

FSH Watch

A publication of the FacioScapuloHumeral Society

Breaking News

New Senate Legislation Shows Solid Federal Commitment To Muscular Dystrophy Research

In April 2001, the *FSH Society, Inc.* played a critical role in developing and shaping new groundbreaking legislation (S.805) for muscular dystrophy research. We are pleased to present the news release at right. For further details please see the article 'Letter from Washington' on page 20 of this newsletter. The *FSH Society* is delighted to have negotiated the situation where all three organizations signed off on the proposed legislation. The *FSH Society* was on top of all the issues at hand and both Capitol Hill and the National Institutes of Health looked to our credibility and guidance in orchestrating the final version of the legislation. All groups respected our position of having spent more than eight years already on the Hill with fifteen congressional testimonies and joined in an unprecedented level of cooperation in reshaping and creating this new legislation.

PRESS RELEASE

Statement of the *FSH Society, Inc.*, the Muscular Dystrophy Association (MDA), and the Parent Project Muscular Dystrophy (PPMD).

New Senate Legislation (S.805) Shows Solid Federal Commitment To Muscular Dystrophy Research

Groups Praise Introduction of MD Care Act

Washington, DC

On May 1, 2001 the hopes of tens of thousands of children and adults living with Muscular Dystrophy and their families were raised by the Senate's introduction of bipartisan Muscular Dystrophy Community Assistance, Research and Education (MD Care) Act (S.805).

The MD Care Act is a breakthrough in securing a real commitment from the federal government toward research, treatment and prevention of various forms of muscular dystrophy

We praise Senators **Paul Wellstone** (D-MN), **Thad Cochran** (R-MS) and **Susan Collins** (R-ME) for their hard work and leadership for standing up for children and adults whose lives have been devastated by muscular dystrophy.

Contact:

Daniel Perez, FSH Society, (781) 860-0501

David Roscow, PPMD, (703) 276-2772

Bob Mackle, MDA, (520) 529-5317

NIH responds to FSH Society's Congressional requests for funding with three research programs

The FSH Society's work in Washington, DC over the last decade comes to fruition as the National Institutes of Health (NIH) announces a series of initiatives to accelerate research on Facioscapulohumeral Muscular Dystrophy (FSHD)

For the first time since its inception, the NIH has requested grant applications whose sole purpose is to explore and develop research that will broaden the base of inquiry on FSHD. Three (3) different major programs have been announced in the last two months guaranteeing funds for research on FSHD.

As you know, a tremendous amount of work, time and effort has gone into making these contracts and programs a reality. This is a direct result of our efforts to inform the NIH of the critical needs in FSHD research and more than six years of testimony given before the U.S. Congress. We are pleased that the hard work of the *FSH Society*, the research and clinical community and the directors and staff of the NIH has resulted in the establishment of dedicated contracts and general research programs as well as a patient registry specifically for FSHD and research on FSHD. These programs effectively represent a fifteen-fold

increase over the NIH's historical spending levels on FSHD. This is the direct result of *FSH Society* efforts.

This is wonderful news for us. Many of us have worked hard to get this far with the NIH and we feel that four coordinated efforts are responsible for this. First, the *FSH Society* testifying before the congressional and senatorial appropriation committees; second, the generous gift of seed money from Mrs. **Marjorie Bronfman** to start a wide array of post doctoral research projects, the Delta Railroad Construction Company research grants, and all the other members of the *Society* for their support of annual research fellowships and projects; third, the help from those of you who contacted your Representatives and Senators; and, fourth, the help from numerous Representatives and Senators who acted on our behalf.

We are also indebted for the strong support

we have received from Senator **Arlen Specter**, Chairman of the Senate Appropriations Subcommittee on Labor, Health and Human Services, Education and Related Agencies and members of the U.S. Senate Appropriations subcommittee and from his staff as well as Representative **John Porter**, Chairman, U.S. House Appropriations Subcommittee on Labor, Health and Human Services, Education and Related Agencies and members of the U.S. House Appropriations subcommittee and from his staff. Without their understanding of our needs and their cooperation in our efforts these grants might not have been developed.

Many of the action items outlined by the international community of researchers, scientists and clinicians working on FSHD during the 2000 International Conferences (May 8-9, 2000) on FSHD in Bethesda, MD are listed. We are deeply indebted to the

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General Counsel

Morgan Downey
 Suite 300, 1250 24th Street N.W.
 Washington, DC 20037
 (202) 466-0580
 (202) 776-7712 Fax

Executive Director

Carol A. Perez, M.Ed.

Boston Office

Carol A. Perez
 FSH Society, Inc.
 3 Westwood Road
 Lexington, MA 02420
 (781) 860-0501
 (781) 860-0599 Fax
 carol.perez@fshsociety.org

San Diego Office

Stephen J. Jacobsen
 FSH Society, Inc.
 1507 Traske Road
 Encinitas, CA 92024
 (760) 632-5411
 stephen.jacobsen@fshsociety.org

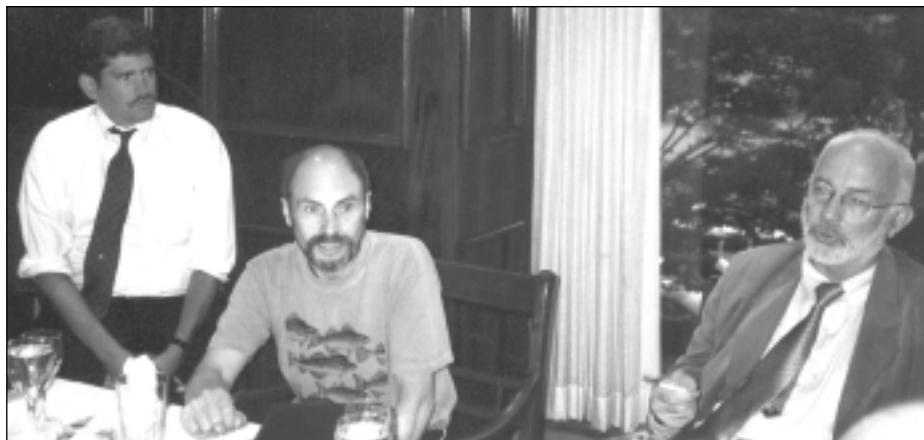
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Letter from the President

This tenth edition of the *FSH Watch* is dedicated to the memory of **Kiichi Arahata** M.D. of Tokyo, Japan and to FSHD research issues. Dr. Arahata was a leading expert in the field of FSHD research and a world renowned

researchers, academic institutions, and many interested individuals.

We continue to accumulate and disseminate high quality information about FSHD.



Meeting in the fall of 1999 between the FSH Society and the Association Française Contre les Myopathies (AFM — French Muscular Dystrophy Association) and Genethon to discuss research priorities and directions for major international efforts on FSHD. Left to right: Daniel Paul Perez, President & CEO, FSH Society, Lexington, Massachusetts, Dr. Louis Kunkel, Children's Hospital, Boston, Massachusetts, Pierre Birambeau, Group President, Association Française Contre les Myopathies (AFM), Evry cedex, France.

authority in muscle disease. Dr. Arahata's sincerity, kindness and presence lit up the room, as the sun passes over a meadow on a cloud-covered day, with an optimism, happiness and a hope that answers would soon be found for patients with FSHD. One of Kiichi's images that stands out clearly in my mind is from the close of one of the FSHD research meetings. It was raining. There was an enormous amount of frenetic activity as members hurriedly departed from the meeting to catch cabs, planes and transportation. Dr. Arahata saw Dr. **Stephen Jacobsen** waiting in the rain, went to him and opened his umbrella to shelter them both. He stayed and waited in the rain with Dr. Jacobsen until the accessible van came. We will miss Kiichi dearly.

The year 2000 was an extraordinary year for FSHD research and the *FSH Society's* efforts to promote FSHD. There have been many exciting developments since our last newsletter. Let me point out some of the enormous gains that the FSH Society has accomplished on a very modest budget for FSHD research and individuals concerned and involved with FSHD in the last eleven years.

We have created a clearinghouse for information on the FSH disorder, related drugs and devices for the treatment of FSHD, and foster communication among individuals, families, caregivers, charitable organizations, government agencies, industry, scientific

We continue to encourage and promote increased scientific and clinical research and development on the causes, alleviation of suffering and the cure of FSHD, including without limitation, the promotion of research and development for the treatment of FSHD for which funding may not otherwise be generally available.

We continue to solicit grants and contributions from private foundations, the pharmaceutical industry and others to support such research and development.

We continue to make grants and awards to qualified applicants to accomplish the much needed research and development.

We continue to represent individuals and families with FSHD not otherwise represented by effective organizations and to work cooperatively and collegially with related organizations, including but not limited to the Muscular Dystrophy Association.

We continue to educate the general public, relevant governmental bodies, and the medical profession about the existence, diagnosis and treatment of FSHD.

This year, testimonies were again submitted before the U.S. House of Representatives and the U.S. Senate regarding appropriations for research on FSHD in 2000 and early 2001 and several more rounds of testimony will occur

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President's Letter

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over the next few months.

We are known by the Muscular Dystrophy Association (MDA), the Association Française Contre les Myopathies (AFM, the French MDA), the National Institutes of Health (NIH) and the key institutes responsible for FSHD research which are the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), as the authority on FSHD research and policy issues. We work very closely with the Stichting FSHD (The Dutch FSHD Foundation) on global plans, priorities and high profile collaborative projects on FSHD. We are also well known and respected by members of the U.S. House of Representatives and the U.S. Senate and key congressional members as the voice for FSHD.

You will find details of the projects the Society has funded and the excellent quality of fellows that we attract to carry out FSHD research on page(s) 41-45 and 49.

We are indebted to Mrs. **Marjorie Bronfman, Larry and Ida Laurello** and the countless number of members and donors who donated to the Research & Education Fund to make this program successful. A review of researchers section and research bibliography in this newsletter demonstrates the impact that we are having globally.

The Scientific Advisory Board (SAB) of the *FSH Society* is unparalleled in its capacity to evaluate research on FSHD. The SAB has diligently carried out its mission of providing strategy for FSHD research, recruiting and attracting qualified researchers, selecting and evaluating research proposals, granting fellowships and monitoring ongoing projects. We are thankful for the excellent leadership provided by Dr. **David Housman** and the expert counsel and advice from the many outstanding members of the SAB.

We have brought together and networked people living with FSHD and involved with FSHD. Through the Internet, our web site (www.fshsociety.org) and chat room ([#fsh_society](http://webboard.novatech.net:7000)) the *Society* is in every corner of the world. Now our extended family, the "Tribe of FSHD," is more than 2000 plus families strong, a far cry from the dozen families of a decade ago.

All aspects of our program are vital to succeeding in conquering FSHD and this newsletter provides a valuable and optimistic view for those involved with FSHD. We are

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Research Fund Donation

From Colorado, **Vickie and Mark Ray's** generous contribution to the Research and Education Fund to support research on FSHD significantly increases the availability of grants. Thank you to the Rays who chose the *FSH Society* to benefit those near and dear to them.

FUNDING

NIH Funding *continued from front page*

research and clinical community for their scientific input and for making this a reality.

The *FSH Society* strongly encourages FSHD researchers to apply for these grants. It is absolutely imperative that the research community continue to grow this area of research by submitting high quality proposals in sufficient quantity.

All three programs are sponsored jointly by the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Arthritis and

Musculoskeletal and Skin Diseases (NIAMS) at the NIH. On November 8, 2000, the first of the three major announcements was made as a one time contract program titled "Request For Applications (RFA) number AR-01-002: Exploratory Research on Facioscapulohumeral Muscular Dystrophy." On December 11, 2000, the second announcement was made in a national news release announcing the establishment of a perpetual National Patient Registry at the University of Rochester Medical School for FSHD under a contract program

numbered contract N01-AR-02250. On January 4, 2001, the third announcement was made as a three year "Program Announcement with Set-Aside (PAS) number PAS-01-041: Therapeutic and Pathogenic Approaches for the Muscular Dystrophies."

We are delighted with these monumentally important and critical steps towards finding solutions for FSHD. The *FSH Society* is pleased to share this information as it represents a major step forward in FSHD research. We hope

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Program announcement summaries

PAS-01-041: A NIH program announcement for Facioscapulohumeral Disease (FSHD)

On January 4, 2001, NIH announced a three year "Program Announcement with Set-Aside (PAS) number PAS-01-041: Therapeutic and Pathogenic Approaches for the Muscular Dystrophies" in the amount of approximately \$5-\$15 million for FY2002-2004.

- strong emphasis is placed on FSHD in the program announcement;
- regular grant application deadlines in February, June and October for three years;
- applications may be submitted by domestic or foreign for-profit and non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of state and local governments, and eligible agencies of the federal government;
- for fiscal years 2002-2004 \$5-\$15 million is available to cover direct costs;
- the mechanisms of support will be the individual research project grant (R01) and the program project grant (P01);
- NIH internet hyperlink: <http://grants.nih.gov/grants/guide/pa-files/PAS-01-041.html>

- grant application deadline March 14, 2001;
- applications may be submitted by domestic or foreign for-profit and non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal government;
- for fiscal year 2001 at least \$1 million is available to cover direct costs and it is anticipated that at least five grants will be awarded;
- three years of support may be requested with each application;
- the applicants may request under the R21 mechanism of funding up to \$150,000 "for support of creative, novel, and/or high risk/high payoff approaches that could produce innovative advances in the field.
- NIH internet hyperlink: <http://grants.nih.gov/grants/guide/rfa-files/RFA-AR-01-002.html>

- information source where researchers can obtain data for analysis associated with FSHD;
- registry's independent scientific advisory committee will make recommendations about enrollment criteria, monitor and improve ways to recruit patients and investigators, and assess progress. It will also revise and extend methods for collecting and handling data and determine possible clinical studies;
- Drs. **Moxley** and **Tawil** at the University of Rochester, Rochester, N.Y. will lead the effort for the registry;
- patient enrollment for the registry is currently projected to begin in fall 2001;
- NIH internet hyperlink: <http://www.nih.gov/news/pr/dec2000/niams-11.htm>

Announcing RFA: AR-01-002 A NIH Request For Application (RFA) for Facioscapulohumeral Disease (FSHD) \$1 million minimum

RFA: AR-01-002: Exploratory Research on Facioscapulohumeral Dystrophy

National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institute of Neurological Disorders and Stroke

N01-AR-02250: National Patient Registry for FSHD Approximately \$400,000 annually perpetually

- registry scientists will seek out and classify patients with clinically diagnosed FSHD, and store their medical and family history data;
- central



Discussing science, research and policy at the National Institutes of Health (NIH) Planning meeting May 9, 2000 in Chevy Chase, Maryland. Left to right: Dr. Kurt Fishbeck, the NIH National Institute of Neurological Disorders and Stroke (NINDS), Dr. Rune Frants, Leiden, The Netherlands.

MISSION

FSH Society Board update

The Board of Directors of the FSH Society has established a **Board Member Emeritus** position to acknowledge extraordinary contributions of members who wish to continue to serve the Society. **Judge William E. Hall**, De Ridder, LA and **Dr. Robert H. Brown**, Boston, MA have accepted their nomination. Dr. Brown will continue to serve as a full member of the Scientific Advisory Board.

Dr. William R. Lewis (Senior) has accepted the **Vice-Chairman** position and the Board has expanded its membership with the acceptance by **E. Ann Biggs-Williams**, **Robert F. Smith** and **Z. John Stekly**.

E. Ann Biggs-Williams: A founding member of the FSH Society and leader of the Society's Gulf Support Group, is a retired college librarian lives Brewton, Alabama. Active in many community organizations as is her husband, Biggs-Williams participated in all our conferences, researched FSHD issues and has significantly broadened our knowledge. While doing graduate work in England, Biggs-Williams became active with the FSHMD Support Group there and linked the FSH Society with the British effort. Diagnosed with FSHD, Biggs-Williams has actively developed resources and networks for FSHD families in the South including DNA testing information.

Robert F. Smith: A partner in the law firm of Smith & Lach in Dennis Port, Massachusetts, raised in the Amherst, Massachusetts and his wife Patti have lived in Harwich, Massachusetts since 1972. Active in his community including the Town of Harwich Finance Committee, his church, political campaigns at the town, state and federal levels and youth organizations, he is also the Founder and President of The Harwich Conservation Trust, a not for profit organization committed to the conservation and protection of open land. Diagnosed with FSHD at the age of 14, Bob is the only member of his family with the disease. He has been active with the FSH Society, Inc. since 1994 when he started attending the New England Support Group, and has served as a facilitator at the Boston and Denver conferences as well as providing support in many areas of the Society's activities.

Z. John Stekly, Sc.D.: A graduate of Massachusetts Institute of Technology in combined electrical and mechanical engineering, Dr. Stekly has been involved in business, technical, and scientific dealings with China, Japan, Western Europe with contacts not only in the U.S. but globally and is a member of the National Academy of Engineering. He co-founded Magnetic Corporation of America, a developer and manufacturer of superconducting materials and magnet systems for all applications including Fusion, High Energy Physics, and M.R.I. Stekly met with the National Institutes of Health regarding the FSH Society and FSHD research. Dr. Stekly and his wife, Suzanne, reside in Wayland, Massachusetts and participate in the New England FSH Support group. With both his wife and son affected by FSHD, he is personally committed to the mission of the Society.



Robert F. Smith, J.D. of Harwich, Massachusetts joins the Board of Directors of the FSH Society, Inc.

About the FSH Society

The Facioscapulohumeral Society (*FSH Society*) is an independent, non-profit and tax-exempt U.S. corporation organized to address issues and needs specifically related to Facioscapulohumeral Muscular Dystrophy (FSHD). Papers certifying its incorporation, bylaws and tax-exempt status are deposited at the Corporation's East and West Coast offices and the office of its General Counsel in Washington, D.C.

FSHD is a muscle disease with a frequency in the population of between four and 10 per 100,000. The disease is inheritable and the responsible gene is located on chromosome 4. The expression of symptoms requires inheritance of the defective gene from only one affected parent, and an individual of either sex has a fifty percent chance of inheriting the gene from that affected parent. The major consequence of inheriting the disease is that of a progressive loss of skeletal muscle, with a usual pattern of initial noticeable weakness of facial, scapular and upper arm muscles and subsequent developing weaknesses of other muscles of the torso and lower limbs. Early facial weaknesses often provide a clue to the physician that distinguishes this disease from other neuromuscular diseases that can be similar in appearance. The age of onset is variable as is the eventual extent and degree of muscle loss, but noticeable muscle weaknesses are usually present by the age of twenty and are recognizable in all but a small percentage of adults who carry the gene. The prognosis includes both a loss of muscular strength that limits personal and occupational activities of most FSHD individuals and a loss of mobility in perhaps twenty percent of the cases. Hearing loss and retinal abnormalities associated with FSHD have been reported, but the frequency of these effects and their relationship, if any, to the causative gene for the muscle defect are uncertain.

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The Facioscapulohumeral Society (*FSH Society*) is an independent, non-profit and tax-exempt 501(c)(3) U.S. corporation organized to address issues and needs specifically related to Facioscapulohumeral Muscular Dystrophy (FSHD). Contributions are acknowledged for tax purposes.

It is the editorial policy to report on developments regarding FacioScapuloHumeral Muscular Dystrophy (FSHD), but not to endorse any of the drugs or treatments discussed. We urge you to consult with your own physician about the procedures mentioned.

The *FSH Watch* is published by the *FSH Society* and distributed by mail to its members and supporters. To be placed on the mailing list or to submit an article please write to: Carol Perez, *FSH Society*, 3 Westwood Road, Lexington, MA 02420. Articles may be edited for space and clarity. Every effort has been made to ensure accuracy in the newsletter. If you wish to correct an error, please write to the above address. Look for us on the internet at: www.fshsociety.org
Editors: Stephen Jacobsen and Daniel Perez

FUNDING

NIH Funding *continued from page 4*

that you will consider making your 2001 membership contribution today and consider a special donation to help the FSH Society continue its advocacy programs and to increase its resources devoted to these vital programs.

*The FSH Society depends on
YOUR contributions to
continue its work!
Please consider a
tax-deductible
contribution today!*



Discussing research issues during the evening of the National Institutes of Health (NIH) Conference on the Cause and Treatment of FSHD May 8, 2000 in Bethesda and Rockville, Maryland. Left to right: Dr. Enzo Ricci, Institute of Neurology, Catholic University, Rome, Italy, Dr. Luciano Felicetti, Istituto de Biologia Cellulare, CNR, Rome, Italy, Dr. Rossella Tupler, Howard Hughes Medical Institute, University of Massachusetts, Worcester, Massachusetts and Biologia Generale e Genetica Medica, Pavia, Italy.

FSH Society at work - A chronology of 2000

by Daniel Paul Perez, President and CEO of the FSH Society

Research Grants

The Scientific Advisory Board (SAB) of the FSH Society, with Dr. **David Housman's** expert leadership, diligently carried out its mission of providing strategy for facioscapulohumeral muscular dystrophy (FSHD) research, recruiting and attracting qualified researchers, selecting research proposals, evaluating research proposals, granting fellowships, and monitoring ongoing projects and research opportunities. We receive counsel and advice from the outstanding members of the SAB, many of whom also advise the Muscular Dystrophy Association (MDA) and serve on the National Institutes of Health (NIH) panels in the area of FSHD research and proposals relating to muscular dystrophy.

The FSH Society's mission with the Mrs. **Marjorie Bronfman's** grant is to attract promising researchers to FSHD research. The FSH Society's Marjorie Bronfman fellowship grant program is part of our overall effort to accelerate funding on FSHD by fostering promising research. The NIH, MDA, and the Association Française Contre les Myopathies (AFM - French Muscular Dystrophy Association) are aware of our commitment to carry out such a program and hopes, as we do, that such funds will give new and existing investigators the opportunity to apply for NIH, MDA and AFM grants.

The FSH Society fellowship grant program

is mutually exclusive with the MDA grant policy in general. The FSH Society fellowships are to be used as stepping-stones to MDA and NIH grants. It is easier for FSH Society grantees to access other funding institutions when those reviewers know that the prestigious FSH Society SAB has already reviewed the research and time to publication is reduced.

The FSH Society research grant program addresses the concerns that:

- each project is conducted under the supervision of a well-respected geneticist and performed at a reputable institution—the grant process, materials and peer review insure this;
- any fellowship awarded falls within the scope of a well-defined research project—considerable information is requested through the letter of intent and the full application regarding this;
- the researcher complies with the terms and condition of his/her grants and submits timely progress reports—the terms and conditions are well stated, clear, in the best interest of the FSHD patient community [patents] and legally binding;
- budgets are adhered to—we request budgets and overlap if it exists and the SAB determines if the fellowship is producing at an according rate; and
- The FSH Society Scientific Advisory Board (SAB) will recommend the timely cut-off of funding if a project is not proceeding satisfactorily—we have had several reviews of nine-month reports and have every indication

from the SAB that it will discontinue any project that is not adequate.

Research Advancements

In less than three and a half years since the FSH Society and Mrs. Marjorie Bronfman began building the foundations for new discoveries in FSHD, we have made remarkable progress. We brought FSHD research planning from a rough sketch to a concrete and tangible blueprint. With the yearly process between the Congress and the National Institutes of Health and numerous iterations of grant application processes through FSHD funding agencies worldwide (MDA, NIH, AFM), there emerged a picture with clarity and definition of what needs to be done in FSHD research. This is directly the result of the FSH Society and the generosity of its supporters.

Through our research programs, we see many things never seen before in FSHD. In recent months, Dr. **Figlewicz**, with Dr. **Winokur**, reports the first tangible evidence of a biochemical pathway failure in FSHD. Drs. Winokur and Figlewicz have found that FSHD muscle is extremely susceptible to oxidative stress.

Dr. **Robert Bloch**, currently a Delta Railroad fellow and applicant for a M&GBF grant reports findings and evidence of muscle structure anomaly in FSHD tissue through

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SOCIETY'S ADVANCES

Chronology, 2000 *continued from page 6*

con-focal laser microscopy and electron microscopy and, "... although still preliminary, our ideas constitute the first specific cell biological model for FSHD and suggest obvious ways that this model can be tested."

Dr. **Silvère van der Maarel** has produced five critical lines of transgenic mice and continues to be prolific in producing insight into FSHD mechanisms. This is another first, since no one else has succeeded in producing these lines of mice.

Dr. Sara Winokur, University of California at Irvine, collaborating with and networking researchers, has begun the process of gene expression array testing with the new technology of gene chips whereby we can study the expression of tens of thousands of genes in a single sample of tissue. Dr. Winokur's work has produced surprising insight into FSHD genes and the mis-regulation of skeletal muscle genes in FSHD. Dr. Winokur's work on FSHD with gene chips is another first. She is pioneering the way for understanding clearly and comprehensively what happens genetically in FSHD.

We can no longer say, "there is no known cause or cure for FSHD" as we gain knowledge and clues about FSHD. We now have a tangible handle on global gene mis-regulation in FSHD. For the very first time, we see visible evidence in photographic form of the possible disruption in the muscle membrane structure where the underlying contractile apparatus binds to the tissue (the sarcolemma) in FSHD. We see, for the very first time, that FSHD muscle cells are organized quite differently from normal muscle cells and are highly sensitive to being destroyed by oxidative stress. We understand, for the very first time, that some of the D4Z4 repeats have a nuclear signal and may have a role in transcription of genes into proteins. We are now able to examine each of the repeats individually and ascertain their function. We see now, for the first time, an entire symphony of genes on a biological array chip; it looks like a chessboard with 100 by 100 squares colored differently and in gradients representing gene expression data. Our research is showing how amazingly

dimensional and profoundly complex the FSHD mechanism is. Although beautifully and utterly complex, we are able to get around this and get a handle on what causes FSHD through more traditional avenues of study by looking at the discrete parts of the problem.

Despite the complexity of this biological architecture around FSHD, we should be able to gain insight into where the muscle is failing and what causes its failure by both understanding how the entire symphony in 4q35 D4Z4 deletions works and by individual areas of investigation. Instead of broken genes, we have found that the structure that holds

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About the FSH Society

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The *FSH Society* was created because of a need for a comprehensive resource for FSHD individuals and families. Purposes of the organization are:

- to encourage and promote scientific and clinical research and development through education of the general public, governmental bodies and the medical profession;
- to support such research and development through solicitation of grants and contributions from private foundations, the pharmaceutical industry and others;
- to accumulate and disseminate information about FSHD;
- to actively cooperate with related organizations and foster communication among all interested parties; and
- to represent individuals and families with FSHD.

The *Society* invites contact from any interested individuals, families, physicians, caregivers, charitable organizations, government agencies, industry, scientific researchers and academic institutions. Any inquiries regarding membership, charitable donations, purposes and goals or other issues pertaining to the *Society* and FSHD, should be addressed to the east or west coast offices.

New York Community Trust Foundation awards \$250,000 grant

In March 2000, at the request of an anonymous donor, The New York Community Trust awarded an annual grant of \$50,000 for five years to the FSH Society, Inc. The Society is truly and deeply touched and amazed with the generosity and respect demonstrated by this gift. Recognizing that this is the highest form of charity, we express our gratitude to our anonymous donor.

Thanks to our anonymous donor and the New York Community Trust, these funds provide the resources to develop our organization into a responsive Society.

President's Letter *continued from page 3*

still working against time to improve the quality-of-life and literally save lives. We are getting the word out that there is a genetic test for FSHD, helping to make the test available and nearing the completion of a brochure on genetic testing for FSHD.

A long time ago, we embarked on the very difficult journey to find clues, search for meaning and to find answers for FSHD. What we are doing is hard but we are winning the battle.

The *FSH Society* makes the difference and we hope that you will choose to walk with us. We hope that the *Society* provides the same shelter and kindness as that of Dr. Kiichi Arahata and his umbrella for those dealing with the very hard realities of FSHD. As always, we thank you for your steadfast support and hope that you will seriously consider continuing with us and generously increasing your financial support. Please join today and make a sizable contribution to make sure that our work continues to make a difference for all those living with FSHD.

Daniel Paul Perez, President & CEO, FSH Society, Inc.

EDUCATION/NIH RESEARCH

National Institutes of Health (NIH) establishes National Patient Registry for FSHD

The FSH Society is delighted to inform you that on December 11, 2000 the National Institutes of Health (NIH) issued a national news release announcing the establishment of a National Patient Registry for FSHD. The NIH National Registry will be for two muscular dystrophy types — facioscapulohumeral (FSHD) and myotonic (DM) muscular dystrophy. The project is funded under NIH contract # N01-AR-02250.

This is in addition to the recent contract request from the NIH For Applications (RFA) number AR-01-002: *Exploratory Research on Facioscapulohumeral Muscular Dystrophy*.

As you know a tremendous amount of work, time and effort has gone into making both of these contracts a reality. This is a direct result of our efforts to inform the NIH of the critical needs in FSHD research and more than six years of testimonies given before the U.S. Congress. We are pleased that the hard work of the FSH Society, the research and clinical community, and the directors and staff at NIH has resulted in the establishment of a patient registry specifically for FSHD and research on FSHD.

The Registry is sponsored jointly by the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). Drs. **Moxley** and **Tawil** at the University of Rochester will lead the effort for the registry. Patient enrollment for the registry is currently projected to begin in fall 2001. Please see inline text and hyper-linked news release for further information.

We are delighted with this monumentally important and critical step towards finding solutions for FSHD.



Contact:

Ray Fleming, Office of Communications and Public Liaison (301) 496-8190
National Registry Established for Two Muscular Dystrophy Types

People with myotonic dystrophy (DM) and facioscapulohumeral dystrophy (FSHD) and their families will benefit from a new national research registry established by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and the National Institute of Neurological Disorders and Stroke (NINDS), both parts of the National Institutes of Health (NIH). The registry will be based at the University of Rochester, Rochester, N.Y.

Registry scientists will seek out and classify patients with clinically diagnosed forms of DM and FSHD, and store their medical and family history data. The registry will also be a central information source where researchers can obtain data for analysis associated with these diseases.

The registry's scientific advisory committee will make recommendations about enrollment criteria, monitor and improve ways to recruit patients and investigators, and assess progress. It will also revise and extend methods for collecting and handling data and determine possible clinical studies.

NIAMS Director **Stephen I. Katz**, M.D., Ph.D., said, "This national registry will be an important resource to provide hope to families and encourage scientists in finding a cure for these two disabling diseases. It will also hasten the course of research for more in-depth answers to what happens in muscular dystrophy."

Richard Moxley III, M.D., is the lead investigator for the registry. "Research has uncovered recent clues to genetic, chromosomal and DNA errors in those with DM and FSHD," he said. "I am pleased to lead scientists in collecting and analyzing new research data for better treatments for these two diseases."

DM and FSHD are two of the nine types of muscular dystrophy. They can be detected through testing at birth, and may be passed from one generation to the next. Both cause progressive, disabling weakness. In addition, DM sometimes results in sudden death.

DM is divided into four different types, all of which are accepted by the registry: congenital, juvenile, adult and late onset. It is marked by a generally slow progression of weakness and muscle wasting affecting the face, feet, hands, neck and glandular system. Muscles are unable to relax properly after contraction. DM affects both males and

females. The cause is unknown.

FSHD is marked by weakness in the facial muscles and weakness and wasting in the shoulders and upper arms. It may progress either slowly or rapidly. FSHD affects both males and females, and a child from an affected parent has a 50 percent risk of inheriting the disease. It is the third most common genetic disease of skeletal muscle. The cause is unknown.

Patient enrollment for the registry is currently projected to begin in fall 2001. The project is funded under NIH contract #N01-AR-02250.

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) is a component of the National Institutes of Health. The mission of the NIAMS is to support research into the causes, treatment and prevention of arthritis and musculoskeletal and skin diseases, the training of basic and clinical scientists to carry out this research, and the dissemination of information on research progress in these diseases. For more information about NIAMS, call our information clearinghouse at (301) 495-4484 or (877) 22-NIAMS (free call) or visit the NIAMS web site at <http://www.nih.gov/niams>.

To be placed on a list to receive information when registry enrollment begins, contact:

Lynn Cos, R.N., C.C.R.C.
Neuromuscular Disease Center
University of Rochester
601 Elmwood Avenue
Box 673

Rochester, NY 14642
716-275-7680,

lynn_cos@urmc.rochester.edu
<http://www.nih.gov/news/pr/dec2000/niams-11.htm>



Discussing FSHD research during the evening of the National Institutes of Health (NIH) Conference on the Cause and Treatment of FSHD May 8, 2000 in Bethesda and Rockville, Maryland. Left to right: Dr. David Housman, M.I.T., Cambridge, Massachusetts, Chairman FSH Society, Scientific Advisory Board; Dr. Kathy Mathews, University of Iowa Hospitals and Clinics, Iowa City, Iowa.

Conference on the Cause and Treatment of Facioscapulohumeral Muscular Dystrophy

Agenda • Lister Hill Auditorium, National Institutes of Health (NIH) – May 8, 2000

- 7:15 Registration and Continental Breakfast
 8:00 Welcome and Opening Remarks:
Stephen I. Katz, M.D., Ph.D. – NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
Gerald D. Fischbach, M.D. – NIH National Institute of Neurological Disorders and Stroke (NINDS)
Stephen Groft, Pharm.D. – NIH Office of Rare Diseases (ORD)
 8:10 Introduction: **Denise Figlewicz, Ph.D.**, Chair
 8:20 The Patient Perspective of FSHD, **Daniel Paul Perez**, President & CEO, FSH Society, Inc.
 8:30 Session 1: Facioscapulohumeral muscular dystrophy (FSHD) phenotype/Clinical studies
 Session Chair: **George W. Padberg, M.D.**
 8:30 FSHD: Clinical criteria, natural history, challenges that remain – **Rabi Tawil, M.D.**
 8:45 Muscle strength training in FSHD – **Elly van der Kooij, M.D.**
 9:00 One year clinical trial of Albuterol in FSH dystrophy – **John Kissel, M.D.**
 9:15 Respiratory insufficiency in facioscapulohumeral dystrophy – **Marielle Wohlgenuth, M.D.**
 9:30 Evidence for cardiac involvement in patients with genetically demonstrated facioscapulohumeral muscular dystrophy – **Pascal LaForet, M.D.**
 9:45 An unusual phenotype in FSHD – **Gaku Yamanaka, M.D.** and **Kiichi Arahata, M.D.**
 10:00 Facioscapulohumeral muscular dystrophy, type 2 (FSLD2) in Russian families – **Valery M. Kazakov, M.D.**
 10:15 A clinical and genetic study of FSHD families with borderline 4q35 EcoRI fragments – **Herbert Schreiber, M.D.** and **Manuela Koch, M.D.**
 10:30 — Coffee Break —
 11:00 Session 2: Molecular diagnostics/Genotype-phenotype studies Session Chair: **Rabi Tawil, M.D.**
 11:00 Guidelines for molecular genetic diagnosis – **Rune R. Frants, M.D.**
 11:15 Control data set of fragment sizes and BlnI-sensitivity type of FIGE—for comparison with parents of new mutation FSHD cases – **Peter Lunt, M.D.**
 11:30 Somatic mosaicism in de novo FSHD families – **Kanako Goto, B.S.** and **Kiichi Arahata, M.D.**
 11:45 Mosaicism and FSHD – **Lionel Van Maldergem, M.D.**
 12:00 Genotype/phenotype correlations – **Maria Manuela, Ph.D.**
 12:15 Nonchromosome 4-linked FSHD – **Marcy Speer, Ph.D.**
 12:30 — Lunch —
 1:30 Session 3: Gene targets of the FSHD mutation/Molecular mechanisms of FSHD pathogenesis Session Chairs: **Jane Hewitt, Ph.D.**, and **Denise Figlewicz, Ph.D.**
 1:30 A dosage test for 4q35;10q26 subtelomeric translocations – **Tsuyoshi Matsumura, M.D.** and **Kiichi Arahata, M.D.**
 1:50 Interchromosomal 4qter-10qter exchanges in normal and FSHD-affected individuals – **Luciano Felicetti, M.D.**
 2:10 Comparative mapping of the FSHD region – **Jane Hewitt, Ph.D.**
 2:30 Studies on the DUX genes and proteins – **Alexandra Belayew, Ph.D.**
 2:50 Update on Myd and Drosophila models – **Kathy Mathews, M.D.**
 3:10 Methylation of the FSHD-associated D4Z4 repeats – **Melanie Ehrlich, Ph.D.**
 3:30 — Coffee Break —
 4:00 Candidate genes and transgenic mouse models – **Silvère van der Maarel, Ph.D.**
 4:20 Analysis of differentially expressed genes in FSHD dystrophic muscle – **Rossella Tupler, M.D.**
 4:40 Microarray analysis of gene expression in FSHD – **Sara T. Winokur, Ph.D.**
 5:00 Gene expression studies in FSHD – **Denise Figlewicz, Ph.D.**
 5:20 Panel Discussion: Future directions for FSHD research Chairs: **Robert C. Griggs, M.D.**, and **Silvère van der Maarel, Ph.D.** Panel Members: **Kiichi Arahata, M.D.**; **Alexandra Belayew, Ph.D.**; **Denise Figlewicz, Ph.D.**; **Rune R. Frants, M.D.**; **Kathy Mathews, M.D.**; and **Sara T. Winokur, Ph.D.**
 6:00 — Adjournment —
 7:00 Dinner sponsored by the FSH Society, Inc.

Opening remarks given by **David Housman**, Chairman FSH Society, Scientific Advisory Board and **Daniel Paul Perez**, President & CEO, FSH Society

May 8, 2000

National Institutes of Health
 Lister Hill Auditorium,
 Bethesda, Maryland

3rd International Conference on the Cause and Treatment of FSHD

by **Daniel Paul Perez**, President & CEO,
 FSH Society

Welcome to the 3rd International Conference on the Cause and Treatment of FSHD. What a pleasure it is to see you all here today. I thank you for coming from all parts of the world and for your dedication and encouragement to all people living with facioscapulohumeral muscular dystrophy.

Let me begin by giving you a patient perspective on facioscapulohumeral disease (FSHD). I am a curious, intense and caring man with FSHD and adjusted to my disease and the issues involved. I am accepting of the uniqueness and challenges that this disease brings to bear. Although I accept my condition, I simply do not accept the loss of control and the unpredictable and uncontrollable nature of this disease. I will not accept indifference, trivializing, benign neglect or apathy towards finding the cause and treatment for FSHD or toward any individual with FSHD by any individual, institution or bureaucracy.

The journey that FSHD patients travel is a journey that no man, woman or child should ever have to travel or endure. It is a journey of alternating darkness and illumination in every realm and aspect of life.

FSH disease is a strong fort, it will last several life times. The insights that this disease yields are a testament to the goodness of human nature and the powerfully triumphant spirit of the human psyche. No one would choose to live a lifetime with devastating disease and debilitating constant decline. To be candid, the losses are utterly unbearable and seeing what this disease does to me and my mother, **Carol**, and others loved and dear to me in the FSH Society is traumatic and hard to take. FSHD is simply what it is. It is a hard way to live.

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A complete copy of the agenda, meeting abstracts and roster for the 2000 FSHD Workshop may be requested through the FSH Society, Inc., 3 Westwood Road, Lexington, MA 02420 USA for US\$20.

EDUCATION/NIH RESEARCH

May 8, 2000

Opening remarks: 3rd International Conference on the Cause and Treatment of FSHD continued from page 9

Those in this room who have known me the longest (other than my family) and who have seen the progression of my disease are Dr. **Jacobsen** and the NIH. I now know that Dr. **Jacobsen** fully knew where I would be heading, having

already traveled the distance and that the NIH is just beginning to realize where I am heading and what this disease is about. I remain optimistic and determined to enjoy life as it is precious and it can be lived under even the most extenuating circumstances.

I knew that our journey would be unique more than a dozen years ago when I founded the *FSH Society*. I had not realized how profoundly different my life would be living and working with others working on this disease. I sincerely enjoy working on the problem of FSHD.

We are here today as a result of more than a decade of persistence and determination on the part of the *FSH Society*. The *FSH Society* is proud to sponsor this conference in conjunction with the National Institute of Neurological Disorders and Stroke (NINDS/NIH), the National Institute of Arthritis, Musculoskeletal and Skin Diseases (NIAMS/NIH), the Office of Rare Disease (ORD/NIH), the Muscular Dystrophy Association (MDA), the Association Française contre les Myopathies (AFM) and the Dutch FSHD foundation.

The *FSH Society* has given 12 Congressional testimonies in seven years and has succeeded in three, and soon to be four, successive years in incorporating report language on FSHD in both U.S. House and U.S. Senate Appropriations Committee Reports accompanying the budget. We have had over one hundred and seventy-five meetings and interactions with the NIH Institutes primarily



The National Institutes of Health (NIH) Planning meeting May 9, 2000 in Chevy Chase, Maryland. Left to right: Dr. Henry Epstein, Baylor College of Medicine, Kees C.J. van der Graaf, Dutch FSHD Foundation, Dr. Denise Figlewicz, University of Rochester, Daniel Paul Perez, FSH Society, Dr. Cheng Zhang, Sun Yat-Sen University of Medical Sciences, Guangzhou, China, Dr. Kurt Fishbeck, the NIH National Institute of Neurological Disorders and Stroke (NINDS), Dr. Jane Hewitt, Nottingham, England, Dr. Rume Frants, Leiden, The Netherlands, Dr. Eric Hoffman, Children's Research Institute, Washington, DC.

responsible for FSHD. We have the distinct honor of working with the prestigious and talented directors and staffs of all three of these institutes for almost a decade.

To date, we have launched ten new fellowships and initiatives in FSHD research which have led to remarkable insight and further progress on finding the solution for FSHD. All of our grantees are here today and we are blessed with their top rate and remarkable intellect, thoughtfulness and sincerity. The *FSH Society* has recently negotiated close to another \$500,000 dollars for fellowships and we will continue the course. I would expressly like to thank Dr. **David Housman** and the members of the Scientific Advisory Board for their dedication and fine insight and judgement on scientific issues.

The meetings today and tomorrow are congressionally mandated and the expectations of the directors and staff of the NIH, researchers, clinicians and patient advocates are clear. Congress expects this meeting to yield a viable road map for research funding mechanisms with the next steps and special opportunities for research on FSHD. Congress has become concerned about what is happening and what is not happening in FSHD. Senator **Arlen Specter** asked me to relay the following to you:

"Please extend my sincere best wishes to the scientists, researchers,

clinicians and leaders from the National Institutes of Health attending the Research Planning Conference on facioscapulohumeral Muscular Dystrophy (FSHD).

"Several years ago, at the behest of you and your colleagues in the *FSH Society*, Congress directed that NIH convene this conference to map out a research strategy on one of the most serious causes of muscular disease in this country, FSHD. Thanks to your

leadership and persistence, this conference is now a reality.

"As you know, my colleagues and I continue to work to significantly expand the biomedical research budget for the National Institutes of Health. I believe society makes the best investment when it helps the health and

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Dr. Valery M. Kazakov, Pavlov's Medical Institute, St. Petersburg, Russia discusses latest research issues among Russian families at the Lister Hill Auditorium on the campus of the National Institutes of Health (NIH) during the day of the Conference on the Cause and Treatment of FSHD May 8, 2000 in Bethesda, Maryland.

EDUCATION/NIH RESEARCH

May 8, 2000

Conference Overview

Lister Hill Auditorium, National Institutes of Health

Sponsored by: The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS); The National Institute of Neurological Disorders and Stroke (NINDS); The NIH Office of Rare Diseases (ORD); The FSH Society, Inc.; The Muscular Dystrophy Association of America

Facioscapulohumeral muscular dystrophy (FSHD) is the third most common genetic disease of skeletal muscle. It has an estimated frequency of one per 20,000. FSHD is inheritable, and a child of either sex has a risk of 50 percent of inheriting the disease from an affected parent. The inheritance of the disease inevitably leads to the expression of symptoms, which include progressive weakening of the muscles of the face, shoulder blades, and upper arms. The specific cause of FSHD is not yet known, but most often it has been associated with a mutation toward the terminal end of the DNA strand of chromosome 4.

In May 2000, the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), together with the National Institute of Neurological Disorders and Stroke (NINDS), the NIH Office of Rare Diseases, the FSH Society, Inc., and the Muscular Dystrophy Association of America, co-sponsored a scientific conference on the cause and treatment of FSHD. Researchers from the U.S., Canada, Europe, South America and Asia met on the NIH campus in Bethesda, MD, to share their latest findings and identify exciting directions for future studies on this disease.

The recommendations that emerged from the conference fall into several categories, including efforts to enhance our understanding of the molecular processes and tissue changes associated with FSHD; ways to explore possible therapies to treat the disorder; and strategies to promote the establishment of population-based studies of the disease, as well as needed research resources. These recommendations will be considered as the NIH develops new program initiatives related to FSHD and other muscular dystrophies. For a complete summary of the conference discussion and related recommendations, please see: <http://www.nih.gov/niams/reports/fshdsummary.htm>

Source: NIH NIAMS Internet web site: <http://www.nih.gov/niams/reports/>

May 9, 2000

NIH executive summary & research plan from conference

Day 1

Facioscapulohumeral muscular dystrophy (FSHD) is the third most common genetic disease of skeletal muscle. It affects approximately one in 20,000 persons. It is inherited in an autosomal dominant way, so that a single copy of the defective DNA may cause disease. Researchers have identified the mutation associated with more than 95% of cases. Though the nature of the DNA mutation is known, it has not yet been possible to identify a gene or mechanism that causes the disease.

The DNA mutation consists of deletions of copies of sections of DNA (called whole repeat units), each called D4Z4, located near the short end of chromosome 4, identified by the term 4q35. Each repeat unit, called D4Z4, consists of 3.3 kilo bases of DNA, meaning that it is a strand of more than three thousand individual nucleotides (the structural units that compose DNA). The number of such repeats in a person unaffected by FSHD ranges from twelve to one hundred. In affected individuals, disease severity increases as the number of repeats decreases below ten.

During the conference, researchers discussed the clinical criteria of FSHD and reported new clinical observations. Clinicians presented the results of a one-year double-blind clinical trial using albuterol, a drug that

normally increases muscle mass. The results of this study in FSHD patients were largely negative, except for slightly improved grip strength and preservation of skeletal muscle mass. Another group assessed the safety and efficacy of muscle strength training in FSHD patients, finding that moderate exercise is safe and dynamic strength training may provide limited gain of dynamic strength specific to the muscles trained. Conferees identified several clinical areas where questions remain, such as determining the incidence of cardiac involvement and tongue and throat weakness in FSHD patients. A further important question is whether males and females have a different relationship between the size of the genetic deletion and clinical manifestations of the disease.

Molecular diagnosis of FSHD is complicated because there is a region of DNA on chromosome 10 which is almost completely identical to the region on chromosome 4 associated with the disease. However, improved biochemical analysis detects slight

differences in the DNA sequence between the regions on chromosomes 4 and 10. Researchers looking at different patient populations and

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Evening of the National Institutes of Health (NIH) Conference on the Cause and Treatment of FSHD May 8, 2000 in Bethesda and Rockville, Maryland. Left to right: Dr. Rune R. Frants, Leiden University Medical Center, Leiden, The Netherlands, Kees C. J. van der Graaf, Stichting FSHD (Dutch FSHD Foundation), Wassenaar, The Netherlands.

EDUCATION/NIH RESEARCH

May 9, 2000

NIH executive summary *continued from page 11*



The National Institutes of Health (NIH) Planning meeting May 9, 2000 in Chevy Chase, Maryland. Left to right: Dr. Alexandra Belayew, Mons, Belgium, Dr. Silwère van der Maarel, Leiden, The Netherlands, Dr. Robert Nussbaum, the NIH National Human Genome Research Institute (NHGRI), Dr. Kathy Mathews, Iowa City, Iowa, Dr. Paul Plotz, the NIH National Institute of Arthritis and Musculoskeletal and Skin Disease (NIAMS), Dr. Kiichi Arahata, NCNP Tokyo, Japan, Morgan Downey, General Counsel, FSH Society, Dr. Richard Lynn, the NIH NIAMS, Dr. H. Lee Sweeney, University of Pennsylvania, Dr. Henry Epstein, Baylor College of Medicine, Dr. Cheng Zhang, Sun Yat-Sen University of Medical Sciences, Guangzhou, China, Dr. Kurt Fishbeck, National Institute of Neurological Disorders and Stroke (NINDS), Dr. Jane Hewitt, Nottingham, England.

unaffected individuals found that genetic events in reproduction frequently result in exchange of genetic material between the similar regions of the two chromosomes. It was suggested that the high frequency of new occurrences of the disease may result from this exchange of DNA between chromosomes 4 and 10. The conferees also addressed the question of the size of the deletion and disease diagnosis, i.e., the smallest region found in asymptomatic family members or control populations. There was general agreement that fewer than eight repeats are uniquely associated with clinical symptoms of FSHD, while more than twelve are relatively rare among FSHD patients. New data presented continue to support the correlation between the size of the DNA deletion and disease severity. Lastly, researchers showed that they could improve molecular diagnostics using a technology called pulsed-field gel electrophoresis, which shows more clearly differences in DNA composition.

There is one family with members who have a clinical phenotype that is virtually indistinguishable from that of FSHD, but whose disease is not linked to the region of chromosome 4 associated with disease in 95% of FSHD patients. This family alone has more than 40 affected individuals and researchers are using it in their search for a second locus for FSHD.

Though no genes have been found in the site of the FSHD genetic defect (4q35), scientists continue to look for genes closer to the center of chromosome 4. They have found a region with the genes ANT and ALP and a newly characterized gene, SMT7. It is likely there are other genes in this area. Expression of the known genes (ANT, ALP, and SMT7) was shown to be significantly higher in skeletal muscle biopsy samples from

FSHD patients compared to controls. Two genes lying closest to the repeats are FRG1 and FRG2. Characterizations of the expression patterns of these two genes, and the roles of their putative gene products, are being carried

out. Researchers are planning on using a mouse model in which it will be possible to cause a higher than normal production of the gene products from genes such as ANT, ALP, and SMT7, which are near the FSHD region of human chromosome 4.

There are several lines of investigation in progress which focus on the D4Z4 repeats themselves. One group has identified a sequence of DNA, which they call DUX4, in the 4q35 region associated with FSHD. These researchers believe that DUX4 may in FSHD patients cause production of a protein that does not appear in unaffected individuals. The DUX4 cDNA sequence and gene product are being studied in cellular and animal models. Another investigator is studying the role of the repeats in chromatin formation (the local chromosome structure based on the DNA strand and associated substances) and repression of adjacent gene transcription, using a fruit fly (*Drosophila*) model in which one can construct strands of genetic material containing different copy numbers and different regions of the 3.3 kilo base repeats. A different approach is based on the observation that chemical attachment of methyl groups to DNA (methylation) is a normal process which can affect the transcription of genes. Studies indicate that the D4Z4 repeats are highly methylated in cells from unaffected people. It

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Discussing FSHD clinical research issues in preparation for the following day's May 9, 2000 planning conference during the evening of the National Institutes of Health (NIH) Conference on the Cause and Treatment of FSHD May 8, 2000 in Bethesda and Rockville, Maryland. Left to right: Dr. Kathy Mathews, University of Iowa Hospitals and Clinics, Iowa City, Iowa; Dr. Richard Lynn the NIH National Institute of Arthritis and Musculoskeletal and Skin Disease (NIAMS); Dr. Henry Epstein, Baylor College of Medicine, Houston; Dr. John Kissel, Ohio State University, Columbus, Ohio.

EDUCATION/NIH RESEARCH

May 9, 2000

NIH executive summary *continued from page 12*

is possible that the deletions in the FSHD region cause a decrease in methylation, which may affect the packing of material attached to the DNA in this region of the chromosome, and disrupt gene expression.

Differential gene expression studies of muscle and regenerative muscle cells (myoblasts) from FSHD patients and controls are now providing the first directions for experiments to explore patho-genetic mechanisms that occur as a consequence of deletion of D4Z4 repeats on chromosome 4. Researchers are studying several proteins, including histone acetyl-transferase (a protein that adds acetyl groups to histones, which appear vital for cellular viability), extra-cellular matrix proteins, and enzymes involved in cell response to the presence of highly reactive oxidative molecules, such as peroxide, which produce oxidative stress. In studies comparing myoblasts (muscle regenerative cells) from people with and without muscle diseases, researchers found that undifferentiated myoblasts from FSHD patients have a unique early sensitivity to highly reactive oxidative molecules, which provides the first biochemical hallmark of the disorder.

Future studies along the many complementary research avenues described at the conference will almost certainly prove fruitful in shedding light on FSHD from the clinical and molecular points of view, clarifying the relationship between genotype and phenotype.

Day 2 Chevy Chase Holiday Inn May 9, 2000

Drs. **Richard Lymn**, NIAMS, and **Giovanna Spinella**, NINDS, opened the second day of the meeting with participant introductions and the background for continuing discussion of FSHD research needs and opportunities. The purpose of the brainstorming session was to build on current knowledge about FSHD and identify research approaches to understanding the riddles of this disease. NIAMS and NINDS invited several researchers expert in areas related to FSHD to bring additional insights into possible approaches to future investigations.

The discussion ranged over possible directions for future research. Major topic areas were approaches to determining pathogenesis, approaches to therapy, and resources needed to move research forward.

Recommendations for future directions, organized by topic, are listed below.

MOLECULAR PROCESSES

Characterize the molecular pathogenesis of FSHD; elucidate the role of the repeats associated with the disease as well as what causes their deletion. FSHD is associated with deletions of copies of whole repeat units from the end (subtelomeric) region of chromosome 4q. The deletion appears to result in global dislocation of gene expression. If the entire region is removed, there are birth defects, but no specific defects on skeletal muscle. Individuals appear to require the existence of 11 or fewer repeat units to be at risk for FSHD.

Determine the relationship between repeat length and its effect on the degree to which disease is manifested (penetrance). Determine also whether the loss of certain repeats is always associated with FSHD clinical expression, since there may be specificity in chromosomal transactions and the resulting development of disease.

Determine the gene sequence and whether the repeats are acting as suppressors or insulating units. The region containing the site associated with at least 95% of FSHD cases is composed almost entirely of the 3.3 kilo base repeats, which are not translated. Few genes have been found near the multi-repeat locus, including FRG1 and FRG2 in adjoining regions, and they do not appear to be related to development of disease. This suggests that FSHD may result from alterations in the chromatin structure, the



Dr. Kathy Mathews, University of Iowa Hospitals and Clinics, Iowa City, Iowa during the evening of the National Institutes of Health (NIH) Conference on the Cause and Treatment of FSHD May 8, 2000 in Bethesda and Rockville, Maryland.

local chromosome structure based on the DNA strand and associated substances. In particular, the data suggest that you need a minimum number of repeats in order to have a compact heterochromatin structure, which is the genetically inert form of chromosome packing. Lack of the compact structure may lead to disease through an unknown mechanism.

Clarify how similarity of regions on chromosomes 4 and 10 may relate to FSHD. There is a region on chromosome 10 that

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Opening remarks *continued from page 10*

well being of each individual. As the NIH budget has grown, the Senate Appropriations Committee is concerned that the benefits of research be available to all Americans. It has appeared to the Committee that, in the past, some neuromuscular disorders including FSHD have not benefited from the increases in research funding.

"We expect that the research plan developed cooperatively on May 8, 2000 and May 9, 2000 by scientists, government leaders and advocates such as yourself will be used by Congress to indicate important areas for future research. I look forward to receiving the report of this conference. It will be an important contribution in setting this and future years' priorities for the NIH."

Last, I would like to thank the organizers and organizing committee of this meeting (the NIH, Dr. **Katz**, Dr. **Lymn**, Dr. **Fischbach**, Dr. **Spinella** and Dr. **Groft** the University of Rochester, Dr. **Figlewicz** and **Tracy Forrester** the FSH Society, **Carol Perez**) for a job well done. I would also like to extend my heartfelt appreciation for the extraordinary effort and remarkable success and insight put forth by this small and international group of researchers and clinicians. We are here today to give credit where it is due and to ensure that your wishes are heard, respected and acted on. Our reception and dinner meeting, following this Conference at the DoubleTree, Rockville is to encourage ongoing dialogue with our invited guests and faculty from the Scientific Community, NIH and the FSH Society.

Thank you.

EDUCATION/NIH RESEARCH

May 22, 2000

Letter sent to NIH directors recapping 3rd International Conference on the Cause & Treatment of FSHD

Stephen Katz, M.D., Ph.D., Director
National Institute of Arthritis and Musculoskeletal and Skin Disease (NIAMS) NIH
Bldg. 31 Room 4C32
31 Center Drive MSC 2350
Bethesda, MD 20892-2350

Gerald Fischbach, M.D., Director
National Institute of Neurological Disorders and Stroke (NINDS), NIH
Bldg. 31 Room 8A52
31 Center Drive, MSC 2540
Bethesda, MD 20892-2540

Stephen C. Groft, Pharm.D., Director
Office of Rare Disorders (ORD), National Institutes of Health
31 Center Drive MSC-2082, Room 1B03
Bethesda, MD 20892-2082

Dear Drs. **Katz**, **Fischbach**, and **Groft**,

I congratulate you on the outcome of the 3rd International Conference on the Cause and Treatment of FSHD on Monday, May 8, 2000, and the subsequent Research Planning Conference held on the following day. I had hoped to see you again before leaving the Washington, D.C. area and to say good-bye and to follow-up with you immediately on the activities. I know that the research community, the clinical community, the observers and the NIH-related experts at the 3rd International Conference on the Cause and Treatment of FSHD held on Monday, May 8, 2000 agreed that it was a truly outstanding, top-rate and excellent meeting. We managed to successfully assemble the leading FSHD researchers from all over the world at the NIH in Bethesda, Maryland and to have them share their findings with each other and the NIH. I thank you and the other directors and staff at the NIH for helping to develop an outstanding and excellent program to aid in your development of a portfolio for FSHD. Again, I regret that we did not have the opportunity to continue our dialogue during the *FSH Society* dinner that evening. The attendees had an opportunity to relax and build and reinforce long distance collaborations and new friendships.

The Research Planning Conference held Tuesday, May 9, 2000 yielded a tremendous amount of energy and a multitude of ideas on how to move forward on the FSHD agenda. The Research Planning Conference format worked very well. It is regrettable that the three of you were unable to be present and that Dr. **Spinella** had to leave early for a family emergency. We hope everything is okay with Dr. Spinella's child. I know that you would have been impressed with how well the FSHD researchers worked with the NIH experts to look at new approaches and avenues and at how more and more energized the room became as they tried to brainstorm on this scientifically intriguing and difficult problem. I was truly impressed with the experts NIH brought in from outside the field including **Paul Plotz**, **Robert Nussbaum**, **Eric Hoffman**, **Lee Sweeney**, **Kurt Fishbeck** and **Henry Epstein**. I believe they were truly impressed with the top rate science and scientific minds working on FSHD as they were able to answer definitely every new suggestion or question posed by them as the world renowned experts in muscle research (NIH related guests) and vice-versa.

Most notable was that for the first time a possible therapeutic approach or cure for FSHD resulting from findings of molecular studies was discussed in the context of this type of scientific meeting. Dr. **David Housman** and Dr. **Kathy Mathews** along with Dr. **Jane Hewitt** and Dr. **Michael Altherr** discussed a strategy for curing and ameliorating FSHD by selective and targeted repair of the deleted repeat sequence through expansion of the array using a combination of AAV and gene therapy. Even more striking was how well the science discussed for a therapeutic approach (cure) fit into the existing portfolio of basic research currently funded by the NIH.

Along with this were many excellent topics and areas for molecular genetics and basic muscle research; and a consensus on the ranking and areas of importance, including:

- **Gene chip, protein chip and expression arrays**

It will be primarily important to understand the gene function and gene dis-regulation of the primary gene(s), such as DUX4, FRG1, FRG2 and others, in the area of FSHD and their characteristics and relation to chromatin structure. Secondary to this, these genes can easily be studied and more carefully examined through the use of gene chips, both DNA and cDNA and expression array technology. The tertiary effect needed to be addressed is how the related proteins in the FSHD region are expressed and functioning. Further to that, it will be important to begin to understand how the proteins involved are functioning through the use of proteomics and proteins array chips and mass spectrometry.

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- **Development of an FSHD animal model with high fidelity to FSHD.**

The development of an animal model for FSHD is critical for understanding muscle pathology and muscle disease. Mouse models have yielded tremendous insight for Limb Girdle and Duchenne muscular dystrophy and for other diseases such as mitochondrial myopathy. A transgenic model is underway and being developed but it was unanimously agreed that an FSHD animal model with a high fidelity is necessary and was an immediate priority for both molecular and clinical work. The mouse was emphasized over other organisms such as worm and monkey.

- **The role of the FSHD deletion/repeats their cause and the consequences of having them.**

Understanding what causes the D4Z4 deletions at 4q35 was clearly distinguished between the consequences of having the FSHD deletion. The research planning committee felt that it was important to gain more insight into what causes the deletion in FSHD and whether it can be prevented from occurring and causing FSHD. Most importantly, it was felt that the consequences of such deletion needed more study and may lead to extremely novel areas of research and insight into human disease.

- **Understanding the inflammatory process in FSHD.**

The role of inflammation and other effects (eye and ear involvement) of FSHD were discussed as being important to examine, but the committee felt that it was unclear as to whether this was a primary or secondary effect, e.g., possibly an auto-immune response is being triggered by proteins expressed at the wrong time on a membrane surface.

The clinicians presented many excellent topics and areas for clinical genetics and basic clinical research; and a consensus on the ranking and areas of importance, including:

- **The importance of the non chromosome 4 linked FSHD phenotype and families.**

The research planning committee felt that a critical key to understanding FSHD may lie within those patients who have classic FSHD but are not linked to chromosome 4. It is felt that these few pedigrees should be approached anew and a major project should be undertaken to re-examine these families from the bottom up both clinically and genetically.

- **Patient Registry and research materials registry.**

The need for comprehensive clinical center(s) with patient registry and FSHD resources and patient locator.

- **Clinical Research Consortium to conduct clinical trials and clinical research.**

The need for a clinical research consortium of several groups working on clinical trials and research for FSHD (steroids, beta agonists (albuterol), alternative medicine and other new compounds). The need to be able to examine various agents and compounds that may be used to treat FSHD including compounds that effect oxidative stress, chromatin structure and methylation of DNA. A working group is needed to be able to execute gene therapy, AAV, stem cell, the feasibility of repair of the repeat sequence and pharmacological studies quickly, safely and accurately.

The scientific community expressed the need to move ahead on this area of research as it extends well beyond just FSHD and the need to understand what exactly is happening with the repeats associated with FSHD. To elaborate, FSHD is a disease with known subtelomeric rearrangements between chromosome 4 and 10 and is a clear model for the study of disease with subtelomeric rearrangements. Subtelomeric rearrangements are associated with many human diseases including mental retardation and cancer (Flint J., Nature Genetics, Vol. 9, 1995, p. 132-140) and the clear dispersal between chromosome 4 and 10 will make for an excellent model to study. Further, FSHD is one of the only known human diseases caused by classical position variegation effect (PEV), and understanding the mechanism associated with FSHD will impact a far greater number of other human diseases caused by PEV and is ideal for epigenetic research.

Dr. Housman stated that the key is in the repeats associated with FSHD. Dr. Housman expressed the immediate need for at least two centers working on FSHD and thought that waiting three to five years would mean a significant lost research opportunity. I know that the NIH experts and FSHD research community were re-energized and excited and optimistic coming out of Tuesday's meeting. However, I was truly concerned about the NIH Program Director's comment that it still may take some time before anything comes forth from this meeting.

It is clear to me that the majority of the planning conference process is now done, pending the final report. The FSHD researchers, NIH experts and NIH staff have clearly identified very tangible ways to make significant advances in FSHD including the means to developing a cure for FSHD. I know that the NIH Institutes have been given a very clear road map for the next one to three years and have been advised that the next five years will be critical to finding a cure for FSHD.

On behalf of the *FSH Society*, I would like to suggest a meeting with the three of you and myself so we may discuss this important issue and how we can capitalize on all the ideas and interest generated at this conference. I will contact your offices to arrange an appropriate time. I am looking forward to working together in the future to promote solutions for FSHD and muscle research.

Sincerely,

Daniel Paul Perez, President and CEO, *FSH Society*, (781) 862-8422 phone, (781) 863-0788 fax

EDUCATION/NIH RESEARCH

NIH still lacks presence in the area of FSHD research

Status report: 2000 NIH research plan

NIH has only funded one new contract towards the effort to "establish a comprehensive portfolio into the causes, prevention, and treatment of FSH disease" even though the previous three years of report language request that this happen. The Congressional Committees have asked NIH several times "to establish a comprehensive portfolio into the causes, prevention, and treatment of FSH disease through all available mechanisms, as appropriate." And still today, currently, not one new P01 or R01 grant will have been issued on FSHD in the entire past year.

The May 8-9, 2000, International Conference on the Cause and Treatment of Facioscapulohumeral Muscular Dystrophy baseline of recommendations by an NIH expert scientific panel on FSHD for evaluating priorities is as follows and to date the NIH has accomplished only one item among this set (see item 11).

Recommendations for future directions, organized by topic, are listed below:

A. Molecular Processes

1. Characterize the molecular pathogenesis of FSHD; elucidate the role of the repeats associated with the disease as well as what causes their deletion;
2. Determine the relationship between repeat length and its effect on the degree to which disease is manifested (penetrance);
3. Determine the gene sequence and whether the repeats are acting as suppressors or insulating units;
4. Clarify how similarity of regions on chromosomes 4 and 10 may relate to FSHD;

B. Tissue Changes

5. Characterize changes in muscle as the disease develops;
6. Determine basis of differential involvement of muscles;
7. Explore the role of inflammation in FSHD;
8. Study properties of muscle cells derived from affected tissue;

C. Possible Therapies

9. It was speculated that it may become possible to repair the disease locus by selected and targeted addition of 3.3 kb repeats to the disease locus on chromosome 4;

10. The modification of cultured FSHD regenerative muscle cells that would reverse their higher sensitivity to oxidative stress. Such cultured cells, with better ability to respond to oxidative stress, might then be used for treatment of patients;

D. Population Based Studies

11. Establish patient registries and recruit additional families for study;
12. Determine if a nonstandard locus produces FSHD;

E. Resources

13. Create new animal models;
14. Facilitate use of differential gene and protein expression techniques;
15. Promote development and use of non-invasive imaging techniques; and
16. Enhance formation of clinical and basic research consortia.

The *FSH Society* will request an earmark of 15 million dollars in its Fiscal Year 2002.

Testimonies before the U.S. House of Representatives and U.S. Senate Appropriations, Subcommittee on Labor, Health and Human Services, Education and Related Agencies to accomplish recommendations put forth by the NIH and scientific community working on FSHD.

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and houses the genes may be damaged and affects how they are accessed.

Imagine genes, as a metaphor, are paintings done by a fantastic master. We find ourselves in an old and beautiful gallery that has stood untouched in stillness and shadows for years and that no curator has dared to enter. Though it is full of beautiful masterpieces, this gallery has severely damaged and cracked walls, the mortar is weak, beams hang down, the roof allows the sunlight and rain through, the floor is rotted and unsafe and yet all of our masterpieces hang at ease in their original places. We have the remarkable task of prioritizing how to fix this situation and restore it to normalcy. We must decide carefully where and how to begin the next level of this major project. Our work with FSHD is exactly the same situation.

In less than three and a half years, the *FSH Society* funded programs resulting in major breakthroughs in understanding what FSHD is.

Research Activities

On March 28, 1999, we presented a document formulated by the SAB, "Strategic Issues and Directions in FSHD Research 1999-2000" which was prepared by **Michael R. Altherr**, Ph.D., Genomics Group at the Los Alamos National Laboratory (LANL). This document has made its way into the list of research priorities and a "research plan" from the NIH. The *FSH Society* has been at every annual October meeting of the American Society of Human Genetics (ASHG), every annual May American Academy of Neurology (AAN) meeting promoting FSHD, and holding

scientific workshops. At these workshops, we have repeatedly brought in various funding agencies including the MDA and the NIH Program Directors at key NIH Institutes involved in FSHD. Every May and October since 1994 we have re-iterated our message and our appeal for the creation of a plan and a list of research priorities by the community involved with FSHD. This physical document evolved over time as we developed the necessary aspects of the plan through *FSH Society* fellowships by planting seeds in major key areas.

On July 20, 1999, at the invitation of its Director, Dr. **Stephen Katz**, the *FSH Society* was invited to present its perspective on the three-to-five year goals on Long Range

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appears to be largely identical (95% homology) to that on chromosome 4 at the FSHD locus (4q35). Studies of affected and unaffected populations show that there is a high amount of exchange between the homologous regions on chromosomes 4 and 10. Although disease has never been associated with alterations on chromosome 10, the frequency of such exchanges may be related to the high proportion of new (i.e., non-familial) cases of FSHD encountered.

TISSUE CHANGES

Characterize changes in muscle as the disease develops. This would be facilitated by non-invasive ways of looking at the muscle and microvasculature in affected and non-symptomatic regions. Studies using improved imaging techniques would provide better assessment of patient muscle, including vasculature, before the development of clinical symptoms. Confirmatory biopsies would be useful, though they are limited by the difficulty of the procedure in affected people and risk-benefit concerns.

Determine the basis of differential involvement of muscles, reflected by the regional pattern of the disease. Comparison of muscle groups might show the cause of relative specificity of affected muscles. Comparing expression patterns of working copies of individual genes (ribonucleic acid or RNA) and protein in affected and non-affected muscle will provide insights into alterations occurring as the disease progresses.

Explore the role of inflammation in FSHD. While FSHD has been described as the most inflammatory form of muscular dystrophy,



Discussing clinical research and genetics issues during the evening of the National Institutes of Health (NIH) Conference on the Cause and Treatment of FSHD May 8, 2000 in Bethesda and Rockville, Maryland. Left to right: Dr. Henry Epstein, Baylor College of Medicine, Houston; Dr. Peter Lunt, Bristol Children's Hospital, Bristol, England; Dr. Peter J. Bridge, Alberta Children's Hospital, Calgary, Alberta, Canada.

there is no evidence that disease severity is lessened by administration of the anti-inflammatory drug prednisone. It is necessary to explore the relationship between inflammatory cells, muscle cell death, and blood vessels. The inflammatory response may affect vasculature, since hearing loss and retinal vasculopathy are widespread in FSHD patients.

Study properties of muscle cells derived from affected tissue. Cells cultured from FSHD muscle show increased sensitivity to oxidative stress. This needs to be followed up by studies verifying that this occurs in vivo and establishing how this cellular phenotype develops.

POSSIBLE THERAPIES

It was speculated that it may become

possible to repair the disease locus by selected and targeted addition of 3.3 kb repeats to the disease locus on chromosome 4. Such targeted gene therapy might prevent development of the FSHD phenotype, but the practical feasibility of such an approach is as yet unknown.

Another approach to explore is the modification of cultured FSHD regenerative muscle cells that would reverse their higher sensitivity to oxidative stress. Such cultured cells, with better ability to respond to oxidative stress, might then be used for treatment of patients. It would be valuable to prevent the reintroduced cells from again developing increased sensitivity.

POPULATION-BASED STUDIES

Establish patient registries and recruit additional families for study. Increase the number of studies on the relationships between genotype and phenotype. This requires accurate and robust genotyping studies comparing disease severity within families. It is difficult to obtain financial support to establish genotype information. There are privacy issues associated with doing this on a broad scale, but establishing a central registry would help.

Determine if a nonstandard locus produces FSHD. There is one family where members have a disease that has characteristics of FSHD, but no defect has been found at the location of chromosome 4 associated with at least 95% of known cases. It is important to characterize the gene defects in this family and see if this provides a better understanding of FSHD disease processes.



Recapping on a successful meeting during the evening of the National Institutes of Health (NIH) Conference on the Cause and Treatment of FSHD May 8, 2000 in Bethesda and Rockville, Maryland. Left to right: Dr. Jane Hewitt, Nottingham University, Nottingham, England, Dr. George W. Padberg, Nijmegen, The Netherlands.

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Planning in Muscle Biology and Muscle Disease Research at the National Institute of Arthritis Musculoskeletal and Skin Diseases (NIAMS). We were the only 501(c)(3) non-profit volunteer health agency invited to present. We presented a very detailed document of priorities in muscle disease and muscle biology research with particular bias and attention to FSHD issues. Much of this presentation was based on the previous *FSH Society*/ASHG workshop meetings, the *FSH Society*/AAN meeting and the "Strategic Issues and Directions in FSHD Research 1999–2000" by Dr. Altherr (LANL). The NIH NIAMS received this thorough and compelling document outlining the research map for FSHD, and the *FSH Society* has been using this list to prioritize its areas of emphasis with new fellowship proposals.

In October 1999, the *Society* furthered this agenda for the NIH research plan and comprehensive portfolio of FSHD research at the *FSH Society*/ASHG meeting in San Francisco. The two program directors responsible for FSHD at two key institutes of the NIH, Dr. **Giovanna Spinella** (Program Director for the National Institute of Neurological Disorders and Stroke (NIH NINDS)) and Dr. **Richard Lymn** (Program Director for NIH NIAMS) were present to hear a clear message that the Congress and the *FSH Society* were growing impatient with the total and complete disregard for three previous years of Congressional Directive that called for a research plan and a research portfolio in FSHD. NIH still felt that it needed to wait for more clarity of the research issues before embarking on a research program in FSHD and deferred action. Concurrently, the NIH decided that the research community should apply for a competitive grant for an FSHD research meeting in May 2000.

It is important to note that the NIH did not put this meeting on its roster as a paid meeting, but rather put it into a competitive process whereby it needed to pass the rigorous evaluation process. Dr. Denise Figlewicz, Marjorie Bronfman fellow FSHS-MB-03, compiled the grant application for the conference in concert with advice from NIH and submitted it for review.

At that time, the *FSH Society* went to Congress to express its outrage at the handling of the process within the NIH and the fourth year of utter disregard for Congressional Directives by not taking a direct role in planning the meeting. Fortunately and not surprisingly, the FSHD symposium grant by Dr.

Figlewicz received in the eleventh hour (a month and some weeks before the actual conference) one of the highest scores ever for a conference grant and the US\$30,000 was awarded from the NIH to the organizers of the meeting.

Without Dr. Figlewicz and without Mrs. Marjorie Bronfman's support for Dr. Figlewicz, we assure you that NIH would have easily been able to score the grant as not fundable. Dr. Figlewicz is an extraordinary scientist in her own right and was one of the few who could carry off and execute this conference. This conference grant was almost identical to the NIH Symposium on FSHD held in May 1997 that was written by the *FSH Society*.

Surprisingly, the NIH initially did not plan to have a meeting for the research planning session of the conference. We wrote to the three Directors of the NIH Institutes (NINDS, NIAMS and the Office of Rare Diseases (ORD)) responsible for the conference, copying key Congressmen, expressing our deep concern that the NIH was failing in its public responsibility and ignoring Congressional

final roster of NIH invited guests and experts was not complete until two weeks prior to the Tuesday, May 9, 2000 meeting. The *FSH Society* went to extraordinary measures and length, working with Dr. **Lymn** (NIH NIAMS), to insure that the top experts in the right areas of FSHD research were present in the room with the independent NIH muscle research experts.

The NIH had originally planned to have an independent panel of experts outside of FSHD assess and make comments on a research plan. The *FSH Society* ensured the presence of FSHD researchers from the minority, going so far as to ask critical key researchers to just show up without invitation. Bronfman grantees, Dr. Denise Figlewicz and Dr. Silvere van der Maarel were present at the planning meeting. The Bronfman grantees and FSHD experts at hand clarified and answered many excellent questions posed by the panelists as seemingly straightforward approaches. The latter did not realize that these approaches had already been tried, exhausted and confounded by the complexity of the FSHD puzzle.

The Third International Conference on the



Two old friends discuss lifelong endeavors on FSHD during the evening of the National Institutes of Health (NIH) Conference on the Cause and Treatment of FSHD May 8, 2000 in Bethesda and Rockville, Maryland. Left to right: Dr. Valery M. Kazakov, Pavlov's Medical Institute, St. Petersburg, Russia, Dr. Kiuchi Arahata, National Institute of Neuroscience, NCNP, Tokyo, Japan.

Directive by not taking an active role in a research plan and for not providing the time and space to generate such a plan.

Soon after this letter arrived on Capitol Hill, the NIH slowly began organizing the format and personnel for that meeting. The

Cause and Treatment of FSHD was held on Monday, May 8, 2000, and the subsequent Research Planning Conference was held on Tuesday, May 9, 2000. The Monday keynote speeches were delivered by Dr. Denise

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Figlewicz, Dr. Stephen Katz (Director, NIH NIAMS), Dr. **Gerald Fischbach** (Director, NIH NINDS), Dr. **Stephen Groft** (Director, NIH ORD) and **Daniel Paul Perez**. All of the *FSH Society* fellows and grantees were present at the Monday meeting. Bronfman and Delta grantees, Drs. van der Maarel, Figlewicz, Winokur, **Gabellini**, **Tupler**, Bloch and **Belayew** presented an impressive array of breakthroughs and leading discoveries.

Dr. **Picketts** has recently entered into collaboration with attendee and presenter, Dr. **Melanie Ehrlich**, a renowned expert in chromatin structure and DNA methylation. The *FSH Society* has enabled Dr. Ehrlich to enter the field by providing a patient sample of one repeat to Dr. Winokur who in turn provided the sample to Dr. Ehrlich for critical examination. We became aware of this critical patient sample through a conversation at a New England support group with a mother whose son had been diagnosed with having only one D4Z4 repeat left on 4q35. I called Dr. Winokur and several other researchers asking them if this was of interest, and, it most certainly was. (We approved Dr. Ehrlich's grant proposal for funding in January, 2001.)

We successfully assembled the leading FSHD researchers from all over the world at the NIH in Bethesda, Maryland where they shared their findings with each other and the NIH. Out of the more than 80 scientists present, the only NIH grantee funded for research on FSHD, Dr. **David Bredt**, University of California, San Francisco (UCSF), did not attend either day to talk about his work on the ALP LIM protein as it relates to FSHD. Dr. Bredt may not see his work as directly related to FSHD. That contradicts the numerous NIH NIAMS responses to Congress stating that Dr. Bredt is the leading and most significant project in their FSHD portfolio.

The Research Planning Conference held Tuesday, May 9, 2000 yielded a tremendous amount of energy and a multitude of ideas on how to move forward on the FSHD agenda. The three directors of the NIH NIAMS, the NIH NINDS and the NIH ORD were unable to be present. We were impressed with how well the FSHD researchers worked with the NIH experts to look at new approaches and avenues and the room became more and more energized as they brainstormed on this scientifically intriguing and difficult problem. I was truly impressed with the experts NIH brought in from outside the field including

Paul Plotz, Robert Nussbaum, Eric Hoffman, H. Lee Sweeney, Kurt Fishbeck and Henry Epstein. I believe the NIH guests were truly impressed with the top rate science and scientific minds working on FSHD. Drs. Figlewicz and van der Maarel were concise and articulate regarding the priorities and needs for FSHD research. Other *FSH Society* fellows, Dr. **Jane Hewitt** on DNA sequencing and Dr. Alexandra Belayew on DUX4 expression were present to cover their respective domains and speciality of research.

Letter to NIH

On May 22, 2000, the *FSH Society* sent a letter to all three directors of the NIH NINDS, the NIH NIAMS and the NIH ORD outlining in detail the significant highlights of the meeting and summarizing the research priorities as presented over the years and from our debriefing comments from key participants



Kiichi Arahata, M.D. discusses research data and findings with the Belgians, Dr. Belayew and Dr. Gabriels, during the evening of the National Institutes of Health (NIH) Conference on the Cause and Treatment of FSHD May 8, 2000 in Bethesda and Rockville, Maryland. Left to right: Dr. Jan Gabriels, University of Leuven, Leuven, Belgium, Dr. Alexandra Belayew, Université de Mons-Hainaut, Mons, Belgium, Dr. Kiichi Arahata, National Institute of Neuroscience, NCNP, Tokyo, Japan as always sharing, teaching and open.

following the May 9, 2000 meeting. We felt it necessary to go on record immediately with a very positive report and avoid having the NIH present a less certain and less definite picture of progress to the Congress and the scientific community at large. The content of this detailed letter has been incorporated almost verbatim into the recent on-line NIH research plan.

The NIH finally published its report on the May 8-9, 2000, FSHD research meeting and subsequent research planning conference on its

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RESOURCES

Create new animal models. Understanding of FSHD would be improved by general availability of a good animal model that has genetic defects and phenotypes that are similar to the human disease. Once a strong colony is established, mice should be readily available to groups with expertise in many areas of muscle biology.

Facilitate use of differential gene and protein expression techniques which can serve as the basis of additional FSHD models, as well as provide directions for new therapeutic approaches.

Promote development and use of non-invasive imaging techniques, such as MRI, in order to analyze the state of tissue in affected and non-affected muscle and during disease progression.

Enhance formation of clinical and basic research consortia. Such consortia could initiate clinical and basic studies, and conduct clinical trials. One specific suggestion was to create centers that would develop and test animal models, establish patient registries, and provide tissue and genotypic analysis.

Source: NIH NIAMS Internet web site:<http://www.nih.gov/niams/reports/>

NIAMS reports and contributions to NIH reports "Conference on the Cause and Treatment of Facioscapulohumeral Muscular Dystrophy" summary of workshop:

<http://www.nih.gov/niams/reports/fshdsummary.htm>

ADVOCACY

Letter from Washington

by Morgan Downey, General Counsel, FSH Society

February 2001 saw increased political activity by advocates for research on Duchenne muscular dystrophy (DMD) in the Nation's Capital.

Spurred on by the Parent Project for DMD, Senator **Arlen Specter** (R-PA) held a hearing on research needs in Duchenne's muscular dystrophy on February 27, 2001. The hearings, part of the Senate Appropriations process, included **Audrey Penn**, Acting Director of the National Institutes of Health, National Institute on Neurological Disorders and Stroke (NINDS/NIH), **Jerry Lewis** of the Muscular Dystrophy Association of America (MDA), parents, researchers and clinicians. Senator Specter promised to look into the low levels of funding which muscular dystrophy has been receiving from NIH during a period when NIH budgets have enjoyed significant growth. The *FSH Society* submitted testimony as well which will be continued before the House of Representatives (see page 21).

Earlier in the month of February, Congressman **Roger Wicker** (R-MS) and some ninety co-sponsors introduced the Duchenne's Muscular Dystrophy Care Act, H.R. 717. The bill would require NIH to establish at least three centers on Duchenne muscular dystrophy research. In addition, the Centers for Disease Control and Prevention epidemiological research on Duchenne muscular dystrophy would be expanded.

In March, Senators **Paul Wellstone** (D-MN), **Thad Cochran** (R-MS) and **Susan Collins** (R-ME) circulated a draft bill which intended to be more broad than the House bill. We were concerned that Congress appreciate that FSHD and Duchenne were different diseases and that approaches in one area did not necessarily mean progress in the other.

In early April, the *FSH Society, Inc.* analyzed the bill and distributed an analysis of the bill to the MDA's lawyer, the Parent Project for Duchenne Muscular Dystrophy representatives, and the NIH legislative staffs expressing our concerns regarding the bill.

Daniel Perez and I met with key Congressional sponsors in the House and Senate in late April with respect to our concerns. We met, as well, with the Directors and Staff of the two key Institutes primarily responsible for muscular dystrophy research, the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). We were able to reach an agreement with all partners that the bill need be modified to address the needs of the entire muscular dystrophy community. The *Society* also requested that five Centers of Research Excellence (CORE) be established instead of three, and that the legislative language stipulate that the NIH was required to maintain a research portfolio in addition to the establishment of centers. Additionally, we opened all sections pertaining to children and boys to include affected adults and both men and women. Finally, we requested and received that the NIH coordination committee called for be comprised of both patients, advocates and federal representatives.

We were very pleased to have had our concerns respected on Capitol Hill and the enthusiastic cooperation of the Parent Project to expand the bill to meet the needs of the entire community.

The *FSH Society*, the Muscular Dystrophy Association, and the Parent Project Muscular Dystrophy are pleased with the new Senate legislation. All three groups jointly praise the Senate's introduction of

bipartisan Muscular Dystrophy Community Assistance, Research and Education (MD Care) Act. The "MD CARE" Act shows a strong and resolved commitment to muscular dystrophy research from the federal government.

All three organizations agree that "the hopes of tens of thousands of children and adults living with Muscular Dystrophy and their families were raised by the Senate's introduction of bipartisan Muscular Dystrophy Community Assistance, Research and Education (MD Care) Act. The MD Care Act is a breakthrough in securing a real commitment from the federal government toward research, treatment and prevention of various forms of muscular dystrophy. We praise Senators Paul Wellstone (D-MN), Thad Cochran (R-MS) and Susan Collins (R-ME) for their hard work and leadership for standing up for children and adults whose lives have been devastated by muscular dystrophy."

The *FSH Society* has welcomed these efforts. For far too long, eight years and fifteen Congressional testimonies, the *FSH Society* has been the only advocate for research in this area. The *FSH Society* will continue to stress the unique aspects of FSHD and for the need for correctly pursuing the course in developing resources for muscular dystrophy research at the federal level.

We encourage you to support the *FSH Society's* efforts in this area. We will keep you informed of developments and the need for support as the bill makes its way through the Congressional process in the coming months. Please encourage your Senators and Representatives to support this legislation.

ADVOCACY

February 27, 2001

FSH Society submits FY2002 testimony on muscular dystrophy before Senate Appropriations Subcommittee

Statement of **Daniel Paul Perez**, President and CEO, Facioscapulohumeral Society (The FSH Society) before United States Senate Committee on Appropriations Subcommittee on Labor, Health, and Human Services and Education and related agencies. Hearing regarding fiscal year 2002 appropriations for NIH research and programs for research on Muscular Dystrophy and Facioscapulohumeral Muscular Dystrophy, February 27, 2001.

Mr. Chairman, it is a great pleasure to submit this testimony to you today.

My name is Daniel Paul Perez, of Lexington, Massachusetts, and I am testifying today as President and Chief Executive Officer (CEO) of the Facioscapulohumeral Muscular Dystrophy Society (FSH Society, Inc.) and as an individual who has this devastating disorder.

We are excited to report that during the past several months, the National Institutes of Health (NIH) have announced a series of initiatives to accelerate research on Facioscapulohumeral Muscular Dystrophy (FSHD). For the first time since its inception, the NIH has requested grant applications whose purpose is to explore and develop research that will broaden the base of knowledge on FSHD. We are indebted to you, Senator **Arlen Specter**, as well as Representative **John Porter**, Chairman, formerly of the U.S. House of Representatives, as well as the directors and staff of the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) at the NIH for this progress.

The FacioScapuloHumeral (FSH) Society, incorporated in 1991, solely addresses specific issues and needs regarding facioscapulohumeral muscular dystrophy (FSHD). We provide public awareness of FSHD by providing information, referral, education, and advocacy on FSHD. Additionally, the FSH Society offers assistance and support to patients, families, physicians, and other professionals. The Society publishes a newsletter with information about advances in research, political action effecting FSHD research, and profiles of people with FSHD. We have awarded \$650,000 in grants toward the prevention, cause and treatment of FSHD for research projects, post-doctoral and research fellowships, and provided training support to institutions and fellowships to individuals in the field of FSHD research worldwide. The FSH Society promotes collaborative research and collects and disseminates research information. The Society organizes and sponsors annual international and national scientific meetings on FSHD as

well as annual international and national patient network day meetings.

FSHD is a neuromuscular disorder that is inherited genetically and has an estimated frequency of one in twenty thousand (1/20,000). FSHD affects 12,500-37,500 persons in the United States. The major consequence of inheriting this disease is that of a clinically unpredictable and progressive and severe loss of skeletal muscle, with the usual pattern of initial noticeable weakness of facial, scapular and upper arm muscles and subsequent developing weaknesses of other skeletal muscles. Retinal and cochlear disease can often be associated with FSHD although the pathogenesis and causative relationship to FSHD remains completely unknown. FSHD wastes the skeletal muscles and gradually but surely brings weakness and reduced mobility. Many with FSHD are severely physically disabled and spend the last 30 years of their lives in a wheelchair. The toll and cost of FSHD physically, emotionally, and financially is enormous. FSHD is a life-long disease that has an enormous cost-of-disease burden and is a life sentence for the innocent patient and involved persons and their children and grandchildren as well.

We are in an unprecedented time with the publication of the entire human genome sequence. We have spent an enormous amount of money in genomic research that is coming to fruition and we hope to begin to realize the payoff for this investment. However, this chapter is not closed and we are not done with understanding FSHD. FSHD is a complex and difficult disease, and the mechanism of this disease is tightly bound to the next steps for genome research. FSHD is an enormously rich disease to study with its involvement in telomeres, repeats, chromosomal "cross-talk", new protein and DNA models for transcription of the genome, and many other new areas outlined for investigation by the entire genome



The FSH Society and the Stichting FSHD (The Dutch FSHD Foundation) discuss the successes of the day and future areas for collaboration, cooperation and mutual benefit for FSHD worldwide at the National Institutes of Health (NIH) Planning meeting May 9, 2000 in Chevy Chase, Maryland. Left to right: Kees C. J. van der Graaf, President, Stichting FSHD, Wassenaar, The Netherlands, Daniel Paul Perez, President & CEO, FSH Society, Lexington, Massachusetts.

community as critical areas for the next steps to understanding how the human genome and physiome works. FSHD may well be the only human disease that can be used as a model for the next generation of novel genomic inquiry.

A decade of progress in FSHD has led to the discovery of a novel genetic phenomena of crossover of subtelomeric DNA between chromosomes (4 and 10) in both normal individuals and diseased individuals and to the discovery that facioscapulohumeral muscular dystrophy may be the only human disease caused by a deletion-mutation causing a position effect variegation (PEV). PEV causes DNA in one part of the genome to affect DNA in other parts of the genome. In FSHD, DNA at the very end of the chromosome (telomere) interferes with DNA upstream towards the center (proximal) of the chromosome. Despite remarkable genetic insight and immense progress by a small team of scientists worldwide, the nature of the gene product(s) remain enigmatic and the biochemical mechanism and cause of this common muscle disease remains absolutely unknown and elusive.

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Congressional Testimony *continued from page 21*

FSHD in particular, and muscular dystrophy in general, appear to be of little interest to the pharmaceutical industry, biotechnology industry and Wall Street. No privately or publicly owned company is currently pursuing FSHD research. Unlike Alzheimer's, Parkinson's disease or breast cancer, with hundreds of millions of research dollars from the NIH supplemented by the enormous investments from the pharmaceutical and biotechnology sector, FSHD has nowhere to go in the private sector. We rely totally on NIH funding and that of voluntary health organizations which raise research funds from the public, to advance knowledge in this field.

Neuromuscular and muscle disease has one of the highest cost-of-disease burdens in the U.S. economy. Yet, of \$20.5 billion annually given to NIH, approximately \$19 million is spent on all muscular dystrophy research and, of that amount, conservatively \$450,000 is currently being spent on the third most prevalent and third largest dystrophy, FSHD. Clearly, the muscular dystrophies are significantly under-funded by NIH. In last year's testimony, we reported the NIH had not responded to the past three years of House and Senate reports accompanying the appropriations bill language. We are pleased to

report a very different picture this year.

The *FSH Society* with the NINDS, the NIAMS and the NIH Office of Rare Diseases (ORD) held "The 3rd International Conference on the Cause and Treatment of FSHD" on Monday, May 8, 2000. The research community, the clinical community, the observers and the NIH-related experts agreed that it was a truly outstanding, top-rate and excellent meeting. We successfully assembled the leading FSHD researchers from all over the world at the NIH in Bethesda, Maryland where they shared their findings with each other and the NIH. The directors and staff at the NIH developed an excellent program to aid in the development of a portfolio for FSHD. The Research Planning Conference held Tuesday, May 9, 2000, generated a multitude of ideas on how to move forward on the FSHD agenda.

On November 8, 2000, the first of three major announcements was made by NIH as "Exploratory Research on Facioscapulohumeral Muscular Dystrophy." On December 11, 2000, the second announcement was made on the establishment of a National Patient Registry at the University of Rochester Medical School for FSHD and Myotonic muscular dystrophy. On January 4, 2001, the third announcement was made for a three year program "Therapeutic

and Pathogenic Approaches for the Muscular Dystrophies."

We are delighted with these steps toward finding solutions for FSHD. We note with cautious optimism that the NIH has begun the process to establish a portfolio in the causes and treatment of FSHD as called for in the past three years of House and Senate Report Language. However, we are only beginning the process. Difficult work lies ahead involving establishing population databases, developing research resources such as a mouse model, understanding the molecular process, understanding tissue changes, the development and clinical trials of possible therapies, and population-based studies.

Mr. Chairman, we are watching with interest the response of the scientific community to the announcements of NIH referenced above. We are concerned that, despite these announcements, the exciting scientific questions about this disease and progress in genomics - and the tremendous need of patients for therapies - that the response of the scientific community will be less than optimal. We hope we are wrong. We are concerned that there is not an attitude of confidence that FSHD, muscular dystrophy or muscle biology is of significant importance at

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Fourth FSH Society Delta Railroad Construction Company Research Fellowship Grant established



Evening of the National Institutes of Health (NIH) Conference on the Cause and Treatment of FSHD May 8, 2000 in Bethesda and Rockville, Maryland. Left to right: Larry Laurello and Ida Laurello of the Delta Railroad Construction Company.

The Delta Railroad Construction Company of Ashtabula, Ohio has established the fourth *FSH Society* Delta Railroad Fellowship Grant for research on Facioscapulohumeral Muscular Dystrophy (FSHD). The *FSH Society* Delta Railroad program continues to help in the FSHD research efforts by awarding research grant(s) that provide needed expansion of current work and innovative approaches in FSHD studies. The *FSH Society* is indebted to the Delta Railroad Construction Company, **Larry and Ida Laurello** and their family for this groundbreaking effort on behalf of the FSHD community. The four Delta Railroad Research Fellowship Grants are yielding tremendous insights in new and novel areas of FSHD research. We hope that this collaboration will continue and that the members of the *Society* will consider matching this gift annually.

ADVOCACY

Natick, Massachusetts, July 8, 2000

A call for political action

A statement to the members and network of the FSH Society by Mr. Ed Schechter

We may leave this meeting without knowing that there is a major gap in the research yet to be done. We may leave this meeting thinking that the researchers whom you have heard today and the others you have not heard are amply funded. Neither of those statements is correct. We will leave this meeting, if you do not hear what I have to say, misinformed about the level of funding for research which is possible on FSHD.

I appeal to you along two lines. First, all of us come from different states; all of us have different representatives in Congress. The National Institute of Health has 17 billion dollars a year to distribute for health research. We do not get any of it. None of it. Now, why don't we get any of it? We don't get any of it because we are a small group; we are spread all around the country. We, fortunately for us but certainly not from the point of view of

interest, don't die of it. We don't get any of it perhaps because we haven't made the right contacts. We don't get any of it perhaps because other people are not concerned. But one of the reasons why we don't get any of it is because we don't put pressure on the people who control the money. That pressure has got to come from all of us.

How many of you have talked to or written to your congressman about this problem? If there are any of you who have never done so, try it. Tell him or her how important it is to you and ask your congressman to pressure other congressmen to make sure we get some bit of that 17 billion dollars. All of you have two senators. There are only 100 of them. We have people in this room represented by perhaps 20 or 30 of them. If you could each write a letter to your senator today and then duplicate that letter again two months from

now, and duplicate it two months after that telling them that it is important to put pressure on the Appropriations Committee of the Senate and its Subcommittee on Labor, Health and Human Services and Education and Related Agencies' Chairman, **Arlen Specter**, to fund research for FSHD, we would be doing ourselves a lot of good, we would be doing our families a lot of good, and we would be doing all the sufferers of FSHD in years to come a lot of good.

Finally, I have to say that we must encourage our own friends, our own relatives, our own associates, and our own families to support FSHD. Not with 25 or 50 dollars a year, but if you have the money and have the desire, for more substantial contributions because the Perezes have done an enormously wonderful job and they need our funding and they need our help.

Congressional Testimony *continued from page 22*

NIH over the long term to justify the investment by researchers in this field. After all it has taken the *FSH Society* since 1994 to encourage Congress and NIH to move this far, we feel the Committee should consider earmarking funding in this area sufficient to encourage researchers to make a commitment to pursue this difficult and often frustrating area of investigation.

We request that the Committee consider earmarking an amount of not less than fifteen (15) million dollars for FSHD research.

The men, women and children who live with the daily consequences of this devastating disease are your friends, neighbors, fellow taxpayers, and contributors to the American way of life. With an historic 88% employment rate and an average educational achievement level of 14 years, we personally bear our burden of the health care costs and training expenses to prepare for and maintain financial and personal independence. We appeal to you today to take our hard-earned tax dollars commensurate with our numbers and valuable contributions to American society and we urge the United States Government to allocate a proportion of our tax burden toward research on FSHD.

Mr. Chairman, we trust your judgement on the matter before us. Please remember, we need your help to ensure that the sun is rising on FSHD and all other muscular dystrophies.

Mr. Chairman, again, thank you for providing this opportunity to testify before your Subcommittee.

FSH Society submits FY2001 language for inclusion in budget report

Senate Appropriations Committee Report on Labor, HHS; House Appropriations Committee Report on Labor, HHS; National Institutes of Health; National Institute of Neurological Disorders and Stroke; National Institute of Arthritis and Musculoskeletal and Skin Disorders; Facioscapulohumeral Muscular Dystrophy and Facioscapulohumeral Disease.

"The Committee is extremely concerned that contrary to the direction indicated by both the U.S. House and Senate for the last several

years, research in facioscapulohumeral muscular dystrophy (FSHD) is at its lowest level ever. The Committee notes that the NIH is not in compliance with the previous three years of Congressional Directive on FSHD and that the NIH has been slow in convening the research planning conference and in developing the comprehensive research plan for FSHD. The Committee is aware that the NIH has not funded any new R01 or P01 projects in FSHD in the past year. The NIH is

requested to report to the Committee immediately after the research planning Conference on May 9, 2000, the steps it will take to create a comprehensive research portfolio in FSHD. A comprehensive portfolio of research at \$5-10 million has been suggested to accelerate efforts in FSHD. NIH is expected to make research in FSHD a high priority for funding immediately by using appropriate mechanisms."

ADVOCACY

FSH Society proposes FY2001 conferee language to be submitted

Calendar Year 2000, fiscal year 2001 Conferee and conference Language submitted by the *FSH Society* to the Unites States House of Representatives and Senate for consideration and inclusion into the report accompanying the budget.

Senate Appropriations Committee Report on Labor, HHS House Appropriations Committee Report on Labor, HHS

National Institutes of Health, National Institute of Neurological Disorders and Stroke, National Institute of Arthritis and Musculoskeletal and Skin Disorders

Facioscapulohumeral Muscular Dystrophy and Facioscapulohumeral Disease (FSHD)

The Conferees are extremely concerned at the slow response of the National Institutes of Health (NIH) to numerous declarations of Congressional interest in the development of a comprehensive research program in

Facioscapulohumeral Muscular Dystrophy (FSHD), a serious and disabling muscular disorder and muscle disease.

The Conferees believe that the current organizational structure at NIH in which responsibility is shared between the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) has not worked well in addressing the research needs in this area.

Therefore, the Conferees direct the Director of NIH to propose a new organizational structure for research on muscle biology and muscle disease, including FSHD, after consultation with interested organizations and parties, to facilitate implementation of the comprehensive research portfolio which Congress expects the NIH to implement.

Senate Appropriations Committee finalized report language for FSHD

The following is the actual text of the final fiscal year 2001 U.S. Senate, Committee on Appropriations, report language accompanying Labor, Health and Human Services and Education and Related Agencies appropriations bill under section for the National Institutes of Health (NIH). The report language is similar for both institutes covering research programs on FSHD, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, and, the National Institute of Neurological Disorders and Stroke (NINDS).

National Institutes of Health (NIH) and National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS):

Facioscapulohumeral muscular dystrophy and facioscapulohumeral disease (FSHD) — The Committee is extremely concerned that funding for FSHD has decreased and that no new projects have been funded over the past year. The Committee requests that the NIH report after the research planning conference on steps it will take to create a comprehensive research portfolio in FSHD. The Committee further urges that NIH make research in FSHD a high priority.

National Institutes of Health (NIH) and National Institute of Neurological Disorders and Stroke (NINDS):

Facioscapulohumeral muscular dystrophy and facioscapulohumeral disease (FSHD) —

The Committee is extremely concerned that funding for FSHD has decreased and that no new projects have been funded over the past year. The Committee requests that the NIH report to the Committee after the upcoming research planning conference on steps it will take to create a comprehensive research portfolio in FSHD. The Committee further urges that NIH make research in FSHD a high priority.

From:

Committee Report 106-293, U.S. Senate Committee on Appropriations, Accompanying Labor, Health and Human Services, Education, and Related Agencies Appropriations Bill.

NIH responds to Appropriations Committee's inquiry

Questions from the Honorable Representative **Randy "Duke" Cunningham** (CA) to **Dr. Ruth Kirschstein**, Director of the National Institutes of Health (NIH) (testifying as a witness for the National Institutes of Health before Representative **John Porter**, Chairman, U.S. House Appropriations Subcommittee on Labor, Health and Human Services, Education and Related Agencies and members of the U.S. House Appropriations subcommittee on February 15, 2000) were answered by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) at the NIH.

Item

Facioscapulohumeral Disease — The committee is concerned that the NIH has not responded to a previous request to develop a plan for enhancing NIH research into Facioscapulohumeral (FSH) Disease. The committee urges NIH to convene a research planning conference and establish a comprehensive portfolio into the causes, prevention and treatment of FSH Disease through all available mechanisms as appropriate. The Director of the Institute is requested to be prepared to testify on the status of the initiative at the fiscal year 2001 appropriations hearing. (p. 97)

Action taken or to be taken

NIAMS supports both extramural and intramural research related to facioscapulohumeral disease (FSHD). In March of 1998, NIAMS together with the National Institute of Neurological Disorders and Stroke (NINDS), issued a special solicitation to encourage investigator-initiated research applications to study the pathogenesis and therapy of various forms of muscular dystrophy in children and adults, including FSHD. A number of projects have been funded as a result of this solicitation, including two by NIAMS that have potential implication for FSHD: both support research on developing safe and effective methods to perform gene therapy on skeletal muscle. With respect to intramural research, NIAMS recently recruited and hired a renowned muscle biologist to head our Laboratory of Physical Biology (LPB) and to strengthen our intramural program on muscle diseases. The LPB has a long and accomplished record in the study of biological

The FSH Society depends on YOUR contributions to continue its work! Please consider a tax-deductible contribution today!

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NIH responds to Appropriations Committee's inquiry *continued from page 24*

systems using leading-edge physical approaches. Muscle contraction, regulation, structure, and function are among the key areas of expertise of laboratory members.

NIAMS staff are currently consulting with members of the extramural community to organize a research planning conference in May of 2000. Researchers in the U.S and Europe will come together to share their latest findings and ideas on this disease.

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Questions from the Honorable Representative **Randy "Duke" Cunningham** (CA) and answers from Dr. **Gerald Fischbach**, Director of the National Institute of Neurological Disorders and Stroke (NINDS), at the National Institutes of Health (NIH) testifying as a witness for the National Institutes of Health before Representative John Porter, Chairman, U.S. House Appropriations Subcommittee on Labor, Health and Human Services, Education and Related Agencies and members of the U.S. House Appropriations subcommittee on February 29, 2000.

Mr. Cunningham: Congress has been indicating consistent and strong support for FSH Disease (facioscapulohumeral muscular dystrophy) research initiatives. Please describe the NINDS research portfolio in this area.

Dr. Fischbach: FSH has proven to be a very difficult disease to understand. As you know, it has been almost ten years since the general location of the gene defect was discovered, a deletion that is a missing piece of chromosome 4. What has confounded further progress is that the defect doesn't seem to be working by directly disrupting a single gene. Instead, some novel mechanism, perhaps affecting the function of nearby genes, seems to be involved and we just don't understand it. We have been trying to stimulate research in this area. In 1997, NINDS together with NIAMS, the Office of Rare Diseases; and the *FSH Society* held a workshop focused on the disease. In 1998, NINDS and NIAMS issued a program announcement, which is still active. In the past year that solicitation brought in two new grants in NIAMS and one in NINDS which are trying to understand what causes the

problems of this disease and find ways for safe therapy. In May, the *FSH Society* with the NINDS and NIAMS will hold another conference. This meeting will bring together people already working on FSH with others in related areas and we are extending this



An international team of renowned neurologists discuss FSHD clinical research issues during the evening of the National Institutes of Health (NIH) Conference on the Cause and Treatment of FSHD May 8, 2000 in Bethesda and Rockville, Maryland. Left to right: Dr. Robert Griggs, University of Rochester School of Medicine, Rochester, New York; Dr. Enzo Ricci, Catholic University, Rome, Italy; Dr. Richard Orrell, Royal Free Hospital School of Medicine, London, England.

conference with a "think tank" to try to identify opportunities to push FSH research forward.

Mr. Cunningham: The Neurology Institute and the Arthritis institute share responsibility in FSH disease and the larger neuromuscular area. How effective has this partnership been? Are there advantages or disadvantages to this approach, relative to having FSH disease research performed entirely within one institute?

Dr. Fischbach: I think in the case of FSH this partnership is working very well. The

program directors at each Institute make a strong effort to ensure that is so. They cooperate extensively on solicitations, workshop planning, and making sure individual grants don't fall through the cracks. And, beyond NIH, the private groups are also an important part of this equation. I should add that both Institutes have moved recently to strengthen our intramural research in areas related to muscle disease, and the new programs complement one another well.

Obviously, splitting responsibility does present potential problems. But, when there is cooperation, the advantages that arise from the added perspective that different institutes and different program directors bring outweighs this. I'd like to take a moment to say that the general issue of cooperation among components of NIH has become increasingly important for several reasons,

including the unexpected directions science often takes. Biology often ignores the divisions of bureaucracy, revealing unexpected connections, and, as we learn more, the underlying unities are becoming more apparent. Enhancing the interaction among the Institutes is one area in which Dr. **Varmus** exerted real leadership, and changed the way NIH operates. I know that Dr. **Kirchstein** (Acting Director NIH), Dr. **Katz** who directs NIAMS, and the other Institute directors share my commitment to Dr. Varmus' vision, and I spoke earlier about our intramural efforts in this regard.

Tides Foundation Grant awarded

The Tides Foundation of San Francisco awarded \$30,000 to the *FSH Society* at the request of a Donor Advised Fund in August 2000. To move quickly and expeditiously, the Board of Directors of the *FSH Society* moved to utilize this award to fund a research grant. **Marcy Speer**, Ph.D., Duke University Medical Center, Durham, North Carolina is the recipient of the first Tides Foundation Research Grant for her project, "Genetic Linkage Studies in Non-chromosome 4 FSHD."

The members of the *FSH Society* express gratitude to the Tides Foundation and for this gift that permits the *FSH Society* to pursue excellence in research and education and to support international collaborative efforts.

ADVOCACY

May 1, 2001

Senator Wellstone introduces Senate Bill 805, the Muscular Dystrophy CARE Act of 2001

by Mr. Wellstone (for himself, Mr. Cochran, Ms. Collins, Mr. Bennett, Mr. Breaux, Mr. Bunning, Mrs. Clinton, Mr. Corzine, Mr. Daschle, Mr. Dayton, Mr. Dorgan, Mr. Hutchinson, Mr. Johnson, Mr. Kerry, Mr. Kohl, Ms. Mikulski, Mr. Sarbanes, Mr. Schumer, Ms. Snowe, Ms. Stabenow, and Mr. Voinovich):

S. 805. A bill to amend the Public Health Service Act to provide for research with respect to various forms of muscular dystrophy, including Duchenne, Becker, limb girdle, congenital, facioscapulohumeral, myotonic, oculopharyngeal, distal, and emery-dreifuss muscular dystrophies; to the Committee on Health, Education, Labor, and Pensions.

Mr. WELLSTONE. Mr. President, this is the Muscular Dystrophy Community Assistance, Research And Education Act of 2001. It really is the MD CARE Act. I thank Senators COCHRAN and COLLINS, especially, for their assistance. There are 20 colleagues who support this legislation. It is about equally divided between Democrats and Republicans, thank God, because of what this piece of legislation is about.

To look at the record of research on these debilitating and deadly diseases is to realize that despite our country's enormous resources, sometimes people are left behind. Today, despite all the advances in medical science, victims of muscular dystrophy—which afflicts tens of thousands of individuals every year in America—have no cure and no effective treatments available to them.

I became engaged with the muscular dystrophy community when I was approached by several families in my home state of Minnesota with children suffering from Duchenne's muscular dystrophy (DMD). DMD is the most prevalent form of muscular dystrophy affecting children and it is the most deadly. Children with DMD are most often not diagnosed before the age of two or three years.

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December 12, 2000

Canada establishes national research organization; FSH Society writes letter expressing concerns

On December 12, 2000, the *FSH Society* sent the following letter to Dr. Alan Bernstein, inaugural President of the newly forming Canadian Institutes of Health Research (CIHR). The Canadian government is establishing its own national research organization modeled very closely after the United States National Institutes of Health (NIH). The *FSH Society* continues to try to make Facioscapulohumeral Muscular Dystrophy (FSHD) research and research issues well known and was concerned that FSHD would have the same placement within mirror institutes in Canada. The responses from respective directors of the CIHR institutes responsible for FSHD are published below. Presently, Canada has an extremely thin portfolio on FSHD and a heavier concentration in other well-known types of muscular dystrophy.

December 12, 2000

Dear Dr. Bernstein,

I had the pleasure of talking with Kelly van Koughnet, Deputy Director, Institutes Liaison Group regarding the situation and placement of muscle disease research and muscular dystrophy research in the newly formed Canadian Institutes of Health Research (CIHR) and my concerns regarding such. In my experience it is extremely disadvantageous to place the core muscle diseases and muscular dystrophies between a "neurology" and an "arthritis" institute in a conglomeration of institutes comprising a national research program.

As President and CEO of the Facioscapulohumeral Muscular Dystrophy (FSHD) Society, I felt it necessary to share my experiences with the United States National Institutes of Health (NIH) and the Congress of the United States to promote the area of muscle disease and muscular dystrophy. Muscle disease, muscular dystrophy and muscular dystrophy research has suffered tremendously by the joint responsibility between the NIH NINDS and the NIH NIAMS. This has been my focus for more than a decade covering 14 Congressional testimonies and numerous meetings and testimonies before the NIH and the Institute of Medicine (IOM). Diseases of motor neuron, neuro-junction and mitochondria do exceptionally well in this style of organization. Diseases of pure myopathy, muscular dystrophy and muscle disease do not. I state this fact without reservation.

I implore you to not make the same mistake as the United States' NIH in this area and feel that it will help with efforts to bring the Canadian MDA and Canadian muscle research to new and higher levels. Please consider the idea that the muscular dystrophies should be placed in a single institute preferably "musculoskeletal" or "neurology."

I have met with, know well and am known by many of the directors of the Institutes of the NIH (NINDS, NIAMS, ORD, NIHGR, CSR) including Acting Deputy Director Ruth Kirchstein.

As mentioned to Dr. van Koughnet, the *FSH Society* promotes and funds research worldwide and we are currently funding research in Canada on FSHD. Further, one of our major post-doctoral and grant fellowship programs is supported by Mrs. Marjorie Bronfman who has a deep respect and interest in the *FSH Society* and the work we do on FSHD. I know that the CIHR, the *FSH Society*, FSHD and muscular dystrophy could mutually benefit one another by a concerted effort to avoid repeating the mistake of allowing this area to "fall between the cracks" of a national research effort.

I would be delighted to talk with you, meet with you or provide more information on how we can work together to make the CIHR a success for muscular dystrophy.

Last, I share with you and wish the utmost success in this bold and exciting initiative.

Sincerely,

Daniel Paul Perez, President and CEO, *FSH Society*, Inc.

ADVOCACY

Canadian response

Response from Cyril B. Frank, MD, FRCSC, Scientific Director, Institute of Musculoskeletal Health and Arthritis (Arthritis Institute), Canadian Institutes of Health Research CIHR (IRSC Instituts de Recherche en Santé du Canada).

January 10, 2001

Dear Mr. Perez:

Thank you for your thoughtful letter, outlining your concerns that myopathic diseases, muscular dystrophy and other muscle diseases may “fall through the cracks” of our new Institute Structure in Canada. This is a concern that I am certain will be shared by many disciplines until our Institutes actually begin to implement new programs — based on input from our entire international research community (such as yourself). Our Advisory Boards will be asked to consider (and prioritize) all factors in setting our annual strategic priorities — making certain that we are sensitive to the needs of all patients, and our entire research community in Canada and beyond.

Speaking from the point of view of my role as the Scientific Director of the Musculoskeletal Health and Arthritis Institute, I would consider it my job to ensure that the muscle diseases that you list do not “fall through the cracks” of my Institute’s agenda. I further believe that the neuromuscular diseases (and related topics) will be embraced within the Neurosciences, Mental Health and Addiction Institute directed by Dr. Quirion.

A point of clarification regarding CIHR (which distinguishes it from NIH) which may also be helpful for you, is that 88% of the research budget will still go through traditional peer-reviewed panels that are not Institute specific (but rather are composed of scientists required for excellent peer-review for each competition). Spontaneous investigator driven muscle research will continue to receive excellent and unbiased peer review at whichever panels are best suited to the proposal (basic or clinical). Institute strategic initiatives will use the other 12% of the budget and, as noted above, muscle research will almost certainly be considered for some targeting (after due consideration).

I am hopeful that this information will help to reassure you that we will give muscle research its due consideration, based on scientific excellence.

Many thanks for your concern and interest in CIHR. Please let me know if I can be of any further assistance.

Sincerely,

Cyril B. Frank, MD, FRCSC, Scientific Director, Institute of Musculoskeletal Health and Arthritis, CIHR

Response from Rémi Quirion, Ph.D., Scientific Director, Professor Department of Psychiatry, McGill University and Scientific Director, Institute of Neurosciences, Mental Health and Addiction (Neurology Institute), Canadian Institutes of Health Research CIHR (IRSC Instituts de Recherche en Santé du Canada).

January 22, 2001

Dear Mr. Perez:

Thank you for the letter addressed to Dr. Bernstein, President of Canadian Institute of Health Research. As Scientific Director of the Institute of Neurosciences, Mental Health and Addiction, I am sympathetic to your concerns and will work with my colleague, Dr. Cyril B. Frank, Director of the Institute of Musculoskeletal Health and Arthritis to sensitize our respective boards to some of the issues raised in your letter. Note however, that the Canadian model differs from that of the NIH with a tendency towards a fewer number of Institutes, some regrouping 4 - 5 of the NIH model (NIAAA, NIE, NIDA, NIMH, NINCDS, etc.)

Yours truly,

Rémi Quirion, Ph.D, Scientific Director, Institute of Neurosciences, Mental Health and Addiction, CIHR

Introduction of Senate Bill 805 *continued from page 26*

Because it is sex-linked, the disease only strikes boys but in reality, it strikes the entire family.

DMD children don’t begin to walk until late, and then in an unusual manner. They frequently fall and have difficulty getting up. Climbing stairs is a major ordeal.

By age 9 these children start to rely on a wheelchair and by their teen years reliance becomes total. Most tragically, the disease is characterized by a continued rapidly progressive muscle weakness that almost always results in death by 20 years of age.

I have three children, ages 36, 31, and 28. I cannot imagine this. Children afflicted with Duchenne Muscular Dystrophy have no ability

to produce the protein dystrophin, the protein that binds the muscle cells together. It is an exceptionally cruel disease that slowly robs boys of their independence and ultimately immobilizes them, leading invariably to an early loss of life.

Sadly, the federal response to this disease has been inadequate. This year, in an NIH budget of more than \$18 billion, research into Duchenne and Becker Muscular Dystrophies totals just \$9.2 million. Only \$17 million was devoted last year to all of the muscular dystrophies combined. If you want to understand why there is nothing available to treat DMD children, you need look no further

than the weak federal response to this disease. The gene that is flawed in this disease is readily identifiable, and has been so for 14 years. Astonishingly, however, the pace of research on DMD actually slowed down after the gene was discovered.

One DMD child back in Minnesota that I have become especially fond of is **Jacob Gunvalsen**. Jacob is an adorable 10-year-old. He loves to play with his siblings out on his parents’ farm, draw pictures for his family’s refrigerator and play video games. Jacob and his mother **Cheri Gunvalsen** have made quite

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CLINICAL

Clinical update on FSHD

by Rabi Tawil, M.D., Associate Professor of Neurology, University of Rochester Medical School, Rochester, NY

The last year of the millennium marked two important milestones in FSHD clinical research. First, large-scale controlled drug trials in FSHD were completed. Both the American and Dutch trials appear to have reached similar conclusions, although the results of the Dutch trial have not been fully presented. The American trial failed to show an improvement in overall strength in the treated individuals although a single muscle, the handgrip, did show significant improvement. Moreover, there was a definite and statistically significant increase in muscle mass. These results are obviously not as exciting as was anticipated but are nevertheless very important. It is clear that muscles of individuals with FSHD are responsive to the anabolic, muscle-building effects of albuterol albeit not sufficiently.

This raises the possibility that a more significant response may be obtained by changing the dosing regimen alone or by combining albuterol with other anabolic agents. Such possibilities are now being investigated. Treatment strategies have, up to now, depended on non-specific ways of building muscle in the hope of slowing disease progression. Ultimately, however, as the precise causes of muscle weakness and wasting are uncovered, more specific treatment strategies can be devised and tested.

Another important milestone in FSHD research is the establishment of the FSHD patient and family registry. The registry, based at the University of Rochester, will provide a significant boost to FSHD research. It is expected to bring in more clinical and basic scientists into the field, which will in turn accelerate our understanding of the disease mechanisms in FSHD. This comes at an important junction in FSHD research. It is becoming increasingly clear that FSHD is a uniquely complex genetic disorder and that understanding this condition will require the concerted efforts of a number of research groups.

September 6-8, 2001

World Muscle Society will emphasize FSHD at upcoming 2001 meeting

The World Muscle Society's 6th International Congress, will be held in Salt Lake City, Utah, USA, September 6-8, 2001. This will be the first North American meeting of this organization, members of which include some of the world's most distinguished muscle disease researchers. The World Muscle Society (WMS) consists of clinician researchers and basic scientists from around the globe. In addition to publishing its journal, *Neuromuscular Disorders*, the other major function of the WMS is to host an annual meeting dedicated to neuromuscular disease. Since the first meeting in London, the WMS has met in Tunisia, Italy, Turkey, and South Africa. Three-quarters of WMS membership is from overseas, and its meetings are remarkable for the efficient exchange of information between laboratories from around the world. Enrollment is capped at 350 individuals, ensuring a small, collegial atmosphere which encourages collaborative efforts.

The *FSH Society* has pledged its support to assist with aspects of the program specifically related to FSHD honoring the memory of **Kiichi Arahata**, M.D. (Tokyo, Japan).

Kevin Flanigan, M.D. is the local organizer of the meeting and he has assembled a United States Organizing Committee which includes some of the most respected names in U.S. muscle disease research: **Marinos Dalakas** (NIH), **Salvatore DiMauro** (Columbia University), **Andrew Engel** (Mayo Clinic), **Susan Iannaccone** (University of Texas at Southwestern), **Jerry Mendell** (Ohio State University).

The program committee for the meeting consists of Dr. Flanigan and the following members of the International Executive Board of the World Muscle Society: **Victor Dubowitz** of London; **Luciano Merlini**, of Milan; **Fernando Tome**, of Paris; and **Thomas Voit**, of Essen. Further information on the WMS, including a complete list of the executive board of the organization, is available on the organization's Web site (<http://www.ior.it/wms/>).

For each annual meeting of the WMS, three primary topics are chosen, although posters and presentations on all topics in

neuromuscular disease are accepted. The topics for the 2001 meeting are

1. **Facioscapulohumeral and other Dominant Muscular Dystrophies;**
2. **Spinal Muscular Atrophy and other Motor Neuropathies;** and
3. **Therapy and Management in Neuromuscular Disorders.**

Each of these will be the main topic for one day of the program, with morning keynote speakers, afternoon platform sessions, and late afternoon poster walkaround sessions devoted to the topic. The meeting is designed to foster

meaningful participation and discussion between researchers who approach each topic from many different disciplines. Posters remain up for the entire meeting,

allowing time for delegates to meet, hear each other out, and return to posters as topics (or strategies, or collaborations) develop during the course of the meeting. As this will be the first North American meeting, we expect an increased representation of North American participants in comparison to past meetings, and anticipate many valuable abstracts and papers of importance to be submitted.

Research professionals are encouraged to register now for the World Muscle Society's Sixth International Congress, to be held at Snowbird (near Salt Lake City), Utah, USA September 6-8, 2001! Register for the meeting and book accommodations on-line via Internet/Web through the Meeting Secretariat web site at:

<http://www.genetics.utah.edu/wms6/>. Register online, or choose to print out the registration form and fax it to the Secretariat; see the web site for details.

Kevin M. Flanigan, M.D., Assistant Professor of Neurology, Pathology, and Human Genetics, University of Utah School of Medicine
email: kevin.flanigan@genetics.utah.edu

FSHD to be one of three primary topics addressed at World Muscle Society meeting

CLINICAL

*Dutch salbutamol (albuterol) study***The Netherlands conducts muscle strength research**

—E. van der Kooi, O.J.M. Vogels, R.J.G. P. van Asseldonk, S.M. van der Maarel, G.W.A.M. Padberg, Center for Neuromuscular Diseases, Neurology Dept., University Medical Center St. Radboud, Nijmegen.

Article from the VSN newsletter:

In this article we shall report on the backgrounds and advances of the two inquiries presently being conducted by the Neurology Department of the University Medical Center St. Radboud in Nijmegen, regarding people afflicted with FSHD. It concerns the research into the natural course of FSHD and the research on the effects of muscle training and Salbutamol on the condition of the muscles.

Inquiry into the Natural (History) Course of FSHD

Twenty years ago Prof. Dr. G.W.A.M. Padberg visited a large number of families in which FSHD was present. He charted whether family members had or did not have FSHD and which muscle groups showed the most problems. He ascertained the extent to which the dystrophy afflicted a particular muscle group by manually estimating the strength of the muscles. This method is still very much in use by neurologists, physiotherapists, and rehabilitation physicians. It allows the physician to quickly make an estimate of the strength of many muscles. The drawback is that minor changes cannot be detected. However this test is appropriate when making comparisons in the change of muscle strength over a twenty year period.

In the inquiry into the natural course the attempt is made to again measure the muscle strength in people who originally participated at the beginning of the study, in order to get an impression of the tempo and patterns of the loss of muscle strength over a longer period.

For the same purpose a group of patients who were visited by Dr. O.F. Brouwer ten years ago will be re-evaluated. The strength of arm and shoulder muscles were measured with the aid of a small instrument—the hand dynamometer. Muscle strength is expressed in kilos Newton which allows for small deviations to show up.

At this point 85% of the 1980 and 1989



The Nijmegen team continues to expand and produce significant research in the clinical aspects of FSHD. Two neurologists discuss the events of the day during the evening of the National Institutes of Health (NIH) Conference on the Cause and Treatment of FSHD May 8, 2000 in Bethesda and Rockville, Maryland. Left to right: Elly L. van der Kooi, University Hospital Nijmegen, St. Radboud, Nijmegen, The Netherlands, Marielle Wohlgenuth, University Hospital Nijmegen, St. Radboud, Nijmegen, The Netherlands.

participants have been visited.

Inquiry into the effects of muscle strength training and Salbutamol

The second inquiry, in which over the past two years 70 patients participated, concerns the effects of muscle strength training and the use of Salbutamol. We here briefly report on the background of this research and to which point it has progressed at present.

Muscle strength training - background and framework

Presently physicians and therapists are unclear on how to advise people afflicted with a muscle disease, such as FSHD, regarding heavy work, strenuous sports and other activities which are demanding on the muscle system. We do not know whether, in the presence of a muscle disease, the extra demands put on the muscle system are extra harmful or, just the opposite, are helpful. According to present insight this will have to be researched for each individual muscle disease, because the different afflictions might well react very differently. One way to research the effects of taxing the muscle system in a good and systematic manner, is to determine the effects of muscle strength training. In the present study of 70 participants with FSHD, one half will be training for the duration of one year under the supervision of Rolf van

Asseldonk. The other half will not be training. After six months, and again after one year, it will be determined which group shows the best results in muscle strength tests, muscle volume measurements, and a number of other tests.

Salbutamol - background and framework

Salbutamol is a medication which already for many years is indicated for the treatment of pulmonary diseases, such as asthma. Top athletes have been using Salbutamol not only to expand the bronchial tubes but also because they believe that it has a muscle strengthening effect. In tests on animals and healthy volunteers this effect was indeed proven. It was also proven that Salbutamol in combination with a program of muscle strengthening exercises resulted in an extra increase in muscle strength and muscle volume.

In a preliminary study, done in 1998 by an American research team, it appeared that the above might also hold true for FSHD patients. After a 12-week consumption of Salbutamol the muscle strength and muscle volume of the 15 participants had improved somewhat. Salbutamol is not a “wonder drug” but it shows few side effects and, possibly, might lead to a better muscle condition in patients with FSHD. The positive results of the preliminary study were the stimulus for a larger American inquiry. This study has 100 participants. One-third receive 16 milligrams Salbutamol SR per day; one-third receive a double dose; the remaining participants receive a placebo (Neppil). The first results, described below, were made public just before the start of the summer. It is expected that a more extensive report on these and other results will appear by the end of this year [2000].

In the Netherlands the aforementioned 70 participants received an evaluation after the first six months—regardless of whether they had received muscle strength training or not either a daily dose of 16 mg. of Salbutamol or a placebo. This means that we can now determine the effects of muscle strength training as well as Salbutamol when used alone, but also the effects of a combination of the two treatments.

Muscle strength training - the first results

So far we have only looked at the results of the tests done in the “strength-measuring

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CLINICAL

Dutch salbutamol study *continued from page 29*

“strength cage” in Nijmegen and the strength tests with the training weights at the participants’ home. We compared the average results from the training group with those from the non-training group. Because the average is a “group” average the result for individual participants may seem to differ.

The strength of the elbow flexors: the training group showed some improvement. In the group which did not train the strength remained unchanged.

The strength of the foot lifters: Both groups showed a marked deterioration. This deterioration proved to be equal in both groups.

After analyzing these results we have the impression that an active use of the muscles — as happens in everyday matters such as working, housework, sport, and hobbies, can have a positive effect on the muscles which (in months) did not measurably deteriorate in strength. In the case of muscles which do measurably deteriorate in strength it seems that neither muscle activity nor inactivity markedly worsens or accelerates the disease process. Why different muscle groups react differently is not yet clear. Further analysis of the results and advice will soon be forthcoming.

Salbutamol - the first results

The following results are from the American study. The results from the Dutch study are presently being analyzed. We have to wait and see whether the results of both studies are in agreement. The American researchers found that after 12 and 24 weeks use of Salbutamol the strength (measured in the “strength measuring cage”) had improved vis-à-vis the situation before Salbutamol use. But after 52 weeks the strength fell back to the level from which it started, and was equal to the strength in the placebo group. Thus the positive effect on muscle strength disappears when Salbutamol is used for an extended period of time. It may well be possible that the muscles develop a tolerance for the medication.

It seems that after 52 weeks Salbutamol still does have a positive effect on muscle volume. In addition to a somewhat larger muscle mass, the muscles appear to be turning less to fat. We shall have to study this effect in greater depth before we can come to a conclusion regarding the value and meaning of this phenomenon. We find ourselves in a good position to study the effects of Salbutamol on muscle and fat mass because we made a CT-scan, especially adapted for the purpose, of all

the participants both before and after the use of Salbutamol. We expect that by the end of the year 2000 we shall have been able to analyze the results of the Dutch study regarding the effects of Salbutamol to a point where, in consultation with the American scientists, we can come to a joint final conclusion.

In conclusion

We hope that on the basis of the above described studies we may gain greater insight into the muscle functioning of patients with FSHD, so that in the future we shall be in a better position to give advice regarding the pros and cons of muscle strength-improving exercises, (heavy) work, sport, and the use of Salbutamol. We hope that the results and experiences from the studies will also have positive consequences for people suffering from muscle diseases other than FSHD.

*FSH Society, translation from the Dutch language of selected contributions to the VSN Newsletter, VSN: Organization Muscle Diseases Netherlands, FSHD, Number 24 - December 2000

This newsletter is a publication by the diagnosis working group Facioscapulohumeral dystrophy (Landouzy-Dejerine disease)

*Article from the VSN newsletter***Expansion of the clinical spectrum of FSHD**

—Anneke J. van der Kooi, Center for neuromuscular diseases, Dept. of Neurology, Academic Medical Center, Amsterdam.

Facioscapulohumeral dystrophy (FSHD) is a muscle disease which usually appears in multiple generations of the same family and which can be passed on from parent to child. The muscle weakness affects, initially, the facial- (facio), scapular- (scapulo) and upper arm (humeral) muscles, followed by weakness in the foot lifting muscles, stomach muscles and hip and upper leg muscles. Complaints usually start around age 15 and often there is a clear difference between the right side and the left side of the body. Electrical muscle tests and a muscle biopsy prove the existence of a dystrophy, but the detected abnormalities are not characteristic for FSHD. In that case a DNA-test is indicated. In 95% of the patients this DNA-test will confirm whether the correct diagnosis was made.

In the Utrecht and Amsterdam neuromuscular centers, six patients were seen in which FSHD presented itself in an atypical

manner but who, on the basis of DNA tests, were nevertheless diagnosed as having FSHD. Three patients showed the beginning of weakness in the foot lifting muscles, one patient had weakness in the upper legs, one patient was unable to walk on tiptoes because of weakness of the calf muscles, and the last one complained about fatigue and muscle pain in the shoulder girdle. None of these patients showed a clear weakness of the facial muscles, and in none of the cases did other family members have the same complaints.

Because of these *rather atypical FSHD-onset symptoms* the initial diagnosis considered other diseases such as, for instance, a hernia, spinal muscle atrophy, and inclusion body myositis. After a very thorough physical examination (performed by a neuromuscular specialist) all patients were determined to have a characteristic facial expression, an abnormal form of the shoulders when lifting the arms, or

winging of the shoulder blades. This led to the thought that FSHD might be present, which in turn led to the request that a DNA-test be performed.

The conclusion can be drawn that in the first instance FSHD does not always present itself in the usual manner. It is not unimaginable that through the application of DNA-testing even more atypical forms in which FSHD can present itself may be found.

FSH Society, translation from the Dutch language of selected contributions to the VSN Newsletter VSN: Organization Muscle Diseases Netherlands – FSHD, Number 24 - December 2000

This newsletter is a publication by the diagnosis working group Facioscapulohumeral dystrophy (Landouzy-Dejerine disease).

CLINICAL

Poster presentation

Results of the Dutch FSHD trial on the efficacy of strength training and albuterol

EL van der Kooi¹, OJM Vogels¹, RJGP van Asseldonk¹, E Lindeman², JC Hendriks³, GW Padberg¹

¹Neuromuscular Centre Nijmegen, University Medical Centre Nijmegen, The Netherlands

²Rehabilitation Centre 'de Hoogstraat', University Hospital Utrecht, The Netherlands

³Department of Medical Statistics, University Medical Centre Nijmegen, The Netherlands

Corresponding author: EL van der Kooi, Neuromuscular Centre Nijmegen, University Medical Centre Nijmegen, PO Box 9101, 6500 HB Nijmegen, The Netherlands Phone: +31-24-3615202 Fax: +31-24-3541122 E-mail: E.vanderKooi@czzzoneu.azn.nl

INTRODUCTION

Decline in muscle strength and mass in FSHD is slowly progressive with large intra- and inter-individual variability. No curative or disease slowing therapy is available. Factors that determine the course of this disorder are largely unknown: genetic and environmental factors are postulated. A factor might be to what extent the dystrophic muscles are (over)used. Observed asymmetric weakness led to the hypothesis that even daily occupations might accelerate progression of muscle weakness.

In contrast, some studies on strength training in neuromuscular patients reported moderate positive effects on muscle strength in the few participating FSHD patients. Due to the small number of FSHD patients (13 in four trials) and the variety in design of the training programs no general conclusions can be drawn. In fact, the effect of physical exertion on muscles in FSHD is still uncertain. Therefore, patients can not be given well-founded advice regarding work, sports and other forms of exertion.

In studies on animals and healthy volunteers beta₂-adrenergic agonists, such as albuterol, increase the muscle strength and mass by different anabolic mechanisms. These effects are greater when combined with strength training. In a pilot study on 15 FSHD patients albuterol induced gain in muscle strength and mass when used for 12 weeks. In a more recent and larger trial patients failed to retain the increased strength after 52 weeks of medication. However, there was (still?) an increase in lean body mass, suggesting an anabolic effect.

OBJECTIVES

Primary Goal:

To evaluate the efficacy of moderate severe, progressive strength training and the beta₂-adrenergic agonist albuterol on skeletal muscle strength, fatigue and muscle mass in patients with facioscapulohumeral muscular dystrophy (FSHD).

Secondary goal:

To study the influence of training on

impairments, disabilities, and handicap.

DESIGN/METHODS

Patients

Seventy genetically confirmed, eligible FSHD patients.

Training Program

- Moderate to high resistance progressive overload
- Elbow flexors (EF) and ankle dorsiflexors (AD)
- Mainly dynamic, few static exercises
- At home: 52 weeks, three times a week, 30 minutes
- Physiotherapist every third week at home
- Non training group instruction: continue the usual amount of physical activity

Albuterol/Placebo

- Albuterol, sustained release, 8 mg bid for 26 weeks
- Identical placebo, 8 mg bid for 26 weeks

Randomization and evaluation

Patients were evenly assigned by randomization to a training (TG) or non-training group (NTG). A second randomization after testing at 26 weeks resulted in four groups. TG and albuterol (TG+A), TG and Placebo (TG+P), NTG+A, NTG+P. Final evaluation took place at 52 weeks by a blinded evaluator.

Analysis

- Generalized linear mixed model
- Correction for dis-balances in treatment groups for potential confounders such as sex, age, length and weight were carried out during analysis (when necessary).

Primary Outcome Measures

- Muscle strength
- Static strength
- MVIC maximum voluntary isometric strength: Maximum Force (MF) and 3-4 seconds
- MVIC maximum voluntary isometric strength: Sustained Force (SF) and 30 seconds

- Dynamic strength
- Weights: One-repetitive maximum (1-RM) was used
- Muscle volume: Estimated by a stereologic CT method

DISCUSSION

In the untreated (NTG+P) trial population there seems to be a measurable tendency of decline in muscle strength over one year. The process is less pronounced for the elbow flexors than for the ankle dorsiflexors. So far this difference in the rate of progression is not understood. However, it seems to be an important factor in the effect of the treatment modes in this trial.

Ankle dorsiflexors:

The impressive loss in strength of the ankle dorsiflexors is neither influenced by training nor the use of albuterol, nor by the combination of these two.

Elbow flexors:

Albuterol, sustained release 8 mg bid, for 26 weeks seems to prevent the moderate loss in muscle strength of the elbow flexors. There is even a small improvement in strength in the albuterol treatment groups. The effect of albuterol on strength is not significantly different in the NTG and TG group.

Training of the elbow flexors did not result in a significant effect on muscle strength as measured by the static strength measurements, but dynamic strength measurements clearly improved. This can be explained by one of the main principles in training: specificity of training.

CONCLUSIONS

In FSHD patients:

- Moderate severe, mainly dynamic strength training can result in very specific, moderate gain of dynamic strength.
- Albuterol when used for 26 weeks induces very moderate gain of strength as compared to the placebo group.
- The effect of both treatment modes seems to be different for different muscle groups and might be dependent on their rate of natural progression.

CLINICAL

November, 1999

FSHD in China

Meeting (November, 1999) with Dr. Cheng Zhang at the Massachusetts General Hospital in Charlestown, MA in the laboratory of FSH Society Scientific Advisory Board member Dr. Robert H. Brown, Jr., M.D., D.Phil. This was the Society's first opportunity to work with physicians working on FSHD in China and their FSHD patients. Left to right: Dr. Cheng Zhang, Sun Yat-Sen University of Medical Sciences, Guangzhou, P.R. China, Daniel Paul Perez, President & CEO, FSH Society, Lexington, Massachusetts.

In November 1999, the FSH Society first met with Dr. Cheng Zhang at the Massachusetts General Hospital in Charlestown, MA in the laboratory of FSH Society Scientific Advisory Board member Dr. Robert H. Brown, Jr., M.D., D.Phil. Dr. Brown and Dr. Zhang have been working together on projects on other neuromuscular diseases and both have a strong interest in FSHD. The initial meeting was congenial and productive and our professional friendship was immediate due to our mutual interests in solving the problem of FSHD. As Neurology Director of one of southern China's largest neurology clinics, Dr. Zhang has been following a large number of FSHD families and patients. This was the Society's first real inroad into FSHD in the country of China as previously we had not been able to locate patients with FSHD or physicians working on FSHD in China. We had finally made a solid contact with an extraordinary physician/clinician researcher with knowledge in both eastern and western medicine.

Shortly after the meeting in November, the FSH Society helped to get the genetic probe for FSHD to Dr. Zhang to allow the beginning of molecular genetic analysis of Chinese FSHD families. In early 2000, Dr. Zhang had completed a preliminary analysis of his families and patients and had proof positive that this population is indeed afflicted with FSHD due to a deletion in the 4q35 region.

At the request of the FSH Society we invited Dr. Zhang to attend the 3rd International Conference on the Cause and Treatment of FSHD on Monday, May 8, 2000, and the subsequent Research Planning Conference held on the following day in Bethesda, Maryland to introduce this new and important dimension to the FSHD work as well as to discuss the use of alternative medicine and Traditional Chinese Medicine treatments of FSHD.

The following is an article from Dr. Cheng Zhang, M.D., Ph.D. on the use of medicinal herbs to treat FSHD in China. It is fascinating to note that the Chinese treatment for muscular dystrophy and FSHD has been around for more than 2000 years.

Treatment of FSHD in traditional Chinese medicine

—Cheng Zhang, M.D., Ph.D., Xiao-yan Guo, Song Ling Chen, Department of Neurology
First Affiliated Hospital, Sun Yan-sen University of Medical Sciences, Guangzhou, Guangdong, 510080, P.R. China

Facioscapulohumeral muscular dystrophy (FSHD) is an autosomal dominant inherited muscular disorder characterized by progressive weakness and atrophy of the facial, shoulder girdle, and upper arm muscles. It is the third most common form of muscular dystrophy, with a prevalence of 1:20,000. FSHD has its onset usually between the first and second decade, and progresses gradually over time. About 10% of patients eventually become wheelchair bound and up to two-thirds of patients have disease-related problems with their daily activities.

In the majority of FSHD families, the gene defect has been located to chromosome 4q35. Genetic linkage analysis showed that most patients with FSHD have a shorter EcoRI and EcoRI/BlnI digestion fragment detected by the chromosome 4qter DNA marker p13E-11.

In China, FSHD was diagnosed based on clinical characters, familial history, and DNA analysis, then treated with Traditional Chinese Medicine (TCM). Some FSHD patients may

slow the progression of muscular dystrophy and weakness.

According to the theory of TCM, FSHD belongs to "WEI" syndrome. "WEI" means muscular dystrophy and flaccidity. Before two thousand years, "WEI" syndrome was treated with Chinese herbs. It was recorded in "The Yellow Emperor's Canon of Internal Medicine," which is one of the most important TCM books.

In the theory of TCM, qi-deficiency of the spleen and kidney (or the deficiency of vital essence of liver and kidney) causes FSHD. According to the theory of TCM, spleen improves the excitement of the cerebral cortex, promoting the tension of skeletal muscles, smooth muscles and supporting tissues, and promoting digestion and absorption. The kidney is the congenital fundamental of constitution. It is in charge of the bone and marrow, and stores reproductive essence and kidney-yin and kidney-yang, as well as supplementing the essence of life.

If a person suffers from qi-deficiency of the spleen and kidney, he may acquire muscular dystrophy; weakness of waist, knees, and girdle; lassitude of the extremities, especially in upper arms; pale tongue with whitish coating; and deficient and weak pulse.

Therefore, for FSHD caused by qi-deficiency of the spleen and kidney, we use the prescription of Buzhongyiqi, which can nourish and enrich the spleen and kidney, invigorating the spleen, replenishing qi and elevating the spleen-yang to treat qi collapse. Usually, we use:

1. Astragalus root acts as a principal drug with the effects of replenishing qi and elevating yang;
2. Prepared licorice root, Ginseng, and Bighead atractylodes rhizome, as assistant drugs, shares the effects of invigorating the spleen and replenishing qi;

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CLINICAL

Double-blind, randomized, controlled trial of albuterol in FSHD

U.S. FSHD albuterol trial

John T. Kissel*, Rabi Tawil+, Michael McDermott+, Wendy M. King*, Shree Pandya+, Jerry R. Mendell*, Robert C. Griggs+, and the FSH-DY Group. The Ohio State University(*), Columbus, Ohio and the University of Rochester(+), Rochester, New York

Recently, the FSH-DY group announced the results of their large study of albuterol in facioscapulohumeral dystrophy (FSHD). The results, which were presented at both the American Academy of Neurology national meeting and at the National Institutes of Health Symposium on FSHD, represent the culmination of a five year effort by the FSH-DY group, which is composed of investigators from the Ohio State University, under the direction of Dr. **John T. Kissel**, and the University of Rochester, under the direction of Dr. **Rabi Tawil**.

The study was based on previous studies indicating that certain drugs called beta2-adrenergic agonists have an anabolic (muscle building) effect and can increase strength in both laboratory animals and healthy adults. Albuterol is one such beta2-adrenergic agonist that is frequently used in this country in patients with asthma and other lung diseases. A previous open-label trial (where both the investigators and patients knew that they were taking the real drug) by the FSH-DY group involving 15 FSHD patients suggested that albuterol might increase muscle mass and strength in these patients.

The larger study was a one-year, prospective, randomized, double-blind, placebo-controlled trial, so that neither the patients nor the investigators or evaluators knew whether they were taking the real drug or a placebo (sugar pill). Ninety adult patients (49 males and 41 females, ages 18-57) were randomized to one of three groups (30 patients each). Two groups took sustained-release albuterol (kindly provided as Proventil Repetabs by the Schering Corporation) at a dose of either 8.0 mg or 16 mg orally every 12 hours; the third group took identical-appearing placebo. All patients took the same number of pills per day.

Assessments were performed at weeks four, 13, 26, and 52. The primary outcome measure was the change from baseline to week 52 in an average strength in 12 muscles, as tested by a computerized muscle strength testing system

(called the MVICT score). Other outcomes examined included the average change in muscle score as measured by so-called manual muscle testing, which involves trained



Discussing clinical and molecular genetics research at the University of Rochester during the evening of the National Institutes of Health (NIH) Conference on the Cause and Treatment of FSHD May 8, 2000 in Bethesda and Rockville, Maryland. Left to right: Dr. Denise Figlewicz, University of Rochester School of Medicine, Rochester, New York, Dr. Rabi Tawil, University of Rochester School of Medicine, Rochester, New York.

investigators pushing and pulling on 38 different muscles in a manner similar to what is done by the doctor in the office. Another important variable examined was the change over the year of treatment in the total body muscle mass as determined by a procedure known as dual-energy X-ray absorptiometry (or DEXA), which is the same basic procedure used to check bone mass in patients with osteoporosis.

Eighty-four patients completed the study. The drug was very well tolerated, and there were no serious adverse events related to the medication. Some side effects were experienced by most patients (about 85%), and included tremor, insomnia, and muscle cramps. The side effects were usually mild and persisted for only a short time, and no patient had to have their dose discontinued or lowered because of side effects.

Unfortunately, when the final data was analyzed, the average change in the computerized MVICT scores was not significantly different between the three groups. In other words, there was no effect of the drug on strength when all the muscles averaged together were analyzed. Similarly, there was no difference in the average strength

as measured by manual testing. There was, however, a statistically significant increase in average grip strength in both low-dose and high dose albuterol groups compared to placebo.

Another interesting finding was that the lean body mass, as measured by DEXA testing, also increased significantly in the high-dose group compared to placebo. In fact the high dose group patients gained an average of 1.57 kilograms of muscle (about 2-1/2 pounds), while the placebo group lost on average 1.02 kilograms (about 2.2 pounds). There was no difference in muscle mass in the low-dose albuterol group compared to placebo.

The "bottom line" is that the long-acting albuterol given for one year did not improve average muscle strength as measured by either computerized or manual testing in patients with FSHD. It did, however, significantly improve grip strength and skeletal muscle mass, suggesting that it does exert some

positive effects on muscle. The reasons for these somewhat differing results are unclear. The most obvious interpretation is that the drug simply doesn't have enough effect on muscle to show up on the testing methods used. An alternative hypothesis is that some of the tested muscles may have been too weak to show a response. Another possibility is that higher doses or a differing dosage schedule (for example, taking the drug for one or two weeks at a time) or even a more potent beta2-agonist might be needed to bring out a better response. The FSH-DY group is currently exploring all of these possibilities, and is planning further clinical trials to investigate these issues.

This study was supported by grants from the Muscular Dystrophy Association, New York State Education Department; NIH Grants NS22099, RR00034, and RR00044.

The FSH-DY group would like to formally thank all of the patients and their families for participating in the study. Without their cooperation and willingness to be involved in projects such as this, there would be no advances in the fight against FSHD.

For an additional albuterol study conducted by the Dutch, please see page 29-31.

PATIENT EDUCATION/AWARENESS

Chronology, 2000 *continued from page 19*

NIH NIAMS Internet web site: <http://www.nih.gov/niams/reports/fshdsummary.htm> during the first week of September, 2000. It remains unclear as to



Discussing the events of the day at the National Institutes of Health (NIH) Planning meeting May 9, 2000 in Chevy Chase, Maryland. Left to right: Carol A. Perez, Executive Director FSH Society, Inc., Dr. Eric Hoffman, Children's Research Institute, Washington, DC, Dr. Stephen J. Jacobsen, Chairman of the Board, FSH Society, Inc.

whether this is construed as the physical hard copy document of a research plan.

NIH Research Program Announced

On November 8, 2000, the first of the three major announcements was made by NIH as "Exploratory Research on Facioscapulohumeral Muscular Dystrophy." On December 11, 2000, the second announcement was made on the establishment of a National Patient Registry at the University of Rochester Medical School for FSHD and Myotonic muscular dystrophy. On January 4, 2001, the third announcement was made for a three year program "Therapeutic and Pathogenic Approaches for the Muscular Dystrophies."

The NIH has rejected five of five grant applications submitted in this fiscal year 2000 including an extremely substantial grant submitted jointly by three researchers. Program Director Dr. Richard Lyman had been advising and consulting with all three researchers from the inception of the idea for this grant until its submission date and thus the grant had been submitted according to the NIH NIAMS guidelines, criteria and suggestions. The researchers are confounded

that some of the critical remarks oppose the NIH NIAMS directive and will resubmit this grant shortly having addressed concerns of the NIH review committee. The FSH Society is concerned that the NIH has once again rejected a grant in FSHD. Of greater concern is that, according to the NIH sources, this grant is by far the best grant application ever seen in the area of FSHD at the NIH. It was submitted by the absolute top and best working on the problem and still not funded.

The above chronology shows how valuable the FSH Society fellowship program has been in rapidly pushing forward the research agenda. The FSH Society has been able to elevate FSHD research into the mainstream consciousness of the research community and funding agencies from its invisible state of a few years prior. We have been able to tap into the collective vision of the FSHD research "nation" with what needs to be done in FSHD research and present the necessary components and objects required for a fully integrated research program. The

process has seen a very definite transformation.

In summary, we hope that the FSH Society members are as pleased as we are with the enormous progress made by the current scientists being funded. Each of the five Bronfman grantees is covering a major program area listed as a priority in our research plan and in the "research plan" as put forth by the NIH NIAMS and the NIH NINDS. Dr. Winokur is working on gene, RNA, cDNA and protein expression studies using high technology assay systems. Dr. van der Maarel has generated five mouse models setting the stage for the introduction and creation of much needed animal models and generating enormous insight into how the deletions occur and the consequences of having the D4Z4 deletions. Dr. Figlewicz has opened the door to understanding the biochemical pathways causing problems in FSHD and has given us tremendous insight into the genetic as well as cellular process in FSHD. Dr. Picketts has begun the extremely complex task of examining how the three-dimensional structure of the chromosome plays a role in FSHD and has joined efforts with two of the top experts in the field. Dr. Gabellini is fast uncovering the role of the D4Z4 repeat as relates to FSHD and is giving us great insight into the consequences of having deletions of the D4Z4 repeats. Dr. Gabellini is on the verge of figuring out how transcription is possibly initiated and promoted in FSHD.

We are driving and shaping the agenda for FSHD research from a number of different angles. We live at a time when remarkable

continued on page 35



Evening of the National Institutes of Health (NIH) Conference on the Cause and Treatment of FSHD May 8, 2000 in Bethesda and Rockville, Maryland. Left to right: Dean Johnsen, Bowie, Maryland, Jan Jacobsen, Encinitas, California, Stephen J. Jacobsen, Chairman of the Board, FSH Society, Encinitas, California.

PATIENT EDUCATION/AWARENESS

Chronology, 2000

continued from page 34

technology is available to help us in our quest for an answer to FSHD. The *Society* has made possible the consideration of FSHD as a disease to be studied using these new technologies and has attracted many new and talented scientists to this new, interesting and novel problem. We are making substantial progress by providing the resources for more traditional methods of scientific study and are making expeditious gains that should have been made several decades ago if not at least one decade ago.

In three and a half years, we have reviewed 25 relevant and high quality applications and now have the certainty that there is no shortage or lack of interest from the research community in the area of FSHD. This gives us firm ground to refute the NIH belief that there is no interest in FSHD.

We hope that you are satisfied with the progress and commitments made to date. It is our hope that you will consider the renewal of a most generous gift with serious thought to increasing the total amount for research. The *Society* has been very successful in achieving its mission and purpose to date but is reaching the limitations of its current organizational structure. The *Society* needs to go much further with respect to building a staffed organization and a Board of Directors and Scientific Advisory Board that has more active and available resources to bring to bear large scale solutions for FSHD. Please consider carefully how much better your family's FSHD interests would be served if this *Society* had the resources to place full time personnel in the field, visiting, phoning, writing, and meeting with our potential supporters in neurological and genetic science, government and business. We count on you to help us.

*The FSH Society depends
on YOUR contributions
to continue its work!
Please consider a
tax-deductible
contribution today!*

Introduction of Senate Bill 805

continued from page 27

an impression on several members of Congress, and Jacob's picture adorns the desks of numerous health care legislative staff throughout Washington. This is because like so many other parents facing the day-to-day experience of living with a child suffering from this debilitating disease, Cheri is focused on leaving no stone unturned in her quest to help improve her son's chance of survival. One day, Jacob drew a picture of himself, and in a cloud above his figure he wrote the words, "What I want most in the world is a cure for Duchenne Muscular Dystrophy." I say to my colleagues, that's what I want, too. Today, we are getting one step closer to making Jacob's wish come true.

David Mesick, also of Minnesota, is the Chairman of the Parent Project Muscular Dystrophy, a national voluntary health organization committed to promoting medical research efforts specific to Duchenne and Becker muscular dystrophies. Through David's leadership and the organization's efforts, the muscular dystrophy community has successfully increased Congress' awareness of this devastating disease. Today, their voices are being heard here on the floor of the Senate. I have been moved by the number of families in Minnesota and elsewhere who have been affected by this disease, and I have been moved even more by their tenacious response. We can support this community by improving federal research efforts and public programs to address the needs of individuals with muscular dystrophy.

Mr. President, passage of this legislation will improve coordination of research not only into Duchenne's, but into all the various forms of Muscular Dystrophy. It authorizes the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) to establish separate Centers of Excellence to promote basic and clinical

research, epidemiology, data collection and assessment on the various forms of muscular dystrophy. These steps are needed to ensure a long-term commitment by the federal government to the treatment and cure of muscular dystrophy. I am neither a scientist nor a physician. But I am told that it is highly probable that sooner or later gene therapy will be able to cure diseases of this nature. For diseases like Duchenne's muscular dystrophy, involving flaws on a single, identifiable gene, the outlook is even more positive. Yet the words 'sooner' and 'later' have profound consequences in the lives of tens of thousands of Americans and their families. With the introduction of the MD CARE Act, we move a step closer to giving those families hope. I encourage my colleagues on the Senate HELP Committee to work steadfastly to move this crucial legislation through the Senate, and I urge all colleagues to support it. I also think of Eric Anderson who is such a good friend of my son. David and Eric came to Washington. So many of the families who came, and many came with their children, were so young and their children were so young. Time is not neutral for them. There is an excellent chance we can make a real breakthrough in finding a cure. It is not too much that these families ask for and it is not too much to pass this legislation and try and push forward a commitment to the funding, a commitment to this research. This is one of those diseases. I hate to label, so few are affected, but for these children and these families, they are not too few in number. These are their lives. These are their hopes. These are their dreams. This is their pain. This is their agony. I want to turn this into hope. I ask all of my colleagues to support this legislation.

I am very pleased this has strong bipartisan support.

FSHD & Chinese medicine *continued from page 32*

3. Functioning as adjuvant drugs, Tangerine peel produces the effect of promoting the flow of qi while Chinese angelica root provides the effect of tonic blood;
4. Cimicifuga rhizome and Bupleurum root are used together as guiding drugs for sending up lucid yang.

According to our experience, the Buzhongyiqi may slow the muscular dystrophy progress in FSHD patients, and improve the weakness in the upper arm and shoulder girdle. But each FSHD patient is a different individual. It is necessary for each FSHD patient to use Bianzhenlunzhi based on the theory of TCM, and modify the drugs, the dose of the drugs, and the dosage forms. Clinically it depends on the concrete condition of the patient's illness.

CLINICAL

Tissue donation needed to further research on FSHD

The Brain and Tissue Bank for Developmental Disorders at the University of Maryland in Baltimore is one of the two tissue repositories that is funded by the National Institute of Child Health and Human Development. The bank is used for the study of childhood disorders that typically start in childhood but may continue into advanced age. The second bank is located at the University of Miami. The purpose of the banks is to make human tissue available for research. Tissue donations are needed from persons with developmental disorders and their relatives, persons of all ages and either sex.

The banks provide information to anyone having questions about tissue donations and maintain a registry of individuals who wish to donate tissue either at the time of surgery or at the time of death. No cost is incurred by families who donate tissues. Currently a number of families with FSHD are registered as potential tissue donors with the bank at the University of Maryland. However, it is necessary to have a larger pool of registrants to assure that sufficient tissue is available for research projects. Advanced planning and registration is always best, however, we can

usually have a successful donation even if notified at the time of passing.

To obtain more information or receive a registration form, please call or write:

Patricia L. W. Nash, PA-C,
Project Coordinator
Brain and Tissue Bank
for Developmental Disorders
University of Maryland
655 W. Baltimore Street, 10-035 BRB
Baltimore, MD 21201-1559
(800) 849-1539; (410) 706-1755;
(410) 706-0020 Fax

FSHD Tissue Donation Facts:

- nine registrants
- one case that has been collected. UMB#862 (collected in 1997)
- one case that is pending
- A few requests about FSHD tissue in the past, nothing very recent, and to date no tissue has been sent out from the one collected case.
- Letter from researchers/clinicians on file at the Brain and Tissue Bank that outlines tissues that would be useful to collect in these cases.

Improved genetic testing available

Recently scientists in Leiden, the Netherlands, discovered new information to further improve and optimize the molecular genetic testing and diagnosis of non-standard cases of FSHD. "Genetic diagnosis of FSHD is based on sizing of the polymorphic *EcoRI* fragment on which the D4Z4 repeat array resides. Use of the combination *EcoRI*, *EcoRI/BlnI* and *XapI* unequivocally allows characterization of each allele, whether homogeneous or hybrid. This is particularly useful in case of co-migrating 4-type and 10-type alleles, for the assignment of hybrid fragments to their original alleles and in case of suspected FSHD with non-standard allele configurations as demonstrated by the exclusion of one patient carrying an apparently short hybrid repeat array." Please see page 59 for more information.

On the issue of anticipation and increased severity down generations in FSHD

Peter W. Lunt, M.D., Bristol UK.

Facioscapulohumeral Muscular Dystrophy: Diagnostic and Molecular Aspects. Deymer F(ed): Neuromuscular Diseases: From Basic Mechanisms to Clinical Management, Monograph Clinical Neuroscience, Basel, Karger, 2000 vol 18. Pp 44-60.

From Monograph Clinical Neuroscience page 48: "Anticipation"

"It is uncertain whether there may be evidence of clinical anticipation in FSHD, whereby the severity tends to increase with successive generations. At present it is not clear how this could come about with a fixed mutation in each family, but the same has been proposed in at least one other neurological condition with a fixed mutation — familial amyloid polyneuropathy. One could hypothesize that the fixed deletional mutation, by affecting chromosome folding or telomeric pairing at meiosis, might be inducing a dynamic expansion (say) in a different type of tandem repeat located more proximally on chromosome 4q, leading to further expansion at subsequent meioses, but this must remain as pure conjecture in the absence of any known dynamic repeat in the 4q35 region. Furthermore, the finding of DNA evidence for somatic and germline mosaicism for a 'severe' mutation as an explanation for minimal symptoms in one parent in some new mutation cases and the knowledge that females generally have milder presentation than males might provide more plausible explanations for at least some cases of apparent anticipation."



Discussing clinical research issues during the evening of the National Institutes of Health (NIH) Conference on the Cause and Treatment of FSHD May 8, 2000 in Bethesda and Rockville, Maryland. Left to right: Dr. Peter Lunt, Bristol Children's Hospital, Bristol, England, Carol A. Perez, Executive Director FSH Society.

CLINICAL

Respiratory insufficiency in FSHD

The following abstract and lecture of interest was presented May 8, 2000 at the FSH Society/National Institutes of Health (NIH) International Conference on the Cause and Treatment of FSHD.

Respiratory Insufficiency in Facioscapulohumeral dystrophy

M. Wohlgenuth, Nijmegen, The Netherlands, E van der Kooij, Nijmegen, The Netherlands, O.J. Vogels, Nijmegen, The Netherlands, R.G. van Kesteren, Utrecht, The Netherlands, S. van der Maarel, Leiden, The Netherlands, G.W. Padberg, Nijmegen, The Netherlands

Objective

A nationwide study was conducted to investigate respiratory insufficiency in FSHD to estimate its prevalence and to recognize the clinical profile of the FSHD patient at risk.

Background

Respiratory failure has been mentioned in only a few severely affected FSHD patients. Adequate studies on prevalence and clinical features are lacking. The FSHD prevalence in the Netherlands is estimated to be 1:20,000 and all neuromuscular patients with ventilatory support are registered at one of the four Dutch Centers for Home Mechanical Ventilation.

Design/Methods

Informed consent was obtained from all registered FSHD patients with ventilatory support. All patients charts were reviewed and all patients were visited at home. Methods included extended history taking, physical examination, DNA test and measurement of Forced Vital Capacity (FVC), Forced Expiratory Volume in 1 Second (FEV1) and static inspiratory and expiratory mouth



Evening of the National Institutes of Health (NIH) Conference on the Cause and Treatment of FSHD May 8, 2000 in Bethesda and Rockville, Maryland. Left to right: Marielle Wohlgenuth, University Hospital Nijmegen, Nijmegen, The Netherlands; Kathy Barrett, University of Rochester School of Medicine, Rochester, New York.

pressures (MIP and MEP). Both spirometry and manometry were compared with a group of ambulant and a group of wheelchair-bound FSHD patients

Results:

Eight out of nine suspected FSHD patients on ventilatory support fulfilled the clinical and genetic criteria for FSHD. The chest autoradiograph of one patient showed emphysema; none of the other patients suffered from pulmonary disease. In one patient polysomnography revealed an obstructive and

central apnea syndrome. Symptoms of nocturnal hypo-ventilation occurred in seven patients and resolved rapidly on ventilatory support. All patients were wheelchair bound and general muscle weakness was profound before respiratory problems began. They all had moderate to severe kyphoscoliosis and severe lumbar lordosis. FVC was less than 40% of predictive value in seven patients and severely decreased MIP and MEP were indicative of respiratory muscle weakness.

In comparison with the ambulant and wheelchair dependent FSHD patients, the patient with early onset of disease, wheelchair dependency and a (kypho-)scoliosis had the most severely restricted lung function.

Conclusions

Respiratory insufficiency requiring ventilatory support is rare in FSHD and its prevalence in the Dutch community is about 1%. The risk profile for ventilation dependency can be delineated as the early onset and wheelchair bounded FSHD patient with severe (kypho-)scoliosis and lumbar lordosis. Annual measurement and Pemax and Pimax is recommended for this patient at risk. Special attention should be paid at symptoms of nocturnal hypo-ventilation. As for other chronic neuromuscular disorders, early recognition of respiratory insufficiency is important and treatment with non invasive ventilatory support improves quality of life and increases functional ability.

Marjorie Bronfman grant for molecular genetics research on FSHD is extended to 2004

The FSH Society is pleased to announce that the Marjorie Bronfman Grant for Molecular Genetics Research on FSHD has been extended to 2004 with an additional \$300,000.

The generosity and commitment of Mrs. **Marjorie Bronfman** to FSHD research permitted the FSH Society, starting in 1998, to award six (6) two-year research fellowships (US\$30,000/year) and two (2) one-year extensions for research projects that show extraordinary promise to find the cause of FSHD. This foresighted contribution significantly impacts progress in FSHD and has already created advances in FSHD research worldwide. The FSH Society is deeply indebted to Mrs. Bronfman and the Marjorie and Gerald Bronfman Foundation for this significant opportunity to advance research by funding up to five more research projects.

The FSH Society is pleased to be able to continue the productive collaboration with Mrs. Marjorie Bronfman to advance FSHD research.

Kiichi Arahata, M.D., 1946-2000

We mourn the passing of our former researcher, friend and colleague. **Kiichi Arahata** died of colon cancer on December 20, 2000 at the age of 54.

After graduation from Juntendo University Medical School in 1971, he was trained in the department of neurology there. Kiichi went to the Mayo Clinic as a research fellow from 1981 to 1983 and visiting scientist from 1985 to 1986 under the distinguished guidance of Professor **Andrew G. Engel**.

Returning home, he moved to the Department of Neuromuscular Research, National Institute of Neuroscience, National Center of Neurology and Psychiatry, Japan, as a section chief. As one of the members of the muscle research group of our institute, Kiichi made very important contributions in exploring the localization of dystrophin at the muscle surface membrane and its defect in Duchenne muscular dystrophy. In 1991, he learned molecular biology at Professor **Louis M. Kunkel's** laboratory in Harvard Medical School as a staff associate.

After being promoted to the Director of the Department, he accomplished many outstanding investigations on various muscular dystrophies, including facioscapulohumeral dystrophy (FSHD), Emery-Dreifuss muscular dystrophy, dysferlinopathy and Fukuyama congenital muscular dystrophy. During the



Kiichi Arahata M.D. lecturing on FSHD (Denver, Colorado 1998).

years, he built a very strong national and international reputation in the field of genetic muscle diseases and his name, integrity and his work became widely known to myologists around the world. His greatest enthusiasm was recently concentrated on the development of DNA Chips for genetic muscle disease research. He was leading the Japanese Muscular Research Group as a chairman since 1999, and served as an executive of the World Muscle Society since 1996.

Even when colon cancer had him deep in its grip, he remained at work and continued his research. On December 15, he presented at the International Symposium in Paris, held in honor of the retirement of Professor **Michel Fardeau**. This was the last opportunity for him to participate in the international meeting. Two days after returning to Japan, he died peacefully.

He was moderate in everything, but a man of remarkable warmth and sensitivity—a true friend in the sense of the word. He was not only brilliant, but also a great teacher and mentor, training many young future promising scientists in and outside of Japan.

We will always recall with pride and gratitude his wisdom, integrity, support and friendship.

FSH Society offers condolences

December 20, 2000

Yukiko K. Hayashi, M.D.

Department of Neuromuscular Research,
National Institute of Neuroscience NCNP

Dear Dr. Hayashi,

This is to the memory of Dr. **Kiichi Arahata**. It was deeply saddening and distressing to receive news of the death of Dr. Arahata. We express our heartfelt sorrow and deepest sympathy to you and Dr. Arahata's family and colleagues.

We are thankful to have been in the company of such an extraordinarily fine and compassionate human being. Dr. Arahata was one of the bravest men that we knew, and our respect for him came from his intellectual, ethical and moral standards of the highest caliber. Our friendship, respect and loyalty to one another was immediate from the first day we met.

We know that the FSHD muscular dystrophy patient and research community has been greatly diminished by the loss of one of its leading scientists and guardians. We feel as though a bright light has gone out throughout the world and will miss Dr. Arahata dearly. We know that Dr. Arahata has left a legacy that will not be denied. We will make sure that Dr. Kiichi Arahata is remembered and honored.

Please accept our heartfelt condolences.
Daniel Paul Perez, President and CEO FSH Society, Inc.

Kiichi Arahata, M.D. memorial fund established



FSHD molecular genetics and genomics researchers have an animated discussion on FSHD issues at the National Institutes of Health (NIH) Planning meeting May 9, 2000 in Chevy Chase, Maryland. Left to right: Dr. Michael R. Altherr, Los Alamos National Laboratory, Los Alamos, New Mexico; Dr. Kiichi Arahata, National Institute of Neuroscience, NCNP, Tokyo, Japan; Dr. Denise Figlewicz, University of Rochester School of Medicine, Rochester, New York; Dr. Jane Hewitt, Nottingham University, Nottingham, England.

The Kiichi Arahata, M.D. Memorial Travel and Education Fellowship Fund established Dr. **Kiichi Arahata** as the most important and active person on FSHD research in Japan, and it appears that at present nobody can do as he had done. Dr. Arahata was extremely well known internationally in the muscle research community for his enormous contributions. Tentatively, the laboratory will continue the clinical and genetic diagnosis of FSHD patients in Japan under the direction of **Yukiko Hayashi**, M.D. It is our duty to help the research continue as there is a rich FSHD resource of clinical and genetic data.

The FSH Society, Inc. announced the establishment of the Kiichi Arahata M.D. Memorial Travel and Education Fellowship Fund to facilitate travel initially by Japanese students/professionals to FSHD meetings and conferences.

This fund was established at the request of Peter Lunt, M.D., Clinical Genetics, Institute of Child Health, Bristol Children's Hospital, St. Michael's Hill, Bristol, BS2 8BJ England.

We encourage professionals, patients and individuals concerned with FSHD to consider helping with this much needed effort by donating to the FSH Society Kiichi Arahata Memorial Fund to continue an excellent FSHD program in Japan.

GENETICS/RESEARCH

Philadelphia, Pennsylvania, October 3, 2000

Current happenings in FSHD molecular genetics

by Sara Winokur, Ph.D., Assistant Professor and FSHD Researcher, University of California, Irvine, California

FSHD Research

Workshop Summary

The past year has seen much progress towards understanding the molecular basis of FSHD. The FSHD Workshop in Philadelphia, Pennsylvania on October 3, 2000 provided a forum for presentation and discussion of recent inroads into FSHD research. More than 40 international clinicians and researchers convened to discuss their findings. Although the specific genes contributing to the disorder have not yet been conclusively identified, much insight has been gained towards understanding the mechanism and diagnosis of FSHD as well as development of model systems to study FSHD.

Silvère van der Maarel (Leiden, The Netherlands) has developed an improved diagnostic tool for FSHD diagnosis that involves the use of the restriction enzyme Xap1 (in addition to EcoR1 and EcoR1/Bln1). This combination allows for unequivocal characterization of both the chromosome 4 and 10 alleles. **Kevin Flanigan** (University of Utah, Utah) discussed his findings indicating an absence of anticipation in a large Utah FSHD family and Antonel Olkers (University of Pretoria, South Africa) presented the molecular diagnosis of FSHD in South African families. **Silvana van Koningsbruggen** (Leiden, The Netherlands) and **Denise Figlewicz** (University of Rochester, New York) presented cellular models for FSHD. Dr. van Koningsbruggen has developed the murine myoblast C2C12 for use in studying the expression of FSHD candidate genes as muscle differentiates. Dr. Figlewicz has utilized human myoblast cell lines to demonstrate that FSHD cells are more susceptible to oxidative stress than normal cells. Dr. **Alexandra Belayew** (University of Mons-Hainaut, Belgium) demonstrated the potential toxicity of a gene DUX4 which may be transcribed from the D4Z4 repeat. **Sara Winokur** (University of California Irvine, California) has found that specific genes encoding a LIM domain appear to be increased in FSHD.

Several new lines of research into the molecular mechanism of FSHD were



Building international relations and partnerships in FSHD research during the evening of the National Institutes of Health (NIH) Conference on the Cause and Treatment of FSHD May 8, 2000 in Bethesda and Rockville, Maryland. Left to right: Dr. Cheng Zhang, Sun Yat-Sen University of Medical Sciences, Guangzhou, P.R. China; Dr. Sara T. Winokur, University of California, Irvine, California.

discussed. These new approaches to studying chromatin structure in FSHD may well lead not only to an understanding of how genes in FSHD are misregulated, but perhaps foster new ideas as to how the disease may be treated therapeutically in the future. Two laboratories (Drs. van der Maarel, **van Overveld** and **Frants** in Leiden, the Netherlands, and, Dr. **Melanie Ehrlich** at Tulane University) discussed their recent results on the methylation status of D4Z4 and whether or not this is altered in FSHD. Although the results are preliminary, data suggests that the D4Z4 repeat is highly methylated in normal tissue, suggesting a condensed structure typical of heterochromatin. Whether or not this structure is unraveled on FSHD chromosomes is a subject of intense focus in FSHD research.

Furthermore, Dr. **Davide Gabellini** (Dr. **Rossella Tupler/Michael Green** laboratory at the University of Massachusetts, Massachusetts) has identified a protein involved in the regulation of genes that binds to the D4Z4 repeat, further suggesting a role for this repeat in the control of gene expression.

The extensive interaction of the 4q and 10q telomeric regions was discussed by Drs.

van Overveld (Leiden, the Netherlands) and **Dr. Luciano Felicetti** (CNR, Rome, Italy). This could have significant repercussion for both the mechanism by which the deletion is generated as well as the expression of genes in both regions. Finally, Dr. **Jane Hewitt** (University of Nottingham, Nottingham, England) presented her and Dr. **Michael van Geel's** (Roswell Park Cancer Institute, Buffalo, New York) physical map and genetic sequence of the region containing the D4Z4 repeat. This analysis has demonstrated that the 4q region is older evolutionary than the 10q region. The FSHD homologous region in the mouse and human show that gene content and order are conserved. As far as gene distribution is concerned, very few genes are localized near the D4Z4 repeat, while there is a gene-rich region beginning about 2 Mb proximal to the repeat. This has important significance in terms of identifying the specific genes affected in FSHD.

A complete copy of the agenda, meeting abstracts and roster for the 2000 FSHD Workshop may be requested through the FSH Society, Inc., 3 Westwood Road, Lexington, MA 02420 USA for US\$20.

GENETICS/RESEARCH

An FSHD research analogy

In our previous *Watch*, we developed a visual picture for the FSHD genetic work on chromosome 4. Imagine a piece of thin copper wire 18 miles long. This will be the DNA of chromosome 4. At each end is a copper ball that looks like a scouring pad with another such ball existing somewhere near the center at mile 10 but not in the center. The balls at



At the Laboratory of Drs. Michael Green, Rossella Tupler and Davide Gabellini in the Howard Hughes Medical Institute, University of Massachusetts, Worcester, Massachusetts. Left to right: Daniel Paul Perez, FSH Society, Dr. Rossella Tupler, Howard Hughes Medical Institute, University of Massachusetts, Dr. Davide Gabellini, Howard Hughes Medical Institute, University of Massachusetts.

the end of the chromosome are known as the telomeres and the ball in the center is known as the centromere of the chromosome. The balls themselves contain heterochromatic material, which is in effect bunched up DNA (permanent heterochromatin). The ten mile side is known as the long arm of the chromosome (the q arm) and the eight mile side is known as the short arm (the p arm).

The long arm and short arm are broken into bands numbered from the center heading out towards the ends. These bands are visible when chromosomes are specially stained in the laboratory. FSHD is thought to be associated with the very last band (band 35) on the long arm (q arm) of chromosome 4. In our analogy, band 35 is a one mile long stretch of copper with 3000 random points which are kinks in the wire. These represent genes and material involved with controlling the genes. Each gene or kink in the wire is unique in definition and may rely on information up and down stream from it.

The last feature that we need to know is the repeats that are associated with the FSHD disease. At the telomere end of the one mile piece of copper wire are anywhere from one to 100 end-to-end one foot segments (D4Z4 region) delineated by notches in the wire. Holding the telomere in one's hand observing band 35, one sees anywhere from one to 100 one foot repeats in the D4Z4 region which appear as one foot spaced notches in the copper wire that we are interested in.

Beyond that is one mile of thin copper wire containing kinks (genes) some of which

may only be a short distance in front of us. This is the 4q35 band with repeats bounded by the telomere. To carry this one step further, the chromosome at various points in time (inter-phase, cell division, cell organization) will bunch up into three-dimensional chromatin.

Chromatin is DNA proteins associated with the chromosome and mRNA

associated with the chromosome. In our analogy, the 18 miles of copper wire will bunch itself up entirely into a copper ball and attract to it food particles and dish detergent (protein and mRNA) at various points in time.

In 95% of the cases, FSHD is genetically linked to a region (D4Z4) close to the telomere on the long arm of chromosome 4. In non-affected individuals, this chromosome region comprises 10 to 100 tandem copies of a DNA element named 3.3 kb repeat. In affected individuals, FSHD is associated with chromosome deletions leaving only one to eight or nine such repeats in D4Z4. Members of the 3.3 kb family are not only found in the D4Z4 region, but also on several different chromosomes. Their number is estimated to be about 500 in the whole genome (across all of the chromosomes), and their function is presently unknown, although they are often associated with heterochromatin, a chromosome structure that blocks gene activity.

Much work is

going into explaining the role of the missing repeats or missing length of the chromosome causing FSHD. The prevailing theory is that the missing repeats cause the telomere to be brought too close to the adjacent genes (the copper ball is now one foot away from the first few kinks causing them not to be easily accessed by our special tools for de-kinking wire). Biologically, this is known as position effect variegation (PEV) and scientists are trying to identify the genes that are most adjacent and in the correct order from the repeats inward. This might cause genes immediately adjacent and also at a very large distance in the genetic world (up to one half a mile away in our example) to be affected in an over-expressed or an under-expressed way.

This is an interesting model as it means that no gene is broken per se but that a gene or many genes may have the quantity of material (protein) they produce higher and/or lower than normal due to the fact this mechanism affects the intermediary product (mRNA) generated by the gene(s). To extend this idea further, some scientists feel that the missing repeats might contain active genes which are stripped away causing lack of function. A third theory is that as the repeats are stripped away, toxic genes within the repeats are expressed or turned on causing damage to muscle cells. A fourth theory is that the heterochromatin plays a crucial role in the activation/de-activation of genes adjacent to it.



Autumn 1999 meeting between the FSH Society and the Association Française contre les Myopathies (AFM — French Muscular Dystrophy Association) and Genethon to discuss research priorities and directions for major international efforts on FSHD. Left to right: The French translator; Bernard Barataud, President AFM/President Genethon, Association Française contre les Myopathies (AFM), Evry Cedex, France; Dr. Robert H. Brown, Jr., Harvard Medical School, Massachusetts General Hospital East, Charlestown, Massachusetts; Dr. David Housman, M.I.T., Cambridge, Massachusetts, Chairman FSH Society, Scientific Advisory Board.

GENETICS/RESEARCH

Marjorie Bronfman fellows highlight recent advances in molecular genetics research on FSHD

We have asked all five Bronfman grantees to provide an interim summary report including: a layman's explanation of the research, a technical explanation, how the project has proceeded according to its original goals, changes in direction if any, how the project led to new areas of research and new areas of funding, significant findings and their impact on FSHD, titles of paper(s) submitted for publication and published under the duration of the grant or as a result of the grant, and their personal perspective of the value of this program towards finding solutions for FSHD. Lastly, we asked each researcher to help us by giving their insight into the human side of research by letting us know how Mrs. Marjorie Bronfman's generosity has been helpful to their research.

The following are the current Marjorie Bronfman grantees and a brief statement on the nature of the work being conducted at the institution.

Grant: FSHS-MB-001

Researcher: Silvère M. van der Maarel, Ph.D.

Institution: Leiden University Medical Center, Dept. of Human Genetics, Wassenaarseweg 72, PO Box 9503, 2300 RA Leiden, The Netherlands

Project Title: Generation of Transgenic Mouse Models for FSHD.

\$30,000 7/1/1998 - 6/30/1999 Year 1

\$30,000 7/1/1999 - 6/30/2000 Year 2

\$30,000 3/31/2001 - 3/30/2002 Year 3

Dr. Silvère M. van der Maarel works for Dr. Rune Frants in Leiden. Dr. Frants is the leading molecular genetics expert in the world on FSHD. In addition to the ongoing studies aiming at the better understanding of the chromatin structure of the 4q (sub)telomere in patients and controls; this project will address creating a series of mouse models involving the FSHD candidate region. This will include lines expressing both the gain-of-function and the loss-of-function in the region of genes in question. These models will enable us to identify the disease gene and will be a unique tool to study FSHD pathology. These models will enable us to study the structure-function relationship in humans. Eventually, suitable FSHD mouse models can be of extreme value for pharmacological purposes. In the gain-of-function experiments the human chromosome 4 genes will be introduced into the mouse to generate the over-expression of genes. In the loss-of-function experiments the equivalent genes will be removed ("knocked out") from the mouse. The human genes in question for FSHD also exist in the mouse on chromosome 8 in reverse order near the centromere. Currently, no other lab is

conducting this much-needed research anywhere in the world. This will result in a clear correlation between defined alterations in gene expression (genetics) and the observed phenotype (symptoms). In the analogy, we are cutting and splicing different sections and sizes of human copper wire without repeats and telomere into the mouse copper wire for gain of function and cutting different sections of mouse copper wire that are the same as the human wire in question for loss of function using very sophisticated biological wire cutters and splicers.

Dr. van der Maarel has been able to create

five publications in two years, three in print and two submitted. It is hoped that one of these construct models will have a high fidelity to the human FSHD mechanism as there are currently no known animal models to study. These are the very first mouse models produced for FSHD research. The creation of an animal model for FSHD research has been one of the top priorities for several years, and now we have such models on hand to be evaluated for fidelity and correctness.

Dr. van der Maarel offers the following comments:

"Facioscapulohumeral muscular dystrophy (FSHD) is a genetic disease that progressively affects the facial, shoulder and upper arm muscles. It can be inherited from one of the parents but it displays also a high frequency of new mutations. It is a dominant disease: a mutation in one of the two homologous chromosomes is sufficient to develop the disease. In FSHD, the mutation has been identified as a partial deletion of a repeat structure near the end of chromosome 4.

"In most genetic disorders resolved so far, the mutation directly affects the **structure** of a gene which results in the absence of the encoded protein, or in the presence of a mutant protein that is incapable of performing its proper function. However, from other organisms it has become evident that some mutations do not affect the structure of the gene, but rather its **regulation**. The conversion from gene to protein is a multi-step process that is tightly regulated. Many genes need to be regulated since their protein products are not always necessary or even deleterious in inappropriate tissues. Thus, the production of proteins from a gene can be temporarily and spatially restricted and aberrations in the production can cause disease.

"It is becoming increasingly evident that FSHD is caused by an improper regulation of the production of proteins from one or more genes in the close vicinity of the mutation. This mutational mechanism poses two difficulties: likely there is no structural mutation in a FSHD causing gene while most mutation detection systems are designed to



Building partnerships towards solutions for FSHD during the evening of the National Institutes of Health (NIH) Conference on the Cause and Treatment of FSHD May 8, 2000 in Bethesda and Rockville, Maryland. Left to right: Kees C. J. van der Graaf, Stichting FSHD (The Dutch FSHD Foundation), Wassenaar, The Netherlands, Dr. Silvère van der Maarel, Leiden University Medical Center, Leiden, The Netherlands.

five constructs or mouse models to examine three very important genes associated with FSHD. FSHD Region Gene 1 (FRG1), FSHD Region Gene 2 (FRG2) are found adjacent to the D4Z4 region and the DoUble homeoboX 4 (DUX4) gene is found within the D4Z4 repeats. These constructs and models are extremely important for studying how these genes work as the mouse grows and develops over time. Dr. van der Maarel has produced

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identify structural mutations, and the improper production of proteins that likely underlies FSHD may be temporally and spatially restricted to tissues and time frames that are virtually impossible to analyze in humans.

"To overcome these problems, we decided to generate a series of mouse models for FSHD. In the past, mice have been shown to be useful to study human myopathies and as a consequence, there is a large body of knowledge on mouse muscle physiology, morphology and pathology. We have chosen to generate mouse models by introducing human genes and chromosomal fragments from the FSHD candidate region in the mouse genome to study their involvement in muscle pathology. The constructs included large chromosomal fragments and three candidate genes for FSHD: *FRG1*, *FRG2*, and *DUX4*. In total, we have successfully generated founder mice for five constructs, while another five constructs are in the process of being generated.

"These founder mice are currently in a breeding program to check the germ-line transmission of the transgenes (since the transgenes have been introduced in a post-fertilization stage, there is not always germ-line transmission of the integrated transgenes). For some of the founder mice, germ-line transmission is established, which means that their offspring also carry the transgene. This offspring is further bred to homozygosity; in these mice two copies of the transgenes are present, each on the homologous chromosome.

"We are currently in the position to analyze these transgenic mice further: where in the construct integrated, are the transgenes expressed, do we observe a (dystrophic) phenotype, do these observations relate to FSHD?

"In summary, two years ago we applied for the initiation of a program to generate transgenic mice to study FSHD. We proposed to make a series of mouse models in which human genes or genomic regions are introduced (gain-of-function), or in which homologous regions in the mouse are deleted (loss-of-function). We realized that this would be an extensive, long-term project which is, to our satisfaction, currently on schedule.

"As a result of new insights in FSHD where it was observed that the protein production of all genes identified so far in the vicinity of the mutation are upregulated rather than downregulated, we decided to focus initially on gain-of-function models. In line

with the proposal, we generated a series of mouse models that carry human chromosomal regions of interest for FSHD pathology. These models will now be scrutinized for their suitability as a model for FSHD."

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Grant: FSHS-MB-002

Researcher: Sara T. Winokur, Ph.D.

Institution: 240 D, Medical Sciences I, Department of Biological Chemistry, University of California Irvine, CA 92697-1700, USA

Project Title: *Analysis of Chromatin Structure and Skeletal Muscle-Specific Gene Expression in Facioscapulohumeral Muscular Dystrophy.*

\$30,000 6/1/1998 - 5/31/1999 Year 1

\$30,000 6/1/1999 - 5/31/2000 Year 2

\$30,000 6/1/2000 - 5/31/2001 Year 3

Dr. Sara T. Winokur works for Dr. Robert K. Moyzis and Dr. Barbara A. Hamkalo who are the leading experts in the study of heterochromatin and telomere. Dr. Winokur had to leave the field of FSHD for two years due to lack of FSHD funding from the MDA while at another institution and was most delighted to have the support to continue her work on FSHD. Although many molecular geneticists studying FSHD agree that a position effect is the most likely mechanism underlying this disease, the chromatin structure and consequent regulation of genes in the region have not been addressed experimentally. This project examines the normal chromatin configuration of the FSHD region and the mechanisms by which perturbations in the structure result in the aberrant regulation of skeletal muscle specific gene(s) responsible for FSHD. Dr. Winokur will be using the latest gene-chip micro-array technology that is not currently available to any other FSHD researcher in the world. In one experiment, we will be able to examine the expression of 6,800 genes and, in another, 42,000 expressed sequence tags (parts of genes). In the analogy, we are trying to determine how the copper scouring pad in the telomere heterochromatin (ball with long wire attached) form and in the chromatin form (entirely bunched up) affects the expression and regulation of all genes related to FSHD using the absolute latest technology which is extremely expensive and originating from the United States. Many important international collaborations will form around this project.

Dr. Winokur provides the following

thoughts in both lay and technical terms in the interim update:

"FSHD appears to result from a very unusual genetic mechanism. The mutation is not within a gene itself, as is usually the case, but rather in the regulation (control) of genes within a region of chromosome 4. My lab is interested in identifying those genes that are affected by this faulty regulatory mechanism. One way to do this is to look at the "expression" of genes, that is, to determine the level at which they are turned on or off in muscle tissue. Any genes that show a different pattern of expression between FSHD and normal muscle are then pursued as to their involvement in the disease process. We are using a technique that allows us to simultaneously examine the expression of >6,000 genes in a single experiment.

"**Undifferentiated Myoblasts:** During the past year, we have conducted global gene expression profiling in FSHD using the Affymetrix GeneChip system. Initial studies focused on undifferentiated myoblast cell lines because of the distinct vacuolar/necrotic phenotype seen in these cells. As detailed in our submitted paper, we found a number of genes involved in the extracellular matrix and cell cycle to be disrupted in FSHD myoblasts. In addition, these studies elucidated the susceptibility of FSHD myoblasts to oxidative stress. These findings were confirmed in cellular assays by our collaborator **Denise Figlewicz**.

"**Differentiated Myoblasts:** We have conducted preliminary analysis of three FSHD vs. two normal myoblast cell lines in the differentiated state. RNA was isolated at a specific time point post serum-deprivation (eight days). Several skeletal muscle genes involved in the calcium signaling were upregulated in the FSHD samples. We are not convinced, however, that this apparent upregulation is not an artifact of the different rates of differentiation amongst the cell lines. We are therefore repeating the differentiated myoblasts studies, isolating RNA at several time points for each cell line. We can therefore perform cluster analysis and determine the slope of expression for each transcript over time. The slope of each transcript over time will then be compared between FSHD and control myoblasts to determine whether the rate of differentiation is merely shifted, or whether specific transcripts do indeed present an aberrant

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expression profile.

"Muscle Biopsy Tissue: We are also currently utilizing muscle biopsy material provided by Dr. **Kevin Flanigan** (University of Utah) and Dr. **Kiichi Arahata** (National Neuroscience Institute NCNP, Tokyo). These consist of both affected and unaffected muscle pairs from several FSHD patients as well as normal and disease controls. These matched sets minimize expression differences due to individual variability. Although too premature to discuss in detail here, we believe that we have uncovered a significant pathway involved in FSHD pathogenesis through these studies. We are currently confirming the deregulation of this gene through an independent technique, Taqman assays. Taqman assays are a means of looking at the accumulation RT-PCR product in real time. Expressed genes are transcribed into mRNA, the mRNA isolated from tissue or cell samples, cDNA is synthesized from this, and then PCR performed using a fluorescent probe. The detection of fluorescence in real time gives a very accurate measure of how much transcript from a specific gene is in this pool of cDNA. Thus, Taqman provides a very accurate measure of gene expression and can be used to independently confirm GeneChip results. One can design a specific probe to any gene of interest (e.g. those that are deregulated in FSHD).

"The Marjorie Bronfman fellowship has been critical for both my role in FSHD research as well as in elucidating key features of the disease. I am exceedingly grateful that this fellowship has enabled me to establish an independent research program in FSHD. This research program, in turn, was instrumental in my joining the faculty of the Department of Biological Chemistry. Without this fellowship, I would not have had the seed money necessary to attract an additional \$300,000 in FSHD research grant funds or to establish my own laboratory at UC Irvine.

"More importantly, this fellowship has enabled us to gain great insight into FSHD pathology through the expression analysis of thousands of genes in this disease. We have identified the first biochemical marker for FSHD: susceptibility to oxidative stress. Delineation of other key components of this process in FSHD will likely reveal critical processes in this disease. In addition, our recent GeneChip studies with FSHD muscle biopsy tissue may well yield key genes and protein complexes central to FSHD."

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Grant: FSHS-MB-003

Researcher: Denise Figlewicz, Ph.D.

Institution: University of Rochester School of Medicine, Department of Neurology, 601 Elmwood Avenue, P.O. Box 673, Rochester, New York 14642, USA

Project Title: *Expression of genes proximal to the D4Z4 deletions: a quantitative study in FSHD patients and controls.*

\$30,000 1/1/1999 - 12/31/1999 Year 1

\$30,000 1/1/2000 - 12/31/2000 Year 2

Dr. **Figlewicz** is one of the leading researchers working on FSHD. Dr. Figlewicz works with Dr. **Tawil** and Dr. **Griggs** at the University of Rochester. Dr. Griggs and Tawil are the leading clinicians on FSHD in the United States. Dr. Figlewicz has extensive experience with Lou Gehrig's Disease (ALS) research. The project will systematically and quantitatively study the expression of all genes lying immediately upstream of or adjacent to the D4Z4 repeats. The study will correlate the changes in gene expression with the number of D4Z4 repeats and parameters of disease severity in different patients. The study will try to determine if the increase in disease severity (which is thought to increase with fewer repeats present) is caused by more significant changes in expression of genes in the FSHD region. Using the analogy, different lengths of copper wire will be used from different patients with different numbers of repeats (1, 2 . . . 7, 8, 9, 10, 20) as the immediate kinks

(genes) are examined for differential activity. At the University of Rochester, Dr. Figlewicz has the largest collection of FSHD cell lines available for this purpose.

Dr. Figlewicz has determined that genes lying upstream of the D4Z4 repeats on chromosome 4q35 are increased in expression in muscle samples from FSHD patients as compared to non-affected individuals. Dr. Figlewicz has quantified several genes which are expressed in muscle and another housekeeping gene, and has found interesting

results with the MyoD transcription factor which promotes the fusion of single undifferentiated muscle cells (myoblasts is upregulated in muscle) as well as with the SuperOxideDismutase 1 gene (SOD1) which alleviates oxidative stress in muscle. Dr. Figlewicz has determined that FSHD myoblasts are extremely susceptible to oxidative stress.

Dr Figlewicz provides the following insights in the interim update:

"The Bronfman fellowship has enabled us to do this work, to carry out this collaboration (with Dr. **Winokur**), and to move rapidly in the direction we consider most important in understanding FSHD . . . Our results show that FSHD myoblasts are very vulnerable to oxidative stress, and can be affected by paraquat concentrations which are only 1/1000 the levels which are harmful to controls. An intracellular molecule, p21, has been shown to signal oxidative stress in certain cell types. We wish to explore whether this signaling pathway may be activated in FSHD



Dr. Denise Figlewicz, University of Rochester School of Medicine, Rochester, New York delivers Illustrated Lecture, Genetic Research on FSHD at the July 8, 2000 FSH Society Network Day, Natick, Massachusetts.

myoblasts; our data thus far suggest that it is. Because elevated levels of p21 may terminate a cell's ability to divide we are now examining this finding further; it might have significant implication for the ability of damaged FSHD muscle to grow new myoblasts and to regenerate."

Dr. Figlewicz's statement above is the very first biochemical hallmark of FSHD. Never

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before have we been able to identify biochemical mechanisms or pathways that are damaged in FSHD. Dr. Figlewicz and Dr. Winokur have recently submitted a paper titled: "Oxidative stress, cell cycle and the extra-cellular matrix are disrupted in FSH muscular dystrophy myoblasts: a micro-array and cell culture analysis."

The FSH Society, Inc. was unique in initially funding this kind of research in the United States.



Grant: FSHS-MB-004

Researcher: David J. Picketts, Ph.D.

Institution: Ottawa General Hospital, Research Institute, 501 Smyth Road, Ottawa, Ontario, K1H 8L6, Canada

Project Title: Utilizing an epigenetic approach to identify the FSHD gene.

\$30,000 5/1/1999 - 4/30/2000 Year 1
\$30,000 5/1/2000 - 4/30/2001 Year 2

Dr. Picketts is studying under Dr. **Robert Korneluk** who is a leading researcher in the field of muscular dystrophy. The fellowship was to begin with Dr. Picketts and transition to Dr. **Storbeck** who is an outstanding young post-doctoral fellow. Unfortunately, Dr. Storbeck was unable to transition into the FSHD research due to the pursuit of prior research and accepting another position in a different area of research. Dr. Picketts has hired and located other personnel to assist in the effort, Mr. **Darren Yip** and Mr. **Patrick Scott**.

The researchers hypothesize that the repeat (D4Z4) deletions cause a molecular defect which impinges on the expression of a nearby gene by causing an alteration in chromatin structure in the region. This alteration of the three dimensional structure of the compact chromosome may ultimately be causing the FSHD disease pathology by incorrectly activating non-muscle genes or inactivating muscle genes. They will examine the configuration of chromatin in normal individuals and compare it to the chromatin of affected individuals who have repeats that have been deleted. Other epigenetic approaches will be used to examine whether the D4Z4 deletion alters replication timing and methylation patterns through 4q35.

The original purpose of Dr. Picketts' project was to characterize the chromatin structure of 4q35 by a combination of assays, including DNase I HyperSensitive Site analysis (HSS) and primary sequence analysis. The SAB was originally primarily concerned with, and remains interested in, knowing the DNase



Evening of the National Institutes of Health (NIH) Conference on the Cause and Treatment of FSHD May 8, 2000 in Bethesda and Rockville, Maryland. Left to right: Dr. Enzo Ricci, Rome, Italy; Dr. Richard Orrell, Royal Free and University College Medical School, London England; Dr. David Picketts, Ottawa Health Research Institute, Ottawa, Ontario Canada

I HSS that are associated with active genes and usually localized at gene regulatory elements. Dr. Picketts is one of the leading experts in this area. Using the analogy, the copper ball scouring pad in both telomere heterochromatin form (ball with long wire attached) and chromatin form (totally bunched up) will be compared between affected individuals and normal individuals. The differences obtained will be explored to see if they affect nearby gene expression either in a temporal or spatial manner. This is the first major molecular genetics research project in Canada to be undertaken in the area of FSHD.

Dr. Picketts states in his interim report: "This award provided us with the seed funding that allowed us to develop another line of research where chromatin was proposed to have a major impact on the disease. Without this funding, the project would not have been initiated. This grant commenced in June, 1999 and through the first year we have been successful in obtaining the resources and personnel required to analyze the chromatin structure of chromosome 4q35. The service laboratory has provided us with extensive DNA and cell samples from patients, however, they did not have the cloned resources required for the research project. Additional reagents were requested from FSHD and other research laboratories worldwide and, we now have many of the reagents we require. Moreover, our demonstration of commitment and resources, including the Marjorie Bronfman Grant, was instrumental in securing one year of seed funding for this project from

the Muscular Dystrophy Association (MDA). This funding was extended for an additional year by MDA in July, 2000. Given the difficulty of the research problem it was unlikely that we would have initiated such a challenging new project without the support provided from this award. In general, I feel that this program has been important in attracting several new investigators to the FSHD field, and the fascination of the problem is more than sufficient to maintain their interest. The novelty of the disease mechanism will also be extremely rewarding when it is defined."

Many important international collaborations have come out of this project. Most notable are with Dr. **Sara Winokur**, Dr. **Melanie Ehrlich** and **Michael van Geel**. Dr. Picketts further states, "... Over the past year I have trained the personnel in my laboratory to perform DNase I HSS assays using erythroid cell lines and probes from the globin genes. In addition, they have been analyzing the primary DNA sequence of 4q35 to develop probes corresponding to both known genes and novel regions for analysis. Many of these probes have now been tested on southern blots and will be used in the upcoming months for DNase I HSS experiments. Since subtle changes in DNase I HSS may be difficult to interpret in patient samples which we will use several somatic cell hybrid cell lines we obtained from Dr. Sara Winokur. These cell lines contain one copy of human chromosome 4, either from a patient or a normal individual.

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Another reagent we have developed in our laboratory was the cloning of fibroblasts from a patient who was a somatic mosaic for a D4Z4 deletion. These two cell lines have an identical genetic background and will be important for comparative studies. We anticipate that we will have a DNase I HSS profile of this region completed within four-seven months. We have initiated a collaboration with Dr. Melanie Ehrlich, an expert in the analysis of DNA methylation status of chromatin. We will compare our results with Dr. Ehrlich's studies to have a broader characterization of the chromatin structure of the region."

The Society anticipates that the areas of sequence analysis for chromatin studies, DNase I HSS Analysis and Repressive function of the D4Z4 repeats will yield insight into the chromatin structure surrounding the FSHD gene and the role of chromatin structure alterations in FSHD disease pathology over the next year. Although his research is extremely slow and complex, it will produce better understanding regarding the scaffolding around which much of the genetic processes are being orchestrated and how they are occurring. No publications have been submitted although the researcher has presented findings at various research conferences.



Grant: FSHS-MB-005

Researcher: Davide Gabellini, Ph.D.

Institution: University of Massachusetts Medical Center, Howard Hughes Medical Institute, 373 Plantation Street, Worcester, MA 01605, USA

Project Title: *Identification and characterization of a protein interacting with the DNA repetitive element causally related to facioscapulohumeral muscular dystrophy.*

\$30,000 1/1/2000 - 12/31/2000 Year 1

\$30,000 1/1/2001 - 12/31/2001 Year 2

Dr. Davide Gabellini works for Dr.

Michael Green and Dr. Rossella Tupler. Dr. Tupler is an aggressive, innovative and leading researcher in FSHD and past FSH Society Delta fellow. Dr. Tupler recently published a landmark paper on the global mis-regulation of genes in FSHD. Dr. Michael Green is a leading expert in genetic transcription. Transcription is the process by which RNA is created from DNA and in turn protein is then created from RNA. Dr. Gabellini is a hard working and outstanding young scientist who has left Italy to pursue interests in FSHD research.

Many molecular geneticists studying

FSHD agree that there is a relationship between the D4Z4 deletions and FSHD. The search to identify the gene(s) responsible for FSHD is ongoing. There is a growing consensus that the deletion of repeats from D4Z4 causes changes in the chromatin dimensional structure and may cause different physical and steric effects changing the original and natural structure. This "remodeling" factor is thought to possibly interfere with gene expression by what is called a position effect variegation (PEV). Again, a position effect is the most likely mechanism underlying this disease; the chromatin structure and consequent regulation of genes in the region have not been addressed experimentally.

Chromatin condensation is a known biological control mechanism for controlling the expression of genes. Further, chromatin functional organization is established by an interaction between DNA sequences and protein complexes and will determine the transcription activity and status of specific chromosomal regions. This project examines the relationship between the D4Z4 repeats and nuclear proteins.

Dr. Gabellini has remarkably discovered that a nuclear signal binds to the D4Z4 region, providing the very first evidence that D4Z4 itself is active and providing a hypothetical regulatory role in chromatin organization. This project investigates the role of D4Z4 and seeks to determine and understand the biological function of a distinct 3.3kb repetitive element and how these repeats affect the chromatin structure.

Using the analogy, we know that most individuals with FSHD (4q35-linked) have only one to nine of the one-foot copper sections left at the end of the 10 miles of the wire. Further, there is a causal relationship between having between one and nine of these one-foot sections and having the FSHD disease. However, we do not know how exactly they cause FSHD.

In this approach, we are trying to determine how the copper scouring pad in the telomere heterochromatin (ball with long wire attached) form transforms itself into the chromatin form (entirely bunched up) and what the role of the one-foot repeat is in this process. We have found that the one-foot repeats have a specific subsection that binds with a specific protein(s) (egg particle) attached to the surface of the scouring pad (chromatin). We know that the three-dimensional result (model) affects the expression and regulation of all genes related

to FSHD using very sophisticated assays. We are trying to answer questions as to whether the one-foot sections are biologically active (produce genetically active components that are spliced from and based on a template from each section of wire), play an active role in orienting the physical structure of the chromosome (do they provide special mechanisms and hold points allowing the wire to wrap on itself?), regulate other genetic material (bind lose egg particles) needed for transcription, or play an inactive role in regulating the structure of the chromosome (just not enough wire left to wrap into a ball).

Dr. Gabellini states in the interim update report:

"The results . . . show that the D4Z4 binding site is able to activate transcription. The transcriptional activation is very specific since it is eliminated by a mutation in the D4Z4 binding site. Taken together our preliminary data indicate that a transcriptional regulator of 27 kilo-Daltons (kDa) specifically binds to D4Z4, providing the first direct evidence of D4Z4 hypothetical role in control of gene expression.

"To identify and characterize the nuclear protein interacting with the DNA element within D4Z4 we will use a classical biochemical purification of the D4Z4-binding protein from HeLa nuclear extracts. Preliminary results indicate that the biochemical purification in combination with the EMSA is very promising and straightforward approach for the isolation of the D4Z4-binding protein.

" . . . Our preliminary results suggest that the D4Z4-binding protein may have a role in regulating gene expression. In order to verify it, we will analyze the effect of the over-expression of the D4Z4-binding protein or of its elimination (using an antisense) on the expression of the 4q35 genes.

"In conclusion, our observation represents a starting point to investigate the role of D4Z4 in determining the 4qter chromatin structure and eventually to understand the biological function of the repetitive element. All this work has only been possible thanks to the commitment and generosity of the Marjorie Bronfman Foundation. We believe that these findings are a crucial point for the delineation of the molecular basis of FSHD pathogenesis. Our project represents a new strategy towards the identification of the molecular defects that are critical for the FSHD pathogenesis. The results of this study will provide the basis to develop an appropriate therapy for FSHD."

FSHD International Consortium Research Meeting

Sponsored by the FSH Society, Inc.

Agenda

October 3, 2000 5:00 – 10:00 p.m. • Philadelphia, Pennsylvania

Co-Chairs: Dr. **Sara Winokur**, University of California, Irvine, Irvine, California, USA
Dr. **Jane Hewitt**, Queen's Medical Centre, Nottingham University, Nottingham, United Kingdom

I. Meeting Introduction and Welcome

Daniel Paul Perez: Welcome and Charge for the Meeting

Rune Frants: FSHD Overview

II. FSHD & Muscle Cellular Studies.

Silvana van Koningsbruggen: C2C12-based model systems to study the biological role of FSHD candidate genes.

Kathy Barrett: FSHD myoblasts possess reduced resistance to oxidative stress.

Patrick Reed: Changes in sarcolemmal organization correlate with severity of myopathy in the mdx mouse.

Sara Winokur: FSHD microarray expression studies & LIM proteins.

Alexandra Belayew: Study of the DUX4 gene present in the D4Z4 repeats of the 4q35 chromosome locus.

III. Guest Speakers I

Robert Bloch: The organization of costameres at the sarcolemma and their relationship to muscle disease.

Laura Palmucci: Apoptosis in normal and denervated muscle, muscular dystrophies and inflammatory disease.

IV. FSHD Chromatin and Repeat Association Studies.

Melanie Ehrlich: The FSHD syndrome-associated 3.3-kb repeat is highly methylated in normal and FSHD tissues and lymphoblastoid cell lines but not in sperm or ICF syndrome cells.

Petra van Overveld: Methylation studies of the D4Z4 repeat in patients with muscular dystrophies.

Davide Gabellini: Analysis of protein-DNA interactions at the level of D4Z4, the DNA repetitive element causally related to facioscapulohumeral muscular dystrophy.

Luciano Felicetti: High frequency of 4qter-10qter subtelomeric exchanges in FSHD Italian families.

Petra van Overveld: Frequent inter-chromosomal repeat array interactions between chromosomes 4 and 10: a model for subtelomeric plasticity.

V. Guest Speakers II

Amy Csink: Trans-sensing in *Drosophila* heterochromatin.

Charles Emerson: Regulation by MyoD/Myf5 enhancer elements.

VI. 4q/10q Genetic Sequence.

Jane Hewitt: Towards a complete BAC contig, draft DNA sequence and transcription map of the FSHD candidate region on human chromosome 4q35.

VII. FSHD Diagnosis, Linkage & Anticipation Studies.

Silvère van der Maarel: XapI improves diagnosis of facioscapulohumeral muscular dystrophy (FSHD).

Antonel Olkers: Segregation of DNA rearrangements at the D4Z4 locus in South African FSHD families.

Kevin Flanigan: Absence of anticipation in reported age of onset in multiple sibships from a large Utah FSHD family.

VIII. Summary & Wrap-up Discussion.



Presentation of South African research at the poster section of the American Society of Human Genetics (ASHG) Meeting, Philadelphia, Pennsylvania, October 2000. Left to right: Carol A. Perez, Executive Director FSH Society; Dr. Meena Upadhyaya, Institute of Medical Genetics, Cardiff, UK; Dr. Annelize van der Merwe, University of Pretoria, South Africa; Dr. Antonel Olkers, University of Pretoria, South Africa.

A complete copy of the agenda, meeting abstracts and roster for the 2000 FSHD Workshop may be requested through the FSH Society, Inc., 3 Westwood Road, Lexington, MA 02420 USA for US\$20.

GENETICS/RESEARCH

Keynote to International Consortium on FSHD October 3, 2000, Philadelphia, Pennsylvania

International Consortium on FSHD held as a satellite symposium to the American Society of Human Genetics

I am **Daniel Perez**, founder, president and CEO of the FSH Society and we are in our eleventh year. Welcome to the International Consortium on Facioscapulohumeral Muscular Dystrophy (FSHD) held as a satellite meeting to the American Society of Human Genetics (ASHG).

The FSH Society is the sponsor of this meeting and is delighted to see so many new researchers and old friends coming together to solve the problem that we live with everyday. We have created a Society of dedicated individuals, both researchers and patients, and we welcome you to our community. Our organization is international because FSHD is found throughout this world and we are delighted with the multi-national presence here.

Your commitment and dedication will result in treatment and cure for tens of thousands of people suffering from the devastating disease called facioscapulohumeral muscular dystrophy. You, who are on the forefront and cutting edge of science and technology with this complicated disorder, are our hope and promise. The FSH Society pledges to you our total commitment to helping you help those of us who live with FSHD everyday, everywhere throughout the world.

I would like to introduce the following people: Special thanks to Dr. **Michael Altherr** and Dr. **Rune Frants** of FSH Society Scientific Advisory Board (SAB). Past and present FSH Society grantees: **Silvère M. van der Maarel**, Ph.D. of Leiden University Medical Center; **Sara T. Winokur**, Ph.D. of University of California; **Denise Figlewicz**, Ph.D. of University of Rochester School of Medicine; **David J. Picketts**, Ph.D. of Ottawa General Hospital; **Davide Gabellini**, Ph.D. of University of Massachusetts Medical Center, Howard Hughes Medical Institute; **Alexandra Belayew**, Ph.D. of Université de Mons-Hainaut; **Rossella Tupler**, M.D., Ph.D., of Howard Hughes Medical Institute, University



The International team of researchers, clinicians, geneticists and funding agencies working on FSHD at the FSH Society workshop held as a Satellite meeting to the American Society of Human Genetics (ASHG) meeting, Philadelphia, Pennsylvania, October 2000.

of Massachusetts Medical Center; **Robert Bloch**, Ph.D. of University of Maryland School of Medicine; **Jane Hewitt**, Ph.D. of Nottingham University; and **Kevin Flanigan**, M.D. of the Eccles Institute of Genetics, University of Utah. Lastly, thank you to Dr. **Winokur**, Dr. **Hewitt** and Dr. **Altherr** for a superb job in organizing this meeting.

The Society continues to expand its

fellowship program and help scientists and laboratories receive the materials, resources and means to work on FSHD. We are pleased to assist in any way we can with resources you need for FSHD and to advocate for funds in all forums.

In less than three years, the FSH Society's program-funded research has resulted in major breakthroughs in actually understanding, and

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Upcoming . . .

Sunday, October 14, 2001 San Diego CA

FSHD/ASHG consortium meeting for FSHD researchers and clinicians

The FSH Muscular Dystrophy (FSHD) consortium workshop will be held as a satellite meeting in conjunction with the American Society of Human Genetics (ASHG) 2001 Annual meeting scheduled to be held in San Diego, California over the dates October 12 - 16, 2001.

The Consortium/Workgroup meeting will be held from 6:30 p.m. - 11:30 p.m. on Sunday, October 14, 2001 at the San Diego Marriott Hotel & Marina. Date is firm but tentative pending final approval from ASHG. Sit down dinner and coffee/tea are provided.

In keeping with the spirit of international representation and collaboration at the meeting, the Co-Chairs of the meeting will be Dr. Sara Winokur and Dr. Rune Frants. It is hoped that we will have a more interactive discussion type and "sparring" component to

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You're invited to:

FSHD consortium satellite meeting to the ASHG 2001 Annual Meeting

Sponsored by: FSH Society, Inc. & MDA
Co-Chairs:

- Dr. Sara Winokur, University of California, Irvine, Irvine, California USA
- Dr. Rune Frants, Leiden University Medical Center, Leiden, The Netherlands

Date: Sunday, October 14, 2001

Time: 6:30 p.m. - 11:30 p.m.

Place: The San Diego Marriott Hotel & Marina, 333 West Harbor Drive, San Diego, CA 92101

GENETICS/RESEARCH

Review of 2001 present clinical and research needs and opportunities on FSHD from the research field

Each year the *FSH Society* defines anew, at the request of the entire international and global molecular genetics and clinical research community, the most crucial issues in FSHD research today and in the coming several years. These following nine areas represent the majority of efforts to be made given recent advances in technology, science and understanding of FSHD.

- A. An international clinical and molecular data (resource) base. Although a complicated issue for several reasons (homogeneity of clinical and genetic data, access etc.), presence of such a facility should greatly improve:
1. our insight in the natural history, and genotype-phenotype relationships as support for patient counseling and management; and
 2. the availability of biological material (DNA, cell lines, muscle biopsies etc.) for research purposes; and the design of (homogeneous) clinical trials.
- B. Non-chromosome 4q families large enough to allow linkage analysis and gene isolation. Identification of a second FSHD gene should greatly facilitate the identification of crucial (rate-limiting) molecular pathways. This might help direct our thinking on (gene) therapy.
- C. Large scale profiling of thousands of components to identify molecular pathways leading to FSHD and targets amenable for intervention. Attention should be given to:
1. RNA (transcriptomics). RNA reflects the steady-state transcription situation, but might be only a meager reflection of the true (patho)biology. This work is ongoing in several centers;
 2. Protein (proteomics). The protein components reflect the real biological executive situation. Proteomics is much more complicated than transcriptomics, but may give much more information; and
 3. Metabolites (metabolomics). In the near future, we will have technologies at our disposal to identify and quantify metabolites, the individual steps (substrates) of metabolic pathways. These compounds may crucially determine the actual pathology and phenotype.
- D. Cellular and animal models. It is very likely that the generation of cellular and animal models will be pivotal, not only for the

generation of therapeutic means, but also to help identify the molecular basis of FSHD itself. In all likelihood, several approaches have to be followed:

1. Transgenic mouse models. Two different approaches can be envisaged: models for individual candidate genes, identified in the chromosome 4q region or elsewhere and general models in which large genomic regions of chromosome 4q and chromosome 10q, including the telomeres are transferred and integrated, preferably at mouse telomeres. These latter models will approximate the human situation and allow studies on the cause and consequences of the inter- and intra-chromosomal interactions and rearrangements in relation to FSHD; and
 2. Other animal models. For specific questions on position effects variegation etc., simpler models, like *Drosophila*, and yeast may be very useful.
- E. Chromatin structure in and adjacent to the region where the FSHD deletions occur. Including:
1. factors predisposing to illegitimate recombination; and
 2. abnormally expressed genes in FSHD.
- F. Better understanding of abnormalities of the small blood vessels of the retina at the back of the eye in FSHD patients. Including;
1. why children with a more severe or even sporadic form of FSHD are more likely to develop this symptomatic form of retinal disease;
 2. an unidentified additional genetic peculiarity which renders some FSHD individuals susceptible to symptomatic retinal disease;
 3. whether retinal, cochlear and skeletal muscle abnormalities in FSHD represent different effects of the same

- mutation or otherwise are the results of abnormalities of adjacent genes; and
4. the possibility that such pleiotropic effects are mediated by inflammation and/or "environmental" factors.
- G. Clinical, molecular genetic study and genotype/phenotype correlation of facioscapulohumeral muscular dystrophy phenotype and facioscapulohumeral muscular dystrophy phenotype.
- H. Clinical trials. It is likely that new clinical trials will be launched on the basis of hints in other (muscular) disorders. Access to well characterized (e.g. with respect to clinical phenotype and genetic constitution) patients cohorts is crucial for proper evaluation.
- I. Molecular pathway-based therapy. Increasing insight in the molecular pathways of FSHD, already available and hopefully even more so in the near future, will form the rationale for novel treatment strategies. It is difficult to predict whether these efforts will be DNA-based or pharmacological. In any case, such experimental approaches have to be developed in (transgenic) animal models; another argument for investing in versatile models.

The *FSH Society* will request an earmark of 15 million dollars in its Fiscal Year 2002 testimonies before the U.S. House of Representatives and U.S. Senate Appropriations, Subcommittee on Labor, Health and Human Services, Education and Related Agencies to accomplish recommendations put forth by the NIH and scientific community working on FSHD. Clearly, the research needed is so extraordinarily expensive as it relates to standard gene discovery process for disease. FSHD is in a new and novel area of molecular genetics and molecular medicine that will have an enormous payoff in many other diseases and our understanding how the human genome functions.

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the efforts of the FSH Society?
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GENETICS/RESEARCH

FSH Society fellowships, fellows & small grants**Grant:** FSHS-MB-001**Researcher:** Silvère M. van der Maarel, Ph.D.**Institution:** Leiden University Medical Center, Dept. of Human Genetics, Wassenaarseweg 72, PO Box 9503, 2300 RA Leiden, The Netherlands**Project Title:** *Generation of Transgenic Mouse Models for FSHD*

\$30,000 7/1/1998 - 6/30/1999 Year 1

\$30,000 7/1/1999 - 6/30/2000 Year 2

\$30,000 3/31/2001 - 3/30/2002 Year 3

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Grant: FSHS-MB-002**Researcher:** Sara T. Winokur, Ph.D.**Institution:** 240 D, Medical Sciences I, Dept. of Biological Chemistry, University of California, Irvine, CA 92697 1700 USA**Project Title:** *Analysis of Chromatin Structure and Skeletal Muscle-Specific Gene Expression in Facioscapulohumeral Muscular Dystrophy*

\$30,000 6/1/1998 - 5/31/1999 Year 1

\$30,000 6/1/1999 - 5/31/2000 Year 2

\$30,000 6/1/2000 - 5/31/2001 Year 3

❖ ❖ ❖

Grant: FSHS-MB-003**Researcher:** Denise Figlewicz, Ph.D.**Institution:** University of Rochester School of Medicine, Dept. of Neurology, 601 Elmwood Ave., PO Box 673, Rochester, NY 14642 USA**Project Title:** *Expression of genes proximal to the D4Z4 deletions: a quantitative study in FSHD patients and controls*

\$30,000 1/1/1999 - 12/31/1999 Year 1

\$30,000 1/1/2000 - 12/31/2000 Year 2

❖ ❖ ❖

Grant: FSHS-MB-004**Researcher:** David J. Picketts, Ph.D.**Institution:** Ottawa General Hospital, Research Institute, 501 Smyth Rd., Ottawa, Ontario, K1H 8L6, Canada**Project Title:** *Utilizing an epigenetic approach to identify the FSHD gene*

\$30,000 5/1/1999 - 4/30/2000 Year 1

\$30,000 5/1/2000 - 4/30/2001 Year 2

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Grant: FSHS-MB-005**Researcher:** Davide Gabellini, Ph.D.**Institution:** University of Massachusetts Medical Center, Howard Hughes Medical Institute, 373 Plantation St., Worcester, MA 01605 USA**Project Title:** *Identification and characterization of a protein interacting with the DNA repetitive**element causally related to facioscapulohumeral muscular dystrophy*

\$30,000 1/1/2000 - 12/31/2000 Year 1

\$30,000 1/1/2001 - 12/31/2001 Year 2

❖ ❖ ❖

Grant: FSHS-MB-006**Researcher:** Fern Tsien, Ph.D. / Melanie Ehrlich, Ph.D.**Institution:** Tulane Cancer Center, Human Genetics/SL31, Tulane Medical School, 1430 Tulane Ave., New Orleans, LA 70112 USA**Project Title:** *DNA Methylation and Chromatin Structure of FSHD-linked Sequences in FSHD Cells, Normal Cells, and Cells from Patients with the ICF Syndrome*

\$35,000 5/1/2001 - 4/30/2002 Year 1

\$35,000 5/1/2002 - 4/30/2003 Year 2

❖ ❖ ❖

Grant: FSHS-DR-001**Researcher:** Alexandra Belayew, Ph.D. / Stephane Plaisance, Ph.D.**Institution:** Lab. Biologie Moléculaire, Université de Mons-Hainaut, Pentagone, avenue du Champ de Mars 6, B - 7000 - Mons, Belgium**Project Title:** *Characterization of a protein expressed from a 3.3 kb element not linked to FSHD*

\$15,000 6/1/1998 - 12/31/1998 Year 1

Small laboratory equipment for research on FSHD.

\$15,000 2/15/2001 - open Year 1

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Grant: FSHS-FS-001**Researcher:** Kevin Flanigan, M.D.**Institution:** Eccles Institute of Genetics, Room 7290, University of Utah, 15 North 2030 E. St., Salt Lake City, Utah 84113 USA**Project Title:** *Small grant proposal for QMA software/system and professional physical therapy resources to help with studies to answer definitively whether anticipation in disease severity**and onset, gender effects, or parent-of origin effects exist in FSHD*

\$8,375 1/1/2000 - 12/31/2000 Year 1

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Grant: FSHS-DR-002**Researcher:** Rossella Tupler, M.D., Ph.D.**Institution:** Howard Hughes Medical Institute, University of Massachusetts Medical Center, Worcester, Massachusetts, USA**Project Title:** *Characterization of differentially expressed genes in facioscapulohumeral muscular dystrophy affected muscles*

\$30,000 6/1/1998 - 5/31/1999 Year 1

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Grant: FSHS-DR-003**Researcher:** Robert Bloch, Ph.D.**Institution:** University of Maryland School of Medicine, 660 W. Redwood St., Baltimore, MD 21201 USA**Project Title:** *Sarcolemmal organization in FSHD and the MYD mouse*

\$30,000 7/1/1999 - 12/31/2000 Year 1

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Grant: FSHS-DR-004**Researcher:** Jane Hewitt, Ph.D.**Institution:** Nottingham University, Division of Genetics, Queen's Medical Centre, Nottingham, NG7 2UH, England**Project Title:** *Fugu rubripes as a model organism for FSHD gene identification*

\$30,000 7/1/2000 - 6/30/2001 Year 1

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Grant: FSHS-TF-001**Researcher:** Marcy Speer, Ph.D.**Institution:** Duke University Medical Center, Box 3445, Durham, NC 27710 USA**Project Title:** *Genetic Linkage Studies in Non-chromosome 4 FSHD*

\$30,000 2/1/2001 - 1/31/2002 Year 1

*We appreciate your
continued support
of the FSH Society and our efforts.*

GENETICS/RESEARCH

A Dutch perspective on FSHD research progress genetic inquiry

Note from the editor*: Those who would like to refresh their memory regarding a number of terms are referred to the following articles in our Newsletter:

- S.M.van der Maarel (1998). Progress of the Genetic Inquiry. *VSN Newsletter FSHD* 19, pp. 3-4.
- C.P.Koetsier (1998). Not every FSHD patient is missing something on chromosome-4, *VSN Newsletter FSHD* 19, pp. 4-5.
- C.P. Koetsier (1999) Heredity in FSHD. *VSN Newsletter FSHD* 21, pp 4-12.

—Silvère M. van der Maarel & Rune R. Frants, for the FSHD team, Leiden University Medical Center.

It is encouraging to observe that the FSHD inquiry is getting more and more attention thanks to the initiatives by the FSHD Foundation [Netherlands] and the *FSH Society* (United States). On both the national and international level more energy is invested in the research regarding FSHD. As a result of this development our research team at the Leiden University Medical Center has grown from three to six researchers during the past few years. Our knowledge regarding the cause and effect of FSHD is therefore growing proportionately. It's not as if all-of-a-sudden we now understand the whole development of the disease, but the stagnation in our knowledge of a few years ago has now turned to progress. Following, point by point, I shall discuss some of the new insights we gained on the national and international level.

- Working in close cooperation with Nijmegen we have gained a better insight into the deletion ('the absence of DNA') by testing the DNA of families where the mutation has arisen for the first time. It was found that often the deletion arises somatically (i.e. after impregnation, in the early stages of embryonic development). The result is that not all cells contain this mutation; these persons therefore carry both 'diseased' as well as 'healthy' cells. This finding is of immediate importance for patients and parents where the mutation arose for the first time (i.e. not for familial FSHD) in connection with the risk of inheriting the disease and the chances of an affected child.

- We have also done a study among the Dutch population regarding the behavior of the repeats (repeated DNA fragments) in the deletion area (the area where DNA is missing), which study resulted in new insights. There is evidence that these repeats behave in a very dynamic way and that about 3% of the healthy Dutch population have a FSHD-like repeat length. This points to a gradual effect of the deletion; it appears that this 3% has certain (genetic) qualities which protect them against the development of the disease. Similar results were found in a study conducted by our French colleagues. They found that FSHD-like repeat structures occur relatively often in the Chinese population without consequences.

This too leads to the conclusion that more (genetic) factors are necessary for the development and/or progression of the disease.

- New insights into the sequence of the repeat structures have made it possible to further refine DNA diagnostics. These diagnostics were already very reliable, but in about 5% of the cases are still very difficult and often not totally clear. We believe that with the new developments the diagnostics for these 5% have again improved considerably and we intend to promote this at future international meetings.

- Also, we and our American colleagues invest a great deal of effort to gain a better understanding of the ultimate consequences of the deletion. DNA is encased in different ways: roughly, an open structure which allows a reading of the genes and a closed structure in which the genes are generally inactive. There are now indications that the FSHD-deletion can alter the structure of the end of chromosome 4 from a rather closed form to a more open one. This could have related consequences for the regulation of neighboring genes.

- Entirely in agreement with this, expression studies of a few candidate genes show that these are regulated differently in FSHD patients than in control individuals. It appears that in muscle cells of FSHD patients the genes in question, FRG1 and FRG2 are more numerous than is normally the case. We are trying to clarify the function of these two genes in order to research their possible connection to FSHD. The proteins coded by these two genes are located in the nucleus of the cell, and the FRG1 protein is even located in special sub-domains of the nucleus. This gives us clues as to the possible functions.

- So called DNA-chips and DNA-arrays are presently much in fashion. These chips and arrays make it possible to, on a small surface, observe the regulation of thousands of genes simultaneously. They are a handy tool to get an overall picture of the changes in the cell as a consequence of the deletion. They are usually unsuitable to determine the primary cause, but they are eminently suitable to

recognize all kinds of secondary disease patterns. It is expected that this can be of special and direct importance for the patient. When pathogenic processes can be recognized they may possibly result in giving us leads for treatment. In cooperation with two American groups we have jumped onto these developments and are applying to the National Institute of Health (NIH) for the financing of a large scale research project.

- The aforementioned project will be complemented by a study of proteins, applying the same strategy. The Dutch FSHD Foundation has initiated a very fruitful cooperation between our department and Unilever Research in which we will concentrate on the development of protein-arrays. As in the study of DNA-arrays this will enable us to analyze the presence of thousands of proteins simultaneously and make a comparison between patients and control individuals. Although part of the techniques for this work will still have to be developed, we have high expectations for a successful cooperation.

- Lastly, during the past two years we have concentrated on the development of research models in mice for FSHD. Already models for other muscle diseases exist which have proven a valuable tool in our efforts to better understand these afflictions. The expectation is that, especially in the case of FSHD, where it proves to be so difficult to hunt down the primary defect, these models will be of great importance. Meanwhile we have a first generation of models which are presently being analyzed for the development of FSHD-characteristic markers.

We hope that the foregoing reports prove that many new initiatives have been taken to gain a better insight into FSHD. Thanks to the financial support from the Princess Beatrix Fund, the FSHD Society, The *FSH Society* (USA), the Muscular Dystrophy Association (USA), the Leiden University Medical Center, and the Gisela Their Fund, six dedicated Leiden scientists, in cooperation with Nijmegen and many other institutions, are trying to better

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GENETICS/RESEARCH

**Dutch progress,
genetic inquiry***continued from page 50*

understand the disease processes in FSHD. This cannot be accomplished without your continued support, motivation and donations, from which we have benefited in the past years. We hope to continue to maintain these good relations with our patients in the coming years and to further work on the many positive developments.

**FSH Society*, translation from the Dutch language of selected contributions to the VSN Newsletter, VSN: Organization Muscle Diseases Netherlands, FSHD, Number 24 - December 2000

This newsletter is a publication by the diagnosis working group Facioscapulohumeral dystrophy (Landouzy-Dejerine disease)

**On 4q35 FSHD fragment sizes
and FSHD molecular deletions**

Peter W. Lunt, Bristol UK. Facioscapulohumeral Muscular Dystrophy: Diagnostic and Molecular Aspects.

Deymer F(ed): Neuromuscular Diseases: From Basic Mechanisms to Clinical Management, Monograph Clinical Neuroscience, Basel, Karger, 2000 vol 18. Pp 44-60.

From Monograph Clinical Neuroscience page 45: "Introduction"

"It is found that the age of onset and severity of clinical presentation correlates broadly and inversely with the size of the residual DNA fragment at 4q35, and, by inference, therefore correlates directly with the number of repeat units deleted. Thus, the smallest residual fragment lengths at 10-17 kb (1-3 repeat copies) are usually associated with a severe infantile or childhood presentation, medium lengths (18-30kb, or 4-7 repeat copies) are often found in the largest recognized

dominant families, while the largest lengths (31-38 kb or 8-10 repeat copies) have been associated with a milder predominantly scapulohumeral presentation, and may have reduced penetrance particularly in females. New mutation cases are seen predominantly with the smallest residual fragment lengths, giving matching clinical severity, and may originate predominantly on the maternal copy of chromosome 4. Study of parental DNA suggests that 20-30% of new mutations occur as somatic and germ-line events in one of the parents, this usually also being the mother."

International Consortium 2000 *cont. from page 47*

for the first time visually seeing, what FSHD is. Our research is showing how amazingly dimensional and profoundly complex the FSHD mechanism is. Despite the complexity of this biological architecture around FSHD, we should be able to gain insight into where the muscle is failing and what causes its failure by understanding how the entire symphony in 4q35 D4Z4 deletions works and by individual areas of investigation.

The *FSH Society* is especially pleased to have both program directors in the area of muscular dystrophy from the two institutes primarily responsible for FSHD at the National Institutes of Health (NIH) present. Welcome Dr. **Giovanna Spinella** of the National Institute of Neurological Disorders and Stroke (NINDS/NIH) and Dr. **Richard Lynn** of the National Institute of Arthritis, Musculoskeletal and Skin Diseases (NIAMS/NIH).

We have been advocating strongly with the Congress of the United States and the NIH for more funds for FSHD and hope to hear from NIH shortly about research opportunities. The *FSH Society* is still extremely concerned about the absence of federal research money for FSHD through the NIH. We view this with alarm and continue to vigorously pursue this concern with the highest levels and with key members of congress.

We are pleased to have Dr. **Sharon Hesterlee**, Research Program Coordinator of the Muscular Dystrophy Association of

America (MDAA) here. The Association Française contre les Myopathies (AFM) is present and supporting this meeting and we understand from its Scientific Director, **François Leterrier**, that a call for research proposals on FSHD is forthcoming.

A special thanks goes to Athena Diagnostics for their support of this meeting. And last, we continue to work closely with the Dutch FSHD foundation on many issues. We ask that you introduce yourselves to Dr. Spinella, Dr. Lynn, Dr. Hesterlee and myself for further information on funding opportunities.

This meeting will be extraordinary with what I understand to be a series of major scientific breakthroughs. The *FSH Society* will continue to work with all of you. The charge of this meeting is to explore the current state of knowledge of FSHD in the context of new discoveries, areas and disciplines of science. It will be critical to generate tonight a clear and written set of research directions and priorities to help facilitate inter-agency and research planning.

I would also like to extend my heartfelt appreciation for the extraordinary effort and remarkable success and insight put forth by this small and international group of researchers and clinicians. We are here today to give credit where it is due and to ensure that your wishes are heard, respected and acted on.

Thank you.

**FSHD/ASHG
meeting 2001***continued from page 47*

the meeting with time for presentations of recent work and significant highlights.

The organizing committee members for the 2001 consortium meeting are Dr. Sara Winokur, Dr. Rune Frants and Mr. Daniel Perez.

Please let Dr. Winokur or Dr. Frants know if you wish to attend (RSVP) and any additional researchers, scientists that you may wish to invite. Last, please let us know of others deemed appropriate to be invited to the meeting. Additionally, please let Dr. Winokur and Dr. Frants know if you have special audio visual needs and/or considerations.

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Bibliography

1999 ■ ■ ■

- Kissel JT. Facioscapulohumeral dystrophy. *Semin Neurol.* 1999;19(1):35-43. Review. PMID: 10711987
- Nitahara K, Sakuragi T, Matsuyama M, Dan K. Response to vecuronium in a patient with facioscapulohumeral muscular dystrophy. *Br J Anaesth.* 1999 Sep;83(3):499-500. PMID: 10655933
- van Santen G, Meuzelaar JJ, Tulleken JE, Zijlstra JG, Meinesz AF, van der Werf TS. [Dyspnea caused by bullae in a muscular dystrophy patient on chronic intermittent ventilatory support]. *Ned Tijdschr Geneesk.* 1999 Dec 11;143(50):2532-6. Dutch. PMID: 10627757
- van der Maarel SM, Deidda G, Lemmers RJ, Bakker E, van der Wielen MJ, Sandkuijl L, Hewitt JE, Padberg GW, Frants RR. A new dosage test for subtelomeric 4;10 translocations improves conventional diagnosis of facioscapulohumeral muscular dystrophy (FSHD). *J Med Genet.* 1999 Nov;36(11):823-8. PMID: 10544225
- Tupler R, Perini G, Pellegrino MA, Green MR. Profound misregulation of muscle-specific gene expression in facioscapulohumeral muscular dystrophy. *Proc Natl Acad Sci U S A.* 1999 Oct 26;96(22):12650-4. PMID: 10535977
- Upadhyaya M, MacDonald M, Ravine D. Prenatal diagnosis for facioscapulohumeral muscular dystrophy (FSHD). *Prenat Diagn.* 1999 Oct;19(10):959-65. PMID: 10521823
- Stout K, van der Maarel S, Frants RR, Padberg GW, Ropers HH, Haaf T. Somatic pairing between subtelomeric chromosome regions: implications for human genetic disease? *Chromosome Res.* 1999;7(5):323-9. PMID: 10515207
- van Geel M, Heather LJ, Lyle R, Hewitt JE, Frants RR, de Jong PJ. The FSHD region on human chromosome 4q35 contains potential coding regions among pseudogenes and a high density of repeat elements. *Genomics.* 1999 Oct 1;61(1):55-65. PMID: 10512680
- Vitelli F, Villanova M, Malandrini A, Bruttini M, Piccini M, Merlini L, Guazzi G, Renieri A. Inheritance of a 38-kb fragment in apparently sporadic facioscapulohumeral muscular dystrophy. *Muscle Nerve.* 1999 Oct;22(10):1437-41. PMID: 10487912
- Gabriels J, Beckers MC, Ding H, De Vriese A, Plaisance S, van der Maarel SM, Padberg GW, Frants RR, Hewitt JE, Collen D, Belayew A. Nucleotide sequence of the partially deleted D4Z4 locus in a patient with FSHD identifies a putative gene within each 3.3 kb element. *Gene.* 1999 Aug 5;236(1):25-32. PMID: 10433963
- Galluzzi G, Deidda G, Cacurri S, Colantoni L, Piazza N, Vigneti E, Ricci E, Servidei S, Merico B, Pachi A, Brambati B, Mangiola F, Tonali P, Felicetti L. Molecular analysis of 4q35 rearrangements in facioscapulohumeral muscular dystrophy (FSHD): application to family studies for a correct genetic advice and a reliable prenatal diagnosis of the disease. *Neuromuscul Disord.* 1999 May;9(3):190-8. PMID: 10382915
- Orrell RW, Tawil R, Forrester J, Kissel JT, Mendell JR, Figlewicz DA. Definitive molecular diagnosis of facioscapulohumeral dystrophy. *Neurology.* 1999 Jun 10;52(9):1822-6. PMID: 10371529
- Bouju S, Pietu G, Le Cunff M, Cros N, Malzac P, Pellissier JF, Pons F, Leger JJ, Auffray C, Dechesne CA. Exclusion of muscle specific actinin-associated LIM protein (ALP) gene from 4q35 facioscapulohumeral muscular dystrophy (FSHD) candidate genes. *Neuromuscul Disord.* 1999 Jan;9(1):3-10. PMID: 10063829
- Grewal PK, van Geel M, Frants RR, de Jong P, Hewitt JE. Recent amplification of the human FRG1 gene during primate evolution. *Gene.* 1999 Feb 4;227(1):79-88. PMID: 9931447
- Copeland SA, Levy O, Warner GC, Dodenhoff RM. The shoulder in patients with muscular dystrophy. *Clin Orthop.* 1999 Nov;(368):80-91. PMID: 10613155
- Fitzsimons RB. Facioscapulohumeral muscular dystrophy. *Curr Opin Neurol.* 1999 Oct;12(5):501-11. Review. PMID: 10590886
- Pomies P, Macalma T, Beckerle MC. Purification and characterization of an alpha-actinin-binding PDZ-LIM protein that is up-regulated during muscle differentiation. *J Biol Chem.* 1999 Oct 8;274(41):29242-50. PMID: 10506181
- Nakayama T, Komiya T, Tyou E, Watanabe S, Kawai M. [Cardiac deformity and dysfunction in facioscapulohumeral dystrophy—electrocardiogram, ECG gate cardiac MRI studies]. *Rinsho Shinkeigaku.* 1999 Jun;39(6):610-4. Japanese. PMID: 10502983
- Munar-Ques M, Pedrosa JL, Coelho T, Gusmao L, Seruca R, Amorim A, Sequeiros J. Two pairs of proven monozygotic twins discordant for familial amyloid neuropathy (FAP) TTR Met 30. *J Med Genet.* 1999 Aug;36(8):629-32. PMID: 10465115
- Sawant MR, Calvert PT. Facioscapulohumeral dystrophy—an indication for internal fixation of clavicle fractures. *J R Soc Med.* 1999 Feb;92(2):88-9. PMID: 10450223
- Zou KH, McDermott MP. Higher-moment approaches to approximate interval estimation for a certain intraclass correlation coefficient. *Stat Med.* 1999 Aug 15;18(15):2051-61. PMID: 10440886
- Furukawa T. [Facioscapulohumeral SMA]. *Ryoikibetsu Shokogun Shirizu.* 1999;(27 Pt 2):382-3. Review. Japanese. PMID: 10434679
- Ricci E, Galluzzi G, Deidda G, Cacurri S, Colantoni L, Merico B, Piazza N, Servidei S, Vigneti E, Pasceri V, Silvestri G, Mirabella M, Mangiola F, Tonali P, Felicetti L. Progress in the molecular diagnosis of facioscapulohumeral muscular dystrophy and correlation between the number of KpnI repeats at the 4q35 locus and clinical phenotype. *Ann Neurol.* 1999 Jun;45(6):751-7. PMID: 10360767
- Letry-Trouillat R, Kuntzer T, Janzer RC, Bogousslavsky J. [Facial myositis: a localized form of generalized myositis]? *Rev Neurol (Paris).* 1999 Mar;155(3):225-8. Review. French. PMID: 10339793
- Burgos-Asurmendi I, Guerra-Gonzalez ML, Canseco-Dansey I, Lojo-Sanchez D, Saez Cuevas E. [Apropos of a case of facioscapulohumeral dystrophy or Landouzy-Dejerine disease]. *Rev Esp Anestesiol Reanim.* 1999 Mar;46(3):132-3. Spanish. No abstract available. PMID: 10228381
- Kohler J, Rohrig D, Bathke KD, Koch MC. Evaluation of the

Bibliography *continued*

facioscapulohumeral muscular dystrophy (FSHD1) phenotype in correlation to the concurrence of 4q35 and 10q26 fragments. *Clin Genet*. 1999 Feb;55(2):88-94. PMID: 10189085

Vogler C, Homan S, Pung A, Thorpe C, Barker J, Birkenmeier EH, Upadhyaya P. Clinical and pathologic findings in two new allelic murine models of polycystic kidney disease. *J Am Soc Nephrol*. 1999 Dec;10(12):2534-9. PMID: 10589692

Kennedy JL, Basile VS, Macchiardi FM. Chromosome 4 Workshop Summary: Sixth World Congress on Psychiatric Genetics, Bonn, Germany, October 6-10, 1998. *Am J Med Genet*. 1999 Jun 18;88(3):224-8. PMID: 10374735

Grewal PK, van Geel M, Frants RR, de Jong P, Hewitt JE. Recent amplification of the human FRG1 gene during primate evolution. *Gene*. 1999 Feb 4;227(1):79-88. PMID: 9931447

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Overveld PG, Lemmers RJ, Deidda G, Sandkuijl L, Padberg GW, Frants RR, van Der Maarel SM. Interchromosomal repeat array interactions between chromosomes 4 and 10: a model for subtelomeric plasticity. *Hum Mol Genet*. 2000 Nov 22;9(19):2879-84. PMID: 11092764.

Lue YJ, Chen SS. The strength and functional performance in patients with facioscapulohumeral muscular dystrophy. *Kaohsiung J Med Sci*. 2000 May;16(5):248-54. PMID: 10969520.

Auer-Grumbach M, Wagner K, Strasser-Fuchs S, Loscher WN, Fazekas F, Millner M, Hartung HP. Clinical predominance of proximal upper limb weakness in CMT1A syndrome. *Muscle Nerve*. 2000 Aug;23(8):1243-9. PMID: 10918262.

van der Kooij AJ, Visser MC, Rosenberg N, van den Berg-Vos R, Wokke JH, Bakker E, de Visser M. Extension of the clinical range of facioscapulohumeral dystrophy: report of six cases. *J Neurol Neurosurg Psychiatry*. 2000 Jul;69(1):114-6. PMID: 10864616.

Felice KJ, North WA, Moore SA, Mathews KD. FSH dystrophy 4q35 deletion in patients presenting with facial-sparing scapular myopathy. *Neurology*. 2000 May 23;54(10):1927-31. PMID: 10822431.

Busse K, Kohler J, Stegmann K, Pongratz D, Koch MC, Schreiber H. An inherited 4q35-EcoRI-DNA-fragment of 35 kb in a family with a sporadic case of facioscapulohumeral muscular dystrophy (FSHD). *Neuromuscul Disord*. 2000 Mar;10(3):178-81. PMID: 10734264.

Saito A, Higuchi I, Nakagawa M, Saito M, Uchida Y, Inose M, Kasai T, Niiyama T, Fukunaga H, Arimura K, Osame M. An overexpression of fibroblast growth factor (FGF) and FGF receptor 4 in a severe clinical phenotype of facioscapulohumeral muscular dystrophy. *Muscle Nerve*. 2000 Apr;23(4):490-7. PMID: 10716758.

van der Maarel SM, Deidda G, Lemmers RJ, van Overveld PG, van der Wielen M, Hewitt JE, Sandkuijl L, Bakker B, van Ommen GJ, Padberg GW, Frants RR. De novo facioscapulohumeral muscular dystrophy: frequent somatic mosaicism, sex-dependent phenotype, and the role of mitotic transchromosomal repeat interaction between chromosomes 4 and 10. *Am J Hum Genet*. 2000 Jan;66(1):26-35. PMID: 10631134.

Finsterer J, Stollberger C. Cardiac involvement in primary myopathies. *Cardiology*. 2000;94(1):1-11. PMID: 11111138.

Tekin NF, Saatci AO, Kavukcu S. Vascular tortuosity and Coats'-like retinal changes in facioscapulohumeral muscular dystrophy. *Ophthalmic Surg Lasers*. 2000 Jan;31(1):82-3. PMID: 10976570.

van Geel M, van Deutekom JC, van Staalduin A, Lemmers RJ, Dickson MC, Hofker MH, Padberg GW, Hewitt JE, de Jong PJ, Frants RR. Identification of a novel beta-tubulin subfamily with one member (TUBB4Q) located near the telomere of chromosome region 4q35. *Cytogenet Cell Genet*. 2000;88(3-4):316-21. PMID: 10828619.

Walter MC, Lochmuller H, Reilich P, Klopstock T, Huber R, Hartard M, Hennig M, Pongratz D, Muller-Felber W. Creatine monohydrate in muscular dystrophies: A double-blind, placebo-controlled clinical study. *Neurology*. 2000 May 9;54(9):1848-50. PMID: 10802796.

Torreggiani WC, Lyburn ID, Harris AC, Rowley VA. Duchenne-Landouzy dystrophy: CT explanation of low serum creatinine level. *AJR Am J Roentgenol*. 2000 May;174(5):1467-8. PMID: 10789819.

Moore DP, Kowalske KJ. Neuromuscular rehabilitation and electrodiagnosis. 5. Myopathy. *Arch Phys Med Rehabil*. 2000 Mar;81(3 Suppl 1):S32-5; quiz S36-44. Review. PMID: 10721759.

Misuri G, Lanini B, Gigliotti F, Iandelli I, Pizzi A, Bertolini MG, Scano G. Mechanism of CO(2) retention in patients with neuromuscular disease. *Chest*. 2000 Feb;117(2):447-53. PMID: 10669689.

Jiao X, Munier FL, Iwata F, Hayakawa M, Kanai A, Lee J, Schorderet DF, Chen MS, Kaiser-Kupfer M, Hejtmancik JF. Genetic linkage of bietti crystallin corneoretinal dystrophy to chromosome 4q35. *Am J Hum Genet*. 2000 Nov;67(5):1309-13. PMID: 11001583.

Hafner FM, Salam AA, Linder TE, Balmer D, Baumer A, Schinzel AA, Spillmann T, Leal SM. A novel locus (DFNA24) for prelingual nonprogressive autosomal dominant nonsyndromic hearing loss maps to 4q35-qter in a large Swiss German kindred. *Am J Hum Genet*. 2000 Apr;66(4):1437-42. PMID: 10739769.

Kondo T, Bobek MP, Quick R, Lamb B, Zhu X, Narayan A, Bouchis D, Viegas-Pequignot E, Ehrlich M, Hanash SM. Whole-genome methylation scan in ICF syndrome: hypomethylation of non-satellite DNA repeats D4Z4 and NBL2. *Hum Mol Genet*. 2000 Mar 1;9(4):597-604. PMID: 10699183.

Number of articles published each year

1991	15	1996	23
1992	18	1997	17
1993	23	1998	26
1994	18	1999	29
1995	28	2000	18

Researchers

SYDNEY, AUSTRALIA

Researcher(s): Robin B. Fitzsimons

Address: 9TH Floor, 229 Macquarie St., Sydney NSW 2000, Australia

Interest(s): Clinical research and retinal, cochlear and skeletal muscle abnormalities in FSHD

Recent notes regarding research

directions: Abnormalities of the small blood vessels of the retina at the back of the eye are present in most patients with FSH, but are usually asymptomatic. Occasionally however, these blood vessels can leak and cause retinal exudates which may even lead to blindness if not treated (with Laser coagulation) in a very timely fashion. It appears that children with a more severe or even sporadic form of FSH are more likely to develop this symptomatic form of retinal disease, but the reason for this is not known. It is therefore important to keep such individuals under especial ophthalmic surveillance. It is also not known whether there is any as yet unidentified additional genetic peculiarity which renders some FSH individuals peculiarly susceptible to symptomatic retinal disease - or indeed whether retinal, cochlear and skeletal muscle abnormalities in FSH represent different effects of the same mutation or otherwise are the results of abnormalities of adjacent genes. If the former hypothesis pertains, then the possibility that such pleiotropic effects are mediated by inflammation and/or 'environmental' factors must be investigated—especially so since there is known to be one set of monozygotic twins who are discordant for retinal manifestations (neither has serious retinal disease, but one had retinal hemorrhages not visible in the other twin).

GERPINNES, BELGIUM

Researcher(s): Pascale Hilbert, Olivier Froment, Daniel Sartenaer

Address: IPG Loverval / Molecular Biology, 41 Allée des Templiers, 6280 Gerpinnes, Belgium

Interest(s): Molecular genetics

LEUVEN, BELGIUM

Researcher(s): Jan Gabriëls, Marie Claire Beckers, Astrid De Vriese, Alexandra Belayew*

Address: Center for Molecular and Vascular Biology, University of Leuven, Herestraat 49, B-3000-Leuven, Belgium

Interest(s): Molecular genetics

* Alexandra Belayew is currently working on FSHD research at the Lab. Biologie Moléculaire, Université de Mons-Hainaut, Mons, Belgium

LOVERVAL, BELGIUM

Researcher(s): Lionel Van Maldergem

Address: Centre de Génétique Humaine, Institut de Pathologie et de Génétique, Allée des Templiers 41, 6280 - Loverval, Belgium

Interest(s): Molecular genetics

MONS, BELGIUM

Researcher(s): Alexandra Belayew, Frédérique Coppée, India Leclercq, Christel Mattéotti, Guy Deneubourg

Address: Lab. Biologie Moléculaire, Université de Mons-Hainaut, Pentagone 3A, Avenue du Champ de Mars, 6, B - 7000 Mons, Belgium

Interest(s): Molecular genetics

Update: Part of the studies presented here was done at the University of Leuven with Marie-Claire Beckers (Ph.D.), Jan Gabriëls (grad student at the time, now Ph.D.), Astrid de Vriese (technician) in the Center for Molecular and vascular Biology headed by Prof. Désiré Collen (M.D., Ph.D.). The second part of the results was obtained at the University of Mons-Hainaut where A. Belayew started the new Laboratory of Molecular Biology, with Frédérique Coppée (Ph.D.), India Leclercq (Ph.D.), Christel Mattéotti (grad student) and Guy Deneubourg (technician). The patient DNA used in these studies was provided through a collaboration with the groups of Profs. R. Frants and G. Padberg (Universities of Leiden and Nijmegen, The Netherlands)

Studies on the DUX4 gene embedded into the 3.3kb repeats of the FSHD locus.

The DUX4 gene. Besides classical genes, the human genome contains a large amount of "junk DNA" i.e. various DNA stretches which are repeated a large number of times and for which no function is known. One family of such elements "the 3.3 kb repeats" has members on several chromosomes in humans, but is absent in mice. Intriguingly, we found a gene embedded within some 3.3 kb repeats: we could show that this gene was active and encoded a protein (DUX1) with two homeodomains, a structure known to bind DNA. Other members of this 3.3 kb repeat family are found on chromosome 4 in the D4Z4 locus that is associated with FSHD. In non-affected individuals the FSHD locus comprises 10-100 copies of the 3.3 kb repeat. In patients, this repeat array has been reduced by a deletion leaving only one to eight copies of this element. We have previously identified a putative DUX4 gene within each of the two 3.3 kb repeats left in the rearranged locus of a patient with FSHD. The DUX4 gene lacks several features normally found in active genes. We investigated whether the DUX4

gene could be active by the following experience. We have injected the two 3.3 kb elements of the same patient locus in a muscle of a mouse leg. We reasoned that if the DUX4 gene could be active in the mouse muscle cells, it would express the DUX4 protein. This protein being human would be recognized as foreign in the mouse that would build antibodies against it. We were able to detect a large amount of such antibodies in the sera of the six mice we had injected, thus demonstrating functionality of the DUX4 gene.

Our hypothesis. Like several researchers in the field, we hypothesize that in non-affected individuals the large number of 3.3 kb elements in D4Z4 are covered by a compact chromatin structure and we think that this prevents DUX4 expression. In patients, the few repeats left might be in a more open chromatin structure and we hypothesize that this allows expression of a DUX4 protein toxic to muscle. Evaluation of this hypothesis is complicated by the presence in the genome of hundreds of 3.3 kb/DUX repeats that are not linked to FSHD, most of which are transcribed, and at least one of which is expressed as a non-pathological protein, DUX1.

The DUX4 protein. We expressed the non-pathological DUX1 protein in bacteria to obtain a large amount of it. A rabbit antiserum was raised against this protein, and can be used as a tool to detect all DUX proteins which are very similar. In order to avoid a non-specific response of the other uncharacterized DUX proteins, we used mouse (lacking the DUX genes) muscle C2C12 cells growing *in vitro* and introduced a gene expressing either DUX1 or DUX4 into them. Using this rabbit serum, and a confocal microscope that provides very large magnification of cells to be observed, we could stain the DUX proteins as a fuzzy ring on the envelope that surrounds the cell nuclei. This localization is similar to those of emerin and lamins, mutations of which are associated with the Emery-Dreyfus muscular dystrophy.

In conclusion, we believe that the results accumulated this year underscore our hypothesis that DUX4 constitutes a new candidate gene for FSHD.

Recent Abstract from October 3, 2000 FSH Society FSHD workshop Philadelphia, PA USA:

Study of the DUX4 gene present in the D4Z4 repeats of the 4q35 chromosome locus. Frédérique Coppée¹, Jan Gabriëls², Christel Mattéotti¹, Guy Deneubourg¹, Ernő Zádor³, Frank Wuytack⁴, László Dux³, Désiré Collen² and Alexandra Belayew¹ 1) Lab. Molecular Biology, Univ. Mons-Hainaut, 7000

Researchers *continued*

Mons, Belgium. 2) Center for Molecular and Vascular Biology, Univ. Leuven, 3000 Leuven, Belgium.

3) Inst. Biochemistry, Albert Szent-Györgyi Medical Univ. 6701 Szeged, Hungary.

4) Lab Physiology, Univ. Leuven, Gasthuisberg, 3000 Leuven, Belgium.

FSHD is linked to partial deletions of a tandem repeat array (D4Z4) in the 4q35 chromosome locus. In non-affected individuals this array comprises 10-100 copies of a 3.3 kb element associated with heterochromatin. In patients this array is reduced to one to eight repeats. We have identified a gene encoding a protein with a double homeodomain (DUX4) within each of the two 3.3 kb elements left in the rearranged locus of a patient with FSHD. This has allowed us to put forward the following hypothesis. In non-affected individuals, the large number of *DUX4* genes present in the D4Z4 repeats are buried in heterochromatin and cannot be expressed. In patients with FSHD, where the number of *DUX4* genes has been reduced by a deletion, the heterochromatin might be loosened, allowing expression in some cells of a *DUX4* protein that would be toxic to muscle. Evaluation of this hypothesis is complicated by the presence in the genome of hundreds of 3.3 kb/*DUX* repeats that are not linked to FSHD, most of which are transcribed, and at least one is expressed as a non-pathological protein, *DUX1*.

All our studies of *DUX4* gene expression have been performed in rodents since they lack the 3.3 kb/*DUX* repeat family. Functionality of the *DUX4* gene was shown by injection into mouse leg muscles of a plasmid containing the 13.5 kb *EcoRI* fragment of the patient locus we had sequenced: six out of six injected mice produced a strong immune response against the human *DUX4* protein demonstrating that it could be expressed from the injected patient DNA. In order to characterize the *DUX4* RNA, we introduced the same DNA fragment in mouse C2C12 cells grown *in vitro*. Since the *DUX4* gene doesn't have a poly A addition signal, and because we have found that other, non-pathologic, *DUX* genes were expressed as poly A- RNAs, we isolated total RNA from these cells. Several transcripts of different sizes were observed on a Northern blot using a PCR fragment overlapping the two homeoboxes as a probe. RT-PCR experiments are in progress to further characterize these RNAs.

The putative toxicity of the *DUX4* protein was evaluated in a model of rat soleus regeneration characterized in Szeged. An expression vector for *DUX4* was injected in the soleus four days after notexin treatment, at a stage of active myoblast proliferation and

early myotube formation. Muscles were harvested four days later and quickly frozen. Hematoxylin staining of the cryosections revealed a strong disorganization in the central part of the muscle, with major cell loss and infiltration by small cells. Further characterization of these muscle sections is ongoing by immunostaining and comparison with *DUX1*-injected controls.

We have previously localized the *DUX* proteins to the nucleoplasm of various cell lines transfected with expression vectors for proteins (either *DUX1* or *DUX4* truncated to its two homeodomains) fused to the green fluorescent protein (EGFP). A rabbit antiserum raised against the *DUX1* protein, and cross-reacting with *DUX4*, was shown to specifically immunostain C2C12 cells expressing either *DUX1*- or *DUX4*-EGFP. When used on cells expressing natural *DUX1* or *DUX4*, this antiserum showed in addition another staining pattern of a fuzzy ring on the nuclear envelope.

SAO PAULO, BRAZIL

Researcher(s): Mayana Zatz, Maria Rita Passos-Bueno, Suely K. Marie, Rita de Cassia M. Pavanello, Maria Tonini, Maria Cerqueira, Maria Manuela

Address: Departamento de Biologia, Instituto de Biosciencias, Universidade de Sao Paulo, Rua de Matao 227 - sala 211, 05508-900, Sao Paulo, SP, Brazil

Interest(s): Molecular genetics, clinical and occupational and genetic testing

ALBERTA, CANADA

Researcher(s): Peter J. Bridge

Address: Molecular Diagnostic Laboratory, Alberta Children's Hospital, 1820 Richmond Rd. S.W., Calgary, Alberta, Canada T2T 5C7

Interest(s): Molecular genetics, clinical and genetic testing

ONTARIO, CANADA

Researcher(s): Robert Korneluk, Alasdair Hunter, Nancy Carson

Address: Dept. of Genetics, Children's Hospital of Eastern Ontario (CHEO), 401 Smyth Rd., Room 3029, Ottawa, Ontario, Canada K1H 8L1

Interest(s): Molecular genetics, clinical and genetic testing

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Researcher(s): David Picketts

Address: Ottawa General Hospital, Research Institute, 501 Smyth Rd., Ottawa, Ontario, Canada K1H 8L6

Interest(s): Molecular genetics and cellular biology

Update: FSHD patients have a reduced

number of D4Z4 repeats at the end of chromosome 4. It has been hypothesized that the reduction in D4Z4 copy number affects the chromatin structure in this region of the genome. Such an alteration in the chromatin configuration could alter the expression of one or more genes, ultimately resulting in FSHD. Our laboratory is interested in examining the normal chromatin structure of 4q35 in muscle and non-muscle cell types as a starting point to identify chromatin changes associated with patient material. As such, we have been methodically screening the region for DNase I hypersensitive sites to generate a "chromatin" map of the region. We have utilized the human genome sequence to identify CpG islands and putative regulatory elements corresponding to genes that have been previously cloned and mapped to 4q35. Appropriate probes have been designed for indirect end-labeling and DNase I hypersensitive site analysis is currently in progress.

GUANGZHOU, CHINA

Researcher(s): Cheng Zhang

Address: Dept. of Neurology, First Affiliated Hospital, Sun Yat-Sen University of Medical Sciences, Zhongshan Road II, Guangzhou, Guangdong, 510080 P.R. China

Interest(s): Clinical research, molecular genetics, clinical and genetic testing

Note: Please see article on the treatment of FSHD with Traditional Chinese Medicine (herbal) on page 32, 35.

BRISTOL, ENGLAND

Researcher(s): Peter Lunt

Address: Bristol Royal Hospital for Sick Children, Clinical Genetics Service, St. Michael's Hill, Bristol BS2 8BJ, England

Interest(s): Molecular genetics and clinical research

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Researcher(s): Philip Jardine

Address: Children's Centre, Frenchay Hospital, Bristol BS16 1LE, England

Interest(s): Molecular genetics and clinical

CAMBRIDGE, ENGLAND

Researchers: Robin B. Fitzsimons

Address: 53 Bateman Street, Cambridge, CB2 1LR, England

Interest(s): Clinical research and retinal, cochlear and skeletal muscle abnormalities in FSHD

CARDIFF, ENGLAND

Researchers: Meena Upadhyaya, Mike Osborn, Peter S. Harper, David N. Cooper

Address: Institute of Medical Genetics,

Researchers *continued*

University of Wales College of Medicine,
Heath Park, Cardiff CF4 4LA, England

Interest(s): Molecular genetics, clinical and genetic testing

Update: FSHD Research Group—Our main research interests include: 1) Study of methylation status of DNA sequences within the FSHD region, specifically targeting known genes or repeat sequences, 2) To investigate the prevalence of subtelomeric exchanges between the homologous 4q35 and 10q26 loci in both normal individuals and FSHD patients and to ascertain their possible role in the etiology of the disorder, 3) To search for potential differences in the expression levels of muscle specific 4q35 located transcribed sequences in both FSHD patients and control subjects.

Our institute is also involved in the molecular testing for FSHD.

LONDON, ENGLAND

Researcher(s): Richard Orrell

Address: University Department of Clinical Neurosciences, Royal Free Hospital School of Medicine, Pond Street, London NW3 2QG, England

Interest(s): Clinical Research



Researcher(s): Michael Rose

Address: King's Neurosciences Centre, Mapother House, De Crespigny Park, Denmark Hill, London SE5 8AZ, England

Interest(s): Clinical

NOTTINGHAM, ENGLAND

Researcher(s): Jane Hewitt, Pam Grewal, Daniel Bolland

Address: Division of Genetics, Queen's Medical Centre, Nottingham University, Nottingham, N97 2UH, England

Interest(s): Molecular genetics, sequencing, genomics and mouse models

Recent Abstract from October 3, 2000
FSH Society FSHD workshop Philadelphia, PA
USA: **Towards a complete BAC contig, draft DNA sequence and transcription map of the FSHD candidate region on human chromosome 4q35**

Jane Hewitt, Pam Grewal, Dan Bolland
Institute of Genetics, Queen's Medical Centre, University of Nottingham, UK

Using a YAC contig and high resolution marker map as a starting point, we have been interrogating the Human Genome Project draft DNA sequence as a means of developing a transcription map of human chromosome 4q35. In conjunction with this we are also developing a mouse BAC contig spanning the homologous region on mouse chromosome 8. The proximal part of chromosome 4q35 is

gene-rich and a summary of transcripts will be presented. There is now draft sequence covering most of this region. In contrast, the distal part of 4q35 (between MTNR1A and FRG1) is poor in genes and contains many duplicated genomic regions as well as a large amount of LINE and LTR sequences. There is not contiguous draft sequence and several BAC clones reputed to map to this region have probably been misassigned. The current status of this region will be presented for discussion of further strategies. The current BAC data for the FSHD homologous region in mouse show that gene content and order are conserved. Furthermore, we have found that the Mtnr1a-Frg1 region in mouse is about the same size as human and also contains a high proportion of LINES and LTRs.

Recent Abstract from October 3, 2000
FSH Society FSHD workshop Philadelphia, PA
USA: **Sequence comparison of 4qter and 10qter**

Michel van Geel (1), Morag C. Dickson (2), Amy F. Beck (1), Lisa J. Heather (2), Daniel J. Bolland (2,3) Rune R. Frants (4), Silvère van der Maarel (4)*, Pieter J. de Jong (1), Jane E. Hewitt (2,3)

*presenting author

(1) Department of Cancer Genetics, Roswell Park Cancer Institute, Buffalo, NY, USA (2) School of Biological Sciences, University of Manchester, Manchester, UK (3) Institute of Genetics, Queens Medical Centre, Nottingham University, Nottingham, UK (4) Leiden University Medical Center, MGC-Department of Human Genetics, Leiden, The Netherlands

A polymorphic 3.3 kb tandem repeated sequence (D4Z4) maps to the subtelomeric region of human chromosome 4q35 and is causally associated with facioscapulohumeral muscular dystrophy. A second tandem repeat locus, closely related to D4Z4, has been mapped to the subtelomeric chromosomal region of 10q26 but is not associated with any disease phenotype. Analysis of the subtelomeric regions of human chromosome 4q and 10q indicate extreme conservation of structure and sequence identity. Although the distal part of 10q has derivative copies in the genome, the proximal part is uniquely associated with this chromosome, unlike the chromosome 4q35, which has duplicated regions stretching over at least 0.5 Mb. This suggests that the chromosome 4q35 is more ancient in comparison to the relatively young 10q26 telomere.

Sequence analysis of an additional independent YAC containing the 4q subtelomeric region demonstrates the presence of an alternative allele. Both alleles, 4qA and 4qB, show a high level of nucleotide identity ((

94%) to the terminal 25 kb of the 4p telomere. Additional pulsed field gel electrophoresis analysis in the Dutch population confirms the existence of the 4qB allele. The proximal boundary of this similarity lies immediately distal to the 3.3 kb tandem repeat. Sequences of the 3.3 kb repeats from the two 4q35 alleles and chromosome 10q reveal very little inter- and intra-chromosomal sequence variation indicating that these repeats are undergoing homogenization. The mechanism behind this subtelomeric homogenization presumably occurs through concerted evolution. Although the underlying molecular defect of the FSHD phenotype is still elusive, the sequenced regions on 4qter and the associated 10q26ter contribute to solving some pieces of this complex puzzle.

EVRY, FRANCE

Researcher(s): Claude Diaz, Annie Barois, Jean Pouget

Address: Association Française contre les Myopathies (AFM) 1, rue l'Internationale BP59 — 91002 Evry Cedex, France

Interest(s): Molecular genetics, clinical, research and medical school education

GARCHES, FRANCE

Researcher(s): J. Andoni Urtizberea

Address: Service de Medecine Physique et Readaptation de l'Enfant, Hopital Raymond Poincare, 92380 Garches, France

Interest(s): Clinical, research and medical school education

Update: We continue to collect a huge amount of patients with the disease (from France mainly but also Spain and Portugal) and we test them for the deletion (over 1000 individuals to my latest collection). Another group in Montpellier (Karima LAOUDJ) is performing differential display in muscle tissue.

MONTPELLIER, FRANCE

Researcher(s): Bouju S, Dechesne C

Address: Laboratoire de Physiopathologie Cellulaire et Moleculaire, INSERM Unite 300, Faculte de Pharmacie, Montpellier, France.

Interest(s): Molecular genetics and cell biology



Researcher(s): Mireille Claustres, Sylvie Tuffery

Address: Association Française Contre les Myopathies (AFM), Montpellier - FRANCE

Interest(s): Molecular genetics and cell biology

Researchers *continued*

PARIS, FRANCE

Researcher(s): Michel Fardeau

Address: AFM - Institut de Myologie, Groupe Hospitalier Pitie-Salpetriere, 75651 Paris Cedex 13, France

Interest(s): Clinical and molecular genetics



Researcher(s): Jean-Claude Kaplan, Yuzhou Zhang

Address: Laboratoire de Biochemie Genetique, Hopital Cochin, 123, Boulevard de Port-Royal, 75014 Paris, France

Interest(s): Molecular genetics



Researcher(s): Marc Jeanpierre

Address: Laboratoire de Genetique, 123, Bd de Port-Royal, 75014 Paris, France

Interest(s): Molecular genetics



Researcher(s): Pascal Laforêt

Address: Groupe Hospitalier Pitié-Salpêtrière, Institut de Myologie, 47, boulevard de l'Hôpital, 75651 Paris Cédex 13

Interest(s): Clinical Research and cardiac issues in FSHD

POITIERS, FRANCE

Researcher(s): Yves Rideau, Gerard Dupont, Ann Delabier, Laurence Dumas, Claire Guillou

Address: Unite Duchenne de Boulogne, Centre Hospitalier Universitaire, BP 577, 86021, Poitiers Cedex, France

Interest(s): Clinical, orthopedic surgery (scapula fixation), corrective procedures for FSHD.

Update: Poitiers University, France offers: 1) Medical actions for FSHD patients: early treatment of usual causes of disability; 2) Scapular winging: surgical fusion of the two scapulae by special technique allowing to preserve shoulder function for longer periods of time; 3) Foot weaknesses: muscle transfer, without any plaster cast immobilization, allowing to significantly prolong a normal gait pattern; 4) Low back problems: research of means of prevention of pain or deformity.

All of these current therapeutic purposes, involving both surgery and rehabilitation adapted to FSHD, were deduced from a continual clinical experience over a thirty year period of time. The results were achieved owing to a multidisciplinary approach. The specialized surgical group is directed by Gerard Dupont M.D. (Poitiers University Hospital - Jean Bernard). The specialized Rehabilitation Medicine group is comprised of Ann Delabier M.D., Laurence Dumas M.D., Claire Guillou M.D., Yves Rideau M.D. and the entire staff

(Poitiers University Hospital — Unite Duchenne de Boulogne)

BERLIN, GERMANY

Researcher(s): Thomas H. Haaf

Address: Max-Planck Institute of Molecular Genetics, Ihnestrasse 73, 14195 Berlin, Germany

Interest(s): Molecular genetics

MARBURG, GERMANY

Researcher(s): Manuela C. Koch

Address: Center of Human Genetics, Bahnhofstrasse 7, 35037 Marburg, Germany

Interest(s): Clinical and Molecular Genetics

Researcher: Herbert Schreiber

Address: Department of Neurology, University of Ulm, Steinhövelstrasse 9, 89075 Ulm, Germany

Interest(s): Clinical phenotype of muscular dystrophies

Update: A causal relationship between the disease FSHD and shortened p13E11/EcoRI-fragments of 10-33 kb has been identified by several research groups. Meanwhile it is well established, that the diagnostic evidence of the shortened fragment reaches its upper limit at a size range around 38 kb. Definitions of the upper threshold vary considerably from 28-41 kb in different research groups. Thus, a more accurate definition of the diagnostic threshold appears necessary. Together with the Neurological Department of Ulm, Germany, we therefore initiated a clinical and molecular genetic study to investigate more carefully patients with a FSHD phenotype and a EcoRI-fragment size above 35 kb. In addition, we will take a closer look at the diagnostic grey zone between 35-80 kb in individuals from the general population.

Reference: Busse K, Köhler J, Stegmann K, Pongartz D, Koch MC, Schreiber H (2000). An inherited 4q35-EcoRI-DNA-fragment of 35 kb in a family with a sporadic case of facioscapulohumeral muscular dystrophy (FSHD). *Neuromuscular Disorders* 10:178-181.

Recent Abstract of Publication: *Neuromuscul Disord* 2000 Mar;10(3):178-81

An inherited 4q35-EcoRI-DNA-fragment of 35 kb in a family with a sporadic case of facioscapulohumeral muscular dystrophy (FSHD).

Busse K, Köhler J, Stegmann K, Pongartz D, Koch MC, Schreiber H. Klinik für Neurologie, Universität Ulm, Steinhövelstrasse 9, D-89075, Ulm, Germany.

We present a case of an adult male patient showing clinical, neurophysiological and histological signs consistent with the

phenotype of facioscapulohumeral muscular dystrophy. On molecular testing with a 4q35-DNA-probe p13E-11 (D4F104S1), the patient, his clinically unaffected mother and two sisters shared a 4q35-EcoRI-DNA-fragment of 35 kb on the transition between FSHD1A-associated and polymorphic fragments. Explanatory hypotheses, such as reduced penetrance in females or a phenotype unlinked to the 4q35-locus are considered. Alternatively, additional changes in the unidentified FSHD1A gene could have caused the phenotype. Thus, in such rare cases, the diagnostic evidence of 4q35-EcoRI-fragments is still limited. PMID: 10734264

SZEGED, HUNGARY

Researcher(s): Laszlo Dux

Address: Department of Biochemistry, University of Szeged, Albert Szent-Györgyi Medical Center, H-6720 Szeged, Dom ter 9, Hungary

Interest(s): Molecular genetics

PAVIA, ITALY

Researcher(s): Rossella Tupler,* Elena Giulotto, Solomon Nergadze, Claus Azzalin

Address: Department of Genetics and Microbiology, University of Pavia, Via Abbiategrasso 207, 27100, Pavia, Italy

Interest(s): Molecular Genetics and clinical

Note: *Rossella Tupler is currently working on FSHD research at the Howard Hughes Medical Institute, Worcester, Massachusetts, USA

ROME, ITALY

Researcher(s): Luciano Felicetti, Patrizia Venditti, Claudia Cappuzzello

Address: Department of Molecular Biology, Istituto di Biologia Cellulare, 43 viale Marx, 00137, Rome, Italy

Interest(s): PFGE analysis of inter-chromosomal 4qter-10qter exchanges in normal individuals; chromatin organization at the 4q35 locus in normal and FSHD affected individuals.

Recent Abstract from October 3, 2000 FSH Society FSHD workshop Philadelphia, PA USA: **High Frequency of 4qter - 10qter subtelomeric exchanges in FSHD Italian Families.**

Galluzzi G. 1-2, Ricci E. 2-3, Colantoni L. 1-2, Rossi M. 2-3, Mangiola F. 2, Tonali P. 3, Felicetti L. 1

1) Institute of Cell Biology, CNR, Rome, Italy; 2) Center for Neuromuscular Diseases, U.I.L.D.M., Rome Section, Italy; 3) Institute of Neurology, Catholic University, Rome, Italy

Sequence homology between 4qter and 10qter loci has been shown to facilitate

Researchers *continued*

interchromosomal exchanges resulting in the reshuffling of 4q-type BlnI-resistant and 10q-type BlnI-sensitive repeats from one chromosome to the other. In order to verify whether the occurrence of interchromosomal exchanges could play a pathogenic role in association with the 4q35 rearrangement responsible for FSHD, we analyzed the segregation of BlnI-resistant and BlnI-sensitive alleles in members of 20 FSHD Italian families for a total of 75 individuals. FicolI-purified leukocytes were included in agarose blocks: DNA extraction and subsequent restriction steps with EcoRI, BlnI and Tru9I were performed directly in agarose. p13E-11 alleles were separated by PFGE and BlnI-resistant and BlnI-sensitive alleles identified by using p13E-11 and KpnI cloned sequences as probes.

We observed the presence of interchromosomal exchanges in 70% of the families studied: the exchanges were found in both affected and unaffected individuals as well as in spouses and included all different types of 4q-10q rearrangements (like *trisomy*, *monosomy* and partial translocations).

Among the 20 probands, ten of them (50%) displayed a subtelomeric translocation: five were *trisomic* and five *monosomic*. All the *monosomic* patients carried only the small BlnI-resistant fragment related to the disease. The larger p13E-11 allele was a hybrid chromosome containing a mixture of BlnI-resistant/BlnI-sensitive repeats, identified only by hybridization with KpnI sequences (*spurious monosomy*). When the parental origin of the translocated allele could be assessed, we observed that in most cases the translocated fragment was inherited from the parent not transmitting the disease.

Our data suggest that the basic mechanism underlying the pathogenesis of the disease is a marked instability of the KpnI subtelomeric repeats of homologous 4qter and 10qter loci, while the small 4q35 fragment causing FSHD is rarely involved in interchromosomal exchanges. Up to now no correlation was found between the presence of translocations and the severity of the clinical phenotype.

Other Abstracts:

1) 3rd International Symposium on the cause and treatment of Facioscapulohumeral Muscular Dystrophy. Bethesda, May 8, 2000 PFGE analysis of interchromosomal 4qter-10qter exchanges in normal and FSHD affected subjects. Felicetti L., Galluzzi G., Bonifazi E., Colantoni L., Rossi M., Mangiola E., Tonali P. and Ricci E. 2) 5th International Congress of Mediterranean Society of Myology. Capri, September 29- October 1, 2000. PFGE analysis of 4q35 rearrangements in FSHD: implications for the molecular mechanism of the disease. Galluzzi G, Colantoni L, Rossi M,

Bonifazi E, Mangiola, Tonali P, Ricci E. and Felicetti L.



Researcher(s): Giuliana Galluzzi, Luca Colantoni, Monica Rossi, Francesca Matullo, Enzo Ricci

Address: U.I.L.D.M, Italian Muscular Dystrophy Association, Center for Neuromuscular Disease, 5, Via P. Santacroce, 00167 Rome, Italy

Interest(s): Molecular diagnosis, family studies and prenatal diagnosis; application of PFGE analysis and study of 4qter-10qter exchanges in FSHD affected individuals



Researcher(s): Enzo Ricci, Mario Pescatori

Address: Institute of Neurology, Catholic University, Largo A. Gemelli, 8, 00168, Rome, Italy

Interest(s): Genotype-phenotype correlations, study of respiratory functions in FSHD patients.

TURIN, ITALY

Researcher(s): Laura M. Palmucci, Tiziana Mongini, Ivana Bosone, Simona Bortolotto, Loredana Chiadò-Piat, Isabella Ugo

Address: Centro Malattie Neuromuscolari, Department of Neuroscience, University of Turin, via Cherasco 15, 10126, Turin, Italy

Interest(s): Molecular genetics, clinical research, cell biology

Update: The people presently involved in my Center for Neuromuscular Diseases are, apart from me, Dr Tiziana Mongini who is a clinical neurologist also involved in research, Dr Ivana Bosone and Dr Simona Bortolotto who are Neurology residents, two PhD (Loredana Chiadò-Piat and Isabella Ugo) and one technician who are involved in the processing of muscle biopsies, immunohistochemistry, Western blotting, molecular biology. At the moment we haven't any special line of research on FSH, we follow FSH patients clinically, we made clinical evaluations and, if necessary, muscle biopsy. Genetic analysis of our patients with FSH is performed by Rossella Tupler with whom we are cooperating. We are now reexamining some FSH patients with the aim of beginning a clinical trial.

Recent Abstract from October 3, 2000 FSH Society FSHD workshop Philadelphia, PA USA: **Muscle apoptosis in humans occurs in normal and denervated muscle, but not in myotonic dystrophy, dystrophinopathies or inflammatory disease.**

Neurogenetics 1997 Sep;1(2):81-7
Migheli A, Mongini T, Doriguzzi C,

Chiado-Piat L, Piva R, Ugo I, Palmucci L
Department of Neuroscience, University of Turin, Italy.

Recent data suggest that death of muscle cells during development and in selected pathological conditions occurs via apoptosis. We investigated the occurrence of apoptosis in normal and pathological human skeletal muscle, using in situ end-labeling (ISEL) to detect DNA fragmentation, and immunohistochemistry for the expression of tissue transglutaminase and interleukin-1beta-converting enzyme (ICE)-like proteases. In normal subjects, apoptotic myonuclei were occasionally observed as evidence of normal tissue turnover. Myonuclear apoptosis due to a deficit of trophic support from nerve cells also occurred in spinal muscular atrophies. No apoptosis of muscle cells was found in dystrophinopathies, myotonic dystrophy and inflammatory myopathies, suggesting that death of myofibers in those conditions is not due to activation of a gene-directed program of death. In dystrophinopathies and inflammatory myopathies, apoptosis was found in interstitial mononuclear cells, as a likely mechanism of clearance of the inflammatory infiltrates.

**Dr. Palmucci has recently investigated apoptosis in FSH muscular dystrophy. Preliminary results suggest that apoptosis may occur in FSHD. This is in contrast to other types of muscular dystrophy and inflammatory muscle disease.*

TOKYO, JAPAN

Researcher(s): Yukiko K. Hayashi, Kiichi Arahata M.D. (Deceased), Toshifumi Tsukahara

Address: Department of Neuromuscular Research, National Institute of Neuroscience, NCNP, 4-1-1 Ogawa-higashi, Kodaira, Tokyo 187-8502, Japan

Interest(s): Molecular genetics, cell biology and clinical research

CHUNGBUK, KOREA

Researcher(s): Min Dong Song
Address: Department of Molecular Biology, Kon-Kuk University, KOREA, #322 Dan weol-dong, choongju, Chungbuk, 380-701, Korea

Interest(s): Molecular genetics and molecular biology

HOUTEN, THE NETHERLANDS

Researchers: C. Theo Verrips
Address: Stichting FSHD (Dutch FSHD Foundation), Bloementuin 6, 3994 ZP Houten, The Netherlands

Interest(s): Molecular genetics and clinical research

Researchers *continued*

LEIDEN, THE NETHERLANDS

Researcher(s): Oebo F. Brouwer

Address: Department of Neurology, University Hospital Leiden, P.O. Box 9600, 2300 RC Leiden, The Netherlands

Interest(s): Molecular genetics



Researcher(s): Egbert Bakker

Address: Leiden University Medical Center, Department of Human Genetics, Wassenaarseweg 72, 2333 AL Leiden, The Netherlands

Interest(s): Molecular genetics and genetic testing



Researcher(s): Rune Frants, Silvère van der Maarel, Marten Hofker, Silvana van Koningsbruggen, Petra van Overveld, Tonnie Rijkers, Richard JLF Lemmers

Address: Department of Human Genetics, Leiden University Medical Center, Wassenaarseweg 72, PO Box 9503, 2300 RA Leiden, The Netherlands

Interest(s): Molecular genetics, cell biology, clinical research, transgenic mice and genetic testing

Update: The Dutch FSHD research group in Leiden and Nijmegen has a long history of FSHD research, both in the clinical and genetic aspects of FSHD. The last year we have focussed on the mechanism by which the deletion occurs. We demonstrated that in at least 50% of individuals with new mutations, the rearrangement occurs after fertilization (somatic). As a result, these individuals have only in a proportion of cells the rearrangement, while the remainder of cells is healthy. This proportion may vary from 20-90% and females seem to exhibit a higher tolerance for disease cells than males. This finding has also important consequences for current risk factors.

From previous studies, we know that the repeats on chromosome 4 may be translocated to chromosome 10. This chromosome carries a highly homologous repeat array structure, and its homology is the basis for the repeat array exchanges we observe in 20% of the population. We now have additional evidence that individuals with translocated repeats from chromosome 4 on chromosome 10, have a higher chance on a rearrangement than individuals with non-translocated repeat arrays. For the first time, we have some insight in the factors that drive the deletion: likely the deletion occurs by a false interaction between identical, rather than highly homologous, repeat arrays on two chromosomes.

A large survey in the Dutch population taught us other aspects of these repeat arrays. It confirmed their dynamic behavior:

translocated repeat arrays are frequently found and also in this control population we found evidence for post-fertilization rearrangements, as described in the first paragraph. In contrast to FSHD, all these rearrangements did not result in FSHD-sized repeat arrays. Nevertheless, we also identified FSHD-sized repeats in apparently healthy individuals. Since these arrays were all in the upper FSHD-range, we hypothesized that there is a reduced penetrance for these larger FSHD-alleles.

In the course of these studies, we embarked on a new consistent DNA difference between chromosome 4 and chromosome 10 repeat units. Several years ago, such consistent DNA difference identified by the Italian group, greatly facilitated FSHD diagnosis since it enables discrimination between repeat units originating from both chromosomes. The difference that we identified recently, has opposite characteristics and we presented these data at the FSHD workshop in Philadelphia since we are convinced that it will make FSHD diagnosis even more reliable.

Two years ago and with support from the *FSH Society*, we initiated a project to generate mouse models for FSHD, which should be regarded as a long term investment. We are well on schedule and have generated several transgenic mice carrying various fragments of the human FSHD candidate region. Currently, these mice are in a breeding program and analyzed for their phenotype. We hope to report soon in more detail on this project.

In collaboration with Drs. Denise Foglewicz (Rochester, NY), Sara Winokur (Irvine, CA) and Theo Verrips (Unilever Research, The Netherlands), and with support of the Dutch Foundation FSHD, we have initiated a new project aiming at a better understanding of pathogenic processes that take place in FSHD. This project combines genomics and proteomics by monitoring RNA and protein in healthy and control tissue. Eventually, it is anticipated that this project will lead to a better understanding of the disease and to development of cellular and animal models to study FSHD.

We are thankful to the FSHD families for their strong commitment to our research activities and their patience. Thanks to the continuous financial support of national and international funding agencies (Prinses Beatrix Fonds, Gisela Thier Fonds, Dutch Foundation FSHD, MDA, and the *FSH Society*), we are able to continue our research activities.

Recent Abstract from October 3, 2000 *FSH Society* FSHD workshop Philadelphia, PA USA: **Methylation studies of the D4Z4 repeat in patients with muscular dystrophies**

Petra G.M. van Overveld1,*, Robert ten Hove1, Richard J.E.L. Lemmers1, Mariëlle

Wohlgemuth2, George W. Padberg2, Rune R. Frants1 and Silvère M. van der Maarel1, Department of Human and Clinical Genetics, Leiden University Medical Center, Leiden, The Netherlands, Department of Neurology, University of Nijmegen, Nijmegen, The Netherlands

*presenting author

It has long been hypothesized that the partial D4Z4 repeat array deletion in FSHD may exert a position effect on nearby genes by unknown chromatin alterations. To prove this hypothesis, we developed a test to study the methylation of affected and unaffected individuals by a combination of (methylation-sensitive) restriction enzymes and the probe p13E-11. This combination allows the analysis of D4Z4 repeats without the interference of homologous repeat units on chromosome 10 or other loci in the genome.

Analysis of a small set of individuals (three FSHD patients, three controls and one Duchenne muscular dystrophy (DMD) patient) demonstrates a differential methylation of the D4Z4 repeat in these individuals. It further supports the hypothesis that partial deletions of the D4Z4 repeat array may result in a mild hypomethylation of the D4Z4 repeat array. Interestingly, also the DMD patient shows a marked hypomethylation of the D4Z4 repeat array suggesting that common factors between both dystrophies may (also) result in a hypomethylated D4Z4 repeat. Studies are ongoing to verify the differential methylation of D4Z4 repeat arrays in FSHD individuals, individuals with other muscular dystrophies and controls.

Recent Abstract from October 3, 2000 *FSH Society* FSHD workshop Philadelphia, PA USA: **XapI improves diagnosis of facioscapulohumeral muscular dystrophy (FSHD).**

Richard JLF Lemmers1, Peggy de Kievit1, Michel van Geel2, Michiel JR van der Wielen1, Egbert Bakker1, George W Padberg3, Rune R Frants1 and Silvère M van der Maarel1

**presenting author

1. Department of Human and Clinical Genetics, Leiden University Medical Center, Leiden, The Netherlands
2. Roswell Park Cancer Institute, Buffalo, USA
3. Department of Neurology, University Hospital Nijmegen, Nijmegen, The Netherlands

Genetic diagnosis of FSHD is based on sizing of the polymorphic *EcoRI* fragment on which the D4Z4 repeat array resides. This is complicated by the co-hybridizing homologous repeat array on chromosome 10 which is also polymorphic and may vary between 1 and

Researchers *continued*

>150 units without pathological consequences. Chromosome 10-derived repeat units are -in contrast to chromosome 4-derived repeat units- sensitive to *BlnI* allowing chromosome-specific allele discrimination. However, frequent translocations of 4-type repeat arrays to chromosome 10 and vice versa, and hybrid arrays consisting of clusters of 4-type and 10-type repeat units further compromises FSHD diagnosis.

Here, we have used *XapI* to further optimize FSHD diagnosis. It displays opposite characteristics of *BlnI* by uniquely digesting 4-type repeat units and leaving 10-type repeat units undigested. Use of the combination *EcoRI*, *EcoRI/BlnI* and *XapI* unequivocally allows characterization of each allele, whether homogeneous or hybrid. This is particularly useful in case of co-migrating 4-type and 10-type alleles, for the assignment of hybrid fragments to their original alleles and in case of suspected FSHD with non-standard allele configurations as demonstrated by the exclusion of one patient carrying an apparently short hybrid repeat array. We strongly advocate the routine use of *XapI* in FSHD diagnosis.

Recent Abstract from October 3, 2000 FSH Society FSHD workshop Philadelphia, PA USA: **Frequent interchromosomal repeat array interactions between chromosomes 4 and 10: a model for subtelomeric plasticity**

Petra G.M. van Overveld (1)*, Richard J.F.L. Lemmers (1), Giancarlo Deidda (1, 2), Lodewijk Sandkuijl (1), George W. Padberg (3), Rune R. Frants (1) and Silvere M. van der Maarel (1)

*presenting author

(1) Department of Human and Clinical Genetics, Leiden University Medical Center, Leiden, The Netherlands (2) National Research Council, Rome, Italy (3) Department of Neurology, University of Nijmegen, Nijmegen, The Netherlands.

To further elucidate the plasticity of subtelomeric D4Z4 domains, we examined the 3.3kb repeat array on chromosome 4 and its homologue on chromosome 10 in 208 Dutch blood donors by pulsed field gel electrophoresis. Previous studies in *de novo* FSHD kindreds demonstrated a frequent mitotic origin of the partial repeat array deletion associated with FSHD. This survey shows that mitotic rearrangements occur frequently since 3% of individuals display somatic mosaicism for a repeat expansion or contraction explaining the high variability of subtelomeric repeat array sizes. In agreement with our study in 50 healthy males, translocated 4-type repeat arrays on chromosome 10 and the reverse configuration of 10-type repeat arrays on chromosome 4 are observed in 24% of individuals. However, the

translocated repeat arrays on chromosome 4 tend to be more heterogeneous (i.e. composed of 4-type and 10-type units) than 4-type repeats on chromosome 10.

The repeat length on chromosome 4 is on average larger than on chromosome 10. But, on both chromosomes we observe a multimodal repeat length distribution with equidistant peaks at intervals of 65kb, possibly reflecting a higher order chromatin structure. Interestingly, in as many as six random blood donors (3%) we identified FSHD-sized 4-type repeat arrays. Assuming that these individuals are clinically unaffected, these results imply an incomplete penetrance in the upper range of FSHD alleles. Overall, the observed dynamic characteristics of these homologous domains may serve as a model for subtelomeric plasticity.

Recent Abstract from October 3, 2000 FSH Society FSHD workshop Philadelphia, PA USA: **C2C12-based model systems to study the biological role of FSHD candidate genes**

S. van Koningsbruggen (1)*, G. Deidda (2), R.W. Dirks (3), A.M. Mommaas (4), J. Onderwater (4), G.W. Padberg (5), R.R. Frants (1), S.M. van der Maarel (1)

*presenting author

(1) Department of Human and Clinical Genetics, Leiden University Medical Center, Leiden, The Netherlands; (2) Institute of Cell Biology, CNR, Rome, Italy; (3) Department of Molecular Cell Biology, Leiden University Medical Center, Leiden, The Netherlands; (4) Center for Electron Microscopy, Leiden University Medical Center, Leiden, The Netherlands; (5) Department of Neurology, University Hospital Nijmegen, Nijmegen, The Netherlands.

There is increasing evidence that FSHD is caused by the regional transcriptional relaxation of chromosome 4qter, as indicated by for example the transcriptional up-regulation of *FRG1* in primary myoblast cultures of FSHD patients. Although *FRG1* is closely localized to the D4Z4 repeat and the *FRG1P* protein is highly conserved between vertebrates and non-vertebrates, its function and potential involvement in FSHD pathology is still unknown. Therefore, we generated polyclonal and monoclonal antibodies against *FRG1P*. Currently, these antibodies are able to identify the transfected protein, but detection of endogenous *FRG1P* is still troublesome. Thus, to obtain more insight in the biological role of *FRG1P*, we studied the subcellular localization in transiently transfected cell lines such as U2OS, COS-1, and rhabdomyosarcoma. *FRG1P* is localized in the nucleoli, speckles and Cajal bodies, suggestive for a dynamic interplay between these three nuclear components.

Since nucleoli can easily be studied in U2OS cells, we stably transfected this cell line to study the localization of *FRG1P* in time and during cell cyclus. Moreover, C2C12, a murine cell line capable to differentiate in myotubes by serum starvation, is a suitable model to study the myogenic properties of our candidate genes. Recently, we succeeded to transiently transfect C2C12 cells in which we confirmed the subnuclear localization of *FRG1P*. The generation of stably transfected C2C12 cell lines will allow the study of *FRG1P* during differentiation. These studies will give us clues for the possible function of *FRG1P* and its involvement in FSHD pathogenesis.

NIJMEGEN, THE NETHERLANDS

Researchers: George W.A.M. Padberg, Oscar J.M. Vogels, Elly L. van der Kooi, Marielle Wohlgenuth

Address: University Hospital Nijmegen, Department of Neurology, Reinier Postlaan 4, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands

Interest(s): Molecular genetics, clinical research, rehabilitation and exercise

Note: Please see article on *Salbutamol* (*Albuterol*) on page 29-30.

Update: Strength Training in Facioscapulohumeral Muscular Dystrophy
EL van der Kooi1, OJM Vogels1, RJGP van Asseldonk1, E Lindeman2, JC Hendriks3, GW Padberg1

1Neuromuscular Centre Nijmegen, University Medical Centre Nijmegen, The Netherlands

2Rehabilitation Centre 'de Hoogstraat', University Hospital Utrecht, The Netherlands
3Department of Medical Statistics, University Medical Centre Nijmegen, The Netherlands

Corresponding author: EL van der Kooi, Neuromuscular Centre Nijmegen, University Medical Centre Nijmegen, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands

Study supported by: The Netherlands Organization for Scientific Research (NWO) and the Prinses Beatrix Fonds

Objective: To evaluate the efficacy of moderate severe, progressive strength training on skeletal muscle strength, fatigue and muscle mass in patients with facioscapulohumeral muscular dystrophy (FSHD). Secondary goal is to study the influence of training on impairments, disabilities, and handicap.

Background: Decline in muscle strength and mass in FSHD is slowly progressive with large intra- and inter-individual variability. Factors that determine the course of this disorder are largely unknown: genetic and environmental factors are postulated. A factor might be to what extent dystrophic muscles are

Researchers *continued*

(over)used. Observed asymmetric weakness led to the hypothesis that even daily occupations might accelerate progression of muscle weakness. In contrast, some studies on the effect of strength training in neuromuscular patients reported moderate positive effects on muscle strength in the few participating FSHD patients. Due to the small number of FSHD patients (13 in four trials) and the variety in design of the training programs no general conclusions could be drawn. In fact, the effect of physical stress on muscles in FSHD is still uncertain. Therefore, patients can not be given well-founded advice regarding work, sports and other forms of exertion.

Design/Methods: Seventy genetically confirmed, eligible FSHD patients were evenly assigned by randomization to a training (TG) or non-training group (NTG). The TG participated in a moderate, progressive strength training program, focussing on elbow flexors and ankle dorsiflexors. The program consisted of mainly dynamic and a few static exercises. Exercises were carried out at home, three times a week for 26 weeks. Every third week the participants were visited by a physiotherapist to optimize training. The NTG was instructed to continue their usual amount of physical activity. Primary outcome measures were muscle strength and mass. Measures used for static strength were maximum voluntary isometric strength (MF) and 30 seconds sustained strength (SF). One-repetitive maximum (1-RM) was used as a measure for dynamic strength. Muscle mass was estimated by a stereologic CT method.

Results: Training was well tolerated. No serious complaints or injuries occurred. For right elbow flexors MF, SF, and 1-RM increased 1, 4, and 29% in the TG versus a 4% (MF) decrease, and 2% (SF) and 8% (1-RM) increase in the NTG. For right ankle dorsiflexors MF, SF and 1-RM showed +2%(MF), -3% (SF) and -26% (1-RM) after training versus -5% (MF), -2% (SF) and -19% (1-RM) in the NTG. Only the 29 versus 8% gain in 1-RM of the elbow flexors proved to be significant. Left side results were comparable. Data on muscle mass, impairments (particularly pain and fatigue), disabilities, and handicap are being currently being analyzed.

Conclusions: In FSHD patients moderate severe, mainly dynamic strength training can result in very specific, moderate gain of dynamic strength, with less generalization to other muscle strength modalities as compared to healthy individuals. No deleterious effects were seen in our training set-up, but monitoring should be advised when starting new forms of moderate intensive physical exertion.

Recent Abstract of Publication: J Neuro

Neurosurg Psychiatry 2000 Jul;69(1):114-6

Extension of the clinical range of facioscapulohumeral dystrophy: report of six cases.

van der Kooij AJ, Visser MC, Rosenberg N, van den Berg-Vos R, Wokke JH, Bakker E, de Visser M

Department of Neurology, Academic Medical Center, University of Amsterdam, The Netherlands.

Consensual diagnostic criteria for facioscapulohumeral dystrophy (FSHD) include onset of the disease in facial or shoulder girdle muscles, facial weakness in more than 50% of affected family members, autosomal dominant inheritance in familial cases, and evidence of myopathic disease in at least one affected member without biopsy features specific to alternative diagnoses. Six patients did not meet most of these criteria but were diagnosed as FSHD by DNA testing, which showed small EcoRI fragments on chromosome 4q. Their clinical signs and symptoms and results of auxiliary investigations are reported. The patients presented with foot extensor, thigh, or calf muscle weakness. None of them had apparent facial weakness, only one complained of weakness in the shoulders, none had a positive family history. Expert physical examination, however, showed a typical facial expression, an abnormal shoulder configuration on lifting the arms, or scapular winging. This raised the suspicion of FSHD, whereupon DNA analysis was done. In conclusion, the clinical expression of FSHD is much broader than indicated by the nomenclature. The possibility to perform DNA tests is likely to greatly expand the clinical range of FSHD. PMID: 10864616

ST. PETERSBURG, RUSSIA

Researcher(s): Valery M. Kazakov, Dimitry Rudenko

Address: Department of Neurology, Pavlov's Medical Institute, Lev Tolstoy str. 6/8, 197089, St., Petersburg, Russia

Interest(s): Clinical genetics and clinical research

Update: Facioscapulohumeral muscular dystrophy, type 2 (FSLD2) (the same as a facioscapulohumeral form of FSHD) in Russian families. Clinical aspects of the phenotype/genotype. Preliminary data.

V. Kazakov1, D. Rudenko1, E. Katsev1, H. Sugita2, K. Goto2, M. Funakoshi2, K. Arahata2

1Department of Neurology, Pavlov State Medical University of St. Petersburg, St. Petersburg, Russia and 2Department of Neuromuscular Research, National Institute of

Neuroscience, NCNP, Tokyo, Japan

In 12 Russian AD FSLD2 families in 33 affected members the probe p13E-11 detected EcoRI/BlnI of DNA fragments size (DFS) between 16-38 kb co-segregated with the disease and linked with 4q35. In 10 families (28 patients) DFS was less than 28 kb (range 16-27 kb) in all symptomatic and presymptomatic (Pr) patients. In two other families (five men) in all symptomatic and Pr patients DFS of 35 and 38 kb was found, respectively.

In all described families which had the same DFS (in seven symptomatic patients it was 23 kb and in other five symptomatic and one Pr it was 27 kb) or different ones (in 10 symptomatic and five Pr it was 16, 17, 20, 22 and 25 kb) and in two other families (three symptomatic and two Pr) with DFS 35 and 38 kb, respectively we observed the similar clinical variability of phenotypes (pattern of muscle involvement), the severity of the disease and daily-life work disability (DLWD) between the patients belonging both to the same family and to the different ones that is within and between families. We didn't find a correlation between DFS and the phenotype, DFS and severity of the disease, DFS and DLWD as well as between DFS and the dynamics of phenotype and severity of the disease and DLWD of seven patients after 24-28 years. A correlation between DFS and the age at onset of the disease, DFS and uptake ratio of radioisotope in muscles was weak and not significant.

We examined clinically and genetically a homogeneous (4q35 linked) group with a great similarity of clinical manifestations between the members of the families. The same muscles and muscle groups were affected. The disease began with the weakness of the facial and shoulder girdle muscles with subsequent involvement of the peroneal group (anterior tibial), proximal parts of the lower limb (posterior group of the thigh), pelvic girdle (gluteus maximus), and not always the upper arm (biceps brachii) muscles. In 10 of 25 symptomatic patients the biceps brachii muscle was weakened in slight degree on one side, only. In the other 11 patients these muscles were preserved although the disease started from childhood. The distribution of the muscular weakness in the members of the families did not overstep the limits of the descending with a "jump" type of the development of the disease. In all the patients the FSP or the (F)SP phenotypes predominated in clinical picture at the different stages of the disease. The received data confirm that the probe p13E-11 can be used for detecting DFS between 16-38 kb (double digestion method) for FSLD2 which

Researchers *continued*

are assigned with chromosome 4q35.

The opinion exists that the sporadic SP forms of FSHD are associated with DFS ranging between 22 to 28 kb (Pou et al., 1999) or between 28 to 35 kb on 4q35 (double digestion method) and represent the mild end of the spectrum of FSHD (Attarian et al., 1999).

However, in patients with typical FSHD the 4q35-linked EcoRI fragment detected by p13E-11 is usually shorter than 40 kb, as well (Padberg, Lunt, Koch, Fardeau, 1997).

Thus it happened so that the FSLD2 and the SP form of FSHD with minimal affection of mimic muscles (if it exists) are "absorbed" by FSHD taking into consideration the DFS. That is why we suppose that the detected DFS cannot be the criterion for establishing the genetic heterogeneity of FSHD. This problem can be finally solved only after the identification of the FSHD genes and characterization of the gene products.

Key words: facioscapulohumeral muscular dystrophy; 4q35; correlations

Letter to the Editor:

What is myopathology: is it the reality or author's personal opinions? (About priority in describing the primary muscle diseases.)

V. Kazakov, Department of Neurology, I. P. Pavlov State Medical University of St. Petersburg, St. Petersburg, Russia

In medical literature on the neuromuscular diseases one may trace the tendency between doctors from different countries transferring the priority of the describing of the primary diseases of muscle i.e. the myopathy from one side to another.

Duchenne in 1848 together with Cruveilhier made the autopsy and microscopic investigations of brain, spinal cord, muscles and nerves including intra-muscular ones in patient Legrand aged 18 with severe affection of the mimic, trunk and limb muscles. The central and peripheral nervous system remained unchanged. The reason of the disease was in the affection of muscles themselves in the majority of which the different stage of fatty transformation was noticed. Duchenne called this new disease "Muscular atrophy with fatty degeneration of muscle" and stressed that muscular atrophy with fatty degeneration could occur without the affection of spinal cord and peripheral nerves. He sent his work, "Muscular atrophy with fatty degeneration," as a competitive one to the French Academy of Sciences and Archives Générales de Médecine on 21 May 1849 (1). This case together with other Duchenne's cases was published by Aran in 1850 (2) and then by Cruveilhier in 1852/1853 (3).

Duchenne (4) in 1849 described three

types of muscular atrophy with changes in the structure of muscle fibres and their transformation into fatty tissue. The first and second types were called "atrophic fatty paralysis." The third type of muscular atrophy which was due to impairment of the nutrition of muscle fibres themselves and in which the muscle weakness appears as a result of the decrease and fatty degeneration of muscle fibres was called by Duchenne "the fatty muscular atrophy or the muscular atrophy with fatty transformation of muscles." This very new and unique type of muscular atrophy was suggested by Duchenne to distinguish it as a special nosological entity.

Meryon in 1851 did the autopsy with microscopic study in patient G.H.P. aged 17 with severe affection of pelvic girdle and shoulder girdle as well as the leg and arm muscles. The brain, and the spinal cord as well as the communicating nerves and the nerves of organic life were perfectly healthy. Microscopic examination of the muscles showed predominantly the fatty and granular degeneration of muscle fibres with destruction of their sarcolemma. Meryon called this disease "Fatty degeneration of the voluntary muscle" (5). This case and other ones was published again in 1852 under the title "On granular and fatty degeneration of the voluntary muscles" (6).

In 1868 Duchenne (7) after careful analysis of Meryon's work (6) wrote: "In this paper Meryon affirms the priority of the discovery of progressive muscular atrophy with fatty degeneration of muscle. However, the honour of the discovery of this disease primarily belongs to France. This is one of some historical questions which is being discussed to day. In May 1849 I have sent my paper to the Academy of Sciences in which on the basis of numerous clinical investigations having collected during many years in the hospitals of Paris I was the first to discover the existence of this disease which I called "muscular atrophy with fatty transformation of muscles." Later, I gave my cases to Aran who published them in Archives Générales de Médecine in 1850 under the title "progressive muscular atrophy taking into consideration my opinion to some extent."

Interestingly, at the same time the English doctors expressed another point of view on the priority of describing the primary diseases of muscle.

For example, Dr. Meryon (1866) (8) reported in Royal Medical and Chirurgical Society about two new cases with granular degeneration of the voluntary muscles. The materials of this Society say, "In conclusion, Dr. Meryon adverted to the question of priority of description of this peculiar form of disease. He

quoted passages from several of the French medical periodicals in relation to this matter. It is unnecessary to report these, though the following fact may be mentioned that at the Academy of Medicine M. Cruveilhier referred to Dr. Meryon's plates in illustration of his (M. Cruveilhier's) own diseased muscles, and called the attention of the Academy to a form of paralysis "non encore décrite" (not described yet -V.K). Dr. Meryon's paper had been published in The Lancet more than a year before, and shortly afterwards appeared also in Society's Transactions."

Dr. Webster, a member of Royal Medical and Chirurgical Society, who listened to Dr. Meryon's cases said: "In reference to the author's statement regarding a recent speaker at the Paris Academy of Medicine, who had claimed the merit of being the first to notice the malady now under discussion, it should be remembered that French medical men rarely read English periodicals and seldom speak the language; . . . Therefore Dr. Meryon need not deem it strange whenever any French observer thinks himself an original discoverer, seeing the circumstances above related may perhaps furnish a satisfactory explanation of the assumption narrated" (8).

It should be noted that the same tendencies may be traced in neuromuscular literature at the present time on the priority of the description of primary diseases of muscle, in general and some types of them, in particular. In the recent article called "Some contributions of Duchenne de Boulogne (1806-75)" (9) we may read: His epitaph we can leave to Charcot who remarked, "How is it that one fine morning Duchenne discovered a disease that probably existed in the time of Hippocrates? Why do we realize things so late, so poorly, with such difficulty . . . because our minds have to take in something that upsets our original set of ideas . . ." However, the author then adds in postscript: "Edward Meryon (1807-) presented a paper to the Royal Medico-chirurgical society on 9 December 1851, which described two typical 'Duchenne' families and one with Becker type dystrophy. He recognized them as primary diseases of muscle and showed postmortem the typical 'granular degeneration.'"

Earlier, the similar opinion was expressed by A. Emery and M. Emery " . . . Meryon made the first systematic clinical and pathological study of the type of dystrophy with whose name Duchenne is usually associated" (10).

However, it is necessary to remark, that Meryon himself did not insist on referring to his cases as pseudohypertrophic paralysis even in 1870 when this disease had been distinguished as nosological entity by

Researchers *continued*

Duchenne and, moreover, Meryon insisted on his priority in describing the new peculiar form of "granular and fatty degeneration of voluntary muscles" in 1851 (11).

Interestingly as well, that Duchenne (7) supposed that Meryon's cases closely resemble the early stage of his own disease but they are not the same as pseudohypertrophic paralysis and differ from it in some clinical and pathological muscle peculiarities.

Also, in Roth's "Muscular tables" (12) as well as in the recent investigation (13) doubts were expressed about possibility of attributing Meryon's cases to pseudohypertrophy. It is well known as well it was Duchenne (1868) (7) who had the priority in distinguishing the pseudohypertrophic muscular dystrophy as a clinical entity in the chaos of muscular atrophies, in defining it as a childhood hereditary disease occurring prevalently in males, in describing all the clinical peculiarities reflecting the different stages of this disease, in carrying out the differential diagnosis from other muscular atrophies of childhood and in discovering the characteristic histological muscle changes.

Moreover, it is well known that the detailed muscular clinical picture with the characteristic pseudohypertrophic muscle pattern and affection of the cardiac muscle of the pseudohypertrophic muscular dystrophy was described for the first time by G. Conte and L. Gioia in 1836 (12-14) and this fact was confirmed by English neurologists V. Dubowitz and A. Emery who together with G. Nigro established the memorial plaque in honour of Gaetano Conte of 28 May 1998 on the grounds of the old Ospedale degli Incurabili in Naples.

However, the name of Meryon's disease instead of Duchenne pseudohypertrophic muscular dystrophy becomes more popular and the priority in discovering the primary muscle diseases is ascribed to Meryon.

Meanwhile, it is impossible to forget that when Meryon from 1851 until 1868 published his small papers on granular and fatty degeneration of the voluntary muscles with short description of the individual cases, at the same time on the basis a large clinical observations using the thorough clinical and electrical examination of the separate muscle and muscle groups, electrodiagnostics, data of autopsy and biopsy, electrical and orthopedic treatment published some world-famous books on neuromuscular diseases, such as: 1. Local electrification, 1855, 1861; 2. Physiological Orthopedics, 1857; 3. The mechanism of human facial expression, 1862 and 4. Physiology of movements, 1867. Not accidentally Charcot (1885) (16) called Duchenne de Boulogne the Great Artist in

neuro-nosography and Roth later (1895) (12) wrote "It was Duchenne who began to distinguish one after another the different and strictly isolated diseases in the chaos of muscular atrophies."

By 1862 Duchenne was elected a Member correspondent of many Academies, Universities and Societies of Medicine, for examples: Moscow, Saint-Petersburg, Kieff (Russia), Rome, Naples, Florence, (Italy), Dresden, Wurtzbourg, Leipzig (Germany), Madrid (Spain), Stockholm (Sweden), Vienna (Austria), Geneva (Switzerland), Paris (France) and others (17).

Actually, Duchenne is a founder of neuromuscular diseases study and he is the first who discovered the primary and secondary diseases of muscle. That is why in many Encyclopedias of different countries ahead the name Duchenne de Boulogne as a rule stands the word Great i.e. Great Duchenne de Boulogne.

PRETORIA, SOUTH AFRICA

Researcher(s): Antonel Olckers, Engela Honey, Clara Schutte, Annelize van der Merwe

Address: Department of Human Genetics, University of Pretoria, P.O. Box 2034, Pretoria, 0001: South Africa

Interest(s): Molecular genetics, molecular biology, clinical and genetic testing

Update: The South African FSHD research team is as follows:

Antonel Olckers, PhD, Head: Molecular Biology Unit; Engela Honey, MBChB, Clinical Geneticist, Department of Human Genetics
Clara Schutte, MBChB, Acting Head: Department of Neurology; Annelize van der Merwe, Research Assistant, Department of Human Genetics

Recent Abstract from October 3, 2000 FSH Society FSHD workshop Philadelphia, PA USA: **Segregation of DNA rearrangements at the D4Z4 locus in South African FSHD families**

A. Olckers¹, A. van der Merwe², S.M. van der Maarel², R.R. Frants² and C.-M. Schutte³.

¹Dept. of Human Genetics, University of Pretoria; South Africa; ²Dept. of Human Genetics, Leiden University Medical Centre, The Netherlands; ³Dept. of Neurology, University of Pretoria, South Africa;

This study is the first to investigate the polymorphic rearrangement at the FSHD locus on 4q35 within the South African population, via the use of probe p13-E11.

The segregation of two distinct FSHD associated haplotypes has been reported in the South African population. In addition, no FSHD associated haplotype was observed in

one family, F40. The absence of linkage in this family to the 4q35 region could, however, not be substantiated via haplotype analysis alone.

Results of Southern Blot analysis in these families are reported here. For the first time, FSHD was confirmed in the families investigated - via the presence of a deletion fragment at the D4Z4 locus. One recombination event between the designated "FSHD haplotype" and the observed deletion fragment was confirmed in family F30. No FSHD associated haplotype was observed in family F40. However, the presence of a deletion fragment was verified in several affected individuals from this family.

Based on Southern Blot analysis at the D4Z4 locus, with probe p13-E11, it is evident that all the South African FSHD families investigated to date display linkage to this FSHD locus on chromosome 4q35.

United States of America

DAVIS, CALIFORNIA

Researcher(s): K. Devereaux; D.D. Kilmer; R.T. Abresch; S.G. Aitkens; G.T. Carter; W.M. Fowler; E.R. Johnson; J. Wright

Address: Research and Training Center on Neuromuscular Disease, Department of Physical Medicine and Rehabilitation, University of California, Davis, TB 191, Davis, CA 95616-8665; and National Institute on Disability and Rehabilitation Research (NIDRR)

Interest(s): Rehabilitation, Occupational and Clinical

IRVINE, CALIFORNIA

Researcher(s): Sara T. Winokur, Mariella Simon, Jeff Ehmsen, George Martin, Michael Altherr*

Address: University of California, Irvine, School of Medicine, Department of Biological Chemistry, 240 D, Medical Science Institute, Irvine CA 92697-1700

Interest(s): Molecular genetics, cell biology, gene and protein microarray chip technologies

Notes: *Michael Altherr is currently with the Genomics and Structural Biology Group, LANL, Los Alamos, NM

Recent Abstract from October 3, 2000 FSH Society FSHD workshop Philadelphia, PA USA: **An update on FSHD microarray and SMT7/LIM gene expression analysis.**

Sara T. Winokur¹, Jeffrey T. Ehmsen¹, Jorge H. Martin¹ Michael R. Altherr², Thomas Brettin² and Kevin Flanigan³.

¹Department of Biological Chemistry,

Researchers *continued*

University of California, Irvine, CA
2McClintock Resource, Los Alamos National
Laboratory, Los Alamos, NM
3Eccles Institute of Genetics, University of
Utah, Salt Lake City, UT

Facioscapulohumeral muscular dystrophy (FSHD) is an autosomal dominant neuromuscular disorder resulting from integral deletions of a 3.3 kb tandem repeat in the subtelomeric of chromosome 4q. This deletion is believed to disrupt chromatin structure in the region, with consequent deregulation of gene expression. We have embarked on global gene expression profiling in FSHD through the use of both GeneChip and cDNA microarrays. Examination of undifferentiated myoblasts revealed disturbances in resistance to oxidative stress and in extracellular matrix components. All primary data from these experiments was recently posted on the web site;

<http://www.genomics.uci.edu> in a collaborative effort with the gene expression database at Los Alamos National Laboratory. Currently, we are generating expression profiles of adult muscle from biopsies of FSHD, normal and disease control tissue. Preliminary analysis reveals a consistent upregulation of a muscle LIM protein. This is of interest, as another muscle LIM protein, actinin-associated LIM protein (ALP) maps to chromosome 4q35. In addition, we have identified several transcripts encoding isoforms of ALP. One of these transcripts was previously termed SMT7. These transcripts are missing the carboxy terminus LIM domain of ALP and have a novel, long (3.5 kb) 3' UTR. Other members of this class of proteins (e.g. Cypher2/ZASP1 and the enigma homolog ENZ) also encode multiple functional isoforms which lack the LIM domain of the full length transcript. These splice variants are believed to negatively modulate the activity of the full-length protein through competitive binding to cytoskeletal proteins in the disk region. We therefore continue to investigate the potential role of ALP/SMT7 isoforms and the upregulated muscle LIM protein in FSHD. In addition, we are using Taqman assays to confirm increased expression levels of the muscle LIM protein (revealed by GeneChip analysis) and to examine ALP/SMT7 variant expression levels in a large panel of FSHD and control muscle.

Supported by an FSH Society, Inc. fellowship (STW), a grant from the Muscular Dystrophy Association (STW) and a University of California/Los Alamos Cooperative Grant (CULAR) (STW and MRA).

SAN FRANCISCO, CALIFORNIA

Researcher(s): David S. Bredt

Address: Department of Physiology, University of California, San Francisco, School of Medicine, Box 0444 Room S-859, 513 Parnasus Avenue, San Francisco, CA 94143-0444

Interest(s): Molecular Genetics, Actinin associated LIM protein (ALP) and facioscapulohumeral (FSH) muscular dystrophy.

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Researcher(s): Clay Bunn

Address: Department of Physiology, Box 0444 Room S-154, University of California, San Francisco, School of Medicine, 513 Parnasus Avenue, San Francisco, CA 94143

Interest(s): Molecular Genetics, Actinin associated LIM protein (ALP) and facioscapulohumeral (FSH) muscular dystrophy.

FARMINGTON, CONNECTICUT

Researcher(s): Kevin Felice

Address: Department of Neurology, University of Connecticut Health Center, 263 Farmington Ave., Farmington, CT 06030-2925

Interest(s): Molecular genetics and clinical research

Recent Publication Abstract: Neurology 2000 May 23;54(10):1927-31

FSH dystrophy 4q35 deletion in patients presenting with facial-sparing scapular myopathy.

Felice KJ, North WA, Moore SA, Mathews KD Department of Neurology, University of Connecticut School of Medicine, Farmington 06030-1840, USA.

Objective: To evaluate the incidence of the facioscapulohumeral dystrophy (FSHD) 4q35 deletion in patients with facial-sparing scapular myopathy.

Background: Scapular winging is typical of FSHD but may also be prominent in other muscle disorders including scapulooperoneal syndromes. With DNA testing, it is possible to determine if patients with facial-sparing scapular myopathy have FSHD.

Methods: Fourteen of 17 unrelated patients with facial-sparing scapular myopathy, seen over a seven-year period at a regional neuromuscular center, agreed to have DNA testing for FSHD. The clinical and laboratory features of these patients were also noted.

Results: Of the 14 patients, 10 (71%) had restriction fragments consistent with the 4q35 deletion. The mean size of the smaller fragment following EcoRI digestion was 29.5 kb (range 20 to 39). The mean age at onset was 19.9 years; at presentation, 44.7 years. Except for the absence of facial weakness, most patients had clinical and laboratory features otherwise consistent with FSHD. Five

patients (50%) had a positive family history of similar weakness. Following removal of outliers, the Pearson correlation coefficient (r) value between EcoRI fragment size and age at onset was 0.64, and between fragment size and limb muscle strength, 0.64.

Conclusion: The FSHD 4q35 deletion was found in 71% of the facial-sparing scapular myopathy patients. They otherwise resemble typical FSHD patients in age at onset, physical characteristics, and association between fragment size and disease severity. PMID: 10822431

CHICAGO, ILLINOIS

Researcher(s): Anthony A. Romeo

Address: Rush Arthritis and Orthopedics Institute, 1725 West Harrison Avenue, Suite 1063, Chicago, IL 60612

Interest(s): Orthopedic Surgery, Scapulothoracic fusion, clinical and genetic research

Update: Title: Evaluation of Muscle Abnormalities in Facioscapulohumeral Dystrophy

Introduction: You are being asked to participate in a research study that will be coordinated at Rush Presbyterian St. Luke's Medical Center in Chicago, Illinois. You are being asked to participate because you have the known diagnosis of Facioscapulohumeral Dystrophy (FSHD) and you are undergoing a surgical stabilization (fusion) of the scapula (shoulder blade) to the chest wall (ribs). During this procedure, muscle must be removed from between the scapula and the ribs. This muscle tissue is normally discarded. However the histological and biochemical analysis of this muscle tissue may provide further insight into the mechanism of disease which results in the clinical syndrome of FSHD.

Purpose and Procedure of the Study:

This study involved research. The purpose of this research is to create a repository of muscle tissue that can be used by the most advanced research centers investigating the underlying ideology of FSHD which may lead to new treatments for patients with FSHD. If you agree to participate, you will undergo a thorough history and clinical examination to define the characteristics of your FSHD. For most patients, this information has already been collected by your treating physician. Furthermore, you will donate one tube of blood which will be used for DNA analysis to define the genetic characteristics of your FSHD. Finally, during the stabilization of your scapula (shoulder blade) to your ribs, the muscle that must be excised to allow for a successful fusion of the scapula to the ribs will

Researchers *continued*

be collected and deposited in a repository which will be a resource for researchers looking into the ideology and potential treatment of FSHD. This process collecting one tube of blood as well as the muscle specimen will be done during your surgical procedure and does not require any added effort on your behalf. At this time, a follow-up examination based specifically on this study is not intended. If there are unique patterns either to the genetic characteristics of your FSHD or the muscle sample, you may be contacted for further information regarding the progression of your symptoms related to your FSHD. Approximately 50 subjects will be enrolled in the study but the repository will continue to grow and become an international resource for tissue samples.

Potential Risks: There are no additional risks to you for participating in the study. The removal of muscle is a standard part of the procedure to fuse the scapula to the ribs. Drawing one tube (10 ccs) of blood is also a common part of surgical treatment.

Possible Benefit: At this time, there are no direct benefits to you for participating in the study other than contributing to the continued investigation of the cause of FSHD which is anticipated will lead to new methods for slowing the progression of the muscular dystrophy and possibly even treating the FSHD. The tissue and blood samples from the study will be used to determine whether there are specific histological or biochemical markers or proteins that may lead to the gradual deterioration of muscle function. Your participation will benefit the physicians and researchers who are trying to improve our understanding of FSHD and in the future will also benefit patients with the diagnosis of FSHD with possible treatment to prevent progression and possibly even lead to a cure for FSHD.

Alternatives to Participation: Instead of participating in this study you have the option to not participate. Your care will not be affected in any way. The surgical procedure and your continued management will be the same as if you had participated in the study.

Cost and Compensation: The cost of the additional laboratory tests, collection of the muscle samples and depositing them into a repository as well as processing them for multiple research centers will be covered by research funding. All costs that are part of your usual medical care will be charged to you or your insurance company. As is normally the case, you will be responsible for all costs for your usual medical care if not paid for by your insurance. You will not be paid for your participation in this study.

Voluntary Participation: All participation is voluntary. There is no penalty to anyone who does not decide to participate. Nor will anyone be penalized if he or she decides to stop participation or removed from any aspect of this research project.

Research Related Injuries: If a physical injury results from your participation in the study, immediate and necessary care will be provided however there is no provision for free medical care or compensation for such an injury from Rush Presbyterian St. Luke's Medical Center or any of the other participating medical centers. The cost for emergency care will be charged to you or your insurance company. You do not waive any legal rights by signing this form.

Confidentiality: To protect your privacy your name, initials, medical record number or any other identifying information will be coded so that your history and physical examination, your blood sample, and your muscle tissue can all be identified as coming from the same individual. However the code will not allow researchers to identify you by name to maintain your privacy. All results from this study will be reported as a group so that no single individual will be identifiable. Records of participation in this study will be maintained and kept confidential to the extent permitted by law. The study investigators, the Rush Institutional Review Board (the board in charge of the protection of human subjects involved in research), and regulatory agencies such as the National Institute for Health may have access to study files for auditing purposes.

Questions: Questions about this study are encouraged. If you have questions about this research project, please contact Dr. Anthony Romeo, MD, at 312/243-4244. Questions about the rights for research subjects may be addressed to the office of research affairs at Rush Presbyterian St. Luke's Medical Center at 312/942-5498.

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Researcher(s): Irwin Siegel
Address: Department of Neurological Sciences, Rush Presbyterian - St. Luke's Medical Center, 1725 Harrison, Suite 1106/1118, Chicago, IL 60612-3824

Interest(s): Orthopedic Surgery, Scapulothoracic fusion and clinical

IOWA CITY, IOWA

Researcher(s): Katherine Mathews
Address: 2503 JCP, Departments of Pediatrics and Neurology, University of Iowa Hospitals and Clinics, Iowa City, Iowa 52246

Interest(s): Molecular genetics, clinical, mouse model and genetic testing

Note: University of Iowa Hospitals and

Clinics pathology department has started to offer DNA testing since August 1998. This is the first DNA testing service established to help families within the United States. The information regarding testing has been placed on the Helix list. Here is the critical information, for professionals: Shipping instructions: 10 ml EDTA (purple top) tube within Iowa: Corporate Express acct # 110554180 1-800-435-9645 outside of Iowa: overnight express to University of Iowa Hospitals and Clinics, Department of Pathology, Microbiology Laboratory, 200 Hawkins Drive, Boyd Tower 6004 GH, Iowa City, IA 52242-1182.

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Researcher(s): Kathleen (Kate) Mills
Address: 220 MRC-Pediatrics, University of Iowa, Iowa City, IA 52242

Interest(s): Molecular genetics, clinical and mouse/animal models

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Researcher(s): Kevin P. Campbell
Address: Howard Hughes Medical Institute Research Laboratories, University of Iowa College of Medicine, 400F Eckstein Medical Research Building, Iowa City, Iowa 52242-1101

Interest(s): Molecular genetics and clinical research

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Researcher(s): Frederica Piccolo, Yvonne M. Kobayashi

Address: Howard Hughes Medical Institute, University of Iowa, Department of Physiology and Biophysics, 400EMBR, Iowa City, IA 52242

Interest(s): Molecular genetics

NEW ORLEANS, LOUISIANA

Researcher(s): Melanie Ehrlich, Fern Tsien

Address: Tulane Cancer Center, Human Genetics/SL31, Tulane Medical School, 1430 Tulane Avenue, New Orleans, LA 70112

Interest(s): Molecular genetics and DNA methylation

Update: Genetically programmed methylation of DNA at cytosine residues is being recognized more and more to play important roles in modulating human gene expression and chromatin structure (1). We have been examining the relationships between DNA methylation and chromosome structure in cancer and in a recessively inherited DNA methylation deficiency disease, the ICF syndrome (immunodeficiency, centromeric region instability, facial anomalies). ICF is a rare disease involving mutations in one of the three DNA methyltransferase genes and a resulting

Researchers *continued*

predisposition to heterochromatin decondensation and rearrangements in undermethylated DNA in the vicinity of the centromeres of chromosomes 1 and 16 (2-4).

We have extended our research to studying methylation of the FSHD-linked D4Z4 repeat in a variety of cell samples. These are normal tissues; lymphoblastoid cell lines from FSHD patients, normal individuals, and ICF patients; and FSHD and normal blood and skeletal muscle samples. We have already demonstrated that D4Z4 repeats are highly methylated at Eag I sites in normal lymphoblastoid cell lines but are hypomethylated in LCLs from patients with the ICF syndrome (5). Because constitutive heterochromatin is so frequently rich in 5-methylcytosine (m5C) residues (6,7) and because DNA methylation has been causally linked to chromatin compaction resulting in repression of transcription (8), it is important to study the methylation status of the D4Z4 repeat in a variety of cell sources. Our preliminary results are consistent with the hypothesis that DNA methylation at the D4Z4 repeats helps to maintain a position effect repressing deleterious expression of the FSHD gene(s) at 4q35 in unaffected individuals.

Fern Tsien, a graduate student who will soon finish her graduate studies is working on this project, with input from Drs. Baodong Sun and Nancy Hopkins in my lab. This research is in collaboration with Drs. Sara Winokur, Denise Figlewicz, and Vettaikorumakankav Vedanarayanan.

URLs: For M. Ehrlich:

www.tmc.tulane.edu/departments/human_genetics/ehrllich/

For the DNA Methylation Society:

www.dnamethylation.org

References:

1. Ehrlich, M. (2000) DNA methylation: normal development, inherited diseases, and cancer. *J. Clin. Ligand Assay*, **23**, 144-146.
2. Tuck-Muller, C.M., Narayan A., Tsien F., Smeets D., Sawyer J., Fiala E.S., Sohn O. and Ehrlich M. (2000) DNA hypomethylation and unusual chromosome instability in cell lines from ICF syndrome patients. *Cytogen. Cell Gen.*, **89**, 121-128.
3. Jeanpierre, M., Turleau C., Aurias A., Prieur M., Ledeist F., Fischer A. and Viegas-Pequignot E. (1993) An embryonic-like methylation pattern of classical satellite DNA is observed in ICF syndrome. *Hum. Molec. Genet.*, **2**, 731-735.
4. Hansen, R.S., Wijmenga C., Luo P., Stanek A.M., Canfield T.K., Weemaes C.M. and Gartler S.M. (1999) The DNMT3B DNA methyltransferase gene is mutated in the ICF immunodeficiency syndrome. *Proc. Natl. Acad. Sci. U S A*, **96**, 14412-14417.
5. Kondo, T., Bobek M.P., Kuick R., Lamb

B., Zhu X., Narayan A., Bourc'his D., Viegas-Pequignot E., Ehrlich M. and Hanash S.M. (2000) Whole-genome methylation scan in ICF syndrome: hypomethylation of non-satellite DNA repeats D4Z4 and NBL2. *Hum. Mol. Genet.*, **9**, 597-604.

6. Gama-Sosa, M.A., Wang R.Y.-H., Kuo K.C., Gehrke C.W. and Ehrlich M. (1983) The 5-methylcytosine content of highly repeated sequences in human DNA. *Nucleic Acids Res.*, **11**, 3087-3095.

7. Sanford, J., Forrester L., Chapman V., Chandley A. and Hastie N. (1984) Methylation patterns of repetitive DNA sequences in germ cells of *Mus musculus*. *Nucleic Acids Res.*, **12**, 2823-2836.

8. Jones, P.L., G.J.C. V., Wade P.A., Vermaak D., Kass S.U., Landsberger N., Strouboulis J. and Wolffe A.P. (1998) Methylated DNA and MeCP2 recruit histone deacetylase to repress transcription. *Nat. Genet.*, **19**, 187-191.

Recent Abstract from October 3, 2000 FSH Society FSHD workshop Philadelphia, PA USA: **The FSHD syndrome-associated 3.3-kb repeat is highly methylated in normal and FSHD tissues and lymphoblastoid cell lines but not in sperm or ICF syndrome cells**

Fern Tsien¹, Baodong Sun¹, Nancy Eddy Hopkins¹, Vettaikorumakankav Vedanarayanan³, Denise Figlewicz⁴, Sara Winokur⁵, and Melanie Ehrlich^{1,2}

¹ Human Genetics Program and 2 Department of Biochemistry, Tulane Medical School, New Orleans, LA 70112; 3 Department of Neurology, University of Mississippi Medical School, Jackson, MS; 4 Department of Neurology, University of Rochester Medical Center, Rochester, NY 14642; 5 Department of Biological Chemistry, University of California, Irvine, CA 92717.

FSHD (facioscapulohumeral muscular dystrophy) patients almost always have <10 copies of the 3.3-kb D4Z4 repeat at one of their allelic 4q35 regions. In contrast, unaffected individuals have 11-90 copies in this subtelomeric region. It has been proposed that this repeat at 4q35 is normally heterochromatic and exerts a genetically programmed position-effect on as yet unelucidated FSHD genes. It is hypothesized that having <10 copies of D4Z4 at 4q35 abrogates this position effect leading to inappropriate gene expression. Because of the frequent association of vertebrate heterochromatin with a high 5-methylcytosine content, we examined the methylation of D4Z4 repeats at Eag I, Sma I, Sac II, and Mlu I sites in normal and FSHD tissues and lymphoblastoid cell lines (LCLs). We demonstrated by Southern blotting, with a subfragment of D4Z4 as a probe, that D4Z4

repeats at 4q35 and at the disease-unrelated 10q26 region are generally highly methylated in various normal somatic tissues and in normal and FSHD LCLs, blood samples, and skeletal muscle biopsies. We will increase the sensitivity and specificity of the methylation analysis to determine if the small percentage of deletion-associated D4Z4 alleles at 4q35 is hypomethylated in FSHD samples. In contrast to the prevalent hypermethylation of D4Z4 repeats, most of these repeats are very undermethylated in sperm and in LCLs from patients with a DNA methyltransferase deficiency disease (ICF; immunodeficiency, centromeric region instability, facial anomalies) involving mutations in *DNMT3B*. Our previous studies on the hypomethylated juxtacentromeric heterochromatin in ICF LCLs suggest that a high 5-methylcytosine content in a long region of tandem repeats can help stabilize heterochromatin, e.g., at 4q35. Cis effects of DNA methylation might be important in FSHD because heterochromatinization is linked to repression of transcription. In addition, adventitious demethylation of these repeats might predispose to intra- or intermolecular recombination and thus help explain the high frequency of new deletions resulting in sporadic FSHD. Also, changes in the methylation status of this repeat at the deletion-associated 4q35 region might modulate the severity of the symptoms and play a role in the anticipation seen in some ICF families.

BALTIMORE, MARYLAND

Researcher(s): Patrick Reed, John Strong, Neil Porter and Robert J. Bloch, Kevin Flanigan*

Address: Department of Physiology, University of Maryland School of Medicine, 660 W. Redwood Street, Baltimore, Maryland 21201

Interest(s): Physiology, cell biology, cytoskeletal proteins, sarcolemmal organization, and mouse model

*See Kevin Flanigan, *University of Utah School of Medicine, Salt Lake City, UT*

Update: We have been studying the organization of the sarcolemma and nearby regions in muscles from patients with FSHD. We have observed frequent interruptions in the organization of the membrane skeleton, which we have traced to the presence of large, membrane-bound vesicles, or "bubbles," that lie between the superficial myofibrils and the sarcolemma. These "bubbles" distend the sarcolemma and appear to interrupt the regular connections that normally link that membrane to the nearby contractile apparatus.

Researchers *continued*

As we have not observed these structures in other myopathies, we believe that they are related to the pathophysiology of FSHD.

Recent Abstract from October 3, 2000 FSH Society FSHD workshop Philadelphia, PA USA: **The Organization of Costameres at the Sarcolemma and their Relationship to Muscle Disease.**

R.J. Bloch, M.W. Williams, A. O'Neill, G.A. Porter, P. Reed, D. Milner, *N. Porter, and Y. Capetanaki, *University of Maryland School of Medicine, Baltimore, MD, and *Baylor University College of Medicine, Houston, TX.

The cytoskeletal proteins at the sarcolemma of fast twitch skeletal muscle fibers are organized into a distinctive, rectilinear array that parallels the organization of the contractile apparatus. The elements of this array, which have been called "costameres," are present at the membrane overlying the Z and M lines of nearby myofibrils. Additional elements are oriented longitudinally. All the membrane skeletal proteins of skeletal muscle, including spectrins and spectrin-associated proteins, and dystrophin and dystrophin associated proteins, are concentrated in costameres.

The three domains of costameres are not identical, however, as they differ in both composition and stability. The domains overlying Z lines (Zdomains) contain both alphaspectrin and betaspectrin, but the longitudinally oriented domains (Ldomains) and the domains overlying M lines (Mdomains) contain betaspectrin without an identifiable alpha subunit. Similarly, Zdomains contain desmin, but the L and Mdomains do not. In keeping with the latter, the sarcolemma of desmin/mice lose Zdomains, while L and Mdomains tend to remain stable. By contrast, in dystrophin-deficient (mdx) mice, L and Mdomains are selectively lost, while the Zdomains tend to be stable. In mice lacking both dystrophin and desmin, none of the domains of costameres remain stable.

These results suggest that the organization of the sarcolemma requires the presence of both membrane skeletal proteins (e.g., dystrophin) and intermediate filament proteins that link the membrane skeleton to nearby myofibrils (e.g., desmin). Loss of essential proteins of either class is linked to myopathy. We are now testing models of the sarcolemma with the aim of determining the biochemical basis for the coordinated organization of sarcolemmal and contractile structures. We have also developed methods to examine the membrane skeleton of frozen biopsies of human muscle, to learn if the same changes in organization occur in human muscular dystrophies.

Supported by the FSH Society, the

Muscular Dystrophy Association, and the NIH.

Guest Speaker October 3, 2000 FSH Society FSHD workshop Philadelphia, PA USA: Bloch, Robert J., Ph.D., Professor, Co-Director, Interdisciplinary Training Program in Muscle Biology, Department of Physiology <http://physiology.umaryland.edu/faculty/rbloch.htm>

My laboratory has been investigating the organization of the postsynaptic membrane of the developing neuromuscular junction, in order to elucidate the cellular and molecular processes involved in synapse formation. Many of our experiments focus on the acetylcholine receptor (AChR), which accumulates at high density in the postsynaptic membrane. We have found that an unusual cytoskeletal structure, consisting in part of actin and spectrin, and resembling the membrane skeleton of the human erythrocyte, is important in binding and immobilizing receptors in the muscle membrane. We have also identified several extracellular and integral membrane proteins that are associated with accumulations of AChR. Our results suggest that some of these proteins are bound together in a large macromolecular complex through their associations with a spectrin-rich membrane skeleton. We are now characterizing the complex formed by these proteins and AChR using intracellular injection of antibodies and fusion proteins, and with the yeast two-hybrid screen.

Related experiments have examined the composition and organization of the plasma membrane of muscle where it makes connections to the contractile apparatus, in structures termed "costameres." Dystrophin, the protein missing in Duchenne's Muscular Dystrophy, is concentrated at costameres. Current efforts are aimed at identifying and characterizing the spectrins and spectrin-associated proteins at costameres and learning how these are affected in DMD. Our results suggest widespread changes in the organization of the sarcolemma in dystrophic muscle.

We are also studying an unusually small form of ankyrin that is highly enriched in the sarcoplasmic reticulum of skeletal and cardiac muscle fibers. We are using cellular transfection, site-directed mutagenesis, the yeast two-hybrid screen, and biochemical techniques to learn how small ankyrin is targeted to calcium-sequestering membrane compartments in muscle, and how it mediates the interactions of these membranes with surrounding structures.

WORCESTER, MASSACHUSETTS

Researcher(s): Rossella Tupler, Michael R. Green, Davide Gabellini

Address: Howard Hughes Medical Institute, Program in Molecular Medicine, University of Massachusetts, 373 Plantation Street, #309, Worcester, MA 01605

Interest(s): Molecular genetics, cell biology, and clinical

Update: A transcriptional regulator binds specifically to D4Z4, the DNA repetitive element causally related to facioscapulohumeral muscular dystrophy.

FSHD, along with the Duchenne and Becker forms, is one of the three major muscular dystrophies. It is transmitted in an autosomal dominant fashion with an almost complete penetrance. The FSHD genetic locus has been mapped in 4q35 by genetic linkage analysis, but positional cloning strategies applied to the FSHD gene search have come out ineffective till now and no candidate gene has been isolated. Interestingly, p13E-11, the most telomeric probe of the 4q35 region, reveals chromosomal rearrangements in familial and sporadic FSHD cases. Those rearrangements correspond to deletions of 3.3 Kb *KpnI* tandemly repeated units occurring in the 4q subtelomeric heterochromatin (D4Z4). The number of 3.3 kb units seems to be crucial in determining the FSHD phenotype and a direct correlation between number of deleted units and clinical severity of the disease has been suggested.

The role of D4Z4 in the development of FSHD has yet to be determined. It has been postulated that heterochromatic elements within the repeat are essential for maintaining or establishing proper chromatin structure of this region. D4Z4 deletions might cause rearrangements of chromatin structure affecting gene expression either within or outside the 4q35 region by position effect. Consistent with this hypothesis, it has been recently observed that FSHD affected muscle undergoes a profound and global transcriptional misregulation of numerous genes.

Chromatin condensation is a known control mechanism of gene expression. In FSHD genes located in 4q35 might be switched on and off depending on the distance from D4Z4 and on the length of the deleted repeat. This hypothesis is consistent with linkage analysis data and with the clinical variability observed among the FSHD patients and could explain the failure of positional cloning techniques, such as exon trapping or cDNA selection, applied to the very distal region of chromosome 4q.

It is known that chromatin functional organization is established by the interaction between definite DNA sequences and protein complexes, and it determines the transcriptional status of specific chromosomal

Researchers *continued*

regions. For this reason, we studied the interaction between D4Z4 DNA elements and nuclear proteins by electro-mobility-shift assay (EMSA). We were aimed at determining if there is any nuclear factor binding a definite sequence within D4Z4. We divided D4Z4 unit into eight subfragments. Each fragment has been used as a probe in EMSA experiments using human extracts. Only one DNA fragment (D4Z4-243) generates a specific bandshift. This finding strongly argues for the presence of definite DNA sequence in D4Z4 that specifically interacts with a nuclear factor. In fact, the result of a competition assay confirms that the DNA-protein interaction is very specific. Moreover, we were able to demonstrate comparable binding activity in several cell lines and in particular human and mouse myogenic cells. The evolutionary conservation of the D4Z4-243 binding activity suggests that the protein(s) binding D4Z4-243 can be involved in the regulation of fundamental functions. Taken together those data indicate that D4Z4 bears specific binding activity, supporting the hypothetical role of D4Z4 in either chromatin organization or modulation of gene expression. For this reason, we decided to further analyze D4Z4-protein interactions by mapping the minimal D4Z4 binding site. To this purpose we have used deoxyribonuclease I (DNase I) *in vitro* footprinting. The result of this assay indicates that a sequence of 27 bp represents the D4Z4 minimal binding site. We confirmed this result by performing EMSA experiments with an oligonucleotide covering the 27 bp sequence and a mutated version of this sequence. To determine the molecular weight of the protein(s) that binds the D4Z4 binding site an UV crosslinking experiments has been performed. A specific protein with an apparent molecular weight of 27 kDa contained in human nuclear extracts is able to binds to the D4Z4 minimal binding site. Moreover, the 27 kDa protein binds the D4Z4 minimal binding site with a high specificity, as indicated by the results of a competition experiments. Interestingly, the same 27 kDa D4Z4-binding protein is present in mouse myoblasts or myotubes nuclear extracts suggesting that it may have an important role in the regulation of basic activities. D4Z4 might directly regulate gene expression having an enhancer or silencer function. In order to verify the role of D4Z4 in gene expression, a reporter system, which utilize a secreted form of human placental alkaline phosphatase (SEAP), has been used to analyze the activity of the D4Z4 recognition site. A trimer of the D4Z4 minimal binding site and its mutant version have been cloned in the pSEAP2 promoter vector, transfected in human myogenic cells and the reporter activity

analyzed. The D4Z4 binding site is able to activate transcription. The transcriptional activation is very specific since is eliminated by a mutation in the D4Z4 binding site.

Taken together, our preliminary data indicate that a transcriptional regulator of 27 kDa specifically binds to D4Z4, providing the first direct evidence of D4Z4 hypothetical role in control of gene expression. To identify and characterize the nuclear protein interacting with the DNA element within D4Z4 we are currently using a classical biochemical purification of the D4Z4-binding protein from human nuclear extracts. Preliminary results indicated that the biochemical purification in combination with the EMSA is very promising and a straightforward approach for the isolation of the D4Z4-binding protein.

In conclusion, our observation represents a starting point to investigate the role of D4Z4 in determining the 4qter chromatin structure and eventually to understand the biological function of the repetitive element. We believe that these findings are a crucial point for the delineation of the molecular basis of FSHD pathogenesis. Our project represents a new strategy towards the identification of the molecular defects that are critical for the FSHD pathogenesis. The results of this study will provide the basis to develop an appropriate therapy for FSHD.

Glossary

Position Effect. The genome of eucaryotes is divided in chromosomes, highly compacted units that allow the very long DNA molecules to fit inside the cell and to be managed easily. The DNA near the ends of the chromosomes (the telomeres) is packaged into particular form of chromatin called heterochromatin. The heterochromatin, is assumed to contains special proteins that make the DNA unusually inaccessible and this packaging is responsible for maintaining the genes close to the telomere in an inactive status, called silencing. The silencing seems to weaken gradually with distance from the telomere. The mechanism of silencing is not known, but it seems likely to involve a cooperative assembly of proteins on the DNA that, once established, is heritable following DNA replication. The silencing nears the telomeres is an example of position effect, in which the activity of a gene is dependent on its position in the genome. Position effects were first recognized in the fruit fly *Drosophila melanogaster*, but they have been observed in a number of other organisms and are thought to reflect the different states of chromatin present at different locations in the genome and the tendency of these states to spread to encompass nearby genes.

Electro-Mobility-Shift-Assay (EMSA). A

DNA molecule is highly negatively charged and will therefore move rapidly toward a positive electrode when it is subjected to an electric field. When analyzed by polyacrylamide-gel electrophoresis, DNA molecules are separated according to their size because smaller molecules are able to penetrate the fine gel meshwork more easily than large ones. While free DNA fragments run rapidly to the bottom of the gel, protein molecules bound to a DNA molecule will cause it to move slowly through the gel; in general the larger the bound protein, the greater the retardation of the DNA molecule. This phenomenon provides the basis for the EMSA, which allows even trace amounts of a sequence-specific DNA-binding protein to be readily detected. In this assay a short DNA fragment of specific length and sequence is radioactively labeled and mixed with a cell extract; the mixture is then loaded onto a polyacrylamide gel and subjected to electrophoresis. If the DNA fragment corresponds to a chromosomal region where a sequence-specific protein binds, autoradiography will reveals a retarded DNA band corresponding to the DNA-protein complex. This assay is generally simpler, faster and more sensitive than other methods. Thus, it is an ideal assay to monitor the purification of DNA-binding proteins. More importantly, the sensitivity of this assay enables femtomole quantities of DNA-binding protein to be detected routinely. In addition to providing quantitative information on the amount of DNA bound to the protein, the use of EMSA provides additional information on the number and type of proteins bound.

DNaseI Footprinting. Deoxyribonuclease I (DNaseI) protection mapping, or footprinting, is a valuable technique for locating the specific binding sites of proteins on DNA. If a DNA fragment is labeled with a radioactive atom only at one end of one strand, the location of any break in this strand can be deduced merely from the size of the labeled fragment that results. The size, in turn, can easily be determined by high-resolution electrophoresis in a polyacrylamide gel. The basis of the assay is that a bound protein protects the DNA region it binds from DNaseI-catalyzed hydrolysis. Binding sites are visualized by autoradiography of the DNA fragments that results from hydrolysis, following separation by electrophoresis on denaturing DNA sequencing gels.

UV Crosslinking. Crosslinking proteins to nucleic acids with UV light is a simple method for rapidly and accurately determining the molecular weight of a DNA-binding protein in a crude extract. Moreover, the specificity of the photoadduct can be rigorously determined

Researchers *continued*

by measuring the ability of an excess of unlabeled competitor DNA to compete for binding sites on the protein. The goal of the UV crosslinking method is to specifically transfer a radioactive label from a DNA-binding site to the binding protein. Irradiation of DNA with UV light produces purine and pyrimidine free radicals. If a protein molecule is in close proximity to the free radical, a covalent bond can be formed, crosslinking the protein to the DNA. Thus, UV crosslinking may be used to selectively label DNA-binding proteins based on their specific interaction with a DNA recognition site. The procedure can be divided into three stages: 1) extract containing the protein of interest is incubated with a radioactive, uniformly labeled DNA fragment that contains a high-affinity binding site for the protein; 2) protein-DNA complexes are crosslinked with UV irradiation and digested with nuclease, leaving only those labeled DNA fragments that are crosslinked and in close contact with the DNA-binding protein; and 3) the molecular weights of the crosslinked proteins are determined by SDS-polyacrylamide gel electrophoresis followed by autoradiography.

SEAP reporter system. The function of a DNA-binding site can be analyzed by checking its influence on the expression of a reporter gene. The Great EscAPE system uses SEAP as a reporter molecule to monitor the activity of DNA-binding sites. The chemiluminescent substrate CSPD enable to monitor expression of the SEAP reporter gene using simple, sensitive, nonradioactive assays of secreted phosphatase activity. In order to determine if a DNA-binding site is able to regulate gene expression, a multimer of the high-affinity binding site is cloned in front of the SEAP gene and transfected in cells. Since the SEAP reporter gene encodes a truncated form of the placental enzyme that lacks the membrane-anchoring domain, thereby allowing the protein to be efficiently secreted from transfected cells, the levels of SEAP activity can be easily detected in the culture medium.

Recent Abstract of Publication:

Proc Natl Acad Sci U S A 1999 Oct 26;96(22):12650-4
Proc Natl Acad Sci U S A 2000 Feb 29;97(5):2397

Profound misregulation of muscle-specific gene expression in facioscapulohumeral muscular dystrophy.

Tupler R, Perini G, Pellegrino MA, Green MR Howard Hughes Medical Institute, Program in Molecular Medicine, University of Massachusetts Medical School, 373 Plantation Street, Suite 309, Worcester, MA 01605, USA.

Facioscapulohumeral muscular dystrophy (FSHD) is a neuromuscular disorder

characterized by an insidious onset and progressive course. The disease has a frequency of about one in 20,000 and is transmitted in an autosomal dominant fashion with almost complete penetrance. Deletion of an integral number of tandemly arrayed 3.3-kb repeat units (D4Z4) on chromosome 4q35 is associated with FSHD but otherwise the molecular basis of the disease and its pathophysiology remain obscure. Comparison of mRNA populations between appropriate cell types can facilitate identification of genes relevant to a particular biological or pathological process. In this report, we have compared mRNA populations of FSHD and normal muscle. Unexpectedly, the dystrophic muscle displayed profound alterations in gene expression characterized by severe underexpression or overexpression of specific mRNAs. Intriguingly, many of the deregulated mRNAs are muscle specific. Our results suggest that a global misregulation of gene expression is the underlying basis for FSHD, distinguishing it from other forms of muscular dystrophy. The experimental approach used here is applicable to any genetic disorder whose pathogenic mechanism is incompletely understood. PMID: 10535977



Researcher(s): Jeanne B. Lawrence
Address: University of Massachusetts Medical Center, Department of Cell Biology, 55 Lake Avenue North, Worcester, MA 01655
Interest(s): Molecular genetics: Organization and expression of muscle genes, transgenes and facioscapulohumeral muscular dystrophy locus

CAMDEN, NEW JERSEY

Researcher(s): Robert Johnson
Address: Coriell Cell Repositories, Coriell Institute for Medical Research, 401 Haddon Avenue, Camden, NJ 08103
Interest(s): Molecular genetics and cell lines

Update: FSHD families set to join the NIGMS Human Genetic Cell Repository
For the past two years the *FSH Society* and the Coriell Cell Repositories in Camden, New Jersey have been working together to bring cell lines from members of 10 families into the National Institute for General Medical Sciences Human Genetic Cell Repository.
<http://locus.umdj.edu/nigms/>

The intention is to establish a valuable resource of FSHD materials open to researchers worldwide for a reasonable cost (\$75 per cell line, \$50 for 50 micrograms of DNA). Researchers can be assured of the quality of the cell lines and DNA from the NIGMS Collection which Coriell initiated at

the invitation of the NIH and has operated for the past 27 years. Each year Coriell distributes over 3000 cell lines and more than 8,000 DNA samples from this unique National collection to more than 25 countries. All cells are free of microbial contamination, including mycoplasma, and have been assigned a microsatellite identity profile. All members of any submitted family are verified for relationship before they are included in the collection. Coriell therefore supplies validated, uncontaminated cell cultures to established researchers who can be certain that the cells they receive are the cells they ordered. The extensive quality control that Coriell uses to assess isolated DNA includes pulse field gel electrophoresis and long range PCR. Finally, a clinical profile of each affected family member from the FSHD collection will be provided in the electronic catalog.

The scientific staff at Coriell have been greatly helped by Officers of the FSHD Society to acquire this important resource for the NIGMS Collection. All of us hope that the materials will be of use in helping to define the molecular basis of this inherited condition.

LOS ALAMOS, NEW MEXICO

Researcher(s): Michael R. Altherr
Address: Genomics Group, LS-3 M888, Los Alamos National Laboratory, Los Alamos, New Mexico 87545

Interest(s): Molecular genetics, genomics, proteomics, DNA chip, chip technologies and informatics

Update: Drs. Sara Winokur (University of California, Irvine) and Michael Altherr (Los Alamos National Laboratory) have been awarded a three-year grant to study gene expression in FSHD. This CULAR (Cooperative UC-Los Alamos Research) grant will allow them to utilize complementary technologies at the different sites in order to perform a comprehensive analysis of gene dysregulation. Dr. Winokur is utilizing the Affymetrix GeneChip system at UC Irvine, while Dr. Altherr is utilizing a cDNA microarray platform. In addition, along with Thomas Brettin at Los Alamos, they have established a database for FSHD gene expression <http://linker.lanl.gov/array/internal> on which will be posted gene expression files and annotation from myoblast and muscle tissue. This web site will be to allow researchers in the field to access and compare FSHD expression data.

Researchers *continued*

NEW YORK, NEW YORK

Researcher(s): Edwin Kolodny

Address: Department of Neurology, NYU School of Medicine, 550 First Avenue, New York, NY 10016

Interest(s): Molecular genetics



Researcher(s): Gregory M. Pastores

Address: NYU Medical Center, Neurogenetics Laboratory, 400 East 34 Street, RR220, New York, NY 10016

Interest(s): Molecular genetics, clinical and genetic testing

ROCHESTER, NEW YORK

Researcher(s): Robert Griggs; Rabi Tawil; Denise Figlewicz; Lynn Cos; Michael McDermott, Janet Sowden, Kathy Barrett, Amanda Haeefe

Address: University of Rochester School of Medicine, Department of Neurology, 601 Elmwood Avenue, P.O. Box 673, Rochester, New York 14642

Interest(s): Molecular genetics and clinical

Update: NIH Grant Number:

1N01AR02250 – **National Registry for Myotonic Dystrophy and Facioscapulohumeral Muscular Dystrophy Patients and Family Members.**

This contract establishes a National Registry for Myotonic Dystrophy and Facioscapulohumeral Dystrophy Patients and Families. Myotonic dystrophy (DM) and Facioscapulohumeral Muscular Dystrophy (FSHD) are the most common forms of adult muscular dystrophy and both cause progressive, disabling weakness. DM can sometimes cause sudden death. The long term goal for the Registry is to facilitate research in DM and FSHD by functioning as a synergistic liaison between families afflicted by these diseases, who are eager to participate in research, and the investigators interested in studying these disorders. The Registry has a multi discipline Scientific Advisory Committee that will establish diagnostic criteria for DM and FSHD, including specific clinical definitions to diagnose patients who do not have DNA proven DM or FSHD. The Registry will solicit, recruit, classify patients, and store medical and family history data for patients with clinically diagnosed DM and FSHD and facilitate research by providing to investigators statistical analysis of Registry data and answers to specific questions about the data; and, by providing for investigators a means to contact individuals and families who have given their consent and are eager to participate in their specific research studies. The Scientific Advisory Committee monitors the function of the Registry, assesses the value of proposed clinical

studies, and to reviews all proposals submitted by investigators who wish to obtain the names of Registry members or accessibility of Registry data for research projects.

Recent Abstract from October 3, 2000 FSH Society FSHD workshop Philadelphia, PA USA: **FSHD Myoblasts possess Reduced Resistance to Oxidative Stress**

K.A. Barrett (1,2), R. Tawil (1), R.C. Griggs(1), D.A. Figlewicz (1,2), (1) Depts. of Neurology; (2) Neurobiology, University of Rochester School of Medicine and Dentistry Rochester, NY 14642

Facioscapulohumeral muscular dystrophy (FSHD), the third most common muscular dystrophy, is inherited in an autosomal dominant manner. A variable deletion in a repeat region (D4Z4) of chromosome 4q35 has been associated with the disorder, however, the pathogenesis of FSHD has yet to be established. To examine resistance to oxidative stress, cells from FSHD patients, normal control individuals and patients with other muscle diseases were evaluated. Myoblasts and myotubes were exposed to various concentrations of the superoxide anion generator, paraquat (0.02mM to 20 mM) for 24 hours, at which time the number of surviving cells was counted. Adjacent wells containing normal growth medium (SkGM) were run simultaneously as controls. In a separate experiment, cells were also exposed to a non-oxidative stressor, the protein kinase inhibitor, staurosporine, and similarly analyzed. The only statistically significant difference was observed for FSHD myoblasts exposed to low concentrations of paraquat (0.02mM and 0.2mM). FSHD myoblasts showed decreased survival rates relative to normal and disease controls. Previous studies have linked increased expression of the cdk (cyclin kinase) inhibitor, p21, to reduced resistance to oxidative stress in fibroblasts.

We have found that FSHD myoblasts under normal growth conditions express higher baseline levels of p21 compared to normal control cells. (22.2% of FSHD myoblast nuclei stain strongly positive for p21, compared to 14.2% of normal myoblast nuclei, $p=0.004$, $n=4$.), consistent with a reduced capability to resist oxidative stress. The ability of reduced glutathione to rescue myoblasts from oxidative stress was then evaluated for normal and FSHD cells. For this assay, cells were grown to approximately 70% confluence and incubated for five hours with a broad concentration range of glutathione ethyl ester (GSH-OEt) or SkGM (control wells) or paraquat. Following the incubation, wells exposed to medium containing GSH-OEt were replaced with medium containing paraquat plus GSH-OEt. Paraquat concentrations were selected such

that survival with paraquat alone was approximately 40%. This corresponded to 20mM for normal cells and 10mM for FSHD cells. Following an overnight incubation, the number of surviving cells was counted using a hemocytometer and expressed relative to the survival in control wells for each individual (wells containing SkGM throughout the study). Full rescue was defined as viability equivalent to that in control wells. The presence of GSH in cells was identified using Cell Tracker (Molecular Probes), a fluorescent intracellular thiol detector. Toxicity of GSH-OEt was evaluated by exposing sister wells to various concentrations of this agent throughout the study. A concentration of GSH-OEt was said to be toxic if the viability in test wells was less than 80% of that in control wells.

For normal cells, concentrations exceeding 8.5 mM were toxic, and full rescue was obtained for a GSH-OEt concentration of 0.85 mM. Similarly, toxic levels and the ability of GSH-OEt to rescue FSHD myoblasts are being studied and compared to values for normal cells. The current study demonstrates an enhanced vulnerability of FSHD myoblasts to oxidative stress, suggesting a biochemical marker for FSHD early in myocyte development.

DURHAM, NORTH CAROLINA

Researcher(s): Marcy Speer, Margaret Pericak-Vance, Jeffery Stajich, Barbara Randolph-Anderson

Address: Duke University Medical Center, CARL Building, Room 026, P.O. Box 3445, Durham, North Carolina 27710

Interest(s): Molecular genetics, clinical research, genomics and non-Chromosome 4 FSHD.

Update: At Duke University Medical Center, we are continuing our efforts to identify the non-chromosome 4-linked form of FSHD. We are continuing to characterize both clinically and molecularly the large family we have been studying and have also identified new families that we are studying. Our studies are focusing on identifying regions of the genome that may harbor the non-chromosome 4 form of the FSHD gene. Our hope is that identifying and learning about the non-chromosome 4 form of FSHD will shed light on the more common, chromosome 4 form of FSHD.

We have recently recruited a new laboratory analyst, Ms. Barbara Randolph-Anderson, who has more than 15 years of experience in molecular biology. She will be leading the day-to-day activities associated with our studies. In addition, both Drs. John

Researchers *continued*

Gilbert and Marcy Speer continue to be actively involved in this work.

Information about our FSHD study and other on-going studies at the Center for Human Genetics can be found at our web site <http://www.chg.mc.duke.edu/>



Researcher(s): John R. Gilbert

Address: Duke University Medical Center, Center for Human Genetics, Box 2903, Durham, North Carolina 27710

Interest(s): Molecular genetics, clinical and genomics

COLUMBUS, OHIO

Researcher(s): John T. Kissel

Address: Department of Neurology, Ohio State University Hospitals, Room 463-Means Hall, 1654 Upham Drive, Columbus, Ohio 43210

Interest(s): Clinical Research and Clinical Trials

Note: Please see article on Albuterol trials on page 33.



Researcher(s): Jerry Mendell

Address: Ohio State University, Dept. of Neurology, 1654 Upham Drive, Columbus, OH 43210

Interest(s): Clinical Research

PHILADELPHIA, PENNSYLVANIA

Researcher(s): Charles P. Emerson, Jr.

Address: Department of Cell and Developmental Biology, University of Pennsylvania School of Medicine, 1157 BRBII/III, 421 Curie Boulevard, Philadelphia, PA 19104-6058

Interest(s): Muscle, cell and developmental biology.

Guest Speaker October 3, 2000 FSH Society FSHD workshop Philadelphia, PA USA: Charles P. Emerson, Jr., Ph.D., Joseph Leidy Professor and Chair, University of Pennsylvania Medical Center, 1157 Biomedical Building II/III, 421 Curie Boulevard Philadelphia, PA 19104-6058 USA

Research Summary: Our research focuses on skeletal muscle as a model cell type for investigations of developmental and cellular regulatory mechanisms. Developmental studies focus on the signal transduction and transcriptional control mechanisms that regulate the expression of the skeletal myogenic master regulatory genes, *Myf5* and *MyoD*, during the determination of skeletal muscle cell lineages in developing vertebrate embryos. Embryological and genetic studies focus on the role of Sonic hedgehog signal transduction through its *Patched* receptor and *Gli* transcription factor effector genes in *Myf5*

transcriptional activation in somites and on the role of mutations in these Sonic hedgehog signal transduction genes in the origins of muscle, skin and neural tumors in adults. Molecular approaches are used to identify and clone specific transcription factors that interact with and regulate the somite expression of the *Myf5* and *MyoD* enhancers in somites. The overall goal of these studies is to define the molecular processes that integrate signal transduction and transcriptional control mechanisms to initiate skeletal lineage determination.

Cell biological studies utilize the power of *Drosophila* genetics and embryology to investigate molecular mechanisms that regulate the expression and contractile functions of muscle-specific myosin isoforms, which in *Drosophila* are produced by regulated alternative exon splicing of transcripts produced by a single muscle Myosin Heavy Chain gene. Transgenic methods are combined with ultrastructural, physiological and biochemical approaches to investigate the functions of myosin structural domains encoded by alternatively-spliced exons. The structural domains of interest are located in the myosin head and are hypothesized to define the kinetic properties of specific myosin isoforms to define the contractile activities of functionally specialized muscles, including those muscles that power flight. In addition, molecular and genetic screens are being used to identify splicing factor genes that control the splicing of alternative myosin exons in these specialized muscles.

PITTSBURGH, PENNSYLVANIA

Researcher(s): Amy Csink

Address: Department of Biological Sciences, Carnegie Mellon University, 4400 Fifth Avenue, Pittsburgh, PA 15213

Interest(s): Chromatin, heterochromatin and chromosome structure and function

Guest Speaker October 3, 2000 FSH Society FSHD workshop Philadelphia, PA USA: Amy K. Csink, Assistant Professor, Ph.D., University of Georgia, Postdoctoral Appointments, University of Missouri, Columbia, Fred Hutchinson Cancer Research Center, Seattle

The DNA of the eukaryotic genome is wrapped around nucleosomes, subdivided into chromosomes and contained within the cell nucleus. Until recently, many studies of eukaryotic gene expression have assumed that a gene's position along a chromosome and within the three dimensional space of the nucleus was of minor importance. However, there is now increased interest in the regulatory effects of many aspects of higher

order chromatin, chromosome and nuclear structure. Early work on the importance of a gene's chromosomal context was done in the fruit fly *Drosophila melanogaster*, where rearrangements that place a gene closer to a part of the chromosome, called heterochromatin, can result in patchy, reversible gene silencing. Heterochromatin makes up a large proportion (in *Drosophila* 20-30%) of eukaryotic genomes and, unlike euchromatin, consists largely of repetitive, non-protein coding sequences. Silencing by heterochromatin is now thought to be relevant to a variety of phenomena such as regulated developmental silencing of genes, mating type silencing in yeast and X chromosome inactivation in mammals. It is the goal of my lab to further understand and characterize the functions, effects and evolution of heterochromatin.

Previous studies of mine have shown that heterochromatin can influence the location of a chromosomal region within the three dimensional space of the nucleus. Using fluorescence in-situ hybridization correlations were found between the association of a euchromatic region with the heterochromatic neighborhood and the phenotypic silencing of a resident gene. Work in my lab combines the powerful tools of modern *Drosophila* genetics and state-of-the-art 3D fluorescence microscopy to investigate the roles of heterochromatin in gene expression and nuclear organization. Future directions will focus on mechanisms by which heterochromatin influences the positioning of a chromosomal region and the properties of the silencing effects of the heterochromatic neighborhood. Methods are being developed to allow us to simultaneously assay gene location and transcriptional activity. Additionally, these methods will be used to evaluate the susceptibility of different promoters to changes in nuclear position.

I also plan to study the evolution of heterochromatic sequences within and between species of *Drosophila*. Heterochromatin is vastly divergent between even closely related species. Since the centromere is located in these regions, I am interested in investigating if such changes alter centromere position or function. I am also interested in how the requirement of at least some heterochromatic sequences for a mitotic "partner protein" may influence the sequence content of heterochromatin.

From: Department of Biological Sciences, Carnegie Mellon, Mellon College of Science.

Researchers *continued*

SALT LAKE CITY, UTAH

Researcher(s): Mary Beckerle

Address: Huntsman Cancer Institute, University of Utah, 2000 Circle of Hope, Salt Lake City, Utah 84112

Interest(s): Cell biology, Actinin-associated LIM protein (ALP)

❖ ❖ ❖

Researcher(s): Kevin Flanigan

Address: Eccles Institute of Genetics, Room 7290, University of Utah School of Medicine, 15 North 2030 East Street, Salt Lake City, Utah 84113

Interest(s): Clinical research and genetics

Recent Abstract from October 3, 2000 FSH Society FSHD workshop Philadelphia, PA USA: **Absence of Anticipation in Reported Age of Onset in Multiple Sibships from a Large Utah FSHD Family**

Kevin M. Flanigan, M.D.; Christin Coffeen, M.S.; Lee Sexton; and Mark Leppert, Ph.D.

Departments of Neurology, Pathology, and Human Genetics University of Utah, Salt Lake City Utah

In 1950, Tyler and Stephens reported a large Utah kindred with FSHD, consisting of 1249 descendants of a single Utah pioneer (*Ann. Int. Med.* 1950;32:640-660). We have extended this pedigree to include 2200 individuals, and demonstrated that affected individuals carry a 4q35 deletion resulting in an allele of ~20 kb with EcoRI/BlnI digestion. We have initiated detailed clinical studies in order to address the presence or absence of reported clinical features, including anticipation. Previous reports of anticipation in age-of-onset and disease severity have been performed in parent-offspring pairs from multiple families, cohorts within which it is difficult to exclude ascertainment bias. We report preliminary results in studies of three large at-risk sibships within this family. Two of these consist of nine siblings, and one of ten. All available at-risk siblings (eight out of nine in family group one; 10 out of 10 in family group two; and seven out of nine in family group three) were genotyped and examined by a single examiner (KMF). Among these sibships, there is no compelling evidence for anticipation—either in reported age of onset or in disease severity—in comparison to the affected parent. This family, representing a genetically homogeneous FSHD cohort, is a unique resource for the study of parent-of-origin, anticipation, and gender effects of FSHD, and ongoing studies in this family should clarify whether these features exist in FSHD.

PATIENT NETWORK DAY

Patient Network Day Agenda

Saturday, July 8, 2000 • Afternoon Program

- 1-5 p.m., Harvard Room, Crowne Plaza Natick, Massachusetts
- | | |
|------------|---|
| 12:00 p.m. | Registration, Reception and Coffee |
| 1:00 p.m. | Welcome and Introductory Remarks, <i>FSH Society</i> |
| 1:15 p.m. | Kathy Mathews, M.D., Illustrated Lecture, Clinical Developments in FSHD |
| 2:00 p.m. | Denise Figlewicz, Ph.D., Illustrated Lecture, Genetic Research on FSHD |
| 2:45 p.m. | Coffee Break |
| 3:00 p.m. | Anthony Romeo, M.D., Lecture, Orthopedics and Scapular Fixation in FSHD |
| 3:45 p.m. | Panel Discussion, Questions and Answers by Invited Faculty |
| 4:30 p.m. | Concluding Remarks, <i>FSH Society</i> |

Saturday, July 8 • Evening Program

6-10 p.m., Natick Room, Crowne Plaza

- | | |
|-----------|--|
| 6:00 p.m. | Reception, Wine and Cheese |
| 7:00 p.m. | <i>FSH Society</i> Annual Achievement Award |
| 7:00 p.m. | Dinner |
| 8:00 p.m. | Entertainment, Brett Leake, nationally renowned comedian |
| 9:00 p.m. | Piano |

July 8, 2000

Opening remarks at the 3rd International Patient Network Day

Welcome to the 3rd International Patient Network Day for FSHD. What a pleasure it is to see you all here today. My name is **Daniel Paul Perez** founder, President and CEO of the *FSH Society*.

I thank you for coming from all parts of the world; for your courage, dedication and encouragement to all people living with Facioscapulohumeral Muscular Dystrophy.

I knew that our journey would be unique more than a dozen years ago when I founded the *FSH Society*. I had not realized how profoundly different my life would be living and working with others working on this disease. I sincerely enjoy working on the problem of FSHD. I remain optimistic and determined to enjoy life as it is precious and it can be lived under even the most extenuating circumstances.

The journey that FSHD patients travel is a journey that no man, woman or child should ever have to travel or endure. FSH disease is a



Daniel Paul Perez, FSH Society, delivers opening remarks and keynote speech at the July 8, 2000 FSH Society Network Day, Natick, Massachusetts.

strong fort, it will last several life times. It is a journey of alternating darkness and illumination in every realm and aspect of life. The insights that this disease yields are a testament to the goodness of human nature and the powerfully triumphant spirit of the human psyche. No one would choose to live a lifetime with devastating disease and debilitating constant decline to gain the fleeting insights into the goodness of human nature. It is a hard way to live.

We are now finding that FSHD is an extraordinarily complex disease mechanism. Remarkably we and the FSHD researchers worldwide have achieved an

understanding of the complexity of the genetic basis and mechanism of FSHD. And even more remarkable, is still how little is known about how this molecular defect causes our disease. The *FSH Society* is determined to push on and to push harder to fund research and to find solutions for FSHD. FSHD is a scientifically fascinating and yet frustratingly difficult and tantalizing disease at the technical level as well as personal level. I am determined with your help personally and

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PATIENT NETWORK DAY

July 8, 2000

Opening remarks at the 3rd International Patient Network Day *continued from page 72*



Audience listens to Lectures at the July 8, 2000 FSH Society Network Day, Natick, Massachusetts.

financially to understand what exactly is happening in FSHD and to begin to change its course.

I remember very clearly why I founded the Society more than ten years ago. For decades I had heard people lament over what a difficult hand I had been dealt and yet it was always left to outside forces to work on this problem. Phrases like: "I pray that." "God willing they'll come up with a cure," "Someone's got to come up with a solution in the lab somewhere," etc., etc. always left it to others. I looked down at myself seeing that I had FSHD, I looked all around me and over my shoulders and saw and realized that there was no one there. It was clearly no one else's problem or concern and understandably so. From that point on, I began taking steps forward and have not looked back. In the FSH Society we hope to earnestly and



Dr. Anthony A. Romeo, Chicago, Illinois, delivers Lecture, Orthopedics and Scapular Fixation in FSHD at the July 8, 2000 FSH Society Network Day, Natick, Massachusetts

sincerely reach our goal knowing full well that we may only reach the mountain top and never see the promise of a cure. But I know that we will be better for trying and my heart tells me that the effort has made the difference.

We are here today as of the result of more than a decade of persistence and determination on the part of the FSH Society. The FSH Society was proud to sponsor the May 8, 2000, 3rd International Conference on the Cause and Treatment of FSHD in conjunction with the National Institutes of Health (NIH), the Association Française contre les Myopathies (AFM) and the Dutch FSHD foundation. These meetings were congressionally mandated thanks to our work. Congress expects a viable road map for research funding mechanisms from the NIH with the next steps and special opportunities for research on FSHD. Congress has become concerned about what is happening and what is not happening in FSHD at the NIH. We expect that a research plan will be developed from the May 8-9, 2000 meetings by scientists, government leaders and advocates such as ourselves to be used by Congress to indicate important areas for future research.

The FSH Society has given 12 congressional testimonies in seven years and has succeeded in three, and soon to be four, successive years in incorporating report and conference language on FSHD in both U.S. House and U.S. Senate Appropriations Committee Reports accompanying the budget. We have had over two hundred meetings and interactions with the NIH Institutes primarily responsible for FSHD.

To date, we have launched 11 new fellowships and initiatives in FSHD research which have led to remarkable insight and further progress on finding the solution for FSHD. All of our grantees were at the 3rd International Conference on the Cause and Treatment of FSHD held at the National Institutes of Health (NIH) in Bethesda,

Maryland on May 8, 2000. The FSH Society has received more monies and pledges for new fellowships and we will continue the course. I thank Mrs. **Marjorie Bronfman**, The Delta Railroad Construction Company, The Sam and Mary Roberts Foundation and our many extremely generous members for making the research happen. I thank Dr. **David Housman** and the members of the Scientific Advisory Board for their dedication and fine insight and judgement on scientific issues.

We are here to continue our work and to further our purpose. Today, we will hear from the top specialists working on FSHD in the areas of molecular genetics, clinical research and

orthopedic medicine. I am deeply appreciative to have **Theodore Munsat, M.D.** with us today as Chair of the afternoon presentations and panel discussion. Dr. Munsat has made enormous contributions to the field of FSHD research and in advancing solutions for FSHD. If it were not for



Dr. Kathy Mathews, University of Iowa Hospitals and Clinics, Iowa City, Iowa presents Illustrated Lecture, Clinical Developments in FSHD at the July 8, 2000 FSH Society Network Day, Natick, Massachusetts.

Dr. Munsat and his unending encouragement we would probably not be here today.

Denise Figlewicz, Ph.D., of the University of Rochester School of Medicine, Rochester, New York will present an Illustrated Lecture, Genetic Research on FSHD. **Kathy Mathews, M.D.**, of the University of Iowa Department of Neurology, Iowa City, Iowa will present "Illustrated Lecture, Clinical Developments in FSHD." **Anthony Romeo, M.D.**, Orthopedic Surgeon, Rush/St.Lukes, Chicago, Illinois will present a Lecture, Orthopedics and Scapular Fixation in FSHD. Following the lectures we will have a panel to answer questions from the audience. I am especially pleased to introduce

continued on page 74

PATIENT NETWORK DAY

July 8, 2000

Opening remarks at the 3rd International Patient Network Day *continued from page 73*



Making new friends and acquaintances at the July 8, 2000 FSH Society Gala, Natick, Massachusetts.

two leading researchers who will be with us today - **Davide Gabellini**, Ph.D., and **Rossella Tupler**, M.D., Ph.D., from the University of Massachusetts, Howard Hughes Medical Institute, Worcester, Massachusetts.

We must realize that despite the

remarkable progress to date by the *FSH Society* and in FSHD research it is of the utmost importance that we be extremely aware that we are still working against enormous odds. We are a grassroots organization and we need your dollars and your political involvement to make

our work possible. We need you to contact your Congressmen, we need you to raise money, we need you to educate your doctors, we need the doctors to educate you. Without your support and the support of your friends we can not continue our work. What we are doing is hard, very hard. Do not accept your condition. Do not accept the loss of control and the unpredictable and uncontrollable nature of this disease. Do not accept indifference, trivializing, benign neglect or apathy towards finding the cause and treatment for FSHD or toward any individual with FSHD by any individual, institution or bureaucracy.

Looking out across this room I realize that we have created a family and a community worldwide of people living with and concerned with FSHD. Each one of us realizes that the lives of FSHD patients and their caregivers are heroic. Each one has taken the responsibility to make the difference. Remember, "If I do not do for myself, who will do it for me? And if I care only for myself, what am I? And if not now, when?"*

**Pirkei Avos 1:14*

July 8 2000

Dr. Munsat receives the first FSH Society Outstanding Achievement Award



Daniel Paul Perez, FSH Society, presents First Annual Achievement Recognition Award for Outstanding Contributions to FSHD to Theodore L. Munsat, M.D at first annual Gala dinner July 8, 2000, Natick, Massachusetts.

On July 8, 2000, the *FSH Society* presented the first Outstanding Achievement Award for outstanding contributions and work on FSHD to **Theodore L. Munsat**, M.D. for his dedication, guidance, wisdom, concern and care for FSHD patients worldwide.

Dr. Munsat, founding Board Member, served on the Scientific Advisory Board and brought the *FSH Society* to the international community of clinicians and scientists. This award is presented with respect and gratitude to Dr. Munsat.

Daniel Paul Perez, President and CEO, *FSH Society, Inc.* presented the award to Dr. Munsat with the following words of appreciation.

"The *FSH Society* is honored to present this (the) first Outstanding Achievement Award for outstanding contributions and work on FSHD to Theodore L. Munsat, M.D. Please accept our many heartfelt thanks for your dedication, guidance, wisdom, concern and care for FSHD patients worldwide.

"This token of our esteem, a Paul Revere bowl, symbolizes the essence of our revolution. Paul Revere was a Bostonian and a silversmith known for his design of this bowl. Revere was also a revolutionary, and brought disparate groups together to change the status quo.

"You, Dr. Munsat, best exemplify those talents and concern. Here, in Boston, you led us into a revolution in patient rights, clinical research and medicine, education, advocacy and information, opened doors for the *FSH Society*, and led us into the international community for FSHD.

"It was your gentle persuasion that gave us the confidence to enter the world of cyberspace and, as both caring physician and scientist, you expanded our world. For this, we thank you."



Theodore L. Munsat, M.D. Chairs Scientific and Medical sessions at the July 8, 2000 FSH Society Network Day, Natick, Massachusetts.

PATIENT NETWORK DAY

(There's more to an FSH Society Network Conference than meets the eye!)

Summer survivor story Boston 2000 from one who survived

—Ann from Alabama a.k.a. Ann Biggs-Williams

Readers of the FSH Society's Internet BBS this summer may have glimpsed references to a "Boston 2000 Adventure." Here's a tongue-in-cheek remembrance from one of the survivors

of the taxi fare, many of the survivors fell into a deep mental and financial depression and vowed to find a more economical route for the 17 miles home to CPBN later in the day. (That

who left CPBN with an unknown escort to meet a mysterious islander at Faneuil Hall. In lieu of Cindy's mysterious absence, the group sought new alliances.

The scheming Ray and L set out by themselves to be the first survivors back to CPBN. Their challenge was to outwit the Massachusetts Bay Transportation Authority (MBTA) "T" (subway) while navigating with a wheelchair. The devious Aussie soon learned that a thick Aussie accent goes a long way in America and the two navigated the maze of accessible and not so accessible subway lines with what later proved to be an amazingly low fare of zero.

Meanwhile the new alliance of the Canadians, the Swede, and the Alabama Belles who came to be known as the "Lost Six" were still examining the T line map, praying for some type of immunity challenge or divine intervention. This group hesitated to board the T. There was a blue line, a red line, a green line, an orange line, and it all became a blur. "Should we invest in a ticket?" they pondered. Then, naively, they purchased a three-day visitor pass with unlimited travel believing it would prove economical for sight seeing the next day. The six explained to the MBTA official that they were all from foreign countries and needed assistance. After inquiring about which countries they were from, the official replied that although he did poorly in geography in school, he really thought Alabama was part of the U.S. The southern belles explained that when it came to traveling on a subway, that experience was indeed foreign to Alabamians.

"Will we survive these mazes?" the six foreigners asked. The two male members of the tribe rose to the occasion and protected the females from the masses of the mass transit with occasional faint "ya'lls" from the southern gals. Which way to go? North, south, east, west? Upstairs, downstairs? Perhaps circles would be the best choice? This group just wanted to return to CPBN, rest, and go see and hear the famous Boston Pops that evening. They thought that Ray and L were already safely back at CPBN.

Meanwhile, the Aussie and L were still navigating the accessibility of the Boston transit. Assuming the "Lost Six" were already back at CPBN headquarters, the thoughtful Aussie called to explain their dilemma of finding an accessible "T" line.



The survivors of July 8, 2000. Left to right: L from PA; Ann Biggs-Williams, Alabama; Anita Norrblom, Väsby, Sweden; Dawn Young, Vancouver, British Columbia, Canada; Craig Young, Vancouver, British Columbia, Canada.

who remained in Natick for some extra days of R&R following the July 8, 2000 FSH Society Network and Gala. It's a story of intrigue and alliances in the face of disability.

Nine FSHD survivors found themselves castaway in the summer of 2000 on the Cutthroat Island of Boston. Their goal, rather than the million dollars sported by ABC during this infamous millennium summer, was to see Boston after attending the FSH Society Network and Gala. How to travel to Boston proper from the secure environs of their home-away-from-home, Crowne Plaza Boston-Natick hereafter referenced as CPBN, was the first major challenge.

The players were: "The Aussie" Ray; "The Swede" Anita; "The Canadians:" Dawn, Craig, and Kevin; "L" from Pa; "Cyber" Cindy from Florida; and "The Alabama Belles:" Evelyn and Ann.

With well wishes from fellow supporters Paul from Florida and the Lovely Annabelle during a farewell Sunday breakfast at CPBN Headquarters, eight of the nine survivors packed their gear and piled into a flotilla van recommended by the ninth survivor, Cindy from Cyberspace, to head to Quincy Market. The sympathetic shuttle driver included in the fare a glimpse of the better known tourist spots of Boston proper. The group was off to a great start with spirits high when they arrived at Quincy Market. However, shocked by the cost

reasoning later proved to be their major mistake.)

Splitting into two tribes, the "Tall Ships Tribe," (Ray, Anita, L, Evelyn and Ann) took off to the waterfront to watch for photo ops of the Tall Ships arriving in the harbor for the Boston 2000 event while the "Souvenir Hunting Canadian Tribe" lived up to its name. "Tall Ships Tribe" Captain Ray Jordan cleverly propelled his wheelchair and parted the swarming hordes of tourists also arriving in Boston for the Tall Ships as they encountered obstacle after obstacle on their way to its harbor destination. Captain Jordan, tiring of navigating the ins and outs of Boston sidewalks and much to the horror of fellow tribe members, decided to traverse the yellow line in the middle of the street to hasten the approach to the harbor. It was the consensus of the tribe that this daring but foolhardy act, accomplished successfully due to the absence of weekday business traffic, qualified the Aussie for at least one immunity vote.

The Tall Ships Tribe reunited with the Souvenir Hunting Canadian Tribe for a Tribal Council Initiation at lunch in an outdoor cafe at Quincy Market. Due to the high cost of the taxi ride, there were mild skirmishes for any food that anyone considered leaving on their plate as the players built their strength in preparation for the day ahead. The two tribes had hoped to encounter FSHDer Cyber Cindy

PATIENT NETWORK DAY

July 8, 2000

Summer survivor story *continued from page 75*

Where was Cyber Cindy? As reported on the FSH BBS, she remained trapped in the privies of Faneuil Hall until a tall, handsome, uniformed rescuer finally assisted in releasing her from her plight. "Taxation without representation," Cindy shouted as she sailed away without sighting either of the two tribes.

With the setting of the sun, the strains of the Boston Pops were diminishing. On arrival at CPBN, the Aussie used his trusty cell phone conch to advise **Carol Perez**, the Jeff Probst of the *FSH Society*, that he and L had no response from the Yanks. It looked like Carol would have to extinguish their tiki torches soon.

Finally the "Lost Six:" the Canadians, the Swede, and the Alabama Belles made it to what they thought was the end-of-the line, only to be met with another commuter challenge—a commuter rail train. More money for another fare! The original cost of the morning taxi was looking better and better. "Inbound, outbound"? "Who cared?" thought the six who collapsed to wait for the next train, mumbling something to fellow commuters about why commuters go postal. Other commuters edged away.

The train arrived and the six rode to their destination only to find a seedy bar. Who would go in? Drawing straws was not an option. It was Alabama Ann who would enter in search of a phone. After being too cordially greeted by several customers, Ann found a phone to call CPBN. A worried Evelyn went to check on Ann and was greeted by a very friendly customer. Evelyn fled. "Wrong train stop," Ann reported when she emerged. "Take a taxi to the next train stop . . ." "Not another taxi fare," moaned the tribe. "The taxi won't take six of us!" "Watch and learn," said the Alabama girl. The southern drawl of the lone phone caller resulted in a taxi's prompt arrival. "I can't take six passengers," the driver exclaimed. "Open that trunk and pack'em in" said Ann. "Two of our folks are going as luggage!"

After a grueling five-minute taxi ride, the tribe phoned CPBN at the next stop. There was a long wait, darkness arrived, rain set in and the cold wind blew in the bleak and desolate station. Natives begin appearing in what seemed to be clandestine operations. "Any one want to go to hear the Pops?" Ann whispered hopefully. "NO!" was the concerted reply. Another call from Dawn to headquarters followed by another. Deathly cold and quiet, the survivors were finally rescued by the CPBN shuttle driver. "The heater, the heater, the

heater," they finally cried in unison as they shivered in the shuttle.

Tired, wet, and cold, the "Lost Six" welcomed the warmth of CPBN and pizza flown in courtesy of the Canadians' grandmother who heard of their plight on the evening news. Another tribal council was held that evening. Word came down from Carol as she extinguished the first tiki flame that by default, L was voted off the island first. She had to return to work on another island the next day.

How to top the adventure of this fateful day? Alarmed that the international guests would leave their fair country with a frustrated view, Dan, Carol, and **Charlie Perez** came to the rescue. The very next day, they whisked the Aussie and the Swede in the luxury of private transportation (adapted vans) to Cambridge, their fair city, close up and personal. That same day, the other five took an escorted tour bus from Harvard Square to see Boston and had a great time. Oh yes, they gladly took a taxi direct to Harvard Square and gave the taxi driver their three-day subway passes as a tip! Their driver, planning to see the Tall Ships, said mass transit was the only way to go. "Yeah, right!" said the five with knowing smiles.

One by one, Perez extinguished the tiki lamps. The tall Swede left on the big white bird to return to her homeland under the cover of darkness. The southern belles left yearning for a place with no mass transit and mumbling to themselves, "the 'T,' the 'T.'" Learning their flight was cancelled due to the mechanical



The survivors of July 8, 2000 following the double yellow line. Left to right: L from PA, Ray Jordan, Australia.

failure, the Belles said, "We don't care, we want to go where there is no mass transit."

We're not sure when Cyber Cindy left, as mystery continued to surround this seasoned traveler. By Wednesday, the Aussie and the Canadians, now called "Clan of Four," who remained decided to honor their newfound global alliance by leaving simultaneously for their homelands and call it a draw. The argument continued as to who was first into the air, Dawn and brood to the north or Ray to the south.

So you see, there is more to an *FSH Society* conference than meets the eye.

Searching for adventure, these nine survivors left the island with plenty to tell. Hosts, Carol, Charles and **Dan Perez** were always there in the background and breathed a collective sigh of relief when all the survivors safely embarked for their homelands. The survivors left with a new found network of friends, worlds of knowledge, hope about FSHD and a memory of Boston that would forever be known as the "Boston Adventure 2000." The survivors recommend that readers start saving their pennies now for the next *FSH Society* Network Conference, stay a few extra days and the seasoned FSHD survivor team will provide an adventure to remember. See you there!

Note: Ann Biggs-Williams, Board Member of the FSH Society and Gulf Coast Support Group leader, is a retired college librarian living in Brewton, Alabama.

Athena Diagnostics supports the work of the FSH Society

Thank you to **Athena Diagnostics**, Worcester, Massachusetts, Corporate sponsor of the 2000 Gala and the 2000 FSHD Workgroup meeting in Philadelphia and to **Vincent Bertolino** and their staff who joined us at both the *FSH Society* Network Conference in Natick and the FSHD Workgroup.

PATIENT NETWORK DAY



Serious and funny, reaching out at the July 8, 2000 FSH Society Gala, Natick, Massachusetts. Left to right: Ann Biggs-Williams, Board of Directors, FSH Society, Alabama, Paul Closson, Florida (middle rear), Brett Leake, renowned comedian, Virginia.

Thanks to those who made it possible

Our thanks to the 2000 Network Conference Committee: **Cheri Hardiman, Karen Johnsen, Theodore L. Munsat, M.D., Carol A. Perez, Jessica Peroni** and the members of the New England FSHD Support Group for their contributions to the success of this meeting. Special thanks to **Athena Diagnostics**, Worcester, MA and **Rehab Seating**, Newton, MA for supporting the 2000 Network Conference and entertainer **Brett Leake** for his benefit performance for the FSH Society. With appreciation to **John Davey**, Manager of the Crowne Plaza - Natick, his management and staff for multiple contributions, hard work and hospitality to our membership and network on this occasion.

2000 FSH Society network meeting & gala dinner

The 2000 International FSH Society Network Information Meeting and Gala Dinner, held on Saturday, July 8, 2000 was a unique opportunity to meet with patients, family members, researchers, clinicians and others concerned with facioscapulohumeral muscular dystrophy (FSHD).

Chaired by Dr. **Theodore L. Munsat**, the afternoon presentations and panel discussions were designed to bring the most current advances in FSHD research to the FSHD community of patients, families, physicians and scientists, and provide forums, both formal and informal, to advance knowledge, understanding, and support networks for all concerned.*

The First Annual Achievement Recognition Award for Outstanding Contributions to FSHD was presented to Theodore L. Munsat, M.D at our first annual Gala dinner. The highlight of this festive evening was the first New England appearance of comedian **Brett Leake** whose performance followed the elegant dinner with music by pianist **Jack Hart**.

**Videotaped copies of the extraordinarily informative and educational afternoon program are available from the office of the FSH Society for US\$30.00.*



Making new friends and acquaintances at the July 8, 2000 FSH Society Network Day, Natick, Massachusetts.

FSH Society welcomes groups

Support groups in Arizona, the Gulf area (Alabama, Louisiana and Mississippi), Michigan and Ohio, Mid Atlantic and New England offer the unique opportunity to meet with others to discuss Facioscapulohumeral Muscular Dystrophy (FSHD) issues. Meetings are generally held every other month covering topics specific to FSHD. The groups have leading researchers and clinicians present the current genetic and clinical information. Experts address nutrition, exercise and coping strategies for FSHD. Individuals, family members and professionals concerned with FSHD are welcome to attend.

Please call **Karen Johnsen**, FSH Society Support Group Coordinator, (301) 262-0701, with any questions or interest in forming a local group, telephone network or pen pal group. In order to preserve confidentiality, the FSH Society will contact members and inform them of groups in their areas.

We have requests to form groups in San Diego, San Francisco and Los Angeles, CA; Palm Beach, FL; Duluth, MN; Kansas City and St. Louis, MO; and Rochester, NY. Information about support groups and networks will be posted on the FSH Society website: www.fshsociety.org

Additional Resources: Videotapes of selected meetings from the Mid Atlantic FSHD Support Group and New England FSHD Support Group are available on loan (\$7.00 postage charge per tape). Tapes include presentations on physical therapy, occupational therapy, massage therapy and a discussion with a physician. Contact **Carol Perez**, East Coast Office of the FSH Society for further details. We are grateful to **Karen Johnsen** and **Robert Smith** for making these materials available.

Pen pal network for our children. Anyone interested may contact **Carol Perez** or **Mary Redick**, 715-426-9986, for the name, age, and address of those involved.

Network for the partners and family Members. **Dean Johnsen**, 301-262-0701, is coordinating a Support Network for the Partners and Family Members of individuals with FSHD.

FSH Society Infantile Facioscapulohumeral (IFSHD) National Network: **Mary Redick**, W11149 County Road M, River Falls, WI 54022 (715-426-9986), coordinates the Infantile Facioscapulohumeral and early onset IFSHD National Network that continues to grow and reach out across the continents. One of the goals in forming this network is to address the unique needs of parents and children living with IFSHD. The Society would like to develop a resource list of those families willing to exchange information about IFSHD and early onset.

- Groups meet in accessible locations

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GROUPS AND SUPPORT

FSH Society groups welcome new members and offer new resources

Support Group Contacts

- Arizona FSH Society Support Group: **Margaret Powers** (480) 325-4526
- Gulf FSHD Support Group: **Ann Biggs-Williams**, (334) 867-2445 includes Alabama, Mississippi, and Louisiana.
- Michigan FSH Society Support Group: **Kristi Myers** (248) 594-5881 includes Indiana, Michigan and Ohio. Meetings are held at both Michigan and Ohio locations.



Mid Atlantic support group meeting at Karen Johnsen's home in Bowie, Maryland for lecture on muscle physiology, May 2000. Left to right: Dr. Neil Porter, University of Maryland, Don Burke, Virginia, Dr. Robert Bloch, University of Maryland.

- Mid Atlantic FSHD Support Group: **Karen Johnsen**, (301) 262-0701 includes Maryland, Virginia, Washington, D.C., Delaware, and Pennsylvania
- New England FSHD Support Group: **Ranae Beeker** and **Carol Perez**, (781) 860-0501 includes Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island and Vermont
- FSH Society's FSHD Chatroom in Cyberspace: www.fshsociety.org: Sundays at 2 and 9 p.m. Eastern USA time to meet with FSHDers and concerned individuals from around the globe.
- FSH Society Network Contacts—United States - Colorado: **Leandra Dean** (719) 594-0503; Pennsylvania (South Central): **Mary Morris-Kelly**, (717) 731- 6211

International FSH Society Network Contacts

- Australia: **Ray Jordan**, 86 Barry Street. Reservoir. Victoria 3073, Australia, Phone: 03 9460 2559, Email: afme@labyrinth.net.au
- Update: MDA Victoria coordinator for FSHD group. Ray attended the FSH Society Network and Gala in Natick, MA USA
- Belgium: Ms. **Denyse Bourgeois**, Rue de Blanc Bois #2, 1360, Perwez, Belgium
- Update: The Belgian group represents all neuromuscular disorders and meets annually. Their publications are in French.
- Canada: **Rosanna Mossa**, 29 Robaldon, Toronto, Ontario M3A5A8, Canada

Update: FSH Society Network Coordinator for Canada - **James** and **Linda Dobson**, Society for Muscular Dystrophy Information International (S.M.D.I.), P.O. Box 479, Bridgewater, Nova Scotia B4V 2X6, Canada Phone: 902-685-3961 Fax: 902-685-3962 e-mail smdi@aura.com The S.M.D.I. International Newsletter and Access-Able Information published quarterly provide an international forum for neuromuscular disorder/disability information

- England: Mrs. **Lorraine Jonas**, Secretary FSHMD Support Group, 8 Caldecote Gardens, Bushey, Herts WD23 4GP, England, Phone: 44

20 8950 7500, Fax: 44 20 8950 7300, E-mail: nmj@brockley.telme.com Web Site: <http://www.binternet.com/~fsh>

Update: FSH-MD Support Group Newsletter and annual meeting in October. Contact Mrs. Jonas for date and location.

- The Netherlands: FSHD Foundation (de Stichting FSHD): **Kees van der Graaf**, Founder. The purpose of the foundation is to stimulate, facilitate and fund scientific (genetic and clinical) research into the causes and etiology of FSHD. A sponsor of the FSH Society's 2000 NIH Science Conference, the

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Chabner vs Mutual of Omaha sets precedent for life insurance rates

Howard Chabner, FSH Society member, won a victory for individuals with facioscapulohumeral muscular dystrophy (FSHD) in California and set a precedent for life insurance rates that may apply to other states. "I don't think of myself as a crusader," Chabner says. "I'm just someone with a disability and legal training, with an opportunity to advance the law. [Insurers] shouldn't charge you a price without having a good reason."

Chabner, a 1982 graduate of the Harvard Law School, practices law in San Francisco. After leaving an in-house position for the law firm world in 1993, Chabner applied for a whole life insurance policy with United of Omaha. Chabner, who has FSHD and uses a wheelchair, was told by the insurance company that because his life expectancy was nine to eleven years shorter than that of other nonsmoking males his age, he would have to pay nearly double the standard life insurance premium though United of Omaha admitted that this condition only reduced his life span by four years. Two of Howard Chabner's grandparents lived into their 90s and doctors expect him to live a long life, too. In rating Chabner, the underwriter relied mainly on an industrial manual.

Sid Wolinsky, director of litigation at Disability Rights Advocates in Oakland, successfully sued on behalf of Chabner (Howard L. Chabner v. United of Omaha Life Insurance Company) and helped establish the precedent that insurance companies cannot discriminate against the disabled by charging them arbitrarily high rates. "As more people with disabilities marry and have families, health and life insurance become even more important," says Wolinsky. "This case helps shake insurance companies loose from outdated stereotypes of disabled people."

In March 2000, the California Ninth Circuit U.S. Court of Appeals ruled in favor of Chabner and affirmed on state law grounds, finding that the double premium was arbitrary and not based on actuarial data or experience. The court held that there was no ADA (federal) violation.

The FSH Society is grateful to Howard Chabner for taking the time to change attitudes and challenge the inequities in the insurance industry for people with FSHD. This ruling was specific to FSHD and California.



Howard Chabner (left) and wife Michelle DeSha (right).

GROUPS AND SUPPORT

Greetings from Frank van Zimmeren

From VSN (Netherlands) Newsletter No. 23, June 2000, FSHD Workgroup

I went to the meetings of the VSN workgroup to see if I could do something useful and fun there. I'm now in charge of keeping an eye on research and this fits my interests perfectly. I want to take this opportunity to openly talk about FSHD and myself. In my view this is best done by telling of my experiences with this disease, so I will start with how I found out I had FSHD.

One day when I was twelve I was unable to do an exercise in the physical education lesson that everybody else could. So I went to my general practitioner doctor (GP) and was, of course, referred to a specialist. You have most likely experienced the same yourself.

A few months later I was told I had an incurable muscular dystrophy and I should try and keep living the way I was. The months before this moment I had been hoping that I would be cured with some pills or, at worst, an operation. But that wasn't to be. My emotions at the time are very hard to describe, but anger and sadness were prevailing. I couldn't handle it, not my emotions nor the fact that my body was different from 'normal.' My self confidence, of which I had very little anyway, was diminished. I couldn't talk about my disease with anyone. I also didn't want anyone to know about it. I even told my parents not to tell anyone! I lived this way for four years, without talking about it, basically behaving like an ostrich. It is a human trait to stick your head in the sand when you experience nasty things. Many of you will recognize this.

At school I hardly had any friends, but that's hardly surprising if you have very little self-esteem and can't talk about your disease. You can't expect your disease not to be a problem in your relationship with other people if it is still a problem for yourself. But time is a

good healer. At a certain point I just couldn't deny the fact anymore that I was less able than others were. By the time I had passed my



Meeting with Frank van Zimmeren on his way through the United States. Left to right: Daniel Paul Perez, FSH Society; Bas Barr, The Netherlands and Frank van Zimmeren, The Netherlands.

school exams I had become a little more 'open.' I took a year off and in this year I changed a lot.

I started to wonder why such a stupid deletion in my DNA could have such a great effect on my body. After a fax to **Cor Koetsier**, he sent me a few editions of the *FSH Watch*, the magazine of the American *FSH Society*. (Cor; I am still grateful for that!) This motivated me to get an Internet connection, and on the Internet I met many people (especially via the *FSH Society's* site) who have FSHD. I think that meeting many people who share the same problems as me, but despite this live very full lives, helped me to become more positive about my situation. Books on eastern philosophy helped me to see life in a larger perspective and concentrate on what I have and CAN do.

At last I could talk to friends about FSHD. I decided to study biology so I could understand the research literature better and hopefully contribute to it some day. You could say I have gone from 'not wanting to know about FSHD' to 'wanting to know all.' I'm convinced there will be a cure for FSHD in the future. How fast this will be depends on how much money there is to finance enthusiastic and inventive researchers. Therefore, I try to support the *FSH Society* and the *FSHD Foundation* as much as possible. Thanks to them, a lot more research is now being done...

but the more the better, of course! It's a shame that a lot of money is needed for this, but it does pay off; better DNA diagnostics for example.

I'm now 20 years old and have studied biology for one and a half years. Since the summer holiday I have had trouble motivating myself to study. This is because my leg muscles are getting weaker and I'm therefore afraid that walking is going to become difficult in the near future. So I want to do fun things now that will be more difficult to do in the future. By fun things I mean experiencing the world (i.e. traveling). So in January I temporarily stopped studying. When you read this I will probably be in the U.S., if I haven't caught malaria in Surinam that is!

So, this was it. Actually I would like to tell you much more, but then where do I stop?! It was difficult to openly talk about myself and keep it short at the same time. The result is a compromise. I hope it was understandable, that you enjoyed reading it and that it maybe even helped you in some way, even if it were only a moment of recognition. In my experience people all have the same fears, anxieties and other feelings.

Elsewhere you will find more from me about horseback riding and the Internet. In the workgroup I now fulfill the task of keeping track of research and keeping the workgroup informed appropriately. I also go to the meetings of the Dutch FSHD Foundation out of personal interest and to maintain ties between the Foundation and us. I'm also a contact person for young people with FSHD. I would like it very much if you would call, fax, e-mail or write to me about things that bug you, with problems, just to chat or whatever you want to talk about. Even if you don't fall into the category of 'young people'! I'm sure we can learn a lot from each other.

I want to do a parachute jump and am looking for people—no, not to catch me if the chute doesn't open!—who would like to jump with me. I will be jumping attached to a professional jumper (tandem jump) because this doesn't require much physically. People who like travelling and have cool plans, ideas or tips are also most welcome to contact me!

Editor's note: In May, 2000 the FSH Society had the pleasure of meeting with Frank on his visit to Boston. This article is excerpted from the VSN FSHD workgroup newsletter (the Netherlands) with Frank's permission.

GROUPS AND SUPPORT

Support Groups *continued from page 79*

Foundation works closely with the *FSH Society* on scientific issues.

- VSN (Muscular Disease Society Netherlands): VSN FSHD Working Group, Gortstraat 115, Veenendaal, Utrecht, The Netherlands 3905 BD

Update: VSN FSHD newsletter covered the Contact Day in 2000. The summary of Research Update appears on page 31.

- South Africa: Mr. **Honiball**, FSHD Coordinator Muscular Dystrophy Foundation SA, P O Box 1535, Pinegowrie 2123 South Africa, Phone: +27 11 789-7634, Fax: +27 11 789-7634, Email: msa@megaweb.co.za

- Sweden: **Anita Norrblom Stallgatan** 12B, S-194 32 Upplands Väsby, Sweden, Phone: +46 8 590 949 62 Email: chat@chatcissi@hotmail.com

Update: Anita attended the 2000 *FSH Society* Network and Gala in Natick, MA USA and welcomes contact to discuss FSHD concerns.

Thank you!

The *FSH Society* wishes to acknowledge the following for their contributions to our efforts.

- Denise Figlewicz, Ph.D. for presentation to July 8, 2000 FSH Network Day

- Davide Gabellini, Ph.D. for panel participation on July 8, 2000 FSH Network Day

- Jane Hewitt, Ph.D., Nottingham, UK for co-chairing the 2000 ASHG FSHD Work Group.

- Thomas A. Kammerer, Rockville DoubleTree for contributions and support to *FSH Society* hosting NIH International Conference on FSHD, May 2000

- Kathy Mathews, M.D. for presentation to July 8, 2000 FSH Network Day

- Mid-Atlantic *FSH Society* Support Group members for hosting researcher's dinner in Maryland

- Ardeth Millner, Lexington, MA, for continued support to the *FSH Society* office

- Theodore L. Munsat, M.D. for chairing the *FSH Society* 2000 Network Conference.

- Anthony A. Romeo, M.D. for presentation to July 8, 2000 FSH Network Day

- Support Group Leaders: Ann Biggs-Williams; Karen Johnsen, Margaret Powers, Ranae Becker; Kristi Myers and Carol Miller who hosted the annual picnic.

- Thilmany Division, International Paper for supplies and mailings for membership mail

- Rossella Tupler, M.D. for panel participation on July 8, 2000 FSH Network Day

- Bev and Jim Weyenberg, Kaukauna, WI for membership and newsletter mailings

- Sarah Winokur, Ph.D., Irvine, CA for co-chairing the 2000 ASHG FSHD Work Group.



Members of the Mid Atlantic support group congregate at Karen Johnsen's home in Bowie, Maryland to hear lecture by Drs. Robert Bloch, Neil Porter and Patrick Reed on muscle physiology, May 2000.

2000 Exhibit Booth Support San Diego, CA 2000

- American Academy of Neurology: Jay Bass, Marilyn Maxwell

Boston, MA 2000

- American Neurology Association: Nancy Baer, Ginny Michael

Philadelphia, PA 2000

- American Society for Human Genetics: Martha Bowditch, Debbie & David Hansen, L from PA, Scott Schultz

Acknowledgements

Special Events

- 2000 Read-A-Thon Fundraiser at the Bear Creek Elementary School in Baltimore, Maryland (fourth year) to support the *FSH Society* and educate their community about FSHD. The school did this to honor **Arlene Endres**, mother of **Jessica Ryley** and teacher at the Bear Creek School.



Ms. Catherine North, Principal, Bear Creek Elementary school with Brandon Mohr, 2nd grade student who brought in the highest dollar amount of contributions for the Bear Creek School Read-a-thon.

- Friends of Christopher Stenmon - Second Annual End of Tax Season (1999) Event in Quincy, MA to support the activities of the *FSH Society*: **Shelley A. Buckingham**, **The Eight-Ball Billiard Parlor**, **Bernadette Finneran**, **Alison E. McLaughlin**, **Mary Oldmixon**, **Paddy Barry's**, **Sarsfield, Inc.**, **Shooters Café**, **Russell C. Stamm**, **Amanda Steen**, **Frances A. Uttring**.

- **June 6, 1999 Run for the *FSH Society***: **Elizabeth McGowan**, Denver, CO Elizabeth completed the run to support the *FSH Society* research fund. Her sponsors were: Joyel M. Bennett - NY, Nilofar Q. Mir, M.D. - NY, David Murphy - MA.

- **June 11, 2000 High Woods Sportsman's Club *FSH Society* Benefit Archery Shoot**, Saugerties, NY: Proceeds from the archery shoot were donated to the *FSH Society's* Research and Education Fund. With special thanks to **John** and **Denise Van Etten** for their good work on our behalf.

- **Holiday Crafts Fundraiser**: **Kim Harwood** of Hermantown, MN contributed proceeds of her 1999 Christmas crafts to the *FSH Society*.

Corporate Sponsors

- Athena Diagnostics - MA
- Cephalon - PA
- Delta Railroad Construction Co. Research Fund - Ashtabula, OH
- Gerald Norton Memorial Corp. - IL
- Schering Plough - NJ

Foundations

- Marjorie and Gerald Bronfman Foundation
- New York Community Trust Foundation
- The Tides Foundation

Corporate Matching Funds

- American International Group, Inc. - NY
- The Lubrizol Corp - OH

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GROUPS AND SUPPORT

Acknowledgements *continued from page 80*

- McKinsey & Co. Inc. Gift of Hope - NY
- Microsoft Matching Gifts Program - NJ
- Research Systems, Inc. - CO
- Spear, Leeds & Kellogg, - NY

United Way

- United Way of Mass Bay - MA
- United Way of Minneapolis Area - MN
- United Way of Chester Cty, Inc. - PA
- United Way of Snohomish Cty - WA

Memberships

Mr. & Mrs. Irving Barocas - NJ; E. Ann Biggs-Williams - AL; Steven Blier - NY; Jerilyn Blom - MN; Kelly & Steve Brooks - FL; Claudine H. Brown - NM; Lori Calandro - MI; Howard Chabner & Michele DeSha - CA; Gary and Arlene Cohen - NY; Josh Comfort - CO; John Damon - MA; Leandra Dean - CO; Larry Dressler - WA; Don Drinkwater - FL;



Ms. Arlene Endres, reading to 5th grade students at the Bear Creek School Read-a-thon for FSHD (May 2000).

Susan Egert - NY; Doris Embry -TX; Frank Gerace - PA; Manuel R. Gomez - DC; Lady Beth Hall - LA; Mr. & Mrs. Bane Hereford - NV; Cliff & Linda Hoover - CA; Isabel & Preston Jeffares - GA; Deanna & James Jones - CA; David J. Klecker - CO; Russ Kleve - OR; Robert Kobrin - MA; Elaine Kolakowski - MD; Lincoln & Irene Lai - CA; Stuart A. Lai - NY; Alan Latman - FL; Richard & Wendy Levinson - NY; Dr. David T. Lokerson - MD; Mr. & Mrs. Donald Lokerson - MD; Wilma Metros - AZ; Steve & Kay Miller - GA; Patrick G. Morris - FL; Mrs. Doris Olds-Eck - MD; Mr. William R. Oviatt - OH; Kristen Paladino - MA; Peter Pogozelski - CT; Ed Ramsey -CA; Syrus Rayhan, M.D. - CA; Mel & Cathy Roberts - NY; Carol Robinson - CA; Jerry & Jane Rocco - CA; Philip & Sybil Rosenberg -NJ; Betty & Ed Schechter - PA; Evelyn Schuster - MA; Kelly Spaninger - PA;

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International Members

- Ruth Moenikes-Peis -Unkel, Germany
- Antoinette Oosthuisen - South Africa; Lynn Whittal - Canada

In Honor Of

- Joseph Daniel Albanio: Grandmother Barbara F. Ambrose - NY
- Kaleb Bates Wolcott: Julie Wolcott -VT; Grandmother, Nan Wolcott Ph.D. - NY
- Ann Biggs-Williams on her 50th: Mother, Mary S. Biggs - AL
- Justin Zachary Cohen: Grandparents, Harriet & Stuart Cohen - NY; Great Aunt, Mrs. Joseph D. Cotler - NY; The Cotler Family - NY Grandmother Rose Kanter- NY- In honor of Justin's birthday: Rose C. Sicker - NY; The Curtis Stoner Family - NJ
- Paul Closson: Sister, Janice Closson Caldwell - MI
- The Len Gilman Family: Dr. & Mrs. Donald Disick - MA; Audrey & Jack Kadis - MA; Evelyn Sheffres - MA
- The kindness of William G. Michael: Henry T. Wiggan - MA
- Kristen Paladino: Cheri Kahle - MA; Wayne Staples - MA
- Jesse Pease: Great grandmother, Helen Sennott - MA; Grandmother, Patricia Tompkins - FL
- Denise & Allison Potapa: Theresa Frizzell - MI
- Carla L. Ramey: Damona Temple #45 Pythian Sisters - OH
- Jess Ryley: John & Carolyn Chesney - FL; Mary E. Doto - NY; Parents, Arlene & Patrick Endres - MD; Rick & Leslie Frye - WA; Great Grandmother Thelma B. Green - MI; James F. Ryley, Jr. - PA; David D. Smith - OH; Grandparents, Gerry & Joanne Smith -MI; Timothy A Smith - TX

Professional Memberships

- William Herzberg, M.D. - Portland, OR - Neurologist with Special Interest in FSHD
- Anthony A. Romeo, M.D.,S.C. - Chicago, IL - Orthopedic surgeon with a special interest in scapular fixation and FSHD.

Research and Education Fund

- Frank C. Heffron - CA
- Richard & Wendy Levinson - NY
- Bob Rowlett - TX honoring Donna Rowlett
- Lynn & Bob Schulteis -NC, honoring "The Cruz Kids"
- Robert G. Trumble - MI
- Mark & Vickie Ray - CO

In Memory

- Kiichi Arahata, M.D.: Dr. Peter Lunt - Bristol, UK; Daniel Paul Perez - MA
- Eleanor Braterman: Sophie, Florence, Sam, Russell and Jerene Braterman - FL; Helen and. Gerald Pease - FL; Mamie Ruth Pease - FL
- Stanford Closson: Janice Closson Caldwell - MI
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- Jules Glick: Anonymous, NY
- Charles Francis Louie: Russell & Selina Lai - CA
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- Ida Murphy to Research Fund: Jo Melanie Calverley- TX; Jo Ann Turner - TX
- Luis J. Perez: Grandson, Daniel P. Perez - MA
- Dorothy Schoeneck, Renee Brown's mother: Makino Die/Mold Group - OH
- Elsie Spivak: Carol Finkel - AZ; Paul & Aimee Grace - MA; New Jersey: Hannah & Ben Baker; Mr. & Mrs. Philip Chappine Sr; Jackie & Hank Herskowitz; Norman & Sonny Kanefsky; Pennsylvania: Neal & Barbara Blatt; Sheila & Lou Cheifetz; Mr. & Mrs. Bernard Elias; Paul & Sheri Goldstein; Merle & Jeff Marder; Joel Neulight; Mr. & Mrs. Jack Persky; Carole S. Rose; Shelley & Harry Ruben; Mr. & Mrs. Harry Satinsky; Ms. Belle Simon; Ms. Terri Wallace

Honoring with Christmas wishes

- Paul & Annabelle Closson to Jason Closson and Janice Caldwell



Ms. Kim Harwood, Hermantown, Minnesota with her 1999 hand sewn Christmas handcrafts.

FSH Society Membership Application—Donation

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- Other \$ _____

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- Please check here if you would like your membership or donation acknowledged in the next issue of the FSH newsletter.

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Please make checks payable to the FSH Society and send contributions to:

Carol A. Perez, Executive Director, FSH Society, Inc. 3 Westwood Road, Lexington MA 02420 USA

Please Note: Checks or money orders from outside the United States should be in US dollars from institutions with US bank affiliations.