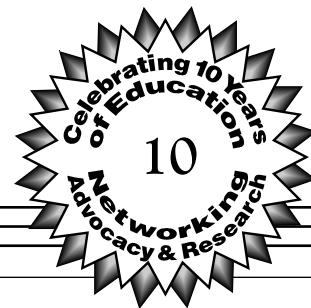


FSH Watch

A publication of the FacioScapuloHumeral Society



NIAMS requests input from the FSH Society on long-range planning issues in the area of muscle biology and muscle disease

On July 20, 1999, the *FSH Society* participated in the Muscle Biology and Muscle Disease long-range research panel at the National Institute of Arthritis, Musculoskeletal and Skin Diseases (NIAMS) in Bethesda, Maryland. At the invitation of **Stephen I. Katz**, M.D., Ph.D., Director of the NIAMS, **Daniel P. Perez**, President of the *FSH Society*, served on this panel and was the only Volunteer Health Organization presenting input on the panel. The NIAMS brought together a small and diverse group representing different interests within muscle disease and muscle biology to help determine long term (two to four years) research opportunities. Dr. Stephen I. Katz, **Richard Lynn**, Ph.D., Director, Muscle Biology Branch and Extramural Program Officer, **Kuan Wang**, Ph.D., Chief, Laboratory of Physical Biology

and Intramural Program officer, **Helen Simon**, Chief of the Office of Program Planning and **Janet Austin**, Director, Office of Communications and Public Liaison (OCPL) were present. The NIAMS indicated that some of the needs presented by the panel may be addressed in a shorter time frame if resources are available.

Both the *FSH Society*, and the director and staff of the NIAMS agreed that the panel yielded insight and progress in understanding issues from varied perspectives. Lastly, the discussion led to excellent progress regarding research opportunities and needs for NIAMS in the area of Muscle Biology and Muscle Disease, including facioscapulohumeral muscular dystrophy.

The NIAMS is requesting input into this

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Molecular genetics advances research

—Sara T. Winokur, Ph.D., Assistant Researcher, University of California, Irvine

The genetic mutation that causes FSHD appears to be a very unusual one. In greater than 95% of individuals with FSHD, a deletion in 3.3 kb repeat sequences has occurred in the DNA near the end (telomere) of chromosome 4q. This region of the chromosome contains many repetitive sequences that do not actually encode genes. These repetitive sequences (including the 3.3 kb repeat) are more likely involved in other functions such as chromosome stability and regulation of where (what tissue) and when (during development) genes are expressed. The type of regulation that likely occurs in the FSHD gene region is called a "position effect," meaning that the genes that are close in position to the repeat sequences will be affected by whether or not there is a deletion in the total number of 3.3 kb repeats. The 3.3 kb repeat, when present in more than eight copies or so (corresponding to an EcoRI

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Elizabeth "Betsy" Conron before submitting Testimony before the United States House of Representatives Subcommittee on Labor, Health and Human Services and Education and Related Agencies regarding appropriations for the National Institutes of Health (NIH) for FSHD research April 29, 1999. Please see related story on page 7.

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You will receive that, and more than you have asked for as well

The Story of Iron John, Jacob and Wilhelm Grimm, Grimms Marchen

—Daniel Paul Perez, President & CEO, FSH Society

From the President,

At the request of the Board of Directors of the *FSH Society*, I accepted the full-time salaried position of President and CEO to bring the *FSH Society* to the next stage of organizational development. I am delighted to have the opportunity to facilitate this transition. Dr. **Stephen J. Jacobsen** has been asked to take the helm of the *FSH Society* as Chairman of the Board and in May, 1999, we completed the changes.

May, 1999, also was the tenth year anniversary of my first meeting with Dr. Jacobsen at the University of California San Diego in La Jolla. The *FSH Society* emerged from our meeting then and today we are advancing our cause with the staffing needed to meet the demands of managing FSHD research issues.

This edition of the *FSH Watch* is dedicated to research and the *FSH Society's* efforts to promote FSHD. We continue to create opportunities for solutions for individuals involved with FSHD. We constantly advocate for research and networking, and we push with diligence for progress on FSHD. Our message is clear: research must be done on FSHD anywhere in the world. The *FSH Society* has done everything possible within the constraint of its current budget to provide the highest quality service, information and efforts for finding a treatment for FSHD. Note that the income of the *FSH Society* in 1998 (excluding gifts specifically ear-marked for research) was US\$87,365.75. Although this money has been carefully monitored and well spent, we need to have staff working full time to become a truly effective organization promoting our cause. We can not do that under our current budget. The Board of Director's takes its fiduciary responsibilities very seriously and has completed the necessary independent audits and maintained a strong financial position to get to the next stage of organizational development. We still need your concerted help to reach our annual goal of US\$400,000 overall with US\$160,000 of that needed in unrestricted funds.

There have been exciting developments since our last newsletter. Testimonies were again submitted this year before the U.S. House of Representatives and the U.S. Senate regarding appropriations for research on FSHD. The *FSH Society* has granted more fellowships to carry out vital research on FSHD. We have had a series of meetings with the Association Française contre les Myopathies (AFM, the

French MDA) which resulted in a direct call for research proposals on FSHD. We have increased our communication and education efforts at the National Institutes of Health (NIH). We were asked to help define the two-to five-year long range goals in Muscle Biology and Muscle Disease at the National Institute for Arthritis Musculoskeletal and Skin Diseases (NIAMS/NIH). The *FSH Society* was the only patient group participating on the muscle planning panel at NIAMS/NIH. Last, we have successfully promoted information on FSHD internationally over the Internet.

The *FSH Society* fellowship program has been overwhelmingly successful and we are making an appeal to the community involved with FSHD to help double the current number of researchers working on FSHD. The fellowship salaries are typically one or two years at US\$30,000 per year. To date, we have funded four (4) two year and three (3) one year fellowships and we continue to have a demand that far outstrips our funding capacity. In this newsletter you will find details of the nature of the projects the *FSH Society* has funded and the excellent quality of fellow that we are attracting to carry out such research. We are indebted to Mrs. **Marjorie Bronfman**, **Larry** and **Ida Laurello** and the countless number of members and donors who have made donations to the Research & Education fund to make this program successful to date.

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 research proposals, 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.

The stories we hear from people living with FSHD span the entire globe. The Internet has brought our Web site (www.fshsociety.org) and chat room ([webboard.novatech.net:7000 #fsh_society](http://webboard.novatech.net:7000/#fsh_society)) into every corner of the world. We know these people who endeavor and persevere with FSHD through the personal triumphs and contributions they make. The spirit of competition and energy resounds in the pages of the *Watch* through fundraising efforts involving physical competition

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Molecular Genetics, *continued from front page*

fragment of greater than approximately 32 kb) seems to form a specialized structure called "heterochromatin" in which the chromosomal DNA is very tightly condensed. In a position effect, this compact structure inhibits genes in the vicinity from being expressed and therefore the corresponding proteins are not produced.

Therefore, this unusual mechanism has made identification of the FSHD gene a challenge for research. The mutation does not appear to be within the gene itself, but rather in repeat sequences which affect a gene somewhere in that vicinity of the chromosome. Therefore, we must examine any and all genes in the FSHD region as to whether those genes have a different pattern of expression, i.e. whether they are turned "on" in FSHD and "off" in normal muscle, or vice versa.

Many FSHD researchers are now taking the approach of examining gene expression in the FSHD gene region. Drs. **Sara Winokur**, **Denise Figlewicz** and **Kiichi Arahata** are utilizing a very powerful technology called microarray analysis to compare the expression pattern of thousands of human genes in FSHD and normal muscle. Dr. Figlewicz is also utilizing a different approach, competitive RT-PCR, to examine the increase in expression of specific genes in the FSHD region. Dr. **Rossella Tupler** has used a third approach, differential display, and found that indeed there are skeletal muscle genes that exhibit increased expression in FSHD. Dr. **Alexandra Belayew** is pursuing the possibility of a gene (*Dux*) actually being expressed from the 3.3 kb repeat. Drs. **Silvere van der Maarel** and **Rune Frants** are examining the expression of *FRG2* (FSHD region gene 2) from the normal and deleted chromosomes. They are also constructing a mouse model of the disease to see whether deletion of the 3.3 kb repeats affects gene expression in the mouse.

Another important direction of research over the past year has been the effort to sequence a large region near the telomere of chromosome 4q. This is invaluable, because new genes in the FSHD region are likely to be uncovered by this approach. **Michel van Geel** and Dr. **Pieter de Jong** have succeeded in sequencing over 400,000 base pairs of DNA from the FSHD region. This is especially remarkable, as generating sequence is encumbered by the large number of repeats in the FSHD region. Dr. **Jane Hewitt** has continued with her studies on the evolution of the FSHD gene region which will help to identify those conserved sequences and genes that function in the disease process.

We must keep in mind, however, that although most of the scientific data points to a position effect as causing FSHD, that this remains a hypothesis until proven unequivocally. Therefore, another important

direction of research will be to study the biochemical and chromosomal basis of gene regulation and position effect in FSHD. The components of heterochromatin in the FSHD region must be identified as this will yield a greater understanding of the disease mechanism. However, the past few months have been an exciting time in FSHD research as new approaches to identifying and characterizing the gene defect have led to greater insight into the disease mechanism and fostered much interaction between the numerous laboratories working to solve the FSHD "puzzle." The direction of scientific research into FSHD will therefore likely focus

on 1) gene expression 2) further sequencing of the FSHD region 3) investigation of heterochromatin and gene regulation and 4) animal models of the disease. The consortium of FSHD researchers will meet at a FSHD workshop in San Francisco on October 19, 1999 to exchange experimental findings and discuss the insight gained over the past year into the FSHD disease process. A detailed summary of the research finding will be published in an upcoming issue of the *FSH Watch*. v

Advances in FSHD research sheds light

by *Rabi Tawil, M.D., Associate Professor of Neurology, University of Rochester School of Medicine and Dentistry*

Several published studies over the past year address clinical issues in FSHD. Two recent articles examine the issue of genetic testing and confirm the accuracy of the DNA testing procedure as currently performed. They also help define the range of mutation sizes seen in FSHD by screening a large number of families. One of the articles also confirms the previous finding of a strong correlation between the size of the mutation and the severity of muscle weakness.

FSHD is not usually thought of as involving the brain. However, a study from Japan reports a high incidence of mental retardation and seizures in individuals with severe FSHD who have very large DNA deletions on chromosome 4. A single previous report, also from Japan, reported the occurrence of seizures in an individual with FSHD. No such association has been observed in other populations.

The large, controlled trial of albuterol being conducted by the Ohio State University and the University of Rochester is entering its final phase. The target enrollment of 90 individuals with FSHD has been reached and final results from the study are expected in early 2000. Another compound, of potential benefit to individuals with FSHD, has recently received attention in the press. Two small studies which included a variety of neuromuscular conditions, including FSHD, demonstrated improvement in overall strength following short-term supplementation with creatine monohydrate. Creatine is a natural substance found in meat and is the first source of energy used by muscle during vigorous exercise. Creatine supplementation in normal athletes, at best, shows only slight improvement in performance during high-intensity, short-term exercise. These studies, although preliminary, suggest that creatine may have added benefits in muscles affected with a dystrophy. Further, long term studies evaluating the effects of creatine in individual neuromuscular disorders are needed to confirm the long term safety and efficacy of creatine monohydrate. v

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NIAMS requests information, *continued from front page*

plan from the public and the NIH Advisory Council on its Internet Web site to develop the final presentation to Dr. **Harold Varmus**, Director of the National Institutes of Health (NIH) later this year.

The following recommendations from over 35 members of the scientific community working on FSHD, the *FSH Society's* Scientific Advisory Board, Board of Directors, members and General Counsel were presented:

State of Understanding of FSHD

Facioscapulohumeral muscular dystrophy (FSHD) is the third most common form of inherited muscle disease following Duchenne and myotonic dystrophy. The incidence of FSHD is conservatively estimated at 1 in 20,000 (or as many as 15,000 cases in North America). The estimated incidence of 1/20,000 may be low and there may be three times as many cases due to the number of sub-clinical and undiagnosed cases. In spite of the great successes in positional cloning in the past decade, the gene responsible for facioscapulohumeral muscular dystrophy (FSHD) has not been identified. The genetic defect associated with FSHD was mapped to the terminus of the long arm of chromosome 4 nearly ten years ago (in 1990) and the identification of a genetic rearrangement, deletion of 3.3 kb repeats, followed quickly in 1993. Since then, progress on FSHD has been painfully slow.

It has been demonstrated that the 3.3 kb repeat is immediately adjacent to the telomere of human chromosome 4q, that it has significant sequence similarity to known classes of constitutive heterochromatin, and that related loci exist throughout the human genome, predominantly in regions known to be heterochromatic. Furthermore, evolutionary studies of the repeat demonstrate the dispersion of the repeat was a relatively recent event in primate evolution. The immediate proximity of the 3.3 kb tandem repeat to the telomere and the sequence similarity to constitutive heterochromatin suggest that this repeat, deleted in FSHD, lies in telomeric heterochromatin. This conclusion is further supported by the fact that, despite intense efforts over the past seven years, there have been no protein coding transcripts identified from this repeat sequence. In addition, interchromosomal translocations suggest that the gene responsible for FSHD lies proximal to, and not within, the repeat itself. Integral deletions of the heterochromatic D4Z4 repeat appear to disrupt the normal expression of these genes, a phenomenon akin to position effect variegation in *Drosophila* and telomere silencing in yeast. Attempts to identify the gene(s) involved in FSHD have been thwarted

by its unusual molecular genetic mechanism and the repetitive nature of the genomic region. It appears that we are dealing with a novel disease mechanism with respect to FSHD that once understood will yield tremendous scientific opportunities in many other areas.

What then are the most significant long range research opportunities and issues for the NIH in the area of Facioscapulohumeral Disease (FSHD) research over the next two to four years (FY 2001-2003)?

Research Opportunities

The first area of opportunities/issues for FSHD Research at the NIH commits to funding FSHD research in the following areas:

1. cloning the gene(s), characterizing the nature of mutations in the gene(s) and regulation of the gene(s);
2. launching a major effort to understand the normal function of the FSHD gene(s) and how its alteration causes the disease;
3. conducting natural history studies to provide a baseline for future therapeutic techniques; and
4. developing therapies based on information in 1, 2, and 3 above.

The second area of opportunities/issues for FSHD Research at the NIH are extramural contact programs or intramural programs for FSHD whose areas of focus are:

5. sequencing the entire 4q35 region 15 to 17 megabases (Mb) from the telomere;
6. expression of the FSHD gene(s),
7. regulation of FSHD gene(s);
8. understanding the whole biochemistry of cells and tissue to yield targets for therapeutic agents;
9. to continue to search for candidate genes, through such approaches as differential display and genomic scanning;
10. to investigate experimentally the position effect hypothesis and its basis in chromatin structure;
11. to further pursue animal models such as the mouse and *Drosophila*;
12. to examine genetic heterogeneity;
13. to examine phenotype/genotype correlations regarding intra/interfamilial variation and nonmendelian inheritance;
14. clinical trials;
15. continued sequencing of the FSHD region;
16. examining the structure/function relationship of the D4Z4 repeat;
17. diagnostic improvements;
18. ethical and legal and societal issues regarding diagnostics;

19. examining the role of non-muscular sensory systems;
20. creating a bank of important reagents, tissue and cell resources;
21. developing cell-based assays for gene expression;
22. developing standard biochemistry techniques and approaches for understanding gene regulation; and
23. to develop new and needed informatics, database and computational biology tools.

Research Projects

The third area of opportunities/issues for FSHD Research at the NIH are the following five (5) "Out-of-the-box (OOTB)" strategies and projects requested as necessary areas for funding by the *FSH Society* Scientific Advisory Board (SAB) to accelerate information and progress on Facioscapulohumeral Disease (FSHD) research.

Project 1. The complete sequencing of chromosomal band 4q35 is ongoing, should continue and should not be distracted by "genome politics." Given the repetitive complexity of the region, sequence-based gene identification may be the only way to identify all of the potential coding segments. In fact, it is not clear that we have in hand the informatics tools necessary to identify genes based solely on sequence but we will not want to wait for the sequence if such tools become available. Furthermore, a variety of efforts utilized clone-based gene finding methodologies (like exon amplification and direct selection). Unfortunately, many of the subsequent products also turned out to be mildly repetitive. Together co-linear genomic sequence and these apparently "transcriptionally" competent sequences may be used to identify protein encoding genetic elements.

Project 2. Cloning syntenic loci from non-human primates. The demonstration that the amplification and dispersion of the D4Z4 repeats is a relatively recent event in primate evolution, and is an important finding. Much of chromosome structure and gene organization is conserved in primates. The further one descends down the primate tree, the fewer the number of copies of D4Z4 repeats. So that, in the rhesus monkey, perhaps only two repeat segments exist. It may be that protein encoding genes that were obscured by the amplification and dispersion of repeats during primate evolution could be isolated by a focused effort in rhesus using the D4Z4 syntenic sites as a nucleation point. Cloning these segments and subsequently employing clone-based and

NIAMS requests information, *continued from page 4*

sequence-based gene finding methods could identify the rhesus homologs of genes important to the pathophysiology of FSHD. The human homologs of these genes could then be identified and the biochemical and physiological properties of the genes assessed.

Project 3. There exists in mice a genetic defect with a dystrophic phenotype that maps in a region syntenic with several loci from 4q35. The D4Z4 locus is not found in mice. Therefore, the mechanism of dystrophy may be quite different. However, the finding of a gene linked to 4q35 loci that contributes to a dystrophic phenotype in the mouse is significant and should be vigorously pursued. The gene should be cloned and human homologs sought. Mechanistically, the role of D4Z4 repeats in chromatin-mediated gene expression is being studied in *Drosophila*. If successful, this approach could be employed in reconstitution experiments to identify components of the process.

Project 4. The ability to track the expression of complete cellular populations of genes in response to specific stimuli is one of the most exciting recent developments in cell biology. A variety of methods have evolved for this purpose, including: differential display, a PCR-based method that identifies differences in mRNAs present in two cell populations; array based hybridization, in which specific nucleic acids are immobilized on a solid support and interrogated by probes derived from specific cell types and imaged digitally; and SAGE, the serial analysis of gene expression, in which the frequency of a specific sequence signatures can be measured.

The use of two-dimensional microarrays is particularly infatuating. Not only because it represents a rapid and quantitative approach for the study of genetic regulatory networks, but also because microarray proponents exalt that the entire coding component of the human genome could be interrogated in a single experiment occupying the space of a postage stamp. Unfortunately, the current costs of manufactured arrays and devices for reading them have limited their widespread availability and use. However, it is likely that these technologies will emerge as important contributors to our understanding of cellular differentiation at the molecular level, whether these differences are cell type (i.e. skin vs. neuron) or cell state (FSHD affected vs. non-affected).

When hybridized with labeled probes synthesized from total cellular mRNA, the microarray provides a snapshot image of the expression level of all the genes represented by the arrayed cDNAs. Using double labeling techniques, microarrays allow the simultaneous

comparison of gene expression generated from two different cellular states providing a powerful means for elucidating the cellular biochemistry of disease in its entirety. The expression of tens of thousands of genes can be simultaneously monitored, so that the basic pathophysiologic process reveals itself through identification of the protein pathways and complexes involved. FSHD is particularly amenable to this approach, as current data implicates a global deregulation of genes effected by deletions of regulatory chromatin in this disease. Microarray analysis is also a potent means of discriminating between the primary cause and secondary effects of muscular dystrophy as well as the evaluation of therapeutic approaches to FSHD.

Project 5. The D4Z4 repeat is likely involved in the regulation of genes in the FSHD region. Heterochromatin is known to regulate gene expression in many other species. Although the DNA components of this heterochromatic complex in FSHD are now well defined, virtually nothing is known about the proteins that are involved in this regulatory complex. Indeed, little is known in general about the mechanism by which higher order chromatin structure regulates gene expression in the human.

Identification of these protein components is critical to our understanding of FSHD and may provide a means in the future to therapeutically approach the aberrant regulation of genes in this disorder. Recent developments employing mass spectrometry (MS) for the analysis of multi molecular complexes provides an approach to the identification of small quantities of proteins isolated from biological systems. As little as one to two ng of protein isolated from a silver-stained 2-D electrophoretic gel can be accurately identified by this approach. It may be possible to isolate FSHD-associated heterochromatic complexes and analyze these by MS.

Research Organization

The NIH needs to re-evaluate and re-assess the research granting process at the NIH for FSHD and the mechanisms in place for facilitating and enhancing research progress on FSHD. The NIH needs to evaluate the process of requesting applications on FSHD, evaluating grants on FSHD and coordinating intramural and extramural efforts on FSHD. The current process is not adequately designed for new, novel, untried and untested research ideas that require "Out-of-the-box" (OOTB) thinking and experimental strategies. The broad-based study sections are not structured to recognize the major difficulties and nuances of the FSHD

problem. To re-iterate, we are dealing with a novel disease mechanism with respect to FSHD and FSHD research is an extraordinarily interesting, challenging and difficult scientific problem with tremendous application to other areas of research.

At present, the NIH conventional funding and broad-based study section evaluation strategy does not readily lend itself to the needed focus on FSHD. The research community needs a clear call for research and a clear assurance that the time consuming and labor intensive effort of writing NIH grants will be met with responsible calls for research through contract, RFA, RFP mechanisms, or any other mechanism that indicates to the research community that there are monies set aside and associated with the request. We were pleased with Program Announcement PA-98-044 titled "*Pathogenesis and Therapy of the Muscular Dystrophies*" but had concerns regarding the routing for grants and evaluation of grants and monies available for applications.

The *FSH Society* suggests that the NIH, with NIAMS leadership, establish a National Task Force on Muscle Biology Research Organization to consider the following questions:

1. Is the current study section organization adequate for muscle biology research proposal evaluation?
2. Does the current division of responsibility between NIAMS and NINDS promote FSHD and muscle biology research? If not, what other organizational options are available?

Since the conventional broad-based study section is inadequately designed for evaluating grants on FSHD or unaware of the complexities of FSHD, a new "special" study section must be created to evaluate research grants on FSHD. A broad-based study section evaluates 80 to 90 grants. We would not request that a new broad-based study section be enacted for FSHD, but would suggest that a new broad-based study section should be created for Muscle Biology and Muscle Diseases. NIH should enact a newly created "special" study section for FSHD that must be comprised of bright, creative, focused and OOTB thinkers capable of evaluating FSHD research. Researchers capable of evaluating FSHD grants in this manner might be **Michael Altherr**, Ph.D. (Los Alamos), **David Housman**, Ph.D. (MIT), **Robert Griggs**, M.D. (University of Rochester), **Doug Marcheuk**, Ph.D. (Duke), **Rita Shiang**, Ph.D. (Virginia Medical College) and **Jeff Murray**, Ph.D. (University of Iowa).

What is the rationale for the creation of a special study section for FSHD? FSHD presents

NIAMS requests information, *continued from page 5*

challenges and issues that are unique in the field of genomics and will yield scientific opportunities in many other areas. FSHD needs a set aside with a special call for research in the areas determined valuable by advisory panels in the form of an RFA. An RFA is needed given the difficulty of the FSHD problem and the need for a concerted and focused effort in this area. The subsequent proposals should then be evaluated by a "special" study section capable of peer reviewing and providing evaluation on the unique and complex aspects of research on FSHD.

Furthermore, NIH should consider the creation of an Office for Muscle Biology and Muscle Disease Research (OMBMD) or an Office for Muscular Dystrophy Research to coordinate inter-institute initiatives. The Office for Muscle Biology and Muscle Disease Research (OMBMD) should be at the Director's level in Building 1 and, following that, should be located at the institute level (NINDS, NIAMS). FSHD research has been significantly impaired by inter-institute competition for jurisdiction over the area and has created the situation of allowing FSHD to "fall through the cracks." Lastly, the NIH needs to investigate the benefits and gain that would be offered by creating a separate Institute at the NIH for Muscle Biology and Muscle Disease Research (NIMBMD). The muscle biology budget is certainly as large if not larger than current small-sized institutes at the NIH.

The fourth area of opportunities/issues for FSHD Research at the NIH should be:

1. the set aside of appropriate funds to address and explore the scientific opportunities and mechanisms of Facioscapulohumeral Disease (FSHD) with the aim of accelerating progress and understanding in this unique area;
2. recruitment of OOTB researchers to help with long range planning, opportunities and issues with respect to FSHD and to evaluate proposals received in the appropriate designated special study section;
3. the issuance of RFAs, RFPs or contracts on FSHD and the creation of programs to attract and expedite extramural grant applications and intramural projects based on input from the special advisory committee on FSHD;
4. the creation of a "special" FSHD study section to evaluate the subsequent grants received for FSHD and its related genomic issues;
5. the creation of a regular broad-based study section for Muscle Biology and Muscle Disease Research;
6. the creation of an Office for Muscle Biology and Muscle Disease Research

at the director's level (Dr. **Harold Varmus**) to coordinate cross institute initiatives; and

7. an evaluation of the feasibility and benefit of the creation of a separate NIH Institute for Skeletal Muscle Biology and Muscle Disease Research.

Current Research Organization Projects

Many projects to enhance FSHD research at the NIH can be implemented in the immediate future. They include the following fifth area of opportunities/issues for FSHD Research at the NIH:

1. implementing the Congressional directive for a research conference on FSHD;
2. the creation of major and minor Centers of Research Excellence (CORE). Minor is \$200,000-\$300,000 per year and major is \$2,000,000-\$3,000,000 per year. Three or four minor centers and one major center need to be established for FSHD,
3. intramural NIH programs for FSHD research; and
4. extramural contract programs for FSHD whose areas of focus are outlined above in the first, second and third areas of opportunity/issues above.

Lastly, joint projects that would be good for the *FSH Society* and NIH include the following sixth area of opportunities/issues for FSHD research at the NIH:

1. the creation of an annual international research planning conference on FSHD;
2. the creation of a FSHD workshop that pulls together researchers in the field of FSHD and from new areas of research to facilitate open exchange of ideas in an environment that is non-threatening to researchers; and
3. the creation of literature, brochures and books on FSHD for the research, medical and patient communities.

Additional thoughts and issues to be included in report to the NIAMS

Clinical research usually involves high profile diseases with a high enough incidence to attract pharmaceuticals and industry investors. Given the set of diseases in muscle disease and the incidence of muscular dystrophy, it is difficult to conduct clinical trials underwritten by industry and the pharmaceuticals. This is further complicated by the fact that it is more difficult to isolate large single entities of a disease for study as the disease become more characterized. Limb Girdle Muscular Dystrophy (LMGD) now has a dozen different sub-types. Programs to encourage industry and

pharmaceutical investment and expansion into FSHD and muscle disease by NIH should be developed. NIH could help with clinical trials in this area.

The genetic information far outstrips the clinical information we have on FSHD and muscle disease. NIH should help to develop programs that help characterize clinical features of FSHD and muscle disease. The genetic information we have needs to better correlate to the phenotype and clinical characteristics of FSHD and muscle disease. We need to know more about these diseases clinically to better understand how to intervene pharmacologically or genetically. NIH needs to establish a patient registry for FSHD and other muscle diseases to assist with this dimension of the problem. Epidemiology studies need to be undertaken now that we have tens of thousands of individuals with FSHD on record.

Muscle biologists and muscle disease experts need to develop surrogate measures and markers to better understand progression and milestones in FSHD and muscle disease. The tools we have now are crude, time consuming and can have difficult chemistry to analyze e.g. using dexascan to calculate lean body mass, urine collection for creatinine. NIH needs to develop technologies and applications to better track muscle disease. Newer technologies such as MRI need to be examined.

NIH can help the clinicians involved with FSHD and muscle disease by forming a multi-centered working group to help strategize and examine problems in muscle disease and to help co-ordinate and initiate new clinical trials, treatments and interventions for FSHD. A muscle study group is needed such as the one for Parkinson's disorder. FSHD needs the resources and expertise associated with a 20- to 30-center group given the clinical and scientific complexity of the FSHD disorder.

Technology transfer and foreign research investment needs to be evaluated in FSHD. Internationally there are agencies that are interested in gene therapy of muscle disease, myology and vectrology with strong desires to harness American research but need assurance that return on investments will be achieved. FSHD could directly benefit from this investment through the NIH if technology transfer and policies issues are adequate for investors and foreign institutions. v

FSH Society statement

Facioscapulohumeral Dystrophy (FSHD) is a muscle disease with a frequency in the population of between 4 and 10 per 100,000. The disease is inheritable; the genetic defect or responsible gene(s) is located on chromosome 4 for most individuals with FSHD. For individuals not linked to chromosome 4, the disease locus is still not yet known. The expression of symptoms requires inheritance of the defective gene from only one affected parent. An individual of either sex has a fifty percent chance of inheriting the gene from that affected parent.

The disease pathology includes 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 distinguish 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.

The Facioscapulohumeral Society (*FSH Society, Inc.*) is an independent, non-profit and

tax-exempt U.S. corporation organized to address issues and needs specifically and solely 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.

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

- to encourage and promote scientific and clinical research and development through education of the general public, government 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. v

FSH Society presents 1999 FY2000 testimony before Congressional Committees

The *FSH Society* successfully launched its 1999 (FY2000) Washington agenda with the testimonies of **Daniel Paul Perez** and **Elizabeth "Betsy" Conron** on April 23, 1999 before the United States Senate and on April 29, 1999 before the United States House of Representatives. The testimonies were presented to both the U.S. Senate and U.S. House Appropriations Committee's, Subcommittee on Labor, Health and Human Services, Education and Related Agencies which set the funding for the National Institutes of Health (NIH) and for neuromuscular research. The *FSH Society* has been working intensively with the members of Congress in both the U.S. House of Representatives and U.S. Senate and wishes to expressly thank the following Congressmen for their responsiveness, professionalism and assistance: Rep. **John Porter** (R-IL), Rep. **Sam Farr** (D-CA), Rep. **Edward J. Markey** (D-MA), Rep. **Randy "Duke" Cunningham** (R-CA), Senator **Arlen Specter** (R-PA), Senator **Edward Kennedy** (D-MA), Senator **John Kerry** (D-MA) and Rep. **Steny Hoyer** (D-MD).

In an eloquent five minute statement presented on April 29, 1999 before the U.S. House Subcommittee, Ms. Conron described what it is like to live with facioscapulohumeral muscular dystrophy (FSHD). Her testimony included a description of FSHD and what it is like to have the disease. Additionally, the testimony pointed out that although the National Institutes of Health (NIH) budget has grown substantially, FSHD research through the NIH has not benefited even with Congressional report language. She stated that despite all of our work with the NIH and Congress that FSHD funding has gone down stating that our situation worsened in 1997 and 1998 when Congressional directives to the NIH regarding FSHD were ignored or no response was given.

In the past years, the *FSH Society* has provided Congress with the clinical picture of the disease, what it is like to live with and have the disease, updated the Subcommittee on recent clinical and genetic advances and presented areas of opportunities with detailed explanation of programs to help accelerate

Dr. Louis Kunkel receives Dana Award

Dr. **Louis Kunkel** of Harvard Medical School and Children's Hospital and Dr. **James Gusella** of Harvard Medical School and Massachusetts General Hospital will share the Dana Award for Pioneering Achievement in Health. Kunkel and Gusella have developed strategies to localize and characterize genes that cause neurological disorders.

Dr. Kunkel is a member of the *FSH Society* Board and Scientific Advisory Board. v



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**

Testimony, continued from page 7

FSHD research. This year, the FSH Society has taken a substantially different approach to past year's testimonies by noting the non-compliance of the NIH with Congressional directives and asking for a five to 10 million dollar earmark for FSHD to move the research ahead at NIH.

Most notable were the time capsule sections of Ms. Conron's testimony which stated the FSH Society's track record of going on record by appearing before Congress and other committees and the comparison of what has happened to her personally during the same six year period.

Ms. Conron had the extraordinary honor of being introduced to Chairman Representative John Porter's (R-IL) Subcommittee by her representative, Representative Sam Farr (D-CA) and special privilege of testifying before Randy "Duke" Cunningham (R-CA) as acting Chair of the Subcommittee. Rep. Cunningham is Dr. **Stephen J. Jacobsen's** Representative in San Diego, California. Even more extraordinary was Representative Farr's introduction of Ms. Conron to the Subcommittee:

Introduction of Elizabeth Conron by Representative Sam Farr:

"Mr. Chairman. Thank you for giving me a moment to introduce today a remarkable woman.

"Elizabeth Conron is the daughter of a constituent of mine, Dr. **William Lewis**. Dr. Lewis saved my life after an auto accident 30 years ago.

"Ironically, I now am able to repay the favor: I get to urge this committee to help save the life of Elizabeth and others like her who suffer from FSHD. FSHD is a debilitating version of muscular dystrophy that gradually destroys a person's ability to use their muscles at all.

"Though there is a body of research on FSHD, not enough work has been done to find a cure or prevention. NIH sorely ignores this disease though it is the third most common form of muscular dystrophy. Most of the research has been underwritten by private donations and foundation grants. Despite the limited dollars in research on this disease, what is known is that the disease is housed on the 4th chromosome. But without more in-depth study and scientific research, it will be difficult to progress much farther in finding a cure or prevention.

"I ask you to hear Elizabeth's story. She is a talented person who has not let the disease debilitate her spirit as it has debilitated her body. Please do what you can to help her and others like her."

The following is the transcript of Ms. Conron's testimony before the U.S. House Appropriations Subcommittee on Labor, Health and Human Services, Education and Related Agencies:

"Mr. Chairman, it is a pleasure to testify today. I am Elizabeth Conron, of Danville, California, a founding member of the FSH Society, who has FSHD.

"Faciocapulohumeral dystrophy or FSHD is an inherited or spontaneous neuromuscular disorder affecting one in twenty thousand people and is the third most prevalent form of muscular dystrophy. FSHD causes progressive and severe loss of skeletal muscle and may be the only dystrophy where the gene has not been identified. FSHD can happen to any of us.

"Diagnosed at Stanford at sixteen, I was physically active until twenty-two. Once an avid snow skier and competitive gymnast, today I walk short distances with assistance.

"FSHD has attacked my major muscle groups. My feet and calf muscles have atrophied so I stand on the outside of my ankles. My hip muscles have weakened so that I no longer rise from a sitting position without assistance. The arch in my back forms the letter "C." I cannot raise my arms above my shoulders. My right hand has weakened and feeding myself is difficult. I now must learn to be left handed. My once big and friendly smile has been replaced with weak and crooked lips. To close my eyes at night, I tape weights to the tops of my eyelids. My joints are swollen and my bones feel as though they rub together.

"Look at me, look at what FSHD has done to me. This is a painful and disabling disease. One by one, we surrender ourselves to wheelchairs. My sister, brother, mother, two aunts and six cousins have FSHD.

"In 1995, I earned a law degree and three American Jurisprudence awards. Writing was so difficult that I had to type my exams and when the elevator broke, classmates carried me up the stairs. This was truly humiliating.

"I have two children – four year old **Caroline** and two year old **William**. My husband and I agonized over the decision to have children. They are adorable and I am a good mom. The uncertainty that FSHD brings to the future of entire families is underestimated and can mean the end of a family line.

"FSHD deprives my family of some basic joys. Caroline and William must climb into my lap so that I can hug them. I can not go on a Ferris wheel with my children, supervise them in a swimming pool or walk along a beach with them. Simply combing Caroline's hair or changing William's diapers are difficult tasks.

"As soon as I make necessary adaptations, I weaken again. I pray that God will stop my FSHD. I have bruised, cut and torn most of my body from falls. I taught Caroline at age 2-1/2 to dial 911 and say, 'Mommy fell and won't wake up.'

"Without a cure for FSHD, I will continue to weaken. Please help me fight this disease

now. If you had FSHD, you would fight to defeat it.

"I am a good person. I did not deserve a lifetime of FSHD. I want to walk with dignity, catch William as he comes down a park slide, button Caroline's dress and hold my husband in my arms. And, I want my smile back.

"Thanks largely to your efforts, Mr. Porter, NIH funding has grown. FSHD research through the NIH has not benefited even with Congressional report language. We have met with the NIH, testified before Congress and FSHD funding has gone down. Our situation worsened in 1997 and '98 when Congressional directives to the NIH regarding FSHD have been ignored or no response given.

"In 1999, no mention was made of FSHD in the draft of the NINDS' *Neuroscience at the New Millennium*. The NINDS has one grant directly titled for FSHD and the NIAMS currently has nothing.

"Mr. Chairman, it is heartbreaking that FSHD, a neurological disease almost exclusively musculoskeletal in effect, can not gain support from the very institutes that have the word 'neurology' and 'musculoskeletal' in their names.

"We have come before you in 1994, '95, '97, '98 and again this year. In 1994, the NINDS and the NIAMS funded \$300-500,000 dollars on FSHD and today are funding less than \$250,000.

"I lost my ability to rise from sitting in 1994, to climb stairs in '95, to drive my car without adaptation in '96, to walk in '97 and to get up after falling in '98. It is now 1999 and I have to move from the home I love due to lack of progress on FSHD. When will the NIH take responsibility for FSHD research?

"Mr. Chairman, you trusted that the IOM and the NIH would set its priorities correctly. We were forced to give testimony from the back of the room at the IOM because it was not wheelchair accessible. Mr. Chairman, the NIH is not listening to Congress or the scientific community and patients regarding FSHD research.

"Mr. Chairman, we request that an amount of not less than five (5) million and not more than ten (10) million dollars be earmarked for FSHD research. We know that this Committee does not like to earmark. The record of five years indicates that the NIH ignores Congressional direction and scientific opportunities. Earmarking appears the only way to get the NIH's attention.

"I am submitting a longer statement from the FSH Society for the record.

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

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Both Representatives Farr and Cunningham thanked Ms. Conron for her excellent and profoundly moving testimony and assured the witness that everything possible would be done to help honor the request. The following is the longer version and written testimony presented by Mr. Perez and Ms. Conron on behalf of the members of the *FSH Society* for the record on April 29, 1999 to the U.S. House of Representatives:

"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 of the *Facioscapulohumeral Society* and as an individual who has this disorder.

"As a chief patient activist for the tens of thousands of individuals living with *Facioscapulohumeral Disease (FSHD)* in the United States, I will continue to argue the case of wanting to live life free from disease.

"My testimony is about the profound and devastating effects of a disease known as *Facioscapulohumeral Disease* which is also known as *FSH Muscular Dystrophy* or *FSHD*, and the urgent need for NIH funding for research on this disorder. In past years (1994, 1995, 1997, 1998) and again this year we will submit testimony before both House and Senate Committees which states that NIH and Congress could help bring about a significant research and scientific discovery program which, with modest investments, would benefit hundreds of thousands of people worldwide.

"The *FSH Society* has previously informed the members of this Committee of the United States Congress on the need and rationale for research on *FSHD*. We have updated you on the most recent developments in clinical medicine with respect to *FSHD*, kept you abreast of the latest breakthroughs in the molecular genetics of the disease and given you insight into the difficulty of living a lifetime with this disease.

"Thanks largely to your efforts, Mr. Porter, NIH research funding continues to grow to its current level of 14 billion annually. Our gratitude fuels our hope for promising research solutions for *FSHD*. Ironically, I must in all candor express our frustration that promising *FSHD* research support and programs have yet to appear from the NIH, even in light of Congressional mandates and report language for such. While NIH has seen a funding increase of 30 percent in the past decade, *FSHD* research through the NIH has not benefited at all. In fact, research funding has gone down, not up. Since the *FSH Society* first testified before Congress in 1994, *FSHD*

research has decreased from between \$300-500,000 to between \$100-250,000. During this time, Congressional directives to NIH regarding the state of *FSHD* research have been either ignored or responded to in an untimely manner. We have met with NIH officials, testified before the Institute of Medicine Committee and taken the path indicated to put forth our goals and the situation has only gotten worse.

"*FSHD* is a neuromuscular disorder that is inherited in an autosomal dominant fashion and has an estimated frequency of one in twenty thousand (1/20,000). Autosomal dominant means that there is a fifty percent chance that a child will inherit the disease from an affected parent. The prevalence could be as much as three times greater than the estimated frequency stated in the literature due to an undetermined number of sub-clinical cases. The major consequence of inheriting this disease is that of a 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. *FSHD* can be extremely severe and in some forms can lead to an early death. *FSHD* can happen to anyone of us.

"In 1997, the *FSH Society* submitted testimony to Chairman John Porter before the U.S. House of Representatives and to Senator Arlen Specter before the U.S. Senate requesting appropriations for research on *FSHD* and the need for Congressional input to the NIH to initiate research in this area.

"Report language was issued on July 22, 1997 stating: '*Facioscapulohumeral disease*— The Committee has heard compelling testimony about *facioscapulohumeral (FSH) disease*, which causes a progressive and severe loss of skeletal muscle. *FSH* research includes aspects such as molecular genetics, neurological function and muscular dystrophy involving multiple NIH Institutes. The Committee encourages NIH to take steps to stimulate research in this area and requests NIH to develop a plan for enhancing NIH research into *FSH* disease, including an assessment of whether an intramural research program in this area would be beneficial.'

"In 1998 the *FSH Society* again submitted testimony to Chairman John Porter before the U.S. House of Representatives and to Senator Arlen Specter before the U.S. Senate requesting appropriations for research on *FSHD* and the need for Congressional input to the NIH to initiate research in this area.

"By this time, NIH responded to the

1997 Congressional language, a year later: 'The NIAMS and the National Institute of Neurological Disorders and Stroke (NINDS) support research on the many forms of muscular dystrophy including *facioscapulohumeral disease (FSHD)*. In 1990, scientists discovered the general location of the defective gene for *FSHD* on chromosome 4. However, much remains to be learned about the functional changes that accompany the disease and treatments. In April, 1997, the NIAMS, NINDS and the NIH Office of Rare Diseases, along with the *Facioscapulohumeral Society*, held a *FSHD* conference designed to identify medical problems associated with the disease and to help focus research efforts by identifying new research opportunities. As the next step in an effort to increase research interest on *FSHD*, NIAMS and NINDS are developing a program announcement to follow up on recommendations from the April meeting. NIAMS, NINDS and the NIH Office of Rare Diseases will continue to work closely on encouraging *FSHD* research and to share relevant scientific advances.'

"One month after our 1998 testimony before the U.S. House of Representatives, NIH issued a program announcement that covered, in part, *FSHD*. PA-98-044 is a response to the 1997 testimony and is over one year late. On

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FSH Society Delta Railroad fellowship recipient Dr. Alexandra Belayew (Leuven, Belgium) presents research findings at the Society-sponsored International FSHD Workshop on October 30, 1998, in Denver, CO.

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March 20, 1998, the NIH issued PA Number: PA-98-044, titled: "Pathogenesis and Therapy of the Muscular Dystrophies." PA-98-044 was sponsored jointly by NINDS and NIAMS and the support mechanisms for grants in this area were the investigator-initiated research project grant (R01) and the program project grant (P01). We were disappointed with the diffusion of our efforts by this program announcement covering not just FSHD but all of the muscular dystrophies.

"Additionally in 1998, we testified before the Institute of Medicine (IOM) responding to its four-part directive from Congress on priority setting for research at the NIH. We were forced to submit the IOM testimony from the back of the auditorium as it was not wheelchair accessible. We testified before the IOM Committee regarding the area of report language: '... We find that the NIH response did not directly address the questions asked by the committee regarding the development of a plan for research in the area of FSHD research and regarding the possibility of intramural research in the area of FSHD research. The response we received did, in fact, dilute our efforts to accelerate and enhance research directly on FSHD by opening up a program announcement to all of the muscular dystrophies when in fact the request was for FSHD research.'

"In 1998, report language appeared in three sections of the U.S. House and U.S. Senate Appropriations budget under NIH, NIAMS and NINDS. The report language is as follows:

'The Committee was pleased with the Institutes' response to last year's request which encouraged NIH to stimulate research in the area of facioscapulohumeral disease (FSHD). However, the committee notes that NIAMS has not responded in developing a plan for enhancing FSHD research, and has not

addressed the question of whether an intramural program in this area would be beneficial. Therefore, the Committee urges NIAMS to conduct a research planning conference in the near future in order to explore scientific opportunities in FSHD research, both intramurally and extramurally.'

"No response was heard from NIH in 1998 for the 1998 language. FSHD researchers expressed disbelief both with the lack of funds and with the grants turned down. In 1998, NINDS and NIAMS funded no less than \$100,000 and no more than \$250,000 on direct FSHD research.

"This year NINDS asked for our input on a draft document titled, 'Neuroscience at the New Millennium' outlining priorities for NINDS 2000-2001. There was not one mention of FSHD nor was there any program that explicitly and suitably covered research on FSHD. My comments to Dr. **Fischbach**, Director of NINDS, and Dr. **Varmus**, Director of NIH, were:

'I have some comments after having reviewed your document "Neuroscience at the New Millennium - Priorities and Plans for the National Institute of Neurological Disorders and Stroke Fiscal Years 2000-2001." It is clear to me, if not completely black and white, that the formulation of the plan does not account for or even give consideration to FSHD and is not adequate with respect to FSHD.

'Of the greatest concern to me is no direct mention of FSHD in any of the sentences, clauses or paragraphs in the document I received, "Neuroscience at the Millennium," despite strong Congressional report language on the issue. I do not see the scope expanding to cover diseases such as FSHD for which there is no known gene—and for which there may never be a gene per se. Where in this program is FSHD covered?

'The NINDS plan is not consistent with recent congressional mandates and report language which instruct NINDS for more involvement in FSHD research. Despite repeated meetings and work with the various institutes at NIH, and assurances the responsibility and jurisdiction with respect to FSHD research is shared across institutes, NINDS does not reflect this in the current document.

'Both the House and Senate Appropriations Reports have language for this fiscal year and the last fiscal year that instructs and authorizes NINDS and NIAMS for plans and priorities with respect to FSHD.'

"In 1999 to date, NINDS has only one newly issued grant in its portfolio that is directly titled for FSHD. When we called NIAMS, the secretary who

answered incorrectly informed us that NIAMS does not do research in muscular dystrophy. In 1999 to date, NIAMS has no grants presently issued with FSHD in their title. NIAMS states that it is beginning the process of organizing the research conference for the spring of 2000 but we have absolutely no indication of movement in this area. NIAMS again points us towards the MDA which has recently started gene therapy trials in limb-girdle muscular dystrophy. FSHD is not limb-girdle muscular dystrophy. NIH must understand that FSHD requires their attention. NIH must understand that FSHD may be the only muscular dystrophy for which the putative gene has not been identified.

"FSHD researchers still express incredulity with the lack of funds and rejection of grants submitted by the top laboratories in the world. In 1999, NIAMS currently has funded \$0 (zero) on direct FSHD research.

"Mr. Chairman, it is ironic that with FSHD being a primary neurological disease which is almost exclusively musculoskeletal in its effects, it can not gain support from the very institutes that have 'neurology' and 'musculoskeletal' in their names.

"Mr. Chairman, we know that the Committee is overwhelmed in hearing from patient groups such as ours. We know that you trusted that the Institute of Medicine (IOM) and the NIH would set its priorities correctly. The truth is that we have come before Congress to testify year after year, given testimony in a wheelchair from the back of the room at the IOM, worked hard to have NIH take a more active, deliberate and responsible role, and yet the NIH is not listening to the Congress, the scientific community and the patients on this issue.

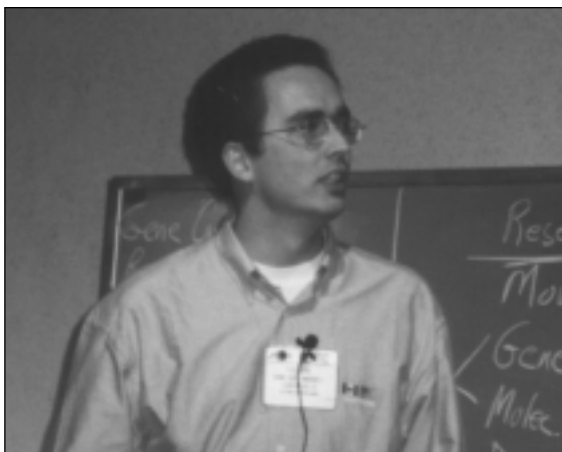
"Mr. Chairman, this is a clear and disturbing trend.

"Although FSHD research may have benefited indirectly from NIH funding of the Human Genome Project, direct funding of FSHD research by the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Arthritis, Musculoskeletal and Skin Diseases (NIAMS) at NIH has been minimal.

"The total NIH funding for directly titled FSHD research currently for the fiscal year 1999 (FY99) is approximately three hundred thousand dollars.

"FSH Muscular Dystrophy has a prevalence of 5-10/100,000 persons, Amyotrophic Lateral Sclerosis (ALS), also known as Lou Gehrig's disease, has a prevalence of 1-2/100,000 persons and Charcot-Marie-Tooth (CMT Type 1, 2, 3) has a prevalence of 1/15,000 persons. Even though FSHD may have a greater prevalence in the population than CMT and be

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FSH Society Marjorie Bronfman fellowship recipient Dr. Silvere van der Maarel (Leiden, Netherlands) presents research findings at the Society-sponsored International FSHD Workshop on October 30, 1998 in Denver, CO.

Testimony, *continued from page 10*

similar in magnitude to ALS, it has received far, far significantly less from NIH funding sources.

"Mr. Chairman, there presently is very little funding of FSHD from NIH—perhaps three hundred thousand dollars. I re-iterate, this is clearly inadequate given the recent advances and the high likelihood of making significant progress in the very near future. With a budget of 14 billion dollars, NIH is spending such a miniscule amount on FSHD research. This tiny amount is utterly unconscionable and defies logic and reason given the prevalence of FSHD and the cost of doing molecular genetics research in 1999.

"Mr. Chairman, we ask the Subcommittee to earmark a dollar amount to FSHD research. We request that an amount of not less than five (5) million and not more than ten (10) million dollars be earmarked for FSHD research. We know that this Committee does not approve of earmarking. However, the record of five years indicates that NIH ignores Congressional direction as well as scientific opportunities. Earmarking appears to be the only way to get NIH's attention.

"The FSHD community demands that the Congress of the United States of America take action on funding research on FSHD. We are asking today for a promise to people living with FSHD which commits to funding FSHD research in the following areas:

1. Cloning the gene, characterizing the nature of mutations in the gene;
2. Launching a major effort to understand the normal function of the FSHD gene and how its alteration causes the disease;
3. Conducting natural history studies to provide a baseline for future therapeutic techniques; and
4. Developing therapies based on information in 1, 2, and 3 above.

"Additionally, the FSHD community is requesting that Congress ask NIH to research and make recommendations on the following:

1. Increasing the number of applications received and accepted from

investigators working on FSHD;

2. Creating a Center of Research Excellence (CORE) for FSHD research;
3. Enacting intramural NIH programs for FSHD research immediately;
4. Extramural contract programs for FSHD; and
5. Programs to attract and expedite extramural grant applications.

"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 historical 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. We urge the United States government to allocate a proportion of our tax burden towards research on FSHD.

"This is the United States of America and, in a country as great as ours with all of its technical means and ability, it should be absolutely clear that the number one priority for individuals with FSHD and the one absolutely commanding imperative for the federal government is to initiate and accelerate in any way possible, research on FSHD. With modest funding and a clear direction from Congress to the NIH to support research on FSHD, significant progress can be made in conquering and eliminating this and other devastating diseases.

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

PA-98-044:**A program announcement for Facioscapulohumeral Disease (FSHD)**

The FSH Society wishes to inform you that on March 20, 1998, the NIH issued PA Number: PA-98-044, titled: "Pathogenesis and Therapy of the Muscular Dystrophies" (the hyperlink to PA-98-044 is <http://www.nih.gov/grants/guide/pa-files/PA-98-044.html>). This is a direct result of efforts to inform NIH of the critical needs in FSHD research and testimonies given before Congress year after year.

Sponsored jointly by NINDS and NIAMS, applications may be submitted by domestic and 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. Racial/ethnic minority individuals, women, and persons with disabilities are encouraged to apply as Principal Investigators.

The support mechanisms for grants in this area will be the investigator-initiated research project grant (R01) and the program project grant (P01) and may include studies in appropriate animal models or preclinical or clinical studies in patients with facioscapulohumeral dystrophy (FSH).

The National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) encourage investigator-initiated research grant applications to study the pathogenesis and therapy of the various forms of muscular dystrophy in children and adults. Responses to this program announcement may include studies in appropriate animal models or preclinical or clinical studies in patients with facioscapulohumeral dystrophy (FSH), limb-girdle muscular dystrophy (LGMD), myotonic dystrophy, congenital muscular dystrophy (CMD), Emery-Dreifuss muscular dystrophy (EMD), Duchenne muscular dystrophy (DMD), Becker muscular dystrophy (BMD), or other forms of muscular dystrophy.

Some possible areas of research that are specific to facioscapulohumeral muscular dystrophy include the continuation of the sequencing of the entire 4q35 region, and the investigation of the position effect hypothesis and its basis in chromatin structure.

As program announcements are usually three years in duration, both the NIH and the FSH Society encourage both researchers and clinicians working on FSHD to apply and continue to apply for these grants. v

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

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1991	15	1996	23
1992	18	1997	17
1993	23	1998	26
1994	18	1999	12 (to date)
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Update: This work was done in collaboration with Jane Hewitt in Nottingham, Rune Frants and Silvere van der Maarel in Leiden, George Padberg in Nijmegen, in addition to people from my group in Leuven.

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. FSHD is associated with chromosome deletions leaving only 1-8 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 about 500 in the whole genome, and their function is presently unknown, although they are often associated with heterochromatin, a chromosome structure that blocks gene activity.

A few 3.3 kb elements from the D4Z4 loci of non-affected individuals have been cloned and sequenced and the sequences made available in computer databases by the groups of Drs J Hewitt and K Arahata. The sequences are very rich in the DNA bases G and C, which makes them difficult to determine. Their analyses showed a complex pattern with several smaller repeated motifs known to occur also elsewhere in the genome. In addition, the 3.3 kb elements were found to putatively encode a large protein with two homeodomains. Such domains can bind DNA regulatory elements, and are known in proteins that activate genes involved in early embryo development. However, no promoter that might drive expression of this putative homeo gene was identified in the 3.3 kb elements.

Two years ago, we cloned, by serendipity, other members of the 3.3 kb repeat family not coming from the D4Z4 region. We have identified among the later some genes with a functional promoter and encoding proteins with two homeodomains: we named those genes DUX1, DUX2, DUX3 (for Double homeoboX). Alignment of the DUX genes with the known sequences of 3.3 kb repeats derived from D4Z4 loci of non-affected individuals identified in some of these a homologous promoter. It was not detected earlier because it is inside the region that putatively encodes a large protein with two homeodomains. Moreover promoters usually comprise a TATAA sequence that was changed here into a

TACAA sequence. Interestingly, a shorter protein with the same two homeodomains is putatively encoded just after this promoter: we named this putative protein DUX4.

In the present study, we investigated whether the 3.3 kb repeats actually present in the D4Z4 locus after the partial deletion linked to FSHD could still include such putative DUX4 genes. To facilitate this study, we needed DNA from a patient with very few 3.3 kb repeats left in his D4Z4 locus. One patient followed by Dr. G. Padberg had only two such elements; its D4Z4 locus had been cloned by the group of Dr. R. Frants and was used as starting material. We determined the complete locus sequence and found that the two 3.3 kb elements were identical, and contained the putative DUX4 gene. In addition, their sequences were nearly identical to those determined previously in non-affected individuals. We then showed that the promoter was active when it was introduced in muscle cells grown in vitro, and that a DUX4 protein could be made in vitro. This is the first demonstration that a putative gene is present in the 3.3 kb repeats of the D4Z4 locus.

In collaboration with Dr J. Hewitt, we made the following hypothesis: in non-affected individuals, the many 3.3 kb repeats in the D4Z4 locus would be covered by heterochromatin and inactive. Deletions of most of the locus observed in patients would destabilize heterochromatin and allow activation of the DUX4 genes in some cells; the resulting DUX4 protein would be toxic to muscle cells. This hypothesis would fit, among others, with the known genetic dominance of FSHD and with the heterogeneity of the symptoms. We want to stress that this is only a hypothesis and that a lot of studies will still be needed to evaluate it.

Abstract of recent publication: Gene 1999 Aug 5;236(1):25-32; *Nucleotide sequence of the partially deleted D4Z4 locus in a patient with FSHD identifies a putative gene within each 3.3 kb element.* Gabriels J, Beckers M, Ding H, De Vriese A, Plaisance S, van der Maarel SM, Padberg GW, Frants RR, Hewitt JE, Collen D, Belayew A; Center for Molecular and Vascular Biology, University of Leuven, Leuven, Belgium

Facioscapulohumeral muscular dystrophy (FSHD) is linked to the polymorphic D4Z4 locus on chromosome 4q35. In non-affected individuals, this locus comprises 10-100 tandem copies of members of the 3.3kb dispersed repeat family. Deletions leaving 1-8 such repeats have been associated with FSHD, for which no candidate gene has been identified. We have determined the complete nucleotide sequence of a 13.5kb EcoRI genomic fragment comprising the only two 3.3kb elements left in the affected D4Z4 locus of a patient with

FSHD. Sequence analyses demonstrated that the two 3.3kb repeats were identical. They contain a putative promoter that was not previously detected, with a TACAA instead of a TATAA box, and a GC box. Transient expression of a luciferase reporter gene fused to 191bp of this promoter, demonstrated strong activity in transfected human rhabdomyosarcoma TE671 cells that was affected by mutations in the TACAA or GC box. In addition, these 3.3kb repeats include an open reading frame (ORF) starting 149bp downstream from the TACAA box and encoding a 391 residue protein with two homeodomains (DUX4). In-vitro transcription/translation of the ORF in a rabbit reticulocyte lysate yielded two (35)S Cys/ (35)S Met labeled products with apparent molecular weights of 38 and 75kDa on SDS-PAGE, corresponding to the DUX4 monomer and dimer, respectively. In conclusion, we propose that each of the 3.3kb elements in the partially deleted D4Z4 locus could include a DUX4 gene encoding a double homeodomain protein.

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Interest(s): Molecular genetics, clinical and occupational and genetic testing

Update: Our group is focused on the following aspects of FSHD: molecular analysis of FSHD, genotype-phenotype correlations, genetic testing and genetic counseling.

Abstract from recent publication: American Journal of Medical Genetics 1998 May 1;77(2):155-61; *The facioscapulohumeral muscular dystrophy (FSHD1) gene affects males more severely and more frequently than females.* Zatz M, Marie SK, Cerqueira A, Vainzof M, Pavanello RC, Passos-Bueno MR
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We investigated 52 families of patients with facioscapulohumeral muscular dystrophy (FSHD1), including 172 patients (104 males and 68 females). Among 273 DNA samples which were analyzed with probe p13E-11, 131 (67 males and 64 females) were shown to carry an EcoRI fragment smaller than 35 kb; 114 among them were examined clinically and neurologically. Results of the present investigation showed that: a) there is no molecular evidence for autosomal or X-linked recessive inheritance of FSHD1; b) an excess of

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affected males, which is explained by a significantly greater proportion of females than males among asymptomatic cases and a significantly greater proportion of affected sons than daughters observed in the offspring of asymptomatic mothers; c) the penetrance of the FSHD1 gene until age 30 was estimated as 83% for both sexes but was significantly greater for males (95%) than for females (69%); d) new mutations occur significantly more frequently in females than males among somatic/germlinal mosaic cases; and e) severely affected cases originated more often through new mutations or were transmitted through maternal than through paternal lines including somatic/germlinal mothers. These observations have important implications for understanding the molecular mechanisms responsible for FSHD1 and for genetic and prognostic counseling according to the gender of the affected patient.

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Update: 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 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

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Interest(s): Clinical

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Interest(s): Molecular genetics and mouse models

Update: We have recently moved from Manchester to Nottingham University and have spent the last few months setting up our new laboratory here. We are continuing our comparative mapping approach to identify candidate genes which might be involved in FSHD. We are concentrating on the mouse and the Japanese puffer fish (*Fugu rubripes*). The *Fugu* genome is much smaller than human but contains a similar number of genes. We hope that this will make it easier to find genes!

We are also continuing to investigate the

evolution of the FSHD-associated repeat because we think this will help us to understand its normal function and why the deletion causes FSHD.

Abstracts of recent publications: Gene 1998 Aug 17;216(1):13-9; *FRG1*, a gene in the FSH muscular dystrophy region on human chromosome 4q35, is highly conserved in vertebrates and invertebrates. Grewal PK, Todd LC, van der Maarel S, Frants RR, Hewitt JE; School of Biological Sciences, The University of Manchester, 3.239 Stopford Building, Oxford Rd, Manchester M13 9PT, UK.

The human *FRG1* gene maps to human chromosome 4q35 and was identified as a candidate for facioscapulohumeral muscular dystrophy. However, *FRG1* is apparently not causally associated with the disease and as yet, its function remains unclear. We have cloned homologues of *FRG1* from two additional vertebrates, the mouse and the Japanese puffer fish *Fugu rubripes*, and investigated the genomic organization of the genes in the two species. The intron/exon structure of the genes is identical throughout the protein coding region, although the *Fugu* gene is five times smaller than the mouse gene. We have also identified *FRG1* homologues in two nematodes: *Caenorhabditis elegans* and *Brugia malayi*. The *FRG1* protein is highly conserved and contains a lipocalin sequence motif, suggesting it may function as a transport protein.

Gene 1999 Feb 4;227(1):79-88; *Recent amplification of the human FRG1 gene during primate evolution*. Grewal PK, van Geel M, Frants RR, de Jong P, Hewitt JE School of Biological Sciences, The University of Manchester, 3.239 Stopford Building, Oxford Road, Manchester M13 9PT, UK.

There is evidence of multiple copies of the FSHD Region Candidate Gene 1 (*FRG1*) in humans. Analysis of human *FRG1* ESTs showed many of them to be non-processed pseudogenes dispersed throughout the genome. To determine when the amplification of *FRG1* occurred, we used a PCR-based approach to identify *FRG1* sequences from great apes, chimpanzee, gorilla and orang-utan, and an Old World monkey, *Macaca mulatta*. In common with humans, multiple copies of *FRG1* were detected in the great apes. However, in *Macaca mulatta*, only two *FRG1* loci were identified, one presumed to be the homologue of the human chromosome 4q gene. This is strikingly similar to the distribution of a dispersed 3.3-kb repeat family in primates. A member of this family, *D4Z4*, maps to the subtelomeric region of 4q, in close proximity to *FRG1*. We propose that an ancestral duplication of distal 4q included *FRG1*. This duplication is present in *Macaca mulatta* whose

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divergence from hominoids is thought to have occurred at least 33 million years ago. We propose that this telomeric region then underwent further amplification and dispersion events in the great ape lineage, with copies of FRG1 and the 3.3-kb repeats being localized in heterochromatic regions.

Mammalian Genome 1998 Aug;9(8):603-7; *High-resolution mapping of mouse chromosome 8 identifies an evolutionary chromosomal breakpoint.* Grewal PK, Bolland DJ, Todd LC, Hewitt JE; School of Biological Sciences, The University of Manchester, 3.239 Stopford Building, Oxford Rd., Manchester M13 9PT, UK.

The central region of mouse Chromosome (Chr) 8, containing the myodystrophy (*myd*) locus, is syntenic with human Chr 4q28-qter. The human neuromuscular disorder facioscapulohumeral muscular dystrophy (FSHD) maps to Chr 4q35, and *myd* has been proposed as a mouse homolog of FSHD. We have employed a comparative mapping approach to investigate this relationship further by extending the mouse genetic map of this region. We have ordered 12 genes in a single cross, 8 of which have human homologs on 4q28-qter. The results confirm a general relationship between the most distal genes on human 4q and the most proximal genes in the mouse 8 syntenic region. Despite chromosomal rearrangements of syntenic groups in this region, conservation of gene order is maintained between the group of genes in the human telomeric region of 4q35 and MMU8. Furthermore, this conserved telomeric HSA4q35 syntenic group maps proximal to the *myd* mutation and is flanked by genes with homologs on HSA8p22. At the proximal boundary of the MMU8 linkage group we have identified a single 300-kb YAC containing the genes *Frgl* and *Pcml*, which have human homologs on 4q35 and 8p22, respectively. Thus, this YAC spans an evolutionary chromosomal breakpoint. As well as providing clues about chromosomal evolution, this map of the FSHD syntenic mouse region should prove invaluable in the isolation of candidate genes for this disease.

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

Update: The Association Française contre

les Myopathies (AFM) recently issued a new monograph (copyright May 1999) on facioscapulohumeral muscular dystrophy (Dystrophie Musculaire Facio-Scapulo-Humerale) in its "Myoline" series on neuromuscular disorders. The monograph (100 pages, 3 ring bound) is available in French and is a comprehensive training manual covering the various aspects FSHD. It is a collection of information and articles for use in the training of medical professionals. Chapters cover the following aspects of FSHD: definition of muscular dystrophy, history of FSHD, epidemiology, physiology and patho-physiology, clinical description of FSHD and associated clinical features, genetics, differential diagnosis issues, methods for quantitatively tracking and treating the disease clinically, occupational and vocational issues, researchers, diagnostic criteria, psychosocial development, and counseling and mental health issues. Interested medical professionals should contact Dr. Claude Diaz at the above address at the AFM in writing or by e-mail at editions-myoline@mail.afm.genethon.fr.

MONTPELLIER, FRANCE

Researcher(s): S. Bouju, C. Dechesne

Address: Laboratoire de Physiopathologie Cellulaire et Moléculaire, INSERM Unite 300, Faculte de Pharmacie, Montpellier, France.

Interest(s): Molecular genetics and cell biology

Abstract of recent publication:

Neuromuscular Disorders 1999 Jan;9(1):3-10; Exclusion of muscle specific actinin-associated LIM protein (ALP) gene from 4q35 facioscapulohumeral muscular dystrophy (FSHD) candidate genes. Bouju S, Pietu G, Le Cunff M, Cros N, Malzac P, Pellissier JE, Pons F, Leger JJ, Auffray C, Dechesne CA; Laboratoire de Physiopathologie Cellulaire et Moléculaire, INSERM Unite 300, Faculte de Pharmacie, Montpellier, France.

Facioscapulohumeral muscular dystrophy (FSHD) is an autosomal dominant disorder for which no candidate gene has yet been identified. The gene corresponding to one of the novel human cDNAs that we cloned on the basis of a muscle restricted expression pattern [Pietu G, Alibert O, Guichard B, et al. Genome Res 1996;6:492-503] was mapped in the region of the FSHD1A genetic locus, i.e. one of the loci involved in this muscular dystrophy. The corresponding encoded protein contains a PDZ and a LIM domain, two protein-protein interaction domains, and was very recently shown to bind alpha-actinin-2 and was named ALP (actinin-associated LIM protein) [Xia H, Winokur S, Kuo W, Altherr M, Bredt D. J Cell Biol 1997;139:507-515]. We

raised a specific polyclonal anti-ALP serum against an ALP recombinant polypeptide to evaluate the size, level of expression and subcellular localization of ALP in three patients, clearly diagnosed with FSHD disease. Quantitative or qualitative alterations of ALP expression have not been detected in any of them, thus prompting us to exclude ALP as a FSHD gene candidate.

PARIS, FRANCE

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Interest(s): Clinical and molecular genetics

Researcher(s): Marc Jeanpierre, Jean-Claude Kaplan

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Interest(s): Molecular genetics

POITIERS, FRANCE

Researcher(s): Yves Rideau, Gerard Duport, 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 Duport 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

Researchers, *continued from page 16*

Duchenne de Boulogne)

BERLIN, GERMANY

Researcher(s): Thomas H. Haaf

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Interest(s): Molecular genetics

MARBURG, GERMANY

Researcher(s): Manuela C. Koch

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Interest(s): Molecular genetics

Abstract of recent publication: Clinical Genetics 1999 Feb;55(2):88-94; *Evaluation of the facioscapulohumeral muscular dystrophy (FSHD1) phenotype in correlation to the concurrence of 4q35 and 10q26 fragments.* Kohler J, Rohrig D, Bathke KD, Koch MC; Medizinisches Zentrum für Humangenetik der Philipps-Universität Marburg, Germany.

Probe p13E-11 (locus D4F104S1) detects two highly homologous polymorphic loci on chromosomes 4q35 and 10q26. Previous reports in the literature have described a correlation of shortened 4q35-specific fragments and facioscapulohumeral muscular dystrophy (FSHD1). We have identified 30 FSHDI families (46 patients) carrying one short 4q35 and one short 10q26 fragment. The clinical data of these patients were compared with those of 47 families (131 patients) showing a single short 4q35 fragment, in order to evaluate a potentially modifying influence of shortened 10q26 fragments on the phenotype. According to our results, the polymorphic locus on 10q26 does not modify the FSHDI phenotype. The normal population (14%) and our FSHDI population (13%) did not significantly differ in the overall frequency of short polymorphic 10q26 fragments. The specificity of the p13E-11/EcoRI-BlnI test for FSHDI was 100%.

PAVIA, ITALY

Researcher(s): Rossella Tupler*, Elena Giulotto, Solomon Nergadze, Claus Azzalin

Address: Università di Pavia, Biologia Generale e Genetica Medica, via Forlanini 14, 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

Update: The research going on in this laboratory on FSHD concerns the genomic

organization of genes differentially expressed in the FSHD muscle. The genes have been isolated by Dr. Rossella Tupler from two cDNA libraries: one representing genes over expressed in FSHD, one representing genes under expressed in FSHD. In collaboration with Dr. Rossella Tupler we are localizing these genes on the human chromosomes, with the goal to find those deriving from the critical region in 4q35, which will be considered candidate genes for the disorder. In addition, we may reveal other chromosomal regions where FSHD related genes are clustered. None of the 21 over expressed genes that we have so far localized derives from the critical region. We intend to continue mapping the over expressed genes and to start the study of the under expressed ones.

ROME, ITALY

Researcher(s): Luciano Felicetti, Giancarlo Deidda

Address: Department of Molecular Biology, Istituto di Biologia Cellulare, 43 viale Marx, 00137, Rome, Italy

Interest(s): Molecular genetics, clinical and genetic testing

ww

Researcher(s): Giulianna Galluzzi, Enzo Ricci, Luca Colantoni

Address: U.I.L.D.M, Italian Muscular Dystrophy Association, Center for Neuromuscular Disease, 5, Via P. Santacroce, 00167 Rome, Italy

Interest(s): Molecular genetics, clinical

Abstract of recent publication:

Neuromuscular Disorders 1999 May; 9(3):190-8; *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.* 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; Institute of Cell Biology, CNR, Rome, Italy.

In the majority of facioscapulohumeral muscular dystrophy (FSHD) families (about 95%) the genetic defect has been identified as a deletion of a variable number of KpnI repeats in the 4q35 region, although no specific transcripts from this locus have been isolated so far. Molecular diagnosis is based on the detection by probe p13E-11 of EcoRI small fragments, in the range 10-28 kb, that are resistant to BlnI digestion. In family studies this probe is used with other 4q35 polymorphic markers to assign the haplotype associated with the disease. So far, we performed DNA analysis in 145 FSHD families and identified the 4q35 DNA rearrangement not only in affected individuals, but also in healthy subjects at risk of transmitting the disease, such as non-

penetrant gene carriers and somatic mosaics. In addition we applied prenatal tests to 19 fetuses, using DNA extracted from chorionic villi samples (CVS) at 10-11 weeks of gestation. The FSHD status, as determined by the presence of BlnI-resistant small fragments associated with the at risk haplotype, was assessed in nine fetuses; in the remaining 10 cases the disease was excluded. Our results show that molecular analysis of 4q35 rearrangements is a reliable indirect method to perform diagnostic, predictive and prenatal tests in FSHD.

ww

Researcher(s): Enzo Ricci

Address: Institute of Neurology, Catholic University, Largo A. Gemelli, 8, 00168, Rome, Italy

Interest(s): Molecular genetics and clinical

Abstract of recent publication: Annals of Neurology 1999 Jun;45(6):751-7; *Progress in the molecular diagnosis of facioscapulohumeral muscular dystrophy and correlation between the number of KpnI repeats at the 4q35 locus and clinical phenotype.* 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; Institute of Neurology, Catholic University, Centre for Neuromuscular Diseases, Rome, Italy.

Genotype analysis by using the p13E-11 probe and other 4q35 polymorphic markers was performed in 122 Italian facioscapulohumeral muscular dystrophy families and 230 normal controls. EcoRI-BlnI double digestion was routinely used to avoid the interference of small EcoRI fragments of 10qter origin that were found in 15% of the controls. An EcoRI fragment ranging between 10 and 28 kb that was resistant to BlnI digestion was detected in 114 of 122 families (93%) comprising 76 familial and 38 isolated cases. Among the unaffected individuals, 3 were somatic mosaics and 7, carrying an EcoRI fragment larger than 20 kb, could be rated as non penetrant gene carriers. In a cohort of 165 patients with facioscapulohumeral muscular dystrophy we found an inverse correlation between fragment size and clinical severity. A severe lower limb involvement was observed in 100% of patients with an EcoRI fragment size of 10 to 13 kb (1-2 KpnI repeats left), in 53% of patients with a fragment size of 16 to 20 kb (3-4 KpnI repeats left), and in 19% of patients with a fragment size larger than 21 kb (>4 KpnI repeats left). Our results confirm that the size of the fragment is a major factor in determining the facioscapulohumeral muscular dystrophy phenotype and that it has an impact on clinical prognosis and genetic counseling of the disease.

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Researchers, continued from page 17

TOKYO, JAPAN

Researcher(s): Kiuchi Arahata M.D., J.H. Lee, Chirhiro Akazawa, Masanori Funakoshi, 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

Abstract of recent publication:

Neuropediatrics 1998 Oct;29(5):239-41; *Two cases of chromosome 4q35-linked early onset facioscapulohumeral muscular dystrophy with mental retardation and epilepsy.* Miura K, Kumagai T, Matsumoto A, Iriyama E, Watanabe K, Goto K, Arahata K; Department of Pediatric Neurology, Central Hospital, Aichi Welfare Center for Persons with Developmental Disabilities, Japan.

Two cases of early onset facioscapulohumeral muscular dystrophy (FSHD) with mental retardation and epilepsy are reported. They were sporadic, unrelated, severely affected females. In both cases, Southern blot analysis of the EcoRI-digested genomic DNA, using probes p13E-11 and pFR-1, detected the shortest 10 kb EcoRI fragments reported to date. Patient 1 showed infantile spasms at the age of 4 months and localization-related epilepsy at the age of 2.5 years. Muscular atrophy in the face, shoulder girdle and upper arms was observed from the age of 4 years. In Patient 2, lack of facial expression was noticed since the age of 1 year, and at 4 years she was noted to have a loss of bilateral upward gaze. She developed localization-related epilepsy at the age of 9 years. From the age of 10 years, weakness of the lower limbs progressed and she became wheelchair-bound at the age of 14 years and 8 months. She had moderate sensorineural hearing loss, a loss of bilateral upward gaze and tongue atrophy. Their Iqs were 33 and 45, respectively. The two patients suggest that mental retardation and epilepsy may be part of the clinical spectrum of FSHD, especially in very early onset patients with large deletions.

CHUNGBUK, KOREA

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Interest(s): Molecular genetics and molecular biology

LEIDEN, NETHERLANDS

Researcher(s): Oebo F. Brouwer

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Interest(s): Molecular genetics

ww

Researcher(s): Egbert Bakker

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Interest(s): Molecular genetics and genetic testing

ww

Researcher(s): Rune Frants, Marten Hofker, Silvere van der Maarel, Silvana van Koningsbruggen, Giancarlo Deidda*, Tonnie Rijkers

Address: Leiden University Medical Center, Department of Human Genetics, Wassenaarseweg 72, PO Box 9503, 2300 RA Leiden, The Netherlands

Interest(s): Molecular genetics, cell biology, clinical, transgenic mice and genetic testing

Note: *Giancarlo Deidda spent the last 1.5 years in our lab. He has done an excellent job and we regret that he had to leave for Italy again on April 1, 1999. We intent to continue our collaboration with him and his group.

Update: *The BglIII/BlnI dosage test for detection of translocated alleles and deletions of p13E-11.* Silvere M. van der Maarel, Giancarlo Deidda, Richard Lemmers, Bert Bakker, George W. Padberg, Rune R. Frants

Last year, we reported on the deletion of the region proximal to the repeat array including D4F104S1 (p13E-11) in two healthy individuals. In one family, the this deletion was transmitted from the father to two of his children. In one child affected with FSHD, the deletion was expanded into the repeat array thereby causing FSHD (Human Molecular Genetics (1998) 7;1207-1214). Recently, we again identified a patient with a partial deletion of the repeat array including the region encompassing p13E-11.

These observations have serious implications since the probe p13E-11 is used worldwide for genetic testing. These results show that the lack of a short fragment in a suspected FSHD individual may be caused by a deletion encompassing the region of the probe itself which would result in a misdiagnosis (no FSHD). Since we have observed the deletion in two unrelated FSHD patients and in the control population, we anticipate a larger number of these unresolved cases. We have identified this type of deletion in 2 out of 40 sporadic patients which would suggest a frequency of 5% in the sporadic FSHD population. Since this type of deletion can be transmitted as shown in our familial case, we also anticipate to find these deletions in FSHD

families. However, the exact frequency of this deletion in the FSHD population must await studies from other laboratories.

To address this novel complication in FSHD diagnosis, we have developed a new test, the BglIII-BlnI dosage test on which we reported on the last FSHD workshop in Denver, Colorado (submitted for publication). This test can be implemented in any laboratory offering genetic testing. It allows the discrimination between translocated repeats (4-type repeats on chromosome 10 and 10-type repeat arrays on chromosome 4) and allows the identification of deletions encompassing p13E-11.

MAASSLUIS, NETHERLANDS

Researchers: C. Theo Verrips

Address: Stichting FSHD (Dutch FSHD Foundation), Hagedoorn 18, 3142 KB, Maassluis, The Netherlands

Interest(s): Molecular genetics

NIJMEGEN, NETHERLANDS

Researchers: George W.A.M. Padberg, Oscar J.M. Vogels, Elly L. van der Kooi

Address: University Hospital Nijmegen, Department of Neurology, Reinier Postlaan 4, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands

Interest(s): Molecular genetics, clinical and rehabilitation

Update Dutch Trial: "The efficacy of strength training and salbutamol in FSHD" At this moment we are conducting a trial to study the efficacy of strength training and/or salbutamol in patients with FSHD. After a qualification and a baseline visit, 70 eligible FSHD patients were randomized into two groups, namely training and non-training.

The strength training consists of a moderate, progressive resistance training program at home. The patients are visited at home every third week by a physiotherapist in order to optimize the training. After 26 weeks all participants will return to our center for testing. A second randomization at that time will result in 4 groups: training & salbutamol/placebo and non-training & salbutamol/placebo. Salbutamol SR (8mg twice a day) is the European name for albuterol. At 52 weeks a final evaluation will take place.

The primary outcome measure of both parts of the trial will be based on the maximum voluntary isometric contraction testing and muscle mass estimates by computed tomography and urinary creatinine excretion. Secondary measurement outcomes include e.g. surface EMG, functional testing, and pain-

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Researchers, *continued from page 18*

fatigue-, disability- and handicap-scales. The trial will be completed in the summer of the year 2000.

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

Update: *Use of Radionuclide Imaging to Estimate Skeletal Muscles in Patients with Facio-Scapulo-Peroneal Muscular Dystrophy (FSPD). Preliminary data* V.M. Kazakov, E.V. Katsev, D.I. Rudenko, V.I. Amosov, V.M. Katsev, L.A. Dmitrieva, Department of Neurology and Department of Radiology, Pavlov's State Medical University, St. Petersburg, Russia

The functional condition of muscles by radioisotope scintigraphy in 22 FSPD patients (10 men and 12 women; aged 16-78) from 10 autosomal dominant families was studied. The patients were divided into two groups. In the first one (FSPD1) 6 pre-symptomatic and 2 patients with slight affection with FSP phenotype were included. The second group (FSPD2) consisted of 14 patients with severe degree of the disease; they had different phenotypes of the disease from FSP to the final one, namely the facio-scapulo-peroneal-femoro (posterior group of muscles)-gluteal (gluteus maximus)-humeral (biceps brachii, slight affection). Molecular genetic analysis showed a short DNA fragment of < 28 kb on chromosome 4q35 in all the patients excluding four pre-symptomatic ones (Dr. Arahata, Tokyo). 95 oncological patients (28 men and 67 women; aged 18-81) were under control. For radionuclide scanning of muscles the Tc-99m-labeled diphosphonates were used. The patients were treated with one intravenous injection of 350-450 MBq radioisotope and after 3 hours the scintigrams of upper arms, thighs and lower legs on gamma-camera were presented. The computer analysis of the scintigrams received included bringing the region of interest (ROI) on the bones and muscles. The uptake ratio (UR) of radioisotope in muscles was being calculated as the relation of mean account of impulses in ROI brought on bones (spina scapulae, diaphysis of humeral, femoral and tibial) and muscles (upper part of trapezius, deltoid, lateral and medial groups of thigh, medial head of gastrocnemius and peroneal), respectively.

In the patients of FSPD1 group the UR of radioisotope in muscles did not differ from the control group. On the other hand, in the patients of FSPD2 group the UR decreased ($p < 0.05$ 0.01) in all the observed muscles as

compared with the control group. The moderate correlation ($P < 0.001$) between UR and muscle strength decrease was found. The correlation between the creatin kinase level and UR was very weak. It is possible that the considerable decrease of UR of radioisotope in muscles of the FSPD2 group patients was due to the inflammatory and metabolic disturbances in muscles. Radionuclide scanning of muscles with quantitative estimation of the data may be used for receiving additional information concerning the localization and severity of the pathological muscle changes in FSPD patients.

PRETORIA, SOUTH AFRICA

Researcher(s): Antonel Olckers, Engela Honey, Clara Schutte, Annelize van der Merwe

Address: Department of Human Genetics, University of Pretoria, PO Box 2034, Pretoria, 0001, South Africa

Interest(s): Molecular genetics, molecular biology, clinical and genetic testing

Update: It is great to be able to tell you that FSHD research is up and running in South Africa. We are funded by the Muscular Dystrophy Foundation of SA, both our local (Gauteng) branch as well as the National branch for research in 1999. We are making remarkable progress despite feeling somewhat isolated here at the tip of Africa.

We have expanded our "team" to include a clinical geneticist to help us with counseling of the patients and families, as well as a neurologist who has also registered a FSHD clinical research project with our Institution. Our goal is to have both the molecular and the clinical programs run parallel, and for both to complement the other. Plans are to attend the FSHD workshop at the American Society for Human Genetics (ASHG) meeting later this year on Tuesday, October 19, 1999 in San Francisco, California, U.S.A.

To this end, our "South African FSHD" research team is as follows: Antonel Olckers, Ph.D., 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

United States of America

DAVIS, CALIFORNIA

Researcher(s): K. Devreux; D.D. Kilmer; R.T. Abresch; S.G. Aitkens; G.T. Carter; W.M. Fowler; E.R. Johnson; J. Wright

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Physical Medicine and Rehabilitation, University of California, Davis, TB 191. Davis, CA 95616-8665; and National Institute on Disability & Rehabilitation Research (NIDRR)

Interest(s): Rehabilitation, occupational and clinical

IRVINE, CALIFORNIA

Researcher(s): Sara T. Winokur, Mariella Simon, Jeff Ehmsen; Michael Altherr*

Address: University of California, Irvine, School of Medicine, Department of Biological Chemistry, D240 Medical Science Institute, Irvine CA 92717

Interest(s): Molecular genetics, cell biology, gene and protein microarray chip technologies

Note: *Michael Altherr is currently with the Genomics and Structural Biology Group, LANL, Los Alamos, NM

Update: The focus of our laboratory is on the identification and characterization of the biochemical pathways and structures responsible for FSHD. Recent developments in microarray technology have enabled global gene expression analysis in any given tissue or cell line. We are using the Affymetrix GeneChip system to quantitatively compare large-scale differential gene expression in FSHD, non-FSHD dystrophic and normal muscle tissue and myoblast cell lines. This will enable us to identify the genes responsible for FSHD as well as better understand the cellular pathophysiology of the disease. Over 42,000 gene transcripts are represented by oligonucleotides on two types of chips: a 6800 chip representing genes for which sequence and functional information is known, and a 35,000 EST chip representing transcripts from as yet uncharacterized genes. The GeneChips are hybridized with amplified cRNA derived from target tissue. Corresponding cDNAs will then be isolated and sequence of the full-length transcripts determined. In addition to quantifying differential gene expression in FSHD and determining the primary cause of this disorder, we propose to examine the regulatory mechanism disrupted by deletions of the heterochromatic repeat D4Z4. Differential gene expression in yeast strains carrying telomeric half-YACs encompassing the FSHD region will be quantitated in an effort to identify yeast homologs of genes involved in heterochromatin formation at the D4Z4 locus. Thus, we will yield immense insight into both the regulatory mechanism and the primary cause of FSHD using this powerful technology.

In addition, we have recently isolated a novel skeletal muscle gene which maps to the FSHD gene region. This gene has a transcript

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size of 7 kb and maps adjacent to ALP. We are currently generating full-length sequence of this gene and investigating its potential role in FSHD. Our chromatin structure studies are also ongoing, and we have recently submitted a paper demonstrating that the D4Z4 repeat is associated with heterochromatic histone subtypes. (Parseghian, MH, Newcomb, RL, Winokur ST and Hamkalo, BA (1999); The distribution of somatic H1 subtypes is nonrandom on active vs inactive chromatin. *Molecular Cell*).

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

CHICAGO, ILLINOIS

Researcher(s): Anthony A. Romeo, Irwin Siegel

Address: Rush Arthritis and Orthopedics Institute, 1725 West Harrison Avenue, Chicago, IL 60612

Interest(s): Orthopedic surgery, scapulothoracic fusion and clinical

IOWA CITY, IOWA

Researcher(s): Katherine Mathews, Kate Mills

Address: Department of Pediatrics, 216 MRC, University of Iowa Hospitals and Clinics, Iowa City, IA 52242

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.

BALTIMORE, MARYLAND

Researcher(s): Robert J. Bloch, Patrick Reed

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

Update: Dr. Neil Porter, a neurologist with whom I have worked for some time, has contacted his colleague, Dr. Kevin Flanigan, at the University of Utah in Salt Lake City. Dr. Flanigan has collected biopsy samples from individuals with clinical diagnoses consistent with FSHD. We are hoping to tap into his collection of biopsied samples. We hope to work out more extensive interactions between his laboratory and other investigators who are studying FSHD.

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 St., #309, Worcester, MA 01605

Interest(s): Molecular genetics, cell biology, and clinical

Update: Facioscapulohumeral muscular dystrophy (FSHD) is a hereditary neuromuscular disorder characterized by an insidious onset and progressive course. Deletions of arrayed 3.3 kb repeat units on the very distal part of the long arm of chromosome 4 are associated with FSHD but otherwise the molecular basis of the disease and its pathophysiology remain obscure. Our major research goal is to uncover the molecular mechanism underlying FSHD dystrophic process. It is known that the molecular basis of biological or pathological mechanisms might be understood through analysis of the gene expression pattern in a specific cell or tissue. The isolation of genes that show a different expression in a particular tissue may allow the characterization of pathways involved in a specific biological function or pathological process.

To define the molecular mechanism responsible for FSHD, we compared messenger-RNA (mRNA) expression patterns of FSHD and normal muscle. Unexpectedly, the FSHD dystrophic muscle displayed profound alterations in gene expression characterized by severe under- or over-expression of specific mRNAs. Intriguingly, many of the misregulated mRNAs are muscle-specific. To verify that deregulated expression of muscle-specific genes distinguishes FSHD from other neuromuscular

diseases, we analyzed the expression of some genes that were differentially expressed in FSHD in Becker Muscular Dystrophy (BMD) and Amyotrophic Lateral Sclerosis (ALS).

These diseases arise from two different types of molecular pathophysiology. In BMD, the dystrophic process results from mutations in the dystrophin gene that alters the interaction between the cytoskeleton and sarcolemma causing muscle degeneration associated with muscle cell death and regeneration. In ALS, an atrophic process occurs in muscle due to lack of electrical stimuli and resultant motor neuron death. Our study shows that expression of the analyzed genes in these other neuromuscular diseases was normal. Furthermore, to verify the generality of the deregulated expression of muscle-specific genes observed in FSHD muscle, we extended the expression analysis to other FSHD patients and a normal control. Our experiments confirmed that the expression of muscle-specific genes is misregulated in FSHD.

In conclusion, our study indicates that a profound misregulation of muscle-specific genes occurs in FSHD dystrophic muscle. This seems to be peculiar to FSHD. Our further studies will focus on the molecular characterization of genes that are specifically misregulated in the FSHD in order to understand their role in FSHD pathogenesis.

vw

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

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

BUFFALO, NEW YORK

Researcher(s): Pieter de Jong, Michel van Geel

Address: Roswell Park Cancer Institute, Department of Human Genetics, Elm & Carlton Streets, Buffalo, NY 14263

Interest(s): Molecular genetics

Abstract of recent publication: *Gene* 1999 Feb 4;227(1):79-88. *Recent amplification of the human FRG1 gene during primate evolution.* Grewal PK, van Geel M, Frants RR, de Jong P, Hewitt JE. School of Biological Sciences, The University of Manchester, 3.239 Stopford

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Researchers, continued from page 20

Building, Oxford Road, Manchester M13 9PT, UK. (See abstract under Nottingham, England.)

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

ww

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; James Forrester; Michael McDermott, Janet Sowden, Kathy Barrett, Robert Orrell

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: Efforts ongoing by molecular genetics team are: Identification of gene fragments which are differentially expressed between FSHD patient and control muscle samples; identification of candidate genes from the FSHD region of 4q35; quantitative study of expression of genes which have already been mapped to 4q35; characterization of biochemical properties in myoblasts cultured from FSHD patient and control muscle. We are getting data for all of these approaches, and should have quite a bit of information in the near future.

We have finished recruiting the 90 patients (45 at Ohio State University and 45 at the University of Rochester) for the albuterol study. The last patient will finish the study in December of 1999. We are anticipating preliminary, understandable results in the spring of 2000.

Researchers at the University of Rochester are in the process of setting up an FSHD muscle tissue bank. This will allow researchers to directly investigate the expression of genes on chromosome 4q adjacent to the 4q35 FSHD-associated deletion.

Researchers at the University of Rochester are looking for individuals with FSHD interested in participating in a research study to determine the cause of FSHD. The study involves a onetime visit to obtain a blood sample and a muscle biopsy. We will accept any volunteers for the muscle biopsy. Of particular

interest are identical twins, only one of who is affected with FSHD. Researchers: Rabi Tawil, MD; Denise Figlewicz, PhD. Contact: Lynn Cos, RN, study coordinator; Telephone (716) 275-7680 or e-mail: Lynn_Cos@urmc.rochester.edu.

Quantitative Analysis of 4q35 genes. Our current experimental work is centered around a hypothetical mechanism: disruption of gene expression at 4q35 may result from telomeric chromatin reorganization due to deletions of integral copies of a 3.3kb repeated element known as D4Z4. We are determining the expression level of genes which lie centromeric to D4Z4; adenine nucleotide translocator gene (ANT1), actin associated LIM protein (ALP), factor eleven (FXI), plasma prekallikrein (KLK3) and FSHD Related Gene 1 (FRG1) using muscle tissue from normal control individuals and from FSHD patients. We have found a three-fold increase in expression of ALP in FSHD patients and a four-fold increase in expression of ANT1 and have found an increase in expression of FRG1. KLK3 and FXI have not yet been quantitated because they are not consistently expressed in muscle tissue.

Abstract from recent publication:

Neurology 1999 Jun 10;52(9):1822-6; *Definitive molecular diagnosis of facioscapulohumeral dystrophy.* Orrell RW, Tawil R, Forrester J, Kissel JT, Mendell JR, Figlewicz DA; Department of Neurology, University of Rochester, NY, USA.

Objective: To establish the usefulness of a molecular diagnostic protocol for the autosomal dominant disease facioscapulohumeral dystrophy (FSHD).

Background: The genetic defect underlying the majority of cases is a deletion on chromosome 4q35 that is not associated with the coding sequence of any known gene. Molecular diagnosis of FSHD involves the visualization of this deletion as a "small" EcoRI restriction fragment. However, molecular diagnostics are complicated because of the homology of the telomeric regions of chromosomes 4q and 10q; the homologous 10q26 EcoRI fragments are also detected, and can fall into the size range considered to be diagnostic for FSHD. It is therefore important to distinguish the 4q35 and 10q26 EcoRI fragments, taking advantage of the presence of additional restriction sites (BlnI) in the alleles of chromosome 10q origin.

Methods: Paired digests of genomic DNA (EcoRI only and EcoRI/BlnI double digest), followed by pulsed field gel electrophoresis (PFGE), were used to establish the molecular diagnosis of FSHD in 82 unrelated index cases (46 familial, 24 proven sporadic with de novo mutations, and 12 with uncertain family history).

Results: In all cases fulfilling FSHD diagnostic criteria, a 4q35 EcoRI allele size of

< or = 38 kb was present. The smallest 4q35 EcoRI allele in 205 normal control subjects was 41 kb. EcoRI alleles < or = 38 kb of chromosome 10q26 origin were present in 11.2% of this control group. In problematic cases, it was possible to resolve the diagnostic question.

Conclusions: The combination of double digestion with EcoRI and BlnI followed by PFGE is the most reliable molecular protocol for distinguishing patients with FSHD.

DURHAM, NORTH CAROLINA

Researcher(s): John R. Gilbert, Margaret Pericak-Vance, Marcy Speer, Jeffery Stajich

Address: Duke University Medical Center, CARL Building, Room 026, P.O. Box 3445, Durham, North Carolina 27710

Interest(s): Molecular genetics, clinical and genomics

Update: Request for participants for genetic study of FSHD. We are continuing to study a large family (with more than 40 family members affected with FSHD) to determine the chromosomal localization of the FSHD gene in this family. We know that the gene in this family is not the same as the chromosome 4 gene in other FSHD families and we are continuing to try to find its location elsewhere in the genome.

Recently, Drs. George Padberg and Rabi Tawil visited members of this family in North Carolina and concurred that the clinical presentation of FSHD was the same as in other, chromosome 4-linked families.

Our hope is that once the gene for this non-chromosome 4 family is localized to a specific area of a chromosome, we can identify it and characterize it, and that by understanding the non-chromosome 4 FSHD gene, we can shed light into how the more common form of FSHD (linked to chromosome 4) works.

COLUMBUS, OHIO

Researcher(s): Jerry Mendell, John T. Kissel

Address: Department of Neurology, Ohio State University Hospitals, Room 463-Means Hall, 1654, Upham Drive, Columbus, Ohio 43210

Interest(s): Clinical

Abstract of recent article: *Muscular Dystrophy: Historical Overview and Classification in the Genetic Era*; John T. Kissel, M.D. and Jerry R. Mendell, M.D., Department of Neurology, The Ohio State University, Columbus, Ohio

Despite recent advances in molecular genetics, it has proven very difficult to arrive at

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Researchers, *continued from page 21*

an accurate and clinically useful classification of the muscular dystrophies. Much of this difficulty arises from confusion related to the term "muscular dystrophy" itself, as well as a general reluctance on the part of the neuromuscular community to abandon traditional, clinically based classifications. Nevertheless, advances in the understanding of the molecular defects of these disorders have permitted a foundation for classification based on molecular biology. This review presents a historical perspective on the classification of the muscular dystrophies, and furnishes the underpinnings of a genetic classification that can be used both at the bedside and in the research laboratory. [Seminars in Neurology 19(1):5-7, 1999. © 1999 Thieme Medical Publishers, Inc.]

SALT LAKE CITY, UTAH

Researcher(s): Mary Beckerle, Pascal Pomies

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) v

The Association Française contre les Myopathies (AFM) makes direct appeal for researchers to submit proposals on FSHD

The following is a request for proposals for research on FSHD from the Association Française contre les Myopathies (AFM) as outlined in a poster titled "Appel D'Offres AFM 1999." The *FSH Society* wishes to expressly thank **Bernard Barataud**, President of the AFM and President of Généthon and **Pierre Birambeau**, Délégué Général chargé du Téléthon du Développement des Affaires Internationales of the AFM for their immediate assistance in establishing significant resources for FSHD research, for their continued support of FSHD and for accelerating the international research effort on FSHD through the AFM, Généthon and related agencies.

Bernard Barataud and Pierre Birambeau of the AFM state that FSHD is an area of scientific interest and opportunity to the AFM and that they are seeking to accelerate research on FSHD. The AFM has not received many applications for research in the area of FSHD from both inside and outside of France and has asked the *FSH Society* for assistance in encouraging FSHD researchers to apply for their specific program announcement in FSHD. There are excellent resources available to neuromuscular researchers worldwide from the AFM and from Généthon.

The call for applications on FSHD can be found at the AFM Internet page address <http://www.afm-telethon.asso.fr/chercheurs.htm>. Please refer to Section 2.) Themes Concernant Spécifiquement les Maladies Neuromusculaires; first group titled, Dystrophies musculaires, myopathies cogenitales et cardiomyopathies (groupe 4) which states that the AFM is particularly interested in groups researching the function of FSHD and the role of molecular

deletions in FSHD.

The following is the actual text of the request:

"2) Themes Concernant Spécifiquement Les Maladies Neuromusculaires. Ces maladies ont été regroupées en quatre groupes : Dystrophies musculaires, myopathies congénitales et cardiomyopathies (groupe 4). - il est fait en particulier appel à des équipes intéressées par l'étude de la fonction de la dystrophine et par la détermination des lésions moléculaires impliquées dans la dystrophie facio- scapulo-humérale (FSH)."

All researchers are encouraged to apply and to contact the Association Française contre les Myopathies (AFM) regarding this program. Applications encouraging international collaborations on FSHD will be considered.

The *FSH Society* will assist any researcher with contacts to the AFM and in locating and obtaining translation services (written and oral), if needed. The *FSH Society* will facilitate contact with the AFM for any researcher if there should be any difficulties obtaining the necessary information regarding this program announcement.

Interested researchers should contact Pierre Birambeau or Pierre Tambourin, Directeur, Général de Genopole, 2 rue Gaston Crémieux, BP 191, 91006 Evry Cedex, France. By telephone at 01 60 87 25 31, by fax at 01 60 87 25 91 or by e-mail at ptambou@genoscope.cns.fr v



Dr. Stephen J. Jacobsen, Daniel Paul Perez, Carol Perez and Dr. Peter Bridge (Alberta, Canada), from left to right at the FSH Society exhibit booth with materials on FSHD and FSHD research opportunities at the American Society of Human Genetics (ASHG) Denver, Colorado, October 1998.

FSH Society issues grants

—Daniel Paul Perez, President & CEO, FSH Society

The following article is an update on the FSH Society fellowship program for researchers and clinicians. The program has been remarkably successful to date in accelerating efforts on and knowledge of FSHD. We hope that this provides insight as to your dollars at work and hope that you will consider generously supporting this program financially. In September, 1997, Mrs. **Marjorie Bronfman** agreed to provide US\$300,000 over a three- to five-year period for research on FSHD contingent on the FSH Society finding suitable research projects and researchers for fellowships. In April, 1997, the Delta Railroad Construction Company (**Larry and Ida Laurello**) agreed to provide US\$30,000 annually for research projects on FSHD to help with accelerating research efforts and advancing knowledge on FSHD.

The Scientific Advisory Board (SAB) and the Board of Directors and staff of the FSH Society have diligently carried out its mission of providing strategy for FSHD research, recruiting and attracting qualified researchers, selecting research proposals, evaluating research proposals, granting fellowships and monitoring ongoing projects and research opportunities. This is largely due to the strong and competent leadership provided by Dr. **David Housman** and the expert counsel and advice received from the many outstanding members of the SAB working under Dr. Housman's direction. It should be noted that several of the members of the SAB are the top advisors to the Muscular Dystrophy Association (MDA) in the area of FSHD research and several are on the National Institutes of Health (NIH) panels for evaluating NIH proposals in FSHD and proposals relating to the Dystrophies.

Of the greatest concern for the FSH Society is the most efficient use of funds and avoiding any overlap or waste when granting our scarce and valuable funds for molecular genetic research to find the cause of FSHD. The reader should be made aware that it is not customary for some granting organizations to fund salaries for researchers. This is important to note as many qualified researchers have had difficulty entering the field of FSHD research since there would be funds for their project but not their salary. The NIH presence in FSHD at present is still sparse but shows immediate signs of change.

The mission of the FSH Society Fellowship Grant Program is to attract promising researchers to the field of facioscapulohumeral muscular dystrophy (FSHD) research. The FSH Society 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 salient point is that the FSH Society's SAB is in close contact with NIH, MDA and the AFM grants, projects and development in the pipeline and avoids funding overlap at all costs. The structure of the grants as fellowship grants is generally mutually exclusive with the MDA grant policy, often augmenting MDA grants at an institution. The FSH Society fellowships are to be stepping stones to MDA and NIH grants. We note that it is easier for researchers to access funding institutions as FSH Society grantees and time to publication is reduced when reviewers know that the research has already been reviewed by the prestigious FSH Society's SAB.

To explain projects chosen in layman's terms, we will develop 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 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 FSH disease. At the telomere end of the 1-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 (interphase, cell division, cell organization) will bunch up into 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 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 (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 the FSH disease. The prevailing theory at the current time 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 they affect the intermediary product (mRNA) generated by the gene(s). To extend this idea further, some of the 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.

To date the FSH Society has had three

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**International Network and Contact Day for
Facioscapulohumeral Muscular Dystrophy (FSHD)**
A meeting of the Facioscapulohumeral Society, Inc., October 31, 1998
Hyatt Regency Hotel, 1750 Welton St., Denver, Colorado • Imperial Ballroom
Sponsored by the FSH Society, Inc.

7:45-8:15 a.m. *Registration and Continental Breakfast*

8:15 a.m. *Welcome*

Conference Issues and Charge to the Panel, Daniel Paul Perez, President, FacioScapuloHumeral Society, Inc., Lexington, MA

I. Clinical and Research Issues in Facioscapulohumeral Muscular Dystrophy

Chair: Paul Schultz, M.D., Director of the Muscle Disease Clinic, Childrens' Hospital, San Diego, CA

8:30 a.m. *Clinical Presentation - Paul Schultz, M.D.*

9:00 a.m. *Physical Therapy - Alicia Ryden, P.T.*

9:20 a.m. *Occupational Therapy - Jill Peck-Murray, OTR*

9:40 a.m. *Orthopedic Surgery - Anthony Romeo, M.D.*

10:10 a.m. *Panel Discussion, Dr. Schultz, Chair*

10:50 a.m. *Break*

11:00 a.m. *Genetic Research - Michael Altherr, Ph.D., Los Alamos National Laboratory, NM*

11:30 a.m. *Specific laboratory investigations (FSH Society Research Grantees):*

- *Stephane Plaisance, Ph.D., University of Leuven, Belgium, Recipient of the FSH Society Delta Railroad Construction Fellowship: Characterization of a Protein Expressed from a 3.3 kb element not linked to FSHD.*
- *Rossella Tupler M.D., Ph.D., Howard Hughes Medical Institute, Worcester, MA, Recipient of the FSH Society Delta Railroad Construction Fellowship Grant: Characterization of differentially expressed genes in facioscapulohumeral muscular dystrophy affected muscles.*
- *Silvere van der Maarel, Ph.D., Leiden University, The Netherlands, Recipient of the FSH Society Marjorie Bronfman Grant: Generation of Transgenic Mouse Models for FSHD.*
- *Sara Winokur, Ph.D., University of California, Irvine, CA, Recipient of the FSH Society Marjorie Bronfman Grant: Analysis of Chromatin Structure and Skeletal Muscle-Specific Gene Expression in Facioscapulohumeral Muscular Dystrophy.*

12:30 p.m. *Panel Discussion - Dr. Altherr, Chair*

Panel Participants: (Additional panelists to be announced) Denise Figlewicz, Ph.D., University of Rochester School of Medicine, Rochester, NY; Rune Frants, Ph.D., Leiden University, Leiden, The Netherlands; Peter Lunt, Ph.D., Bristol Royal Hospital for Sick Children, United Kingdom

1-2:00 p.m. *Lunch in the Imperial Ballroom Foyer*

II. FSH Society Future Directions and Developing Programs to Meet FSHD Specific Needs

2:30-3:15 p.m. *Workshop I: Neurology and Occupational Therapy; Paul Schultz, M.D., Director of the Muscle Disease Clinic, Childrens' Hospital, San Diego, CA*

3:30-4:15 p.m. *Jill Peck-Murray, OTR, Childrens' Hospital, San Diego, CA*

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2:30-3:15 p.m. *Workshop II: Orthopedics and Physical Therapy; Anthony Romeo, M.D., Orthopedic Surgeon Rush/St.Lukes, Chicago, IL*

3:30-4:15 p.m. *Alicia Ryden, P.T., Childrens' Hospital, San Diego, CA*

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2:30-3:15 p.m. *Workshop III: Helping Us Help Ourselves: Support Groups and Internet; Karen Johnsen, FSH Society Board Member, Leader, Mid-Atlantic Group, Bowie, MD*

3:30-4:15 p.m. *Robert Smith, Esq., Member, New England, FSHD Support Group, Harwich, MA*

◆◆◆

2:30-3:15 p.m. *Workshop IV: Helping Us Help Ourselves: The Significant Others Group of Spouses, Siblings, Caregivers, Family and Friends; Dean Johnsen, FSH Society co-leader, Mid-Atlantic Group, Bowie, MD*

3:30-4:15 p.m. *Patti Smith, Member, New England, FSHD Support Group, Harwich, MA*

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2:30-3:15 p.m. *Workshop V: Genetic Research and DNA testing for FSHD; Sara Winokur, Ph.D., University of California, Irvine, CA*

3:30-4:15 p.m. *Peter Lunt, Ph.D., Clinical Genetics (first session), Bristol BS2 8BJ, England; Meena Upadhyaya, Ph.D., Institute of Medical Genetics (second session), University of Wales College of Medicine, Cardiff, England*

3:15 p.m. *Break*

3:30-4:15 p.m. *Second session: Concurrent Workshops; Group*

4:30 p.m. *Concluding Remarks - Imperial Ballroom*

5:00 p.m. *Adjournment*

1998 Network Conference report

by Carol Perez, M.Ed., C.R.C., Executive Director, FSH Society

On Saturday, October 31, 1998, we had close to one hundred participants (one-third each researchers/clinicians, patients, family and friends). Attendees came from as far as Australia, Japan, Europe and from just around the corner. The presentations by Dr. Schultz and his faculty were outstanding. Michael Altherr chaired the researchers and our grantees' part of the program with an international panel of experts.

The afternoon sessions were very lively. Patti Smith and Dean Johnsen led the Significant Others group. Karen Johnsen and Bob Smith ably organized the support groups discussions. Dr. Romeo and Alicia Ryden were teamed for the orthopedic and PT session with emphasis on scapular fixation procedure. Dr. Schultz ran the workgroup on Neurology with Jill Peck Murray who did consultations including activities of daily living. Dr. Sara Winokur shared the session on genetics and molecular biology with Dr. Peter Lunt and Dr. Meena Upadhyaha of England who have had direct experience with the DNA test for FSHD.

We are very grateful to Dr. Schultz and Dr. Jacobsen for the excellent program; thank you to Dr. Altherr and his panelists, our grantees and Drs. Romeo, Winokur, Lunt and Upadhyaya for their presentations. Our gratitude to Dail Neugarten who worked diligently with ASHG and NSGC to accomplish the booths that preceded the Network Conference and with the Hyatt staff to ensure a successful conference. With thanks also to the members of the Society who covered the exhibits under Dail's leadership: Hank and Charles Torri, Mary Bellows, Leandra Dean, and Carolyn Brink. Friday evening, Karen and Dean Johnsen, Ann Biggs Williams, and Patti and Bob Smith hosted the hospitality room. To Frank Bishop, we owe our appreciation for videotaping the proceedings and to the Smiths and Johnsens for the Saturday workshops.

The informal meetings and collaborative efforts by the researchers during the conference were of immense value to furthering communication between countries and groups. v



From left to right: Dr. Kiichi Arahata (Tokyo, Japan), Marc Jeanpierre (Paris, France), Dr. Rune Frants (Leiden, Netherlands), Dr. Silvere van der Maarel (Leiden, Netherlands), Dr. Giancarlo Deidda (Leiden, Netherlands/Rome, Italy), Dr. Peter Lunt (Bristol, England), Dr. Michael Altherr (Chair, Los Alamos, NM), Dr. Elena Giulotto (Pavia, Italy), Dr. Rossella Tupler (Worcester, MA/Pavia, Italy) listen to lectures and presentations on research from fellow members of the international scientific community at the October 30, 1998, International Workshop on FSHD.

Perez welcomes participants to the 1998 Network Conference

The following was given before The FSH Society's 1998 Network Conference at the Hyatt Regency Imperial Ballroom, October 31, 1998, Denver, Colorado

I thank Dr. Paul Schultz for chairing today's conference; Dr. Stephen Jacobsen and Michael Altherr for help organizing today's program and Dail Neugarten and the Colorado FSH Society Support members for hosting and representing the Society during this past week's National Society of Genetics Counselors and the American Society of

Human Genetics.

I welcome and thank all of you for being here today. The challenge before the FSHD community in today's meeting is to continue the dialogue that began just nine years ago at the first meeting of the FSH Society. The FSH Society is an independent grassroots volunteer health organization solely dedicated to finding the cause, treatment and cure for facioscapulohumeral muscular dystrophy. Supported by contributions and membership

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FSH Society President Perez addresses International Workgroup

The following statement was given by Daniel Paul Perez, President FSH Society, Inc. before the International Workgroup on FSHD held as a Satellite Symposium to the American Society of Human Genetics (ASHG) conference held October 30, 1998, in Denver, Colorado.

"... As it has been a year since our last meeting, I would like to update all of you on the progress of the Facioscapulohumeral Society during that period. For those of you not familiar with the FSH Society, we are a 501(c)(3) non-profit solely dedicated to FSH Muscular Dystrophy. The Society is a decade-old grassroots volunteer health organization comprised of individuals concerned and living with FSHD. Our newsletter, patient brochure, fact sheet and information about FSH Society grants are available at this meeting. We work to distribute information about FSHD worldwide. We are not limited by geographical boundaries nor are our grants. In the last two years, we have published and distributed 8,000 copies of our patient brochure and nearly the same for our newsletter, the FSH Watch. In the last year, we have developed a brochure for genetic testing and are currently in the process of refining it.

Over the last year, we have advocated for the FSHD research, clinical and patient communities at all levels. We are making a difference.

Some highlights

In 1997, I asked this very same group to come up with a list of research initiatives to be carried to NIH. The FSH Society carried this list, put together by you, to the highest levels of Congress and the NIH in the weeks that followed last year's workgroup meeting which was sponsored by the FSH Society.

The result: The NIH issued Program Announcement PA-98-044, titled: "Pathogenesis and Therapy of the Muscular Dystrophies." Although this program covered many of the dystrophies, it was the direct result of our efforts to inform NIH of the critical needs in FSHD research and testimonies given before Congress year after year.

I encourage all of you to consider applying for PA-98-044 which contains the list of objectives set forth by this group last year. The response to date has not been deafening according to NIH, and it should be. We were disappointed with the diffusion of our efforts by a program announcement covering not just

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Perez addresses International Workgroup, *continued from page 25*

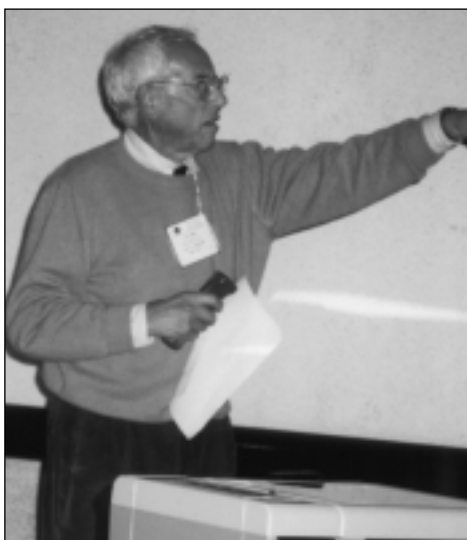
FSHD but all of the muscular dystrophies and individuals at NIH have voiced the same.

We again went before Congress on behalf of all concerned with FSHD by submitting two more testimonies before the House and Senate early this year. Additionally, we testified before the Institute of Medicine (IOM) responding to its four-part directive from Congress on priority setting for research at the NIH. The *FSH Society* again was heard and affirmed at the highest levels of Congress and the NIH as saying that not enough is being done to enhance research on FSHD.

Two weeks ago, we succeeded in report language in three sections of the House and Senate Appropriations budget under NIH, NIAMS and NINDS. The report language is even stronger than we imagined. The language in the NIAMS section is as follows:

"The Committee was pleased with the Institute's response to last year's request which encouraged NIH to stimulate research in the area of facioscapulohumeral disease (FSHD). However, the committee notes that NIAMS has not responded in developing a plan for enhancing FSHD research, and has not addressed the question of whether an intramural program in this area would be beneficial. Therefore, the Committee urges NIAMS to conduct a research planning conference in the near future in order to explore scientific opportunities in FSHD research, both intramurally and extramurally."

In the next few weeks to months, we will be meeting with NIH and Congress to discuss FSHD research directions. I am optimistic that this next year will see tremendous gains, as we have gained the ear of several powerful Congressmen who are not as patient as the *Society*.



Dr. Luciano Felicetti (Rome, Italy) presents research findings at the Society-sponsored International FSHD Workshop on October 30, 1998, in Denver, CO.



From left to right: Dr. Luciano Felicetti (Rome, Italy), Dr. Alexandra Belayew (Leuven, Belgium), Dr. Rune Frants (Leiden, the Netherlands), Dr. Jane Hewitt (Nottingham, England behind in photo), Dr. Denise Figlewicz (Rochester, NY), Dr. Peter Lunt (Bristol, England), Dr. Kiichi Arahata (Tokyo, Japan). Researchers answer questions from the audience during the October 31, 1998, International Network Day. Dr. Michael Altherr (Los Alamos, NM) Chair, Research program.

By the end of today's meeting, I hope we can update the list of top fifteen research priorities and enlist those interested in assisting NIH with the research planning conference. This is a model that has worked successfully in enhancing research for such diseases as Parkinson's.

Even more noteworthy is the FSH Society Research Fellowship Program that was launched this year under the direction of Dr. **David Housman**. This could not have been done without the generosity and commitment of Mrs. **Marjorie Bronfman** and the Delta Railroad Construction Company to FSHD research. We have issued four fellowships, with two more to be awarded in the next few weeks and a seventh to be awarded within the first quarter of 1999. Seven fellows; truly remarkable. Mrs. Marjorie Bronfman is extremely pleased with the success of the program to date and indications are that this gift will be renewed on a regular basis for the purpose of research fellowships.

... We have met with **Pierre Birambeau**, General Secretary of the AFM, Association Française contre les Myopathies, and **Kees van der Graaf**, President of the Dutch FSHD Foundation. Pierre Birambeau would be very interested in hearing from researchers regarding FSHD research and in sponsoring European conferences on FSHD.

The *FSH Society* is sponsoring this meeting ... with the hope of providing the space and forum for free interchange of ideas. ... Last year's meeting in Baltimore was truly remarkable in spirit and we are extraordinarily pleased with the unprecedented level of cooperation and collaboration among the international community on FSHD. We are amazed at the number of new and uncharted

areas that have come forth out of the creative and innovative thinking within this research community both in genetic and clinical areas during the last year. We are even more amazed at the gains made given the difficulty and scarcity of funding in this area.

Now, the *FSH Society* will turn its efforts to asking the same of the research agencies funding research on FSHD. We will be asking the NIH, MDA and AFM to increase the overall level of spending to the three- to five-million-dollar range from its current level of mid-six figures. The *FSH Society* will be devoting more full time resources toward this effort in the next few months.

... It is important to emphasize the extraordinary international character that the meetings tonight and tomorrow have. And more importantly, we thank people in this room such as **Kiichi Arahata, Peter Lunt, Meena Upadhyaya, Kathy Mathews, Denise Figlewicz, Alexandra Belayew** and so many of you for your continuous support and encouragement over the years.

The *FSH Society* is aware of how remarkable and yet frustrating the FSHD problem is, and fully realizes that the absolute best and brightest minds are working on FSHD. We encourage you to continue, despite the difficulties, as we would encourage any patient to strive to hope despite the difficulty of having FSHD. At two thousand families strong, we are striving to effect change for all working on FSHD.

Please remember that it is no small success to affect FSHD, and that your endeavor keeps the hope alive for those of us living everyday with FSHD. We have made the commitment to you for this very reason. v

Perez welcomes participants, *continued from page 25*

donations, the *Society* is comprised of individuals concerned and living with FSHD. As a clearinghouse for information about FSHD, wherever there is FSHD in the world (and we know it is everywhere in this world), wherever there are families, doctors, researchers, and individuals living with FSHD, the *FSH Society* responds. Today, you represent the FSHD community. One third of you are researchers and clinicians from all points of the globe. One third of you are people who have this devastating and misunderstood disease and one third are family and friends living daily with the constant challenges FSHD presents in the clinic, in the laboratory, in the workplace and the home. You have come from as far as Australia and Japan and from just around the corner to join in this dialogue.

To update you on the progress of the Facioscapulohumeral Society

In the area of information and education:

Our newsletter, patient brochure, fact sheet and information about the *FSH Society* are in your folders. We work to distribute information about FSHD worldwide. We are not limited by geographical boundaries nor are our grants. In the last two years, we have published and distributed 8,000 copies of our patient brochure and nearly the same for our newsletter, the *FSH Watch*. In the last year, we have developed a brochure for genetic testing and are currently in the process of refining it.

The *FSH Society* Web site, support groups, FSHD networks and collaboration with FSHD groups around the world have become the catalyst for the FSHD community.

Examples:

- Dr. **Dexter Sun** has facilitated contact with physicians following large families with FSHD in northern and southern China giving us inroads into China.
- **Ray Jordan** represented the FSHD community at the Australian conference on FSHD.
- **Catello Labriola** translates our newsletters into Italian for the Italian Web site.
- Dr. **Antonel Olckers** has a grant to research FSHD in Pretoria, South Africa.
- Members in France are translating our materials into French and Portuguese.
- Drs. **Arahata** and **Funakoshi** from Japan revisited their FSHD data after meeting with the families with Infantile FSHD at our last conference and found that the parent's sense that IFSHD was "different" was true.
- Dr. **Felicetti's** (Italy) and Dr. **Frants'** (Netherlands) support of DNA testing at our 1997 Network Conference in

Boston was the catalyst that made the test available not only in the United States, but raised the issue worldwide.

- Over the last year, we have advocated for the FSHD research, clinical and patient communities at all levels. We are making a difference.

In the area of research

- In 1997, the *FSH Society* carried the list of research initiatives for FSHD developed by researchers at the workgroup meeting which was sponsored by the *FSH Society*, to the NIH and the highest levels of Congress. Our members wrote to their congressman; we testified before Congress.

The result: The NIH issued Program Announcement PA-98-044, titled: "*Pathogenesis and Therapy of the Muscular Dystrophies*" which contains that list of objectives. Although this program covered many of the dystrophies, it was the direct result of our efforts to inform NIH of the critical needs in FSHD research, and testimonies given before Congress year after year. Last night, at the FSHD Work Group meeting cosponsored by the *FSH Society*, the 1998 FSHD research priority list was again updated by the research community.

Congressional testimony

In 1998, we again went before Congress on behalf of all concerned with FSHD by submitting two more testimonies before the House and Senate early this year. Our members wrote to their congressman. Additionally, we testified before the Institute of Medicine (IOM) responding to its four-part directive from Congress on priority-setting for research at the NIH. The *FSH Society* again was heard and affirmed at the highest levels of Congress and the NIH as saying that not enough is being done to enhance research on FSHD.

The result: Two weeks ago, we succeeded in getting report language into three sections of the House and Senate Appropriations budget under NIH, NIAMS and NINDS. The report language as follows is even stronger than we imagined:

"The Committee was pleased with the Institute's response to last year's request which encouraged NIH to stimulate research in the area of facioscapulohumeral disease (FSHD). However, the committee notes that NIAMS has not responded in developing a plan for enhancing FSHD research, and has not addressed the question of whether an intramural program in this area would be beneficial. Therefore, the Committee urges NIAMS to conduct a research planning conference in the near future in order to explore scientific opportunities in FSHD research, both



From left to right: Dr. Paul Schultze (San Diego, CA), Chair, and lecturer Jill Peck-Murray (San Diego, CA) at the 1998 International Network Day.

intramurally and extramurally."

In the next few weeks to months, we will be meeting with NIH and Congress to discuss FSHD research directions. I am optimistic that this next year will see tremendous gains, as we have gained the ear of several powerful congressmen who are not as patient as the *Society*.

Research Fellowship Program

The *FSH Society* Research Fellowship Program was launched this year under the direction of Dr. **David Housman**. This could not have been done without the generosity and commitment of Mrs. **Marjorie Bronfman** and the **Laurello** family's Delta Railroad Construction Company Grant for FSHD research. We have issued four fellowships, with two more to be awarded in the next few weeks and a seventh to be awarded within the first quarter of 1999. Seven fellows; truly remarkable. Mrs. Marjorie Bronfman and Larry Laurello are extremely pleased with the success of the program. Today, you will hear from the current recipients of the *FSH Society* grants.

Kees van der Graaf, President of the Dutch FSHD Foundation, is committed to supporting today's conference. The FSHD Foundation also funds FSHD research. The *FSH Society* and the FSHD Foundation continue to work closely sharing a commitment to FSHD research. We worked with Dr. **Robin Fitzsimons** to ensure the success of the FSHD satellite meeting in Australia this summer and thank Dr. **Upadhyaya** for the summary of that meeting in your conference folder.

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NIH/NINDS requests researchers to submit grants on FSHD

The National Institutes of Health/National Institute of Neurological Disorders and Stroke (NIH/NINDS) wishes to restate their interest in receiving FSHD related applications from domestic and foreign researchers. As a note, only two of the 25 grants mentioned below were related to FSHD. NIH/NINDS encourages the FSHD research community to pursue funding opportunities in this area.

The National Institute of Neurological Disorders and Stroke (NINDS) strongly encourages researchers studying FSH dystrophy to submit grant applications. Very few FSH dystrophy applications have been received, possibly because there is a perception in the research community that muscular dystrophy applications do not get a fair review at the NIH. However, an informal study of applications for grants to study neuromuscular disorders assigned to the NINDS in the last two years showed that 11 of 25 applications were paid, a success rate (44%) significantly higher than other applications assigned to the NINDS. The NINDS will fund more studies in FSH dystrophy if researchers submit more applications! v

Inquiries regarding programmatic issues may be directed to:

Paul L. Nichols, Ph.D.

Division of Convulsive, Infectious, and Immune Disorders
National Institute of Neurological Disorders and Stroke
Federal Building, Room 504
Bethesda, MD 20892-9160
Telephone: (301) 496-9964
Fax: (301) 402-2060
E-mail: pn13w@nih.gov

or:

Inquiries regarding fiscal issues may be directed to:

Ms. Dawn Richardson

Grants Management Branch
National Institute of Neurological Disorders and Stroke
Federal Building, Room 1004
Bethesda, MD 20892
Telephone: (301) 496-9231
Fax: (301) 402-0219
E-mail: da8h@nih.gov



From left to right: Dr. Rune Frants (Leiden, the Netherlands), Dr. Jane Hewitt (Nottingham, England), Dr. Denise Figlewicz (Rochester, NY behind in photo), Dr. Peter Lunt (Bristol, England), Dr. Kiichi Arahata (Tokyo, Japan). Researchers answer questions from the audience during the October 31, 1998, International Network Day. Dr. Michael Altherr (Los Alamos, NM) chaired the research part of the program with an international panel of experts.

Perez welcomes participants, continued from page 27

In the clinical area

We are grateful to **Peter Lunt** and Meena Upadhyaya of the United Kingdom, **Rune Frants** from the Netherlands, and **Robert Korneluk** of Canada for providing DNA testing to the FSHD community in the United States when it was unavailable, and to **Dr. Kathy Mathews** of Iowa for making this diagnostic test available within the United States in August, 1998.

We helped recruit participants for the albuterol and other clinical studies and responded to the hundreds of inquiries from around the world.

... We are extraordinarily pleased with the unprecedented level of cooperation and collaboration among the international community on FSHD, and the creative and innovative thinking both in genetic and clinical areas during the last year. We are even more

amazed at the gains made given the difficulty and scarcity of funding in this area.

... The FSH Society is aware of how remarkable and yet frustrating the FSHD problem is and fully realizes that the absolute best and brightest minds are working on FSHD. At two thousand families strong, we are striving to effect change for all working on FSHD.

Today we will cover a lot of territory. Please keep in mind that our survival depends on your commitment. For the FSH Society to continue to address FSHD issues, we need the financial support of every FSHD community member now to support the people who have become your resource. v

*Would you like to support
the efforts of the FSH Society?
Pull out the envelope inserted into the middle of
this newsletter, fill it out and send it in today!*

FSH grants, *continued from page 23*

rounds of grants and a fourth is pending. The round one (1) application date was February 1, 1998. In round one, seven letters of intent were received; five applications were requested and reviewed. Four research grants were recommended for funding on March 23, 1998. The round two application date was August 1, 1998. In round two (2), we received four letters of intent and four applications were requested and reviewed. Two research grants were recommended for funding on December 17, 1998. The round three application date was February 1, 1999. In round three (3), five letters of intent were received, five applications were requested. One research grant was recommended for funding on May 27, 1999. The round four (4) application date was August 1, 1999. Five letters of intent were received in round four, and five applications were requested for review. Reviewers will be assigned and an SAB meeting will be convened shortly.

To date we have issued four Marjorie Bronfman Fellowships at two years at US\$30,000 per year. We will be issuing the fifth Marjorie Bronfman Grant during the next round if the SAB recommends an application as meeting the standard of Marjorie Bronfman grants previously issued. If there are no applications that are fundable and acceptable per the SAB, we will wait until the February, 2000 round. To date, we have issued three Delta Railroad Construction Company Fellowships at one year at US\$30,000 per year. The FSH Society has issued 100% of the US\$90,000 from the Delta Railroad Construction Company.

Marjorie Bronfman Grants Awarded

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: Silvere M. van der Maarel, Ph.D.
Institution: Department of Human Genetics, Sylvius Laboratory Leiden University, 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

Dr. **Silvere 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 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 of 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. There is no other lab currently 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.

Grant: FSHS-MB-002

Researcher: Sara T. Winokur, Ph.D.

Institution: Department of Biological Chemistry, University of California Irvine, Irvine, California, U.S.A.

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

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 which is not available currently to any other FSHD researcher in the world. In one experiment, she 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 how 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.

Grant: FSHS-MB-003

Researcher: Denise Figlewicz, Ph.D.

Institution: Department of Neurology; University of Rochester School of Medicine, Rochester, New York 14642

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 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

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FSH Society Marjorie Bronfman fellowship recipient Dr. Sara Winokur, (Irvine, CA) presents research findings at the Society-sponsored International FSHD Workshop on October 30, 1998, in Denver, CO.

FSH grants, *continued from page 29*

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. Dr. Figlewicz has the largest collection of FSHD cell lines available at the University of Rochester for this purpose. The *FSH Society* is unique in 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, Ottawa, Ontario, 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 and Dr. Storbeck are studying with Dr. Robert Korneluk who is a leading researcher in the field of muscular dystrophy. The fellowship is to begin with Dr. Picketts and transition to Dr. Storbeck who is an outstanding young post-doctoral fellow. 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. 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. 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 undertaken in the area of FSHD. This project had been tentatively approved before the MDA funded this institution and the *FSH Society* may have been instrumental in helping Ottawa receive interim funding from the MDA. Many important international collaborations will come out of this project.

Delta Railroad Construction Company Grants Awarded

The following are the current Delta Railroad Construction Company grantees and a brief statement on the nature of the work being conducted at the institution.

Grant: FSHS-DR-001

Researcher: Stephane Plaisance, Ph.D./Alexandra Belayew, Ph.D.

Institution: Center for Molecular and Vascular Biology, University of Leuven, Leuven, Belgium

Project Title: *Characterization of a protein expressed from a 3.3 kb element not linked to FSHD.*

\$30,000 6/1/1998 - on hold pending relocation Year 1

Dr. Plaisance and Dr. Belayew have demonstrated that a new member of the 3.3 kb dispersed repeat family not mapping to the FSHD locus is an active gene. It encodes a novel transcription factor with a double homeodomain (DUX1) that is mostly expressed in skeletal muscle and heart, and presents the highest similarity with the Pax3 homeodomain. This is the first indication that some of these 3.3kb elements might not constitute inactive or "junk" DNA.

Additionally, the sequence alignment with the known 3.3kb repeats from the FSHD locus identify similar promoter and coding features. The Leuven group is known for its expertise in the field of transcriptional regulation and it will focus on the biological activity of DUX1 and search for its target genes. In parallel, a search for homologous protein encoding genes was initiated in the 4q35 locus of FSHD patients.

Grant: FSHS-DR-002

Researcher: Rossella Tupler, M.D., Ph.D.

Institution: Howard Hughes Medical Institute, University of Massachusetts Medical Center, Worcester, Massachusetts, U.S.A.

Project Title: *Characterization of differentially expressed genes in facioscapulohumeral muscular dystrophy affected muscles.*

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

Dr. Tupler, M.D., Ph.D. is currently working for Dr. Michael Green at the University of Massachusetts Medical School at the Howard Hughes Research Institute. Dr. Green is a leading authority and researcher in the field of transcription. Dr. Tupler is investigating the deregulation of the molecular machinery in FSHD muscle by comparing messenger RNA (mRNA) obtained from muscle biopsies of a normal individual and a FSHD individual. Performing subtractive hybridization experiments, the researchers were able to locate several transcripts that should correspond to differentially expressed genes in tissues examined. The main goal of this project is to identify, among the several differentially expressed genes, those that are critical for the FSHD pathogenesis. The research will help us to understand the molecular mechanism causing FSHD by either confirming the pathogenic role of the 4q subtelomeric heterochromatin or revealing mutations in candidate genes and the isolation of the gene(s) responsible for FSHD. The research will also help with understanding the biological function of genes whose expression is

deregulated in the FSHD muscle cell and help to establish the basis for future therapeutic approaches.

Grant: FSHS-DR-003

Researcher: Robert J. Bloch, Ph.D., Professor, Department of Physiology

Institution: University of Maryland School of Medicine, Baltimore, Maryland, U.S.A.

Project Title: *Sarcolemmal organization in FSHD and the MYD mouse.*

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

Dr. Robert Bloch is a highly respected and very innovative researcher in the field of cytoskeletal proteins and their relation to the pre- and post-synaptic organization of synapses at neuromuscular junctions. One of the hurdles to understanding the molecular basis of FSHD is the identification of an appropriate animal model. Recent studies have suggested that the myodystrophic (myd) mouse may serve as such a model.

The myd mutation is located in a region of the mouse genome that is syntenic with the locus that is affected in humans with FSHD. The altered musculature of myd mice resembles that seen with FSHD and damage to the sarcolemma of myd muscle is consistent with the muscle weaknesses seen in FSHD. Dr. Bloch proposes to test the myd model by comparing the organization of the sarcolemma of skeletal muscles taken from myd mouse and from FSHD patients. Using immunological techniques and confocal laser scanning

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FSH Society Delta Railroad fellowship recipient Dr. Rossella Tupler (Worcester, MA/Pavia, Italy) presents research findings at the Society-sponsored International FSHD Workshop on October 30, 1998, in Denver, CO.

FSH grants, *continued from page 30*

microscopy, Dr. Bloch has shown that dystrophinopathies cause significant changes in the organization of the sarcolemma. These changes are very likely to compromise the integrity of the sarcolemma leading to the formation of lesions and ultimately to degeneration.

The general aim of the project is to learn if the organization of the sarcolemma in skeletal myofibers from myd or FSHD samples is normal or abnormal compared to appropriate controls. The specific aims are to characterize any reorganization of the membrane skeleton of myd muscle fibers and to determine if the changes in the sarcolemma of myd muscle are similar in nature and extent to those seen in FSHD muscle.

The SAB is quite pleased with the quality and content of proposals received. Additionally, the projects fall within the scope of a well defined research strategy outlined by the members of the SAB. We have asked the *FSH Society's* SAB to formulate a "Strategic Issues and Directions in FSHD Research 1999-2000" document. A draft of "Strategic Issues and Directions in FSHD Research 1999-2000" was prepared by **Michael R. Altherr**, Ph.D., Genomics Group at the Los Alamos National Laboratory on March 28, 1999, and was submitted for consideration, discussion and modification by the entire SAB. The strategy document was subsequently relayed to the National Institutes for Arthritis and Musculoskeletal and Skin Diseases (NIAMS) at the National Institutes of Health (NIH) during the Muscle Biology and Muscle Disease long range planning meeting held on July 20, 1999, in Bethesda, Maryland (see related story).

The Board of Directors of the *FSH Society* and the SAB are quite pleased with the success and results of the *FSH Society* fellowship program. We know that Mrs. Marjorie Bronfman and the Laurello's are equally satisfied with the progress and commitments made to date. It is our hope that the readers of this newsletter consider the renewal of their most generous gift with serious thought to increasing the total amount for research under this program. We would also like to stress the immediate need for monies for the August, 1999, fellowship round and future rounds of this program as the demand of qualified researchers far outstrips our capacity. Please consider making a donation to the *FSH Society Research and Education Fund* for the fellowship program. We need to raise an additional US\$150,000 annually to cover possible gaps in the program and to double the effort to date. v

Then and now: *FSH Society addresses the IOM*

by Karen Johnsen, *FSH Society board member*

This is an interesting story about the *FSH Society* once again being on the mark and going on record regarding the priority setting process at the NIH in the area of FSHD research. In April, 1998, the *FSH Society* was asked by the Institute of Medicine (IOM), which is part of the National Academy of Sciences (NAS), to give testimony regarding the IOM's four (4) part charge from the Congress of the United States to assess the process of assessing scientific opportunity at the NIH and for NIH responsiveness to public input in areas of scientific opportunity.

Karen Johnsen, member of the Board of Directors of the *FSH Society*, gave the following testimony compiled by the *Society* and answered the four questions posed to us by **Bruce Alberts**, President of the NAS and IOM. Karen eloquently delivered our statement in person even though she had to submit testimony from the back of the auditorium as it was not wheelchair accessible. As untenable as the situation is, it was a telling commentary on how volunteer health organizations and patient groups are being treated in the research priority setting process. Bruce Alberts, the president of the NAS, heard from the *FSH Society* on this one.

The following was presented by Karen Johnsen, of Bowie Maryland, in April, 1998, to the IOM:

"The *FSH Society*, Inc which represents patients and concerned individuals with facioscapulohumeral muscular dystrophy, adds the following constructive written comments with regard to the subcommittee of The Institute of Medicine's four part charge from congress:

1. Regarding the factors and criteria used by NIH to make funding allocations on facioscapulohumeral muscular dystrophy:

"The *FSH Society* is a strong supporter of the NIH process but finds that the criteria and factors used by NIH to be ineffective for the area of facioscapulohumeral muscular dystrophy. FSHD is the third most common form of muscular dystrophy and has received no or little attention from NIH under its current system of factors and criteria used by NIH.

"As severe and prevalent as FSHD is, there is still an extraordinary gap between the demand for research allocations from the research, clinical, vocational and patient communities and the allocation from NIH towards this type of research.

"The policy and system for ranking priority

research on chronic and debilitating disease has not shown to be effective to date. The *FSH Society* was extremely surprised at NIH lack of awareness regarding FSHD and the impact of FSHD on the public health system prior to the existence of the *FSH Society*.

"The factors and criteria used by NIH to make funding decisions need to be modified to better prioritize research on non-fatal lifelong chronic debilitating genetic diseases by fully recognizing the impact and toll of such diseases on the public health and their proneness to repeatedly falling through the cracks in funding agencies.

2. Regarding the process by which the funding decisions are made:

"The process by which the funding decisions are made have not been effective for the area of facioscapulohumeral muscular dystrophy. Although the peer review system is one that the *FSH Society* is in full agreement with, we find that it has repeatedly been a barrier to allowing FSHD research to even be born into existence due to the total emphasis on scientific merit and criticism without consideration to the broader reasons for research in the area under consideration e.g. there is no existing support anywhere from NIH currently in this area but it impacts 20,000 Americans with the disease. It takes a long time for good research to develop and those programs that are further along on the evolutionary path of the research cycle have extraordinary advantages over little known areas.

"Under-represented or new areas of research should have policies and mechanisms that allow these struggling or burgeoning areas of research to survive the peer review process. The peer review process needs better checks and balances and should require some level of representation or review from patient advocacy groups.

3. Regarding the mechanisms for public input:

"The *FSH Society* finds the current mechanism of public input adequate and has seen NIH make tremendous gains in this area over the past three years.

4. Regarding the impact of congressional statutory directives:

"The *FSH Society* has seen report language written for the area of FSHD research included in the congressional budget and NIH response to the report language. It is still too early to

IOM, *continued from page 31*

comment on the impact of the report language specifically in the area of FSHD research.

"Regarding the area of report language, we find that the NIH response did not directly address the questions asked by the committee regarding the development of a plan for research in the area of FSHD research and regarding the possibility of intramural research in the area of FSHD research. The response we received did, in fact, dilute our efforts to accelerate and enhance research directly on FSHD by opening up a program announcement to all of the muscular dystrophies when, in fact, the request was for FSHD research.

"On August 3, 1999, the Washington Fax and Information Service (<http://www.washingtonfax.com>) ran an article quoting Bruce Alberts regarding the NIH study sections. Excerpts from the article are found to the right." v

Brain and Tissue banks for developmental disorders available to researchers

The Brain and Tissue Banks for Developmental Disorders at the University of Maryland in Baltimore and the University of Miami are tissue resources established to further research aimed at improved understanding, care and treatment of developmental disorders. The Brain and Tissue Banks were funded by the National Institute of Child Health and Human Development to serve as intermediaries between people who wish to have tissue donated for research upon the time of their death, and the researchers who need this tissue for their vital work. If you are interested in becoming a registered donor, or if you have any questions or concerns regarding the donation process, please contact Sally Wisniewski, Project Coordinator, at 1-800-847-1539. Thank you for taking the time to consider the possibilities offered to humanity through the great gift of tissue donation. v

Internet sites:

<http://www.som1.umaryland.edu/btbank>

or:

<http://www.som1.umaryland.edu/btbank/family>

NIH "Panel On Scientific Boundaries For Review" Releases Draft Report — Panel Calls For Changes In Peer Review and its Culture

An expert panel has proposed revamping both the peer review system and the peer review "culture" at the National Institutes of Health (NIH) in order to make it friendlier to risk takers, more cognizant of "emerging" disciplines and better able to link basic with applied research.

The Panel on Scientific Boundaries for Review, established last year by the NIH Center for Scientific Review (CSR) advisory group, issued a draft report late last week that seeks to address common criticisms of a system that evaluates some 30,000 grant proposals each year and is viewed as the cornerstone of NIH's much-lauded research enterprise. (see Washington Fax 1/14/99)

While praising the system as "outstandingly successful," the so-called "Boundaries Panel," chaired by National Academy of Sciences President Bruce Alberts, also notes that "rapid progress in biomedicine and its accelerating rate of change now challenge (NIH peer review) to keep pace."

On a more blunt note, the report gives credence to the most frequent charge levied against the agency's peer review system, declaring that "the panel is concerned that in practice the present system tends to discourage risk taking and to undervalue new ideas."

"We urge that reviewers endorse the importance of ideas that are original and have yet to be tried," the report states. "Peer reviewers should eschew the common current tendency to find fault or to identify minor errors. Instead, they should strive to assess the potential impact of the proposed research and to encourage good ideas and novel concepts, even if they appear to be risky. Countering the conservatism of the peer review system is a critical issue that should become a long-term focus for the CSR."

The report also notes that researchers variously complain that the system fails to give emerging fields and "high impact" science enough attention, that it puts too much stock in preliminary data and that it does not properly serve "clinical investigators, behavioral scientists, bioengineers and developers of technology and instrumentation."

The panel states that its overall goal is to help develop a review process that "encourages risk-taking and innovation and is flexible and responsive enough to keep up with the many new opportunities developed by the striking advances in biomedical science."

The panel seeks to accomplish its mission by pursuing a reworking of the CSR's Integrated Review Groups (IRGs)—the clusters of scientifically-related study sections that assess the merit of grant applications—and by pushing for changes in the peer review "culture."

The new configuration of IRGs, which the panel would like to see implemented between 2000 and 2002 and which have yet to be fleshed out with study sections, would continue some of the current system's emphasis on hard-core fundamental research. Five of the 21 new IRGs would deal with work that "has no immediate or specific application to human health." But 15 of the groups would be organized so as to link, wherever possible, basic and applied work by having it reviewed within the same IRG.

"As a result, all types of research related to a given system or disease will be clustered in an IRG devoted to that system or disease," the report states. "For example, the IRG for cardiovascular science would include basic studies of heart and vessel development and physiology, studies of pathophysiology of the heart and vasculature and clinical studies pertaining to specific cardiovascular diseases and their treatment."

The panel believes that an IRG responsible for reviewing both basic and applied proposals would make "high-level communication between basic and disease-oriented researchers" a matter of routine in the NIH review process. In such an environment, the report states, "ambitious and interdisciplinary research proposals" may get more attention while investigators may be more likely to submit "broader and more innovative research" projects.

The panel also believes that in a multi-disciplinary review group, reviewers would quickly see how basic work under their aegis applies to "disease problems." Similarly, the report notes that reviewers would have a feel for the kinds of basic research needed to address knowledge gaps plaguing clinical investigators.

In addition to the structural innovations, the panel also endorses "cultural changes" in the peer review process, many of which address the issue of NIH's willingness to fund cutting-edge research. The report notes that such changes need not wait for a restructuring of the IRGs but could be implemented immediately.

For example, the report criticizes "the practice of NIH study sections" to "narrowly" interpret the concept of "hypothesis-driven research" as a "formal exercise in the proposal and proof of a well-circumscribed idea." v

NIAMS and NINDS offer career development research award programs

The National Institute of Arthritis, Musculoskeletal and Skin disease (NIAMS) and the National Institute for Neurological Disorders and Stroke (NINDS) of the National Institutes of Health (NIH) has asked the *FSH Society* to make investigators working on FSHD aware of the existence of valuable career development research award programs for the clinician and researcher working on FSHD. The awards are specifically known as the K23, K24, K25, K30 and F32 awards. These awards fall specifically within the jurisdiction of NIAMS, NINDS and the NIH. The NIH also requests and suggests that clinicians and researchers refer to the Center for Scientific Review at NIH (CSR NIH) Referral and Review page for information on study sections and the CSR study section roster index of CSA members who may be able to help with the grants application process at <http://www.drg.nih.gov/refrev.htm>.

- **Overall Career Development Award**
Site: <http://www.nih.gov/training/careerdevelopmentawards.htm>
- **Mentored Patient-oriented Research Career Development Award (K23):**
<http://www.nih.gov/grants/guide/pa-files/PA-98-052.html>

The purpose of the Mentored Patient-oriented Research Career Development Award (K23) is to support the career development of investigators who have made a commitment to focus their research endeavors on patient-oriented research. This mechanism provides support for a period of supervised study and research for clinically trained professionals who have the potential to develop into productive, clinical investigators focussing on patient-oriented research.

For the purposes of this award, patient-oriented research is defined as research conducted with human subjects (or on material of human origin such as tissues, specimens, and cognitive phenomena) for which an investigator directly interacts with human subjects. This area of research includes:

1. mechanisms of human disease;
2. therapeutic interventions;
3. clinical trials; and
4. the development of new technologies.

- **Midcareer Investigator Award in Patient-oriented Research (K24):**
<http://www.nih.gov/grants/guide/pa-files/PA-98-053.html>

The purpose of the Midcareer Investigator Award in Patient-Oriented Research (K24) is to provide support for clinicians to allow them protected time to devote to patient-oriented research and to act as mentors for beginning clinical investigators. The target candidates are outstanding clinical scientists engaged in patient-oriented research who are within 15 years of their specialty training, who can demonstrate the need for a period of intensive research focus as a means of enhancing their clinical research careers, and who are committed to mentoring the next generation of clinical investigators focussing on patient-oriented research. The award is intended to further the research and mentoring endeavors of outstanding patient-oriented investigators, enable them to expand their potential to make significant contributions to their field of patient-oriented research, and to act as mentors for beginning clinicians.

For the purposes of this award, patient-oriented research is defined as research conducted with human subjects (or on material of human origin such as tissues, specimens, and cognitive phenomena) for which an investigator directly interacts with human subjects. This area of research includes:

1. mechanisms of human disease;
2. therapeutic interventions;
3. clinical trials; and
4. the development of new technologies.

- **Mentored Quantitative Research Career Development Award (K25):**
<http://www.nih.gov/grants/guide/pa-files/PA-99-087.html>

Research at the borders of disciplines and from fresh perspectives often produces surprising and exciting results. Increasingly, teams of scientists from diverse disciplines converge on a common research questions. Individuals who can independently bridge different disciplines, as well as those who are able to function as leading members of multidisciplinary research teams are playing ever more valuable roles at the forefront of biomedicine.

The purpose of the Mentored Quantitative Research Career Development Award (K25) is to engender and foster such activities by supporting the career development of investigators with quantitative scientific and engineering backgrounds outside of biology or medicine who have made a commitment to focus their research endeavors on behavioral and biomedical research (basic or clinical). This mechanism is aimed at research-oriented scientists with experience at the level of junior

faculty (e.g., early- to mid-levels of assistant professor or research assistant professor ranks). This award provides support for a period of supervised study and research for professionals with such backgrounds who have the potential to integrate their expertise with biomedicine and develop into productive investigators.

Examples of quantitative scientific and technical backgrounds outside of biology or medicine considered appropriate for this award include, but are not limited to: mathematics, statistics, computer science, informatics, physics, chemistry, and engineering.

- **Clinical Research Curriculum Award (K30):** <http://www.nih.gov/grants/guide/rfa-files/RFA-OD-98-007.html>

The National Institutes of Health (NIH) invites educational and research institutions to apply for the new Clinical Research Curriculum Award (CRCA) (K30). This program will be supported by all NIH Institutes and Centers.

The CRCA is an award to institutions and addresses, in part, the NIH's initiative to improve the quality of training in clinical research. The NIH recognizes that highly trained clinical researchers are needed in order to capitalize on the many profound developments and discoveries in fundamental science and to translate them to clinical settings.

This RFA is intended to stimulate the inclusion of high-quality, multidisciplinary didactic training as part of the career development of clinical investigators. The CRCA supports the development or improvement of core courses designed as in-depth instruction in the fundamental skills, methodology, theories, and conceptualizations necessary for the well-trained, independent, clinical researcher.

While many NIH programs support research experiences for new clinicians, not all of these trainees have the opportunity to receive formal course work in the design of clinical research projects, hypothesis development, biostatistics, epidemiology, and the legal, ethical and regulatory issues related to clinical research. This award is intended to support the development of new didactic programs in clinical research at institutions that do not currently offer such programs or, in institutions with existing didactic programs in clinical research, to support or expand their programs or to improve the quality of instruction. The goal of this program is to improve the training of the participants so that, upon completion of their training, they can

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Career development programs, *continued from page 33*

more effectively compete for research funding.

For the purpose of this award, clinical research includes: patient-oriented research, epidemiologic and behavioral studies, and outcomes or health services research. The NIH defines patient-oriented research as research conducted with human subjects (or on material of human origin such as tissues, specimens, and cognitive phenomena) for which an investigator directly interacts with human subjects. This area of research includes the development of new technologies, mechanisms of human disease, therapeutic interventions and clinical trials.

- **Research Service Awards for Individual Postdoctoral Fellows**

(F32): <http://www.nih.gov/grants/guide/pa-files/PA-99-025.html>

The Congress of the United States enacted the National Research Service Act (NRSA) Program in 1974 to help ensure that highly trained scientists will be available in adequate numbers and in appropriate research areas to carry out the Nation's biomedical and behavioral research agenda. Under this congressional authority, the National Institutes of Health (NIH) awards NRSA individual postdoctoral fellowships (F32) to the most promising applicants to support full-time research training related to the mission of the NIH constituent institutes and centers. v

NIH/NIAMS requests researchers to submit grants on FSHD

The National Institutes of Health (NIH) strongly encourages investigators studying FSH dystrophy to submit applications for research funding. A program announcement (PA-98-044) issued in March of 1998 by the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) calls for applications on the "Pathogenesis and Therapy of the Muscular Dystrophies," including FSHD. Responses to this announcement may include projects with appropriate animal models, as well as pre-clinical or clinical studies in patients with FSH. The support mechanisms for awards in this area are investigator-initiated research project grants (R01) and program project grants (P01). Listed below are key programmatic and fiscal contacts at NIH for this announcement.

The agency is also working with the FSHD scientific community to plan a research planning conference in the spring of 2000 to explore further opportunities in FSHD research, both extramurally and intramurally. The conference will provide a forum for FSH researchers to share their latest findings with their colleagues and to identify promising directions for future studies on this disease. v

Inquiries regarding programmatic issues may be directed to:

Paul L. Nichols, Ph.D.

Division of Convulsive, Infectious, and Immune Disorders
National Institute of Neurological Disorders and Stroke
Federal Building, Room 504
Bethesda, MD 20892-9160
Telephone: (301) 496-9964
Fax: (301) 402-2060
E-mail: pn13w@nih.gov

or:

Richard W. Lymn, Ph.D.

Muscle Biology Program
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Natcher Building Room 5AS49E
Bethesda, MD 20892-6500
Telephone: (301) 594-5128
Fax: (301) 480-4543
E-mail: rl28b@nih.gov

Inquiries regarding fiscal issues may be directed to:

Ms. Dawn Richardson

Grants Management Branch
National Institute of Neurological Disorders and Stroke
Federal Building, Room 1004
Bethesda, MD 20892
Telephone: (301) 496-9231
Fax: (301) 402-0219
E-mail: da8h@nih.gov

or:

Ms. Sally A. Nichols

Grants Management Officer
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Natcher Building, Room 5AS 49F
Bethesda, MD 20892-6500
Telephone: (301) 594-3535
Fax: (301) 480-5450
E-mail: nicholss@ep.niams.nih.gov

FSH Society research grant & fellowship applications process

The Facioscapulohumeral (FSH) Society offers basic research grants and fellowships to support research about understanding the molecular genetics and cause of Facioscapulohumeral Muscular Dystrophy (FSHD).

Support from the **Marjorie Bronfman Grant for Molecular Genetics Research on FSHD** is for research projects that will contribute to identifying and understanding the basic defect in FSHD. The maximum award for the regular research grant is \$30,000.00. Grants are usually for one year, with the possibility of renewal for a second and third year.

The Society also offers a special Delta Railroad Construction Grant for innovative proposals accelerating the discovery of a treatment and cure for FSHD. A Delta Award can be funded for one year for up to \$30,000.00 per year.

Specific areas of interest include tissue, cell and molecular biology studies toward the etiology of and treatment for FSHD. Proposals are sought for research that involves isolation and characterization of the causative gene(s), the development of animal models for FSHD and understanding of the genetic, neuromuscular and developmental mechanisms of the disease. Further, there is interest in the development of gene therapy, and other therapeutic programs that may arise from that understanding.

To obtain an application, please submit a letter of intent, consisting of a single page introductory cover letter plus a one or two page descriptive summary of the proposed research. A considered and concise rationale for a research project can easily lend itself to one page. The letter of intent may be submitted at any time to the *FSH Society*, and should be brought to the attention of **Dr. David Housman**, Scientific Advisory Board Chairman. The Scientific Advisory Board will determine if the proposal falls within the funding interests of the *FSH Society*. If so, application materials will be provided to the applicant.

As the Society has limited funds, funded grants should be considered "seed money" to develop new and promising research. The Society anticipates that promising research will be strengthened by these grants and will compete successfully for funds from other institutions, such as the NIH or MDA, with larger funding resources. Indirect costs are not allowed, but fringe benefits are considered part of the personnel costs and are acceptable. v

More resources soon available for FSHD researchers!

FSHD Cell Lines are being moved to the Coriell Cell Repository

by Stephen J. Jacobsen, Ph.D., Chairman of the Board, FSH Society

The hitter in search of the long ball looks for that perfect fast ball or hanging curve; the attorney in search of an acquittal looks for that one irrefutable piece of evidence; the molecular biologist in search of a treatment or cure for an inherited disease looks for the gene. The search for an FSHD gene is the Grail of the FSH Society.

Frozen viable B cell cultures from many individuals and families with FSHD are the key resource for scientists doing DNA studies in their search for the FSHD gene and mechanism. These cultures initiate from cells in only one to two tablespoons of a blood donation and can ultimately provide sufficient DNA for many researchers throughout the world. One such important cell bank is at the University of Rochester in New York and the Genome Therapeutics Corporation (GTC) in Massachusetts. The bank was the result of my studies, funded by the Muscular Dystrophy Association, at the University of California, San Diego, in the late 1980's and early 1990's. The bank was the primary source of experimental material for the important FSHD molecular genetic studies of Dr. **Barbara Weiffenbach** at GTC. With the end of those

studies, the Society has hoped that this important resource could be made available to other researchers for their FSHD studies.

The National Institute of General Medical Sciences provides a resource for storage of such cultures: the NIGMS Human Cell Culture Collection at the Coriell Cell Repository in Camden, New Jersey. The Coriell Cell Repository stores important collections and makes them available to qualified researchers studying a variety of diseases. I discussed the FSHD cell bank with Dr. **Robert Johnson**, the Director of Coriell. He and their scientific advisory board felt that an FSHD collection would be an important addition to the repository. GTC accepted our request to transfer cultures. We have initiated the work to transfer cultures of 10 FSHD families from GTC to Coriell, with the approval of Dr. **Weiffenbach** and the kind assistance of Mr. **Dana Torrey** at GTC.

I will contact the individual participants in these families and obtain permission for the transfer of their cultures. In the event that some cultures have lost their viability, those individuals will be asked for a small blood donation to begin their cultures again. Correlation of clinical features of the disease with molecular findings is becoming an

important part of FSHD research. Each participant will be requested to have their physician, familiar with FSHD in their family, fill out an FSHD questionnaire for clinical information important as part of FSHD research. The questionnaire provides the essential medical verification status of that family member concerning FSHD and may be helpful in the research for not only a better understanding of FSHD, but also valuable predictive and genetic counseling information.

If you participated in that research project, please contact one of our offices if you have not yet heard from me. Please call (760) 632-5411 in San Diego or (781) 860-0501 in Boston or e-mail daniel.perez@fshsociety.org. Additional contact information can be found in the front of this newsletter. This is another example of your dollars at work as we at the FSH Society help with the transfer of valuable resources to a national and permanent repository to save extremely valuable research material. We at the FSH Society continue in our goal to make, preserve and keep all the possible resources available to those searching for answers to FSHD. We can do this work because of your support. I urge you to help the FSH Society in this endeavor and its many others with your financial support. v

What's new @ www.fshsociety.org

by Daniel P. Perez, President & CEO, FSH Society

The FSH Society Internet Web site has moved to its own home (domain) at www.fshsociety.org. Our collaboration and work still continues with the NIDRR Rehabilitation Research and Training Center in Neuromuscular Diseases at UC Davis. However, due to a gap in the NIDRR/RRTC grant from the NIH and a broadening of the scope of the work in neuromuscular diseases in general at UC Davis, we decided to move to our new home. On January 15, 1999, we moved to our new home complete with Bulletin Board and Chat systems. Please be sure to re-bookmark The FSH Society at its new location at www.fshsociety.org. The FSH Society Web site is still going strong and we are seeing a tremendous increase in both domestic and international traffic. We are getting the word out about FSHD!

The home page at www.fshsociety.org contains a rich resource of material for those interested in FSHD. For those not familiar with the site The FacioScapuloHumeral Muscular Dystrophy Society home page contains the following:

Information on the FSH Society which

includes the introduction to the FSH Society and FSHD, the FSH Society membership application and donation form and an on-line form to request FSH Society membership materials.

Information on FacioScapuloHumeral Muscular Dystrophy (FSHD) in the form of the FSH Society patient brochure on FacioScapuloHumeral Muscular Dystrophy (FSHD). We will have the new brochure on genetic testing for FSHD available sometime in the near future.

Information and hyperlinks to the FSH Society Online Conferences which include the new and improved FSHD bulletin board and chat and how to access chat with your own Internet Relay Chat (IRC) software or mIRC via the IRC FSHD channel ([webboard.novatech.net:7000 #fsh_society](http://webboard.novatech.net:7000/#fsh_society)). We decided to use the O'Reilly WebBoard. For those not familiar with the concept of bulletin board systems and chat, O'Reilly offers the following summary of its WebBoard product in its on-line help and tutorial system that we strongly encourage on-line users to familiarize themselves with: "You can share information by



Paul (Paul from Florida) and Annabelle Closson at the October 31, 1998, International Network Day.

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President's Letter, *continued from page 2*

(marathons, races) and mental competition (gin rummy contests, read-a-thons, school fairs) and more. We are moved by the indestructible spirit of the race car driver in Italy racing to defeat Muscular Dystrophy, remark at the tireless efforts of promoting disability issues and rights through Miss Wheelchair Maryland and how this benefits those with FSHD, and the unique character of support groups around the country as detailed by a reporter with FSHD. Our annual scientific symposium and network days join researcher and the patient in a dialogue to help in the fight against FSHD.

The *FSH Society* is a rich resource for patient material and for providing help and contacts for those needing day-to-day support, advice, coping strategies and real world solutions. The hard reality of FSHD imposes a unique set of demands for those living with FSHD. We at the *FSH Society* are working hard to create the possibilities that will conquer FSHD.

The *FSH Watch* is a mosaic. Each piece of information gives better definition to the entire picture of FSHD. Combining all will truly tell us the scope, breadth and area that FSHD spans. All aspects of our program are vital to succeeding in conquering FSHD. We hope that this newsletter provides a valuable and optimistic view for those involved with FSHD.

In this newsletter you will see that the complexities and variability of FSHD emerge in

every arena. FSHD is an extremely challenging and unique problem. FSHD may be the only human disease currently known to be caused by position effect or by one piece of DNA in the genome affecting other pieces of DNA in the genome. In short, it is possible that FSHD will open up whole new research areas in biology and a new class of disease to study. We are working hard with the research funding agencies worldwide to convey the need for special and focused efforts on this difficult and extremely challenging area of science. Clinically the disease presents an almost endless array of characteristics (phenotype) and strong challenges in correlating, tracking and relating these to the molecular level (genotype).

Some organizations save trees, rivers and the environment. We are working to preserve important human B cell cultures, the source of DNA for FSHD studies, by facilitating the transfer of cell lines to the nationally renowned Coriell Cell Repository. We are working against time to make lives better and to save lives. We are helping researchers get the valuable tissues they need by making known the resources and services available from the Brain and Tissue Banks. We are helping researchers with any request that they may have related to FSHD. 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.

I recently read "*Iron John, A Book About Men*," by Robert Bly. In it, he uses the Grimms fairy tale about a genie like wild man named 'Iron John' to illustrate a boy's passage from childhood to manhood and the steps, transitions and fears that accompany it. The tale is a rich metaphor and clearly mirrors the trials and tribulations of those living with and working on FSHD. For so long, FSHD has been a journey that few have taken. It is no accident that for almost one hundred years FSHD existed in the center of a forest that sat in deep stillness and solitude that very few researchers and clinicians dared to enter. Then just a decade ago, Dr. Jacobsen and I asked if there was anything that we could do. We have set foot into the forest knowing that we have undertaken a very difficult and risky journey to find clues, search for meaning and to find answers for FSHD. We now know that the *FSH Society* has made the difference and hope that you will choose to walk with us. As always, we thank you for your steadfast support and hope that you will consider continuing and increasing your financial support. v

Marjorie Bronfman Grant for Molecular Genetics Research on FSHD continues through 2001

The *FSH Society* is pleased to announce that the Marjorie Bronfman Grant for Molecular Genetics Research on FSHD has been extended for an additional one-year period. The pledge now extends to the year 2001 with an additional \$100,000.

The generosity and commitment of Mrs. **Marjorie Bronfman** to FSHD research permitted the *FSH Society*, starting in 1998, to award five (5) two-year research fellowships (US\$30,000/year) to date 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 for this significant opportunity to advance research.

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

Research projects will be selected by the Scientific Advisory Board of the *FSH Society* in accordance with the procedures described on page 34 of this newsletter. These fellowships are available to researchers worldwide. v

Third Delta Railroad FSH Society Research Grant Established

The Delta Railroad Construction Company of Ashtabula, Ohio, has established the third *FSH Society* Fellowship Grant for innovative research on Facioscapulohumeral Muscular Dystrophy (FSHD). The *FSH Society* Scientific Advisory Board (SAB) evaluates innovative research methods and approaches in FSHD and awards the Delta grant to provide needed expansion of current work in FSHD studies. The third Delta award has been awarded to **Robert J. Bloch**, Ph.D., Professor, Department of Physiology, University of Maryland School of Medicine, Baltimore, Maryland, for his project titled: "*Sarcolemmal organization in FSHD and the MYD mouse*." Dr. Bloch is highly respected and internationally renowned as a researcher in the field of cytoskeletal proteins. The *FSH Society* is indebted to the Delta Railroad Construction Company, **Larry** and **Ida Laurolo**, and their family for their continued commitment towards understanding and finding a cure for FSHD. v

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

Web site, *continued from page 35*

posting messages directly to WebBoard conferences (and reading responses). When you need to make a file available to your conference-mates, simply attach the file to a message. If you or others in your group travel, WebBoard lets you participate by e-mail, both reading and responding to posted messages. And, if you need or want to discuss something in real time, WebBoard's chat provides instant interaction." The chat room and BBS are open 24 hours a day 7 days a week (24x7) and we have regular chat session times at 2pm EST and 9pm EST on Sundays (-0400 GMT daylight savings). We are trying a new time of 2pm EST Sundays to make it easier for international users of the system.

Information on FSHD in the form of on-line FSH Society publications and information includes all back issues of the *FSH Watch* (Vol. 5, No. 1, Spring 1998, Vol. 4, No. 1, Summer 1997, Vol. 3, No. 2, Fall 1996 / Winter 1997, Vol. 3, No. 1, Spring 1996, Vol. 2, No. 2, Fall 1995, Vol. 2, No. 1, Spring 1995, Vol. 1, No. 2, Fall 1994, Vol. 1, No. 1, Spring 1994) and a copy of this current issue of the *FSH Watch* Vol. 6, No. 1. Please be sure to get the word out about this rich resource of information on FSHD to your family, friends, doctors, and anyone who may have an interest in FSHD. We also encourage you to refer new members and individuals on the BBS and in the chat to this area of the Web site, which contains a wealth of information.

We are considering a site makeover in the near future and invite any fellow members to help us code and redesign the new site. To date we have chosen simplicity, speed and search engine compatibility/performance over graphics. Web designers and Web architects who would like to volunteer their time and services are encouraged to contact us. Given the amount of time and resources needed to maintain this Web site, we fully appreciate the contributions and donations made to date to the Society to support this important and timely resource. Please consider making a donation to the FSH Society Internet fund.

We look forward to seeing you on-line. v

Pen pals wanted

- **Andrew Levinson**, 12, in New York would like e-mail pals: IAMBUZZZ@aol.com Andrew would like to chat with other kids who also have FSHD.

- **Pernilla Westman-Steffanson**, Wieselgrensgatan 8A, Gothenburg 417 17, Sweden. Pernilla, 30, would like contact with others in the United States who also have FSHD.

Ms. Wheelchair Maryland, Inc. donates \$5000 for research to the FSH Society

—by Doris Olds Eck

A mother's dedication:

My decision to give this donation from the Ms. Wheelchair Maryland, Inc. Program to the FSH Society for research is a direct response to my family's history. I have watched three of my children suffer from this muscle-deteriorating disease (Faciocapulohumeral muscular dystrophy).

My daughter, **Karen Johnsen**, was a beautiful talented vivacious child, singing, playing a guitar and an outstanding majorette. It was heartbreaking to see her starting to stumble, fall down, become unable to play a guitar, perform as a majorette and unable to wear a bathing suit without feeling self-conscious. Finally, Karen needed to use a wheelchair for mobility, not to mention her pain, mentally as well as physically. I am very proud of Karen who has become more beautiful as the years go by, both physically and spiritually, becoming a wonderful role model for all to follow. She has overcome both the limitations set for her by FSHD and her triumph over cancer. She leads a very active life as a wife, mother of a son who has inherited the same disease, as well as working. Karen gives more to society than some with no physical challenges.

I had to go through the same heartbreak with my son, **Rob**. An outstanding athlete in every sport he participated in, receiving outstanding trophies in all until his senior year in high school when Rob finally realized that he no longer had the muscles to continue. He was ridiculed as a teen and called names such as "Lips" because of changes in his physique due to FSHD. He, too, has grown into a handsome and productive person and father to his beautiful daughter, **Hailey**. Rob did not allow this disease to stop him. He has a beautiful voice and spends his spare time, when not working and being a father, entertaining young people by singing with a band.

Then along came **Ron**, my youngest son. For a long time, I was in denial thinking that he was not affected. I now know that he also has FSHD.

It is very important that we do everything possible to wipe out this disease that takes away part of a person's dignity and life. To this end

I have, with the approval of the Ms. Wheelchair Maryland Committee, given this donation of five thousand dollars to the FSH Society for FSHD research.

Karen and I worked very hard throughout 1993-1999 to bring recognition to women who have made great achievements in spite of their physical and/or mental disabilities. I thank the Board of Ms. Wheelchair Maryland, Inc. and **Robert Watson**, Executive Director of DateAble, Inc. for their support of this contribution to the FSH Society.

Please see it in your hearts to give generously to the FSH Society to support research to wipe out FSHD.

Note: Doris Olds Eck, past president of the Ms. Wheelchair Maryland Committee, is a member of the FSH Society. Her daughter, Karen Johnsen (past Ms. Wheelchair Maryland) is a board member of the FSH Society and leader of the Mid Atlantic FSH Society Support Group. v



Doris Olds Eck (standing), past president of the Ms. Wheelchair Maryland Committee and a member of the FSH Society and her daughter, Karen Johnsen (past Ms. Wheelchair Maryland and Board Member of the FSH Society). The Ms. Wheelchair Maryland, Inc. brought recognition to women who have made great achievements in spite of their physical and/or mental disabilities.

Winning the race

—Luigi Giuliani, Rome, Italy, Italian racing car driver with FSHD

The driver

I have always been interested in speed and risk. As a child I always dreamed that I would become a racing driver. At 14 I enrolled myself in an aeronautical high school. I wanted to be a commercial airplane pilot but shortly thereafter I was diagnosed with muscular dystrophy. Thankfully, the “facioscapulohumeral” type. Luckily in those years I had the chance to ride on motorbikes and to experience the sense of freedom that only that vehicle can give. This precious driving experience proved to be useful for driving fast powerful cars. My love for speed remained unchanged, as did my desire to become a sports car driver. Years were passing by; my physical situation was progressively getting worse. My dreams were still there. Nineteen-ninety-five was the year in which they established the Italian championship for the “Touring” category reserved for physically challenged drivers. I had been waiting 20 years for this time!

Championship

The Italian sports authorities recognize the unique championship. All the drivers have some disability. The cars are Fiat Punto 75 empowered with a modified engine that can drive the car up to 190 Km/h. The suspensions are hardened; the control devices are adjusted for the specific driver. The races are held in the major Italian circuit and are very demanding because of the competitiveness of the drivers who participate in it.

The race preparation

In 1996, I followed the racing season of the Italian championship. I then decided to buy a racing Fiat Punto 75. I was going to be the first race car driver in Italy, and perhaps in the world, affected with muscular dystrophy!

After long months spent in adapting the seat and other instruments to my needs, the season was opening. The first trials in the racing circuit of Rome were held at Vallelunga. I felt great emotion for my debut on the track: I had to see that everything was OK, the necessary strength in my arms and legs, the anchoring on the seat, all systems were designed specifics for my needs.

Many days of trials and mechanical adjustments were necessary in order to

adjust the driving control devices. Nothing was left to chance: switches and gear lever (the car is equipped with an automatic clutch) had to be adjusted. The results on the track were encouraging. At every lap I was improving. I was then ready for my racing debut. MD for me was like a bad dream and for this adventure it was defeated and didn't present any obstacles to me. Lastly I was preparing for the race. I was intensifying my physical training with daily walks and swimming. Incredibly, I was increasing physical endurance like a normal sportsman.

The race

It was already halfway through the season of the “Fiat Autonomy Trophy 1997” (this is the championship name) and I could not compete for financial reasons. I never imagined that I would have to spend so much for a race. I then decided to take part in the last race of the championship. The race was scheduled for the ninth of November at the Magione circuit, near Perugia. I arrived early in the morning and my car was already there in line with other cars. As the cars got on the track for the trial laps, it started to rain. I was not doing badly for a beginner such as myself! I did some laps at low speed in order to check the grip of the

track. As soon as I started to speed up, my car spun and I found myself facing the other cars. No problem. I put the car in first gear and straightened it out. At the free trials, I was racing with cars in much faster categories than mine. I was very tense and had difficulty concentrating. I was always looking in the mirror to get out of the way of the faster cars. Anyway, the free trials were very useful for adjusting to the track: Everything is OK even in the faster turns where the G-force is higher.

Sunday morning: Official trials. The Fiat Punto are the first to compete. At last we have 20 minutes of trials for our category alone. It is the first time that I am racing with my direct competitors. All of my competitors have some kind of stable physical handicap, such as paraplegia or amputation or polio. They are very skilled and very expert. They have been competing since the beginning of the year with perfectly adjusted cars. My desire to compete is so high that I compete with anyone who is near me. My lap time is second to last. I should have checked the tire pressure and other important things but the mechanic was not there. This will affect my competitiveness but this type of car is very durable. The few minutes before

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Race car driver Luigi Giuliani (Rome, Italy) in his racing Fiat Punto 75.

Race, *continued from page 38*

the start of the race, I concentrate on what I have to do: 12 laps at maximum speed. The race will start: after one lap behind the "pace car" we can start when the traffic light is green. As I am getting through the last turn of the recognition lap, the light turns green and the fastest cars are already far ahead. My objective is to finish the race without committing any errors and most of all without getting tired. It was raining and this made my objective more difficult to reach. Just before a turn, I made a mistake with the gear lever, so I found myself in last position.

I challenged the car just in front of me. I am just behind it when it veers off the track and came back on. I had to brake quickly in order not to crash into him. I was surprised at how I responded so quickly. I continued to challenge my competitor and at the next turn, his car spun around. I now could overtake him and leave him behind. Now, I can concentrate more on the driving. At every lap I check how many laps are left and am surprised at how well my strength is holding up. At the 12th lap I see my objective as a race car driver. It is to be a person who promotes the image of competition for individuals with dystrophy, not only in wheelchairs but also on four wheels that run at top speed in the safety granted by our modern racetracks.

Conclusion

The price for reaching these objectives is high due to technical support. All of these efforts were done without the help of the UILDM (Italian Muscular Dystrophy Association) or of the "telethon." The most important thing is that the results of my experience can be shared with all other individuals with dystrophy who drive or would like to drive. I have already helped someone in Rome and I can, together with racing technology, help others. I am sorry that there are so many people with FSHD or other dystrophies who are unable to drive because there is no one to help them. Without someone helping me with this project, my car will remain in the garage and nothing will change for people with dystrophy. I welcome the help and support of others who believe in my goals and objectives. v

Note: Luigi Giuliani is a member of the FSHD international network.
Luigi Giuliani, Via del Canale dello Stagno, 40
00124 Roma, Casalpalocco, Italia.

**In her own words: Betsy Conron
successfully juggles life and FSHD**

by Elizabeth Conron, FSH Society member

As part of its ongoing mission, the FSH Society feels that it is important for Congress and the NIH to fully understand the personal aspects of the disease and to offer help to individuals to empower themselves by educating others about this poorly understood disease. The following is presented by **Elizabeth Conron**, of Danville, California, who is testifying as the daughter and sister of members of the Board of Directors of the FSH Society, as a founding member of the FSH Society, and as an individual who has this disorder.

"I have FSHD. This diagnosis was a shock to my family and me since no one in our family had been previously recognized to have this disease. Diagnosed at Stanford University at the age of sixteen, I remained physically active until the age of twenty-two. I was a cheerleader, an avid snow skier, captain of my high school swim team and a competitive gymnast. Today, I can only walk short distances with assistance.

"This disease has affected most of the major muscle groups in my body. I can no longer flex my feet and my shins and calf muscles have atrophied to the point that I can only stand on my outside ankles. My thigh and hip muscles have weakened so that I can no longer arise from a sitting position without assistance and great body contortions. The arch in my back is so severe that I can form the letter "C" with it. I can no longer raise my arms above shoulder height. I have difficulty with shoulder dislocation. I can no longer feed myself with my right hand. The fingers in my right hand have weakened so severely that I now must learn to be left-handed. My once big and friendly smile has been replaced by crooked, weak lips and I cannot close my eyes at night without taping weights on my eyelids. People stare at my bizarre gait and body contortions. FSHD has replaced and is replacing my once strong and vital muscles with fat. My joints are swollen from the effects of FSHD and my bones, with no muscles, feel as though they are rubbing together. FSHD is a very painful and disabling disease for me.

"My family now knows that my sister and one of my brothers have FSHD as do my mother, two aunts and six cousins. We have watched our family deteriorate physically as one by one we surrender ourselves to wheelchairs. Nonetheless, our spirits remain strong and our mental capacity sharp. We are committed to being productive and contributing members in our communities.

"I earned a law degree in 1995, a feat that was truly a physical challenge for me. I stayed focused and worked hard, ultimately earning

three American Jurisprudence awards for achieving the highest scores and I served as Student Body Secretary and then Vice President. When the elevator malfunctioned, I hated it. Fellow classmates would carry me upstairs in a piggyback fashion that humiliated me. I was forced to type my exams due to my weakened right hand. Typing was difficult — I used my left hand and only the index finger from my right hand to hit the keys. Despite the difficulties FSHD posed for me, I worked hard to make a contribution to the law school.

"I have two children — four year old **Caroline** and two year old **William**. For me, the issue of children and FSHD has caused the greatest hardship. For fifteen years, my beloved and devoted husband and I agonized over the decision to have children. My desire to be a mother would not be denied. My children are adorable and I am a good mother. My inability to do so many things for and with my children causes me grief. When I take my son William to the park, I can not get into the sandbox with the play equipment due to the wheelchair. I miss the play groups and birthday parties in other homes due to the lack of wheelchair accessibility. I can not be on a Ferris wheel with my children, supervise them in a swimming pool or walk along a beach with them. Simply combing Caroline's hair is a difficult task. I do not have the arm strength to pick up and hug my children. To receive physical affection, Caroline and William climb into my lap and I drape my arms around them.

"Caroline attends preschool and I volunteered to serve as a room mom and work in the classroom. I always look for opportunities to contribute to her well being. I was told that I could injure a child by rolling over a foot with my wheelchair and it was 'suggested' that I not go into the classroom. I am the only mother prohibited from volunteering in the classroom.

"Often, I lie awake at night and worry about what new weaknesses I will have when I awaken in the morning. I pray that God will stop the progression of FSHD in my body so that I can attempt to adjust to my current level of weakness. As soon as I make the needed adaptations to my life, I weaken again. After thirteen years, we are forced to move since our current home with its narrow doors and hallways is not wheelchair accessible and I can no longer walk in my home. Falling has become a regular event. I have bruised, cut or bent most of my body from my numerous falls and felt it necessary to teach Caroline at age 2, to dial 911 and say, 'Mommy fell and she won't wake up.'

"I have seen others with FSHD whose basic

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Conron, *continued from page 39*

functions such as bathing and feeding require assistance as well as the use of a wheelchair. Am I emotionally and spiritually strong enough to accept these challenges? I will have a meaningful life. I know that with no treatment or cure for FSHD, I will weaken and not be able to lift my arm from my lap. I will fight against this disease. If you had FSHD, would you not fight to defeat it too? In 1990, I along with a half dozen others with FSHD became the founding members of the national *FSH Society*. Today, our organization represents over 1300 families. We are committed to advancing

scientific and clinical research and providing support to families and individuals living with FSHD.

"Sometimes I watch able-bodied people move about so effortlessly and I wonder if they have any idea how fortunate they are to be able to do such basic things as walk, bend over to tie a shoe, or scratch their heads. I wonder, sometimes, if what is happening to me is just a bad dream. Inside this diseased body is a good person, a young woman who wants so much to be active again. I want to be able to walk with dignity, to catch William as he comes down a

park slide, to button Caroline's dress, and to hold my husband in my arms. And I want my smile back.

"We are an incredible group of people with a passion to serve our communities and our country. Our drive is limited only by our physical weaknesses. I pray for your help. We need you to help us overcome the devastating effects of FSHD." v

I have muscular dystrophy, but I'm lucky

By Rich Holmes, staff writer

Unless we met at the gym or beach, you probably wouldn't notice much different about my physical appearance. A slight limp, perhaps.

You wouldn't say I have muscular dystrophy. But I do. I'm one of the lucky ones.

I don't have Duchenne muscular dystrophy—the horror that strikes young boys and usually kills them in their 20s. That's the well-publicized variety many people think of when they hear the words, "muscular dystrophy."

Muscular dystrophy is a term applied to a range of inherited neuromuscular disorders. Some are gender-specific, some not. My disease goes by the mouthful, "facioscapulohumeral muscular dystrophy" or FSHD. It was formerly known as Landouzy-Dejerine muscular dystrophy. The nomenclature and the way researchers classify dystrophy keeps changing as they discover more about these diseases.

The name FSHD designates some of the main areas of the body it affects: the face and shoulders. But it also wastes the muscles of the arms, legs, abdomen, and neck. It doesn't affect the heart or IQ as Duchenne and some other dystrophies do. I belong to a subgroup that doesn't have facial involvement. Those who do have facial muscles affected can have trouble whistling, smiling and keeping their eyes shut while sleeping. Their faces lose some ability to express emotion.

Many mild cases

The disease is relatively rare: estimates of incidence range from 1 in 500,000 to 1 in 20,000. Many mild cases undoubtedly go unreported. It's an inherited disorder that both sexes equally develop; it's also believed that some cases result from spontaneous mutation. It's chronic—it generally progresses slowly, although it can have periods of rapid progression.

The degree to which it manifests itself varies widely—even within families. Some people with FSHD barely notice the impairment; some are so weak they rely on crutches, canes, and electric wheelchairs. It can

shorten lifespan. Generally, those most severely affected show symptoms as young children.

More typically, FSHD first becomes noticeable in the teens and 20s, although the disease has been eroding muscles before then.

I was in junior high school, around the onset of puberty, when my friends noticed my shoulder blades sticking out. My mother and father thought I had poor posture. My father—a doctor—didn't recognize this symptom.

Ironically, after I was diagnosed in my late 30s, I realized that my late father also had FSHD, although to a lesser degree. I had inherited it from him. But as a kid, I thought: This is just the way I am, somewhat weaker than my friends. I was more concerned then about the appearance of my shoulder blades.

Back then, the weakness wasn't very pronounced. I could run, lift weights, (though less than my friends), do my share of physical labor. By college, I was using one hand to brace the other arm when combing my hair. I didn't think much about it.

Not athletic

By the time I was in my mid 20s, I realized I wasn't a jogger—I could walk faster than run. Sit-ups had become very difficult. And pushups? Forget it. Still, I didn't think there was anything wrong with me—just an out-of-shape guy who never was athletic.

The discovery came in the aftermath of a car accident about four years ago. My car had been rear-ended; I had whiplash and underwent some chiropractic treatments. One night I reached for a beer stein (my first of the evening) and nearly slobbered it all over myself. A week later my right arm gave way again as I picked up a ketchup bottle while seated at the kitchen table. I figured the accident had pinched a nerve in my neck, affecting my right arm.

The chiropractor did some diagnostic measurements and ordered a blood test. It came back with a high level of protein—an indicator of muscular dystrophy. She referred me to a neurologist. After a brief exam, he said I had muscular dystrophy. I scheduled a second

opinion with the head of neurology at Brigham and Women's Hospital in Boston. He confirmed the diagnosis and pronounced mine a mild to moderate case. I might require foot braces in my retirement, he said.

Age can be an equalizer

The diagnosis scared me, but I soon found out why he seemed unimpressed with my case.

I attended several meetings of a support group for people in New England who have FSHD. It was led by an indomitable woman in an electric wheelchair, severely affected but filled with drive. Others in the group ranged in disability, but I was definitely among the least impaired.

Since strength is to men what beauty is to women, I do find the weakness frustrating. But at 42, age is a great equalizer, and many of my middle-age contemporaries also must deal with some physical infirmity.

There are things I can't do. I can't run, hop, or stand on tiptoe. Climbing a vertical ladder is next to impossible, as is pulling myself out of the water and up into a boat. I can't hold anything above my shoulders. I can't pick up my kids or play with them as exuberantly as I'd like to. The droop in my right foot wears away the heel of my shoes and occasionally trips me up. And the dystrophy makes me clumsy, so that I always seem to be dropping things or chipping dishes as I put them away in the cupboard. My hands sometimes shake. I can get easily fatigued and sore.

On the other hand, there's so much I can do. My physical limitations mean nothing at work. I enjoy swimming, riding my bike and hiking. This past winter, I was thrilled to ski with my family; previous attempts had been exhausting and painful. A switch to better equipment made all the difference. v

From the "Cape Cod Times", Tuesday, July 7, 1998. Rich Holmes is a Times page designer and member of the FSH Society

Group Update

FSH Society Groups Welcome New Members and Offer New Resources

Support groups in the Gulf area (Alabama, Louisiana and Mississippi), Mid-west (Illinois), Michigan, Mid Atlantic, New England, Nevada and Tri State (New York area) offer the unique opportunity to meet 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. To preserve confidentiality, the FSH Society will contact members and inform them of groups in their areas.

We have requests to form groups in Phoenix, AZ; 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 Web site: 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 (\$6.00 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.

- **Pen pal network for our teens.**

Anyone interested may contact **Karen Johnsen**, (301) 262-0701, for names of those interested in receiving correspondence.

- **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

Support Group Contacts

- **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 FSHD Support Group:** Karen Johnsen, (301) 262-0701, includes Maryland, Virginia, Washington, D.C., Delaware, and Pennsylvania
- **New England FSHD Support Group:** Carol Perez, (781) 860-0501, includes Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island and Vermont
- **Tri State (New York) FSH Society Support Group:** Marilyn Meisel, (718) 357-5079, includes New York, New Jersey and Connecticut
- **FSH Society's FSHD Chatroom in Cyberspace:** Ready to use chat software is available at www.fshsociety.org by clicking on hyperlink "FSHD Bulletin Board and Chat." Or use your own Internet Relay Chat (IRC) software or mIRC via the IRC FSHD channel ar ([#fsh_society](http://webboard.novatech.net:7000)).

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, e-mail: afme@labyrinth.net.au

Update: MDA Victoria coordinator for FSHD group. Ray attended the International Conference on FSHD in Sydney in August 1998.

- **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 & Linda Dobson, Society for Muscular 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.com

Update: 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, 2, Hamlyn Close, Edgware, Middlesex, HA8 8DB, England; phone: 0181-958-788, fax: 0181-958-2198; e-mail: nmj@brockley.telme.com; Web site: <http://www.britinternet.com/~fsh>

Update: FSH-MD Support Group Newsletter Issue 4 reported on the October, 1998, annual meeting. Contact Mrs. Jonas for annual conference dates.

- **France:** **Catherine LHeureux-Rouslin**, 16, Rue du Parc Royal, 75003 Paris, France
- **Netherlands:** **Albert Gielis**, C. Beerninckstraat 102, 3641 DE Mijdrecht, The Netherlands; Home: +31-297-286126; fax: +31-297-283530; e-mail: L.Gielis@vici.nl

- **Dutch FSHD Foundation (de Stichting FSHD):** **Kees C. J. van der Graaf**, President and Founder, Stichting FSHD, Kievitslaan 34, 2243 GD Wassenaar, The Netherlands; phone: 31 70 511 8466; fax: 31 70 511 0041. 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 1998 Conference, the 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 20 covered the Contact Day in 1998. Dr. van der Maarel discussed his research (FSH Society grant) and Dr. Frants reported on improved techniques for DNA testing. Dr. Padberg and Dr. Brouwer are completing a nine and 18 year follow up study to measure disease progression in FSHD families. Additionally, the salbutamol (albuterol) and muscular strength training study will be completed in 1999.

- **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; e-mail: mdsa@megaweb.co.za

Acknowledgements

Foundation Grants

- Marjorie Bronfman Grant extension to 2001. Please see story on page 36.
- Delta Railroad Construction, Ashtabula, Ohio, 1999 research grant. Please see story on page 36.

Special Events

- The Whitford Country Club in Exton, PA held the second annual Charity Gin Rummy Challenge to support the *FSH Society*. The *FSH Society* thanks Mary Larsen who organized this successful event, the Whitford Country Club and local businesses for their contributions.
- **1998 Read-A-Thon Fundraiser at the Bear Creek Elementary School:** The Bear Creek Elementary School in Baltimore, Maryland held a 1998 Read-A-Thon Fundraiser 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.
- **1999 Friends of Christopher Stenmon:** Friends of Christopher Stenmon sponsored an end-of-tax-season event in Quincy, Massachusetts to support the activities of the *FSH Society*.
- **FSH Society Bulletin Board/Internet Fund: Donated funds from BBS posters:** "Without *FSH Society's* BBS, I would never have learned of this possible medical

breakthrough—it really belongs to you folks. Thank you so much. Keep up the good work!"
—Russ Kleve, Oregon

- **June 6, 1999 Run for FSH Society—** Elizabeth McGowan, Denver, CO: Elizabeth completed the run to support FSHD research. Her sponsors were: **California:** Sile C. Dooley. **Colorado:** George & Rayna Godfrey; Elizabeth McGowan; Marina Papirova. **Connecticut:** Michelle R. Durwin; Christina S. McGowan; Mr. Wray. **Washington, DC:** Mary E. Abdella; Samiya Mir. **Massachusetts:** Meredith L. Brand; Edward & Linda Colozzi; Donald & Maureen Jensen; Benjamin D. Locke; Renee M. Martin; Elizabeth & John Riley; Elizabeth Thompson; Deanna L. Vanwinkle. **New York:** Joyel M. Bennett; Michael A. Cappelto; Mr. & Mrs. John Frein; Barbara Kershaw; Amy E. Lewis; Kathleen Martin; Kimberly A. Martin; Lisa D. May; Charles F. McGowan; Evonne M. Miller; Erik Swart. **North Carolina:** Mr. & Mrs. Scott Tyler. **Ohio:** Richard & Pamela Friedauer. **Pennsylvania:** Lisa Bramham. **Virginia:** Colleen Sullivan; Colleen Sullivan's father; Terence P. Szuplat
- 1999 Read-A-Thon Fundraiser at the Bear Creek Elementary School: The Bear Creek Elementary School in Baltimore, Maryland held the annual Read-A-Thon Fundraiser to support the *FSH Society* honoring their teacher, Arlene Endres, mother of Jessica Ryley.

Corporate Sponsors

- **Athena Diagnostics, MA:** 1998 *FSH Society* Network Conference
- **The FSHD Foundation, The Netherlands:** 1998 *FSH Society* Network Conference
- **NEO Products Corporation, TN:** in Honor of Jessica Ryley
- **Schering-Kenilworth Pharmaceutical Division, Union, NJ:** Support of *FSH Watch* VOL. 6, 1

Corporate Matching Funds

- Chubb & Son Inc. - Warren, NJ
- The Lubrizol Corporation - Wickliffe, OH
- Microsoft Matching Gifts Program - Princeton, NJ
- Pitney Bowes, Inc. - Stamford, CT
- The Prudential 1998 Community Giving Campaign - Princeton, NJ
- Spear, Leeds & Kellogg, - New York, NY

United Way

- Mr. Edward K. Cummins - RI
- Quorum Health Resources, MA

Research and Education Fund Donors

- Steve Chestnut Memorial Fund for FSHD Research: Mr. & Mrs. Glen Chestnut & Family; Raleigh & Cheris Koehn; Scott & Lisa Saylor
- Ms. Wheelchair Maryland, Inc. Please see story on page 37.
- Jerry & Jane Rocco - CA;

Research and Education Fund in Honor of:

- Justin Cohen- Grandparents Mrs. & Mrs. Stuart Cohen - NY
- Jessie Pease- "Anonymous"; Great Grandmother Helen Sennott - MA
- Jessica Ryley's 21st Birthday- Great Grandmother Thelma B. Green

Memberships

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Winners, *FSH Charity Gin Rummy Challenge*, December 6, 1998. Left to right: Winner Pat Brown, Runner-up Marion Weaver, Consolation Winner Mike Larsen and Consolation Runner-up Tim McClatchy

Acknowledgements, *continued from page 42*

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- Justin Zachary Cohen: Grandparents Mrs. & Mrs. Stuart Cohen - NY; Great aunt, Mrs. Joseph D. Cotler NY; Grandmother Rose Kanter - NY—in honor of Justin's birthday: Dr. & Mrs. Mark A. Montera - NY
- The "Cruz Kids": Lyn & Bob Schulteis - NC

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- Mr. & Mrs. John Ruvolo on the occasion of their fiftieth anniversary: Grace

Corradino - NY

- Jessica Ryley: Mary E. Doto - NY; Parents Arlene & Patrick Endres - MD; Rick & Leslie Frye - WA; James F. Ryley, Jr. - PA; David, Mary Sue, Melissa & Delmar Smith - OH; Grandparents Gerry & Joanne Smith - MI; Timothy A. Smith - TX

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- Margaret Yeagle Xeros: Mr. & Mrs. Paul Closson

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- Bev & Jim Weyenberg, Kaukauna, WI for membership and newsletter mailings. v

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