

Testimony of Daniel Paul Perez, Co-Founder & Director Emeritus, FSHD Society before
U.S. House Appropriations Subcommittee on Labor, HHS, Education and Related Agencies
May 3, 2024

Honorable Chairman Aderholt, Ranking Member DeLauro, and distinguished members of the Subcommittee, thank you for this opportunity to testify. We are requesting a FY2025 appropriation of **\$40 million** to the *agency* U.S. DHHS National Institutes of Health (**NIH**) for research programs on **facioscapulohumeral muscular dystrophy** (*hereafter called FSHD*).

I am co-founder, Director emeritus, past -Chairman, -President & CEO, and -CSO of the FSHD Society. As a patient with FSHD, my life's work on FSHD disease and its funding spans nearly every research lab, biotechnology and pharma company working today on FSHD globally. My efforts through the FSHD Society have led to understanding how FSHD1¹ and FSHD2^{2,3} work. I was a key architect of the Muscular Dystrophy Community Assistance, Research and Education Amendments of 2001 (MD-CARE Act, Public Law 107-84). I have served on the Muscular Dystrophy Coordinating Committee (MDCC) since its inception in 2001 and am the longest serving member. MDCC is a Federal Advisory Committee designed to coordinate activities relating to the various forms of muscular dystrophy across the NIH and with other Federal health agencies.

Since 1994, the FSHD Society and I have 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 insights into the difficulty of living a lifetime with this disease.

FSHD is a heritable disease and one of the most common neuromuscular disorders with a prevalence of 1:8,000.⁴ It affects nearly one million children and adults of both sexes worldwide. FSHD is characterized by progressive loss of skeletal muscle strength that is asymmetric in pattern and widely variable. Muscle weakness typically starts at the face, shoulder girdle and upper arms, often progressing to the legs, torso and other muscles. In addition to affecting any skeletal muscle, it can bring with it respiratory failure and breathing issues⁵⁻⁷, mild-profound hearing loss⁸, eye problems and cardiac bundle blockage and arrhythmias^{9,10}. FSHD causes significant disability and death according the U.S. Centers for Disease Control and Prevention (CDC), National Center on Birth Defects and Developmental Disabilities, Atlanta, and others^{11,12}.

FSHD is associated with epigenetic changes on the tip of human chromosome 4q35, in the D4Z4 DNA macrosatellite repeat array region, leading to an inappropriate gain of expression (function) of the D4Z4-embedded **double homeobox 4** (DUX4) gene¹³⁻¹⁶. DUX4 is a transcription factor that kick starts the embryonic genome during the 2- to 8-cell stage of development¹⁷. Ectopic expression of DUX4 in skeletal muscle is associated with the disease and the disease's pathophysiology that leads to muscle death. DUX4 is never expressed in 'healthy' muscle. FSHD has had few clinical trials, there is no cure or therapeutic options. DUX4 requires and needs to activate direct transcriptional targets for DUX4-induced gene aberration and muscle toxicity¹⁸.

Our patient community through its fundraising efforts and intensive research-integration has pioneered inroads to treating FSHD using genomic sequencing, genomic medicine, gene editing and next generation diagnostics. All with the goal of reducing DUX4 in its DNA or RNA or protein state, or the effects of DUX4-driven toxicity e.g. modulating DUX4 repressive pathways, targeting DUX4 mRNA, DUX4 protein, or cellular downstream effects of DUX4 expression. In the past five years, gains were made in expanding basic research, better understanding of natural history and disease heterogeneity, biomarkers and outcomes assessments, therapeutic compounds/interventions and clinical trial design¹⁹.

We describe the advances in the last year as remarkable³⁶⁻⁴⁷. Since 2023 to the present, there have been 177 articles published on FSHD (PubMed search terms: fshd or facioscapulohumeral or landouzy-dejerine), 187 articles published on human DUX4 or mouse Dux (PubMed search terms: DUX4 or Dux); and, 61 articles on DUX4 translocations in cancer (PubMed search terms: DUX4 cancer). New and notable discoveries in FSHD to highlight are as follows: long-range sequencing²⁰, evolution of DUX4 and DUXC family²¹, RNA processing and novel peptide translation²², protein modifications of DUX4²³, SMCHD1 structure and function²⁴, virus induction of DUX4 expression²⁵, animal models¹⁹, and clinical studies²⁶. These discoveries combined with earlier research data allow us to further define and to suggest a model of disease progression.

Potential therapeutics are currently in clinical trials and the prospects of a first therapy within the next 12-24 months is tangible. However, more approaches are in the discovery and development pipelines and a true cure is still many years off and depends upon increasing our knowledge of the disease and learning from these initial clinical trials. More than \$1 billion from investment banks, venture capital, private/philanthropic investors across more than 30 companies recently flowed into companies working on FSHD therapies. Though DUX4 is clearly the target – we are still flying blind when it comes to measuring ectopic DUX4 in human muscle and understanding the normal function of DUX4. What emerges -- is, on one end of the spectrum an overarching need for far more basic and mechanistic research e.g. better understanding of the fundamental mechanisms of FSHD disease, including muscle disease. Secondly, in the most important place of getting therapies to patients, is the need to eliminate projects that will never succeed in practice/clinic i.e. ‘does this have a pathway to clinic?’

Now, along with our FY2025 request we highlight three broad areas of highest priority where Congress can kindly implore through report language, that the NIH increase its portfolio of grants and expand on its FSHD research projects spending.

Table 1. FSHD Research Areas in Need of Accelerated and Increased NIH Funding

- **Maintaining basic research on developmental and disease-associated DUX4** expression, dynamics and activity. These studies have added tremendously to planning therapeutic interventions in FSHD.
- **Validating protocols for fast and limited scale human trials** based on molecular or MRI or other markers of disease activity in FSHD. Helping to create and identify viable biomarkers that could be exploited in clinical trials or engineering specific biomarkers and models associated with the onset, and progression of FSHD1 and FSHD2. Many different interventions will be coming to trial and more thought and validation should be put into how to determine effectiveness of the intervention very early with a small number of subjects.
- **Developing non-human animal models** suitable for a broad range of different therapeutic interventions in FSHD. Improved preclinical and large animal models that accurately reflect mechanisms of disease onset and progression. The mouse models are good for some interventions but do not broadly represent disease progression. The FSHD community is very interested in the pig models that are in development, and other animal models might be good as well.

When we merge the advances in the last year with earlier studies the data begins to form better models of disease progression. Like brushstrokes on a canvas shape turns to form and a picture emerges. Mechanisms of progression take on better definition and hypothetical models of disease progression need to be considered and explored. The advances in the last year helps connect the dots from findings decades past and coming in from new and unexpected directions such as cancers -- B Cell Acute Lymphoblastic Leukemia (ALL)²⁷, Ewing-like Sarcoma²⁸, and CIC-DUX4 Sarcoma²⁹.

Mechanistic aspects of FSHD progression have become better defined. Areas of interest in FSHD are: methylation profiles, accumulation of epigenetic memory^{17,30,31}, positive autoregulation of DUX4^{18,32}, translational reprogramming³³, ribonucleoprotein complexes, and DNA double-strand breaks.

Areas of interest as potential therapeutics for FSHD, involve getting at FSHD via DUX4

(expression, mRNA, protein), via amplification (auto-regulation, feed-forward), accumulated memory (epigenetic, circuits), and via suppression of the muscle program. Therapeutic approaches for attacking cancer must be considered as well via targeting translocations (expression, mRNA, protein) by Immune Signaling Interferon Stimulated-Gene induction³⁴ and by using Full-length DUX4 expression in cancer³⁵.

Currently active projects listed in NIH RePORT as being applicable to FSHD are \$16.330 million FY2024 (1May2024) vs. \$16.557 million year-ago FY2023 and \$17.507 the year before in FY2022 (source: NIH Research Portfolio Online Reporting Tools (RePORT) 'FSHD or facioscapulohumeral or landouzy-dejerine'). The NIH is currently the principal worldwide source of funding of basic biomedical research on FSHD. Currently annual funding directly dedicated for FSHD listed in NIH RCDC is estimated at \$10 million.

Table 2. FSHD Research Dollars (millions) & FSHD Percentage of Total NIH Muscular Dystrophy Funding
Sources: NIH/OD Budget Office & NIH OCPL & NIH RePORT / RCDC (e=estimate, a=actual)

Fiscal Year	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023e	2024e
All MD (\$ millions)	\$75	\$76	\$78	\$77	\$79	\$81	\$81	\$83	\$95	\$82	\$78	\$81	\$83
FSHD (\$ millions)	\$5	\$5	\$7	\$8	\$9	\$11	\$11	\$10	\$9	\$9	\$10	\$10	\$10
FSHD (% total MD)	7%	7%	9%	10%	11%	14%	14%	12%	9%	11%	13%	12%	12%

Honorable Chairman, thanks to Congress' work in enacting the MD CARE Act, funding the NIH, and with communications with NIH-leadership and program/legislative staff -- several dystrophies now have FDA approved treatments. NIH has been especially thoughtful with its expenditure and approach to research on muscular dystrophy.

I have not delved into the catastrophic nature of FSHD physically, emotionally and financially in this testimony to spare the heartache and have simply stated the facts of the present condition and paradigm of FSHD scientific evolution. The facts speak loudly that NIH has taken its foot off the accelerator and the opportunity to improve the lives of millions of individuals internationally are being missed if not ignored. I wish to stress that we need funding now more than ever.

It is imperative to increase our efforts in the areas mentioned herein -- gains in these areas will help ascertain if therapies are effective, safe and not cost-prohibitive. We request for FY2025, increasing NIH FSHD research funding/appropriation of the standard portfolio to \$40 million.

Honorable Chairman, thank you for this opportunity to update you with this testimony.

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