

Testimony of Daniel Paul Perez, Co-Founder & Director Emeritus FSHD Society before
U.S. Senate Appropriations Subcommittee on Labor, HHS, Education and Related Agencies
May 11, 2022

Honorable Chairwoman Murray, Ranking Member Blunt, and distinguished members of the Subcommittee, thank you. We are requesting the FY2023 appropriation of an *amount* of **\$25 million** for the *agency* U.S. DHHS National Institutes of Health (**NIH**) to sustain and continue its research *program* on facioscapulohumeral muscular dystrophy (*hereafter called* **FSHD**). We are requesting an additional **\$5 million** for specifically targeted FSHD research through the NIH as requested herein.

Madam Chairman, this is my sixty-third testimony before the U.S. Congress' Appropriations Subcommittee on this matter. I have been professionally engaged in FSHD research since 1987, with a focus on funding research on the fundamental pathophysiology, molecular biology and genetics of the disease. I am co-founder, past -Chairman, -President & CEO, and -CSO of FSHD Society, and have been involved in the evolution and design of FSHD research, gene mapping and genetics more or less from its inception to the present. My work and the FSHD Society's funding spans nearly every research lab working on FSHD, the tactical and strategic planning that have led to understanding how FSHD1¹ and FSHD2^{2,3} work, Muscular Dystrophy Community Assistance, Research and Education Amendments of 2001 (MD-CARE Act, Public Law 107-84), advocacy and policy, and the relationship of the scientific community to the larger societal context in which FSHD is embedded.

I am approaching near thirty years of testifying as a patient with FSHD for Appropriation of funding for FSHD. I have had this disease for twice that time. That is a long time to live with a disease of this burden. I have now seen, experienced the entire effects, and borne almost the full brunt of what FSHD can do to you. FSHD is a heritable disease and one of the most common neuromuscular disorders with a prevalence of 1:8,000.⁴ It affects 934,000 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, Georgia and others.^{11,12}

The NIH is currently the principal worldwide source of funding of biomedical research on FSHD. Currently annual funding specifically targeted for FSHD listed in NIH RCDC is \$10 million. Given the remarkable advances and momentum in FSHD research in the past eight years; it is appalling that FSHD funding has not grown according to NIH RCDC. This indicates a mismatch between NIH funding mechanisms and the external community working on FSHD.

FSHD Research Dollars (in millions) & FSHD as a Percentage of Total NIH Muscular Dystrophy Funding

Sources: NIH/OD Budget Office & NIH OCPL & NIH RePORT RCDC (e=estimate, a=actual)

Fiscal Year	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021e	2022e
All MD (\$ millions)	\$86	\$75	\$75	\$76	\$78	\$77	\$79	\$81	\$81	\$83	\$95	\$97	\$102
FSHD (\$ millions)	\$6	\$6	\$5	\$5	\$7	\$8	\$9	\$11	\$11	\$10	\$9	\$9	\$10
FSHD (% total MD)	7%	8%	7%	7%	9%	10%	11%	14%	14%	12%	9%	9%	10%

Currently active projects listed in NIH RePORTer as having application to FSHD are \$17.507 million FY2022 (actual 04May2022), a 17.2% portion of the estimated \$102 million spent on all muscular dystrophies. A year ago at this time in fiscal year 2021 the NIH portfolio of active projects was \$16.554 million (actual 23June2021), a 17.1% portion of the estimated \$97 million spent on all muscular dystrophies. (source: NIH Research Portfolio Online Reporting Tools (RePORT) keyword 'FSHD or facioscapulohumeral or landouzy-dejerine').

In my role, I provide initiator and seed funding to bring new ideas and researchers online and am asked to evaluate and compare the various research projects we have funded and understand their commonalities and differences. I have, if I had to estimate, made a fairly extensive study of five to six hundred FSHD projects and proposals. My effort to solve FSHD has been persistent in yielding refined advances, it is novel and original, and is clearly driven by an overall sense of goals and concepts that are meaningful to patients and their families. The research we've started is forward-looking, as illustrated by the number of industry and philanthropic partners/researchers that have picked up on this seminal work and contributed to it.

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 development¹⁷⁻¹⁹. 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^{20-26,27,28}, and currently there is no cure or therapeutic option available to patients. DUX4 requires and needs to activate its direct transcriptional targets for DUX4-induced gene aberration and muscle toxicity²⁹⁻⁴². The genetics of FSHD are so remarkable, that NIH Director Dr. Francis Collins said on the front page of the New York Times, "If we were thinking of a collection of the genome's greatest hits, this [FSHD] would go on the list."⁴³ Add to this that FSHD was the sole disease mentioned in the recent tour de force Science publication "The complete sequence of a human genome." The paper is proof that scientists were able to sequence every base in the genome using at least one of six methods! FSHD was highlighted as having a bunch of newly assembled paralogs in the assembly; some of which showed evidence of being transcriptionally active. Great exposure for FSHD! This article will be read by the majority of genomics researchers worldwide - so should definitely increase awareness.⁴⁴

Blocking DUX4's DNA, DUX4's RNA or DUX4's protein ability to activate its targets has profound therapeutic relevance⁴⁵⁻⁴⁸. The FSHD scientific community has in recent years pioneered inroads to treating FSHD using the enormous potential of genomic sequencing, genomic medicine, gene editing and next generation diagnostics. All with the central paradigm of the reduction of: DUX4, DUX4 expression, DUX4 protein activity, or the effects of DUX4-mediated toxicity. Strategies include modulating DUX4 repressive pathways, targeting DUX4 mRNA, DUX4 protein, or cellular downstream effects of DUX4 expression.

Our FY2022 testimony on FSHD was quite comprehensive in scope, complete with 82 references, with a broad call to action in research areas from bench-side to clinic. Rather than restating – we ask the Committee to urge NIH to move forward on the many priorities listed.

In FY2023, we request NIH to additionally make an immediate and targeted push to answer the following three questions. Answers to these questions will help remove the obstacles to measuring disease progression, help measure if novel therapeutics are making a difference in stopping the disease and elucidate if muscle can grow again and be restored. At present, measuring disease progression and the effectiveness and safety of drugs remains ambiguous and the path forward deep and hard-going for industry, clinical partners and patients.

Three Key Research Questions

How does DUX4 expression lead to pathophysiology? We know a lot of what can happen when DUX4 is expressed in a cell (mostly forced experimental expression), but not a lot about what happens when an FSHD muscle cell expresses DUX4 that leads to pathology.

Can FSHD muscle pathology be reversed once DUX4 expression starts the pathogenic cascade in a particular muscle? This is a key question when looking to improve outcomes with either muscle building or DUX4 halting therapies.

Is there a systemic effect of local DUX4 expression that leads to amplification of muscle decline, either immune or some extracellular signaling? Answering this question will help delineate where along the travels of DUX4 from its birth and death in muscle we can intercept and control the disease process.

New data/information generated on the basic mechanism of DUX4 and how it causes muscle disease has the potential to focus the design of future clinical trials on muscles and measurements that will increase the rigor of the design and decrease the number of individuals necessary for initial tests of drug activity. It is absolutely necessary to increase our resolution, clarity and understanding of what DUX4 is and what it does to muscle in FSHD. The gains in this area will effectively unpin or untether FSHD from the difficulty category of “slowly progressing neuromuscular diseases remaining recalcitrant” to timely ascertainment that a clinical intervention can work.

We request for FY2023, increasing NIH FSHD research funding/appropriation of the standard portfolio to \$25 million. The growth has been slow, continuous and prone to year-to-year fluctuations downward and upward according to NIH funding data. Additionally, we request a one-time boost of \$5 million to solicit applications to answer the three questions of key import. At this moment in time, FSHD needs an infusion of both longstanding and immediate discovery NIH grants both submitted and funded. NIH needs to increase funding by adding exploratory / developmental research grants (parent R21) and research project grants (parent R01). This is NIH’s wheelhouse and forte without a doubt.

Madam Chairman, thank you for this opportunity to update you on FSHD with this testimony.

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