# U.S. DHHS National Institutes of Health (NIH) FY2019 budget Appropriations request for NIH funding of research on facioscapulohumeral muscular dystrophy (FSHD)

Witness appearing before the Senate Appropriations Subcommittee on Labor, HHS, Education and Related Agencies

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***Agency:*** *National Institutes of Health (NIH).* ***Account:*** *National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institute of Neurological Disorders and Stroke (NINDS), Eunice Kennedy Shriver National, Institute of Child Health and Human Development (NICHD), National Heart, Lung and Blood (NHLBI) and other Institutes as appropriate.* ***FY2019 Program / Amount Language:*** *Scientific opportunities and recent breakthroughs alongside community defined research priorities in facioscapulohumeral disease (FSHD) call for more funding on the disorder. The Committee strongly encourages the NIH to significantly increase funds to $29 million on basic and exploratory research efforts and to accelerate clinical trials readiness funding to foster access to treatment of facioscapulohumeral muscular dystrophy (FSHD) and other FSHD-related-epigenetic diseases.*

Honorable Chairman Blunt, Ranking Member Murray and distinguished members of the Subcommittee, thank you for the opportunity to submit testimony. We kindly request $29 million for FY2019 of NIH funding for research on facioscapulohumeral disease (FSHD).

FSHD, a heritable disease, is the most common form of muscular dystrophy with a prevalence of 1:8,000.[1] It affects 934,000 children and adults of both sexes worldwide. FSHD is characterized by progressive loss of muscle strength that is asymmetric and widely variable. Muscle weakness typically starts at the face, shoulder girdle and upper arms, often progressing to the legs, torso and other muscles. FSHD can cause significant disability and, in severely affected individuals, premature death that is mainly through respiratory failure. In addition to affecting muscle, it can bring with it hearing loss, eye problems, asymptomatic cardiac arrhythmias and respiratory insufficiency.

I started my journey in 1989 to raise the understanding and visibility of FSHD. I naively believed in those years that if you had a chronic and debilitating disease that someone somewhere would be funding research and working on a cure. We had not yet discovered that it would happen ever so gradually and that it would take years of personal endeavor and self-advocacy by people directly concerned with the disease to advocate for funding and research. I co-founded the FSH Society in 1991, we are a small group of affected, dedicated and talented individuals working to alter the course of a disease. We testify each year and are still here working hard for a sense of agency and survival against extraordinary odds.

At any age an individual with FSHD should be recognized as a lifelong survivor of severe trauma and tension. Patients and their families deal with the continuing, unrelenting and unending loss caused by FSHD from birth, over the months and through the years. Not for a moment is there a reprieve from continual loss of physical ability; not for a moment is there a time to mourn the loss; not for a moment is there relief from the physical and mental pain that is a result of this disease. There is no known treatment for this disease.

FSHD insidiously and systematically deprives patients and their families of the full range of choices in life. FSHD affects the way you walk, the way you dress, the way you work, the way you wash, the way you sleep, the way you relate, the way you parent, the way you love, how and where you live, and the way people perceive and treat you. Individuals manifesting signs of the FSHD disorder cannot smile; or hold a baby in their arms; cannot close their eyes fully either when awake or when asleep; can no longer run or walk on the beach or climb stairs. Every day they are keenly aware of the things that they may not



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be able to do tomorrow. This is the reality for the near 41,000 people living with FSHD in the United States of America.

Meticulous scientific efforts by world-class FSHD researchers and clinicians working with partial seed funding from the FSH Society, the NIH and others have yielded significant scientific discoveries advancing epigenetic and human disease knowledge. FSHD is the only human disease known to be caused by the contraction of repetitive "junk' DNA. Its cause is found within a stretch of 'junk DNA' thought previously to have no biological function. A contraction of this array of macrosatellite repeats called 'D4Z4' located near the chromosome 4q telomere causes the production of a transcription factor called *DUX4*. This transcription factor is a gene which when overexpressed makes a protein product DUX4 that causes skeletal muscle death and degeneration. FSHD-patients' 'junk' DNA contains a gene *DUX4* that is normally turned on in initial stage embryonic development and shuts off before the embryo even implants in the uterus, and as an adult it is packed away in the 'junk'. In FSHD, when this 'junk' array of DNA is shortened, contracted or modified, the gene *DUX4* is made accessible, and is toxic to skeletal muscle.[2,3,4,5]

The fact that reanimated 'junk' DNA can cause disease in a Mendelian fashion is so astounding NIH Director Dr. Francis Collins emphasized its significance on the front page of the *New York Times*, saying "If we were thinking of a collection of the genome's greatest hits, this [FSHD] would go on the list."[6] This past March, NIH funded extramural researchers highlighted groups of proteins that normally turn *DUX4* off and on (NuRD$^{Dux4\text{off}}$, CAF-1$^{Dux4\text{off}}$ and MBD3L2$^{Dux4\text{on}}$) in development. Researchers found that when MBD3L2 turns *DUX4* on in a muscle cell it spreads down the muscle fiber from nucleus to nucleus in culture.[7] Though in actual muscle tissue these cells may not be as close to one another or touching one another -- it might perhaps explain why only muscles are affected in FSHD, as muscle-cell nuclei unlike other cells do not have walls between them. It helps us rationalize a mechanism whereby when at any given time we only view under the microscope one in 1,000 cells expressing DUX4. Controlling MBD3L2 theoretically may affect spreading and progression. Last month, a paper came out in *Molecular Therapy* on FSHD screens and FSHD candidate targets showing that FSHD causing targets can be repressed by different methods in skeletal myocytes without major effects on certain critical muscle genes. Both small molecules and CRISPR gene editing techniques were independently used. This project funded by NIH NIAMS and industry provides data demonstrating that expression of DUX4-fl toxic variant is regulated by multiple epigenetic pathways, and highlights multiple viable, druggable candidates for therapeutic target development.[8]

The National Institutes of Health (NIH) is the principal worldwide source of funding of research on FSHD. Currently active projects are $13.654 million FY2018 (actual), a portion of the estimated $85 million spent on all muscular dystrophies.

This Subcommittee and **Congress in partnership with NIH, patients and scientists have made truly outstanding progress in understanding and treating the nine major types of muscular dystrophy.** Congress is responsible for this success by its sustaining support of the overall NIH budget, and enacting the Muscular Dystrophy Community Assistance, Research and Education Amendments of 2001 (MD-CARE Act, Public Law 107-84). Several years past, NIH leadership and staff published the *'2015 NIH Action Plan for the Muscular Dystrophies'* – a research plan -- written by the federal advisory committee mandated by MD CARE Act, called the MDCC, along with working groups of outside scientific experts in the field. It specifies eighty-one objectives, in six sections (mechanism, screening, treatments, trial readiness, access to care, infrastructure including workforce) in need of funding and further development.[9]

Since inception, the FSH Society has provided approximately $9.834 million in seed funds and grants to pioneering FSHD researchers and created an international network of patients and researchers. Recent



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papers have emerged with findings on potential FSHD targets, validated candidate targets, cell and animal models, biomarkers, muscle pathophysiology and cell biology, genetics of FSHD, FSHD stem cell biology, MRI, surrogate outcome measures, drug discovery and development work -- therapeutic studies using small molecules, studies in gene therapy, genetic engineering, CRISPR, antisense oligonucleotide (ASO), morpholino, and LNA gapmers to name a crowd of exciting priorities and concepts. FSH Society funded researchers have shown through peer review publications proof-of-concept in-vivo and in-vitro studies that the DUX4 gene and protein can be turned off! [10, 11, 12]

With more grant applications the NIH can increase the amount of research funding on FSHD without having to increase the NIH budget or take money from other promising areas of research. Better data, higher quality science, and focus allows for more efficiency out of a slowly increasing budget, while achieving the goals of the NIH Action Plan for muscular dystrophy.

**We must keep moving forward.** At the FSH Society's most recent annual International Research Consortium meeting in Boston, Massachusetts (a meeting funded in part by the NIH NICHD University of Massachusetts Medical School Wellstone Center for FSHD) over 110 researchers from around the world gathered to present the latest data and discuss research strategies. The FSHD clinical and research community listed 2016-2018 priorities in the following Table I as:

**Table I. 2017/2018 Research Priorities**

**Molecular mechanisms**

Priority 1: Understanding genetic toxicity in FSHD
Priority 2: Understanding DUX4/Dux4 and how to silence it. How to silence the *DUX4* RNA
Priority 3: Understanding what real pathophysiology is in FSHD
Priority 4: Studying relationship to other markers and correlation between the expression and activity, transcriptional activity of *DUX4*

**Genetics and epigenetic**

Priority 5: Studies that focus on the uniformity in genetic testing and subgrouping of patients
Priority 6: Understanding epigenetic regulation of the repeats to help better understand the disease process and the disease mechanism
Priority 7: Research on modifiers of the disease mechanism

**Clinical and therapeutic studies**

Priority 8: Generating and identifying surrogate outcome biomarkers
Priority 9: Establishing validated outcome measures
Priority 10: More research with natural history studies
Priority 11: Studies to identify, validate, and determine the best standard measurements critical for trial preparedness in FSHD

**Models**

Priority 12: Research to ensure clinician-researchers are measuring the same kinds of things which translate into usable tools for our therapeutic industry
Priority 13: Development, characterization and use of animal models: whole animal; mice; fish; pig mammal
Priority 14: Emphasis on development, characterization and use of FSHD human cellular models
Priority 15: Research on models to develop how to deliver, how to formulate, how to turn the conceptual entity into an effective therapeutic use of the entity, all require something that you can test
(Source: http://www.fshsociety.org/)

**NIH funding for muscular dystrophy.** Mr. Chairman, these major advances in scientific understanding and epidemiological surveillance are not free. They come at a significant cost. Since passing the MD CARE Act in 2001, funding at NIH for FSH muscular dystrophy has remained far too level given the remarkable and exponential rate of discoveries in the past three years.



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**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 *(a=actual, e=estimate, ee=estimate enacted)*

| **Fiscal Year** | **2006** | **2007** | **2008** | **2009** | **2010** | **2011** | **2012** | **2013** | **2014** | **2015** | **2016** | **2017e** | **2018e** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| All MD ($ millions) | $39.9 | $47.2 | $56 | $83 | $86 | $75 | $75 | $76 | $78 | $77 | $79 | $81 | $85ee |
| FSHD ($ millions) | $1.7 | $3 | $3 | $5 | $6 | $6 | $5 | $5 | $7 | $8 | $9 | $11 | $13.7a |
| FSHD (% total MD) | 4% | 5% | 5% | 6% | 7% | 8% | 7% | 7% | 9% | 10% | 11% | 14% | 16% |

There are 28 active projects NIH-wide totaling $13.654 million as of April 18, 2018, versus 28 active projects NIH-wide totaling $12.751 million as of March 3, 2017, and 32 active projects NIH-wide totaling $12.616 million on April 14, 2016 (source: NIH Research Portfolio Online Reporting Tools (RePORT) http://report.nih.gov keyword 'FSHD or facioscapulohumeral or landouzy-dejerine'). NIH's 28 projects cover 2 F31, 1 K22, 1 K23, 12 R01, 1 R13, 4 R21, 1 R56, 1 P01, 1 P50, 2 U01, and 2 U54 grants.

**What we need.** Specifically, NIH needs to increase its current portfolio by funding substantial additional R01 and R21 style grants. The engine of federal research runs on the basic building blocks of workforce training, exploratory/developmental research grants (parent R21) and research project grants (parent R01). NIH can help by issuing targeted funding announcements covering FSHD such as Program Announcement (PA) and similar calls for applications. A request for applications (RFA) on FSHD for R01 and R21 grants will yield results in FSHD and illustrate to NIH leadership the pent up demand for funding and let us know that leadership has listened to our concerns. These types of efforts help convey to FSHD and allied researchers that NIH has an elevated interest.

**What we are asking for.** We request for FY2019, a doubling of the NIH FSHD research portfolio to $29 million. We are very appreciative of the slow but steady year-to-year increases and thank NIH and Congress. This year FSHD needs an investment in centers, collaborative research grants – and, most importantly, a rapid ramp up of basic grants and exploratory research awards along with the expansion of post-doctoral and clinical training fellowships. The NIH research plan for FSHD calls for and needs these additional funds to succeed. The opportunities before us in FSHD are quite significant at all levels – the time to move forward with purpose and expeditiously is now. Mr. Chairman, thank you for this opportunity to testify before your committee. Thank you as always for your kind consideration and help.

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