Testimony of Daniel Paul Perez, President & CEO, e-mail: daniel.perez@fshsociety.org
FSH Society, 450 Bedford Street, Lexington, MA 02420, phone: (781) 275-7781, before the United States House Appropriations Committee, Subcommittee on Labor, Health and Human Services, Education and Related Agencies on the subject of **$21 million** in **FY2016** Appropriations for U.S. DHHS National Institutes of Health **NIH** Research Programs on **Facioscapulohumeral Muscular dystrophy (FSHD)** April 29, 2015

Agency: *National Institutes of Health (NIH).*
Account: *NINDS, NIAMS, NICHD, NHLBI, NHGRI and others as appropriate.*
Suggested FY 2016 Report Language*: The Committee encourages the NIH to foster opportunities for multidisciplinary research on facioscapulohumeral muscular dystrophy (FSHD), a common and complex form of muscular dystrophy, commensurate with its prevalence and disease burden. The Committee hopes such advances will be utilized to help advance treatments and access to therapies for this grave disease.*

Honorable Chairman Cole and Ranking Member DeLauro, thank you for the opportunity to submit this testimony. Facioscapulohumeral muscular dystrophy (FSHD) may be the most common muscular dystrophy with a prevalence of 1:8,000.[1] For approximately 870,000 men, women, and children worldwide the major consequence of inheriting this condition may be a lifelong progressive loss of all skeletal muscles. The National Institutes of Health (NIH) is the principal source of funding of research on FSHD currently at the $7 million level. I am pleased to report that your help and investment has produced remarkable scientific returns.

1. **Congress has made a major difference.** I have testified approximately fifty times. When I first testified, we did not know the genetic mechanism of this disease. Now we do. Now we can target it. When I first testified, FSHD was considered rare; now it may be the most prevalent form of muscle disease. Congress is responsible for this success, through its sustaining support of the NIH and the enactment of the Muscular Dystrophy CARE Act. We are aware that MD Care Act does not set the amount of spending on FSHD or the other dystrophies at the NIH and we recognize that funding levels are determined in the appropriations process and the numbers of grant applications received and funded by the NIH on FSHD. With this understanding, we are requesting that Congressional appropriations ask NIH to seize on great

opportunities to advance treatments for FSHD that will not require increasing the NIH budget, nor diminish other research while gaining more efficiency out of a non-growing research budget.

2. Quantum leaps in our understanding of FSHD. The past four and a half years have seen remarkable contributions made by a very small but extremely dedicated tribe of researchers funded by NIH and non-profits.

TABLE 1

- On August 19, 2010, American and Dutch researchers published a paper which dramatically expanded our understanding of the mechanism of FSHD.[2] A front page story in the *New York Times* quoted the **NIH Director Dr. Francis Collins** saying, "If we were thinking of a collection of the genome's greatest hits, this would go on the list." [3]
- Two months later, another paper was published that made a second critical advance in determining the cause of FSHD. The research shows that FSHD is caused by the inefficient suppression of a gene that may be normally expressed only in early development. [4]
- On January 17, 2012, an international team of researchers based out of Seattle discovered a stabilized form of a normally suppressed gene called DUX4 affects many different germline genes, retro-elements, and immune mediators; all potential targets. [5]
- Six months later, another high profile paper produced by a Senator Paul A. Wellstone Muscular Dystrophy Cooperative Research Center of the NIH (mandated by MD CARE Act), used sufficiently "powered" large collections of genetically matched FSHD cell lines generated by the NIH center that are both unique in scope and shared with all researchers worldwide, to improve on the Seattle group's finding by postulating that DUX4-fl (full-length) expression is necessary but not sufficient by itself for FSHD muscle pathology. [6]
- On July 13, 2012, a team of researchers from the United States, Netherlands and France identified mutations in a gene called SMCHD1 causing 85% of another form of FSHD called FSHD1B or FSHD2. This paper furthers our understanding of the molecular pathophysiology of FSHD. This work too was supported in part by a program project grant from NIH. [7]
- On September 25, 2014, researchers from United States, France, Spain, Netherlands and United Kingdom narrow the focus mechanistically opening the possibility of all types of FSHD having an epigenetic basis. [8]
- On March 29, 2015, different researchers involved with the NIH Senator Paul A. Wellstone Cooperative Research Center using its large collection of different FSHD patient samples and different techniques arrive at the same answer that there is an underlying principle of epigenetics defining asymptomatic or non-manifesting and playing a role in disease severity. [9]

Many of these findings have their origins in seed funding from the FSH Society to researchers who have then used preliminary data to secure funding from the NIH. In simpler terms, our own genes within us are being inappropriately expressed in muscle tissue at a time and place where they do not normally reside or function by a confluence of events in a variety of ways giving rise to the decay and destruction of skeletal muscle; and we begin to focus on the very narrow stretch of DNA down to the nucleotide level in an area adjacent to the toxic gene inappropriately turned on so-named DUX4-fl (full-length). Think of it as the opposite of cancer rather than runaway genes causing unbridled cell growth; runaway genes are causing unbridled cell death. What is fascinating is, though one has all the requisites to have FSHD (e.g. the presence of a

chromosome 4qA containing a DUX4 polyadenylation signal; and either a truncation of D4Z4; or a SMCHD1 mutation with D4Z4 repeat array with array sizes at the lower end of the normal repeat size spectrum) there are modifiers that allow a person to have symptoms of FSH disease whilst other genetically tested positive relatives are spared of disease symptoms e.g. methylation and modifiers. We can see clearly now that the stability of epigenetic repression by the region just upstream of DUX4 gene on the very last distal D4Z4 repeat, regardless of which route DUX4-fl was stabilized and presented FSHD1, FSHD2, FSHD3, etc., is a key regulator that can be modified perhaps via its methylation level/status. FSHD2 modifies FSHD1 in individuals who carry both mutations presenting even more severe disease. Even more remarkably, we have compounds and techniques to modify and target modifiers and expression of DUX-fl, and still the FSHD research and clinical enterprise is starved for federal funding from NIH! In 2014, the FSH Society funded projects to silence the DUX4 gene using leading-edge genome-editing technologies (CRSPR/Cas, TALEN), helped support efforts in development efforts and models to test anti-sense oligonucleotide (ASO) and morpholino and we aided the development of animal models and a novel method that we believe will revolutionize FSHD diagnostics. We are thrilled that our grantees and colleagues have data that proves that DUX4-fl and cascading events can be turned off.

3. We must keep moving forward. In October 2014 the FSH Society held its annual FSHD International Research Consortium meeting. The meeting was funded in part by the NIH NICHD University of Massachusetts Medical School Wellstone center for FSHD. Nearly 85 researchers gathered to present latest data and discuss research strategies. The discussion agenda focused on being prepared for intervention development and clinical readiness. To keep focused we followed the path: Genetics > Mechanisms and targets > Models > Patients. The priorities

stated for 2015, at the October 18, 2014, FSH Society FSHD IRC meetings can be found at: http://www.fshsociety.org/international-research-consortium/

Additionally, on March 17th, 2015, the FSH Society presented to the MDCC its concern about the small number of NIH grants and that much greater funding is required to address the most pressing challenges for FSHD research, including research on topics listed in Table 2.

TABLE 2

- Mechanisms of DUX4 toxicity
- More molecular, imaging and functional markers of disease progression
- Modifiers of disease: genetic, chemical, and lifestyle
- Preclinical models validated to represent aspects of FSHD pathophysiology
- Better animal models based on low expression of DUX4 as seen in patients
- Mechanisms of pathology in patients' muscles
- Normal functions of DUX4 in tissues other than muscle
- Methods of administering anti-DUX4 agents to muscle
- Muscle regeneration capacity in FSHD muscles
- Large animal models (monkey, marmoset)
- Biomarkers that can indicate impact of therapeutic agents.

4. NIH Funding for Muscular Dystrophy. Mr. Chairman, since Congress passed the MD CARE Act in 2001, research funding at NIH for muscular dystrophy has increased 4-fold from $21 million. While FSHD funding has increased 14-fold from $500,000 during this period. The FSHD funding level at the NIH has been basically flat for the past seven years.

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)

Fiscal Year	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015e**	**2016e**
All MD ($ millions)	$38.7	$39.5	$39.9	$47.2	$56	$83	$86	$75	$75	$76	$78	$79	$81
FSHD ($ millions)	$2.2	$2.0	$1.7	$3	$3	$5	$6	$6	$5	$5	$7	$7	$7
FSHD (% total MD)	6%	5%	4%	5%	5%	6%	7%	8%	7%	7%	9%	9%	9%

We have communicated to the NIH leadership and the Muscular Dystrophy Coordinating Committee (MDCC) federal advisory committee mandated by the MD CARE Act our grave concern that FSHD research is way too under-represented and needs a proactive effort on the part of NIH. At the March 17, 2015, MDCC meeting we re-iterated to Alan E. Guttmacher, MD., Director, NICHD and Chair of the MDCC and all MDCC members that we are fully supportive of the Action Plan for Muscular Dystrophy; while at the same time we requested that NIH redress the imbalance of

funding in the muscular dystrophy portfolio with respect to FSHD. The NIH should address this issue head-on. In the last year alone, incredible opportunities for public, private and non-profit entities engaged in FSHD research and clinical research have emerged. Oddly these discoveries clearly belonging to the leading edge of human genetics and our understanding the epigenome and treating epigenetic diseases are sitting idle at NIH. NIH needs to see through the thick fog of fiscal distress and recognize that opportunities for the development of effective treatments for FSHD and epigenetic diseases have never been greater. While all muscular dystrophy research funding at NIH increased by $41 million ($39.9M 2006 to $81M 2016e); FSHD increased by $5.3 million ($1.7M to $7M). There is a real paradox in FSHD's order of magnitude difference in growth, being equally devastating and burdensome as the disease receiving the most funding in this category called muscular dystrophy, and though it functions in the exact same U.S. federal research infrastructure. **We request for FY2016, an NIH FSHD research portfolio of $21 million correlating to 25% of the current estimated muscular dystrophy funding at NIH.** NIH can to convey to researchers that it has a specific interest in FSHD. There are no quotas on peer-reviewed research above pay line at the NIH, and NIH can help. This is the time to fully and expeditiously exploit the advances in scientific opportunities for which the American taxpayer has paid. Thank you for this opportunity to testify before your committee.

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