Testimony of **Daniel Paul Perez**, President & CEO, **FSH Society, Inc.**
Telephone: (781) 275-7781, e-mail: daniel.perez@fshsociety.org before the
United States Senate Appropriations Committee
Subcommittee on Labor, Health and Human Services, and Education
On the subject of **$12 million FY2014 Appropriations for U.S. DHHS National Institutes of Health (NIH) Research Programs on Facioscapulohumeral Muscular Dystrophy (FSHD)**
May 6, 2013

Honorable Chairwoman Mikulski and Ranking Member Harkin, thank you for the opportunity to submit this testimony. I am Daniel Paul Perez, of Bedford, Massachusetts, President and CEO of the FSH Society, Inc. and an individual who has lived with facioscapulohumeral muscular dystrophy (FSHD) for 51 years. For hundreds of thousands of men, women, and children worldwide the major consequence of inheriting this form of muscular dystrophy is a lifelong progressive loss of all skeletal muscles. FSHD is a crippling and life shortening disease. No one is immune. It is both genetically and spontaneously transmitted to children. It can affect multiple generations and entire family constellations.

The National Institutes of Health (NIH) is the principal source of funding of research on Facioscapulohumeral Muscular Dystrophy (FSHD) currently at the $6 million level. Over many years, this Committee has supported the incremental growth in funding for FSHD research. I am pleased to report that this modest investment has produced huge scientific returns.

1. Congress has made a major difference in muscular dystrophy

I have testified many times before Congress. When I first testified, we did not know the mechanism of this disease. Now we do. When I first testified, we assumed that FSHD was a rare form of muscular dystrophy. Now we understand it to be one of the most prevalent forms of muscular dystrophy. Congress is responsible for this success, through its sustaining support of the National Institutes of Health (NIH), and the enactment of the Muscular Dystrophy CARE Act. I am testifying in order to document this success and call on Congress to continue the momentum of discovery you have set in motion.

Congress enacted The Muscular Dystrophy Community Assistance, Research and Education Amendments of 2001 (the MD-CARE Act, Public Law 107-84) on December 18, 2001. It was reauthorized in 2008 and new efforts are underway to reauthorize the MD-CARE Act as it will expire in 2013. We are hopeful that this reauthorization bill will receive the same overwhelming bi-partisan support enjoyed in earlier enactments.

2. Quantum leaps in our understanding of FSHD have occurred in past three years

The past three years have seen remarkable contributions made by researchers funded by NIH.

- On August 19, 2010, American and Dutch researchers published a paper which dramatically expanded our understanding of the mechanism of FSHD.[1] 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."[2]

Patients, professionals, and other parties interested in FSHD can contact us at FSH Society, Inc., 450 Bedford Street, Lexington, MA 02420 USA. Phone (781) 275-7781, fax (781) 275-7789, e-mail: daniel.perez@fshsociety.org. Internet: http://www.fshsociety.org

- Two months later, another paper was published that made a second critical advance in determining the cause of FSHD.[3] The research shows that FSHD is caused by the inefficient suppression of a gene that may be normally expressed only in early development.
- On January 17, 2012, an international team of researchers based out of Seattle discovered a gene called DUX4 required to develop chromosome 4-linked FSHD.[4]
- Six months later, another high profile paper produced by the NIH funded University of Massachusetts Senator Paul D. Wellstone Cooperative Research Center for FSHD, 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 expression is necessary but not sufficient by itself for FSHD muscle pathology.[5] This work was also supported by a NIH cooperative research center grant mandated by MD CARE Act.
- On July 13, 2012, a team of international researchers from the, United States, Netherlands and France identified mutations in a gene causing 80% of another form of FSHD. 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.[6]
- On April 4, 2013, an international team published a mouse model that appears more promising than previous models of FSHD. The result of a decade's worth of work, during which scientific understanding of FSHD exploded. "We hope that in the near future these mouse models will serve an important purpose in drug development programs for FSHD," remarked senior author Silvère van der Maarel of Leiden University in the Netherlands. The herculean project was initiated in 2003, by the FSH Society's Marjorie Bronfman Fellowship grant. The patient-driven charity was seeking a definitive mouse model based on a genetic unit called D4Z4. Normally, people have ten or more of these units, repeated one after the other near the tip of chromosome 4. The majority of FSHD patients, in contrast, have fewer than ten D4Z4 units. The newly published mouse model contains 2.5 copies of the D4Z4 unit, a truncated number comparable to that seen in human FSHD patients. The D4Z4 unit contains the gene called DUX4, which is toxic to muscle cells.[7] This work was also supported by NIH grants.

I am proud to say that many of these researchers have started their efforts in FSHD with seed funding from the FSH Society and have received continued support from the FSH Society, the National Institutes of Health, and the Muscular Dystrophy Association and other partners. This shows the power of the collaboration among funders, patient groups and researchers to advance the search for cures and treatments.

3. Remarkable progress in FSHD research and the need to keep moving forward

Given the recent developments, there is a need to ramp up the preclinical enterprise and build/organize infrastructure needed to conduct clinical trials. Our immediate priorities should be to confirm the new hypotheses and targets. We need to be prepared for this new era in the science of FSHD, by accelerating efforts in the following **five** areas: [8]

Patients, professionals, and other parties interested in FSHD can contact us at FSH Society, Inc., 450 Bedford Street, Lexington, MA 02420 USA. Phone (781) 275-7781, fax (781) 275-7789, e-mail: daniel.perez@fshsociety.org. Internet: http://www.fshsociety.org

Table 1.

1. Genetics / epigenetics. There is general acceptance that transcriptional deregulation of D4Z4 is central to FSHD1 and FSHD2. The FSHD2 gene SMCHD1 explains approximately 80% of FSHD2. There is a need for better understanding of the factors that modulate DUX4 activity and disease penetrance.

2. FSHD molecular networks. D4Z4 chromatin relaxation on FSHD-permissive chromosome-4 haplotypes leads to activation of downstream molecular networks. In addition to considering DUX4 as the "target" and downstream targets, the upstream processes and targets – triggering of activation – are equally important. Hence, understanding what DUX4lf does as a target and targets up- and down-stream of it are priorities. Detailed studies on these processes are crucial for insight in the molecular mechanisms of FSHD pathogenesis and may contribute to explaining the large intra- and interfamily clinical variability. Importantly such work may lead to intervention (possibly also prevention) targets. Additional FSHD genes and modifiers are still likely to exist. Apart from chromatin modifiers, these include, but are not limited to, CAPN3 and the FAT1 gene that was recently suggested to be involved in FSHD.

3. Clinical trial readiness. It is now broadly accepted that deregulation of the expression of D4Z4 / DUX4 is at the heart of FSHD1 and FSHD2. This finding opens perspectives for intervention along different avenues. Intervention trials are envisaged within the next several years. The FSHD field needs to be prepared for this crucial step. There is an increasing need to improve the translational process. This includes, but is not limited to, the need for consensus on data capture and storage, overcoming national and international barriers, definition of natural history, identification of (meaningful) and sensitive outcome measures, biomarkers, and meaningful functional measures. There is a need to work more closely with FDA to help define acceptable measures for trials.

4. Model systems. There was already a good set of cellular and models, based on different pathogenic (candidate gene) hypotheses. This was further expanded during the last year. The phenotypes are very diverse and often difficult to compare with the human FSHD phenotype. Many basic questions remain unanswered and dearly need to be answered for further translational studies: when and where is DUX4 expressed in skeletal muscle and what regulates DUX4 activity. It was recognized that there still exists a gap in our knowledge linking the basic genetic and molecular findings with the observed muscle pathology. The University of Massachusetts NIH Sen. Wellstone center and the University of Rochester continue to generate human cellular resources. These resources continuously deserve attention and need to be replenished. Recent progress in ES-cell technology, including iPS lines, allows for inter-group distribution and dedicated molecular (epi)genetic studies.

5. Sharing. Timely sharing of information and resources remains a critical contributor to the progress in the field. Sharing of resources other information remains a priority (e.g. protocols, guide to FSHD muscle pathology, etc.).

We would be pleased to provide the Committee with detailed information on each of these areas. The pace of discovery and numbers of experts in the field of biological science and clinical medicine working on FSHD are rapidly expanding. Many leading experts are now turning to work on FSHD not only because it is one of the most complicated and challenging problems seen in science, but because it represents the potential for great discoveries, insights into stem cells and transcriptional processes and new ways of treating human disease.

4. NIH Funding for Muscular Dystrophy

Mr. Chairman, these major advances in scientific understanding and epidemiological surveillance are not free. They come at a cost. Since Congress passed the MD CARE Act, research funding at NIH for muscular dystrophy has increased 4-fold. While FSHD research funding has increased 12-fold during this period, the level of funding is still exceedingly modest.

Patients, professionals, and other parties interested in FSHD can contact us at FSH Society, Inc., 450 Bedford Street, Lexington, MA 02420 USA. Phone (781) 275-7781, fax (781) 275-7789, e-mail: daniel.perez@fshsociety.org. Internet: http://www.fshsociety.org

FSHD Research Dollars (in millions) & FSHD as a Percentage of Total NIH Muscular Dystrophy Funding
Sources: NIH/OD Budget Office & NIH OCPL & NIH RCDC RePORT
(e = estimate; as FY2012 actuals not available on-line as of March 12, 2013)

Fiscal Year	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012e**
All MD ($ millions)	$12.6	$21	$27.6	$39.1	$38.7	$39.5	$39.9	$47.2	$56	$83	$86	$75	$75
FSHD ($ millions)	$0.4	$0.5	$1.3	$1.5	$2.2	$2.0	$1.7	$3	$3	$5	$6	$6	$6
FSHD (% total MD)	3%	2%	5%	4%	6%	5%	4%	5%	5%	6%	7%	8%	8%

Despite the great success of the past two and a half years in the science of FSHD brought about by Congress we are concerned that the budget cuts required by the sequester are coming at a time when many of the FSHD research projects are ending. It is likely that new research projects will not be funded or existing programs will not be renewed. This is a perfect storm that could have devastating effects on FSHD research efforts. I served on the federal advisory committee MDCC for nine years until 2011. We have conveyed to the Executive Secretary of the MDCC our grave concern that the current portfolio of research on FSHD has a disproportionate number of FSHD grants near the end or in the last year of their grant cycles. While most are competitively renewable this occurrence could not have happened at a worst time with sequestration making meat axe cuts across all federal agencies.

We request for FY2014, a doubling of the facioscapulohumeral muscular dystrophy (FSHD) research budget to $12 million dollars. This will allow an expansion of the U.S. DHHS NIH Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers, an increase in research awards, expansion of post-doctoral and clinical training fellowships, and a dedicated center to design and conduct clinical trials on FSHD.

We are aware of the great pressures on the federal budget, but cutting the NIH budget and research funding for FSHD at this time would be the wrong decision. We have come so far with such modest funding. This is not the time to lessen our endeavor. This is the time to fully and expeditiously exploit the advances for which the American taxpayer has paid.

Thank you for this opportunity to testify before your committee.

Footnotes:

1. Lemmers, RJ, et al, A Unifying Genetic Model for Facioscapulohumeral Muscular Dystrophy *Science* 24 September 2010: Vol. 329 no. 5999 pp. 1650-1653
2. Kolata, G., Reanimated 'Junk' DNA Is Found to Cause Disease. *New York Times*, Science. Published online: August 19, 2010 http://www.nytimes.com/2010/08/20/science/20gene.html
3. Snider, L., Geng, L.N., Lemmers, R.J., Kyba, M., Ware, C.B., Nelson, A.M., Tawil,R., Filippova, G.N., van der Maarel, S.M., Tapscott, S.J., and Miller, D.G. (2010). Facioscapulohumeral dystrophy: incomplete suppression of a retrotransposed gene. *PLoS Genet*. 6, e1001181
4. Geng et al., DUX4 Activates Germline Genes, Retroelements, and Immune Mediators: Implications for Facioscapulohumeral Dystrophy, *Developmental Cell* (2012), doi:10.1016/j.devcel.2011.11.013
5. Jones TI, et al, Facioscapulohumeral muscular dystrophy family studies of DUX4 expression: evidence for disease modifiers and a quantitative model of pathogenesis. *Hum Mol Genet*. 2012 Oct 15;21(20):4419-30. Epub 2012 Jul 13.
6. Lemmers, RJ, et al, Digenic inheritance of an SMCHD1 mutation and an FSHD-permissive D4Z4 allele causes facioscapulohumeral muscular dystrophy type 2. *Nat Genet*. 2012 Dec;44(12):1370-4. doi: 10.1038/ng.2454. Epub 2012 Nov 11.
7. Krom YD, Thijssen PE, Young JM, den Hamer B, Balog J, et al. (2013) Intrinsic Epigenetic Regulation of the D4Z4 Macrosatellite Repeat in a Transgenic Mouse Model for FSHD. *PLoS Genet* 9(4): e1003415. doi:10.1371/journal.pgen.1003415
8. 2012 FSH Society *FSHD International Research Consortium*, held November 6, 2012 co-sponsored by DHHS NIH NICHD Boston Biomedical Research Institute Senator Paul D. Wellstone MD CRC for FSHD. To read the expanded summary and recommendations of the group see: http://www.fshsociety.org/pages/sciConsortium.html

Patients, professionals, and other parties interested in FSHD can contact us at FSH Society, Inc., 450 Bedford Street, Lexington, MA 02420 USA. Phone (781) 275-7781, fax (781) 275-7789, e-mail: daniel.perez@fshsociety.org. Internet: http://www.fshsociety.org