

**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
FY2013 Appropriations for National Institutes of Health (NIH) for research on
Facioscapulohumeral Muscular Dystrophy (FSHD) – April 26, 2012**

Honorable Chairmen Inouye and Harkin and Ranking Members Cochran and Shelby, 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 49 years. For hundreds of thousands of men, women, and children 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.

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, if not the most, prevalent form of muscular dystrophy. Congress is responsible for this success, through its sustaining support of the National Institutes of Health (NIH), enactment of the Muscular Dystrophy CARE Act and the collaborations of NIH, the Centers for Disease Control and Prevention (CDC), patient groups, and researchers, both here and internationally.

I am testifying in order to document this success and call on Congress to take advantage of the system of discovery it has set in motion.

1. Mechanism of FSHD has been Described

On August 19, 2010, Dutch and American researchers published a paper which dramatically expanded our understanding of the mechanism of FSHD.¹ The 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

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 led by Stephen J. Tapscott, M.D., Ph.D., of the Seattle Fred Hutchinson Center's Biology Division, published a third major advance further elucidating the mechanisms that can cause the disease genes and proteins that damage FSHD muscle cells. The research also discovered that one of the genes required for FSHD, called, DUX4 regulates cancer/testis antigens.⁴ Cancer and testis antigens are abnormally expressed in various tumor types, including melanoma and carcinomas of the bladder, lung and liver. This allows for the potential of using these antigens to create cancer vaccines.

This past week has brought five publications with significant developments on FSHD. On this day, April 26, 2012, another major breakthrough was announced. Researchers who began their careers with FSH Society fellowships reported in *Cell* of an epigenetic activatory long non-

coding RNA (lncRNA) switch involved in FSHD and human genetic disease. This opens the potential to control FSHD by going after the master switch that regulates DUX4 and other genes that are necessary to cause FSHD. The master switch is a non-protein encoding lncRNA that has a normal developmental function and that can cause disease by allowing normally quiescent genes to produce too much protein at the wrong time and wrong place.⁵ This study published in *Cell* is important for several reasons. First, it further defines a mechanism of disease that could help explain the workings of diseases other than FSHD, including some forms of diabetes or cancer. Second, it clarifies the mechanism at work in FSHD and has identified specific therapeutic targets to achieve a treatment for FSHD.

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.

The renowned FSH Society Scientific Advisory Board (SAB) led and chaired by M.I.T. Professor David E. Housman, Ph.D. has made great strides in the past twenty years. FSHD had long been thought of as a Mendelian disease caused by a defect in a single gene inherited in an autosomal dominant fashion. Two decades of work by a small group of patients and scientists have shown that, FSHD, is free of damage from any protein-encoding gene on the chromosomes that define human life. FSH Society seed funding has allowed researchers to understand how FSHD works, first in the cell, then at the chromosome level, then at a specific address on the chromosome called 4q35, then by discovering that the disease is associated with a shortening or modification of repetitive sequences of DNA at 4q35 called D4Z4, then by studying the expression of genes and different types of RNA messages from within each repeat of D4Z4, and finally how D4Z4 repeat sequences regulate gene expression and that mutations and changes of such elements can influence the progression of a human genetic disease.

Even with these breakthroughs, much work remains to be done. Given the recent developments in our definition of FSHD, the current potential is even greater for intervention strategies, therapeutics, and the planning and conducting of trials. We need to be prepared for this new era in the science of FSHD by accelerating efforts in the following four areas:⁶

1. Genetics / epigenetics

It is now broadly accepted that the dysregulation of the expression of D4Z4/DUX4 plays a major role in FSHD1 (FSHD1A) and FSHD2 (FSHD1B). Additional FSHD (modifier) loci are likely to exist.

FSHD molecular networks. The relaxation of the chromatin structure on permissive chromosome 4 haplotypes leads to activation of downstream molecular networks. Importantly, the upstream processes – triggering of activation – are equally important. Detailed studies on these processes are crucial for insight into the molecular mechanisms of FSHD pathogenesis and may contribute to explaining the large intra- and interfamily clinical variability. Importantly such work will lead to intervention (possibly also prevention) targets.

Additional FSHD genes. FSHD2 is characterized by hypomethylation of D4Z4 on chromosome 4 as well as chromosome 10. This also leads to bursts of DUX4 expression. Identification of the responsible factor (gene) and molecular mechanisms is of utmost importance.

2. Clinical trial readiness

It is now broadly accepted that dysregulation of the expression of D4Z4/DUX4 is at the heart of FSHD1 and FSHD2. This finding opens perspectives for intervention along different avenues.

Clinical Trial Readiness. Intervention trials are envisaged within the next several years. The FSHD field needs to be prepared for this crucial step. To design and coordinate this important translational process, it was envisaged to install an international task force Clinical Trial Readiness (FSHD-CTR), with a proven FSHD-clinician as leader.

Biomarkers. Sensitive biomarkers are needed to monitor intervention: they may also improve diagnosis.

3. Model systems

There are a plethora of cellular and animal models, based on different pathogenic (candidate gene) hypotheses. Moreover, the phenotypes are very diverse and often difficult to compare with the human FSHD phenotype.

FSHD Model Data Base. The importance of a systematic database was recognized. This data base should contain detailed information on the molecular characteristics of the model (design and phenotype).

Human pathology and bio-banking. Importantly, this data base should also contain well-documented muscle pathology data of patients – astonishingly difficult to find in the literature. Human cellular resources continuously deserve attention.

4. Sharing

Timely sharing of information and resources significantly contributes to the progress in the field. There are several initiatives that create large repositories of data and resources. Their websites should be used for sharing of information (e.g. protocols, guide to FSHD muscle pathology (images), model systems, contact information, reagents, and resources).

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 multiple human diseases.

2. Surveillance Systems have Improved Understanding of Prevalence

The consortium, Orphanet, has issued new prevalence data for hundreds of orphan diseases in Europe. That report ranks FSHD as the most prevalent form of muscular dystrophy.⁷

Likewise, the U.S. Centers for Disease Control and Prevention (CDC) has presented new data on the prevalence of muscular dystrophies which shows FSHD with the second highest prevalence rate 4.4/100,000 (the first was myotonic muscular dystrophy.)^{8,9} This enhanced understanding is due to Congress' foresight in charging CDC to enhance its surveillance of muscular dystrophy. We cannot say whether FSHD is becoming more prevalent, if the prevalence of other dystrophies such as Duchenne's 2.1/100,000 is declining or if older information was just inaccurate.⁹ But we can say that Congressional action is producing better information enabling all of us to make decisions.

3. Funding Picture has Improved but More is Needed

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 low.

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

Source: National Institutes of Health (NIH) FSHD Funding & Appropriations
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

We request for FY2013, a doubling of the facioscapulohumeral muscular dystrophy (FSHD) or facioscapulohumeral disease research budget at the NIH to \$12 million dollars. This will allow an expansion of the DHHS NIH Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers, an increase in much needed research awards, expansion of post-doctoral and clinical training fellowships, and a dedicated center to design and conduct clinical trials on animal models of FSHD. We need to translate discoveries and treatments for FSHD that, according to Dr. Collins “if we were thinking of a collection of the genome’s greatest hits, this would go on the list,”² can be rapidly realized if FSHD is one of the diseases that the NIH National Center for Advancing Translational Sciences (NCATS), chooses to work on.

Mr. Chairman, the patients and researchers of the FSH Society are grateful for the support from Congress and the tremendous efforts of many people at the NIH Office of the Director, the National Institute of Arthritis and Musculoskeletal and Skin Disease, the National Institute on Neurological Disorders and Stroke and the National Institute for Child Health and Human Development. 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.

As president of a patient organization which raises about one million dollars a year for research, I can tell you that the private sector cannot touch the level of funding NIH provides. And we fully appreciate your support.

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., Philippova, 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. Cabianca et al., A Long ncRNA Links Copy Number Variation to a Polycomb/Trithorax Epigenetic Switch in FSHD Muscular Dystrophy, *Cell* (2012), doi:10.1016/j.cell.2012.03.035
6. 2011 FSH Society FSHD International Research Consortium, held November 7-8, 2011 at 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/assets/pdf/IRCWorkshop2011WorkingConsensusOfPrioritiesGalley.pdf>
7. Prevalence of rare diseases: Bibliographic data, Orphanet Report Series, Rare Diseases collection, November 2011, Number 1 : Listed in alphabetical order of diseases, http://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf
8. Centers for Disease Control and Prevention. November 7-8, 2011, CDC meeting “Defining a public health approach for muscular dystrophy: A model for conditions with high impact/low prevalence”
9. Centers for Disease Control and Prevention. Prevalence of Duchenne/Becker muscular dystrophy among males aged 5-24 years - four states, 2007. *MMWR Morb Mortal Wkly Rep.* 2009 Oct 16; 58(40): 1119-22