



Muscular Dystrophy Coordinating Committee
Natcher Conference Center Room D
Bethesda, Maryland
March 17, 2015

Daniel Paul Perez
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Comments on the Draft Action Plan

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A Brief Overview of FSH Society

- FSH Society formed in 1991 by two patients
- Daniel Paul Perez, President & CEO, co-founder
- Invested nearly \$5.5 million FSHD research fellowships and grants
- Majority of our grants are fellowships and startup funds
- First MD organization with single disease focus
- First to initiate and seed fund many investigators and projects; ante up
- 90% of our Board affected or has a family members who is affected
- 2014, RFA genomic engineering CRISPR/Cas9, TALEN, AAV
- Society involved with drafting the first Action Plan
- First MD-patient advocate to open dialogue with NIH and Institutes
- First on the Hill
- Introduced first MD CARE Act bill ideas with PPMD and MDA



Thoughts, comments and endorsement of 2015 NIH Action Plan

CON / DISLIKE

- Dense impenetrable document (mea culpa, helped write first version in 2005). Will it inspire anyone?
- Reads like abstracts of the last 200 proposals
- Does not bring in other fields – genome engineer, germline bio, RNA transcription, epigenetic, etc.
- Document meant to help researchers identify grant opportunity. How do you communicate with them?
- Need to set clear and measurable goals for NIH
- **How do we address emerging priorities and redress funding disparities for each muscular dystrophy:**
 - infrastructure to support basic research through clinical trials;
 - training and support of new investigators;
 - access to research data, specimens, mentors, etc.
- **Needs to address getting the maximum efficiency out of a non-growing NIH and federal research budget**



Thoughts, comments and endorsement of 2015 NIH Action Plan

PRO / LIKE

- NIH working groups comprised of best, brightest and most talented experts
- Comprehensive and thorough plan
- More coverage for multiple dystrophies by individual areas
- Emphasizes relevant and key scientific areas for FSHD
- **FSH Society fully supports and endorses plan**
- Brings in other key federal agencies who can be of enormous help
- NIH leadership and program staff have done an outstanding job with the plan



FSHD Grants at NIH 1990-2015

NIH Research Portfolio Online Reporting Tools (RePORT) <http://report.nih.gov>
Projects as of January 1, 1990 – March 7, 2015

In last 25 years, 76 grants:

F32, K08, K23 -- three training grants

18 R21 – less than one R21 per year

25 R01 – one R01 per year

No grants ever on FSHD from key institutes studying heart, lung, blood, hearing, and vision



FSHD Grants at NIH

Source: NIH Research Portfolio Online Reporting Tools (RePORT) <http://report.nih.gov>

Projects as of January 1, 1990 – March 7, 2015

Institute		Number	Type
NIH National Institute on Aging (NIA)	AG	n=1	R21
NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)	AR	n=30	F32 K23 N01 R01=12 R13 R21=7 R55 RC2 U01=2 U54
NIH National Institute of Environmental Health Sciences (NIEHS)	ES	n=1	R01
NIH National Institute of General Medical Sciences (NIGMS)	GM	n=4	R01=4
NIH EKS National Institute of Child Health and Human Development (NICHD)	HD	n=3	R03=2 U54
NIH National Heart, Lung and Blood Institute (NHLBI)	HL	n=0	
NIH National Library of Medicine (NLM)	LM	n=1	R01
NIH National Institute of Nursing Research (NINR)	NR	n=1	RC2
NIH National Institute of Neurological Disorders and Stroke (NINDS)	NS	n=21	K08 P01=2 R01=6 R13 R21=10 U54
NIH National Human Genome Research Institute (NHGRI)	HG	n=1	R01
National Center for Research Resources (NCRR) (dissolved 12/2011)	RR	n=13	M01=13
		n=76	
3 Training grants F32, K08, K23			
18 R21			
25 R01			

Active FSHD Grants at NIH as of March 2015

NIH Research Portfolio Online Reporting Tools (RePORT) <http://report.nih.gov>
Active Projects as of March 12, 2015

In August 2010, 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 [FSHD genetic mechanism] would go on the list.”**

More NIH funding for FSHD needed! **\$7 million FSHD** / \$79 million MD

Within 26 Active Projects:

F32 -- **one training grant**

6 R21, 12 R01, 1 P01, 2 U01, 2 U54

NHGRI = 1 R01

NHLBI = 0

NICHD = no R21, no R01



FSHD Grants at NIH

Source: NIH Research Portfolio Online Reporting Tools (RePORT) <http://report.nih.gov>
Active Projects as of March 12, 2015

Institute		Number	Type
NIH National Institute on Aging (NIA)	AG	n=1	R21
NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)	AR	n=11	F32 R01=6 R21=1 U01=2 U54
NIH National Institute of Environmental Health Sciences (NIEHS)	ES	n=0	
NIH National Institute of General Medical Sciences (NIGMS)	GM	n=3	R01=3
NIH EKS National Institute of Child Health and Human Development (NICHD)	HD	n=2	R03=1 U54
NIH National Human Genome Research Institute (NHGRI)	HG	n=1	R01
NIH National Heart, Lung and Blood Institute (NHLBI)	HL	n=0	
NIH National Library of Medicine (NLM)	LM	n=1	R01
NIH National Institute of Nursing Research (NINR)	NR	n=0	
NIH National Institute of Neurological Disorders and Stroke (NINDS)	NS	n=7	P01=1 R01=1 R21=4 U54
		n=26	
1 F32			
1 R03			
6 R21			
12 R01			
1 P01			
2 U01			
3 U54			

FSHD Breakthroughs 2010-Present

On August 19, 2010, American and Dutch researchers published a paper which dramatically expanded our understanding of the mechanism of FSHD. 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.”** Deletion chromosome 4 and 4qA161

Lemmers, RJ, et al, A Unifying Genetic Model for Facioscapulohumeral Muscular Dystrophy *Science* 24 September 2010: Vol. 329 no. 5999 pp. 1650-1653

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>

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. Deletion 4 and 4qA161 yields DUX4

Facioscapulohumeral dystrophy: incomplete suppression of a retrotransposed gene.

Snider L, Geng LN, Lemmers RJ, Kyba M, Ware CB, Nelson AM, Tawil R, Filippova GN, van der Maarel SM, Tapscott SJ, Miller DG.

PLoS Genet. 2010 Oct 28;6(10):e1001181. doi: 10.1371/journal.pgen.1001181.

PMID: 21060811



On January 17, 2012, an international team of researchers based out of Seattle discovered a **stabilized** form of a **normally suppressed gene called DUX4** required to develop chromosome 4 linked FSHD. Deletion 4, 4qA161, PAS = DUX4lf

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

Six months later, another high profile paper produced by a **Senator Wellstone Cooperative Research Center** of the NIH, 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**. This work was also supported by a NIH U54 center grant mandated by MD CARE Act. Deletion 4, 4qA161, PAS = DUX4lf but not always FSHD

Facioscapulohumeral muscular dystrophy family studies of DUX4 expression: evidence for disease modifiers and a quantitative model of pathogenesis.

Jones TI, Chen JC, Rahimov F, Homma S, Arashiro P, Beermann ML, King OD, Miller JB, Kunkel LM, Emerson CP Jr, Wagner KR, Jones PL.

Hum Mol Genet. 2012 Oct 15;21(20):4419-30. Epub 2012 Jul 13.

PMID: 22798623



On July 13, 2012, a team of researchers from the, United States, Netherlands and France identified **mutations in a gene on chromosome 18 called SMCHD1** causing 80% of **another form of FSHD** called **FSHD2**. This paper furthers our understanding of the molecular pathophysiology of FSHD. Another locus controlling DUX4, gene maintains D4Z4 DUX4 region on chromosome 4

Digenic inheritance of an SMCHD1 mutation and an FSHD-permissive D4Z4 allele causes facioscapulohumeral dystrophy type 2.

Lemmers RJ, Tawil R, Petek LM, Balog J, Block GJ, Santen GW, Amell AM, van der Vliet PJ, Almomani R, Straasheijm KR, Krom YD, Klooster R, Sun Y, den Dunnen JT, Helmer Q, Donlin-Smith CM, Padberg GW, van Engelen BG, de Greef JC, Aartsma-Rus AM, Frants RR, de Visser M, Desnuelle C, Sacconi S, Filippova GN, Bakker B, Bamshad MJ, Tapscott SJ, Miller DG, van der Maarel SM.

Nat Genet. 2012 Dec;44(12):1370-4. doi: 10.1038/ng.2454. Epub 2012 Nov 11.

On September 25, 2014, researchers identify an epigenetic basis for wide variability in onset and disease progression seen in FSHD individuals.

Researchers begin to think of **FSHD1 manifesting, FSHD1 non-manifesting and FSHD2 SMCHD1 mutation plus D4Z4 repeat array. SMCHD1 (FSHD2) as a modifier of FSHD1**. Deletion 4 and 4qA161 and PAS and now methylation

Inter-individual differences in CpG methylation at D4Z4 correlate with clinical variability in FSHD1 and FSHD2.

Lemmers RJ, Goeman JJ, van der Vliet PJ, van Nieuwenhuizen MP, Balog J, Vos-Versteeg M, Camano P, Ramos Arroyo MA, Jerico I, Rogers MT, Miller DG, Upadhyaya M, Verschuuren JJ, Lopez de Munain Arregui A, van Engelen BG, Padberg GW, Sacconi S, Tawil R, Tapscott SJ, Bakker B, van der Maarel SM.

Hum Mol Genet. 2015 Feb 1;24(3):659-69. doi: 10.1093/hmg/ddu486. Epub 2014 Sep 25. PMID: 25256356



On October 28, 2014, researchers publish the foundation for developing the **next generation of FSHD genetic testing and diagnosis**. **The basis for FSHD will be found in epigenetic regulation. FSHD is a model disease.**

Facioscapulohumeral Muscular Dystrophy As a Model for Epigenetic Regulation and Disease.
Himeda CL, Jones TI, Jones PL. Antioxid Redox Signal. 2014 Oct 22.

Identifying diagnostic DNA methylation profiles for facioscapulohumeral muscular dystrophy in blood and saliva using bisulfite sequencing.
Jones TI, Yan C, Sapp PC, McKenna-Yasek D, Kang PB, Quinn C, Salameh JS, King OD, Jones PL.
Clin Epigenetics. 2014 Oct 29;6(1):23. doi: 10.1186/1868-7083-6-23. eCollection 2014. PMID: 25400706

On March 15, 2015, researchers detail **sorting out** of an artifact that prevented from testing the **antisense oligonucleotides against DUX4**. Multiple efforts underway using AAV, morpholino, preliminary unpublished data with antisense compounds active in reducing DUX4 and in knocking out DUX4.

Aberrant Splicing in Transgenes Containing Introns, Exons, and V5 Epitopes: Lessons from Developing an FSHD Mouse Model Expressing a D4Z4 Repeat with Flanking Genomic Sequences.
Anseau E, Domire JS, Wallace LM, Eidahl JO, Guckes SM, Giesige CR, Pyne NK, Belayew A, Harper SQ.
PLoS One. 2015 Mar 5;10(3):e0118813. doi: 10.1371/journal.pone.0118813. eCollection 2015.
PMID: 25742305

Epigenetic status of the D4Z4 region determines disease in FSHD. We may see as high as 20-30% non-manifesting FSHD1 carriers.



FSHD is linked to the 4qA subtelomere and the epigenetic status of the 4q35 D4Z4 array

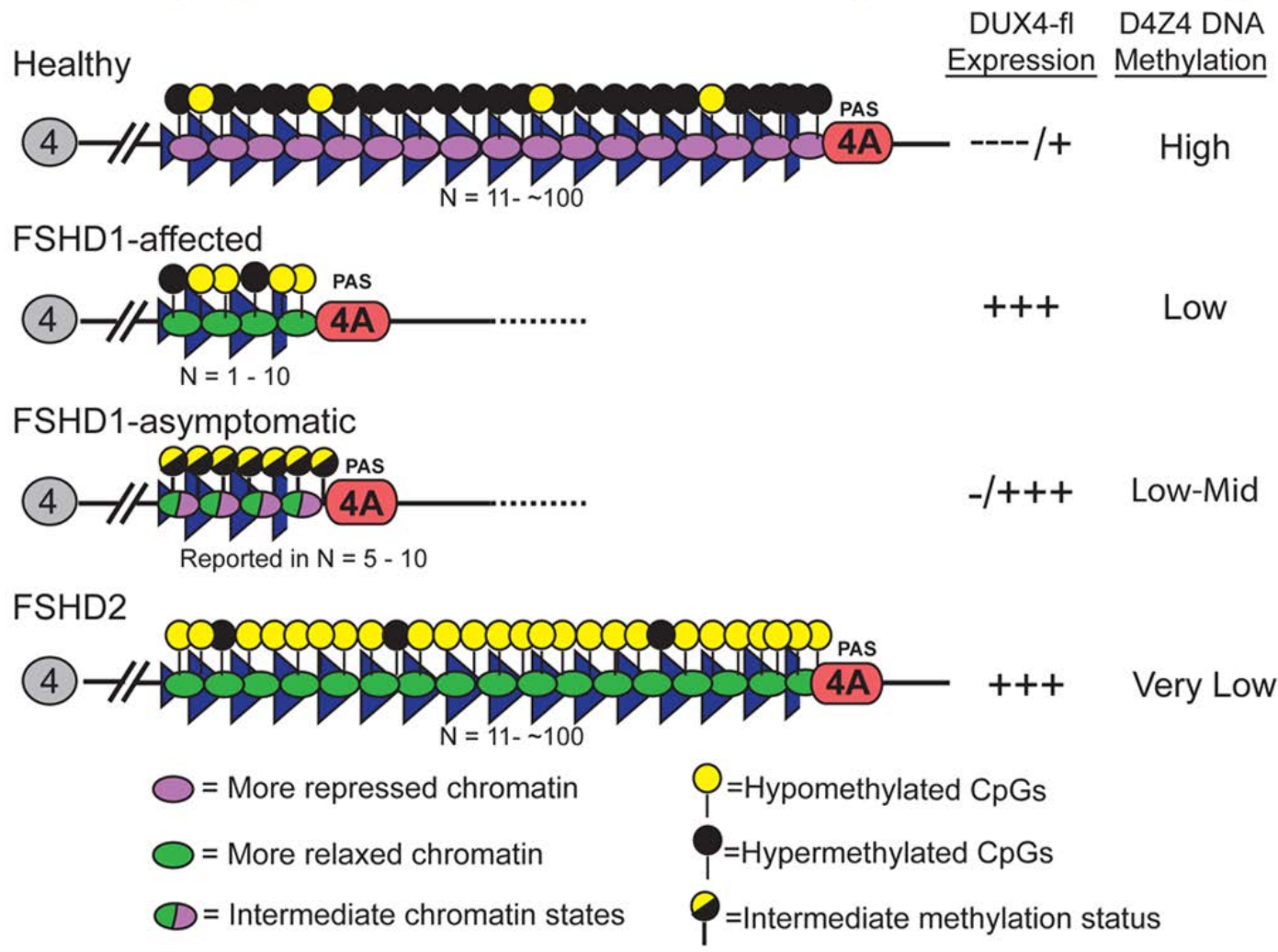


FIGURE. The D4Z4 repeat region at location 4q35 on chromosome 4 differs markedly among healthy, FSHD1, and FSHD2 individuals. Healthy individuals have numerous D4Z4 repeats which are highly methylated (black dots). FSHD1-affected individuals have few repeats, and these are hypomethylated (light dots). FSHD1 non-manifesting, or unaffected, individuals, also have few repeats, but these have higher methylation (half-filled dots). FSHD2 individuals have many D4Z4 repeats, like healthy individuals, but they are severely hypomethylated. Figure courtesy of Peter L. Jones, Ph.D.

In The Last Year Clinically

- A prevalence of 1/8,333, suggests that FSHD may be one of the most prevalent neuromuscular disorders.
- Significant association between the presence of hearing loss and FSHD deletion size. **Clues within non-muscular manifestation?** NHLBI.
- Cardiac ECG demonstrated incomplete right bundle branch block (RBBB) in 33%, complete RBBB in 4%, and other minor abnormalities in 16% without cardiac symptoms. Echocardiography normal. No significant changes eight years of follow-up. Prevalence of incomplete RBBB in the absence of cardiomyopathy suggests a selective involvement of the His-Purkinje system in FSHD. **Clues within non-muscular manifestation?** NHLBI.
- Restrictive respiratory involvement in 10% FSHD1 and 25% FSHD2. 50% Sleep disordered breathing. Opportunities for NHLBI.



Population-based incidence and prevalence of facioscapulohumeral dystrophy.

Deenen JC, Arnts H, van der Maarel SM, Padberg GW, Verschuuren JJ, Bakker E, Weinreich SS, Verbeek AL, van Engelen BG.

Neurology. 2014 Sep 16;83(12):1056-9. doi: 10.1212/WNL.0000000000000797. Epub 2014 Aug 13.

PMID: 25122204

Clinical and genetic features of hearing loss in facioscapulohumeral muscular dystrophy.

Lutz KL, Holte L, Kliethermes SA, Stephan C, Mathews KD.

Neurology. 2013 Oct 15;81(16):1374-7. doi: 10.1212/WNL.0b013e3182a84140. Epub 2013 Sep 16.

PMID: 24042093

High prevalence of incomplete right bundle branch block in facioscapulohumeral muscular dystrophy without cardiac symptoms.

van Dijk GP, van der Kooi E, Behin A, Smeets J, Timmermans J, van der Maarel S, Padberg G, Voermans N, van Engelen B.

Funct Neurol. 2014 Jul-Sep;29(3):159-65.

PMID: 25473735

Restrictive lung involvement in facioscapulohumeral muscular dystrophy.

Scully MA, Eichinger KJ, Donlin-Smith CM, Tawil R, Statland JM.

Muscle Nerve. 2014 Nov;50(5):739-43. doi: 10.1002/mus.24218. Epub 2014 Sep 29.

PMID: 24639337



Newly redesigned website www.fshsociety.org features four areas of research priorities as outlined by the entire FSHD research community at our latest annual FSHD research workshop (**Genetics, Mechanisms and targets, Models, Patients - trial preparedness**)

In addition, we need to **work towards accelerating efforts** in the following areas:

- Mechanisms of DUX4 toxicity.
- Need more molecular, imaging, and functional markers of FSHD and disease progression.
- Study modifiers of FSHD: genetic, chemical, and lifestyle.
- Develop and deploy preclinical models validated to represent specific aspects of FSHD patho-physiology.
- Attain pharmacological inhibition of DUX4 protein activity/expression.
- Create better animal models for FSHD based on patient-like, i.e. low level, expression of DUX4.
- Study the mechanism of pathology in patient muscle - is the disease caused by loss of progenitor cells? loss



of muscle fibers? infiltration of immune cells? an immune reaction against testis-antigens?

- DUX4 normal functions in tissues other than muscle: if we inhibit DUX4 in FSHD muscles, we need to make sure this inhibition doesn't cause problems in other tissues!
- Develop administration methods (muscle targeting) for antiDUX4 agent.
- Need to understand muscle regeneration capacity after DUX4 inhibited in patients: fibrosis, satellite cell niche, satellite cell proliferation / differentiation capacity.
- Large animal model: monkey, marmoset?
- Develop FSHD biomarkers and altered signaling pathways for easy follow up of an impact of therapeutic agents.

