

Progress in FSHD Research

**Presentation to the
Muscular Dystrophy
Coordinating Committee**

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Facts and Figures

- Facioscapulohumeral Muscular Dystrophy (FSHD) is caused by a genetic defect. It is transmitted in an autosomal dominant fashion. 30% of cases arise spontaneously.
- An estimated 500,000 people worldwide have FSHD, and 1-2% of the population carries the genetic risk.
- A progressive, lifelong disease, it affects all skeletal muscles – typically the face, shoulders, arms, back and legs.
- Symptoms may be evident at birth or during childhood, but more often appear during teenage and adult years.
- FSHD can be profoundly disabling, causing a loss of facial expression, difficulties with speech and hearing, and an inability to lift objects or walk.



Facts and Figures

- One of the most common muscular dystrophies
- Prevalence estimated at 1:15,000 to 1:20,000
- Significantly underdiagnosed
- ~24% of patients will require a wheelchair
- Respiratory involvement ~10% of moderately affected adults
- Can be severely disabling and life-shortening
- Can also affect infants and young children



Disease-Specific Pathogenic Mechanisms



Define the molecular pathogenetic mechanisms that lead to facioscapulohumeral muscular dystrophy (Long Term; High Risk).

- FSHD Type 1 (95% of FSHD) linked to contraction of D4Z4 microsatellite repeats on chromosome 4
- About half of FSHD Type 2 linked to mutations in SMCHD1 (Structural Maintenance of Chromosomes flexible Hinge Domain containing 1)
- Disease-modifying gene for FSHD1 identified: it's SMCHD1
- Consensus that DUX4 is a key player. Necessary but not sufficient.
- Transcriptional regulators of DUX4 (PARP1, Bromodomain and extra terminal proteins, DME1, DME2)
- Downstream targets (apoptosis, autophagy, oxidative stress)

Disease-Specific Pathogenic Mechanisms

Establish mouse (and cellular) models for FSHD specific to emerging candidate genes and/or disease genomics, to understand the epigenetic mechanisms and for the development of novel intervention strategies (Long Term; Intermediate Risk).

- D4Z4 transgenic mice recapitulate key molecular features, but phenotype lacks muscle pathology
- DUX4 Zebrafish exhibit muscle pathology
- Mouse xenograft with human muscle
- Induced pluripotent stem cell lines
- SMCHD1 epigenetic modifications to D4Z4 region
- Antisense, TALENS, CRISPR technologies for DUX4 silencing

Technology for Diagnostic Testing

Develop minimally invasive diagnostic techniques for muscular dystrophies where appropriate.

- Potential blood biomarkers
- Gene expression profiling
- Magnetic resonance imaging

Develop definitive gene tests for muscular dystrophies for which genetic testing is not yet available.

- Commercial genetic test for FSHD1 now exists
- Genetic test for FSHD2 is available through research labs

Establish mechanisms for muscular dystrophy patients to obtain accurate genetic counseling.

- Genetic counseling available through test labs.

Resources for the Research Community Related to Diagnosis

Support disease-specific registries with detailed genetic, structural and functional information regarding phenotypic effects in other organ systems, as well as structural and functional information regarding phenotypic effects in other organ systems, as well as pathological and clinical information. Foster cooperation between registries, neuromuscular research centers, and academic diagnostic centers.

- National registry at the University of Rochester
- TREAT-NMD & Muscular Dystrophy Campaign UK registries
- Wellstone Centers registry and biospecimen repository.
- The FSH Society organizes an annual meeting to foster information exchange and cooperation among research and clinical centers.
- FSHD Champions group of international funders on coordination of registries.

Resources for the Research Community Related to Diagnosis



Optimize utilization of muscle biopsy materials for research by:

1) Developing IRB language to assist investigators with use of archived or prospectively collected diagnostic muscle biopsies.

- Fields and Wellstone centers have IRB-approved protocols on muscle biopsies.

2) Fostering shared use of stored and prospectively collected diagnostic muscle biopsies by the research community.

- Wellstone Center cell lines from FSHD muscle biopsies are being distributed.

Epidemiology Studies Neonatal Testing



Establish current and accurate incidence and prevalence data for genetically confirmed forms of muscular dystrophy.

- The FSH Society has worked with the Centers for Disease Control to support initiatives in this area. **More work needed on FSHD.**

Develop methods for newborn screening of the muscular dystrophies. Explore the social and ethical issues involved in offering neonatal screening for muscular dystrophy and develop techniques that would make screening practical.

- Newborn Screening workshop held. Complicated for FSHD.

Therapy for Muscular Dystrophy



Examine the efficacy of existing anti-inflammatory drugs for treatment of muscular dystrophy.

- Sacconi study examined outcomes in FSHD patients who had been misdiagnosed with polymyocytis and treated with prednisone.

Identify alternative mechanisms of myostatin inhibition and establish their potential as therapeutics through preclinical testing in animal models of various types of muscular dystrophy.

- Acceleron's myostatin inhibitor trial.

Define, through basic and preclinical translational studies, the therapeutic potential of alternative muscle progenitor cells.

- Induced pluripotent stem cells lines have been established. Genomic engineering methods to correct genetic defect in cells are in development.

Therapy for Muscular Dystrophy

Define, through basic and preclinical translational studies, the therapeutic potential of embryonic stem cells.

- Work on ESC's has been conducted.

Improve the efficiency of gene therapy delivery in the muscular dystrophies, while minimizing the immune response to both gene product and delivery vehicle.

- Work in AAV in various mouse models.

Expand high-throughput, small molecule screening efforts for promising therapeutic targets and identify novel targets for drug development.

- First high-throughput small molecule screening study was published this year (Kyba et al.)

Quality of Life Measures

Identify and evaluate the quality of life and burden of disease measurement tools that are currently available.

- Meetings held on this issue at NIH and CDC.

Develop disease-specific quality of life and burden of disease measures where gaps in existing measures are found.

- QOL and disease burden assessment tools are making progress.

Clinical Endpoints

Determine the sensitivity of clinical endpoints to changes in disease severity.

Determine the magnitude of changes in endpoints which are clinically meaningful to patients and family members.

Study the interrelationship of clinical endpoints for specific muscular dystrophies.

- Clinical endpoints research is ongoing, and involves several muscular dystrophies.

Develop standardized data collection approaches nationally using clinically meaningful, readily obtainable parameters; develop a minimum data set for national data gathering efforts.

- FSHD Clinical Trial Network is pursuing these objectives.

Consensus Guidelines for Clinical Management



Develop consensus guidelines for the clinical management of other muscular dystrophies.

- A consensus guideline for FSHD has been written; awaiting publication by AAN. Members of the FSHD Champions provided feedback and plan to help disseminate the new guidelines when they are published.

Benefits and Risks of Exercise and Physical Activity



Determine the benefits and risks of varied exercise approaches in muscular dystrophies and develop scientifically based recommendations concerning optimal exercise, physical activity, and recreation.

- Randomized, controlled clinical trial has demonstrated significant benefit of aerobic exercise combined with cognitive behavioral therapy in reducing chronic fatigue in FSHD.

Understanding and Managing the Secondary Consequences

Assess the prevalence of secondary conditions in muscular dystrophy using existing longitudinal data collection efforts.

- Respiratory involvement, hearing loss & impaired speech.

Assess the natural history of secondary conditions in muscular dystrophy using existing longitudinal data collection efforts.

- Ongoing.

Assess the effectiveness of clinical management approaches to prevent and treat secondary conditions using existing multi-center collaborative networks and clinically meaningful outcomes.

- Only informally; an area that needs to be addressed.

Define the neuropsychological and neurobehavioral profiles that impact on quality of life and caregiver burden and identify useful interventions.

- An area that needs to be addressed for FSHD.

Patient & Family Education, Social Participation, Physician Training



Establish annual educational conferences for patients and families focused on specific muscular dystrophies.

- FSH Society, FSHD Global, UK group. FSH Society live streams.

Identify strategies to improve patient integration into educational systems.

- FSH Society brochure for schools; live streamed a patient meeting in Baltimore on patient integration into colleges.

Identify strategies to improve vocational outcomes and reduce social isolation.

- Peer support network; Facebook, Yahoo and Twitter online communities are very active, serving about 3,000 patients. More work needed re: vocational outcomes.

Develop strategies to improve physician effectiveness in communicating with and managing the care of patients with muscular dystrophy.

- Biennial meeting is open to clinicians; we provide educational material to physicians; we live-stream lectures with experienced clinicians and respond to phone and email inquiries from physicians.

Preclinical Research Infrastructure

Facilitate research (discovery, validation, and dissemination) of the biochemical pathways involved in muscular dystrophy.

- Major focus of all of the FSHD funding organizations.

Establish standardized endpoints for preclinical trials in both mouse models, and the dog model, and ensure that facilities are available that enable testing of drugs and other therapeutic approaches.

- The FSHD field has not yet produced a mouse model based on the genetic mechanism that recapitulates the phenotype. Significant work is still needed.

Create a mechanism to maintain mouse models of muscular dystrophy at approved vendors in a live state, available for easy and rapid importation into academic colonies.

- This is a requirement for FSH Society grants.

Preclinical Research Infrastructure



Develop optimized models for mechanistic studies of specific muscular dystrophies, including models appropriate for therapeutic development screens.

- Mixed success with DUX4 mouse model. Zebrafish is another interesting potential assay.

Encourage the development of cell-based assays that target aspects of pathogenesis and pathophysiology in the muscular dystrophies, to enable high throughput drug screening.

- This is a major focus of grant funding. Some interesting assays are already in use for high-throughput drug screening. Focus to date is on DUX4 toxicity; more diverse assays would be ideal.

Clinical Research Infrastructure



Establish a focus panel for molecular diagnostics of the muscular dystrophies, with the charge of developing consensus standards and approaches for molecular testing, screening, interpretation of results, and genetic counseling.

Identify, develop, and encourage the use of standardized instruments to measure quality of life, cognitive, and central nervous system function using existing databases and potentially develop new common element databases to extend research capabilities.

- Good progress on both of these objectives. Work under way to develop consensus; additional validation research still needed. Coordinated by FSHD Clinical Trials Network.

Communication & Education



Design and implement a web site that provides information and links to all existing resources in both the USA and internationally.

- 14 websites that provide patient education, and an umbrella site for the FSHD Champions is in development, which will link to all of the organizations' sites.

Establish a USA equivalent of the European Neuromuscular Centre's disease focus meetings to link to and communicate with European and other international networks or groups.

- FSH Society's annual International Research Consortium and the FSHD Champions meetings perform some of these functions; an International FSHD Clinical Trials Network is under way.

Communication & Education



Increase the number and scientific breadth of basic scientists and clinicians involved in translational research in the muscular dystrophies.

- Good progress. FSH Society fellowships and RFAs encourage scientists and clinicians to enter the field and get involved in translational research. Scientific advisory board reaches out to scientists outside of FSHD field. Society advocates for inclusion of FSHD sessions at major conferences. Annual International Research Consortium provides opportunities to introduce scientists in industry and basic research to FSHD research.

Provide a publicly accessible listing of available training grants and resources so that opportunities for physicians and scientists are transparent.

- Website lists grant opportunities worldwide.

Stimulate international collaborations and infrastructure sharing to ensure that opportunities are exploited and resources are used to maximum advantage, particularly in cases of novel opportunity or for the rare and/or understudied muscular dystrophies.

- International Research Consortium and Champions organization were established to achieve this aim..



FSHD Champions

Informal alliance of FSHD advocacy and funding organizations from around the world. Mission is to promote transparency and coordination to optimize use of funding, share best practices and leverage resources. Founded in 2012, working group meets monthly. Members meet annually.



FSHD Research Priorities

DUX4

DUX 4 expression is necessary but not always sufficient to cause FSHD. Research should focus on upstream and downstream molecular pathways and mechanisms as they form the most plausible intervention targets.

- The DUX4 interactome
- Understanding DUX4 manifestation and variation
- Additional genetic heterogeneity; non-FSHD1 and FSHD2
- Understanding pathophysiology of FSHD: connection to DUX4, heterogeneity, asymmetry, role of inflammation; infiltrates and etiology

FSHD Research Priorities

Disease models

The field needs improved and specific in vivo (animal) models for mechanistic and intervention studies. At this stage it is not sensible to give strict recommendations.

- Inducible (conditional) models seem necessary to dissect spatial and temporal effects of the DUX4 pathway.
- For specific questions, simpler models, like zebra fish may have unique potential.
- Availability of higher vertebrate models (e.g. dog, primates, etc.) may be helpful to study intervention effects prior to human trials.

FSHD Research Priorities

Intervention

Although DUX4 over-expression is crucial, various biological and chemical (pharma) strategies can be envisaged to intervene with the overall expression mechanism. Strategies include:

- DUX4 silencing by directly by targeting the mRNA or the protein, or indirectly by modulating the transcription machinery, including the chromatin structure.
- Intervening in specific molecular subpathways (upstream and downstream) of the DUX4 cascade.

FSHD Research Priorities

Clinical studies and trial readiness

- Well documented natural history with reliable endpoints; modulating mechanisms/genes
- Increasing data depth of patient databases with extensive (follow-up) clinical data
- Prepare for clinical trials: reliable and meaningful outcome measures; with access to discreet patient populations and disease mechanism of action classes.
- Better data on prevalence
- Improve rates of diagnosis
- Broadly disseminate new standard of care guidelines
- Therapy; proof-of-principle experiments
- Focus on translational research; from clinic to bench and back

FSHD Research Dollars



| Fiscal Year | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014e | 2015e |
|----------------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|--------------|--------------|
| All MD (\$ millions) | \$39.1 | \$38.7 | \$39.5 | \$39.9 | \$47.2 | \$56 | \$83 | \$86 | \$75 | \$75 | \$76 | \$78 | \$78 |
| FSHD (\$ millions) | \$1.5 | \$2.2 | \$2.0 | \$1.7 | \$3 | \$3 | \$5 | \$6 | \$6 | \$5 | \$5 | \$6 | \$6 |
| FSHD (% total MD) | 4% | 6% | 5% | 4% | 5% | 5% | 6% | 7% | 8% | 7% | 7% | 8% | 8% |

Sources: NIH/OD Budget Office & NIH OCPL & NIH RCDC Report
(e = estimate)

Building on progress

- FSHD is still a small field. The loss of even one scientist or lab due to lack of funding is devastating.
- We cannot afford to slow down. Patients need treatments in their lifetimes.
- With enough funding, we could have the first effective FSHD treatments in the next 5-10 years.

Thank You

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