# Facioscapulohumeral Muscular Dystrophy (FSHD): Overview and Emerging Treatment Strategies

A Resource for Clinicians

## Background

- FSHD is one of the most common adult-onset muscular dystrophies and affects the muscles of the face (facio), shoulders (scapulo), and upper arms (humeral).
- Genetic testing is required to confirm FSHD diagnosis and can be challenging; a genetic counselor can facilitate the process and select sponsored programs are available.
- FSHD is optimally managed via multidisciplinary care. There are no approved therapies (as of 2023), but several interventional clinical trials are underway to evaluate potential drug candidates.
- Information in this document highlights key points from an MDA mini-webinar with a neurologist with extensive FSHD expertise. **View the companion mini-webinar here.**

## Overview

### Description

- Slow progression
- Variable symptoms
- Gradual muscle weakness that typically starts in the face, shoulders and upper arms
- Asymmetric weakness

### Epidemiology

- One of the most common adult-onset muscular dystrophies
- Prevalence: 1 in 8,000 to 1 in 20,000 people

### Onset

- Can occur anytime from infancy to middle age
- Most people begin experiencing symptoms by their 20s

### Prognosis

- People who develop symptoms at an early age often experience more severe disease, sometimes leading to wheelchair dependence
- Typically not life-threatening
- Does not significantly affect life span

Tawil R. *Handb Clin Neurol.* 2018;148:541-548. doi:10.1016/B978-0-444-64076-5.00035-1

## Etiology: The Role of DUX4[1,2]

### DUX4

- Transcription factor involved in embryonic development
- Multiple DUX4 copies contained in microsatellite (D4Z4) units on chromosome 4
- **11-150 repeats**

### Inappropriate DUX4 Expression

- Shortened D4Z4 repeats (**1-10**)
- Results in DUX4 expression
- In FSHD1, repeat size correlates with symptom severity and onset

### Downstream impact

- Inflammation
- Muscle atrophy
- Increased susceptibility to oxidative stress
- Disrupted myogenesis

1. Tawil R. Handb Clin Neurol. 2018;148:541-548. doi:10.1016/B978-0-444-64076-5.00035-1 2. Statland JM. Muscle and Nerve. 2013; 49(4):520-527. doi: 10.1002/mus.23949.

In FSHD, inappropriate expression of DUX4 in skeletal muscles activates genetic programs that lead to downstream functional consequences.

Developed with the expertise of Rabi Tawil, MD, University of Rochester Medical Center
Last Reviewed: June 2023

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## Clinical Features: A "Typical" Pattern with Wide-Ranging Variability

### Primary Abnormalities

- Distinctive pattern of weakness
- Face and shoulders typically involved early on, with a characteristic shoulder profile
- Progresses to involve muscles of the trunk and lower extremities

### Symptom Variability

- Variable progression in muscle groups in same individual
- Wide–ranging severity: Minimal symptoms to wheelchair bound (20% > age 50)
- Restrictive lung disease in ~10-20% of individuals
- Non-skeletal muscle involvement:
  - Hearing loss
  - Coats disease: retinal hemorrhage that can result in blindness
  - Cognitive impairment (mainly in childhood- onset disease)

Tawil R. *Handbook Clin Neurol.* 2018;148:541-548. doi:10.1016/B978-0-444-64076-5.00035-1 .

Genetic testing is required to confirm the diagnosis of FSHD. Sponsored testing is available for select mutations.

## Guidelines for Genetic Confirmation

**FSHD1:**

- D4Z4 repeat of 10-40 kb (equivalent to 1-10 repeats)
- A variant (permissive)

**FSHD2:**

- D4Z4 repeat of 10-60 kb (equivalent to 10-20 repeats)
- A variant (permissive)
- Hypomethylation
- Confirmed by mutation in:
  - SMCHD1 (most common; sponsored testing available), DNMT3B, LRIF1

## Management: Multidisciplinary Care and Monitoring

### Rehabilitation/Holistic Care

- Pain management
- Physical therapist to manage progressive weakness, advise on exercise programs and the use of assistive devices

### Specialist Care

- Periodic monitoring of lung function in more severely affected individuals
- Evaluation by experienced surgeon for possible scapular fixation
- Access to a genetic counselor

**Severe, early-onset FSHD may require:**

- additional therapy for muscle weakness
- additional monitoring of breathing and hearing function

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## Ongoing Studies (as of June 2023)*

### MOVE-FSHD (NCT04635891)

- Collecting motor and functional outcomes specific to FSHD over time

### FSHD Registry

- Participants enroll by downloading and completing a form
- Registered participants receive updates on enrolling trials

### Interventional Trials

- **REACH:** Losmapimod, Phase 3
- **FORTITUDE:** AOC1020, Phase 1/2
- **MANOEUVRE:** GYM329, Phase 2

*Visit clinicaltrials.gov for the most up-to-date information

1. FSHD CTRN webpage. https://www.kumc.edu/fshd-clinical-trial-research-network/about.html 2. ClinicalTrials.gov (MOVE-FSHD). https://clinicaltrials.gov/ct2/show/NCT04635891.3. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT05397470. 4. Clinicaltrials.gov (FORTITUDE). https://clinicaltrials.gov/ct2/show/NCT05747924. 5. Clinicaltrials.gov (MANOEUVRE). https://clinicaltrials.gov/ct2/show/NCT05548556 Accessed June 2023.

## Resources and Additional Reading

### Select Publications


- Tawil R. 171st ENMC international workshop: Standards of care and management of facioscapulohumeral muscular dystrophy. *Neuromuscul Disord*. 2010 Jul;20(7):471-5. doi: 10.1016/j.nmd.2010.04.007.
- Tihaya MS. FSHD muscular dystrophy: the road to targeted therapies. *Nat Rev Neurol.* 2023;19(2):91-108.


### Sponsored Genetic Testing Programs

INVITAE

**Invitae Detect Muscular Dystrophy**

- Includes testing for FSHD2 (***SMCHD1* only**)
- Does **not** include testing for FSHD1

### Clinical Trial Resources

- MOVE FSHD natural history study
- FSHD Registry
- MDA Clinical Trial Updates and Finder

1. Invitae. https://www.invitae.com/en/sponsored-testing/detect-mdys. 2. Clinical trials.gov (MOVE FSHD). https://clinicaltrials.gov/ct2/show/NCT04635891 Accessed June 2023. 3. University of Rochester webpage. FSHD Registry. https://www.urmc.rochester.edu/neurology/national-registry/join.aspx 4. MDA. Clinical Trial Finder. https://www.mda.org/research/clinical-trials

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