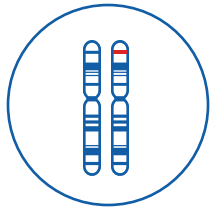
Facioscapulohumeral muscular dystrophy: disease background

Facioscapulohumeral muscular dystrophy (FSHD)

One of the most common inherited muscle disorders[1]

Prevalence of 4.7–12 per 100,000 of the population[2,3]

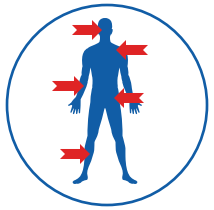


Driven by aberrant expression of the *DUX4* gene[1]

Mostly autosomal dominant inheritance (10–30% of cases are de novo)[1]

Age of onset varies from infant to late adulthood[1]

Typically manifests between ages of 15 and 30 years[1]



Characterized by a distinct, asymmetric pattern of muscle weakness[1]

Face, shoulder, upper arms, and sometimes axial and leg muscles[1]

Disease progression is non-linear and can occur throughout a patient's lifetime[1]

Muscle-by-muscle involvement with periods of stabilization and rapid decline[1]

Most patients with typical age of onset have normal lifespans[1]

Approximately 20% of patients will become wheelchair dependent[1]

Infantile FSHD (age <10 years at onset) is associated with severe symptoms[1]

- *Severe generalized muscle weakness*
- *Extramuscular features, including:*
  - *Sensorineural hearing loss*
  - *Retinal vasculopathy*
  - *Right bundle branch block (incomplete)*
  - *Restrictive lung disease*
  - *Cognitive impairment and epilepsy*

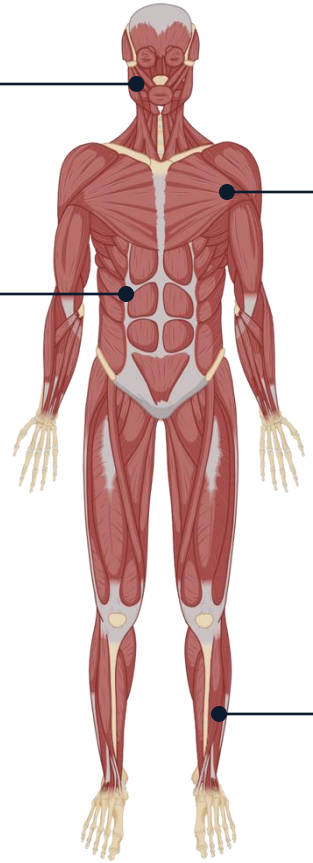
There is currently no disease-modifying therapy available for FSHD[1]

DUX4, double homeobox protein 4.

1. Tihaya MS, et al. *Nat Rev Neurol*. 2023;19:91–108; 2. Deenen JC, et al. *J Neuromuscul Dis.* 2025:22143602241313118; 3. Deenen JC, et al. *Neurology* 2014;83:1056–1059.

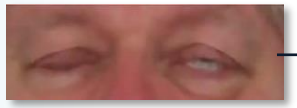
FSHD is characterized by a distinct asymmetrical pattern of muscle weakness and atrophy

Although FSHD is associated with a distinct pattern of muscle weakness, the degree of involvement is highly variable between patients and between different muscles in the same patient[1–3]*

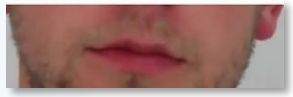


Facial muscles[1–3]

Weakness of the orbicularis oculi results in difficulty in closing both eyes[3]

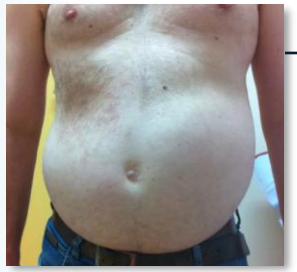


Mouth is asymmetrical in resting position[3]

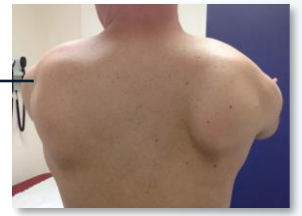


Abdominal and pelvic girdle muscles[1–3]

Horizontal anterior axillary fold visible on both sides of the trunk – abdomen protrudes asymmetrically[3]

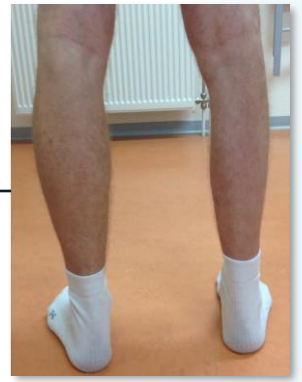


Shoulder girdle/ upper arm muscles[1–3]



Asymmetrical bilateral scapular winging[3]

Leg muscles[1–3]



Atrophy of calf muscles[3]

*Photographs shown do not represent full spectrum of clinical features.

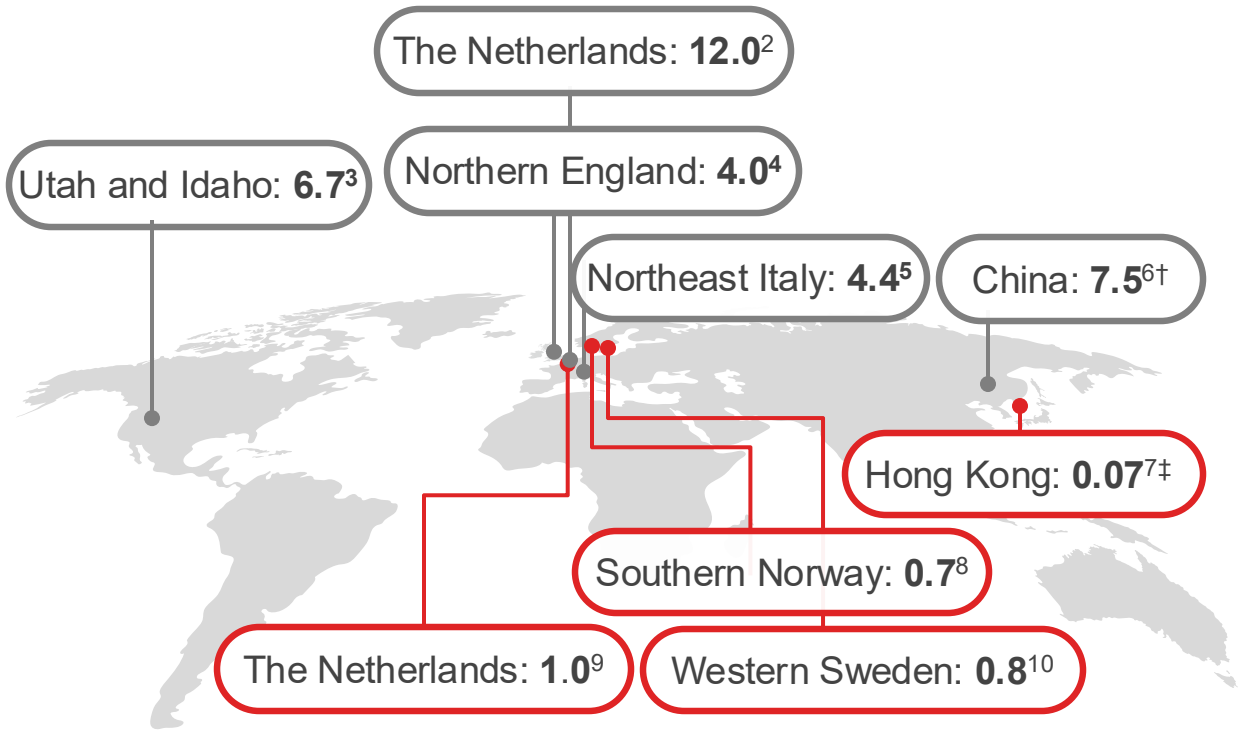
FSHD, facioscapulohumeral muscular dystrophy.

1. Tihaya MS, et al. *Nat Rev Neurol*. 2023;19:91–108; 2. Statland JM, Tawil R. *Continuum (Minneap Minn)*. 2016;22:1916–1931; 3. Mul K, et al. *Pract Neurol.* 2016;16:201–207.

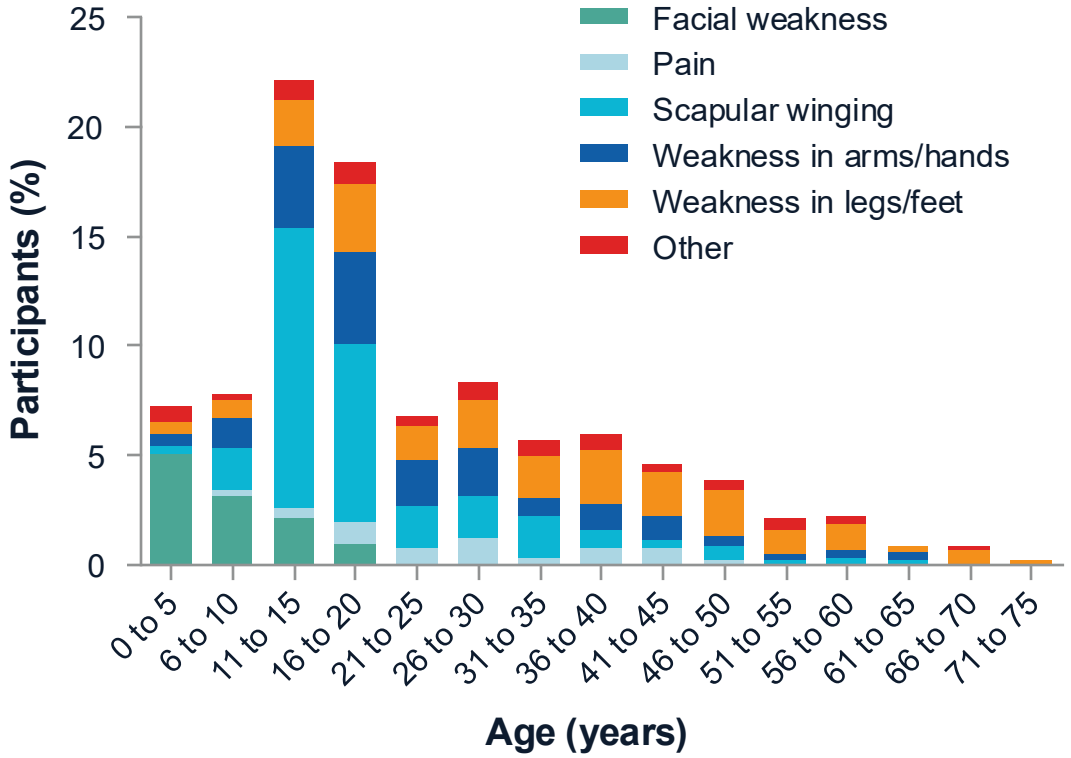
FSHD is one of the most prevalent inherited muscle disorders, with a pattern of onset that varies according to age

The global prevalence of FSHD is around 5–12 per 100,000 individuals[1,2]

Reported FSHD prevalence in the literature (cases per 100,000 overall and in children*)



Age of onset of symptoms[11¶]



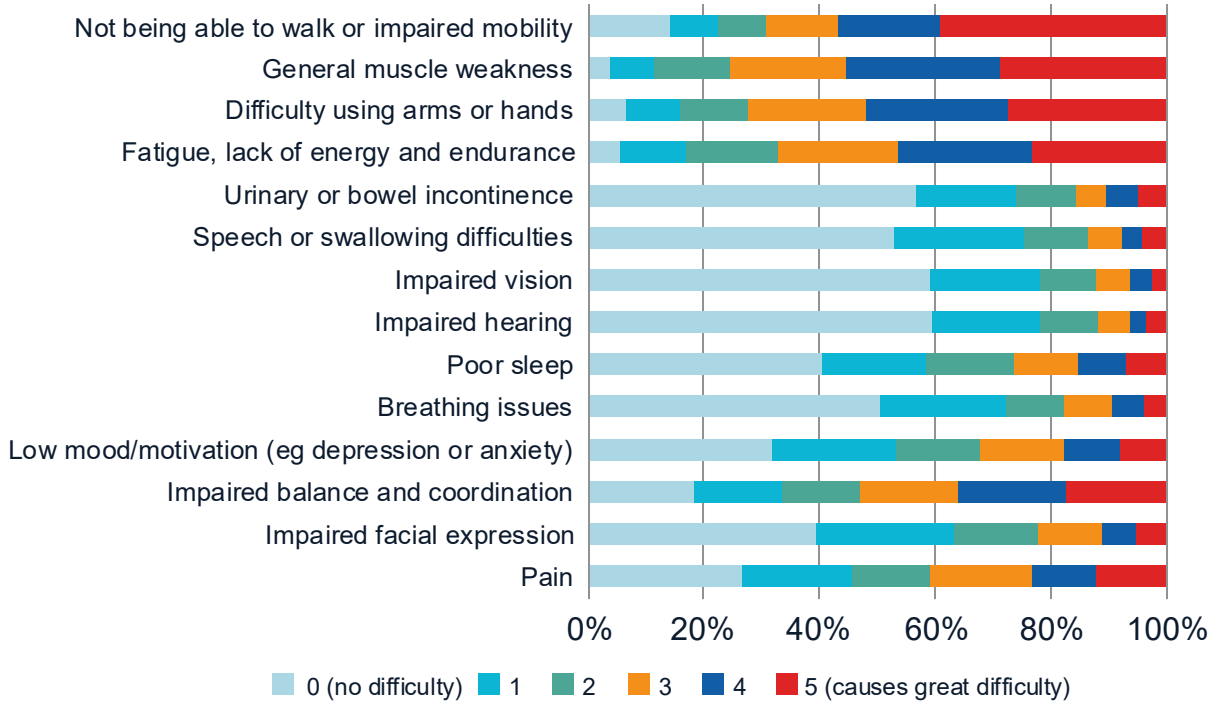
*Defined as age <19 years in references 7–9 and <16 years in reference 10; †Genetically confirmed FSHD1; ‡1 case in 1,335,469. ¶Image used with permission of The Author(s), from McNiff MM, et al. *J Neuromuscul Dis*. 2024;11:459–472; permission conveyed through Copyright Clearance Center. FSHD, facioscapulohumeral muscular dystrophy.

1. Mul K. *Continuum (Minneap Minn)*. 2022;28:1735–1751; 2. Deenen JCW, et al. *Neurology*. 2014;83:1056–1059; 3. Flanigan KM, et al. *Neuromuscul Disord*. 2001;11:525–529; 4. Norwood FL, et al. *Brain*. 2009;132:3175–3186; 5. Mostacciuolo ML, et al. *Clin Genet*. 2009;75:550–555; 6. Wang Z, et al. *Lancet Reg Health West Pac*. 2021;18:100323; 7. Chung B, et al. *J Child Neurol*. 2003;18:217–219; 8. Tangsrud SE and Halvorsen S. *Clin Genet*. 1988;34:145–152; 9. Goselink RJM, et al. *Ann Neurol*. 2018;84:627–637;10. Darin N and Tulinus M. *Neuromuscul Disord*. 2000;10:1–9; 11. McNiff MM, et al. *J Neuromuscul Dis*. 2024;11:459–472.

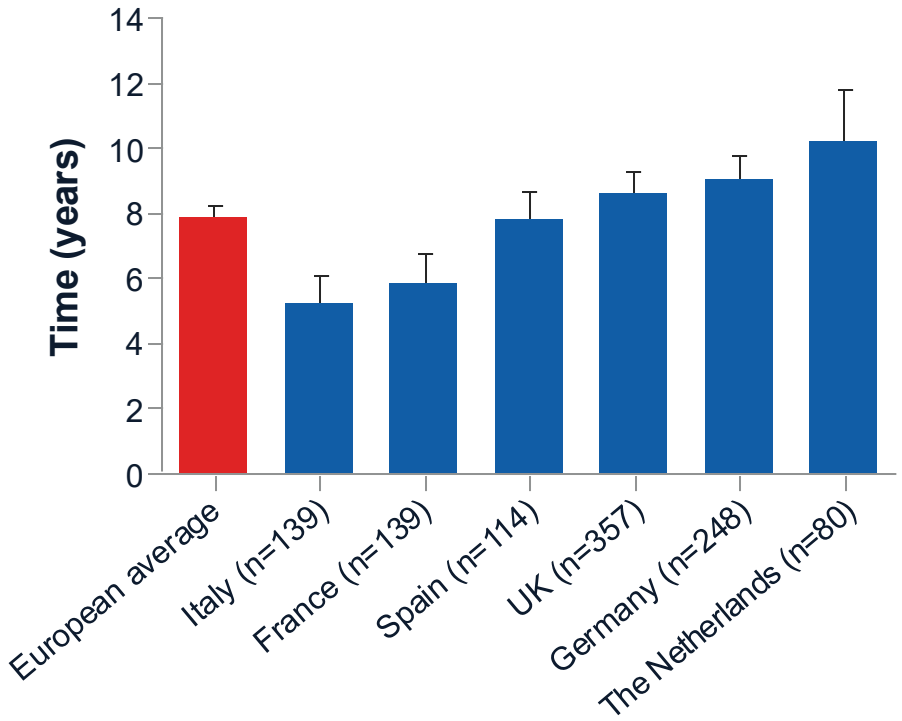
Patients with FSHD experience a variety of symptoms that impact their daily life but they may experience a significant delay in diagnosis

European survey of 1147 patients* with FSHD from 26 countries

Symptoms causing difficulty in daily life



Time to FSHD diagnosis based on survey responses



Impaired mobility was reported to cause the greatest difficulty in daily life
It takes 7.9 years on average for patients to receive a diagnosis

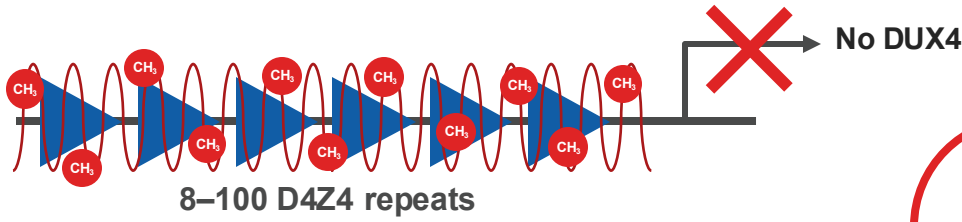
*The majority of respondents were patients (92%); caregivers represented 5% of participants, and 3% identified as both a patient and a caregiver. Error bars show ±SEM.
FSHD, facioscapulohumeral muscular dystrophy; SEM, standard error of the mean.

McNiff MM, et al. *J Neuromuscul Dis.* 2024;11:459–472.

FSHD results from epigenetic de-repression of the *DUX4* gene in skeletal muscle

Healthy individuals[1,2]

D4Z4 tandem repeats, which are characterized by high CpG methylation, prevent DUX4 transcription by maintaining closed chromatin

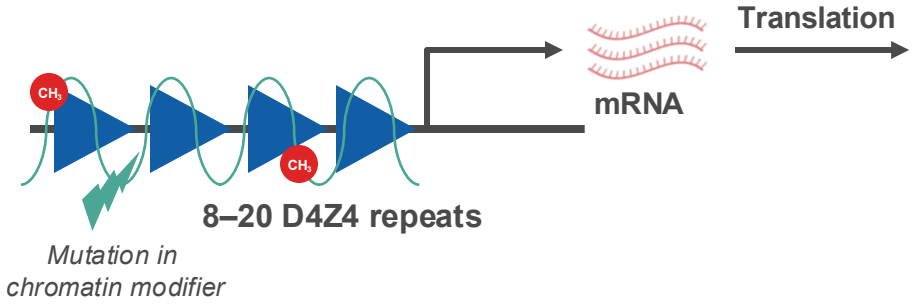


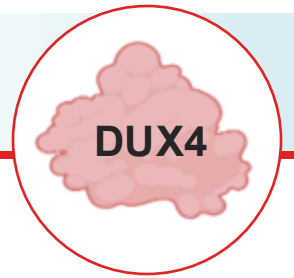
FSHD1 (~95% of patients)[1,2]

Contraction in D4Z4 repeats leads to partial loss of D4Z4 methylation, opening of chromatin and transcription of DUX4

FSHD2 (~5% of patients)[1,2]

A mutation in chromatin modifier genes such as SMCHD1 (>85% of FSHD2 cases), DNMT3B or LRIF1, de-represses DUX4 via hypomethylation, despite a short D4Z4 array within the normal range



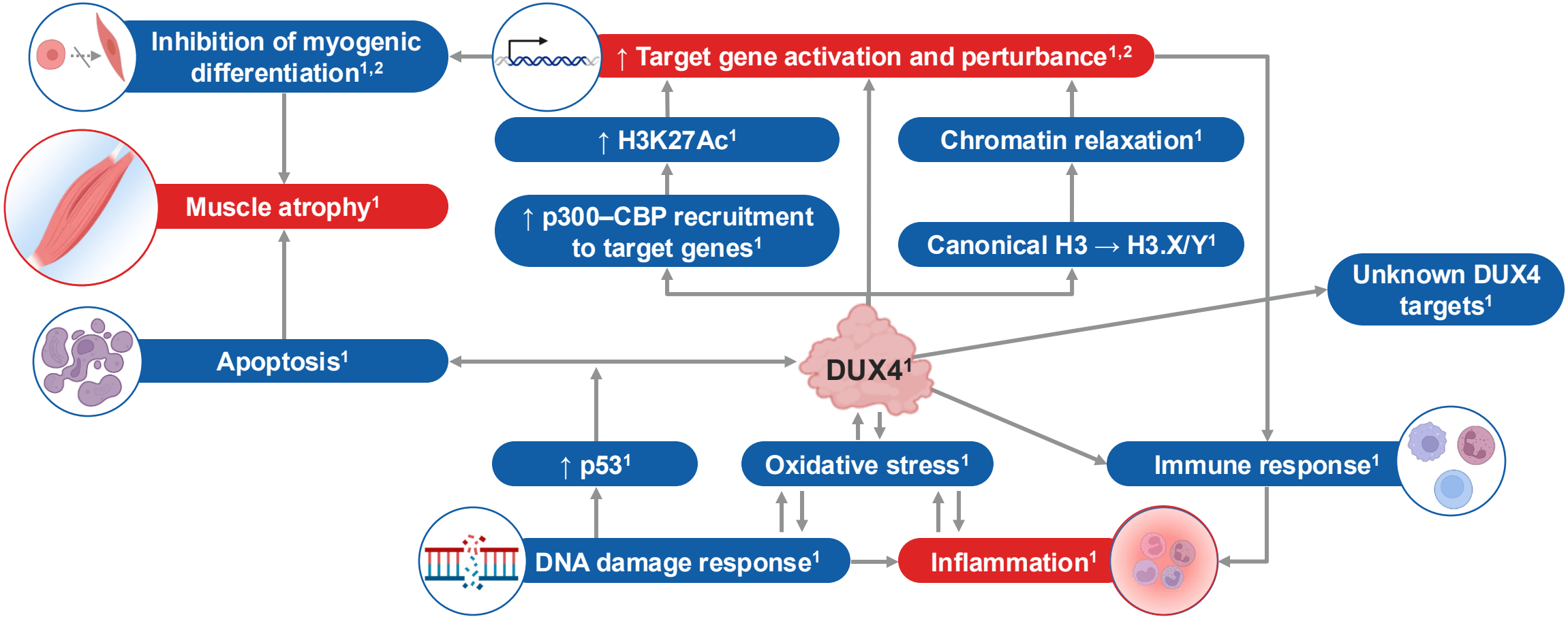


- Transcription factor involved in embryonic genome activation[1]
- Suppressed in most adult somatic tissues (except thymus and testes)[1,2]
- Expressed sporadically and at low levels in FSHD skeletal myocytes[1,2]
- Expression of DUX4 protein in skeletal muscle can be indirectly derived from transcriptional regulation of its target genes[1]
- DUX4 dose-dependently activates persistent downstream targets, causing cytotoxicity[1]
- FSHD disease severity is inversely correlated with D4Z4 repeat counts[1,2]

CpG, cytosine–guanine dinucleotide; DNA, deoxyribonucleic acid; DNMT3B, DNA-methyltransferase 3 beta; DUX4, double homeobox protein 4; FSHD, facioscapulohumeral muscular dystrophy; LRIF1, ligand-dependent nuclear receptor interacting factor 1; mRNA, messenger ribonucleic acid; SMCHD1, Structural Maintenance of Chromosomes flexible Hinge Domain Containing 1.

1. Tihaya MS, et al. *Nat Rev Neurol*. 2023;19:91–108; 2. Mul K. *Continuum (Minneap Minn)*. 2022;28:1735–1751.

Aberrant expression of *DUX4* in skeletal muscle leads to transcriptional deregulation, inflammation, and muscle atrophy



In FSHD, DUX4 is associated with activation of pathways toxic to muscle tissue, including oxidative stress and DNA damage, inhibition of myogenic differentiation, impaired transcript quality control, and inflammation, leading to muscle cell apoptosis and atrophy[1,2]

CBP, cyclic adenosine monophosphate response element binding protein (CREB) binding protein; DUX4, double homeobox protein 4;FSHD, facioscapulohumeral muscular dystrophy; H, histone; H3K27Ac, histone H3 lysine 27 acetylation.

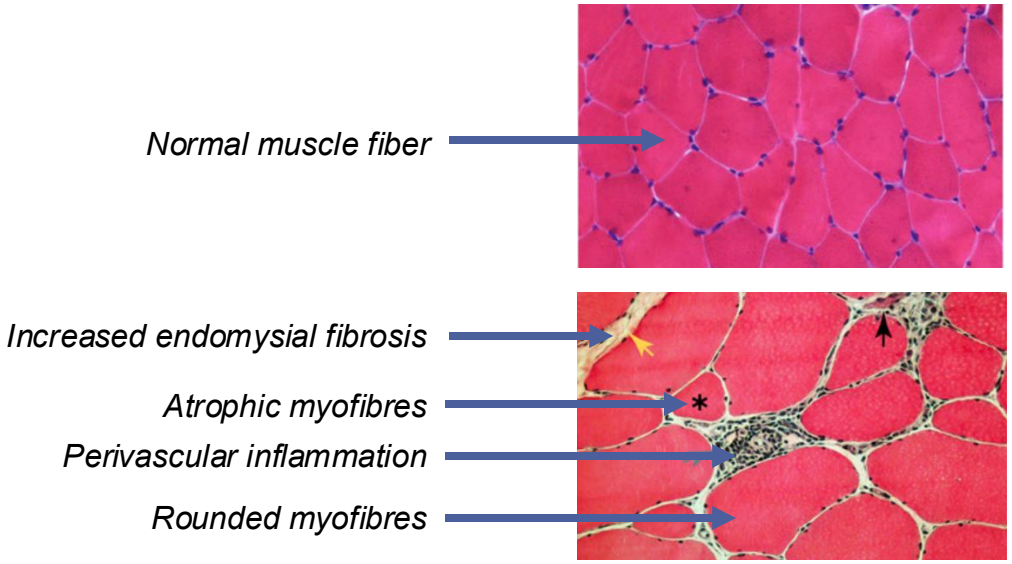
Image adapted from Tihaya MS, et al. *Nat Rev Neurol*. 2023;19:91–108 and Mocciaro E, et al. *Cells*. 2021;10:3322

1. Tihaya MS, et al. *Nat Rev Neurol*. 2023;19:91–108; 2. Mocciaro E, et al. *Cells*. 2021;10:3322.

FSHD shows distinctive pathological features that can be used to measure disease progression

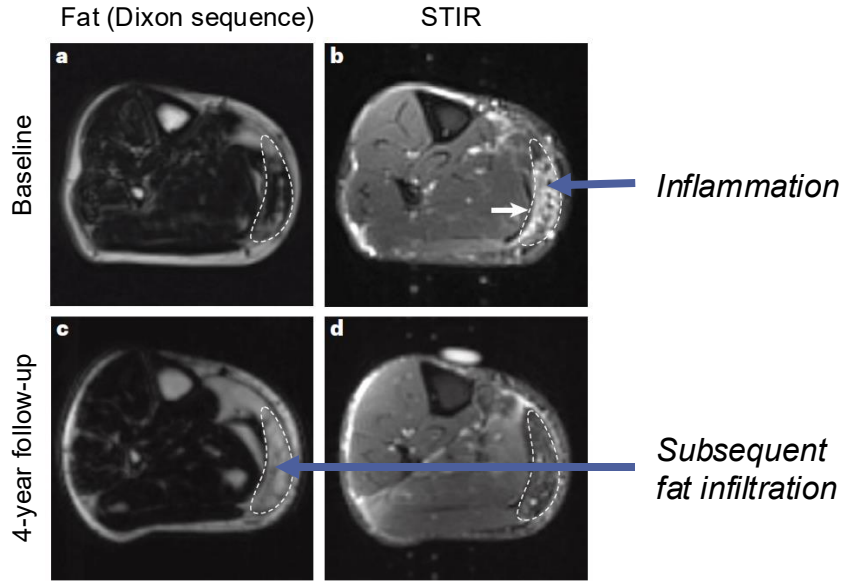
FSHD muscle biopsies are characterized by fibrosis, fiber size variation, apoptosis of fibers and/or myonuclei, inflammation, and fatty infiltration[1–3]

Morphological features of healthy skeletal muscle (top) vs skeletal muscle from an FSHD biopsy (below)[4*]



Pathological changes in FSHD muscle can be visualized on muscle MRI using short-tau inversion recovery (STIR) scans[1–3]

Progression of FSHD as measured by MRI[1†]



Progression of FSHD is believed to follow a non-linear pattern, where discrete bursts of *DUX4* expression lead to muscle inflammation, followed by rapid fatty replacement[1]

Muscles with hyperintense STIR+ lesions have a higher likelihood of inflammatory muscle pathology and increased expression of DUX4 targets[1,5]

DUX4, double homeobox 4; FSHD, facioscapulohumeral muscular dystrophy; MRI, magnetic resonance imaging.

*Images reproduced from Banerji CRS, Zammit PS. *EMBO Mol Med*. 2021;13:e13695, licensed under a CC-BY 4.0 Creative Commons license; doi: 10.15252/emmm.202013695.

†Images used with permission of Springer Nature Limited, from Tihaya MS, et al. *Nat Rev Neurol*. 2023;19:91–108; permission conveyed through Copyright Clearance Center.

1. Tihaya MS, et al. *Nat Rev Neurol*. 2023;19:91–108; 2. Mul K. *Continuum (Minneap Minn)*. 2022;28:1735–1751; 3. Hubregtse L, et al. *Neuromuscul Disord*. 2024;36:6–15; 4. Banerji CRS, Zammit PS. *EMBO Mol Med*. 2021;13:e13695; 5. Monforte M, et al. *Neuromuscul Disord*. 2023;33:65–75.

DUX4-related gene expression biomarkers have been identified in FSHD samples, but require further study

DUX4 expression is currently an unreliable biomarker in FSHD[1,2]

- It occurs randomly in short bursts and in very few myonuclei[1,2]
- Its GC-rich sequence is similar to many other RNAs, making it hard to assay[1]

Development of reliable therapeutic biomarkers is a major unmet need in FSHD[1]

- Ongoing research is investigating inflammatory biomarkers (SLC34A2 and IL-6), micro-RNAs, proteomics, and gene expression profiles[1]

Gene expression biomarker research in FSHD has focussed on two types of signatures: DUX4 targets and PAX7 targets[1-3]

- Validation of FSHD biomarkers in independent patient cohorts will be required before they can be used in clinical trials[1,2]

DUX4 and PAX7 signatures have been characterized in samples from patients with FSHD

DUX4 target gene signatures

- Genes activated directly by DUX4, or indirectly through downstream signalling[1,2]
- May detect early changes in FSHD muscle[2,3]

PAX7 target gene signature (PAX7 score)

- Genes controlled by PAX7 (a protein structurally similar to DUX4), which are affected when DUX4 is present[1,2]
- May be associated with FSHD disease progression[2,3]

C, cytosine; DUX4, double homeobox 4; FSHD, facioscapulohumeral muscular dystrophy; G, guanine; IL-6, interleukin-6; micro-RNA, micro ribonucleic acid; PAX7, paired box 7; RNA, ribonucleic acid; SLC34A2, solute carrier family 34 member 2.

1. Montagnese F, et al. *Neuromuscul Disord*. 2023;33:447–462; 2. Tihaya MS, et al. *Nat Rev Neurol*. 2023;19:91–108;
3. Wong CJ, et al. *Hum Mol Genet*. 2020;29:1030–1043.

Summary

- FSHD is one of the most common muscular dystrophies affecting children and adults[1]
- There are currently no approved pharmacologic treatments for FSHD[2]
- FSHD is caused by aberrant expression of *DUX4*, which leads to cytotoxicity in skeletal muscle cells[2]
- *DUX4* expression influences muscle differentiation and muscle atrophy, and *DUX4*-related gene expression biomarkers have been identified in FSHD samples[2]

DUX4, double homeobox 4 gene; FSHD, facioscapulohumeral muscular dystrophy; mRNA, messenger ribonucleic acid; siRNA, small interfering RNA; TfR1, transferrin receptor 1.

1. Statland JM, Tawil R. *Continuum (Minneap Minn)*. 2016;22:1916–1931; 2. Tihaya MS, et al. *Nat Rev Neurol*. 2023;19:91–108.