



Genetics Medical Center

Clinician Information



**FACIOSCAPULOHUMERAL MUSCULAR  
DYSTROPHY (FSHD)**

## ■ SYMPTOMS AND RED FLAGS

Facioscapulohumeral muscular dystrophy (FSHD) affects the muscles of the face (facio-), the shoulder girdle (scapulo-) and the upper arms (humeral). Also affected are the muscles of the trunk and extremities:

### Face

- ▶ **Asymmetrical facial muscle weakness** is a typical first symptom which patients may not be aware of due to its very slow progression. In 25 % of the patients, facial weakness is very discreet.
- ▶ Lack of facial expression. Difficulty whistling. 'Signe de cils' – an inability to bury the eyelashes completely when attempting to close the eyes tightly. More severely affected patients sleep with eyes partially open, which leads to irritated conjunctiva in the morning. Extraocular muscles are not involved; therefore, there is regular oculomotor function.

### Shoulder girdle

- ▶ **Scapula alata** – often asymmetrical
- ▶ **Difficulty with overhead work** such as hair washing or combing
- ▶ "**Popeye arms**" and "**Poly-Hill phenomenon**" by selective involvement of the biceps and triceps while sparing of the deltoids and forearm muscles until late in the disease

### Trunk

- ▶ Weakness of abdominal muscles as typical and early sign
- ▶ Upward movement of the umbilicus on flexing the neck in the supine position – **Beevor's sign**
- ▶ Difficulties in rising from a supine to a sitting position and later on in turning from one side to the other when supine
- ▶ Characteristic **lumbar hyperlordosis**
- ▶ Weakness of M. erector spinae leads to "**bent-spine-syndrome**" or **Camptocormia**.
- ▶ Respiratory muscles are not primarily affected. Patients rarely require ventilator assistance.

### Lower Extremities

- ▶ Weakness of the tibialis anterior muscle, eventually causing foot drop, as a classical feature in the early stage of the disease

## Pain and Fatigue

Chronic pain, moderate to severe, in 75 % of patients, frequently pertaining to the lower back, legs, shoulder region and neck. Many patients also complain of fatigue symptoms.

## Systemic Involvement

Usually no cardiomyopathy. Increased prevalence of (incomplete) right bundle branch block. Retinal vasculopathy is associated with FSHD but is mostly subclinical. Only in the case of very severe forms of progression may treatment be necessary. High-frequency hearing loss also mostly subclinical. However, hearing loss requiring hearing aids may develop in patients with severe, early onset of disease.

## GENETIC BACKGROUND

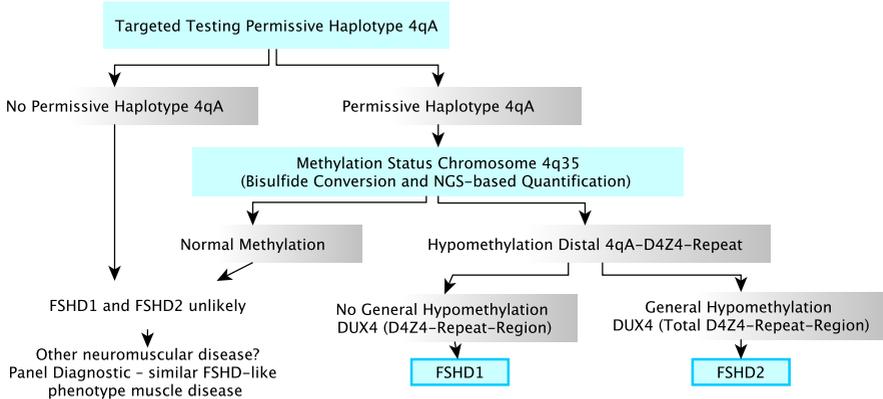
*FSHD is associated with the hypomethylation of a chromosome segment (D4Z4 macrosatellite repeat) on chromosome 4 (4q35). Thus, the gene expression in this chromosome segment is not switched off as would actually be the case with normal methylation. This leads to aberrant transcription and expression of a protein (DUX4) that is toxic to skeletal muscles and is considered pathophysiologically responsible for the neuromuscular phenotype.*

*The mechanisms leading to chromosomal hypomethylation and aberrant gene expression on chromosome 4 are complex. The most common cause is the shortening of the D4Z4 repeat (repeat contraction) to less than 11 units (FSHD1). More rarely, hypomethylation is primarily based on mutations in genes (especially SMCHD1) coding for chromatin-regulating proteins (FSHD2).*

*The prerequisite for FSHD is that the patient has a so-called permissive haplotype, i.e. a specific genomic constellation in which a Poly-A signal is present that makes it possible to stabilize the DUX4 mRNA and thus ultimately express DUX4 protein. If no permissive haplotype is detectable, this makes FSHD1 or FSHD2 unlikely.*

## ■ DIAGNOSTIC STRATEGY

### Diagnostic Algorithm



The diagnostic strategy is based on the detection of an FSHD-permissive haplotype and an aberrant methylation status of the FSHD locus on chromosome 4q35. Predictive/prenatal analyses additionally require the direct detection of D4Z4 repeat contraction by Southern blot, requiring 8 ml fresh EDTA blood.

### Mutation Detection Rate

The absence of a permissive haplotype or a normal methylation pattern on chromosome 4q35 largely excludes FSHD1 or FSHD2. If the clinical picture is nevertheless suggestive, FSHD-like neuromuscular diseases (e.g. other scapulo-peroneal syndromes) should be considered, which can be detected by an NGS panel diagnostic.

### Clinical Utility

- ▶ Genetic classification allows differentiation from acquired clinical conditions.
- ▶ Depending on the genetically defined form (FSHD1 or FSHD2), the risk of recurrence for family members and offspring differs, as do the possibilities of prenatal or preimplantation diagnosis.
- ▶ Even if there is currently no therapy available that addresses the (genetic) cause, the genetic classification of the disease permits the adaptation of follow-up examinations to the known associated disease risks.
- ▶ Genetic diagnosis facilitates the inclusion in patient registries and in therapy studies.

### REFERENCES

Mul K, et al. Pract Neurol 2016;16:201–207.  
GeneReviews® [<https://www.ncbi.nlm.nih.gov/sites/books/NBK1443>].

## FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY (FSHD)

### Leading Symptoms

Slowly progressive, often asymmetrical weakness of selective muscle with normal to moderately elevated CK. Initially, often foot drop; further on, selective atrophy of the facial musculature, the shoulder girdle, upper arm, as well as the abdominal musculature as typical first symptoms.

### Genetic Causes

Hypomethylation of the D4Z4 macrosatellite repeat on chromosome 4q35 caused by a contraction of the D4Z4 repeat to less than 11 repeat units or by a pathogenic variant in the *SMCHD1* gene (more rarely in the *DNMT3B* gene), with simultaneous presence of a so-called permissive allele.

### Frequency

After myotonic dystrophies, FSHD is the most frequent muscular dystrophy in adults. The incidence is 0.4-1:10,000.

### Inheritance

Autosomal dominant inheritance with reduced penetrance. Approx. 70-90 % of all FSHD1 patients have inherited the D4Z4-repeat contraction from one parent; approximately 10-30 % have a new mutation.

Most patients with FSHD2 have a heterozygous mutation of the *SMCHD1* gene, more rarely of the *DNMT3B* gene. Since two independently segregating genetic traits (both permissive haplotype and heterozygous *SMCHD1* mutation or *DNMT3B* mutation) must be present for clinical symptoms to occur, inheritance in FSHD2 is digenic.

### Progression

Very variable and often relapsing course. Severe early childhood to very mild forms, with few symptoms into old age. Intrafamily variability also possible. First manifestation from early childhood to advanced age, often disease onset in young adulthood (before the age of 20). Higher penetrance in the male sex. One in five patients at the age of 50 years is dependent on a wheelchair. Life expectancy is generally not shortened.

## SELF-HELP GROUPS / USEFUL ADDRESSES

- ▶ Orphanet. [www.orpha.net](http://www.orpha.net)
- ▶ Treat-NMD Neuromuscular Network; FSHD-Patient Registry: [www.fshd-registry.org](http://www.fshd-registry.org)

On our website, you will find information on other clinical topics as well as information about our company and services.

Visit us at [www.mgz-muenchen.com](http://www.mgz-muenchen.com)



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