Facioscapulohumeral Muscular Dystrophy

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KEYWORDS

• Muscular dystrophy • Facioscapulohumeral muscular dystrophy • D4Z4 deletion • DUX4 • SMCHD1 mutation

KEY POINTS

- Clinically, Facioscapulohumeral muscular dystrophy types 1 and 2 are similar: often asymmetric and descending weakness affecting the face, shoulder, and arms followed by the distal lower extremities and pelvic girdle.
- Facioscapulohumeral muscular dystrophy patients with the largest contractions are more likely to have symptomatic extramuscular involvement that includes retinal vascular disease, hearing loss, and, rarely, cognitive impairment or seizures.
- Facioscapulohumeral muscular dystrophy type 1 is caused by a deletion in the number of the macrosatellite repeat (D4Z4) elements on chromosome 4q35; this leads to decreased DNA methylation and opening of the chromatin structure.
- Facioscapulohumeral muscular dystrophy type 2 is caused by mutations in genes elsewhere in the genome that lead to decreased methylation in the same D4Z4 region on chromosome 4q35.
- The opening of the chromatic structure seen in both Facioscapulohumeral muscular dystrophy types 1 and 2 results in de-repression of the DUX4 gene, a transcriptional factor believed to cause disease through a toxic gain-of-function mechanism.
- The identification of a proposed disease mechanism opens the door to future disease-directed therapies.

INTRODUCTION

Facioscapulohumeral muscular dystrophy (FSHD), one of the most prevalent adult muscular dystrophies (1:15,000–1:20,000), is characterized by asymmetric and often descending weakness affecting the face, shoulder, and arms followed by weakness of the distal lower extremities and pelvic girdle.[1,2] FSHD is categorized as type 1 or

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type 2 based on the underlying genetic lesions. Approximately 95% of patients will have disease inherited in an autosomal dominant fashion associated with loss of part of a repeated sequence in the D4Z4 region on chromosome 4q35.[3,4] An additional 5% of patients will have disease with a variable inheritance pattern caused by a D4Z4 deletion-independent pathway.[5] Recent advances suggest both FSHD types 1 and 2 exert their effects through a common pathophysiologic pathway: de-repression of the retrogene *DUX4* believed to cause disease in a toxic-gain-of-function manner.[6] Studies have suggested FSHD1 and FSHD2 are clinically identical; although, the number of FSHD2 patients studied has been limited. Approximately 20% of FSHD patients greater than 50 years of age will require the use of a wheelchair.[2,7] FSHD1 patients with the largest contractions are more likely to have extramuscular manifestations of FSHD, which include symptomatic retinal vascular disease and hearing loss.[8,9] The elucidation of a proposed common molecular mechanism behind both FSHD types 1 and 2 has opened the door to research in potential disease-directed therapies.

CLINICAL FINDINGS

Both FSHD types 1 and 2 are clinically similar, characterized by:

- Symptom onset typically in the first or second decade of life but can present later in life
- Often marked side-to-side asymmetry
- Facial weakness seen as inability to squeeze the eyes shut or furrow the brow, a transverse smile, or flattening when puckering the lips
- Shoulder weakness often with scapular winging and flattening of the clavicles
- Arm weakness including the biceps and triceps often with forearm sparing
- Asymmetric abdominal weakness seen on examination as a positive Beevor's sign
- Usually distal lower extremity weakness before proximal, starting with a foot drop

FSHD can go on to affect most any skeletal muscle but typically spares extraocular muscles, cardiac muscles, and bulbar muscles. Debilitating paraspinal muscle weakness can develop, which can be an initial presentation.[10] Although the most common presentation is with facial and shoulder weakness and a descending pattern of progression, several initial presentations have been described, including bent spine and less-specific limb girdle patterns. The rate of progression has been evaluated in a large prospective natural history study, which found a loss of strength using combined quantitative strength testing and manual muscle testing of about 1% to 4% per year.[11] Although not life limiting, FSHD can cause significant lifetime morbidity.[2,7,12] The 6-year risk of wheelchair use overall is about 24%. Risk of wheelchair use shows a bimodal distribution: FSHD1 patients with the largest D4Z4 deletions (1–3 remaining repeats) have the highest risk, which peaks in the second and third decades, followed by a slow age-dependent increase in the risk. Respiratory involvement is seen in about 10% of patients, most commonly in the most severely affected or wheelchair-bound patients. Atrial arrhythmias are seen in about 5% of FSHD patients but are rarely symptomatic.

Extramuscular manifestations are also rarely symptomatic and include retinal vascular changes and hearing loss. Approximately half of FSHD patients show peripheral retinal vascular abnormalities on fluorescein angiography, but symptomatic retinal vasculopathy (Coat's syndrome) is only seen in approximately 1% of patients, typically patients with the largest D4Z4 deletions.[9,13,14] High-frequency hearing loss is reported