REVIEW ARTICLE

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Facioscapulohumeral Muscular Dystrophies

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ABSTRACT

PURPOSE OF REVIEW: Facioscapulohumeral muscular dystrophy (FSHD) is a common muscular dystrophy affecting both pediatric and adult patients. This article reviews the phenotype and pathophysiology of the disease as well as the recent efforts in clinical outcome measures and clinical trials.

RECENT FINDINGS: As the name implies, FSHD involves weakness of facial muscles, muscles that fix the scapula, and muscles overlying the humerus (biceps and triceps). The distinctive phenotype of FSHD occurs secondary to two different genetic mechanisms. FSHD type 1 (FSHD1) is due to a deletion on chromosome 4q, leading to hypomethylation and derepression of *DUX4*. FSHD type 2 (FSHD2) is due to mutations in *SMCHD1* with resulting hypomethylation of the same subtelomeric region of chromosome 4q and derepression of *DUX4*. Understanding the central role of *DUX4* has opened up the possibility of disease-modifying treatments. In preparation for clinical trials of novel agents, researchers are in the process of validating a number of clinical trial outcome measures including MRI, the 6-minute walk test, the FSHD Composite Outcome Measure, reachable workspace, electrical impedance myography, and the FSHD Health Index.

SUMMARY: The treatment of FSHD is currently supportive only. While past clinical trials in FSHD have been largely disappointing, novel agents in development, including antisense oligonucleotides, gene therapy, and small molecules, hold promise for future meaningful therapies.

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INTRODUCTION

Facioscapulohumeral muscular dystrophy (FSHD) is one of the most common muscular dystrophies. Recent studies suggest that it has a prevalence from 1 in 8333 to 1 in 15,000 depending on the population.[1] The disorder gets its name from the muscles preferentially affected: those of the face, those that fix the scapula, and those overlying the humerus (ie, biceps and triceps). FSHD has a wide range of onset and severity, including rapidly progressive infantile or early onset, slowly progressive young-adult onset, and asymptomatic carriers of the alleles. Few treatment options, beyond supportive care, are available for patients with FSHD.

The two commonly recognized forms of the disease are FSHD type 1 (FSHD1) and FSHD type 2 (FSHD2). FSHD1 encompasses 95% of the disease population and is inherited in an autosomal dominant fashion. FSHD2 comprises the remaining 5% and is a digenic disorder. The pathophysiology of FSHD is just

becoming elucidated. The unifying hypothesis is that mutations leading to FSHD result in the inappropriate expression of a normally dormant transcription factor, double homeobox 4 (DUX4). The growing understanding of the pathophysiology of FSHD has led to the development of disease-specific drugs and preparation for future clinical trials.

This article summarizes the genetic basis and describes the phenotype of FSHD, discusses outcome measures that are being developed for FSHD, and concludes with a discussion of current and future therapies for FSHD.

KEY POINT

- **The two forms of facioscapulohumeral muscular dystrophy are type 1 (95% of cases) and type 2 (5% of cases). The presentations of both types are identical.**

GENETIC BASIS OF DISEASE

The genetics of FSHD are complex and have only recently been elucidated. FSHD is inherited in an autosomal dominant manner. FSHD1 was mapped to chromosome 4q35,[2] a region with large, 3.2-kilobase (kb) repetitive units termed D4Z4 repeats (FIGURE 7-1). Normally, between 11 and 100 repeats are present on each 4q35 chromosome; however, in patients with FSHD, 1 to 10 D4Z4 repeats are present.[3] This deletion of repetitive units is associated with hypomethylation of the region.[4] With hypomethylation, the chromatin is relaxed, allowing transcription of the normally dormant gene *DUX4* from the terminal D4Z4 repeat.[5] However, for the *DUX4* transcript to be polyadenylated and stabilized, the deletion must be in the correct context of one of two alleles (A and not B).[5,6] In this setting, FSHD1 ensues. 95% of all FSHD is FSHD1.

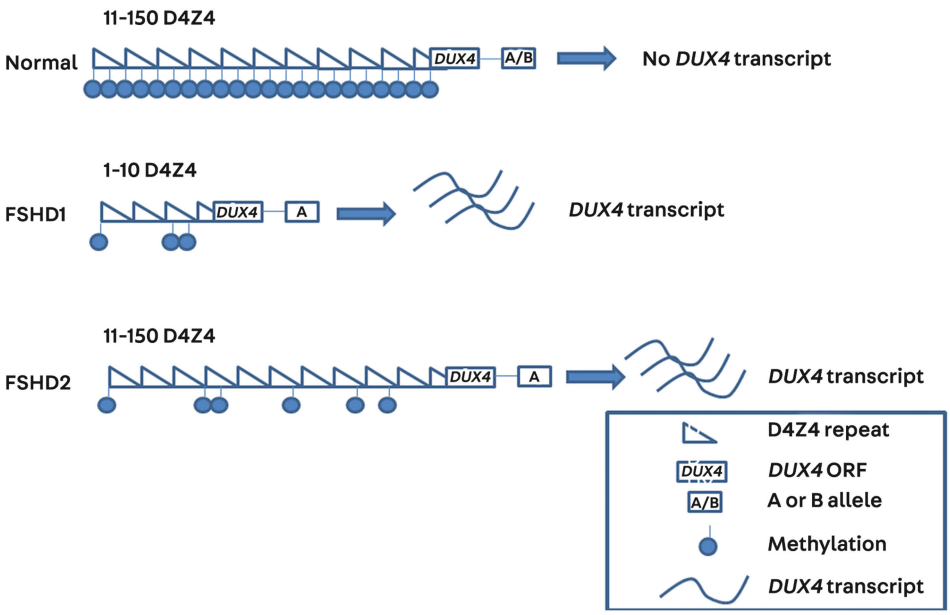

FIGURE 7-1

The molecular mechanism of facioscapulohumeral muscular dystrophy (FSHD). Normally, the 4q chromosome contains 11 to 150 D4Z4 repeats and is highly methylated. In this setting, the *DUX4* locus is silent. In FSHD type 1 (FSHD1), there is a contraction of D4Z4 repeats, and in the presence of an A allele, *DUX4* is transcribed. In FSHD type 2 (FSHD2), there is hypomethylation of the D4Z4 repeats due to a mutation in *SMCHD1*, and in the presence of the A allele on chromosome 4, *DUX4* is similarly transcribed. DUX4 is a transcription factor that turns on a host of genes, and DUX4 along with the protein products of its target genes are thought to be responsible for muscle pathology.

ORF = open reading frame.

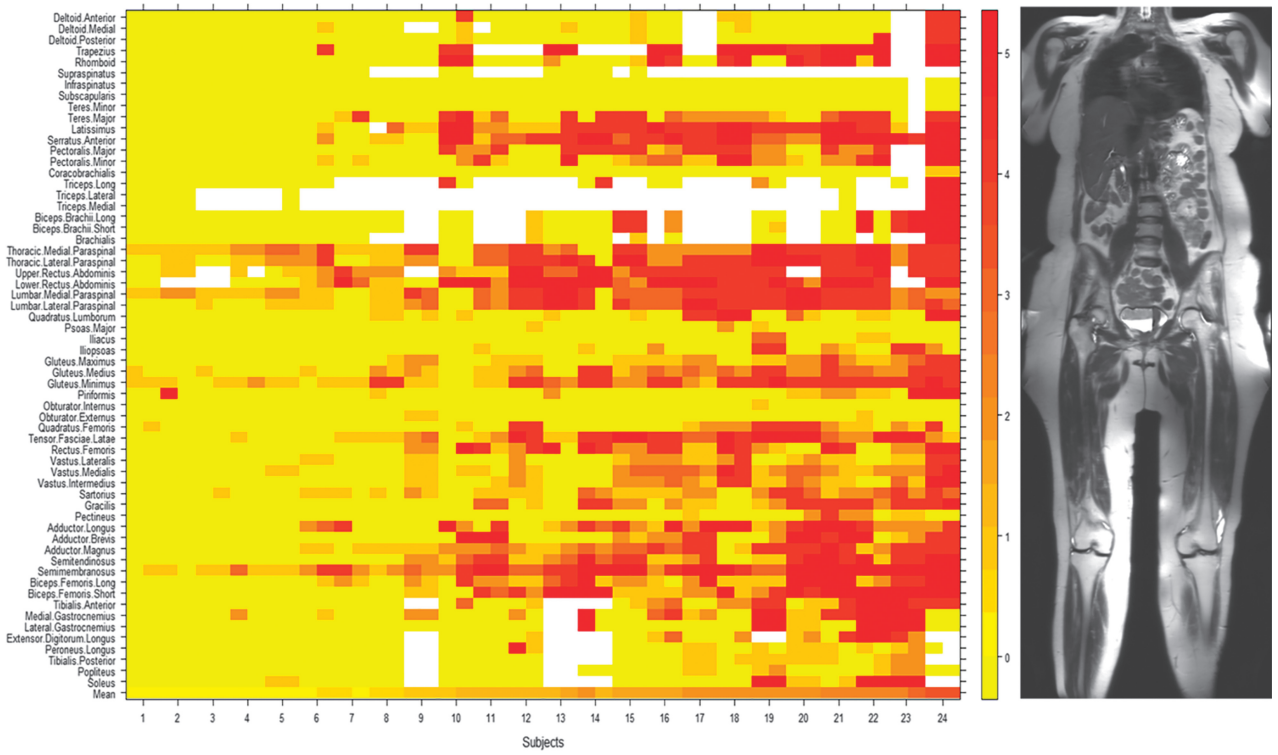

FIGURE 7-2

MRI findings in facioscapulohumeral muscular dystrophy. Heat map of fat infiltration scores in 24 individuals with facioscapulohumeral muscular dystrophy. Fat infiltration scores on T1-weighted MRI (from 0 to 5) and their corresponding colors are shown in the numbered bar on the right. Patients are arranged (left to right) from lowest to highest mean MRI score. Muscles on the left and right sides of the body are placed to the left and right sides, respectively, of the labeled tick marks for each subject. Notice that some muscles such as the semimembranosus, paraspinals, and rectus abdominis are nearly uniformly affected (*red*) while others such as the infraspinatus, subscapularis, and obturators are nearly uniformly unaffected (*yellow*).

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FSHD2 (5% of FSHD) is also the result of hypomethylation of the D4Z4 region of chromosome 4q35. However, in this case, hypomethylation is not associated with a D4Z4 contraction. About 80% of patients with FSHD2 have a separate mutation in *SMCHD1*, a hypermethylating enzyme with a normal role in X chromosome inactivation.[7] Mutations in *SMCHD1* (and presumably other yet-to-be-defined loci) result in hypomethylation of the D4Z4 region, which leads to *DUX4* transcript expression in the context of the A allele. Thus, the unifying genetic model of FSHD is hypomethylation of the D4Z4 region of chromosome 4q35, leading to expression of *DUX4*.

The function of DUX4 protein is incompletely understood. Normally, DUX4 is expressed exclusively in development and in the spermatogonia of adult testes. In FSHD, DUX4 is misexpressed in a very small percentage of myogenic cells (approximately 1:1000).[8] It is toxic to cells and leads to apoptosis.[9,10] DUX4 is a transcription factor, and misexpression of DUX4 in FSHD is associated with the regulation of hundreds of genes. These genes include germline genes, retroelements, immune mediators, and those responsible for RNA metabolism.[11,12] The specific target gene(s) responsible for DUX4-mediated toxicity have not been

conclusively identified but are believed to make the myogenic cells more susceptible to oxidative stress.[13] Theories of FSHD pathophysiology include DUX4-mediated cytotoxicity, DUX4 causing a regenerative defect, and DUX4 triggering an inflammatory response. These mechanisms are not mutually exclusive.

CLINICAL PRESENTATION

FSHD1 and FSHD2 present similarly. The onset and severity vary widely. The most classic onset is in teenage or early adult years, but the disorder ranges from infantile onset in FSHD1 to nonmanifesting carriers of the disease. The disorder is slowly progressive, with many patients not changing substantially over a year's time. However, some exhibit the rapid loss of select muscles over a few months. Symptoms are most often first noticed in the muscles of the face and scapular region. However, MRI findings suggest that hamstring and abdominal muscles may be some of the first to be affected (FIGURE 7-2[14]).[15] Patients present with wide open eyes and often have a history of sleeping with their eyes partially open. They have an inability to pucker (FIGURE 7-3A) and may never learn to whistle. They frequently have a transverse or asymmetric smile. Babies with early-onset FSHD have a reduced ability to suck and may not develop a social smile (CASE 7-1).

The muscles of scapular fixation (the rhomboids and serratus anterior) are weak, causing the medial border of the scapula to "wing" and the rostral border to rise up, producing a poly-hill sign on arm abduction (FIGURE 7-3B–D). Individuals with FSHD frequently have an inability to slowly abduct or extend their arms to 180 degrees, although they may be able to do so by throwing their arms up. Pectoralis weakness is accompanied by horizontal clavicles and deep axillary creases. The biceps and triceps are disproportionately involved compared to the deltoid and forearm flexors. Weakness of the tibialis anterior results in footdrop. Paraspinal and abdominal muscle weakness leads to lordosis and a protuberant abdomen (FIGURE 7-3E). The umbilicus moves rostrally when the individual attempts to sit up, in what is called the Beevor sign (FIGURE 7-3F). Eventually, muscles including the forearm flexors and extensors and knee flexors and extensors may become weak. Weakness and wasting are frequently asymmetric.

Associated Symptoms

Up to one-third of patients with FSHD who are nonambulatory have respiratory involvement.[18] The greatest impairment is found in those who are wheelchair dependent and have kyphoscoliosis.[18] Early manifestations include nocturnal hypoventilation. Respiratory insufficiency requiring ventilator support is rare.[19]

Cardiomyopathy is not associated with FSHD. Various studies have suggested that conduction defects or arrhythmias are more prevalent in FSHD than the general population.[20–22] In one study, incomplete right bundle-branch block was found in one-third of patients, but no progression was observed during 8 years of follow-up.[22]

FSHD1 is associated with a retinal vasculopathy. In one study, half of all patients with FSHD had mild retinal abnormalities such as telangiectasias or microaneurysms.[23] In its severe form, this vasculopathy can mimic Coats disease with neovascularization, retinal detachment, and neovascular glaucoma. Severe retinal vasculopathy is a rare finding in FSHD (0.8% of the population) and is most frequently associated with early-onset FSHD with large 4q35 deletions.[24]

Hearing loss has been considered an associated symptom of FSHD. For typical patients with FSHD, hearing loss was not found to be more common than in

KEY POINTS

- **Both facioscapulohumeral muscular dystrophy types 1 and 2 are due to hypomethylation of the subteleomeric region of chromosome 4q, leading to aberrant expression of a normally silent transcription factor DUX4.**
- **Facioscapulohumeral muscular dystrophy presents with asymmetric weakness of the orbicularis oculi, orbicularis oris, rhomboids, serratus anterior, biceps, triceps, paraspinals, rectus abdominis, and tibialis anterior. Eventually, other muscles of the arms and legs may become involved.**

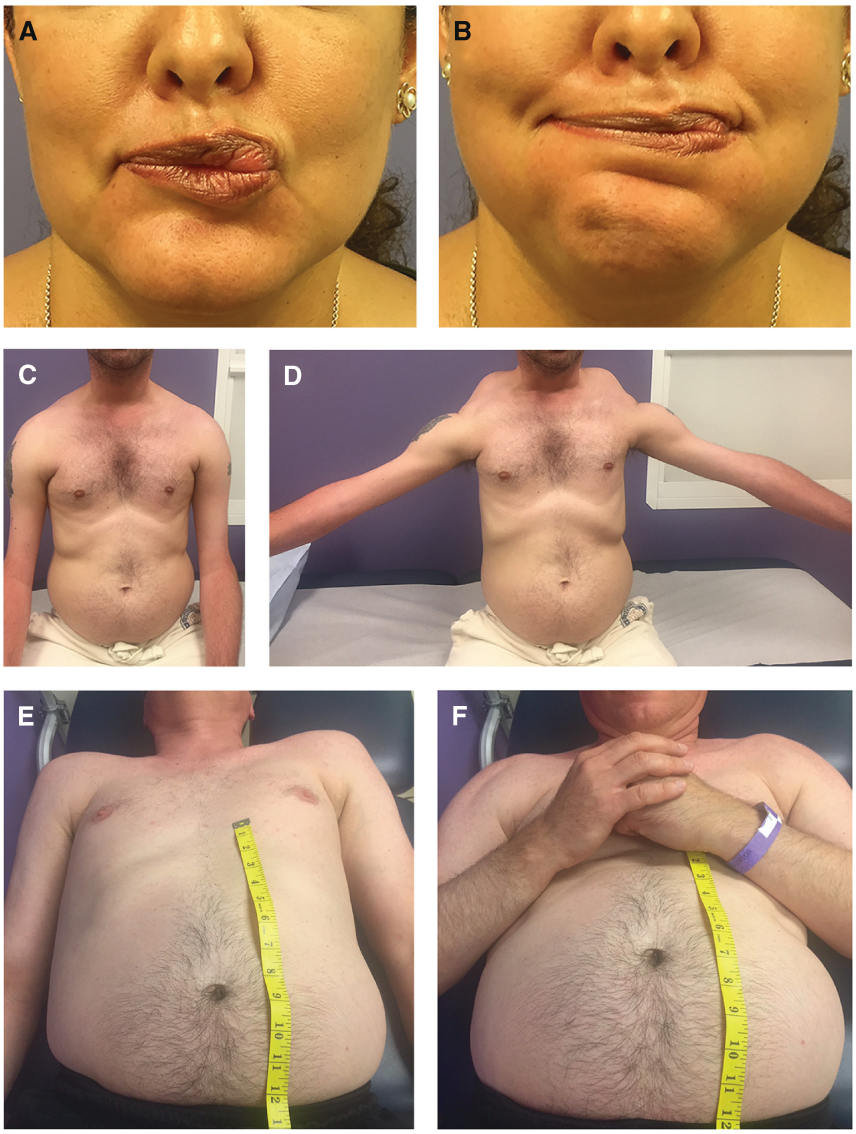

FIGURE 7-3

The facioscapulohumeral muscular dystrophy phenotype. *A*, Asymmetry of mouth when attempting to pucker. *B*, An inability to puff out the cheeks with air. *C*, Sloped shoulders, horizontal clavicles, prominent axially creases, and biceps atrophy. *D*, Poly-hill sign when attempting to abduct the arms caused by elevation of the scapula. *E*, Protuberant abdomen caused by rectus abdominis muscle weakness. *F*, Beevor sign of the umbilicus moving rostrally when the patient attempts to sit up.

patients without FSHD.[25,26] Similar to retinal vasculopathy, high-frequency hearing loss is most common in those with large 4q35 deletions.[27]

Musculoskeletal pain is a frequent manifestation of FSHD. In a recent study, 88.6% of patients with FSHD reported pain at the time of the study,[28] most frequently in the shoulders and lower back. Chronic pain in FSHD impairs quality of life and should be addressed by treating physicians.

Diagnostic Evaluation

The clinical presentation of FSHD is distinct from most other neuromuscular disorders. It should be considered in the setting of eyelid closure weakness

(without ptosis), scapular winging, and asymmetric limb weakness without contractures. It sometimes can be confused for limb-girdle muscular dystrophy (especially calpainopathy with associated scapular winging), Pompe disease, inclusion body myositis, or polymyositis (CASE 7-2). Creatine kinase levels will be normal to mildly elevated.

EMG plays little role in the diagnosis of FSHD. EMG will show nonspecific myopathic features (small, polyphasic motor units) and occasional irritability (fibrillations and positive sharp waves). Similarly, muscle biopsy is rarely indicated in the diagnosis of FSHD. Muscle biopsies are marked by nonspecific myopathic features of variation in fiber size, internalized nuclei, rare necrotic

CASE 7-1

A 7-year-old boy was brought into clinic by his parents because of episodes of tripping and falling. He was born healthy at full term. However, his mother noted that he had a poor suck as an infant and always slept with his eyes partly open. He met his motor milestones on time but walked on his tip toes. He had difficulty blowing out his birthday candles and could not whistle. He never learned to do a sit-up. He had high-frequency hearing loss and a speech impediment for which he was receiving speech therapy. His mother had a diagnosis of facioscapulohumeral muscular dystrophy (FSHD) but had onset in her late teenage years and was still walking in her forties.

On examination, he was significantly underweight for his height. He could not fully close his eyes or puff out his cheeks. He had wasting of the pectoralis, shoulder girdle, and biceps muscles, and had a pectus excavatum. The deltoid muscle was relatively preserved. A poly-hill sign was noted when he attempted to abduct his arms, and he had profound scapular winging. He could only raise his arms over his head by throwing them up in the air. He had fair strength in his lower arms, hip girdle, and knee extensors but had left greater than right weakness of his knee flexors and dorsiflexors. He walked with prominent lumbar lordosis and a steppage gait.

Genetic testing identified a short 4qA35 fragment size of 11 kilobases (kb) (approximately 2 repeats) consistent with a diagnosis of FSHD type 1.

COMMENT

This case is an example of early-onset FSHD. Early-onset FSHD is defined as signs or symptoms of facial weakness before the age of 5 and signs or symptoms of scapular weakness before the age of 10.[16] Early-onset FSHD is estimated to occur in 10% of all cases of FSHD and is associated with the smallest number of residual D4Z4 repeats (typically 1 to 3). It has a more severe phenotype than classic FSHD, with 40% of patients becoming wheelchair dependent during childhood.[17] It is also associated with higher rates of high-frequency hearing loss (40%), such as in this child, and retinal abnormalities (37%).[17] This case is also an example of the phenotypic heterogeneity seen within families and the observation that within families males are often more severely affected than females.

and atrophied fibers, and, in up to one-third of cases, endomysial inflammation with CD4 or CD8 cells.[29] Biopsies from more severely affected muscles are marked by fibrosis and fatty infiltration.

Genetic testing for FSHD is commercially available and is sensitive and specific. The most common protocol is to assess first for a contraction of the 4q35 subtelomeric region through pulsed field electrophoresis followed by Southern blotting of various restriction fragments that distinguish a D4Z4 contraction on chromosome 4 from a homologous (and nonpathogenic) region on chromosome 10. This is then followed by haplotype testing. Healthy individuals have a restriction fragment greater than 38 kb, and patients with FSHD1 have an allele size of approximately 10 kb to 38 kb (corresponding to 1 to 10 D4Z4 repeats) in the setting of the A haplotype. If a 4qA contraction is not identified, then the methylation status of the 4q35 subtelomeric region is

CASE 7-2

A 61-year-old woman presented for evaluation of slowly progressive weakness. As a child she was not a good athlete but did learn to ride a bike and whistle. She had normal strength until 5 years prior to presentation, when she noticed an inability to lift her head from her pillow. She was evaluated by a rheumatologist and had a muscle biopsy that showed primary inflammation around non-necrotic fibers and muscle fiber atrophy. She was given the working diagnosis of polymyositis and treated with corticosteroids, methotrexate, and mycophenolate mofetil without benefit.

On presentation to neurology, she had wide open eyes with sclera underneath her iris visible; however, she was able to fully close her eyes. She was unable to puff out her cheeks with air and was unable to whistle. On motor examination, her muscle bulk was decreased both proximally and distally. She had prominently sloped shoulders and mild scapular winging. She was unable to abduct her arms to 90 degrees. Strength testing revealed asymmetric left greater than right weakness of the elbow flexors and extensors, hip flexors, knee flexors and extensors, and foot dorsiflexors. She had a positive Beevor sign. Her gait was marked by lordosis, waddle, and mild footdrop.

Genetic testing identified a short 4qA35 fragment size of 27 kilobases (kb) (approximately 7 repeats) consistent with a diagnosis of facioscapulohumeral muscular dystrophy type 1 (FSHD1).

COMMENT

The differential for FSHD includes limb-girdle muscular dystrophy (especially limb-girdle muscular dystrophy type 2A due to calpain mutations, which is also marked by scapular winging), Pompe disease, mitochondrial myopathy, and polymyositis. This case was complicated by the presence of primary inflammation on muscle biopsy, which can be seen in as many as one-third of FSHD cases.[29] The lack of response to immunosuppression as well as facial, distal, and asymmetric weakness suggested that the diagnosis was in fact FSHD.

assessed. Very low methylation (less than 20%) in the setting of the A haplotype is sufficient to yield a diagnosis of FSHD2. Most of these cases will be due to mutations in *SMCHD1*, which is the final gene to be assessed.

CURRENT THERAPY

While no drugs have been approved to increase muscle mass and strength in patients with FSHD, several actions can be taken to reduce morbidity. The American Academy of Neurology (AAN) provided recommendations on the current treatment of FSHD based on a systematic review of the evidence.[30] These recommendations, plus some additional recommendations for exercise and bone health, are summarized in the following sections.

Vision and Hearing

All newly diagnosed patients with FSHD should have a dilated eye examination to look for evidence of reversible retinal vascular disease. Since retinal disease is almost exclusively found in those with large deletions in chromosome 4q (eg, allele sizes of 10 kb to 20 kb), it is recommended that these patients be referred to a retina specialist.[30] Hearing loss is also associated with large deletions. All patients with early-onset FSHD should be screened for hearing loss prior to starting school.[30] Adults should be tested if they are symptomatic.

Pulmonary

All patients with FSHD should have pulmonary function testing at baseline. Pulmonary function testing should be performed annually in patients with severe proximal weakness, kyphoscoliosis, wheelchair dependence, or comorbid conditions that may affect ventilation.[30] Patients should be referred to a sleep medicine specialist for evaluation of possible nocturnal noninvasive ventilator support if the forced vital capacity is less than 60% or if the patient has excessive daytime somnolence, frequent nocturnal arousals, or morning headaches.[30]

Pain Management

All patients with FSHD should be questioned regarding their level of pain. Physical therapy, nonsteroidal antiinflammatory medications, and antidepressants such as duloxetine may be helpful in reducing chronic pain.

Surgical Scapular Fixation

Surgical fixation of the scapula to the rib cage can be helpful in reducing scapular winging, improving pain, and facilitating arm abduction to 90 degrees. The patient has to have sufficient deltoid strength to profit from the procedure. To determine if a patient might benefit from scapular fixation, an improvement in shoulder range of motion is sought from fixing the scapula manually in a simple bedside maneuver. Surgical scapular fixation is an extensive procedure and should be undertaken only in specific patients with preserved deltoid strength. The surgeon should be familiar with FSHD and be experienced with scapular fixations. Side effects may include pain, hemothorax, pneumothorax, infection, and reduced lung capacity. Some restriction of movement may also occur as the patient will no longer be able to throw the arm up overhead for 180-degree abduction.

KEY POINTS

- Facioscapulohumeral muscular dystrophy has few associated signs and symptoms. In those with large deletions, an increased risk of retinal vasculopathy and hearing loss is present.
- The diagnosis of facioscapulohumeral muscular dystrophy rests on the recognition of the clinical phenotype and genetic testing. Creatine kinase is normal to mildly elevated, and EMG and muscle biopsy are nonspecific and not indicated.
- Patients with large deletions in chromosome 4q should be seen by a retina specialist and have a hearing examination.
- Surgical scapular fixation is an extensive procedure and should be undertaken only in specific patients with preserved deltoid strength and should be carried out by experienced surgeons.

Bracing

Footdrop and tripping can be significantly alleviated with ankle-foot orthosis. The gait and dorsiflexion strength of all patients with FSHD should be assessed, with bracing recommended in the setting of footdrop.

Exercise

The AAN recommends that patients with FSHD engage in low-intensity aerobic exercise[30] to reduce muscle atrophy and increase bone density at a minimum and to decrease fatigue and increase strength, as has been observed in some studies. A cycling program of 30 minutes a day, 3 times a week, is a reasonable exercise routine.[31–33]

Bone Health

Bone health is important to prevent morbidity. Low bone density can lead to fractures and impaired mobility. In a study of bone health in patients with FSHD, one-third had low vitamin D_3 levels.[34] All patients with FSHD should have their vitamin D_3 level checked and supplemented as needed to yield vitamin D_3 in the normal range. Dietary calcium intake should be calculated and supplemented to reach the recommended dietary allowance (1000 mg/d to 1200 mg/d for most adults). Bone loss is exacerbated with weakness and loss of ambulation.[34] Dual energy x-ray absorptiometry scans should be performed annually in those who display significant weakness, fall frequently, or are wheelchair dependent.

CLINICAL OUTCOME ASSESSMENTS

To date, relatively few clinical trials studying FSHD have been conducted. However, as the pathophysiology of the disorder has been elucidated, disease-specific therapies directed at DUX4 toxicity are being developed. As the field prepares for new clinical trials in FSHD, the need for reliable, valid, and responsive clinical outcome assessments has become apparent.

Magnetic Resonance Imaging

There is an increasing use of MRI in the diagnosis and management of acquired myopathies. Standard MRI sequences can identify regions of healthy muscle, acute intramuscular inflammation, and infiltration of fat and fibrosis. Patterns of muscle involvement can be recognized to differentiate the various genetic myopathies. Although a distinctive pattern of muscle involvement occurs, MRI is not used in the diagnosis of FSHD because of the superior specificity of genetic diagnosis. Instead, MRI has the potential to be a powerful clinical outcome measure. It is noninvasive and nonirradiating and is independent of daily clinical variations in symptoms, patients' effort, and learning effects. MRI can be performed in most patients irrespective of disease severity, unlike some muscle function tests that cannot be performed in individuals who are severely affected. In addition to volumetric measurements of muscle mass, MRI can measure fatty infiltration of muscle on T1-weighted images. It can also measure intramuscular edema or inflammation by hyperintensity of short tau inversion recovery (STIR) images.

Whole-body MRI provides important information on the selectivity of muscle involvement (FIGURE 7-2).[15] T1-weighted images are scored for the degree of intramuscular fat infiltration. Interestingly, a hamstring muscle, the semimembranosus, is the most frequently and severely affected muscle

in patients with FSHD.[15,35–37] Along with the rectus abdominis, the semimembranosus is affected more than 70% of the time, the paraspinal and serratus anterior muscles are affected 60% to 70% of the time, and the gluteus minimus, latissimus dorsi, adductors, and trapezius are affected 50% to 60% of the time.[38] Spared muscles include the tibialis posterior, peroneus, iliopsoas, and iliacus.[38] Asymmetry in muscle involvement is common. Patients who are asymptomatic may have substantial muscle involvement on MRI.[15,39]

Longitudinal studies confirm that FSHD is a slowly progressive disorder, with most patients not showing progression of fatty infiltration over 6.9 to 13.8 months of follow-up.[40] Areas of hyperintensity on STIR sequences suggest another pathologic stage prior to the end-stage T1-weighted hyperintensity. Biopsy of STIR hyperintense areas revealed active inflammatory cell infiltration.[39,41] It has been suggested that the inflammation of STIR positivity precedes the fatty replacement of T1-weighted hyperintensity,[42] although a recent study suggests the progression is more complex.[40] A model that correlates with many patients' subjective experience is that of long periods of stability interspersed with acute onset of inflammation and rapid progression to fatty infiltration. If this model is correct, then STIR hyperintense muscles might be ones to direct therapies to prior to end-stage irreversible fatty replacement.

For MRI to be a good biomarker of disease activity, it is important that it is correlated to muscle function. Indeed, several cross-sectional studies have shown that the degree of fatty infiltration correlates with muscle strength and function.[15,37,43,44] Longitudinal studies suggest that quantitative MRI is more sensitive to change than most conventional muscle tests. Over the course of 1 year, clinical scores did not change significantly, while fat infiltration could be measured to increase significantly.[45,46]

Muscle Strength

Strength can be measured by manual muscle testing, which is scored according to the Medical Research Council scale or by maximum voluntary isometric contraction testing through handheld or fixed dynamometry. In a natural history study assaying strength every 6 months for 3 years, strength by composite maximum voluntary isometric contraction testing and manual muscle testing were found to be decreased over the course of 1 year.[47] The mean change in maximum voluntary isometric contraction testing was –0.29 and in manual muscle testing was –0.07.[47] From the maximum voluntary isometric contraction testing and manual muscle testing variance, it was estimated that a sample size of 160 patients per arm would be needed to have 80% power to detect stabilization of the disease over 1 year.[47] This calculation is complicated by the fact that those in clinical trials (with albuterol and the antimyostatin drug MYO-029) had an increase in their strength at 6 months regardless of taking the drug or placebo,[48] which underscores the importance of a placebo arm in FSHD trials.

Six-Minute Walk Test

The 6-minute walk test measures both strength and endurance. Originating in cardiopulmonary trials, it has subsequently been used as an outcome measure in a variety of neuromuscular diseases including spinal muscular atrophy, Duchenne muscular dystrophy (DMD), inclusion body myositis, and Pompe disease.[49–52] It was the primary outcome measure for approval of alglucosidase

KEY POINTS

- Bone health is important to prevent morbidity. Vitamin D_3 levels should be checked in all patients with facioscapulohumeral muscular dystrophy and supplemented as needed. For those with significant weakness, bone density should be followed by annual dual energy x-ray absorptiometry scans.
- The rectus abdominis and semimembranosus are among the most severely affected muscles in patients with facioscapulohumeral muscular dystrophy, as noted on MRI.
- On imaging, muscle affected by facioscapulohumeral muscular dystrophy may follow a pathologic progression from normal signal intensity to short tau inversion recovery hyperintensity to T1-weighted hyperintensity.

alfa for adult-onset Pompe disease and of eteplirsen for DMD.[52,53] In a study from two centers, the mean results of the 6-minute walk test in ambulatory patients with FSHD was 404.3 meters, clearly impaired from the mean of 571 meters in the healthy population.[54,55] The minimal detectable change, or magnitude of change in which one could be 95% certain that the change exceeds measurement error, was 34.3 meters.[55] The test-retest reliability was excellent with an intraclass correlation coefficient of 0.99.[55] There was a moderate to strong relationship to other measures of muscle strength and function.[55] Comparing the first 2 minutes to the last 2 minutes of the test showed that fatigue was not a major factor in the population as a whole, but for those who walked less than the mean, a statistically significant difference was found between the first and last 2 minutes of the test.[55] Clinical trials that wish to examine both strength and fatigue may need to include only participants who had a 6-minute walk test of less than 400 meters. Longitudinal data are now needed to determine how sensitive the 6-minute walk test is to change over time.

Reachable Workspace

To focus on shoulder girdle weakness, one of the primary impairments of FSHD, an outcome measure evaluating the area through which an individual can move one's arms (or reachable workspace) was developed.[56] The test makes use of a markerless, three-dimensional vision-based sensor system.[56] Normalization of reachable workspace by each individual's arm length allows for comparison between different height/arm lengths.[56] Reachable workspace can discriminate between FSHD and normal controls and between different degrees of disease severity when compared to the FSHD clinical score of Lamperti and colleagues.[57] Quantitative upper extremity strength (maximum voluntary isometric contraction testing of elbow flexion and shoulder abduction) is correlated with reachable workspace.[58] The reachable workspace outcome measure is expected to have a good correlation to activities of daily living such as getting a dish out of a cabinet or brushing one's hair. As with the 6-minute walk test, it will be important to determine how sensitive this measure is to change over time.

Facioscapulohumeral Muscular Dystrophy Composite Outcome Measure

To provide a more comprehensive measure of function throughout the body, the FSHD Composite Outcome Measure was developed. This is an 18-item evaluator-administered instrument where each item is rated on a scale from 0 (unaffected) to 4 (severely impaired/unable to complete). The outcome measure tests areas identified by patients to be of importance including leg function, shoulder and arm function, trunk function, hand strength, and balance/mobility. The FSHD Composite Outcome Measure showed excellent test-retest reliability with an intraclass correlation coefficient of 0.96. There was moderate to strong cross-sectional association to disease severity, disease duration, and muscle strength. The FSHD Composite Outcome Measure is one of two primary outcome measures (along with electrical impedance myography) in an ongoing multicenter, prospective, 18-month natural history study of 160 patients.[59]

Electrical Impedance Myography

Electrical impedance myography is a noninvasive technique that measures muscle composition. Similar to MRI, it does not require patient effort, is

independent of learning, and is resistant to the placebo effect. It has been used as an outcome measure in other neuromuscular diseases such as amyotrophic lateral sclerosis and DMD. Multifrequency, low-intensity, alternating electrical currents pass through various muscles from electrodes applied to the skin, from which impedance is measured. Muscle and fat have different impedance to current flow. Studies in FSHD have shown good reliability for trunk, arm, and leg muscles with intraclass correlation coefficients between 0.89 and 0.98.[60] Facial muscle reliability was less.[60] Fifty kHz reactance showed moderate to strong correlations with other FSHD disease measures such as the strength, time to ascend four stairs, and the 6-minute walk test.[60] Unfortunately, the electrical impedance myography was not found to be very responsive to change, with no change observable over a 1-year period.[61]

Facioscapulohumeral Muscular Dystrophy Health Index

The FSHD Health Index was developed in response to the 2009 US Food and Drug Administration (FDA) guidelines encouraging industry use of patient-reported outcome measures to gauge treatment benefit or risk in clinical trials.[62] The FSHD Health Index is an FSHD-specific patient-reported outcome measure composed of 116 items developed from qualitative interviews of patients followed by a cross-sectional validation study.[63,64] Fourteen subscales measure the patient's perception of ambulation and mobility, hand function, shoulder and arm function, emotional health, back/chest/abdomen strength, fatigue, pain, eating function, ability to do activities, communication ability, satisfaction in social situations, performance in social situations, body image, and cognition.[64] Test-retest reliability in 22 subjects was excellent (intraclass correlation coefficient of 0.945).[64] Test of responsiveness is still ongoing, but the FSHD Health Index appears to be capable of measuring small increments in disease burden over a 6- to 12-month period.[64]

The field of FSHD research is developing a number of clinical outcome measures and assessment tools. One of the challenges in the field is that no universally accepted outcome measure exists for trials in FSHD. What is desired from any outcome measure is reliability, concordant validity, and responsiveness. Most FSHD clinical outcome assessments have shown excellent reliability. Many are validated or in the process of being validated by an ongoing natural history study.[59] Next for the field is to show that these outcome measures are responsive over the course of a typical 6-month or 1-year clinical trial.

CLINICAL TRIALS

Previous clinical trials of repurposed or novel therapeutics in FSHD were mostly underpowered with disappointing results. However, with the recent understanding of the pathophysiology of FSHD, several promising drugs directly targeting DUX4 are in development.

Past

Initial trials in FSHD were pilot open-label trials. Given the beneficial effects of corticosteroids in DMD, a trial of 1.5 mg/kg/d prednisone was trialed in eight subjects.[65] No improvement in strength was seen by 12 weeks.[65] Hypothesizing that calcium dysregulation leads to cell death in FSHD, researchers conducted a pilot study of the calcium channel blocker diltiazem in 20 subjects.[66] No improvement in muscle mass, strength, or function were found at 24 weeks.[66]

Given the natural history of FSHD, it is now appreciated that these early trials were underpowered to detect anything other than a large increase in strength or function. Therefore, it remains an open question whether immune modulation in particular would benefit patients with FSHD.

β_2-Adrenergic agonists exert an anabolic effect on normal muscle and in settings of muscle wasting.[67] To determine if albuterol would lead to increased muscle mass and strength in patients with FSHD, a randomized, double-blind, placebo-controlled trial of 8 mg or 16 mg 2 times a day was conducted.[68] After 1 year, the high-dose group showed an increase in lean body mass by dual energy x-ray absorptiometry.[68] No improvement was noted in composite quantitative muscle testing or manual muscle testing scores, although a significant increase in grip strength was noted at 1 year.[68] A randomized, double-blind, placebo-controlled trial paired strength training of elbow flexors and ankle dorsiflexors for the first 26 weeks followed by the addition of 8 mg 2 times a day albuterol versus placebo.[69] Muscle volume by stereologic CT was similarly increased in subjects treated with albuterol.[69] Elbow flexion as well as strength in several untrained muscles increased while strength in foot dorsiflexors did not.[69] Hypothesizing that desensitization of the β_2-adrenergic receptors might be blunting a response, a randomized, double-blind, placebo-controlled trial was conducted with periodic 8 mg 2 times a day albuterol of 3 weeks on and 1 week off for 6 months.[70] Unfortunately, no significant change was noted in quantitative muscle testing, manual muscle testing, or timed motor test.[70] In summary, although β_2-adrenergic agonists are associated with increased muscle mass, insufficient evidence supports that this translates to increased strength in patients with FSHD.

Myostatin is a member of the transforming growth factor beta superfamily and a negative regulator of muscle growth.[71] Inhibition of myostatin leads to increased muscle mass as well as decreased fibrosis in animal models of muscular dystrophy.[72–76] MYO-029 is a neutralizing antibody to myostatin that was trialed in 116 adult subjects with muscular dystrophy, approximately one-third of whom had FSHD.[77] In this randomized, double-blind, placebo-controlled dose escalation trial, this agent had a good safety and tolerability profile with the exception of cutaneous hypersensitivity that limited dose escalation.[77] At 6 months, no increase in muscle strength or function was found.[77] Increased lean body mass was found in some dosing cohorts by dual energy x-ray absorptiometry but not by MRI.[77] Again, this study was underpowered to detect a change in strength or function in the FSHD cohort. Newer-generation myostatin inhibitors with higher binding affinity are currently in clinical trials.

A broader transforming growth factor beta inhibitor has recently been trialed that targets myostatin and activins. ACE-083 is a recombinant fusion protein consisting of the modified form of human follistatin linked to the human immunoglobulin Fc domain. In postmenopausal women, IM injection of ACE-083 led to an increase in muscle volumes of the rectus femoris and tibialis anterior by 14.5% and 8.9%, respectively.[78] In an open-label study in patients with FSHD, subjects received ACE-083 injected into the tibialis anterior or biceps every 3 weeks for a total of 5 doses.[79] There was an increased muscle mass of 6.7% and a decreased fat fraction of –4.8% over time compared with –0.5% and –0.8%, respectively, in the contralateral untreated muscle.[79] Unfortunately, a randomized, double-blind, placebo-controlled phase 2 trial of ACE-083 in FSHD showed statistically significant increases in mean total muscle volume but failed to translate to statistically significant improvements in functional tests.[80]

One of the consequences of DUX4 expression appears to be increased oxidative stress.[81] Antioxidants have the potential to reduce reactive oxygen species and oxidative stress. In a trial of vitamin C, vitamin E, zinc gluconate, and selenomethionine, subjects were randomly assigned in a double-blind trial to receive either antioxidants or placebo.[82] The results of the 2-minute walk test did not differ between groups.[82] However, the maximum voluntary contraction and the endurance of the quadriceps were significantly improved in antioxidant-treated versus placebo-treated individuals.[82] These study results from 53 subjects warrant a larger study evaluating function in the setting of antioxidants.

Muscle from patients with FSHD frequently displays lymphocytic infiltration on muscle biopsy and STIR hyperintensity correlating with inflammation on MRI.[29,39,41] ATR1940 is a physiocrine (physiologically active cytokine) that modulates immune responses to muscles preclinically.[83] A randomized, double-blind, placebo-controlled, multiple ascending dose study was conducted in participants with FSHD with STIR hyperintensity and minimal fatty infiltration on lower extremity muscle MRI.[83] No differences in MRI findings and manual muscle testing were found between groups.[83] The study did find an improvement in all dosing cohorts compared to baseline in the Individualized Neuromuscular Quality of Life Questionnaire and at the highest dose an improvement in the Individualized Neuromuscular Quality of Life Questionnaire compared to placebo.[83] At the time of this article's publication, additional clinical development of ATR1940 is not being pursued without a significant collaboration or strategic partnership.

Several studies have described potential benefits to exercise in patients with FSHD. Bankolé and colleagues[32] randomly assigned patients with FSHD to combined aerobic and interval training versus no treatment for 24 weeks. They reported improvement in peak oxygen uptake (VO_2 peak), maximal aerobic power, quadriceps strength, and the 6-minute walk test.[32] Andersen and colleagues[31] randomly assigned participants to aerobic exercise plus protein supplement, exercise plus placebo, or no treatment for 12 weeks. Improved fitness (VO_2 max), workload (Wmax), 6-minute walk test, and self-assessed health and physical capacity were reported.[31] No additional benefits were found from protein supplementation.[31] Voet and colleagues[33] randomly assigned participants to aerobic exercise, cognitive-behavioral therapy, or no treatment for 16 weeks and reported reduced chronic fatigue and increased physical activity by an actometer in subjects receiving exercise or cognitive-behavioral therapy. No improvement was appreciated in aerobic capacity, quadriceps strength, or distance walked.[33] All three studies used cycling as the form of exercise but with different regimens. It is possible that variability in the findings of these studies can be ascribed to the various exercise regimens. In any event, it appears that exercise does not harm FSHD muscle and potentially provides some benefits.

Future

With the understanding that DUX4 is the major trigger of FSHD, the field is now poised to develop therapies specific to the pathophysiology of FSHD. Therapies targeting DUX4 with antisense oligonucleotides, gene therapy, and small molecules are currently being developed.

Antisense oligonucleotides are short fragments of nucleic acid. They are complementary to specific messenger RNAs and inhibit their expression. The

KEY POINTS

- **β_2-Adrenergic agonists have been trialed in patients with facioscapulohumeral muscular dystrophy, and while they show increased muscle mass, they have had mixed results in showing increased strength.**
- **Aerobic exercise in the form of cycling has shown mixed results with some improvement in fitness and strength observed in patients with facioscapulohumeral muscular dystrophy.**
- **Future therapies for patients with facioscapulohumeral muscular dystrophy include antisense oligonucleotides, gene therapy, and small molecules all targeting DUX4.**

backbone of the oligonucleotide can be altered to make the molecule more stable or have more cell-penetrating abilities. Phosphorodiamidate morpholinos are antisense oligonucleotides in which the deoxyribose moiety is replaced by a morpholine ring and the charged phosphodiester intersubunit linkage is replaced by an uncharged phosphorodiamidate linkage. Phosphorodiamidate morpholinos have been directed against DUX4 in in vitro and in vivo studies. In FSHD muscle cell cultures and in mice engrafted with FSHD tissue, phosphorodiamidate morpholinos downregulated DUX4 and DUX4 target genes without off-target effects. Particularly effective were phosphorodiamidate morpholinos directed to the polyadenylation region of DUX4.[84,85] While phosphorodiamidate morpholinos have good stability, they have poor cell-penetrating ability. This is particularly an issue with FSHD muscle that does not have the same degree of membrane fragility as is seen in DMD. Delivery of antisense oligonucleotides with greater cell-penetrating abilities, such as with peptide-conjugated phosphorodiamidate morpholinos or through exosomes is needed to overcome this hurdle.

MicroRNAs are naturally occurring, small, noncoding RNAs that are present in the genomes of all eukaryotic organisms, ranging from single-celled algae to humans. MicroRNAs function to silence expression of other genes in a sequence-specific fashion through a process called RNA interference. Importantly, natural microRNAs can be modified and redirected to target disease genes. These designed microRNAs, often called artificial microRNAs or microRNA shuttles, can be engineered in a laboratory and packaged within adeno-associated viral vectors for use in preclinical and clinical gene therapy studies. Several adeno-associated viral vector serotypes have high tropism for muscle and can deliver therapeutic gene products via IM injection or to virtually the entire musculature of a mouse, large animal model, or human following a single systemic administration. For FSHD, artificial microRNAs (miDUX4) were designed to silence the toxic *DUX4* gene and delivered to mouse muscles expressing DUX4. In a proof-of-concept study, adeno-associated viral vector–miDUX4 reduced DUX4 protein levels and protected adeno-associated viral vector–DUX4 mice from muscle pathology and grip strength deficits.[86] In a follow-up toxicology study, high doses of a lead miDUX4 sequence were shown to be safe when delivered via IM or IV routes of administration.[87] These results are encouraging to the future development of gene therapy for FSHD.

Several groups have been able to take advantage of pharmacologic screens of chemical libraries that repress DUX4 downstream targets, either through inhibiting DUX4 expression or inhibiting DUX4 activity. Campbell and colleagues[88] identified inhibitors of the bromodomain and extraterminal family of proteins and agonists of the β_2-adrenergic receptor that suppress expression of DUX4 messenger RNA. Two companies have identified compounds through screens with DUX4 producing cells and now have drugs in development. These compounds are entering early phase clinical trials and will directly address the primary pathophysiology of FSHD.

CONCLUSION

FSHD is one of the most common muscular dystrophies. It has a wide range of severity but is marked by face, shoulder girdle, arm, trunk, and leg weakness.

The pathophysiology of the disorder is becoming elucidated as dependent on the aberrant expression of the transcription factor DUX4 and its multiple downstream targets. In parallel, clinical outcome measures are being developed so the field is well poised to conduct successful clinical trials in FSHD. Although past trials in FSHD have been largely disappointing, the future looks promising with several strategies directly targeting DUX4 activity. The hope is that these new trials will bring novel therapies to the clinic, resulting in meaningful change in the lives of those with FSHD.

USEFUL WEBSITES

FRIENDS OF FSH RESEARCH
The Friends of FSH Research website provides information and news about facioscapulohumeral muscular dystrophy and lists research and grant opportunities.
fshfriends.org

FSHD GLOBAL RESEARCH FOUNDATION LTD
The FSHD Global Research Foundation Ltd website offers information about research and grant opportunities for researchers as well as information on living with facioscapulohumeral muscular dystrophy and finding care for patients and families.
fshdglobal.org

FSHD SOCIETY
The FSHD Society is a research-focused organization for facioscapulohumeral muscular dystrophy that provides resources for researchers and patients.
fshsociety.org

MUSCULAR DYSTROPHY ASSOCIATION
The Muscular Dystrophy Association website offers patients, caregivers, and researchers information about patient care, family support, and scientific breakthroughs related to neuromuscular disease.
mda.org

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