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Facioscapulohumeral Muscular Dystrophy

Synonym: FSH Muscular Dystrophy

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Summary

Clinical characteristics

Facioscapulohumeral muscular dystrophy (FSHD) typically presents with weakness of the facial muscles, the stabilizers of the scapula, or the dorsiflexors of the foot. Severity is highly variable. Weakness is slowly progressive and approximately 20% of affected individuals eventually require a wheelchair. Life expectancy is not shortened.

Diagnosis/testing

The diagnosis of FSHD1 is established in a proband with characteristic clinical features by identification of a heterozygous pathogenic contraction of the D4Z4 repeat array in the subtelomeric region of chromosome 4q35 on a chromosome 4 permissive haplotype. The diagnosis of FSHD2 is established in a proband by identification of hypomethylation of the D4Z4 repeat array in the subtelomeric region of chromosome 4q35 on a chromosome 4 permissive haplotype. Hypomethylation of the D4Z4 repeat array can be the result of a heterozygous pathogenic variant in *SMCHD1* or *DNMT3B*.

Management

Treatment of manifestations: Consultation with a physical therapist to establish appropriate exercise regimen; ankle/foot orthoses to improve mobility and prevent falls; occupational and speech therapy in individuals with infantile onset; surgical fixation of the scapula to the chest wall may improve range of motion of the arms over the short term; management of chronic pain by physical therapy and medication; monitoring respiratory function; lubricants to prevent drying of the sclera or taping the eyes shut during sleep to treat exposure keratitis; treatment for retinal vasculopathy as per ophthalmologist; standard treatment of sensorineural hearing loss.

Surveillance: Annual physical therapy assessment; Pain should be assessed at regular visits to the primary care physician or physical therapist; screening for hypoventilation in individuals with abnormal PFTs, severe proximal weakness, kyphoscoliosis, wheelchair dependence, or comorbid disease affecting ventilation;

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pulmonary consultation for FVC <60%, excessive daytime somnolence or nonrestorative sleep, and prior to surgical procedures requiring anesthesia; annual dilated ophthalmoscopy in individuals with early childhood-onset FSHD with large pathogenic contraction of D4Z4 and adults with visual symptoms; audiometry in infants at each visit and annually in children.

Genetic counseling

FSHD1 is inherited in an autosomal dominant manner. Approximately 70%-90% of individuals have inherited the disease-causing deletion from a parent, and approximately 10%-30% of affected individuals have FSHD as the result of a *de novo* deletion. Offspring of an affected individual have a 50% chance of inheriting the deletion. Prenatal testing for a pregnancy at increased risk is possible if the D4Z4 pathogenic contraction has been identified in the family. FSHD2 is inherited in a digenic manner.

Diagnosis

Evidence-based guidelines for diagnosis of FSHD are available (see Figure 1) [Tawil et al 2015].

Suggestive Findings

Facioscapulohumeral muscular dystrophy (FSHD) **should be suspected** in individuals with the following:

- Weakness that predominantly involves the facial, scapular stabilizer, or foot dorsiflexor muscles without associated ocular or bulbar muscle weakness. Weakness is often asymmetric.
- Progression of weakness after pregnancy [Ciafaloni et al 2006]
- Prior diagnosis with inflammatory myopathy that was refractory to immunosuppression
- Family history of FSHD

Supportive Findings

Serum concentration of creatine kinase (CK) is normal to elevated in individuals with FSHD and usually does not exceed three to five times the upper limit of the normal range. Serum concentration of CK >1500 IU/L suggests an alternate diagnosis.

EMG can show mild myopathic changes in symptomatic muscles.

Muscle biopsy most often shows nonspecific chronic myopathic changes. Mononuclear inflammatory reaction, typically perivascular, is present in muscle biopsies in up to 40% of individuals with FSHD. Rarely, the inflammatory reaction is intense enough to suggest an inflammatory myopathy. Muscle biopsy is now performed only in individuals in whom FSHD is suspected but not confirmed by molecular genetic testing.

Establishing the Diagnosis

The diagnosis of FSHD **is established** in a proband who has **one of the following** identified on molecular genetic testing (see Table 1; Figure 1):

- **FSHD1** (~95% of FSHD). A heterozygous pathogenic contraction of the D4Z4 repeat array in the subtelomeric region of chromosome 4q35 on the permissive chromosome 4 haplotype
- **FSHD2** (~5% of FSHD). Hypomethylation of the D4Z4 repeat array in the subtelomeric region of chromosome 4q35 on the permissive chromosome 4 haplotype as a result of one of the following:
  - A heterozygous *SMCHD1* pathogenic (or likely pathogenic) variant (<5% of individuals with FSHD; ~85% of individuals with FSHD2) [Lemmers et al 2015]
  - A heterozygous *DNMT3B* pathogenic (or likely pathogenic) variant (3 families reported) [van den Boogaard et al 2016]

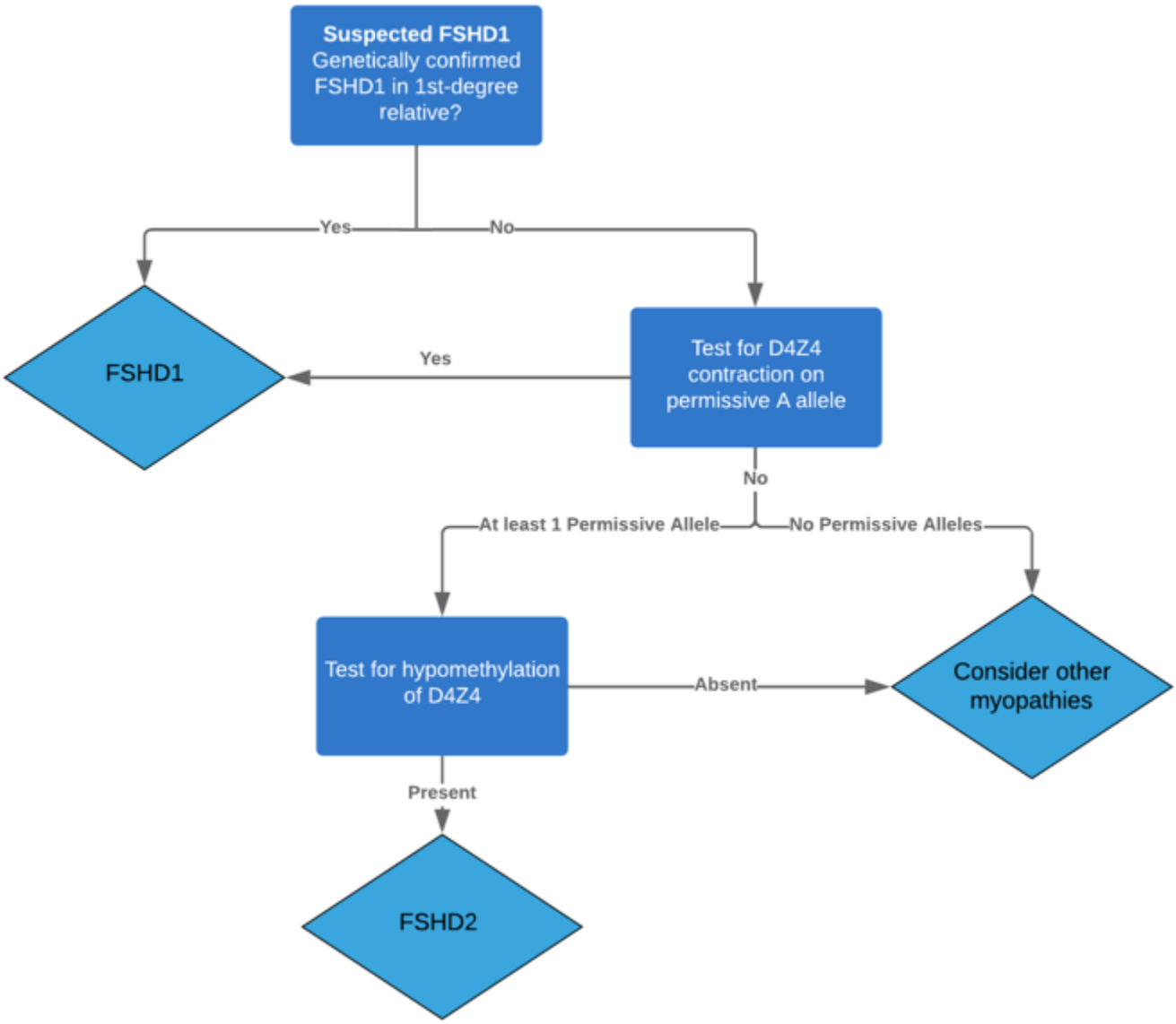

Figure 1. Molecular genetic testing for a heterozygous pathogenic variant in *SMCHD1* or *DNMT3B* can be pursued in individuals with at least one permissive chromosome 4 haplotype (e.g., 4A161, 4A159, 4A168, 4A166H) and hypomethylation of D4Z4.

- Unknown cause of hypomethylation of D4Z4 repeat array at 4q35 (2 families) [Lemmers et al 2012a]

Allele sizes

- **Normal alleles.** A D4Z4 locus with ≥12 repeat units (i.e., fragments of ≥43 kb using EcoRI and the p13E-11 probe), or a D4Z4 locus with any number of repeat units on a non-permissive haplotype
- **Contracted, reduced-penetrance alleles.** A D4Z4 locus that has ten or 11 repeat units AND is on a permissive haplotype
- **Contracted, full-penetrance alleles.** A D4Z4 locus that has ≤9 repeat units AND is on a permissive haplotype

Note: (1) Penetrance of allele sizes is dependent on multiple factors (see Penetrance) and patient-specific manifestations may vary from the categories below. (2) Per ACMG variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both

are considered diagnostic and both can be used for clinical decision making. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants.

Molecular genetic testing approaches can include **targeted analysis** for the repeat size of D4Z4 repeat array in the subtelomeric region of chromosome 4q35 and **haplotype analysis**, **DNA methylation studies**, and **single-gene testing**.

Targeted Analysis and Haplotype Analysis

Targeted analysis. Testing is targeted for the abnormally contracted D4Z4 repeat array in the subtelomeric region of chromosome 4q35. Note: Contraction of an almost identical D4Z4 repeat array at 10q26 is not associated with FSHD (see Molecular Genetics).

Note: Targeted testing is typically done by Southern blotting (Table 1); molecular combing techniques have also been described. Molecular combing has a higher resolution than Southern blotting: in individuals with a normal D4Z4 repeat array by Southern blot testing, molecular combing has been used to identify a short D4Z4 repeat array (5-6 repeat units), which may not be recognized by Southern blot [Lemmers et al 2018]. However, molecular combing may not be clinically available.

Haplotype analysis. Haplotype analysis is recommended concurrently with testing for a D4Z4 contraction to determine if an abnormal allele is present on a permissive or non-permissive haplotype distal to the last D4Z4 repeat (see Molecular Genetics). In individuals with a contracted D4Z4 repeat array (see **Allele sizes**), a permissive haplotype is required to confirm FSHD1.

Examples of chromosome 4q35 permissive (known as 4A or A) and non-permissive (known as 4B or B) haplotypes:

- Permissive: 4A161, 4A159, 4A168, 4A166H
- Non-permissive: 4A166, 4B

Note: The presence of a typical FSHD clinical profile without a contracted repeat but with at least one allele with a permissive haplotype, raises the possibility of FSHD2.

DNA Methylation Studies

In individuals who do not have a contracted D4Z4 repeat array identified and have at least one repeat array with a permissive chromosome 4 haplotype, D4Z4 methylation analysis should be done next. D4Z4 hypomethylation suggests the presence of a heterozygous *SMCHD1* or *DNMT3B* pathogenic variant.

Single-Gene Testing

Sequence analysis of *SMCHD1* and *DNMT3B* should be done in individuals with D4Z4 hypomethylation to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. If no pathogenic variant is found perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.

Table 1. Molecular Genetic Testing Used in Facioscapulohumeral Muscular Dystrophy

Locus/ Gene [1]	Method	Pathogenic Variants/Alterations [2] Detected	Proportion of FSHD-Related Alterations Detected [3]
D4Z4	Targeted analysis for pathogenic variants [4]	Pathogenic contraction of number of D4Z4 repeats [5, 6, 7]	~95%
	Haplotype analysis	Analysis to confirm that the D4Z4 pathogenic contraction occurred on a permissive haplotype [8]	Not applicable
	Methylation analysis	D4Z4 hypomethylation (<25% methylation) [9]	~5%
SMCHD1	Sequence analysis [10]	*SMCHD1* sequence variants	~4% [11]
	Gene-targeted deletion/ duplication analysis [12]	*SMCHD1* deletion/duplication	See footnote 13.
DNMT3B	Sequence analysis [10]	*DNMT3B* sequence variants	3 families [14]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. The ability of the test method used to detect a variant that is present in the indicated gene/locus
4. Molecular genetic testing to determine the length or number of repeat units of the D4Z4 locus has typically relied on Southern blot analysis, typically with a probe (e.g., p13E-11) immediately proximal to D4Z4. Standard DNA diagnostic testing (defined here as linear gel electrophoresis and Southern blot analysis) uses the restriction enzyme *Eco*RI, which recognizes the D4Z4 locus on chromosomes 4 and 10. Pulsed-field gel electrophoresis and Southern blot analysis requires *Eco*RI/*Hin*dIII double digestion for a better resolution of DNA fragments between 20 and 50 kb. An *Eco*RI/*Bln*I double digestion further fragments the chromosome 10 array, allowing one to distinguish D4Z4 arrays located on chromosome 4 from the similar benign arrays on chromosome 10. Molecular combing, which has a higher resolution than Southern blotting [Nguyen et al 2017, Lemmers et al 2018, Nguyen et al 2019] has also been described, but may not be clinically available.
5. Detection of the pathogenic contraction of the D4Z4 locus by Southern blot analysis requires high-quality DNA; a false negative test result can be caused by poor-quality DNA that was sheared into small fragments.
6. In approximately 3% of the European families with FSHD1 the D4Z4 contraction on chromosome 4q35 is not visible using the standard genetic test because a deletion encompasses the region of the molecular diagnostic probe p13E-11. These individuals require additional testing to visualize the contracted D4Z4 repeat and resolve the size of the repeat [Lemmers et al 2003, Ehrlich et al 2007].
7. A combination of Southern blotting and molecular combing detected complex rearrangements of 4q35 with duplication of D4Z4 array [Nguyen et al 2017, Lemmers et al 2018] and a 4q deletion proximal to D4Z4 [Nguyen et al 2019].
8. 4A161 is most common permissive haplotype, but others are reported (4A159, 4A168, 4A166H) [Lemmers et al 2010a]. All individuals with FSHD carry a permissive haplotype. Because 66% of controls also carry a permissive haplotype, this analysis (without sizing of the repeat array) is often not informative. Lemmers et al developed a clinically available diagnostic test to discriminate both haplotype variants using *Hin*dIII-digested DNA and specific probes for 4A and 4B [Lemmers et al 2002, Lemmers et al 2007].
9. D4Z4 methylation values below the threshold of 25% are indicative of FSHD. However, the CpG methylation at the D4Z4 repeat array is also determined by the size of the D4Z4 arrays on chromosomes 4q and 10q. Contracted D4Z4 arrays on chromosomes 4q and 10 have a significantly lower level of methylation than normal-sized arrays. D4Z4 methylation levels should always be evaluated with respect to the repeat size. A Southern blot-based method has been developed that measures the total D4Z4 methylation at chromosomes 4q and 10q by using methylation-sensitive restriction enzyme (*Fse*I) in the promoter region of *DUX4* [Lemmers et al 2012b]. The average methylation of D4Z4 in control individuals is 45%, while in individuals with FSHD2 the methylation level drops below 25%, with an average of 11% [Lemmers et al 2012b].
10. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
11. 51 families of 60 with FSHD2 were found to have an *SMCHD1* pathogenic variant with D4Z4 DNA hypomethylation [Lemmers et al 2015].
12. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications.
13. Deletions including *SMCHD1* and other genes have been reported as 18p- syndrome [Lemmers et al 2015].
14. van den Boogaard et al [2016]

Clinical Characteristics

Clinical Description

Facioscapulohumeral muscular dystrophy (FSHD) is characterized by progressive muscle weakness involving the face, scapular stabilizers, upper arm, lower leg (peroneal muscles), and hip girdle [Wang & Tawil 2016]. Asymmetry of facial, limb, and shoulder weakness is common [Kilmer et al 1995]. Typically, individuals with FSHD become symptomatic in their teens, but age of onset is variable. More than 50% of individuals with FSHD demonstrate findings by age 20 years. Individuals with severe infantile FSHD have muscle weakness at birth. In contrast, some individuals remain asymptomatic throughout their lives. Progression is usually slow; however, many affected individuals describe a stuttering course with periods of disease inactivity followed by periods of rapid deterioration. Eventually 20% of affected individuals require a wheelchair.

Scapular winging is the most common initial finding; preferential weakness of the lower trapezius muscle results in characteristic upward movement of the scapula when attempting to flex or abduct the arms. The shoulders tend to slope forward with straight clavicles and pectoral muscle atrophy.

Affected individuals show facial weakness, with symptoms more pronounced in the lower facial muscles than the upper. Some affected individuals recall having facial weakness before the onset of shoulder weakness. Earliest signs are often difficulty whistling or sleeping with eyes partially open in childhood. Individuals with FSHD are often unable to purse their lips, turn up the corners of their mouth when smiling, or bury their eyelashes when attempting to close their eyelids tightly. Extraocular, eyelid, and bulbar muscles are spared.

The deltoids remain minimally affected until late in the disease; however, the biceps and triceps are selectively involved, resulting in atrophy of the upper arm and sparing of the forearm muscles. The latter results in the appearance of "Popeye arms." In more severely affected individuals, distal upper extremity weakness typically involves the wrist and finger extensors.

Abdominal muscle weakness results in protuberance of the abdomen and exaggerated lumbar lordosis. The lower abdominal muscles are selectively involved, resulting in a Beevor's sign (upward displacement of the umbilicus upon flexion of the neck in a supine position).

The legs are variably involved, with peroneal muscle weakness with or without weakness of the hip girdle muscles, resulting in foot drop.

Sensation is preserved; reflexes are often diminished when the reflex involves weak muscles.

Respiratory dysfunction is relatively uncommon. Individuals who had pulmonary function testing by spirometry showed a restrictive lung disease pattern in 38% [Moreira et al 2017], which was likely a result of expiratory weakness. Respiratory support with noninvasive ventilation is uncommon (1%-3%) [Santos et al 2015].

Other manifestations. Retinal vasculopathy characterized by failure of vascularization of the peripheral retina, telangiectatic blood vessels, and microaneurysms can be demonstrated by fluorescein angiography in 40%-60% of affected individuals [Padberg et al 1995]. Vision is usually unaffected by this particular vascular malformation, but an exudative retinopathy clinically indistinguishable from Coats disease that can result in retinal detachment and vision loss has also been described. Bindoff et al [2006] reported two sisters with infantile-onset FSHD who had tortuous retinal vessels, small aneurysms, and yellow exudates.

Approximately 15% of individuals with FSHD have an abnormal audiogram. An abnormal audiogram was identified in up to 32% of individuals with a large pathogenic contraction of D4Z4 (D4Z4 fragments <20 kb) [Lutz et al 2013].

Both the exudative retinopathy and symptomatic sensorineural hearing loss are seen almost exclusively in individuals with a large pathogenic contraction of D4Z4 (1-3) repeats) or in individuals with early-onset disease [Lutz et al 2013, Statland et al 2013].

A predilection for atrial tachyarrhythmias has been reported in about 5% of cases, but symptoms are rarely experienced [Laforêt et al 1998, Galetta et al 2005, Trevisan et al 2006].

Chronic pain is likely underrecognized in affected individuals, with a prevalence as high as 77% [van der Kooi et al 2007].

Atypical presentations. Clinical variants of typical FSHD in individuals with a pathogenic contraction of the D4Z4 locus in the subtelomeric region of chromosome 4q35 include the following:

- Scapulohumeral dystrophy onset with facial sparing
- Infantile onset with severe rapidly progressive disease and a large pathogenic contraction of D4Z4 (D4Z4 fragments in the 9-21 kb range) was observed in 4% of individuals studied [Klinge et al 2006]. Felice et al [2005] and Bindoff et al [2006] have also reported individuals with infantile onset and mild-to-moderate cognitive deficiency and possible epilepsy [Bindoff et al 2006, Hobson-Webb & Caress 2006, Quarantelli et al 2006].

Mosaicism for FSHD-associated alleles. Approximately half of *de novo* cases of FSHD (i.e., affected offspring of unaffected parents) show a mosaic distribution of D4Z4 repeat array lengths in peripheral blood. This mosaicism likely results from a postzygotic array contraction during the first few cell divisions in embryogenesis. In such cases, a proportion of cells have two normal-sized D4Z4 alleles, while the remaining cells have one normal-sized D4Z4 allele and one pathogenic contracted D4Z4 allele [Lemmers et al 2004]. Depending on when in embryogenesis the pathogenic contraction occurs at the D4Z4 locus and the proportion of cells with the contracted D4Z4 repeat, individuals with mosaicism can be affected or asymptomatic. FSHD with somatic mosaicism of D4Z4 array lengths is more penetrant in males than in females [van der Maarel et al 2000].

Genotype-Phenotype Correlations

D4Z4 repeat array contraction size. Evidence-based guidelines published in 2015 recommend that a large pathogenic contraction of D4Z4 (D4Z4 fragments of 10-20 kb) should alert clinicians to the increased likelihood of significant disability, earlier onset of symptoms, and increased likelihood of extramuscular manifestations [Tawil et al 2015].

Allele size explains roughly 10% of variability in phenotype [Mul et al 2018]. A correlation has been reported between the degree of the pathogenic contraction of the D4Z4 locus and the age at onset of symptoms [Zatz et al 1995], age at loss of ambulation [Lunt & Harper 1991], and muscle strength as measured by quantitative isometric myometry [Tawil et al 1996], particularly in affected females [Tonini et al 2004a]. Individuals with a large contraction of D4Z4 (1-3 repeats) have a higher probability of earlier-onset disease and more rapid progression than those with smaller contractions of the D4Z4 locus [Bindoff et al 2006, Hobson-Webb & Caress 2006, Klinge et al 2006, Nikolic et al 2016, Goselink et al 2019]. However, significant variation exists even with small repeats, and others have not been able to confirm a correlation between disease severity and degree of D4Z4 pathogenic contractions [Butz et al 2003].

A study of Italy's National Registry concluded that 76% of early-onset (age <10 years) disease was a result of *de novo* pathogenic variants. However, neither *de novo* pathogenic variants nor earlier disease onset were associated with a more severe phenotype [Nikolic et al 2016], contrasting with other studies showing that earlier onset is associated with more severe symptoms [Mah et al 2018, Goselink et al 2019]. Caution must be noted as this correlation may represent an ascertainment bias, where more mild forms of FSHD are detected when inheritance of a known pathogenic variant in a family is suspected.

Mosaicism. The phenotypic severity of individuals with mosaic distributions of one or more array sizes, which is typically less than that of individuals without mosaicism, may reflect the proportion of cells carrying the pathogenic contracted D4Z4 locus in addition to the degree of the contraction of the D4Z4 locus in those cells.

Compound heterozygosity. Two unrelated affected individuals homozygous for a D4Z4 pathogenic contraction were reported by Wohlgemuth et al [2003], suggesting that the presence of two FSHD-associated alleles can be compatible with life. However, both families demonstrated reduced penetrance for FSHD, leaving open the possibility that in other genetic/environmental settings, compound heterozygosity could be a lethal condition. In support of this possibility, the authors report a phenotypic dosage effect in both of the compound heterozygotes, compared to other family members.

Homozygosity. Tonini et al [2004b] reported an individual homozygous for the contraction on two D4Z4 4A alleles whose clinical phenotype is not more severe than those of some of his heterozygous relatives. Within the same family, the authors also observed a large number of asymptomatic or minimally affected heterozygotes, reflecting the wide range of clinical variability that can occur in a given kindred.

Penetrance

Penetrance is increased with smaller D4Z4 repeat arrays; however, significant variation exists. In one study, penetrance of FSHD was found to vary by age and sex; it was 83% by age 30 years, but significantly greater for males (95%) than for females (69%) [Zatz et al 1998, Wohlgemuth et al 2018]. The effect of the affected individual's sex on penetrance and disease variability is uncertain, with data showing a lack of significant effect of lifetime estrogen exposures [Mul et al 2018] or methylation status between sexes [Lemmers et al 2015]. Effects from epigenetic factors such as methylation status (for both FSHD1 and 2) and other unknown environmental or genetic factors likely contribute [Mul et al 2018].

Anticipation

Absence of anticipation in large multigenerational families has been reported [Flanigan et al 2001].

Nomenclature

The term "Landouzy-Dejerine muscular dystrophy," used in the past for a syndrome similar or identical to FSHD, is no longer in use.

Persons with FSHD are sometimes included under the descriptive terms "scapulo-humeral" or "scapulo-peroneal syndromes."

Prevalence

The estimated prevalence of FSHD is between four and ten per 100,000 population. Sposìto et al [2005] found a prevalence in central Italy of 4.6:100,000. Lunt and Harper noted reports of 1:435,000 population in Wisconsin and figures for Europe from 1:17,000 to 1:250,000 population [Lunt & Harper 1991]. In Wales, the prevalence was 4.4:100,000 population. In Netherlands, the prevalence of FSHD may be 2.4:20,000 population, higher than prior estimates [Deenen et al 2014].

Genetically Related (Allelic) Disorders

Mutation of *SMCHD1* is also known to be associated with Bosma arhinia microphthalmia syndrome (OMIM 603457).

Mutation of *DNMT3B* is also known to be associated with immunodeficiency-centromeric instability-facial anomalies syndrome 1 (OMIM 242860).

No phenotypes other than those discussed in this *GeneReview* are associated with the pathogenic contraction of the D4Z4 locus in the subtelomeric region of chromosome 4q.

Differential Diagnosis

Disorders that are similar clinically to facioscapulohumeral muscular dystrophy (FSHD) but easily differentiated by their distinct muscle histopathology include the following:

- Myofibrillar myopathy (previously called desmin-storage myopathy)
- Inclusion body myositis including inclusion body myopathy 2 (See *GNE*-Related Myopathy.)
- Mitochondrial myopathies
- Adult acid maltase deficiency (See Pompe Disease.)
- Congenital myopathies
- Polymyositis

More troublesome are the following disorders in which the distribution of weakness and pathologic findings can be difficult to distinguish easily from FSHD. Molecular genetic testing allows definitive diagnosis of these conditions:

- Limb-girdle muscular dystrophies
- Scapuloperoneal muscular dystrophy syndromes, including myotonic dystrophy type 1 and myotonic dystrophy type 2 (also known as PROMM), which have mild facial weakness and nonspecific histopathologic changes that cannot be differentiated from FSHD

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with facioscapulohumeral muscular dystrophy (FSHD), the evaluations summarized in Table 2 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 2. Recommended Evaluations Following Initial Diagnosis in Individuals with Facioscapulohumeral Muscular Dystrophy

System/Concern	Evaluation	Comment
Musculoskeletal	Physical exam	To assess strength & functional limitations
	Eval for PT & need for assistive devices	
Neurodevelopmental	OT & speech therapy assessment	In persons w/infantile onset
Respiratory	Eval for hypoventilation; screen for daytime somnolence, nonrestorative sleep	• Baseline PFTs • Pulmonary/sleep eval if abnormal PFTs or sleep symptoms
Ophthalmologic	Ophthalmologic eval	• In persons w/large pathogenic contraction of D4Z4 (D4Z4 fragments of 10-20 kb) or visual symptoms • For presence of retinal vasculopathy
Audiologic	Assessment of hearing	• In all affected infants & children • In adults w/symptomatic hearing loss
Other	Consultation w/clinical geneticist &/or genetic counselor	

OT = occupational therapy; PFT = pulmonary function test; PT = physical therapy

Treatment of Manifestations

Standards of care and management of facioscapulohumeral muscular dystrophy were agreed upon at the 171st ENMC International Workshop. A consensus on the following topics and the recommendations from that conference [Tawil et al 2010] are outlined in Table 3.

Table 3. Treatment of Manifestations in Individuals with Facioscapulohumeral Muscular Dystrophy

Manifestation/ Concern	Treatment	Considerations/Other
Weakness	PT	• Establish appropriate exercise regimens (e.g., moderate weight training, aerobic training). • Identify assistive devices that may ↑ mobility & ↓ risk of falls at home.
	Ankle/foot orthoses	To improve mobility & prevent falls in those w/foot drop
	OT & speech therapy	In persons w/infantile onset
Limited range of motion	Surgical fixation of scapula to chest wall	Offered cautiously w/careful consideration of risk & benefit in context of person's symptoms
Pain	PT; pain medication	• NSAIDs for acute pain • Antidepressants or anti-seizure medication for chronic pain
Hypoventilation	Ventilatory support (e.g., BiPAP)	As necessary
Exposure keratitis	Ocular lubricants	In severe cases taping the eyes shut during sleep may be required.
Exudative retinopathy	Treatment per ophthalmologist	May be prevented by early intervention w/laser treatment
Hearing loss	Standard therapies	Incl amplification if necessary

OT = occupational therapy; PT = physical therapy

Surveillance

Table 4. Recommended Surveillance for Individuals with Facioscapulohumeral Muscular Dystrophy

System/Concern	Evaluation	Frequency
Musculoskeletal	PT assessment	Annually or more frequently as determined by disease severity
	Pain assessment	W/each visit to primary care physician & PT
Respiratory	Screening for hypoventilation	• Regular monitoring for persons w/abnormal PFTs, severe proximal weakness, kyphoscoliosis, wheelchair dependence, or comorbid disease affecting ventilation • Pulmonary consultation for FVC <60%, excessive daytime somnolence, or nonrestorative sleep; & before surgical procedures requiring anesthesia
Ophthalmologic	Dilated ophthalmoscopy	• Annually in those w/large pathogenic contraction of D4Z4 (D4Z4 fragments of 10-20 kb) • In adults only if visual symptoms develop
Audiology	Audiometry	• W/each visit in infants w/early-onset FSHD • Annually in children until starting school • In adults only if symptoms of hearing loss reported
Cardiology	Cardiac eval	If overt signs or symptoms of cardiac disease (regular screening not required)

FVC = forced vital capacity; PFT = pulmonary function test; PT = physical therapy/therapist

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Outcome of 105 pregnancies in 38 women with FSHD was generally favorable [Ciafaloni et al 2006]. However, rates for low-birth-weight infants, augmented extraction procedures such as forceps and vacuum assisted deliveries, delivery by cæsarean section, and anesthetic complications were higher than for the general population. Worsening of weakness occurred in 24% of the pregnancies, beginning during the pregnancy and generally not resolving after delivery.

Therapies Under Investigation

Genetic treatments such as RNAi treatment to silence *DUX4* have been evaluated in preclinical studies, though no human trials are currently underway [Wallace et al 2017]. Losmapimod is an inhibitor of p38α/β mitogen-activated protein kinase (MAPK) shown in preclinical studies to reduced *DUX4* expression. The medication has been previously studied in Phase I trials in other diseases, and Phase II trials are currently enrolling for FSHD [Ino et al 2015, Oliva et al 2019].

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Facioscapulohumeral muscular dystrophy 1 (FSHD1) is inherited in an autosomal dominant manner. Facioscapulohumeral muscular dystrophy 2 (FSHD2) is inherited in a digenic manner.

Risk to Family Members – FSHD1 (Autosomal Dominant Inheritance)

Parents of a proband

- Most individuals diagnosed with FSHD have a parent with clinical findings of FSHD and one D4Z4 allele with a pathogenic contraction (70%-90% of individuals with FSHD).
- Approximately 10%-30% of probands with FSHD have the disorder as the result of a D4Z4 *de novo* pathogenic contraction [Mostacciuolo et al 2009].
- Clinical evaluation and/or molecular genetic testing are recommended for the parents of a proband who has an apparent *de novo* pathogenic contraction.
- If the pathogenic contraction found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic contraction in the proband or germline mosaicism in a parent. Germline mosaicism has been reported [Köhler et al 1996] but the incidence is unknown.
- The family history of some individuals diagnosed with FSHD1 may appear to be negative because of failure to recognize the disorder in family members, an asymptomatic parent who has a deletion of the

region subtelomeric to the D4Z4 locus where the probe hybridizes (and is therefore probe negative [Nguyen et al 2017]), early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Also, if the parent is the individual in whom the pathogenic contraction first occurred, the parent may have somatic mosaicism for the contraction and may be mildly/minimally affected. Therefore, an apparently negative family history cannot be confirmed until appropriate evaluations have been performed.

Sibs of a proband. The risk to the sibs of a proband depends on the genetic status of the parents:

- If a parent of the proband is affected and/or is known to have the pathogenic contraction, the risk to the sibs of inheriting the D4Z4 pathogenic contraction is 50%.
- If the proband has a known D4Z4 pathogenic contraction that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism [Köhler et al 1996].
- If the parents have not been tested for the D4Z4 pathogenic contraction but are clinically unaffected, the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for FSHD because of the possibility of reduced penetrance in a parent or the possibility of parental germline mosaicism.

Offspring of a proband. Each offspring of an affected individual has a 50% chance of inheriting the D4Z4 pathogenic contraction.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected and/or has a D4Z4 pathogenic contraction, the parent's family members are at risk.

Risk to Family Members – FSHD2 (Digenic Inheritance)

FSHD2 results from double heterozygosity for an *SMCHD1* or *DNMT3B* pathogenic variant and an FSHD-permissive *DUX4* allele (*SMCHD1*, *DNMT3B*, and the *DUX4*-permissive allele segregate independently).

Parents of a proband

- The parents of a proband with FSHD2 may be heterozygous for either an FSHD2-related pathogenic variant in *SMCHD1* or *DNMT3B* or an FSHD-permissive *DUX4* allele. Parents who are heterozygous for either an FSHD2-related pathogenic variant or an FSHD-permissive *DUX4* allele are asymptomatic and not at risk of developing the disorder.
- Alternatively, one parent has double heterozygosity for both an FSHD2-related pathogenic variant and an FSHD-permissive *DUX4* allele (and is clinically affected) and the other parent has neither an FSHD2-related pathogenic variant nor an FSHD-permissive *DUX4* allele.
- Molecular genetic testing is recommended for the parents of a proband to confirm their genetic status and allow reliable recurrence risk assessment.

Sibs of a proband

- If each parent has one causative allele (or one parent has double heterozygosity for both causative alleles), each sib at conception has a 25% chance of having FSHD2, a 50% chance of being heterozygous for either an FSHD2-related pathogenic variant or an FSHD-permissive *DUX4* allele, and a 25% chance of being unaffected and having neither an FSHD2-related pathogenic variant nor an FSHD-permissive *DUX4* allele.
- Sibs who are heterozygotes for either an FSHD2-related pathogenic variant or an FSHD-permissive *DUX4* allele are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. Assuming that the proband's reproductive partner is not affected and not heterozygous for either an *SMCHD1* or *DNMT3B* pathogenic variant or an FSHD-permissive *DUX4* allele, each child of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic heterozygote, and a 25% chance of being unaffected and not a heterozygote.

Other family members. Each sib of a heterozygous parent has a 50% chance of having either an *SMCHD1* or *DNMT3B* pathogenic variant or an FSHD-permissive *DUX4* allele.

Related Genetic Counseling Issues

Predictive testing (i.e., testing of asymptomatic at-risk individuals)

- Predictive testing for at-risk relatives is possible once the FSHD-causing variant(s) have been identified in an affected family member.
- Potential consequences of such testing (including but not limited to socioeconomic changes and the need for long-term follow up and evaluation arrangements for individuals with a positive test result) as well as the capabilities and limitations of predictive testing should be discussed in the context of formal genetic counseling prior to testing.

Predictive testing in minors (i.e., testing of asymptomatic at-risk individuals age <18 years)

- For asymptomatic minors at risk for adult-onset conditions for which early treatment would have no beneficial effect on disease morbidity and mortality, predictive genetic testing is considered inappropriate, primarily because it negates the autonomy of the child with no compelling benefit. Further, concern exists regarding the potential unhealthy adverse effects that such information may have on family dynamics, the risk of discrimination and stigmatization in the future, and the anxiety that such information may cause.
- For more information, see the National Society of Genetic Counselors position statement on genetic testing of minors for adult-onset conditions and the American Academy of Pediatrics and American College of Medical Genetics and Genomics policy statement: ethical and policy issues in genetic testing and screening of children.

In a family with an established diagnosis of FSHD, it is appropriate to consider testing of symptomatic individuals regardless of age.

Considerations in families with apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant or clinical evidence of the disorder, it is likely that the proband has a *de novo* pathogenic variant. However, possible non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) or undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

Prenatal Testing and Preimplantation Genetic Testing

Once the FSHD-causing variant(s) have been identified in an affected family member, prenatal testing for a pregnancy at increased risk is possible.

Preimplantation genetic testing (PGT) may be an option for families in which the FSHD-causing variant(s) have been identified. However, no method for PGT is currently reliable.

The current diagnostic method for FSHD is based on genetic linkage and requires detailed chromosome analysis including D4Z4 array sizing of both parents, after which the segregation of a pathogenic chromosome in the fetal material is followed using DNA markers. However, one study tested several polymorphic markers in the D4Z4 region at a considerable distance from the array (0.55-1.88 Mb) that showed a relatively high recombination risk, making the application to PGT unreliable [Barat-Houari et al 2010]. Another study used DNA markers much closer to the D4Z4 repeat array with a very low risk of recombination [Tsumagari et al 2010]. This method enables the detection of the permissive haplotype but does not distinguish between a person carrying the common 4A161 permissive haplotype and those carrying the haplotype and associated FSHD-causing array contraction, thus reducing the sensitivity of this approach considerably, given the high frequency of permissive haplotypes in European and Asian populations.

Note: PGT for FSHD2 with a defined *SMCHD1* or *DNMT3B* pathogenic variant is theoretically possible as only DNA from a single cell is needed to determine if the embryo is carrying the pathogenic variant; however, there are currently no studies that address this possibility.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Friends of FSH Research**
  www.fshfriends.org
- **FSHD Canada Foundation**
  1100 1st Street SE
  Suite 201
  Calgary Alberta T2G 1B1
  Canada
  Phone: 403-470-0141
  www.fshd.ca
- **FSHD Global Research Foundation**
  PO Box A296
  Sydney South NSW 1235
  Australia
  Phone: 61 2 8007 7037
  Fax: 61 2 8007 7038
  Email: admin@fshdglobal.org
  www.fshdglobal.org
- **FSHD Society**
  450 Bedford Street
  Lexington MA 02420
  Phone: 781-301-6060
  www.fshdsociety.org
- **National Library of Medicine Genetics Home Reference**

Facioscapulohumeral muscular dystrophy

- **Japan Muscular Dystrophy Association**
  Japan
  Phone: 03-6907-3521
  www.jmda.or.jp

- **National Registry of Myotonic Dystrophy and FSHD Patients and Family Members**
  National Registry of Myotonic Dystrophy and FSHD
  601 Elmwood Avenue
  Box 673
  Rochester NY 14642
  Phone: 888-925-4302
  Fax: 585-273-1255
  Email: dystrophy_registry@urmc.rochester.edu
  National Registry for Myotonic Dystrophy (DM) & Facioscapulohumeral Dystrophy (FSHD)

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Facioscapulohumeral Muscular Dystrophy: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
DNMT3B	20q11.21	DNA (cytosine-5)-methyltransferase 3B	DNMT3Bbase: Mutation registry for ICF syndrome	DNMT3B	DNMT3B
DUX4L1	4q35.2	Double homeobox protein 4			DUX4L1
SMCHD1	18p11.32	Structural maintenance of chromosomes flexible hinge domain-containing protein 1	SMCHD1 @ LOVD	SMCHD1	SMCHD1
Unknown	4q35	Unknown			

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Facioscapulohumeral Muscular Dystrophy (View All in OMIM)

158900	FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY 1; FSHD1
158901	FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY 2, DIGENIC; FSHD2
601278	FSHD REGION GENE 1; FRG1
602900	DNA METHYLTRANSFERASE 3B; DNMT3B
606009	DOUBLE HOMEOBOX PROTEIN 4; DUX4
614982	STRUCTURAL MAINTENANCE OF CHROMOSOMES FLEXIBLE HINGE DOMAIN-CONTAINING PROTEIN 1; SMCHD1

Molecular Pathogenesis

FSHD results from expression of a gene that is not typically expressed in somatic tissue. This happens because of an opening of the chromatin structure either as a result of loss of D4Z4 copy number repeats or hypomethylation of D4Z4 due to a pathogenic variant in *SMCHD1* or *DNMT3B* that results in reduced methylation. FSHD1 (from D4Z4 array contraction) and FSHD2 (with resultant D4Z4 array hypomethylation; [Lemmers et al 2012b]) ultimately lead to the inappropriate expression of *DUX4*; the two pathomechanisms lead to similar clinical features.

Each 3.3-kb D4Z4 repeat unit has an open reading frame (named *DUX4*) that encodes two homeoboxes (see Figure 2) [Hewitt et al 1994, Gabriëls et al 1999]. Immediately distal to the D4Z4 region on the 4A variant is an additional *DUX4* exon that carries the polyadenylation signal of the gene required for stable gene expression [Lemmers et al 2010a]. Only transcripts that are spliced with the additional *DUX4* exon are stabilized sufficiently for protein production; therefore, 4A haplotypes can be permissive to *DUX4* expression.

Chromosome variants 4A and 4B (sometimes referred to as 4qA and 4qB) are almost equally common in the population and can be further divided into at least nine distinct haplotypes [Lemmers et al 2007, Lemmers et al 2010b]. FSHD1 is associated with contractions of the D4Z4 repeat array on the polyA exon encoding 4A variant [Lemmers et al 2002, Lemmers et al 2010a]:

- 4A161 is the most common 4A haplotype.
- 4A159, 4A163, 4A166H, and 4A168 are less common permissive haplotypes.
- Contraction of the D4Z4 allele on 4A166, a less common 4A haplotype found in two Dutch families, is not associated with FSHD.
- Contraction of the D4Z4 allele on 4B haplotypes is non-pathogenic.

In FSHD2, chromatin relaxation results from a heterozygous pathogenic variant in *SMCHD1*. SMCHD1 regulates chromatin repression at the inactive X chromosome and autosomal transgenes, like D4Z4, by CpG DNA methylation [Blewitt et al 2008]. Similar to FSHD1, FSHD2 requires a haplotype that is permissive to *DUX4* expression. *SMCHD1* can also be a modifier in FSHD1 families, as has been shown in two families with FSHD in which pathogenic variants for both FSHD1 and FSHD2 have been identified [Larsen et al 2015].

Mechanism of disease causation. Gain of function as a result of inappropriate expression of *DUX4*

Gene/locus-specific laboratory technical considerations. Testing for FSHD requires non-sequencing-based techniques such as Southern blotting, haplotype analysis, and methylation analysis (see Table 1), which are not widely performed by clinical laboratories. Other technical challenges include:

- **D4Z4 variant on chromosome 10.** A repeat sequence almost identical to D4Z4 has been identified on chromosome 10q26; contractions of this repeat are not associated with FSHD. The chromosome 10 *DUX4*-like gene in the D4Z4 array has nucleotide variants in the polyadenylation signal, which prevent the production of a stable DUX4 transcript [Lemmers et al 2010a].
- **Translocated alleles.** Approximately 20% of the general population carries either a chromosome 4q35-type D4Z4 repeat array on chromosome 10 or a D4Z4 array that consists of both 4q35- and 10q26-type sequence repeats on chromosome 4q35 [van Deutekom et al 1996, Lemmers et al 2010b]. Translocated arrays on chromosome 10q are non-permissive to FSHD, while the contractions on the hybrid arrays on chromosome 4q35 cause FSHD [Buzhov et al 2005, Lemmers et al 2010a]. Therefore, the finding of a D4Z4 array that appears to be contracted in an individual who carries these translocations must be interpreted with caution and reconciled with clinical findings [Lemmers et al 2010b, Lemmers et al 2012b]. Although these are commonly known as "translocated alleles," the mechanism is unknown.

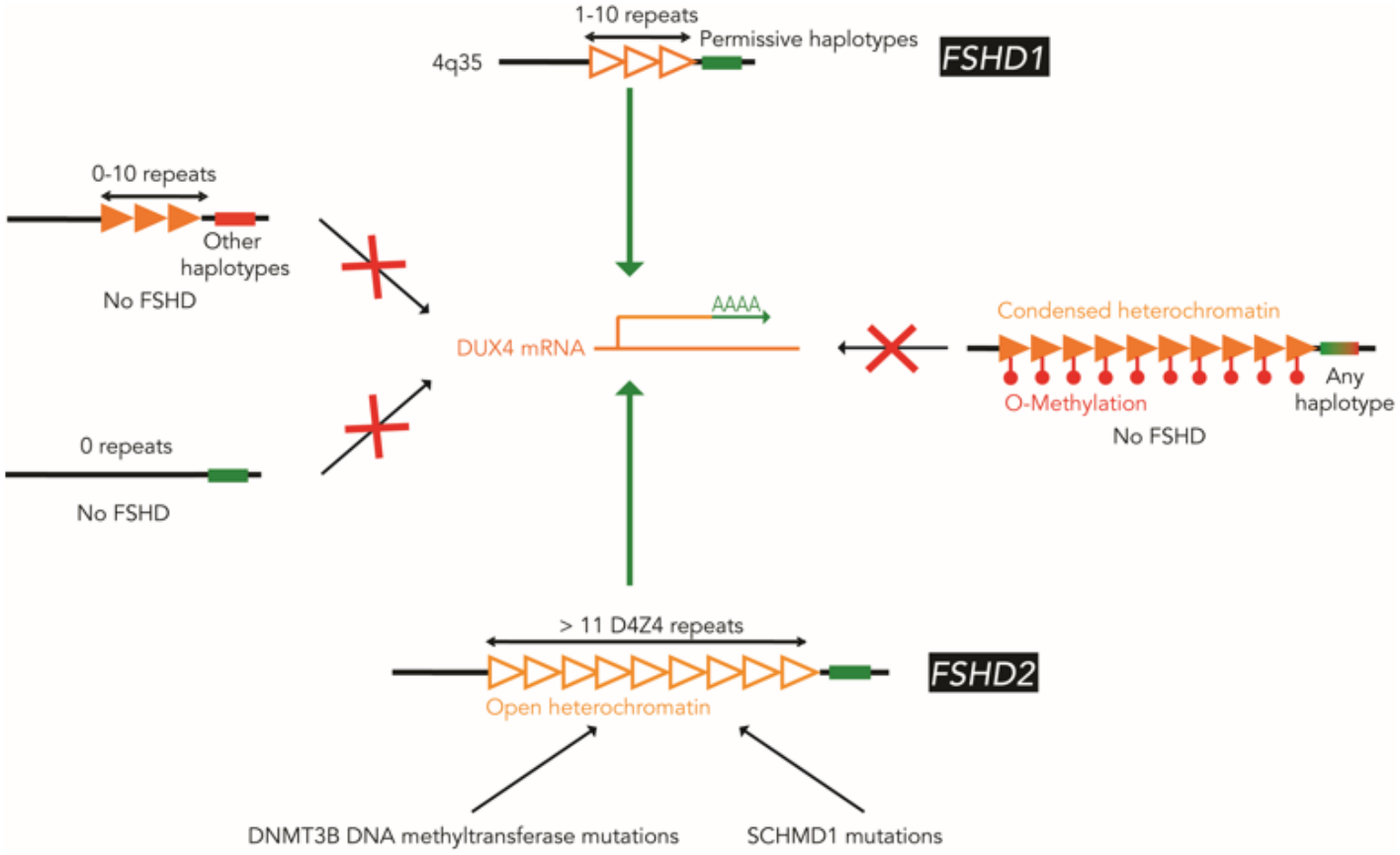

Figure 2. Schematic comparison of the structure of the normal D4Z4 allele and the pathogenic contracted D4Z4 allele that causes FSHD1. The normal D4Z4 allele has between 11 and 100 units of the 3.3-kb repeat sequence (depicted by triangles), whereas the pathogenic contracted FSHD1-causing D4Z4 allele has a contracted D4Z4 repeat array of between one and ten units on a permissive chromosome 4 haplotype (e.g., 4A161, 4A159, 4A168, 4A166H).

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Chapter Notes

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