Facioscapulohumeral Muscular Dystrophy Genetic Testing

MOL.TS.290.A
v1.0.2025

Introduction

Facioscapulohumeral muscular dystrophy genetic testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedure addressed by this guideline	Procedure code
D4Z4 region (FSHMD1A) deletion analysis	81404
D4Z4 region (FSHMD1A) methylation analysis	81479
FSHMD1 characterization of 4qA/4qB haplotypes	81404
SMCHD1 sequencing	81479
SMCHD1 deletion/duplication analysis	81479

Criteria

Introduction

Requests for facioscapulohumeral muscular dystrophy (FSHD) testing are reviewed using the following criteria.

Known Familial Mutation Analysis

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous genetic testing that would detect the familial mutation, AND

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- Diagnostic Testing for Symptomatic Individuals:
  - D4Z4 deletion and permissive 4A haplotype in a 1st, 2nd, or 3rd degree biologic relative with a clinical diagnosis of FSHD, or
  - Abnormal D4Z4 methylation or disease-causing SMCHD1 mutation and permissive 4A haplotype in a 1st, 2nd, or 3rd degree biologic relative with a clinical diagnosis of FSHD, OR
- Presymptomatic Testing for Asymptomatic Individuals:
  - Member is 18 years of age or older, AND
  - One of the following has been identified in a 1st, 2nd, or 3rd degree biologic relative:
    - D4Z4 deletion and permissive 4A haplotype in a 1st, 2nd, or 3rd degree biologic relative with a clinical diagnosis of FSHD, or
    - Abnormal D4Z4 methylation or disease-causing SMCHD1 mutation and permissive 4A haplotype in a 1st, 2nd, or 3rd degree biologic relative with a clinical diagnosis of FSHD, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

D4Z4 Targeted Analysis and Haplotyping

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No redundant previous FSHD related testing, AND
- Diagnostic Testing for Symptomatic Individuals:
  - The member has a probable clinical diagnosis of FSHD based on the following:
    - Weakness of facial muscles, or
    - Either weakness of scapular stabilizers or foot dorsiflexors, and
    - Member has the following:
      - No involvement of the extrinsic ocular muscles (responsible for eyeball movement), and
      - Muscle biopsy, if available, is not consistent with another diagnosis, and
      - EMG, if available, does not show myotonia or neurogenic changes, and
      - Creatine kinase, if performed, is less than 1500 IU/L, AND

- The member does not have a known underlying cause for their symptoms, AND

- Rendering laboratory is a qualified provider of service per the Health Plan policy.

D4Z4 Methylation Analysis

- Previous Genetic Testing:
  - No redundant previous FSHD related testing, AND
- Diagnostic Testing for Symptomatic Individuals:
  - The member meets the above criteria for D4Z4 deletion and haplotype analysis, and
  - The member has previously had negative D4Z4 deletion testing, and
  - The member has a permissive 4A haplotype, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

SMCHD1 Analysis

- Previous Genetic Testing:
  - No redundant previous FSHD related testing, AND
- Diagnostic Testing for Symptomatic Individuals:
  - The member meets the above criteria for D4Z4 methylation analysis, and
  - The member has low D4Z4 methylation analysis results (less than 25%), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

What is Facioscapulohumeral Muscular Dystrophy?

Definition

Facioscapulohumeral muscular dystrophy (FSHD) is both a genetic and epigenetic condition characterized by progressive, asymmetrical muscle weakness involving facial, scapular, and humeral muscle groups early followed by distal then proximal lower extremities.[1,2] There is significant variability in phenotype even for affected individuals within the same family. There are two types of FSHD (FSHD1 and FSHD2) that are clinically identical, but distinguished by their different genetic causes.

Prevalence

Prevalence is estimated between 4-10 per 100,000.[3] Approximately 95% of FSHD cases are FSHD1; the remaining cases are FSHD2.[2]

Symptoms

Signs and symptoms can begin anytime between childhood and adulthood. More than 50% of individuals with FSHD demonstrate findings by age 20 years, but some individuals remain asymptomatic throughout their lives.[3] Around 5% of affected individuals show symptoms before age 5.[1] There is a severe infantile form of FSHD in which muscle weakness is present from birth.[3]

Symptoms of FSHD include:[1-4]

- Progressive facial muscle weakness (seen by difficulty closing the eyes, raising the eyebrows, whistling, frowning, puffing the cheeks, or showing teeth)
- Progressive shoulder girdle muscle weakness and atrophy
- Upper arm weakness and atrophy (“Popeye arms”), often asymmetric
- Pelvic muscle weakness and atrophy develop later
- Gait weakness, foot drop, calf hypertrophy
- Scapular winging
- Exercise intolerance
- Pain
- Extra-muscular manifestations include hearing loss (common) and vision deterioration (rare)

Severity ranges from almost asymptomatic weakness to severe restrictions of activities of daily living with approximately 20% of individuals requiring a wheelchair. Initial presentation is most often with facial and shoulder weakness, but can be variable including bent spine and less specific limb girdle patterns.[2]

Cause

FSHD is caused by inappropriate expression of the DUX4 gene in muscle cells. The DUX4 gene is located within a microsatellite region called D4Z4, and relaxation of the chromatin in this region is believed to cause the aberrant expression.[3]

In FSHD1, the chromatin relaxation is caused by a deletion or contraction of a repeated stretch of DNA (called the D4Z4 repeat). Symptoms arise when this deletion occurs in the context of a permissive nearby haplotype (called 4A). Inheritance with another haplotype results in non-penetrance of the deletion, and FSHD1 is not likely.

In FSHD2, the chromatin relaxation is caused by the loss of methylation at D4Z4. This is commonly caused by a mutation in the SMCHD1 gene or, very rarely, the DNMT3B gene.[2,3]

Inheritance

The pattern of inheritance differs between FSHD1 and FSHD2.

FSHD1 is inherited in an autosomal dominant pattern, with symptoms only occurring when the D4Z4 deletion occurs in the presence of the permissive haplotype. Without the presence of a specific chromosome 4A haplotype, a D4Z4 region deletion will not lead to the FSHD1 disorder.

FSHD2 inheritance is digenic, with symptoms only occurring when a mutation in SMCHD1 or DNMT3B occurs with the permissive 4A haplotype. The inheritance is not simply autosomal dominant, as SMCHD1 and DNMT3B sort independently from the permissive 4A haplotype locus: they are not always inherited together or from the same parent, as is the case with FSHD1.

Between 10 and 30% of individuals diagnosed with FSHD have no family history. In these putative non-familial cases the genetic change occurred either de novo or the parents may be mosaic for the causative genetic change.

Diagnosis

Diagnosis of FSHD is suggested by clinical phenotype and inheritance pattern, and confirmed by molecular testing. Because of the complex inheritance, careful correlation between clinical presentation and molecular result is essential.

- Diagnostic features should include a facial, scapular, humeral, and/or peroneal distribution of weakness and atrophy. Presence of a clinical phenotype more consistent with FSHD than other myopathies is an important diagnostic consideration. Note, myotonic dystrophy type 1 and 2 are very similar to FSHD and may only be distinguished by molecular testing.
- Biochemical abnormalities are nonspecific but point in the direction of muscle damage. Creatine kinase (CK) is normal to elevated, but it is not typically greater than 1500 IU/L.[3]
- EMG shows mild myopathic changes.
- Muscle biopsy is usually reserved for cases in which molecular testing is inconclusive. If a muscle biopsy is performed, results typically show nonspecific, chronic myopathic changes and dystrophy. Occasionally there can be inflammatory changes present significant enough to suggest an inflammatory myopathy.

The University of Rochester's National Registry of Myotonic Dystrophy and Facioscapulohumeral Muscular Dystrophy defines definite FSHD diagnosis as:[5]

- Weakness of facial muscles, and
- Either of the following
    - Scapular weakness, or
    - Foot dorsiflexor weakness, AND
- Absence of eye involvement (ptosis or extraocular muscle weakness), and
- Absence of an alternative diagnosis on muscle biopsy, and

- EMG results that do not demonstrate myotonia or neurogenic changes

Probable FSHD diagnosis is defined as either:[4]

- Weakness of facial muscles, or
- Either of the following
  - Scapular weakness, or
  - Foot dorsiflexor weakness, and
- Absence of eye involvement (ptosis or extraocular muscle weakness), and
- Absence of an alternative diagnosis on muscle biopsy, and
- EMG results that do not demonstrate myotonia or neurogenic change

OR

- Weakness of facial muscles, and
- Either of the following
  - Scapular weakness, or
  - Foot dorsiflexor weakness, and muscle biopsy and/or EMG results are not available

A molecular diagnosis of FSHD1 is achieved with the detection of a heterozygous pathogenic contraction of D4Z4 on the permissive 4A haplotype. A molecular diagnosis of FSHD2 is established when hypomethylation of the D4Z4 repeat is detected on the permissive 4A haplotype.[3]

Treatment

There are no disease-modifying treatments currently available for FSHD. Management is symptom driven and primarily consists of support needed to address loss of strength. Hearing loss and rarer sequelae such as vision impairment or decreased lung function should be assessed and addressed as needed.

Standard of care and management guidelines for confirmed FSHD diagnosis include:[6]

- Evaluation by physical therapy to address functional limitations
- Help determining standard follow-up schedules to monitor for complications (such as pulmonary function testing and ophthalmologic screenings), and the need for assistive devices
- Assessments for hearing and vision loss and other orthopedic interventions
- Pain management to avoid compounding existing mechanical limitations

FSHMD

Survival

FSHD is not typically life shortening, but does lead to increased morbidity.

Test information

Introduction

Testing for FSHD may include known familial mutation analysis, targeted analysis with haplotyping, methylation analysis, next generation sequencing, and/or deletion/duplication analysis.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

FSHD1 Testing: Targeted Analysis and Haplotyping

Molecular testing for FSHD starts with assessment for the more common FSHD1. This testing consists of detecting contractions of the D4Z4 locus (reported as a number of D4Z4 repeats) and determination of the associated haplotype, using Southern blot analysis and optical genome mapping.[7]

- The normal range is defined as 12-100 repeat units.
- The FSHD-associated repeat range is defined as 1-10; however, to be pathogenic, the contraction needs to occur in the context of the permissive 4A haplotype.
- Borderline repeat lengths between 8 and 11 can display reduced penetrance and may require consideration of clinical phenotype and additional molecular testing to confirm a diagnosis as they may or may not be associated with FSHD1 in a given individual, even in the presence of the 4A haplotype.[8]

This analysis will detect causative variants in 95% of clinically affected individuals.[3]

FSHD2 Testing: Methylation Analysis and SMCHD1 Sequencing

Molecular testing for FSHD2 consists of determining the methylation status of the D4Z4 region.

- D4Z4 methylation (methylation-sensitive restriction enzyme and Southern blot): methylation levels below 25% are consistent with an FSHD2 diagnosis. Again, to be pathogenic, the hypomethylation needs to occur in the context of the permissive 4A haplotype.

- If hypomethylation is identified, SMCHD1 next generation sequencing may be performed to determine the causative mutation.
- SMCHD1 deletion/duplication analysis will find gene rearrangements that are too large to be detected by sequencing. Large deletions in SMCHD1 are infrequently reported; therefore, deletion/duplication analysis is done as second tier testing in FSHD2.
- DNMT3B gene sequencing may detect rare causative mutations.

This analysis will detect causative variants in less than 5% of clinically affected individuals.[3]

Guidelines and evidence

American Academy of Neurology

The American Academy of Neurology Evidenced-based Guideline for Clinicians (AAN, 2015; reaffirmed 2021) considered the following to be Level B practice recommendations:[6]

- “Clinicians should obtain genetic confirmation of FSHD1 in patients with atypical presentations and no first-degree relatives with genetic confirmation of the disease.”
- “Large D4Z4 deletion sizes (contracted D4Z4 allele of 10-20 kb) should alert the clinician that the patient is more likely to develop more significant disability and at an earlier age. Patients with large deletions are also more likely to develop symptomatic extramuscular manifestations.”

European Neuromuscular Center

The 268th European Neuromuscular Center International Workshop: Genetic diagnosis, clinical classification, outcome measures, and biomarkers in Facioscapulohumeral Muscular Dystrophy (2023) stated the following:[8]

- "Genetic testing is the preferred tool to confirm a diagnosis of FSHD in a patient with suggestive clinical features."
- This workshop provided expert opinion on the complexities of FSHD genetic testing, including: the advantages and disadvantages of the different genetic testing modalities, the variability in penetrance and expression for repeat sizes in an intermediate range, and opportunities for biomarker use in FSHD detection and management.

Note This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for facioscapulohumeral muscular dystrophy testing will ensure that testing will be available to those members most likely to benefit from a

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genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

References

1. Kniffin CL. FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY 1; FSHD1 OMIM 158900. Online Mendelian Inheritance In Man (OMIM) OMIM 158900 (updated 10/11/2023).

2. Statland J, Tawil R. Facioscapulohumeral muscular dystrophy. *Neurol Clin*. 2014;32:721-728. doi:10.1016/j.ncl.2014.04.003.

3. Preston M, Tawil R, and Wang L. Facioscapulohumeral muscular dystrophy. 1999 Mar 8 [Updated 2020 Feb 6]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1443/.

4. Loonen TGJ, Horlings CGC, Vincenten SCC, et al. Characterizing the face in facioscapulohumeral muscular dystrophy. *J Neurol*. 2021;268(4):1342-1350. doi: 10.1007/s00415-020-10281-z

5. University of Rochester National Registry of Myotonic Dystrophy and Facioscapulohumeral Muscular Dystrophy Patients and Family Members Physician Checklist FSHD. Version 2. Revised: 03/05/2018. Available at: https://www.urmc.rochester.edu/MediaLibraries/URMCMedia/neurology/documents/Physician-check-list-FSHD-7-25-11.pdf.

6. Tawil R, Kissel JT, Heatwole C, et al. Evidence-based guideline summary: Evaluation, diagnosis and management of facioscapulohumeral muscular dystrophy: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the Practice Issues Review Panel of the American Association of Neuromuscular & Electrodiagnostic Medicine. *Neurology*. 2015;85:357-364. doi:10.1212/WNL.0000000000001783. Reaffirmed 2021.

7. Stence AA, Thomason JG, Pruessner J, et al. Validation of Optical Genome Mapping for the Molecular Diagnosis of Facioscapulohumeral Muscular Dystrophy. *J Mol Diagn*. 2021 Nov;23(11):1506-1514. doi:10.1016/j.jmoldx.2021.07.021.

8. Montagnese F, de Valle K, Lemmers RJLF, et al. 268th ENMC workshop - Genetic diagnosis, clinical classification, outcome measures, and biomarkers in Facioscapulohumeral Muscular Dystrophy (FSHD): Relevance for clinical trials. *Neuromuscul Disord*. 2023;33(5):447-462. doi:10.1016/j.nmd.2023.04.005

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