Test Specific Guidelines

Facioscapulohumeral Muscular Dystrophy Genetic Testing

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Introduction

Facioscapulohumeral muscular dystrophy genetic testing is addressed by this guideline.

Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

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

What Is Facioscapulohumeral Muscular Dystrophy?

Definition

Facioscapulohumeral muscular dystrophy (FSHD) is both a genetic & epigenetic condition characterized by progressive muscle weakness involving facial, scapular, and humeral muscle groups early, and pelvic and peroneal muscle groups later.[1,2] 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] There is a severe infantile form of FSHD in which muscle weakness is present from birth.[3]

Symptoms of FSHD include:

Progressive facial muscle weakness (seen by difficulty with whistling) and 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.

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:[4]

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

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 FSDH diagnosis include:[5]

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

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.[6]

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 of 10 or 11 require clinical phenotype to interpret, as they may or may not be associated with FSHD in a given individual, even in the presence of the 4A haplotype. These are considered reduced penetrance alleles.

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 contraction 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

Introduction

The following section includes relevant guidelines and evidence pertaining to FSHD testing.

American Academy of Neurology

The American Academy of Neurology Evidenced-based Guideline for Clinicians (2015) considered the following to be Level B practice recommendations:[5]

"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

According to the 171st European Neuromuscular Center International Workshop: Standards of Care and Management of FSHD (2010): if a physician suspects FSHD clinically, genetic testing is the preferred diagnostic test.[7,8]

Criteria

Introduction

Requests for 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

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 ocular muscles (including extraocular weakness or ptosis), 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.

References

Introduction

This guideline cites the following references.

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