Friedreich Ataxia Genetic Testing

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Friedreich ataxia (FRDA) 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.

Procedures addressed by this guideline	Procedure codes
FXN gene analysis; evaluation to detect abnormal (expanded) alleles	81284
FXN gene analysis; characterization of alleles (eg, expanded size)	81285
FXN gene analysis; full gene sequence	81286
FXN gene analysis; known familial variant(s)	81289
FXN gene analysis, deletion/duplication	81479
Genomic Unity FXN analysis	0233U

Criteria

Requests for Friedreich ataxia (FRDA) testing are reviewed using the following criteria.

Known Familial Mutation Analysis

- Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- No previous FXN gene analysis performed that would detect the familial mutation, AND
- Known disease-causing mutation in FXN gene identified in 1st degree relative(s), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy

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GAA Trinucleotide Repeat 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 GAA repeat analysis of FXN performed, and
  - Member does not have a known mutation in both copies of the FXN gene, AND
- Individual has been diagnosed with cerebellar ataxia, regardless of age of onset, AND
- Family history is consistent with autosomal recessive inheritance (including simplex cases), AND
- The member does not have a known underlying cause for their ataxia (e.g. alcoholism, vitamin deficiencies, multiple sclerosis, vascular disease, tumors, known mutation), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy

Sequence Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - Member does not have a known mutation in both copies of the FXN gene, and
  - No previous sequencing analysis of the FXN gene, and
  - Previous GAA trinucleotide repeat analysis was performed and revealed a GAA expansion on only one allele, and
  - Meets criteria for GAA trinucleotide repeat analysis, and
  - Testing is needed to confirm the diagnosis of Friedreich Ataxia, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy

Deletion/duplication Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - Member does not have a known mutation in both copies of the FXN gene, and
  - Previous GAA trinucleotide repeat analysis was performed and revealed a GAA expansion on only one allele, and
  - Previous GAA sequencing was performed and did not identify a mutation on either FXN allele, and

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  - Meets criteria for GAA trinucleotide repeat analysis, and
  - Testing is needed to help confirm the diagnosis of Friedreich Ataxia, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy

Other Considerations

FRDA testing may be performed as part of a multigene, multisyndrome panel. For information on multigene, multisyndrome panel testing, please refer to the guideline *Hereditary Ataxia Multigene Panel Genetic Testing,* as this testing is not addressed here.

What is Friedreich Ataxia?

Friedreich ataxia (FRDA) is an inherited neuromuscular condition.

Prevalence

FRDA is the most common inherited ataxia in European, Middle Eastern, south Asian (Indian subcontinent), and North African populations.[1] The prevalence is 2:100,000-4:100,000.[1] The carrier frequency is 1:60-1:100.[1]

Symptoms

FRDA is characterized by progressive ataxia (lack of coordination of muscle movements) of the limbs and gait, dysarthria (difficulty articulating speech), absent lower limb reflexes, sensory loss, and muscle weakness.[1-3] About two-thirds of individuals with FRDA also have cardiomyopathy (weakening of the heart muscle).[1] Approximately 30% of individuals with FRDA have diabetes mellitus.[1] Other features include pes cavus, sensorineural hearing loss, and optic atrophy.[3]

Symptoms typically present before 25 years of age, with the mean age of symptom onset between 10 and 15 years.[1,2] However, about 25% of affected individuals have an atypical form with later onset and/or retained reflexes.[1] Shorter GAA repeat expansions tend to be associated with later onset of symptoms.[1,3]

Cause

FRDA is caused by mutations in the FXN gene. Most mutations in the FXN gene cause a section of DNA, called a GAA triplet repeat, to expand.[1] The GAA expansion results in reduced levels of the protein, frataxin.[3] A minority (less than 5%) of affected people have a different type of mutation in the FXN gene.[1]

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Inheritance

FRDA is an autosomal recessive disorder.

Autosomal recessive inheritance

In autosomal recessive inheritance, individuals have 2 copies of the gene and an individual typically inherits a gene mutation from both parents. Usually only siblings are at risk for also being affected. Males and females are equally affected. Individuals who inherit only one mutation are called carriers. Carriers do not typically show symptoms of the disease, but have a 50% chance, with each pregnancy, of passing on the mutation to their children. If both parents are carriers of a mutation, the risk for each pregnancy to be affected is 1 in 4, or 25%.

Diagnosis

The diagnosis of FRDA is confirmed when disease-causing mutations are found in both copies of the FXN gene (biallelic mutations).[1] Approximately 96% of individuals with FRDA have disease-causing GAA triplet repeat expansions in both FXN genes.[1] About 4% have a single disease-causing GAA triplet repeat expansion and a second FXN gene mutation not in the GAA repeat region.[1] In this case, different genetic testing, such a next generation sequencing, is required to identify the second mutation.

The main result categories are based on the number of GAA triplet repeats:[1]

- 5 to 33 GAA repeats: normal range
- 34 to 65 repeats: described as normal, but possibly unstable with regard to reproductive risk; have rarely been reported in individuals presenting with atypical FRDA
- 44 to 66 repeats: borderline; the "shortest repeat length associated with disease (i.e., the exact demarcation between normal and full-penetrance alleles) has not been clearly determined."[1]
- 66 or more repeats: disease-causing; usually people with typical FRDA have 600 to 1200 repeats.[1] "The age of onset, presence of leg muscle weakness/wasting, duration until wheelchair use, and prevalence of cardiomyopathy, pes cavus, and scoliosis have all shown statistically significant inverse correlations with the size of the expanded GAA repeat." [1]

Single or multi-exon deletions or duplication of FXN are rare but have been reported.[1]

Very few people who have been clinically diagnosed with FRDA have no GAA expansion in the FXN gene, though some are reported with only one mutation identified.[1] These people may have mutations in another gene, although another disease causing gene has not yet been identified.[1,4]

Management

Management of FRDA is largely supportive, and includes the use of walking aids and wheelchairs for ambulation, physical therapy, speech therapy, occupational therapy, and other assistive devices.[1]

Survival

The survival range for FRDA varies. The mean age of death is 36.5 years, with a median age of 30 years.[1] Some individuals have been documented to live into their 60s and 70s. Cardiac issues, particularly progressive heart failure, arrhythmias, and cardioembolic stroke attributable to atrial fibrillation, are the most common cause of death among individuals with FRDA.[3] Potential therapeutic targets focused on two general principles, increasing frataxin expression and reducing oxidative stress, are currently under investigation.[3]

Test Information

Testing for FRDA may include known familial mutation analysis and trinucleotide repeat testing. If needed for affected individuals with only one expanded repeat identified, next generation sequencing and/or deletion/duplication analysis can be subsequently performed.

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.

Analysis for known familial mutations is typically performed by trinucleotide repeat expansion analysis. Some mutations may require sequencing or deletion/duplication analysis.

Trinucleotide Repeat Testing

Repeat expansion genetic testing allows for the determination of the size of a repeated DNA sequence. This testing may involve more than one test methodology. Smaller repeat expansions are typically identified using certain types of polymerase chain reaction (PCR), while larger expansions may require Southern blot. More comprehensive repeat expansion testing that utilizes next generation sequencing and exome sequencing methods is under development.

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Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

Guidelines and Evidence

American College of Medical Genetics and Genomics

An overview published by the American College of Medical Genetics (ACMG, 2013) stated the following regarding testing for hereditary ataxias:[5]

- “Establishing the diagnosis of hereditary ataxia requires:
  - Detection on neurological examination of typical clinical signs including poorly coordinated gait and finger/hand movements, dysarthria (incoordination of speech), and eye movement abnormalities such as nystagmus, abnormal saccade movements, and ophthalmoplegia.
  - Exclusion of nongenetic causes of ataxia (see Differential Diagnosis below).
  - Documentation of the hereditary nature of the disease by finding a positive family history of ataxia, identifying an ataxia-causing mutation, or recognizing a clinical phenotype characteristic of a genetic form of ataxia.”
- “Differential diagnosis of hereditary ataxia includes acquired, nongenetic causes of ataxia, such as alcoholism, vitamin deficiencies, multiple sclerosis, vascular disease, primary or metastatic tumors, and paraneoplastic diseases associated with occult carcinoma of the ovary, breast, or lung, and the idiopathic degenerative disease multiple system atrophy (spinal muscular atrophy). The possibility of an acquired cause of ataxia needs to be considered in each individual with ataxia because a specific treatment may be available.”
- "Testing strategy when the family history suggests autosomal recessive inheritance

- A family history in which only sibs are affected and/or when the parents are consanguineous suggests autosomal recessive inheritance. Because of their frequency and/or treatment potential, FRDA, A-T, AOA1, AOA2, AVED, and metabolic or lipid storage disorders such as Refsum disease and mitochondrial diseases should be considered."

- "Testing simplex cases. A simplex case is a single occurrence of a disorder in a family, sometimes incorrectly referred to as a 'sporadic' case.
  - If no acquired cause of the ataxia is identified, the probability is ~13% that the affected individual has SCA1, SCA2, SCA3, SCA6, SCA8, SCA17, or FRDA, and mutations in rare ataxia genes are even less common.
  - Other possibilities to consider are a de novo mutation in a different autosomal dominant ataxia, decreased penetrance, alternative paternity, or a single occurrence of an autosomal recessive or X-linked disorder in a family such as fragile X-associated tremor/ataxia syndrome.
  - Although the probability of a positive result from molecular genetic testing is low in an individual with ataxia who has no family history of ataxia, such testing is usually justified to establish a specific diagnosis for the individual's medical evaluation and for genetic counseling.
  - Always consider a possible nongenetic cause such as multiple system atrophy, cerebellar type in simplex cases."

European Federation of Neurological Sciences

- The European Federation of Neurological Sciences (EFNS, 2014) stated the following regarding testing for ataxia:[4]
  - For symptomatic individuals with a family history consistent with autosomal recessive cerebellar ataxia, the first step in the suggested diagnostic approach included analysis for FRDA.
    - "Step 1: mutation analysis of the FRDA gene for Friedreich's ataxia (although one can refrain from this in the case of severe cerebellar atrophy), and biochemical testing that includes cholestanol, vitamin E, cholesterol, albumin, creatine kinase (CK) and a-fetoprotein. Also consider doing nerve conduction studies/EMG (presence versus absence of peripheral neuropathy, axonal versus demyelinating) and referral to an ophthalmologist (retinitis pigmentosa, cataract, cherry red spot etc.) (Table S2) (good practice point)."
  - "In the case of sporadic ataxia and independent from onset age, we recommend routine testing for SCA1, SCA2, SCA3, SCA6, and DRPLA (in Asian patients) (level B), the step 1 panel of the recessive ataxia workup, i.e mutation analysis of the FRDA gene (level B), and biochemical testing that includes cholestanol, vitamin E, cholesterol, albumin, CK, and α-fetoprotein."
- For the diagnosis of FRDA, guidelines from the European Federation of Neurological Societies (EFNS, 2010) created by consensus of expert members following literature

review recommended: "In cases presenting with early onset ataxia, peripheral sensory neuropathy, and absence of marked cerebellar atrophy at MRI, genetic test for FRDA mutation is recommended (Class B)."[2]

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 Friedreich Ataxia testing will ensure that testing will be available to those members most likely to benefit from a 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

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