Friedreich Ataxia Genetic Testing

Introduction

Friedreich ataxia 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.

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What is Friedreich Ataxia

Definition

Friedreich ataxia (FRDA) is an inherited neuromuscular condition.

Incidence and Prevalence

FRDA is the most common inherited ataxia in European, Middle Eastern, Asian Indian, and North African populations. The prevalence is 2:100,000-4:100,000.

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. About two-thirds of individuals with FRDA also have cardiomyopathy (weakening of the heart muscle). Approximately 30% of individuals with FRDA have diabetes mellitus.
Symptoms typically present before 25 years of age, and most commonly between 10 and 15 years. However, about 25% of affected individuals have an atypical form with later onset and/or retained reflexes.

Cause

Friedreich ataxia 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. However, a minority of affected people have a different mutation in the FXN gene.

Inheritance

FRDA is an autosomal recessive disorder. An affected individual must inherit FXN gene mutations from both parents. Full siblings of an affected individual have a 25% risk to be affected. Individuals who inherit only one mutation are called carriers. Carriers do not show symptoms, but have a 50% chance of passing on the mutation to their children. Two carriers have a 25% chance of having a child with the disorder.

Diagnosis

The diagnosis of FRDA is confirmed when disease-causing mutations are found in both copies of the FXN gene. 96% of individuals with FRDA have disease-causing GAA triplet repeat expansions in both FXN genes. About 4% have a single disease-causing GAA triplet repeat expansion and a second FXN gene mutation not in the GAA repeat region. Different genetic testing is required to identify the second mutation.

Very few people who have been clinically diagnosed with FRDA have no GAA expansion in the FXN gene. These people may have mutations in another gene, although another disease causing gene has not yet been identified.

Treatment

Treatment of FRDA is largely supportive, and includes the use of walking aids and wheelchairs for ambulation, speech therapy, occupational therapy, and other assistive devices.

Survival

The survival range for FRDA varies. The mean age of death is 36.5 years, with a median age of 30 years. Some individuals have been documented to live into their 60s and 70s. Cardiac issues are the most common cause of death among individuals with FRDA.
Test Information

Introduction

Testing for FRDA is performed by determining the number of GAA repeats in the FXN gene. If needed, FXN sequencing or FXN deletion/duplication analysis can be subsequently performed.

Trinucleotide repeat expansion

The main result categories are based on the number of GAA triplet repeats:\(^1\)

- 5 to 33 GAA repeats is the normal range
- 34 to 65 repeats do not usually cause typical Friedreich ataxia. However, this range may be unstable and can lead to atypical disease or an increased risk for a person's child to be affected.
- 44 to 66 repeats is considered borderline given that the "shortest repeat length associated with disease has not been clearly determined."\(^1\)
- 66 or more repeats are disease-causing. Usually people with typical Friedreich ataxia have 600 to 1200 repeats. Smaller numbers of repeats may lead to later onset disease.

Sequencing

About 4% of people with Friedreich ataxia have only one GAA expansion mutation on initial testing. For these people, subsequent FXN gene sequencing is needed to identify the second gene mutation.\(^1\)

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/Duplication analysis

Single or multi-exon deletions or duplication of FXN are rare but have been reported.\(^1\)

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, MLPA, and NGS data analysis.

These assays detect gains and losses too large to be identified through sequencing technology, often single or multiple exons or whole genes.

Known familial mutation analysis

Known familial mutation analysis is performed when a causative mutation has been identified in a close relative of the individual requesting testing.
Analysis for known familial mutations is typically performed by trinucleotide repeat expansion analysis. Some mutations may require Sanger sequencing or deletion/duplication analysis.

**Guidelines and Evidence**

**Introduction**

This section includes relevant guidelines and evidence pertaining to genetic testing for FRDA.

**European Federation of Neurological Sciences**

- The European Federation of Neurological Sciences (EFNS, 2014) stated the following regarding testing for ataxia:
  - “In the case of a family history compatible with an autosomal recessive cerebellar ataxia, we recommend a three-step diagnostic approach.”
    - “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).”
    - “Step 2: mutation analysis of the SACS, POLG, Aprataxin (APTX) and SPG7 genes (taking into account specific phenotypes, as given in Table S2), and biochemical testing for white cell enzymes, phytanic acid and long chain fatty acids (good practice point).”
    - “Step 3: referral to a specialized centre, e.g. for skin or muscle biopsy targeted at diagnoses such as Niemann Pick type C, recessive ataxia with coenzyme Q deficiency [aarF domain containing kinase 3 (ADCK3)/autosomal recessive spinocerebellar ataxia 9 (SCAR9)] and mitochondrial disorders, or for extended genetic screening using gene panel diagnostics (good practice point).”
  - “In the case of sporadic ataxia and independent from onset age, we recommend routine testing for SCA1, SCA2, SCA3, SCA, and DRPLA (in Asian patients) (level B), the step one 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 alpha-fetoprotein.”
- For the diagnosis of Friedreich ataxia, guidelines from the European Federation of Neurological Societies (EFNS, 2010) created by consensus of experts members
following literature review recommend: "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)."

American College of Medical Genetics

The American College of Medical Genetics (ACMG, 2013) states the following regarding testing for hereditary ataxias:

- "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.
  - 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."

Criteria

Introduction

Requests for FRDA testing are reviewed using these 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 have identified the known 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

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
  - No known mutation identified by previous analysis, 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
  - 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
  - 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

Exclusions and Other Considerations

For requests for multigene panels, please see the guideline *Hereditary Ataxia Multigene Panel Testing*.

References

Introduction

These references are cited in this guideline.

