

# **Test Specific Guidelines**



# Hereditary Ataxia Multigene Panel Genetic Testing

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Introduction

Hereditary ataxia multigene panel 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.

Procedures addressed by this guideline	Procedure codes
<u>Genomic Unity Ataxia Repeat</u> Expansion and Sequence Analysis	<u>0216U</u>
Genomic Unity Comprehensive Ataxia Repeat Expansion and Sequence Analysis	<u>0217U</u>
Hereditary Ataxia Multigene Panel	<u>81479</u>
<u>Hereditary Ataxia Multigene Panel</u> (including sequencing of at least 15 genes)	<u>81443</u>

## What Are Hereditary Ataxias?

#### **Definition**

<u>The hereditary ataxias are a group of genetic disorders. They are characterized by</u> <u>slowly progressive uncoordinated, unsteady movement and gait, and often poor</u> <u>coordination of hands, eye movements, and speech. Cerebellar atrophy is also</u> <u>frequently seen.<sup>1</sup></u>

#### **Prevalence**

<u>Prevalence estimates vary. The prevalence is approximately 2.7/100,000 and 3.3/100,000 for autosomal dominant and autosomal recessive hereditary ataxias,</u>

# respectively.<sup>2</sup> One study in Norway estimated the prevalence of hereditary ataxia at 6.5 per 100,000 people.<sup>3</sup>

#### Symptoms

Although hereditary ataxias are made up of multiple different conditions, they are characterized by slowly progressive uncoordinated, unsteady movement and gait, and often poor coordination of hands, eye movements, and speech. Cerebellar atrophy is also frequently seen.<sup>1</sup>

#### <u>Cause</u>

<u>Hereditary ataxias are caused by mutations in one of numerous genes.<sup>1</sup> The</u> <u>following genes are associated with hereditary ataxia; however, this list is not</u> <u>intended to be all inclusive: ATN1, ATXN1, ATXN2, ATXN3, CACNA1A, ATXN7, TBP,</u> <u>and FMR1. Several of the ataxias are caused by nucleotide repeat expansions.</u> <u>Testing for these conditions is performed by expansion analysis to identify the</u> <u>number of repeats. Expansion analysis can be performed for diagnostic testing,</u> <u>presymptomatic testing, as well as prenatal testing.</u>

#### **Inheritance**

Most hereditary ataxias, including the spinocerebellar ataxias (SCA), dentatorubral-pallidoluysian atrophy (DRPLA), and episodic ataxia (EA) types 1 and 2, are inherited in an autosomal dominant manner. A few of the hereditary ataxias, including Friedreich ataxia and ataxia telangiectasia, are inherited in an autosomal recessive manner. Fragile X tremor/ataxia syndrome is an X-linked ataxia.<sup>1</sup>

#### <u>Diagnosis</u>

The diagnosis of hereditary ataxia is suspected based on clinical and family history, neurological exam, and neuroimaging studies.<sup>1</sup> Acquired causes of ataxia — including alcoholism, vitamin deficiencies, multiple sclerosis, vascular disease, and tumors — should be ruled out.<sup>1</sup>

Molecular genetic testing can be used to establish a specific diagnosis. In the absence of a family history, it can be difficult to differentiate the type or subtype of hereditary ataxia based on clinical features.<sup>1</sup> One study found that in approximately 13% of apparently sporadic ataxias, a causative genetic change was identified.<sup>4</sup>

#### <u>Management</u>

<u>Treatment of ataxia is largely supportive, and includes the use of canes and walkers for ambulation, speech therapy, and other assistive devices.<sup>1</sup></u>



#### <u>Survival</u>

The survival range of the hereditary ataxias varies across the multiple conditions included in this group.

## **Test Information**

#### **Introduction**

<u>Testing for hereditary ataxias may include known familial mutation analysis, single gene testing, nucleotide repeat expansion analysis, or multigene panel testing. This guideline only addresses multigene panel testing.</u>

#### Multi-Gene Testing Panels

<u>The efficiency of NGS has led to an increasing number of large, multi-gene</u> <u>testing panels. NGS panels that test several genes at once are particularly well-</u> <u>suited to conditions caused by more than one gene or where there is</u> <u>considerable clinical overlap between conditions making it difficult to reliably</u> <u>narrow down likely causes. Additionally, tests should be chosen to maximize the</u> <u>likelihood of identifying mutations in the genes of interest, contribute to</u> <u>alterations in patient management, and/or minimize the chance of finding variants</u> <u>of uncertain clinical significance.</u>

## **Guidelines and Evidence**

#### Introduction

This section includes relevant guidelines and evidence pertaining to hereditary ataxia testing.

European Federation of Neurological Sciences

<u>The European Federation of Neurological Sciences (EFNS, 2014) stated the</u> <u>following regarding testing for hereditary ataxias:<sup>5</sup></u>

<u>"In the case of a family history that is compatible with an autosomal dominant</u> cerebellar ataxia, screening for SCA1, SCA2, SCA3, SCA6, SCA7, and SCA17 is recommended (Level B). In Asian patients, DRPLA should also be tested for."

"If mutation analysis is negative, we recommend contact with or referral to a specialized clinic for reviewing the phenotype and further genetic testing (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 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."

AmeriHealth Caritas

#### **Selected Relevant Publications**

De silva R, Greenfield J, Cook A, et al. (2019) recommended referral to clinical genetics services and/or genetic testing as part of the diagnostic work-up for adults with progressive ataxia. They recommended the following as secondary [first line] care:<sup>6</sup>

"Genetic tests for FRDA, SCA 1, 2, 3, 6, 7 (12,17) and FXTAS"

Hadjivassiliou M, Martindale J, Shanmugarajah P, et al (2017) stated the following with regard to testing for hereditary ataxias:<sup>4</sup>

"We have shown that patients with early onset idiopathic ataxia (irrespective of family history) are much more likely to have a genetic aetiology (81%) than those with late onset idiopathic ataxia (55%). One possible selection criterion for genetic testing is early onset ataxia. Additional selection criteria may include the presence of other clinical features, for example, 1% of patients with histologically suspected/genetically confirmed mitochondrial disease had ataxia with other clinical features, diabetes, myoclonus, etc) and only 9% pure ataxia."

"Furthermore, the presence of severe cerebellar atrophy without any clinical correlation and with well-preserved spectroscopy of the cerebellum often suggests that the ataxia is long standing (maybe even early onset) and slowly progressive. Patients should therefore be offered genetic testing. The pattern of cerebellar involvement on MR spectroscopy may also direct to a particular diagnosis. Most genetic ataxias involve both the hemispheres and the vermis while the majority of immune-mediated acquired ataxias (eg, gluten ataxia, anti-GAD ataxia and primary autoimmune cerebellar ataxia) have a predilection for the vermis."

Jayadev S and Bird T (2013) stated the following: 7

The "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."

Regarding establishing the diagnosis of hereditary ataxias:

"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."

"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."

<u>Regarding testing when the family history suggests autosomal dominant</u> <u>inheritance:</u>

"An estimated 50–60% of the dominant hereditary ataxias can be identified with highly accurate and specific molecular genetic testing for SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, SCA10, SCA12, SCA17, and DRPLA; all have nucleotide repeat expansions in the pertinent genes."

"Because of broad clinical overlap, most laboratories that test for the hereditary ataxias have a battery of tests including testing for SCA1, SCA2, SCA3, SCA6, SCA7, SCA10, SCA12, SCA14, and SCA17. Many laboratories offer them as two groups in stepwise fashion based on population frequency, testing first for the more common ataxias, SCA1, SCA2, SCA3, SCA6, and SCA7. Although pursuing multiple genes simultaneously may seem less optimal than serial genetic testing, it is important to recognize that the cost of the battery of ataxia tests often is equivalent to that of an MRI. Positive results from the molecular genetic testing are more specific than MRI findings in the hereditary ataxias. Guidelines for genetic testing of hereditary ataxia have been published."

"Testing for the less common hereditary ataxias should be individualized and may depend on factors such as ethnic background (SCA3 in the Portuguese, SCA10 in the Native American population with some exceptions [Fujigasaki et al., 2002]); seizures (SCA10); presence of tremor (SCA12, fragile X-associated tremor/ataxia syndrome); presence of psychiatric disease or chorea (SCA17); or uncomplicated ataxia with long duration (SCA6, SCA8, and SCA14). Dysphonia and palatal myoclonus are associated with calcification of the dentate nucleus of cerebellum (SCA20)."

"If a strong clinical indication of a specific diagnosis exists based on the affected individual's examination (e.g., the presence of retinopathy, which suggests SCA7) or if family history is positive for a known type, testing can be performed for a single disease."

Regarding testing 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."

Regarding testing for a simplex 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."

# <u>Criteria</u>

Introduction

<u>Requests for hereditary ataxia multigene panel testing are reviewed using these criteria.</u>

Multigene Panel Testing

Genetic counseling:

<u>Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND</u>

Previous Genetic Testing

No previous testing of requested genes, and

No known mutation identified by previous analysis, and

No known familial mutation in a gene known to cause ataxia, AND

**Diagnostic Testing for Symptomatic Individuals** 

Individual has been diagnosed with cerebellar ataxia, regardless of age of onset, AND

Documentation from ordering provider indicating how test results will be used to directly impact medical care for the individual (e.g. change in surveillance or treatment plan), 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, etc), AND

Family and medical history do not point to a specific genetic diagnosis or pattern of inheritance for which a more focused test or panel, such as a nucleotide repeat analysis panel, would be appropriate, AND

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

**Billing and Reimbursement Considerations** 

Gene panels that are specific to hereditary ataxias will only be considered for reimbursement. This testing will only be considered for reimbursement when billed with an appropriate panel CPT code: 81443, 81479, 0216U, or 0217U. Analysis of individual genes will not be reimbursed separately.

Test methodology should be appropriate to the disease-causing mutations that are commonly reported for the disorder in question (e.g., sequencing only panels will not detect triplet repeat or large deletion/duplication mutations).

For information on spinocerebellar ataxia (SCA) panel testing, please refer to the guideline Spinocerebellar Ataxia Genetic Testing, as this focused testing is not addressed here.

#### **References**

Introduction

These references are cited in this guideline.

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