Spinocerebellar Ataxia Genetic Testing

Introduction

Spinocerebellar ataxia (SCA) 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.

<table>
<thead>
<tr>
<th>Procedures addressed by this guideline</th>
<th>Procedure codes</th>
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<tr>
<td>ATXN1 gene analysis, evaluation to detect abnormal (eg, expanded) allele</td>
<td>81178</td>
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<tr>
<td>ATXN2 gene analysis, evaluation to detect abnormal (eg, expanded) allele</td>
<td>81179</td>
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<tr>
<td>ATXN3 gene analysis, evaluation to detect abnormal (eg, expanded) allele</td>
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<td>ATXN7 gene analysis, evaluation to detect abnormal (eg, expanded) allele</td>
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<td>ATXN8 gene analysis, evaluation to detect abnormal (eg, expanded) alleles</td>
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<td>ATXN10 gene analysis, evaluation to detect abnormal (eg, expanded) alleles</td>
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<tr>
<td>CACNA1A gene analysis; evaluation to detect abnormal (eg, expanded) alleles</td>
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<tr>
<td>CACNA1A gene analysis; full gene sequence</td>
<td>81185</td>
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<td>CACNA1A gene analysis; known familial variant</td>
<td>81186</td>
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<tr>
<td>PPP2R2B gene analysis, evaluation to detect abnormal (eg, expanded) alleles</td>
<td>81343</td>
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<td>TBP gene analysis, evaluation to detect abnormal (eg, expanded) alleles</td>
<td>81344</td>
</tr>
<tr>
<td>Unlisted molecular pathology procedure</td>
<td>81479</td>
</tr>
</tbody>
</table>
What is spinocerebellar ataxia

Definition

Spinocerebellar ataxias (SCA) are a group of autosomal dominant ataxias that have a range of phenotypes. There are various subtypes of SCA, which are denoted by numbers (e.g. SCA1, SCA3, etc.)

Incidence and Prevalence

The prevalence of autosomal dominant cerebellar ataxias, as a whole, is 1-5:100,000.¹ SCA3 is the most common autosomal dominant form of ataxia. This is followed by SCA1, SCA2, SCA6, and SCA7.¹ The prevalence of specific subtypes of SCA vary by region. SCA3 is most common is Portugal.¹

Symptoms

Although the specific phenotype of each subtype varies, most individuals with SCA have “progressive adult-onset gait ataxia (often with hand dysmetria) and dysarthria associated with cerebellar atrophy on brain imaging.”¹ The age of onset for the different subtypes also overlaps, which makes it difficult to distinguish between subtypes based on clinical phenotype only.¹,² See the table below for the various subtypes of SCA and the associated clinical features.

Cause

SCAs are caused by mutations in one of numerous genes. See the table below for the various subtypes of SCA and the associated genes.

Inheritance

SCAs are inherited in an autosomal dominant pattern. Children of an individual with an SCA have a 50% chance of inheriting the mutation. Anticipation is also observed in some of the SCAs. This means that as the disease passes through generations, the severity can increase and the age of onset can decrease.

Diagnosis

Molecular genetic testing can be used to establish a specific diagnosis, which aids in understanding the prognosis and risk assessment for family members.¹

Treatment

Treatment of ataxia is largely supportive, and includes the use of canes and walkers for ambulation, speech therapy, and other assistive devices.¹
<table>
<thead>
<tr>
<th>SCA subtype</th>
<th>Gene Associated</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCA1</td>
<td>ATXN1</td>
<td>Progressive cerebellar ataxia, dysarthria, deterioration of bulbar functions, pyramidal signs, peripheral neuropathy&lt;sup&gt;2,3&lt;/sup&gt;</td>
</tr>
<tr>
<td>SCA2</td>
<td>ATXN2</td>
<td>Progressive ataxia and dysarthria, nystagmus, slow saccadic eye movements, peripheral neuropathy, decreased DTRs, dementia&lt;sup&gt;2,4&lt;/sup&gt;</td>
</tr>
<tr>
<td>SCA3</td>
<td>ATXN3</td>
<td>Gait problems, speech difficulties, clumsiness, visual blurring, diplopia, hyperreflexia, progressive ataxia, nystagmus, dysarthria, pyramidal and extrapyramidal signs; lid retraction, nystagmus, decreased saccade velocity; amyotrophy fasciculations, sensory loss&lt;sup&gt;2,5&lt;/sup&gt;</td>
</tr>
<tr>
<td>SCA4</td>
<td>16q22.1</td>
<td>Sensory axonal neuropathy, deafness; may be allelic with 16q22-linked SCA&lt;sup&gt;2&lt;/sup&gt;</td>
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<tr>
<td>SCA5</td>
<td>SPTBN2</td>
<td>Early onset, slow course&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>SCA6</td>
<td>CACNA1A</td>
<td>Progressive cerebellar ataxia, dysarthria, nystagmus, sometimes episodic ataxia, very slow progression&lt;sup&gt;2,6&lt;/sup&gt;</td>
</tr>
<tr>
<td>SCA7</td>
<td>ATXN7</td>
<td>Progressive cerebellar ataxia, dysarthria, dysphagia, cone-rod and retinal dystrophy with progressive central visual loss resulting in blindness&lt;sup&gt;2,7&lt;/sup&gt;</td>
</tr>
<tr>
<td>SCA subtype</td>
<td>Gene Associated</td>
<td>Clinical Features</td>
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</tr>
<tr>
<td>SCA8</td>
<td>ATXN8</td>
<td>Principally cerebellar ataxia, slowly progressing ataxia, scanning dysarthria, truncal instability, hyperactive tendon reflexes, decreased vibration sense; rarely, cognitive impairment&lt;sup&gt;2,8&lt;/sup&gt;</td>
</tr>
<tr>
<td>SCA10</td>
<td>ATXN10</td>
<td>Progressive cerebellar ataxia, scanning dysarthria, dysphagia, upper-limb ataxia, generalized motor seizures and/or complex partial seizures, most families are of Native American background&lt;sup&gt;2,9&lt;/sup&gt;</td>
</tr>
<tr>
<td>SCA11</td>
<td>TTBK2</td>
<td>Progressive cerebellar ataxia, abnormal eye signs (jerky pursuit, horizontal and vertical nystagmus), mild, remain ambulatory&lt;sup&gt;2,10&lt;/sup&gt;</td>
</tr>
<tr>
<td>SCA12</td>
<td>PPP2R2B</td>
<td>Slowly progressive ataxia; action tremor in the 30s; hyperreflexia; subtle Parkinsonism possible; cognitive/psychiatric disorders including dementia&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>SCA13</td>
<td>KCNC3</td>
<td>Ranges from progressive childhood-onset cerebellar ataxia, cerebellar dysarthria, occasional seizures to adult-onset progressive ataxia, mild intellectual disability, short stature&lt;sup&gt;2,11&lt;/sup&gt;</td>
</tr>
<tr>
<td>SCA subtype</td>
<td>Gene Associated</td>
<td>Clinical Features</td>
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<tr>
<td>SCA14</td>
<td>PRKCG</td>
<td>Progressive cerebellar ataxia, dysarthria, nystagmus, axial myoclonus, cognitive impairment, tremor, sensory loss, Parkinsonian features including rigidity and tremor\textsuperscript{2,12}</td>
</tr>
<tr>
<td>SCA15</td>
<td>ITPR1</td>
<td>Progressive gait and limb ataxia, ataxic dysarthria, titubation, upper limb postural tremor, mild hyperreflexia, gaze-evoked nystagmus, and impaired vestibuloocular reflex gain\textsuperscript{2,13}</td>
</tr>
<tr>
<td>SCA16</td>
<td>ITPR1</td>
<td>Head tremor; reported in one Japanese family\textsuperscript{2}</td>
</tr>
<tr>
<td>SCA17</td>
<td>TBP</td>
<td>Ataxia, dementia, mental deterioration; occasional chorea, dystonia, myoclonus, epilepsy; Purkinje cell loss, intranuclear inclusions with expanded polyglutamine\textsuperscript{2,14}</td>
</tr>
<tr>
<td>SCA18</td>
<td>7q22-q32</td>
<td>Ataxia with early sensory/motor neuropathy, nystagmus, dysarthria, decreased tendon reflexes, muscle weakness, atrophy, fasciculations, Babinski responses\textsuperscript{2}</td>
</tr>
<tr>
<td>SCA19/22</td>
<td>KCND3</td>
<td>Slowly progressive, rare cognitive impairment, myoclonus, hyperreflexia\textsuperscript{2}</td>
</tr>
<tr>
<td>SCA subtype</td>
<td>Gene Associated</td>
<td>Clinical Features</td>
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</tr>
<tr>
<td>SCA20</td>
<td>11q12</td>
<td>Progressive ataxia, dysarthria, palatal tremor (myoclonus), and/or abnormal phonation clinically resembling spasmodic adductor dysphonia, hyperreflexia, bradykinesia; calcification of the dentate nucleus.²,¹⁵</td>
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<tr>
<td>SCA21</td>
<td>TMEM240</td>
<td>Mild cognitive impairment²</td>
</tr>
<tr>
<td>SCA23</td>
<td>PDYN</td>
<td>Dysarthria, abnormal eye movements, reduced vibration and position sense; reported in one Dutch family; neuropathology²</td>
</tr>
<tr>
<td>SCA25</td>
<td>SCA25</td>
<td>Sensory neuropathy; reported in one French family²</td>
</tr>
<tr>
<td>SCA26</td>
<td>EEF2</td>
<td>Dysarthria, irregular visual pursuits; reported in one Norwegian-American family; MRI: cerebellar atrophy²</td>
</tr>
<tr>
<td>SCA27</td>
<td>FGF14</td>
<td>Early-onset tremor; dyskinesia, cognitive deficits; reported in one Dutch family²</td>
</tr>
<tr>
<td>SCA28</td>
<td>AFG3L2</td>
<td>Young-adult onset, progressive gait and limb ataxia resulting in coordination and balance problems, dysarthria, ptosis, nystagmus, and ophthalmoparesis, increased tendon reflexes; reported in two Italian families²,¹⁶</td>
</tr>
<tr>
<td>SCA29</td>
<td>ITPR1</td>
<td>Learning deficits²</td>
</tr>
<tr>
<td>SCA30</td>
<td>4q34.3-q35.1</td>
<td>Hyperreflexia²</td>
</tr>
<tr>
<td>SCA31</td>
<td>BEAN1</td>
<td>Normal sensation²</td>
</tr>
<tr>
<td>SCA subtype</td>
<td>Gene Associated</td>
<td>Clinical Features</td>
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<tr>
<td>SCA35</td>
<td>TGM6</td>
<td>Hyperreflexia, Babinski responses; spasmodic torticollis²</td>
</tr>
<tr>
<td>SCA36</td>
<td>NOP56</td>
<td>Late-onset, slowly progressive cerebellar syndrome typically associated with sensorineural hearing loss, muscle atrophy and denervation, especially of the tongue, as well as pyramidal signs, muscle fasciculations, hyperreflexia²,¹⁷</td>
</tr>
<tr>
<td>SCA37</td>
<td>1p32</td>
<td>Abnormal vertical eye movements¹</td>
</tr>
<tr>
<td>SCA38</td>
<td>ELOVL5</td>
<td>Adult onset, axonal neuropathy¹</td>
</tr>
<tr>
<td>SCA40</td>
<td>CCDC88C</td>
<td>Adult onset, brisk reflexes, spasticity¹</td>
</tr>
<tr>
<td>SCA42</td>
<td>CACNA1G</td>
<td>Mild pyramidal signs, saccadic pursuit¹</td>
</tr>
</tbody>
</table>

**Test Information**

**Introduction**

Testing for SCA may include known familial mutation analysis, expansion analysis, sequencing, deletion/duplication analysis, or multi-gene panel testing. Test methods vary by gene.

**Expansion analysis**

Several of the SCAs are caused by triplet repeat expansions. Testing for these conditions is performed by expansion analysis to identify the number of repeats. Expansion analysis can be performed for diagnostic testing, presymptomatic testing, as well as prenatal testing.

**Sequencing**

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 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**

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

Known familial mutation analysis is performed when a causative mutation has been identified in a close relative of the individual requesting testing.

**Guidelines and Evidence**

**Introduction**

This section includes relevant guidelines and evidence pertaining to SCA testing.

**European Federation of Neurological Sciences**

The European Federation of Neurological Sciences (EFNS, 2014) stated the following with regards to testing for autosomal dominant cerebellar ataxia:

- “In the case of a family history that is compatible with an autosomal dominant 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.”

**American College of Medical Genetics**

The American College of Medical Genetics (ACMG, 2013) stated the following 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."

- “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."

- "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."

For testing when the family history suggests autosomal dominant inheritance, ACMG recommends the following:

- "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 the 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."
For testing simplex cases, ACMG recommends the following:

- "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."

Peer-reviewed literature

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

- “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 (eg, deafness, diabetes, myoclonus, etc) and only 9% pure ataxia."\(^{19}\)

- “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."\(^{19}\)

Criteria

Introduction

Requests for SCA testing are reviewed using these 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 gene analysis of requested gene that would have identified the mutation, AND

- Presymptomatic Testing for Asymptomatic Individuals:
  - Member is 18 years of age or older, and
  - Known disease-causing mutation in SCA gene identified in 1\textsuperscript{st} or 2\textsuperscript{nd} degree relative(s), OR

- Diagnostic Testing for Symptomatic Individuals:
  - Known disease-causing mutation in SCA gene identified in 1\textsuperscript{st} or 2\textsuperscript{nd} degree relative(s), AND

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

Single gene testing

- 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 testing of requested gene(s), and
  - No mutation identified by previous analysis, if performed, 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, and
  - Medical history points to the specific subtype of SCA requested (e.g. age of onset, distinguishing features present, etc), 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 history is consisted with an autosomal dominant inheritance pattern (including simplex cases), AND
• Rendering laboratory is a qualified provider of service per the Health Plan policy

**Multigene panel testing**

• Genetic counseling:
  o Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

• Previous Genetic Testing:
  o No previous testing of requested genes, and
  o No mutation identified by previous analysis, if performed, and
  o No known familial mutation in a gene known to cause ataxia, AND

• Diagnostic Testing for Symptomatic Individuals:
  o 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 history is consistent with an autosomal dominant inheritance pattern (including simplex cases), AND

• Medical history does not point to a specific genetic diagnosis for which a more focused test or panel would be appropriate, AND

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

**Billing and reimbursement considerations**

For broader hereditary ataxia panel testing requests, see *Hereditary Ataxia Multigene Panel Testing* guideline.

Gene panels that are specific to SCA will be eligible for reimbursement according to the criteria outlined in this guideline. When multiple CPT codes are billed for components of a panel and there is a more appropriate CPT code representing the panel, eviCore will redirect to the panel code(s).
If the laboratory will not accept redirection to a panel code, the medical necessity of each billed component procedure will be assessed independently.

- In general, only a limited number of panel components that are most likely to explain the member’s presentation will be reimbursable. The remaining panel components will not be reimbursable.
- When the test is billed with multiple stacked procedure codes, only the following genes may be considered for reimbursement:
  - ATXN1 (SCA1)
  - ATXN2 (SCA2)
  - ATXN3 (SCA3)
  - CACNA1A (SCA6)
  - ATXN7 (SCA7)
  - TBP (SCA17)

References

Introduction

These references are cited in this guideline.


