Spinocerebellar Ataxia Repeat Expansion Analysis

DISORDER ALSO KNOWN AS
SCA, Hereditary Ataxia, Spinocerebellar Degeneration

PANEL GENE LIST
ATXN1, ATXN2, ATXN3, ATXN7, ATXN8, CACNA1A

CLINICAL FEATURES
The Spinocerebellar Ataxias (SCAs) are a clinically and genetically heterogeneous group of neurodegenerative disorders classified into subtypes based on age of onset, mode of inheritance, and clinical features. Clinical features of SCA include poor coordination, unsteady gait, dysarthria, dysphagia, and abnormal eye movement. Sensory neuropathy, spasticity, and hyperreflexia have also been noted.[1,2] Many of these features are due to cerebellar atrophy, which can be identified by brain MRI.[3] Although less common, cognitive and behavioral issues are also reported for some types of SCA.[2] Considerable phenotypic overlap exists between the autosomal dominant SCAs; however, distinguishing features have been noted for almost all subtypes.[2,3] Age of disease onset is variable for this group of disorders, but symptoms typically present in the 3rd to 4th decades of life.[2] Treatment is primarily supportive in most forms of inherited SCA.[3]

The prevalence of the autosomal dominant cerebellar ataxias is estimated to be 1-5:100,000 individuals in the general population.[4] Most individuals with autosomal dominant ataxia have an affected parent, although occasionally the family history is negative due to reduced penetrance or late onset of the disorder in a parent.[3] SCA3 is the most common form of autosomal dominant ataxia worldwide, although prevalence of each subtype varies by ethnicity.[3]

INHERITANCE PATTERN/GENETICS
Ataxias can be either genetic or non-genetic in nature. The SCAs evaluated by this panel are inherited in an autosomal dominant and/or autosomal recessive manner and are caused by both coding and non-coding CAG polynucleotide repeat expansions.[3] Repeat expansions are generally meiotically unstable, which can result in expansion of the repeat during transmission from parent to offspring. Disease severity and age of onset are loosely based on repeat number for some of the genes evaluated (ATXN1, ATXN2, ATXN3, ATXN7), but not others (CACNA1A).[5-9] For subtypes that display anticipation, the mildest, latest onset forms are associated with the smallest number of repeats and the most severe, earliest-onset forms are associated with the greatest number of repeats.[1,2] Although anticipation has been observed in families with ATXN8 expansions, all repeat lengths have shown reduced penetrance and may not result in disease at any age.[10] For all SCA subtypes, repeat length should not be used to predict disease onset or prognosis.[2]

TEST METHODS
Using genomic DNA from the submitted specimen, standard PCR fragment analysis is performed to identify alleles with 100 or fewer repeats and repeat primed PCR is used to identify alleles with >100 repeats, as well as determine the number of repeats in alleles with 100 or fewer repeats. Nucleotide repeat numbers of 50 or fewer are reported with an accuracy of +/- 2 repeats and repeat numbers from 51-100 are reported with an accuracy of +/- 5 repeats. Internal standards are analyzed along with clinical samples to evaluate assay performance. The exact number of repeats cannot be determined for alleles with greater than 100 repeats. Southern blot analysis is required to determine the number of repeats in alleles larger than this and is not completed as part of this test.

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CLINICAL SENSITIVITY

The clinical sensitivity of this assay depends on the clinical phenotype of the patient. SCA types 1, 2, 3, 6, 7, and 8 are estimated to account for 65% of the autosomal dominant SCAs, worldwide.[3] The technical sensitivity of fragment analysis is estimated to be greater than 95%.

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Repeat Analysis of 6 Genes

Gene	Disease Associations	Inheritance	Diagnostic Yield in Selected Population(s)
ATXN1	SCA1	AD	6% of AD ataxia worldwide* [3]Most common AD ataxia in Siberia[5]
ATXN2	SCA2	AD	15% of AD ataxia worldwide* [3]Most common AD ataxia in Korea[6]
ATXN3	SCA3	AD	21% of AD ataxia worldwide* [3]Most common AD ataxia worldwide[7]
ATXN7	SCA7	AD	5% of AD ataxia worldwide* [3]Common in Scandinavian, South African, and Mexican populations[11]
ATXN8	SCA8	AD	3% of AD ataxia worldwide* [3,10]Common form of ataxia in Finland[10]
CACNA1A	SCA6	AD	15% of AD ataxia worldwide* [3]~31% of AD ataxia in Japan[9]

Abbreviations:
SCA – Spinocerebellar Ataxia
AD – Autosomal Dominant

*Diagnostic yield varies widely based on population[3]

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