Spinocerebellar Ataxia Type 1 Repeat Analysis

DISORDER ALSO KNOWN AS
SCA1

CLINICAL FEATURES
SCA1 is a neurodegenerative disorder presenting with balance issues and slurred speech.[1,2]As the disease progresses, individuals experience worsening cerebellar ataxia, dysarthria, dysphagia, impaired gait, decreased or absent deep tendon reflexes, hypermetric saccades, nystagmus, and muscle atrophy.[1,2] Decline in executive function, attention, and memory have been noted and is more rapid in SCA1 as compared to the other SCAs.[3,4] Significant degeneration of cerebellar Purkinje cells and brainstem atrophy are often identified by MRI.[5,6]

The age of onset of SCA1 is typically in the third or fourth decade, though childhood and late-adult onset have been reported.[1] The average disease duration is approximately 15 years (ranging from 10-30 years); individuals with juvenile onset disease experience a more rapid progression.[1,7]

The overall prevalence of SCA1 is estimated to be 1-2:100,000 individuals and accounts for 6% of autosomal dominant cerebellar ataxia worldwide, but varies by ethnic origin and geographic location.[1]

Inheritance Pattern/Genetics
SCA1 is an autosomal dominant disorder caused by the expansion of a CAG trinucleotide repeat in exon 8 of the *ATXN1* gene.[1] Molecular genetic testing identifies an expansion in more than 99% of affected individuals.[1]

The clinical subtypes associated with disease alleles fall along a spectrum that is loosely based on CAG repeat number; where the mildest, latest onset forms are associated with the smallest number of repeats and the more severe, earliest-onset forms are associated with the greatest number of repeats.[1] Most individuals with 35 or fewer repeats are unaffected, while pathogenic alleles have 47 or more repeats.[1] Alleles with 36-46 repeats are considered of uncertain significance although the presence of CAT interruptions have been reported to influence disease association.[1] Evaluation of CAT interruptions is not completed as part of this analysis. Anticipation has been observed in SCA1, with expansions more likely to occur when paternally transmitted, while contractions are more typical of maternal transmission.[1]

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.

CLINICAL SENSITIVITY
The clinical sensitivity for analysis of the CAG repeat in *ATXN1* depends on the clinical phenotype of the patient. All individuals with SCA type 1 have an expansion of the CAG repeat in exon 8 of the *ATXN1* gene, which is detectable by this targeted analysis. The technical sensitivity of fragment analysis is estimated to be greater than 95%.

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