Spinocerebellar Ataxia Type 7 Repeat Analysis

DISORDER ALSO KNOWN AS
SCA7

CLINICAL FEATURES
SCA7 is a neurodegenerative disorder that typically presents with vision concerns or poor coordination in adults, and hypotonia and muscle weakness in children.[1] As the disease progresses, SCA7 is characterized by progressive cerebellar ataxia, dysarthria, dysphagia, dysmetria, dysdiadochokinesia, and progressive cone-rod retinal dystrophy in adults.[1] Disease duration in adults is approximately 20 years, but tends to be variable.[1,2] The infantile-onset form of SCA7 has an aggressive course with rapid decline, resulting in failure to thrive, muscle weakness and wasting, developmental delay and regression, retinal degeneration, and cerebellar degeneration.[1] Retinopathy resulting in vision loss and/or blindness is a characteristic feature of SCA7.[1,2] However, the cerebellar and brain stem degeneration noted in the infantile-onset form SCA7 can be so rapid that visual symptoms may not be evident.[1,3]

The overall prevalence of SCA7 is estimated to be 1:100,000 individuals and accounts for approximately 5% of autosomal dominant SCAs worldwide, but varies by ethnic origin and geographic location.[1,4]

INHERITANCE PATTERN/GENETICS
SCA7 is an autosomal dominant disorder caused by the expansion of a CAG trinucleotide repeat in the coding sequence of exon 1 of the *ATXN7* 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, earlier-onset form is associated with the greatest number of repeats.[1] Individuals with 19 or fewer CAG repeats are unaffected.[1] Alleles with 20-27 CAG repeats are uncommon in the general population and it is unknown if they are associated with disease.[1] Premutation alleles with 28-33 CAG repeats are not associated with symptoms of SCA7, however, they are meiotically unstable and expansion of these alleles has been observed in their transmission from parent to offspring, more commonly with paternal transmission. Therefore, offspring of these individuals have an increased risk of inheriting an expanded allele and being affected.[5] Alleles with 34-36 CAG repeats are associated with incomplete penetrance and a milder phenotype, while alleles with 37 or more are fully penetrant and pathogenic.[1,6] Anticipation has been observed in SCA7 and in general, larger repeat numbers are associated with earlier disease onset and faster disease progression.[7]

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.4

CLINICAL SENSITIVITY
The clinical sensitivity for analysis of the CAG repeat in *ATXN7* depends on the clinical phenotype of the patient. All individuals with SCA type 7 have an expansion of the CAG repeat in the coding sequence of exon 1 of the

ATXN7, which is detectable by this targeted analysis. The technical sensitivity of fragment analysis is estimated to be greater than 95%.

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