Spinocerebellar Ataxia Type 6 Repeat Analysis

CLINICAL FEATURES

SCA6 is a neurodegenerative disorder characterized by slowly progressive cerebellar ataxia, dysarthria, and nystagmus.[1] Age of onset and disease progression are typically later and slower than other forms of adult onset SCA. Symptoms may present between 19-71 years of age, although the mean age of onset is 43-52 years.[1,2] Affected individuals demonstrate a long disease course of greater than 25 years, typically compatible with a normal lifespan.[2,3,4]

Most individuals present with gait disturbance, or more rarely, dysarthria. As the disease progresses, intention tremor, upper limb incoordination, dysarthria, and dysphagia become more evident. Gaze-evoked and downbeat nystagmus are present in most individuals with SCA6; while diplopia is present in approximately half of affected individuals.[1] Hyperreflexia, dystonia, and sensory issues have also been reported.[1,3,4] Cerebellar atrophy is frequently noted on brain MRI, but the brainstem is usually unremarkable or only mildly affected. Neuronal loss is widespread but usually less severe than in other types of SCA.[3,4] Clinical features and age of onset are highly variable for this disorder, even within the same family. The overall prevalence of SCA6 is estimated to be 0.02-0.31:100,000 individuals, but varies by ethnic origin and geographic location.[1]

INHERITANCE PATTERN/GENETICS

SCA6 is an autosomal dominant disorder caused by the expansion of a CAG trinucleotide repeat in the 3' UTR of the *CACNA1A* gene.[1,4] 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.[1,5] Normal alleles have 18 or fewer repeats, and pathogenic alleles have 20 or greater repeats. Premutation alleles with 19 CAG repeats are not typically associated with clinical features; however, they are meiotically unstable and expansion of this allele into the pathogenic range has been observed in their transmission from parent to offspring.[6,7] The clinical significance of these alleles should be interpreted within the context of clinical presentation and family history. Anticipation has not been reported for SCA6, and is attributed to the small size and stability of the CAG repeat observed in affected individuals.[1,5]

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 *CACNA1A* depends on the clinical phenotype of the patient. All individuals with SCA type 6 have an expansion of the CAG repeat in the 3' UTR of the CACNA1A 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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