Spinocerebellar Ataxia Type 3 Repeat Analysis

DISORDER ALSO KNOWN AS
SCA3, Machado-Joseph Disease

CLINICAL FEATURES
SCA3, also known as Machado-Joseph disease, generally presents with gait disturbance, speech difficulties, and clumsiness.[1] As the disease progresses, cerebellar ataxia and pyramidal signs become more evident.[1] Individuals with late stage disease typically have impaired ambulation, severe dysarthria, ophthalmoparesis, dysphagia, dystonic posturing, and muscle atrophy.[1,2] Neuropathology demonstrates atrophy of the cerebellum and brainstem on brain MRI, with widespread neuronal loss.[1,3] SCA3 has been categorized into subtypes based on age of onset and clinical features. Type I (dystonic-rigid form; 13% of cases) is characterized by spasticity, rigidity, ophthalmoparesis, and an earlier age of onset. Type II (ataxia with pyramidal signs; 57% of cases) is characterized by adult onset of ataxia, spasticity, and hyperreflexia. Type III (peripheral amyotrophy; 30% of cases) is characterized by late onset of ataxia, peripheral polyneuropathy, and parkinsonism.[1] Clinical features are variable even within the same family. Features are progressive with an average disease duration of 10 years; ranging from 1-20 years.[4]

SCA3 is the most common autosomal dominant ataxia accounting for approximately 21% worldwide, but varies by ethnic origin and geographic location.[5]

INHERITANCE PATTERN/GENETICS
SCA3 is an autosomal dominant disorder caused by the expansion of a CAG trinucleotide repeat in the coding sequence of exon 10 of the *ATXN3* 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. Individuals with 44 or fewer CAG repeats are unaffected.[6]Alleles with 45-59 CAG repeats are uncommon in the general population and it is unknown if they are associated with disease.[6] Alleles with 60 or more CAG repeats are fully penetrant and pathogenic.[6] A nticipation has been observed in SCA3 and larger repeat sizes are generally associated with earlier onset and faster disease progression.[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 *ATXN3* depends on the clinical phenotype of the patient. All individuals with SCA type 3 have an expansion of the CAG repeat in the coding sequence of exon 10 of the *ATXN3* 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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