Spinocerebellar Ataxia Type 2 Repeat Analysis

DISORDER ALSO KNOWN AS

SCA2

CLINICAL FEATURES

SCA2 is a slowly progressive neurodegenerative disorder presenting with coordination and balance issues.[1] SCA2 is characterized by ataxia, dysarthria, dysphagia, and oculomotor dysfunctions including nystagmus, slow saccadic eye movements, and ophthalmoparesis.[1,2] Tremor, peripheral neuropathy, decreased muscle tone, and dystonia or chorea have also been reported later in the disease course. Dementia and intellectual impairment have been reported in some individuals with L-dopa-responsive parkinsonism, and an increased risk for amyotrophic lateral sclerosis (ALS) has been identified.[1,3,4] Neuropathology demonstrates marked atrophy of the cerebellum, pons, medulla oblongata, and spinal cord on brain MRI, with significant loss of cerebellar Purkinje cells.[1,2,5] In addition, an infantile onset neurodevelopmental phenotype including developmental delay, visual impairment, hypotonia, seizures, abnormal movements, and/or cerebellar atrophy has also been reported in a number of individuals.[8]

The mean age of onset is in the fourth decade with a 10-15 year disease duration, although rapid progression of symptoms has been noted in individuals presenting before 20 years of age.[1,2,4]

SCA2 accounts for approximately 15% of autosomal dominant ataxias worldwide, but varies by ethnic origin and geographic location.[6] It is the most common autosomal dominant ataxia in Korea, and has a large founder population in Cuba.[6]

INHERITANCE PATTERN/GENETICS

SCA2 is inherited in an autosomal dominant manner; caused by the expansion of a CAG trinucleotide repeat in exon 1 of the ATXN2 gene.[1] Molecular genetic testing identifies an expansion in more than 99% of affected individuals.[1]

Most individuals with 30 or fewer CAG repeats are unaffected.[1] Alleles with 31-32 repeats are uncommon in the general population and it is unknown if they are associated with disease.[1] Alleles with 33-34 repeats are associated with incomplete penetrance, while alleles with 35 or more are fully penetrant and pathogenic.[1] CAA interruptions within the CAG repeat may enhance the meiotic stability of the repeat, but are not expected to have an effect on pathogenicity.[1] Evaluation of CAA interruptions is not completed as part of this analysis. Anticipation has been reported for SCA2, and is most often noted with paternal 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.

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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 ATXN2 depends on the clinical phenotype of the patient. All individuals with SCA type 2 have an expansion of the CAG repeat in exon 1 of the ATXN2 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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