Spinocerebellar Ataxia Type 8 Repeat Analysis

DISORDER ALSO KNOWN AS
SCA8

CLINICAL FEATURES
SCA8 is a slowly progressive cerebellar ataxia usually presenting with gait instability and dysarthria.[1] Clinical features of SCA8 include gait ataxia, dysarthria, limb-dysmetria, and nystagmus.[1-4] S canning dysarthria with a characteristic drawn-out slowness of speech is a distinctive finding.[1] Issues with executive function, attention, and information processing have been noted.[4,5] Cerebellar atrophy, specifically in the cerebellar hemisphere and vermis are typically identified on neuroimaging.[3,4] SCA8 typically presents in adulthood, although onset ranges from 1 to 73 years.[1,3] Disease progression is over decades regardless of age of onset, and lifespan is not typically reduced.[2,3]

SCA8 accounts for approximately 3% of autosomal dominant cerebellar ataxia wordwide.[1,6]

INHERITANCE PATTERN/GENETICS
SCA8 is an autosomal dominant disorder caused by the expansion of a TAG-CAG repeat present in the open reading frame of the *ATXN8* gene, which is overlapping and anti-parallel to the CTA-CTG repeat in the *ATXN8OS* gene.[1] Molecular genetic testing identifies an expansion in more than 99% of affected individuals.[1]

Most individuals with 50 or fewer repeats are unaffected, while pathogenic alleles have 80 or more repeats. Alleles with 51-79 repeats have uncertain significance, as they have been observed in affected individuals and unaffected relatives of affected individuals. Intervening TAG repeats have been reported in affected and unaffected individuals, and may account for the variability and incomplete penetrance of alleles with more than 50 repeats.[1] Evaluation of TAG interruptions is not completed as part of this analysis. Expansions are more likely to occur during maternal transmission, while contractions are more typical of paternal transmission.[3]However, incomplete penetrance is seen with all repeat lengths; therefore, repeat length is not predictive of disease course.[1] In addition, individuals with homozygous expansions appear to have similar clinical course to those with heterozygous expansions.[1,2]

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 51-1 00 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 *ATXN8* depends on the clinical phenotype of the patient. All individuals with SCA type 8 have an expansion of the CAG repeat in the *ATXN8* 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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REFERENCES:

1. Ayhan et al. (1993) Spinocerebellar Ataxia Type 8. 2001 Nov 27 [Updated 2014 Apr 3]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019. (Available from: https://www.ncbi.nlm.nih.gov/books/NBK1268/): (PMID: 20301445)
2. Ikeda Y et al. Spinocerebellar ataxia type 8: molecular genetic comparisons and haplotype analysis of 37 families with ataxia. American Journal Of Human Genetics. 2004 Jul 75(1):3-16 (PMID: 15152344)
3. Day JW et al. Spinocerebellar ataxia type 8: clinical features in a large family. Neurology. 2000 Sep 12 55(5):649-57 (PMID: 10980728)
4. Juvonen V et al. Clinical and genetic findings in Finnish ataxia patients with the spinocerebellar ataxia 8 repeat expansion. Annals Of Neurology. 2000 Sep 48(3):354-61 (PMID: 10976642)
5. Lilja A et al. Cognitive impairment in spinocerebellar ataxia type 8. Journal Of The Neurological Sciences. 2005 Oct 15 237(1-2):31-8 (PMID: 15958266)
6. Bird et al. (1993) Hereditary Ataxia Overview. 1998 Oct 28 [Updated 2018 Sep 27]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019. (Available from: https://www.ncbi.nlm.nih.gov/books/NBK1138/): (PMID: 20301317)