

ASPA Gene Analysis in Canavan Disease

Clinical Features:

Canavan disease (CD) is a neurodegenerative leukodystrophy that typically presents as a neonatal/infantile (severe) form with onset of symptoms at 2-4 months that include poor head control, macrocephaly, truncal hypotonia, and developmental delay. Severe CD is associated with delayed motor skills and the inability for these children to sit, stand, walk or talk. Many severe patients also have optic atrophy. Over time, spasticity develops and sleep disturbance, seizures and feeding difficulties may be present. Spongy degeneration of the white matter is present, with swollen astrocytes and elongated mitochondria. The life expectancy of patients with the severe form is variable with survival reported from months to past the teen years.¹ A much more rare mild/juvenile form of CD also exists that is characterized by mild developmental delay that may go unrecognized. CD occurs in all ethnic groups, but it is most common in the Ashkenazi Jewish population where the carrier rate has been estimated at 1 in 40 to 1 in 82.¹

CD is caused by variants in the ASPA gene that encodes the aspartoacylase (ASPA) enzyme that hydrolyzes N-acetyl aspartic acid (NAA) to aspartate and acetate in oligodendrocytes. Deficient ASPA activity results in the accumulation of NAA in the brain. Patients with severe CD are usually diagnosed by the presence of increased levels of NAA in urine, while in patients with mild CD NAA levels in urine may only be mildly elevated; therefore, the diagnosis of mild CD may depend upon identification of disease-causing variants in the ASPA gene. Measurement of ASPA enzyme activity is possible in skin fibroblasts (activity is not detectable in leukocytes) but the reliability of this test has been questioned since enzyme activity is affected by culture conditions.¹ The ASPA gene is located on chromosome 17pter-p13 and has 6 exons.

Inheritance Pattern/Genetics:

Autosomal Recessive

Test Methods:

Variant analysis of the ASPA gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of coding exons and corresponding intron/exon boundaries. In addition, targeted array CGH analysis with exon-level resolution (ExonArrayDx) is performed concurrently to evaluate for a deletion or duplication of one or more exons of this gene. A variant/deletion is confirmed by repeat analysis using sequencing, restriction fragment analysis, quantitative PCR or oligo-array comparative genome hybridization (ExonArrayDx), as appropriate.

Test Sensitivity:

In 23 patients with CD, sequence analysis and deletion/duplication testing of the ASPA gene identified variants on greater than 95% of alleles (44/46).²

At this time, more than 70 variants have been identified in the ASPA gene including missense, nonsense, splicing, small deletions/insertions and large deletions. In one study of 23 non-Ashkenazi Jewish patients from diverse ethnic backgrounds, large deletions that would not be detected by sequence analysis were identified in over 10% of ASPA alleles (5/46).² Two variants, p.Glu285Ala and p.Tyr231Stop, account for 98% of disease-causing alleles in the Ashkenazi Jewish population, and a p.Ala305Glu variant accounts for 20%-60% of disease-causing alleles in non-Ashkenazi Jewish patients.^{3, 4} Most other variants appear to be private or confined to small geographic areas.² Individuals homozygous for p.Glu285Ala, p.Tyr231Stop or p.Ala305Glu usually have a severe CD phenotype as do individuals who are either homozygous or compound heterozygous for a large deletion.¹ Mild CD has been associated with the presence of at least one “mild” variant: p.Tyr288Cys, p.Arg71His or p.Pro257Arg.¹

References:

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