ASL Gene Analysis in Argininosuccinic Aciduria

Clinical Features:
Argininosuccinic aciduria (ASA) is a disorder of the urea cycle. Patients may present at any age, but onset is typically in the neonatal period or late infancy. The neonatal presentation is characterized with a normal delivery followed by lethargy, vomiting, poor feeding, hypothermia, hyperventilation, decreased consciousness and coma, while later-onset patients usually present with episodic hyperammonemia, or with cognitive impairment, irritability, behavioral problems or intellectual disability without documented hyperammonemia. Trichorrhexis nodosa may occur, but usually in severe cases.

Genetics:
ASA is caused by variations in the *ASL* gene that encodes the argininosuccinate lyase enzyme which catalyzes the cleavage of argininosuccinate to fumarate and arginine; the forth step in the urea cycle in the liver. In other tissues, the ASL enzyme is involved in the conversion of citrulline to arginine. Deficiency of argininosuccinate lyase leads to the accumulation of argininosuccinic acid and hyperammonemia. The *ASL* gene is located on chromosome 7q11.21 and has 17 exons (the first codes only for the 5' UTR). The incidence of ASA has been estimated at approximately 1 in 70,000 live births.[1]

Inheritance Pattern:
Autosomal Recessive

Test Methods:
Variation analysis of the *ASL* gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of the 16 coding exons, and corresponding intron/exon boundaries. If sequencing identifies a variation on only one allele of the *ASL* gene, and if clinically indicated, reflex deletion/duplication testing (ExonArrayDx) will be performed at no additional charge to evaluate for a deletion/duplication of one or more exons of this gene. Variations found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method.

Test Sensitivity:
In 27 patients of European ancestry diagnosed with ASA based on complete absence or severely reduced ASL activity in cultured fibroblasts, variations were identified on 54/54 *ASL* alleles.[1] The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

Variant Spectrum:

At this time, over 60 pathogenic variants have been described in the *ASL* gene consisting of predominately missense variants.[4,5,7] Nonsense, splice site and small deletions and insertions have also been described. Large, exon-level deletions have also been reported.[2, 6] A nonsense variant, Q354X (c.1060 C>T), was found in 26 of 35 patients with ASA from Saudi Arabia.[3] Patients homozygous for Q354X were found to have a higher incidence of hyperammonemia compared to patients with other variants.[3] Other genotype-phenotype correlations have been reported including for the R12Q (c.35 G>A) missense change associated with an attenuated disease-presentation.[7]

References:

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7. Balmer et al. (2014) Human Mutation 35 (1):27-35 (PMID: 24166829)