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 fourth 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:
Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the ASL gene are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to the reference sequence based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot
identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

**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:**

4. Imtiaz BMC Res Notes 18:79