ARG1 Gene Analysis in Arginase Deficiency

Clinical Features:
Arginase deficiency is a very rare inborn error of the urea cycle. The first symptoms are often identified between 2 and 4 years and include clumsiness, spasticity and diminished growth. In untreated individuals symptoms are progressive resulting in loss of psychomotor function, spasticity, hyperactive deep-tendon reflexes, developmental delay, poor growth and seizures. Unlike the other defects of ureagenesis, patients with arginase deficiency rarely present in the neonatal period with acute episodes of hyperammonemia and, if they do, the episodes are generally less severe. A minority of patients have persistent or intermittent episodes of irritability, nausea, poor appetite and vomiting, which may progress to lethargy. Typically, hepatomegaly is present during acute episodes of hyperammonemia but is otherwise absent.

Genetics:
Arginase deficiency is caused by pathogenic variants in the ARG1 gene that encodes the liver arginase enzyme that is the sixth and final enzyme of the urea cycle catalyzing the hydrolysis of arginine to urea and ornithine. Plasma amino acid analysis in affected patients show elevated arginine levels and, if the patient is chronically hyperammonemic, glutamine elevations. Urine orotic acid is also frequently elevated and elevated arginine levels are detected in cerebrospinal fluid. Arginase activity is very low or absent in red blood cells and in the liver. Many affected individuals are now detected by newborn screening. The ARG1 gene is located on chromosome 6q23 and has 8 exons.

Inheritance Pattern:
Autosomal Recessive

Test Methods:
Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the ARG1 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:**

ARG1 variants include missense, nonsense, splicing and small deletions and insertions. Large deletions have also been described.\(^2,6\) There is considerable genetic heterogeneity in arginase deficiency with the majority of variants being private. Common variants have been identified in specific populations including in Portugal (R21X) and Brazil (T134I) where affected individuals were all homozygotes.\(^3,5\) In one study, a correlation between pathogenic variants and phenotype was reported but not corroborated in another report.\(^1,3\)

**References:**