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:
Variant analysis of the *ARG1* gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of coding exons and corresponding intron/exon boundaries. If sequencing identifies a variant on only one allele of the *ARG1* 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. Variants 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:
There have been very few large studies of patients with arginase deficiency. One study of 11 patients identified an *ARG1* pathogenic variant on 21/22 alleles, while a second study of 16

patients identified *ARG1* variants on 32/32 alleles.[1, 5] The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

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:

1. Uchino et al., (1995) Hum Genet 96:255-260.
2. Korman et al., (2004) Prenat Diagn 24:857-860.
3. Cardoso et al., (1999) Hum Mutat 14:355-6.
4. Crombez, E. and Cederbaum, S. (2005) Mol Genet Metab 84:243-251.
5. Carvalho et al., (2012) Gene 509:124-130.
6. Mohseni et al., (2014) Gene 533:240-245.