IVD Gene Analysis in Isovaleric Acidemia

Clinical Features:
Isovaleric acidemia (IVA) is an inborn error of leucine metabolism. The acute neonatal phenotype usually presents within the first 2 weeks of life with poor feeding, vomiting, decreased levels of consciousness, seizures, acidosis and hyperammonemia. A characteristic smell of “sweaty socks” may also be present during an acute illness. A chronic intermittent presentation may occur that is characterized by recurrent episodes of ketoacidosis, vomiting, lethargy, coma and varying degrees of developmental delay. Patients who survive the acute neonatal presentation have a similar clinical course as those with the chronic phenotype. Since the inception of MS/MS based newborn screening, a group of potentially asymptomatic patients has emerged with a mild biochemical phenotype.¹

Inheritance:
Autosomal Recessive

Genetics:
IVA is caused by variants in the IVD gene that encodes the isovaleryl-CoA dehydrogenase enzyme, which catalyzes the third step in the catabolism of leucine. Accumulation of isovaleryl-CoA derivatives particularly urinary isovalerylglucose, a stable compound, is characteristic of IVA. The IVD gene is located on chromosome 15q14-q15 and has 12 exons. Based on recent newborn screening reports, the incidence of IVA in the United States is approximately 1 in 250,000.¹

Test Methods:
Tiered testing of the IVD gene is available, if requested. A single variant in exon 9, A314V (c.932 C>T) or A282V if numbering from the processed protein, has been found in approximately two-thirds of newborns identified with IVA by newborn screening and is homozygous in approximately 25% of these patients.¹ Sequencing of this exon is available as a first step in the analysis in individuals identified by newborn screening, if specifically requested. Variant analysis of the IVD gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of exons 1-12, and the corresponding intron/exon boundaries. If sequencing identifies a variant on only one allele of the IVD 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 or another appropriate method.
Test Sensitivity:
Variant analysis is expected to identify a sequence variant in approximately 95% of patients with IVA.\textsuperscript{2,3,4} The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

Variant Spectrum:
Missense and splicing variants, small deletions and insertions, and exonic deletions have been reported in \textit{IVD} in association with IVA.\textsuperscript{6} There are greater than 30 variants described, the vast majority of which are private. A single variant in exon 9, A314V (c.932 C\textsuperscript{->}T) or A282V if numbering from the processed protein, was found in approximately two-thirds of newborns identified with IVA by newborn screening. Thus far, all of the newborns harboring A314V, including compound heterozygotes for this variant, have a mild biochemical phenotype and have remained asymptomatic with no or limited treatment. Other than the A314V variant, genotype-phenotype correlations are not well established.\textsuperscript{1,5,6}

References: