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 isovalerylglycine, 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.[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 *IVD* in association with IVA.[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->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.[1,5,6]

References:

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3. Lin, WD et al., (2007) Mol Genet Metab 90 :134-139 (PMID: 17027310).
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5. Vockley, J and Ensenauer R. (2006) Am J Med Genet C Semin Med Genet 142:95-103 (PMID: 16602101).
6. Couce et al. (2017) J. Hum. Genet. 62 (3):355-360 (PMID: 27904153).