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. Affected individuals 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 individuals 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

Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the IVD 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

Missense and splicing variants, small deletions and insertions, and exonic deletions have been reported in IVD in association with IVA.[3] 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.[1] 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.[1-3]

REFERENCES:

1. Ensenauer R. et al., (2004) Am J Hum Genet 75 :1136-1142 (PMID: 15486829).
2. Vockley, J and Ensenauer R. (2006) Am J Med Genet C Semin Med Genet 142:95-103 (PMID: 16602101).
3. Couce et al. (2017) J. Hum. Genet. 62 (3):355-360 (PMID: 27904153)

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