Methylglutaconic Aciduria Nuclear Gene Panel

Sequence Analysis and Exon-Level Deletion/Duplication Testing of 14 Nuclear Genes

Panel Gene List: *AGK, ATP5E, ATPAF2, AUH, CLPB, DNAJC19, HMGCL, HTRA2, OPA3, POLG, SERAC1, SUCLA2, TAZ, TMEM70*

Clinical Features:
3-Methylglutaconic aciduria is a clinically and genetically heterogeneous disorder where tissues with higher requirements for oxidative metabolism, such as the central nervous system, cardiac, and skeletal muscle are predominantly affected.[1] The phenotypic presentation varies from a mild form that includes delayed development of language and hyperchloremic acidosis associated with gastroesophageal reflux, to a much more severe phenotype that includes seizures, cerebellar findings, and atrophy of the basal ganglia.[2,3]

Genetics:
Most nuclear mitochondrial diseases are associated with autosomal recessive inheritance. The *TAZ* gene is associated with X-linked inheritance and the *HTRA2, OPA3*, and *POLG* genes are associated with both autosomal dominant and recessive inheritance.

Test Methods:
Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel 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 reference sequences 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. For the *HTRA2* gene, sequencing but not deletion/duplication analysis, was performed. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data. 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.

Clinical Sensitivity:

This panel of genes account for more than 95% of nuclear gene variants currently known to be associated with inherited 3-methylglutaconic aciduria. Methylglutaconic aciduria may also be caused by variants in mtDNA.[4] It is estimated that this panel would detect the disease-causing vairant(s) in almost all patients with methylglutaconic aciduria type I, II, III, V and >50% patients with methylglutaconic aciduria type IV.[3]

References:

1. Gunay-Aygun et al. (2005) Mol. Genet. Metab. 84 (1):1-3 (PMID: 15719488)
2. Gibson et al. (1998) J. Inherit. Metab. Dis. 21 (6):631-8 (PMID: 9762598)
3. Wortmann et al. (2013) J. Inherit. Metab. Dis. 36 (6):923-8 (PMID: 23296368)
4. Gibson et al. (1992) J. Pediatr. 121 (6):940-2 (PMID: 1447663)