Lactic Acidosis/ Pyruvate Metabolism Nuclear Gene Panel

Sequence Analysis and Exon-Level Deletion/Duplication Testing of 130 Nuclear Genes

Panel Gene List: *ACAD9, AGK, AIFM1, ATP5E, ATPAF2, BCS1L, BOLA3, C12orf65, CARS2, COQ2, COQ4, COQ7, COQ8A, COQ9, COX10, COX14, COX15, COX6B1, CYC1, DARS2, DGUOK, DLAT, DLD, DNM1L, EARS2, ECHS1, ELAC2, ETFA, ETFB, ETFDH, ETHE1, FARS2, FBXL4, FDX1L, FH, FOXRED1, GFER, GFM1, GTPBP3, GYG2, HMGCL, HTRA2, IBA57, ISCU, LARS, LARS2, LIAS, LIPT1, LRPPRC, LYRM4, LYRM7, MFF, MPC1, MPV17, MRPL12, MRPL44, MRPS16, MRPS22, MRPS7, MTFMT, MTO1, NARS2, NDUFA1, NDUFA10, NDUFA11, NDUFA9, NDUFAF1, NDUFAF3, NDUFAF5, NDUFAF6, NDUFB3, NDUFB9, NDUFS1, NDUFS2, NDUFS3, NDUFS4, NDUFS6, NDUFS7, NDUFS8, NDUFV1, NFS1, NFU1, PARS2, PC, PCCA, PCCB, PDHA1, PDHB, PDHX, PDP1, PDSS1, PDSS2, PNPT1, POLG, POLG2, PUS1, RARS2, RMND1, RNASEH1, RRM2B, SARS2, SCO2, SDHAF1, SERAC1, SFXN4, SLC25A26, SLC25A3, SLC25A4, SUCLA2, SUCLG1, SURF1, TARS2, TAZ, TK2, TMEM70, TPK1, TRMT10C, TRMU, TRNT1, TSFM, TTC19, TUFM, TWNK, TYMP, UQCC2, UQCC3, UQCRB, UQCRC2, UQCRQ, YARS2*

Clinical Features:

Pyruvate is the end product of glycolysis and provides energy to the cells through the citric acid cycle.[1, 2] Disorders of pyruvate metabolism result in a heterogeneous group of conditions characterized by dysfunction in organ systems with high energy demand.[1,2] Common features of these disorders include lactic acidosis, encephalopathy, hypotonia, Leigh syndrome, myopathy and cardiomyopathy.[1,2] The clinical features of other mitochondrial disorders resulting in lactic acidosis may overlap those of disorders of pyruvate metabolism.

Genetics:

To date, around 200 nuclear genes have reported disease-causing variants associated with a primary mitochondrial disorder. Disorders due to nuclear gene variants that affect mitochondrial function may be inherited in an autosomal dominant, autosomal recessive or X-linked manner.

Test Methods:

Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the genes tested 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; 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. Due to the presence of non-functional pseudogenes, regions of the *GYG2* and *PDSS1* genes are not fully sequenced by this method. For the *COQ7, COX8A, HTRA2, RNASEH1, SLC25A26,* and *TRMT10C* genes, sequencing but not deletion/duplication analysis, was performed.

Clinical Sensitivity:

This panel includes all known genes with reported variants associated with deficiency in pyruvate metabolism (*BOLA3, DLAT, DLD, IBA57, ISCU, LIAS, LIPT1, MPC1, NFU1, PDHA1, PC, PDHB, PDHX, PDP1,* and *TPK1*) and almost all of the nuclear genes with reported variants associated with a primary mitochondrial disorder that includes lactic acidosis/lactic academia as one of the clinical features. [2]

This panel is expected to identify a disease causing variant(s) in all patients with pyruvate dehydrogenase complex (PDHc) deficiency and the majority of patients with lactic acidosis or lactic academia.[3]

References:

1. Gray et al. (2014) Cell. Mol. Life Sci. 71 (14):2577-604 (PMID: 24363178)
2. Sperl et al. (2014) Journal Of Inherited Metabolic Disease : (PMID: 25526709)
3. Tarnopolsky et al. (2005) Med Sci Sports Exerc 37 (12):2086-93 (PMID: 16331134)