Lactic Acidosis/ Pyruvate Metabolism Nuclear Gene Panel

Sequence Analysis and Exon-Level Deletion/Duplication Testing of 152 Nuclear Genes

Panel Gene List: *ACAD9, AGK, AGL, AIFM1, ATP5E, ATPAF2, B4GALT1, BCKDHA, BCKDHB, BCS1L, BOLA3, C12orf65, CA5A, CARS2, COG4, COG8, COQ2, COQ4, COQ7, COQ8A, COQ9, COX10, COX14, COX15, COX6B1, CYC1, DARS2, DBT, DGUOK, DLAT, DLD, DNM1L, EARS2, ECHS1, ELAC2, ETFA, ETFB, ETFDH, ETHE1, FARS2, FBXL4, FDX1L, FH, FOXRED1, GFER, GFM1, GTPBP3, GYG2, HADHA, HADHB, HLCS, HMGCL, HMGCS2, HSD17B10, HTRA2, IBA57, ISCU, LARS, LARS2, LDHA, LIAS, LIPT1, LRPPRC, LYRM4, LYRM7, MFF, MLYCD, 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, PFKM, PNPT1, POLG, POLG2, PUS1, RARS2, RMND1, RNASEH1, RRM2B, SARS2, SCO2, SDHAF1, SERAC1, SFXN4, SLC25A13, SLC25A19, SLC25A26, SLC25A3, SLC25A4, SLC2A2, SLC35A2, SLC37A4, SLC7A7, SUCLA2, SUCLG1, SURF1, TARS2, TAZ, TK2, TMEM70, TPK1, TRMT10C, TRMU, TRNT1, TSFM, TTC19, TUFM, TWNK, TYMP, UQCC2, UQCC3, UQCRB, UQCRC2, UQCRQ, YARS2*

Clinical Features:

Mitochondrial disorders are clinically heterogeneous and result from dysfunction of the mitochondrial respiratory chain, which can be caused by variants in mitochondrial DNA (mtDNA) or in nuclear genes. Mitochondrial disorders may affect a single organ, but many involve multiple organ systems particularly those that are highly dependent on aerobic metabolism (brain, skeletal muscle, heart, kidney and endocrine system). Patients may present at any age; however, individuals with nuclear DNA variants generally present in childhood and those with mtDNA variants generally present in late childhood or in adults. Some affected individuals exhibit clinical features that fall into a discrete clinical syndrome, such as Leber Hereditary Optic Neuropathy (LHON), Kearns-Sayre syndrome (KSS), chronic progressive external ophthalmoplegia (CPEO), mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS), myoclonic epilepsy with ragged-red fibers (MERRF), neurogenic weakness with ataxia and retinitis pigmentosa (NARP) or Leigh syndrome (LS). However, often the clinical features are highly variable and non-specific and many affected persons do not fit into one particular category. Similar clinical features can be caused by mtDNA variants or nuclear gene variants. Common features of mitochondrial disease may

include ptosis, external ophthalmoplegia, proximal myopathy, exercise intolerance, cardiomyopathy, sensorineural deafness, optic atrophy, pigmentary retinopathy, diabetes mellitus, encephalopathy, seizures, dementia, migraine, stroke-like episodes, ataxia, spasticity, chorea and dementia. It has been estimated that approximately 7% of patients diagnosed with autism may have an underlying disorder of mitochondrial function [1]. The prevalence of mitochondrial disorders has been estimated 1/5000 to 1/8500. [2-5] This panel includes all known genes with reported variants associated with deficiency in pyruvate metabolism 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. Several other genes are also included because variants in these genes are associated with clinical features that are indistinguishable from that of a primary mitochondrial disorder including lactic acidosis.

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 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. 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, SCO2, SLC25A26,* and *TRMT10C* genes, 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 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. Oliveira et al. (2005) Dev Med Child Neurol 47 (3):185-9 (PMID: 15739723)
2. Chinnery P. Mitochondrial Disorders Overview 2000 Jun 8 [Updated 2014 Aug 14]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1224/
3. Tarnopolsky et al. (2005) Med Sci Sports Exerc 37 (12):2086-93 (PMID: 16331134)
4. van Adel et al. (2009) Journal Of Clinical Neuromuscular Disease 10 (3):97-121 (PMID: 19258857)
5. Zhu et al. (2009) Acta Biochim. Biophys. Sin. (Shanghai) 41 (3):179-87 (PMID: 19280056)