Mitochondrial Encephalopathy/ Leigh Syndrome Nuclear Gene Panel

Sequence Analysis and Exon-Level Deletion/Duplication Testing of 134 Nuclear Genes

Panel Gene List: *AARS2, ACAD9, ACO2, AFG3L2, AIFM1, APOPT1, ATP5A1, ATP5E, ATPAF2, AUH, BCS1L, BOLA3, C12orf65, COQ2, COQ4, COQ6, COQ7, COQ8A, COQ9, COX10, COX14, COX15, COX20, COX6B1, COX8A, CYC1, DARS2, DGUOK, DLAT, DLD, DNM1L, EARS2, ECHS1, ETFDH, ETHE1, FARS2, FASTKD2, FBXL4, FH, FOXRED1, GCDH, GFER, GFM1, GFM2, GTPBP3, GYG2, HMGCL, HTRA2, IARS2, IBA57, ISCA2, LARS2, LIAS, LIPT1, LRPPRC, LYRM7, MARS2, MFF, MFN2, MPC1, MPV17, MRPL44, MRPS22, MTFMT, MTPAP, NARS2, NDUFA1, NDUFA10, NDUFA11, NDUFA12, NDUFA2, NDUFA4, NDUFA9, NDUFAF1, NDUFAF2, NDUFAF3, NDUFAF4, NDUFAF5, NDUFAF6, NDUFAF7, NDUFB11, NDUFB3, NDUFS1, NDUFS2, NDUFS3, NDUFS4, NDUFS6, NDUFS7, NDUFS8, NDUFV1, NDUFV2, NFU1, NUBPL, PC, PCCA, PCCB, PDHA1, PDHB, PDHX, PDP1, PDSS1, PDSS2, PET100, PNPT1, POLG, RARS2, RMND1, RRM2B, SCO1, SCO2, SDHA, SDHAF1, SERAC1, SLC19A3, SLC22A5, SLC25A46, SUCLA2, SUCLG1, SURF1, TACO1, TARS2, TK2, TMEM70, TPK1, TRMU, TSFM, TTC19, TUFM, TWNK, TYMP, UQCC2, UQCC3, UQCRQ, VARS2*

Clinical Features:

Leigh syndrome is an early-onset progressive neurodegenerative disorder with a characteristic neuropathology consisting of focal, bilateral lesions in one or more areas of the central nervous system, including the brainstem, thalamus, basal ganglia, cerebellum, and spinal cord.[1] The lesions are areas of demyelination, gliosis, necrosis, spongiosis, or capillary proliferation.[1] The clinical features of mitochondrial encephalopathy may overlap that of Leigh syndrome. [1,2,3]

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, PDSS1*, and *TSFM,* and genes are not fully sequenced by this method. For the *COQ7, COX8A, HTRA2, NDUFB11, RNASEH1, SCO2, SDHA,* and *SLC25A46* genes, sequencing but not deletion/duplication analysis, was performed.

Clinical Sensitivity:
Variant(s) in about 134 genes have been reported to be associated with Leigh syndrome or mitochondrial encephalopathy. The genes included in this panel include more than 95% of known nuclear gene variants associated with Leigh syndrome, Leigh-like syndrome, and mitochondrial encephalopathy. It is estimated that this panel would detect the disease-causing variants(s) in more than 50% of patients with familial Leigh syndrome.[1,2,3]

References:

1. Baertling et al. (2014) J. Neurol. Neurosurg. Psychiatry 85 (3):257-65 (PMID: 23772060)
2. Tucker et al. (2010) Curr Neurol Neurosci Rep 10 (4):277-85 (PMID: 20446063)
3. Gerards et al. (2016) Mol. Genet. Metab. 117 (3):300-12 (PMID: 26725255)