

## Mitochondrial Focused Nuclear Gene Panel

### Sequence Analysis and Exon-Level Deletion/Duplication Testing of 202 Nuclear Genes

**Panel Gene List:** *AARS2, ABCB7, ACAD9, ACO2, AFG3L2, AGK, AIFM1, ALAS2, APOPT1, ATP5A1, ATP5E, ATP7B, ATPAF2, AUH, BCS1L, BOLA3, C12orf65, C19orf12, CARS2, CLPB, COA5, COA6, COASY, COQ2, COQ4, COQ6, COQ7, COQ8A, COQ8B, COQ9, COX10, COX14, COX15, COX20, COX6A1, COX6B1, COX8A, CYC1, DARS2, DGUOK, DLAT, DLD, DNA2, DNAJC19, DNM1L, EARS2, ECHS1, ELAC2, ETFA, ETFB, ETFDH, ETHE1, FARS2, FASTKD2, FBXL4, FDX1L, FH, FLAD1, FOXRED1, GARS, GCDH, GFER, GFM1, GFM2, GLRX5, GTPBP3, GYG2, HARS2, HMGCL, HTRA2, IARS2, IBA57, ISCA2, ISCU, LAMP2, LARS, LARS2, LIAS, LIPT1, LRPPRC, LYRM4, LYRM7, MARS2, MFF, MFN2, MGME1, MICU1, MPC1, MPV17, MRPL12, MRPL3, MRPL44, MRPS16, MRPS22, MRPS7, MTFMT, MTO1, MTPAP, NARS2, NDUFA1, NDUFA10, NDUFA11, NDUFA12, NDUFA2, NDUFA4, NDUFA9, NDUFAF1, NDUFAF2, NDUFAF3, NDUFAF4, NDUFAF5, NDUFAF6, NDUFAF7, NDUFB11, NDUFB3, NDUFB9, NDUFS1, NDUFS2, NDUFS3, NDUFS4, NDUFS6, NDUFS7, NDUFS8, NDUFV1, NDUFV2, NFS1, NFU1, NR2F1, NUBPL, OPA1, OPA3, OTC, PARS2, PC, PCCA, PCCB, PDHA1, PDHB, PDHX, PDP1, PDSS1, PDSS2, PET100, PNPT1, POLG, POLG2, PRKAG2, PUS1, QARS, RARS, RARS2, RMND1, RNASEH1, RRM2B, SARS2, SCO1, SCO2, SDHA, SDHAF1, SERAC1, SFXN4, SLC19A2, SLC19A3, SLC22A5, SLC25A26, SLC25A3, SLC25A38, SLC25A4, SLC25A46, SPAST, SPG7, SUCLA2, SUCLG1, SURF1, TACO1, TARS2, TAZ, TFAM, TIMM8A, TK2, TMEM126A, TMEM126B, TMEM70, TPK1, TRIT1, TRMT10C, TRMU, TRNT1, TSFM, TTC19, TUFM, TWNK, TYMP, UQCC2, UQCC3, UQCRB, UQCRC2, UQCRQ, VARS2, WDR45, WFS1, YARS2*

#### **Clinical Features:**

Mitochondrial disorders are clinically heterogeneous and result from dysfunction of the mitochondrial respiratory chain, which can be caused by pathogenic 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<sup>1</sup>. The prevalence of mitochondrial disorders has been estimated 1/5000 to 1/8500<sup>2-5</sup>.

### 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*, *PDSS1*, *TSMF*, and *NR2F1* genes are not fully sequenced by this method. For the *COQ7*, *COX8A*, *HTRA2*, *NDUFB11*, *RNASEH1*, *SCO2*, *SDHA*, *SLC25A26*, *SLC25A46*, *TFAM*, *TMEM126B*, and *TRMT10C* genes, sequencing but not deletion/duplication analysis, was performed. In addition, for the *COA5* gene deletion/duplication analysis may only be able to detect full gene events. 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:**

The 202 genes in this panel include more than 95% of the known nuclear gene variants associated with primary mitochondrial disorders. This panel is estimated to identify disease-causing variants(s) in approximately 40-60% patients with a primary mitochondrial disorder. <sup>2, 6, 7, 8</sup>

### **References:**

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5. Zhu et al. (2009) *Acta Biochim. Biophys. Sin. (Shanghai)* 41 (3):179-87 (PMID: 19280056)
6. Koenig et al. (2008) *Pediatr. Neurol.* 38 (5):305-13 (PMID: 18410845)
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8. Taylor et al. (2014) *JAMA* 312 (1):68-77 (PMID: 25058219)