Mitochondrial Disorders (mtDNA) Sequencing and Deletion Analysis by NGS

Patient: [redacted] DOB: [redacted] Age: 38 Sex: M **Patient Identifiers:** [redacted] **Visit Number (FIN):** [redacted]	Client: Physician:	ARUP Test Code: 3001965 Collection Date: 08/03/2023 Received in lab: 08/07/2023 Completion Date: 08/18/2023

Test Information

Test performed at GeneDx.

Patient Report

Patient's results from GeneDx continue on following page(s).

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Jonathan R. Genzen, MD, PhD, Laboratory Director

Chart continues on following page(s)

[redacted]

GeneDx

DOB [redacted]

Accession [redacted]

Submitter Patient ID(s) [redacted]

Sample	Testing	Provider
Source: Blood in EDTA	Date Started: 10-AUG-2023	Account #:
Date Collected: 03-AUG-2023	Date Reported: 18-AUG-2023	A.R.U.P Laboratories
Date Received: 08-AUG-2023		

Test(s) Requested

Mitochondrial Disorders / Sequence Analysis and Deletion Testing of the Mitochondrial Genome

Result: Positive: See Interpretation

Gene	Mode of Inheritance	Variant	Heteroplasmy (%)	Classification
MT-ND6	Maternal	m.14484 T>C p.(M64V)	Homoplasmic	Pathogenic Variant

Interpretation

This individual is homoplasmic for a pathogenic variant in the MT-ND6 gene, which is commonly associated with Leber's hereditary optic neuropathy (LHON). LHON-causing mtDNA variants have markedly reduced penetrance as approximately 50% of males and 90% of females who harbor a primary LHON-causing mtDNA pathogenic variant do not develop blindness (PMID: 20301353). As no clinical information was provided for this patient, the interpretation of this result is deferred to the ordering clinician.

Recommendation(s)

- Clinical correlation and genetic counseling are recommended to discuss the implications of this test report.
- There are no recommendations for ongoing surveillance of asymptomatic individuals who harbor LHON-pathogenic variants; however, if any visual problems arise, these individuals should seek medical attention immediately (PMID: 20301353).
- Mitochondrial DNA disorders are maternally inherited. Testing appropriate matrilineal relatives for the pathogenic variant in the MT-ND6 gene is available.

Resources

MyGene2 is a portal through which families with rare genetic conditions who are interested in sharing their health and genetic information can connect with other families, clinicians, and researchers. If you are interested in learning more and/or participating, please visit www.mygene2.org.

GenomeConnect is an NIH initiative created to enable individuals and families with the same genetic variant or medical history to connect and share de-identified information. If you are interested in participating, please visit www.genomeconnect.org.

MT-ND6

GENE SUMMARY

The MT-ND6 gene encodes for subunit 6 of mitochondrial complex I (NADH:ubiquinone oxidoreductase). The mitochondrial genome (mtDNA) contains 37 genes encoding proteins, tRNA and rRNA molecules, all of which are essential for normal mitochondrial function. Mitochondrial disorders are clinically heterogeneous and result from dysfunction of the mitochondrial respiratory chain. 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), and patients may present at any age. Some affected individuals

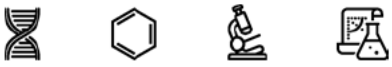

exhibit clinical features that fall into a discrete clinical syndrome, such as Leber Hereditary Optic Neuropathy (LHON), Kearns-Sayre syndrome (KSS), chronic progressive external ophthalmoplegia (CPEO), mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS), myoclonic epilepsy 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. Common features of mitochondrial disease may include cardiomyopathy, sensorineural deafness, ptosis, external ophthalmoplegia, proximal myopathy, exercise intolerance, optic atrophy, pigmentary retinopathy, diabetes mellitus, encephalopathy, seizures, dementia, migraine, stroke-like episodes, ataxia, spasticity, chorea and dementia. Variants in mtDNA arise de novo or are maternally inherited and can be associated with late-onset disease and reduced penetrance. Usually, mtDNA variants affect only a fraction of the mtDNA; the coexistence of normal and mutant mtDNA is called heteroplasmy. When the percentage of mutant mtDNA (variant load) reaches a certain threshold that varies by tissue type, age, and specific mtDNA variant the function of that tissue may become impaired (PMID: 14743651). While the threshold resulting in clinical symptoms is specific for each mtDNA variant, it is considered to be between 60%-80% heteroplasmy for most pathogenic mtDNA variants (PMID: 28415858). Pathogenic mtDNA variants in protein encoding genes can present at higher levels of heteroplasmy in post-mitotic tissues such as skeletal muscle, heart, and brain than in rapidly replicating cells such as blood or buccal (PMID: 14743651).

m.14484 T>C: p.(Met64Val) (ATG>GTG) in the MT-ND6 gene (NC_012920.1)

- Commonly associated with Leber's hereditary optic neuropathy (LHON) at near homoplasmic levels in blood (Wallace et al., 1988); however, approximately 50% of males and 90% of females who harbor a primary LHON-causing mtDNA pathogenic variant do not develop blindness (Yu-Wai-Man, P. and Chinnery, P. 2016)
- Most affected individuals harbor this variant at greater than 70% heteroplasmy in blood (Yu-Wai-Man, P. and Chinnery, P. 2016)
- Cardiac arrhythmias have been reported to be more common in Finnish individuals with LHON than in controls; however, this finding has not been replicated in other populations (Nikoskelainen et al., 1994; Bower et al., 1992)
- Published functional studies using cybrid cell lines demonstrate m.14484T>C causes a complex I dysfunction that leads to a decrease in respiratory capacity (Cruz-Bermudez et al., 2016)
- Smoking has been reported to have a consistent role in increasing disease penetrance in LHON. Asymptomatic LHON carriers are advised to avoid smoking and to moderate alcohol consumption (Kirkman et al., 2009)

We interpret this as a Pathogenic Variant.

Additional Comments

This individual's haplogroup and a table of observed variants are also provided.* The observed variants have not been reported to be associated with a disorder of mitochondrial metabolism when present in association with this individual's specific haplogroup.

Genes Evaluated

Mitochondrial Genome

Methods

Genomic DNA was extracted from the submitted specimen, and the entire mitochondrial genome was amplified and sequenced using Next Generation sequencing. DNA sequence was assembled and analyzed in comparison with the revised Cambridge Reference Sequence (rCRS GeneBank number NC_012920) and the reported variants listed in the MITOMAP database (http://www.mitomap.org). Next-generation sequencing may not detect large-scale mtDNA deletions present at 5% heteroplasmy or lower or mtDNA point variants present at 1.5% heteroplasmy or lower. Alternative sequencing or other detection methods may be used to analyze or confirm mtDNA variants. 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. Available evidence for variant classification may change over time and the reported variant(s) may be reclassified according to our mitochondrial variant classification aligned with the ACMG/AMP Standards and Guidelines for variant classification (PMID: 25741868), which may lead to issuing a revised report.

Disclaimer

Genetic testing using the methods applied at GeneDx is expected to be highly accurate. Normal findings do not rule out the diagnosis of a genetic disorder since some genetic abnormalities may be undetectable by this test. The methods used cannot reliably detect deletions of 20bp to 500bp in size, or insertions of 10bp to 500bp in size. Sequencing

cannot detect low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect mosaicism and cannot identify balanced chromosome aberrations. Regions of certain genes have inherent sequence properties (for example: repeat, homology, or pseudogene regions, high GC content, rare polymorphisms) that yield suboptimal data, potentially impairing accuracy of the results. Inaccurate results may occur in the setting of allogeneic bone marrow/stem cell transplantation, active or chronic hematologic conditions, recent blood transfusion, suboptimal DNA quality, or in other rare circumstances. Rarely, incidental findings of large chromosomal rearrangements outside the gene of interest may be identified. As the ability to detect genetic variants and naming conventions can differ among laboratories, rare false negative results may occur when no positive control is provided for testing of a specific variant identified at another laboratory. In addition, the chance of an erroneous result due to laboratory errors incurred during any phase of testing cannot be completely excluded. Interpretations are made with the assumption that any clinical information provided, including family relationships, are accurate. Consultation with a genetics professional is recommended for interpretation of results.

This test was developed and its performance characteristics determined by GeneDx. This test has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. The test is used for clinical purposes and should not be regarded as investigational or for research. The laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing.

References

Lek et al. (2016) Nature 536 (7616):285-91 (PMID: 27535533);Stenson et al. (2014) Human genetics 133 (1):1-9 (PMID: 24077912);Landrum et al. (2016) Nucleic Acids Res. 44 (D1):D862-8 (PMID: 26582918);Lott et al. (2013) Curr Protoc Bioinformatics 44 :1.23.1-26 (PMID: 25489354);Richards et al. (2015) Genetics In Medicine: 17 (5):405-24 (PMID: 25741868);Longo N. (2003) Neurol Clin. 21 (4):817-31 (PMID: 14743651);Craven L et al. (2017) Annu Rev Genomics Hum Genet. 18 :257-275 (PMID: 28415858); Wallace et al., (1998) Science 242:1427-30. Yu-Wai-Man, P. and Chinnery, P. (Updated [June 23, 2016]). Leber's Hereditary Optic Neuropathy. In: GeneReviews at Genetests: Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1997-2014. Available at http://www.genetests.org. Cruz-Bermúdez et al. (2016) PLoS ONE 11 (1):e0146816 (PMID: 26784702); Nikoskelainen et al. (1994) Clin Neurosci 2:115-20; Bower et al. (1992) Lancet 339 (8806):1427-8 (PMID: 1350847); Kirkman et al. (2009) Brain 132 (Pt 9):2317-26 (PMID: 19525327)

Report Electronically Signed By

Renkui Bai M.D., Ph.D., FACMG
Director, Clinical Genetics

[redacted]

GeneDx

DOB [redacted] Accession [redacted]

Submitter Patient ID(s) [redacted]

MTDNA BENIGN/LIKELY BENIGN VARIANTS

Functional Location	Variant Change	Amino Acid Change	Frequency (Gen. Pop)
MT-DLOOP	m.64 C>T	non-coding	1518/49135
MT-DLOOP	m.73 A>G	non-coding	37469/49135
MT-DLOOP	m.94 G>A	non-coding	201/50175
MT-DLOOP	m.146 T>C	non-coding	9497/49135
MT-DLOOP	m.153 A>G	non-coding	1660/49135
MT-DLOOP	m.235 A>G	non-coding	1510/49135
MT-DLOOP	m.263 A>G	non-coding	46799/49135
MT-RNR1	m.663 A>G	rRNA	1396/49135
MT-RNR1	m.750 A>G	rRNA	48276/49135
MT-RNR1	m.1438 A>G	rRNA	46721/49135
MT-RNR2	m.1736 A>G	rRNA	1382/49135
MT-RNR2	m.2706 A>G	rRNA	38981/49135
MT-RNR2	m.3106del	In Frame	common
MT-ND1	m.4248 T>C	Synonymous	1776/49135
MT-ND2	m.4769 A>G	Synonymous	55528/56895
MT-ND2	m.4824 A>G	Missense	1441/49135
MT-ND2	m.5291 T>C	Synonymous	50/49135
MT-CO1	m.7028 C>T	Synonymous	39824/49135
MT-CO2	m.7604 G>A	Missense	18/49135
MT-CO2	m.7861 T>C	Synonymous	279/49135
MT-CO2	m.8027 G>A	Missense	1619/49135
MT-ATP6	m.8794 C>T	Missense	1391/49135
MT-ATP6	m.8860 A>G	Missense	48479/49135
MT-ATP6	m.9067 A>G	Missense	36/56895
MT-CO3	m.9254 A>G	Synonymous	406/49135
MT-ND4	m.11453 G>A	Missense	17/56895
MT-ND4	m.11719 G>A	Synonymous	38205/49135
MT-ND4	m.12007 G>A	Synonymous	3088/49135

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MT-ND5	m.12705 C>T	Synonymous	20517/49135
MT-ND6	m.14551 A>G	Synonymous	9/51192
MT-CYB	m.14766 C>T	Missense	37907/49135
MT-CYB	m.15326 A>G	Missense	48493/49135
MT-TP	m.15978 C>T	tRNA	151/50175
MT-DLOOP	m.16111 C>T	non-coding	1313/49135
MT-DLOOP	m.16209 T>C	non-coding	1299/49135
MT-DLOOP	m.16223 C>T	non-coding	19551/49135
MT-DLOOP	m.16290 C>T	non-coding	1927/49135
MT-DLOOP	m.16319 G>A	non-coding	2906/49135
MT-DLOOP	m.16362 T>C	non-coding	8667/49135
Haplogroup (HG): A2q1			

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