Client: Example Client ABC123
123 Test Drive
Salt Lake City, UT 84108
UNITED STATES

Physician: Doctor, Example

Patient: Patient, Example

DOB	1/29/1985
Gender:	Male
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Mitochondrial Disorders (mtDNA) Sequencing and Deletion Analysis by NGS

ARUP test code 3001965

Ordering Physician Name	Not Provided
Ordering Physician Phone Number	Not Provided
EER Mito Disorders, mtDNA, Seq/Del	See Note Authorized individuals can access the ARUP Enhanced Report using the following link: [redacted]
Mito Disorders, mtDNA, Seq/Del	*

Positive: See Interpretation

Date Test(s) Started: 10-AUG-2023 13:23:39
Sample Source: Blood in EDTA Date Collected: 03-AUG-2023 Date Received:
08-AUG-2023 Testing Date Started: 10-AUG-2023 Date Reported: 18-AUG-2023
Provider Account #: A.R.U.P Laboratories Additional Provider:
Test(s) Requested Mitochondrial Disorders / Sequence Analysis and Deletion
Testing of the Mitochondrial Genome
Result: Positive: See Interpretation
GeneMode of InheritanceVariantHeteroplasmy (%)Classification
MT-ND6Maternalm.14484 T>C
p.(M64V)HomoplasmicPathogenic 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

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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%

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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

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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-Bermudez 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)
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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
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

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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
Report electronically signed by: Renkui Bai M.D., Ph.D., FACMG
Performed by: GeneDx
207 Perry Parkway
Gaithersburg, MD 20877

Anne Maddalena, Ph.D.,FACMG,

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Ordering Physician Name	23-215-115571	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Ordering Physician Phone Number	23-215-115571	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
EER Mito Disorders, mtDNA, Seq/Del	23-215-115571	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Mito Disorders, mtDNA, Seq/Del	23-215-115571	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

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