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

Physician: Doctor, Example

Patient: Patient, Example

DOB	2/12/1986
Gender:	Female
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	[redacted] Performed by: GeneDx 207 Perry Parkway Gaithersburg, MD 20877 Anne Maddalena, Ph.D.,FACMG,
Ordering Physician Phone Number	[redacted] Performed by: GeneDx 207 Perry Parkway Gaithersburg, MD 20877 Anne Maddalena, Ph.D.,FACMG,
EER Mito Disorders, mtDNA, Seq/Del	See Note Access ARUP Enhanced Report using either link below: -Direct access: [redacted] -Enter Username, Password: https://erpt.aruplab.com Username: [redacted] Password: [redacted]
Mito Disorders, mtDNA, Seq/Del	**POSITIVE** *

Date Test(s) Started: 7/30/2020 12:32:00
Test(s) Requested Mitochondrial Disorders / Sequence Analysis and Deletion
Testing of the Mitochondrial Genome
Clinical Indication Not provided
Result(s): POSITIVE
GeneMode of InheritanceVariantHeteroplasmy (%)Classification
MT-TL1Maternalm.3243 A>G
Approximately 52%Pathogenic Variant
MT-CO3Maternalm.9286 T>C
p.M27T
HomoplasmicVariant of Uncertain Significance
Interpretation A heteroplasmic pathogenic variant was detected in the MT-TL1

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gene. The presence of this variant is expected to be consistent with a
diagnosis of a mitochondrial disorder in this individual.
This individual is homoplasmic for a variant of uncertain significance in the
MT-CO3 gene. This result does not establish a molecular diagnosis of a
mitochondrial-DNA disorder in this individual.
Recommendation(s) Clinical correlation and genetic counseling are recommended.Mitochondrial DNA disorders are maternally inherited. Testing
appropriate matrilineal relatives for the m.3243 A>G variant (Test #453) is
available.
Testing of affected or older unaffected matrilineal relatives may help to
further clarify the pathogenicity of the m.9286 T>C variant.
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-TL1 m.3243 A>G in the MT-TL1 gene (NC_012920.1)Associated with various
phenotypes including Mitochondrial Encephalomyopathy, Lactic Acidosis, and
Stroke-like episodes (MELAS) (m.3243 A>G accounts for approximately 80% of
MELAS cases), Leigh syndrome, Maternally Inherited Diabetes and Deafness (MIDD)
(m.3243 A>G present in approximately 2%-7% of patients with MIDD), and
hypertrophic cardiomyopathy (HCM) (m.3243 A>G present in approximately 10% of
Finnish patients with HCM) (Longo, N. 2003; Majamaa et al., 1998)Heteroplasmy
levels are usually significantly higher in the affected tissues than in blood,
and in some patients m.3243 A>G may be undetectable in blood but present at
much higher levels in urinary sediment or muscle (Shanske et al., 2004)Histochemical, immunohistochemical, and single-fiber PCR analysis studies
in multiple patients with MELAS found that high heteroplasmy levels in muscle
are associated with ragged-red fibers and with partial cytochrome c oxidase
deficiency, which directly correlates the m.3243 A>G variant with causing
muscle mitochondrial proliferation, partial respiratory-chain impairment and
decreased mitochondrially synthesized protein content (Moraes et al., 1992)
We interpret this as a Pathogenic Variant.
MT-CO3 m.9286 T>C: p.Met27Thr (M27T) (ATG>ACG) in the MT-CO3 gene (NC_012920.1)Observed in homoplasmic state in the blood of an individual who
had analysis of the mitochondrial genome performed by an outside laboratory.
This individual's mother was not evaluated (Tang et al., 2013)Observed in
12/49135 [0.02%] individuals in large population cohorts

(MitoMap)In-silico
analyses, including protein predictors and evolutionary conservation, support
that this variant does not alter protein structure/function
We interpret this as a Variant of Uncertain Significance.
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
re-classified according to our mitochondrial variant classification aligned
with the AMP/ACMG guidelines for variant classification (Richards et al. 2015),
which may lead to re-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 with this test.
The methods used may not detect mtDNA sequence variants with a heteroplasmy
lower than 1.5%. For mtDNA large deletions, levels of heteroplasmy of 5% or
lower may not be detected and the standard deviation for heteroplasmy of
large-scale deletions is estimated to be 5%. False negative results may also
occur in the setting of bone marrow transplantation, recent blood transfusion,
or suboptimal DNA quality. 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. The chance of a false positive or false
negative 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 N Am 21: 817- 831 (PMID 14743651). Majamaa et al., (1998) Am J Hum
Genet 63: 447-454 (PMID 9683591); Shanske et al. (2004) Am. J. Med. Genet. A
130A (2): 134-7 (PMID: 15372523); Moraes et al. (1992) Am. J. Hum. Genet. 50
(5): 934-49 (PMID: 1315123) Tang et al. (2013) Human Mutation 34 (6): 882-93
(PMID: 23463613);
Report electronically signed by: Hong Cui PhD, FACMG
Performed by: GeneDx
207 Perry Parkway
Gaithersburg, MD 20877

Anne Maddalena, Ph.D.,FACMG,

H=High, L=Low, *=Abnormal, C=Critical

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Ordering Physician Name	20-206-402403	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Ordering Physician Phone Number	20-206-402403	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
EER Mito Disorders, mtDNA, Seq/Del	20-206-402403	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Mito Disorders, mtDNA, Seq/Del	20-206-402403	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

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