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

Physician: Doctor, Example

Patient: Patient, Example

DOB	11/24/1969
Gender:	Male
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Mitochondrial Disorders Panel (mtDNA and Nuclear Genes)

ARUP test code 3001959

Ordering Physician Name	NOT PROVIDED Performed by: GeneDx 207 Perry Parkway Gaithersburg, MD 20877 Anne Maddalena, Ph.D.,FACMG,
Ordering Physician Phone Number	NOT PROVIDED Performed by: GeneDx 207 Perry Parkway Gaithersburg, MD 20877 Anne Maddalena, Ph.D.,FACMG,
EER Mito Disorders, mtDNA/Nuclear Genes	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 and Nuclear Genes	NEGATIVE Date Test(s) Started: 9/14/2020 16:21:00 Test(s) Requested Combined Mito Genome Plus Mito Focused Nuclear Gene Panel / Sequencing and Deletion Analysis of the Mitochondrial Genome and Sequencing and Deletion/Duplication Analysis of 202 Nuclear Genes Result(s): NEGATIVE - see table below Variant(s) of uncertain significance that do not establish a molecular diagnosis are listed in the table below. Interpretation No pathogenic variant associated with a disorder of mitochondrial metabolism was identified by this analysis; therefore, we cannot

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confirm a diagnosis of a mitochondrial disorder in this individual. The
combination of full sequence analysis and deletion testing of the mitochondrial
genome plus analysis of the 202 nuclear genes is estimated to identify
pathogenic variant(s) in approximately 60-80% of patients with a primary
mitochondrial disorder (Chinnery P. 2014; Koenig et al., 2008; Zeviani et al.,
2004; Taylor et al., 2014).
This negative result does not rule out a genetic basis for a diagnosis of a
mitochondrial disorder in this patient. It is possible that this patient has a
pathogenic variant in a portion of a nuclear gene that is not included in the
analysis or in a nuclear gene that is not included in this panel. Furthermore,
the percentage of mutant mtDNA (the degree of variant heteroplasmy) varies
among tissues so that mtDNA variants may be detected in some tissues, but not
others. Therefore it is usually best to test an involved tissue, such as muscle
or liver.
Recommendation(s) Genetic counseling is recommendedThe level of variant
heteroplasmy may differ among tissues so that mtDNA variants may be detected in
some tissues, but not others. Therefore it is usually best to test an involved
tissue, such as muscle or liver. If clinically indicated, full sequence
analysis and deletion testing of the mitochondrial genome can be repeated on a
muscle biopsy (approximately 50mg).The MitoXpanded panel, which includes
concurrent patient and parent sequencing of approximately 1800 genes associated
with mitochondrial disorders or a similar phenotype is also available. Whole
exome sequencing could also be considered. Please visit our website for
additional information: http: //www.genedx.com.
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.
Variants of Uncertain Significance (See Below)
GeneMode of InheritanceVariantZygosityClassification
MRPS7Autosomal Recessivec.550 A>G
p.M184VHeterozygousVariant of Uncertain Significance*
*Reported as homozygous in two siblings with congenital sensorineural deafness,
lactic acidemia, and reduced mitochondrial complex I, III and IV activity in
fibroblasts (Menezes et al. 2015).
At this time, the above variants are classified as variants of uncertain
significance as they do not meet criteria to be classified

otherwise. This
table may include single heterozygous variants of uncertain significance (VUS)
in autosomal recessive genes, VUS in genes associated with dual inheritance
that are unlikely to be related to the referring phenotype, and/or VUS or
unclassified variants in the mitochondrial DNA observed at low levels of
heteroplasmy. For variants identified in the nuclear genome, information on
population data and in-silico analysis can be found in the supplemental variant
information tables at the end of the report.

Genes Evaluated AARS2, ABCB7, ACAD9, ACO2, ADCK4, AFG3L2, AGK, AIFM1, ALAS2,
APOPT1, ATP5A1, ATP5E, ATP7B, ATPAF2, AUH, BCS1L, BOLA3, C10ORF2, C12ORF65,
C19ORF12, C20ORF7, C8ORF38, CARS2, CLPB, COA5, COA6, COASY, COQ2, COQ4, COQ6,
COQ7, COQ8A, 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,
MT-ATP6, MT-ATP8, MT-CO1, MT-CO2, MT-CO3, MT-CYB, MT-DLOOP, MTFMT, MT-ND1,
MT-ND2, MT-ND3, MT-ND4, MT-ND4L, MT-ND5, MT-ND6, MTO1, MTPAP, MT-RNR1, MT-RNR2,
MT-TA, MT-TC, MT-TD, MT-TE, MT-TF, MT-TG, MT-TH, MT-TI, MT-TK, MT-TL1, MT-TL2,
MT-TM, MT-TN, MT-TP, MT-TQ, MT-TR, MT-TS1, MT- TS2, MT-TT, MT-TV, MT-TW, MT-TY,
NARS2, NDUFA1, NDUFA10, NDUFA11, NDUFA12, NDUFA2, NDUFA4, NDUFA9, NDUFAF1,
NDUFAF2, NDUFAF3, NDUFAF4, 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

Methods Genomic DNA was extracted from the submitted specimen. For skin punch
biopsies, to analyze the nuclear genome, fibroblasts were cultured and used for
DNA extraction. For the nuclear genome, the DNA was enriched for the complete
coding regions and splice junctions of the genes on this panel using a
proprietary targeted capture system developed by GeneDx for next-generation
sequencing with CNV calling (NGS-CNV). The enriched targets were simultaneously

sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads were assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data were analyzed to identify sequence variants and most deletions and duplications involving coding exons at the exon-level; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Due to the presence of non-functional pseudogenes, regions of the GYG2, NR2F1, PDSS1 and TSFM genes were not fully sequenced by this method. For the COQ7, COX8A, HTRA2, NDUFB11, RNASEH1, SCO2, SDHA, SLC25A26, SLC25A46, TFAM, TMEM126B and TRMT10C gene(s), sequencing but not deletion/duplication analysis, was performed. Alternative sequencing or copy number detection methods were used to analyze regions with inadequate sequence or copy number data by NGS. Sequence variants are reported according to the Human Genome Variation Society (HGVS) guidelines. Copy number variants are reported based on the probe coordinates, the coordinates of the exons involved, or precise breakpoints when known. The entire mitochondrial genome from the submitted sample 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 in both the nuclear and mitochondrial genomes 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) in nuclear genes may be re-classified according to the AMP/ACMG guidelines for variant classification, while the reported variant(s) in mtDNA may be re-classified according to our mitochondrial variant classification guidelines aligned with the AMP/ACMG guidelines (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 by this test. The methods used cannot reliably detect deletions of 20bp to 500bp

in size, or
insertions of 10bp to 500 bp 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.
Rarely, incidental findings of large chromosomal rearrangements outside the
gene of interest may be identified. 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. For mitochondrial DNA (mtDNA) deletions,
this test will detect almost all disease-associated heteroplasmy reported to
date; 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%. For mtDNA sequence variants, novel variants with a heteroplasmy lower than
1.5% may not be detected. 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 Chinnery P. Mitochondrial Disorders Overview 2000 Jun 8 [Updated
2014 Aug 14]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews
[Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018.
Available from: https: //www.ncbi.nlm.nih.gov/books/NBK1224/; Koenig et al.
(2008) Pediatr. Neurol. 38 (5): 305-13 (PMID: 18410845); Zeviani et al. (2004)
Brain 127 (Pt 10): 2153-72 (PMID: 15358637); Taylor et al. (2014) JAMA 312 (1):
68-77 (PMID: 25058219) Menezes et al. (2015) Hum. Mol. Genet.

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

24 (8): 2297-307
(PMID: 25556185)
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Gene: Coding DNAMRPS7: c.550 A>G
Variant (Protein)p.Met184Val (M184V)
ClassificationVariant of Uncertain Significance
ZygosityHeterozygous
Chr: Position17: 73261825
dbSNPrs115047866
gnomAD_Freq0.0008
gnomAD_AMR0.00084669
gnomAD_NFE0.00124187
gnomAD_AFR0.00020051
gnomAD_EAS0.00000000
gnomAD_FIN0.00011946
gnomAD_Other0.00000000
gnomAD_SAS0.00049010
gnomAD_ASJ0.00009664
gnomAD_Hom0
Provean-3.06 (D)
ClinVarLikely pathogenic
This supplement provides evidence to support the classification of each
reportable variant in the attached result report. This information is provided
as a resource. It is not inclusive of all available information used by GeneDx
for variant classification, and individual data elements may be weighted
differently to derive the classification. This information is subject to change
over time and may differ from what is currently available. Results should
always be interpreted in the context of the patient's clinical presentation.Blank fields indicate that no data was available at time of
analysis.dbSNP - NCBI repository for single base nucleotide substitutions and
short deletion and insertion polymorphismsThe Genome Aggregation Database
(gnomAD) combines exome and genome sequencing data from a variety of
large-scale sequencing projects, including approximately 15,000 genomes and
123,000 exomes (Lek et al., 2016).The gnomAD set integrates data from the 1000
Genomes project as well as individuals recruited for disease-specific studies,
including cancer and cardiovascular diseases. Genotype quality metrics and site
quality metrics for a specific variant are available at http://gnomad.broadinstitute.org/.gnomAD_Freq - variant allele frequency (in
percent) from approximately 15,000 genomes and 123,000 exomes in the Genome
Aggregation DatabasegnomAD_AMR- variant frequency (in percent) for individuals
of Latino ancestrygnomAD_NFE - variant frequency (in percent) for non-Finnish
individuals of European ancestrygnomAD_AFR - variant frequency (in percent) for
individuals of African ancestrygnomAD_EAS - variant frequency (in percent) for
individuals of East Asian ancestrygnomAD_FIN - variant frequency (in percent)
for Finnish individuals of European ancestrygnomAD_Other - variant frequency
(in percent) for individuals of other ancestrygnomAD_SAS - variant frequency
(in percent) for individuals of South Asian ancestrygnomAD_ASJ- variant
frequency (in percent) for individuals of Ashkenazi Jewish

ancestrygnomAD_Hom -
The number of individuals who are homozygous for the
variantPROVEAN (Protein
Variation Effect Analyzer) - predicts whether an amino acid
substitution or
indel affects the biological function of a protein using a delta
alignment
score from -14 to +14 (more negative=more damaging) with a
predefined threshold
of -2.5. If the PROVEAN score is equal to or below -2.5, the
variant is
predicted to have a deleterious effect. If the PROVEAN score is
greater than
-2.5, the variant is predicted to have a neutral effect.Note
that other
published in silico algorithms, including those that predict
splicing impact,
may be considered for variant analysis. In silico scores used by
GeneDx are
precomputed and may change over time. In silico models use
algorithms that
predict the effect a variant may have on the protein, but they
do not provide
direct evidence regarding the actual impact on protein structure
or function.
In silico models should be interpreted with caution and only be
used in
combination with other available evidence to support the
classification of any
variant.ClinVar - Classification of variant in ClinVar database,
an NCBI
archive of human variants with supporting evidence of phenotypic
association.REFERENCES:
1. gnomAD: Lek et al. (2016) Nature 536 (7616): 285-91 (PMID:
27535533). 2.
PROVEAN: Choi et al. (2012) PLoS ONE 7 (10): e46688 (PMID:
23056405). 3.
ClinVar: Landrum et al. (2014) Nucleic Acids Res. 42 (1): D980-5
(PMID:
24234437).
Report electronically signed by: Hong Cui PhD, FACMG
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Anne Maddalena, Ph.D.,FACMG,

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

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Ordering Physician Name	20-220-137652	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Ordering Physician Phone Number	20-220-137652	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
EER Mito Disorders, mtDNA/Nuclear Genes	20-220-137652	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Mito Disorders, mtDNA and Nuclear Genes	20-220-137652	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

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