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

Physician: Doctor, Example

Patient: Patient, Example

DOB	4/11/2023
Gender:	Female
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	SEE NOTE
Ordering Physician Phone Number	SEE NOTE
EER Mito Disorders, mtDNA/Nuclear Genes	See Note Authorized individuals can access the ARUP Enhanced Report using the following link: [redacted]
Mito Disorders, mtDNA and Nuclear Genes	**Positive** *

Date Test(s) Started: 11-MAY-2023 17:38:52
Sample Source: Blood in EDTA Date Collected: 20-APR-2023 Date Received:
25-APR-2023 Testing Date Started: 11-MAY-2023 Date Reported: 22-JUN-2023
Provider Account #: A.R.U.P Laboratories Additional Provider:
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 188 Nuclear Genes
Result: Positive
GeneMode of InheritanceVariantZygosityClassification
PDHA1X-Linkedc.904 C>T
p.(R302C)HeterozygousPathogenic Variant
SCO2Autosomal dominant, Autosomal recessivec.737 C>T
p.(S246L)HeterozygousVariant of Uncertain Significance
Variant(s) of uncertain significance that do not establish a molecular
diagnosis are listed in the table below.
Interpretation This individual is heterozygous for a pathogenic variant in the
PDHA1 gene, which is consistent with pyruvate dehydrogenase deficiency. This
individual is heterozygous for a variant of uncertain significance in the SCO2
gene, which does not establish a molecular diagnosis in this individual.
Recommendation(s) Genetic counseling is recommended to discuss the implications

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

of these results.Targeted testing of the parents of this
individual will help
determine if the variant in the PDHA1 gene was inherited or
arose de novo.
Molecular prenatal diagnosis may be considered for the pathogenic
variant.Please contact GeneDx to discuss testing requirements
prior to
submitting fetal samples. Targeted testing of family members for
the variant in
theSCO2 gene may be considered to determine if the variant is
segregating with
the phenotype in this family. If desired, please contact GeneDx
to discuss
which family members may be the most informative for testing.
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.
PDHA1 Gene SummaryThe X-linked PDHA1 gene encodes the E1-alpha
subunit of the
pyruvate dehydrogenase (PDH) complex, which is located in the
mitochondrial
matrix and catalyzes the irreversible oxidative decarboxylation
of pyruvate to
acetyl-CoA (MIM 312170). The majority (>80%) of PDH complex
deficiencies result
from pathogenic variants in the PDHA1 gene, which cause a
spectrum of clinical
disorders that vary in age-of-onset, symptoms, and severity
(PMID: 16904023,
20002461). At the severe end of the spectrum, patients may
present with
neonatal severe lactic acidosis leading to early death. In other
cases,
individuals may have hypotonia, lethargy, seizures, intellectual
disability,
and spasticity. Some individuals are diagnosed with Leigh
syndrome, while
others have a milder presentation with intermittent lactic
acidosis and
cerebellar ataxia, or there may be neurologic dysfunction with
or without
structural brain abnormalities (MIM 312170). Heterozygous
females exhibit a
broad range of presentations, from severely affected to
unaffected.p.(Arg302Cys) (CGT>TGT): c.904 C>T in exon 10 of the
PDHA1 gene
(NM_000284.3)Observed in multiple unrelated female patients from
different
ethnic backgrounds with pyruvate dehydrogenase complex (PDHc)
deficiency
(Quintana et al., 2010; Glushakova et al., 2011; Dahl et al.
1992) and in a
male patient who was mosaic for the variant (Quintana et al.,
2010); has not
been observed in controlsDe novo variant with confirmed
parentage in a patient
with clinical features consistent with pyruvate dehydrogenase
deficiency
previously tested at GeneDxPublished functional studies
demonstrate that

colonies harboring the R302C variant had no functional enzyme activity
(Drakulic et al., 2018)In silico analysis supports that this missense variant
has a deleterious effect on protein structure/functionNot observed at
significant frequency in large population cohorts (gnomAD)We interpret this as
a Pathogenic Variant.
SCO2 Gene Summary The SCO2 gene encodes a metallochaperone involved in the
delivery of copper to Complex IV (COX) of the respiratory chain (PMID:
10749987). Pathogenic variants in the SCO2 gene are most commonly associated
with an autosomal recessive form of early-onset cardioencephalopathy
characterized by early mortality (PMID: 10749987). Affected individuals
typically develop respiratory insufficiency, hypotonia, lactic acidosis,
seizures and hypertrophic cardiomyopathy, with severe COX deficiency observed
in heart and skeletal muscle (PMID: 10749987). Nearly all reported patients
carry at least one copy of the common c.1541 G>A (E140K) pathogenic variant
(PMID: 10749987, 16326995). Patients homozygous for E140K have a delayed onset
of disease and a more prolonged survival, while patients with one copy of E140K
in combination with a more deleterious pathogenic variant follow a severe
clinical course, which sometimes mimicks spinal muscular atrophy type I
(Werdnig-Hoffman disease) (PMID: 14994243, 16326995). Patients with bi-allelic
variants in SCO2 and axonal neuropathy (Charcot Marie Tooth disease type 4)
with decreased copper levels were recently described; neither have developed
cardiomyopathy (PMID: 29351582). In addition, heterozygous variants in SCO2
have been reported in association with early-onset high-grade myopia (PMID:
23643385, 25525168). p.(Ser246Leu) (TCG>TTG): c.737 C>T in exon 2 of the SCO2
gene (NM_005138.2) Has not been previously published as pathogenic or benign
to our knowledge Not observed at significant frequency in large population
cohorts (gnomAD) In silico analysis supports that this missense variant has a
deleterious effect on 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.
Additional Variants of Uncertain Significance (See Below)
Gene Mode of Inheritance Variant Zygosity Classification
COASY Autosomal recessive c.1183 G>A
p.(A395T) Heterozygous Variant of Uncertain Significance
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, VUS in candidate
genes that have been suggested to be associated with autosomal recessive or
dual inheritance human disease, and 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, ATP5F1A, ATP5E, ATP7B, ATPAF2, AUH, BCS1L, BOLA3, C10ORF2, C12ORF65,
C19ORF12, C20ORF7, C8ORF38, CARS2, CLPB, COA6, COASY, COQ2, COQ4, COQ6, COQ7,
COQ8A, COQ9, COX10, COX15, COX20, COX6A1, COX6B1, CYC1, DARS2, DGUOK, DLAT,
DLD, DNA2, DNAJC19, DNM1L, EARS2, ECHS1, ELAC2, ETFA, ETFB, ETFDH, ETHE1,
FARS2, FASTKD2, FBXL4, FDX2, FH, FLAD1, FOXRED1, GARS, GCDH, GFER, GFM1, GFM2,
GLRX5, GTPBP3, HARS2, HMGCL, HTRA2, IARS2, IBA57, ISCA2, ISCU, LAMP2, LARS,
LARS2, LIAS, LIPT1, LRPPRC, LYRM4, LYRM7, MARS2, MFF, MFN2, MGME1, MICU1, MPC1,
MPV17, MRPL3, MRPL44, MRPS16, MRPS22, 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, NDUFA12,
NDUFA2, NDUFA9, NDUFAF1, NDUFAF2, NDUFAF3, NDUFAF4, NDUFB11, NDUFB3, NDUFS1,
NDUFS2, NDUFS3, NDUFS4, NDUFS6, NDUFS7, NDUFS8, NDUFV1, NDUFV2, NFU1, NR2F1,
NUBPL, OPA1, OPA3, OTC, PARS2, PC, PCCA, PCCB, PDHA1, PDHB, PDHX, PDP1, PDSS1,
PDSS2, PET100, PNPT1, POLG, POLG2, PRKAG2, PUS1, QARS, RARS1, 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, TIMM8A, TK2, TMEM126A, TMEM126B,
TMEM70, TPK1, TRIT1, TRMT10C, TRMU, TRNT1, TSFM, TTC19, TUFM, TWNK, TYMP,
UQCC2, UQCRB, UQCRC2, VARS2, WDR45, WFS1, YARS2
Methods Genomic DNA was extracted directly from the submitted specimen or, if
applicable, from cultured fibroblasts. 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. Alternative sequencing or
copy number
detection methods were used to analyze or confirm 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 genome 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
variant(s) in nuclear genes may be reclassified according to the
ACMG/AMP
Standards and Guidelines (PMID: 25741868), while the reported
variant(s) in
mtDNA may be reclassified according to our mitochondrial variant
classification
guidelines aligned with the ACMG/AMP Standards and Guidelines
which may lead to
issuing a revised report. If included in this test, the
following gene specific
information applies. Gene specific exclusions for exon-level
deletion/duplication testing for this panel are: SCO2 and SDHA,
no copy number
testing; COX6A1, GTPBP3, NDUFAF4, NDUFB3, NR2F1, SLC25A26, TAZ,
and TYMP genes,
only whole gene deletions or duplications may be detected.
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.
Unless indicated in the test methods, the following may not be
detected: mosaic
variants, pure heterodisomy, balanced chromosomal aberrations,
nucleotide
repeat expansion/contraction, abnormal DNA methylation, and

variants located in
regions not evaluated by this test or that cannot be detected by the
methodology used. Regions of certain genes have technical limitations and
inherent sequence properties that yield suboptimal data, potentially impairing
accuracy of the results (for example: repetitive DNA, homology or pseudogene
regions, high GC content). Unless otherwise indicated, sequence analysis cannot
reliably detect deletions of 20bp to 500bp in size, or insertions of 10bp to
500bp in size; deletions/insertions of less than 500 bp cannot be reliably
detected by exon-level array. Rarely, incidental findings of large chromosomal
rearrangements outside the gene(s) of interest may be identified. The zygosity
reported reflects the presumed germline status of this individual, but may be
limited by depth of read coverage and/or parental genotype data at the time of
reporting. The chance of a false positive or false negative result due to
laboratory errors incurred during any phase of testing cannot be completely
excluded. 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. False negative results may also occur in the setting of
bone marrow transplantation, recent blood transfusion, or suboptimal DNA
quality. DNA extracted using external methodologies may negatively affect test
performance. In individuals with active or chronic hematologic neoplasms or
conditions, there is a possibility that testing may detect an acquired somatic
variant, leading to a false positive result. The clinical sensitivity of this
test depends in part on the patient's clinical phenotype, and is expected to be
highest for individuals with clearly defined disease and/or family history of
disease. Interpretations are made with the assumption that any clinical
information provided, including family relationships, is 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
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(5): 820-6 (PMID: 23643385);Jiang D et al. (2015) Investigative ophthalmology
& visual science. 56 (1): 339-45 (PMID: 25525168);Rebelo AP et al. (2018)
Brain. 141 (3): 662-672 (PMID: 29351582);Brown RM et al. (2006) Dev Med Child
Neurol. 48 (9): 756-60 (PMID: 16904023);Quintana E et al. (2010) Clin Genet. 77
(5): 474-82 (PMID: 20002461); Drakulic et al. (2018) Cell. Mol. Life Sci. 75
(16): 3009-3026 (PMID: 29445841); Dahl et al. (1992) J. Inherit. Metab. Dis. 15
(6): 835-47 (PMID: 1293379); Glushakova et al. (2011) Molecular Genetics And
Metabolism 104 (3): 255-60 (PMID: 21846590); Quintana et al. (2010) Clin.
Genet. 77 (5): 474-82 (PMID: 20002461); Stenson et al. (2014) Hum. Genet. 133
(1): 1-9 (PMID: 24077912)
###
Variant Table
Gene: Coding DNAPDHA1: c.904 C>TCOASY: c.1183 G>ASCO2: c.737 C>T
Variant (Protein)p.(Arg302Cys) ((R302C))p.(Ala395Thr)
((A395T))p.(Ser246Leu)
((S246L))
ClassificationPathogenic VariantVariant of Uncertain SignificanceVariant of
Uncertain Significance
ZygosityHeterozygousHeterozygousHeterozygous
Chr: PositionX: 1937703817: 4071686222: 50962104
dbSNPrs137853252rs139263701rs139003628
gnomAD_Freq0.00060.0000
gnomAD_AMR0.000127490.00000000
gnomAD_NFE0.001108180.00001760
gnomAD_AFR0.000243720.00000000
gnomAD_EAS0.000000000.00000000
gnomAD_FIN0.000000000.00000000
gnomAD_Other0.000154800.00000000
gnomAD_SAS0.000000000.00000000
gnomAD_ASJ0.000000000.00000000
gnomAD_Hom00
Provean-7.77 (D)-1.46 (N)-2.98 (D)
ClinVarPathogenicUncertain significance
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 at the classification. This information is subject to
change 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 were available at time of analysis.

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

dbSNP - NCBI repository for single base nucleotide substitutions and short
deletion and insertion polymorphisms https: //www.ncbi.nlm.nih.gov/snp/The
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, including individuals recruited for
disease-specific studies such as cancer and cardiovascular diseases. (PMID
32461654).gnomAD_Freq - variant allele frequency (in percent) from
approximately 15,000 genomes and 123,000 exomes in the Genome Aggregation
Database. Select ancestries include: gnomAD_AMR (Admixed American/Latino);
gnomAD_AFR (African); gnomAD_EAS (East Asian); gnomAD_FIN (Finnish of European
ancestry); gnomAD_NFE (non-Finnish of European ancestry); gnomAD_SAS (South
Asian); gnomAD_ASJ (Ashkenazi Jewish). gnomAD_Hom - number of individuals
homozygous for the variant.gnomAD_AMR- variant frequency (in percent) for
individuals of Latino ancestryPROVEAN (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 (< or =
-2.5, predicted deleterious; >-2.5, predicted neutral).Other published in
silico algorithms, including those that predict splicing impact, may be
considered for variant analysis. In silico scores may change. In silico models
use algorithms that predict the effect a variant may have on the protein. Thus,
predictions should be interpreted with caution and only be used in combination
with other available evidence to support the classification of any variant
(PMID 23056405).ClinVar - Classification of variant in ClinVar database, an
NCBI archive of human variants with supporting evidence of phenotypic
association. https: //www.ncbi.nlm.nih.gov/clinvar/ (PMID 26582918).

MTDNA BENIGN/LIKELY BENIGN VARIANTS " style="cursor: pointer;" contenteditable="true">
Functional Location Variant Change Amino Acid Change Frequency (Gen. Pop)
MT-DLOOP m.73 A>G non-coding 37469/49135
MT-DLOOP m.119 T>C non-coding 75/50175
MT-DLOOP m.189 A>G non-coding 2719/49135
MT-DLOOP m.195 T>C non-coding 9537/49135
MT-DLOOP m.204 T>C non-coding 3142/49135
MT-DLOOP m.207 G>A non-coding 2295/49135
MT-DLOOP m.227 A>G non-coding 165/50175
MT-DLOOP m.263 A>G non-coding 46799/49135
MT-DLOOP m.503 A>G non-coding 19/51673
MT-RNR1 m.709 G>A rRNA 6395/49135
MT-RNR1 m.750 A>G rRNA 48276/49135
MT-RNR1 m.1243 T>C rRNA 776/49135
MT-RNR1 m.1438 A>G rRNA 46721/49135
MT-RNR2 m.2706 A>G rRNA 38981/49135
MT-RNR2 m.3106del In Frame common
MT-ND1 m.3505 A>G Missense 701/49135
MT-ND2 m.4769 A>G Synonymous 55528/56895

MT-ND2 m.5046 G>A Missense 868/49135
MT-ND2 m.5460 G>A Missense 3179/49135
MT-CO1 m.7028 C>T Synonymous 39824/49135
MT-CO2 m.7864 C>T Synonymous 211/50175
MT-CO2 m.8251 G>A Synonymous 2823/49135
MT-ATP6 m.8860 A>G Missense 48479/49135
MT-ATP6 m.8994 G>A Synonymous 808/49135
MT-ND4 m.11204 T>C Missense 147/49135
MT-ND4 m.11674 C>T Synonymous 561/49135
MT-ND4 m.11719 G>A Synonymous 38205/49135
MT-ND4 m.11914 G>A Synonymous 5367/49135
MT-ND4 m.11947 A>G Synonymous 533/49135
MT-ND5 m.12414 T>C Synonymous 670/49135
MT-ND5 m.12648 A>G Synonymous 11/50175
MT-ND5 m.12705 C>T Synonymous 20517/49135
MT-ND5 m.14148 A>G Extended Protein 315/49135
MT-CYB m.14766 C>T Missense 37907/49135
MT-CYB m.15326 A>G Missense 48493/49135
MT-CYB m.15884 G>C Missense 535/49135
MT-DLOOP m.16223 C>T non-coding 19551/49135
MT-DLOOP m.16292 C>T non-coding 1218/49135
MT-DLOOP m.16519 T>C non-coding 30962/49135
Haplogroup (HG): W1c1
Report electronically signed by: Hong Cui PhD, 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	23-110-122946	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Ordering Physician Phone Number	23-110-122946	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
EER Mito Disorders, mtDNA/Nuclear Genes	23-110-122946	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Mito Disorders, mtDNA and Nuclear Genes	23-110-122946	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART