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

Physician: Doctor, Example

Patient: Patient, Example

DOB	5/25/1996
Sex:	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

EER Mito Disorders, mtDNA/Nuclear Genes

See Note

Authorized individuals can access the ARUP Enhanced Report with an ARUP Connect account using the following link.

Your local lab can assist you in obtaining the patient report if you don't have a Connect account.

Mito Disorders, mtDNA and Nuclear Genes

Positive *

Date Test(s) Started: 5/5/2025 18:23:10
Sample Source: Blood in EDTA Date Collected: 4/25/2025 Date Received: 5/2/2025
Testing Date Started: 5/5/2025 Date Reported: 5/28/2025
Provider Account #:
[redacted] A.R.U.P Laboratories Additional Provider:
Test(s) Requested Combined Mito Genome Plus Mito Nuclear Gene Panel /
Sequencing and Deletion Analysis of the Mitochondrial Genome and Sequencing and
Deletion/Duplication Analysis of Nuclear Genes
Result: Positive
Gene Mode of Inheritance Variant Heteroplasmy (%) Classification
MT-ND4 Maternal m.11232 T>C
p.(L158P) Homoplasmic Likely Pathogenic Variant
Gene Mode of Inheritance Variant Zygosity Classification
SPG7 Autosomal dominant, Autosomal recessive c.847 G>A
p.(G283R) Heterozygous Variant of Uncertain Significance
Interpretation A likely pathogenic variant was identified in the MT-ND4 gene.
When observed at this level of heteroplasmy, this variant is expected to be
associated with a mitochondrial disorder(s).
The variant(s) of uncertain significance in the SPG7 gene(s) do not establish a
molecular diagnosis.
Recommendation(s) Genetic counseling is recommended to discuss the implications
of these results.Correlation of these findings with the clinical features of
this proband is recommended.Mitochondrial DNA disorders are maternally
inherited. Testing for the MT-ND4 variant in matrilineal relatives may be
considered.Targeted testing of the parents of this proband and/or other family
members, if available, may help determine if the variant in the SPG7 gene

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

segregates with the phenotype and may assist in further interpretation. To inquire if individuals from this family may be eligible for targeted testing at no additional charge, please contact GeneDx with a pedigree or a summary of the health status of the available relative(s).
MT-ND4 Gene Summary The MT-ND4 gene encodes for subunit 4 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.11232 T>C: p.(Leu158Pro) (CTT>CCT) in the MT-ND4 gene
(NC_012920.1) Identified in an individual with chronic progressive external
ophthalmoplegia, diabetes, elevated serum lactate, and ragged red fibers on
muscle biopsy. Variant was observed at approximately 40% heteroplasmy in muscle
and not observed in blood (PMID: 14581685) Identified homoplasmic on a post
mortem whole exome sequencing with mitochondrial genome analysis in a female
child who presented with hearing impairment and subsequently developed
metabolic acidosis, hyperlactatemia, and died after an anesthetic procedure for
cerebral magnetic resonance imaging (Candelo E et al. (2023) Research Square)
Identified homoplasmic in blood in unrelated patients referred for genetic
testing at GeneDx with acute hypoxic or ischemic encephalopathy following
anesthesia Single fiber analysis found this variant at higher levels in COX-
fibers (60.4%) than COX+ fibers (16.2%) (PMID: 14581685) Not observed in large
population cohorts (MITOMAP) In silico analyses, including protein predictors
and evolutionary conservation, support a deleterious effect We interpret this
as a Likely Pathogenic Variant.
SPG7 Gene Summary The SPG7 gene encodes paraplegin, a component of the enzyme
that is involved with the degradation of misfolded proteins and regulation of
ribosome assembly (PMID: 20301286). Pathogenic variants in the SPG7 gene cause
spastic paraplegia 7, a typically adult-onset disorder characterized by
progressive bilateral lower limb weakness and spasticity (PMID: 20301286).
Additional features such as hyperreflexia in the arms, dysphagia, ataxia,
nystagmus and strabismus, decreased hearing, motor and sensory neuropathy, and
amyotrophy may also be present (PMID: 20301286). A wide range of pathogenic
variants, including deletion and duplications of the SPG7 gene, have been
reported in association with spastic paraplegia (HGMD). Spastic paraplegia 7 is
typically associated with autosomal recessive inheritance, and most carriers of
pathogenic variants in the SPG7 gene are asymptomatic (PMID: 22571692).
However, some heterozygotes have been reported to have isolated optic
neuropathy or a more mild presentation of spastic paraplegia (PMID: 23065789,
11222789, 22571692). Although pathogenic variants in SPG7 are a known cause of
spastic paraplegia, recent studies indicate that autosomal recessive
SPG7-related disorders may also include a predominant cerebellar ataxia
phenotype (PMID: 25681447, 27081526, 22964162). Additionally, there is
increasing evidence to suggest that individuals with heterozygous or compound

heterozygous variants in the SPG7 gene may also present with dystonia and/or
parkinsonism-like symptoms (PMID: 35586535, 37648940).
p.(Gly283Arg) (GGA>AGA):
c.847 G>A in exon 6 of the SPG7 gene (NM_003119.2) 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 In silico analysis supports a deleterious effect on splicing
Has not been previously published as pathogenic or benign to our knowledge We
interpret this as a Variant of Uncertain Significance.
Additional Variants of Uncertain Significance (See Below)
Gene Mode of Inheritance Variant Zygosity Classification
AUH Autosomal recessive c.769 G>A
p.(V257I) Heterozygous Variant of Uncertain Significance
BCS1L Autosomal recessive c.530 G>A
p.(R177H) 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)
or two VUS present on the same allele (in cis) in genes associated with
autosomal recessive inheritance, 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. If provided, this
individual's mother was not evaluated for the presence of these variant(s). 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, AFG3L2, AGK, AIFM1, ALAS2, ATP5F1A,
ATP5F1E, ATP7B, ATPAF2, AUH, BCS1L, BOLA3, C19ORF12, CARS2, CLPB, COA6, COA8,
COASY, COQ2, COQ4, COQ6, COQ7, COQ8A, COQ8B, 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, GARS1, GCDH, GFER, GFM1, GFM2, GLRX5, GTPBP3, HARS2, HMGCL, HTRA2,
IARS2, IBA57, ISCA2, ISCU, LAMP2, LARS1, LARS2, LIAS, LIPT1, LRPPRC, LYRM4,
LYRM7, MARS2, MFF, MFN2, MGME1, MICU1, Mitochondrial Genome, MPC1, MPV17,
MRPL3, MRPL44, MRPS16, MRPS22, MTFMT, MTO1, MTPAP, MTRFR, NARS2, NDUFA1,
NDUFA10, NDUFA12, NDUFA2, NDUFA9, NDUFAF1, NDUFAF2, NDUFAF3, NDUFAF4, NDUFAF5,
NDUFAF6, 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, QARS1, 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,
TAFAZZIN, TARS2, TFAM, 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 toreference 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 2% heteroplasmy
or lower. Sensitivity of testing may be reduced for insertions and deletions in
repetitive regions. 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. Haplogroup and homoplasmic
likely benign and benign variants are included in a supplemental

table. Nuclear
and heteroplasmic 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 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 otherwise indicated, 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. Copy number assessment methods 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. DNA
extracted at other laboratories may negatively affect test performance. 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. The clinical sensitivity of this test depends in
part on the patient's clinical presentation and is expected to be highest for
individuals with a clearly defined phenotype and/or family history.
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
ClinVar https: //www.ncbi.nlm.nih.gov/clinvar/
ClinGen Dosage Sensitivity https:
//search.clinicalgenome.org/kb/gene-dosage
Database for Genomic Variants (DGV) http:
//dgv.tcag.ca/dgv/app/home
DECIPHER https: //www.deciphergenomics.org/
gnomAD https: //gnomad.broadinstitute.org/
MITOMAP https: //www.mitomap.org/MITOMAP
OMIM https: //www.omim.org/
Provean https: //www.jcvi.org/research/provean
The Human Gene Mutation Database (HGMD) https:
//www.hgmd.cf.ac.uk/ac/index.php
To find publications referenced in the report using PubMed ID
(PMID), please
search PubMed (https: //pubmed.ncbi.nlm.nih.gov/).
###
Variant Table
Gene: Coding DNAAUH: c.769 G>ABCS1L: c.530 G>ASPG7: c.847 G>A
Variant (Protein)p.(Val257Ile) ((V257I))p.(Arg177His)
((R177H))p.(Gly283Arg)
((G283R))
ClassificationVariant of Uncertain SignificanceVariant of
Uncertain
SignificanceVariant of Uncertain Significance
ZygosityHeterozygousHeterozygousHeterozygous
Chr: Position9: 939831612: 21952655116: 89595973
dbSNPrs749920943rs143968821
gnomAD_Freq0.00000.0000
gnomAD_AMR0.000086730.00000000
gnomAD_NFE0.000000000.00001759
gnomAD_AFR0.000061520.00000000
gnomAD_EAS0.000000000.00005437
gnomAD_FIN0.000000000.00000000
gnomAD_Other0.000325840.00000000
gnomAD_SAS0.000032660.00006534
gnomAD_ASJ0.000000000.00000000
gnomAD_Hom00
Provean-0.79 (N)-4.83 (D)-3.75 (D)
ClinVarUncertain significanceUncertain 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. 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

Functional Location	Variant	Change	Amino Acid Change	Frequency (Gen. Pop)
MT-DLOOP	m.73	A>G	non-coding	37469/49135
MT-DLOOP	m.263	A>G	non-coding	46799/49135
MT-DLOOP	m.489	T>C	non-coding	12687/49135
MT-RNR1	m.750	A>G	rRNA	48276/49135
MT-RNR1	m.1438	A>G	rRNA	46721/49135
MT-RNR2	m.2092	C>T	rRNA	426/49135
MT-RNR2	m.2706	A>G	rRNA	38981/49135
MT-RNR2	m.3010	G>A	rRNA	7061/49135
MT-RNR2	m.3106del	In Frame	common	
MT-ND1	m.3335	T>C	Missense	54/49135
MT-TM	m.4435	A>G	tRNA	52/50175
MT-ND2	m.4769	A>G	Synonymous	55528/56895
MT-ND2	m.4883	C>T	Synonymous	2373/49135

MT-ND2 m.5178 C>A Missense 2350/49135
MT-ND2 m.5273 A>G Synonymous 2/51836
MT-CO1 m.7028 C>T Synonymous 39824/49135
MT-ATP8 m.8414 C>T Missense 1945/49135
MT-ATP6 m.8701 A>G Missense 16496/49135
MT-ATP6 m.8860 A>G Missense 48479/49135
MT-CO3 m.9540 T>C Synonymous 16490/49135
MT-ND3 m.10398 A>G Missense 21770/49135
MT-ND3 m.10400 C>T Synonymous 10506/49135
MT-ND4 m.10873 T>C Synonymous 16474/49135
MT-ND4 m.11719 G>A Synonymous 38205/49135
MT-ND5 m.12705 C>T Synonymous 20517/49135
MT-ND6 m.14668 C>T Synonymous 2041/49135
MT-CYB m.14766 C>T Missense 37907/49135
MT-CYB m.14783 T>C Synonymous 10482/49135
MT-CYB m.15043 G>A Synonymous 11642/49135
MT-CYB m.15164 T>C Missense 8/56895
MT-CYB m.15301 G>A Synonymous 14238/49135
MT-CYB m.15326 A>G Missense 48493/49135
MT-DLOOP m.16176 C>T non-coding 303/49135
MT-DLOOP m.16223 C>T non-coding 19551/49135
MT-DLOOP m.16261 C>T non-coding 3689/49135
MT-DLOOP m.16325 T>C non-coding 1630/49135
MT-DLOOP m.16327 C>T non-coding 2119/49135
MT-DLOOP m.16362 T>C non-coding 8667/49135
Haplogroup (HG): D1
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
EER Mito Disorders, mtDNA/Nuclear Genes	25-115-152751	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Mito Disorders, mtDNA and Nuclear Genes	25-115-152751	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

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