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

Physician: Doctor, Example

Patient: Patient, Example

DOB	Unknown
Gender:	Unknown
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Exome Sequencing, Proband

ARUP test code 2006336

Exome Sequencing Specimen, Patient	DNA

Exome Sequencing Interpretation, Patient

Positive

TEST PERFORMED
Exome Sequencing, Proband

Exome sequencing was performed on the patient using DNA extracted from whole blood. Parental samples were not available to aid result interpretation.

RESULT
Positive. One pathogenic variant was identified in the LMNA gene that is predicted to provide an explanation for this individual's phenotype.

One pathogenic variant was detected in the SDHB gene. The American College of Medical Genetics and Genomics (ACMG) recommends reporting likely pathogenic and pathogenic variants that are identified in this gene by whole exome sequencing even though this variant may not be related to the primary indication for testing.

INDICATION FOR TESTING
According to information provided to ARUP, this patient is a 10-year-old with a waddling gait during an annual physical examination. The parents also reported that the child sometimes toe walked and appeared to have joint stiffness resulting in difficulties stretching their arms. Testing revealed elevated creatine kinase (CK) levels. The family reported a maternal cousin with atrial fibrillation. The maternal grandfather reportedly died while swimming, but no further details were available. The paternal grandfather developed dilated cardiomyopathy at the age of 80 after prolonged chemotherapy.

INTERPRETATION
One pathogenic variant was identified in the LMNA gene. Pathogenic variants in LMNA are associated with autosomal dominant Emery-Dreifuss muscular dystrophy 2 (MIM: 181350) and congenital muscular dystrophy (MIM: 613205), dilated cardiomyopathy 1A (MIM: 115200), as well as autosomal recessive Emery-Dreifuss muscular dystrophy 3 (MIM: 616516).

PATHOGENIC VARIANT
Gene: LMNA (NM_170707.2)
Variant: c.1072G>A; p.Glu358Lys - Heterozygous
Chr1(GRCh37):g.156105827
Frequency: rs60458016; absent from gnomAD
Conservation: highly conserved amino acid (Alamut software

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

v2.11.0)
Computational prediction programs: Deleterious (REVEL: 0.953)
Inheritance pattern: Autosomal dominant

One pathogenic variant, c.1072G>A; p.Glu358Lys, was identified in the lamin A/C (LMNA) gene by massively parallel sequencing. Pathogenic variants in LMNA are associated with autosomal dominant Emery-Dreifuss muscular dystrophy 2 (MIM: 181350) and congenital muscular dystrophy (MIM: 613205), dilated cardiomyopathy 1A (MIM: 115200), as well as autosomal recessive Emery-Dreifuss muscular dystrophy 3 (MIM: 616516). This individual's future offspring have a 50 percent chance of inheriting this variant.

The LMNA c.1072G>A; p.Glu358Lys variant is reported in the literature in several individuals with laminopathies including in at least one individual where the variant was reported de novo (Choi 2019, Komaki 2011, Mitsuhashi 2010, Pasqualin 2014, van Rijsingen 2013, Zwerger 2013). The variant is reported as pathogenic by several sources in the ClinVar database (Variation ID: 14525). In support of the prediction of this variant being deleterious, cells expressing this variant exhibit altered LMNA localization and are more sensitive to strain (Zwerger 2013). Based on available information, this variant is classified as pathogenic.

MEDICALLY-ACTIONABLE SECONDARY FINDING

PATHOGENIC VARIANT
Gene: SDHB (NM_003000.2)
Variant: c.343C>T; p.Arg115Ter - Heterozygous
Chr1(GRCh37):g.17355175
Frequency: rs751000085; gnomAD: 2 out of 251,464 chromosomes, overall MAF 0.0008%
Inheritance pattern: Autosomal dominant

One pathogenic variant, c.343C>T; p.Arg115Ter, was detected in the succinate dehydrogenase complex, subunit B, iron sulfur protein (SDHB) gene by massively parallel sequencing. Pathogenic germline variants in SDHB are associated with autosomal dominant paragangliomas (MIM: 115310) and pheochromocytoma (MIM: 171300). This result is consistent with a diagnosis of hereditary paraganglioma-pheochromocytoma syndrome; clinical manifestations and penetrance are variable. This individual's offspring have a 50 percent chance to inherit the pathogenic variant.

The SDHB c.343C>T; p.Arg115Ter variant is reported in the medical literature in several individuals and segregates with disease in at least one family (Bayley 2006, Benn 2006, Hensen 2012, Niemeijer 2017, Ricketts 2010). The variant is reported as pathogenic by several sources in the ClinVar database (Variation ID: 197210). This variant induces an early termination codon and is predicted to result in a truncated protein or mRNA subject to nonsense-mediated decay. Based on available information, this variant is considered to be pathogenic.

No additional pathogenic variants were identified in genes that were reviewed related to the following HPO terms: HP:0030234 (Highly elevated creatine kinase), HP:0001387 (Joint stiffness), HP:0008180 (Mildly elevated creatine kinase), HP:0040083 (Toe walking), HP:0002515 (Waddling gait). Please note that adequate sequencing coverage has not been verified for each of these genes.

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of medical screening and management. Targeted testing for the identified LMNA and SDHB variants in parental samples may be useful to clarify whether they are inherited or de novo. The patient should also be offered prenatal diagnostic options when he/she is of reproductive age. At-risk relatives should be offered carrier testing for the identified pathogenic LMNA and

SDHB variants (Familial Mutation, Targeted Sequencing; ARUP test 2001961).

NOTES
Approximately 95.5% of bases in the coding exome were covered by more than 10 sequencing reads.

REFERENCES
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Benn DE et al. Clinical presentation and penetrance of pheochromocytoma/paraganglioma syndromes. J Clin Endocrinol Metab. 2006 Mar;91(3):827-36.

Choi SA et al. Importance of early diagnosis in LMNA-related muscular dystrophy for cardiac surveillance. Muscle Nerve. 2019;60(6):668-672.

Hensen EF et al. High prevalence of founder mutations of the succinate dehydrogenase genes in the Netherlands. Clin Genet. 2012 Mar;81(3):284-8.

Mitsuhashi H et al. Specific phosphorylation of Ser458 of A-type lamins in LMNA-associated myopathy patients. J Cell Sci. 2010;123(Pt 22):3893-3900.

Niemeijer ND et al. The phenotype of SDHB germline mutation carriers: a nationwide study. Eur J Endocrinol. 2017 Aug;177(2):115-125.

Ostlund C et al. Properties of lamin A mutants found in Emery-Dreifuss muscular dystrophy, cardiomyopathy and Dunnigan-type partial lipodystrophy. J Cell Sci. 2001;114(Pt 24):4435-4445.

Pasqualin LM et al. Congenital muscular dystrophy with dropped head linked to the LMNA gene in a Brazilian cohort. Pediatr Neurol. 2014;50(4):400-406.

Ricketts CJ et al. Tumor risks and genotype-phenotype-proteotype analysis in 358 patients with germline mutations in SDHB and SDHD. Hum Mutat. 2010 Jan;31(1):41-51.

van Rijsingen IA et al. Gender-specific differences in major cardiac events and mortality in lamin A/C mutation carriers. Eur J Heart Fail. 2013;15(4):376-384.

Zwerger M et al. Myopathic lamin mutations impair nuclear stability in cells and tissue and disrupt nucleo-cytoskeletal coupling. Hum Mol Genet. 2013;22(12):2335-2349.

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Exome Sequencing, Proband

CHARACTERISTICS: The purpose of exome sequencing is to determine the patient's diagnosis when a genetic condition is suspected. The exome includes all known human genes and accounts for approximately 1-2 percent of the human genome. However, it is estimated that the exome harbors approximately 85 percent of genetic disease-causing variants.

CLINICAL SENSITIVITY: A diagnosis is determined in up to 35 percent of patients when parental samples are submitted for targeted sequencing and in 20 percent of cases when parental samples are unavailable.

METHODOLOGY: Targeted capture of all (or selected) coding exons and exon-intron junctions of the targeted genes, followed by massively parallel sequencing. Sanger sequencing was performed as necessary to confirm reported variants. Human genome build 19 (Hg 19) was used for data analysis.

ANALYTICAL SENSITIVITY: The analytical sensitivity of this test is approximately 98 percent for single nucleotide variants (SNVs) and greater than 93 percent for Insertions / duplications / deletions from 1-10 base pairs in size. Deletions/duplication greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced.

LIMITATIONS OF ANALYSIS: A negative result does not exclude all genetic diagnoses. The human exome is not able to be completely analyzed as some genes have not been identified while others, due to technical limitations, cannot either be sequenced or interpreted. Some pathogenic variants reside in regions outside the exome. This test only detects variants within the coding regions and intron-exon boundaries of the targeted genes. Mitochondrial DNA is not analyzed. Chromosomal phase of identified variants may not be determined. Deletions / duplications / insertions of any size may not be detected by massively parallel sequencing. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions. This assay may not detect low-level somatic variants associated with disease.

LIMITATIONS FOR REPORTING AND INTERPRETATION: Only variants in genes suspected to be associated with the patient's symptoms are reported, with the exception of secondary pathogenic findings, if elected. Additionally, de novo and/or rare compound heterozygous variants in genes of unknown clinical relevance may be reported. Incorrect reporting of biological relationships among family members may affect result interpretation. Mode of inheritance, reduced penetrance, and genetic heterogeneity could reduce clinical sensitivity. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation.

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the US Food and Drug Administration. This test was performed in a CLIA certified laboratory and is intended for clinical purposes.

Counseling and informed consent are recommended for genetic testing. Consent forms are available online.

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

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Exome Sequencing Specimen, Patient	21-123-112625	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Exome Sequencing Interpretation, Patient	21-123-112625	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