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

Physician: Doctor, Example

Patient: Patient, Example

DOB	12/9/2016
Gender:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	01/01/2017 12:34

Aortopathy Panel, Sequencing and Deletion/Duplication

ARUP test code 2006540

Aortopathy Panel Specimen: Whole Blood

Aortopathy Panel Interpretation: Positive

INDICATION FOR TESTING
Patient referred for testing due to prominent forehead, long fingers, and suspected congenital contractural arachnodactyly.

RESULT
One pathogenic variant was detected in the FBN1 gene.

PATHOGENIC VARIANT
Gene: FBN1 (NM_000138.4)
Nucleic Acid Change: c.364C>T; Heterozygous
Amino Acid Alteration: p.Arg122Cys
Inheritance: Autosomal Dominant

INTERPRETATION
One pathogenic variant, c.364C>T; p.Arg122Cys, was detected in the FBN1 gene by massively parallel sequencing and confirmed by Sanger sequencing. Pathogenic FBN1 variants are most commonly causative for Marfan syndrome (MFS); clinical manifestations are variable. Additionally, other phenotypes including neonatal Marfan syndrome, mitral valve prolapse syndrome, MASS syndrome, thoracic aortic aneurysms and aortic dissections (TAAD), Shprintzen-Goldberg syndrome, Weill-Marchesani syndrome as well as autosomal dominant ectopia lentis are also associated with FBN1 pathogenic variants. Future offspring of this individual have a 50 percent chance of inheriting the causative variant.

No additional pathogenic variants were identified in the other targeted genes by massively parallel sequencing or deletion/duplication analysis. Please refer to the background information included in this report for a list of the genes analyzed and limitations of this test.

Evidence for variant classification:
The FBN1 c.364C>T; p.Arg122Cys variant (rs137854467) has been reported in multiple families with clinical symptoms suggestive of Marfan syndrome, and is strongly associated with ectopia lentis (Black 1998, Comeglio 2002, Jin 2007, Loeys 2001, Stahl-Hallengran 1994). It is reported in ClinVar as pathogenic (Variation ID: 16440) and is absent from general population databases (1000 Genomes Project, Exome Variant Server, and Genome Aggregation Database), indicating it is not a common polymorphism. The variant changes an arginine in an EGF-like domain into a cysteine residue, which meets the revised Ghent nosology criteria of a causative Marfan syndrome variant (Loeys

2010). Based on available information, this variant is considered to be pathogenic.

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of medical screening and management. At risk family members should be offered testing for the identified pathogenic FBN1 variant (Familial Mutation, Targeted Sequencing, ARUP test code 2001961).

COMMENTS
Benign variants are not included in this report, but are available upon request.

REFERENCES
Black C et al. Correlation of a recurrent FBN1 mutation (R122C) with an atypical familial Marfan syndrome phenotype. Hum Mutat. 1998; Suppl 1:S198-200.

Comeglio P et al. Identification of FBN1 gene mutations in patients with ectopia lentis and marfanoid habitus. Br J Ophthalmol. 2002; 86(12):1359-62.

Jin C et al. Novel FBN1 mutations associated with predominant ectopia lentis and marfanoid habitus in Chinese patients. Mol Vis. 2007; 13:1280-4.

Loeys B et al. Genotype and phenotype analysis of 171 patients referred for molecular study of the fibrillin-1 gene FBN1 because of suspected Marfan syndrome. Arch Intern Med. 2001; 2001 Nov 12;161(20):2447-54.

Loeys B et al. The revised Ghent nosology for the Marfan syndrome. J Med Genet. 2010; 47(7):476-85.

Stahl-Hallengren C et al. An extra cysteine in one of the non-calcium-binding epidermal growth factor-like motifs of the FBN1 polypeptide is connected to a novel variant of Marfan syndrome. J Clin Invest. 1994; 94(2):709-13.

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Aortopathy Panel, Sequencing and Deletion/Duplication

CHARACTERISTICS: Life-threatening aortic dilatations, dissections, and/or rupture, including syndromic and familial connective tissue disorders caused by variants identified in multiple genes.

EPIDEMIOLOGY: The prevalence of Marfan syndrome (MFS) is 1 in 5,000 to 1 in 10,000; Homocystinuria due to cystathionine beta-synthase deficiency (HCY) is 1 in 1,800 to 1 in 800,000 depending on the ethnic population; Ehlers-Danlos syndrome, type I/II (EDS I/II) is 1 in 20,000; Ehlers-Danlos syndrome, type IV (EDS IV) is at least 1 in 250,000; thoracic aortic aneurysm and dissection (TAAD) has an incidence of 9-16/100,000 individuals/year and is familial in approximately 20 percent of cases.

CAUSE: Pathogenic germline variants in genes associated with MFS, HCY, EDS, TAAD, congenital contractural arachnodactyly (CCA) and Loeys-Dietz syndrome (LDS).

INHERITANCE: X-linked for FLNA, autosomal recessive for CBS, EFEMP2, PLOD1, and SLC2A10; autosomal dominant for the other tested genes.

PENETRANCE: Complete for MFS, EDS IV, EDS VI, CCA, and LDS, with rare exceptions; reduced for TAAD and EDS I/ II.

GENES TESTED: ACTA2, CBS, COL3A1, COL5A1, COL5A2, EFEMP2, FBN1, FBN2, FLNA, LOX**, MYH11, MYLK, PLOD1, PRKG1, SKI, SLC2A10, SMAD3, SMAD4, TGFB2, TGFB3, TGFBR1, TGFBR2

** - Deletion/duplication detection is not available for this gene.

METHODOLOGY: Targeted capture of all coding exons and exon-intron junctions of the targeted genes, followed by massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage and confirm reported variants. A custom tiled comparative genomic hybridization array (aCGH) was used to detect large deletions or duplications in the indicated subset of genes. Human genome build 19 (Hg 19) was used for data analysis.

ANALYTICAL SENSITIVITY: The analytical sensitivity of this test is approximately 99 percent for single nucleotide variants (SNVs) and greater than 93 percent for insertions/duplications/deletions from 1-10 base pairs in size. Variants greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced.

LIMITATIONS: A negative result does not exclude a heritable form of MFS, HCY, EDS, TAAD, CCA, or LDS. This test only detects variants within the coding regions and intron-exon boundaries of the targeted genes. Regulatory region variants and deep intronic variants will not be identified and breakpoints of large deletions/duplications will not be determined. Single exon deletions/duplications or deletions/duplications less than 1kb may not be detected. Deletions/duplications/insertions of any size may not be detected by massive 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. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Non-coding transcripts were not analyzed.

Single exon deletions/duplications will not be called for the following exons:
COL3A1(NM_000090) 6,7,9,13;COL5A1(NM_000093) 1,16,20;COL5A2(NM_000393) 36;MYH11(NM_001040113) 42;PRKG1(NM_006258) 8,17;TGFBR1(NM_004612) 1

Test developed and characteristics determined by ARUP Laboratories. See Compliance Statement C: aruplab.com/CS

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Aortopathy Panel Specimen	18-344-107874	12/10/2018 12:01:00 PM	12/10/2018 12:01:14 PM	12/10/2018 1:08:00 PM
Aortopathy Panel Interpretation	18-344-107874	12/10/2018 12:01:00 PM	12/10/2018 12:01:14 PM	12/10/2018 1:08:00 PM

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