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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

Aortopathy Panel, Sequencing and Deletion/Duplication

ARUP test code 2006540

Aortopathy Panel Specimen: Whole Blood

Aortopathy Panel Interpretation: Positive

RESULT
One pathogenic variant was detected in the FBN1 gene.

PATHOGENIC VARIANT
Gene: FBN1 (NM_000138.5)
Nucleic Acid Change: c.4621C>T; Heterozygous
Amino Acid Alteration: p.Arg1541Ter
Inheritance: Autosomal dominant

INTERPRETATION
One pathogenic variant, c.4621C>T; p.Arg1541Ter, was detected in the FBN1 gene by massively parallel sequencing. Pathogenic FBN1 variants are most commonly causative for Marfan syndrome (MFS); clinical manifestations are variable. Additionally, other phenotypes including 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 pathogenic FBN1 variants. This individual's offspring have a 50 percent chance of inheriting the pathogenic variant.

Please refer to the background information included in this report for a list of the genes analyzed, methodology, and limitations of this test.

Evidence for variant classification:
The FBN1 c.4621C>T; p.Arg1541Ter variant (rs794728228) is reported in the literature in several individuals affected with Marfan syndrome (Comeglio 2007, Halliday 1999, Loeys 2001, Loeys 2004). This variant is also reported in ClinVar (Variation ID: 200052), but is absent from the Genome Aggregation Database, indicating it is not a common polymorphism. This variant induces an early termination codon, and functional analyses show the variant mRNA is subject to nonsense-mediated decay, resulting in undetectable levels of FBN1 mRNA (Magyar 2009). 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 Targeted Sequencing, ARUP test code 3005867).

COMMENTS

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

Likely benign and benign variants are not reported.
Variants in the following region(s) may not be detected by NGS with sufficient confidence in this sample due to technical limitations:
NONE

REFERENCES
Comeglio et al. The importance of mutation detection in Marfan syndrome and Marfan-related disorders: report of 193 FBN1 mutations. Hum Mutat. 2007; 28(9): 928. PMID: 17657824.
Halliday et al. Molecular analysis of eight mutations in FBN1. Hum Genet. 1999; 105(6): 587-597. PMID: 10647894.
Loeys 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; 161(20): 2447-2454. PMID: 11700157.
Loeys et al. Comprehensive molecular screening of the FBN1 gene favors locus homogeneity of classical Marfan syndrome. Hum Mutat. 2004; 24(2): 140-146. PMID: 15241795.
Magyar et al. Quantitative sequence analysis of FBN1 premature termination codons provides evidence for incomplete NMD in leukocytes. Hum Mutat. 2009; 30(9): 1355-1364. PMID: 19618372.

This result has been reviewed and approved by Desi DeMille
BACKGROUND INFORMATION: Aortopathy Panel, Sequencing and Deletion/Duplication

CHARACTERISTICS: Aortopathy disorders are associated with aneurysm, dissection and/or rupture of the aorta. Clinical presentation may include thoracic aortic aneurysm and dissection (TAAD). Syndromic forms include Marfan syndrome (MFS), Loeys-Dietz syndrome (LDS), Ehlers-Danlos syndrome (EDS: classic, vascular, and kyphoscoliotic types), Shprintzen-Goldberg syndrome, multisystemic smooth muscle dysfunction syndrome, Meester-Loeys syndrome, congenital contractual arachnodactyly (CCA), arterial tortuosity syndrome, periventricular nodular heterotopia 1, cutis laxa type 1B, juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome, and aortic valve disease 1. Homocystinuria due to cystathionine beta-synthase deficiency (HCY) has phenotypic overlap with MFS.

EPIDEMIOLOGY: The prevalence of Marfan syndrome (MFS) is 1 in 5,000 to 1 in 10,000; HCY is 1 in 1,800 to 1 in 335,000 depending on the ethnic population; EDS, classic type (cEDS, type I/II) is 1 in 20,000; EDS, vascular type (vEDS, type IV) is at least 1 in 200,000. 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 aortopathy disorders

INHERITANCE: Commonly autosomal dominant. X-linked for BGN and FLNA. Autosomal recessive for CBS, EFEMP2, PLOD1, and SLC2A10.

PENETRANCE: Complete for MFS, vEDS, PLOD1-associated kEDS, CCA, and LDS, with rare exceptions; reduced for TAAD and cEDS.

GENES TESTED: ACTA2, BGN, CBS*, COL1A1, COL1A2*, COL3A1, COL5A1*, COL5A2, EFEMP2, FBN1, FBN2, FLNA, FOXE3*, LOX, MFAP5, MYH11, MYLK*, NOTCH1*, PLOD1, PRKG1, SKI, SLC2A10, SMAD2, SMAD3, SMAD4, TGFB2, TGFB3**, TGFBR1, TGFBR2.

*One or more exons are not covered by sequencing and/or deletion/duplication analysis for the indicated gene; see limitations section below.

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

METHODOLOGY: Probe hybridization-based 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 to confirm reported variants that do not meet acceptable quality metrics. A proprietary bioinformatic algorithm was used to detect large (single exon-level or larger) deletions or duplications in the indicated genes. Large deletions/duplications were confirmed using an orthogonal exon-level microarray. Human genome build 19 (Hg 19) was used for data analysis.

ANALYTICAL SENSITIVITY: The analytical sensitivity is approximately 99 percent for single nucleotide variants (SNVs) and greater than 93 percent for insertions/duplications/deletions (indels) from 1-10 base pairs in size. Indels greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced. Deletions of 2 exons or larger are detected with sensitivity greater than 97 percent; single exon deletions are detected with 62 percent sensitivity. Duplications of 3 exons or larger are detected at greater than 83 percent sensitivity. Specificity is greater than 99.9 percent for all variant classes.

LIMITATIONS: A negative result does not exclude a heritable aortopathy disorder. This test only detects variants within the coding regions and intron-exon boundaries of the targeted genes. Deletions/duplications/insertions of any size may not be detected by massively parallel sequencing. Regulatory region variants and deep intronic variants will not be identified. Precise breakpoints for large deletions or duplications are not determined in this assay and single exon deletions/duplications may not be detected based on the breakpoints of the rearrangement. The actual breakpoints for the deletion or duplication may extend beyond or be within the exon(s) reported. This test is not intended to detect duplications of 2 or fewer exons in size, though these may be identified. Single exon deletions are reported but called at a lower sensitivity. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations caused by the presence of pseudogenes, repetitive, or homologous regions. This test is not intended to detect low-level mosaic or somatic variants, gene conversion events, complex inversions, translocations, mitochondrial DNA (mtDNA) mutations, or repeat expansions. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Noncoding transcripts were not analyzed.

The following regions are not sequenced due to technical limitations of the assay:
CBS(NM_001321072) exon(s) 1
COL5A1(NM_000093) exon(s) 1
COL5A1(NM_001278074) exon(s) 1
FOXE3(NM_012186) partial exon(s) 1(Chr1:47882098-47882163)

Single exon deletions/duplications will not be called for the following exons:
CBS(NM_001321072) 1; COL1A2(NM_000089) 3; COL5A1(NM_000093) 1; COL5A1(NM_001278074) 1; MYLK(NM_053025) 13; MYLK(NM_001321309) 12; MYLK(NM_053026) 12; MYLK(NM_053027) 13; MYLK(NM_053028) 12; NOTCH1(NM_017617) 1

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
Aortopathy Panel Specimen	22-294-117783	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Aortopathy Panel Interpretation	22-294-117783	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