Client: ARUP Example Report Only
500 Chipeta Way
Salt Lake City, UT 84108
UNITED STATES

Physician: ARUP, ARUP

Patient: FBN1 NGS, POSITIVE EXAMPLE

DOB

Sex:	Female
Patient Identifiers:	44176
Visit Number (FIN):	44503
Collection Date:	11/14/2022 14:03

Marfan Syndrome (FBN1) Sequencing and Deletion/Duplication

ARUP test code 3004102

Marfan Syndrome (FBN1) Specimen	Whole Blood
Marfan Syndrome (FBN1) Interpretation	Positive

INDICATION FOR TESTING
Confirm a suspected diagnosis of Marfan syndrome.

RESULT
One pathogenic variant was detected in the FBN1 gene.

PATHOGENIC VARIANT
Gene: FBN1 (NM_000138.4)
Nucleic Acid Change: c.3373C>T; Heterozygous
Amino Acid Alteration: p.Arg1125Ter
Inheritance: Autosomal Dominant

INTERPRETATION
One copy of a pathogenic variant, c.3373C>T; p.Arg1125Ter, 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 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. Offspring of this individual have a 50 percent chance of inheriting the causative variant.

No additional pathogenic variants were identified by massively parallel sequencing or deletion/duplication analysis. Please refer to the background information included in this report for the clinical sensitivity and limitations of this test.

Evidence for variant classification: The FBN1 c.3373C>T; p.Arg1125Ter variant (rs727505006) is reported in the literature in individuals with clinical findings of Marfan syndrome (Becerra-Munoz 2018, Mannucci 2020, Overwater 2018, Rommel 2005, Weerakkody 2016), and is classified as pathogenic by multiple laboratories in ClinVar (Variation ID: 179632). This variant is absent from general population databases (Exome Variant Server, Genome Aggregation Database), indicating it is not a common polymorphism. 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.

RECOMMENDATIONS

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

Genetic consultation is indicated, including a discussion of medical screening and management. At-risk family members should be offered a clinical evaluation for Marfan syndrome. If it is unclear whether or not they are affected, targeted testing for the identified pathogenic variant should be offered (Familial Mutation, Targeted Sequencing, ARUP test code 2001961).

COMMENTS
Likely benign and benign variants are not included in this report.

REFERENCES
Becerra-Munoz VM et al. The importance of genotype-phenotype correlation in the clinical management of Marfan syndrome. Orphanet J Rare Dis. 2018 Jan 22;13(1):16. PMID: 29357934.

Mannucci L et al. Mutation analysis of the FBN1 gene in a cohort of patients with Marfan Syndrome: A 10-year single center experience. Clin Chim Acta. 2020 Feb;501:154-164. PMID: 31730815.

Overwater E et al. Results of next-generation sequencing gene panel diagnostics including copy-number variation analysis in 810 patients suspected of heritable thoracic aortic disorders. Hum Mutat. 2018 Sep;39(9):1173-1192. PMID: 29907982.

Rommel K et al. Identification of 29 novel and nine recurrent fibrillin-1 (FBN1) mutations and genotype-phenotype correlations in 76 patients with Marfan syndrome. Hum Mutat. 2005 Dec;26(6):529-39. PMID: 16220557.

Weerakkody RA et al. Targeted next-generation sequencing makes new molecular diagnoses and expands genotype-phenotype relationship in Ehlers-Danlos syndrome. Genet Med. 2016 Nov;18(11):1119-1127. PMID: 27011056.

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Marfan Syndrome (FBN1) Sequencing and Deletion/Duplication

CHARACTERISTICS: Marfan syndrome is a connective tissue disorder affecting the ocular, skeletal, and cardiovascular systems with a high degree of clinical variability. Common ocular findings include myopia, ectopia lentis, retinal detachment, glaucoma, and early cataracts. Skeletal involvement may include bone overgrowth and joint laxity, disproportionally long extremities, pectus excavatum/carinatum, and scoliosis. Cardiovascular findings include aortic dilatation/dissection, mitral and/or tricuspid valve prolapse, and enlargement of the proximal pulmonary artery. Cardiovascular disease management is necessary to decrease morbidity and early mortality.

EPIDEMIOLOGY: Prevalence is 1 in 5,000 to 1 in 10,000.

CAUSE: Pathogenic germline variants in the FBN1 gene

INHERITANCE: Autosomal dominant. De novo pathogenic variants are causative for 25 percent of cases.

PENETRANCE: Complete, but age dependent.

CLINICAL SENSITIVITY: 95-98 percent.

GENE TESTED: FBN1 (NM_000138)

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 confirmed using an orthogonal exon-level microarray. Human genome build 19 (Hg 19) was used for data analysis.

ANALYTICAL SENSITIVITY/SPECIFICITY: 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 diagnosis of Marfan syndrome or other FBN1-related disorders. This test only detects variants within the coding regions and intron-exon boundaries of the FBN1 gene. 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.

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.

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Marfan Syndrome (FBN1) Specimen	22-318-114358	11/14/2022 2:03:00 PM	11/14/2022 2:05:14 PM	11/14/2022 2:14:00 PM
Marfan Syndrome (FBN1) Interpretation	22-318-114358	11/14/2022 2:03:00 PM	11/14/2022 2:05:14 PM	11/14/2022 2:14:00 PM

END OF CHART

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