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Patient Report

Patient Age/Gender: Male

Specimen Collected: 22-Jun-21 16:01

Marfan Syndrome (FBN1) by NGS, DelDup | **Received: 24-Jun-21 09:40** | **Report/Verified: 24-Jun-21 10:14**

Procedure	Result	Units	Reference Interval
Spcm FBN1	See Note		
FBN1 Interp	Positive f1 i1		

Result Footnote

f1: FBN1 Interp

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
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.

*=Abnormal, #=Corrected, C=Critical, f=Result Footnote, H-High, i-Test Information, L-Low, t-Interpretive Text, @=Performing lab

Result Footnote

f1: FBN1 Interp

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 Pinar Bayrak-Toydemir, MD, PhD

Test Information

i1: FBN1 Interp

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.

Test Information

i1: FBN1 Interp

METHODOLOGY: 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. Multiplex ligation-dependent probe amplification (MLPA) was used to detect large deletions or duplications.

ANALYTICAL SENSITIVITY/SPECIFICITY: The analytical sensitivity of sequencing 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. The analytical sensitivity for MLPA is 99 percent.

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. Regulatory region variants and deep intronic variants will not be identified and breakpoints of large deletions/duplications will 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 mosaic or somatic variants associated with disease. 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.