MAYO CLINIC

1-800-533-1710

FBN1 Full Gene Analysis

MFBNG

PATIENT NAME				ORDER NUMBER
ABNORMAL, MFBNG				**M229000170**
PATIENT ID SA00154614	DATE OF BIRTH 01/01/1980	AGE 42 Y	SEX Female	REQUESTED BY CLIENT CLIENT
COLLECTED 9/28/2022, 11:00 AM	RECEIVED 9/29/2022, 8:29 AM	REPORTED 9/30/2022, 10:53 AM		
The collected, received, and reported dates and times on the report are in the time zone of the performing location. 7028846 MCL RochesterCampus Rochester MN 55901				CLIENT ORDER NUMBER SA00154614 CLIENT MRN SA00154614

TEST DESCRIPTION

Evaluation of FBN1 gene associated with Marfan syndrome and other hereditary connective tissue disorders

SPECIMEN

DNA (ul)

RESULT SUMMARY

Pathogenic Variant Detected

RESULT

Gene (Transcript)	Variant	Zygosity	Classification
FBN1 (NM_000138.4)	c.1787G>A p.Cys596Tyr (p.C596Y) Chr15(GRCh37):g.48800829C>T	Heterozygous	Pathogenic

The following heterozygous PATHOGENIC variant was detected: FBN1 (NM_000138.4), Chr15 (GRCh37):g.48800829C>T, c.1787G>A, p.Cys596Tyr (p.C596Y)

No additional reportable variants were detected within all other tested genes. See the Method section for a complete list of genes evaluated by this assay.

INTERPRETATION

FBN1: c.1787G>A (p.Cys596Tyr): The heterozygous c.1787G>A (p.Cys596Tyr) variant in the FBN1 gene (MIM: 134797) is classified as pathogenic. The FBN1 gene encodes fibrillin-1. Pathogenic variants in this gene have mainly been associated with autosomal dominant Marfan syndrome (MFS). This variant removes a cysteine residue within the domain and may cause protein misfolding by loss or gain of disulfide bonds. FBN1 missense variants affecting cysteine residues are considered strongly predictive of pathogenicity according to the revised Ghent nosology for Marfan syndrome (1). The p.Cys596Tyr variant has been previously reported in two to three individuals with a diagnosis of MFS (1-3). This variant was also reported to segregate with features of MFS in three family members (3). Finally, this variant has not been observed in exome and/or genome sequencing data gathered from large, multi-ethnic cohorts, suggesting it is a rare variant (4). Taken together, this result is supportive of a diagnosis of Marfan syndrome for this individual. Clinical correlation is recommended.

This result should be interpreted in the context of clinical findings, family history, and other laboratory testing.

Consultation with a genetics professional is recommended for interpretation of this result and to determine whether reproductive risk assessment and familial testing may be of benefit to this family. Genetic testing for family members is available by ordering FMTT / Familial Mutation, Targeted Testing for the specific variant(s) detected. Please contact the laboratory at 1-800-533-1710 or the online test catalog at www.mayocliniclabs.com for information about FMTT.

REFERENCES:

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1. Katzke S, Booms P, Tiecke F, et al. TGGE screening of the entire FBN1 coding sequence in 126 individuals with marfan syndrome and related fibrillinopathies. Hum Mutat. 2002;20(3):197-208. doi:10.1002/humu.10112 (PMID: 12203992)
2. Somers AE, Hinton RB, Pilipenko V, Miller E, Ware SM. Analysis of TGFBR1*6A variant in individuals evaluated for Marfan syndrome. Am J Med Genet A. 2016;170(7):1786-1790. doi:10.1002/ajmg.a.37668 (PMID: 27112580)
3. Hernándiz A, Zúñiga A, Valera F, et al. Genotype FBN1/phenotype relationship in a cohort of patients with Marfan syndrome. Clin Genet. 2021;99(2):269-280. doi:10.1111/cge.13879 (PMID: 33174221)
4. gnomAD Browser: gnomad.broadinstitute.org/; Karczewski K, Francioli LC, MacArthur DG, et al. The mutational constraint spectrum quantified from variation in 141,456 humans. Nature. 2020; 581(7809):434-443 (PMID 32461654)

METHOD

Next generation sequencing (NGS) and/or Sanger sequencing was performed to test for the presence of variants in coding regions and intron/exon boundaries of the genes analyzed, as well as some other regions that have known pathogenic variants. The human genome reference GRCh37/hg19 build was used for sequence read alignment. At least 99% of the bases are covered at a read depth over 30X. Sensitivity is estimated at above 99% for single nucleotide variants, above 94% for indels less than 40 base pairs (bp), above 95% for deletions up to 75 bp and insertions up to 47 bp. NGS, and/or a polymerase chain reaction (PCR)-based quantitative method was performed to test for the presence of deletions and duplications in the genes analyzed. See the Genes Analyzed field for a list of genes tested.

There may be regions of genes that cannot be effectively evaluated for sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high GC content, and repetitive sequences. Confirmation of select reportable variants was performed by alternate methodologies based on internal laboratory criteria. See www.mayocliniclabs.com (TEST ID MFBNG) for details regarding genes with regions not routinely covered.

GENES ANALYZED

FBN1

DISCLAIMER

Clinical Correlations
An online research opportunity called GenomeConnect (genomeconnect.org), a project of ClinGen, is available for the recipient of this genetic test. This patient registry collects de-identified genetic and health information to advance the knowledge of genetic variants. Mayo Clinic is a collaborator of ClinGen. This may not be applicable for all tests.

If testing was performed because of a clinically significant family history it is often useful to first test an affected family member. Detection of a reportable variant(s) in an affected family member would allow for more informative testing of at risk individuals.

To discuss the availability of further testing options or for assistance in the interpretation of these results, Mayo Clinic Laboratory genetic counselors can be contacted at 1-800-533-1710.

Technical Limitations
Next generation sequencing may not detect all types of genomic variants. In rare cases, false negative or false positive results may occur. The depth of coverage may be variable for some target regions, but assay performance below the

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minimum acceptable criteria or for failed regions will be noted. Given these limitations, negative results do not rule out the diagnosis of a genetic disorder. If a specific clinical disorder is suspected, evaluation by alternative methods can be considered.

There may be regions of genes that cannot be effectively evaluated for sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high GC content, and repetitive sequences. Confirmation of select reportable variants was performed by alternate methodologies based on internal laboratory criteria.

Additionally, low level mosaic variants may not be detected.

This test is not designed to differentiate between somatic and germline variants. If there is a possibility that any detected variant is somatic, additional testing may be necessary to clarify the significance of results.

Genes may be added or removed based on updated clinical relevance. Please refer to the Targeted Genes and Methodology Details for the FBN1 Full Gene Analysis in the Special Instructions section of the Test Catalog for the most up to date list of genes included in this test.

Reclassification of Variants Policy
See www.mayocliniclabs.com (TEST ID MFBNG) for information regarding the laboratory's policy for reclassification of variants.

Variant Evaluation
Variant curation is performed using published ACMG-AMP recommendations as a guideline. Other gene-specific guidelines may also be considered. Variants classified as benign or likely benign are not reported.

Results from in silico evaluation tools may change over time and should be interpreted with caution and professional clinical judgment.

TEST CLASSIFICATION
This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

RELEASED BY

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