MAYO CLINIC

1-800-533-1710

Postmortem Aortopathy Gene Panel

PMAOG

PATIENT NAME				ORDER NUMBER
TESTRNV, TESTING A				**N425000323**
PATIENT ID X100430252	DATE OF BIRTH 02/19/1968	AGE 55 Y	SEX Male	REQUESTED BY CLIENT TESTING
COLLECTED 9/25/2023, 7:00 AM	RECEIVED 9/25/2023, 2:00 PM	REPORTED 10/1/2023, 2:58 PM		
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 X100430252 CLIENT MRN 321

TEST DESCRIPTION

Evaluation of 31 genes associated with Marfan syndrome, Loeys-Dietz syndrome, Ehlers-Danlos syndrome, heritable thoracic aortic disease/aortopathy and related conditions

SPECIMEN

Tissue Scroll

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 PATHOGENIC variant was detected:
FBN1 (NM_000138.4), chr15(GRCh37):g.48800829C>T, c.1787G>A, p.Cys596Tyr (p.C596Y), heterozygous

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

INTERPRETATION

FBN1 c.1787G>A (p.Cys596Tyr), PATHOGENIC
The heterozygous c.1787G>A (p.Cys596Tyr) missense 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). Other associated autosomal dominant conditions include familial ectopia lentis, MASS syndrome, Marfan lipodystrophy syndrome, Weill-Marchesani syndrome, and several others. This variant removes a cysteine residue within the domain and may cause protein misfolding by loss or gain of disulfide bonds (1). The p.Cys596Tyr variant has been previously reported in two to three individuals with a diagnosis of MFS (2,3). This variant was also reported to segregate with features of MFS in three family members (3). This variant is absent from large control databases (4,5). This result is supportive of a diagnosis of autosomal dominant Marfan syndrome or other FBN1-related condition 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

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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:
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) dbSNP: www.ncbi.nlm.nih.gov/snp
5) gnomAD Browser: gnomad.broadinstitute.org/

ADDITIONAL INFORMATION

TISSUE ID: Testing5-3029565

METHOD

Next generation sequencing (NGS) was performed to test for the presence of sequence variants in coding regions and intron/exon boundaries of the genes analyzed. The human genome reference GRCh37/hg19 build was used for sequence read alignment. See the Genes Analyzed field for a list of genes tested.

There may be regions of genes that cannot be effectively evaluated as a result of technical limitations of the assay, including regions of homology, high GC content, and repetitive sequences. See www.mayocliniclabs.com (TEST ID PMAOG) for details regarding genes with regions not routinely covered.

GENES ANALYZED

ACTA2, ADAMTS10, ADAMTS17, AEBP1, BGN, COL1A1, COL1A2, COL3A1, COL5A1, COL5A2, EFEMP2, FBN1, FBN2, FLNA, LOX, MED12, MFAP5, MYH11, MYLK, NOTCH1, PRKG1, SKI, SLC2A10, SMAD2, SMAD3, SMAD4, SMAD6, TGFB2, TGFB3, TGFBR1 and TGFBR2

DISCLAIMER

Sample Quality:

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This test is intended for use when EDTA whole blood is not available and formalin-fixed, paraffin-embedded (FFPE) tissue is the only available sample. DNA extracted from FFPE tissue can be degraded, which results in a higher failure rate for next-generation sequencing when compared to DNA extracted from whole blood. Due to the quality of DNA extracted from FFPE, the acceptable coverage threshold may be lower than that of the equivalent blood assays. Coverage of at least 20X is expected for most regions assessed but may be adjusted on a case-by-case basis at the discretion of the laboratory director.

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 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.

Deletion/duplication analysis is not performed due to technical limitations of the FFPE sample type. In addition, there may be regions of genes that cannot be effectively evaluated for sequencing analysis as a result of technical limitations of the assay, including regions of homology, high GC content, and repetitive sequences. Confirmation of NGS results by Sanger sequencing is typically not performed for this test. 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 Postmortem Aortopathy Gene Panel 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

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See www.mayocliniclabs.com (TEST ID PMAOG) 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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