MAYO CLINIC LABORATORIES

Test Definition: PMAOG

Postmortem Aortopathy Gene Panel, Tissue

Overview

Useful For

Providing a comprehensive postmortem genetic evaluation in the setting of a sudden death attributed to thoracic aortic dissection or with a personal or family history suggestive of Marfan syndrome, Loeys-Dietz syndrome, thoracic aortic aneurysm and dissections, vascular Ehlers-Danlos syndrome, or a related condition

Identifying a disease-causing variant in the decedent, which may assist with risk assessment and predictive testing of at-risk family members

Genetics Test Information

This test utilizes next-generation sequencing to detect single nucleotide variants and deletions-insertions (delins) in 31 genes associated with Marfan syndrome, Loeys-Dietz syndrome, Ehlers-Danlos syndrome, heritable thoracic aortic disease/aortopathy and related conditions with overlapping clinical presentation: *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*. See Method Description for additional details.

Identification of a disease-causing variant may assist with familial risk assessment, screening, and genetic counseling for Marfan syndrome, Loeys-Dietz syndrome, Ehlers-Danlos syndrome, and hereditary aortopathies.

Special Instructions

- Informed Consent for Genetic Testing
- Informed Consent for Genetic Testing for Deceased Individuals
- Informed Consent for Genetic Testing (Spanish)
- Connective Tissue/Cerebrovascular Disease Genetic Testing Patient Information

Method Name

Sequence Capture and Targeted Next-Generation Sequencing (NGS)

NY State Available

Yes

Specimen

Specimen Type

Varies

Ordering Guidance

This test is intended for use when whole blood is not available, and formalin-fixed, paraffin-embedded (FFPE) tissue is the only available specimen. If whole blood is available, consider either MFRGG / Marfan, Loeys-Dietz, and Aortopathy

Gene Panel, Varies or CAORG / Comprehensive Marfan, Loeys-Dietz, Ehlers-Danlos, and Aortopathy Gene Panel, Varies.

Targeted testing for familial variants (also called site-specific or known variants testing) is available for the genes on this panel. See FMTT / Familial Variant, Targeted Testing, Varies. To obtain more information about this testing option, call 800-533-1710.

Specimen Required

Specimen Type: Tissue block
Collection Instructions: Submit a formalin-fixed, paraffin-embedded tissue block
Additional Information: Testing will be attempted on blocks of any age but may be canceled if adequate DNA concentration cannot be obtained.

Forms

1. **New York Clients-Informed consent is required.** Document on the request form or electronic order that a copy is on file. The following documents are available:
-Informed Consent for Genetic Testing (T576)
-Informed Consent for Genetic Testing (Spanish) (T826)
-Informed Consent for Genetic Testing for Deceased Individuals (T782)
2. Connective Tissue/Cerebrovascular Disease Genetic Testing Patient Information
3. If not ordering electronically, complete, print, and send a Cardiovascular Test Request (T724) with the specimen.

Specimen Minimum Volume

See Specimen Required

Reject Due To

All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Ambient (preferred)		
	Refrigerated		

Clinical & Interpretive

Clinical Information

Sudden cardiac death (SCD) is estimated to occur at an incidence of between 50 to 100 per 100,000 individuals in North America and Europe each year, claiming between 250,000 and 450,000 lives in the United States annually. In younger individuals (15-35 years of age), the incidence of SCD is between 1 to 2 per 100,000 young individuals. Sudden cardiac death, particularly in young individuals, may suggest an inherited form of heart disease. In some cases of sudden death, autopsy may identify a structural abnormality, such as aortic aneurysm or dissection. Postmortem diagnosis of a hereditary form of aortic aneurysm/dissection may assist in confirmation of the cause of death, as well as risk assessment in living family members.

Inherited forms of aortic disease, or aortopathies, may be associated with isolated thoracic aortic aneurysms and

dissections or conditions with multi-system involvement. This gene panel includes genes for multiple conditions that may have aortopathy as a feature, including Marfan syndrome, Loeys-Dietz syndrome, Ehlers-Danlos syndrome, arterial tortuosity syndrome, and heritable thoracic aortic disease (also known as familial thoracic aortic aneurysm/dissection: FTAAD). Other heritable conditions with overlapping clinical presentations are also covered by this panel. Confirming a genetic diagnosis in the setting of aortopathy may aid in differentiating the genetic etiology of complex or ambiguous clinical presentations, treatment decisions, and genetic counseling.

Marfan syndrome (MFS) is an autosomal dominant genetic disorder affecting the connective tissue that occurs in approximately 1 to 2 per 10,000 individuals. It is characterized by the presence of skeletal, ocular, and cardiovascular manifestations and is caused by variants in the *FBN1* gene. Skeletal findings may include tall stature, chest wall deformity, scoliosis, and joint hypermobility. Lens dislocation (ectopia lentis) is the cardinal ocular feature with mitral valve prolapse and aortic root dilatation/dissection the main cardiovascular features.(1)

Loeys-Dietz syndrome (LDS) is an autosomal dominant connective tissue disease with significant overlap with Marfan syndrome but may include involvement of other organ systems and is primarily caused by variants in *TGFBR1* and *TGFBR2*.(2,3) Features of LDS that are not typical of MFS include craniofacial and neurodevelopmental abnormalities and arterial tortuosity with increased risk for aneurysm and dissection throughout the arterial tree. Variants in the *SMAD3* gene have been reported in families with an LDS-like phenotype with arterial aneurysms and tortuosity and early onset osteoarthritis. Variants in the *TGFB3* gene have also been reported in families with an LDS-like phenotype, although these individuals tended to not have arterial tortuosity.

FTAAD is a genetic condition primarily involving dilatation and dissection of the thoracic aorta but may also include aneurysm and dissection of other arteries. This condition has a highly variable age of onset and presentation and may involve additional features, such as congenital heart defects and other features of connective tissue disease or smooth muscle abnormalities depending on the causative gene. The gene most commonly involved in FTAAD is *ACTA2*.(4,5)

Vascular Ehlers-Danlos syndrome (also known as vEDS or EDS IV) is an autosomal dominant connective tissue disease caused by variants in the *COL3A1* gene. vEDS may present with characteristic facial features, thin, translucent skin, easy bruising, and arterial, intestinal, and uterine fragility. Arterial rupture may be preceded by aneurysm or dissection or may occur spontaneously.(6) Classic Ehlers-Danlos syndrome types I and II (also known as cEDS) are caused by variants in the *COL5A1* and *COL5A2* genes and may develop aortic root dilation and, more rarely, spontaneous vessel rupture. Vascular fragility has also been demonstrated in a rare form of cEDS (known as COL1A1-cEDS, classic-like EDS syndrome with propensity to arterial rupture, or vascular-like EDS) due to variants in the *COL1A1* gene.(7)

Other genes included on this panel cause conditions with clinical overlap with those above. Examples include genes associated with rare, autosomal recessive forms of Ehlers-Danlos syndrome, the *FLNA* gene associated with periventricular nodular heterotopia, the *FBN2* gene associated with congenital contractural arachnodactyly, the *SLC2A10* gene associated with autosomal recessive arterial tortuosity syndrome, and the *NOTCH1* gene associated with aortic valve disease and severe valve calcification. Currently, expert consensus indicates *NOTCH1* variants may be predictive of thoracic aortic enlargement without evidence of progression to aortic dissection.(8-12)

Reference Values

An interpretive report will be provided.

Interpretation

All detected variants are evaluated according to American College of Medical Genetics and Genomics

recommendations.(13) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Cautions

Clinical Correlations:
Test results should be interpreted in the context of clinical findings, family history, and other laboratory data. Misinterpretation of results may occur if the information provided is inaccurate or incomplete.

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 in an affected family member would allow for more informative testing of at-risk individuals.

To discuss the availability of additional testing options or for assistance in the interpretation of these results, contact Mayo Clinic Laboratories genetic counselors at 800-533-1710.

Technical Limitations:
Next-generation sequencing (NGS) 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.

There may be regions of genes that cannot be effectively evaluated by sequencing as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. Confirmation of NGS results by Sanger sequencing is typically not performed for this test.

Deletions-insertions (delins) of 40 or more base pairs, including mobile element insertions, may be less reliably detected than smaller delins.

Deletion/duplication analysis is not performed due to technical limitations of the formalin-fixed paraffin-embedded specimen type.

This test is not designed to detect low levels of mosaicism or 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. For detailed information regarding gene specific performance and technical limitations, see Method Description or contact a laboratory genetic counselor.

Reclassification of Variants**:**
Currently, it is not standard practice for the laboratory to systematically review previously classified variants on a regular basis. The laboratory encourages healthcare providers to contact the laboratory at any time to learn how the classification of a particular variant may have changed over time. Due to broadening genetic knowledge, it is possible that the laboratory may discover new information of relevance to the patient. Should that occur, the laboratory may issue an amended report.

Variant Evaluation:
Evaluation and categorization of variants are performed using published American College of Medical Genetics and Genomics and the Association for Molecular Pathology recommendations as a guideline.(13) Other gene-specific guidelines may also be considered. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Variants classified as benign or likely benign are not reported.

Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and periodic updates to these tools may cause predictions to change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Rarely, incidental or secondary findings may implicate another predisposition or presence of active disease. Incidental findings may include, but are not limited to, results related to the sex chromosomes. These findings will be carefully reviewed to determine whether they will be reported.

Clinical Reference

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Performance

Method Description

Next-generation sequencing (NGS) is 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 disease-causing 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 20X. Sensitivity is estimated at above 99% for single nucleotide variants and above 94% for deletions-insertions (delins) less than 40 base pairs.

There may be regions of genes that cannot be effectively evaluated by sequencing as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. Confirmation of NGS results by Sanger sequencing is typically not performed for this test.(Unpublished Mayo method)

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*

PDF Report

Supplemental

Day(s) Performed

Varies

Report Available

28 to 42 days

Specimen Retention Time

FFPE tissue block: Client provided paraffin blocks (FFPE) will be returned to client after testing is complete; Extracted DNA: 3 months.

Performing Laboratory Location

Mayo Clinic Laboratories - Rochester Main Campus

Fees & Codes

Fees

- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact Customer Service.

Test Classification

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

CPT Code Information

81410

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
PMAOG	Postmortem Aortopathy Gene Panel	106052-4

Result ID	Test Result Name	Result LOINC® Value
620569	Test Description	62364-5
620570	Specimen	31208-2
620571	Source	31208-2
620572	Result Summary	50397-9
620573	Result	82939-0
620574	Interpretation	69047-9
620575	Additional Results	82939-0
620576	Resources	99622-3
620577	Additional Information	48767-8
620578	Method	85069-3
620579	Genes Analyzed	82939-0
620580	Disclaimer	62364-5
620581	Released By	18771-6