MAYO CLINIC
Mayo Medical Laboratories

TEST ID: PMMFR

POSTMORTEM MARFAN AND RELATED PANEL

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, or a related disorder
- Identification of a pathogenic variant in the decedent, which may assist with risk assessment and predictive testing of at-risk family members

GENETICS TEST INFORMATION

This test includes next-generation sequencing and supplemental Sanger sequencing to evaluate for variants in the *ACTA2*, *CBS*, *COL3A1*, *FBN1*, *FBN2*, *MYH11*, *MYLK*, *SKI*, *SLC2A10*, *SMAD3*, *TGFB2*, *TGFBR1*, and *TGFBR2* genes.

Targeted testing for familial variants (also called site-specific or known mutation testing) is available for all genes on this panel; see **KVAR1 / Known Variant Analysis-1 Variant**, **KVAR2 / Known Variant Analysis-2 Variants**, or **KVAR3 / Known Variant Analysis-3+ Variants**. Contact Mayo Medical Laboratories to confirm the appropriate test code for targeted testing if testing for a gene not included on this panel is needed.

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 (ages 15–35), 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.

Marfan syndrome (MFS) is an autosomal dominant genetic disorder affecting the connective tissue and 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, and aortic root dilatation/dissection and mitral valve prolapse are the main cardiovascular features. Diagnosis is based on the revised Ghent nosology and genetic testing of *FBN1*. Management aims to monitor and slow the rate of aortic root dilatation, and initiate appropriate medical and/or surgical intervention as needed. Other phenotypes associated with the *FBN1* gene include autosomal dominant ectopia lentis (displacement of the lens of the eye), familial thoracic aortic aneurysm and dissections (TAAD), isolated skeletal features of MFS, MASS phenotype (mitral valve prolapse, aortic diameter increased, stretch marks, skeletal features of MFS), Shprintzen-Goldberg syndrome (Marfanoid-craniosynostosis; premature ossification and closure of sutures of the skull), and autosomal dominant Weill-Marchesani syndrome (short stature, short fingers, ectopia lentis).

REFERENCE VALUES

An interpretive report will be provided.

ANALYTIC TIME

6 weeks

SPECIMEN REQUIRED

PREFERRED

Type
Tissue

Container/Tube
Tissue block

ACCEPTABLE

Type
Blood spot

Container/Tube
Whatman FTA Classic Card or Whatman Protein Saver 903 Card

Specimen Volume
3–5 blood spots

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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*. 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 a LDS-like phenotype with arterial aneurysms and tortuosity and early onset osteoarthritis.

Thoracic aortic aneurysm and dissections (TAAD) is a genetic condition primarily involving dilatation and dissection of the thoracic aorta, but may also include aneurysm and dissection of other arteries. TAAD 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 familial TAAD is *ACTA2*, followed by *TGFBR1* and *TGFBR2*, and *MYH11*. Variants in the *MYLK* gene have been reported in a small subset of families with familial TAAD. *TGFB2* variants have also been reported in families with TAAD and systemic features that overlap with LDS and MFS.

The *COL3A1* gene causes Ehlers Danlos syndrome type IV (vascular type), an autosomal dominant connective tissue disease 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.

Autosomal dominant variants of the *FBN2* gene are known to cause congenital contractural arachnodactyly (CCA), which has several overlapping features with Marfan syndrome, including dolichostenomelia, scoliosis, pectus deformity, arachnodactyly, and a risk for thoracic aortic aneurysm.

Variants of the *CBS* gene cause homocystinuria an autosomal recessive disorder of amino acid metabolism with clinical overlap with Marfan syndrome; including lens dislocation and skeletal abnormalities, as well as increased risk for abnormal blood clotting.

Variants in the *SKI* gene cause Shprintzen-Goldberg syndrome (SGS), an autosomal dominant condition with overlap with LDS and MFS. Distinguishing features of SGS include hypotonia and intellectual disability. Aortic root dilatation is less frequent in SGS than in LDS or MFS but, when present, it can be severe.

Homozygous and compound heterozygous loss of function variants in the *SLC2A10* gene have been described in arterial tortuosity syndrome, a condition characterized by generalized tortuosity and elongation of all major arteries in addition to other connective tissue disease features.

Many of these described disorders have distinct genetic causes but may present phenotypically similarly, leading to difficulty in accurate diagnosis. However, gene-based management strategies have been described for some of these disorders. Therefore, comprehensive genetic analysis may be useful for accurate diagnosis and gene-based management.

INTERPRETATION

Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

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