Cardiovascular Diseases Genetic Testing Program

Thoracic Aortic Aneurysm Panel

The Thoracic Aortic Aneurysm Panel offers Next Generation Sequencing of 14 genes associated with syndromic and non-syndromic forms of thoracic aortic aneurysm and dissections (TAAD). TAAD is characterized by aneurysm and dissection primarily of the thoracic aorta, but can involve other arteries including abdominal aortic aneurysms, cerebral aneurysms, and peripheral artery aneurysms. Even in the absence of obvious connective tissue disease, thoracic aortic aneurysms are often associated with genetic/familial predisposition. Most commonly, Familial TAAD is associated with dilation, aneurysm, and/or dissection of the ascending aorta. This is typically associated with an autosomal dominant inheritance pattern with reduced penetrance. *ACTA2* is the gene most commonly implicated in Familial TAAD, accounting for up to 14% of cases. In total, the genetic basis of Familial TAAD is identifiable in approximately 20% of cases.

Several syndromic conditions are known to be associated with TAAD. This panel includes genes associated with connective tissue related disorders including Marfan syndrome, Loeys-Dietz syndrome, Ehlers-Danlos syndrome Type IV (Vascular Type EDS), Arterial Tortuosity syndrome, Shprintzen-Goldberg syndrome, Aneurysm-Osteoarthritis syndrome, Congenital Contractural Arachnodactyly and Homocystinuria. In addition to TAAD, additional cardiac features of these conditions can include arterial tortuosity, mitral valve prolapse, and congenital heart defects. Non-cardiac features may include skeletal anomalies, craniofacial manifestations, cutaneous findings, and in some instances, developmental delay.

TAA Panel Includes:

- ACTA2
- CBS
- COL3A1
- FBN1
- FBN2
- FLNA
- MYH11
- MYLK
- SKI
- SLC2A10
- SMAD3
- TGFB2
- TGFBR1
- TGFBR2

Molecular Genetics Laboratory

Shipping Instructions

Please enclose a test requisition form with sample. All information must be complete before sample can be processed. Samples may be shipped at room temperature by overnight Federal Express to arrive Monday through Friday.

Ship to:

Molecular Genetics Lab
Cincinnati Children's Hospital
3333 Burnet Ave. NRB 1042
Cincinnati, OH 45229

Phone: 513-636-4474
Fax: 513-636-4373

Methodology:

Next Generation Sequencing: All coding exons, as well as their flanking regions, of the genes listed in the panel are enriched from the patient's genomic DNA and sequenced using a solid-state sequencing-by-synthesis process. DNA sequences are assembled and compared to the published genomic reference sequences in Genome Reference Consortium Build 37. Dideoxy DNA sequencing is used to provide data for bases with insufficient coverage and to confirm the reported variants from next-generation sequencing. This assay does not detect variants in the promoter regions, deep intronic regions, or other regulatory elements, and does not detect large deletions or mosaicisms. Variants are reported according to HGVS nomenclature (www.hgvs.org/mutnomen).

Sensitivity & Accuracy:

Validation testing indicates an analytic sensitivity of greater than 99% and an analytic specificity of 100%.

References:

1. Coady MA, Davies RR, et al. Familial patterns of Thoracic Aortic Aneurysms. *Archives of Surgery*. 1999;134:361-367.
2. Zhu L, Vranckx R, et al. Mutations in myosin heavy chain 11 cause a syndrome associating Thoracic Aortic Aneurysm/aortic dissection and patent ductus arteriosus. *Nature Genetics*. 2006;38:343-349.
3. Brautbar A, LeMaire SA, et al. *FBN1* mutations in patients with descending thoracic aortic dissections. *American Journal of Medical Genetics Part A*. 2010;152A:413-416.
4. Guo DC, Pannu H, et al. Mutations in smooth muschle α-actin (ACTA2) lead to thoracic aortic aneurysms and dissections. *Nat Gen* 2007:36(12):1448-935.
5. Mtys G, Arnold E, et al. Identification and in silico analyses of novel TGFβR2 and TGFβR2 mutations in Marfan syndrome-related disorders. *Hum Mutat.* 2006:27(8):760-9.
6. Milewicz DM, Tran-Fadulu V (2006) Thoracic aortic aneurysms and aortic dissections. In GeneReviews at GeneTests http://www.genetests.org.
7. Mizuguchi T, Matsumoto N. Recent progress in genetics of Marfan syndrome and Marfan-associated disorders. *J Hum Genet* 2007:52:1-12

Specimen:

Peripheral blood in EDTA tube
Adult: 5-10mL
Child: 3-5mL
Infant: 1-3mL
For other specimen types, please contact us at 513-636-4474

Turnaround Time:

Full Panel Analysis 8-10 weeks
Known Mutation Analysis 1-2 weeks

CPT Codes:

Full Panel Analysis: 81410
Additional Family Members: 81403

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