Cardiovascular Diseases Genetic Testing Program

ACTA2 – Familial Thoracic Aortic Aneurysms and Aortic Dissections

Familial Thoracic Aortic Aneurysms and Aortic Dissections (TAAD) is defined as the presence of dilation and/or dissection of the ascending aorta in the absence of any connective tissue abnormalities and in the presence of a positive family history. It is estimated that 20% of thoracic aortic aneurysms and dissections result from a genetic predisposition[1]. TAAD has been linked to several genes including *TGFBR1*, *TGFBR2*, *MYH11*, *FBN1*, and *ACTA2*. *ACTA2* encodes a smooth muscle protein called alpha-actin, which is a major contractile protein in smooth muscle. Mutations in the *ACTA2* gene affect both the structure and the assembly of the actin filaments and have a dominant negative affect, leading to impaired contractility. The *ACTA2* gene contains 9 exons and is located on chromosome 10q22-q24.

Causative mutations can be identified in approximately 18% of individuals with TAAD. Mutations in *ACTA2* account for the majority of cases (14%), while mutations in *TGFBR2*, *TGFBR1*, and *MYH11* account for 2.5%, 1%, and less than 1%, respectively[2]. TAAD has an autosomal dominant pattern of inheritance. Most affected individuals have a parent who is also affected.

Aortic aneurysms and dissections can also be associated with genetic syndromes. Before testing the *ACTA2* gene it is important to rule out any underlying connective tissue disorders.

Indication

ACTA2 gene testing is utilized to confirm a diagnosis of TAAD in patients with clinically evident disease. Genetic testing allows for early identification and diagnosis of individuals at greatest risk prior to the expression of typical clinical manifestations.

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:

All 9 exons of the *ACTA2* gene, as well as the exon/intron boundaries and portion of untranslated regions of the gene are amplified by PCR. Genomic DNA sequences from both forward and reverse directions are obtained by automatic fluorescent detection using an *ABI PRISM® 3730 DNA Analyzer*. Sequence variants different from National Center for Biotechnology Information GenBank references are further evaluated for genetic significance. If a mutation is identified, a known familial mutation analysis will be available for additional family members.

Sensitivity & Accuracy:

Greater than 98.5% of the mutations in exons 1-9 of *ACTA2* are detectable by sequence based methods. Sequencing does not detect deletions or duplications.

References:

1. Coady MA, Davies RR, Roberts M, Goldstein LJ, Rogalski MJ, Rizzo JA, Hammond GL, Kopf GS, Elefteriades JA. Familial patterns of Thoracic Aortic Aneurysms. *Archives of Surgery*. 1999;134:361-367.

2. Guo DC, Pannu H, Tran-Fadulu V, Papke CL, Yu RK, Avidan N, Bourgeois S, Estrera AL, Safi HJ, Sparks E, Amor D, Ades L, McConnell V, Willoughby CE, Abuelo D, Willing M, Lewis RA, Kim DH, Scherer S, Tung PP, Ahn C, Buja LM, Raman CS, Shete SS, Milewicz DM. Mutations in smooth muscle alpha-actin (*ACTA2*) lead to Thoracic Aortic Aneurysms and Dissections. *Nature Genetics*. 2007;39:1488-1493.

3. Brautbar A, LeMaire SA, Franco LM, Coselli JS, Milewicz DM, Belmont JW. *FBN1* mutations in patients with descending thoracic aortic dissections. *American Journal of Medical Genetics A*. 2010;152A:413-416.

Specimen:

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

Turnaround Time:

Full Mutation Analysis 2-4 weeks
Known Mutation Analysis 1-2 weeks

CPT Codes:

Full Gene Sequencing	81405
Additional Family Members	81403

Molecular Genetics Laboratory | Cincinnati Children's Hospital
3333 Burnet Ave. | Cincinnati, OH 45229
Phone: 513-636-4474 | Fax: 513-636-4373