TAADNext: Analyses of 22 Genes Associated with Thoracic Aortic Aneurysms and Dissections

RESULTS

Pathogenic Mutation(s): None Detected
Variant(s) of Unknown Significance: None Detected
Gross Deletion(s)/Duplication(s): None Detected

SUMMARY

NEGATIVE: No Clinically Significant Variants Detected

INTERPRETATION

- No pathogenic mutations, variants of unknown significance, or gross deletions or duplications were detected.
- Risk Estimate: low likelihood of variants in the genes analyzed contributing to this individual's clinical history.
- Genetic counseling is a recommended option for all individuals undergoing genetic testing.

Genes Analyzed: ACTA2, COL3A1, COL5A2, FBN1, FBN2, MED12, MYH11, MYLK, NOTCH1, PLOD1, PRKG1, SKI, SLC2A10, SMAD3, TGFB2, TGFBRI and TGFBRII (sequencing and deletion/duplication); CBS, COL5A1, FLNA, SMAD4 and TGFB3 (sequencing only).

COMMENT: You may wish to contact Dr. Dianna M. Milewicz and her research staff of the University of Texas Health Science Center at Houston, regarding a study of the genes that, when altered, lead to aortic aneurysms and dissections and related vascular diseases. Participation in research is optional. You or your patient may contact the study coordinator's office at (713) 500-7072 or email at info@JohnRitterResearchProgram.org.

Order Summary: The following products were included in the test order for this individual. Please note: tests on hold and those that have been cancelled (including reflex testing steps cancelled due to a positive result in a preceding test) are excluded. For additional information, please contact Ambry Genetics.
- TAADNext (Product Code 8789)
**ASSAY INFORMATION**

**General Information:** Marfan syndrome (MFS) is an autosomal dominant disorder characterized by cardiovascular, skeletal, and ocular findings. Diagnosis can be challenging due to phenotypic variability and overlap with related disorders. One of the major features of MFS is an increased risk for aortic aneurysms and dissections, which, if untreated, can be fatal. Approximately 13,000 Americans die each year from aortic aneurysms. Identifying at-risk individuals is complicated by the fact that sudden death is often the first major clinical sign. Some conditions overlap clinically with MFS, but do not include the same level of risk for aneurysms. These include Shprintzen-Goldberg syndrome, homocystinuria, and congenital contractual arachnodactyly. MFS is the most common form of syndromic thoracic aortic aneurysms and dissections (TAAD). Other syndromic TAAD conditions include Loewy-Dietz syndrome, Ehlers-Danlos syndrome (EDS), arterial tortuosity syndrome, and Lujan-Fryns syndrome. Familial non-syndromic TAAD is characterized by aneurysms without other manifestations and typically follows an autosomal dominant pattern of inheritance. Up to 20% of individuals with TAAD have a first-degree relative with thoracic aortic disease. Several genes have been associated with familial non-syndromic TAAD or familial aortic valve abnormalities, which lead to an increased risk for TAAD. Sporadic forms of TAAD have also been reported. Early diagnosis of MFS, familial TAAD, and other related syndromes is essential for improved prognosis, management, and genetic counseling. Identifying the specific genetic cause will help stratify risks, direct management options, and dramatically improve outcome.

**Methodology:** TAADNext is a comprehensive analysis of 22 genes associated with TAAD. Genomic deoxyribonucleic acid (gDNA) is isolated from the patient's specimen using a standardized kit and quantified. Sequence enrichment of the targeted coding exons and adjacent intronic nucleotides is carried out by a bait-capture methodology using long biotinylated oligonucleotide probes, and is followed by polymerase chain reaction (PCR) and Next-Generation sequencing. Additional Sanger sequencing is performed for any regions missing or with insufficient read depth coverage for reliable heterozygous variant detection. Suspect variant calls other than “likely benign” or “benign” are verified by Sanger sequencing. Gross deletion/duplication analysis for 17 genes (excluding CBS, COL5A1, FLNA, SMAD4, and TGFBR3) is also performed utilizing a targeted chromosomal microarray. Sequence analysis is based on the following NCBI reference sequences: ACTA2 NM_001613.2, CBS NM_000071.2, COL3A1 NM_000090.3, COL5A1 NM_000993.4, COL5A2 NM_000393.3, FBN1 NM_000138.4, FBN2 NM_0001993.4, FLNA NM_001456.3, MED12 NM_005120.2, MYH11 NM_002474.2, MYLK NM_053025.3, NOTCH1 NM_017617.3, PLOD1 NM_000302.3, PRKG1 NM_006258.3, SKI NM_003036.3, SLC2A10 NM_030777.3, SMAD3 NM_005902.3, SMAD4 NM_00359.5, TGFBR2 NM_000328.3, TGFBR3 NM_003239.2, TGFB1 NM_004612.2, TGFB2 NM_003242.5.

**Analytical Range:** TAADNext targets detection of DNA sequence mutations in 22 genes (ACTA2, CBS, COL3A1, COL5A1, COL5A2, FBN1, FBN2, FLNA, MED12, MYH11, MYLK, NOTCH1, PLOD1, PRKG1, SKI, SLC2A10, SMAD3, SMAD4, TGFB2, TGFB3, TGFB1, and TGFB2) by either Next-Generation or Sanger sequencing of all coding domains and well into the flanking 5' and 3' ends of all the introns and untranslated regions. Gross deletion/duplication analysis determines gene copy number for the covered exons and untranslated regions of 17 genes (excluding CBS, COL5A1, FLNA, SMAD4, and TGFBR3). If FBN1 or COL3A1 gene sequence and deletion/duplication analysis is requested, then only the specific gene is analyzed.

**Expected (Normal) Value:** Diagnostic or Family History: 0, 1, or more mutation(s) detected.

**Result Reports:** In result reports, alterations in the following classifications are always reported, and are based on the following definitions and clinical recommendations:

- **Pathogenic Mutation:** alterations with sufficient evidence to classify as pathogenic (capable of causing disease). Targeted testing of at-risk relatives and appropriate changes in medical management for pathogenic mutation carriers recommended. Previously described pathogenic mutations, including intronic mutations at any position, are always reported when detected.
- **Variant, Likely Pathogenic (VLP):** alterations with strong evidence in favor of pathogenicity. Targeted testing of at-risk relatives and appropriate changes in medical management for VLP carries typically recommended. Previously described likely pathogenic variants, including intronic VLPs at any position, are always reported when detected.
- **Variant, Unknown Significance (VUS):** alterations with limited and/or conflicting evidence regarding pathogenicity. Familial testing via the Family Studies Program recommended. Medical management to be based on personal/family clinical histories, not VUS carrier status. Note, intronic VUSs are always reported out to 5 basepairs from the splice junction when detected.

Alterations of unlikely clinical significance (those with strong/very strong evidence to argue against pathogenicity) are not routinely included on results reports. These include findings classified as “likely benign” and “benign” alterations.

Assay Information Continued on Next Page
Resources: The following references are used in variant analysis and classification when applicable for observed genetic alterations.

7. Exome Variant Server, NHLBI Exome Sequencing Project (ESP) [Internet], Seattle WA. Available from: evs.gs.washington.edu/EVS.

Disclaimer: This test was developed and its performance characteristics were determined by Ambry Genetics Corporation. It has not been cleared or approved by the US Food and Drug Administration. The FDA does not require this test to go through premarket FDA review. It should not be regarded as investigational or for research. Any questions, suggestions, or concerns regarding interpretation of results should be forwarded to a genetic counselor, not be regarded as investigational or for research.

ASSAY INFORMATION (Supplement to Test Results - Continued)

- Toll Free:(866)262-7943 Ph:(949)900-5500 Fx:(949)900-5501 www.ambrygen.com 15 Argonaut, Aliso Viejo, CA 92656
- Laboratory Director: Trieu Timothy D. Vo, PhD, DABMG, FACMG CLIA# 05D0981414 Page 3/3

Therefore, it is important to consider these limitations when interpreting the results of the test.