R125 Thoracic Aortic Aneurysm and Dissection

Background

This gene panel is based on the Genomics England PanelApp Thoracic Aortic Aneurysm and Dissection gene panel version 1.2 and is designed to assist in the diagnosis of genetic forms of thoracic aortic aneurysm and dissection.

This panel includes genes where variants can cause various disorders relating to defects in the connective tissue; the tissue that connects, supports, binds or separates other tissues or organs. This group of disorders have different combinations of symptoms with varying degrees of severity, but they all involve medical problems affecting the heart. The syndromes covered by this panel include Marfan, and various forms of Loeys-Dietz and Ehlers-Danlos (we also offer a separate panel for Ehlers-Danlos syndromes, which covers all forms of this condition, R101 Ehlers Danlos syndromes). Inheritance patterns vary depending upon the specific type and the variant involved, although many are autosomal dominant, which means that there is a 50% chance of a parent with the gene variant passing it onto their child. See the support links below for more details about this group of syndromes.

Genes

For a full list of genes included in this panel please see Genomics England PanelApp R125 Thoracic Aortic Aneurysm and Dissection, latest signed off version: 1.2 (19 Feb 2020).

Recommended Clinical Referral Criteria

For testing criteria, please refer to the NHS England rare and inherited diseases eligibility criteria for Thoracic Aortic Aneurysm and Dissection (R125) at the following link: https://www.england.nhs.uk/publication/national-genomic-test-directories/

Genomic analysis

Diagnostic screening by whole exome sequence analysis

Whole exome next generation sequencing on the Illumina NovaSeq 6000 using Nonacus Cell3 Target ExomeCG. Sequences are aligned to human genome assembly GRCh38 and variants called by the Illumina DRAGEN (Dynamic Read Analysis for GENomics) Bio-IT Platform (v3.7, Illumina), with additional processing by an in-house bioinformatics pipeline. The sensitivity for detecting small variants (SNVs and indels) is 99.87% and 96.23% respectively at an average read coverage of 100X. Variants are called within the coding exons +/-20 bp of flanking regions of the genes on PanelApp [R125 Thoracic Aortic Aneurysm and Dissection version 1.2] gene panel. This NGS assay aims to cover the all coding regions and 5 bp of flanking intron to a minimum vertical depth of 20X. This test does not exclude variants in regions not analysed such as promoters and deep intronic regions. This analysis has been validated to detect small variants (SNVs and indels), copy number variants and structural variants. Only pathogenic, likely pathogenic and variants of uncertain significance considered to be clinically actionable are reported. Variants are classified using the most recent version of the ACMG/AMP and ACGS guidelines. This test will detect mosaicism down to 20% allele frequency. Recessive carrier status may not be disclosed.

This test is not yet accredited by United Kingdom Accreditation Service (UKAS) to ISO15189.

Limitations of panel:

This test cannot be used for the detection of repeat expansions, copy number variants or variants in mitochondrial DNA (mtDNA). The test does not identify balanced translocations or complex inversions, and it may not detect low-level mosaicism or inter-locus gene conversion.
The sensitivity to detect variants may be limited in genes where some, or all, of the gene is duplicated in the genome or the gene has suboptimal coverage. Specific regions include TNXB. Please contact the laboratory for additional details.

It is possible that as part of this test, incidental or secondary findings that are not of direct relevance to the clinical features in the patient may be identified. These will not be reported in the patient's initial result.

If the patient or family wish to receive information about additional, clinically actionable findings unrelated to the patient's clinical features, they can discuss this during a follow-up appointment with Clinical Genetics.

Family follow-up: Testing for known familial (likely) pathogenic variants in any of the genes in this panel of genes

Sample Requirements
Blood – 5ml in EDTA (1ml neonates/infants);
Please contact lab prior to sending a prenatal sample.
Please label samples with three identifiers and date of collection

All samples must be accompanied by request form
Consent for testing & DNA storage is assumed when request for test received

Test (price available on request)	TAT (calendar days)
Whole exome panel screen	84
Testing for known familial variants in panel genes	42
Testing for known familial (likely) pathogenic variants in panel genes during the prenatal period, if appropriate (please contact the laboratory in advance to arrange this)	3

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http://medicalgenomicswales.co.uk

Links

Orphanet - http://www.orpha.net/
OMIM - http://www.omim.org/
Genetic Test Registry - http://www.ncbi.nlm.nih.gov/gtr/

Support
Marfan Association UK - http://www.marfan-association.org.uk
The Marfan Trust - http://www.marfantrust.org/