AWMGS
All Wales Medical Genomics Service

R101 Ehlers Danlos syndromes

Background

This gene panel is based on the Genomics England PanelApp version 2.3 and is designed to assist in the diagnosis of genetic forms of Ehlers-Danlos syndromes.

Ehlers-Danlos syndromes is a group of genetic disorders affecting the connective tissue. Symptoms can include loose joints, stretchy skin and abnormal scar formation, and complications can include aortic dissection, joint dislocation and osteoarthritis. EDS is caused by pathogenic variants in one of a number of genes, and the specific gene affected determines the type of EDS. Inheritance patterns vary depending upon the type of EDS, as does prognosis and life expectancy. However, all physical signs and symptoms caused by this group of disorders are as a result of faulty or reduced amounts of collagen. There is no known cure for these disorders and treatment is of a supportive nature including physiotherapy, close monitoring and physical braces and supports for joints.

Genes

For a full list of genes included in this panel please see Genomics England PanelApp R101 Ehlers Danlos syndromes gene panel, signed off version: 2.3 (04/03/2020).

Recommended Clinical Referral Criteria

For testing criteria, please refer to the NHS England rare and inherited diseases eligibility criteria for Ehlers-Danlos syndromes (R101) at the following link:
https://www.england.nhs.uk/publication/national-genomic-test-directories/

Genomic testing

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, 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 [R101 Ehlers Danlos syndromes version 2.3] 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 only been validated to detect small variants (SNVs and indels). Copy number variants and structural variants will not be detected on this analysis. 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.

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. Specifically, the TNXB gene; this gene has suboptimal coverage (mean coverage >20x = 87.3%). 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

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

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

Contact Details
All Wales Genomics Laboratory, Institute of Medical Genetics, University Hospital of Wales, Heath Park,
Cardiff CF14 4XW
Telephone: 02921844023

Lab.genetics.cav@wales.nhs.uk
https://medicalgenomicswales.co.uk

Links

Orphanet – https://www.orpha.net/

OMIM - https://omim.org/

Genetic Testing Registry - http://www.ncbi.nlm.nih.gov/gtr/

Support
Ehlers-Danlos Support UK - https://www.ehlers-danlos.org/