AWMGS
All Wales Medical Genomics Service

R87 Cerebral malformations

Background

This gene panel is based on the Genomics England PanelApp version 5.17 and is designed to assist in the diagnosis of genetic forms of cerebral malformations.

Lissencephaly is as an 'umbrella' term used to describe a range of rare brain disorders where the whole or parts of the surface of the brain appear smooth. Polymicrogyria is characterized by an excessive number of small convolutions on the surface of the brain, and again is found in a number of diseases. In these brain malformation disorders, a wide range of other abnormalities can be present depending upon the particular condition. A proportion of cases have a genetic cause. Identification of a causative sequence variant provides information on prognosis, avoids unnecessary investigations, informs treatment and is useful for genetic counselling. This panel of genes is designed to assist in the diagnosis of genetic forms of cortical brain malformation disorders.

Genes

For a full list of genes included in this panel please see Genomics England PanelApp R87 Cerebral malformations, latest signed off version: 5.17 (4 Mar 2020)

Recommended Clinical Referral Criteria

For testing criteria, please refer to the NHS England rare and inherited diseases eligibility criteria for Cerebral malformations (R87) at the following link: https://www.england.nhs.uk/publication/national-genomic-test-directories/

Genomic analysis

Diagnostic screening by 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 when within the coding exons +/-20 bp of flanking regions. of the genes on PanelApp R87 Cerebral malformations 5.17 gene panel. This NGS assay aims to cover 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 will not be detected in 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.

Dosage analysis of the relevant genes for all coding exons of the genes *PAFAH1B1 (LIS1)* and *DCX,* and selected exons of the genes *FLNA, POMGNT1* and *POMT1* is undertaken using MRC-Holland MLPA kit P061.

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: *B3GALNT2*, *OCLN*, *TUBB2A* and *TUBB2B* genes. Please contact the laboratory for additional details. The genes *TUBB2A* and *TUBB2B* can be screened using Sanger sequencing if clinically indicated, please contact the laboratory to discuss your requirements.

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 a request form

Consent for testing & DNA storage is assumed when request for test received

Contact Details

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https://medicalgenomicswales.co.uk

Links

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

Support

https://www.epilepsy.org.uk/
https://contact.org.uk/conditions/west-syndrome/
https://contact.org.uk/conditions/ohtahara-syndrome/
https://www.youngepilepsy.org.uk/