Cortical Brain Malformations Panel

Background

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.

This service is the front-line test for suspected genetic forms of cortical brain malformations and replaces single gene Sanger sequencing requests.

Genes

For a full list of genes included in this panel please see below.

Recommended Clinical Referral Criteria

For testing criteria, please refer to the NHS England Cerebral Malformations testing criteria (Test R87) in the 'Rare and inherited disease eligibility criteria' document at the following link: https://www.england.nhs.uk/publication/national-genomic-test-directories/

Genomic analysis

Diagnostic screening by sequence analysis:

Next Generation Sequencing (NGS) Target genes are enriched using an Illumina TruSight One assay and sequenced on an Illumina HiSeq. This assay aims to cover the coding sequence and 5bp of flanking intron to a minimum vertical depth of 20X. Where this is not achieved (i.e. % horizontal coverage is less than 100%) due to design or patient-specific gaps then Sanger sequencing is available for the genes in **bold** and may be available for gaps in other genes, on request. The selection of gaps to be filled may be guided by the patient's phenotype or by interaction with the referring clinician

Dosage analysis – by MLPA for all coding exons of the genes *PAFAH1B1 (LIS1)* and *DCX,* and selected exons of the genes *FLNA, POMGNT1* and *POMT1*

Family follow-up: Testing for known familial mutations in any of the genes in the panel

Full Gene List

ACTB	CASK	FKTN	LAMC3	PEX10	PEX26	GTDC2	**TUBB2B**
ACTG1	CCND2[1]	FLNA	LARGE	PEX11B	PEX3	POMT1	TUBB3
ADGRG1	COL4A1	GPSM2	NDE1	PEX12	PEX5	POMT2	VLDLR
AKT3	COL4A2	GRIN1	NEDD4L	PEX13	PEX6	RELN	WDR62
ARFGEF2	DAG1	ISPD	OCLN	PEX14	PEX7	SCN3A	
ARX	**DCX**	KIFBP (KIAA1279)	OPHN1	PEX16	PIK3CA	SRPX2	
ASPM	DYNC1H1	LAMA2	**PAFAH1B1**	PEX19	PIK3R2	**TUBA1A**	
B3GNT1	FKRP	LAMB1	PEX1	PEX2	POMGNT1	TUBA8	

[1] *CCND2* is not present on our NGS platform but Sanger sequencing of exon 5 (mutation hotspot) is included in the analysis.

Please note: The genes **TUBB2A** (615763), **TUBG1** (615412) and **TUBB4A** (612438) can be screened using Sanger sequencing if clinically indicated, please see below.

For cases where Cortical Brain Malformations NGS panel analysis has not identified a genetic cause of the patient's condition, bi-directional sequence analysis of the entire coding regions of those genes in the table and paragraph above marked in **BOLD** are available as second line tests for patients referred through the specialty of Clinical Genetics. This testing strategy is available by arrangement only. Please contact the laboratory to discuss your requirements.

Test (Price available on request)	TAT (calendar days)
Cortical brain malformation disorders panel screen, including MLPA analysis of *PAFAH1B1 (LIS1), DCX, FLNA, POMGNT1* and *POMT1*	84
Testing for known familial variants in any of the genes listed above	42
Testing for known familial (likely) pathogenic variants in any of the genes listed above in the prenatal period (please contact the laboratory in advance to arrange this)	3

Contact Details
All Wales Genomics Laboratory,
Institute of Medical Genetics,
University Hospital of Wales,
Heath Park,
Cardiff CF14 4XW
Tel: 029 2074 2641
Fax: 029 2074 4043
lab.genetics@wales.nhs.uk
https://medicalgenomicswales.co.uk
Accredited to ISO 15189:2012
(8988)

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

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