R59 Early Onset or Syndromic Epilepsy Service

Background

This service's gene panel is based on the Genomics England PanelApp gene panel: Early Onset or Syndromic Epilepsy version 6.0 and is designed to assist in the diagnosis of genetic forms of early onset or syndromic epilepsy. Gene panel analysis is complemented by copy number variant (CNV) analysis using single nucleotide polymorphism (SNP) array, where requested.

Genetic epilepsy syndromes include epileptic encephalopathies, benign familial neonatal or infantile seizures, generalized epilepsy with febrile seizures plus or other syndromic epilepsies or early onset seizures. Identification of a causative variant provides information on prognosis, avoids unnecessary investigations, informs treatment and is useful for genetic counselling.

Genes

For a full list of genes included in this panel please see Genomics England PanelApp R59 Early Onset or Syndromic Epilepsy, signed off version: 6.0, 7th August, 2024.

Recommended Clinical Referral Criteria

Early onset or syndromic epilepsy disorders:

- Onset under 2 years, **OR**
- Clinical features suggestive of specific genetic epilepsy, for example Dravet syndrome, **OR**
- Additional clinical features: intellectual disability, autism spectrum disorder, structural abnormality (e.g. dysmorphism, congenital malformation), unexplained cognitive/memory decline
- Testing may occasionally be appropriate where age of onset is between 2 and 3 years and following clinical agreement by a specialist MDT.

For further information please refer to the NHS England National Genomic Test Directory, Testing Criteria for Rare and Inherited Disease for Early onset or Syndromic Epilepsy (R59) 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 or NextSeq 550 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 R59 Early onset or syndromic epilepsy v6.0 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 (CNVs), short tandem repeat (STR) expansions and structural variants will not be detected in this sequencing 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.

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

Copy number variant (CNV) testing by genome-wide microarray analysis:

Please note that copy number variant analysis is not included as part of the epilepsy sequencing gene panel test. Should CNV analysis, via SNP array, be clinically appropriate, please state that this testing is required on the referral form.

For further information, please refer to the AWMGS information for: Single nucleotide polymorphism (SNP) array Service for Developmental Disorders and Epilepsy/Seizure Disorders:

https://medicalgenomicswales.co.uk/images/awmgsdownload/PD-GEN-INFSNPArray1.pdf

Limitations of gene panel test:

This test cannot be used for the detection of short tandem repeat (STR) expansions, copy number variants (CNV) 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 where the gene has suboptimal coverage using our testing platform. Specific regions include: *ADARB1, ARV1, CELF2, CNPY3, DHPS, DTYMK, FUT8, GABRG2, GBA*, GOSR2, IKBKG*, OCLN, PHACTR1, PIGU, SLC9A6, TUBB2A*[$], *TUBB2B*[$], *UFM1, USP18, ZNF142* and *HECTD4* genes. Please contact the laboratory for further details, if required.

[$]The genes *TUBB2A* and *TUBB2B* can be sequenced to completion using Sanger sequencing if clinically indicated, please contact the laboratory to discuss your requirements.

*Alternative testing of the *GBA* gene may be available for individuals with a suspected diagnosis of Gaucher's disease. In addition, for *IKBKG*-related disorders, a single gene test may be more appropriate. Please contact the laboratory for further information.

This test will not detect short tandem repeat (STR)/nucleotide expansions. Two STR expansions listed in the targets for the PanelApp R59 Early Onset and Syndromic Epilepsy panel for genes: *ATN1* and *CSTB* **will not be detected as part of this test.** Similarly, the recurrent polyalanine expansions variants in the *ARX* gene, which present on this gene panel, **will not be detected as part of this test.**

The gene *ATN1*, is associated with seizure disorders: Congenital hypodontia, epilepsy, developmental delay, and digital anomalies (CHEDDA) (OMIM# 618494) and *ATN1*-related Dentatorubral-Pallidoluysian Atrophy (DRPLA) (OMIM# 125370). While pathogenic sequence variants associated with CHEDDA may be detected by this test, an STR expansion in the *ATN1* gene

which accounts for 100% of cases of DRPLA will not be detected. **Targeted testing for repeat expansion in the *ATN*1 gene is available, upon request.**

CSTB-related myoclonic epilepsy of Unverricht and Lundborg (ULD/EPM1A, OMIM #245800), is attributable to either biallelic abnormal STR expansions in *CSTB* or compound heterozygosity for an STR expansion and a sequence variant/SNV in the *CSTB* gene in nearly all cases. **Targeted testing for repeat expansions in the *CSTB* gene is available, upon request.**

The gene *ARX* is associated with a range of neurodevelopmental seizure disorders. Recurrent polyalanine repeat expansions in the *ARX* gene are associated with a proportion of patients with seizure and developmental phenotypes, without brain malformations: Developmental and epileptic encephalopathy 1 (OMIM# 308350) and Intellectual developmental disorder, X-linked 29 (OMIM# 300419) as well as Partington syndrome (intellectual disability with focal dystonia) (OMIM# 309510) where this is the most common cause of the disorder. While pathogenic sequence variants in *ARX* may be detected by this gene panel test, the recurrent polyalanine repeat expansions will not be detected as part of this test. **Targeted testing for polyalanine repeat variants in the *ARX* gene is available, upon request.**

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.

Family follow-up:

Testing for known familial (likely) pathogenic variants in any of the genes in this panel of genes is available.

Test (price available on request)	**TAT (Calendar days)**
Whole exome gene panel screen	84
Genome-wide SNP array analysis for CNV	84
Testing for known familial variants in panel genes	42
Predictive testing for familial (likely) pathogenic variants in the postnatal period	14
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

All Wales Medical Genomics Service
Wales Genomic Health Centre
Cardiff Edge Business Park
Longwood Drive
Whitchurch
Cardiff
CF14 7YU
lab.genetics.cav@wales.nhs.uk
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

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