Congenital Malformation Syndromes and/or Dysmorphism
Whole Genome Sequencing / Whole Exome Sequencing Service

BACKGROUND

Congenital malformations and dysmorphisms are structural or functional defects affecting the formation of single or multiple organs and systems within the body, and are present from birth. Research has shown that WGS can increase the diagnostic yield of congenital malformation and/or dysmorphisms in comparison to traditional array and gene panel testing (Sweeney *et al* 2021, PMID: 33888711; 100,000 Genomes Project Pilot Investigators 2021, PMID: 34758253).

Whole genome sequencing (WGS) is a technology that examines the entirety of one's genome and look for changes in many different genes and non-protein coding regions at the same time. Whole exome sequencing (WES) looks at changes across all of the protein-coding regions of genes in a genome. WGS and WES can replace genetic tests that were previously targeted at just one gene (single gene tests).

Routine WGS is available for patients with congenital malformation and/or dysmorphisms with a likely underlying genetic cause on a **trio basis only**, i.e. the proband and **BOTH** their parents.
Routine WES (as a trio or singleton) is available for patients with congenital malformations and/or dysmorphisms in specified cases. Please see below for specific testing criteria for WES testing.
The equivalent NHSE Test Directory code for this test is R27.

Please contact the laboratory as soon as possible if your request is clinically urgent.

RECOMMENDED CLINICAL REFERRAL CRITERIA

Routine WGS/WES testing is **ONLY** available through referral from Clinical Genetics.

Essential Criteria for WGS (ALL to be fulfilled)

- The patient presents with multi-system congenital malformation and/or dysmorphism with or without intellectual disability
- Suspected underlying monogenic cause
- DNA sample is available from **both** parents and they are willing to consent to testing

Essential Criteria for WES

- **Singleton** analysis of the Intellectual disability gene panel plus one of the following panels, RASopathies, Clefting, Skeletal Dysplasia and/or Severe Microcephaly, for patients with multi-system congenital malformation and/or dysmorphism but parental samples are **not** available.
- A **specific diagnosis** is suspected, tested as one of the following panels: RASopathies, Clefting, Skeletal Dysplasia or Severe Microcephaly. A panel must be indicated upon request. This is test is performed as a singleton.
- Fetal malformation with a likely genetic cause (non-urgent, e.g. where there is imminent fetal loss or termination of pregnancy, or miscarriage has already occurred) as a **trio.** If the parents are now pregnant and testing not previously performed on the proband, please contact the laboratory for urgent testing. Please note, fetal malformation testing is only an option if a fetal blood sample is available. For fetal tissue samples, other testing options are available. Please contact the laboratory for further discussion.
- **Re-analysis of in-house trio WES data** from the Fetal Anomalies sequencing service, performed prenatally, following birth of a child with congenital malformation and/or dysmorphism.

GENES

For a full list of genes included in this panel please see the R27 Paediatric disorders NHS Genomic Medicine Service (GMS) Panel App panel or the RASopathies, Clefting, Skeletal Dysplasia or Severe Microcephaly panels. Please contact the laboratory to obtain information about the version of the gene panel used for the analysis. It's important to note that we always aim to use the latest GMS Signed Off versions of gene panels to ensure the most up-to-date analysis. Only green genes on the panel will be included.

GENOMIC ANALYSIS

Diagnostic screening by sequence analysis:
Next Generation Sequencing (NGS) of the **whole genome** using Illumina PCR-Free assay and sequenced on Illumina NovaSeq 6000 platform. Sequences are aligned to human genome assembly GRCh38 (hg38). This aims to cover 97% of coding region exons ±20 base pairs to a minimum vertical depth of 20X, whilst 89% of the entire genome will be covered at a minimum of 20X.

Next Generation Sequencing (NGS) enrichment of the **whole exome** using Nonacus Cell3™ Target ExomeCG kit and sequenced on Illumina NovaSeq 6000 platform. Sequences are aligned to human genome assembly GRCh38 (hg38). This aims to cover 95% of coding region exons ±5 base pairs to a minimum vertical depth of 20X.

Where **trio** samples are available variants in green genes from the 'Paediatrics Disorders' (R27) PanelApp gene panel will be analysed followed by a gene agnostic approach to identify potential causative variants.

Where **singleton** testing **only** is possible either the Intellectual Disability (R29) and/or RASopathies, Clefting, Skeletal Dysplasia (R104) or Severe Microcephaly (R88) panels on PanelApp will be analysed, where specified.

Copy number variants will be detected using array technology as well as WGS.

Please refer to PD-GEN-WGSTestInfo and PD-GEN-WESTestInfo for more information.

Family follow-up: Testing for known familial variants in any of the genes in the panel using Sanger sequencing

REPORTING TIMES

Analysis	TAT (calendar days)
Routine Whole Genome Sequencing / Whole Exome Sequencing	84
Family follow-up	42
Urgent Whole Genome /Exome Sequencing	14

Prices are available on request

Sample Requirements	Contact Details
▪ **CHILD** – >1ml blood, EDTA (preferred) & LiHep ▪ **MATERNAL** blood sample – 3-4ml, EDTA & LiHep ▪ **PATERNAL** blood sample – 3-4ml, EDTA & LiHep Please label samples with three identifiers and date of collection **All samples must be accompanied by a fully completed Intellectual Disability & Congenital Malformations and/or Dysmorphism sequencing request form**	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.cav@wales.nhs.uk medicalgenomicswales.co.uk

Links
Orphanet http://www.orpha.net/ **OMIM** http://www.omim.org/ **GeneReviews** http://www.genetests.org/ **Decipher** http://decipher.sanger.ac.uk/ **National Genomic Test Directory** https://www.england.nhs.uk/wp-content/uploads/2018/08/rare-and-inherited-disease-eligibility-criteria-v2.pdf **PanelApp Paediatric Disorders Panel** https://panelapp.genomicsengland.co.uk/panels/486