Intellectual Disability
Whole Genome Sequencing / Whole Exome Sequencing Service

BACKGROUND

The Intellectual Disability (ID) sequencing service provides testing for patients presenting with unexplained ID, learning difficulties and/or global developmental delay where clinical features are suggestive of an underlying monogenic disorder. This service offers whole genome sequencing (WGS) or whole exome sequencing (WES) to patients. WGS and WES can replace multiple genetic tests that were previously targeted at just one gene (single gene tests).

WGS is a technology that examines the entirety of one's genome for changes in many different genes and non-protein coding regions at the same time. This service is performed as **trio** testing, i.e. **BOTH** parents and proband samples are required for testing. Research from the 100,000 Genomes Project has shown that trio WGS can provide a diagnostic yield of 40-55% for NHS patients with ID (100,000 Genomes Project Pilot Investigators *et al* 2021, PMID: 34758253).

WES examines changes across all of the protein-coding regions of genes in a genome. Routine WES is available for singleton patients with ID, where a trio is unavailable.

The equivalent NHSE Test Directory code for this test is R29.

GENES

For a full list of genes included in this panel please see the R29 Intellectual Disability NHS Genomic Medicine Service (GMS) Panel App panel. 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.

RECOMMENDED CLINICAL REFERRAL CRITERIA

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

- The patient presents with unexplained Intellectual Disability and/or global developmental delay.
- Suspected underlying monogenic cause.
- For WGS, DNA samples must be available from **both** parents and they are willing to consent to testing (**trio basis, i.e. the proband and BOTH their parents**).
- Where parental samples are not available, singleton testing on WES is available (see GENOMIC ANALYSIS below for further information).

WGS/WES testing is only an option if a **blood** sample is available. If a blood sample is not available, please contact the laboratory for further discussion.

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 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 technical information.

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

REPORTING TIMES

Analysis	Reporting time (calendar days)
Routine Whole Genome Sequencing (WGS) / Whole Exome Sequencing	84
Family follow-up	42

Prices are available on request

Sample Requirements	Contact Details
▪ **CHILD** – >1ml blood in EDTA (preferred) & LiHep ▪ **MATERNAL** blood sample – 3-4ml, EDTA & LiHep ▪ **PATERNAL** blood sample – 3-4ml, EDTA & LiHep Please label samples with at least 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 https://medicalgenomicswales.co.uk

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