AWMGS
All Wales Medical Genomics Service

# R15 Primary immunodeficiency

## Background

This gene panel is based on the Genomics England PanelApp '**Primary immunodeficiency or monogenic inflammatory bowel disease'** GMS signed-off version 4.0 and represents primary immunodeficiency disorders including: immunodeficiencies affecting cellular and humoral immunity, combined immunodeficiency with or without associated/syndromic features; Predominantly antibody deficiencies; Diseases of immune dysregulation; Congenital defects of phagocyte number or function; Defects in intrinsic and innate immunity; autoinflammatory disorders; and complement deficiencies.

## Genes

This panel of 321 (Green) genes is designed to assist in the molecular diagnosis of primary immunodeficiency disease. For a full list of genes included in this panel please see Genomics England PanelApp R15 Primary Immunodeficiency, latest signed off version: 4.0 (22 March 2023).

## Recommended Clinical Referral Criteria

For testing criteria, please refer to the NHS England rare and inherited diseases eligibility criteria for Primary Immunodeficiency (R15) at the following link: https://www.england.nhs.uk/wp-content/uploads/2018/08/rare-and-inherited-disease-eligibility-criteria-v4.pdf

## 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 within the coding exons +/-20 bp of flanking regions. 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 only been validated to detect small variants (SNVs and indels). Copy number variants and structural variants will not be detected on 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.

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. We aim to have more than 95% coverage of each gene on the panel. However, some of the genes on this panel have no coverage or suboptimal coverage. Please refer to the table below for details:

| % Coverage | Relevant Genes |
|---|---|
| Low/ no coverage | C4A, C4B, IGHM, TRAC |
| 50 - 60% | IKBKG, NCF1 |
| 80 - 89% | CD55, CFI, USP18 |
| 90 - 95% | CORO1A, CSF2RA, CXCR4, RFXANK, TNFRSF1A, IL6R, IL12RB1 |

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**
All Wales Genomics Laboratory,
Institute of Medical Genetics,
University Hospital of Wales,
Heath Park,
Cardiff CF14 4XW
Tel: 029 2184 4023

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/
NHSE PanelApp - https://nhsgms-panelapp.genomicsengland.co.uk/panels/398/v4.0

Support
http://www.immunodeficiencyuk.org/