# Severe Combined Immunodeficiency (SCID) Panel

## PANEL GENE LIST

*ADA, AK2, ATM, CD3D, CD3E, CD3Z, CORO1A, DCLRE1C (ARTEMIS), DOCK8, FOXN1, IL2RG, IL7R, JAK3, LIG4, NHEJ1, ORAI1, PNP, PRKDC, PTPRC, RAC2, RAG1, RAG2, RMRP, STIM1, TBX1, TBX1, ZAP70*

## CLINICAL FEATURES

Severe combined immunodeficiency (SCID) can be caused by pathogenic variants in a variety of genes. Although the clinical presentation can vary depending on which gene carries a pathogenic variant, there are several common characteristics observed throughout the different forms of SCID. Patients will typically present in infancy with severe, persistent infections of bacterial, viral, fungal and/or protozoal origin. In addition, these individuals have poor wound healing and failure to thrive. In states where newborn screening includes the TREC test for poor maturation of T cells, presymptomatic infants may be identified.[1] T-cell lymphopenia is common to almost all forms of SCID, while the presence/absence of B-cells and NK-cells varies and can be used to help determine appropriate genetic testing. The prevalence of SCID in the general population is approximately 1/50,000 live births, with males showing a higher prevalence as the most common form of SCID is X-linked.[2]

## GENETICS

Leukocyte Profile and Associated Genes

T/B/NK Deficient SCID: ADA, AK2

T/B Deficient SCID: DCLRE1C, LIG4, NHEJ1, PRKDC, RAC2, RAG1, RAG2

In addition to their inclusion on the Comprehensive SCID panel, the above 9 genes are also offered as a B-negative sub-panel.

T/NK Deficient SCID: IL2RG, JAK3

T Deficient SCID: CD3D, CD3E, CD3Z, CORO1A, IL7R, ORAI1, PNP, PTPRC, RMRP, ZAP70

In addition to their inclusion on the Comprehensive SCID panel, the above 12 genes are also offered as a B-positive sub-panel.

SCID differential genes: ATM, DOCK8, FOXN1, STIM1, TBX1

The above 5 genes are offered as part of both the comprehensive SCID panel and the B-positive SCID sub-panel due to immunodeficiency phenotypes which overlap with SCID.

## TEST METHODS

Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the genes tested are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV).

The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size. For the TBX1 gene, sequencing but not deletion/duplication analysis is performed. For the DCLRE1C gene, deletion/duplication analysis does not include exons 4 and 6-9.

| Gene | Inheritance Pattern | Pathogenic Variant Spectrum | Frequency in SCID |
|---|---|---|---|
| IL2RG | X-linked | Missense (~33%), nonsense (~19%), small deletions (~19%) splice-site (~17%), small insertion/insertion-deletions (~9%), large deletions (rare) | ~40% [2] |
| ADA | Autosomal recessive | Missense, nonsense, frameshift, large deletions (rare) | ~16-20% [2,3] |
| IL7R | Autosomal recessive | Missense, nonsense, frameshift, one deep intronic pathogenic variant* | ~10% [2,4,5] |
| JAK3 | Autosomal recessive | Missense, nonsense, frameshift, large deletions | 5-10% [3,4] |
| PNP | Autosomal recessive | Missense, splice-site, small deletions | 4% [2] |
| RAG1/2 | Autosomal recessive | Missense, nonsense, frameshift, large deletions (~1-2%) | 3.5% [3] |
| CD3D/E/Z | Autosomal recessive | Nonsense, splice-site (CD3D/E), frameshift (CD3E/Z) | ~1.5-3% [3,6] |
| DCLRE1C | Autosomal recessive | Missense, nonsense, frameshift, splice-site, small/large deletions. | 1-2% [3] |
| AK2 | Autosomal recessive | Missense, nonsense, splice-site, small/large deletions (8-12%) | Rare |
| NHEJ1 | Autosomal recessive | Missense, nonsense, frameshift, splice-site, small/large deletions | Rare |

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|---|---|---|---|
| LIG4 | Autosomal recessive | Missense, nonsense, small deletions | Rare |
| RAC2 | Autosomal dominant | Single missense pathogenic variant (D57N) | Rare |
| PTPRC | Autosomal recessive | 3 pathogenic variants (one splice-site, one small deletion, one large deletion) | Rare |
| ZAP70 | Autosomal recessive | Missense, splice-site, small deletion | Rare |
| RMRP | Autosomal recessive | Regulatory (point pathogenic variants, small insertions/deletions) | Rare in SCID, ~90% in individuals Cartilage-Hair Hypoplasia (CHH) |
| PRKDC | Autosomal recessive | Missense, one large deletion | Rare |
| CORO1A | Autosomal recessive | Missense, frameshift, small deletions, one large deletion | Rare |
| ORAI1 | Autosomal recessive | Missense, one small insertion | Rare |
| ATM | Autosomal recessive (AT) Autosomal dominant (cancer risk) | Missense, nonsense, splice-site, frameshift, small insertions/deletions, large deletions | Ataxia-telangiectasia, increased cancer risk |
| DOCK8 | Autosomal recessive | Large deletions, single base-pair substitutions, small deletions. | Hyper-IgE syndrome |
| FOXN1 | Autosomal recessive | One missense, one nonsense, one frameshift | T-cellimmunodeficiency,congenitalalopecia, and naildystrophy[7] |
| STIM1 | Autosomal recessive | Missense, one each of: splicing, frameshift, small insertion, large deletion | T-cellimmunodeficiency,hepatosplenomegaly, autoimmunehemolytic anemia,thrombocytopenia,muscularhypotonia, anddefective enameldentition[8] |
| TBX1 | Autosomal dominant | Missense,small deletions/insertions, large deletions/duplications, frameshift | DiGeorge/Velocardiofacial syndrome |

## REFERENCES:

1.Puck, JM, 2007, Population-based newborn screening for severe combined immunodeficiency: steps toward implementation, JAllergy Clin Immunol 120:760-768.
2.Aloj G, et al., 2012, Severe Combined Immunodeficiencies: New and Old Scenarios, Internat Revs of Immunol 31:43-65.
3.Buckley, RH, 2004, The multiple causes of human SCID, J Clin Imm 114:1409-11.
4.Roberts, JL, 2004, Janus kinase 3 (JAK3) deficiency: clinical, immunologic, and molecular analyses of 10 patients and outcomes ofstem cell transplantation, Blood 103:2009-2018.
5.Butte MJ et al., 2007, IL-7 receptor deficient SCID with a unique intronic mutation and post-transplant autoimmunity due to chronicGVHD, Clinical Immunology 125(2):159-64.
6.Fischer A et al., 2005, Severe combined immunodeficiency, a model disease for molecular immunology and therapy, Immunological Reviews. 203:98-109.
7.Frank J et al., 1999, Exposing the human nude phenotype, Nature. 1999 398:473-4.
8.Picard C et al., 2009, STIM1 mutation associated with a syndrome of immunodeficiency and autoimmunity, The New England Journal Of Medicine. 360:1971-80.

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