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 from the submitted specimen, the coding regions and splice junctions of the 26 genes (ADA, AK2, ATM, CD3D, CD3E, CD3Z, CORO1A, DCLRE1C, DOCK8, FOXN1, IL2RG, IL7R, JAK3, LIG4, NHEJ1, ORAI1, PNP, PTPRC, PRKDC, RAC2, RAG1, RAG2,

RMRP, STIM1, TBX1, and ZAP70) will be enriched using a proprietary targeted capture system developed by GeneDx. These targeted regions will be sequenced simultaneously by massively parallel (NextGen) sequencing on an Illumina platform with paired-end reads. Bi-directional sequence will be assembled, aligned to reference gene sequences, and analyzed for sequence variants. Capillary sequencing is used to confirm all potentially pathogenic variants and to obtain sequence for regions where fewer than 15 reads were achieved by NextGen sequencing. Concurrent deletion/duplication testing will be performed for the included genes using exon-level oligo array CGH (ExonArrayDx). Please note, due to the presence of an unprocessed pseudogene that contains homologous regions to exons 4 and 6-9 of the DCLRE1C gene, it is not possible to accurately identify deletions/duplications affecting these exons with array technology. In addition, the array technology used for this panel will not accurately identify deletions and duplications involving the TBX1 gene. Confirmation of copy number changes will be performed by MLPA, qPCR, or repeat array CGH analysis.

Previously offered single gene testing of the ADA, DCLRE1C, DOCK8, IL2RG, IL7R, JAK3, RAG1, RAG2, and TBX1 genes remains available.

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
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-cell immunodeficiency, congenital alopecia, and nail dystrophy[7]
STIM1	Autosomal recessive	Missense, one each of: splicing, frameshift, small insertion, large deletion	T-cell immunodeficiency, hepatosplenomegaly, autoimmune hemolytic anemia, thrombocytopenia, muscular hypotonia, and defective enamel dentition[8]
TBX1	Autosomal dominant	Missense, small deletions/insertions, large deletions/duplications, frameshift	DiGeorge/Velocardiofacial syndrome

References:

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