Severe Combined Immunodeficiency Panel

Indications for Ordering

Confirm suspected severe combined immunodeficiency (SCID)

Test Description

- Targeted capture of all coding exons and intron/exon boundaries followed by massively parallel sequencing
  - Reported variants are confirmed by Sanger sequencing
- Deletion/duplication analysis by tiled, custom-designed comparative genomic hybridization (CGH) array

Tests to Consider

Primary test

Severe Combined Immunodeficiency (SCID) Panel, Sequencing and Deletion/Duplication, 19 Genes 2010219

- Preferred test for individuals with
  - Clinical phenotype of SCID, Omenn syndrome, or other combined immunodeficiency disorders
  - Abnormal newborn screen T-cell receptor excision circles (TREC) test result suggestive of SCID

Related tests

Screening for immunodeficiency

- CBC with Platelet Count and Automated Differential 0040003
- CD4+ T-Cell Recent Thymic Emigrants (RTEs) 2010179
- Lymphocyte Subset Panel 7 – Congenital Immunodeficiencies 0095899
- Lymphocyte Antigen and Mitogen Proliferation Panel with Cytokine Response 2013117
- Immunoglobulins (IgA, IgG, IgM), Quantitative 0050630
- Familial Mutation, Targeted Sequencing 2001961
  - Useful when a pathogenic familial variant identifiable by sequencing is known

Disease Overview

Incidence – ≥1/50,000 births

Age of onset – usually 3-6 months of age

Symptoms

- Recurrent and/or severe infections
  - Candidiasis
  - *Pneumocystis jirovecii*
- Chronic diarrhea
- Failure to thrive
- Chronic pulmonary insufficiency
- Laboratory abnormalities
  - Increased IgE level
  - Increased absolute eosinophil
  - Severe neutropenia
  - Autoimmune cytopenias
  - Absence of granulopoiesis
- Lymphadenopathy
- Allergic manifestations
  - Eczema
  - Asthma
  - Urticaria
  - Food allergy
- Hepatitis, vasculitis
- Noninfectious granulomas
- Sensorineural deafness
- Severe skin disease
  - Rash
  - Palmar and plantar warts

Genetics

Genes – see table for genes tested and for gene-specific information

Mutations

- Mutations in multiple genes appear to cause overlapping phenotypes for SCID
  - Other genetic and/or environmental factors may influence severity of clinical phenotype
- In vivo somatic spontaneous mutation reversion has been documented in *ADA* gene
- Female germline mosaicism has been documented in X-linked SCID

Test Interpretation

Clinical sensitivity – ~90%

Results

- Positive
  - Detection of two pathogenic mutations on opposite chromosomes in a gene with autosomal recessive (AR) inheritance
    - Confirms diagnosis of SCID
  - Detection of a single pathogenic mutation in an X-linked gene in males
    - Confirms diagnosis of SCID
  - Detection of one pathogenic mutation in an AR gene
    - Individual is a carrier
  - Detection of one pathogenic mutation in an X-linked gene in females
    - Individual is a carrier
- Negative
  - No pathogenic mutation detected
    - Reduces, but does not exclude, a diagnosis of SCID
- Inconclusive
  - Variants of uncertain clinical significance may be identified

Limitations

- Not determined or evaluated
  - Mutations in genes not included on the panel
  - Deep intronic and regulatory region mutations
  - Breakpoints for large deletions/duplications
- Deletions/duplications will not be detected in
  - Exon 1 in *ADA* gene
  - Exon 11 in *CORO1A* gene
  - Exons 4, 6, and 8 in *DCLRE1C* gene
  - Exons 3, 6, and 9 in *JAK3* gene
- Small deletions or insertions may not be detected
- Diagnostic errors can occur due to rare sequence variations
- Lack of a detectable gene mutation does not exclude a diagnosis of SCID

Gene Symbol	Gene Name	NM #	OMIM #	Phenotype/Disorder	Inh.*	Incidence/ Prevalence	% of Condition Attributed to Mutations in Gene
ADA	Adenosine deaminase	000022	608958	• SCID, T-cell/B-cell/ NK-cell negative, due to ADA deficiency • SCID due to ADA deficiency – delayed onset	AR	• 1-9 /million live births; higher in populations with high degree of consanguinity	~15%
AK2 (ADK2)	Adenylate kinase 2	001625	103020	• Reticular dysgenesis	AR	Rare	Unknown
CD247 (CD3Z)	CD247 molecule	198053	186780	• Immunodeficiency due to defect in CD3-zeta	AR	Rare	Unknown
CD3D	CD3d molecule, delta (CD3-TCR complex)	000732	186790	• CD3-delta deficiency	AR	Rare	Unknown
CD3E	CD3e molecule, epsilon (CD3-TCR complex)	000733	186830	• CD3-epsilon deficiency	AR	Rare	Unknown
CORO1A	Coronin, actin binding protein, 1A	007074	605000	• SCID due to CORO1A deficiency	AR	Rare	Unknown
DCLRE1C (ARTEMIS)	DNA cross-link repair 1C	001033855	605988	• Omenn syndrome • Severe combined SCID, Athabaskan type	AR	1/2,000 in Athabaskan-speaking populations	~1%
FOXN1 (WHN)	Forkhead box N1	003593	600838	• T-cell immunodeficiency • Congenital alopecia • Nail dystrophy	AR	Rare	Unknown
IL2RG	Interleukin 2 receptor, gamma	000206	308380	• SCID • Combined immunodeficiency, moderate	XL	~1/50,000-100,000 live births	~50%
IL7R	Interleukin 7 receptor	002185	146661	• SCID, T cell-negative, B-cell positive, NK-cell positive	AR	Rare	~10%
JAK3	Janus kinase 3	000215	600173	• SCID, T-cell negative, B-cell positive, NK-cell negative	AR	1/500,000 live births	~6.5%
LIG4	Ligase IV, DNA, ATP-dependent	002312	601837	• SCID with sensitivity to ionizing radiation • LIG4 syndrome	AR	Rare	Unknown
NHEJ1	Nonhomologous end-joining factor 1	024782	611290	• SCID with microcephaly, growth retardation, and sensitivity to ionizing radiation	AR	Rare	Unknown
PNP	Purine nucleoside phosphorylase	000270	164050	• Purine nucleoside phosphorylase deficiency	AR	Rare	Unknown

Gene Symbol	Gene Name	NM #	OMIM #	Phenotype/Disorder	Inh.*	Incidence/ Prevalence	% of Condition Attributed to Mutations in Gene
PRKDC (DNA-PKcs)	Protein kinase, DNA-activated, catalytic polypeptide	006904	600899	• DNA-PKcs-deficiency	AR	Rare	Unknown
PTPRC (CD45)	Protein tyrosine phosphatase, receptor type, C	002838	151460	• SCID, T-cell negative, B-cell positive, NK-cell positive	AR	Rare	Unknown
RAG1	Recombination activating gene 1	000448	179615	• SCID, T-cell negative, B-cell negative, NK-cell positive • Omenn syndrome • Alpha/beta T-cell lymphopenia with gamma/delta T-cell expansion, severe cytomegalovirus infection, and autoimmunity • Combined cellular and humoral immune defects with granulomas	AR	~1/100,000 live births	~Up to 3%
RAG2	Recombination activating gene 2	000536	179616	• SCID, T-cell negative, B-cell negative, NK-cell positive • Omenn syndrome • Combined cellular and humoral immune defects with granulomas	AR	~1/100,000 live births	~Up to 3%
RMRP	RNA component of mitochondrial RNA processing endoribonuclease	NG_017041. 1 Chr9:35657748-35658015	157660	• Anauxetic dysplasia • Cartilage-hair hypoplasia • Metaphyseal dysplasia without hypotrichosis	AR	Rare	Unknown
*Inh. = Inheritance, AR = autosomal recessive, XL = X-linked							