Severe combined immunodeficiency (SCID) represents a group of rare, sometimes fatal, congenital disorders characterized by little or no immune response. The defining feature of SCID, commonly known as "bubble boy" disease, is a defect in the specialized white blood cells (B- and T- lymphocytes) that defend us from infection by viruses, bacteria, and fungi. Without a functional immune system, SCID patients are susceptible to recurrent infections such as pneumonia, meningitis, and chicken pox, and can die before the first year of life. SCID occurs with an estimated incidence of 1 in 75,000 births and is considered a pediatric emergency because of the potentially lethal outcome of recurrent or persistent infections suffered by SCID patients. Several monogenic causes with different modes of inheritance have been identified for SCID. Depending on the underlying genetic defect, different primary phenotypes associated with SCID have been characterized. Genetic testing for SCID can allow distinction between the various forms of this syndrome. Knowledge of the defective gene may have implications for treatment and prognosis. This knowledge may also enable more effective genetic counseling, in addition to facilitating identification of asymptomatic carriers and timely initiation of treatment in affected descendants of carriers.

T?B?+ SCID is the most common type of SCID. It is most often caused by X-linked recessive mutations in IL2RG, which encodes the ? chain (?c) common to several cytokine receptors such as IL-2R, IL-4R, IL-7R, IL-9R, IL-15R, and IL-21R. T?B?+ SCID has also been associated with autosomal recessive mutations in other autosomal genes. Mutations in these genes lead to defective signaling through the ?c receptors, resulting in an absence of both T cells and NK cells. B cells are present at normal levels, but have impaired function.

T?B? SCID is caused by autosomal recessive mutations in several genes, some of which are necessary for antigen receptor rearrangement, RAG1, RAG2, and DCLRE1C (ARTEMIS). Defects in these genes lead to impaired development of both B and T cells, while NK-cell development is normal.

If the patient’s phenotype is more well-defined as either SCID B+ or SCID B-, phenotype-specific panels are available.

References:

- OMIM.
- GeneReviews.

Genes

ADA, CD247, CD3D, CD3E, DCLRE1C, FOXX1, IL2RG, IL7R, JAK3, LI4, NHEJ1, ORAI1, PNP, PTPRC, RAG2, RAG1, RAG2, STAT5B, STIM1, TBX1, ZAP70

Indications

This test is indicated for:

- Confirmation of a clinical diagnosis of Severe Combined Immunodeficiency (SCID) B+.
- Confirmation of a clinical diagnosis of Severe Combined Immunodeficiency (SCID) B-.

Methodology

Next Generation Sequencing: In-solution hybridization of all coding exons is performed on the patient's genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient's gene sequences are then compared to a standard reference sequence. Potentially causative variants and areas of low coverage are Sanger-sequenced. Sequence variations are classified as pathogenic, likely pathogenic, benign, likely benign, or variants of unknown significance. Variants of unknown significance may require further studies of the patient and/or family members.

Copy Number Analysis: Comparative analysis of the NGS read depth (coverage) of the targeted regions of genes on this panel was performed to detect copy number variants (CNV). The accuracy of the detected variants is highly dependent on the size of the event, the sequence context and the coverage obtained for the targeted region. Due to these variables and limitations a minimum validated CNV size cannot be determined; however, single exon deletions and duplications are expected to be below the detection limit of this analysis.

Detection

Next Generation Sequencing: Clinical Sensitivity: Unknown. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient’s clinical/biochemical phenotype.

Analytical sensitivity for sequence variant detection is ~99%.
Copy Number Analysis: The sensitivity and specificity of this method for CNV detection is highly dependent on the size of the event, sequence context and depth of coverage for the region involved. The assay is highly sensitive for CNVs of 500 base pairs or larger and those containing at least 3 exons. Smaller (< 500 base pairs) CNVs and those that involving only 1 or 2 exons may or may not be detected depending on the sequence context, size of exon(s) involved and depth of coverage.

**Specimen Requirements**

Submit only 1 of the following specimen types

**Type: Whole Blood (EDTA)**

**Specimen Requirements:**
- EDTA (Purple Top)
- Infants and Young Children (2 years of age to 10 years old): 3-5 ml
- Older Children & Adults: 5-10 ml
- Autopsy: 2-3 ml unclotted cord or cardiac blood

**Specimen Collection and Shipping:**
Ship sample at room temperature for receipt at EGL within 72 hours of collection. Do not freeze.

**Type: DNA, Isolated**

**Specimen Requirements:**
- Microtainer
- 8µg
- Isolation using the Perkin Elmer™Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.

**Specimen Collection and Shipping:**
Refrigerate until time of shipment in 100 ng/µL in TE buffer. Ship sample at room temperature with overnight delivery.

**Type: Saliva**

**Specimen Requirements:**
- Oragene™ Saliva Collection Kit
- Orangene™ Saliva Collection Kit used according to manufacturer instructions. Please contact EGL for a Saliva Collection Kit for patients that cannot provide a blood sample.

**Specimen Collection and Shipping:**
Please do not refrigerate or freeze saliva sample. Please store and ship at room temperature.

**Related Tests**

- Severe Combined Immunodeficiency (SCID) B-: Sequencing Panel
- Severe Combined Immunodeficiency (SCID) B+: Sequencing Panel
- Severe Combined Immunodeficiency (SCID) B+/B-: Deletion/Duplication Panel