TEST ID: SCDGP
SEVERE COMBINED IMMUNODEFICIENCY (SCID) GENE PANEL

USEFUL FOR

- Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of severe combined immunodeficiency (SCID), combined immunodeficiency (CID), T-cell lymphopenia/deficiency, bare lymphocyte syndrome (BLS), or EBV-associated primary immunodeficiency (PID)
- Establishing a diagnosis and, in some cases, allowing for appropriate management and surveillance for disease features based on the gene involved
- Identifying pathogenic variants within genes known to be associated SCID, CID, T-cell lymphopenia/deficiency, BLS, or EBV-associated PID allowing for predictive testing of at-risk family members

CLINICAL INFORMATION

Severe combined immunodeficiency (SCID) is characterized by the absence of, or dysfunction of T lymphocytes, which affects both cellular and humoral adaptive immunity, resulting in a severe form of inherited primary immunodeficiency that may be life-threatening. In classic form, SCID presents in infancy with persistent respiratory and gastrointestinal infections, failure to thrive, or graft-versus-host disease (due to engraftment of maternal T cells). The absence of lymphoid tissue, immunoglobulins, and T lymphocytes may also be noted. Typically, patients will have less than 300 autologous CD3 T cells/mcL blood and will require immediate medical intervention.

Atypical or leaky SCID tends to present later (ie, over 12 months of age) with recurrent, severe, and prolonged viral infections, bronchiectasis, autoimmune manifestations including cytopenias, and failure to thrive. Patients may display partial or restricted antigen-specific antibody responses. Leaky SCID is also related to hypomorphic variants in genes normally associated with classic SCID, as indicated above.

Omenn syndrome, a form of leaky SCID that typically presents in infancy, is characterized by erythroderma, alopecia, hepatosplenomegaly, and lymphadenopathy. Laboratory findings may include elevated IgE, eosinophilia, and lymphocytosis. Omenn syndrome is due to genetic variants in at least 7 different genes that allow for partial activity, although disease severity is likely only partially attributable to genotype. While RAG1 and RAG2 hypomorphic variants are most often associated with leaky SCID or Omenn syndrome, patients may have variants affecting other genes/proteins, such as Artemis or Interleukin-7 receptor (IL-7R) alpha. There may be forms of leaky SCID with hypomorphic variants in these genes that do not have the associated Omenn syndrome phenotype.

REFERENCE VALUES

An interpretive report will be provided.

ANALYTIC TIME

6 weeks

04/2018

CONTENT AND VALUES SUBJECT TO CHANGE. SEE THE MAYO MEDICAL LABORATORIES TEST CATALOG FOR CURRENT INFORMATION.
SCID can be classified as T-B+ or T-B- SCID, with further subdivision possible based on the presence or absence of NK cells. T-B+ SCID, characterized by impaired development of mature T-cells along with present but non-functional B-cells, is most often caused by genetic variants that affect cytokine-mediated signaling. X-linked SCID is due to mutations in the IL2RG gene, which encodes the common gamma chain that is a part of the IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 receptors. Autosomal recessive forms due to variants in JAK3 or IL7R also disrupt cytokine signaling. Genetic variants in one of the four CD3 genes (CD3G, CD3D, CD3E, and CD247[CD3Z]) inhibit CD3 signaling and also cause T-B+ SCID. T-B+ SCID may also be due to coronin-1A deficiency causing disruption of thymic egress of T cells and defective T cell locomotion, or due to CD45 deficiency (caused by variants in PTPRC). Patients with coronin-1A deficiency may also have other syndromic manifestations.

T-B-SCID is typically characterized by a defect in V(D)J recombination. V(D)J recombination begins with proteins encoded by RAG1 and RAG2 forming a heterodimer and making a single-stranded nick and forming hairpin structured ends between a coding element (V, D, or J segment) and the recombination signal sequence. Then, in the processing phase, the DNA-protein kinase complex (including a protein encoded by PRKDC) binds to and opens the hairpin structure by phosphorylating Artemis (encoded by DCLRE1C). Prior to ligation of the open ends by LIG4/XRCC4 and Cernunnos/XLF (encoded by NHEJ1), additional editing takes place. Adenosine deaminase (ADA) deficiency, which results in accumulation of metabolic by-products that are toxic to lymphocytes, and results in T-B- and NK-SCID. It accounts for approximately 15% of cases and is inherited as an autosomal recessive condition, which may include neurological problems (ie, cognitive impairment, hearing/visual impairment, and movement disorders) in addition to SCID. Reticular dysgenesis, due to genetic variants in AK2, is the most severe form of combined immunodeficiency and is characterized by congenital agranulocytosis, lymphopenia, lymphoid and thymic hypoplasia, along with bilateral sensorineural deafness.

Subsets of T cells may be decreased due to genetic variants in certain genes, without an appreciable effect on other T cell subsets. For example, genetic variants in CD8A, ZAP70, TAP1, TAP2, or TAPBP can result in absent or reduced CD8+ T cells in the presence of normal quantity of CD4+ T cells. In contrast, genetic variants in CIITA, RFXANK, RFx5, or RFXAP result in absent or reduced CD4+ T cells. These genes are associated with Bare Lymphocyte Syndromes types 1 and 2 respectively, or MHC class I and II deficiencies. In addition, variants in ITK, MAGT1, RHOH, STK4, TRAC, LCK, MAL1, IL21, IL21R, TNFRSR4 (OX40), IKBKB, CD27, or CTPS1 are thought to generally result in combined immunodeficiency that is generally less clinically profound than severe combined immunodeficiency.

Several combined immunodeficiencies are associated other features and syndromes. Variants in WAS and WIPF1 present with combined immunodeficiency and congenital thrombocytopenia, while variants in RBM8A are associated with thrombocytopenia-absent radius (TAR) syndrome. DNA repair defects are commonly observed along with combined immunodeficiency in Ataxia-telangiectasia (due to variants in ATM). Thymic defects with additional congenital anomalies may be observed in DiGeorge syndrome (represented on this panel by TBX1), CHARGE syndrome (due to variants in CHD7 or SEMA3E), and patients with genetic variants in FOXN1. Immune-osseous dysplasias along with combined immunodeficiency may be observed in cartilage hair hypoplasia (due to variants in RMRP), while those with variants in STAT5B may have growth hormone insensitivity. Combined immunodeficiency (CID) along with defects of vitamin B12 and folate metabolism may be observed in patients with genetic variants in SLC46A1 or MTHFD1. Anhidrotic ectodermal dysplasia with immunodeficiency results from genetic variants in IKBKGN (NEMO) or NFKBIA (IKBA). Calcium channel defects are an associated feature in those with variants in ORAI1 or STIM1. In addition to CID, patients with variants in TTC7A may have multiple intestinal atresias. Barth syndrome along with combined immunodeficiency can be observed in patients with variants in TAZ. Some of these defects can be identified by newborn screening (NBS) for SCID, while others do not present with severe enough T cell lymphopenia in the neonatal period to be identified by NBS.