Autoimmune Lymphoproliferative Syndrome (ALPS) Test

Clinical Features:

Autoimmune lymphoproliferative syndrome (all types) generally presents in early childhood, and is characterized by chronic, non-malignant lymphadenopathy, usually with autoimmunity. The underlying cause is a defect in lymphocyte apoptosis, or programmed cell death, leading to persistence of mature T and B cells, including the usually rare CD4/CD8-double-negative T (DNT) cell. The formal diagnostic triad for ALPS is elevated DNT cells, hepato/splenomegaly, and defective in vitro lymphocyte apoptosis. Autoimmunity may be present, most often directed against erythrocytes, platelets and neutrophils. In some patients, skin rashes, glomerulonephritis, arthritis, Guillan-Barré syndrome and autoimmune hepatitis may occur. The disorder can vary significantly in severity, even within families. Some individuals have only positive laboratory findings, typically including DNT cells, autoantibodies (such as Coombs positivity), hypergammaglobulinemia (IgG, IgM, IgA), elevated serum IL-10, and elevated serum vitamin B12. ALPS patients and their variant-bearing relatives have a significantly increased risk for both Hodgkin and non-Hodgkin lymphoma. The majority of ALPS patients have variants in the FAS (TNFRSF6) gene and are referred to as Type IA. ALPS Type IB is caused by variants in the FASL gene, which are rare. ALPS cases associated with CASP10 (Type IIA) and CASP8 (Type IIB) variants are also make up a smaller proportion of ALPS, although they are more common than Type IB. ALPSIIB has been called Caspase-8 Deficiency State (CEDS) because two published siblings have immunodeficiency in addition to ALPS.[1]

Test Methods:

Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel 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. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data. 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 FAS gene, sequencing but not deletion/duplication analysis is performed.

Test Sensitivity:

ALPS Type IA, caused by variants in the FAS gene, is the most common form of ALPS and represents approximately 72% of ALPS cases.[9] The majority of variants are detectable by sequencing, but a few cases (<5%) have large insertions or deletions.

ALPS Type IB, caused by variants in the FASL gene, is a cause of a small portion of ALPS cases.[10-13]

ALPS Type II is estimated to account for up to 10% of ALPS cases, although published cases are relatively rare. The two involved genes CASP10 and CASP8 have been found to harbor missense variants in a handful of published families.[2-4,8] An additional 2 patients had missense variants in CASP10 along with variants in FAS.[5] Sequencing of the coding regions as performed at GeneDx is expected to detect greater than 99% of variants in the ALPS genes if they are present.

Gene	Protein	Inheritance	Disease Associations	Sensitivity
FAS	Fas cell surface death receptor	AD; AR (rare)	ALPS Type IA	72%[9]
CASP10	Caspase 10	AD; multigeneic with FAS (rare)	ALPS Type II	<5%[2,3,9]
CASP8	Caspase 8	AR	ALPS Type II	Rare[4,8]
FASL	Fas ligand	AD; AR	ALPS Type IB	Rare[10-13]

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