FAS (TNFRSF6) Gene Analysis in
Autoimmune Lymphoproliferative Syndrome (ALPS) Type 1A

Disorder also known as:
Canale-Smith Syndrome

Clinical Features:
Autoimmune lymphoproliferative syndrome type 1A (ALPS 1A) 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.

Inheritance Pattern/Genetics:
Autosomal dominant, although homozygous or compound heterozygous variants have been reported.

Test Methods:
Analysis is performed by bi-directional sequencing of the 9 coding regions and intron/exon boundaries of the FAS. A variant found in the proband (first person of a family to be tested) will be confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method.

Test Sensitivity:
ALPS Type 1A is the most common form of ALPS and by definition is caused by variants in FAS. Over 95% of cases have variant types that are readily detected by sequencing.

Missense and nonsense variants predominate but splice-site variants and small insertions and deletions have also been reported. Very few cases have large insertions or deletions.
References: