CASP10 and CASP8 Gene Analysis in Autoimmune Lymphoproliferative Syndrome (ALPS) Type IIA and IIB

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. The majority of ALPS patients have variants in the FAS (TNFRSF6) gene and are referred to as Type IA. ALPS cases associated with CASP8 and CASP10 variants are extremely rare and less well understood. ALPS2B has been called Caspase-8 Deficiency State (CEDS) because the two published siblings have immunodeficiency in addition to ALPS.1

Inheritance Pattern/Genetics:
CASP10 is autosomal dominant or multigenic with FAS (TNFRSF6) variants in 5 families; CASP8 is autosomal recessive in 1 family.

Test Methods:
Analysis is performed by bi-directional sequencing of the coding regions and intron/exon boundaries of the CASP10 gene (exons 2-10) or CASP8 gene (exons 3-10). Variants found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method.

Test Sensitivity:
ALPS Type II is estimated to account for up to 10% of ALPS cases, although published cases are rare. The two involved genes CASP10 and CASP8 have been found to harbor missense variants in three2,3 or one5 published families, respectively. An additional 2 patients had missense variants in CASP10 along with variants in TNFRSF65. Sequencing of the coding regions as performed at GeneDx is expected to detect 99% of such variants if they are present.
The CASP8 and CASP10 variants associated with ALPS to date have been single base missense variants. Interpretations may be limited by the small numbers of comparable patients.

References:
2. Wang, J., et al., Inherited caspase 10 mutations underlie defective lymphocyte and dendritic cell apoptosis in autoimmune lymphoproliferative syndrome type II. Cell 47-58, 1999