



Division of Human Genetics

## Autoimmune Lymphoproliferative Syndrome

Genes Tested:

TNFRFS6 (FAS), TNFSF6 (FASLG), CASPASE 10 (CASP10)

### Molecular Genetics Laboratory

CLIA#: 36D0965791

Phone: (513) 636-4474

Fax: (513) 636-4373

Email: [moleculargenetics@cchmc.org](mailto:moleculargenetics@cchmc.org)

Additional information and test requisitions are available at:

[www.cchmc.org/molecular-genetics](http://www.cchmc.org/molecular-genetics)



*Helping you fit the pieces together*

### Shipping Instructions

Please enclose test requisition with sample. All information must be completed before sample can be processed.

Place samples in Styrofoam mailer and ship at room temperature by overnight Federal Express to arrive Monday through Friday

Ship to:

Cytogenetics and Molecular Genetics Laboratories

3333 Burnet Avenue NRB 1042

Cincinnati, OH 45229

513-636-4474

ALPS is a primary immunodeficiency disorder of defective FAS-mediated apoptosis (restimulation-induced cell death). Patients with ALPS develop chronic/recurrent lymphadenopathy, [hepato] splenomegaly, and autoimmune disease affecting blood cells and other tissues. There is a highly increased risk of lymphoma in ALPS patients.

Mutations in FAS are identified in 70-80% of patients with an ALPS phenotype. A small minority of ALPS patients have identified mutations in genes other than FAS, such as the FAS ligand (FASLG) gene (ALPS type Ib), and caspase-10 (CASP10) gene (ALPS type II). Individuals with ALPS type III, which accounts for about 20%-25% of patients, do not have identified mutations in any of these genes. Somatic mutations in FAS (limited to double negative T cells) have also been identified in a minority of ALPS patients.

#### FAS:

Most patients with ALPS type Ia have a heterozygous mutation in the FAS gene, located at 10q24.1, which encodes the protein tumor necrosis factor receptor superfamily member 6 (TNFRSF6). In most patients, ALPS Ia is inherited as an autosomal dominant disorder. All known mutations in FAS result in defective FAS-mediated apoptosis. However, mutations affecting the intracellular domain (exons 7-9) are much more likely to be associated with an ALPS phenotype than are those mutations which affect the extracellular domain (exons 1-6). Homozygous or compound heterozygous mutations in FAS result in a very severe clinical phenotype which is classified as ALPS 0, while the phenotype in patients with somatic mutations in FAS, classified as ALPS I SM, may be clinically indistinguishable from that of typical ALPS I patients. The presence of additional, unidentified genetic or environmental modifiers may be necessary to effect the development of the ALPS phenotype in individuals with FAS mutations.

#### FASLG:

Approximately 1% of reported patients with an ALPS phenotype have a mutation in the FASLG gene, located at 1q23 and which encodes the protein tumor necrosis factor ligand superfamily member 6 (TNFSF6), also known as Fas ligand. ALPS type Ib, both autosomal dominant and autosomal recessive inheritance patterns have been described. Thus, it is possible that both haplo-insufficiency, as well as dominant negative interference are associated with ALPS type Ib. There is currently no consistent information regarding family or penetrance studies for this form of ALPS, although, due to the fact that Fas ligand forms trimers similarly as Fas, it is speculated that missense mutations may have more severe effects than mutations that disrupt the FasLG protein more globally. The presence of additional, unidentified genetic or environmental modifiers may be necessary to affect the development of the ALPS phenotype in individuals with FASLG mutations.

#### CASP10:

Approximately 2% of reported patients with an ALPS phenotype have a mutation in the CASP10 gene, located at 2q33-q34 and which encodes the protein apoptosis related cysteine protease, also known as Caspase-10. Most patients with ALPS type II have a heterozygous mutation in CASP10. The presence of additional, unidentified genetic or environmental modifiers may be necessary to affect the development of the ALPS phenotype in individuals with CASP10 mutations.

## DIAGNOSTIC TESTING:

Consistent laboratory abnormalities in ALPS patients include defective in vitro FAS-mediated apoptosis, the presence of double-negative (CD4/CD8-negative) T-cells, expressing the alpha/beta T-cell receptor, hyperimmunoglobulinemia, cytokine alterations, autoantibodies, and elevated vitamin B12.

### Clinical testing for ALPS should include:

- Full sequence analysis of FAS gene; if normal, consideration of FASLG, CASP10 sequence analysis and FAS mutation analysis in double negative T cells
- ALPS panel by flow cytometry (and plasma cytokines, vitamin B12)
- FAS-apoptosis assay (where available)

## INDICATIONS:

- Confirmation of diagnosis in a symptomatic individual
- Identification of at-risk individuals for future medical management
- Prenatal diagnosis of an at-risk fetus, after identification of a mutation in a proband (by previous arrangement only)

## SPECIMEN:

At least 3 mls whole blood in purple top (EDTA) tube. Label tube with patient's name, birth date, and date of collection. Buccal swabs are required for analysis in patients who have undergone transplantation and may facilitate DNA isolation in patients undergoing chemotherapy or in individuals with leukopenia. Please call for a free buccal swab collection kit.

## METHODOLOGY:

Testing is performed by PCR-based sequencing of the entire coding regions and intron/exon boundaries of the FAS, CASP10 or FASLG genes. Testing may be ordered sequentially or tandemly.

## SENSITIVITY:

Approximately 75% of patients with ALPS have a mutation in FAS, while mutations in FASLG and CASP10 have been reported in < 5% of ALPS patients. PCR-based sequencing detects the majority of reported mutations in these genes. Gross deletions and rearrangements are reported in less than 10% of patients with ALPS and are not detected by this test methodology. Similarly, somatic FAS mutations in double negative T cells have been reported in some patients with ALPS and are not routinely detected. For patients with classic ALPS and a normal FAS study, somatic mutation analysis is available on a fresh sample and at an additional charge. Please contact the Diagnostic Immunology Laboratory at 513-636-4685 to arrange for this testing.

## TURN-AROUND TIME:

One Month

## COST:

Please call 1-866-450-4198 for current pricing.

## CPT CODES:

FAS	83890, 83898(x9), 83894(x9), 83891(x9), 83904(x18), 83912
FASLG	83890, 83898(x5), 83894(x7), 83891(x5), 83904(x12), 83909(x12), 83912
CASP10	83890, 83898(x9), 83894(x11), 83891(x9), 83904(x23), 83909(x23), 83912

Family specific mutation analysis 83890, 83898, 83894, 83891, 83904, 83912