GeneReviews

GENEReviews

Funded by the NIH · Developed at GeneTests (www.genetests.org), University of Washington, Seattle

Autoimmune Lymphoproliferative Syndrome

[*ALPS, Canale-Smith Syndrome. Includes: CASP10-Related Autoimmune Lymphoproliferative Syndrome, FAS-Related Autoimmune Lymphoproliferative Syndrome, FASLG-Related Autoimmune Lymphoproliferative Syndrome*]

Jack JH Bleesing, MD, PhD
Assistant Professor of Pediatrics, Division of Hematology/Oncology
Cincinnati Children's Hospital
Jack.Bleesing@cchmc.org

Judith Johnson, MS, CGC
Program Coordinator, Diagnostic Center for Heritable Immunodeficiencies
Cincinnati Children's Hospital
JudithA.Johnson@cchmc.org

Kejian Zhang, MD, MBA
Assistant Professor of Pediatrics
Director, Molecular Genetics Laboratory
Division of Human Genetics
Cincinnati Children's Hospital
kejian.zhang@cchmc.org

Initial Posting: July 9, 2007.
Last Revision: July 9, 2007.

Summary

Disease characteristics. **A**utoimmune **l**ympho**p**roliferative **s**yndrome (ALPS), caused by defective lymphocyte homeostasis, is characterized by (1) non-malignant lymphoproliferation (lymphadenopathy, hepatosplenomegaly with or without hypersplenism) that usually improves with age; (2) lifelong autoimmune disease, mostly directed towards blood cells; and (3) lifelong increased risk of both Hodgkin and non-Hodgkin lymphoma. In ALPS Ia, the most common and best characterized type of ALPS, non-malignant lymphoproliferation typically manifests in the first years of life, inexplicably waxes and wanes, and then decreases without treatment at the beginning of the second decade of life; however, often neither splenomegaly nor the overall expansion of lymphocyte subsets in peripheral blood decrease. Although autoimmunity is often not present at the time of diagnosis or at the time of the most extensive lymphoproliferation, autoantibodies are often detected years before autoimmune disease manifests clinically. ALPS 0, characterized by severe lymphoproliferation before, at, or shortly after birth, usually results in death at an early age. ALPS Ia-SM (somatic mutations), resulting from somatic *FAS* mutations in selected cell populations, notably the alpha/beta double-negative T cells (α/β-DNT cells), is similar to ALPS Ia.

Diagnosis/testing. The diagnosis of ALPS is based on clinical findings, laboratory abnormalities including defective in vitro tumor necrosis factor receptor superfamily member 6 (Fas)-mediated apoptosis and T cells that express the alpha/beta T-cell receptor but lack both CD4 and CD8 (so-called α/β-DNT cells), and identification of mutations in genes relevant for the Fas pathway of apoptosis. Mutations in *FAS (TNFRSF6*) are associated with ALPS 0, ALPS Ia, and ALPS Ia-SM. Mutations in *FASLG (TNFSF6*) and *CASP10* have been identified in a few individuals with ALPS. Molecular genetic testing of *FAS* and *CASP10* is available clinically. Testing of *FASLG* is available on a research basis only.

GeneReviews GeneReviews GeneReviews GeneReviews

Management. Lymphoproliferation can be suppressed with corticosteroids, cyclosporine, tacrolimus, and mycophenolate mofetil. Because lymphadenopathy and organomegaly invariably return once these agents are discontinued, one approach is to use immunosuppressive therapy only for severe complications of lymphoproliferation (e.g., airway obstruction) and/or autoimmune manifestations. Lymphoma is treated with conventional protocols. Bone marrow (stem cell) transplantation (BMT/SCT), the only curative treatment for ALPS, has to date mostly been performed on those with severe clinical phenotypes such as ALPS 0. Surveillance involves clinical assessment, imaging and laboratory studies for manifestations of lymphoproliferation and autoimmunity, and specialized imaging studies to detect malignant transformation. Splenectomy to control autoimmune cytopenias is discouraged because it typically does not lead to permanent remission of autoimmunity and may be associated with an increased risk of infections. Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) should be used with caution as they can interfere with platelet function. If the disease-causing mutation has been identified in a family member with ALPS, it is appropriate to perform molecular genetic testing on at-risk relatives to allow early diagnosis and treatment.

Genetic counseling. ALPS Ia is inherited in an autosomal dominant manner. Most individuals diagnosed with ALPS Ia have a parent with a *FAS* mutation. A proband with ALPS Ia may have the disorder as the result of somatic mosaicism or a *de novo* mutation; the proportion of ALPS Ia caused by either somatic mosaicism or *de novo* mutations is currently unknown. Each child of an individual with ALPS Ia has a 50% chance of inheriting the *FAS* mutation. ALPS 0 is thought to be the consequence of homozygous (or compound heterozygous) *FAS* mutations. The parents of a child with ALPS 0 are obligate heterozygotes and therefore have one *FAS* mutant allele. Prenatal diagnosis for pregnancies at increased risk for (a) *FAS* mutation(s) or a *CASP10* mutation is possible if the disease-causing mutation(s) has/have been identified in an affected family member.

Diagnosis

Clinical Diagnosis

The diagnosis of autoimmune lymphoproliferative syndrome (ALPS) is based on a constellation of clinical findings, laboratory abnormalities, and identification of mutations in genes relevant for the tumor necrosis factor receptor superfamily member 6 (Fas) pathway of apoptosis.

ALPS should be considered in individuals with (combinations of) the following [Bleesing 2003, Rieux-Laucat et al 2003]. See also Table 2.

- **Chronic non-malignant lymphoproliferation**
  - Chronic and/or recurrent lymphadenopathy
  - Splenomegaly with/without hypersplenism
  - Hepatomegaly
  - Lymphocytic interstitial pneumonia (LIP) (less common)
- **Autoimmune disease**
  - **Cytopenia,** particularly combinations of autoimmune hemolytic anemia (AIHA), immune thrombocytopenia (ITP), and autoimmune neutropenia

    Note: The combination of AIHA and ITP is often referred to as Evans syndrome.

GeneReviews GeneReviews GeneReviews GeneReviews

  - **Other** including autoimmune hepatitis, autoimmune glomerulonephritis, autoimmune thyroiditis and, less commonly, uveitis and Guillain Barré syndrome

- **Lymphoma,** both Hodgkin lymphoma and non-Hodgkin lymphoma
- **Skin rashes,** often but not exclusively of an urticarial nature
- **Family history** of ALPS or ALPS-like features

Testing

Although no specific laboratory abnormality alone is diagnostic of ALPS, the detection of the following facilitates the diagnosis [Bleesing 2003]:

- Defective Fas-mediated apoptosis in vitro
- T cells that express the alpha/beta T-cell receptor but lack both CD4 and CD8 (so-called alpha/beta double-negative T cells [α/β-DNT cells] in peripheral blood or tissue specimens. Detected by flow cytometric immunophenotyping, these terminally differentiated in vivo-activated T cells are rare in healthy individuals and other immune-mediated (lymphoproliferative) disorders; typically they constitute less than 1%-2% of the lymphocyte pool.

Note: The finding of α/β-DNT cells in individuals with clinical evidence of ALPS and somatic mutations in *FAS* who did not display defective in vitro Fas-mediated apoptosis suggests that the presence of α/β-DNT cells is the only consistent laboratory finding shared by individuals with ALPS [Rössler et al 2005].

Laboratory findings in ALPS [Le Deist et al 1996; Sneller et al 1997; Lim et al 1998; Carter et al 2000; Bleesing, Brown, Dale et al 2001; Bleesing, Brown, Straus et al 2001; Lopatin et al 2001; Bleesing et al 2002; Bleesing 2003; Bleesing 2005; Maric et al 2005]

Hematology

- Lymphocytosis, lymphopenia (primary or secondary in response to treatment)
- Coombs-positive hemolytic anemia
- Dyserythropoiesis
- Reticulocytosis
- Thrombocytopenia
- Neutropenia
- Eosinophilia

Immunology

- Expansion of other lymphocyte subsets
  - Gamma/delta-DNT cells
  - $CD8^+/CD57^+$ T cells
  - $HLA\text{-}DR^+$ T cells
  - $CD5^+$ B cells
- Decreased numbers of $CD4^+/CD25^+$ T cells
- Decreased numbers of $CD27^+$ B cells

GeneReviews GeneReviews GeneReviews GeneReviews

- Elevated concentration of IL-10 in serum/plasma
- Elevated concentrations of IgG, IgA, and IgE; normal or decreased concentrations of IgM
- Autoantibodies (most often positive direct or indirect antiglobulin test, antiplatelet antibody, antineutrophil antibody, antiphospholipid antibody, antinuclear antibody, rheumatoid factor)
- Lymph node pathology (paracortical expansion with immunoblasts/plasma cells and DNT cells in interfollicular areas, florid follicular hyperplasia, progressive transformation of germinal centers [PTGC])
- Other: increased soluble CD25, CD27, CD30, and tumor necrosis factor ligand superfamily member 6 (Fas ligand, or FasL); monoclonal gammopathy; decreased antibody responses to polysaccharide antigens

Chemistry

- Liver function abnormalities (in case of autoimmune hepatitis)
- Proteinuria (in case of glomerulonephritis)
- Elevated concentration of vitamin B_{12}

Normal findings in ALPS

- Neutrophil function
- Complement concentrations and function
- In vitro proliferative responses of T-cells (e.g., in response to common mitogens or antigens)
- NK-cell and cytotoxic T-lymphocyte (CTL) function; possibly decreased CTL activity in ALPS on the basis of defective FasL (i.e., ALPS Ib)
- Antibody responses to protein antigens (e.g., diphtheria, tetanus)

Note: (1) The abnormal and normal laboratory findings above have been most reliably established for individuals with ALPS caused by mutations in *FAS* (ALPS Ia). (2) Cell surface expression of Fas (CD95) can be normal, increased, or decreased and is in general not helpful in the diagnosis of ALPS. (3) When interpreting laboratory data of individuals with (suspected) ALPS, the influence of concurrent immunosuppressive agents at the time of testing needs to be considered.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Genes. Germline mutations in the three following genes are known to be associated with ALPS. Additionally, somatic mutations in *FAS* in selected cell populations, including α/β-DNT cells, produce a phenotype similar to that caused by *FAS* germline mutations.

FAS (TNFRSF6)

GeneReviews GeneReviews GeneReviews GeneReviews

- **ALPS 0** is associated with homozygous (or rarely compound heterozygous germline mutations) in *FAS* [Rieux-Laucat et al 1995, Kasahara et al 1998, van der Burg et al 2000].
- **ALPS Ia** is associated with heterozygous *FAS* germline mutations; it accounts for approximately 75% of individuals with ALPS [Bleesing 2003, Rieux-Laucat et al 2003].
- **ALPS Ia-SM.** Somatic mutations in selected cell populations, including α/β-DNT cells, have been identified in individuals with ALPS with a phenotype similar to that caused by *FAS* germline mutations [Holzelova et al 2004, Rössler et al 2005].

FASLG (TNFSF6)

- **ALPS Ib** is associated with germline mutations in *FASLG*, the gene encoding tumor necrosis factor ligand superfamily member 6 (FasL). Three affected individuals have been reported to date [Wu et al 1996, CIS 1999, Del-Rey et al 2006].

CASP10

- **ALPS II** is associated with mutations in *CASP10* (the gene encoding caspase-10) [Wang et al 1999]. Two affected individuals were originally reported in 1999; in one, ALPS has subsequently been determined not to be caused by the reported homozygous *CASP10* mutation, while two additional individuals (out of a group of 32 probands with ALPS) have been identified with heterozygous missense mutations in *CASP10* [Zhu et al 2006].

Other loci. Approximately 20%-25% of individuals with ALPS currently lack a genetic diagnosis. They are classified as having either:

- ALPS III, if all known genetic defects have been ruled out;

OR

- ALPS non-Ia, if only *FAS* mutations have been ruled out [Dianzani et al 1997, Ramenghi et al 2000, Hundt et al 2002, van der Werff ten Bosch et al 2002, Bleesing 2003].

Note: Depending on the criteria used to define ALPS (e.g., with regard to demonstration of defective Fas-mediated apoptosis), defects in other genes or gene products inside or outside the Fas/FasL pathway may be associated with ALPS [Chun et al 2002]. No independently confirmed and published information has associated other Fas pathway-related genes with ALPS.

Clinical uses

- Diagnostic confirmation in symptomatic individuals
- Presymptomatic diagnosis
- Prenatal diagnosis

Clinical testing

- ***FAS.*** *FAS* germline mutations have been identified throughout the entire coding region and exon/intron boundaries. Sequencing of the entire coding region and intron/exon boundaries of the *FAS* gene detects about 90% of all reported mutations [NHGRI].
- ***CASP10.*** Sequence analysis of the entire coding region of the *CASP10* gene is available clinically. The mutation detection rate is not known. Furthermore,

GeneReviews GeneReviews GeneReviews GeneReviews

CASP10 mutations have been reported in in only two families; one was later found to have another mutation in the *TNFRSF1A* gene, consistent with a diagnosis of TNF receptor-associated periodic syndrome.

Research testing

- **Detection of *FAS* somatic mutations** requires specialized genetic testing of α/β-DNT cells sorted by flow cytometric immunophenotyping. Currently, such testing is not available on a clinical basis.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in ALPS

ALPS Type	Test Method	Mutations Detected	Mutation Detection Rate	Test Availability
ALPS Ia	Sequence analysis	*FAS*	90%	Clinical Testing
ALPS Ib		*FASLG*	Unknown	Research only
ALPS II		*CASP10*		Clinical Testing

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

A diagnostic approach to ALPS includes a combination of the following:

1. Confirm the presence of chronic non-malignant lymphoproliferation.
2. Identify the presence of T cells that express the alpha/beta T-cell receptor but lack both CD4 and CD8 (alpha/beta double-negative T cells [α/β-DNT cells]) in peripheral blood or tissue specimens.
3. Identify defective Fas-mediated apoptosis in vitro.
4. Perform molecular genetic testing of *FAS*.
5. If chronic non-malignant lymphoproliferation and α/β-DNT cells are present, defective Fas-mediated apoptosis in vitro is absent, and a germline mutation in *FAS* is not detectable, consider the possibility of a somatic mutation in *FAS*.
6. If a mutation in *FAS* is not identified, consider molecular genetic testing of *CASP10*.

Genetically Related (Allelic) Disorders

No phenotype other than ALPS is known to be associated with germline or somatic mutations in *FAS*.

***FASLG*, *CASP10*.** Only a few individuals with mutations in *FASL* and *CASP10* have been reported; thus, it is currently unknown whether clinical phenotypes other than ALPS may be associated with mutations in *FASLG* or *CASP10*.

GeneReviews GeneReviews GeneReviews GeneReviews

Clinical Description

Natural History

Autoimmune lymphoproliferative syndrome (ALPS) can be considered a prototypic disorder of defective lymphocyte homeostasis [Canale & Smith 1967, Sneller et al 1992, Fisher et al 1995, Rieux-Laucat et al 1995].

The manifestations are lymphadenopathy, hepatosplenomegaly with or without hypersplenism, and autoimmune disease, mostly directed toward blood cells. In addition, the risk of lymphoma is increased. See Table 2.

Table 2. Summary of Clinical Manifestations of ALPS

Lymphoproliferation of non-malignant lymphoid cells • Lymphadenopathy • Splenomegaly (+/- hypersplenism) • Hepatomegaly
Autoimmunity • Autoimmune hemolytic anemia • Autoimmune thrombocytopenia • Autoimmune neutropenia • Glomerulonephritis • Autoimmune hepatitis • Guillain Barré syndrome • Uveitis, iridocyclitis
Neoplasia (including benign tumors) • Lymphoma (Hodgkin and non-Hodgkin lymphoma) • Carcinoma (thyroid, breast, skin, tongue, liver) • Multiple neoplastic lesions (thyroid/breast adenomas, gliomas)
Other and/or infrequent findings • Urticaria and other skin rashes • Vasculitis • Panniculitis • Arthritis and arthralgia • Recurrent oral ulcers • Humoral immunodeficiency • Pulmonary infiltrates • Premature ovarian failure • Hydrops fetalis • Organic brain syndrome (mental status changes, seizures, headaches)

Much remains to be learned about the natural history and prognosis of ALPS. While non-malignant lymphoproliferative manifestations are likely to regress or improve over time, autoimmunity shows no permanent remission with advancing age. Moreover, the risk for development of lymphoma likely appears to be lifelong. Thus, in the absence of curative treatment, the overall prognosis for ALPS remains guarded, necessitating long-term clinical studies to better understand its natural history [Rieux-Laucat et al 1999, Bleesing 2003, Rieux-Laucat et al 2003].

GeneReviews GeneReviews GeneReviews GeneReviews

ALPS Ia. ALPS Ia is the most common and best characterized type of ALPS. The following are the main consequences of perturbed lymphocyte homeostasis in ALPS Ia.

- **Chronic non-malignant lymphoproliferation.** Expansion of antigen-specific lymphocyte populations that are not eliminated through apoptosis leads to expansion of the lymphoid compartment, resulting in lymphadenopathy, splenomegaly, hypersplenism and, less frequently, hepatomegaly. In most individuals with ALPS Ia, this finding typically manifests in the first years of life. In some individuals, splenomegaly is the predominant or only manifestation of lymphoproliferation [Bleesing 2003, Rieux-Laucat et al 2003].

  For many individuals with ALPS Ia, lymphadenopathy tends to decrease early in the second decade, while splenomegaly often does not. Furthermore, long-term follow-up in several individuals has shown that diminution of lymphadenopathy is not accompanied by significant changes in the overall expansion of lymphocyte subsets in peripheral blood [Bleesing, Brown, Straus et al 2001]. The lymphoproliferation waxes and wanes for reasons that are not entirely clear. Intercurrent viral and bacterial infections can decrease lymphadenopathy, reflecting activation of other (intact) apoptosis pathways.

  The overall prognosis of lymphoproliferation is relatively good and few individuals require long-term treatment with immunosuppressive agents to control lymphoproliferation [Bleesing 2003, Rieux-Laucat et al 2003].

  Laboratory findings of lymphoproliferation are the expansion of most lymphocyte subsets including the pathognomonic α/β-DNT cells as well as other T- and B-cell subsets.

- **Autoimmunity,** a common feature of ALPS, is often not present at the time of diagnosis or at the time of the most extensive lymphoproliferation. The reason for the delay in onset is unclear but may be related to age-dependent acquisition of secondary pathogenic factors that interact with defective Fas-mediated apoptosis. In many individuals with ALPS, autoantibodies can be detected years before the appearance of clinical manifestations of autoimmune disease [Bleesing 2003, Rieux-Laucat et al 2003].

  Although autoimmune manifestations can also wax and wane, current knowledge suggests that autoimmune disease poses a lifelong burden.

  Autoimmunity most often involves combinations of Coombs-positive hemolytic anemia and immune thrombocytopenia (together referred to as Evans syndrome); autoimmune neutropenia is less common. The observation of primary lymphopenia, contrasting with the typical presence of lymphocytosis, suggests the possibility of autoimmune lymphopenia (as seen in other autoimmune diseases).

  Autoimmune cytopenias may be difficult to distinguish from the effects of concomitant hypersplenism; examination of blood smears for evidence of hemolysis and measurement of autoantibodies and the degree of reticulocytosis may help in establishing the distinction.

  Additional autoimmune features can be found, often in patterns that appear to be family-specific, suggesting the influence of other (background) genes [Pensati et al 1997, Rieux-Laucat et al 1999, Vaishnaw et al 1999, Kanegane et al 2003].

  Laboratory findings include, among others: autoantibodies detected by direct and indirect antiglobulin tests (Coombs' test), antiplatelet antibodies, antineutrophil antibodies, antinuclear antibodies (ANA), and antiphospholipid antibodies.

GeneReviews GeneReviews GeneReviews GeneReviews

- **Lymphoma.** Individuals with ALPS Ia are at an increased risk for both Hodgkin and non-Hodgkin lymphoma, underscoring the role of Fas as a tumor-suppressor gene. Based on calculations in one study, the increased risk is 14-fold and 51-fold for non-Hodgkin and Hodgkin lymphoma, respectively [Straus et al 2001].

  Lymphoma can originate from B and T cells and does not appear to be related to EBV infection (based on absence of EBV in tumor biopsies).

  Current experience suggests that lymphomas can occur at any age in ALPS Ia and do respond to conventional chemotherapeutic treatment. Individuals with other forms of ALPS may also be at an increased risk for lymphoma; however, further data are needed to provide a detailed risk assessment. Because of the frequent concomitant presence of benign (i.e., "typical") lymphadenopathy and splenomegaly, distinguishing a "good" node from a "bad" node is a diagnostic challenge. Important clues are B-type symptoms including fever, night sweats, itching, and weight loss.

  A number of studies have looked at associations between Fas and neoplasms, including somatic mutations in solid tumors, leukemias, and lymphomas. For further discussion, see Muschen et al (2002), Houston & O'Connell (2004), Poppema et al (2004), and Peter et al (2005).

ALPS 0

- **Chronic non-malignant lymphoproliferation.** Individuals with homozygous or compound heterozygous *FAS* mutations often present with severe lymphoproliferation before, at, or shortly after birth [Rieux-Laucat et al 1995, Le Deist et al 1996, Kasahara et al 1998, van der Burg et al 2000].
- **Autoimmunity.** In several individuals reported, the delay between onset of autoimmunity and lymphoproliferation was minimal, while in others this was not the case. The rarity of and poor prognosis in ALPS 0 make it difficult to draw firm conclusions regarding autoimmunity in this type of ALPS [Rieux-Laucat et al 1995, Le Deist et al 1996, Kasahara et al 1998, van der Burg et al 2000].
- **Lymphoma.** Because of the severity of ALPS, affected individuals typically succumb to lymphoproliferation and/or autoimmunity at an early age.

ALPS Ia-SM (provisional classification). Somatic *FAS* mutations in selected cell populations, notably the α/β-DNT cells, have been identified in individuals with ALPS. The clinical phenotype is similar to that caused by *FAS* germline mutations. The population of α/β-DNT cells is expanded; however, as a consequence of technical aspects of the assay, Fas-mediated apoptosis of lymphocytes in vitro is not defective [Holzelova et al 2004, Rössler et al 2005]; apoptosis may, however, be defective in vivo.

Pathogenesis of ALPS. The phenotype of ALPS results from defective apoptosis of lymphocytes mediated through the Fas/Fas ligand (FasL) pathway. This pathway limits the size of the lymphocyte compartment by eliminating/removing autoreactive lymphocytes; therefore, defects in this pathway lead to expansion of antigen-specific lymphocyte populations. Fas also appears to play a role in suppression of malignant transformation of lymphocytes, although it remains to be firmly established whether this involves the Fas/FasL pathway in a similar way.

Genotype-Phenotype Correlations

ALPS Ia. Although the death domain (DD) of ALPS — the intracellular domain of Fas that connects cell surface-expressed Fas to the intracellular (death) signal transduction pathway — is a mutational hotspot, genotypes resulting from mutations in any domain of Fas lead to the

GeneReviews GeneReviews GeneReviews GeneReviews

same clinical phenotype of ALPS, as far as lymphoproliferation and autoimmunity are concerne. Lymphomas, in contrast, seem thus far to be associated only with mutations affecting the intracellular domains of Fas, though independent confirmation is required [Straus et al 2001].

Despite this similar clinical phenotype, in vitro Fas-mediated apoptosis is less defective in individuals with mutations affecting extracellular domains than in those with mutations affecting intracellular domains [Bleesing, Brown, Straus et al 2001].

ALPS II. Genotype-phenotype correlation is not well established for *CASP10* mutations.

Penetrance

ALPS Ia. A distinction needs to be made between the penetrance of the cellular phenotype (defective Fas-mediated apoptosis) and the penetrance of the clinical phenotype (i.e., ALPS).

Family studies to date show that penetrance for the defective Fas-mediated apoptosis cellular phenotype approximates 100% — i.e., every individual heterozygous for an inherited (germline) disease-causing mutation has defective apoptosis — whereas the penetrance for the clinical phenotype is reduced because a significant proportion of relatives heterozygous for the disease-causing mutation have no clinical symptoms of ALPS. In addition, other relatives display laboratory features of ALPS (e.g., expansion of lymphocyte subsets and/or autoantibodies) without clinical evidence of either lymphoproliferation or autoimmunity [Infante et al 1998; Jackson et al 1999; Bleesing, Brown, Straus et al 2001].

The factors that determine the penetrance of clinical ALPS are not entirely understood, but it appears that penetrance is determined by the location and type of mutation; however, further study and independent confirmation are needed [Rieux-Laucat et al 1999, Le Deist & Fisher 2001]. The highest penetrance (70%-90%) for the clinical phenotype occurs with missense mutations affecting the intracellular domains, followed by mutations leading to truncation of the intracellular domains [Jackson et al 1999]. The penetrance for the clinical phenotype with extracellular mutations is about 30%.

The reduced penetrance for ALPS in some families suggests that one or more additional pathogenic factors interact with defective Fas-mediated apoptosis. On the other hand, the high penetrance for the clinical phenotype in certain families associated with specific types of *FAS* mutations (e.g., missense mutations affecting the death domain) cast doubt on that assumption by suggesting that under certain conditions, a single defect in Fas-mediated apoptosis is sufficient to cause ALPS [Infante et al 1998, Jackson et al 1999, Le Deist & Fisher 2001].

Anticipation

Anticipation has not been documented in ALPS.

Prevalence

The prevalence of ALPS is unknown. It is a rare condition with a worldwide distribution and no predilection of race or ethnicity. It is likely as rare as other primary immunodeficiency disorders that cause disease in a heterozygous state.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

GeneReviews GeneReviews GeneReviews GeneReviews

The main considerations in the differential diagnosis for autoimmune lymphoproliferative syndrome (ALPS) are other immunodeficiency disorders characterized or complicated by lymphoproliferation, autoimmune disease, and lymphoma. These include the following:

- **Common variable immunodeficiency disease (CVID)** has an estimated incidence of one in 50,000 and occurs equally in males and females. Symptoms include recurrent infections (especially of the respiratory tract) at any age. The genetic etiology of most CVID is currently unknown. From a clinical and immunologic standpoint, CVID can be roughly classified into two groups, depending on the presence or absence of mature B cells in peripheral blood. Individuals with CVID with B cells (but absent or decreased memory B cells) are at an increased risk for autoimmune disease that often targets blood cells and for chronic lymphoproliferation including lymphadenopathy, splenomegaly, and lymphoma [Warnatz et al 2002, Piqueras et al 2003]. CVID with present B cells should be regarded in the differential diagnosis of ALPS, while the variant characterized by low or absent B cells and generally low levels of immunoglobulins should not.

  The overlap between ALPS and CVID is also illustrated by the report of two individuals with CVID who were found to have heterozygous mutations in *CASP8* [Chun et al 2002].

- **Hyper IgM (HIGM) syndrome.** Several non-X-linked forms of hyper IgM syndrome have now been identified. In varying degrees, they share features with the X-linked form, XHIGM (HIGM1), caused by mutations in *TNFSF5 (CD40L)* [Winkelstein et al 2003]. Shared features include recurrent bacterial infections, such as otitis media, sinusitis, and pneumonias. Autoimmune hematologic disorders including neutropenia, thrombocytopenia, and hemolytic anemia are also found. Other complications may include lymphomas and other malignancies as well as gastrointestinal complications. Serum concentration of IgM is elevated while other immunoglobulinlevels are normal; specific antibody responses are defective. In contrast to HIGM1, T-cell function in ALPS is typically within normal limits, reflected in an absence of opportunistic infections.

  HIGM2 is caused by mutations in the gene *AICDA*, encoding activation-induced cytidine deaminase. Inheritance is usually autosomal recessive, but in rare cases autosomal dominant [Revy et al 2000, Lee et al 2005]. Recurrent bacterial, respiratory, and gastrointestinal infections are typical; opportunistic infections are rare. Lymphoid hyperplasia, seen in ALPS, has been reported in HIGM2 [Revy et al 2000, Lee et al 2005]. *AICDA* mutations typically affect only B-cell differentiation.

  HIGM3, HIGM4, and HIGM5 are other forms of non-X-linked hyper IgM syndrome. Their inclusion in the differential diagnosis of ALPS is less clear on the basis of known clinical presentation and inheritance pattern [Ferrari et al 2001, Imai et al 2003].

- **X-linked lymphoproliferative syndrome (XLP)** is associated with an inappropriate immune response to Epstein-Barr virus (EBV) infection resulting in unusually **severe and often fatal infectious mononucleosis**; **dysgammaglobulinemia**; and/or **lymphoproliferative disorders**, typically of B-cell origin. Clinical manifestations of XLP vary, even among affected family members. The most common presentation is a near-fatal or fatal EBV infection associated with an unregulated and exaggerated immune response with widespread proliferation of cytotoxic T cells, EBV-infected B cells, and macrophages. Mortality is greater than 90%. In about one-third of males with XLP, hypogammaglobulinemia of one or more immunoglobulin subclasses is diagnosed prior to EBV infection or in rare survivors of EBV infection. The prognosis for males with this phenotype is more favorable if they are managed with regular intravenous immune globulin (IVIG). Lymphomas or other lymphoproliferative

GeneReviews GeneReviews GeneReviews GeneReviews

disease occur in about one-third of males with XLP, some of whom have hypogammaglobulinemia or have survived an initial EBV infection. The lymphomas seen in XLP are typically high-grade B-cell lymphomas, non-Hodgkin type, often extranodal, and particularly involving the intestine. Allogeneic bone marrow transplantation is the only curative therapy for XLP. Average life expectancy without curative bone marrow transplantation has been estimated as less than ten years. XLP is caused by hemizygous mutations in *SH2D1A*.

- **Wiskott-Aldrich syndrome (WAS)** typically manifests in infancy with thrombocytopenia, eczema, and recurrent bacterial and viral infections, particularly recurrent ear infections. At least 40% of males who survive the early complications develop one or more autoimmune conditions such as hemolytic anemia, immune thrombocytopenic purpura (ITP), immune-mediated neutropenia, arthritis, vasculitis of small and large vessels, and immune-mediated kidney and liver disease. Individuals with WAS, particularly those who have been exposed to EBV, have an increased risk of developing lymphomas, which often occur in unusual, extranodal locations such as the brain, lung, or gastrointestinal tract. Inheritance is X-linked.
- **Lymphoma** without other manifestations of ALPS has been observed in families with ALPS Ia. Thus, both B-cell and T-cell lymphoma should be considered in the differential diagnosis of ALPS [van der Werff ten Bosch et al 1999, Poppema et al 2004].

Management

Evaluations Following Initial Diagnosis

At initial diagnosis of autoimmune lymphoproliferative syndrome (ALPS), an inventory should be made regarding the presence and extent of lymphoproliferation and/or autoimmunity.

- Complete blood counts and flow cytometric immunophenotyping of lymphocytes, in combination with physical examination and imaging studies provide a detailed assessment of lymphadenopathy and hepatosplenomagaly.
- The presence of autoimmunity likely will be evident from the complete blood counts and the presence of autoantibodies (see Testing).
- The presence of significant lymphadenopathy may also prompt more extensive diagnostic procedures to detect lymphoma, especially if constitutional symptoms (e.g., fever, night sweats, weight loss) are present.

Treatment of Manifestations

In the absence of curative treatment, current management is focused on the control and/or treatment of manifestations of lymphoproliferation and/or autoimmunity and the treatment of lymphoma [Rieux-Laucat et al 1999, van der Werff ten Bosch et al 2001, van der Werff ten Bosch et al 2002, Bleesing 2003, Rieux-Laucat et al 2003, Rao et al 2005].

Manifestations of lymphoproliferation can be suppressed with the use of immunosuppressive agents, such as corticosteroids, cyclosporine, tacrolimus, and mycophenolate mofetil. The benefits of immunosuppression, however, are balanced by the side effects. Moreover, it has become clear that lymphadenopathy, as well as organomegaly, invariably return once immunosuppression is discontinued [Bleesing 2003]. Thus, one approach is to use immunosuppressive therapy only for severe complications of lymphoproliferation (e.g., airway obstruction) and/or autoimmune manifestations.

GeneReviews GeneReviews GeneReviews GeneReviews

Autoimmune manifestations typically respond to short courses of immunosuppressive agents. Mycophenolate mofetil is effective in chronic recalcitrant autoimmune cytopenias and may spare steroid usage [Rao et al 2005]. Rituximab has been used successfully in the treatment of refractory cytopenias in ALPS, although it remains to be seen how long affected individuals remain in clinical remission.

Lymphoma is treated according to conventional protocols. The presence of defective Fas-mediated apoptosis does not appear to hinder the response to chemotherapeutic agents or radiation.

Prevention of Primary Manifestations

Bone marrow (stem cell) transplantation (BMT/SCT) is currently the only curative treatment for ALPS. Because of the risks associated with BMT, it has so far been performed mostly in individuals with ALPS with severe clinical phenotypes, such as those with homozygous mutations in *FAS* (ALPS 0). It is likely, however, that individuals with undiagnosed forms of ALPS, including ALPS Ia, have been transplanted.

Successful (reported) BMT in several individuals indicates that defective Fas-mediated apoptosis does not pose a barrier to this treatment option [Benkerrou et al 1997, Sleight et al 1998].

Surveillance

Clinical assessment, imaging, and laboratory studies outlined in Evaluations Following Initial Diagnosis can be used in surveillance for manifestations of lymphoproliferation and autoimmunity.

Specialized imaging studies such as combined CT and PET scanning in combination with clinical and laboratory surveillance may be helpful in detection of malignant transformation [Rao et al 2006].

Agents/Circumstances to Avoid

Splenectomy to control autoimmune cytopenias is discouraged because it typically does not lead to permanent remission of autoimmunity and may be associated with an increased risk of infections [Author, unpublished observation].

The use of over-the-counter medications such as aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) should be discussed with a physician as some of these medications can interfere with platelet function.

Testing of Relatives at Risk

It is appropriate to perform molecular genetic testing on relatives at risk for ALPS Ia or ALPS II if the disease-causing mutation has been identified in the proband.

Relatives who have the family-specific mutation should:

- Be advised of their increased risk for ALPS or ALPS-related manifestations if the type and location of the *FAS* mutation (i.e., missense mutations affecting the intracellular domains) is predicted to have a high penetrance for clinical ALPS;
- Undergo ALPS-specific evaluations at initial diagnosis (e.g., enumeration of α/β-DNT cells, detection of autoantibodies, IL-10 measurement) (see Evaluations Following Initial Diagnosis);

- Be advised that ALPS-specific evaluations or other assessments may need to be repeated at regular intervals, particularly if the family member is young and/or if new health-related issues consistent with ALPS or ALPS-related complications (e.g., lymphoma) become apparent (see Surveillance).

Therapies Under Investigation

Mini-transplants. The advent of less toxic BMT conditioning regimens (i.e., reduced-intensity transplants, or "mini-transplants") may make BMT a realistic treatment option for individuals with ALPS who are not considered candidates for conventional BMT because of the associated risks.

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

High-dose intravenous immune globulin (IVIG) does not appear to be as effective in inducing permanent or long-term remission in ALPS as it is in isolated immune thrombocytopenia (ITP).

Mode of delivery. No evidence suggests that C-section reduces the risk of morbidity and mortality in newborns with ALPS, though the possible presence of autoimmune cytopenias such as immune thrombocytopenia in a newborn with ALPS 0 could pose a risk of increased bleeding in the neonate.

Gene therapy. No studies regarding gene therapy to treat ALPS Ia are ongoing; the highly regulated expression and activity of Fas pose substantial difficulties for gene therapy.

Genetics clinics, staffed by genetics professionals, provide information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section may include disease-specific and/or umbrella support organizations.

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

GeneReviews GeneReviews GeneReviews GeneReviews

Mode of Inheritance

ALPS Ia, ALPS Ib, and ALPS II are inherited in an autosomal dominant manner.

ALPS 0 is thought to be the consequence of homozygous (or compound heterozygous) mutations.

Risk to Family Members — ALPS Ia, ALPS Ib, ALPS II

Parents of a proband

- Most individuals diagnosed with ALPS Ia have a parent who has a *FAS* mutation. Individuals who are heterozygous for a *FAS* mutation all have defective Fas-mediated apoptosis but may have no clinical symptoms of ALPS (see Penetrance).
- A proband with ALPS Ia may have the disorder as the result of somatic mosaicism. The proportion of cases caused by somatic mosaicism is currently unknown.
- A proband with ALPS Ia may have the disorder as the result of a new gene mutation. However, the proportion of cases caused by *de novo* mutations is largely unknown.

Note: Although most individuals diagnosed with ALPS have a parent with a *FAS* mutation, the family history may appear to be negative because of reduced penetrance of the clinical symptoms of ALPS (as opposed to the nearly complete penetrance of apoptosis in individuals with a *FAS* mutation), failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, molecular genetic testing is the most accurate means of determining the mutational status of at-risk individuals.

Sibs of a proband

- The risk to the sibs of the proband depends upon the genetic status of the proband's parents.
- If a parent of the proband has a *FAS* or a *CASP10* mutation, each sib has a 50% chance of inheriting the *FAS* or *CASP10* mutation. The risk of developing ALPS-related complications however depends on the nature of the mutation, as well as the presence of other, as-yet incompletely understood genetic or environmental factors.
- If the *FAS* or *CASP10* mutation found in the proband cannot be detected in the DNA of either parent, the risk to sibs is low but greater than that of the general population, because the possibility of germline mosaicism exists.

Offspring of a proband. Each child of an individual with ALPS Ia or II has a 50% chance of inheriting the *FAS* or *CASP10* mutation. The risk of that child developing ALPS-related complications is dependent on the nature of the mutation as well as the presence of other, as-yet incompletely understood genetic or environmental factors.

Other family members of a proband. The risk to other family members depends upon the genetic status of the proband's parents. If a parent is found to have a *FAS* or *CASP10* mutation, his or her family members may have inherited the same mutation and are potentially at some increased risk of developing ALPS-related complications.

Note: Mutations in *FASLG* and *CASP10* are also associated with ALPS (types 1 and 2, respectively). Both are likely disease-causing in the heterozygous state. No additional information (i.e., penetrance, mutation rate, clinical variability) useful for genetic counseling purposes is currently available.

GeneReviews GeneReviews GeneReviews GeneReviews

Risk to Family Members — ALPS 0

Parents of a proband

- The parents of a child with ALPS 0 are obligate heterozygotes and therefore have one *FAS* mutant allele.
- Heterozygotes may present with ALPS-related symptoms or may be clinically asymptomatic.

Sibs of a proband

- At conception, each sib of a child with ALPS 0 has an overall 75% chance of having one or two *FAS* mutations; a 25% chance of inheriting two *FAS* mutations, which would most likely result in a severe ALPS 0 phenotype; a 50% chance of inheriting a single *FAS*, which could result in clinical manifestations of ALPS Ia or II; and a 25% chance of inheriting one normal *FAS* allele from each parent and having no clinical manifestations of ALPS.
- Once an at-risk sib is known to be unaffected with ALPS 0, the risk of his/her being a heterozygote for a mutation is 2/3.
- Heterozygotes may present with ALPS-related symptoms or may be clinically asymptomatic.

Offspring of a proband. Individuals with ALPS 0 typically die at an early age and thus are not likely to reproduce.

Other family members of a proband. If a parent of the proband has a *FAS* mutation, his/her sibs are at 50% risk of having the mutation.

Related Genetic Counseling Issues

Testing at-risk asymptomatic family members. Testing of at-risk asymptomatic family members for *FAS* or *CASP10* mutations is available once the disease-causing mutation(s) is (are) identified in the proband. Although the factors that determine the penetrance of clinical ALPS are not entirely understood, penetrance appears to be determined by the location and type of mutation. Results of testing of at-risk asymptomatic family members may be helpful in predicting phenotype.

Molecular genetic testing of asymptomatic individuals should only be undertaken following thorough genetic counseling and assessment of family-specific risks; medical specialists can assess individuals found to have a *FAS* or *CASP10* mutation for lifelong risk for and management of an ALPS-related disorder.

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA banking for a list of laboratories offering this service.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk for (a) *FAS* mutation(s) or a *CASP10* mutation is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis

GeneReviews GeneReviews GeneReviews GeneReviews

usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. The disease-causing allele(s) of an affected family member must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation(s) has/has been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Autoimmune Lymphoproliferative Syndrome

Gene Symbol	Chromosomal Locus	Protein Name
CASP10	2q33-q34	Caspase-10
FAS	10q24.1	Tumor necrosis factor receptor superfamily member 6
FASLG	1q23	Tumor necrosis factor ligand superfamily member 6

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Autoimmune Lymphoproliferative Syndrome

134637	TUMOR NECROSIS FACTOR RECEPTOR SUPERFAMILY, MEMBER 6; TNFRSF6
134638	TUMOR NECROSIS FACTOR LIGAND SUPERFAMILY, MEMBER 6; TNFSF6
601762	CASPASE 10, APOPTOSIS-RELATED CYSTEINE PROTEASE; CASP10
601859	AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME; ALPS
603909	AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME, TYPE IIA; ALPS2A

Table C. Genomic Databases for Autoimmune Lymphoproliferative Syndrome

Gene Symbol	Entrez Gene	HGMD
CASP10	843 (MIM No. 601762)	CASP10
FAS	355 (MIM No. 134637)	FAS
FASLG	356 (MIM No. 134638)	FASLG

For a description of the genomic databases listed, click here.

Molecular Genetic Pathogenesis

Autoimmune lymphoproliferative syndrome (ALPS) can be considered a prototypic disorder of defective lymphocyte homeostasis [Canale & Smith 1967, Sneller et al 1992, Fisher et al 1995, Rieux-Laucat et al 1995]. Although it appears that the full clinical spectrum of ALPS may depend on the interplay of several pathogenic factors, defective activation induced cell death (AICD), also known as apoptosis or cellular suicide, through the Fas/FasL pathway is central in the etiology of ALPS [Lenardo et al 1999]. The two existing mouse models of lymphoproliferative disease show features similar (though not identical) to features of ALPS [Watanabe-Fukunaga et al 1992, Takahashi et al 1994].

GeneReviews GeneReviews GeneReviews GeneReviews

As in the mouse models, the genetic background may determine penetrance of the clinical manifestations of ALPS, as well as the age of onset and/or severity of these manifestations. The genetic background may concern detrimental (loss-of-function) mutations affecting other tumor necrosis factor receptor superfamily member 6 (Fas) pathway components, as demonstrated by individuals with tumor necrosis factor ligand superfamily member 6 (FasL) and caspase-10 defects. Alternatively, genes relevant to Fas-independent apoptosis pathways may be affected. Finally, the genetic background may operate at the level of genes that encode regulators of other aspects of lymphocyte function and survival. The presence of clinical manifestations of ALPS at birth makes environmental influences less likely; the occurrence of murine ALPS in Fas-mutant mice kept in a germ-free environment is consistent with this assumption.

The discovery of individuals with ALPS with somatic mutations in *FAS* may offer new insights as the presence of mutations in some, but not all, lymphocyte subsets could allow dissection of the molecular mechanisms of ALPS in a manner that cannot be achieved in individuals with germline mutations in *FAS*.

FAS

Normal allelic variants: *FAS* consists of nine exons. Exons 1 and 2 encode a signal sequence that, upon trafficking of the Fas protein to the cell surface, is cleaved off. Exons 3, 4 and 5 encode three extracellular cysteine-rich domains (CRD). Exon 6 encodes the transmembrane domain (TM). The intracellular domains of Fas are encoded by exons 7-9, with exon 9 representing the death domain (DD) that interacts with the intracellular, apoptosis-inducing signal transduction pathway [Jackson et al 1999].

Genomic DNA of *FAS* spans about 25 kb. To date, at least eight alternatively spliced transcript variants encoding seven distinct normal allele variants have been observed. These have been documented by biochemical and functional testing in vivo and are highly unlikely to have pathologic effects on *FAS* expression.

Pathologic allelic variants: To date, about 60 pathologic variants have been identified. Mutations have been found throughout the entire coding region and exon/intron boundaries. These allele variants would lead to the absence of functional proteins or result in truncated proteins.

Most of the (reported) *FAS* mutations affect the intracellular domains of Fas, with approximately 60% of those located in the death domain. Mutations include missense mutations, nonsense mutations, splicing defects, small deletions/insertions, gross deletions and complex deletion/duplications.

Normal gene product: The *FAS* gene encodes a 16-amino acid signal sequence, followed by a mature protein of 319 amino acids with a single transmembrane domain and a molecular mass of approximately 36 kd.

The protein encoded by *FAS* is a member of the TNF-receptor superfamily and contains a death domain; it has been shown to play a central role in the physiologic regulation of programmed cell death. The interaction of Fas with its ligand allows the formation of a death-inducing signaling complex that includes Fas-associated death domain protein (FADD), caspase-8 and caspase-10. The autoproteolytic processing of the inductor caspases in the complex triggers a downstream effector caspase cascade, leading to apoptosis. Fas has also been shown to activate NF-kappaβ, MAPK3/ERK1, and MAPK8/JNK, leading to the transduction of proliferating signals in normal diploid fibroblast and T cells.

GeneReviews GeneReviews GeneReviews GeneReviews

Abnormal gene product: The fact that heterozygous mutations lead to defective Fas-mediated apoptosis can be explained by dominant negative interference by the abnormal Fas protein in many cases of ALPS Ia. Because Fas and FasL form homotrimers, the contribution of the mutant *FAS* allele versus the normal *FAS* allele to these trimers results in a normal Fas trimer (consisting of three normal proteins) in only one out of eight, and an abnormal Fas trimer (in which at least one of the proteins is mutated) in seven out of eight possible configurations, assuming equal amounts of mutant and wild type Fas protein [Fisher et al 1995, Jackson et al 1999]. Dominant-negative interference by abnormal Fas chains has been demonstrated for mutations affecting the death domain as well as for other intracellular mutations [Jackson et al 1999, Martin et al 1999].

Extracellular heterozygous mutations affecting the FasL-binding domain (CRD2 and CRD3) are also associated with dominant-negative interference because Fas proteins self-associate into trimers prior to FasL interaction. The result, as with intracellular mutations, is the assembly of faulty Fas trimers that dominantly interfere with Fas-mediated apoptosis in seven out of eight configurations [Siegel et al 2000]. For other extracellular heterozygous mutations, including mutations that affect the domain of the protein that regulates self-association into trimers, defective apoptosis can be explained by interference of truncated and/or soluble fragments of mutant Fas, or by haploinsufficiency, in which the total amount of Fas generated is below a threshold needed for physiologic induction of apoptosis [Roesler et al 2005].

In individuals with homozygous or compound heterozygous mutations, defective Fas-mediated apoptosis can be explained by loss-of-function [van der Burg et al 2000]. In contrast to those with heterozygous mutations, these individuals display absent or reduced surface expression of Fas on lymphocytes.

FASLG

Normal allelic variants: *FASLG* spans about 8 kb and comprises four exons. No normal allelic variants have been reported to date.

Pathologic allelic variants: To date, only three pathologic alleles have been reported. Wu et al (1996) described an 84-bp deletion resulting in a 28-amino acid in-frame deletion within exon 4 of *FASLG* in a person with lymphadenopathy. The second mutation, T(-844)C, is in the promoter region of *FASLG* [Zhang et al 2005]. The third mutation, a homozygous C-to-A substitution at cDNA nucleotide 740 (p.Ala247Glu), was found in an individual with ALPS who demonstrated both defective FasL-mediated apoptosis and defective Fas-dependent cytotoxic function [Del-Rey et al 2006].

Normal gene product: The *FASLG* cDNA codes a protein of 281 amino acids. Fas ligand (FasL) is a type II transmembrane protein that belongs to the tumor necrosis factor family. It is expressed in activated splenocytes and thymocytes, consistent with its involvement in T-cell mediated cytotoxicity and in several non-lymphoid tissues (e.g., testis, liver, lung, ovary, heart), where its function is unclear.

Abnormal gene product: A study of peripheral blood mononuclear cells from the individual with the 84-bp deletion revealed decreased FasL activity, decreased activation-induced cell death, and increased T-cell proliferation after activation [Wu et al 1996]. The individual with the homozygous missense mutation (p.Ala247Glu) showed decreased Fas-mediated cell death and Fas-dependent cytotoxicity [Del-Rey et al 2006]. Compared to controls, the T(-844)C mutation resulted in increased expression of FasL in many types of human cancers including lung cancer [Zhang et al 2005].

CASP10

GeneReviews GeneReviews GeneReviews GeneReviews

Normal allelic variants: *CASP10* contains 11 exons and spans about 48 kb [Hadano et al 2001]. There are two isoforms of *CASP10* transcripts. The $CASP10_L$ isoform encodes an insertion of 43 amino acids at the end of the prodomain, but its C terminus is the same as the short *CASP10* isoform [Vincenz & Dixit 1997]. The two isoforms are expressed equally. In addition, one common polymorphic variant of *CASP10* (1208A>G) was observed in 5% of normal controls and had no effect on apoptotic function of caspase-10 [Wang et al 1999].

Pathologic allelic variants: To date, seven *CASP10* mutations have been reported in eight individuals [Wang et al 1999, Park et al 2002, Shin et al 2002]. Two missense mutations, p.Leu242Phe and p.Ile406Leu, were identified in one and two kindreds, respectively, with ALPS IIa characterized by abnormal lymphocyte and dendritic cell homeostasis and immune regulatory defects [Wang et al 1999, Zhu et al 2006]. The other five somatic mutations in *CASP10* were suspected to be responsible for development of non-Hodgkin lymphoma (NHL) and gastric cancers [Park et al 2002, Shin et al 2002].

Note: The previously reported homozygous p.Val367Ile mutation by Wang et al (1999) has subsequently been deemed not be associated with ALPS II [Wang et al 1999, Zhu et al 2006].

Normal gene product: The physiologic function of caspase-10 is poorly understood. Gene transfection assays verified its function as a death-inducing caspase [Chaudhary et al 1997, Pan et al 1997, Schneider et al 1997, Vincenz & Dixit 1997]. Moreover, Wang et al (2001) showed that caspase-10 can function independently of caspase-8 in initiating Fas- and tumor necrosis factor-related apoptosis.

Abnormal gene product: The p.Leu242Phe and p.Val367Ile mutations result in decreased caspase activity and dominantly interfere with death receptor-induced apoptosis, particularly that stimulated by FasL and TRAIL. Wang et al (1999) and Shin et al (2002) expressed some *CASP10* mutants in 293 cells and found that apoptosis was suppressed, possibly contributing to the pathogenesis of some human non-Hodgkin lymphomas.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

National Institute of Allergy and Infectious Diseases
Autoimmune Lymphoproliferative Syndrome

American Autoimmune Related Diseases Association, Inc.
22100 Gratiot Ave
East Detroit MI 48021
Phone: 800-598-4668; 586-776-3900
Fax: 586-776-3903
Email: aarda@aol.com
www.aarda.org

Immune Deficiency Foundation
40 W Chesapeake Ave Suite 308
Towson MD 21204
Phone: 800-296-4433; 410-321-6647
Fax: 410-321-9165

Email: idf@primaryimmune.org
www.primaryimmune.org

Jeffrey Modell Foundation/National Primary Immunodeficiency Resource Center
747 Third Avenue 34A
New York NY 10017
Phone: 800-533-3844; 212-819-0200
Fax: 212-764-4180
Email: info@jmfworld.org
www.info4pi.org

Primary Immunodeficiency Diseases Registry (PIDR)
Phone: 800-296-4433
Primary Immunodeficiency Registry

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

Literature Cited

Benkerrou M, Le Deist F, de Villartay JP, Caillat-Zucman S, Rieux-Laucat F, Jabado N, Cavazzana-Calvo M, Fischer A. Correction of Fas (CD95) deficiency by haploidentical bone marrow transplantation. Eur J Immunol. 1997;27:2043–7. [PubMed: 9295043]

Bleesing JJ. Autoimmune lymphoproliferative syndrome (ALPS). Curr Pharm Des. 2003;9:265–78. [PubMed: 12570831]

Bleesing JJ. Sorting out the causes of ALPS. J Pediatr. 2005;147:571–4. [PubMed: 16291343]

Bleesing JJ, Brown MR, Dale JK, Straus SE, Lenardo MJ, Puck JM, Atkinson TP, Fleisher TA. TcR-alpha/beta(+) CD4(-)CD8(-) T cells in humans with the autoimmune lymphoproliferative syndrome express a novel CD45 isoform that is analogous to murine B220 and represents a marker of altered O-glycan biosynthesis. Clin Immunol. 2001;100:314–24. [PubMed: 11513545]

Bleesing JJ, Brown MR, Novicio C, Guarraia D, Dale JK, Straus SE, Fleisher TA. A composite picture of TcR alpha/beta(+) CD4(-)CD8(-) T Cells (alpha/beta-DNTCs) in humans with autoimmune lymphoproliferative syndrome. Clin Immunol. 2002;104:21–30. [PubMed: 12139944]

Bleesing JJ, Brown MR, Straus SE, Dale JK, Siegel RM, Johnson M, Lenardo MJ, Puck JM, Fleisher TA. Immunophenotypic profiles in families with autoimmune lymphoproliferative syndrome. Blood. 2001;98:2466–73. [PubMed: 11588044]

Canale VC, Smith CH. Chronic lymphadenopathy simulating malignant lymphoma. J Pediatr. 1967;70:891–9. [PubMed: 4165068]

Carter LB, Procter JL, Dale JK, Straus SE, Cantilena CC. Description of serologic features in autoimmune lymphoproliferative syndrome. Transfusion. 2000;40:943–8. [PubMed: 10960521]

Chaudhary PM, Eby M, Jasmin A, Bookwalter A, Murray J, Hood L. Death receptor 5, a new member of the TNFR family, and DR4 induce FADD-dependent apoptosis and activate the NF-kappaB pathway. Immunity. 1997;7:821–30. [PubMed: 9430227]

Chun HJ, Zheng L, Ahmad M, Wang J, Speirs CK, Siegel RM, Dale JK, Puck J, Davis J, Hall CG, Skoda-Smith S, Atkinson TP, Straus SE, Lenardo MJ. Pleiotropic defects in lymphocyte activation caused by caspase-8 mutations lead to human immunodeficiency. Nature. 2002;419:395–9. [PubMed: 12353035]

Clinical Immunology Society. CIS annual meeting. 1999

GeneReviews GeneReviews GeneReviews GeneReviews

GeneReviews GeneReviews GeneReviews GeneReviews

Del-Rey M, Ruiz-Contreras J, Bosque A, Calleja S, Gomez-Rial J, Roldan E, Morales P, Serrano A, Anel A, Paz-Artal E, Allende LM. A homozygous Fas ligand gene mutation in a patient causes a new type of autoimmune lymphoproliferative syndrome. Blood. 2006;108:1306–12. [PubMed: 16627752]

Dianzani U, Bragardo M, DiFranco D, Alliaudi C, Scagni P, Buonfiglio D, Redoglia V, Bonissoni S, Correra A, Dianzani I, Ramenghi U. Deficiency of the Fas apoptosis pathway without Fas gene mutations in pediatric patients with autoimmunity/lymphoproliferation. Blood. 1997;89:2871–9. [PubMed: 9108407]

Ferrari S, Giliani S, Insalaco A, Al-Ghonaium A, Soresina AR, Loubser M, Avanzini MA, Marconi M, Badolato R, Ugazio AG, Levy Y, Catalan N, Durandy A, Tbakhi A, Notarangelo LD, Plebani A. Mutations of CD40 gene cause an autosomal recessive form of immunodeficiency with hyper IgM. Proc Natl Acad Sci U S A. 2001;98:12614–9. [PubMed: 11675497]

Fisher GH, Rosenberg FJ, Straus SE, Dale JK, Middleton LA, Lin AY, Strober W, Lenardo MJ, Puck JM. Dominant interfering Fas gene mutations impair apoptosis in a human autoimmune lymphoproliferative syndrome. Cell. 1995;81:935–46. [PubMed: 7540117]

Hadano S, Yanagisawa Y, Skaug J, Fichter K, Nasir J, Martindale D, Koop BF, Scherer SW, Nicholson DW, Rouleau GA, Ikeda J, Hayden MR. Cloning and characterization of three novel genes, ALS2CR1, ALS2CR2, and ALS2CR3, in the juvenile amyotrophic lateral sclerosis (ALS2) critical region at chromosome 2q33-q34: candidate genes for ALS2. Genomics. 2001;71:200–13. [PubMed: 11161814]

Holzelova E, Vonarbourg C, Stolzenberg MC, Arkwright PD, Selz F, Prieur AM, Blanche S, Bartunkova J, Vilmer E, Fischer A, Le Deist F, Rieux-Laucat F. Autoimmune lymphoproliferative syndrome with somatic Fas mutations. N Engl J Med. 2004;351:1409–18. [PubMed: 15459302]

Houston A, O'Connell J. The Fas signalling pathway and its role in the pathogenesis of cancer. Curr Opin Pharmacol. 2004;4:321–6. [PubMed: 15251123]

Hundt M, Posovszky C, Schmidt RE. A new disorder of lymphocyte apoptosis: combination of autoimmunity, infectious lymphadenopathy, double negative T cells, and impaired activation-induced cell death. Immunobiology. 2002;206:514–8. [PubMed: 12607726]

Imai K, Catalan N, Plebani A, Marodi L, Sanal O, Kumaki S, Nagendran V, Wood P, Glastre C, Sarrot-Reynauld F, Hermine O, Forveille M, Revy P, Fischer A, Durandy A. Hyper-IgM syndrome type 4 with a B lymphocyte-intrinsic selective deficiency in Ig class-switch recombination. J Clin Invest. 2003;112:136–42. [PubMed: 12840068]

Infante AJ, Britton HA, DeNapoli T, Middelton LA, Lenardo MJ, Jackson CE, Wang J, Fleisher T, Straus SE, Puck JM. The clinical spectrum in a large kindred with autoimmune lymphoproliferative syndrome caused by a Fas mutation that impairs lymphocyte apoptosis. J Pediatr. 1998;133:629–33. [PubMed: 9821419]

Jackson CE, Fischer RE, Hsu AP, Anderson SM, Choi Y, Wang J, Dale JK, Fleisher TA, Middelton LA, Sneller MC, Lenardo MJ, Straus SE, Puck JM. Autoimmune lymphoproliferative syndrome with defective Fas: genotype influences penetrance. Am J Hum Genet. 1999;64:1002–14. [PubMed: 10090885]

Kanegane H, Vilela MM, Wang Y, Futatani T, Matsukura H, Miyawaki T. Autoimmune lymphoproliferative syndrome presenting with glomerulonephritis. Pediatr Nephrol. 2003;18:454–6. [PubMed: 12736807]

Kasahara Y, Wada T, Niida Y, Yachie A, Seki H, Ishida Y, Sakai T, Koizumi F, Koizumi S, Miyawaki T, Taniguchi N. Novel Fas (CD95/APO-1) mutations in infants with a lymphoproliferative disorder. Int Immunol. 1998;10:195–202. [PubMed: 9533447]

Le Deist F, Emile JF, Rieux-Laucat F, Benkerrou M, Roberts I, Brousse N, Fischer A. Clinical, immunological, and pathological consequences of Fas-deficient conditions. Lancet. 1996;348:719–23. [PubMed: 8806292]

Le Deist F, Fischer A. Autoimmune lymphoproliferative syndrome. Created on-line for Orphanet: http://orphanet.infobiogen.fr/data/patho/GB/uk-ALPS.html. 2001

Lee WI, Torgerson TR, Schumacher MJ, Yel L, Zhu Q, Ochs HD. Molecular analysis of a large cohort of patients with the hyper immunoglobulin M (IgM) syndrome. Blood. 2005;105:1881–90. [PubMed: 15358621]

GeneReviews GeneReviews GeneReviews GeneReviews

Lenardo M, Chan KM, Hornung F, McFarland H, Siegel R, Wang J, Zheng L. Mature T lymphocyte apoptosis--immune regulation in a dynamic and unpredictable antigenic environment. Annu Rev Immunol. 1999;17:221–53. [PubMed: 10358758]

Lim MS, Straus SE, Dale JK, Fleisher TA, Stetler-Stevenson M, Strober W, Sneller MC, Puck JM, Lenardo MJ, Elenitoba-Johnson KS, Lin AY, Raffeld M, Jaffe ES. Pathological findings in human autoimmune lymphoproliferative syndrome. Am J Pathol. 1998;153:1541–50. [PubMed: 9811346]

Lopatin U, Yao X, Williams RK, Bleesing JJ, Dale JK, Wong D, Teruya-Feldstein J, Fritz S, Morrow MR, Fuss I, Sneller MC, Raffeld M, Fleisher TA, Puck JM, Strober W, Jaffe ES, Straus SE. Increases in circulating and lymphoid tissue interleukin-10 in autoimmune lymphoproliferative syndrome are associated with disease expression. Blood. 2001;97:3161–70. [PubMed: 11342444]

Maric I, Pittaluga S, Dale JK, Niemela JE, Delsol G, Diment J, Rosai J, Raffeld M, Puck JM, Straus SE, Jaffe ES. Histologic features of sinus histiocytosis with massive lymphadenopathy in patients with autoimmune lymphoproliferative syndrome. Am J Surg Pathol. 2005;29:903–11. [PubMed: 15958855]

Martin DA, Zheng L, Siegel RM, Huang B, Fisher GH, Wang J, Jackson CE, Puck JM, Dale J, Straus SE, Peter ME, Krammer PH, Fesik S, Lenardo MJ. Defective CD95/APO-1/Fas signal complex formation in the human autoimmune lymphoproliferative syndrome, type Ia. Proc Natl Acad Sci U S A. 1999;96:4552–7. [PubMed: 10200300]

Muschen M, Rajewsky K, Kronke M, Kuppers R. The origin of CD95-gene mutations in B-cell lymphoma. Trends Immunol. 2002;23:75–80. [PubMed: 11929130]

Pan G, Ni J, Wei YF, Yu G, Gentz R, Dixit VM. An antagonist decoy receptor and a death domain-containing receptor for TRAIL. Science. 1997;277:815–8. [PubMed: 9242610]

Park WS, Lee JH, Shin MS, Park JY, Kim HS, Lee JH, Kim YS, Lee SN, Xiao W, Park CH, Lee SH, Yoo NJ, Lee JY. Inactivating mutations of the caspase-10 gene in gastric cancer. Oncogene. 2002;21:2919–25. [PubMed: 11973654]

Pensati L, Costanzo A, Ianni A, Accapezzato D, Iorio R, Natoli G, Nisini R, Almerighi C, Balsano C, Vajro P, Vegnente A, Levrero M. Fas/Apo1 mutations and autoimmune lymphoproliferative syndrome in a patient with type 2 autoimmune hepatitis. Gastroenterology. 1997;113:1384–9. [PubMed: 9322534]

Peter ME, Legembre P, Barnhart BC. Does CD95 have tumor promoting activities? Biochim Biophys Acta. 2005;1755:25–36. [PubMed: 15907590]

Piqueras B, Lavenu-Bombled C, Galicier L, Bergeron-van der Cruyssen F, Mouthon L, Chevret S, Debre P, Schmitt C, Oksenhendler E. Common variable immunodeficiency patient classification based on impaired B cell memory differentiation correlates with clinical aspects. J Clin Immunol. 2003;23:385–400. [PubMed: 14601647]

Poppema S, Maggio E, van den Berg A. Development of lymphoma in Autoimmune Lymphoproliferative Syndrome (ALPS) and its relationship to Fas gene mutations. Leuk Lymphoma. 2004;45:423–31. [PubMed: 15160902]

Ramenghi U, Bonissoni S, Migliaretti G, DeFranco S, Bottarel F, Gambaruto C, DiFranco D, Priori R, Conti F, Dianzani I, Valesini G, Merletti F, Dianzani U. Deficiency of the Fas apoptosis pathway without Fas gene mutations is a familial trait predisposing to development of autoimmune diseases and cancer. Blood. 2000;95:3176–82. [PubMed: 10807785]

Rao VK, Carrasquillo JA, Dale JK, Bacharach SL, Whatley M, Dugan F, Tretler J, Fleisher T, Puck JM, Wilson W, Jaffe ES, Avila N, Chen CC, Straus SE. Fluorodeoxyglucose positron emission tomography (FDG-PET) for monitoring lymphadenopathy in the autoimmune lymphoproliferative syndrome (ALPS). Am J Hematol. 2006;81:81–5. [PubMed: 16432855]

Rao VK, Dugan F, Dale JK, Davis J, Tretler J, Hurley JK, Fleisher T, Puck J, Straus SE. Use of mycophenolate mofetil for chronic, refractory immune cytopenias in children with autoimmune lymphoproliferative syndrome. Br J Haematol. 2005;129:534–8. [PubMed: 15877736]

Revy P, Muto T, Levy Y, Geissmann F, Plebani A, Sanal O, Catalan N, Forveille M, Dufourcq-Labelouse R, Gennery A, Tezcan I, Ersoy F, Kayserili H, Ugazio AG, Brousse N, Muramatsu M, Notarangelo LD, Kinoshita K, Honjo T, Fischer A, Durandy A. Activation-induced cytidine deaminase (AID) deficiency causes the autosomal recessive form of the Hyper-IgM syndrome (HIGM2). Cell. 2000;102:565–75. [PubMed: 11007475]

GeneReviews GeneReviews GeneReviews GeneReviews

Rieux-Laucat F, Blachere S, Danielan S, De Villartay JP, Oleastro M, Solary E, Bader-Meunier B, Arkwright P, Pondare C, Bernaudin F, Chapel H, Nielsen S, Berrah M, Fischer A, Le Deist F. Lymphoproliferative syndrome with autoimmunity: A possible genetic basis for dominant expression of the clinical manifestations. Blood. 1999;94:2575–82. [PubMed: 10515860]

Rieux-Laucat F, Fischer A, Deist FL. Cell-death signaling and human disease. Curr Opin Immunol. 2003;15:325–31. [PubMed: 12787759]

Rieux-Laucat F, Le Deist F, Hivroz C, Roberts IA, Debatin KM, Fischer A, de Villartay JP. Mutations in Fas associated with human lymphoproliferative syndrome and autoimmunity. Science. 1995;268:1347–9. [PubMed: 7539157]

Roesler J, Izquierdo JM, Ryser M, Rosen-Wolff A, Gahr M, Valcarcel J, Lenardo MJ, Zheng L. Haploinsufficiency, rather than the effect of an excessive production of soluble CD95 (CD95{Delta} TM), is the basis for ALPS Ia in a family with duplicated 3' splice site AG in CD95 intron 5 on one allele. Blood. 2005;106:1652–9. [PubMed: 15870181]

Rossler J, Enders A, Lahr G, Heitger A, Winkler K, Fuchs H, Kopp M, Niemeyer C, Ehl S. Identical phenotype in patients with somatic and germline CD95 mutations requires a new diagnostic approach to autoimmune lymphoproliferative syndrome. J Pediatr. 2005;147:691–4. [PubMed: 16291365]

Schneider P, Thome M, Burns K, Bodmer JL, Hofmann K, Kataoka T, Holler N, Tschopp J. TRAIL receptors 1 (DR4) and 2 (DR5) signal FADD-dependent apoptosis and activate NF-kappaB. Immunity. 1997;7:831–6. [PubMed: 9430228]

Shin MS, Kim HS, Kang CS, Park WS, Kim SY, Lee SN, Lee JH, Park JY, Jang JJ, Kim CW, Kim SH, Lee JY, Yoo NJ, Lee SH. Inactivating mutations of CASP10 gene in non-Hodgkin lymphomas. Blood. 2002;99:4094–9. [PubMed: 12010812]

Siegel RM, Frederiksen JK, Zacharias DA, Chan FK, Johnson M, Lynch D, Tsien RY, Lenardo MJ. Fas preassociation required for apoptosis signaling and dominant inhibition by pathogenic mutations. Science. 2000;288:2354–7. [PubMed: 10875918]

Sleight BJ, Prasad VS, DeLaat C, Steele P, Ballard E, Arceci RJ, Sidman CL. Correction of autoimmune lymphoproliferative syndrome by bone marrow transplantation. Bone Marrow Transplant. 1998;22:375–80. [PubMed: 9722073]

Sneller MC, Straus SE, Jaffe ES, Jaffe JS, Fleisher TA, Stetler-Stevenson M, Strober W. A novel lymphoproliferative/autoimmune syndrome resembling murine lpr/gld disease. J Clin Invest. 1992;90:334–41. [PubMed: 1386609]

Sneller MC, Wang J, Dale JK, Strober W, Middelton LA, Choi Y, Fleisher TA, Lim MS, Jaffe ES, Puck JM, Lenardo MJ, Straus SE. Clincal, immunologic, and genetic features of an autoimmune lymphoproliferative syndrome associated with abnormal lymphocyte apoptosis. Blood. 1997;89:1341–8. [PubMed: 9028957]

Straus SE, Jaffe ES, Puck JM, Dale JK, Elkon KB, Rosen-Wolff A, Peters AM, Sneller MC, Hallahan CW, Wang J, Fischer RE, Jackson CM, Lin AY, Baumler C, Siegert E, Marx A, Vaishnaw AK, Grodzicky T, Fleisher TA, Lenardo MJ. The development of lymphomas in families with autoimmune lymphoproliferative syndrome with germline Fas mutations and defective lymphocyte apoptosis. Blood. 2001;98:194–200. [PubMed: 11418480]

Takahashi T, Tanaka M, Brannan CI, Jenkins NA, Copeland NG, Suda T, Nagata S. Generalized lymphoproliferative disease in mice, caused by a point mutation in the Fas ligand. Cell. 1994;76:969–76. [PubMed: 7511063]

Vaishnaw AK, Toubi E, Ohsako S, Drappa J, Buys S, Estrada J, Sitarz A, Zemel L, Chu JL, Elkon KB. The spectrum of apoptotic defects and clinical manifestations, including systemic lupus erythematosus, in humans with CD95 (Fas/APO-1) mutations. Arthritis Rheum. 1999;42:1833–42. [PubMed: 10513797]

van der Burg M, de Groot R, Comans-Bitter WM, den Hollander JC, Hooijkaas H, Neijens HJ, Berger RM, Oranje AP, Langerak AW, van Dongen JJ. Autoimmune lymphoproliferative syndrome (ALPS) in a child from consanguineous parents: a dominant or recessive disease? Pediatr Res. 2000;47:336–43. [PubMed: 10709732]

van der Werff ten Bosch J, Delabie J, Bohler T, Verschuere J, Thielemans K. Revision of the diagnosis of T-zone lymphoma in the father of a patient with autoimmune lymphoproliferative syndrome type II. Br J Haematol. 1999;106:1045–8. [PubMed: 10520011]

van der Werff ten Bosch J, Otten J, Thielemans K. Autoimmune lymphoproliferative syndrome type III, an indefinite disorder. Leuk Lymphoma. 2001;41:501–11. [PubMed: 11378568]

van der Werff Ten Bosch J, Schotte P, Ferster A, Azzi N, Boehler T, Laurey G, Arola M, Demanet C, Beyaert R, Thielemans K, Otten J. Reversion of autoimmune lymphoproliferative syndrome with an antimalarial drug: preliminary results of a clinical cohort study and molecular observations. Br J Haematol. 2002;117:176–88. [PubMed: 11918552]

Vincenz C, Dixit VM. Fas-associated death domain protein interleukin-1beta-converting enzyme 2 (FLICE2), an ICE/Ced-3 homologue, is proximally involved in CD95- and p55-mediated death signaling. J Biol Chem. 1997;272:6578–83. [PubMed: 9045686]

Wang J, Chun HJ, Wong W, Spencer DM, Lenardo MJ. Caspase-10 is an initiator caspase in death receptor signaling. Proc Natl Acad Sci U S A. 2001;98:13884–8. [PubMed: 11717445]

Wang J, Zheng L, Lobito A, Chan FK, Dale J, Sneller M, Yao X, Puck JM, Straus SE, Lenardo MJ. Inherited human Caspase 10 mutations underlie defective lymphocyte and dendritic cell apoptosis in autoimmune lymphoproliferative syndrome type II. Cell. 1999;98:47–58. [PubMed: 10412980]

Warnatz K, Denz A, Drager R, Braun M, Groth C, Wolff-Vorbeck G, Eibel H, Schlesier M, Peter HH. Severe deficiency of switched memory B cells (CD27(+)IgM(-)IgD(-)) in subgroups of patients with common variable immunodeficiency: a new approach to classify a heterogeneous disease. Blood. 2002;99:1544–51. [PubMed: 11861266]

Watanabe-Fukunaga R, Brannan CI, Copeland NG, Jenkins NA, Nagata S. Lymphoproliferation disorder in mice explained by defects in Fas antigen that mediates apoptosis. Nature. 1992;356:314–7. [PubMed: 1372394]

Winkelstein JA, Marino MC, Ochs H, Fuleihan R, Scholl PR, Geha R, Stiehm ER, Conley ME. The X-linked hyper-IgM syndrome: clinical and immunologic features of 79 patients. Medicine (Baltimore). 2003;82:373–84. [PubMed: 14663287]

Wu J, Wilson J, He J, Xiang L, Schur PH, Mountz JD. Fas ligand mutation in a patient with systemic lupus erythematosus and lymphoproliferative disease. J Clin Invest. 1996;98:1107–13. [PubMed: 8787672]

Zhang X, Miao X, Sun T, Tan W, Qu S, Xiong P, Zhou Y, Lin D. Functional polymorphisms in cell death pathway genes FAS and FASL contribute to risk of lung cancer. J Med Genet. 2005;42:479–84. [PubMed: 15937082]

Zhu S, Hsu AP, Vacek MM, Zheng L, Schaffer AA, Dale JK, Davis J, Fischer RE, Straus SE, Boruchov D, Saulsbury FT, Lenardo MJ, Puck JM. Genetic alterations in caspase-10 may be causative or protective in autoimmune lymphoproliferative syndrome. Hum Genet. 2006;119:284–94. [PubMed: 16446975]

Chapter Notes

Revision History

- 9 July 2007 (cd) Revision: sequence analysis and prenatal diagnosis available clinically for *CASP10*
- 14 September 2006 (me) Review posted to live Web site
- 2 December 2005 (jj) Original submission