Autoimmune lymphoproliferative syndrome, type Ia

GENERAL INFORMATION

Description:

Defects in TNFSF6 are a cause of autoimmune lymphoproliferative syndrome (ALPS). There are several types of ALPS: type I ALPS (a and b) is associated with Fas and Fas ligand defects and type II ALPS is caused by defects in other apoptosis genes (CASP10). ALPS can be caused by autosomal recessive (ALPS 0) or by autosomal dominant inheritance of Fas mutations (ALPS Ia) and Fas ligand (ALPS Ib).

Alternative names:

- ALPS1A, ALPS Ia, ALPS type Ia
- Lymphoproliferative syndrome with autoimmunity
- Canale-Smith syndrome (CSS)
- Apoptosis mediator APO-1/Fas defects
- defective CD95

Classification:

- Defects in lymphocyte apoptosis
  - Autoimmune lymphoproliferative syndrome

Inheritance:

Autosomal dominant/Autosomal recessive (rare severe cases)

OMIM:

- #601859 Autoimmune lymphoproliferative syndrome
- #601859 Autoimmune lymphoproliferative syndrome, type II
- *134637 Tumor necrosis factor receptor superfamily, member 6; TNFRSF6
- *601762 Caspase 10, apoptosis-related cysteine protease; CASP10

Cross references:

Phenotype related immunodeficiencies:

- IDR factfile for Apopotosis mediator APO-1/ Fas defect

Incidence:

Incidence unknown.

CLINICAL INFORMATION

Description:

Patients present nonmalignant lymphadenopathy and splenomegaly, autoimmune phenomena and in some cases even malignancy. Autoimmune manifestations include hemolytic anemia and thrombocytopenia. In rare cases, there are systemic manifestations like vasculitis, arthritis and glomerulonephritis. ALPS 0 patients have the severe form of disease, characterized by neonatal or prenatal onset with marked hyperlymphocytosis. Most cases of ALPS Ia are with delayed onset.

Diagnosis:

Diagnostic laboratories:

Clinical:

- Lymphoproliferative disorders, eMedicine
- Autoimmune lymphoproliferative syndrome, ORPHANET

Genetic:

- TNFRSF6, IDdiagnostics

Therapeutic options:

- In patients with massive lymphoproliferation, chemotherapy with prednisone, cyclophosphamide and vincristine has been unsuccessful. Allogenic bone-marrow transplantation is the only cure for complete Fas deficiency. In case of hypersplenism, splenectomy is often performed. Severe autoimmune manifestation can be treated with steroids and cyclophosphamide.
- Lymphoproliferative disorders, eMedicine

Research programs, clinical trials:

- European Initiative for Primary Immunodeficiencies
- APLSbase, Jennifer Puck, National Human Genome Research Institute
- Pyrimethamine to Treat Autoimmune Lymphoproliferative Syndrome, ClinicalTrial.gov
- Study of Autoimmune Lymphoproliferative Syndrome (ALPS), ClinicalTrial.gov
- Genetic Analysis of Immune Disorders, ClinicalTrial.gov

GENE INFORMATION

Names:

HUGO name: TNFRSF6
Alias(es): APO-1, APT1, CD95, FAS, FAS1, apoptosis (APO-1) antigen 1, tumor necrosis factor receptor superfamily, member 6, Tumor necrosis factor receptor superfamily member 6 precursor, FASL receptor, Apoptosis-mediating surface antigen FAS, Apo-1 antigen

Localization:

Reference sequences:

DNA: Z96050 (EMBL) , **cDNA:** X89102 (EMBL) , **Protein:** AAC16237 (Entrez) Other Sequences

Chromosomal Location:

10q23-q24.1

Maps:

TNFRSF6 (Map View)

Variations / Mutations:

- ALPSbase; ALPSbase at NHGRI
- TNFSF6base: Mutation registry for Autoimmune lymphoproliferative syndrome, type 1B (ALPS1B); IDbases

Other gene-based resources:

Ensembl: OTTHUMG00000018701, GENATLAS: TNFRSF6, GeneCard: TNFRSF6, Entrez Gene: 355, euGenes: 355, GDB: 132671

PROTEIN INFORMATION

Description:

Protein function:

Receptor for TNFSF6. The adaptor molecule FADD recruits Caspase-8 to the activated receptor. The resulting death-inducing signaling complex performs Caspase-8 proteolytic activation which initiates the subsequent cascade of caspases (aspartate-specific cysteine proteases) mediating apoptosis. Fas-mediated apoptosis may have a role in the induction of peripheral tolerance, in the antigen-stimulated suicide of mature T-cells, or both. The secreted isoforms 2 to 6 block apoptosis (in vitro).

Subcellular location:

Type I membrane protein (isoform 1); secreted (isoforms 2 to 6).

Protein function:

6 isoforms: 1, 2/del2/d, 3/del3/e, 4/b, 5/c and 6/tmdel/a are produced by alternative splicing.

Structures (PDB):

1DDF Fas Death Domain, NMR, Minimized Average Structure

Domains:

Extracellular domain: 17-173

Cytoplasmic domain: 191-335

Death domain: 230-314

Other features:

Signal peptide: 1-16

Tumor necrosis factor receptor superfamily member 6: 17-335

Disulfide bonds: 59-73, 63-82, 85-101, 104-119, 107-127, 129-143, 146-157, 149-165

Other related resourses:

PIR: A40036, InterPro: IPR000488; Death, InterPro: IPR001368; TNFR_c6, Pfam: PF00020; TNFR_c6, Pfam: PF00531; death, SMART: SM00005; DEATH, SMART: SM00208; TNFR, PROSITE: PS00652; TNFR_NGFR_1, PROSITE: PS50050; TNFR_NGFR_2, PROSITE: PS50017; DEATH_DOMAIN

Expression pattern for human:

Tissue	Exp. (%)	Clones
lung, cell line	17.87	1:876
blood, white cells	17.20	1:910
eye, retina	17.11	11:10065
fibrosarcoma	8.38	1:1867
leukocyte	5.23	3:8982
leukopheresis	3.43	1:4557
human skeletal muscle	2.91	2:10746
human lung epithelial cell lines untreated lps 6hr to lps	2.49	1:6278
kidney, pooled	2.11	1:7404
CNS, multiple sclerosis lesions	2.00	1:7823

Animal models:

Mouse:

MGD: ; Tnfrsf6

Fly:

euGenes: ; CG10465

OTHER RESOURCES

Societies:

General:

- International Patient Organization for Primary Immunodeficiencies
- Immune Deficiency Foundation
- March of Dimes Birth Defects Foundation
- NIH/National Institute of Allergy and Infectious Diseases
- European Society for Immunodeficiencies

Other information sources:

- Autoimmune lymphoproliferative syndromes: genetic defects of apoptosis pathways