Familial haemophagocytic lymphohistiocytosis type 2

GENERAL INFORMATION

Description:

Defects in PRF1 are a cause of familial hemophagocytic lymphohistiocytosis type 2, a rare and lethal autosomal recessive disorder of early childhood characterized by excessive immune activation. Patients have a nonmalignant accumulation and multivisceral infiltration of activated T lymphocytes and histiocytes (macrophages).

Alternative names:

- FHL2
- HPLH2, HLH
- Familial erythrophagocytic lymphohistiocytosis 2
- Familial histiocytic reticulosis 2
- Hemophagocytic lymphohistiocytosis

Classification:

- Defects of phagocyte function
  - Familial haemophagocytic lymphohistiocytosis
    - Familial haemophagocytic lymphohistiocytosis type 2

Inheritance:

Autosomal recessive

OMIM:

- #267700 Reticulosis, familial histiocytic
- *170280 Perforin 1; PRF1

Cross references:

Phenotype related immunodeficiencies:

- Familial haemophagocytic lymphohistiocytosis type 1
- Familial haemophagocytic lymphohistiocytosis type 3

Incidence:

1:50,000 births

CLINICAL INFORMATION

Description:

The symptoms may vary widely. The most common findings are unexplained high fever, irritability, general pain, oedema, hepatosplenomegaly, cytopenia (thrombocytopenia, anemia). This macrophage activation syndrome occurs after a healthy period of several months after the birth to more rarely several years, and is usually triggered by viral infection. Other early symptoms include skin rash, lymph node enlargement, and neurologic abnormalities (bulging fontanel, neck stiffness, hypotonia, hypertonia, convulsions, cranial nerve palsy, ataxia, hemiplagia/tetraplagia, blindness and unconsciousness). Median survival is of 2 months.

Diagnosis:

Diagnostic laboratories:

Clinical:

- Familial hemophagocytic lymphohistiocytosis (FHL), ORPHANET

Genetic:

- IDdiagnostics, PRF1

Therapeutic options:

- Treatment with epipodophyllotoxins, immunosuppressive agents, corticotherapy and anti thymocyte immunoglobulin (ATG) control macrophage activation and precede bone marrow transplantation. Intrathecal injections of methotrexate prevent or cure neuromeningeal disorders.
- Lymphohistiocytosis, eMedicine
- The Role of Blood and Marrow Transplantation as Treatment for Hemophagocytic Lymphohistiocytosis (HLH)
- Current Treatment Protocols, Histiocyte Society

Research programs, clinical trials:

- European Initiative for Primary Immunodeficiencies

GENE INFORMATION

Names:

HUGO name: PRF1
Alias(es): HPLH2, P1, PFP, PERFORIN 1 PRECURSOR, perforin 1 (pore forming protein), perforin 1 (preforming protein), Perforin 1 precursor, Lymphocyte pore forming protein, Cytolysin

Localization:

Reference sequences:

DNA: M31951 (EMBL) , **cDNA:** M28393 (EMBL) , **Protein:** P14222 (SWISSPROT) Other Sequences

Chromosomal Location:

10q22

Maps:

PRF1 (Map View)

Variations / Mutations:

- PRF1base; Mutation registry for familiar haemophagocytic lymphohistiocytosis, type II (FHL2)

Other gene-based resources:

Ensembl: ENSG00000180644, GENATLAS: PRF1, GeneCard: PRF1, UniGene: 2200, Entrez Gene: 5551, euGenes: 5551, GDB: 118853

PROTEIN INFORMATION

Description:

Protein function:

In the presence of calcium, perforin polymerizes into transmembrane tubules and is capable of lysing non-specifically a variety of target cells.

Subcellular location:

Cytoplasmic granules of cytolytic T-lymphocytes.

Induction:

Repressed by contact with target cells.

Domains:

Egf-like domain: 373-408

C2 domain domain: 416-498

Other features:

Signal peptide : 1-21

Perforin 1: 22-555

Disulfide bond : 257-279

N-linked (glcnac...) glycosylation sites: 205, 549

Other related resourses:

PIR: A37181, InterPro: IPR000008; C2, InterPro: IPR006209; EGF_like, InterPro: IPR001862; MAC_perforin, Pfam: PF00168; C2, Pfam: PF01823; MACPF, SMART: SM00239; C2, SMART: SM00457; MACPF, PROSITE: PS00279; MAC_PERFORIN, PROSITE: PS00022; EGF_1, PROSITE: PS01186; EGF_2, PROSITE: PS50004; C2_DOMAIN_2

Expression pattern for human:

Tissue	Exp. (%)	Clones
natural killer cells, cell line	50.11	12:5412
lymphocyte	11.60	1:1949
leukocyte	7.61	3:8915
hepatocellular carcinoma, cell line	6.89	4:13130
lung focal fibrosis	5.85	1:3864
leukopheresis	5.81	2:7777
rpe and choroid	4.97	1:4545
human skeletal muscle	2.12	1:10654
poorly differentiated adenocarcinoma with signet ring cell features	1.26	1:17880
2 pooled tumors (clear cell type)	1.10	1:20589

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

Disease specific:

- Histiocyte Society
- Histiocytosis Association of America
- Histiocyte Society of Germany
- The Histiocytosis Association of Canada
- Artemis Society, Greek histiocytosis support group
- Associazione Italiana Ricerca Istiocitos (AIRI)