Familial hemophagocytic lymphohistiocytosis 3

GENERAL INFORMATION

Description:

Defects in UNC13d are a cause of familial hemophagocytic lymphohistiocytosis type 3 (FHL3). FHL3 is phenotypically homogeneous and indistinguishable from HPLH2/FHL2. Patients have a nonmalignant accumulation and multivisceral infiltration of activated T lymphocytes and histiocytes (macrophages). Familial hemophagocytic lymphohistiocytosis is a genetically heterogeneous condition characterized by defective cytotoxicity.

Alternative names:

- HPLH3
- FHL3
- Familial erythrophagocytic lymphohistiocytosis type 3
- Familial histiocytic reticulosis 3
- Hemophagocytic lymphohistiocytosis
- Hemophagocytic lymphohistiocytosis/UNC13D

Classification:

- Defects of phagocyte function
  - Familial haemophagocytic lymphohistiocytosis, FHL3

Inheritance:

Autosomal recessive

OMIM:

- #608898 Hemophagocytic lymphohistiocytosis, familial, 3; HPLH3
- *608897 UNC13D

Cross references:

Phenotype related immunodeficiencies:

- IDR factfile for Familial haemophagocytic lymphohistiocytosis type 1
- IDR factfile for Familial haemophagocytic lymphohistiocytosis type 2

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:

- GeneTests
- IDdiagnostics, UNC13D

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)

Research programs, clinical trials:

- European Initiative for Primary Immunodeficiencies 2001-2004, coord.Edvard Smith.
- Current Treatment Protocols, Histiocyte Society

GENE INFORMATION

Names:

HUGO name: UNC13D
Alias(es): FLJ00067, Munc13-4 , unc-13 homolog D , FLJ00067 protein (Fragment)

Localization:

Reference sequences:

DNA: AJ578444 (EMBL) AK024474 (EMBL) BC067084 (EMBL) , **cDNA:** X58957 (EMBL) , **Protein:** Q9H7K5 (SWISSPROT)

Chromosomal Location:

17q25.3

Maps:

UNC13D (Map View)

Markers:

D16S325, D1S1423, D11S3114, D11S3316, PMC156606P1

Variations / Mutations:

- UNC13Dbase; Mutation registry for Familial hemophagocytic lymphohistiocytosis 3

Other gene-based resources:

Ensembl: ENSG00000092929, GENATLAS: UNC13D, GeneCard: UNC13D, UniGene: 41045, Entrez Gene: 201294, euGenes: 201294, HomoloGene: 26714

PROTEIN INFORMATION

Description:

Protein function:

Seems to play a role in vesicle maturation during exocytosis. Is involved in regulation of cytolytic granules secretion.

Subcellular location:

Cytoplasmic and membrane-associated. Colocalizes with cytotoxic granules at the plasma membrane.

Tissue specificity:

Expressed at high levels in spleen, thymus and leukocytes. Also expressed in lung and placenta, and at very low levels in brain, heart, skeletal muscle and kidney.

Similarity:

Belongs to the UNC-13 family.

Domains:

C2 domain 1 domain: 98-221

C2 domain 2 domain: 912-1019

Other features:

Other related resourses:

InterPro: IPR010439; DUF1041, Pfam: PF06292; DUF1041, PROSITE: PS50004; C2_DOMAIN_2

Expression pattern for human:

Tissue	Exp. (%)	Clones
larynx epithelium	94.05	1:24
thymus	1.47	2:3074
blood	0.78	16:46017
stomach	0.69	22:71656
spleen	0.55	3:12346
pancreas	0.53	16:67592
eye	0.28	16:128990
cervix	0.28	4:32826
lymph_node	0.22	11:113869
mixed	0.17	23:314320

Animal models:

Mouse:

MGD: ; Unc13d

OTHER RESOURCES

Societies:

General:

- International Patient Organization for Primary Immunodeficiencies
- Immune Deficiency Foundation
- 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)