X-linked hyper-IgM syndrome (CD40L deficiency)

GENERAL INFORMATION

Description:

X-linked immunodeficiency with hyperimmunoglobulin M (XHIM) is caused by the absence of CD40 ligand (TNFSF5 or CD154), which is normally expressed on activated CD4+ T cells. Absence of TNFS5 interrupts B cells differentiation by somatic hypermutation and heavy-chain switch from IgM to other immunoglobulin isotypes. Somatic hypermutation and immunoglobulin class switching are required to make high-affinity functional antibodies.

Alternative names:

- XHIM
- Hyper-IgM immunodeficiency, X-linked
- Hyper-IgM syndrome 1
- Hyper-IgM syndrome; HIGM; IHIS
- Immunodeficiency 3 Dysgammaglobulinemia, type 1
- Tumor necrosis factor superfamily member 5 (CD40L, CD154)

Classification:

- Combined B and T cell immunodeficiencies
  - Hyper-IgM syndrome

Inheritance:

X-linked

OMIM:

- #308230 Immunodeficiency with hyper-IgM, type 1; HIGM1
- *300386 Tumor necrosis factor ligand superfamily, member 5

Cross references:

Incidence:

1/1,000,000 live births in males

CLINICAL INFORMATION

Description:

Patients with XHIM have recurrent bacterial and opportunistic infections starting in the first year of life. Pneumocystis Carinii pneumonia is a common presenting infection. Other patients may have chronic, profuse diarrhea requiring parenteral nutrition. Over 50% of patients have chronic or intermittent neutropenia, often associated with oral ulcers. Cryptosporidium infection may lead to severe bile duct disease and hepatic cancer. Serum concentration of IgG is usually less than 200 mg/dl; IgM may be low, normal or elevated. Atypical cases may present with recurrent infections, anemia or hepatitis in the second or third decade of life. XHIM has a higher risk of malignancy than other antibody deficiencies. Lymphomas affect patients with XHIM as they do patients with common variable immunodeficiency (CVID), but the incidence of adenocarcinomas of the liver and biliary track is particularly high; these latter malignancies are suspected to be related to the high incidence of viral hepatitis. Diarrhea and cholangitis are caused by Cryptosporidium.

Diagnosis:

Diagnostic laboratories:

Clinical:

- X-linked Immunodeficiency With Hyper IgM, eMedicine
- Combined B-cell and T-cell disorders, eMedicine

Genetic:

- TNFSF5, IDdiagnostics
- University of Tennessee, GeneTest
- Cincinnati Children's Hospital Medical Center, GeneTest
- North East Thames Regional Clinical Molecular Genetics Laboratory (London), EDDNAL
- Centro de Genética Humana - Laboratório de Biologia Molecular (Lisboa), EDDNAL
- Laboratorio di Genetica Pediatrica Angelo Nocivelli - University of Brescia, EDDNAL

Therapeutic options:

- Intravenous gamma-globulin (IVIg) should be started early. Treatment of infections with antibiotics like amoxicilin, amoxicillin-clavulanic acid, and cefuroxime axetil. If there is a chronic pulmonary infection, acute severe pneumonia, or sepsis intravenous ceftriaxone may be required. All water should be boiled to be free of Cryptosporidium. Severe cases might benefit from bone marrow transplantation. Some successful transplants have been until now. For liver disease secondary to Cryptosporidium liver transplantation may be required.
- X-linked Immunodeficiency With Hyper IgM, eMedicine
- Treatment of CD40 ligand deficiency by hematopoietic stem cell transplantation
- Combined B-cell and T-cell disorders, eMedicine

Research programs, clinical trials:

- Pilot Study of Allogeneic Bone Marrow Transplantation Plus Cyclosporine and Mycophenolate Mofetil to Induce Mixed Hematopoietic Chimerism in Patients With Primary T-Cell Immunodeficiency Disorders, ClinicalTrial.gov
- Center for Cancer Research, National Cancer Institute
- Institute of Child Health, University College London

GENE INFORMATION

Names:

HUGO name: TNFSF5
Alias(es): CD154, CD40L, CD40LG, HIGM1, IGM, IMD3, TRAP, gp39, hCD40L, CD40 antigen ligand, tumor necrosis factor superfamily, member 5, CD40 ligand, TNF-related activation protein, TRAP, T cell antigen GP39

Localization:

Reference sequences:

DNA: D31793 (EMBL) D31794 (EMBL) D31795 (EMBL) D31796 (EMBL) D31797 (EMBL) , **cDNA:** X68550 (EMBL) , **Protein:** P29965 (SWISSPROT) Other Sequences

Chromosomal Location:

Xq26.3-q27.1

Maps:

TNFSF5 (Map View), CHLC.UTR_01701_L07414, L07414, GDB:340965

Variations / Mutations:

- CD40Lbase; Mutation registry for X-linked hyper-IgM syndrome (XHIM)
- ; HGMD
- The European CD40L Defect Database; The European CD40L Defect Database
- SNP:959 at NCBI; SNP:959 at NCBI

Other gene-based resources:

Ensembl: ENSG00000102245, GENATLAS: TNFSF5, GeneCard: TNFSF5, UniGene: 652, Entrez Gene: 959, euGenes: 959, GDB: 120632

PROTEIN INFORMATION

Description:

Structures (PDB):

1ALY	Crystal Structure Of Human Cd40 Ligand
1CDA	Cd40 Ligand Complex With The Membrane-Bound Glycoprotein Cd40 (Theoretical Model)

Domains:

Intracytoplasmic domain (IC): 1-22

Transmembrane domain (TM): 26-46

Tumor necrosis factor homology domain (TNFH): 123-261

Extracellular unique domain (ECU): 47-261

Other features:

Disulfide bonds: 178-218
Other related resourses:

InterPro: IPR003263; TNF_5, InterPro: IPR003636; TNF_abc, Pfam: PF00229; TNF, SMART: SM00207; TNF, PROSITE: PS00251; TNF_1, PROSITE: PS50049; TNF_2

Expression pattern for human:

Tissue	Exp. (%)	Clones

Animal models:

Mus musculus (Mouse):

MGD: ; Tnfsf5

Rattus norvegicus (Rat):

Bos taurus (Bovine):

Canis familiaris (Dog):

Felis silvestris catus (Cat):

Gallus gallus (Chicken):

Aotus trivirgatus (Night monkey) (Douroucouli):

Callithrix jacchus (Common marmoset):

Macaca mulatta (Rhesus macaque), and Cercocebus torquatus atys (Red-crowned mangabey) (Sooty mangabey):

Macaca nemestrina (Pig-tailed macaque):

Sus scrofa (Pig):

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:

- The TNF Nomenclature Scheme by HGNC
- IMMUNODEFICIENCY WITH HYPER-IgM (HIM)