CD40 deficiency

GENERAL INFORMATION

Description:

Defects in TNFRSF5 are the cause of type 3 hyper-IgM immunodeficiency characterized by an inability of B cells to undergo isotype switching, one of the final differentiation steps in the humoral immune system, an inability to mount an antibody-specific immune response, and a lack of germinal center formation.

Alternative names:

- Hyper-IgM syndrome type 3, HIGM3
- Tumor necrosis factor receptor superfamily member 5 (CD40)

Classification:

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

Inheritance:

Autosomal recessive

OMIM:

- #606843 Immunodeficiency with hyper-IgM, type 3
- *109535 Tumor necrosis factor receptor superfamily, member 5; TNFRSF5

Cross references:

Incidence:

1/2,000,000 births/year

CLINICAL INFORMATION

Description:

HIGM3 is characterized by hypogammaglobulinemia with normal or elevated levels of IgM. The clinical features of HIGM3 are similar to those of X-linked HIGM1. Patients have susceptibility to bacterial and opportunistic infections, such as Pneumocystis Carinii. There is often neutropenia and thrombocytopenia. Also patients present autoimmune disease of all types. There will be a normal or high IgM, with low IgG and IgA. T-cell function may be normal or poor. The complications include lymphomas, opportunist pneumonias, autoimmune disease, aplastic anaemia, infection of biliary tree with Cryptosporidium leading to severe cholangitis and liver failure.

Diagnosis:

Diagnostic laboratories:

Clinical:

- Hyper-IGM syndrome, autosomal recessive, ORPHANET
- Combined B-cell and T-cell disorders, eMedicine

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.
- Hypogamaglobulinemia, eMedicine
- 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
- European Initiative for Primary Immunodeficiencies

GENE INFORMATION

Names:

HUGO name: CD40
Alias(es): Bp50, TNFRSF5, p50, CD40 antigen, tumor necrosis factor receptor superfamily, member 5, Tumor necrosis factor receptor superfamily member 5 precursor, CD40L receptor, B-cell surface antigen CD40, CDw40

Localization:

Reference sequences:

DNA: AL035662 (EMBL) , **cDNA:** X60592 (EMBL) , **Protein:** P25942 (SWISSPROT) Other Sequences

Chromosomal Location:

20q12-q13.2

Maps:

TNFRSF5 (Map View)

Variations / Mutations:

- TNFRSF5base; Mutation registry for CD40 deficiency

Other gene-based resources:

Ensembl: ENSG00000101017, GENATLAS: TNFRSF5, GeneCard: TNFRSF5, UniGene: 472860, Entrez Gene: 958, euGenes: 958, GDB: 215268

PROTEIN INFORMATION

Description:

Protein function:

Receptor for TNFSF5/CD40l.

Subcellular location:

Type I membrane protein (isoform I); secreted (isoform II).

Protein function:

At least 2 isoforms; I) and II; are produced by alternative splicing.

Structures (PDB):

1CDF TNFRSF5

Domains:

Extracellular domain: 20-193

Cytoplasmic domain: 216-277

Other features:

Signal peptide: 1-19

Tumor necrosis factor receptor superfamily member 5: 20-277

Disulfide bonds: 26-37, 38-51, 41-59, 62-77, 83-103, 105-119, 111-116, 125-143

Other related resourses:

InterPro: IPR001368; TNFR_c6, Pfam: PF00020; TNFR_c6, SMART: SM00208; TNFR, PROSITE: PS00652; TNFR_NGFR_1, PROSITE: PS50050; TNFR_NGFR_2

Expression pattern for human:

Tissue	Exp. (%)	Clones
human eye anterior segment	15.74	1:1978
tonsil, enriched for germinal center B-cells	7.67	9:36522
B-cells	7.53	4:16533
leukocyte	6.93	2:8982
mixed	5.16	10:60341
lung metatastic chondrosarcoma	4.83	1:6448
foreskin, melanocyte	4.62	2:13478
lymph	4.35	9:64395
kidney, pooled	4.21	1:7404
B cells germinal	4.13	1:7537

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:

- Understanding Hyper-IgM syndrome, PIA
- Hyper IgM Syndrome, Genetic Information and Patient Services, Inc. (GAPS)