Omenn syndrome

GENERAL INFORMATION

Description:

Omenn syndrome is a rare autosomal recessive disease. The defect of this syndrome affects the maturation of both B and T lymphocytes and the activation of the T cell subset is secondary to a partially defective V(D)J recombination process.

Alternative names:

- Reticuloendotheliosis, familial, with eosinophilia
- Severe combined immunodeficiency with hypereosinophilia
- Combined immunodeficiency and reticuloendotheliosis with eosinophilia

Classification:

- Combined B and T cell immunodeficiencies
  - T⁻B⁻ Severe combined immunodeficiency (SCID)

Inheritance:

Autosomal recessive

OMIM:

- #603554 Omenn syndrome

Cross references:

Phenotype related immunodeficiencies:

- IDR factfile for RAG1 deficiency
- IDR factfile for RAG2 deficiency

Incidence:

1/100000

CLINICAL INFORMATION

Description:

Patients with Omenn syndrome present with early onset generalized erythodermia, lymphadenopathy, hepatosplenomegaly, protracted diarrhea, failure to thrive, eosinophilia, increased Ig E levels, defective B and T lymphocyte function, greatly increased numbers of T lymphocytes, and death usually before 5 - 6 months of age. Additional findings include lymphocytosis and histiocytosis within skin and other tissues. Protein loss due to diarrhea and exudative erythrodermia often leads to generalized edema. The presence of a massive inflamatory infiltrate confers to the skin a unique appearance and consistency (pachydermia). Alopecia is a frequent finding. Infections and severe malnutrition are the main causes of death. Septicemia often arising from skin infections is common.

Diagnosis:

Diagnostic laboratories:

Clinical:

- Omenn syndrome, ORPHANET

Genetic:

- RAG1, IDdiagnostics
- RAG2, IDdiagnostics

Therapeutic options:

- Bone marrow transplantation is the only treatment of SCID. Other recommendations include intravenous gamma-globulin infusion, irradiation of all blood products, antibiotherapy.
- BMT, supportive treatment, prophylaxis of infection and tailored conditioning regimen, National Marrow Donor Program
- Omenn syndrome, 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
- Yale University
- Recombination and expression of antigen receptor genes
- Howard Hughes Medical Institute

GENE INFORMATION

Names:

HUGO name: RAG1
HUGO name: RAG2
Alias(es): recombination activating gene 1, V(D)J recombination activating protein 1 (RAG-1)
Alias(es): recombination activating gene 2, V(D)J recombination activating protein 2 (RAG-2)

Localization:

Reference sequences:

DNA: (IDbases) , **cDNA:** M29474 (EMBL) , **Protein:** P15918 (SWISSPROT)

Reference sequences:

DNA: M94633 (EMBL) , **cDNA:** M94633 (EMBL) , **Protein:** P55895 (SWISSPROT)

Chromosomal Location:

11p13

Chromosomal Location:

11p13

Maps:

SHGC-6028, STS-M29474, RAG1, RAG1 (Map View)

Maps:

RAG2 (Map View), Rag2

Variations / Mutations:

- RAG1base; Mutation registry for autosomal recessive RAG1 deficiency
- Polymorphisms/Variations; Polymorphisms/ Variations
- RAG2base; Mutation registry for autosomal recessive RAG2 deficiency

Other gene-based resources:

Ensembl: ENSG00000166349, GENATLAS: RAG1, GeneCard: RAG1, UniGene: 73958, Entrez Gene: 5896, euGenes: 5896, GDB: 120334, Ensembl: ENSG00000175097, GENATLAS: RAG2, GeneCard: RAG2, UniGene: 159376, Entrez Gene: 5897, euGenes: 5897, GDB: 125186

PROTEIN INFORMATION

Description:

Protein function:

During lymphocyte development, the genes encoding immunoglobulins and T cell receptors are assembled from Variable (V), Diversity (D), and Joining (J) gene segments. This combinatorial process, known as V(D)J recombination, allows the generation of an enormous range of binding specificities from a limited amount of genetic information. The RAG1/RAG2 complex initiates this process by binding to the conserved Recombination Signal Sequences (RSS) and introducing a double-strand break between the RSS and the adjacent coding segment. These breaks are generated in two steps, nicking of one strand (hydrolysis), followed by hairpin formation (transesterification). RAG1/2 has also been shown to function as a transposase in vitro, and to possess RSS-independent endonuclease activity (end processing) and hairpin opening. RAG1 alone can bind to RSS but stable, efficient binding requires RAG2. All known catalytic activities require the presence of both proteins.

Subcellular location:

Nuclear

Cofactor:

Binds 1 magnesium or manganese ion per subunit (by similarity)

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Structures (PDB):

1RMD Rag1 Dimerization Domain

Domains:

Invertase/Homeodomain: 392-448

RAG2-interacting domain: 504-1008

Core domain: 392-1011

SRP1 interacting domain: 1-129

RCH1 interacting domain:: 333-1043

Other features:

Basic region 1: 142-147

Basic region 2:: 222-226

Basic region 3:: 244-252

Basic region 4:: 829-843

Basic region 5: 972-975

zing ring finger:: 291-333

InterPro: IPR001841; Znf_ring, PROSITE: PDOC00449; Zinc finger RING type signature and profile, Pfam: PF00097; zf-C3HC4, Blocks: IPB001841; Znf_ring, Smart: SM00184; RING

zing finger A:: 352-381

zing finger B:: 726-757

Other related resourses:

PIR: A33754, PROSITE: PS00518; ZF_RING_1, PROSITE: PS50089; ZF_RING_2

Other related resourses:

InterPro: IPR004321; RAG2, Pfam: PF03089; RAG2

Expression pattern for human:

Animal models:

Mus musculus (Mouse):

MGD: MGI:97848; Rag1

Oryctolagus cuniculus (Rabbit):

Gallus gallus (Chicken):

Xenopus laevis (African clawed frog):

Oncorhynchus mykiss (Rainbow trout) (Salmo gairdneri):

Mus musculus (Mouse):

MGD: MGI:97849; Rag2

Oryctolagus cuniculus (Rabbit):

Gallus gallus (Chicken):

Xenopus laevis (African clawed frog):

Oncorhynchus mykiss (Rainbow trout) (Salmo gairdneri):

OTHER RESOURCES

Societies:

General:

- European Society for Immunodeficiencies
- A.I.P. : Associazione Immunodeficienze Primitive - ONLUS
- International Patient Organization for Primary Immunodeficiencies
- Immune Deficiency Foundation
- The Jeffrey Modell Foundation
- March of Dimes Birth Defects Foundation
- NIH/National Institute of Allergy and Infectious Diseases

Disease specific:

- The SCID Homepage

Other information sources:

- Severe Combined Immunodeficiency, Patient and Family Handbook
- Severe Combined Immunodeficiency, KidsHealth