RAG1 deficiency

GENERAL INFORMATION

Description:

The functional failure of one of the constituents of the V(D)J recombinase machinery, such RAG1 or RAG2, results in a severe combined immunodeficiency without B and T cells. The RAG1 and RAG2 deficiency is an autosomal recessive disease.

Alternative names:

- SCID
- Recombination defect
- Complete RAG1 deficiency
- SCID with RAG1 deficiency

Classification:

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

Inheritance:

Autosomal recessive

OMIM:

- #601457 Severe combined immunodeficiency, B cell-negative
- *179615 Recombination-activationg gene 1; RAG1

Cross references:

Incidence:

~ 1/100,000 live births.

CLINICAL INFORMATION

Description:

The clinical description is relatively uniform. No symptoms are detected during pregnancy, birth and within the first few weeks of life. In the majority of cases, the symptoms start within the second or third month of birth. Infectious complications with a high preponderence of opportunistic infections are the hallmark of the disease. The clinical signs are characterized by chronic respiratory disease, recurrent acute pneumonia, therapy-resistant mucocutaneous candidiasis, eczematous dermatitis and systemic bacterial infections. The recurrent infections in addition to chronic enteritis lead to a therapy-resistant growth failure. Intracellular parasites (Listeria, Legionella), viruses (EBV) and cytomegaloviruses (CMV) cause lethal complications. All SCID children die within few months if they are not provided with haematopoietic stem cells. The physical examination of completely RAG deficient patients reveals unusual infections and a characteristic absence of lymphatic organs. In most cases cervical lymph nodes and tonsils are undetectable.

Diagnosis:

Diagnostic laboratories:

Clinical:

- Severe combined immunodeficiency, eMedicine

Genetic:

- RAG1, 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.
- National Marrow Donor Program
- Severe combined immunodeficiency, 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
- European Initiative for Primary Immunodeficiencies

GENE INFORMATION

Names:

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

Localization:

Reference sequences:

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

Chromosomal Location:

11p13

Maps:

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

Variations / Mutations:

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

Other gene-based resources:

Ensembl: ENSG00000166349, GENATLAS: RAG1, GeneCard: RAG1, UniGene: 73958, Entrez Gene: 5896, euGenes: 5896, GDB: 120334

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)

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

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):

OTHER RESOURCES

Societies:

General:

- European Society for Immunodeficiencies
- International Patient Organization for Primary Immunodeficiencies
- Immune Deficiency Foundation
- March of Dimes Birth Defects Foundation
- NIH/National Institute of Allergy and Infectious Diseases

Disease specific:

- FMF community

Other information sources:

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