JAK3 deficiency

GENERAL INFORMATION

Description:

Defects in JAK3 are a cause of autosomal recessive T-cell negative/B-cell positive severe combined immunodeficiency (T-B+ SCID), a condition characterized by the absence of circulating mature T-lymphocytes and NK cells, normal to elevated numbers of nonfunctional B-lymphocytes, and marked hypoplasia of lymphoid tissues.

Alternative names:

- Autosomal recessive T-B+ SCID due to JAK3
- Janus kinase 3

Classification:

- Combined B and T cell immunodeficiencies
  - T⁻B⁺ SCID

Inheritance:

Autosomal recessive

OMIM:

- #600802 Severe combined immunodeficiency, autosomal recessive, T-negative/B-positive type
- *600173 Janus kinase 3; JAK3

Cross references:

Phenotype related immunodeficiencies:

- IDR factfile for X-linked SCID(gamma-chain deficiency)

Incidence:

1/500,000 live births

CLINICAL INFORMATION

Description:

The clinical features of JAK3 deficiency are similar with the features commonly observed in infants with X-linked SCID. This deficiency occurs since the first months of life, with recurrent bacterial or viral (Cytomegalovirus, Pneumocystis Carinii) infections, sometimes BCG-itis if the infant had received BCG vaccination during the neonatal period, severe diarrhoea and failure to thrive. Peripheral nodes are undetectable. Unless treated by successful bone marrow transplantation, JAK3 deficiency is a lethal disorder.

Diagnosis:

Diagnostic laboratories:

Clinical:

- Severe combined immunodeficiency, eMedicine

Genetic:

- JAK3, IDdiagnostics
- Laboratorio di Genetica Pediatrica Angelo Nocivelli - University of Brescia, EDNAL
- North East Thames Regional Clinical Molecular Genetics Laboratory (London), EDNAL

Therapeutic options:

- Bone marrow transplantation. Other recommendations include intravenous gamma-globulin infusion, irradiation of all blood products, agressive treatment of infections with antibacterials, antifungals, and antivirals. Nutritional support. Gene therapy is predicted to work for JAK3 mutations based on murine studies.
- Severe combined immunodeficiency, eMedicine
- BMT for Severe Combined Immunodeficiencies
- Gene therapy of human severe combined immunodeficiency (SCID)-X1 disease

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
- European Initiative for Primary Immunodeficiencies

GENE INFORMATION

Names:

HUGO name: JAK3
Alias(es): JAKL, L-JAK, Janus kinase 3 (a protein tyrosine kinase, leukocyte), Tyrosine-protein kinase JAK3, Leukocyte janus kinase

Localization:

Reference sequences:

DNA: U70065 (EMBL) , **cDNA:** U31601 (EMBL) , **Protein:** P52333 (SWISSPROT) Other Sequences

Chromosomal Location:

19p13.1

Maps:

JAK3 (Map View), RH67783, RH98718, RH70552, SHGC-35252

Variations / Mutations:

- JAK3base; Mutation registry for autosomal recessive severe combined JAK3 deficiency

Other gene-based resources:

Ensembl: ENSG00000105639, GENATLAS: JAK3, GeneCard: JAK3, UniGene: 515247, Entrez Gene: 3718, euGenes: 3718, GDB: 376460

PROTEIN INFORMATION

Description:

Protein function:

Tyrosine kinase of the non-receptor type, involved in the interleukin-2 and interleukin-4 signaling pathway. Phosphorylates STAT6, IRS1, IRS2 and PI3k

Catalytic activity:

ATP + a protein tyrosine = ADP + protein tyrosine phosphate

Subcellular location:

Wholly intracellular, possibly membrane associated (by similarity)

Post-translational modification:

Tyrosine phosphorylated in response to IL-2 and IL-4

Protein function:

3 isoforms; 1/JAK3b/breast-JAK3, 2/JAK3s/ spleen-JAK3 and 3/JAK3m/activated monocytes-JAK3; are produced by alternative splicing. Isoform 1 may be defective as it lack some part of the kinase domain

Domains:

SH2 (atypical) domain: 375-475

Protein kinase 1 domain: 521-781

Protein kinase 2 domain: 822-1111

Other features:

ATP nucleotide phosphate-binding region: 828-836

ATP binding site: 855

Other related resourses:

InterPro: IPR000299; Band_4.1, InterPro: IPR000719; Euk_pkinase, InterPro: IPR000980; SH2, InterPro: IPR001245; Tyr_pkinase, Pfam: PF00017; SH2, Pfam: PF00069; pkinase, SMART: SM00295; B41, SMART: SM00252; SH2, SMART: SM00219; TyrKc, PROSITE: PS00107; PROTEIN_KINASE_ATP, PROSITE: PS00109; PROTEIN_KINASE_TYR, PROSITE: PS50011; PROTEIN_KINASE_DOM, PROSITE: PS50001; SH2

Expression pattern for human:

Tissue	Exp. (%)	Clones
trachea	94.74	1:22
adipose, white adipose tissue	2.11	1:987
leukocyte	0.46	2:8982
spleen	0.29	1:7229
B cells germinal	0.28	1:7537
B-cells	0.25	2:16533
lymph, T-cell	0.25	1:8503
lymph	0.23	7:64395
aorta	0.20	1:10275
small intestine	0.18	1:11480

Animal models:

Mouse::

MGD: ; IL7R

FlyBase::

euGenes: ; FlyBase

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

Disease specific:

- The SCID Homepage

Other information sources:

- Severe combined immunodeficiency, Patient and Family Handbook, IDF
- Severe combined immunodeficiency (SCID), JMF
- Severe combined immunodeficiency, KidsHealth