Leukocyte adhesion deficiency I

GENERAL INFORMATION

Description:

Leukocyte adhesion deficiency type I is caused by a mutation in the common chain of the #2 integrin family CD18. There are three #2 integrins with different α chains but a common β chain, called CD18. Defects in CD18 determine the loss of β2 integrin and the clinical symptoms. Neutrophils are unable to aggregate and do not bind to intercellular adhesion molecules on endhothelial cells. When there is no infection, the neutrophil count is about twice the normal level. LAD I has been described in more than 300 patients worldwide.

Alternative names:

- LAD1
- Lymphocyte function-associated antigen 1 immunodeficiency
- LFA1 immunodeficiency
- Leukocyte adhesion deficiency type 1, CD18 (integrin beta2)
- Rambam-Hasharon syndrome

Classification:

- Defects of Phagocyte Function
  - Leukocyte adhesion defects

Inheritance:

Autosomal recessive

OMIM:

- #116920 Leukocyte adhesion deficiency, type I; LAD
- *600065 Integrin, beta-2; ITGB2

Cross references:

Phenotype related immunodeficiencies:

- IDR factfile for Leukocyte adhesion deficiency II

Incidence:

Incidence is not known.

CLINICAL INFORMATION

Description:

LAD1 patients have recurrent bacterial infections, impaired pus formation and impaired wound healing. Patients have a history of delayed separation of the umbilical cord, severe periodontitis, often with early tooth decay, and recurrent infections of the oral and genital mucosa, skin, and intestinal and respiratory tract. The bacterial infections are localized and difficult to detect until they have progressed to an extensive life-threatening level. Typical infections are omphalitis, perirectal and labial cellulitis, associated with extreme neutrophilia, otitis media with minimal inflammation, and other necrotic skin infection. The most common infectious agents are Staphylococcus species, gram-negative bacteria and fungal organisms (candida species). Infected foci contain few neutrophils and heal slowly, with enlarging borders and dysplastic scars. Severe gingivitis and periodontitis are major features among all patients who survive infancy. The severity of clinical infections complications is related to the degree of CD18 deficiency. Patients with less than 1% of the normal CD18 surface expression have a severe form of disease with earlier, more frequent, and more serious episodes of infection, often leading to death in infancy. Patients with some surface expression of CD18 (2,5-10%) have a moderate to mild phenotype with fewer serious infections and survival into adulthood.

Diagnosis:

Diagnostic laboratories:

Clinical:

- Leukocyte adhesion deficiency, ORPHANET
- Leukocyte adhesion deficiency, eMedicine

Genetic:

- Leukocyte Adhesion Deficiency, Type 1, GeneTest

Therapeutic options:

- Antibiotic therapy initiated early, in case of acute infection. Granulocyte transfusion in case of life-threatening situations when all other measures have failed. Bone marrow transplantation is the only definitively corrective treatment.
- Leukocyte adhesion deficiency, eMedicine

Research programs, clinical trials:

- Use of G-CSF to Obtain Blood Cell Precursors, ClinicalTrials.gov
- Follow-Up of a Phase-I Gene Therapy Trial of Patients with Leukocyte Adherence Deficiency, Clinical Research Studies, NIH
- European Initiative for Primary Immunodeficiencies

GENE INFORMATION

Names:

HUGO name: ITGB2
Alias(es): CD18, LAD, LCAMB, LFA-1, MF17, cell surface adhesion glycoprotein, Integrin, beta 2, antigen CD18 (p95), lymphocyte function-associated antigen 1, macrophage antigen 1 (mac-1) beta subunit), Integrin beta-2 precursor, Cell surface adhesion glycoproteins LFA- 1/CR3/ p150,95 beta-subunit, Complement receptor C3 beta- subunit

Localization:

Reference sequences:

DNA: AL163300 (EMBL) , **cDNA:** M15395 (EMBL) , **Protein:** P05107 (SWISSPROT) Other Sequences

Chromosomal Location:

21q22.3

Maps:

ITGB2 (Map View)

Variations / Mutations:

- ITGB2base; Mutation registry for leucosyte adhesion deficiency I (LAD-I)

Other gene-based resources:

Ensembl: ENSG00000160255, GENATLAS: ITGB2, GeneCard: ITGB2, UniGene: 375957, Entrez Gene: 3689, euGenes: 3689, GDB: 120574

PROTEIN INFORMATION

Description:

Protein function:

Integrin #-l/#-2 is a receptor for ICAM1, ICAM2, ICAM3 and ICAM4. Integrins #-m/#-2 and #-x/#-2 are receptors for the IC3B fragment of the third complement component and for fibrinogen. Integrin #-x/# 2 recognizes the sequence g-p-r in fibrinogen #-chain. Integrin #-m/#-2 recognizes P1 and P2 peptides of fibrinogen gamma chain. Integrin #-m/#-2 is also a receptor for Factor X. Integrin #-d/# 2 is a receptor for ICAM3 and VCAM1.

Subunit:

Heterodimer of an # and a # subunit. #-2 associates with either #-l, #-m, #-x or #-d.

Subcellular location:

Type I membrane protein

Domains:

Extracellular domain: 23-700

Cytoplasmic domain: 724-769

Vwfa-like domain: 124-363

4 cysteine-rich tandem repeats domain: 449-617

Other features:

Signal peptide: 1-22

Integrin beta-2: 23-769

Other related resourses:

PIR: IJHULM, InterPro: IPR002369; Integrin_B, InterPro: IPR001169; Integrin_beta_C, InterPro: IPR003659; Plexin-like, InterPro: IPR002035; VWF_A, Pfam: PF00362; integrin_B, SMART: SM00187; INB, SMART: SM00423; PSI, SMART: SM00327; VWA, PROSITE: PS00243; INTEGRIN_BETA, PROSITE: PS00022; EGF_1, PROSITE: PS01186; EGF_2

Expression pattern for human:

Tissue	Exp. (%)	Clones
thyroid gland	12.92	2:1136
whole blood	12.01	4:2445
nasopharynx	11.36	1:646
smooth muscle	11.34	1:647
subchondral bone	5.51	1:1332
lung with fibrosis	4.96	1:1479
muscle	4.25	13:22471
B-cells	3.55	8:16533
blood	3.48	6:12646
T cells from T cell leukemia	3.06	1:2397

Animal models:

Mouse:

MGD: ; Itgb2

Fly:

euGenes: ; mys

C. elegans:

euGenes: ; pat-3

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:

- Leukocyte adhesion deficiency web site