

Dianzani Autoimmune Lymphoproliferative Disease (DALD)

Identity

Note Variant of the [Autoimmune Lymphoproliferative Syndrome \(ALPS\)](#)

Inheritance Possibly, an oligogenic disease.

Clinics

Phenotype and clinics	Paediatric onset with: 1) Autoimmunity, that is predominantly haematological, but any other autoimmunity can be displayed; 2) Enlargement of the spleen and/or lymph nodes due to accumulation of polyclonal lymphocytes; 3) Decreased function of the Fas death receptor. These patients lack the peripheral blood expansion of T cells expressing the TCR alpha/TCR beta but not CD4 and CD8 (double-negative T cells), that are present in the typical form of ALPS.
Neoplastic risk	2.5 fold increased risk of cancer (both haematological and not haematological).
Treatment	Immune suppression.
Evolution	Autoimmunity may remit in adulthood but lymphoproliferation generally persists. Increased risk of lymphomas and other cancers in adulthood.
Prognosis	Good on survival, but the autoimmune haemolytic anemia may be occasionally lethal.

Genes involved and Proteins

Note The disease is due to inherited defects decreasing function of the Fas (CD95) death receptor, involved in switching off the immune response by triggering apoptosis of activated lymphocytes. The mutation possibly hits unknown genes involved in Fas signalling. The Fas, Fas ligand, caspase-10, caspase-8 genes, that can be involved in ALPS are not mutated.
The genetic background may influence the disease onset. Variants of the gene of osteopontin or perforin (see above) can act as predisposition factors.

Gene Name

[OPN](#)

Location 4q21-q25

DNA/RNA

Description Encoded in 7 exons spanning 5.4-8.2 Kb.

Protein

Description Protein of 287-314 aa. Several OPN forms originate from alternative splicing, phosphorylation, glycosylation, and proteolytic cleavage and mediate partly distinct functions.

Expression Constitutively expressed by bone and several epithelial tissues, whereas in endothelial cells, macrophages and smooth muscle cells, it is mainly expressed upon activation in inflammatory contexts. Moreover, it is expressed by activated T-cells.

Localisation Secreted cytokine.

Function Functions as a free cytokine in body fluids or an immobilized extracellular matrix molecule in mineralized tissues. Plays a role in cell-to-cell and cell-to-extracellular matrix interaction by binding to several integrins and the CD44v6-7 isoforms, triggering signals involved in cell activation and migration. Involved in bone remodeling, tissue repair, and cell migration. It potentiates T-cell proliferation, IFN-gamma production, and CD40L expression, which in turn favor B-cell proliferation and antibody production.

Mutations

Germinal Polymorphic variants of the gene have been associated with increased susceptibility to develop DALD. Four polymorphisms, corresponding to position +282T/C (exon VI), +750C/T (exon VII, coding region), +1083A/G and +1239A/C (3' UTR) (ATG = +1), form 3 haplotypic combinations:
Haplotype-A (282T-750C-1083A-1239A),
Haplotype-B (282C-750T-1083A-1239C),
Haplotype-C (282C-750T-1083G-1239C).
Subjects carrying haplotype-B and/or -C have a 8-fold higher risk of developing DALD than haplotype-A homozygotes. Haplotype-B and -C causes production of increased levels of osteopontin, possibly because of higher stability of its mRNA.

Gene Name [PRF1](#)

Location 10q22

Note Biallelic mutations of PRF1 cause the familial hemophagocytic lymphohistiocytosis (HLH), an immune deficiency ascribed to decreased capacity of cytotoxic lymphocytes (CD8+ T cells and NK cells) to kill virus-infected cells.

DNA/RNA

Description Encoded in 3 exons spanning 5.4 Kb.

Protein

- Description** Protein of 436 aa.
- Expression** Expressed by cytotoxic effector lymphocytes (activated cytotoxic T cells and NK cells).
- Localisation** It is stored in the lytic granules and secreted against the target cell.
- Function** It polymerizes on the membrane of target cells and forms pores.
- Homology** High sequence homology to the C9 complement component.

Mutations

- Germinal** Several PRF1 mutations have been associated with HLH and lymphomas. These mutations can inhibit either expression or function of perforin. The A91V amino acid substitution decreases perforin function by altering its conformation, decreasing its cleavage to the active form, and increasing its degradation. Carriers of this variation show decreased NK activity. A91V is relatively frequent in control population (4.6%), but it has been associated with HLH, when combined with a second PRF1 variation. By contrast, it may favor DALD development when inherited defects hitting Fas function are also present. Its presence, in fact, increases the risk of DALD by 3 fold.

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