WHIM syndrome

GENERAL INFORMATION

Description:

The syndrome of warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis (WHIM) is an autosomal dominant immunologic disorder in which mature neutrophil fail to exit the bone marrow and B- and T-cell abundance or function is variably deficient. The syndrome is cause by mutations in CXCR4, a chemokine receptor expressed by hematopoietic and non-hematopoietic cells. The ligand CXCL12 (SDF-1) is a homeostatic chemokine with a central role in hematopoietic cells homing to and release from bone marrow. Neutrophils and lymphocytes from affected patients present a chemotaxis towards CXCL12 that could explain the innapropriate retention of mature neutrophils in the bone marrow causing the peripheral neutropenia.

Alternative names:

- WHIM
- WARTS, hypogammaglobulinemia, infections, and 'myelokathexis'
- WARTS, hypogammaglobulinemia, recurrent bacterial infections, and myelokathexis
- Warts, hypogammaglobulinemia, infections, and myelokathexis syndrome

Classification:

- Defects of innate immune system, receptors and signaling components

Inheritance:

Autosomal dominant

OMIM:

- #193670 WHIM syndrome
- *162643 Chemokine, CXC motif, receptor 4; CXCR4

Cross references:

Phenotype related immunodeficiencies:

- IDR factfile for X-linked hypogammaglobulinemia with growth hormone deficiency

Incidence:

Incidence is not known.

CLINICAL INFORMATION

Description:

Patients have neutropenia, hypogammaglobulinemia and extensive human papillomavirus (HPV) infection. Despite the peripheral neutropenia, bone marrow aspirates from affected individuals contain abundant mature myeloid cells, a condition termed myelokathexis. Recurrent bacterial infections are typically minor and responsive to oral antibiotics, as the resultant inflammatory state induces neutrophil release from the bone marrow. Respiratory infections (sinusitis, otitis and pneumonia) and cellulitis are common infections complications. Late in life most of the patients develop widespread and recalcitrant warts with common Human Papilloma Virus. Cell blood counts show an absolute neutrophil count usually bellow 300/µl, a variable degree of lymphopenia, but normal hemoglobin levels and platelets.

Diagnosis:

Diagnostic laboratories:

Clinical:

- WHIM syndrome, ORPHANET

Genetic:

- Children Cancer Research Institute, Vienna, EDDNAL

Therapeutic options:

- Infectious episodes are reduced by monthly injections of intravenous immunoglobulin. Neutrophil counts and marrow cytology are normalized by daily injections of G-CSF or GM-CSF. Warts are generally therapy-resistant, requiring laser ablation for management. There is a high risk of malignant transformation of genital HPV infection that requires careful monitoring.
- Neutropenia, eMedicine

Research programs, clinical trials:

- European Initiative for Primary Immunodeficiencies

GENE INFORMATION

Names:

HUGO name: CXCR4
Alias(es): D2S201E, HM89, HSY3RR, LESTR, NPY3R, NPYR, NPYY3, NPYY3R, fusin, chemokine (C-X-C motif) receptor 4, neuropeptide Y receptor Y3, C-X-C chemokine receptor type 4, Stromal cell- derived factor 1 receptor, SDF-1 receptor, Leukocyte-derived seven transmembrane domain receptor, LCR1, FB22, NPYRL, CD184 antigen

Localization:

Reference sequences:

DNA: AF005058 (EMBL) , **cDNA:** NM_003467 (EMBL) , **Protein:** P30991 (SWISSPROT) Other Sequences

Chromosomal Location:

2q21

Maps:

CXCR4 (Map View)

Variations / Mutations:

- CXCR4base; Mutation registry for WHIM syndrome

Other gene-based resources:

Ensembl: ENSG00000121966, GENATLAS: CXCR4, GeneCard: CXCR4, UniGene: 421986, Entrez Gene: 7852, euGenes: 7852, GDB: 230002

PROTEIN INFORMATION

Description:

Protein function:

Receptor for the c-x-c chemokine sdf-1. Transduces a signal by increasing the intracellular calcium ions level. Involved in haematopoiesis and in cardiac ventricular septum formation. Plays also an essential role in vascularization of the gastrointestinal tract, probably by regulating vascular branching and/or remodelling processes in endothelial cells. Could be involved in cerebellar development. In the CNS, could mediate hippocampal-neuron survival. Acts as a primary receptor for some HIV-2 isolates and as a co-receptor with CD4 for HIV-1 x4 viruses (lymphocyte-tropic HIV-1 viruses, also called syncytium-inducing (si) strains). Promotes env-mediated fusion of the virus.

Subcellular location:

Integral membrane protein.

Post-translational modification:

Sulfated

Protein function:

Was originally thought to be a receptor for neuropeptide y, type 3 (npy3-r).

Domains:

Extracellular domain: 1-39

Cytoplasmic domain: 64-79

Extracellular domain: 100-110

Cytoplasmic domain: 133-154

Extracellular domain: 176-200

Cytoplasmic domain: 221-240

Extracellular domain: 262-285

Cytoplasmic domain: 306-352

Other features:

Disulfide bond : 109-186

N-linked (glcnac...) glycosylation sites: 11

Other related resourses:

PIR: A45747, InterPro: IPR000276; GPCR_Rhodpsn, Pfam: PF00001; 7tm_1, PROSITE: PS00237; G_PROTEIN_RECEP_F1_1, PROSITE: PS50262; G_PROTEIN_RECEP_F1_2

Expression pattern for human:

Tissue	Exp. (%)	Clones
germinal center B-cells	10.98	1:623
breast tumor	8.12	1:843
normal endometrium, late proliferative phase, cycle day 13	6.55	1:1044
myeloid cells, 18 pooled CML cases, BCR/ABL rearrangement positive, includes both chronic phase and myeloid blast crisis	5.63	2:2431
thyroid	5.11	1:1339
moderately differentiated adenocarcinoma	4.44	2:3082
lymphoma, follicular mixed small and large cell	3.67	5:9317
lung tumor	3.53	1:1939
lymphocyte	3.51	1:1949
serous papillary carcinoma, high grade, 2 pooled tumors	2.19	5:15638

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