Severe congenital neutropenias, including Kostmann syndrome

GENERAL INFORMATION

Description:

Autosomal dominant or sporadic congenital neutropenia (SCN1) is caused by mutation in the neutrophil elastase gene (ELA2; 130130). Mutations in the protooncogene GFI1 (600871, which targets ELA2, also cause neutropenia (SCN2). As in the case of the ELA2 mutations, those in GFI1 causing neutropenia are heterozygous. Autosomal recessive severe congenital neutropenia (SCN3; 610738) is caused by homozygous mutations in the HAX1 gene. Kostmann disease (SCN3) is characterized by an absolute neutrophil count (ANC) less than 500/mm3. Severe persistent neutropenia results in an increased susceptibility to frequent bacterial infections. The main feature is cytological: granulocyte are blocked at the promyelocytic stage, eosinophilia and monocytosis.

Alternative names:

- SCN
- Infantile genetic agranulocytosis
- Kostmann disease
- Genetic infantile agranulocytosis

Classification:

- Defects of phagocyte function
  - Neutropenia
    - Cyclic neutropenia and severe congenital neutropenias. Include Kostmann syndrome

Inheritance:

Autosomal dominant

OMIM:

- #202700 Neutropenia, congenital, autosomal dominant or sporadic
- *130130 Elastase 2; ELA2
- *138971 Colony-stimulating factor 3, granulocyte; CSF3R
- *600871 Growth factor-independent 1; GFI1

Cross references:

Phenotype related immunodeficiencies:

- IDR factfile for Cyclic neutropenia

Incidence:

1-2: 1,000,000

CLINICAL INFORMATION

Description:

Severe neutropenia is brought to clinical attention after an initial infection, which typically occurs shortly after birth. Patients have temperature instability in newborn period, fever, irritability. Due to neutropenia, recurrent infections occur in various locations, mostly cutaneo-mucous, ENT (ear, nose, throught) and pulmonary. Stomatological signs appear after age 2, with erosive gingivitis, haemorrhage and pain, associated to papilla on the tongue and mucous membranes. Some patients can present myelodysplastic syndrome.

Diagnosis:

Diagnostic laboratories:

Clinical:

- Kostmann syndrome, ORPHANET
- Kostmann disease, eMedicine

Genetic:

- Laboratorio di Genetica Pediatrica Angelo Nocivelli - University of Brescia, EDDNAL

Therapeutic options:

- Treatment with recombinant human granulocyte colony-stimulating factor (GCSF) elevates the granulocyte counts, diminishes the number of new infections and improve survival and quality of life. Some patients develop leukemia or myelodysplastic syndrome. Bone marrow transplantation could be an option.
- Kostmann disease, eMedicine

Research programs, clinical trials:

- European Initiative for Primary Immunodeficiencies.
- Study of Unrelated Allogeneic Bone Marrow Transplantation in Patients With Benign Congenital Bone Marrow Failure Disorders, ClinicalTrials.gov

GENE INFORMATION

Names:

HUGO name: CSF3R
Alias(es): GCSFR, Colony stimulating factor 3 receptor (granulocyte), Granulocyte colony stimulating factor receptor precursor

Localization:

Reference sequences:

DNA: S71484 (EMBL) , **cDNA:** X55721 (EMBL) X55720 (EMBL) M59818 (EMBL) M59819 (EMBL) M59820 (EMBL) , **Protein:** AAN05790 (NCBI)

Chromosomal Location:

1p35-p34.3

Maps:

CSF3R (Map View)

Other gene-based resources:

Ensembl: ENSG00000119535, GENATLAS: CSF3R, GeneCard: CSF3R, UniGene: 524517, Entrez Gene: 1441, euGenes: 1441, GDB: 126430

PROTEIN INFORMATION

Description:

Protein function:

Receptor for granulocyte colony-stimulating factor (G-CSF). In addition it may function in some adhesion or recognition events at the cell surface.

Subunit:

Dimer

Subcellular location:

Type I membrane protein. The GCSFR-2 form, which lacks the transmembrane domain, may represent a soluble form of the receptor.

Structures (PDB):

1AZ7 .

Domains:

Extracellular domain: 25-627

Cytoplasmic domain: 651-836

Ig-like c2-type domain domain: 25-117

Fibronectin type-III 1 domain: 121-227

Fibronectin type-III 2 domain: 228-332

Fibronectin type-III 3 domain: 333-428

Fibronectin type-III 4 domain: 429-525

Fibronectin type-III 5 domain: 526-621

Other features:

Signal peptide: 1-24

Granulocyte colony stimulating factor receptor: 25-836

Disulfide bonds: 131-142, 248-295, 266-309
N-linked (glcnac...) glycosylation sites: 51, 93, 128, 134, 389, 474, 579, 610
Other related resourses:

PIR: JH0329, InterPro: IPR002996; CR1A, InterPro: IPR003961; FN_III, InterPro: IPR003529; Hemtopoptn_L_F2, Pfam: PF00041; fn3, SMART: SM00060; FN3, PROSITE: PS01353; HEMATOPO_REC_L_F2

Expression pattern for human:

Tissue	Exp. (%)	Clones
spleen	19.77	5:7229
leukocyte	15.91	5:8982
whole blood	11.69	1:2445
osteoarthritic cartilage	9.53	1:2999
ovary (pool of 3)	6.53	1:4380
aorta	5.56	2:10275
bone marrow stroma	5.36	1:5331
placenta	5.23	17:92983
pool, placenta	4.85	2:11794
prostate, epithelium	3.07	1:9299

Animal models:

Mouse:

MGD: ; Csf3r

OTHER RESOURCES

Societies:

General:

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

Disease specific:

- Neutropenia Support Association, Canada
- Severe Chronic Neutropenia International Registry, USA
- Severe Chronic Neutropenia International Registry, Germany