Atlas of Genetics and Cytogenetics in Oncology and Haematology

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Gene Section

Mini Review

JAK3 (janus kinase 3 or just another kinase 3)

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Identity

Hugo: JAK3
Other names: JAK-3; JAK_HUMAN; L-JAK; LJAK; EC 2.7.10.2
Location: 19p13.1
Local order: chr19: 17788,324-17819800.

DNA/RNA

Description

JAK3 is a functioning gene that comprises 23 exons spanning roughly 21 kb of genomic DNA with an open reading frame of 3372 bp.

Transcription

4025 bp mRNA. 7 transcript variants encoding 7 distinct proteins.

Protein

Note: 3 isoforms produced by alternative splicing: JAK3S, JAK3B, JAK3M.

Description

1124 amino acids, 125099 Da. JAK3 is comprised of 7 JAK homology (JH) domains. JH1 contains the C terminus kinase domain and an SH2 or SH3 binding motif; JH2 contains a pseudokinase domain tandemly linked to the N site of the JH1 domain; 5 more JH domains. The N terminus region (JH6 and JH7) is critical for receptor binding and signal transduction.

Expression

JAK3 is expressed in 12 normal human tissues (bone marrow, spleen, thymus, brain, spinal cord, heart, skeletal muscle, liver, pancreas, prostate, kidney, and lung). JAK3S is more commonly seen in hematopoietic cells, whereas JAK3B and JAK3M are detected in cells of hematopoietic or epithelial origin.

Localisation

Intracellular, membrane-associated through association with interleukin (IL) receptor common gamma chain (gamma-c).

Function

Tyrosine kinase of the non-receptor type. Involved in the signaling of ILs that contain the gamma-c chain in their respective receptors, including IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21. Induces tyrosine phosphorylation of a number of proteins, of which most widely studied are signal transducers and activators of transcriptions (STAT). JAK3 has also been shown to phosphorylate insulin receptor substrate-1 (IRS-1), IRS-2, and PI3K/Akt.

Homology

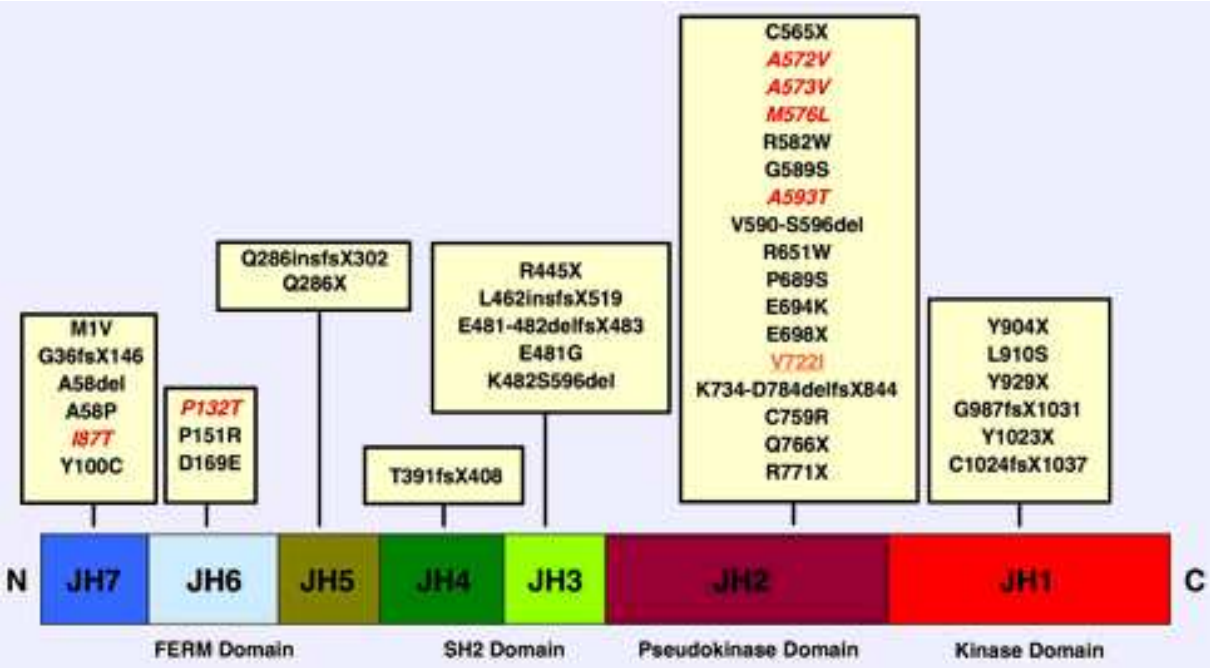
JAK3 is the most recently identified member of the mammalian Janus kinase subfamily (TYK2, JAK1, JAK2, and JAK3); JAK3 paralogs to JAK1 and JAK2; human JAK3 orthologs to murine Jak3.

Mutations

Note: Mostly point mutations were identified affecting all 7 structural JH domains of JAK3.

Somatic

Mutations of JAK3 were generally associated with the same cellular phenotype of the more frequently encountered X-linked SCID due to gamma-c deficiency. It was confirmed with the identification of 34 mutations in JAK3-SCID patients from Europe and the US. JAK3-SCID is inherited as autosomal recessive disease. It is estimated to account for approximately 7-14% of heritable SCID. JAK3 mutations are seemingly sporadic, and neither preferential gene locations (i.e. gene 'hot-spots') nor founder effects have yet been documented.



Different mutations identified in all of the 7 domains of JAK3. The mutations in 'black color' are the mutations reported in JAK3-SCID; 'red color and italic' identifies mutations reported in acute megakaryoblastic leukemia; and 'orange color and underline' highlights one mutation that has been reported in both JAK3-SCID and acute megakaryoblastic leukemia.

The majority of JAK3-SCID patients are compound heterozygotes, having inherited a distinct mutation from each parent, although some individuals are homozygous for their mutations as a result of parental consanguinity. Most mutations have dramatic effects on protein expression of JAK3, but some missense mutations or small in-frame deletions allow for some protein expression. These mutations affect kinase activity, receptor binding, and intracellular trafficking.
In addition, 7 mutations of JAK3 have been recently described in 5 patients with acute megakaryoblastic leukemia with or without Down syndrome. These mutations are in general activation mutations. The Down syndrome patients presented initially with transient myeloproliferative disease.

Implicated in

Severe combined immunodeficiency (SCID)

Note: 34 unique mutations of JAK3 have been identified in cases of JAK3-SCID, occurring in all of its 7 structural JH domains. No hotspots have been reported and multiple types of mutations have been identified: 21 missense/nonsense mutations, 7 splice site mutations, 3 small deletions, 2 gross deletions and 1 insertion.

Disease

Defects in JAK3 are associated with the autosomal recessive T-cell negative/B-cell positive type of severe combined immunodeficiency (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.

Prognosis

SCID due to JAK3 deficiency is generally a lethal disorder. The advent of hematopoietic stem cell transplant revolutionized the outcome of JAK3-SCID, and at present it is still the treatment of choice.

Acute megakaryoblastic leukemia

Note: 7 unique mutations of JAK3 have also been identified in patients with acute megakaryoblastic leukemia. These mutations occur in the JH2, JH6, and JH7 domains.

Disease

Also, defects in JAK3 have been recently described in some cases of acute megakaryoblastic leukemia with or without Down syndrome. Acute megakaryoblastic leukemia is a type of acute leukemia where more than 50% of the blasts are of megakaryocytic lineage. The exact role of JAK3 in this disease is not completely known.

Prognosis

Acute megakaryoblastic leukemia demonstrates a bad clinical outcome.

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