Gene Section
Mini Review

JAK2 (janus kinase 2)
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Identity
Hugo: JAK2
Location: 9p24

DNA/RNA
Description
25 exons spanning roughly 140 kb of genomic DNA; 5402 bp pre-mRNA; 6 different transcripts, putatively encoding 4 different protein isoforms.

Protein
Description
1132 amino acids; 130.7 kDa; JAK2 contains a central Src homology 2 (SH2) domain, and two C-terminal domains: a tyrosine kinase domain JH1 (also termed PTK or TyrKc domain), and a tyrosine kinase-like domain JH2 (also termed STYKc).

Expression
Wide.

Localisation
Intracellular, possibly membrane associated.

Function
Protein tyrosine kinase of the non-receptor type that associates with the intracellular domains of cytokine receptors; JAK2 is the predominant JAK kinase activated in response to several growth factors and cytokines such as IL-3, GM-CSF and erythropoietin; it has been found to be constitutively associated with the prolactin receptor and is required for responses to gamma interferon.

Homology
JAK2 belongs to the janus kinase subfamily; so far four mammalian JAKs have been identified (JAK1, JAK2, JAK3, and TYK2); human JAK2 is >90% identical to the mouse and the rat JAK2 homologs.

Mutations
Somatic
A high proportion (>50%) of patients with myeloproliferative disorders (MPD; polycythemia vera, essential thrombocytopenia, idiopathic myelofibrosis - see below) carry a dominant gain-of-function V617F mutation in the JH2 kinase-like domain of JAK2. This mutation leads to deregulation of the kinase activity, and thus to constitutive tyrosine phosphorylation activity. The incidence of the V617F mutation in different studies ranges from 65-97% in polycythemia vera, from 41-57% in patients with essential thrombocytopenia, and from 23-95% in polycythemia vera.
patients with idiopathic myelofibrosis. In MPD the mutation is heterozygous in most patients and homozygous only in a minor subset. Mitotic recombination probably causes both 9p LOH and the transition from heterozygosity to homozygosity. The same mutation was also found in roughly 20% of Ph-negative atypical CML, in more than 10% of CMML, in about 15% of patients with megakaryocytic AML (AML M7), and 1/5 patients with juvenile myelomonocytic leukemia (JMML). The V617F mutation seems to occur exclusively in hematopoietic malignancies of the myeloid lineage.

**Implicated in**

\[ t(8;9)(p21-22;p24)/acute leukaemias → PCM1-JAK2 \]

**Disease**

Myeloid and lymphoid malignancies; predominantly atypical CML, but also found in chronic eosinophilic leukemia (CEL), (secondary) AML, and MDS/MPD; thirteen cases described to date, all male, except for one childhood female case with erythroid leukemia with multiple bone tumors.

**Prognosis**

Highly variable; allogeneic stem cell transplantation may be the only curative treatment.

**Hybrid/Mutated Gene**

5’ PCM1 - 3’ JAK2; only in some cases the reciprocal 5’ JAK2 - 3’ PCM1 is present.

**Abnormal Protein**

Almost the entire PCM1 protein containing multiple coiled-coil domains is fused to the tyrosine kinase C-terminal domains (JH2 and JH1) of JAK2.

**Oncogenesis**

Dimerization or oligomerization of the PCM1-JAK2 chimera through one or more of the coiled-coil motifs of PCM1 probably results in the constitutive activation of the tyrosine kinase domain of JAK2.

\[ t(9;12)(p24;p13) acute leukaemias → JAK2/ETV6 \]

**Disease**

Myeloid and lymphoid leukaemias; only three cases described to date; one case each: childhood T-ALL, pre-B-ALL, atypical CML.

**Prognosis**

Unknown.

**Hybrid/Mutated Gene**

5’ ETV6 - 3’ JAK2

**Abnormal Protein**

In the atypical CML the N-terminal HLH of ETV6 is fused to the tyrosine kinase C-terminal domains (JH2 and JH1) of JAK2; in the B-ALL the same ETV6 domain is fused to part of the JH2 and the complete JH1 domain, and in the T-ALL case to the JH1 domain.

**Oncogenesis**

It may be speculated that the HLH domain of ETV6 provides a dimerization interface to the kinase domain of JAK2, which activates JAK2; ETV6-JAK2 transgenic mice - generated using a T-ALL specific fusion construct - develop fatal CD8+ acute T-cell leukemia.

\[ t(9;22)(p24;q11.2)/MPD → JAK2-BCR \]

**Disease**

Atypical CML; only one case described to date.

**Hybrid/Mutated Gene**

5’ BCR - 3’ JAK2; absence of the reciprocal 5’ JAK2 - 3’ BCR.

**Abnormal Protein**

The N-terminal coiled-coil domain of BCR is fused to the JH1 tyrosine kinase C-terminal domain of JAK2.

**Oncogenesis**

Constitutive activation of the tyrosine kinase domain of JAK2 mediated through oligomerization through the coiled-coil domain of BCR.

**Polycythemia vera/Essential thrombocytopenia/Idiopathic thrombocytopenia/Idiopathic myelofibrosis**

Note: the V617F mutation in JAK2 could form the basis for a new molecular classification of myeloproliferative disorders.

**Disease**

Chronic myeloproliferative syndromes.

**Oncogenesis**

A significant percentage of patients with myeloproliferative disorders carries a dominant gain of function V617F mutation in JAK2; this mutation seems to lead to deregulation of the kinase activity of JAK2, and thus to constitutive tyrosine phosphorylation activity, providing hematopoietic cells with a proliferative and survival advantage.
### Breakpoints

<table>
<thead>
<tr>
<th>Breakpoint</th>
<th>Chromosome Location</th>
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<tbody>
<tr>
<td>8p21 (PCML)</td>
<td>JAK2 and partners. Editor 08/2004; last update 08/2005.</td>
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<tr>
<td>9p24 (JAK2)</td>
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<tr>
<td>12p13 (ETV6)</td>
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### References


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