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Gene Section
Review

JAK1 (Janus kinase 1)

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Identity

Other names: EC 2.7.10.2; JAK-1; JAK1A; JAK1B; JTK3

HGNC (Hugo): JAK1

Location: 1p31.3

DNA/RNA

Description

25 exons spanning roughly 135 kb of genomic DNA.

Transcription

5053 bp pre-mRNA; 1 transcript described.

Protein

Description

1154 amino acids; 133,3 kDa; JAK1 contains a N-terminal FERM domain, responsible of the binding to the receptor, a central Src homology 2 (SH2) domain, and two C-terminal domains: a tyrosine kinase domain JH1 and a pseudokinase domain JH2.

Expression

Ubiquitous.

Localisation

Intracellular, associated to cytokine receptors.

Function

JAK1 is a non-receptor tyrosine kinase that associates to cytokine receptors without intrinsic kinase activity to mediate cytokine-induced signal transduction; JAK1 associates with numerous cytokine receptors chains and is involved in signaling by the majority of cytokines: the gamma-C family (IL-2, IL-4, IL-7, IL-9, IL-15, IL-21), the gp130 family (IL-6, OSM, LIF, ...), interferons, ...

Homology

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

Implicated in

Acute lymphoblastic leukemia T cell type (T-ALL) and Acute lymphoblastic leukemia B cell type (B-ALL)

Prognosis

JAK1 mutations are associated with advanced age, poor response to therapy and overall prognosis (Flex et al., 2008).

Oncogenesis

Somatic JAK1 mutations occur in T cell acute lymphoblastic leukemia (ALL). These mutations seem to be more frequent among adult T-ALL patients, but the frequency varies between studies: 8/38 (21.0%; adult; Flex et al., 2008), 1/49 (2.0%; children; Flex et al., 2008), 2/11 (27.3%; adult; Jeong et al., 2008), 4/108 (3.7%; adult; Asnafi et al., 2009). These mutations represent gain of function mutations that participate in the leukemogenic process by inducing the constitutive activation of the JAK-STAT pathway.

Amino acid substitution	Proof of hyperactivity	domain	reference
S512L		SH2	Flex et al., 2008
A634D	Yes	Pseudokinase	Flex et al., 2008
Y652H		Pseudokinase	Asnafi et al., 2009
V658F	Yes	Pseudokinase	Jeong et al., 2008
R724H	Yes	Pseudokinase	Flex et al., 2008
R724Q		Pseudokinase	Asnafi et al., 2009
T782M		Pseudokinase	Jeong et al., 2008
L783F		Pseudokinase	Jeong et al., 2008
R879S		Kinase	Flex et al., 2008
R879C	Yes	Kinase	Flex et al., 2008
R879H		Kinasee	Flex et al., 2008

Table 1: Somatic mutations in JAK1 found in T-ALL patients.

Amino acid substitution	Proof of hyperactivity	domain	reference
K204M		FERM	Flex et al., 2008
L624_R629>W	Yes	Pseudokinase	Mullighan et al., 2009
A634D	Yes	Pseudokinase	Flex et al., 2008
S646F	Yes	Pseudokinase	Mullighan et al., 2009
L653F		Pseudokinase	Flex et al., 2008
V658F	Yes	Pseudokinase	Mullighan et al., 2009
R724H	Yes	Pseudokinase	Flex et al., 2008

Table 2: Somatic mutations in JAK1 found in B-ALL patients.

Amino acid substitution	Proof of hyperactivity	domain	reference
T478S		SH2	Xiang et al., 2008
V623A		Pseudokinase	Xiang et al., 2008
V658F	Yes	Pseudokinase	Jeong et al., 2008

Table 3: Somatic mutations in JAK1 found in AML samples.

Amino acid substitution	Proof of hyperactivity	domain	reference
Q644H;V645F		Pseudokinase	Xie et al., 2009

Table 4: Somatic mutations in JAK1 found in hepatocellular carcinomas.

Amino acid substitution	Proof of hyperactivity	domain	reference
H647Y		Pseudokinase	Jeong et al., 2008

Table 5: Somatic mutations in JAK1 found in breast cancer samples.

Amino acid substitution	Proof of hyperactivity	domain	reference
P782M		Pseudokinase	Jeong et al., 2008

Table 6: Somatic mutations in JAK1 found in non-small cell lung cancer samples.

JAK1 mutations were found in 3 B-cell ALL samples after the resequencing of 173 B-ALL (Flex et al., 2008) and in 3 samples after the resequencing of 187 high risk childhood B-ALL (Mullighan et al., 2009). No mutations were found after the resequencing of 69 B-ALL (Jeong et al., 2008).
JAK1 mutants induce the activation of different cytokine-receptor complexes like the IL-9 receptor or the IL-2 receptor, that will induce the constitutive activation of the JAK-STAT pathway.

Acute myeloid leukemia (AML)

Oncogenesis

JAK1 mutaions were found in two AML samples after the resequencing of 94 AML (Xiang et al., 2008) and in one AML sample after the resequencing of 105 AML.

Hepatocellular carcinoma

Oncogenesis

JAK1 mutations were found in one hepatocellular carcinoma sample after the screening of 84 hepatocellular carcinomas.

Breast cancer

Oncogenesis

JAK1 mutation was found in a breast cancer sample after the resequencing of 90 breast cancers.

Non-small cell lung cancer

Oncogenesis

JAK1 mutation was found in a non-small cell lung cancer sample after the resequencing of 47 non-small cell lung cancer samples.

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