**JAG1 (jagged 1 (Alagille syndrome))**

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**Identity**

Hugo: JAG1

Other names: JAGGED1; HJ1; hJ1; JAGL1

Location: 20p12.1-11.23

Local order: telomere PLCB1, PLCB4, PAK7, SNAP25, MKKS, JAG1 centromere.

**DNA/RNA**

<table>
<thead>
<tr>
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The gene spans 36 kb on the short arm of chromosome 20. It contains 26 exons (size from 28 bp to 2 kb) and 25 introns (size from 89 bp to nearly 9 kb): table 1. Intron 19 contains a CA dinucleotide repeat which is a highly polymorphic marker: D20S1154 (12 alleles with heterozygosity of 85.8% and PIC of 0.844).

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**Transcription**

JAG1 is transcribed from centromere to telomere. The 26 exons are coding; exon 1 is coding on the last 81 bases, and exon 26 on the first 455 bases. The transcript size is 5.5 kb.

**Protein**

**Description**

Glycosylated transmembrane protein; 1218 amino acids.

Predicted glycosylation sites: 960; 991; 1045; 1064.

Apparent size on Western blot: about 180 kDa.
Figure 1. Schematic representation of the JAG1 protein (1218 amino acids). It contains signal peptide: SP (1-33), delta, serrate, lag-2 domain; DSL (185-229), 16 EGF-like repeats (230-856; cf table 3), cysteine-rich region: CR (863-1002), transmembrane domain: TM (1068-1093), intracellular (cytoplasmic) part: IC (1094-1218).

Table 2. EGF-like repeats of the human JAG1 protein. A: the 16 EGF motifs are aligned. A 24-amino acid insertion is present in EGF10 (in grey, as in human JAG2 protein). The numbers above the sequences refer to cysteine residues (C in blue). Each EGF-like repeat contains 6 cysteine residues, able to make disulfide bond bridges: 1st with 3th; 2nd with 4th and 5th with 6th. Some of these repeats are calcium-binding EGF-like domains, which have at their amino-terminus, negatively charged or polar residues such as aspartic acid (D), glutamic acid (E), glutamine (Q), and asparagine (N). B: consensus sequence of an EGF-like repeat. x is any amino acid. Three glycine (G) residues are conserved (in green). The amino acid Z (in yellow) could be either phenylalanine (F), tryptophan (W), tyrosine (Y) or histidine (H).

Expression
Very wide; in heart, arteries, kidney, lung, pancreas, skeletal muscle, central nervous system, limb bud, etc. during embryonic and fetal development; in adult tissues; in tumors.

Localisation
Transmembrane plasma protein.

Function
Ligand of the NOTCH family of receptors. The Notch signaling pathway plays a crucial role during embryonic pattern formation, controls many conserved cell determination events and defines a fundamental mechanism controlling cell fate. It is involved in lineage cell decisions in a variety of tissues. It plays a role in hematopoiesis, vascular development and angiogenesis, myogenesis, neurogenesis, somitogenesis; kidney, eye, ear, and tooth development etc.

Homology
Serrate in D. melanogaster; Lag-2 in C. elegans; Jagged 1a and jagged 1b in zebrafish (D. rerio); Jagged2 ou serrateB in zebrafish (D. rerio);
JAG1 (jagged 1 (Alagille syndrome))

Mutations

Note: Heterozygous mutations in JAG1 gene cause Alagille syndrome.
Five per cent are deletions on the short arm of chromosome 20 that could be visible in cytogenetics: the whole gene or part of the gene, or a region larger than the gene can be deleted: del(20p), del(20)(p11.2), del(20)(p12.3-p11.23), del(20)(p13-p12.2), ins(7;20), t(2;20).
Ninety five per cent are point intragenic mutations that are spread over the entire gene, with the exception of the part of the gene encoding the intracellular part of the protein (see the structure of the protein in Figure 2). Seventy per cent of mutations are nonsense or frameshift mutations leading to premature stop codons; 15% are missense mutations and 14% are splice site mutations (Figure 3). The most frequent mutation (‘delCAGT’ in exon 17) accounts for 5% of all mutations.
Some AGS probands present with no mutation in the DNA of the 26 exons and exon boundaries of JAG1. In those instances, no prenatal diagnosis can be performed.

Germinal
Most mutations (70%) are de novo.

Somatic
Cases of mosaicisms are described.

Implicated in

Alagille syndrome (AGS)

Disease
Syndrome associating 5 major features (complete syndrome): paucity of interlobular bile ducts, pulmonary artery stenosis, butterfly-like vertebrae, posterior embryotoxon and a peculiar face. Only the 2 first ones are symptomatic. Incomplete syndrome is very frequent. AGS presents with a highly variable expressivity and nearly complete penetrance.

Figure 3. Distribution of 344 intragenic JAG1 mutations in Alagille patients. We summarized all the mutations published so far and unpublished results from our laboratory and from A. Mantel (Hospital of Kremlin-Bicêtre). Seventy five per cent mutations (257/344) are different at the DNA level. Sequencing exons 2, 4, 6, 9, 17, 23, and 24 which correspond to 35% of cDNA, detect 53% of all mutations. The signal peptide is encoded by exon 1, and the DSL domain by part of exon 4, the 16 EGF-like repeats correspond to exons 5-21, the cysteine-rich region partially overlaps exons 22-24, and the transmembrane domain and the intracellular region are encoded by exon 26.
**References**


Lu F, Morrisette JJ, Spinner NB. Conditional JAG1 mutation shows the developing heart is more sensitive than developing liver to JAG1 dosage. Am J Hum Genet 2003;72:1065-70.


This article should be referenced as such: