Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section

Review

JAG1 (jagged 1 (Alagille syndrome))

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Published in Atlas Database: October 2005

Online updated version: http://AtlasGeneticsOncology.org/Genes/JAG1ID41029ch20p12.html
DOI: 10.4267/2042/38289

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

Exon no	Nucleotide polymorphism	Amino acid
2	518C/T	F35
2	680G/A	G89
2	683G/T	G90
2	707C/T	S98
4	1001C/T	C196
5	1157A/G	P248
6	1178T/C	Y255
7	1337C/T	N308
11	1802C/T	S463
13	1991C/T	I526
13	2120G/A	T569
17	2627A/C	T738
18	2644G/A	R/Q744
20	2795C/T	S794
22	3025C/G	P/R871
23	3179C/T	D922
26	3830C/T	Y1139
26	3941T/C	Y1176

Table 1. Polymorphisms in the cDNA of JAG1. GenBank Accession no : HSU73936.

Description

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).
Size of exons and introns of the human JAG1 gene
exon 1: 494; intron 1: 443; exon 2: 306; intron 2: 8686; exon 3: 52; intron 3: 5240; exon 4: 255; intron 4: 2009; exon 5: 61; intron 5: 3799; exon 6: 131; intron 6: 217; exon 7: 120; intron 7: 436; exon 8: 114; intron 8: 1220; exon 9: 114; intron 9: 611; exon 10: 114; intron 10: 414; exon 11: 47; intron 11: 338; exon 12: 174; intron 12: 438; exon 13: 151; intron 13: 856; exon 14: 165; intron 14: 854; exon 15: 114; intron 15: 501; exon 16: 114; intron 16: 99; exon 17: 114; intron 17: 163; exon 18: 117; intron 18: 478; exon 19: 28; intron 19: 493; exon 20: 86; intron 20: 1176; exon 21: 114; intron 21: 595; exon 22: 110; intron 22: 89; exon 23: 234; intron 23: 215; exon 24: 132; intron 24: 179; exon 25: 151; intron 25: 827; exon 26: 1979.
Polymorphisms were described in the cDNA sequence (table 1).

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.

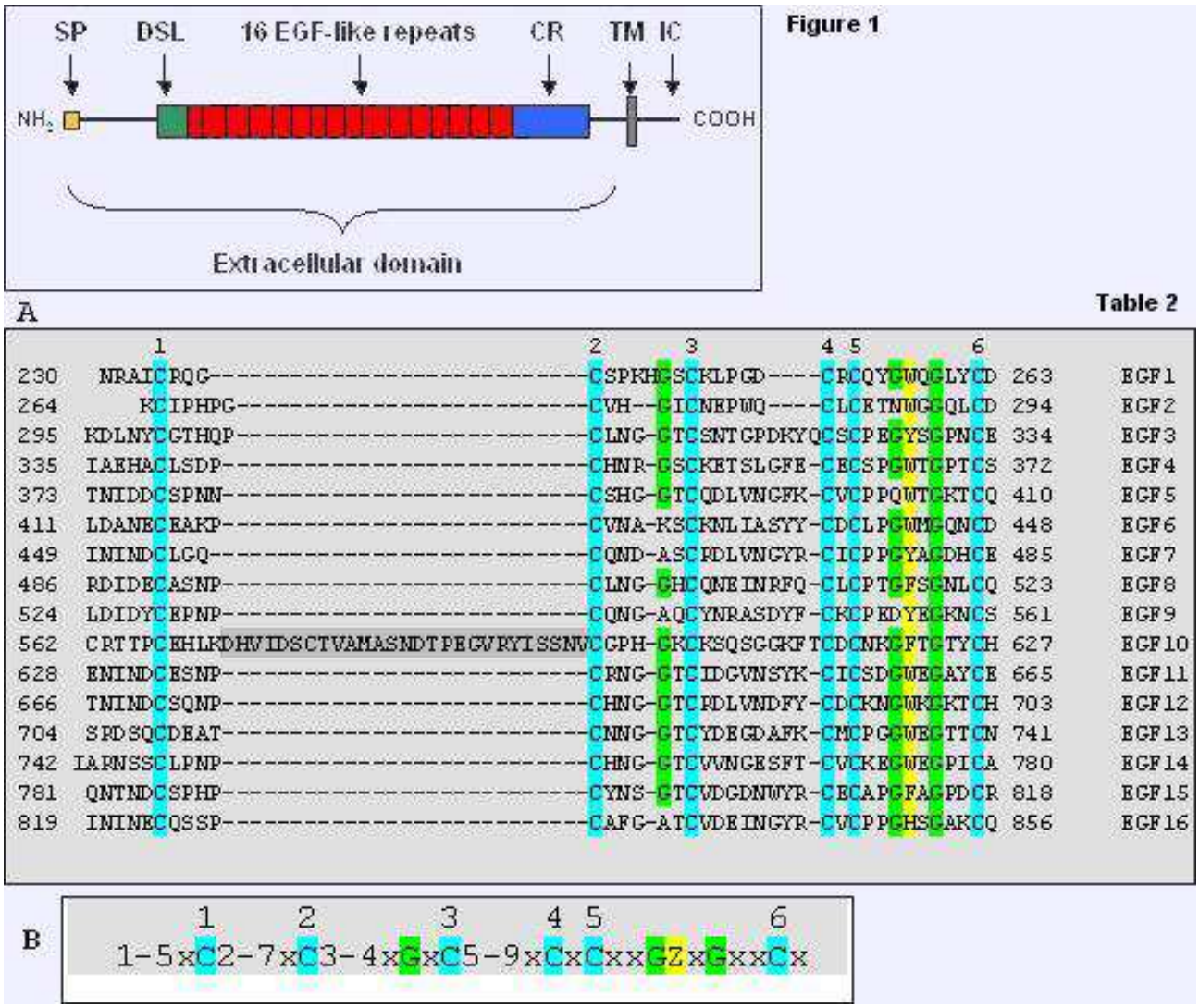

Figure 1. Schematic representation of the JAG1 protein (1218 amino acids). It contains signal peptide: SP (1-33), delta, serrate, lag-2 domain: DSL (185-229), 16 EGF-like repeats (230-856; cf table 3), cysteine-rich region: CR (863-1002), transmembrane domain: TM (1068-1093), intracellular (cytoplasmic)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

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);

X-serrate-1 in tadpole (Xenopus laevis);
C-serrate-1 and C-serrate-2 in chicken (Gallus gallus);
Jagged1 and jagged2 in mouse (Mus musculus);
Jagged1 and jagged2 in rat (Rattus norvegicus);
Jagged1 and jagged2 in dog (Canis familiaris);
Partial jagged1 in Bos Taurus;
JAGGED2 in Homo sapiens.

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.

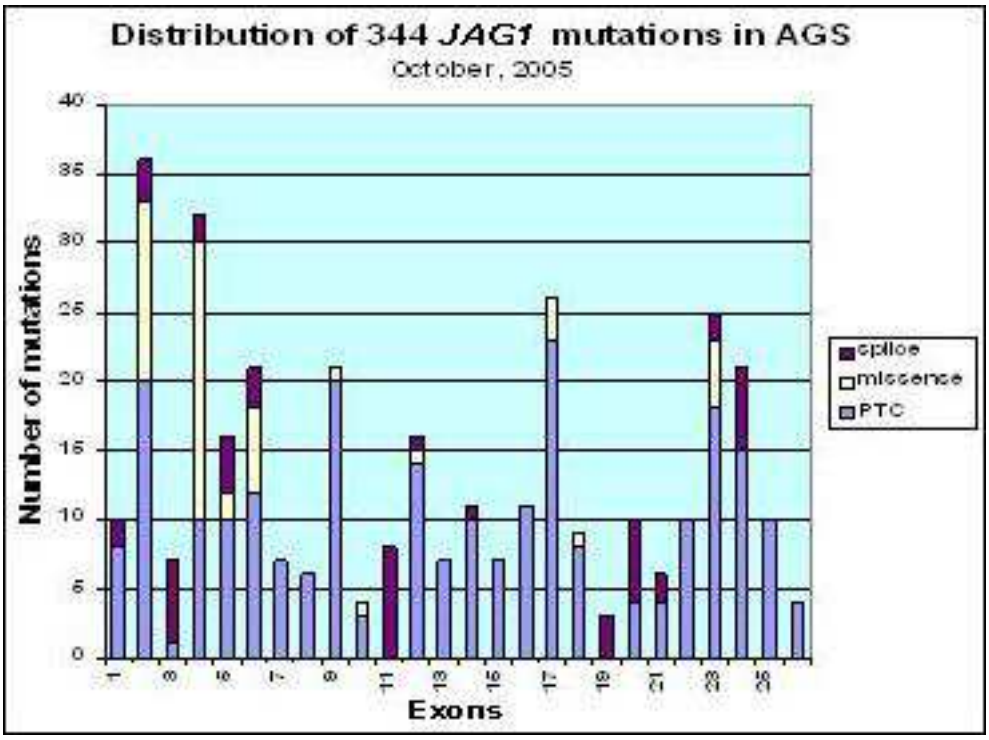

Figure 3. Distribution of 344 intragenic JAG1 mutations in Alagille patients. We summarized all the mutations published so far and unpublished results from our laboratory and from A. Mantel (Hospital of Kremlin-Bicêtre). Seventy five per cent mutations (257/344) are different at the DNA level. Sequencing 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.

Tetralogy of Fallot

Disease

The heterozygous mutation (G274D) in EGF2 of JAG1 has been reported in one family: affected family members also had characteristic facies.

Familial deafness, congenital heart defects, and posterior embryotoxon

Disease

The heterozygous mutation (C234Y) in EGF1 of JAG1 has been reported in one family.

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This article should be referenced as such:
Meunier-Rotival M, Driancourt C, Boyer-Di Ponio J. JAG1 (jagged 1 (Alagille syndrome)). Atlas Genet Cytogenet Oncol Haematol.2006;10(2):79-82.