

Cancer Prone Disease Section

Mini Review

Alagille syndrome (AGS)

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Identity

Other names: Alagille-Watson syndrome (AWS); arteriohepatic dysplasia (AHD); cholestasis with peripheral pulmonary stenosis; hepatic ductular paucity, syndromatic

Note: 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. Other features have been described involving kidney, cardiac and vascular anomalies including tetralogy of Fallot, ear, pancreas, intestine etc.

Inheritance: autosomal dominant with a highly variable expressivity and nearly complete penetrance; frequency is about 1/70,000-100,000 live newborns; 60-70% are sporadic cases.

Clinics

Phenotype and clinics

- liver: jaundice, pruritus, xanthomas, bile duct paucity, biochemical cholestasis and hypercholesterolemia. Liver transplantation is performed in about 25% cases.
- cardiovascular system: peripheral pulmonary stenosis, coarctation of aorta, tetralogy of Fallot, ventricular or atrial septal defects, patent ductus arteriosus, truncus arteriosus, right ventricle hypoplasia.
- systemic vascular system: coarctation of aorta, middle aortic syndrome, arterial hypoplasia (hepatic, renal, carotid, celiac), moyamoya disease, hypoplastic portal vein branch, intracranial bleeding.
- vertebrae and skeleton: butterfly-like vertebrae, spina bifida, abnormal progression of interpedicular distances, shortening of distal phalanges and metacarpal bones, clinodactily.

- eye: posterior embryotoxon, retinal pigmentation, iris strands, cataract, myopia, strabismus, glaucoma, optic disc drusen, fundus hypopigmentation, blindness.
- kidney: mesangiolipidosis, tubular dysfunction, tubulointerstitial nephritis, renal hypoplasia, renal agenesis, horseshoe kidney, cysts.
- ear: temporal bone abnormalities, chronic otitis media, deafness.
- larynx: high pitched voice.
- pancreas: diabetes, exocrine pancreatic insufficiency.
- gut: small bowel atresia or stenosis.
- lung: tracheal and bronchial stenosis.
- face: prominent forehead, deep-set eyes, mild hypertelorism, straight nose, small pointed chin.
- growth retardation.
- mental retardation (?).

Neoplastic risk

Very rare hepatocellular carcinoma.

Treatment

No specific treatment.

Prognosis

Major contributors to morbidity arise from bile duct paucity or cholestatic liver disease (including liver transplantation), cardiac disease, and renal disease.

Cytogenetics

3-7% of patients with Alagille syndrome have deletions of part or totality of the JAG1 gene in 20p and, in rare instances translocations : del(20p), del(20)(p11.2), del(20)(p12.3-p11.23), del(20)(p13-p12.2), ins(7;20), t(2;20).

Other findings

Note: There is no phenotype-genotype correlation.

Genes involved and Proteins

JAGGED1

Location: 20p12.1-11.23

DNA/RNA

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).

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.

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 membrane receptors.

Homology:

- serrate in *D. melanogaster*.

- lag-2 in *C. elegans*.

- jagged 1a and jagged 1b in zebrafish (*D. rerio*).

- jagged 2 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*.

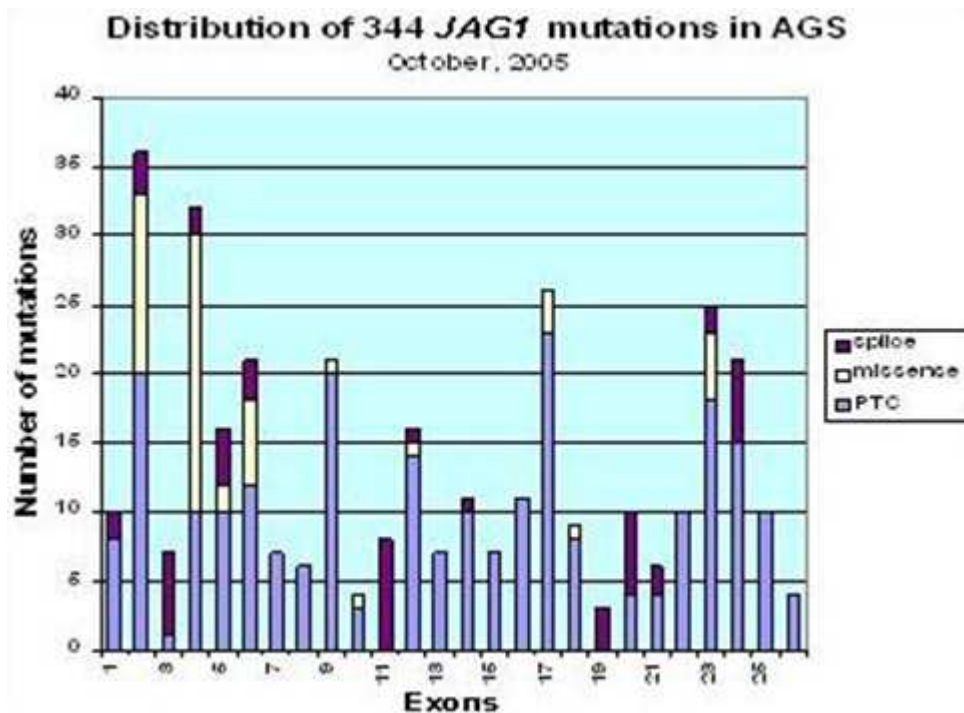
JAGGED2 in *Homo sapiens*.

Mutations

95% of mutations are intragenic mutations located in the part of the JAG1 gene encoding extracellular and transmembrane domains of the protein. They are point mutations or small deletions/insertions, leading to frame-shift mutations, premature stop codons, splice site mutations, and missense mutations.

3-7% of mutations are deletions of part or totality of the JAG1 gene in 20p and, in rare instances translocations. Some AGS cases 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.

Somatic: Mosaicism has been reported.



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 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.

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