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Alagille Syndrome

Synonyms: Arteriohepatic Dysplasia, Syndromic Bile Duct Paucity

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Summary

Clinical characteristics

Alagille syndrome (ALGS) is a multisystem disorder with a wide spectrum of clinical variability; this variability is seen even among individuals from the same family. The major clinical manifestations of ALGS are bile duct paucity on liver biopsy, cholestasis, congenital cardiac defects (primarily involving the pulmonary arteries), butterfly vertebrae, ophthalmologic abnormalities (most commonly posterior embryotoxon), and characteristic facial features. Renal abnormalities, growth failure, behavioral differences, splenomegaly, retinal changes, and vascular abnormalities may also occur.

Diagnosis/testing

The diagnosis of ALGS is established in a proband who meets clinical diagnostic criteria and/or has a heterozygous pathogenic variant in *JAG1* or *NOTCH2* identified by molecular genetic testing.

Management

Targeted therapy: Ileal bile acid transporter inhibitors (maralixabat and odevixibat) to increase excretion of bile acids.

Supportive care: Management by a multidisciplinary team according to clinical manifestations (clinical genetics, gastroenterology/hepatology, nutrition, cardiology, ophthalmology, nephrology, transplant hepatology, and child development); choleretic agents (ursodeoxycholic acid), other medications (cholestyramine, rifampin,

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naltrexone) for pruritus and xanthomas; liver transplantation for refractory cholestasis and/or end-stage liver disease; optimized nutrition and replacement of fat-soluble vitamins as needed; treatment of cardiovascular manifestations in a center with experience with ALGS; low vision services as needed; standard treatment for hepatocellular carcinoma and renal and neurologic involvement.

Surveillance: Monitor liver function per gastroenterologist/hepatologist; serum alpha-fetoprotein and liver ultrasound every six months; at each visit, assess growth, blood pressure, and for recurrent fractures; nutrition assessment as needed; assessment for vascular manifestations per cardiologist; vision assessment per ophthalmologist; basic metabolic panel every six months; assess developmental progress and for attention and executive function impairment annually.

Agents/circumstances to avoid: Contact sports; alcohol consumption if liver disease is present.

Genetic counseling

ALGS is inherited in an autosomal dominant manner. Approximately 40% of individuals have an inherited pathogenic variant and about 60% have a *de novo* pathogenic variant. Parental somatic/germline mosaicism has been reported. Offspring of an individual with ALGS have a 50% chance of inheriting the *JAG1* or *NOTCH2* pathogenic variant. Prenatal testing for pregnancies at increased risk and preimplantation genetic testing are possible if the causative genetic alteration has been identified in an affected family member. Because ALGS is associated with highly variable expressivity with clinical features ranging from subclinical to severe, clinical manifestations cannot be predicted by molecular genetic prenatal testing.

Diagnosis

Clinical diagnostic criteria for Alagille syndrome (ALGS) have been published [Mitchell et al 2018].

Suggestive Findings

ALGS **should be suspected** in individuals with any combination of the following histologic findings, major clinical features, and/or family history.

The histologic finding of bile duct paucity (an increased portal tract-to-bile duct ratio) on liver biopsy. Although considered to be the most important and constant feature of ALGS, bile duct paucity is only identified in 65% of biopsies done in the first three months of life. In the newborn, a normal ratio of portal tracts to bile ducts, bile duct proliferation, or histology suggestive of neonatal hepatitis may be observed. Eventually, bile duct paucity is present in about 95% of individuals [Vandriel et al 2023]. Since liver disease is often present from infancy, this percentage may be an overestimate due to ascertainment bias.

Major clinical features

- Cholestasis
- Cardiac defect (most commonly stenosis of the peripheral pulmonary artery and its branches)
- Skeletal abnormalities (most commonly butterfly vertebrae identified in AP chest radiographs)
- Ophthalmologic abnormalities (most commonly posterior embryotoxon)
- Characteristic facial features (most commonly triangular-shaped face with a broad forehead and a pointed chin, bulbous tip of the nose, deep-set eyes, and hypertelorism) (See Figure 1.)

Family history is consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations). Absence of a known family history does not preclude the diagnosis.

Figure 1. Typical facial features of Alagille syndrome. Note broad forehead, deep-set eyes, and pointed chin.

Establishing the Diagnosis

The clinical diagnosis of ALGS can be **established** in a proband based on clinical diagnostic criteria [Mitchell et al 2018, Kohut et al 2021], or the molecular diagnosis can be established in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *JAG1* or *NOTCH2* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *JAG1* or *NOTCH2* variant of uncertain significance does not establish or rule out the diagnosis.

Clinical diagnosis. The clinical diagnosis of ALGS can be established in an individual with bile duct paucity and any three of the five major clinical features described in suggestive findings, or one of the five major clinical features in an individual with a family history of ALGS.

Molecular diagnosis. Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Option 1

Serial single-gene testing. Sequence analysis of *JAG1* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis of *JAG1* to detect exon and whole-gene deletions or duplications. Sequence analysis of *JAG1* is performed first. If no pathogenic variant is found, *NOTCH2* molecular genetic testing should be considered when the diagnosis is strongly suspected on clinical grounds, but no *JAG1* pathogenic variant (by either sequence or deletion/duplication analysis) was identified.

Note: (1) If a deletion involving the entire *JAG1* gene is identified, a full cytogenetic study may be considered to determine if a rare chromosome rearrangement (translocation or inversion) is present. (2) The presence of developmental delay and/or hearing loss in addition to the features commonly seen in ALGS may increase the suspicion of a chromosome deletion, and a chromosomal microarray analysis (CMA) would be recommended.

A multigene panel that includes *JAG1*, *NOTCH2*, and other genes of interest (see Differential Diagnosis) may be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. (5) Some pathogenic variants may not be detectable by routine sequence analysis including copy neutral inversions and pathogenic variants within the promoter. For individuals with a clinical diagnosis and no identifiable *JAG1* or *NOTCH2* pathogenic variant, alternative methodologies such as genome sequencing (with focus on *JAG1* and *NOTCH2*) or RNA sequencing may be useful [Rajagopalan et al 2021].

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the diagnosis of ALGS is not considered because an individual does not meet the clinical diagnostic criteria, **comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most used; **genome sequencing** is also possible and is being increasingly utilized.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Alagille Syndrome

Gene [1, 2]	Proportion of ALGS Attributed to Pathogenic Variants in Gene	Proportion of Probands with a Pathogenic Variant [3] Detectable by Method	
		Sequence analysis [4]	Gene-targeted deletion/duplication analysis [5]
JAG1	94.3% [6]	88% [6]	12% [6]
NOTCH2	2.5 [6]	<100% [6]	1 individual [7]
Unknown [8]	3.2% [6]	NA	

ALGS = Alagille syndrome; NA = not applicable

1. Genes are listed in alphabetic order.

2. See Table A. Genes and Databases for chromosome locus and protein.

3. See Molecular Genetics for information on variants detected in this gene.

4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.

5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications.

6. Gilbert et al [2019]

7. One individual with a 5.9-kb deletion including exons 31 and 34 has been reported after genome sequencing [Rajagopalan et al 2021].

8. Individuals with a clinical diagnosis of ALGS but without a detectable pathogenic variant in either *JAG1* or *NOTCH2* have been hypothesized to have a pathogenic variant in *JAG1* or *NOTCH2* that is not yet detectable with current molecular genetic testing [Authors, personal observation]. It is also possible that another gene related to the Notch signaling pathway, or a variant in an untranslated regulatory region, may be responsible, although this has not yet been reported.

Clinical Characteristics

Clinical Description

Alagille syndrome (ALGS) is a multisystem disorder with a wide spectrum of clinical variability ranging from life-threatening liver or cardiac disease to only subclinical manifestations (e.g., butterfly vertebrae, posterior embryotoxon, characteristic facial features) [Mitchell et al 2018, Kohut et al 2021]. Some individuals present with an isolated feature (e.g., cardiac disease, aneurysmal disease) [Gilbert & Loomes 2021, Althali & Hentges 2022, Rodrigues Bento et al 2022]. Clinical variability is seen even among individuals from the same family [Kamath et al 2003].

To date, more than 700 individuals with ALGS have been found to have a pathogenic variant in *JAG1 or NOTCH2* [Gilbert et al 2019]. Table 2 lists the phenotypic features associated with this condition.

Table 2. Alagille Syndrome: Frequency of Select Features

Feature	% of Persons w/Feature	Comment
Hepatic abnormality	95%	Bile duct paucity; conjugated hyperbilirubinemia; chronic cholestasis characterized by pruritus, xanthomas, & fat-soluble vitamin deficiencies; end-stage liver disease
Cardiac manifestations	90%-97%	Most commonly including peripheral pulmonary stenosis & tetralogy of Fallot
Posterior embryotoxon	78%-89%	
Vertebral anomalies	33%-93%	
Characteristic facies	20%-90%	
Renal manifestations	39%	Renal malformations & kidney disease
Vascular	15%-30%	Intracranial bleeds, systemic vascular anomalies, & other, including moyamoya disease

McElhinney et al [2002], Kohut et al [2021], Vandriel et al [2023]

Onset. Individuals with ALGS who have severe liver or cardiac involvement are most often diagnosed in infancy. In those individuals with subclinical or mild hepatic manifestations, the diagnosis may not be established until later in life.

Hepatic manifestations. While some individuals with *JAG1* or *NOTCH2* pathogenic variants have no detectable hepatic manifestations, in most affected people, liver disease presents within the first three months of life. In a recent report on a large cohort of children with ALGS, 85% had a history of neonatal cholestasis [Gilbert & Loomes 2021, Althali & Hentges 2022, Rodrigues Bento et al 2022, Vandriel et al 2023]. The severity of liver disease ranges from asymptomatic elevations of liver enzymes to jaundice, chronic cholestasis, and end-stage liver disease. The high prevalence of liver disease in some series is likely affected by ascertainment bias; individuals with liver disease are more readily identified by gastroenterologists and/or hepatologists. In other series, in which enrollment is not driven by organ system, a lower rate of liver disease has been observed (e.g., 61% of individuals with ALGS were reported to have liver disease in a study by da Palma et al [2021]).

Jaundice and conjugated hyperbilirubinemia may be present in the neonatal period. Increased serum concentrations of bile acids, alkaline phosphatase, gamma-glutamyl transpeptidase, triglycerides, and the aminotransferases are also commonly observed. Impaired bile salt secretion can lead to fat-soluble vitamin deficiencies and malnutrition.

Cholestasis manifests as pruritus, increased serum concentration of bile acids, growth failure, and xanthomas. Pruritus is reported to occur in 74% of children at a median age of onset of 12 months [Vandriel et al 2023]. Xanthomas are reported to occur in 24% of children with ALGS with a median age of onset of 25 months [Vandriel et al 2023]. A recent report indicated that 50.4% of individuals with a history of neonatal cholestasis will undergo a liver transplant by age 18 years. The median age for liver transplant was age 2.8 years, with 72% occurring in the first five years of life [Vandriel et al 2023]. The primary indication for liver transplant included cholestasis (72%) and portal hypertension (30%) [Vandriel et al 2023]. Portal hypertension as the primary indication for liver transplant was more common in older individuals. More than half of individuals had more than one indication for transplant. Survival after transplant was 88% at age 20 years [Vandriel et al 2023]. While it is difficult to predict whether a child with cholestasis will have improvement or progression of liver disease, a total bilirubin of <5.0 mg/dL between age six and 12 months was associated with better native liver survival [Mouzaki et al 2016, Vandriel et al 2023].

Liver biopsy typically shows paucity of the intrahepatic bile ducts, which may be progressive. In infants younger than age six months, bile duct paucity is not always present, and the liver biopsy may demonstrate ductal proliferation, resulting in the possible misdiagnosis of ALGS as biliary atresia.

An increased risk for hepatocellular carcinoma (HCC) has been identified in children and adults with *JAG1*- and *NOTCH2*-related ALGS, even in the absence of additional features of ALGS [Schindler et al 2021, Vázquez Rodríguez et al 2022]. This suggests that individuals with ALGS and apparently nonpenetrant family members with the ALGS-related *JAG1* or *NOTCH2* pathogenic variant should undergo surveillance for early detection of HCC.

Cardiovascular manifestations. The pulmonary vasculature (pulmonary valve, pulmonary artery, and its branches) is most commonly involved, with structural abnormalities seen in up to 94% of individuals [Kohut et al 2021]. Pulmonic stenosis (peripheral and branch) is the most common cardiac finding (67%) [Emerick et al 1999]. The most common complex cardiac defect is tetralogy of Fallot, seen in 7%-16% of individuals [Emerick et al 1999]. Other cardiac malformations include (in order of decreasing frequency) ventricular septal defect, atrial septal defect, aortic stenosis, and coarctation of the aorta [Tretter & McElhinney 2018].

Other vascular abnormalities. Neurovascular accidents, reported at rates as high as 15% [Emerick et al 1999], accounted for 34% of mortality in one large study [Kamath et al 2004, Kohut et al 2021]. Renovascular anomalies, middle aortic syndrome, and moyamoya disease [Woolfenden et al 1999, Rocha et al 2012] have been reported. Anomalies of the basilar, carotid, and middle cerebral arteries also occur [Kamath et al 2004, Emerick et al 2005]. Affected individuals with a *JAG1* pathogenic variant from two unrelated families had isolated aneurysmal disease without other features of ALGS, demonstrating variable expressivity of ALGS [Rodrigues Bento et al 2022].

Ophthalmologic manifestations. The most common ophthalmologic finding in individuals with ALGS is posterior embryotoxon. Posterior embryotoxon, a prominent Schwalbe ring, is a defect of the anterior chamber of the eye. Most accurately identified on slit lamp examination, posterior embryotoxon does not affect visual acuity but is useful as a diagnostic aid. Posterior embryotoxon is also present in approximately 8%-15% of individuals in the general population.

Other defects of the anterior chamber seen in individuals with ALGS include Axenfeld anomaly and Rieger anomaly. Ocular ultrasonographic examination in 20 children with ALGS found optic disk drusen in 90%. Retinal pigmentary changes are also common (32% in one study) [Hingorani et al 1999, El-Koofy et al 2011]. Additional eye anomalies have also been described [Makino et al 2012].

While for many individuals the visual prognosis is good, recently additional abnormalities have been recognized such as peripheral chorioretinal changes (including atrophy with accompanying loss of function in the visual

field) and other retinal pigmentary changes, macular atrophy, and progressive decreases in vision in some individuals [da Palma et al 2021, Paez-Escamilla et al 2022].

Skeletal manifestations. The most common radiographic finding is butterfly vertebrae, a clefting abnormality of the vertebral bodies that occurs most often in the thoracic vertebrae. Butterfly vertebrae are usually asymptomatic. The incidence in the general population is unknown but suspected to be low.

Other skeletal manifestations in individuals with ALGS have been reported less frequently [Zanotti & Canalis 2010]. Craniosynostosis (unilateral coronal) has been reported in 0.9% of individuals with ALGS, compared to 0.03% in the normal population [Kamath et al 2002, Yilmaz et al 2013]. Individuals with ALGS have a high risk for bone fractures with significant bone mineral deficiency, quantified by dual-energy x-ray absorptiometry (DXA) analysis [Loomes et al 2019].

Facial features. The constellation of facial features observed in children with ALGS includes a broad forehead, deep-set eyes with moderate hypertelorism, pointed chin, and a concave or straight nasal ridge with a bulbous tip. These features give the face the appearance of an inverted triangle. The typical facial features are almost universally present in ALGS (see Figure 1). Additional features include oral and dental manifestations such as jaw morphology alterations, abnormal dental structure, tooth discoloration, and gingival inflammation, hypothesized to be a result of exposure to high levels of bilirubin during timing of dental calcification and/or treatment-associated medications [Reynal et al 2023].

Although the facial phenotype in ALGS is specific to the syndrome and is often a powerful diagnostic tool, Lin et al [2012] showed that North American dysmorphologists had difficulty assessing the facial features in a cohort of Vietnamese children with ALGS, suggesting that the value of this diagnostic tool is variable across populations.

Renal abnormalities can include both structural (small hyperechoic kidney, ureteropelvic obstruction, renal cysts) and functional (most commonly renal tubular acidosis). Renal dysplasia is the most common renal abnormality, followed by renal tubular acidosis [Kohut et al 2021]. Hypertension and renal artery stenosis have also been noted in adults with ALGS [Salem et al 2012].

Growth failure has been observed in up to 50%-90% of individuals with ALGS; although not well understood, it has been attributed to malnutrition/malabsorption as well as cholestasis [Emerick et al 1999, Arvay et al 2005, Kamath et al 2015].

Neurodevelopmental manifestations. Mild delays of gross motor skills were identified in 16% of affected individuals. Mild intellectual disability was identified in 2% by Emerick et al [1999]. Individuals with ALGS are at an increased risk for attention and executive function impairment, and early screening for identification of these deficits is recommended to maximize developmental outcomes [Leung et al 2022].

Other features

- Delayed puberty and high-pitched voice [Turnpenny & Ellard 2012]
- Splenomegaly [Emerick et al 1999, Subramaniam et al 2011]

Life span in ALGS may be reduced, with the primary cause of death occurring from liver transplant-related complications, cardiac disease, severe liver disease, and intracranial bleeding [Emerick et al 1999, Kamath et al 2004, Cho et al 2015, Vandriel et al 2023]. A recent study reported an overall mortality rate of 8.5%, with the majority occurring in the first five years of life [Vandriel et al 2023].

Phenotype Correlations by Gene

Although very few individuals with *NOTCH2* pathogenic variants have been described to date, it has been reported that individuals with *NOTCH2*-related ALGS have a lower prevalence of cardiac, vertebral, and facial anomalies than those with *JAG1*-related ALGS [Kamath et al 2012; Vandriel et al, unpublished data].

Genotype-Phenotype Correlations

No genotype-phenotype correlations for *JAG1* or *NOTCH2* have been identified.

Penetrance

ALGS associated with pathogenic variants in either of the known causative genes (*JAG1* and *NOTCH2*) demonstrates highly variable expressivity with clinical features ranging from subclinical to severe.

JAG1. To determine the range and frequency of clinical findings in individuals with a *JAG1* pathogenic variant and, hence, the penetrance, Kamath et al [2003] studied 53 *JAG1* variant-confirmed relatives of probands with ALGS. Their findings identified two such individuals with no features of ALGS – a 96% penetrance rate.

NOTCH2. Penetrance appears complete in the individuals so far identified with *NOTCH2* pathogenic variants [Kamath et al 2012, Gilbert et al 2019].

Prevalence

The prevalence of ALGS is estimated at 1:30,000-50,000 live births [Saleh et al 2016]. Advances in molecular genetic testing have aided in increasing the detection rate for the disease; however, due to the variable phenotype, it likely remains underdiagnosed [Kamath et al 2003].

Genetically Related (Allelic) Disorders

Other phenotypes associated with germline pathogenic variants in *JAG1* and *NOTCH2* are summarized in Table 3.

Table 3. Allelic Disorders

Gene	Phenotype
JAG1	*JAG1*-related autosomal dominant Charcot-Marie-Tooth hereditary neuropathy (OMIM 619574). This disease-gene relationship is based on a single study & the proposed mechanism is similar to what is seen for some missense variants in ALGS. Additional studies are needed to confirm this association.
NOTCH2	Specific germline pathogenic variants in *NOTCH2* are known to be associated with Hajdu-Cheney syndrome (serpentine fibula polycystic kidney syndrome) (OMIM 102500), an autosomal dominant disorder that causes focal bone destruction, osteoporosis, craniofacial dysmorphology, renal cysts, cleft palate, and cardiac defects. The *NOTCH2* pathogenic variants identified in individuals with Hajdu-Cheney syndrome were all localized in the last exon (exon 34) of *NOTCH2* and appear to have a different mechanism of action than ALGS-related *NOTCH2* pathogenic variants.

ALGS = Alagille syndrome

Contiguous gene deletions. Individuals with ALGS with additional abnormalities, including developmental delay, hearing loss, and autism, may have a larger deletion of chromosome 20p12 encompassing the entire *JAG1* gene as well as other genes in the region [Kamath et al 2009]. In multiple instances, mosaicism for a 20p deletion has been reported in the asymptomatic parents of children diagnosed with ALGS [Giannakudis et al 2001, Laufer-Cahana et al 2002].

Sporadic splenic marginal zone lymphoma (SMZL) occurring in the absence of any findings of ALGS may contain somatic variants in *NOTCH2* that are **not** present in the germline. In these circumstances predisposition to SMZL is not heritable [Kiel et al 2012].

Differential Diagnosis

Bile duct paucity is not seen exclusively in Alagille syndrome (ALGS). Other causes of bile duct paucity include single-gene disorders (see Table 4), chromosome abnormalities (Down syndrome), infectious diseases (congenital cytomegalovirus, congenital rubella, congenital syphilis, hepatitis B), and immunologic disorders (graft-vs-host disease, chronic hepatic allograft rejection, primary sclerosing cholangitis). These can be distinguished from ALGS by history, by the presence of other findings, or by genetic testing.

Intrahepatic cholestasis. Selected examples of inherited disorders associated with intrahepatic cholestasis are listed in Table 4. These conditions are largely confined to the liver, but some are associated with extrahepatic manifestations.

Neonatal cholestasis. More than 100 specific causes of neonatal cholestasis exist. Differential diagnosis depends on clinical presentation and includes infectious, metabolic, genetic, or endocrine disorders as well as structural anomalies. Evaluation typically focuses on treatable causes including sepsis, hypothyroidism, and single-gene disorders such as classic galactosemia. Biliary atresia is the most common identifiable cause of neonatal cholestasis and should be diagnosed early, as surgical intervention at a young age is associated with better outcomes.

Posterior embryotoxon can be seen in a number of genetic disorders but is a frequent finding in Axenfeld-Rieger syndrome. It is also observed in 8%-15% of the general population. ALGS can be distinguished by the presence of other findings or by genetic testing.

Pulmonic vascular system abnormalities are seen in isolation as well as in single-gene and chromosomal disorders (e.g., Down syndrome). These other syndromes can be distinguished by other associated clinical findings and/or genetic testing (see Table 4).

Several of the **cardiac defects** described in ALGS, particularly ventricular septal defect and tetralogy of Fallot, are commonly seen in individuals with 22q11.2 deletion syndrome. Individuals with this diagnosis have also been reported as having butterfly vertebrae and poor growth, two common features of ALGS. Liver disease is not part of the 22q11.2 deletion syndrome; genetic testing can be used to distinguish the two disorders.

Table 4. Selected Genes of Interest in the Differential Diagnosis of Posterior Embryotoxon and Pulmonic Vascular System Abnormalities

Key Overlapping Clinical Feature	Gene / Genetic Mechanism	Disorder	MOI
Posterior embryotoxon	*FOXC1*	Axenfeld-Rieger syndrome (OMIM PS180500)	AD
	PITX2		
Pulmonic vascular system abnormalities	Deletion of WBSCR on chromosome 7q11.23	Williams syndrome	AD
	NF1	Neurofibromatosis 1 & NF1 phenotypic variants (NF1-Noonan syndrome & Watson syndrome)	AD

Table 4. continued from previous page.

Key Overlapping Clinical Feature	Gene / Genetic Mechanism	Disorder	MOI
	BRAF *KRAS* *LZTR1* *MAP2K1* *MRAS* *NRAS* *PTPN11* *RAF1* *RASA2* *RIT1* *RRAS2* *SOS1* *SOS2*	Noonan syndrome	AD (AR) [1]
	PTPN11 *RAF1* *BRAF* *MAP2K1*	Noonan syndrome with multiple lentigines	AD

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; WBSCR = Williams-Beuren syndrome critical region

1. Noonan syndrome is most often inherited in an autosomal dominant manner. Noonan syndrome caused by pathogenic variants in *LZTR1* can be inherited in either an autosomal dominant or an autosomal recessive manner.

Management

No clinical practice guidelines for Alagille syndrome (ALGS) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with ALGS, the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 5. Alagille Syndrome: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Gastrointestinal	Eval by gastroenterologist to incl: • Total & conjugated/direct bilirubin • Liver enzymes (incl GGT) • Clotting studies	If determined necessary by gastroenterologist, additional studies incl: • Serum bile acids • Lipid panel • Fat-soluble vitamin levels • Hepatic ultrasound • Tc-99m DISIDA scintigraphy • Liver biopsy
Cardiovascular	Complete cardiology eval	Incl echocardiogram
Eyes	Ophthalmologic eval	Look for anterior chamber anomalies.
Skeletal	AP & lateral chest radiographs to evaluate for presence of butterfly vertebrae	
Renal	Evaluate w/renal function studies & renal ultrasound	

Table 5. continued from previous page.

System/Concern	Evaluation	Comment
Growth	Measurement of growth parameters & plotting on age-appropriate growth charts	
Development	Screening developmental eval	Perform more detailed eval if significant delays are identified.
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of ALGS to facilitate medical & personal decision making
Family support & resources	By clinicians, wider care team, & family support organizations	Assessment of family & social structure to determine need for: • Community or online resources such as Parent to Parent • Social work involvement for parental support • Home nursing referral

ALGS = Alagille syndrome; GGT = gamma-glutamyl transpeptidase; MOI = mode of inheritance

Treatment of Manifestations

There is no cure for ALGS.

Targeted Therapy

In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure. —ED

Severe cholestasis and pruritus are often the most debilitating manifestations of ALGS and are a frequent indication for liver transplantation. Ileal bile acid transport inhibitors are a new class of medications that have recently been approved for treatment of cholestatic pruritus in ALGS. Orally administered and minimally absorbed, these drugs result in a medical interruption of the enterohepatic circulation, increasing excretion of bile acids in the stool. Maralixibat is currently FDA approved for treatment of children older than age three months and odevixibat for children older than age 12 months [Shneider et al 2018, Baumann et al 2021, Gonzales et al 2021, Shneider et al 2022]. Additional studies have shown that clinical response to maralixibat treatment is associated with improved event-free survival and quality of life [Kamath et al 2023, Sokol et al 2023]. Additional therapies are listed in Table 6.

Supportive Care

A multidisciplinary approach to the management of individuals with ALGS is often beneficial because of the multisystem involvement. Evaluation by specialists in clinical genetics, gastroenterology/hepatology, nutrition, cardiology, ophthalmology, nephrology, transplant hepatology, and child development may be indicated, depending on the age and specific difficulties of the individual [Kamath et al 2010] (see Table 6).

Table 6. Alagille Syndrome: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Pruritus & xanthomas	Choleretic agents (ursodeoxycholic acid), ileal bile acid transport inhibitors, & other medications (cholestyramine, rifampin, naltrexone)	Combination of therapies often required; biliary diversion may be performed for severe pruritus refractory to medical therapy.
Refractory cholestasis / End-stage liver disease	Liver transplantation	A liver specialist familiar w/ALGS is recommended in the treatment of hepatic manifestations.
Hepatocellular carcinoma	Standard treatments per hepatologist/ oncologist	
Poor growth	Optimized nutrition; replacement of fat-soluble vitamins as needed	Nasogastric feeds or gastrostomy tube may be required to maintain caloric intake.
Cardiovascular manifestations	Treatment per cardiologist & cardiothoracic surgeon at center w/experience in treatment of ALGS [1]	
Ophthalmologic/ Vision	Low vision services as needed for those w/ loss of visual function	Ocular issues in those w/ALGS rarely require treatment, as visual prognosis is good. However, some persons have peripheral chorioretinal changes incl atrophy (w/accompanying loss of function in the visual field) & other retinal pigmentary changes, macular atrophy, & progressive decrease in vision.
Renal manifestations	Treatment as needed per nephrologist	
Neurodevelopmental manifestations	Developmental & educational support as needed	

ALGS = Alagille syndrome
1. Moore et al [2022], Felmly et al [2023]

Surveillance

To date, surveillance guidelines for ALGS have not been published. In the absence of published guidelines, recommendations to monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations are based on the authors' personal experience managing individuals with this disorder (see Table 7).

Table 7. Alagille Syndrome: Recommended Surveillance

System/Concern	Evaluation	Frequency
Liver disease	Assess liver function	Per gastroenterologist/hepatologist
Hepatocellular carcinoma	Serum alpha-fetoprotein & ultrasound of liver	While no formal guidelines are available, one recent study has recommended screening every 6 mos at all ages. [1]
Growth/Nutrition	Monitor growth using standard growth charts.	At each visit
	Nutrition assessment	As needed

Table 7. continued from previous page.

System/Concern	Evaluation	Frequency
Cardiac manifestations	Assess for signs/symptoms of vascular manifestations.	• Per cardiologist • Note: At this time, the efficacy of presymptomatic screening for vascular anomalies in persons w/ALGS has not been formally evaluated. The possibility of a vascular accident should be considered in any symptomatic person, & MRI, magnetic resonance angiography, &/or angiography to identify aneurysms, dissections, or bleeds should be pursued aggressively as warranted.
Vision deficits	Vision assessment	Per ophthalmologist
Skeletal manifestations	Asses for recurrent fractures.	At each visit
Renal disease	Assess blood pressure.	
	Basic metabolic panel	Every 6-12 mos
Development	• Assess developmental progress. • Assess for attention & executive function impairment.	Annually

1. Ayoub et al [2023]

Agents/Circumstances to Avoid

Contact sports should be avoided by all individuals, especially those with chronic liver disease, splenomegaly, and vascular involvement.

Individuals with liver disease should avoid alcohol consumption.

Evaluation of Relatives at Risk

For early diagnosis and treatment. It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from prompt initiation of treatment and preventive measures. Evaluations can include:

- Molecular genetic testing if the *JAG1* or *NOTCH2* pathogenic variant in the family is known;
- Measurement of liver enzymes, cardiac evaluation, eye examination, skeletal survey, and evaluation of facial features if the *JAG1* or *NOTCH2* pathogenic variant in the family is not known.

For liver donation. A potential related liver donor (e.g., parent or other family member) should be evaluated for ALGS to exclude the diagnosis in the donor. If the pathogenic variant in the proband is known, targeted genetic testing for the known pathogenic variant should be done in the potential donor. If a pathogenic variant has not been identified in the proband, any potential donor should have a thorough clinical evaluation (liver enzymes, cardiac evaluation, eye examination, skeletal survey, and evaluation of facial features) [Kasahara et al 2023].

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Liver and cardiac features should be monitored to ensure that portal hypertension and cardiac dysfunction do not worsen during pregnancy [Ferrarese et al 2015].

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Alagille syndrome (ALGS) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Approximately 40% of individuals diagnosed with ALGS have an affected parent.
- Approximately 60% of affected individuals have ALGS as the result of a *de novo* genetic alteration [Vandriel et al, unpublished data].
- If a molecular diagnosis has been established in the proband and the proband appears to be the only affected family member (i.e., a simplex case), molecular genetic testing is recommended for the parents of the proband to evaluate their genetic status and inform recurrence risk assessment. If the causative genetic alteration has not been identified in the proband, recommendations for the evaluation of parents include liver function testing, cardiac evaluation, radiographs of the spine, ophthalmologic examination, and evaluation of facial features by a clinical geneticist.
- If the *JAG1* or *NOTCH2* pathogenic variant identified in the proband is not detected in either parent, and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
    - The proband has a *de novo* pathogenic variant.
    - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism [Giannakudis et al 2001, Laufer-Cahana et al 2002].* The frequency of parental somatic/germline mosaicism was approximately 8% in a study of families with *JAG1*-related ALGS [Giannakudis et al 2001]. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.

      * Parents with somatic mosaicism for an ALGS-causing genetic alteration may be mildly/minimally affected.
- The family history of some individuals diagnosed with ALGS may appear to be negative because of failure to recognize the disorder in family members or reduced penetrance. Therefore, an apparently negative family history cannot be confirmed without appropriate clinical evaluation of the parents and/or molecular genetic testing (to establish that neither parent is heterozygous for the pathogenic variant identified in the proband).

Sibs of a proband. The risk to the sibs of the proband depends on the clinical/genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the *JAG1* or *NOTCH2* pathogenic variant identified in the proband, the risk to the sibs is 50%. Significant intrafamilial variability is observed in ALGS; the clinical manifestations in heterozygous sibs cannot be predicted and may range from mild or subclinical features to severe heart and/or liver disease.
- If the proband has a known *JAG1* or *NOTCH2* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is greater than that of the general population because of the possibility of parental germline mosaicism [Giannakudis et al 2001, Laufer-Cahana et al 2002].
- If the parents have not been tested for the ALGS-related genetic alteration but are clinically unaffected, sibs are still presumed to be at increased risk for ALGS because of the possibility of reduced penetrance in a heterozygous parent or parental mosaicism.

Offspring of a proband

- Offspring of an individual with ALGS have a 50% chance of inheriting the *JAG1* or *NOTCH2* pathogenic variant.
- The clinical manifestations in heterozygous offspring cannot be predicted and range from mild or subclinical features to severe heart and/or liver disease.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected or has the *JAG1* or *NOTCH2* pathogenic variant, other members of the parent's family are at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the *JAG1* or *NOTCH2* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible. Note: Because *JAG1*- and *NOTCH2*-related ALGS demonstrate highly variable expressivity with clinical features ranging from subclinical to severe, clinical manifestations cannot be predicted by molecular genetic prenatal testing.

Fetal ultrasound examination. In fetuses at 50% risk for ALGS, fetal echocardiogram may detect a significant structural defect of the heart; however, a normal fetal echocardiogram does not eliminate the possibility of ALGS or the possibility of a structural cardiac abnormality in the fetus.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Alagille Syndrome Alliance**
  Phone: 901-286-8869
  Email: alagille@alagille.org
  www.alagille.org
- **MedlinePlus**
  Alagille syndrome
- **American Liver Foundation**
  Phone: 800-465-4837 (HelpLine)
  www.liverfoundation.org
- **Canadian Liver Foundation**
  Canada
  Phone: 800-563-5483
  Email: clf@liver.ca
  www.liver.ca
- **Childhood Liver Disease Research Network (ChiLDReN)**
  Phone: 720-777-2598
  Email: joan.hines@childrenscolorado.org
  www.childrennetwork.org
- **Children's Liver Disease Foundation**
  United Kingdom
  Phone: +44 (0) 121 212 3839
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  www.childliverdisease.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Alagille Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
JAG1	20p12.2	Protein jagged-1	CCHMC - Human Genetics Mutation Database (JAG1) JAG1 @ LOVD	JAG1	JAG1

Table A. continued from previous page.

NOTCH2	1p12	Neurogenic locus notch homolog protein 2	NOTCH @LOVD	NOTCH2	NOTCH2

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Alagille Syndrome (View All in OMIM)

118450	ALAGILLE SYNDROME 1; ALGS1
600275	NOTCH RECEPTOR 2; NOTCH2
601920	JAGGED 1; JAG1
610205	ALAGILLE SYNDROME 2; ALGS2

Molecular Pathogenesis

JAG1 and *NOTCH2* encode for a ligand and a receptor protein, respectively, involved in the Notch signaling pathway. Notch signaling is highly ubiquitous, with defects resulting in a variety of human diseases. The name "Notch" derives from the characteristic notched wing found in fruit flies carrying only one functional copy of the gene. Homozygous pathogenic variants in *Notch* in fruit flies are lethal, and the flies show hypertrophy of the nervous system. The finding that pathogenic variants in *JAG1* cause Alagille syndrome (ALGS) indicates that Notch signaling is important in the development of the affected organs (i.e., liver, heart, kidney, facial structures, skeleton, and eye).

The JAG1 and NOTCH2 proteins are both single-pass, transmembrane proteins. Binding of the extracellular region of JAG1 to the extracellular region of NOTCH2 prompts cleavage of the intracellular domain of NOTCH2, which translocates to the nucleus to regulate the expression of Notch signaling target genes, including those belonging to the *HES* and *HEY* gene families.

During cholangiocyte specification, mesenchymal cells surrounding the portal vein express JAG1, while the hepatocytes express NOTCH2. Mouse studies have demonstrated a requirement of Notch signaling for liver development.

Mechanism of disease causation. The disease mechanism of ALGS is haploinsufficiency, and the majority of disease-associated *JAG1* variants (~87%) are loss-of-function variants. Many missense variants in *JAG1*, particularly those that involve loss of a cysteine, result in proteins that are unable to signal with NOTCH2 and/or are improperly trafficked and not expressed on the cell membrane.

Disease-associated *NOTCH2* variants are predominantly missense, and the pathogenicity of these variants is less understood.

***NOTCH2*-specific laboratory considerations.** *NOTCH2NLR*, a pseudogene containing five exons – the first four corresponding to the first four exons of *NOTCH2* and the fifth corresponding to an intronic region of *NOTCH2* – interferes with analysis of *NOTCH2*.

Chapter Notes

Author Notes

Melissa Gilbert (gilbertma@chop.edu) and Nancy Spinner (spinner@chop.edu) are actively involved in research on understanding missense mutations for proper classification and to better understand Jagged-Notch signaling.

Melissa Gilbert (gilbertma@chop.edu) and Nancy Spinner (spinner@chop.edu) are working on utilization of novel technologies to diagnose affected individuals with clinical Alagille syndrome who do not have a pathogenic variant identified.

Contact Melissa Gilbert (gilbertma@chop.edu) to inquire about review of variants of uncertain significance.

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