Review Article

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Genetics Section

Alagille Syndrome: A Narrative Review of Molecular Pathogenesis, Clinical Manifestations, Diagnosis and Management

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ABSTRACT

Alagille Syndrome (ALGS) is a rare multisystem disorder of autosomal dominant type which is primarily caused due to mutations in the JAG1 gene and, less commonly, NOTCH2, both integral to Notch signalling. Clinically, ALGS is further characterised by cholestatic liver disease because of intrahepatic bile duct paucity, along with some cardiac and skeletal abnormalities, ocular defects, renal involvement, and distinct facial features. Diagnosis of ALGS depends upon the presence of at least three of five main clinical features, which are later supported through liver biopsy, genetic testing, and imaging. Differential diagnosis of ALGS includes biliary atresia, Progressive Familial Intrahepatic Cholestasis (PFIC), neonatal hepatitis, and syndromes with overlapping phenotypes such as Noonan and Kabuki syndromes. Management in such cases is largely supportive, which mainly focuses on relieving cholestasis and pruritus, along with proper nutritional adequacy, and addressing systemic complications. Liver transplant is reserved only for end-stage disease or intractable symptoms. A multidisciplinary approach is an essential aspect of treatment to improve patient outcomes, along with quality of life.

Keywords: Bile duct paucity, Cholestasis, JAG1 mutation, Multisystem disorder, Notch signal

INTRODUCTION

Alagille syndrome (ALGS) is a rare, autosomal dominant disorder which is characterised by highly variable clinical features within the same family [1]. ALGS was described in 1969 by a French paediatric hepatologist named Daniel Alagille, who reported a distinctive clinical syndrome in 30 children approximately [2]. These patients presented with hypoplastic intrahepatic bile ducts and a consistent constellation of extrahepatic abnormalities, including cardiac defects, skeletal anomalies, and a characteristic facial feature, which led Alagille and colleagues to propose a unified developmental disorder, initially termed "syndromic bile duct paucity" or arteriohepatic dysplasia [3,4].

Before advancements in molecular testing, the prevalence of ALGS was estimated to be approximately 1 in 70,000-100,000 live births, which was based solely on clinically relevant features of neonatal cholestasis [5]. However, genetic screening of relatives later on revealed that many individuals are carrying pathogenic variants (JAG1 or NOTCH2 mutations) which lacked the full clinical syndrome; this further led to a revised prevalence estimate closer to 1 in 30,000 live births [6]. Most commonly, ALGS arises due to variations in JAG1, which is found in most cases, while mutations in NOTCH2 are found rarely in very few cases [2,7]. Both of these genes encode critical components of the pathway related to Notch signalling, central to the embryological development of the liver, heart, skeleton, kidneys, and eyes [7]. Loss-of-function variants in JAG1 result in haploinsufficiency, which further impairs the formation of the bile duct and leads to intrahepatic bile duct paucity and thus causes neonatal cholestasis [8,9].

Clinical Features of Alagille Syndrome

Alagille Syndrome (ALGS) is an autosomal dominant disorder which is often caused due to pathogenic variants in JAG1 and, more rarely, NOTCH2, both components of the pathway related to Notch signalling [10]. The hallmark clinical manifestation is cholestatic liver disease due to intrahepatic bile duct paucity, which further leads to neonatal or early infancy jaundice, persistent pruritus, acholic (pale) stools, hepatomegaly, splenomegaly, and xanthomas from cholesterol deposition in skin [11,12]. The consequent malabsorption of fat-soluble vitamins often causes failure to thrive, rickets, delayed growth, and malnutrition [13].

Beyond the hepatic picture, ALGS also features congenital cardiac anomalies, most commonly stenosis of the peripheral pulmonary artery, along with Tetralogy of Fallot [14]. Ocular findings in such cases can include posterior embryotoxon and anterior segment anomalies; skeletal anomalies such as butterfly vertebrae are typical but usually asymptomatic [15,16]. Patients suffering from ALGS often exhibit a triangular facies, broad forehead, deep-set eyes, small pointed chin, sometimes termed "cholestasis facies" though not specific to ALGS alone [13,17]. Renal and vascular involvement also occurs, which ranges from renal dysplasia or nephrocalcinosis to cerebrovascular anomalies, thus further highlighting the variable expressivity of ALGS [18]. Clinical features of Alagille syndrome according to systemic involvement are detailed in [Table/Fig-1].

System involved	Clinical features
Genetics	Autosomal dominant; pathogenic variants in JAG1 (common) and NOTCH2 (rare); both part of the Notch signaling pathway
Hepatic	• Cholestatic liver disease due to intrahepatic bile duct paucity • Neonatal/early infancy jaundice • Persistent pruritus • Acholic (pale) stools • Hepatomegaly • Splenomegaly • Xanthomas due to skin cholesterol deposition
Nutritional/Metabolic	• Malabsorption of fat-soluble vitamins • Failure to thrive • Rickets • Delayed growth • Malnutrition
Cardiac	• Peripheral pulmonary artery stenosis (most common) • Tetralogy of Fallot

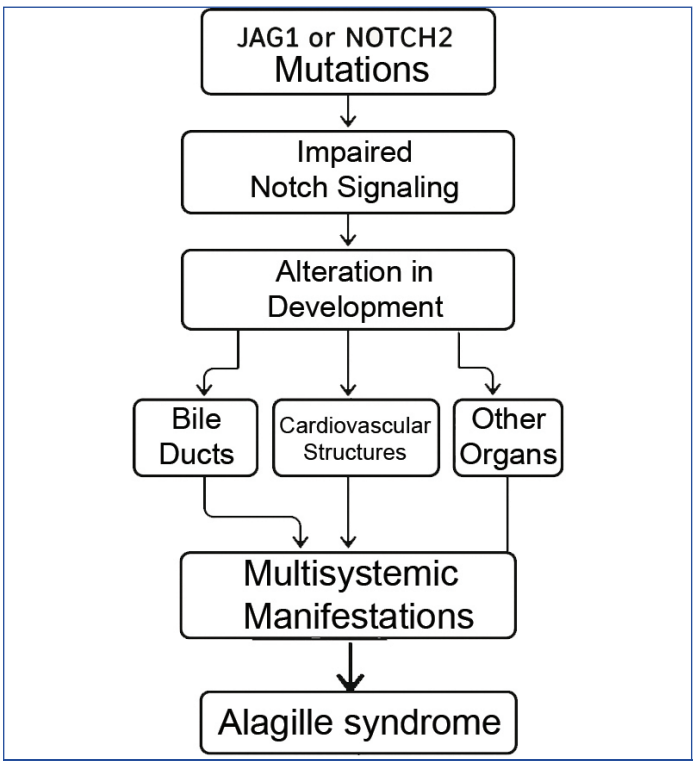
Ocular	• Posterior embryotoxon • Anterior segment anomalies
Skeletal	• Butterfly vertebrae (typically asymptomatic)
Facial Features	• Triangular facies • Broad forehead • Deep set eyes • Small, pointed chin (sometimes called "cholestasis facies")
Renal	• Renal dysplasia • Nephrocalcinosis
Vascular/ Neurological	• Cerebrovascular anomalies

[Table/Fig-1]: Clinical features of Alagille syndrome according to systemic involvement.

Role of JAG1 and NOTCH2 Mutations in Pathogenesis of ALGS

ALGS is primarily caused due to mutations in the JAG1 gene (chromosome 20p12) and, less frequently, in the NOTCH2 gene (chromosome 1p12-p11), both of which are important components of the pathway related to Notch signalling [19]. This pathway governs cell fate decisions during organogenesis and stages of development of the embryo, including the formation of bile ducts, cardiovascular structures, skeleton, and the eye [19,20]. JAG1 encodes a ligand which further activates Notch receptors, particularly NOTCH2, by juxtacrine signalling [21]. Pathogenic mutations in JAG1, which are mostly frameshift, nonsense, or missense variants, can lead to haploinsufficiency, thereby causing disruption of Notch signalling and results in the multisystemic manifestations of ALGS [9,22].

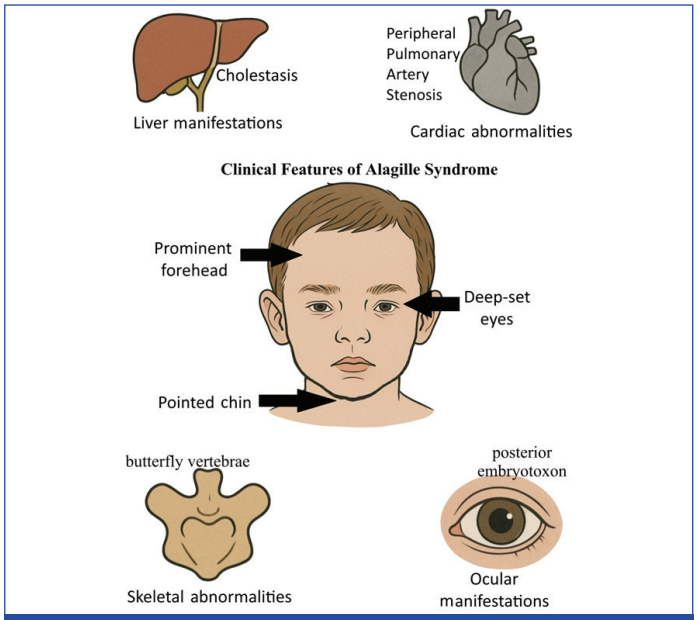
The impaired Notch signalling due to JAG1 or NOTCH2 mutations causes alteration in the development of bile ducts through defective ductal plate remodelling in the liver, which underlies the characteristic paucity of intrahepatic bile ducts [19,23]. Additionally, some of the animal models, such as Jag1 heterozygous mice and conditional Notch2 knockouts, have also demonstrated that disrupted Notch signalling impairs morphogenesis of the bile duct and cardiovascular patterning [24,25]. Thus, the molecular pathogenesis of ALGS is an example showing how disruption in a developmental signalling pathway can lead to a broad spectrum of congenital anomalies across multiple organ systems [24]. Pathogenesis of Alagille Syndrome is depicted through a flowchart [Table/Fig-2] [9,19-25].



Table/Fig-2]: Pathogenesis of Alagille syndrome.
Self-made flowchart by the author, prepared with reference to articles [9,19-25].

Clinical, Genetic, and Imaging-based Diagnosis of Alagille Syndrome

Clinical spectrum in diagnosis of Alagille syndrome: ALGS is diagnosed based on clinical features, genetic testing, histopathologic examination, and imaging findings [26]. The classic diagnostic criteria of ALGS includes presence of at least three of five major clinical features from following: cholestasis (which is typically due to bile duct paucity), cardiac anomalies (most commonly involving peripheral pulmonary artery stenosis), skeletal abnormalities (such as butterfly vertebrae), ocular abnormalities (posterior embryotoxon), and characteristic facial features (prominent forehead, deep-set eyes, and pointed chin) [26,27]. Liver biopsy showing a paucity of interlobular bile ducts in the presence of cholestasis further supports the diagnosis of ALGS, especially in infants who are presented along with jaundice and pruritus [16,28]. A Bahrain cohort study by Isa HM et al., highlighted presentation at birth with cholestasis and dysmorphism, frequent congenital heart disease, and the Biliary Atresia-ALGS (BA-ALGS) diagnostic pitfall; international natural-history work delineated paediatric liver outcomes [29]. Adult-focused bibliometric synthesis by Vandriel SM et al., shows growing attention to adult manifestations and surveillance [30]. Together, these support a clinicopathologic approach that weighs multi-organ features while rapidly confirming molecularly [29,30]. Clinical features in the diagnosis of Alagille syndrome are depicted in [Table/Fig-3] [16,26-30].



[Table/Fig-3]: Clinical features in the diagnosis of Alagille syndrome.
Self-made image by the author, prepared with reference to articles [16,26-30].

Genetic basis for diagnosis of Alagille syndrome: Wherever ALGS is suspected, sequencing and deletion/duplication analysis of JAG1 is recommended in such cases [28]. Usage of Next-Generation Sequencing (NGS) panels, which include genes of the Notch signalling pathway, helps in enhancing the accuracy of diagnosis, particularly in atypical or incomplete presentation of ALGS [31]. Early genetic diagnosis thus not only confirms clinical suspicion but also facilitates family counselling and prenatal testing in applicable cases [13,31]. An 18-month-old girl reported by Laufer-Cahana A et al., inherited a submicroscopic 20p deletion, including the JAG1 locus, from her apparently healthy mother, who was a mosaic (deletion present in ~45% of her blood cells); this case underscores that parental mosaicism can underlie de novo-like presentations and carries critical implications for recurrence risk [32]. A unique case detailed by Zheng Y et al., described a patient with dual pathogenic variants, one in NOTCH2 and another in RASA1, thus presenting with combined Capillary Malformation-Arteriovenous Malformation (CM-AVM) and ALGS-like vascular anomalies affecting liver, heart, and skin; exome sequencing enabled this rare co-occurrence to be

diagnosed properly [33]. Regularly updated guidance (GeneReviews) and recent reviews (2023-2025) reinforce this framework, noting the need for modifier-gene studies and functional work [34].

Imaging-based diagnosis of Alagille syndrome: Hepatobiliary scintigraphy and Magnetic Resonance Cholangiopancreatography (MRCP) can reveal anomalies in the bile duct, while echocardiography is done for congenital heart defects [26,35,36]. Ophthalmologic slit-lamp examination can identify posterior embryotoxon, and skeletal examination can be done for the detection of butterfly vertebrae [19]. A paediatric case report described by Farina R et al., the patient shows hypoplasia of the common bile duct with gallbladder dimorphism on MRCP, a pattern that mimicked biliary atresia but, combined with systemic features, led to an ALGS diagnosis rather than unnecessary surgery [37]. A recent case report by Kato N et al., underscores the role of multimodal ocular imaging in Alagille syndrome, describing a 29-year-old woman with a heterozygous JAG1 variant, in whom ophthalmic evaluation revealed posterior embryotoxon, iris atrophy, peripheral retinal pigmentary changes, and optic disc elevation [38]. Ultra-widefield Optical Coherence Tomography (OCT) demonstrated retinal thinning with choroidal hyper-reflectivity, and anterior-segment OCT confirmed bilateral iris atrophy [38]. Skeletal imaging, which is obtained during evaluation of cholestasis or growth delay, typically demonstrates butterfly vertebrae, a classic radiographic feature reported across multiple case series involving ALGS [36,39].

Differential Diagnosis of Alagille Syndrome

Biliary atresia is the most immediate condition to differentiate from ALGS due to its surgical urgency [40]. Unlike ALGS, biliary atresia typically shows absent or hypoplastic extrahepatic bile ducts, which are observed on hepatobiliary scintigraphy and intraoperative cholangiography [40,41]. Additionally, liver biopsy in biliary atresia often shows proliferation of bile duct along with portal fibrosis, whereas ALGS is characterised by bile duct paucity [40,42].

Progressive Familial Intrahepatic Cholestasis (PFIC) also shows similarities with ALGS, such as pruritus and cholestasis, but genetic testing can help differentiate it accordingly [43]. PFIC involves mutations in ATP8B1, ABCB11, or ABCB4, and unlike ALGS, it lacks multisystem disease involvement [43]. Neonatal hepatitis can also mimic ALGS clinically, but biopsy in neonatal hepatitis usually shows giant cell transformation and lobular disarray rather than bile duct paucity, and it often lacks extrahepatic manifestations [41].

Noonan and Kabuki syndrome can also be confused with ALGS due to shared facial dysmorphism and congenital heart defects [44]. However, genetic testing is decisive mutations in PTPN11, SOS1 (Noonan), or KMT2D and KDM6A (Kabuki) are distinct from the JAG1 or NOTCH2 mutations found in ALGS [45]. However, Noonan syndrome lacks involvement of the liver, and Kabuki syndrome often includes features such as intellectual disability and immune dysfunction, which are not prominent in ALGS [46,47]. Differential diagnosis of Alagille syndrome and distinguishing features are mentioned in [Table/Fig-4].

Conditions	Key similarities with ALGS	Distinguishing features	Diagnostic tools
Biliary atresia	Cholestasis in infancy	Absent/hypoplastic extrahepatic bile ducts; bile duct proliferation with portal fibrosis (on biopsy); surgical emergency	Hepatobiliary scintigraphy, intraoperative cholangiography, liver biopsy
Progressive Familial Intrahepatic Cholestasis (PFIC)	Pruritus, cholestasis	Genetic mutations in ATP8B1, ABCB11, or ABCB4; no multisystem involvement	Genetic testing
Neonatal hepatitis	Neonatal cholestasis	Giant cell transformation, lobular disarray on biopsy; absence of bile duct paucity; lacks extrahepatic features	Liver biopsy
Noonan syndrome	Facial dysmorphism, Congenital heart defects	Mutations in PTPN11, SOS1; lacks liver involvement	Genetic testing
Kabuki syndrome	Facial dysmorphism, Congenital heart defects	Mutations in KMT2D or KDM6A; associated with intellectual disability, immune dysfunction—features not typical in ALGS	Genetic testing

[Table/Fig-4]: Differential diagnosis of Alagille syndrome and distinguishing features.

Comprehensive Management and Emerging Therapeutics in Alagille Syndrome

The treatment of ALGS is largely supportive and symptom-driven, as there is no definitive treatment for the given condition [48]. Management of ALGS is focused mainly on addressing the cholestatic liver disease [48]. Medical therapies include ursodeoxycholic acid to enhance bile flow and cholestyramine, rifampin, naltrexone, or antihistamines to relieve intractable pruritus associated with bile salt accumulation [27,49,50]. Fat-soluble vitamin supplementation (A, D, E, K) is also important in such cases due to malabsorption from cholestasis, and nutritional support is essential to ensure appropriate growth and development [51]. In refractory cases of pruritus or progressive liver dysfunction, there is a need for partial external biliary diversion or liver transplantation [51].

Liver transplantation is only indicated in patients with end-stage liver disease, intractable pruritus, frequent cholangitis, or significant growth failure despite maximal medical therapy [52]. Outcomes after having a transplant are generally favourable, although some patients may have extrahepatic complications due to the multisystemic nature of ALGS [52]. Given the cardiac defects like peripheral pulmonary artery stenosis in ALGS, preoperative cardiac evaluation and multidisciplinary coordination are crucial before performing surgery on the patient [53]. Renal dysfunction in ALGS needs appropriate nephrological follow-up [19,54]. Advances in genetic testing and targeted molecular therapies are currently under investigation, and their clinical application remains limited at this stage [54]. A multidisciplinary approach is required for good outcomes, along with quality of life in affected individuals [53].

CONCLUSION(S)

Alagille Syndrome (ALGS) is a genetic disorder which is characterised by multisystem features such as cholestatic liver disease, cardiac defects, skeletal abnormalities, and different facial features, primarily due to mutations in the JAG1 and NOTCH2 genes affecting the Notch signalling pathway. Diagnosis of ALGS depends upon clinical criteria, genetic testing, and imaging, while its management is largely supportive, which targets symptoms and nutritional needs of the patient. Liver transplant may be necessary in severe cases. Continued research into targeted molecular therapies and a proper multidisciplinary care approach are important aspects for good outcomes and quality of life in patients with ALGS.

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