

Alagille Syndrome: A Comprehensive Review of Clinical Heterogeneity, Genetic Mechanisms, and Evolving Therapeutic Strategies

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Abstract

Alagille Syndrome is a rare, autosomal dominant, multisystem disorder, mainly associated with mutations in the JAG1 gene and, to a lesser extent, NOTCH2. It is associated with bile duct paucity and a spectrum of cholestasis, congenital heart defects (especially peripheral pulmonary stenosis), skeletal defects, ocular defects (posterior embryotoxon), renal defects, and characteristic facial features. Clinical presentation is highly variable, even within the same family carrying identical genetic mutations, which complicates diagnosis and treatment. Progress in molecular genetics, particularly regarding the Notch signalling pathway, has enhanced diagnostic accuracy and clarified disease pathogenesis. Hepatic manifestations, usually presenting in infancy, may progress to end-stage liver disease requiring transplantation. Cardiac and vascular anomalies are significant contributors to poor survival and represent a special management concern. A common and complex presentation includes neuropsychological delay, growth failure, and nutritional deficiencies, all of which require management by a multidisciplinary team. In atypical or mild cases, genetic testing has emerged as an important diagnostic tool. Management focuses on symptom control, nutritional support, and organ-specific interventions, and new drugs targeting bile acid metabolism and the Notch pathway show promise. This review provides a thorough overview of Alagille Syndrome, highlighting its clinical heterogeneity, underlying genetic mechanisms, diagnostic dilemmas, and evolving therapeutic approaches.

Introduction

Alagille Syndrome is a rare, inherited multisystem disease with variable clinical manifestations and severity. The syndrome was first described by the French hepatologist Daniel Alagille in 1969, in a group of patients who had intrahepatic bile duct hypoplasia, with involvement of other organs. Later research showed that other clinical features are also common, including cholestasis, congenital heart defects, skeletal abnormalities, posterior embryotoxon of the eyes, and peculiar facial features. These features were hallmarks that prompted the historical diagnostic criterion of at least 3 of 5 clinical features plus bile duct paucity on liver biopsy. Before the development of molecular diagnosis, the estimated prevalence of clinically apparent ALGS was about 1/70,000 live births. This syndrome represents 10 to 15% of the causes of neonatal cholestasis (1 case out of 100,000 births), with no gender predominance¹⁻³. However, this figure significantly underestimated the true prevalence due to the variable expressivity and incomplete penetrance of the disease. With the emergence of genetic testing, particularly the identification of pathogenic variants in genes associated with the Notch signalling pathway, a more accurate incidence rate of around 1 in 30,000 live births has been proposed⁴.

Genetically, ALGS is primarily caused by mutations in the JAGGED1 (JAG1) gene, located on chromosome 20p11.2-20p12^{5-6,8}. This gene encodes a ligand in the Notch signalling pathway, which is crucial for cell fate determination and organogenesis. Approximately 90%-95% of individuals diagnosed with ALGS have detectable pathogenic variants in JAG1, most commonly resulting in haploinsufficiency due to loss-of-function mutations or deletions. A smaller proportion (1%-2.5%) of cases is attributed to mutations in NOTCH2, a gene encoding one of the receptors in the same pathway. Mutations in NOTCH2

are especially linked to an increased occurrence of renal malformations. Both JAG1 and NOTCH2 are central players in the Notch signalling pathway, which is important in the regulation of embryonic development and tissue differentiation. Following the interaction of ligand with receptor, the pathway begins with a cascade of events, including proteolytic cleavage and nuclear entry of the Notch intracellular domain, which in turn regulates gene transcription. Disruption of this tightly regulated process accounts for the diversity of manifestations seen in ALGS^{7-9,11}.

One of the unique characteristics of ALGS is the diversity in phenotype even within individuals with the same genetic mutation¹⁰. This heterogeneity makes it difficult to diagnose and treat the disease and has led to the suggestion that other genetic and/or epigenetic modifiers might play a role in disease severity. Whilst haploinsufficiency is known to be the primary pathogenic mechanism, the reasons for the variable clinical phenotypes are not fully understood. The role of secondary genetic modifiers and environmental factors in disease expression is being actively studied. Previously known as arteriohepatic dysplasia because of its liver and vascular defects, ALGS is now known to involve multiple organ systems: liver, heart, skeleton, kidneys, eyes, and the central nervous system. Extrahepatic manifestations range from subtle to life-threatening, but hepatic involvement is a constant feature, especially bile duct paucity and resultant cholestasis. Such complexity requires a multidisciplinary approach to diagnosis and care¹¹⁻¹⁴.

Recent progress in genetic analysis and greater knowledge of the Notch signalling pathway have improved earlier and more accurate diagnosis of ALGS in recent years. Molecular confirmation of new mutations in JAG1 or NOTCH2, in addition to or instead of traditional clinical parameters, is now the "gold standard" for diagnosis. Furthermore, targeted therapies are being continually tested to address the genetic causes of ALGS rather than simply treating symptoms. The objective of this review is to give a current overview of Alagille Syndrome, covering its historical background, clinical presentation, genetic background, and new therapeutic options.

Pathogenesis of Alagille Syndrome

Bile duct paucity, although no longer an essential diagnostic requirement, remains a prominent finding in 80-90% of individuals with ALGS. This narrowing of the bile ducts is usually gradual, occurring over time in infancy, and is correlated with liver function, although not all patients progress along this pathway. There is no evidence of a lack of bile duct formation, but rather a lack of clarity regarding the mechanisms of bile duct loss. The role of JAG1 in bile duct development in infancy remains to be fully understood. Others have noted fewer portal tracts or ductular proliferation in infants with the disease, but the cause of this is not clear¹⁵⁻¹⁶. Patients with this condition have very diverse clinical manifestations, raising important questions about the direct role of gene mutation in these manifestations and how they might be affected by other complications such as cholestasis. There has been some discussion as to whether facial dysmorphism in ALGS might be a consequence of liver disease, but clinical experts have always been able to differentiate the features of ALGS from those of

other cholestatic diseases, lending support to a direct genetic contribution. In light of the ubiquity of vascular defects in ALGS, researchers have suggested that impaired development of blood vessels may be an underlying cause of the disease¹⁷. Formation of bile ducts appears to be closely linked with that of intrahepatic arteries, with the Notch signalling pathway playing a role. JAG1 and NOTCH2 are at the heart of this pathway, which is essential for the development of blood vessels and are involved in the development of Alagille syndrome (ALGS)¹⁸.

JAG1 gene involvement

Most cases of ALGS are associated with mutations in the JAG1 gene. The gene contains 26 exons and produces the protein JAGGED1, which binds to Notch receptors 1-4 and activates downstream pathways that affect cell development and differentiation. Other disorders, such as spondylocostal dysostosis and CADASIL, are also caused by disruptions in this pathway. In animal models, complete loss of JAG1 function results in embryonic lethality due to severe vascular defects. Mice with one working copy of Jag1 have only eye problems, whereas mice with both Jag1 and Notch2 mutations have phenotypes very similar to those of ALGS in humans. More than 400 different mutations in JAG1 have been identified so far, the majority of which result in truncated, non-functional proteins. These mutations are not found in specific "hotspot" regions of the gene¹⁹⁻²¹. Up to 7% of patients have deletions in chromosome region 20p12, where JAG1 is located²². Large deletions are associated with additional issues such as learning difficulties, although clinical presentations between mutation and deletion cases are largely similar, suggesting that haploinsufficiency (having only one working gene copy) is the main disease mechanism. About 60% of cases arise from new (de novo) mutations, and germline mosaicism, where a parent carries the mutation in a portion of their reproductive cells, may occur in approximately 8% of cases, which is important during genetic counselling. There is limited correlation between specific JAG1 mutations and disease severity, though some specific mutations have been linked to isolated cardiac malformations²³⁻²⁴.

NOTCH2 gene contribution

Like JAG1, the NOTCH2 gene encodes a receptor in the Notch signalling pathway and includes 34 exons. Based on animal models showing that mutations in both Jag1 and Notch2 produce ALGS-like features, researchers investigated NOTCH2 in patients lacking JAG1 mutations. Only two families with NOTCH2-related ALGS have been described so far. Affected individuals had classical ALGS symptoms, with moderately severe kidney involvement. There is insufficient evidence to draw clear genotype-phenotype relationships for NOTCH2 at present. Additionally, a small percentage of patients fulfilling ALGS diagnostic criteria do not have detectable mutations in either JAG1 or NOTCH2, suggesting the existence of additional, unidentified genetic causes. One such ALGS-like disorder, seen in a Canadian family, followed an autosomal recessive inheritance pattern and involved bile duct loss, liver dysfunction, and pulmonary stenosis, but was not associated with either of the known ALGS genes²⁵.

20p12.2 microdeletion and genotype-phenotype correlation in ALGS

In Alagille Syndrome individuals presenting with developmental delay or hearing impairment, an interstitial microdeletion at chromosome 20p12.2 encompassing the JAG1 gene should be considered. This region is regarded as critical for ALGS manifestation. Deletions on the short arm of chromosome 20 were observed in 21 individuals. Among them, 11 exhibited normal developmental outcomes, with deletions spanning 95 kb to 4 Mb, all located within a 5.4 Mb region associated with JAG1. The other 10 individuals had larger deletions, ranging from 3.28 Mb to 14.62 Mb, extending beyond this critical region, and consistently showed developmental delays²⁰⁻²¹.

Genotype-phenotype associations

The genotype-phenotype correlation in ALGS has yet to be clearly established, although some discrepancies have been noted. In one case with missense mutations of the JAG1 gene, no liver defect was seen, but a cardiac defect was present. The limited sample size did not allow for definitive conclusions, but those with a NOTCH2 mutation tended to have more renal defects. As a result, there is currently no clear link between mutation type and clinical course, and genetic information cannot presently be used to guide clinical management. Furthermore, there is genetic heterogeneity, with some patients meeting the classic diagnostic criteria for ALGS lacking detectable NOTCH2 or JAG1 mutations or deletions. Features seen in a case series of a Native Canadian family without mutations in either known ALGS gene included bile duct paucity, cholestasis, and pulmonary stenosis, pointing to the existence of other, unknown genetic factors^{25,26}.

Diagnosis

Today, Alagille syndrome is defined by its clinical and genetic characteristics, but some complications remain in making the diagnosis. Previously regarded as an ALGS hallmark, histological evidence of bile duct paucity on liver biopsy is present in a range of conditions other than ALGS, including Down syndrome, cystic fibrosis, congenital infections, alpha-1 antitrypsin deficiency, and syndromes such as Zellweger and Ivemark. Furthermore, this histological characteristic is variable and can change with time. The clinical finding of cholestasis is therefore now generally considered a valid clinical marker, reducing the need for liver biopsy to establish the diagnosis. However, congenital heart defects such as pulmonary stenosis can also occur as an isolated defect or as part of other syndromes, such as those due to mutations in the RAS-MAPK pathway or 22q11 deletions. Peripheral pulmonary stenosis (PPS), however, is somewhat characteristic of ALGS and should raise the possibility of this diagnosis, especially where Williams syndrome is not a likely alternative. While liver disease and PPS are among the most common findings reported in ALGS, presentation is quite variable among individuals²⁷.

Kamath et al.¹³ carried out a cohort study evaluating individuals who tested positive for ALGS-associated mutations and were family members of 34 probands. Of these, only 21% showed clear clinical signs of ALGS, 32% showed mild signs, and 47% showed no signs, two of whom were completely asymptomatic. A total of 241 people were referred for genetic testing at the Exeter Molecular Genetics Laboratory in the United Kingdom; 44 probands, along with 23 family members, were found to have a JAG1 mutation. The mutation detection rate was 54% among those with 3 classic ALGS symptoms and 34% among those with 1 or 2 of the features.

These findings suggest that:

- JAG1 mutation detection is not guaranteed even in clinically clear ALGS cases.
- A significant number of patients with fewer clinical signs may still test positive genetically.
- Physicians should maintain a high index of suspicion and a low threshold for genetic testing, even in atypical cases.

Due to the difficulties in diagnosis, revised clinical criteria and a diagnostic algorithm were proposed by Kamath et al.¹³ to facilitate assessment. Warthen et al.²⁸ observed a mutation detection rate of 94% in a highly selected group, but rates may be lower in routine clinical practice. In fact, as many as 40% of suspected ALGS cases do not have a detectable JAG1 mutation, depending largely on the strictness of the clinical criteria used for screening²⁹⁻³⁰.

Clinical Features and Their Management

Alagille Syndrome is a multisystem genetic condition that exhibits high clinical heterogeneity, ranging from severe liver or cardiac disease to less severe, subclinical abnormalities such as elevated liver enzymes, heart murmurs, butterfly vertebrae, posterior embryotoxon, or characteristic facies. This variation can make diagnosis difficult, even among family members carrying the same mutation; in one study, almost half of mutation-positive relatives did not meet the traditional clinical criteria, emphasizing the need to look beyond clinical findings alone. Historically, ALGS was diagnosed based on the presence of cholestasis with bile duct paucity and at least three of five key features: cardiac defects (often peripheral pulmonary stenosis), vertebral anomalies, ocular findings, facial dysmorphism, and liver involvement.

Hepatic features

Liver involvement is a central and often early manifestation of Alagille Syndrome, occurring in the majority of affected individuals. Chronic cholestasis, typically beginning in the neonatal period or within the first few months of life, presents with jaundice due to conjugated hyperbilirubinemia, and elevated gamma-glutamyl transferase (GGT), serum bile acids, and cholesterol levels³¹⁻³². Common symptoms

include pruritus, xanthomas, fat-soluble vitamin deficiencies (A, D, E, K), and growth failure due to impaired bile flow and nutrient malabsorption. Histologically, the hallmark feature is a paucity of intrahepatic bile ducts; however, in early infancy, liver biopsies may show ductal proliferation with portal inflammation, potentially mimicking biliary atresia and leading to misdiagnosis³³. Notably, bile duct paucity becomes more evident after six months of age. While liver biopsy is not mandatory when clinical cholestasis and a confirmed genetic mutation are present, it remains a useful diagnostic and prognostic tool. About a quarter of patients with ALGS develop significant liver disease characterized by cirrhosis and liver failure requiring transplantation³⁴⁻³⁶. Unfavourable hepatic parameters are those that remain elevated to the end of the study period, such as total and conjugated bilirubin, serum cholesterol, and the presence of xanthomas. Hepatic malignancies, including hepatocellular carcinoma (HCC), have been described and are rare even in mildly affected patients, suggesting that alterations in Notch signalling might play a role in this process. A small but growing group of patients develops liver disease in adulthood that was not evident at birth but rather emerged in childhood, and this presentation remains rare³⁷⁻³⁸.

Management:

Treatment of cholestasis associated with ALGS is generally symptomatic and aimed at relieving itching by treating with drugs such as ursodeoxycholic acid, cholestyramine, rifampicin, naltrexone, and ondansetron. More recently, new drugs like maralixibat, an apical ileal bile acid transporter (ASBT) inhibitor, have been found to decrease serum bile acids and itchiness³⁹⁻⁴⁰. Plasmapheresis or partial biliary diversion can be performed if the symptoms do not respond to other treatment, in order to help control symptoms but these procedures do not improve the course of the disease. Indications for liver transplantation (LT) include end-stage liver disease (ESLD), intractable itching, severe xanthomas, recurrent fracture, or hepatocellular carcinoma (HCC)⁴¹. Post-LT outcomes are excellent, with no disease recurrence in the graft. Special considerations include vascular anomalies and renal dysfunction, necessitating tailored immunosuppression to prevent nephrotoxicity. Living donors must be carefully screened due to ALGS's autosomal dominant inheritance. Growth failure, though common, is largely genetic and not an absolute indication for LT⁴²⁻⁴³.

Cardiac abnormalities

Cardiac anomalies are present in approximately 90-97% of individuals with Alagille Syndrome, ranging from benign heart murmurs to complex structural defects. The pulmonary vasculature is most commonly affected, with peripheral pulmonary stenosis (PPS) observed in over two-thirds of cases. Tetralogy of Fallot (TOF) is the most frequently reported complex congenital heart defect, occurring in 7-16% of patients. Other cardiac abnormalities include ventricular septal defect, atrial septal defect, aortic stenosis, and coarctation of the aorta, in decreasing order of frequency³⁹. In some individuals, congenital heart disease may be the sole clinical manifestation of ALGS, particularly in families with JAG1 mutations but no hepatic involvement; JAG1 mutations have been identified in patients with

isolated TOF and multi-generational PPS⁴⁰. Structural heart defects, especially TOF associated with PPS, are a major determinant of early mortality in ALGS, while hepatic complications more commonly contribute to later deaths. Survival is significantly impacted by intracardiac disease, with six-year survival reduced to 40% in affected individuals compared with 95% in those without cardiac involvement. Although no correlation has been established between mutation type and cardiac phenotype, JAG1 plays a critical role in vascular development, as shown in mouse models with endothelial-specific Jag1 deletions⁴⁴.

Management:

Corrective cardiac surgery is critical in ALGS to minimize the infant mortality, especially in the setting of tetralogy of Fallot (TOF). Narrowing of the proximal or lobar branches of the artery may be treated conservatively, but if the narrowing is marked, interventional or surgical arterioplasty with or without stenting may be required. In patients with liver transplantation (LT), cardiac conditions must be carefully evaluated since the presence of right-sided heart lesions could worsen intraoperative complications, graft failure or hepatic congestion. Elevated right ventricular pressures, indicated by tricuspid regurgitation, necessitate pre-LT evaluation via right heart catheterization. Pressures exceeding 50% of systemic levels require intervention. A mean pulmonary artery pressure exceeding 45–50 mmHg is generally considered an absolute contraindication for liver transplantation. In cases where the pressure ranges between 35–45 mmHg, patients are first managed with specific pharmacological therapy aimed at lowering pulmonary pressures before proceeding with transplantation. In rare cases, combined heart-liver transplantation may be considered for patients with complex cardiac anomalies and end-stage liver disease⁴⁶⁻⁵⁰.

Ophthalmic and Skeletal features

An anteriorly displaced, thickened line at the peripheral cornea (posterior embryotoxon) is the most commonly observed eye abnormality in patients with Alagille syndrome, occurring in about 78%-90% of cases. Although characteristic of this syndrome, it can also be detected in 8%-15% of the general population and is present in up to 70% of individuals with 22q11 deletion syndrome⁵¹⁻⁵². Additional eye abnormalities may include irregularities of the iris, such as hypoplasia with a mosaic pattern, abnormally small cornea, reduced depth of the anterior chamber, and structural changes such as keratoconus. Some individuals may exhibit congenital macular degeneration, misalignment of the eyes, corneal calcium deposits, or lens opacities. Changes in the retinal pigment epithelium and variations in the optic nerve head are also commonly observed. Optic disc drusen is reported in up to 95% of cases, typically bilateral, and is not observed in non-ALGS liver disease. Retinal pigmentary changes occur in about one-third of patients and are unrelated to vitamin A or E levels⁵³.

Skeletal abnormalities in ALGS vary widely, from mild vertebral anomalies to severe osteopenia with pathological fractures⁵⁴. A common imaging feature is the presence of butterfly vertebrae, resulting

from a midline cleft in the vertebral bodies, seen in 33%-93% of cases; these may also appear in other syndromes such as Kabuki syndrome or VACTERL association. Additional skeletal features include shortened distal phalanges, clinodactyly of the fifth finger, bilateral radio-ulnar synostosis, and supernumerary digital flexion creases, seen more often in ALGS than in the broader population. Pathological fractures, particularly in the lower limbs, affect around 28% of patients⁵⁵, often after minimal trauma. Bone mineral density and content are significantly reduced, especially in children over five years of age⁵⁶, though these normalize when adjusted for body size. However, persistent low bone strength is linked to elevated serum bile acids and bilirubin. Chronic cholestasis, insufficient vitamin D levels, and inherent bone weakness associated with disrupted Notch signalling all contribute to this condition⁵⁷⁻⁵⁸.

Management:

In patients with chronic cholestasis, supplementation with vitamin D (800–1200 IU/day of cholecalciferol), calcium (50–100 mg/kg/day), and phosphorus (25–50 mg/kg/day) is essential⁵⁹. Bisphosphonates such as alendronate can enhance bone mineral density and reduce fracture risk before and after liver transplantation. However, they should only be initiated after ensuring adequate vitamin D levels and with concurrent calcium supplementation to prevent symptomatic hypocalcemia⁶⁰.

Neurocognitive and psychosocial impact

Children with ALGS frequently have lower IQ than those with other cholestatic disorders, with 16% having gross motor delay and up to 10% having intellectual disability⁶¹. Attention and emotional issues, as well as eating disorders, are increasingly prevalent. Liver transplantation (LT) is frequently performed, and although cognition may not be impaired by transplantation itself, delayed liver transplantation may worsen cognitive outcome⁶². Pruritus, dysmorphic features, xanthomas, cardiac complications, and mental health problems all negatively affect quality of life. The emotional burden on patients and caregivers is substantial, and psychological support for the family is essential⁶³. Learning difficulties are reported with variable frequency across cohorts, an observation that may in part reflect ascertainment bias, and are more frequently observed in individuals with 20p12 deletions than in those without such genetic abnormalities⁶³.

Renal anomalies

Renal involvement occurs in 40-70% of individuals with Alagille syndrome and is included in the updated diagnostic criteria⁴⁵. It includes structural abnormalities, such as renal dysplasia, cysts, hypoplasia, hydronephrosis, and vascular anomalies, as well as functional issues such as renal tubular acidosis, glomerulopathy, and interstitial nephritis. NOTCH2 and JAGGED1, key genes in nephron development, are implicated in these abnormalities. Up to 74% of patients can develop renal tubular dysfunction. Even with

normal imaging, reduced eGFR and persistent proteinuria can occur, possibly due to lipid-induced mesangiolipidosis and glomerular damage, especially in ALGS type 2 ⁶⁴⁻⁶⁵.

Management:

Patients with ALGS need ongoing nephrology care. Structural kidney defects require antibiotic prophylaxis and corrective surgery. Post-transplant, renal-sparing immunosuppression is essential, even with normal eGFR ⁴³. In end-stage renal disease, kidney transplantation—or combined liver-kidney transplant if needed—may be required to optimize outcomes and preserve long-term renal function.

Vascular abnormalities

Vascular abnormalities are common in Alagille syndrome, primarily due to defects in the JAGGED1 and NOTCH2 genes, which are vital for angiogenesis. These anomalies can involve the cerebral, renal, pulmonary, and abdominal vasculature. Cerebral complications such as aneurysms, dolichoectasia, and moyamoya arteriopathy (MMA) are reported in 4-38% of patients, often affecting the posterior circulation ^{64,66}. Up to 25% of patients may be asymptomatic despite having cerebrovascular abnormalities. MRI and MRA are recommended screening tools, especially around age 8 or before major surgeries. MMA is associated with strokes or transient ischemic attacks in children and haemorrhagic strokes in adults. Mid-aortic syndrome (MAS), involving stenosis of the aorta and major abdominal arteries, should be suspected in ALGS patients with unexplained hypertension ⁶⁶. Intracranial bleeding, sometimes triggered by minor trauma, occurs in 15% of patients and accounts for 25-50% of ALGS-related deaths. Structural and functional vascular anomalies, such as renovascular disease, coarctation, and aneurysms, further elevate risk. Routine vascular imaging is essential, particularly before liver transplantation (LT), as nearly 65% of patients may require arterial reconstruction ^{67,68}.

Management:

Corrective surgery is essential for symptomatic cerebral aneurysms or those at high risk of rupture. In cases of moyamoya arteriopathy (MMA) detected on imaging, revascularization procedures such as pial or dural synangiosis are recommended ⁶⁶. For children undergoing major surgeries like liver transplantation (LT), existing cerebrovascular anomalies must be addressed beforehand. Similarly, patients with mid-aortic syndrome (MAS) should be managed with percutaneous transluminal angioplasty or surgical intervention to correct the vascular narrowing ⁶⁸.

Conclusions

Alagille Syndrome is a multisystem, complex genetic disorder with considerable clinical variability, predominantly caused by mutations in the JAG1 gene and, less commonly, NOTCH2. It can impact multiple organs, including the liver, heart, eyes, kidneys, skeleton, and blood vessels. Given its varied presentation, early diagnosis is crucial, relying on genetic testing combined with careful clinical

assessment. Management is multidisciplinary, with emphasis on symptomatic treatment, nutritional support, and surgery, including liver or heart transplantation when required. New advances in molecular genetics and targeted therapies offer future possibilities for individualized treatment. Comprehensive, lifelong care remains key to improving outcomes and quality of life for patients with ALGS.

Learning challenges:

A study reported a more incidence intellectual disability in ALGS, this may be influenced by ascertainment bias. Around 16% of patients may exhibit motor developmental delays. Learning difficulties are more frequently observed in individuals with deletions in chromosome 20p12 compared to those without such genetic abnormalities ⁶⁹.

Abbreviations

ALGS

Alagille Syndrome

ASBT

Apical sodium-dependent bile acid transporter

eGFR

Estimated glomerular filtration rate

ESLD

End-stage liver disease

GGT

Gamma-glutamyl transferase

HCC

Hepatocellular carcinoma

JAG1

Jagged1 gene

LT

Liver transplantation

MAS

Mid-aortic syndrome

MCT

Medium-chain triglyceride

MMA

Moyamoya arteriopathy

MRA

Magnetic resonance angiography

MRI

Magnetic resonance imaging

NOTCH2

Neurogenic locus notch homolog protein 2 gene

PPS

Peripheral pulmonary stenosis

TOF

Tetralogy of Fallot

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F.K. conceived the idea for the review and led the literature search, data synthesis, and drafting of the manuscript. D.S. supervised the project, contributed to the conceptual framework, and critically revised the manuscript for important intellectual content. M.K., K.P., and B.K. contributed to the literature search and data collection, and assisted in drafting sections of the manuscript. All authors read, reviewed, and approved the final version of the manuscript.

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