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Original Article

Clinical and Genetic Characteristics of Alagille Syndrome in Adults

Jianguo Li[1,2#], Haicong Wu[3#], Shuru Chen[1,2], Jiahui Pang[1,2], Heping Wang[1,2], Xinhua Li[1,2*] and Weiqiang Gan[1,2*]

[1]Department of Infectious Diseases, The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, China; [2]Guangdong Key Laboratory of Liver Disease Research, The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, China; [3]Department of Hepatobiliary Medicine, 900th Hospital of Joint Logistics Support Force, Fuzong Clinical Medical College of Fujian Medical University, Fuzhou, Fujian, China

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Abstract

Background and Aims: Alagille syndrome (AGS) is an autosomal dominant multisystem disorder caused by mutations in the *JAG1* and *NOTCH2* genes. AGS has been rarely reported in adult patients, mainly because its characteristics in adults are subtle. The study aimed to improve the understanding of adult AGS by a descriptive case series. ***Methods:*** Eight adults diagnosed with AGS at our hospital between June 2016 and June 2019 were included in the study. Clinical data, biochemical results, imaging results, liver histopathology, and genetic testing were analyzed. ***Results:*** Three female and five male patients with a median age of 24.5 years at the time of diagnosis were included in the analysis. The clinical manifestations were adult-onset (62.5%, 5/8), cholestasis (50%, 4/8), butterfly vertebrae (62.5%, 5/8), systolic murmurs (12.5%, 1/8), typical facies (12.5%, 1/8), posterior embryotoxon, and renal abnormalities (0/8). Genetic sequencing showed that all patients had mutations, with four occurring in the *JAG1* gene and four in the *NOTCH2* gene. Six were substitution mutations, one was a deletion mutation, and one was a splicing mutation. Five had been previously reported; but the others, one *JAG1* mutation and two *NOTCH2* mutations were unique and are reported here for the first time. ***Conclusions:*** The clinical manifestations highlighted by the current diagnostic criteria for most adults with AGS are atypical. Those who do not meet the criteria but are highly suspicious of having AGS need further evaluation, especially genetic testing.

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Keywords: Alagille syndrome; Clinical features; *JAG1*; *NOTCH2*; Adult.

Abbreviations: AGS, Alagille syndrome; ALP, alkaline phosphatase; GGT, glutamyl transpeptidase; PIBD, paucity of intrahepatic bile duct; ULN, upper limit of normal.

[#]Contributed equally to the article.

[*]**Correspondence to:** Xinhua Li and Weiqiang Gan, Department of Infectious Diseases and Key Laboratory of Liver Disease of Guangdong Province, The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong 510630, China. ORCID: https://orcid.org/0000-0002-6748-9803 (XL), https://orcid.org/0000-0002-8934-2829 (WG). Tel: +86-20-85252372, Fax: +86-20-85252250, E-mail: lixinh8@mail.sysu.edu.cn (XL), ganweiq@mail.sysu.edu.cn (WG)

Introduction

Alagille syndrome (AGS) is an autosomal dominant multisystem disorder with variable phenotypic penetrance. It is caused by mutations in genes active in the intercellular NOTCH signaling pathway, including *JAG1* encoding the JAGGED1 ligand[1,2] and *NOTCH2* encoding the *NOTCH2* receptor.[3] Of the two genes, *JAG1* mutations are responsible for about 95% of AGS cases.[4] The *JAG1* gene contains 26 exons, is located on chromosome 20p12.2, and encodes the JAGGED1 ligand. The ligand binds to the NOTCH transmembrane receptor encoded by *NOTCH2* gene. The NOTCH intercellular signaling pathway has been shown to be related to cell fate during development in both invertebrates and vertebrates. The NOTCH proteins are involved in the regulation of development of various mammalian organs such as liver, heart, skeleton, kidney, and others (Fig. 1).[5,6] The classical diagnosis of AGS[7] is based on the presence of bile duct paucity in liver biopsies and at least three of the following five features, chronic cholestasis, cardiac disease (most commonly peripheral pulmonary stenosis), skeletal anomalies (typical butterfly vertebrae), ocular abnormalities (primarily posterior embryotoxon), and characteristic facial features (broad forehead, deep-set eyes, straight nose, pointed chin). AGS is almost exclusively diagnosed as cholestasis in infancy or early childhood. The prevalence is estimated as one case per 70,000 live births,[8] but the availability of molecular genetics for diagnosis has increased the estimate to 1 in 30,000 live births.[9] That may still be an underestimate, as some patients do not present with liver disease in infancy. In China, AGS is considered a rare disease, no reports clearly show the disease burden, and is often misdiagnosed in adults for reasons that include lack of awareness and the variable clinical findings. We conducted this retrospective study of AGS in adult patients to better understand the disease and establish a better diagnostic algorithm.

Methods

Patients

Eight adult patients with AGS from the Department of Infectious Diseases of the Third Affiliated Hospital of Sun Yat-sen University between June 2016 and June 2019 were included

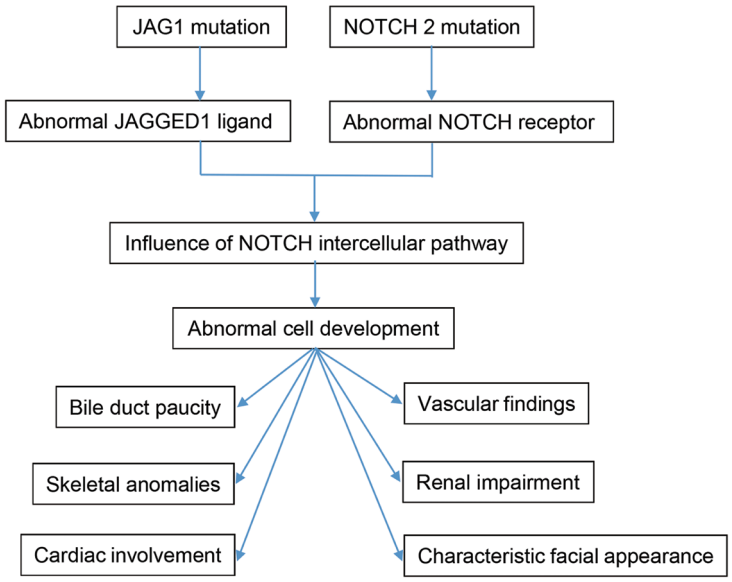

Fig. 1. Role of the *JAG1* and *NOTCH2* mutations in the pathogenesis of Alagille syndrome (AGS).

in the study. The diagnosis of AGS was based on the revised criteria described by Turnpenny *et al*,[10] which include presence of a variant of *JAG1* or *NOTCH2* combined with a positive family history or one of the following, chronic cholestasis, skeletal abnormalities, peculiar facies, ocular abnormalities, renal involvement, or cardiovascular disorders. Informed consent to use the test results for medical research was obtained from the patients. The study conformed to the ethical principles of the Declaration of Helsinki and Good Clinical Practice, as well as Chinese regulatory requirements.

Clinical data were obtained from the patients' medical records, and included demographic characteristics, symptoms, physical examination results, complications, and laboratory data. The patient characteristics included in the physical examination results were facial features, and the presence of heart murmurs and symptoms typical of chronic hepatitis (e.g., jaundice, liver palms, spider angiomas). Routine evaluation included ultrasonography of the liver and kidneys, radiography of the spine, echocardiography, and spiral computed tomography of the chest. Routine blood and urine routines were performed to rule out common liver diseases and to assess liver and renal function. Cholestasis was defined as serum direct/conjugated bilirubin >1.0 mg/dL (17 μmol/L)[11] or serum alkaline phosphatase (ALP) >1.5 times the upper limit of normal (ULN) and glutamyl transpeptidase (GGT) >3 times the ULN.[12]

Percutaneous liver biopsy

Percutaneous liver biopsies were performed in four cases and the fixed, paraffin-embedded tissue was sectioned and stained for hematoxylin and eosin, Masson trichrome, cytokeratin-7, and cytokeratin-19. The histology was reviewed by liver pathologists. Bile duct paucity was defined as the absence of interlobular bile ducts in at least 50% of the portal tracts in liver specimens containing ten or more portal tracts.[13]

Genetic variation analysis

Genomic DNA was extracted from 3 mL of peripheral blood leucocytes with QIAamp Blood Midi Kits (Qiagen, Hilden, Germany) following the manufacturer's instructions. Genes related to the target regions were selected for the panel. Biotinylated 60mer probes (P039-Exome; MyGenostics Inc., Beijing, China) were designed to align with the exons of the genes. Samples were organized into Illumina sequencing libraries, which were enriched for target region-associated genes with the MyGenostics Target Region Enrichment protocol. The captured libraries were sequenced with an Illumina HiSeq 2000 Sequencer (FC-404-2004; Illumina, San Diego, CA, USA).

Statistical analysis

Continuous variables were reported as means and SD or medians. Categorical variables (e.g., age and sex) were reported as numbers and percentages (%). The statistical analysis was performed with SPSS Statistics version 20 (IBM Corp., Armonk, NY, USA).

Results

Clinical characteristics

The patient characteristics are shown in Table 1. Five men and three women with a median age of 24.5 (16–56) years of age at the time of diagnosis were included. One patient (case 1) had positive family history with her mother diagnosed with clinically and genetically confirmed AGS-related cirrhosis. One patient had characteristic facial features, with a broad forehead and posterior embryotoxon. Three patients (37.5%, 3/8) had jaundice since childhood but had not received definitive diagnoses. Five patients (62.5%, 5/8) developed jaundice or hepatic dysfunction in adulthood. Seven patients (87.5%, 7/8) presented with abnormal liver function, half of whom had significant jaundice. Seven patients presented with splenomegaly, but case 3 did not. Systolic murmurs were present in the aortic and pulmonary valve regions in case 2. No sign of structural cardiac disease or vascular malformation was found in any patient. Butterfly vertebrae were found in five of the eight

Table 1. Clinical characteristics of eight adult patients with Alagille syndrome (AGS)

Case	1	2	3	4	5	6	7	8
Sex	Female	Female	Male	Male	Male	Male	Female	Male
Age (years)	16	18	35	36	19	20	56	39
Chief complaint	Jaundice	Skin pigmentation, pruritus	Abnormal LF*	Abnormal LF*	Jaundice/emaciation/ Loss of appetite	Jaundice	Hypodynamia, distention	Jaundice
Onset duration	1 year	10 years	3 years	10 years	8 years	3 days	6 months	1 month
Family history	P	N	N	N	N	N	N	N
Liver	Cholestasis	Bile duct paucity[a]	Cholestasis	Portal hypertension	Bile duct paucity[a]	Cholestasis	Portal hypertension[a]	Bile duct paucity[a]
Angiocarpy	N	Cardiac Murmur	NA	HAF	N	N	N	N
Skeletal	N	BV	BV	BV	N	BV	BV	N
Ocular	N	N	NA	NA	N	N	N	N
Facial	N	P	N	N	N	N	N	N
Kidney	N	N	NA	Kidney Stone	N	N	N	Kidney Stone
Splenomegaly	P	P	NA	P	P	P	P	P
Other features	N	N	N	Decompensated, hepatitis B, LC/ thalassemia	N	HBcAb+	Thalassemia	Cholecystolithiasis

BV, butterfly vertebra; HAF, hepatic arteriovenous fistula; LC, liver cirrhosis; N, negative; NA, not available; P, positive. [a]Patients with percutaneous liver biopsy.

patients (62.5%, Fig. 2). Only one patient had facies characteristic of AGS (prominent forehead and wide intercanthal distance). Posterior embryotoxon was either not reported (2/8 cases) or absent (6/8 cases). No renal abnormalities were found, but kidney stones were present in two cases. Concomitant diseases included decompensated cirrhosis associated with hepatic B in one case, thalassemia in two, and cholecystolithiasis in one.

Biochemical results

Six patients had elevated total and direct bilirubin, four of whom had abnormal ALP/GGT values, and three had elevated serum total bile acid (TBA). Two of the eight patients had elevated alanine aminotransferase (ALT) and four had elevated aspartate aminotransferase (AST). Serum albumin and international normalized ratio (data not shown) were normal in all patients except in case 4 with hepatitis B-related cirrhosis. Two patients had elevated blood lipids (Table 2).

Histological results

PIBD was found in three patients (cases 2, 5, and 8). PIBD was absent in case 7, who had butterfly vertebrae, abnormal ALP and GGT level, cirrhotic changes ultrasound, and *JAG1* mutation was found. Other histological findings included hepatocyte lipofuscin and glycogenosome deposition (Fig. 3).

Genetic variation in AGS

Alterations in the *JAG1* gene (50%, 4/8) and *NOTCH2* gene (50%, 4/8) were identified, and included substitutions in six cases, a deletion in one, and a splice mutation in one. One of the four different *JAG1* gene mutations was novel (c.133G>A) and two of the *NOTCH2* gene mutations were novel, c.6487G>A, and c.2480-4C>G (splicing). The three novel mutations were confirmed by searching the Human Gene Mutation Database updated on 4 November 2021 and the ClinVar database. The missense and splicing mutations were verified by Sanger sequencing. Genetic testing of both parents of three involved patients showed the mutations were derived from mothers. The mother of another patient was negative for the mutation; the father was not tested. The parents of the other four cases were not tested (Table 3).[14–17]

Discussion

AGS is a genetic disorder caused by mutations in *JAG1* and *NOTCH2*, which are components of the NOTCH signaling pathway associated with the development of multiple organs,[18,19] including bile duct and cardiovascular system[20,21] Because the disease is most common in childhood and highly variable across patients,[22] AGS is underdiagnosed in adults, especially those without a family history. The patients in this study were from 16 to 56 years of age. Most previously published studies describe pediatric patients. With the exception of some case reports, few summaries of the clinical features of AGS in adults are available. To the best of our knowledge, our study is the largest diagnostic series of adult AGS in China.

According to the traditional diagnostic algorithm, AGS should manifest as bile duct paucity and at least three other features, cholestasis, characteristic facies, vertebral anom-

Table 2. Biochemical characteristics of eight adult patients with Alagille syndrome (AGS)

Case	ALT (U/L)	AST (U/L)	ALP (U/L)	GGT (U/L)	TBA (μmol/L)	TBil (μmol/L)	DBil (μmol/L)	ALB (g/L)	CHE (U/L)	TG (mmol/L)	CHO (mmol/L)
1	9	25	67	11	14.6	83.7↑	61.2↑	48	8,573	0.76	3.21
2	20	40↑	168↑	132↑	44.6↑	18.3	6.5	45.7	6,462	1.17	6.63↑
3	27	29	60	23	0.3	47.5↑	17.2↑	52.6	8,095	0.71	4.55
4	23	33	NA	23	NA	48.3↑	11.6↑	34.2↓	NA	0.52	3.12
5	5	12	53	6	3.3	40↑	15.2↑	44.5	6,822	0.58	3.36
6	194↑	77↑	133	99↑	329↑	335.2↑	193.2↑	49.4	4,888	1.13	1.53
7	23	48↑	161↑	82↑	7.7	9.3	2.5	44.3	6,450	1.69	5.43
8	57↑	92↑	140↑	28	136.4↑	548.6↑	442↑	42.9	6,548	5.9↑	5.7↑

ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHE, cholinesterase; CHO, cholesterol; DBil, direct bilirubin; GGT, glutamyl transpeptidase; NA, not available; TBA, total bile acid; TBil, total bilirubin; TG, triglyceride. ↑, elevated; ↓, decreased.

alies, ocular abnormalities, and cardiovascular malformations. In our cohort, only case 2 met these criteria. The diagnostic criteria for AGS have changed considerably with the development of molecular testing. Kamath *et al*.[23] and Turnpenny *et al*.[10] revised the diagnostic criteria for AGS to include one or more characteristic clinical features and mutations in *JAG1* or *NOTCH2*. Those with a family history of AGS and defects, even in the absence of some clinical manifestations, should be considered to have AGS and evaluated regularly.

As reported in other large cohorts,[22,24] butterfly vertebrae were common in our patients, occurring in five (62.5%). However, in contrast to previously reported high cholestasis rates, we found that only 50% of the cases had cholestasis. More importantly, the percentages of congenital cardiac disease (12.5%), vascular anomalies (0%), posterior embryotoxon (0%), and typical facial features (12.5%) were also low in our cohort. It is possible that the lesions in these patients were mild and difficult to identify. Another possibility is that the manifestations of AGS are not the same in adults as in children. Previous studies[22,25] have reported renal anomalies in 40–70% of clinically diagnosed AGS, including renovascular disease, tubulointerstitial nephritis, and renal dysplasia or agenesis. Some studies[26] proposed that renal abnormalities should be considered as a disease-defining criterion for AGS. However, in this study, renal function (blood urea nitrogen and creatinine) and routine urine tests were normal, and renal ultrasonography found no structural abnormalities of the kidneys.

Children with AGS present with growth and mental retardation.[27] Chronic disease and malabsorption of fat because of cholestasis may be causative factors. Other abnormalities, such as pancreatic insufficiency, hypothyroidism, small bowel stenosis, atresia, and tracheal stenosis, have

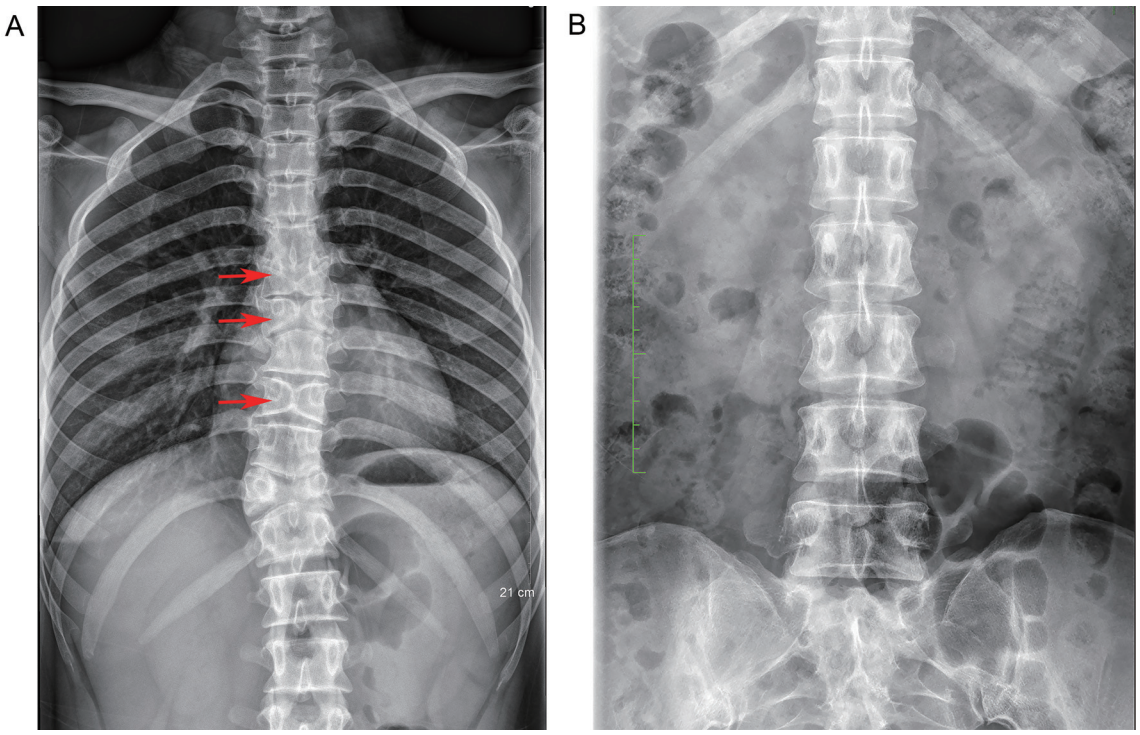

Fig. 2. Butterfly vertebrae in the thoracic and upper lumbar regions. X-ray images of (A) case 2 showing butterfly vertebrae (red arrows) and (B) of normal control.

Table 3. Distribution of mutations in eight adult patients with Alagille syndrome (AGS)

Case	Gene	Mutation	Exon	Predicted Effect	Source	Related Reports
1	*NOTCH2*	c.6487G>A	Exon34	p.D2163N	Mother	Novel
2	*JAG1*	c.1485_1486del	Exon12	p.C496F fs*9	Mother	Crosnier, 1999[14]
3	*JAG1*	c.133G>A	Exon2	p.V45M	NA	Novel
4	*JAG1*	c.133G>T	Exon2	p.V45L	NA	Kohsaka, 2002[15]
5	*NOTCH2*	c.6056G>A	Exon34	p.R2019Q	NA*	Eurofins NTD, 2018[16]
6	*NOTCH2*	c.2480-4C>G	Exon16	splicing	Mother	Novel
7	*JAG1*	c.133G>T	Exon2	p.V45L	NA	Kohsaka, 2002[15]
8	*NOTCH2*	c.2042T>A	Exon13	p.I681N	NA	Kamath, 2012[17]

NA, Not available. *The mother of case 5 had a negative genetic result; the father was not tested.

also been reported in AGS.[28,29] However, there were no similar findings in our study. Two cases had thalassemia, which we believe may be explained by the high incidence of the disease in Guangdong Province.[30] The clinical features of AGS vary widely.[31] Some patients have only mild elevations of serum bilirubin, bile acids, or liver transferases, but others have severe cholestasis that eventually leads to liver failure. In our study, all patients had hepatic involvement, but cholestasis occurred in only 50%, consistent with the guidelines for the evaluation of cholestatic jaundice in infants.[11] However, in adults, the European Association for the Study of the Liver recommends levels of ALP >1.5 ULN and γGGT >3 ULN as biochemical thresholds for diagnosing cholestatic liver diseases.[12] From that perspective, none of our cases met the requirements for the diagnosis of cholestasis.

Bile duct paucity is recognized as a necessary feature of AGS, but some patients are reluctant to undergo a liver biopsy because of its invasiveness, and not all patients who undergo liver biopsy show the absence of intrahepatic bile ducts. In our study, one of the four patients with a liver biopsy did not have bile duct loss, which may have been due to sampling error (Fig. 3). Therefore, liver biopsy is not the gold standard for diagnosis. In addition, the clinical manifestations of some patients, especially adults, are not typical, leading to misdiagnosis. Currently, genetic testing is an important diagnostic tool and perhaps should be considered the gold standard for diagnosis. AGS is a multisystem disorder caused by heterozygous mutations in the *JAG1* and *NOTCH2* genes.[32] Our study found greater involvement of *NOTCH2* mutations than it's been previously reported. In our study mutant *NOTCH2* accounted for half of the cases, but in previous reports, *JAG1* accounted for a larger proportion, 70–94% of the cases.[33–35] Perhaps the difference resulted from the older age of onset in our patients or racial differences. As few reports of specific genetic mutations and variations in adults with AGS have been published,[36,37] more studies including patients from different regions and nationalities are needed to verify the results.

The genotype-phenotype correlations in the literature[34] are not well documented. We found wide variation in phenotypic expression in our cohort. It was interesting to note the trend in increased bilirubin levels associated with *NOTCH2*, and that all patients with *JAG1* mutations had butterfly vertebrae, and that only one case with a *NOTCH2* mutation had butterfly vertebrae. In addition, one patient with a *JAG1* mutation had abnormal cardiac sounds and characteristic facial features, but the other patients did not. However, because of the small sample size, no conclusions can be drawn. Studies of links between genotypes and phenotypes in AGS are ongoing, but no clear connections have been found. Factors that may contribute to the variability of genotypes known to be involved, probably involve a second gene that modifies the effects of a *JAG1* or *NOTCH2* mutation.[32] The search for those genes is underway, and there is evidence that the post-translational addition of sugar moieties (glycosylation and fucosylation) to JAG1 protein has an impact on JAG1-mediated NOTCH signaling. The genes may be involved include Lunatic Fringe (*LFNG*), Radical Fringe (*RFNG*), and Manic Fringe (*MFNG*).[38] Ryan *et al*. found that those genes affected the postnatal growth of bile ducts in mice that were haploinsufficient for both *JAG1* and one of the other three genes.

Currently there is no novel treatments for AGS, not to mention genetic therapy. The best option for improving quality of life is to diagnose AGS as early as possible and initiate symptomatic treatment to slow the disease process. Lack of branching and elongation of bile ducts has been reported during postnatal liver growth in a patient with AGS.[39] Theoretically, novel treatments targeting the NOTCH signaling pathway might promote formation of new bile ducts, thus improving the symptoms of cholestatic liver disease caused by AGS. The aim of treatment would be to increase the expression of JAGGED1 ligand or the *NOTCH2* receptor. Such studies are underway to address the urgent need for those with early stages of liver cholestasis. For those who develop into end stage liver disease, liver transplant will be required. For younger patients, the predicted probability of survival to 20 years of age in all patients is 75%. The probability of survival to age 20 is 80% in patients who did not require liver transplantation.[22] However, similar survival estimates of adult patients is not available, more studies are required, and antenatal screening of parents for AGS-related mutations is necessary.

Conclusions

In summary, retrospective study of eight adult AGS patients identified a novel *JAG1* mutation and two novel *NOTCH2* mutations. Abnormal liver function was the most common initial presenting symptom. Cholestasis was not always the most frequent biochemical characteristic, and bile duct paucity was not seen in some patients. Traditional diagnostic criteria were not appropriate for adults with AGS, in whom the diagnosis should rely more on genetic testing than on clinical features.

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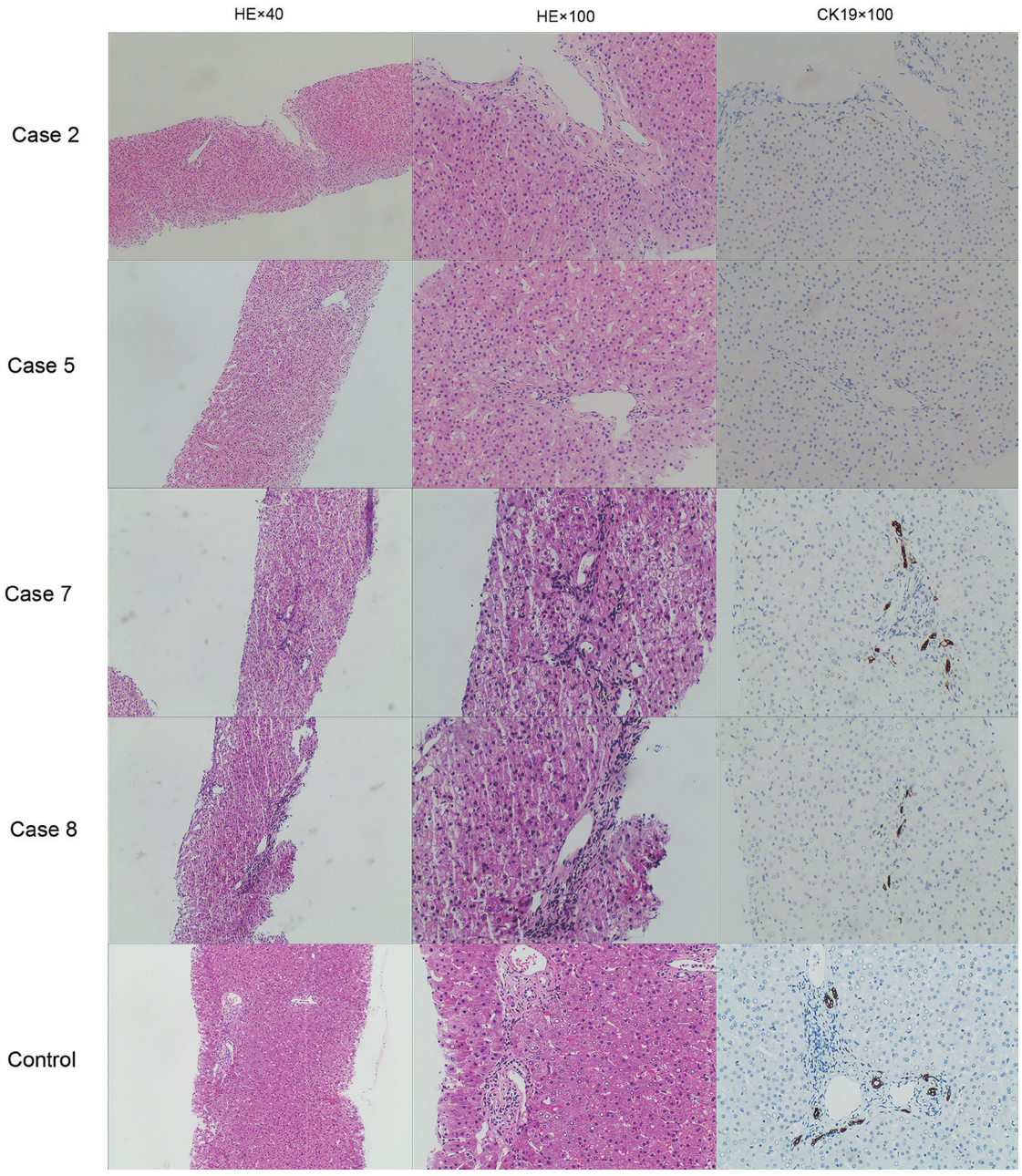

Fig. 3. Liver biopsies of four patients with Alagille syndrome (AGS). Compared with normal control tissue, intrahepatic bile ducts were absent in cases 2 and 5, case 8 had an obvious decrease of bile ducts and case 7 had similar bile ducts.

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Drafting of the manuscript (JL), data collection and analysis (HW), figure preparation and verification of the original data (SC), preparation of the tables and verification of the original data (JP), revision of the manuscript for important intellectual content (WG), and design of the study and review of the final manuscript (XL).

Data sharing statement

The datasets used in the study are available from the corresponding author on reasonable request.

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