

# Diverse renal manifestations of Alagille syndrome in Korean children

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**Purpose:** To determine the prevalence, clinical manifestations, and outcomes of renal involvements in pediatric Alagille syndrome (ALGS).

**Methods:** A total of 21 patients diagnosed with ALGS at age under 18 years who visited Samsung Medical Center from March 1999 to March 2022 were enrolled. ALGS was diagnosed either by clinical manifestations, targeted *JAG1* sequencing, and/or liver biopsy. Medical records including sex, age, renal manifestations, urinalysis, serum creatinine, *JAG1* sequencing, and ultrasonography were retrospectively reviewed.

**Results:** The male to female ratio was 9:12. The mean age of patients at confirmative diagnosis of ALGS was 18.4 months. Sanger sequencing was performed for 17 patients. Sixteen of 21 patients (76.1%) showed *JAG1* mutations. Renal involvement was found in 10 patients (47.6%). The most common type of anomaly was renal dysplasia (40%). One patient having renal dysplasia was pathologically confirmed with glomerular lipid deposition. Two patients (20%) manifested nephrocalcinosis/nephrolithiasis. Among eight renal-involved patients who survived, four (50%) progressed to chronic kidney disease stage 3. Two of these chronic kidney disease patients were diagnosed with hepatorenal syndrome. The other four patients had renal functions preserved, including two without any interventions and two who underwent urological interventions.

**Conclusions:** The current study revealed a high prevalence of renal involvement in Korean pediatric ALGS with diverse phenotypes.

**Keywords:** Alagille syndrome; Child; Nephrocalcinosis; Renal insufficiency, chronic

## Introduction

Alagille syndrome (ALGS) is an autosomal dominant cholestatic liver disease involving multiple organs. Classic diagnosis of ALGS has been made clinically with at least three of the following features: (1) cholestatic liver disease secondary to intrahepatic bile duct paucity; (2) cardiac anomalies (pulmonary artery stenosis or hypoplasia); (3) skeletal involvements (butterfly vertebrae); (4) ocular disorders (posterior embryotoxon); and

(5) characteristic facial features (prominent forehead, deep-set eyes with hypertelorism, pointed chin) [1-4]. Reported prevalence of ALGS ranges from 1:70,000 to 1:100,000 of live births [5].

ALGS is known to be caused by mutations in either *JAG1* or *NOTCH2* gene (accounting for 94% or 2%, respectively) [3,6-9]. *JAG1* and *NOTCH2* genes play a crucial role in cell signaling of the Notch signaling pathway (NSP) during embryonic development of several organs including the liver and kidney [6,10,11]. Crosnier et al. [11] presented that *JAG1* expression is a contrib-

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uting factor to normal development of organs affected in ALGS including kidney. McCright [12] described that NSP is fundamental for kidney development. Several studies have demonstrated the role of NSP especially in differentiation of nephron structures [13,14]. The NSP mediates epithelial specification and vascularization, eventually resulting in the formation of renal collecting system, mature glomerulus, and tubules [3]. Although the classic clinical criteria of ALGS do not comprise renal phenotypes, the role of signaling pathway supports the structural and functional renal involvement prevalent in ALGS. Furthermore, Kamath et al. [3] correlated renal dysplasia and proteinuria owing to abnormal expressions of both *JAG1* and *NOTCH2* in proximal nephrons and renal tubular acidosis (RTA) due to anomalous *JAG1* expression in collecting duct.

Previously, renal involvements encompassing structural abnormalities and impaired function have been documented in almost 40% of ALGS patients with *JAG1* mutations [3,4]. Variable renal manifestations have been observed. The most prevalent renal finding is renal dysplasia with or without cysts followed by RTA and vesicoureteral reflux (VUR) [3,4]. However, only a few studies have characterized and described renal phenotypes.

The objective of this study was to determine the prevalence, clinical manifestations, and outcomes of renal involvement in pediatric ALGS.

## Methods

### Study population

A total of 21 patients diagnosed with ALGS at age under 18 years who visited Samsung Medical Center from March 1999 to March 2022 were enrolled. ALGS was diagnosed either by clinical manifestations, targeted sequencing of *JAG1*, and/or liver biopsy. A retrospective review of medical records was performed. Clinical data included sex, age, renal manifestations, laboratory findings such as urinalysis, serum creatinine, *JAG1* sequencing, ultrasonography and/or computed tomography of kidney, and operation history of liver transplantation.

### Definitions

Renal dysplasia is a histological diagnosis. It generally refers to an abnormal differentiation or organization of renal structure, with or without the presence of renal cysts, ectopic tissue and impaired function [4,15]. In this study, renal dysplasia was defined by increased echogenicity on ultrasound with or without renal cysts and decreased kidney size [4,15]. VUR was diagnosed

using voiding cystourethrogram (VCUG), a gold standard for diagnosis [16]. Glomerular filtration rate (GFR) was estimated using the Schwartz equation [17]. Chronic kidney disease (CKD) was classified according to the 2012 Kidney Disease: Improving Global Outcomes CKD guideline [18]. Hepatorenal syndrome (HRS) is a kind of pre-renal failure due to significant decrease of renal perfusion occurring in patients with persistent portal hypertension [19]. New definition categorizes HRS into three groups: HRS-acute kidney injury (AKI), HRS-acute kidney disease (AKD), and HRS-CKD [20]. HRS-AKD and HRS-CKD are grouped together as HRS-non-AKI. HRS-CKD indicates patients with cirrhosis and estimated GFR <60 mL/min/1.73 m<sup>2</sup> for more than 3 months.

### Genetic tests

Sanger sequencing for *JAG1* mutations was utilized as a confirmative diagnostic tool of ALGS from 2006 in this center. Four patients who visited the center in the early 2000s were diagnosed with ALGS based on clinical manifestations and pathologic findings of liver without genetic study.

## Results

### Demographic data

A total of 21 patients diagnosed with ALGS at age under 18 years who visited Samsung Medical Center from March 1999 to March 2022 were included in this analysis. Male to female ratio was 9:12. Confirmative diagnosis of ALGS was made at a mean age of 18.4 months (Table 1).

### Sanger sequencing for *JAG1*

Sanger sequencing was done for 17 patients. Sixteen of 21 patients (76.1%) were found to have *JAG1* mutations while one

**Table 1.** Demographics and clinical data

Characteristic	Value
Sex (male:female)	9:12
Age at diagnosis of Alagille syndrome (mo)	18.4 (0.3–46.2)
Confirmative diagnostic tool	
<i>JAG1</i> sequencing	16 (76.1)
Liver biopsy	4 (19.0)
Clinical diagnosis <sup>a)</sup>	1 (4.76)
Liver transplantation	13 (61.9)

Values are presented as mean (range) or number (%).

<sup>a)</sup>The patient was also performed *JAG1* sequencing but the result was negative.

patient was negative for mutations (Table 1). Frameshift type accounted for 37.5% of detected *JAG1* mutations, followed by missense and nonsense type mutations (Table 2).

### Extrahepatic manifestations

The most common extrahepatic manifestation was cardiac findings (95.2%) mostly involving pulmonary arteries. Skeletal involvements such as butterfly vertebrae and ocular anomalies, generally posterior embryotoxon, were shown in 42.8% and 19.0% of patients, respectively (Table 3).

**Table 2.** Types of *JAG1* mutations

<i>JAG1</i> mutation type	Location	No. (%)		
Missense	c.476G>T	4 (25.0)		
	c.550C>T			
	c.550C>T			
	c.1156G>A			
Nonsense	c.703C>T	4 (25.0)		
	c.2079T>A			
	c.2277C>A			
	c.3172C>T			
Frameshift		6 (37.5)		
	Deletion		c.994_998delAACTG	4
			c.1620delC	
			c.1630delG	
			c.2874_2875delTG	
	Insertion		c.2410_2411insGT	1
Duplication		c.1160dupG	1	
Splicing site alteration	c.3199+1G>A	1 (6.25)		
Missense and frameshift	c.925G>A	1 (6.25)		
	c.2637delC			

Renal involvement was found in 10 patients (47.6%), which was more prevalent than skeletal or ocular manifestations. Concurrent with previous studies, renal dysplasia (40%) was the most common type of renal anomalies. Others such as RTA, VUR/ureterovesical junction obstruction (UVJO), and nephrocalcinosis (NC)/nephrolithiasis (NL) showed even distribution. One patient with renal dysplasia had undergone diagnostic nephrectomy for incidentally detected renal mass. Xanthogranulomatous pyelonephritis and glomerular lipid deposition were pathologically confirmed (Table 3).

### Renal manifestations and outcomes

Details including outcomes of 10 patients with renal phenotypes are organized in Table 4. Among these 10 patients, seven were found to have *JAG1* mutation and the other three were not performed genetic test. The mean interval time from con-

**Table 3.** Extrahepatic manifestations of Alagille syndrome patients

Extrahepatic manifestations of Alagille syndrome	No. (%)
Cardiac	20 (95.2)
Skeletal	9 (42.8)
Ocular	4 (19.0)
Renal <sup>a)</sup>	10 (47.6)
Renal dysplasia	4
Renal tubular acidosis (proximal)	2
Vesicoureteral reflux/ureterovesical junction obstruction	2
Nephrocalcinosis/nephrolithiasis	2
Glomerular lipid deposition	1

<sup>a)</sup>Glomerular lipid deposition was diagnosed simultaneously in one patient with renal dysplasia.

**Table 4.** Alagille syndrome patients with renal involvements and the outcomes

No.	Sex	<i>JAG1</i> mutation	Time to renal diagnosis (mo) <sup>a)</sup>	Renal finding	Renal outcome
1	F	Not tested	132.8	Renal dysplasia	Renal function preserved
2	M	Not tested	110.2	Nephrolithiasis	ESWL
3	M	Not tested	10.2	Nephrocalcinosis	Expired
4	M	c.2079T>A	39.2	Renal dysplasia	CKD stage 3
5	M	c.2874_2875delTG	2.8	Vesicoureteral reflux	Deflux <sup>b)</sup> injection
6	M	c.476G>T	25.7	Renal tubular acidosis	CKD stage 3
7	M	c.2277C>A	3.9	Renal tubular acidosis	Expired
8	F	c.925G>A c.2637delC <sup>c)</sup>	28.4	Renal dysplasia	CKD stage 3 HRS-CKD
9	F	c.1160dupG	5.6	Ureterovesical junction obstruction	Renal function preserved
10	M	c.3172C>T	0.2	Renal dysplasia Glomerular lipid deposition	CKD stage 3 HRS-CKD

F, female; M, male; ESWL, extracorporeal shock wave lithotripsy; CKD, chronic kidney disease; HRS, hepatorenal syndrome.

<sup>a)</sup>Interval time between confirmative diagnosis of Alagille syndrome and renal diagnosis. <sup>b)</sup>Deflux: hyaluronic acid/dextranome gel used to treat vesicoureteral reflux. <sup>c)</sup>There is no available description whether the variants were cis- or trans-mutations.

firmative diagnosis of ALGS to discovering renal involvement was 35.9 months. Renal phenotypes were categorized into four groups: renal dysplasia, RTA, VUR/UVJO, and NC/NL.

All four patients with renal dysplasia had cystic kidney lesions and increased renal echogenicity on ultrasound. One of these four patients showed abnormal urinary finding as proteinuria. For all patients with renal dysplasia, there was no evidence of prenatal renal diagnosis and no definite causes of CKD other than ALGS at the time of diagnosis. Proximal RTA was noted as an initial renal finding in two patients. One of them expired shortly due to hepatic failure. Urinary tract anomalies were seen in two patients. Of these two patients, one was revealed bilateral VUR with grades 4 and 5 each after recurrent urinary tract infection (UTI) and needed urological intervention by injecting hyaluronic acid/ dextranome gel to relieve the reflux. The other patient was incidentally detected unilateral UVJO and suspected VUR coexisting with hydronephrosis on abdominal sonography. However, VCUG was not done since there was no event of UTI. NC and NL occurred each in one patient and extracorporeal shock wave lithotripsy (ESWL) was performed in the patient with NL.

Eventually, none of 10 patients with renal involvement progressed to end-stage kidney disease (ESKD). However, excluding two patients who expired from hepatic failure, half patients (4/8, 50%) progressed to CKD stage 3 with estimated GFR of 30 to 59 mL/min/1.73 m<sup>2</sup>. Three of four CKD patients had renal diagnosis of dysplasia. Among the four CKD patients, two were diagnosed with HRS-CKD according to the new classification. Four patients preserved their renal functions, including two without any interventions and two who underwent urological interventions.

## Discussion

This study was performed on a group of 21 pediatric patients who met ALGS criteria. Results of this study revealed that the overall prevalence of renal manifestations was 47.6%. To date, only a few studies have tried to analyze the incidence of renal involvements in pediatric ALGS. Through the 1980s and 1990s, the frequency range of renal involvement was suggested to be from 19% to 74% [21-23]. Recently in 2012, Kamath et al. [4] published the largest retrospective cohort study including 187 ALGS patients with renal involvement. The prevalence of renal anomalies or diseases was assumed to be 39% in that study with the

most common phenotype being renal dysplasia, followed by RTA, VUR, and urinary obstruction. In 2018, Di Pinto and Adragina [24] also performed a retrospective study on the presence and outcomes of renal manifestations in 21 children with ALGS and found that the incidence of renal involvement was 85.7%, with renal dysplasia being the most frequent renal anomaly. Renal involvements in the current research also showed a high incidence.

Among the 17 children from this center who had Sanger sequencing done for *JAG1* mutation, 16 (76.1%) were confirmed to have gene mutations. Genotype-phenotype correlation analysis was not performed due to small number of the patients.

The most common type of renal anomalies was renal dysplasia (40%), consistent with previous studies [4,24]. One patient with renal dysplasia was pathologically confirmed xanthogranulomatous pyelonephritis with glomerular lipid deposition. This finding was consistent with earlier reports showing that glomerular lipid deposition was a consequence of abnormal lipid metabolism of ALGS [10,25,26].

Striking point of this study was the prevalence of NC/NL. NC and NL have not often been documented as typical renal anomalies in ALGS patients. However, two (20%) out of 10 renal-involved patients in the present study showed significant renal stones or calcification. One patient with NL needed ESWL but no causative factors were discovered since stone analysis was not done at the time and there was no evidence of either tubular dysfunction or UTI. The other patient with incidentally detected NC could possibly manifested tubular dysfunction regarding the low urinary osmolality and specific gravity. Moreover, when closely examining the other eight patients classified to have other main types of renal involvement, two patients with renal cystic lesions also had histories of transient renal stones. The high incidence of NC/NL was consistent with previous studies suggesting relations between renal cystic lesions and tendency of forming kidney stones [27-29].

During the follow-up, four renal-involved patients who are alive have progressed to CKD stage 3. Of these four CKD patients, three had renal dysplasia and one had RTA. However, two of these four patients had HRS during the clinical course. According to Kamath et al. [4], percentages of patients with CKD and ESKD requiring kidney transplant were 5.4% and 4.1%, respectively. Given that 50% of our patients with renal involvement proceeded to CKD and only 25% preserved renal function without any interventions, the prognosis of sequential renal

disease in pediatric ALGS was considered to be poor. Still, the mean time to renal diagnosis was almost three years. In contrast, all patients were screened for cardiac anomalies during initial evaluation. Regarding the incidence and prognosis of renal manifestations, all clinicians involved in managing ALGS should team up with nephrologists closely from the initial diagnosis. Although renal anomaly is not included in the classic criteria, watchful follow-up of renal manifestations in pediatric ALGS is needed.

However, the current study has some limitations. First, this study was performed as a single-center retrospective review. The study population was small in size and there were missing records such as urine chemistry. Also, the onset of renal diagnosis including renal dysplasia was not clear since most of patients were incidentally detected abnormal sonographic findings during the course ALGS. Therefore, the interval time to renal diagnosis could be measured longer than the actual time from the onset. Second, genetic confirmation was done with Sanger sequencing, targeting only *JAG1* mutation. Thus, ALGS patients without *JAG1* mutation were not genetically analyzed.

In summary, we found a high prevalence of renal involvements in Korean pediatric ALGS with diverse phenotypes, highlighting the importance of nephrologic evaluation and follow-up. There has been a lack of publication documenting renal phenotypes of pediatric ALGS, especially in Asia. This is the first study to represent renal anomalies accompanied by ALGS in Korean children. Further study with multicenter large sample is needed afterward. Furthermore, with commercialization of advanced genetic analysis, genotype-phenotype correlation of renal manifestations in ALGS might be possible in the future.

## Ethical statements

The Institutional Review Board of Samsung Medical Center approved this study (IRB No. 2022-06-083-001). Informed consent was obtained from all participants.

## Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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None.

## Author contributions

Conceptualization: JJ, MJK, HC

Formal analysis: JJ

Investigation: JJ, MJK

Methodology: JJ, HC

Project administration: HC

Visualization: JJ, HC

Writing-original draft: JJ

Writing-review & editing: MJK, HC

All authors read and approved the final manuscript.

## References

1. Alagille D, Odievre M, Gautier M, Dommergues JP. Hepatic ductular hypoplasia associated with characteristic facies, vertebral malformations, retarded physical, mental, and sexual development, and cardiac murmur. *J Pediatr* 1975;86:63-71.
2. Kohut TJ, Gilbert MA, Loomes KM. Alagille syndrome: a focused review on clinical features, genetics, and treatment. *Semin Liver Dis* 2021;41:525-37.
3. Kamath BM, Spinner NB, Rosenblum ND. Renal involvement and the role of Notch signalling in Alagille syndrome. *Nat Rev Nephrol* 2013;9:409-18.
4. Kamath BM, Podkameni G, Hutchinson AL, Leonard LD, Gerfen J, Krantz ID, et al. Renal anomalies in Alagille syndrome: a disease-defining feature. *Am J Med Genet A* 2012;158A:85-9.
5. Danks DM, Campbell PE, Jack I, Rogers J, Smith AL. Studies of the aetiology of neonatal hepatitis and biliary atresia. *Arch Dis Child* 1977;52:360-7.
6. Li L, Krantz ID, Deng Y, Genin A, Banta AB, Collins CC, et al. Alagille syndrome is caused by mutations in human *Jagged1*, which encodes a ligand for Notch1. *Nat Genet* 1997;16:243-51.
7. McDaniell R, Warthen DM, Sanchez-Lara PA, Pai A, Krantz ID, Piccoli DA, et al. NOTCH2 mutations cause Alagille syndrome, a heterogeneous disorder of the notch signaling pathway. *Am J Hum Genet* 2006;79:169-73.
8. Oda T, Elkahloun AG, Pike BL, Okajima K, Krantz ID, Genin A, et al. Mutations in the human *Jagged1* gene are responsible for Alagille syndrome. *Nat Genet* 1997;16:235-42.
9. Gilbert MA, Bauer RC, Rajagopalan R, Grochowski CM, Chao G, McEldrew D, et al. Alagille syndrome mutation update: comprehensive overview of *JAG1* and *NOTCH2* mutation frequencies and insight into missense variant classification. *Hum Mutat* 2019;40:2197-220.
10. Bissonnette ML, Lane JC, Chang A. Extreme renal pathology in

- Alagille syndrome. *Kidney Int Rep* 2016;2:493-7.
11. Crosnier C, Attie-Bitach T, Encha-Razavi F, Audollent S, Soudy F, Hadchouel M, et al. JAGGED1 gene expression during human embryogenesis elucidates the wide phenotypic spectrum of Alagille syndrome. *Hepatology* 2000;32:574-81.
  12. McCright B. Notch signaling in kidney development. *Curr Opin Nephrol Hypertens* 2003;12:5-10.
  13. Cheng HT, Kim M, Valerius MT, Surendran K, Schuster-Gossler K, Gossler A, et al. Notch2, but not Notch1, is required for proximal fate acquisition in the mammalian nephron. *Development* 2007;134:801-11.
  14. Surendran K, Boyle S, Barak H, Kim M, Stomberski C, McCright B, et al. The contribution of Notch1 to nephron segmentation in the developing kidney is revealed in a sensitized Notch2 background and can be augmented by reducing Mint dosage. *Dev Biol* 2010;337:386-95.
  15. Goodyer P, Gupta IR. Renal dysplasia/hypoplasia. In: Avner E, Harmon WE, Niaudet P, Yoshikawa N, Emma F, Goldstein SL, editors. *Pediatric nephrology*. 7th ed. Berlin: Springer; 2016. p. 115-34.
  16. Mattoo TK, Mathews R, Gupta IR. Vesicoureteral reflux and renal scarring in children. In: Avner E, Harmon WE, Niaudet P, Yoshikawa N, Emma F, Goldstein SL, editors. *Pediatric nephrology*. 7th ed. Berlin: Springer; 2017. p. 1715-48.
  17. Schwartz GJ, Haycock GB, Edelmann CM Jr, Spitzer A. A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. *Pediatrics* 1976;58:259-63.
  18. CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* [Internet]. 2013 [cited 2022 Oct 31];3:1-150. Available from: [https://kdigo.org/wp-content/uploads/2017/02/KDIGO\\_2012\\_CKD\\_GL.pdf](https://kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf).
  19. Liu PM, de Carvalho ST, Fradico PF, Cazumba ML, Campos RG, Simoes E Silva AC. Hepatorenal syndrome in children: a review. *Pediatr Nephrol* 2021;36:2203-15.
  20. Angeli P, Garcia-Tsao G, Nadim MK, Parikh CR. News in pathophysiology, definition and classification of hepatorenal syndrome: a step beyond the International Club of Ascites (ICA) consensus document. *J Hepatol* 2019;71:811-22.
  21. Alagille D, Estrada A, Hadchouel M, Gautier M, Odievre M, Dommergues JP. Syndromic paucity of interlobular bile ducts (Alagille syndrome or arteriohepatic dysplasia): review of 80 cases. *J Pediatr* 1987;110:195-200.
  22. Hoffenberg EJ, Narkewicz MR, Sondheimer JM, Smith DJ, Silverman A, Sokol RJ. Outcome of syndromic paucity of interlobular bile ducts (Alagille syndrome) with onset of cholestasis in infancy. *J Pediatr* 1995;127:220-4.
  23. Quiros-Tejeira RE, Ament ME, Heyman MB, Martin MG, Rosenthal P, Hall TR, et al. Variable morbidity in alagille syndrome: a review of 43 cases. *J Pediatr Gastroenterol Nutr* 1999;29:431-7.
  24. Di Pinto D, Adragna M. Renal manifestations in children with Alagille syndrome. *Arch Argent Pediatr* 2018;116:149-53.
  25. Habib R, Dommergues JP, Gubler MC, Hadchouel M, Gautier M, Odievre M, et al. Glomerular mesangiolipidosis in Alagille syndrome (arteriohepatic dysplasia). *Pediatr Nephrol* 1987;1:455-64.
  26. Russo PA, Ellis D, Hashida Y. Renal histopathology in Alagille's syndrome. *Pediatr Pathol* 1987;7:557-68.
  27. Nishiura JL, Neves RF, Eloi SR, Cintra SM, Ajzen SA, Heilberg IP. Evaluation of nephrolithiasis in autosomal dominant polycystic kidney disease patients. *Clin J Am Soc Nephrol* 2009;4:838-44.
  28. Garcia-Nieto V, Negrete-Pedraza F, Lopez-Garcia M, Luis-Yanes MI. Are simple renal cysts in childhood associated with kidney stones? *Nephrourol Mon* 2012;4:596-8.
  29. Torres VE, Wilson DM, Hattery RR, Segura JW. Renal stone disease in autosomal dominant polycystic kidney disease. *Am J Kidney Dis* 1993;22:513-9.