Genetic, Clinical, and Pathologic Backgrounds of Patients with Autosomal Dominant Alport Syndrome

Naohiro Kamiyoshi, Kandai Nozu,* Xue Jun Fu,* Naoya Morisada,* Yoshimi Nozu,* Ming Juan Ye,* Aya Imafuku,† Kenichiro Miura,‡ Tomohiko Yamamura,* Shogo Minamikawa,* Akemi Shono,* Takeshi Ninchoji,* Ichiro Morioka,* Koichi Nakanishi,§ Norishige Yoshikawa,§ Hiroshi Kaito,* and Kazumoto Iijima**

Abstract

Background and objectives Alport syndrome comprises a group of inherited heterogeneous disorders involving CKD, hearing loss, and ocular abnormalities. Autosomal dominant Alport syndrome caused by heterozygous mutations in *collagen 4A3* and/or *collagen 4A4* accounts for <5% of patients. However, the clinical, genetic, and pathologic backgrounds of patients with autosomal dominant Alport syndrome remain unclear.

Design, setting, participants, & measurements We conducted a retrospective analysis of 25 patients with genetically proven autosomal dominant Alport syndrome and their family members (a total of 72 patients) from 16 unrelated families. Patients with suspected Alport syndrome after pathologic examination who were referred from anywhere in Japan for genetic analysis from 2006 to 2015 were included in this study. Clinical, laboratory, and pathologic data were collected from medical records at the point of registration for genetic diagnosis. Genetic analysis was performed by targeted resequencing of 27 podocyte-related genes, including Alport–related *collagen* genes, to make a diagnosis of autosomal dominant Alport syndrome and identify modifier genes or double mutations. Clinical data were obtained from medical records.

Results The median renal survival time was 70 years, and the median age at first detection of proteinuria was 17 years old. There was one patient with hearing loss and one patient with ocular lesion. Among 16 patients who underwent kidney biopsy, three showed FSGS, and seven showed thinning without lamellation of the glomerular basement membrane. Five of 13 detected mutations were reported to be causative mutations for autosomal recessive Alport syndrome in previous studies. Two families possessed double mutations in both *collagen 4A3* and *collagen 4A4*, but no modifier genes were detected among the other podocyte–related genes.

Conclusions The renal phenotype of autosomal dominant Alport syndrome was much milder than that of autosomal recessive Alport syndrome or X–linked Alport syndrome in men. It may, thus, be difficult to make an accurate diagnosis of autosomal dominant Alport syndrome on the basis of clinical or pathologic findings. No modifier genes were identified among the known podocyte–related genes.

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*Department of Pediatrics, Kobe University Graduate School of Medicine, Kobe, Japan; †Department of Nephrology, Toranomon Hospital, Tokyo, Japan; ‡Department of Pediatrics, The University of Tokyo, Tokyo, Japan; and §Department of Pediatrics, Wakayama Medical University, Wakayama, Japan

Correspondence: Dr. Kandai Nozu, Department of Pediatrics, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo, Kobe 6500017, Japan. Email: nozu@med.kobe-u.ac.jp

Introduction

Alport syndrome is a hereditary disorder involving CKD progressing to ESRD, sensorineural hearing loss, and ocular abnormalities (1). Alport syndrome has three genetic modes of inheritance: X–linked Alport syndrome (XLAS), autosomal recessive Alport syndrome (ARAS), and autosomal dominant Alport syndrome (ADAS). XLAS is caused by mutations in the *collagen 4A5* (*COL4A5*) gene encoding the type 4 collagen α5–chain and accounts for approximately 80% of patients with the disease. ARAS occurs in about 15% of patients as a result of homozygous or compound heterozygous mutations in the *COL4A3* or *COL4A4* gene, whereas ADAS occurs in <5% of patients and arises as a result of heterozygous mutations in the *COL4A3* and/or *COL4A4* gene encoding the type 4 collagen α3– or α4–chain, respectively (2). However, heterozygous mutations in *COL4A3* or *COL4A4* are also found in about 40% of patients with thin basement membrane nephropathy (TBMN) (3). Although most affected individuals develop hematuria in childhood, proteinuria, renal failure, and extrarenal disorders are not observed in patients with TBMN, and the molecular mechanisms responsible for the different clinical courses of ADAS and TBMN remain unclear. Recent studies have revealed correlations between FSGS and heterozygous mutations in *COL4A3* or *COL4A4* (3,4), and 10% of patients diagnosed with familial FSGS showed heterozygous mutations in these two genes (5). A recent study using next generation sequencing (NGS) analysis revealed high proportions of mutations in *COL4A3* and *COL4A4* and a higher incidence of ADAS than previously reported (6). However, studies of ADAS are limited, and the clinical phenotype and genetic and pathologic backgrounds remain unclear (7–12). In this study, we provide the first clarification of

the genetic, clinical, and pathologic backgrounds of ADAS in a relatively large number of patients.

Materials and Methods

Diagnostic Criteria for ADAS

All patients diagnosed with ADAS in this study satisfied one of the following criteria: (*1*) hematuria and proteinuria or ESRD with renal pathology showing thickening and thinning with lamellation in the glomerular basement membrane (GBM; basket weave change [BWC]) and heterozygous mutations in *COL4A3* and/or *COL4A4*; (*2*) hematuria and proteinuria with renal pathology showing thin basement membrane (TBM) and a family history of ESRD, with heterozygous mutations in *COL4A3* and/or *COL4A4*; and (*3*) siblings or consanguineous family members of patients with ADAS diagnosed with criteria 1 or 2 and at least showing hematuria, including patients for whom genetic tests were not available. These criteria ensured that at least one person in the family had received a kidney biopsy and had TBM leading to a pathologic diagnosis of ADAS.

Patients

Patients with suspected Alport syndrome after pathologic examination who were referred to our hospital for genetic diagnosis from 2006 to 2015 were included in this study. Clinical, laboratory, and pathologic data were collected from medical records at the point of registration for genetic diagnosis. Detailed family histories were gathered from the patients and/or their parents. Information on hearing loss was obtained from medical records. All patients were evaluated for ocular lesions by an ophthalmologist before genetic analysis. In Japan, annual urinary screening is available for all students and most adults, and family members with urinary abnormalities of at least hematuria were included in the analysis of renal survival. Patient age was determined at the time of registration for genetic testing. We conducted a retrospective study of 72 patients with renal manifestations, including 25 genetically diagnosed patients with ADAS and 47 family members from 16 unrelated families. The family trees for all families are shown in Supplemental Figure 1. Age at registration for genetic analysis, age at reaching ESRD, or age at death without ESRD are shown for all 72 patients. Of these 72 patients, 19 (26%) had already developed ESRD. Clinical and laboratory data and pathologic findings were obtained from medical records. The degree of urinary protein excretion was evaluated by urinary protein-to-creatinine ratio. eGFRs were calculated using the Schwartz equation (13,14) or GFR-estimating equations for Japanese individuals (15) for patients <18 and ≥ 18 years old, respectively.

Genetic Analyses

Sanger Sequencing. Sanger sequencing for *COL4A3* and *COL4A4* was performed by PCR and direct sequencing of genomic DNA for all exons and exon-intron boundaries. Most patients in this study had undergone Sanger sequencing for the diagnosis of ADAS before NGS analysis. Blood samples were collected from patients and family members, and genomic DNA was isolated from peripheral blood leukocytes using the Quick Gene Mini 80 System (Fujifilm, Tokyo, Japan) according to the manufacturer's instructions. For genomic DNA analysis, all 52 specific exons of *COL4A3* and 48 exons of *COL4A4* were amplified by PCR as described previously (16). The PCR-amplified products were then purified and subjected to direct sequencing using a Dye Terminator Sequencing Kit (Amersham Biosciences, Piscataway, NJ) with an automatic DNA sequencer (model ABI Prism 3130; PerkinElmer, Waltham, MA).

Targeted Resequencing. NGS samples were prepared using a HaloPlex Target Enrichment System Kit by following the manufacturer's instruction (Agilent Technologies, Santa Clara, CA). Briefly, digested 225 ng genomic DNA were hybridized at 54°C for 16 hours with custom–designed NGS probes to capture 27 genes, such as *COL4A3*, *COL4A4*, *COL4A5*, and other FSGS–causative genes. Amplified target libraries were sequenced with 150-bp pair-end reads on a MiSeq Platform (Illumina, San Diego, CA) followed by variant analysis on a SureCall 3.0 (Agilent Technologies).

We analyzed 25 patients with ADAS, including at least one from each of 16 families.

Haplotype Analyses. Haplotype analysis was performed for families 122 and 140, both of which possessed double mutations in both *COL4A3* and *COL4A4* with identical substitutions and were, thus, suspected of having a common ancestor. The target fragments on chromosome 2 were amplified by AmpliTaq Gold (Thermo Fisher Scientific, Vernon Hills, IL) using microsatellite markers D2S163, D2S126, D2S133, D2S2354, D2S362, D2S396, D2s233, and D2s206. PCR fragment size was analyzed using an ABI PRISM 310 Genetic Analyzer (Applied Biosystems, Foster City, CA) followed by allele binning using GeneMapper (Thermo Fisher Scientific).

Statistical Analyses

Statistical analysis was performed using JMP (JMP, Version 11 Package for Windows; SAS Institute Inc., Cary, NC). The occurrence of events (age at detection of proteinuria and age at ESRD) was analyzed according to the Kaplan–Meier method. We defined the outcomes as age at ESRD for renal survival analysis and detection of proteinuria for proteinuria–free survival analysis. We considered patients who died without ESRD as censored patients. Deaths in patients who had already developed ESRD were treated as having reached the outcome at the age of developing ESRD. Patients who had not reached ESRD at the point of registration for genetic analysis were also treated as censored patients.

Ethical Considerations

All procedures were reviewed and approved by the Institutional Review Board of Kobe University School of Medicine. Informed consent was obtained from all patients or their parents.

Results

Clinical Features

The clinical features of the 25 patients with genetically proven ADAS are shown in Table 1, and all family trees are shown in Supplemental Figure 1. The cohort included 11 men and 14 women, with a mean age of 33.4 years old (range =5–82 years old). Proteinuria was detected in

Table 1. Clinical findings

Patient ID	Age, yr	Sex	Height, cm	BW, kg	Proteinuria Detected Age, yr	ESRD Detected Age, yr	Hearing Loss Detection Age, yr	Ocular Lesion	sCr, mg/dl	sAlb, g/dl	U-P/C, g/g	eGFR, ml/min per 1.73 m^2
72	14	W	155.6	47.4	—	—	—	—	0.49	4.8	0.04	131.1
122	35	M	183	66.0	9	—	—	—	1.27	4.3	0.45	53.8
122A	39	W	156	51.0	2	—	—	—	ND	ND	ND	ND
122C	62	M	163	66.0	17	57	—	—	ND	ND	ND	ND
124	45	W	158	40.0	17	—	—	—	0.74	4.0	0.73	66.8
129	43	M	170	77.0	42	—	—	—	0.77	4.7	0.22	88.3
140	16	M	180.4	105.3	6	—	—	—	0.81	4.2	0.92	80.9
140A	47	M	172	89.8	9	33	—	—	ND	ND	ND	ND
148	46	W	153.6	38.7	35	—	—	—	0.69	3.7	2.1	71.7
148A	20	W	149	40.7	—	—	—	—	0.57	4.5	0.02	112.2
148B	18	W	164.7	50.4	—	—	—	—	0.51	4.5	0.02	130.6
148C	11	M	150.4	35.4	—	—	—	—	0.62	4.5	0.03	84.9
153	48	W	154.5	49.3	9	—	—	—	0.9	3.8	1.86	53.0
153E	82	M	160	44.0	32	63	—	AMD	8.84	3.2	ND	ND
154	26	W	161	67	16	—	—	—	0.68	4.8	0.71	86.8
161	26	M	177	74.0	5	—	—	—	0.9	4.6	1.5	83.7
175	31	W	159.6	54.4	5	—	—	—	0.92	3.6	1.0	58.1
175A	5	W	100.9	15.5	—	—	—	—	0.34	4.4	0.0	103.8
175B	5	W	106	17.5	—	—	—	—	0.28	4.6	0.0	132.5
198	36	M	167	62	11	—	—	—	3.0	3.6	2.0	20.9
205	45	M	174.3	67.0	20	—	—	—	1.67	3.9	1.0	37
279	29	M	175.0	72.0	17	—	—	—	0.91	3.8	1.3	81.8
285	25	W	152.0	46.0	—	—	—	—	0.41	4.2	0.0	155
297	11	W	143.8	26.5	6	—	—	—	0.60	3.9	0.4	98.8
305	69	W	157.0	51.0	44	—	65	—	1.76	3.6	3.6	22.9

ID, identification; BW, body weight; sCr, serum creatinine level; sAlb, serum albumin level; U-P/C, urinary protein-to-creatinine ratio; W, woman or girl; M, man or boy; ND, not detected until now; AMD, age–related macular degeneration.

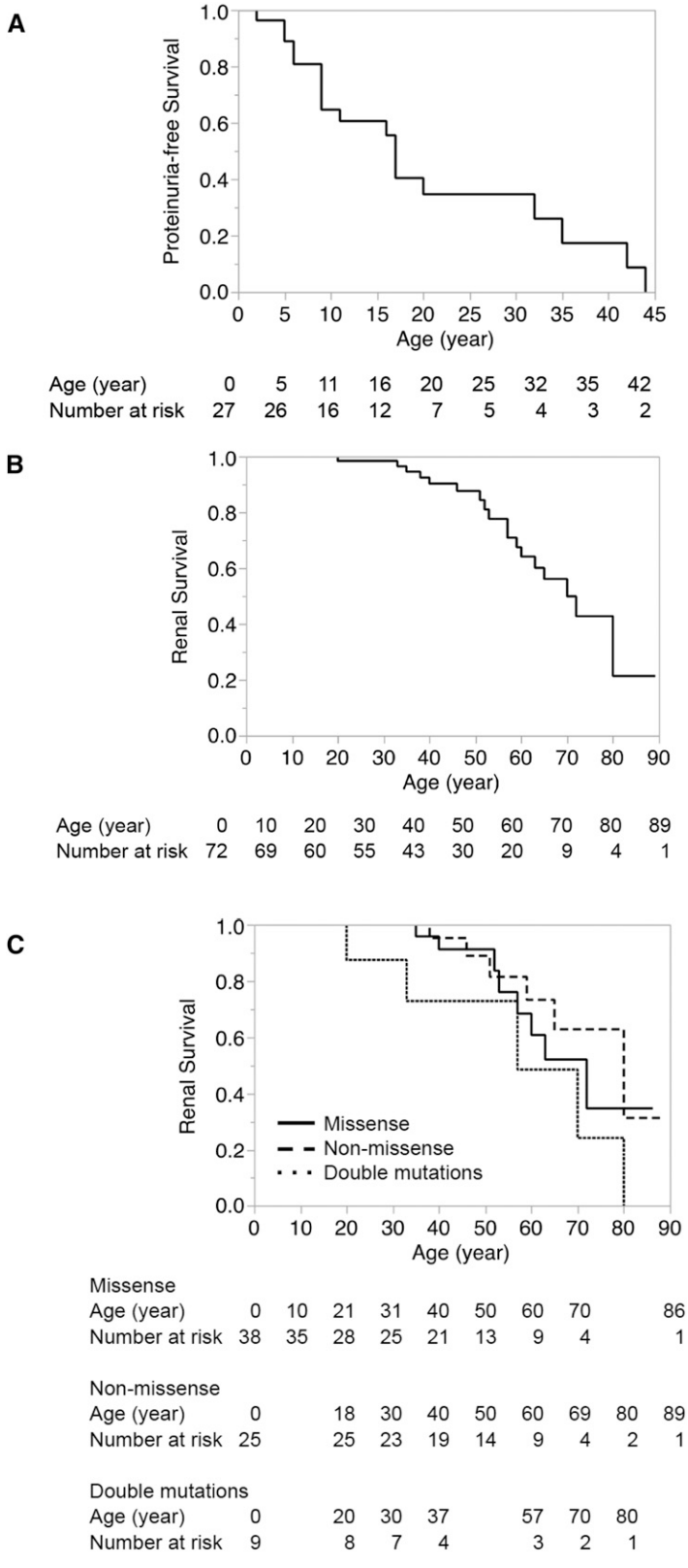

Figure 1. | **Probability of each clinical sign in autosomal dominant Alport syndrome cases.** (A) Probability of developing proteinuria in 24 patients. (B) Probability of developing ESRD in 72 patients. (C) Probability of developing ESRD according to the type of mutation (38 missense, 25 nonmissense, and nine double mutations). The median ages for developing proteinuria and ESRD were 17 and 70 years old, respectively. Differences between types of mutation were not significant (P=0.18).

18 patients, and the median age for developing proteinuria was 17.0 years old (Figure 1A). Although the proteinuria–free survival curve shows the time to proteinuria detection rather than time to onset, all students in Japan receive urinary screening every year, and most adults also receive urinary screening through their employers or public health organizations. The age at detection of proteinuria is, thus, relatively accurate. Seven patients showed normal renal function (age range =5–25 years old), 14 showed mild to severe renal dysfunction, and three patients reached ESRD at 33, 57, and 63 years old (Table 1). One patient had hearing loss, and one ocular lesion was detected. We also assessed a total of 172 patients with ADAS and family members for renal disease and detected renal disorders in 72 individuals, including ESRD in 19 patients. The median renal survival time in this study was 70.0 years (Figure 1B).

Pathologic Findings

The pathologic findings are shown in Table 2. Renal biopsy was performed in 16 patients from 16 families. All of these patients had both hematuria and proteinuria at the time of kidney biopsy. The mean age at renal biopsy was 32.3 years old (range =11–61 years old). Five biopsies showed minimal glomerular change, eight showed diffuse mesangial proliferation, and three showed FSGS, by light microscopy. Immunofluorescence staining revealed IgM deposits in three patients and IgA and C3 deposits in two patients. BWC was detected by electron microscopy in nine patients, and seven patients showed isolated TBM. Immunohistochemical staining of collagen-α5(4) showed normal expression in 15 patients and was not examined in one patient. Seven patients underwent multiple renal biopsies before diagnosis.

Mutation Detection

The detected mutations are shown in Table 3. Thirteen different mutations, including 10 missense mutations leading to glycine substitutions, an 18-bp deletion mutation, a splice-site mutation, and a 1-bp deletion mutation were identified, all in the collagenic domain. Eight of the mutations were novel mutations. Among the 16 families with ADAS, six had mutations in *COL4A3*, eight had mutations in *COL4A4*, and two had mutations in both *COL4A3* and *COL4A4* with identical substitutions suspicious of a common ancestor. Five mutations were reported to be causative mutations for ARAS in previous studies (17,18).

NGS Analyses

We conducted comprehensive analyses of 25 patients from 16 families by targeted resequencing. We targeted 27 causative genes for inherited FSGS and Alport syndrome (Supplemental Table 1). Identical variants in *COL4A3* and/or *COL4A4* were detected by both Sanger method and targeted resequencing in all patients. We also detected 168 variants in exonic region in 26 genes (Supplemental Table 2), and those were not pathogenic variants.

We failed to identify any other variants considered to be modifier genes or double mutations that might have increased the severity of the phenotype.

Haplotype Analyses

Two families had double mutations in both *COL4A3* and *COL4A4*, with identical substitutions of p.Gly1406Glu in *COL4A3* and p.Gly957Arg in *COL4A4*. We, therefore, performed microsatellite analysis to identify any founder effect between these two families using eight markers spanning 22.5 Mb centered on the *COL4A3* and *COL4A4* region on chromosome 2. A haplotype (gray in Figure 2) spanning 13.4 Mb including *COL4A3* and *COL4A4* was conserved in both families, suggesting that the disease-associated segment might have been inherited from the same founder.

Table 2. Pathologic findings

Patient ID	Age at Biopsy, yr	Light Microscopy	Immunofluorescence Staining	Electron Microscopy	α5-Staining	No. of Biopsies
72	14	MGA	Negative	TBM, BWC	Positive	1
122	35	DMP	Negative	TBM	Positive	1
124	45	MGA	IgM	TBM	Positive	2
129	43	DMP	ND	TBM	Positive	1
140	16	FSGS	IgM	TBM	Positive	1
148	46	FSGS	Negative	TBM, BWC	Positive	1
153	48	DMP	ND	TBM, BWC	Positive	1
154	24	DMP	IgA, C3	BWC	Positive	2
161	26	MGA	Negative	TBM, BWC	Positive	1
175	31	DMP	Negative	TBM, BWC	Positive	4
198	17	DMP	Negative	TBM, BWC	ND	4
205	45	FSGS	IgM, Fib	TBM	Positive	2
279	30	MGA	IgA, C3	TBM	Positive	2
285	25	DMP	Negative	TBM	Positive	1
297	11	MGA	IgG, C1q	TBM, BWC	Positive	1
305	61	DMP	Negative	TBM, BWC	Positive	2

ID, identification; MGA, minimal glomerular abnormality; TBM, thin basement membrane; BWC, basket weave change; DMP, diffuse mesangial proliferation; Fib, fibrinogen; ND, not determined.

Table 3. ***Collagen 4A3*** **and** ***collagen 4A4*** **mutations**

Patient ID	Mutation 1				Mutation 2				Previous Report of ARAS
	Gene	Position (Exon)	Nucleotide Change	Amino Acid Change	Gene	Position (Exon)	Nucleotide Change	Amino Acid Change	
72	*COL4A4*	29	c.2510G>C	p.Gly837Ala					Yes
122	*COL4A3*	47	c.4217G>A[a]	p.Gly1406Glu	*COL4A4*	32	c.2869G>A	p.Gly957Asp	Yes
124	*COL4A4*	22	c.1323_1340del[a]	18-bp Deletion					
129	*COL4A3*	35	c.2980+2T>A[a]	Exon skipping					
140	*COL4A3*	47	c.4217G>A[a]	p.Gly1406Glu	*COL4A4*	32	c.2869G>A	p.Gly957Asp	Yes
148	*COL4A4*	25	c.1808A>G[a]	p.Asp603Gly					
153	*COL4A4*	24	c.1733G>T	p.Gly577Val					Yes
154	*COL4A4*	31	c.2726G>A[a]	p.Gly909Glu					
161	*COL4A3*	26	c.1855G>A	pGly619Arg					Yes
175	*COL4A3*	40	c.3499G>A	p.Gly1167Arg					Yes
198	*COL4A3*	26	c.1901G>A	p.Gly634Glu					
205	*COL4A3*	26	c.1855G>A	p.Gly619Arg					Yes
279	*COL4A4*	20	c.1323_1340del[a]	18-bp Deletion					
285	*COL4A4*	30	c.2641del C[a]	p.His881fs					
297	*COL4A4*	27	c.2084G>A[a]	p.Gly695Asp					
305	*COL4A3*	40	c.3464G>A[a]	p.Gly1155Asp					

ID, identification; ARAS, autosomal recessive Alport syndrome; *COL4A4*, *collagen 4A4*; *COL4A3*, *collagen 4A3*.
[a]Novel mutation.

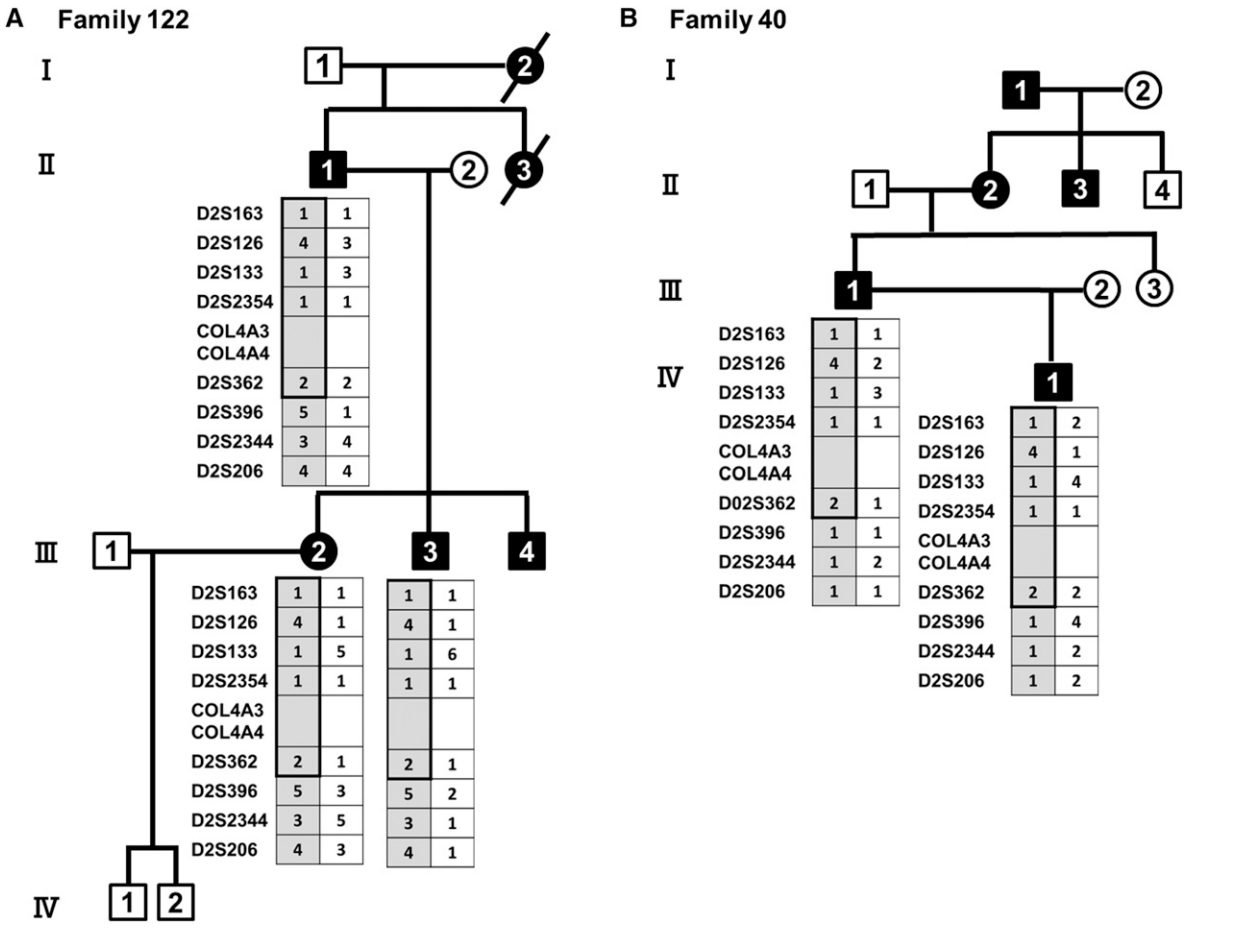

Figure 2. | **Haplotype analysis of two families harboring p.Gly1406Glu in *collagen 4A3* (*COL4A3*) and p.Gly957Arg in *COL4A4* mutations.** Haplotypes of (A) family 122 and (B) family 140. The haplotype from D2S163 to D2S362 (gray with black frame), spanning 13.4 Mb, was conserved in both families. Squares indicate men, and circles indicate women. lack symbols indicate affected individuals, oblique bars indicate deceased individuals, roman numerals represent generations, and numbers identify family members.

Genotype-Phenotype Correlations

We compared renal survival curves for patients with missense mutations, nonmissense mutations, and double mutations (Figure 1C). There were no significant differences among these three groups (P=0.18).

Discussion

This study is one of the largest to examine the clinical manifestations, pathologic characteristics, and genetic backgrounds of patients with ADAS. We conducted genetic analyses in patients with clinical manifestations, pathologic findings, and family histories consistent with Alport syndrome throughout Japan. To date, we have confirmed a genetic diagnosis of Alport syndrome in 305 families and detected ADAS in 16 families, giving a proportion of ADAS of 5.25%, consistent with a previous report (2).

In our study, the median age for developing proteinuria was 17 years old, and the median renal survival time was 70 years. In contrast, previous studies reported median renal survival rates in men with XLAS or ARAS of 25 and 21 years old, respectively (18,19). Marcocci *et al.* (10) observed proteinuria in 50% of patients with ADAS, but only one patient developed proteinuria at younger than 20 years old; however, nine patients reached ESRD, and only one reached ESRD before 40 years of age, consistent with our results. Overall, these results indicate that renal manifestations in individuals with ADAS are mild and slowly progressive compared with those in men with XLAS and individuals with ARAS.

Only one patient in our cohort developed hearing loss (at age 61 years old), and one developed suspected age–related macular degeneration (at age 82 years old). Marcocci *et al.* (10) reported that 13.3% of patients with ADAS developed sensorineural hearing loss and that only one developed bilateral cataract, which was assumed to be caused by postrenal transplantation steroid treatment. Jais *et al.* (19) reported hearing loss and specific ocular changes in 79% and 35.2%, respectively, among men with XLAS, whereas Oka *et al.* (18) reported hearing loss in 40% and ocular lesions in 10% of Japanese patients with ARAS. These results indicate that extrarenal manifestations are relatively rare in patients with ADAS. Overall, the clinical manifestations in patients with ADAS, especially in younger patients, seem to be much milder than those in men with XLAS and patients with ARAS.

Sixteen patients in this study (one from each family) underwent kidney biopsy. Light microscopy revealed FSGS in three of these 16 patients. Previous studies of large Greek Cypriot pedigrees led to the suggestion of a causal relationship between heterozygous *COL4A3*/*COL4A4* mutations and FSGS (20,21). Malone *et al.* (5) analyzed a familial FSGS cohort and found *COL4A3* or *COL4A*4 variants in seven of 70 families. Xie *et al.* (4) identified heterozygous *COL4A3* mutations in five (12.5%) FSGS families, whereas Gast *et al.* (22) reported *COL4A3* or *COL4A*4 variants in four patients from three families among a total of 80 patients (5%) with FSGS. This suggests that some patients with ADAS might be diagnosed as having familial FSGS. Immunohistochemical staining of α5(4) showed normal expression in glomeruli in all patients in this study. We previously also showed normal expression of α5(4) in GBM in 29% of patients with XLAS and 20% of patients with ARAS (16,18). A normal distribution of α5(4) cannot, thus, be used to establish the inheritance mode for ADAS. Although GBM alterations were detected in all patients by electron microscopy, seven patients showed isolated TBM. The mean ages at renal biopsy were 34.1 years old (range =16–45 years old) in patients with isolated TBM and 30.9 years old (range =11–61 years old) in patients with BWC, suggesting that the different findings between TBM and BWC are unlikely to be caused by different ages at renal biopsy in patients with ADAS. Furthermore, multiple renal biopsies were performed before reaching a definite diagnosis in seven of the 16 patients. These results indicate that it may be difficult to make a precise diagnosis of Alport syndrome on the basis of clinical and pathologic findings.

Six patients in this study had heterozygous mutations in *COL4A3*, eight patients had heterozygous mutations in *COL4A4*, and two patients had heterozygous mutations in both *COL4A3* and *COL4A4*. The mutation sites were scattered throughout the genes with no accumulation in any specific region as in the previous study (10). Broad differences in phenotypes were observed among unrelated families, even among families with identical variants, and we were unable to establish any genotype-phenotype correlations in this cohort. Two families had double mutations with identical substitutions in both genes in the *cis* position, and microsatellite analysis in these families identified a founder effect. Mencarelli *et al.* (23) recently reported that digenic inheritance in ADAS was associated with a poorer prognosis, intermediate between ADAS and ARAS. The two families in our study comprised eight patients, five of whom developed ESRD at the ages of 20, 33, 57, 70, and 80 years old. Renal phenotype, thus, varied in these families, and we were unable to identify any correlation between phenotype severity and double mutations.

Five mutations detected in patients with ADAS in this study were previously reported as causative mutations for ARAS (11,18). Interestingly, the heterozygous carrier parents of these mutations in those reports were asymptomatic or only presented with microhematuria. Strasser *et al.* (24) reported that digenic mutations in *COL4A5* and *MYH9* affected severity of Alport syndrome symptoms. We, therefore, conducted targeted resequencing to search for modifier genes among podocyte-related genes reported as causative genes of familial FSGS or congenital nephrotic syndrome. As a result, we could not identify any variants likely to act as modifier genes in this study (Supplemental Table 2). These findings indicate that the heterozygous mutations in *COL4A3* or *COL4A4* may cause ESRD on their own, although secondary factors, such as environmental factors or unknown genetic changes, might also contribute to the phenotype of kidney disease in patients with ADAS.

In conclusion, the results of this study clarify the natural history of ADAS. Patients with ADAS show nonspecific clinical manifestations, except for hematuria at a young age. Pathologically, one half of the examined patients showed isolated TBM, and all showed normal α5(4), highlighting the difficulty of establishing a precise diagnosis of ADAS on the basis of clinical and pathologic findings, especially in the early phase of the disease. Some patients with ADAS may be incorrectly diagnosed with familial FSGS or even IgA nephropathy. The phenotype of ADAS varies, regardless of the genetic background, with no identifiable phenotype-genotype correlations, indicating the existence of secondary factors affecting the phenotype of kidney disease in patients with ADAS.

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