

# Mother–Son Kidney Transplantation in Patients With X-Linked Alport Syndrome



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Received 6 January 2021; revised 19 February 2021; accepted 22 February 2021; published online 12 March 2021

*Kidney Int Rep* (2021) 6, 1454–1458; <https://doi.org/10.1016/j.ekir.2021.02.037>

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## INTRODUCTION

Alport syndrome (AS) is a hereditary disease that is characterized by progressive kidney disease, sensorineural hearing loss, and ocular lesions.<sup>1</sup> The responsible genes for AS are *COL4A3*, *COL4A4*, and *COL4A5*. In approximately 60% to 70% of cases, AS is caused by mutations in *COL4A5*, referred to as X-linked AS (XLAS); in contrast, autosomal dominant AS and autosomal recessive AS, which are caused by mutations in *COL4A3* or *COL4A4*, account for 20% to 30% and 10% of cases, respectively.<sup>2,3</sup>

More than 90% of male patients with XLAS are reported to develop end-stage kidney disease (ESKD) by 40 years of age.<sup>4</sup> Kidney transplantation is well tolerated in XLAS because anti-glomerular basement membrane (GBM) glomerulonephritis is reported to occur after transplantation in approximately 4% of patients with XLAS.<sup>5,6</sup> However, the number of kidney transplants from deceased donors in Japan was 1.83 donors per million population, which was much lower than that in Western countries, according to the International Registry in Organ Donation and Transplantation database.<sup>7</sup> Living donors should be carefully selected because the proband's mother is usually an AS patient herself. Indeed, 12% of female XLAS patients are reported to develop ESKD by 40 years of age.<sup>8</sup>

We report the long-term outcomes of 2 patients with genetically confirmed XLAS who received living kidney transplantation from their mothers.

## CASE REPORTS

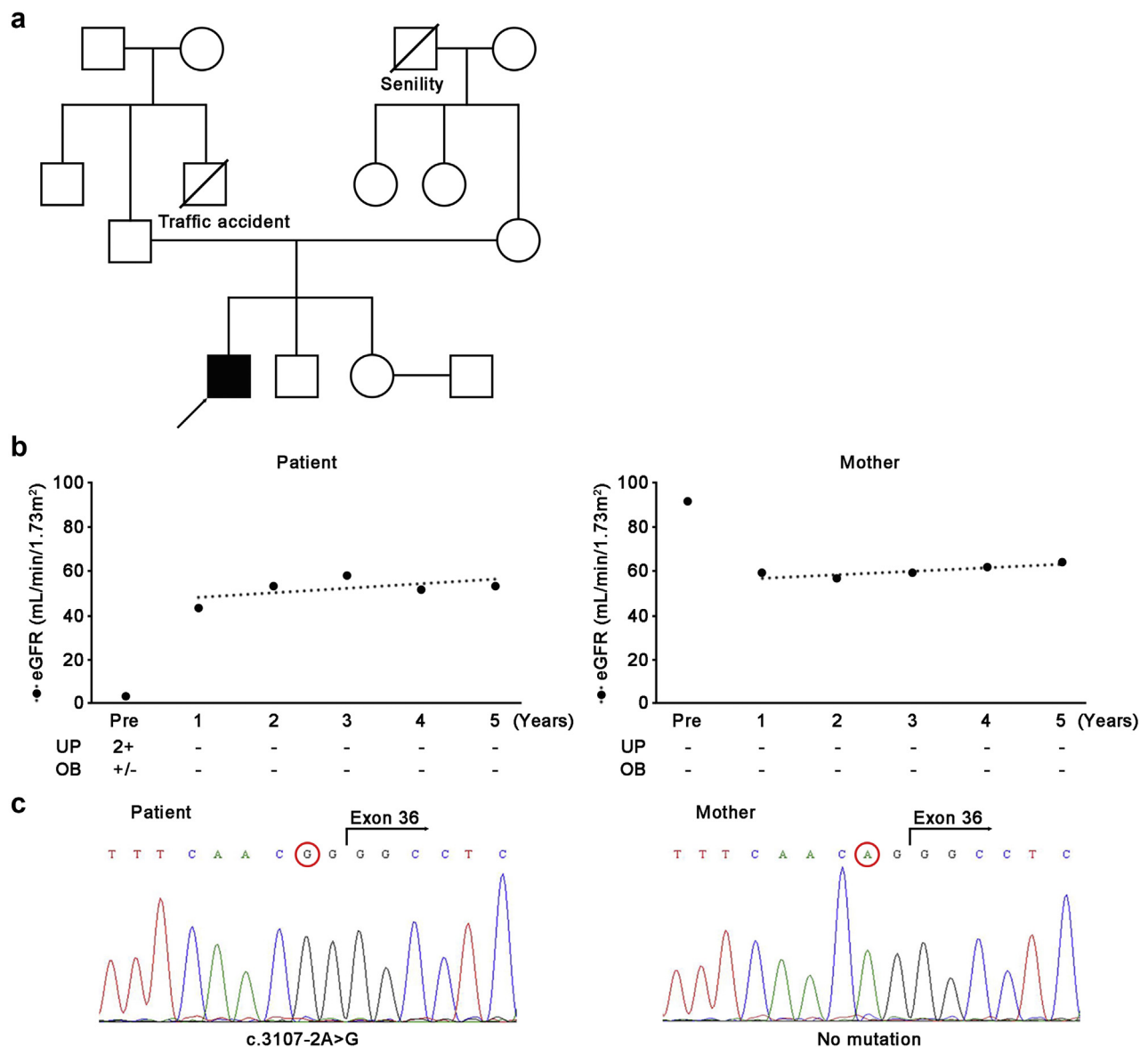
### Case 1

Case 1 is a 39-year-old Japanese man in whom microhematuria had been pointed out during early

childhood. He was diagnosed with AS based on the results of a kidney biopsy specimen at 5 years of age. He developed bilateral sensorineural hearing loss without ocular lesions at 20 years of age and started hemodialysis because of ESKD at 28 years of age. Although an X-linked mode of inheritance was suspected, none of the patient's relatives, including his mother, had kidney disease (Figure 1a). He visited an outpatient clinic for genetic counseling; a genetic analysis was not performed at that time. Since his mother had normal urinalysis results, living kidney transplantation from his mother was performed when he and his mother were 34 and 59 years of age, respectively. His kidney function after transplantation was good and dialysis therapy was discontinued. Neither he nor his mother had proteinuria or microhematuria after kidney transplantation (Figure 1b). The estimated glomerular filtration rate (eGFR) values of the patient at 1 and 5 years were 43.3 and 53.5 ml/min/1.73m<sup>2</sup>, respectively, while those of his mother were 59.2 and 64.2 ml/min/1.73m<sup>2</sup> (Figure 1b). The changes in the eGFR of the patient and his mother were +2% per year and +1.5% per year at 5 years after transplantation without proteinuria or microhematuria. Subsequently, a genetic analysis identified a splice-site mutation at c.3107-2A > G in *COL4A5* in the patient but not the mother (Figure 1c); this was considered a *de novo* mutation.

### Case 2

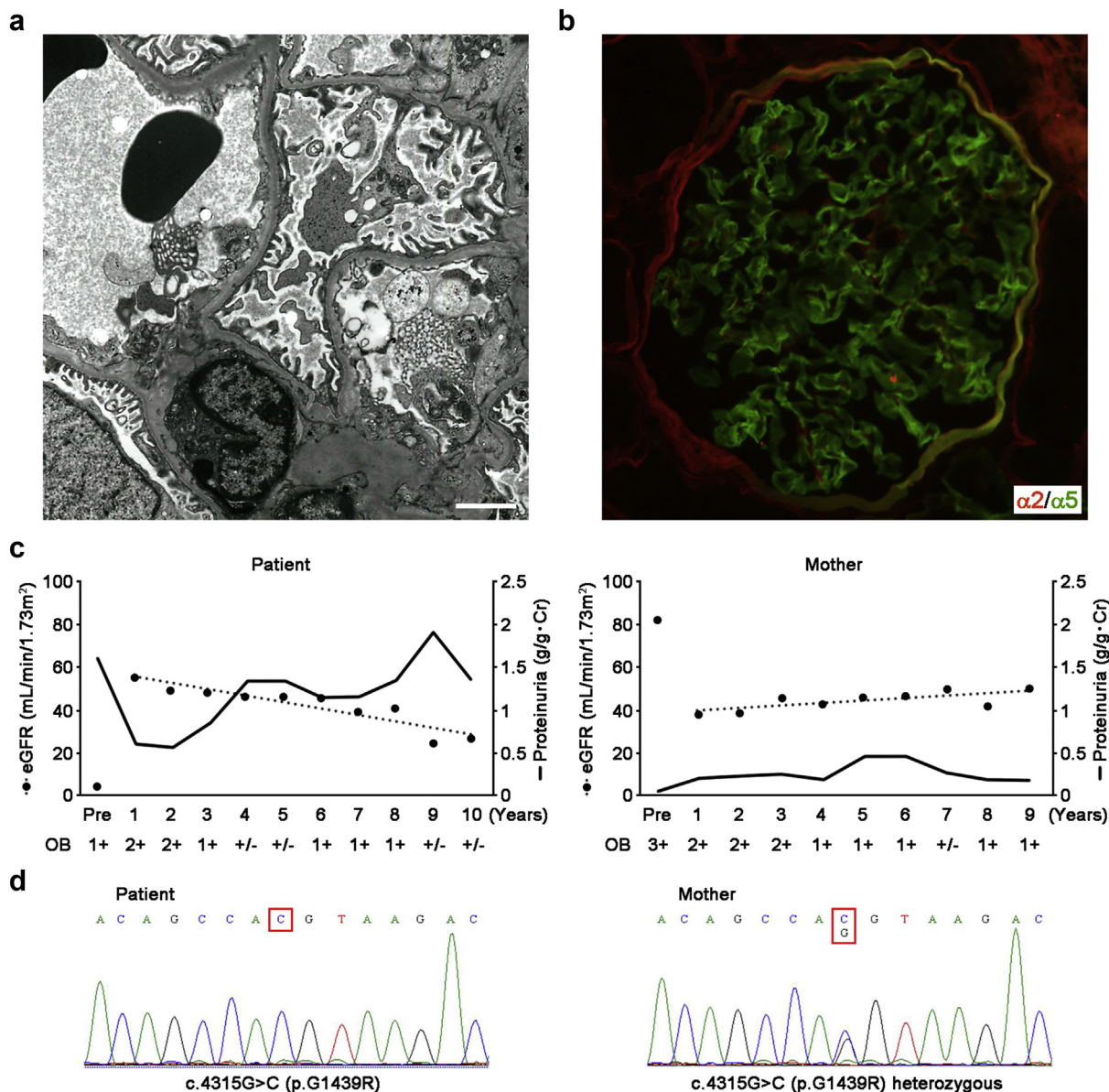
Case 2 is a 36-year-old Japanese man who underwent an operation to treat stenosis of the left ureterovesical junction at 5 years of age. Microhematuria and proteinuria had been pointed out at 9 years of age and he was diagnosed with AS because of typical irregular



**Figure 1.** Case 1: the patient and his mother. (a) The pedigree chart showed a sporadic pattern. (b) Kidney function 5 years after transplantation. The changes in the estimated glomerular filtration rate (eGFR) of the patient and his mother were +2% per year and +1.5% per year 5 years after transplantation without proteinuria or microhematuria. (c) *COL4A5* c.3107-2A>G was only observed in the patient. OB, occult blood; UP, urinary protein.

thickening of the GBM in kidney biopsy specimens. He had bilateral sensorineural hearing loss without any ocular lesions. His kidney function gradually worsened, and hemodialysis was initiated at 23 years of age. His relevant family history included microhematuria in his mother, while his maternal grandmother developed ESKD at approximately 80 years of age. There were no donor candidates in his family other than his mother; his father had already died of cancer. As his mother strongly wished to donate her kidney, an investigation was performed to determine whether she could meet the donor criteria. Although microhematuria had been pointed out in a health check, she had not undergone a detailed examination. She did not have hypertension

and had no problems during 2 pregnancies. Her urinary sediment showed 5 to 9 red blood cells per high power field and her urinary protein was 0.1 g/day. Her serum creatinine, eGFR, and creatinine clearance values were 0.57 mg/dl, 82.3 ml/min/1.73m<sup>2</sup>, and 116.0 ml/min, respectively. She did not have sensorineural hearing loss or ocular lesions. A kidney biopsy specimen was obtained. Light microscopy revealed no major abnormalities in the biopsy specimen. Electron microscopy showed thinning of the GBM (Figure 2a). An immunofluorescence study revealed that the  $\alpha 5$  chain distribution in the glomeruli was almost intact with type IV collagen  $\alpha 2$  and  $\alpha 5$  chains, while the  $\alpha 5$  chain distribution was partially decreased in the



**Figure 2.** Case 2: the patient and his mother. (a) Electron microscopy revealed thinning of the glomerular basement membrane in the patient's mother. Bar = 2  $\mu$ m. (b) In the patient's mother, a double immunofluorescence study to detect type IV collagen  $\alpha$ 2 and  $\alpha$ 5 chains showed that the  $\alpha$ 5 chain distribution in the glomeruli was almost intact while the  $\alpha$ 5 chain distribution was partially decreased in the Bowman basement membrane. (c) The clinical course of the patient and his mother. The change in the estimated glomerular filtration rate (eGFR) of the patient was  $-3\%$  per year 10 years after transplantation while that of his mother was  $+1.1\%$  per year 9 years after transplantation. Proteinuria in case 2 increased from 0.6 to 1.35 g/g Cr 10 years after transplantation while that in his mother was unchanged. (d) c.4315G>C (p.G1439R) in *COL4A5* was identified in the patient and his mother was found to be heterozygous for the same mutation. OB, occult blood.

Bowman basement membrane (Figure 2b). From these observations, it was considered that there was no contraindication to living kidney transplantation from the mother and the operation was performed when the patient and his mother were 26 and 59 years of age, respectively. Although proteinuria (0.62 g/day) was observed after transplantation, the patient's kidney function was good, and his serum creatinine level 2 months after the operation was 1.2 mg/dl. His eGFR was 55.5 ml/min/1.73m<sup>2</sup> 1 year after transplantation and gradually declined to 26.4 ml/min/1.73m<sup>2</sup> 10 years

after transplantation (Figure 2c). The change in the eGFR of the patient was  $-3\%$  per year 10 years after transplantation. The eGFR values of his mother were 38.4 ml/min/1.73m<sup>2</sup> 1 year after transplantation and 50.4 ml/min/1.73m<sup>2</sup> 9 years after transplantation (Figure 2c). The change in eGFR of his mother was  $+1.1\%$  per year 9 years after transplantation. The proteinuria in case 2 increased from 0.6 g/g Cr to 1.35 g/g Cr 10 years after transplantation, while that in his mother showed no change from 0.2 g/g Cr to 0.18 g/g Cr 9 years after transplantation. He received

**Table 1.** Summary of the reported mothers in mother–son kidney transplantation in X-linked Alport syndrome

Cases, year	Age at tx, yr	Kidney biopsy	OB	UP	Hearing loss	Ocular lesion	Follow-up period after tx, yr	eGFR change after tx
Sessa et al., 1995 <sup>53</sup>	46	Thin GBM	+	–	+	–	2	Stable
Yachnin et al., 2002 <sup>54</sup>	44	Basket-weaving feature	+	–	–	–	4.5	Stable
Gross et al., 2009 <sup>55</sup>								
Patient 1	62	NA	+	<0.3 g/day	–	–	2	–35%
Patient 3	56	NA	+	–	–	–	6	–10%
Patient 4	54	NA	+	–	–	–	3	–25%
Patient 5	56	Thin GBM, GBM splitting	+	–	–	–	14	–60%
Patient 6	62	NA	+	–	–	–	8	–10%
Mother of case 1	59	NA	–	–	–	–	5	+7.5%
Mother of case 2	59	Thin GBM	+	0.1 g/day	–	–	10	+9.9%

eGFR, estimated glomerular filtration rate; GBM, glomerular basement membrane; NA, not available; OB, occult blood; Tx, transplantation; UP, urinary protein.

telmisartan and amlodipine to treat hypertension and proteinuria after kidney transplantation. A biopsy specimen of the transplanted kidney was obtained 4 years after transplantation because the kidney started to show calcineurin inhibitor toxicity with arteriosclerotic lesions, and the amount of tacrolimus was gradually decreased. Antihypertensive drugs, including an angiotensin II receptor blocker with dietary sodium restriction, were continued in case 2. A genetic analysis was performed later and revealed a missense mutation at c.4315G>C (p.G1439R) in *COL4A5* (Figure 2d). A heterozygous missense mutation was identified at c.4315G>C (p.G1439R) in *COL4A5* in his mother (Figure 2d), which suggested that she was a female patient with XLAS.

## DISCUSSION

We experienced 2 cases of genetically confirmed XLAS in which the patients received living kidney transplantation from their mothers. Cases 1 and 2 were followed up for 5 and 10 years after transplantation, respectively.

A sporadic pattern was long suspected in case 1 and a genetic analysis confirmed a *de novo* splice-site point mutation at c.3107-2A>G in *COL4A5*, which was predicted to skip exon 36 and cause a frameshift in the collagenous domain of type IV collagen  $\alpha 5$  chain. The mutation was reported to be “pathogenic” in the ClinVar database.<sup>9</sup> The mother of the patient in case 1 showed no mutation in *COL4A5*, and therefore it is plausible that the donated kidney worked well and that she was also healthy with a single kidney. In case 1, the changes in eGFR in the patient and his mother 5 years after transplantation were +2% per year and +1.5% per year, respectively. The genetic analysis had a beneficial effect on her mental status because she was afflicted by a feeling of remorse that she carried the origin of the mutation. The rate of *de novo* mutation in humans is reported to be 1 in 100,000,000<sup>51</sup> and it is

reported that *de novo* mutations are detected in 12% of patients with XLAS.<sup>4</sup>

In contrast, a genetic analysis in case 2 identified a missense point mutation at c.4315G>C (p.G1439R) in *COL4A5*, which was reported to be “likely pathogenic” as c.4297G>C (p.G1433R) in the ClinVar database. After a stringent examination of the mother before kidney transplantation, she was chosen as a donor. If a genetic analysis had been performed in advance, it is possible that this approach would not have been recommended. However, she might have still wished to be a donor if she had known aware of the results of her genetic analysis.<sup>52</sup> In case 2, although the proteinuria and eGFR values of the patient’s mother were unchanged, they worsened in the patient. A biopsy specimen of the transplanted kidney was obtained, and it revealed calcineurin inhibitor toxicity with arteriosclerotic lesions rather than glomerular lesions, which are typical of AS. These results were reminiscent of a previous report in that the kidney function of one son who received a kidney from his mother worsened because of recent viral infection or because of the use of immunosuppressive agents, while the kidney function of the patient’s mother remained stable 2 years after transplantation.<sup>53</sup>

There have been 9 cases of mother–son kidney transplantation among patients with XLAS, including the 2 present cases, and the present and previously reported mothers are summarized in Table 1.<sup>53–55</sup> Although the mother of case 2 had a stable eGFR 10 years after kidney donation, this does not mean that kidney donation by women with XLAS carries no risk of developing chronic kidney disease or kidney failure. Indeed, the kidney function worsened in 3 of the 9 mothers after kidney transplantation (Table 1). Recent opinion about donor selection suggested that female XLAS patients >45 years of age without overt proteinuria or hearing loss could be considered as donors of last resort.<sup>56</sup> As the mother of case 1 had normal urinalysis results without microhematuria and the pedigree chart showed a sporadic pattern, kidney transplantation from

**Table 2.** Teaching points

Donor patients with XLAS should be carefully selected because the proband's mother is usually a patient with XLAS

12% of female patients with XLAS are reported to develop end-stage kidney disease by 40 years of age

A genetic diagnosis before kidney transplantation as well as careful evaluations with kidney biopsy would be useful if a mother is considered a donor for a patient with XLAS

Genetic testing for any family member who is considering being a donor, including sisters, should also be considered

XLAS, X-linked Alport syndrome.

the mother was performed on the assumption that case 1 had a *de novo* mutation. Pretransplant genetic testing in case 1 would have demonstrated the absence of a *COL4A5* variant in the mother and alleviated concern about the extraordinary risks associated with kidney donation. In contrast, the mother of case 2 had micro-hematuria and electron microscopy showed thinning of the GBM, which are typical findings in female patients with XLAS. The waiting time for deceased donor kidney transplant was 12.3 years because of a shortage of the potential deceased donors in Japan.<sup>57</sup> Since there were no donor candidates among the relatives of case 2, including the father, she was chosen as a donor of last resort; she was >45 years of age without overt proteinuria or hearing loss. In case 2 the mother would have had the information needed to make a fully informed decision about kidney donation if pretransplant genetic testing had been performed. While it has been reported that the mutation types of AS recipients do not affect the patient or graft survival after kidney transplantation,<sup>58</sup> no reports have described an association between genotype and the outcome after kidney transplantation in mothers who are donors for XLAS patients. Since *de novo* mutations are reported in 12% of XLAS patients, obtaining genetic information as well as kidney biopsy specimen results would be useful for delineating the long-term risks of the mothers if they are chosen as donors. The only justification for not performing genetic testing of at-risk potential related donors for AS patients is that such testing is simply not possible because of local circumstances in the current era.

The genetic analyses of the 2 present families were performed after kidney transplantation. In conclusion, a genetic diagnosis before transplantation as well as careful evaluations with kidney biopsy should be performed if a mother is considered to be a donor for a patient with XLAS. Genetic testing for any family member who is considering being a donor, including sisters, should also be considered (Table 2).

## DISCLOSURES

All the authors declared no competing interests.

## PATIENT CONSENT

The authors obtained consent from the patients discussed in the report.

## AUTHOR CONTRIBUTIONS

KK, KN, AH, and MF participated in the acquisition of clinical data. KK, KN, RS, TM, TI, and KD carried out analysis of the patient's clinical course and data interpretation. KK wrote a draft of the manuscript and KN, AH, MF, RS, TM, TI, and KD revised it critically. All authors read and approved the final manuscript.

## SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References.

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