A novel COL4A5 splicing variant causing X-linked Alport syndrome: A case report

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Alport syndrome is a hereditary disorder characterized by renal impairment, hearing loss, and ocular symptoms and is caused by COL4A3, COL4A4, and COL4A5 mutations. Historically, Alport syndrome has been diagnosed on the basis of either a combination of histopathological examination and genetic analysis or histopathological examination followed by genetic analysis. In recent years, because of advances in genetic analysis technology, the diagnosis can be made either by histopathological analysis or genetic analysis alone.

In patients with Alport syndrome, renal impairment progresses, leading to end-stage renal failure. Previously, no treatment was administered to prevent renal impairment. However, in recent years, the protective effect of angiotensin-converting enzyme (ACE) inhibitors on renal function has been reported, and new drugs such as bardoxolone and gene therapy are under development. Early diagnosis and treatment are crucial to improve renal function prognosis.

In Japan, routine urinary screening in 3-year-old children is useful to detect congenital anomalies of the kidneys and urinary tract. Hematuria is considered a significant indicator, whereas hematuria is considered a clinically less useful indicator because serious illness is not often found in children with isolated hematuria.

We report here the case of a 3-year-old child who was diagnosed with X-linked Alport syndrome by genetic analysis after hematuria was detected in routine urinary screening. This case demonstrates the usefulness of genetic analysis and urinary screening in the early diagnosis and treatment of Alport syndrome.

A 3-year-old boy was referred to Fujita Health University Hospital for further examination after isolated hematuria was identified in a routine urinary screening for 3-year-old children. His height was 93.8 cm, his weight was 12.7 kg, and his blood pressure was 70/54 mmHg. Physical examination revealed no abnormalities on chest auscultation or edema. Laboratory findings demonstrated normal renal function (estimated glomerular filtration rate, 108 ml/min/1.73 m²), urinalysis showed occult blood (3+), 50–99 RBCs/high power field, and a protein/creatinine ratio of 0.16 g/gCr (Table 1). Various types of casts were observed. His mother had had hematuria with normal renal function since childhood, and his maternal grandmother had undergone hemodialysis for end-stage renal failure owing to diabetic nephropathy (Fig. 1).

After genetic counseling, we obtained consent for genetic analysis from the patient’s parents, and we performed genetic analysis of COL4A3, COL4A4, and COL4A5 using a next-generation sequencing. The results revealed a novel hemizygous variant with a canonical splicing site, NM_033380.3:c. 1032 + 1 G > A, which caused a splicing abnormality in COL4A5. He was diagnosed with X-linked Alport syndrome.

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X-linked Alport syndrome before the onset of proteinuria owing to the identification of a novel variant in COL4A5. Genetic analysis of Alport syndrome is useful for the early diagnosis, treatment, and prognosis of Alport syndrome.

In the present case, hematuria was identified in the patient during a routine urinary screening performed in 3-year-old children, leading to the diagnosis of Alport syndrome and thus allowing early treatment initiation. In Japan, routine urinary screening in 3-year-old children is useful to identify congenital anomalies of the kidneys and urinary tract. In Alport syndrome, hematuria is present from infancy, and at 3 years of age, affected patients often have marked hematuria, even in the absence of proteinuria. Therefore, it is possible to screen for Alport syndrome by identifying hematuria during routine urinary screening in 3-year-old children. However, because Alport syndrome was found in only 0.0032% of all urine samples from 3-year-old children and there was previously no known effective treatment, screening for Alport syndrome during routine urinalysis in 3-year-old children has never been considered. In recent years, the protective effect of ACE inhibitors on renal function has been reported. In addition, other drugs, such as bardoxolone and gene therapy, are under development. This development indicates the recognition of the relevance of the disease and the need for an early diagnosis to improve renal prognosis. In most patients with Alport syndrome, renal function is preserved at the age of 3 years; therefore, an early diagnosis of Alport syndrome based on hematuria in routine urinary screening in 3-year-old children is useful to preserve renal function. Thus, the significance of hematuria in the routine urinary screening of 3-year-old children should be reconsidered.

In conclusion, we identified a novel COL4A5 splicing variant causing X-linked Alport syndrome in a 3-year-old child, and we demonstrated the usefulness of genetic analysis and urinary screening in 3-year-olds for the early diagnosis and treatment of Alport syndrome.

HGV DATABASE
The relevant data from this Data Report are hosted at the Human Genome Variation Database at https://doi.org/10.6084/m9.figshare.hgv.3219.
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Competing interests

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