A novel truncating *PAX2* mutation in a boy with renal coloboma syndrome with focal segmental glomerulosclerosis causing rapid progression to end-stage kidney disease

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Abstract

Renal coloboma syndrome (RCS, MIM#120330), also known as papillorenal syndrome, is an inherited autosomal dominant disease characterized by ocular and/or renal involvement due to *PAX2* mutation. The renal involvement typically consists of a hypo/dysplastic kidney and/or vesicoureteral reflux. Recent studies reported that missense *PAX2* mutations cause familial focal segmental glomerular sclerosis (FSGS) without renal morphological malformations. To date, the reports of genotype–phenotype correlation including pathological findings regarding *PAX2* mutations are scarce. We report a case of RCS with a novel *PAX2* mutation that was pathologically diagnosed as FSGS and rapidly progressed to end-stage kidney failure (ESKD) with a review of past literature. A 6-year-old boy, who had bilateral coloboma and loss of vision in the left eye, was noted non-nephrotic proteinuria and renal dysfunction via school urine screening. Abdominal ultrasound showed no renal and urinary tract malformations and kidney biopsy showed FSGS. Genetic analysis revealed a novel insertion-deletion mutation in *PAX2* (NM003987.4: c.70_72delinsA; p.Gly24Argfs*29). His kidney function deteriorated gradually during the following 2 years and kidney transplantation was performed at 9 years of age. In previous reports describing *PAX2* mutations with FSGS, affected individuals with missense *PAX2* mutations developed ESKD in adulthood, whereas one case with truncating *PAX2* mutations developed ESKD in childhood similar to the current case. Our case highlighted the association of truncating *PAX2* mutations with the risk of rapid progression to ESKD. Thus, *PAX2* mutations should be included in genetic screening for such cases even in the absence of renal and urinary tract malformations.

Keywords *PAX2* · Renal coloboma syndrome · Focal segmental glomerulosclerosis · Truncating mutation

Abbreviations

FSGS Focal segmental glomerulosclerosis
RCS Renal coloboma syndrome
VUR Vesicoureteral reflux

Introduction

Renal coloboma syndrome (RCS, MIM#120330), also known as papillorenal syndrome, is an autosomal dominantly inherited disease associated with abnormal ocular and kidney findings attributable to the paired box protein

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2 (*PAX2*) gene [1, 2]. Common renal findings seen in RCS are renal hypodysplasia (65%), vesicoureteral reflux (VUR) (14%), renal cysts (8%), multicystic dysplastic kidneys (6%), and other congenital anomalies of the kidney and urinary tract [2]. Phenotypic variability is reported in patients with RCS, ranging from typical RCS with congenital anomalies of the kidney and urinary tract (CAKUT) to focal segmental glomerulosclerosis (FSGS) without renal morphological abnormalities [2, 3].

A few reports demonstrated that histological findings of patients with RCS were suggestive of FSGS [4–7] and recent studies suggested that *PAX2* mutations also cause familial FSGS [8, 9]. However, despite many reports of pathogenic variants in the *PAX2* gene, a review of all reported cases to date does not reveal a consistent genotype–phenotype correlation and there have been no reports of a genotype–phenotype correlation including pathological findings [7]. Here we report a case of RCS with pathological findings of FSGS in which genetic analysis revealed a truncating *PAX2* mutation. The patient rapidly progressed to end-stage kidney disease (ESKD). We also review previous literature on *PAX2* mutation and/or FSGS and speculate.

Case report

A 6-year-old boy, born to healthy parents, had a healthy brother and no remarkable family history. Coloboma of both his eyes was noted; his left eye had a functional ocellus but no vision. No history of urinary tract infections was noted and he showed normal neurological development. At 6 years of age, proteinuria was first identified in a school urinalysis screening along with chronic kidney disease. His urinary protein level was 0.5 g/day, and his serum creatinine (Cre) and cystatin C (CysC) levels were slightly elevated (0.75 mg/dL and 1.09 mg/L, estimate glomerular filtration rate [eGFR] 53.02 and 87.7 mL/min/1.73m², respectively). The patient's height and weight were 114.3 cm (− 0.5 standard deviations [SD]) and 19.9 kg, respectively. Abdominal ultrasound showed normal-sized kidneys (right kidney, 6.5 × 3.0 cm [− 0.6 SD]; left kidney, 7.0 × 4.0 cm [− 0.3 SD]) and no signs of hydronephrosis. Voiding cystourethrography showed only grade 1 VUR. The kidney biopsy showed 21 acquisition glomeruli and most glomeruli showed a variety of sclerotic lesions (6 global, 8 segmental) with glomerular hyalinization (Fig. 1a, b). Tubular atrophy or expansion was present but no basal membrane findings suggestive of nephronophthisis were noted. Primitive duct or chondrification which was commonly observed in the dysplastic kidney

Fig. 1 Pathological findings of the first and second kidney biopsy. Specimens of periodic acid-silver staining under light microscopy. **a**, **b** Masson trichrome (MT) stain and periodic acid methenamine silver (PAM) stain of the first kidney biopsy suggestive of focal segmental

glomerulosclerosis (FSGS) (**a** original magnification, ×100, **b** original magnification, ×200). **c–e** MT and PAM stain of the second kidney biopsy showing crescent formation upon FSGS (**c** original magnification, ×100, **d**, **e** original magnification, ×200)

was not seen. Thus, a pathological diagnosis was FSGS not otherwise specified (NOS by Columbia classification).

Genetic analysis revealed a novel insertion-deletion mutation (NM003987.4: c.70-72delinsA; Gly24Argfs*29) in exon 2 of the *PAX2* gene, resulting in a truncated protein. No mutation was found in *WT1* or *NPHS2*. After a diagnosis of FSGS was confirmed, treatment with angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) was initiated. Thereafter, at 8 years of age, 2 weeks after a routine follow-up which showed Cre 2.09 mg/dL (eGFR 24.1) and CysC 3.0 (eGFR 26.90), he suddenly exhibited edema. The laboratory investigation revealed drastic worsening of kidney function (BUN 111.7, Cre 5.02 mg/dL [eGFR 11.7], CysC 4.42, [eGFR 15.75]). The second kidney biopsy showed ten acquisition glomeruli and six glomeruli showed global sclerosis (Fig. 1c); two glomeruli showed endocapillary proliferative glomerulonephritis and acute tubular damage with neutrophilic infiltration suspected to be post-infectious glomerulonephritis, superimposed on FSGS. (Fig. 1d, e). Three months later, at 9 years of age, the patient underwent living donor kidney transplantation from his mother, and no recurrence of ESKD has been observed since then.

Discussion

The current case exhibited a typical ocular-renal phenotype consistent with a diagnosis of RCS with a truncating *PAX2* mutation. Laboratory and imaging examinations findings were not suggestive of a CAKUT phenotype, while the kidney biopsy indicated FSGS. Reports of kidney biopsy findings of patients with RCS are relatively rare, probably because such patients are thought to be easy to diagnose based on kidney morphological evaluations prior to a kidney biopsy. We should, however, note that patients with *PAX2* mutation can have FSGS with or without the ocular/CAKUT phenotype.

In the current case, a novel truncating *PAX2* mutation (c.70-72delinsA:Gly24Argfs*29) was found in exon 2, which contains the paired box domain and comprising mutations most frequently seen in patients with RCS. According to the Leiden Open Variation Database (www.lovd.nl/PAX2) and the Human Gene Mutation Database

(<https://www.hgmd.cf.ac.uk/ac/index>), approximately 100 pathogenic variants have been reported in the *PAX2* gene so far. Truncating mutations were most frequently found in patients with typical RCS, whereas missense mutations were more frequently associated with the phenotype of familial FSGS [8]. Barua et al. speculated that *PAX2* missense variants lead to an expanded phenotypic spectrum including FSGS owing to their haploinsufficiency and/or dominant-negative effects based on an in silico analysis and functional study [8]. Previously reported patients with biopsy proven FSGS with *PAX2* mutations are listed in Table 1. Patients with missense mutations of *PAX2* showed clinical diagnosis of FSGS (Pedigree 1–7), whereas patients with truncating mutations exhibited classical RCS with coloboma findings (Pedigree 9–15). Our case with a frameshift mutation (pedigree 11) rapidly progressed to ESKD at 8 years of age. In addition, another case (pedigree 9) of truncating *PAX2* mutation (c.69-70InsG: p.Val26Glyfs*28) progressed to ESKD at as early as 4 years old [9]. In contrast, familial FSGS patients with missense *PAX2* mutations developed ESKD in adulthood (30–70 years old). Although we had to consider the possibility that ACEI/ARB use might worsen his kidney function in our case, we could say that affected individuals with truncating *PAX2* mutations have a tendency of early progression to ESKD compared to those of with missense *PAX2* mutations.

Currently, there are no formal criteria for the clinical diagnosis of RCS. Therefore, the disease entity and the correlation between RCS and *PAX2* mutation are not thoroughly understood [10]. There is phenotypically heterogeneity and show a wide variation in the clinical presentation in affected individuals with *PAX2* mutations [7]. Our case findings highlight the importance of urinalyses screening programs for children because non-symptomatic proteinuria was the only renal finding in this case. It is important to make an accurate diagnosis of RCS based on pathological findings coupled with genetic analysis. Accumulation of further cases and pathological analysis would help clarify the pathogenesis.

In conclusion, when encountering patients with FSGS of unknown etiology with or without ocular abnormalities, *PAX2* mutations should be screened for even in the absence of evidence of renal malformation.

Table 1 Clinical features and type of PAX2 mutation of pedigrees with proven FSGS

Pedigree no	Age of onset or diagnosis (years)	Affected family members (n)	Patients with ESKD (n)	Age of development of ESKD (years)	Clinical diagnosis	Coloboma	Patients with biopsy (n)	Type of mutation	Mutation	Amino acid	Exon	Report
1	36	4	NA	NA	FSGS	–	NA	Missense	c.167G>A	p.Thr150Ala	2	Barua et al. (2014) [8]
2	7	1	NA	NA	FSGS	–	NA	Missense	c.239 C>T	p.Pro80Leu	3	Barua et al. (2014) [8]
3	10–35	3	1	39	FSGS	–	2	Missense	c.254G>T	p.Gly85Val	3	Vivante et al. (2019) [9]
4	18	3 ^a	2 ^a	50, 70	FSGS	–	1	Missense	c.275C>T	p.Thr92Met	3	Vivante et al. (2019) [9]
5	31–32	5	4	30–36	FSGS	–	3	Missense	c.448A>G	p.Thr150Ala	4	Barua et al. (2014) [8]
6	8	2	1	NA	FSGS	–	1	Missense	c.491C>A	p.Thr164Asn	4	Barua et al. (2014) [8]
7	17–68	6	2	40, 58	FSGS	–	2	Missense	c.565G>A	p.Gly189Arg	5	Barua et al. (2014) [8]
8	20	2	1	27	FSGS	–	1	Splice	c.862-1G>A	?	8	Vivante et al. (2019) [9]
9	1	1	1	4	RCS	+	1	Frameshift	c.69-70InsG	p.Val26Glyfs*28	2	Vivante et al. (2019) [9]
10	14	1	0	–	RCS	+	1	Frameshift	c.57-58 ins GTGAACC	Q22Rfs*34	2	Okumura et al. (2015) [3]
11 (Current case)	6	1	1	8	RCS	+	1	Frameshift	c.70_72delinsA	p.Gly24Argfs*29	2	
12	10	1	1	18	RCS	+	1	Frameshift	c.76dup	p.Val26Glyfs*28	2	Schimmmenti et al. (1997) [5]
13	38	1	1	NA	RCS	+	1	Frameshift	c.224-225 ins AC	G76Pfs*8	3	Okumura et al. (2015) [3]
14	15–24	3	1	42	RCS	+	3	Nonsense	c.310C>T	p.Arg104*	3	Barua et al. (2014) [8]
15	28	1	0	–	RCS	+	1	Nonsense	c.1023C>A	Y341*	9	Okumura et al. (2015) [3]

ESKD end-stage kidney disease, NA data not available

^aPAX2 mutation was confirmed only in the index patient. However, his mother and maternal grandfather progressed to ESKD

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Compliance with ethical standards

Conflict of interest None of the authors have any conflicts of interest to declare.

Ethical approval This study was approved by the ethics committee of the National Center for Child Health and Development in accordance with the ethical standards of the institutional committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent for publication A consent for publication was obtained from the parent.

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