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GENOTYPE-PHENOTYPE ANALYSES OF PEDIATRIC PATIENTS WITH PAX2 MUTATIONS

JI HYUN KIM[1], Yo Han Ahn[2], Hee Gyung Kang[1], Il Soo Ha[1], Hae Il Cheong[1]
[1]Department of Pediatrics-Nephrology, Seoul National University Hospital, Korea, Republic of
[2]Department of Pediatrics-Nephrology, Seoul National University Bundang Hospital, Korea, Republic of

Objectives: Two typical phenotypes of *PAX2* mutations are renal coloboma syndrome (RCS) and focal segmental glomerulosclerosis type 7 (FSGS7). Although most cases with FSGS7 manifest isolated glomerulopathy, some patients have accompanying ocular abnormalities. In this study, geneotype-phenotype analyses were performed in pediatric patients with *PAX2* mutations.

Methods: A total of 14 Korean pediatric patients with *PAX2* mutations were recruited. Mutational analyses were done using Sanger or targeted exome sequencing. The ocular manifestations were reviewed by an ophthalmologist using a 5-point scale grading.

Results: The patients were subgrouped into RCS (n = 9), FSGS7 (n=4), and isolated renal hypoplasia (n = 1) based on their phenotypes. Seven different PAX2 mutations were detected, including 3 known and 4 novel mutations. The c.76dupG mutation was common in 8, including 6 RCS, 1 FSGS7, and 1 isolated renal hypoplasia patient. 8 of 9 with RCS and 2 of 4 with FSGS7 had truncating mutations. All 8 RCS with truncating mutations had severe ocular abnormalities, while remaining 1 RCS with a missense mutation had mild unilateral ocular involvement. Among 4 with FSGS7, 2 with truncating mutations had ocular involvement (overlapping phenotype of FSGS7 and RCS), while the other 2 with missense mutations manifested isolated glomerulopathy. Renal biopsy was performed in 3 with FSGS7 and 2 with RCS, which revealed nonspecific changes in one and secondary FSGS due to renal hypoplasia in the other. Ten progressed end-stage renal disease, 3 were in chronic kidney disease stage 3, and 1 maintained normal renal function at the last follow-up.

Conclusions: Some may manifest overlapping phenotypes of RCS and FSGS7. Most patients with RCS had truncating mutations, while a half with FSGS7 had missense mutations. Patients with truncating mutations were prone to develop ocular abnormalities. Typical extra-renal manifestations provide useful clues for differential diagnosis in patients with steroid-resistant nephrotic syndrome/FSGS or renal hypoplasia.

Figure1. genotypes of patients

	Pt	Gender	cDNA	Protein	Domain	Diagnosis
RCS	1	M	c.76dupG	p.V26Gfs*28	N-terminal paired domain	Sanger
	2	M	c.76dupG	p.V26Gfs*28	N-terminal paired domain	Sanger
	3	M	c.76dupG	p.V26Gfs*28	N-terminal paired domain	Sanger
	4	F	c.76dupG	p.V26Gfs*28	N-terminal paired domain	Sanger
	5	M	c.76dupG	p.V26Gfs*28	N-terminal paired domain	Sanger
	6	M	c.310C>T	p.R104*	C-terminus	Sanger
	7	M	c.754C>T	p.R252*		Sanger
	8	M	c.76dupG	p.V26Gfs*28	N-terminal paired domain	TES
	9	M	c.344G>C	p.R115P	C-terminus	TES
FSGS7	10	M	c.76dupG	p.V26Gfs*28	N-terminal paired domain	TES
	11	**M**	**c.222_225dup4**	**p.G76Dfs**	**N-terminal paired domain**	**TES**
	12	F	c.74G>A	p.G25E	N-terminal paired domain	TES
	13	M	c.563A>G	p.N188S	Octapeptide motif	TES
RH	14	M	c.76dupG	p.V26Gfs*28	N-terminal paired domain	Sanger

RH, renal hypoplasia; Patients 1 and 2 are siblings
Truncating mutations; Non-truncating mutations; Novel mutations

Figure2. ocular and renal phenotypes

	Pt	Ocular manifestations				Renal manifestations		
		R	L	B	Others	Renal USG	Biopsy	Renal outcome
RCS	1	1	3	4		Hypoplasia	nonsp	ESRD at 12 yrs
	2	2	4	6	L) retinal detachment	Hypoplasia + horseshoe		ESRD at 18 yrs
	3	2	4	6	L) chorioretinal atrophy	Hypoplasia	2° FSGS	ESRD at 15 yrs
	4	4	3	7		Hypoplasia		ESRD at 9 yrs
	5	4	4	8	B) chorioretinal atrophy	Large echogenic BK		ESRD at 7 yrs
	6	4	3	7	R) chorioretinal atrophy	Hypoplasia		ESRD at 1 yrs
	7	4	4	8		Hypoplasia		CKD3 (18-yr-old)
	8	4	1	5		Hypoplasia		ESRD at 3 yrs
	9	0	2	2		Hypoplasia		ESRD at 11 yrs
FSGS7	10	1	4	5		No anomaly	FSGS	ESRD at 16 yrs
	11	**2**	**2**	**4**		**No anomaly**	**FSGS**	**CKD3 (24-yr-old)**
	12	0	0	0		No anomaly	FSGS	ESRD at 15 yrs
	13	0	0	0		No anomaly	Not done	Normal GFR (6-yr-old)
RH	14	0	0	0		Hypoplasia		CKD3 (9-yr-old)