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Genotype-phenotype analysis in patients with PAX2 pathogenic variants: beyond renal coloboma syndrome

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Objectives : PAX2-related disorders include two distinct syndromes, renal coloboma syndrome (RCS), characterized by congenital anomalies of the kidney and urinary tract (CAKUT) and abnormalities of the optic disc, and hereditary focal segmental glomerulosclerosis (FSGS) type 7. We evaluated genotype-phenotype correlations, including long-term clinical outcomes, in patients with PAX2 pathogenic variants.
Methods : In this multicenter retrospective study, among 27 patients with PAX2 pathogenic variants detected from 2004–2022, 19 had RCS, 4 had FSGS, and 4 had isolated CAKUT. Based on variant types, patients were classified into predicted loss of function (pLoF) (n=22) and missense (n=5) variant groups.
Results : The pLoF variants mostly led to RCS (81.8%), while missense variants primarily caused FSGS (n=2) and isolated CAKUT (n=2) (80.0%) (P=0.034). Kidney failure developed in 14 patients, with a median age of 14.5 (95% confidence interval 11.9–17.1) years, showing no difference in kidney survival between the pLoF and missense variant groups. However, variants in the paired domain of PAX2 resulted in kidney failure more rapidly than variants in other sites (log-rank test, P=0.025). Regarding ocular manifestations, the pLoF variant group exhibited more common, earlier onset and severe involvement compared to the missense variant group (log-rank test, P=0.038).
Conclusions : pLoF variants in PAX2 were associated with severe ocular involvement not confined to the optic disc, and variants in the paired domain were related to poor long-term kidney outcomes. Our findings support genotype-phenotype correlations in the ophthalmology field and emphasize the impact of the paired domain on kidney outcomes in patients with PAX2 pathogenic variants.

Fig1_KSN_PAX.png

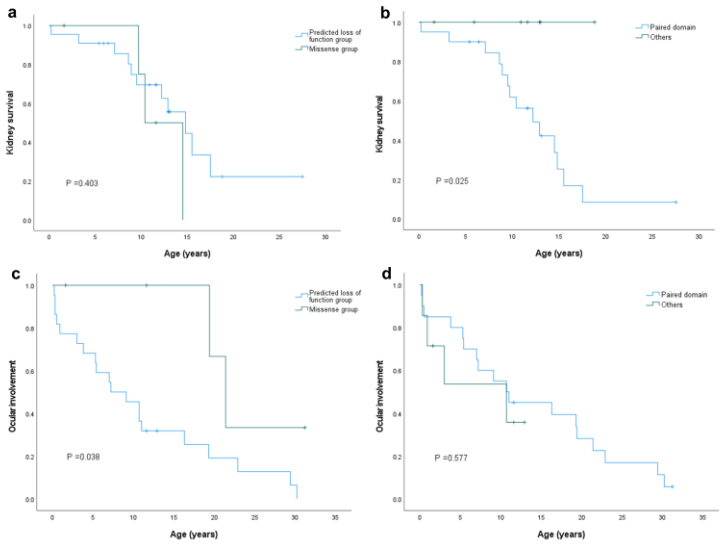

Fig1_KSN_PAX.png

Table 1. Comparison of patient phenotypes according to the genotype of *PAX2* pathogenic variants

	Predicted loss of function (n=22)	Missense (n=5)	*P* value
Sex, male:female	16:6	3:2	0.616
Age at onset, years	1.8 (0.1–6.6)	7.0 (0.1–7.8)	0.726
Age at genetic diagnosis, years	12.4 (8.8–16.5)	19.0 (10.9–23.1)	0.492
Age at the last follow up, years	17.0 (11.4–29.4)	23.8 (11.6–24.4)	0.876
Initial manifestations			0.283
Ocular symptoms	7 (31.8)	0	
Kidney symptoms	15 (68.2)	5 (100.0)	
Clinical phenotype			0.034
Renal coloboma syndrome	18 (81.8)	1 (20.0)	
Focal segmental glomerulosclerosis	2 (9.1)	2 (40.0)	
Isolated CAKUT	2 (9.1)	2 (40.0)	
Developmental delay	4 (18.2)	0	0.561
Kidney manifestations			
Age at kidney manifestations, years	5.7 (0.1–9.7)	7.0 (0.1–7.8)	0.679
Proteinuria at initial diagnosis	21 (95.5)	5 (100.0)	1.000
CKD at initial diagnosis	18 (81.8)	4 (80.0)	1.000
Median age at the onset of CKD, years (95% CI)[a]	6.6 (0.0–14.5)	5.1 (0.0-15.8)	0.274
Median age at kidney failure, years (95% CI)[a]	14.8 (10.1–19.5)	10.4 (7.3–13.5)	0.403
Ocular manifestations[b]	44 eyes	10 eyes	
Optic disc anomaly			<0.001
Anomalous optic disc	42 (95.5)	1 (10.0)	
Normal optic disc	2 (4.5)	9 (90.0)	
Central retinal artery			0.018
Absence	30 (68.2)	2 (20.0)	
Partial	6 (13.6)	3 (30.0)	
Complete	8 (18.2)	5 (50.0)	
Number of cilioretinal vessel	8.0 (10–7.5)[c]	7.5 (8.0–6.2)	0.048
Presence of retinopathy	16 (38.1)	0 (0.0)	0.011
Visual acuity[d], mean (maximum-minimum)	20/22.5 (20/20–light perception)	20/20 (20/20–20/30)	0.041
Visual outcome ≥20/40[d]	31/42 (72.5)	10/10 (100)	0.096
Median age at the diagnosis of ocular involvement, years (95% CI)[a]	7.2 (2.3–12.1)	21.4 (18.2–24.6)	0.038

Values are expressed as numbers (%) and medians (interquartile range), except for visual acuity.

CAKUT, congenital anomalies of the kidney and urinary tract; CKD, chronic kidney disease; CI, confidence interval

[a]It is estimated by Kaplan-Meier analysis. [b]Ocular manifestations were analyzed separately in both eyes of patients.

[c]Case 15 could not count cilioretinal vessels due to severe retinal anomalies.

[d]Snellen visual acuity was observed in 42 and 10 eyes in the pLoF and missense groups, respectively.