SUPPLEMENTAL MATERIAL

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Supplementary Table S1. Ophthalmologic findings of patients with *PAX2* mutations

Case	Sex	Mutation	Age at diagnosis or work up (years)	Ocular symptoms	Optic disc (R/L)	Central retinal artery (R/L)	Numbers of cilioretinal artery[a] (R/L)	Visual acuity (R/L)	Others (R/L)
Renal coloboma syndrome									
1	M	c.76dupG	7.2	Strabismus	E+PPA+VS /E+PPA	Absence/ Absence	8/7	20/20 20/200	-/RD
2	M	c.76dupG	3.8	Nystagmus	E+PPA /E+PPA	Absence/ Absence	8/7	20/63 20/320[b]	-/RD
3	M	c.76dupG	0.2	Microphthalmia	E+PPA /E+PPA	Partial/ Absence	6/8	20/20 CF	-/CRA
4	F	c.76dupG	7.0	Work up	E+PPA /E+PPA	Absence/ Absence	9/8	20/16 20/16	VFD/ VFD
5	M	c.76dupG	0.5	Nystagmus	E+PPA /E+PPA	Absence/ Absence	6/5	UC[c] UC	CRA/ CRA
6	M	c.310C>T	0.3	Nystagmus	Rudimentary OD /E+PPA	Absence/ Absence	8/9	20/200 20/25	CRA/-
7	M	c.754C>T	3.0	Nystagmus	Rudimentary OD /E+PPA	Absence/ Absence	8/10	UC[c] UC	CRA/ CRA
8	M	c.76dupG	9.1	Work up	E+PPA /E+PPA	Partial/ Partial	11/8	20/20 20/20	VFD/ VFD
9	M	c.344G>C	19.4	Work up	E+PPA /E+PPA	Absence/ Absence	11/8	20/20 20/20	-/-
10	M	c.535_546delinsT	0.9	Work up	E+PPA /E+PPA	Absence/ Absence	10/8	UA UA	CRA/-
11	M	c.76dupG	11.0	Work up	E+PPA /E+PPA	Absence/ Absence	11/12	20/16 20/32	-/RS[d]
12	F	c.76dupG	5.3	Work up	E/E	Absence/ Absence	14/10	20/20 20/20	-/-
13	M	c.343C>T	10.7	Work up	E+PPA /E+Seg hypo	Absence/ Absence	11/10	20/80 20/40	-/RS
14	F	c.860delA	10.7	Work up	Normal /E+PPA+Peripapillary RS+RS	Complete/ Absence	9/17	20/20 20/32	RS/RS
15	M	c.754C>T	0.3	Nystagmus Microphthalmia	PHPV /Rudimentary OD	Absence/ Absence	UC/UC[e]	LP (-) LP (-)	PHPV /Retina aplasia

16	M	c.76dupG	5.4	Work up	E+PPA /E+PPA	Absence/ Partial	14/11	20/30 20/30	-/-
17	F	c.76del	16.3	Work up	Hypo /Hypo+PPA	Complete/ Absence	3/8	20/20 20/20	-/-
18	F	c.76dupG	30.2	Decreased visual acuity	E+HypoVS+PPA /E+VS+PPA	Absence/ Absence	11/12	20/125 20/20	RS/-
19	M	c.361_373dup	29.4	Work up	E+PPA /E+PPA	Absence/ Absence	10/11	20/20 20/20	Corneal dystrophy
Focal segmental glomerulosclerosis									
20	M	c.76dupG	19.3	Work up	Seg hypo /E+PPA	Partial/ Partial	12/9	20/16 20/20	VFD/ VFD
21	M	c.223_226dup	22.9	Work up	Seg hypo+Peripapillary RS+VS	Complete/ Complete	6/8	20/25 20/20	-/-
22	F	c.74G>A	21.4	Work up	/Seg hypo Normal /Seg hypo+PPA	Complete/ Complete	2/7	20/20 20/20	-/-
23	M	c.419G>A	10.1	Work up	Normal /Normal	Partial/ Partial	6/8	20/20 20/20	-/-
Isolated congenital anomalies of the kidney and urinary tract									
24	M	c.686-1G>T	11.0	Work up	Normal /Normal	Absence/ Absence	8/7	20/16 20/16	-/-
25	F	c.832C>T	7.5	Work up	Normal /Seg hypo	Complete/ Complete	4/6	20/20 20/20	-/-
26	F	c.1052G>T	0.1	Work up	Normal /Normal	Complete/ Complete	UA/UA	UA UA	-/-
27	M	c.206T>C	30.9	Work up	Normal /Normal	Partial/ Complete	9/5	20/20 20/20	-/-

R, right; L, left; E, Optic disc excavation; PPA, peripapillary atrophy; VS, vitreous strand on optic disc; RD, retinal detachment; CF, counting fingers; CRA, chorioretinal atrophy; VFD, visual field defect; UC, uncheckable; OD, Optic disc; RS, retinoschisis; Hypo, hypoplasia; Seg hypo, segmental hypoplasia; LP, light perception; PHPV, persistent hyperplastic primary vitreous; UA, unavailable data.

[a]Based on the maximum number of ciliioretinal vessels in both eyes. [b]Underwent retinal surgery due to rhegmatogenous retinal detachment.

[c]Un-checkable due to development delay. [d]Spontaneously restored retinal structure.

[e]Un-checkable due to severe retinal anomalies.

Supplementary Table S2. Genetic diagnosis of patients with *PAX2* mutations

Case	cDNA	Protein	Mutation location	Segregation	Frequency in gnomAD	Mutation taster	ACMG classification[a]	ACMG criteria	Genetic test	Age at genetic dianosis (years)	Previously published
Renal coloboma syndrome											
1	c.76dupG	p.Val26Glyfs*28	Paired domain	Maternal germline	0	DC	Pathogenic	PVS1, PM2, PM6, PP5	Sanger	20.0	1
2	c.76dupG	p.Val26Glyfs*28	Paired domain	Maternal germline	0	DC	Pathogenic	PVS1, PM2, PM6, PP5	Sanger	16.5	1
3	c.76dupG	p.Val26Glyfs*28	Paired domain	De novo	0	DC	Pathogenic	PVS1, PM2, PM6, PP5	Sanger	12.8	1
4	c.76dupG	p.Val26Glyfs*28	Paired domain	De novo	0	DC	Pathogenic	PVS1, PM2, PM6, PP5	Sanger	13.9	1
5	c.76dupG	p.Val26Glyfs*28	Paired domain	De novo	0	DC	Pathogenic	PVS1, PM2, PM6, PP5	Sanger	1.9	1
6	c.310C>T	p.Arg104*	Paired domain	De novo	0	DC	Pathogenic	PVS1, PM2, PM6, PP5	Sanger	9.9	1
7	c.754C>T	p.Arg252*	Homeodomain	De novo	0	DC	Pathogenic	PVS1, PM2, PM6, PP5	Sanger	15.1	-
8	c.76dupG	p.Val26Glyfs*28	Paired domain	De novo	0	DC	Pathogenic	PVS1, PM2, PM6, PP5	TES	15.1	2
9	c.344G>C	p.Arg115Pro	Paired domain	NA	0	DC	Likely pathogenic	PM1, PM2, PP3, PP5	TES	19.0	2
10	c.535_546delinsT	p.Asn179Trpfs*17	Between paired and octapeptide domains	NA	0	DC	Likely pathogenic	PVS1, PM2	TES	4.2	-
11	c.76dupG	p.Val26Glyfs*28	Paired domain	NA	0	DC	Pathogenic	PVS1, PM2, PP5	Sanger	0.3	-
12	c.76dupG	p.Val26Glyfs*28	Paired domain	NA	0	DC	Pathogenic	PVS1, PM2, PP5	WES	5.3	-
13	c.343C>T	p.Arg115*	Paired domain	De novo	0	DC	Pathogenic	PVS1, PM2, PM6, PP5	TES	10.0	-
14	c.860delA	p.Gln287Argfs*10	Between octapeptide and homeodomain	NA	0	DC	Pathogenic	PVS1, PM2, PP5	WES	10.5	-
15	c.754C>T	p.Arg252*	Homeodomain	Paternal	0	DC	Pathogenic	PVS1, PM2, PP1, PP5	TES	11.9	-
16	c.76dupG	p.Val26Glyfs*28	Paired domain	NA	0	DC	Pathogenic	PVS1, PM2, PP5	WES	5.4	-
17	c.76delG	p.Val26Cysfs*3	Paired domain	NA	0	DC	Pathogenic	PVS1, PM2, PP5	WES	16.0	-
18	c.76dupG	p.Val26Glyfs*28	Paired domain	NA	0	DC	Pathogenic	PVS1, PM2, PP5	WES	42.4	-
19	c.361_373dup	p.Asp125Glyfs*5	Paired domain	NA	0	DC	Likely pathogenic	PVS1, PM2	TES	32.8	-
Focal segmental glomerulosclerosis											
20	c.76dupG	p.Val26Glyfs*28	Paired domain	NA	0	DC	Pathogenic	PVS1, PM2, PP5	TES	26.3	3
21	c.223_226dup	p.Gly76Aspfs*27	Paired domain	De novo	0	DC	Pathogenic	PVS1, PM2, PM6	TES	24.6	3

22	c.74G>A	p.Gly25Glu	Paired domain	NA	0	DC	Likely pathogenic	PM1, PM2, PM5, PP3	TES	23.1	3
23	c.419G>A	p.Arg140Gln	Paired domain	NA	0	DC	Likely pathogenic	PM1, PM2, PM5, PP3	TES	10.9	3
Isolated congenital anomalies of the kidney and urinary tract											
24	c.686-1G>T	-	Intron 6	Maternal	0	DC	Pathogenic	PVS1, PM2, PP1	WES	10.5	4
25	c.832C>T	p.Gln278*	Between homeodomain and transactivation domain	NA	0	DC	Likely pathogenic	PVS1, PM2	TES	8.8	-
26	c.1052G>T	p.Gly351Val	Transactivation domain	Paternal	0	DC	Likely pathogenic	PM1, PM2, PP1, PP3	TES	0.9	-
27	c.206T>C	p.Leu69Pro	Paired domain	NA	0	DC	Likely pathogenic	PM1, PM2, PP3, PP5	WES	30.4	-

RCS, renal coloboma syndrome; FSGS, focal segmental glomerulosclerosis; RHD, renal hypodyplasia; NA, not available; gnomAD, Genome Aggregation Database; ACMG, American College of Medicine Genetics; DC, disease-causing; TES, targeted exome sequencing; WES, whole exome sequencing; PVS, pathogenic very strong; PM, pathogenic moderate; PP, pathogenic supporting;

The reference sequence of *PAX2* gene is NM_003990.5

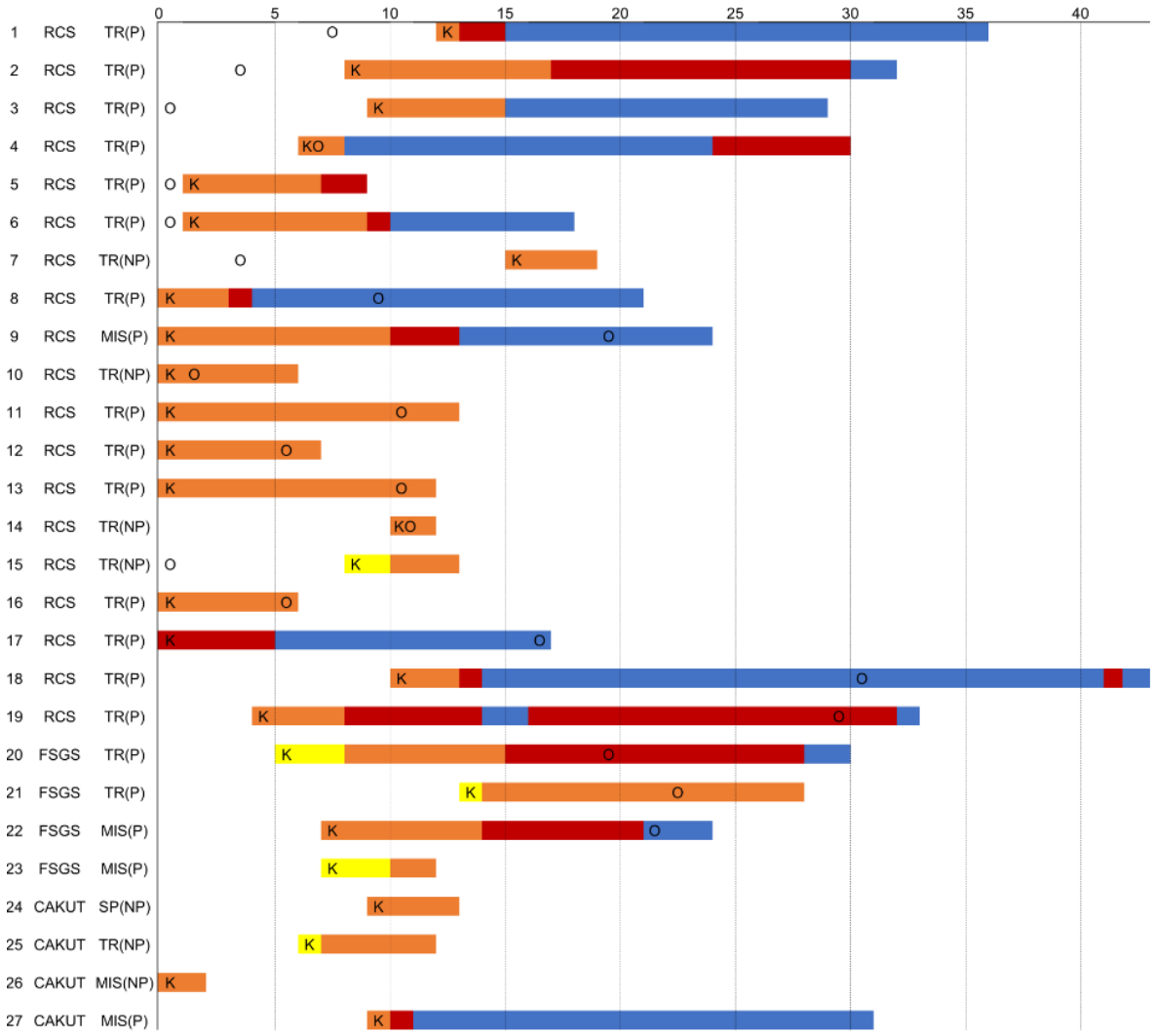
[a]Pathogenicity according to ACMG guidelines: pathogenic criterion; very strong (PVS1), strong (PS1-4), moderate (PM1-6), or supporting (PP1-5), and benign criterion; strong (BS1-4) or supporting (BP1-6)

Supplementary Table S3. Targeted and whole exome sequencing methods

	Covered genes	Exome capture	Sequencing	Human reference genome
TES				
CAKUT	60	Twist custom panel (Twist Bioscience, San Francisco, CA, USA)	MiSeq platform (Illumina, San Diego, CA, USA)	GRCh37/hg19
SRNS	57	SureSelect XT customized kit (Agilent Technologies, Santa Clara, CA, USA)	HiSeq 2500 platform (Illumina, San Diego, CA, USA)	GRCh37/hg19
Cystic kidney disease	89	Targeted gene panel (Twist Bioscience, San Francisco, CA, USA)	NovaSeq 6000 platform (Illumina, San Diego, CA, USA)	GRCh37/hg19
WES	all human genes (approximately 22,000)	SureSelect kit (Version C2; Agilent Technologies, Santa Clara, CA, USA)	NovaSeq 6000 platform (Illumina, San Diego, CA, USA)	GRCh37/hg19

TES, targeted exome sequencing; CAKUT, congenital anomalies of the kidney and urinary tract; SRNS, steroid-resistant nephrotic syndrome; WES, whole exome sequencing

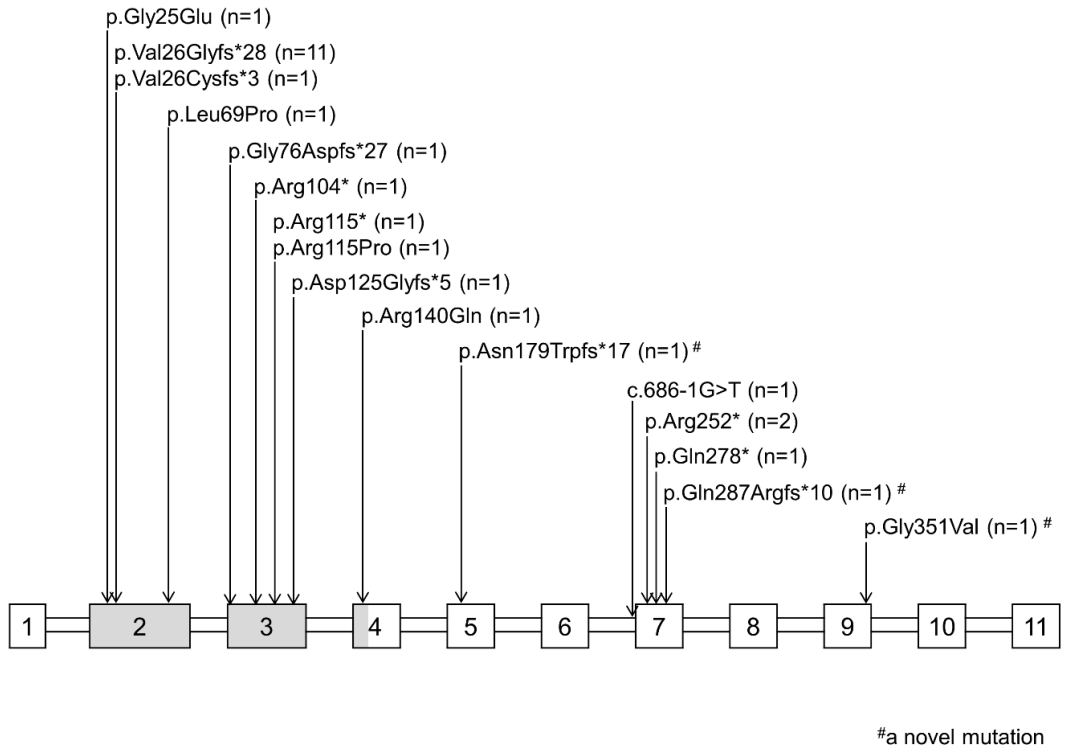
Supplementary Fig. S1. Synopsis of the clinical course in patients with *PAX2* mutations



The first and second columns indicate patient ID and clinical diagnosis. The third column describes the type and site of *PAX2* mutations. The symbols denote the time of initial kidney and ocular manifestations. The yellow bars denote the time before the development of CKD, the orange bars denote the period with CKD, the red bars show dialysis periods, and the blue bars show transplantation periods.

RCS, renal coloboma syndrome; FSGS, focal segmental glomerulosclerosis; CAKUT, isolated congenital anomalies of the kidney and urinary tract; TR, truncating; P, paired domain; MIS, missense; NP, non-paired domain; SP, splicing; K, kidney; O, ocular; CKD, chronic kidney disease

Supplementary Fig. S2. The location of mutations in the *PAX2* gene



The gray colored boxes show the paired domain of the PAX2 protein.

#a novel mutation

References

1. Cheong HI, Cho HY, Kim JH, Yu YS, Ha IS, Choi Y. A clinico-genetic study of renal coloboma syndrome in children. *Pediatr Nephrol.* 2007;22(9): 1283-1289.

2. Ahn YH, Lee C, Kim NKD, et al. Targeted Exome Sequencing Provided Comprehensive Genetic Diagnosis of Congenital Anomalies of the Kidney and Urinary Tract. *J Clin Med.* 2020;9(3): 751.

3. Park E, Lee C, Kim NKD, et al. Genetic Study in Korean Pediatric Patients with Steroid-Resistant Nephrotic Syndrome or Focal Segmental Glomerulosclerosis. *J Clin Med.* 2020;9(6): 2013.

4. Jung J, Lee JH, Park YS, et al. Ultra-rare renal diseases diagnosed with whole-exome sequencing: Utility in diagnosis and management. *BMC Med Genomics.* 2021;14(1): 177.