Supplementary Table S1: Genotype-phenotype correlation in 12 families with two recessive *NPHP2/INVS* mutations[1]

Family individual	Nucleotide change	Amino acid change[2]	Kidney Dysplast. Degen.	Eye Dysplast. Degen.	CNS Dysplast. Degen.	Liver Dysplast. Degen.	Clinical diagnosis	Others	Ref. No.
Patients with 2 truncating mutations									
A128-21	c.1453del1 c.2059del1	p.Q485fsX509 (h) p.R687fsX732 (h)	PKD, ESRD 7 mo	-	-	-	NPHP	HC	12
A8-21	c.1807C>T	p.R603X (H)	PKD, ESRD 14 mo	-	-	-	NPHP	VSD, SI	9
A205-21 A205-22 A205-23	c.2695C>T	p.R899X (H)	-23: PKD, ESRD 19 mo, normal kidneys, r.k. 6.1 cm, l.k. 7.0 cm	-	-	-	-21: autism -22: CF -23: NPHP	-	12
A6-21	c.1453del1 c.2695C>T	p.Q485fsX509 (h) p.R899X (h)	PKD, ESRD <2 yr	-	-	-	NPHP	-	9
A995-22	c.2695C>T c.2719C>T	p.R899X (h) p.R907X (h)	PKD, ESRD 1 yr 7 mo	ONA	hydrocephalus		JBTS?	asthma	-
A1423-21 A1423-23	c.2716G>T	p.E906X (H)	PKD, ESRD 1 yr (-21), 1 yr 7 mo (-23)	-	-	-	NPHP	-	novel
A2035-21 A2035-22	c.2716G>T	p.E906X (H)	PKD, ESRD 1 yr 4 mo	-	-	-	NPHP	-21: AC	novel
A12-21 A12-22	c.2719C>T	p.R907X (H)	PKD, ESRD 2 yr 6 mo	-	-	-	NPHP	-	9
F103-21	c.2719C>T	p.R907X (H)	PKD, ESRD <2 yr	TRD	-	-	SLSN	-	-
F868-21 F868-23	c.2719C>T c.2747dup1	p.R907X (h) p.K916fsX1002 (h)	PKD, ESRD 5 yr (-21), 3 yr (-23), enlarged kidneys, r.k. 8.6 cm, l.k. 8.6 cm (-23)	-	-	-	NPHP	-	9
Patients with 1 truncating mutation									
A9-21	c.1186C>T c.1445C>G	p.R396X (h) p.P482R (h)	PKD, ESRD <2 yr	-	-	-	NPHP	-	9
Patients without truncating mutations									
A7-21	c.1478T>C	p.L493S (H)	PKD, ESRD 4 yr	-	-	-	NPHP	-	9

[1]Clinical data partially reported (Otto *et al*. 2003, Otto *et al* 2008); [2]Truncating mutations and missense mutations are shown in red and black fonts, respectively; Dysplastic phenotypes are shown in purple characters and degenerative phenotypes in green characters; cDNA mutation numbering is based on human reference sequence NM_014425.2. AC, aortic contraction; CF, cystic fibrosis; ESRD, end-stage renal disease; HC, hypertrophic cardiomyopathy; JBTS, Joubert syndrome; NPHP, nephronophthisis; ONA, optic nerve atrophy; PKD, polycystic kidney disease; SI, *situs inversus*; SLSN, Senior-Løken syndrome; TRD, tapeto-retinal degeneration; VSD, ventricular septal defect.

Supplementary Table S2: Genotype-phenotype correlation in 8 families with two recessive *NPHP3* mutations[1]

Family individual	Nucleotide change	Amino acid change[2]	Kidney Dysplast. Degen.	Eye Dysplast. Degen.	CNS Dysplast. Degen.	Liver Dysplast. Degen.	Clinical diagnosis	Others	Ref. No.
Patients with 2 truncating mutations									
A1937-24	c.3235C>T	p.Q1079X (H)	nphp, ESRD 8 yr 7 mo	-	MTS, VH, MR	-	JBTS	-	novel
A1633-22	c.3702del1	p.K1234fsX1246 (H)	enlarged kidneys, passed away at day 3	-	CVH	-	MKS	ASD, double outlet RV, PVS, PH, asplenia, SA, congenital contractures (oligohydramnios)	novel
F86-21 F86-22	c.3775C>T	p.R1259X (H)	nphp, ESRD 12 yr (-21), 13 yr (-22); -21: small kidneys	-	-	-	NPHP	-	12
A14-21	c.1275del1	p.I426fsX444 (H)	nphp, ESRD <12 yr	-	-	-	NPHP	-	7
Patients with 1 truncating mutation									
F23-21 F23-22 F23-23	c.1079T>C c. 1381G>T	p.S360T (h) p.E461X (h)	nphp	-	-	LF	NPHP	-	7
A11-21	c. 435_438del4 c.3571-1G>C	p.S146fsX148 (h) oblig. splice site (h)	nphp	-	-	LF	NPHP	-	6
Patients with only splice site mutations									
F624-21 F624-22	c.3812+1G>A	oblig. splice site (H)	nphp, ESRD 7 yr (-21), 10 yr (-22)	-	-	-	NPHP	-	7
A1125-21 A1125-22	c.3812+2T>C	oblig. splice site (H)	nphp, ESRD 3 yr 8 mo (-21), 4 yr (-22)	-	-	-	NPHP	-	12

[1]Clinical data partially reported (Olbrich *et al.* 2003, Hoefele *et al* 2007, Otto *et al* 2008); [2]Truncating mutations, missense mutations and splice site mutations are shown in red, black and blue fonts, respectively; Dysplastic phenotypes are shown in purple characters and degenerative phenotypes in green characters, ESRD onset <4 yrs is considered to be dysplastic; cDNA mutation numbering is based on human reference sequence NM_153240.3. ASD, atrial septal defect; CVH, cerebellar vermis hypoplasia; ESRD, end-stage renal disease; JBTS, Joubert syndrome; LF, liver fibrosis; MKS, Meckel-Gruber syndrome; MR, mental retardation; MTS, molar tooth sign; NPHP, nephronophthisis; PH, pulmonary hypoplasia; PVS,

pulmonary valve stenosis; RV, right ventricle; SA, *situs ambiguous.*

Supplementary Table S3: Genotype-phenotype correlation in 22 families with two recessive *NPHP4* mutations[1]

Family individual	Nucleotide change	Amino acid change[2]	Kidney Dysplast. Degen.	Eye Dysplast. Degen.	CNS Dysplast. Degen.	Liver Dysplast. Degen.	Clinical diagnosis	Others	Ref. No.
Patients with 2 truncating mutations									
F892-21 F892-22	c.148del1 c. 1892_1895del4	p.V50fsX79 (h) p.Q631fsX699 (h)	nphp, small kidneys	-	-	-	NPHP	chronic bronchitis	5
F1241-21	c.175C>T	p.R59X (H)	nphp	-	-	-	NPHP	-	12
A2305-21 A2305-23	c.305del1	p.N102fsX177 (H)	nphp, -21: large kidneys, -23: normal kidney size	-	-	-	NPHP	-	-
F32-21 F32-22	c. 1334_1335delinsTC>AA	p.F445X (H)	nphp, ESRD 20 yr (-21), 19 yr (-22)	-	-	-	NPHP	-	8
F88-22	c.1462C>T	p.R488X (H)	nphp, small kidneys, ESRD 14 yr	-	-	-	NPHP	-	5
F60-31 F60-32 F60-33 F60-34	c.1972C>T	p.R658X (H)	nphp, ESRD 10 yr (-31), 22 yr (-32), 17 yr (-33), 6 yr (-34)	TRD (-31, -32) -33: LCA -34: coloboma	-	-	SLSN	-	8
F3-21 F3-23	c.2335C>T	p.Q779X (H)	nphp, ESRD 30 yr (-21), 28 yr (-22)	LCA	-	LF	SLSN	deafness	8
F622-22 F622-23	c.2368G>T	p.E790X (H)	nphp, ESRD 8 yr (-22), 9 yr (-23)	-	-	-	NPHP	-	8
F1270-22 F1270-23	c.2368G>T	p.E790X (H)	nphp, small kidneys, -23: ESRD 14 yr	-	-	-	NPHP	-23: mild HI	12
A2324-21 A2324-23	c. 2618_2619insA	p.H873fsX886 (H)	nphp, ESRD 7 yr	-21: TRD	MR, -21: OMA	-	-23: JBTS	-	novel
F617-21	c. 2598_2607dup10	p.R870fsX890 (H)	nphp, ESRD 17 yr, small kidneys	TRD	DD	-	Usher syndrome	splenomegaly, deafness	5
F1183-21	c.3010dup1	p.T1004fsX1102 (H)	nphp, ESRD 13 yr	-	-	-	NPHP	-	12

F698-21 F698-22	c.3068G>A c. 3403del1	p.W1023X (h) p.R1135fsX1144 (h)	nphp, ESRD 21 yr (-21), 11 yr (-22)	-	-	-	NPHP	-	15
F704-22	c. 3149_3150insC	p.Q1050fsX1102 (H)	nphp, small kidneys, ESRD 9 yr	-	-	-	NPHP	-	5
F30-22 F30-23 F30-24	c.3272del1	p.V1091fsX1121 (H)	nphp, ESRD 18 yr (-22), 22 yr (-21, -23); -23: small kidneys	-24: TRD	-	-	SLSN	-	8
A206-21 A206-22	c.3272dup1	p.V1091fsX1102 (H)	nphp, ESRD 16 yr, small kidneys	-22: coloboma	-	-	-21: NPHP -22: PRS	-	12

Family individual	Nucleotide change	Amino acid change[2]	Kidney Dysplast. Degen.	Eye Dysplast. Degen.	CNS Dysplast. Degen.	Liver Dysplast. Degen.	Clinical diagnosis	Others	Ref. No.
Patients with 1 truncating mutation									
F461-31 F461-33 F461-34	c.2044C>T c. 2542C>T	p.R682X (h) p.R848W (h)	nphp, small kidneys	-	-	-	NPHP	-	8
F962-21 F962-22 F962-23	c.305del1 c.3364A>C	p.N102fsX177 (h) p.T1122P (h)	nphp, ESRD 13 yr (-22)	-	-	-	NPHP	-	15
Patients without truncating mutations									
F720-21	c.1405C>T c. 1961C>G	p.R469W (h) p.A654G (h)	nphp, enlarged kidneys	-	-	LF?	NPHP	-	5
F456-21	c.2836A>G	p.T946A (H)	nphp, small kidneys, ESRD 24 yr	TRD	-	-	SLSN	-	5
F24-21 F24-22	c.2260G>A c. 2144-1G>C	p.G754R (h) oblig. splice site (h)	nphp	-	-	-	NPHP	-	8
Patients with only splice site mutations									
F444-21 F444-22	c.1955+1G>A c.3472+1G>A	oblig. splice site (h) oblig. splice site (h)	nphp, ESRD 33 yr (-21), 23 yr (-22)	-	-	-	NPHP	-	8

[1]Clinical data partially reported (Otto *et al* 2002, Hoefele *et al* 2005, Otto *et al* 2008, Otto *et al* 2010); [2]Truncating mutations, missense mutations and splice site mutations are shown in red, black and blue fonts, respectively; Dysplastic phenotypes are shown in purple characters and degenerative

phenotypes in green characters; cDNA mutation numbering is based on human reference sequence NM_015102.2. DD, developmental delay; ESRD, end-stage renal disease; HI, hearing impairment; JBTS, Joubert syndrome; LCA, Leber's congenital amaurosis; LF, liver fibrosis; MR, mental retardation; NPHP, nephronophthisis; OMA, oculomotor apraxia type Cogan; PRS, papillo-renal syndrome; SLSN, Senior-Løken syndrome; TRD, tapeto-retinal degeneration.

Supplementary Table S4: Genotype-phenotype correlation in 25 families with two recessive *NPHP5/IQCB1* mutations[1]

Family individual	Nucleotide change	Amino acid change[2]	Kidney	Eye	CNS	Liver	Clinical diagnosis	Others	Ref. No.
			Dysplast. / Degen.	Dysplast. / Degen.	Dysplast. / Degen.	Dysplast. / Degen.			
Patients with 2 truncating mutations									
F1-21 F1-22	c.424_425del2	p.F142fsX146 (H)	nphp, ESRD 15 yr (-21), 12 yr (-22)	TRD	-	-	SLSN	-	10
A567-21	c.424_425del2	p.F142fsX146 (H)	nphp, ESRD 47 yr	TRD	-	-	SLSN	-	12
F399-21	c.424_425del2	p.F142fsX146 (H)	nphp, ESRD 32 yr	TRD	-	-	SLSN	father has cystic kidneys, bronchitis	10
F408-21	c.424_425del2	p.F142fsX146 (H)	nphp, ESRD 8 yr	TRD	-	-	SLSN	-	10
F409-21	c.424_425del2	p.F142fsX146 (H)	nphp, ESRD <17 yr	TRD	-	-	SLSN	asthma	10
F53-22	c.445_448del4	p.L149fsX179 (H)	nphp	TRD	-	-	SLSN	-	10
F269-21	c.445_448del4 c.825_828del4	p.L149fsX179 (h) p.R275fsX280 (h)	nphp, ESRD 37 yr	TRD	-	-	SLSN	carcinoma in the r.k., tumor in the left ovary	10
F2-21	c.994C>T	p.R332X (H)	nphp	TRD	-	-	SLSN	-	10
F189-21	c.994C>T	p.R332X (H)	nphp, ESRD <13 yr	TRD	-	-	SLSN	-	10
A371-21	c.825_828del4 c.1069C>T	p.R275fsX280 (h) p.Q357X (h)	nphp	TRD	-	-	SLSN	-	-
A19-21	c.825_828del4 c.1069C>T	p.R275fsX280 (h) p.Q357X (h)	nphp, ESRD <15 yr	TRD	-	-	SLSN	-	10
F64-23 F64-24	c. 1074_1075dup2	p.A359fsX361 (H)	nphp, ESRD <20 yr	TRD	-	-	SLSN	-	-
F1146-21 F1146-22	c. 1074_1075dup2	p.A359fsX361 (H)	nphp, ESRD 12 yr (-21), 13 yr (-22)	TRD	-	-	SLSN	-	10
A1175-21	c.1332G>A	p.W444X (H)	nphp, ESRD 7 yr	TRD	-	-	SLSN	-	10
F353-21	c.1363C>T	p.R455X (H)	nphp, ESRD 6 yr	TRD	-	-	SLSN	-	novel
F1395-21	c.1381C>T	p.R461X (H)	nphp, ESRD 14 yr, small kidneys	TRD	-	-	SLSN	-	12
A132-41 A132-45 A132-46	c.1381C>T	p.R461X (H)	nphp, ESRD <12 yr (-41), <8 yr (-45), <6 yr (-46)	TRD	-	-	RHYNS syndrome	-	10
A389-26	c.1465C>T	p.R489X (H)	nphp, ESRD <8 yr	TRD	-	-	SLSN	-	12

F14-22 F14-23	c. 1518_1519del2	p.H506fsX518 (H)	nphp, ESRD <11 yr (-22), <14 yr (-23)	LCA	-	-	SLSN	-	-
F50-21 F50-23	c. 1518_1519del2	p.H506fsX518 (H)	nphp, ERD 12 yr (-21), >13 yr (-23)	TRD	-	-	SLSN	-	10
F54-21	c. 1518_1519del2	p.H506fsX518 (H)	nphp, ESRD <24 yr		-	-	SLSN	-	10
Family individual	**Nucleotide change**	**Amino acid change[2]**	**Kidney** Dysplast. Degen.	**Eye** Dysplast. Degen.	**CNS** Dysplast. Degen.	**Liver** Dysplast. Degen.	**Clinical diagnosis**	**Others**	**Ref. No.**
F1175-21	c. 1518_1519del2	p.H506fsX518 (H)	nphp, small kidneys, ESRD <10 yr	TRD	-	-	SLSN	ES	12
F1298-22	c. 1518_1519del2	p.H506fsX518 (H)	nphp, ESRD 15 yr, normal kidney size	TRD	-	-	SLSN	-	10
Patients with only splice site mutations									
A364-23	c.488-1G>A	oblig. splice site (H)	nphp, normal kidney size	TRD	-	-	SLSN	-	12
A1538-21 A1538-22	c.1130-1G>C	oblig. splice site (H)	nphp, ESRD <12 yr, -21: small kidneys, -22: normal kidney size	TRD	-	-	SLSN	-21: syndactyly	novel

[1]Clinical data partially reported (Otto *et al* 2005, Otto *et al* 2008); [2]Truncating mutations, missense mutations and splice site mutations are shown in red, black and blue fonts, respectively; Dysplastic phenotypes are shown in purple characters and degenerative phenotypes in green characters; cDNA mutation numbering is based on human reference sequence NM_001023570.1. ES, epileptic seizure; ESRD, end-stage renal disease; LCA, Leber's congenital amaurosis; NPHP, nephronophthisis; RHYNS, retinitis pigmentosa-hypopituitarism-nephronophthisis-mild skeletal dysplasia; SLSN, Senior-Løken syndrome; TRD, tapeto-retinal degeneration.

Supplementary Table S5: Genotype-phenotype correlation in 19 families with two recessive *NPHP6*/*CEP290* mutations[1]

Family individual	Nucleotide change	Amino acid change[2]	Kidney	Eye	CNS	Liver	Clinical diagnosis	Others	Ref. No.
			Dysplast. Degen.	Dysplast. Degen.	Dysplast. Degen.	Dysplast. Degen.			
Patients with 2 truncating mutations									
F57-21	c.1A>G, c. 1419_1423del5	start codon defect (h) p.K473fsX478 (h)	nphp	TRD, keratoconus	-	-	SLSN	ES	4
A197-21	c. 3175_3176insA c. 7341_7342insA	p.I1059fsX1069 (h) p.L2448fsX2455 (h)	nphp, ESRD 9.5 yr	retinal phenotype	-	-	JBTS	-	17
A1713-21 A1713 -22	c.5182G>T c.6277del1	p.E1728X (h) p.V2093fsX2096 (h)	nphp	LCA	mild CM	-	JBTS?	-	15
A1388-21	c.136G>T c. 5649_5650insA	p.E46X (h) p.L1884fsX1906 (h)	nphp, enlarged kidneys, ESRD 7 yr 5 mo	OA	CVA, MR	-	JBTS	deafness	15
A372-21 A372-22	c.3811C>T c. 5734del1	p.R1271X (h) p.W1912fsX1923 (h)	nphp	coloboma, LCA	MR	-	JBTS	-	4
F63-21	c.4656del1 c. 5668G>T	p.K1552fsX1556 (h) p.G1890X (h)	nphp, ESRD 12 yr	TRD	CVA, EC, MR	-	JBTS	-	17
A1715-21	c.5311G>T c. 5445_5448del4	p.E1771X (h) p.L1815fsX1818 (h)	nphp	TRD	MR	-	JBTS	-	15
F89-21	c. 5515_5518del4 c. 5649_5650insA	p.E1843fsX1849 (h) p.L1883fsX1906 (h)	nphp, ESRD 11 yr	ONA	CVA, MR	-	JBTS	-	17
F15-21 F15-24	c. 5649_5650insA c.5850del1	p.L1884fsX1906 (h) p.F1950fsX1964 (h)	nphp	LCA	cerebellar involvement	-	JBTS?	-	15
F394-27	c.5668G>T	p.G1890X (H)	nphp, enlarged kidneys, ESRD 3 yr	coloboma	CVH, microcephaly, MR	-	JBTS	ataxia	15
F700-24 F700-26	c.5668G>T	p.G1890X (H)	nphp, ESRD 10 yr (-24)	sight problem	MR; -24: CVH, -26: CVA, EC	-	JBTS	-24: ES	17
F944-31 F944-32	c.5668G>T	p.G1890X (H)	nphp, ESRD 13 yr (-31), 11 yr (-32)	-	-	-	JBTS	-	17

A1188-21	c.5668G>T	p.G1890X (H)	nphp, normal kidney size	-	CVA, MR	-	JBTS	-	15
A989-21	c.4882C>T c.5941G>T	p.Q1628X (h) p.E1981X (h)	nphp, ESRD 5 yr 2 mo	TRD	CVA, MR	LF	JBTS	-	4
Patients with 1 truncating mutation									
A2029-21	c.1189G>A c. 5668G>T	p.G397S (h) p.G1890X (h)	nphp, ESRD 2 yr	LCA	brain anomaly, MTS, MR	-	JBTS	-	15
F101-21	c.5163del1 c.1066-1G>A	p.T1721fsX1723 (h) oblig. splice site (h)	nphp	TRD	-	-	SLSN	-	4

Family individual	Nucleotide change	Amino acid change[2]	Kidney Dysplast. Degen.	Eye Dysplast. Degen.	CNS Dysplast. Degen.	Liver Dysplast. Degen.	Clinical diagnosis	Others	Ref. No.
Patients without truncating mutations									
F335-21 F335-22	c.2915T>C	p.L972P (H)	-21: nphp, ESRD <13 yr; -22: no nphp	TRD	-	-	SLSN	-	15
Patients with only splice site mutations									
F4-21 F4-22	c.2218-4 _2222del9	oblig. splice site (H)	nphp, ESRD 11 yr (-21), 13 yr (-22)	TRD	-	-	SLSN	-	17
A2182-21 A2182-22	c.2217+1G>T	oblig. splice site (H)	nphp, ESRD 13 yr (-21), 8 yr (-22)	TRD	microcephaly, MR	-	JBTS	-	novel

[1]Clinical data partially reported (Sayer *et al* 2006, Helou *et al* 2007, Otto *et al* 2010); [2]Truncating mutations, missense mutations and splice site mutations are shown in red, black and blue fonts, respectively; Dysplastic phenotypes are shown in purple characters and degenerative phenotypes in green characters, ESRD onset <4 yr is considered to be dysplastic; cDNA mutation numbering is based on human reference sequence NM_025114.3. CM, celebellum malformation; CVA, cerebellar vermis aplasia; CVH, cerebellar vermis hypoplasia; EC, encephalocele occ.; ES, epileptic seizure; ESRD, end-stage renal disease; JBTS, Joubert syndrome; LCA, Leber's congenital amaurosis; LF, liver fibrosis; MR, mental retardation; MTS, molar tooth sign; NPHP, nephronophthisis; OA, occular albinism; ONA, optic nerve atrophy; SLSN, Senior-Løken syndrome; TRD, tapeto-retinal degeneration.

Supplementary Table S6: Genotype-phenotype correlation in 8 families with two recessive *NPHP8*/*RPGRIP1L* mutations[1]

Family individual	Nucleotide change	Amino acid change[2]	Kidney Dysplast. Degen.	Eye Dysplast. Degen.	CNS Dysplast. Degen.	Liver Dysplast. Degen.	Clinical diagnosis	Others	Ref. No.
Patients with 1 truncating mutation									
A2424-21	c. 721_724del4 c.1829A>C	p.N241fsX265 (h) p.H610P (h)	PKD	-	DWM, EC	-	MKS	polydactyly	15
A188-23	c.1841A>C c. 2050C>T	p.T615P (h) p.Q684X (h)	no nphp at age 5 yrs	-	MTS, DD, small EC, strabismus, abnormal eye movement, bilateral ptosis	-	JBTS/MKS?	postaxial hand polydactyly, dysmorphic features	1
A177-21	c.1975T>C c.2413C>T	p.S659P (h) p.R805X (h)	nphp, ESRD <5 yr	-	MTS	CLF	COACH syndrome	BDA	3
Patients without truncating mutations									
F138-21 F138-22	c.1843A>C	p.T615P (H)	nphp, ESRD 10 yr, small kidneys	-	CVA; -21: mutism, MR, OMA	-	JBTS	-	19
A166-22 A166-23	c.1843A>C	p.T615P (H)	nphp, ESRD 4 yr 2 mo, normal kidney size	-	-22: MR, -23: MTS	-	JBTS	-	19
A762-21	c.1897T>C	p.C633R (H)	nphp, small kidneys, ESRD 9 yr 8 mo	-	OMA	-	NPHP	-	19
A1367-21 A1367-22	c.2083G>C	p.A695P (H)	nphp, ESRD 9r (-21), 8 yr (-22)	-	OMA, Nys	-	NPHP	scoliosis	11
A1685-21 A1685-22	c.2450A>G	p.Y817C (H)	nphp, ESRD 17 yr (-21), 15 yr (-22)	-	MR, OMA	-	JBTS?	-	novel

[1]Clinical data partially reported (Arts *et al* 2007, Wolf *et al* 2007, Delous *et al* 2007, Otto *et al* 2010, Doherty *et al* 2010); [2]Truncating mutations and missense mutations are shown in red and black fonts, respectively; Dysplastic phenotypes are shown in purple characters and degenerative phenotypes in green characters, ESRD onset <4 yrs is considered to be dysplastic; cDNA mutation numbering is based on human reference sequence NM_015272.2. BDA, bile ductile abnormality; CLF, congenital liver fibrosis; COACH, cerebellar vermis hypo/aplasia-oligophrenia-congenital ataxia-ocular coloboma-hepatic fibrosis; CVA, cerebellar vermis aplasia; DD, developmental delay; DWM, Dandy-Walker malformation; EC, encephalocele occ.; ESRD, end-stage renal disease; JBTS, Joubert syndrome; MKS, Meckel-Gruber syndrome; MR, mental retardation; MTS, molar

tooth sign; NPHP, nephronophthisis; Nys, nystagmus; OMA, oculomotor apraxia type Cogan.

Supplementary Table S7: Genotype-phenotype correlation in 7 families with two recessive *NPHP10*/*SDCCAG8* mutations[1]

Family individual	Nucleotide change	Amino acid change[2]	Kidney Dysplast. Degen.	Eye Dysplast. Degen.	CNS Dysplast. Degen.	Liver Dysplast. Degen.	Clinical diagnosis	Others	Ref. No.
Patients with 2 truncating mutations									
F159-21 F159-22	c.421-?_740+?del	p.E141_R247del107fs (H)	nphp, ESRD 11 yr (-21), 7 yr (-22)	-21: TRD -22: normal	-	-	SLSN?	-22: GS	14
F336-21 F336-22	c.1339_340insG	p.E447fsX463 (H)	nphp, ESRD 7 yr (-21), 4 yr (-22)	flat ERG (-21: 13 yr, -22: 6 yr)	-21: mild MR	-	SLSN?	-	14
A1365-21 A1365-22	c.1420del1	p.E474fsX493 (H)	nphp, ESRD 4 yr (-21), 14 yr (-22)	TRD, -21: 30% vision (14 yr), -22: blind (7 yr)	-	-	SLSN	-	14
F1054-21 F1054-22	c.1796T>G	p.L599X (H)	nphp, ESRD <10 yr (-21), <9 yr (-22)	-	-	-	NPHP	-21: POS	14
F195-21	c.1946_1949del4	p.C649fsX658 (H)	nphp, ESRD 22 yr	TRD	-	-	SLSN	-	14
Patients with 1 truncating mutation									
AR37-25 AR37-27	c.696T>G c.740+1del1	p.Y232X (h) oblig. splice site (h)	nphp, -25: ESRD 22 yr, -27: no ESRD	TRD, -27: SNB	-25: PN -27: MR	-	SLSN?	-25: OB, HP	14
Patients with only splice site mutations									
A2290-21	c.1068+1G>A	oblig. splice site (H)	nphp, ESRD 14 yr	TRD	cystic brain lesion	-	SLSN?	-	14

[1]Clinical data partially reported (Otto *et al* 2010); [2]Truncating mutations, missense mutations and splice site mutations are shown in red, black and blue fonts, respectively; Dysplastic phenotypes are shown in purple characters and degenerative phenotypes in green characters; cDNA mutation numbering is based on human reference sequence NM_006642.2. ERG, electroretinogram; ESRD, end-stage renal disease; GS, generalized seizures; HP, hypogenitalism; MR, mental retardation; NPHP, nephronophthisis; OB, obesity; PN, peripheral neuropathy; POS, polycystic ovary syndrome; SLSN, Senior-Løken syndrome; SNB, stationary night blindness; TRD, tapeto-retinal degeneration.

Supplementary Table S8: Genotype-phenotype correlation in 20 families with two recessive *NPHP11*/*TMEM67*/*MKS3* mutations[1]

Family individual	Nucleotide change	Amino acid change[2]	Kidney Dysplast. Degen.	Eye Dysplast. Degen.	CNS Dysplast. Degen.	Liver Dysplast. Degen.	Clinical diagnosis	Others	Ref. No.
Patients with 1 truncating mutation									
F56-21	c.130C>T c. 2461G>C	p.Q44X (h) p.G821R (h)	nphp	coloboma, ONA, TRD	CVH, MR	-	JBTS	ataxia	13
A77-21	c.622A>T c. 2168A>G	p.R208X (h) p.Y723C (h)	nphp, ESRD 7 yr, normal kidney size	ONA	CVH, DWM, MR	LF	MKS?	SAS	15
A144-21	c.622A>T c. 2498T>C	p.R208X (h) p.I833T (h)	nphp	-	CVA, MR	LF	JBTS	-	13
A971-21	c.622A>T c. 1843T>C	p.R208X (h) p.C615R (h)	nphp, ESRD 7 yr	-	CVH, MR	cholangiopathy, hepatomegaly, LF?	JBTS	-	15
A3208-21 A3208-22	c.1351C>T c.2018T>C	p.R451X (h) p.V673A (h)	nphp, ESRD 19 yr	coloboma	CVH, CH, MR, absences	-	JBTS	-	15
F480-22	c.1387C>T c.2891C>T	p.R463X (h) p.T964I (h)	nphp	-	-	-	JBTS?	-	15
Patients without truncating mutations									
F278-21	c.755T>C c. 1843T>C	p.M252T (h) p.C615R (h)	nphp, ESRD 2 yr, very small kidneys	-	MR	LF, cholangiodysplasia	JBTS	ataxia	15
F190-22	c.755T>C c. 1843T>C	p.M252T (h) p.C615R (h)	nphp, small kidneys, ESRD <7 yr	coloboma	MR, OMA	LF	JBTS?	ataxia	13
F90-21	c.755T>C c. 1843T>C	p.M252T (h) p.C615R (h)	nphp, small kidneys, ESRD 5.5 yr	TRD	CVA, MR	LF	JBTS	polydactyly	15
F96-21 F96-22	c.755T>C c. 2498T>C	p.M252T (h) p.I833T (h)	nphp, ESRD 22 yr	coloboma	CVH, MR	-	JBTS	ataxia	15
A1011-21	c.868G>T c. 1843T>C	p.W290L (h) p.C615R (h)	nphp, ESRD 8 yr	-	OD	LF	NPHP/JBTS	-	13
F631-21	c.1045T>C c.1843T>C	p.L349S (h) p.C615R (h)	nphp	coloboma	MR	LF	JBTS	-	15
F519-21	c.1843T>C	p.C615R (H)	nphp, enlarged kidneys, ESRD 6 yr	-	MR	LF	JBTS	splenomegaly, EDS	13

F585-21	c.1843T>C	p.C615R (H)	nphp, ESRD 6 yr	TRD	general BA	LF	JBTS?	-	13
F315-21	c.1843T>C c.1911C>A	p.C615R (h) p.F637L (h)	nphp, ESRD <9 yr	-	CVA, MR	LF	JBTS	-	15

Family individual	Nucleotide change	Amino acid change[2]	Kidney	Eye	CNS	Liver	Clinical diagnosis	Others	Ref. No.
			Dysplast. / Degen.	Dysplast. / Degen.	Dysplast. / Degen.	Dysplast. / Degen.			
A1371-21 A1371-22	c.1888T>C	p.S630P (H)	nphp, ESRD 8 yr (-21), <10 yr (-22)	LCA, -21: coloboma	CVA, -21: PR, strabismus, ptosis	LF	NPHP	-21: ataxia -22: HI	13
F563-21 F563-22 F563-23	c.2461G>A	p.G821S (H)	nphp, ESRD 14 yr (-21), >8 yr (-22), 9 yr (-23)	-	-	LF	NPHP	-	13
F1039-21	c.2461G>C	p.G821R (H)	nphp, ESRD 10 yr	-	mild BA	LF	JBTS?	myopic, moronic	13
F459-21 F459-22	c.986A>C c.2556+1G>A	p.K329T (h) oblig. splice site (h)	nphp, passed away at 46 yr	coloboma	CVH, MR	LF	JBTS?	ataxia	15
A123-21	c.1769T>C c.1961-2A>C	p.F590S (h) oblig. splice site (h)	nphp	coloboma	MTS, MR, Nys, OMA, DD, hypotonia	CLF, hepatomegaly	COACH syndrome	EV	2

[1]Clinical data partially reported (Brancati *et al* 2009, Otto *et al* 2009, Otto *et al* 2010); [2]Truncating mutations, missense mutations and splice site mutations are shown in red, black and blue fonts, respectively; Dysplastic phenotypes are shown in purple characters and degenerative phenotypes in green characters, ESRD onset <4 yrs is considered to be dysplastic; cDNA mutation numbering is based on human reference sequence NM_153704.5. BA, brain atrophy; CH, cerebellar hypoplasia; CLF, congenital liver fibrosis; CVA, cerebellar vermis aplasia; CVH, cerebellar vermis hypoplasia; DD, developmental delay; DWM, Dandy-Walker malformation; EDS, Ehlers-Danlos syndrome; ESRD, end-stage renal disease; EV, esophageal varices; HI, hearing impairment; JBTS, Joubert syndrome; LF, liver fibrosis; MR, mental retardation; MTS, molar tooth sign; NPHP, nephronophthisis; Nys, nystagmus; OD, oculocerebral disease; OMA, oculomotor apraxia type Cogan; ONA, optic nerve atrophy; PR, psychomotor retardation; SAS, subvalvular aortic stenosis; TRD, tapeto-retinal degeneration.

Supplementary Table S9: Genotype-phenotype correlation in 6 families with two recessive *AHI1* mutations[1]

Family individual	Nucleotide change	Amino acid change[2]	Kidney Dysplast. Degen.	Eye Dysplast. Degen.	CNS Dysplast. Degen.	Liver Dysplast. Degen.	Clinical diagnosis	Others	Ref. No.
Patients with 2 truncating mutations									
F400-21	c. 365_688del324 c.443dup1	p.Q123-L230del (h) p.N148fsX149 (h)	no nphp	coloboma	MTS	-	JBTS	-	18
A185-21	c.736A>T c. 2495T>G	p.K246X (h) p.L832X (h)	nphp, MCDK	TRD	MTS, OMA, Nys	-	NPHP/JBTS	diabetes	16
A191-21	c.1267C>T c. 2212C>T	p.Q423X (h) p.R738X (h)	nphp	TRD	MTS, OMA, Nys	-	NPHP/JBTS	tachypnea	16
F799-22 F799-24	c. 2368_2369insT	p.N790fsX791 (H)	nphp, ESRD 16 yr (-24), no nphp 20 yrs (-22)	-	MR, PDD, OMA, Nys	-	JBTS?	ataxia	18
A2045-21	c.2172del1	p.I724fsX729 (H)	nphp, ESRD 17 yr	-	-	-	NPHP/JBTS	-	novel
Patients with only splice site mutations									
A176-21	c.2036+1 G>T	oblig. splice site (H)	nphp	TRD	MTS, Nys	-	NPHP/JBTS	tachypnea	16

[1]Clinical data partially reported (Utsch *et al* 2006, Parisi *et al* 2006); [2]Truncating mutations and splice site mutations are shown in red and blue fonts, respectively; Dysplastic phenotypes are shown in purple characters and degenerative phenotypes in green characters; cDNA mutation numbering is based on human reference sequence NM_017651.3. ESRD, end-stage renal disease; JBTS, Joubert syndrome; MCDK, multicystic dysplastic kidneys; MR, mental retardation; MTS, molar tooth sign; NPHP, nephronophthisis; Nys, nystagmus; OMA, oculomotor apraxia type Cogan; PDD, Psychomotor developmental delay; TRD, tapeto-retinal degeneration.

Supplementary Table S10: Genotype-phenotype correlation in 3 families with two recessive *CC2D2A* mutations[1]

Family individual	Nucleotide change	Amino acid change[2]	Kidney Dysplast. Degen.	Eye Dysplast. Degen.	CNS Dysplast. Degen.	Liver Dysplast. Degen.	Clinical diagnosis	Others	Ref. No.
Patients with 1 truncating mutation									
A2426-21	c.685_687del3 c.3893T>A	p.E229del (h) p.V1298D (h)	PKD	-	EC	-	MKS	bone-cartilage junction disarray	15
F434-21	c.517C>T c.1676T>C	p.R173X (h) p.L559P (h)	nphp, kidney problem >3 yr	-	CVH, MR, OMA	-	JBTS	ataxia, muscle hypotonia	15
A2421-21	c.3544T>C c.3774_3775insT	p.W1182R (h) p.E1259fsX1260 (h)	PKD	-	EC	-	MKS	hepatic developmental defects	15

[1] Clinical data partially reported (Otto *et al* 2010); [2] Truncating mutations and missense mutations are shown in red and black fonts, respectively; Dysplastic phenotypes are shown in purple characters and degenerative phenotypes in green characters, ESRD onset <4 yrs is considered to be dysplastic; cDNA mutation numbering is based on human reference sequence NM_001080522.1. CVH, cerebellar vermis hypoplasia; EC, encephalocele occ.; ESRD, end-stage renal disease; JBTS, Joubert syndrome; MKS, Meckel-Gruber syndrome; MR, mental retardation; OMA, oculomotor apraxia type Cogan.

References

1. Arts HH, Doherty D, van Beersum SEC *et al.* Mutations in the gene encoding the basal body protein RPGRIP1L, a nephrocystin-4 interactor, cause Joubert syndrome. *Nat Genet* 2007; **39**: 882-888.

2. Brancati F, Iannicelli M, Travaglini L *et al.* MKS3/TMEM67 mutations are a major cause of COACH Syndrome, a Joubert Syndrome related disorder with liver involvement. *Hum Mutat* 2009; 30: 432-442.

3. Doherty D, Parisi MA, Finn LS *et al.* Mutations in 3 genes (MKS3, CC2D2A and RPGRIP1L) cause COACH syndrome (Joubert syndrome with congenital hepatic fibrosis). *J Med Genet* 2010; **47**: 8-21.

4. Helou J, Otto EA, Attanasio M *et al*. Mutation analysis of NPHP6/CEP290 in patients with Joubert syndrome and Senior-Loken syndrome. *J Med Genet* 2007; **44:** 657-663.

5. Hoefele J, Sudbrak R, Reinhardt R *et al*. Mutational analysis of the NPHP4 gene in 250 patients with nephronophthisis. *Hum Mutat* 2005; **25:** 411.

6. Hoefele J, Wolf MT, O'Toole JF *et al*. Evidence of oligogenic inheritance in nephronophthisis. *J Am Soc Nephrol* 2007; **18:** 2789-2795.

7. Olbrich H, Fliegauf M, Hoefele J *et al*. Mutations in a novel gene, NPHP3, cause adolescent nephronophthisis, tapeto-retinal degeneration and hepatic fibrosis. *Nat Genet* 2003; **34:** 455-459.

8. Otto EA, Hoefele J, Ruf R *et al*. A gene mutated in nephronophthisis and retinitis pigmentosa encodes a novel protein, nephroretinin, conserved in evolution. *Am J Hum Genet* 2002; **71:** 1167-1171.

9. Otto EA, Schermer B, Obara T *et al*. Mutations in INVS encoding inversin cause nephronophthisis type 2, linking renal cystic disease to the function of primary cilia and left-right axis determination. *Nat Genet* 2003; **34:** 413-420.

10. Otto EA, Loeys B, Khanna H *et al*. A novel ciliary IQ domain protein, NPHP5, is mutated in Senior-Loken syndrome (nephronophthisis with retinitis pigmentosa), and interacts with RPGR and calmodulin. *Nat Genet* 2005; **37:** 282-288.

11. Delous M, Baala L, Salomon R *et al.* The ciliary gene RPGRIP1L is mutated in cerebello-oculo-renal syndrome (Joubert syndrome type B) and Meckel syndrome. *Nat Genet* 2007; **39**: 875-881.

12. Otto EA, Helou J, Allen SJ *et al*. Mutation analysis in nephronophthisis using a combined approach of homozygosity mapping, CEL I

endonuclease cleavage, and direct sequencing. *Hum Mutat* 2008; **29:** 418-426.

13. Otto EA, Tory K, Attanasio M *et al.* Hypomorphic mutations in meckelin (MKS3/TMEM67) cause nephronophthisis with liver fibrosis (NPHP11). *J Med Genet* 2009; **46**: 663-670.

14. Otto EA, Hurd TW, Airik R *et al*. Candidate exome capture identifies mutation of *SDCCAG8* as the cause of a retinal-renal ciliopathy. *Nat Genet* 2010; **42:** 840-850.

15. Otto EA, Ramaswami G, Janssen S *et al*. Mutation analysis of 18 nephronophthisis associated ciliopathy disease genes using a DNA pooling and next generation sequencing strategy. *J Med Genet* 2011; **48:** 105-116.

16. Parisi MA, Doherty D, Eckert ML *et al.* AHI1 mutations cause both retinal dystrophy and renal cystic disease in Joubert syndrome. *J Med Genet* 2006; **43**: 334-339.

17. Sayer JA, Otto EA, O'Toole JF *et al.* The centrosomal protein nephrocystin-6 is mutated in Joubert syndrome and activates transcription factor ATF4. *Nat Genet* 2006; **38**: 674-681.

18. Utsch B, Sayer JA, Attanasio M *et al.* Identification of the first AHI1 gene mutations in nephronophthisis-associated Joubert syndrome. *Pediatr Nephrol* 2006; **21**: 32-35.

19. Wolf MT, Saunier S, O'Toole JF *et al.* Mutational analysis of the RPGRIP1L gene in patients with Joubert syndrome and nephronophthisis. *Kidney Int* 2007; **72**: 1520-1526.