SUPPLEMENTAL INFORMATION

Somatic Mutations in Renal Cyst Epithelium in Autosomal Dominant Polycystic Kidney Disease

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SUPPLEMENTAL FIGURES

Supplemental Figure 1

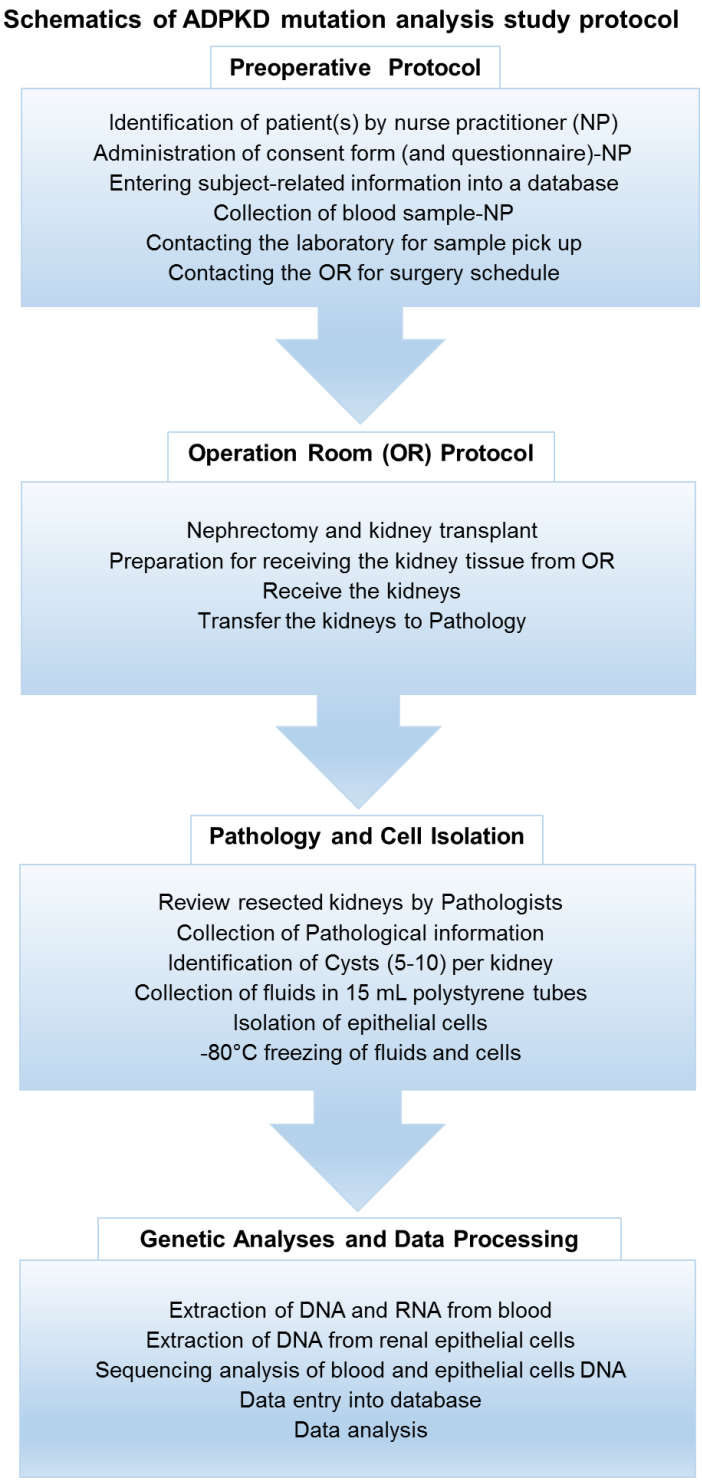
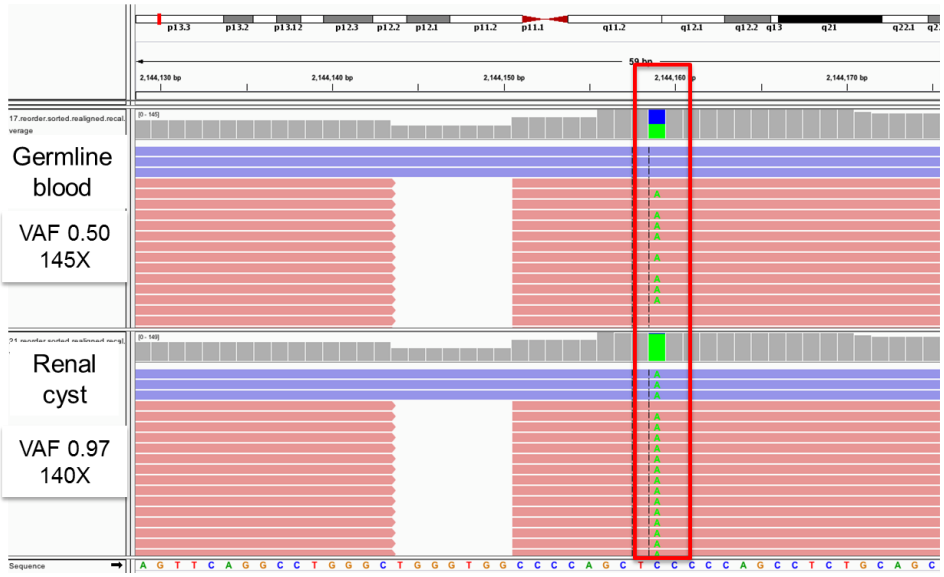


Figure S1. Schematic diagram of the ADPKD mutation analysis study protocol. The study population comprised nine patients with ADPKD scheduled for a living kidney transplant and native kidney removal at the NYPH/WCM campus. The clinical eligibility for nephrectomy was determined by the transplant surgeon prior to enrollment. Prospective study subjects were identified during the pre-transplant evaluation period, following by eligibility assessment and obtaining of informed consent from all subjects. After surgery and pathologist's gross-examination, renal cysts were identified and cyst criteria recorded followed by isolation of the cyst epithelia according to standard procedure (see Methods). Isolated cells were collected by centrifugation and stored at -80°C for further analyses.

Supplemental Figure 2

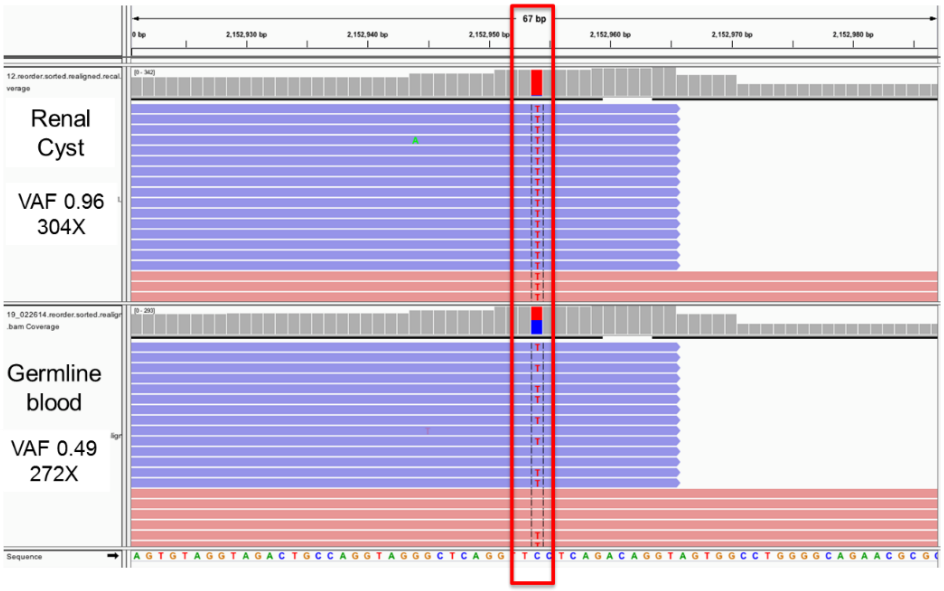
a.

PKD1 c.G10549T: p.E3517X (LOH); Ex35
(RP9001591, Cyst L11/B21)



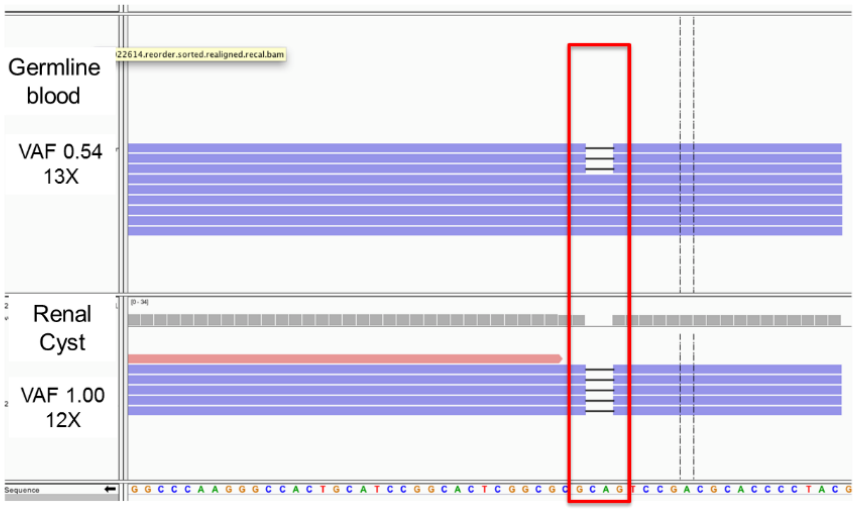
b.

PKD1 c.10084del, p.Gln3362Serfs*35: Ex22
(CDS001574, R10/B12)



c.

PKD1 c.3929_3930del, p.Asp1310Glyfs*120 (LOH); Ex15
(BJA001578, R11/A24)



d.

PKD1 c.9504C>G,p.F3168L (LOH); Ex27
(DR9001565, L3 /A15)

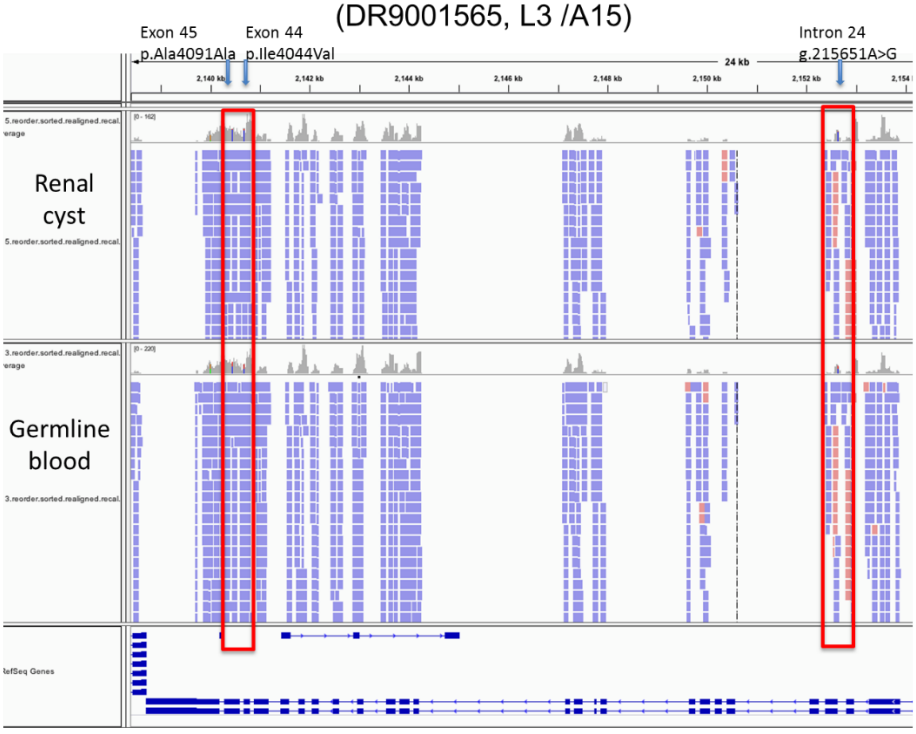


Figure S2. Blood and renal cyst DNAs heterozygous and homozygous for c.6364delG, p.V2122fs, respectively, detected by whole exome sequencing (WES) analysis. *PKD1* WES reads are piled up and are shown in Integrative Genomics Viewer (IGV). The mutation total coverage and variant allele frequency (VAF) are displayed for each sample.

WES analysis of PBL constitutional DNA shows no coverage at the mutation site, but *PKD1* Analysis results of renal cyst DNA clearly show LOH for selected SNPs (see table below for coverage and VAF data) at flanking exonic regions of *PKD.* Shown here are *PKD1* exons 23 through 46.

				Germline DNA		Cyst DNA (A15)	
chr16	location	*PKD1* Exon/Intron	Nomenclature	Coverage depth	VAF	Coverage depth	VAF
chr16	2152651	Intron24	g.215651A>G	69	57%	58	88%
chr16	2140680	Exon44	p.Ile4044Val/c.12130A>G	71	52%	70	84%
chr16	2140454	Exon45	p.Ala4091Ala/c.12273A>G	87	59%	69	91%

Supplemental Figure 3

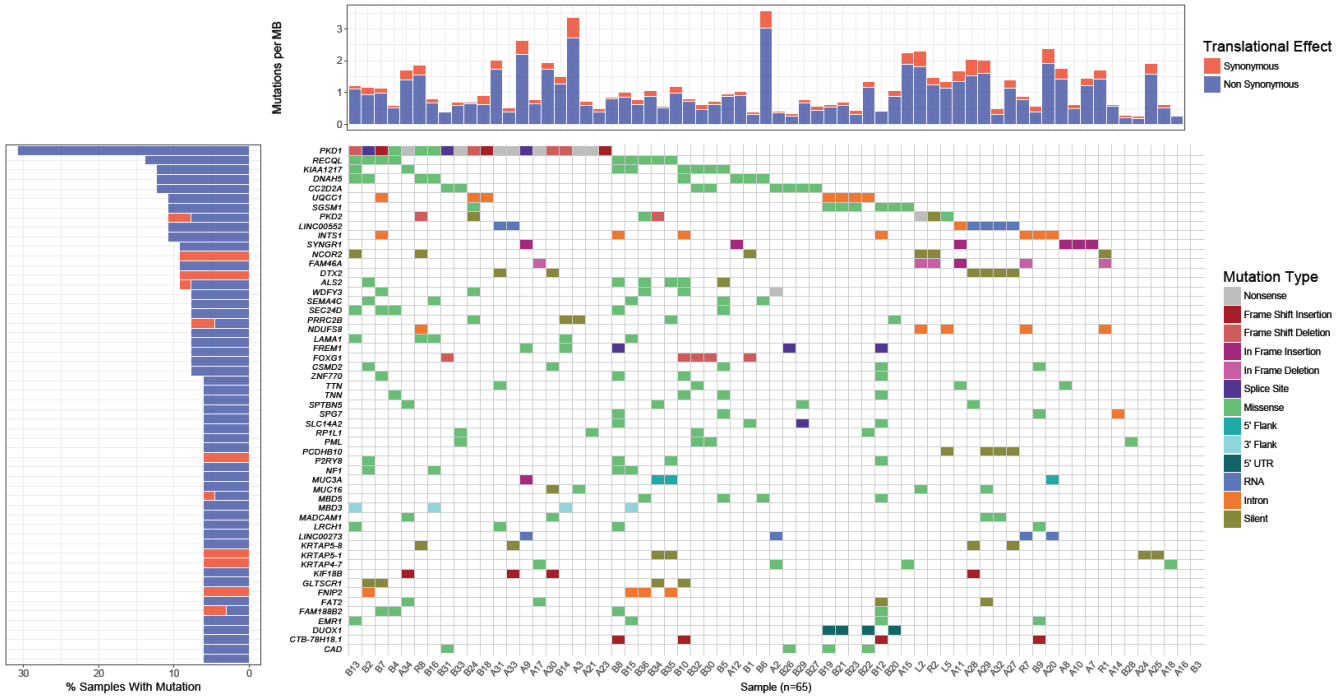
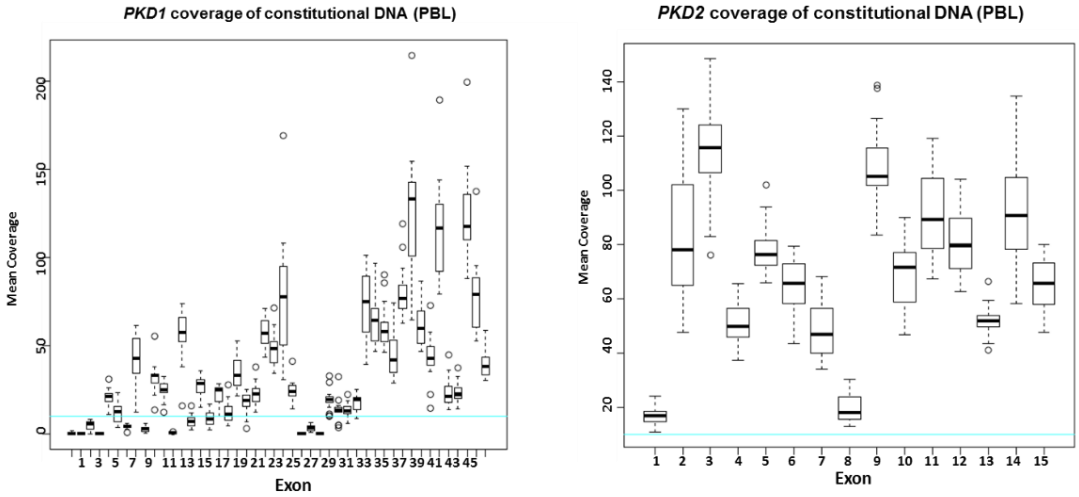


Figure S3. Distribution of somatic changes by alteration type and by cyst across all patients. Alterations are colored according to mutation type.

Supplemental Figure 4

a. *PKD1* and *PKD2* gene coverage in peripheral blood lymphocytes (PBL)



b. *PKD1* and *PKD2* gene coverage in renal cyst epithelia

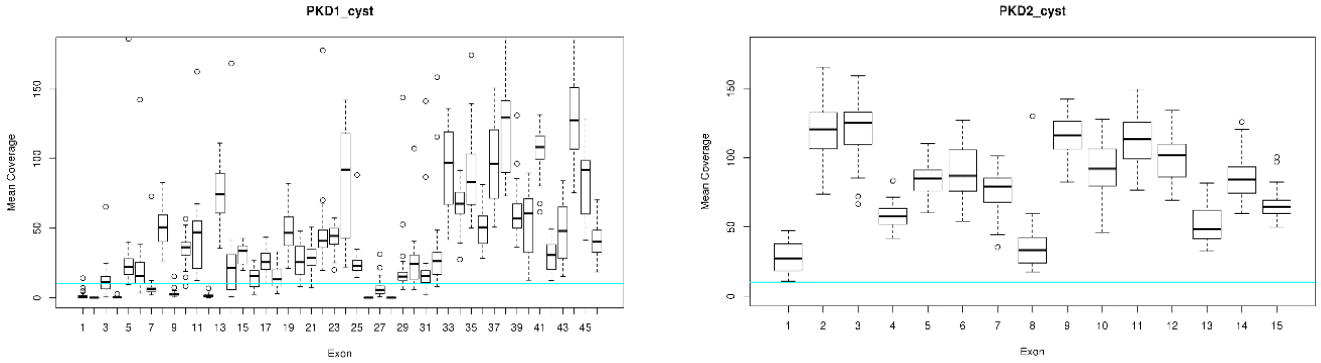
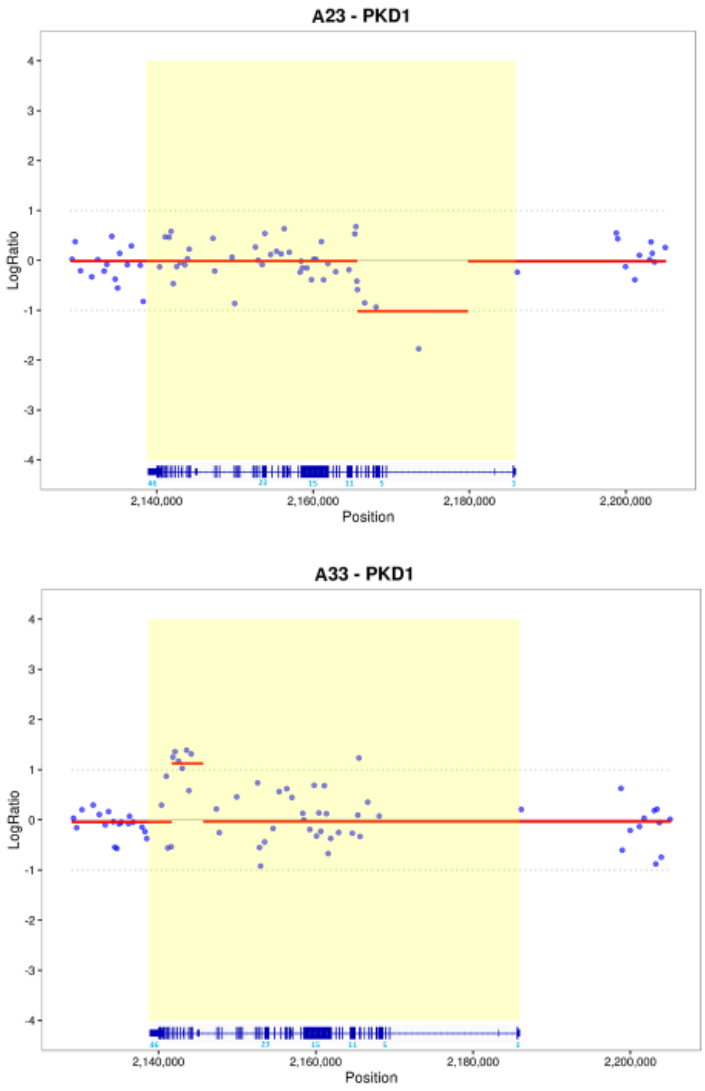
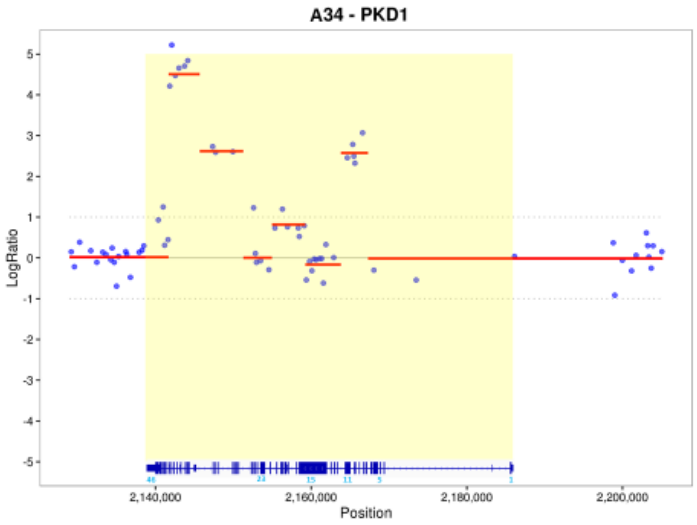


Figure S4. *PKD1 and PKD2* gene coverage by Exon using (a) constitutional peripheral blood lymphocytes (n=18) and (b) renal cyst epithelia cells (n=65). HMW gDNA. PBL, peripheral blood lymphocytes.

Supplemental Figure 5




A34 - PKD1
LogRatio
Position
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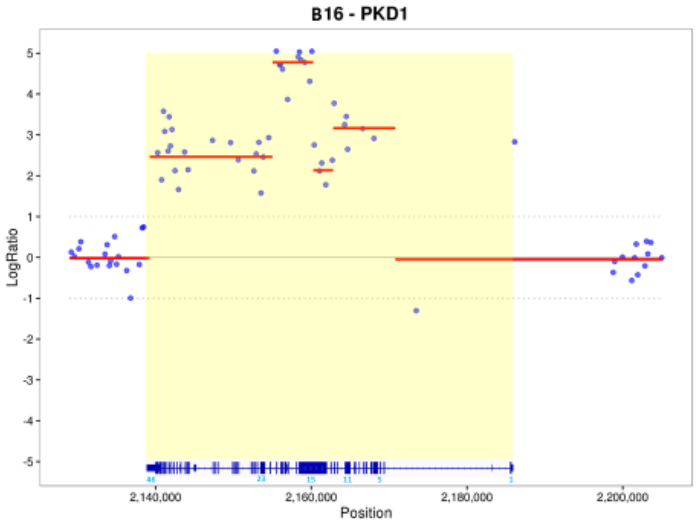
2,160,000
2,180,000
2,200,000


B16 - PKD1
LogRatio
Position
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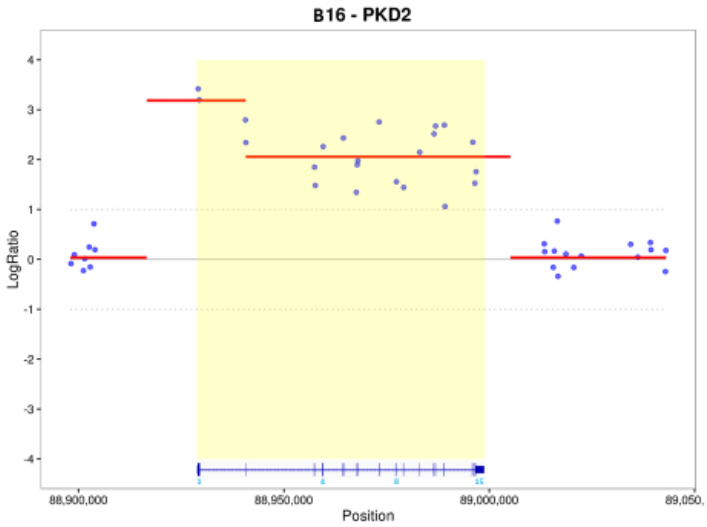
B16 - PKD2
LogRatio
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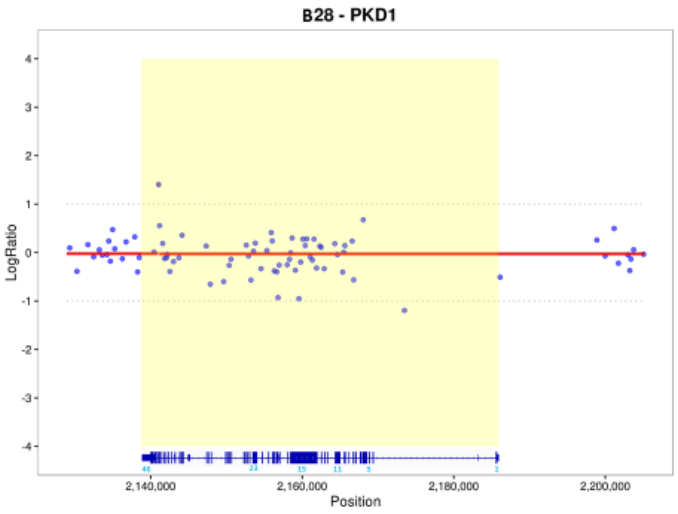
89,000,000
89,050,


B28 - PKD1
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0
-1
-2
-3
-4
2,140,000
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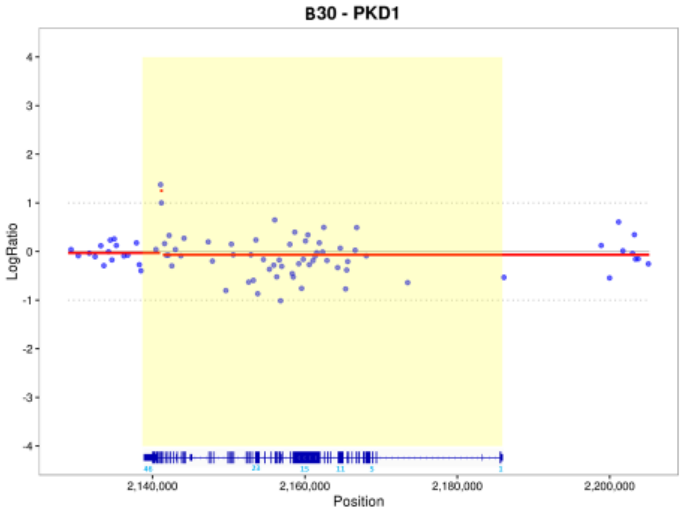
2,200,000
Position


B30 - PKD1
LogRatio
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1
0
-1
-2
-3
-4
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2,200,000
Position

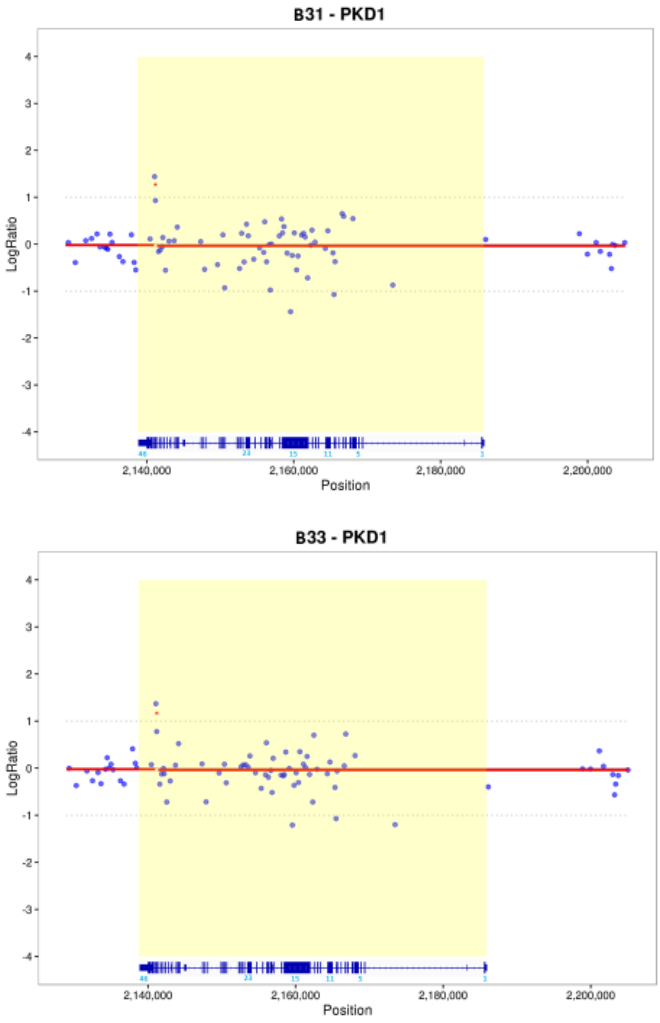


Figure S5. Copy number variations (CNVs) in *PKD1* and *PKD2*. Shown here are plots of CNV analysis identified in selected cyst samples (Table 3 in the manuscript) presented as Log2 Ratio of fold-change at target PKD gene regions. Such alterations can typically affect a single gene to thousands of genes.

Supplemental Figure 6

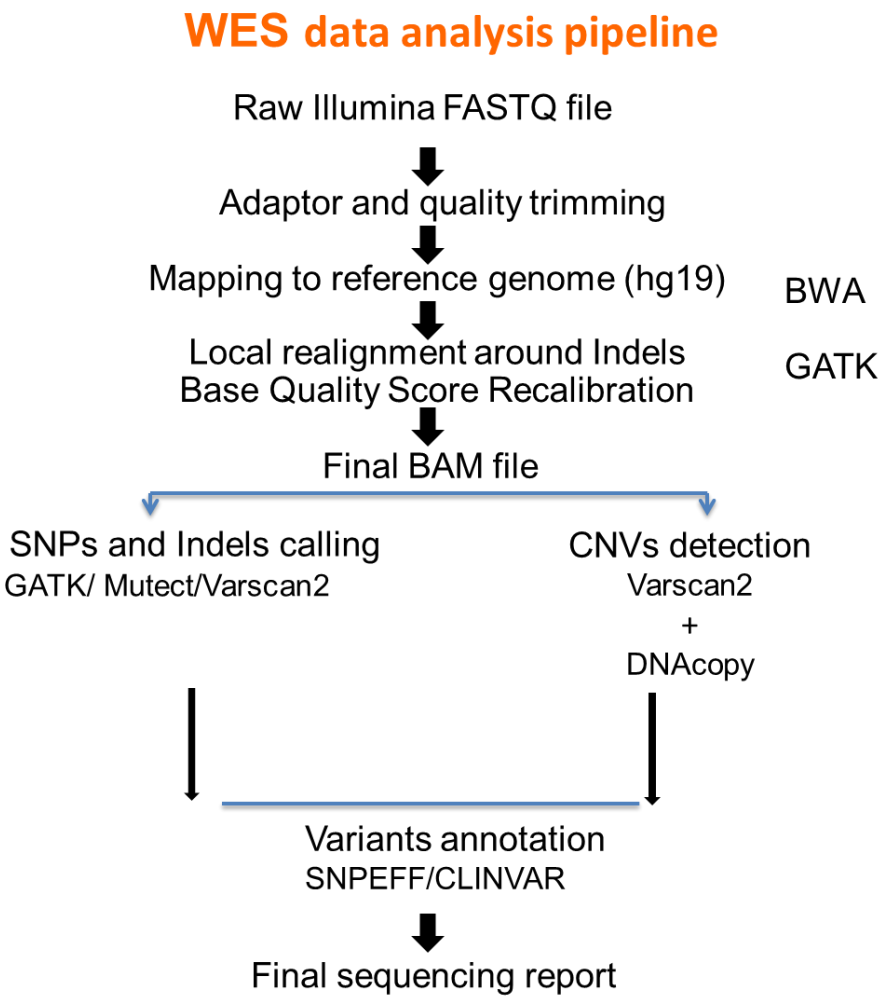
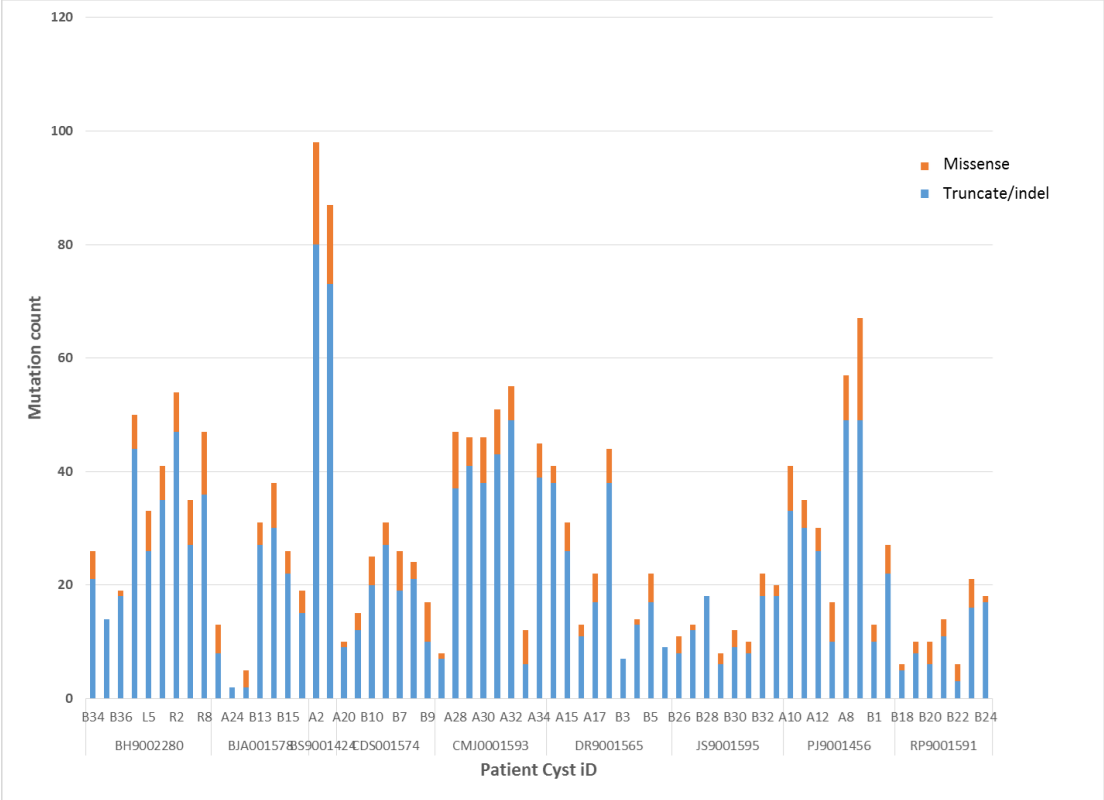


Figure S6. Illustration of the data analysis pipelines. Listed are the analysis steps and the corresponding software/application programs involved.

Supplemental Figure 7

a.



b.

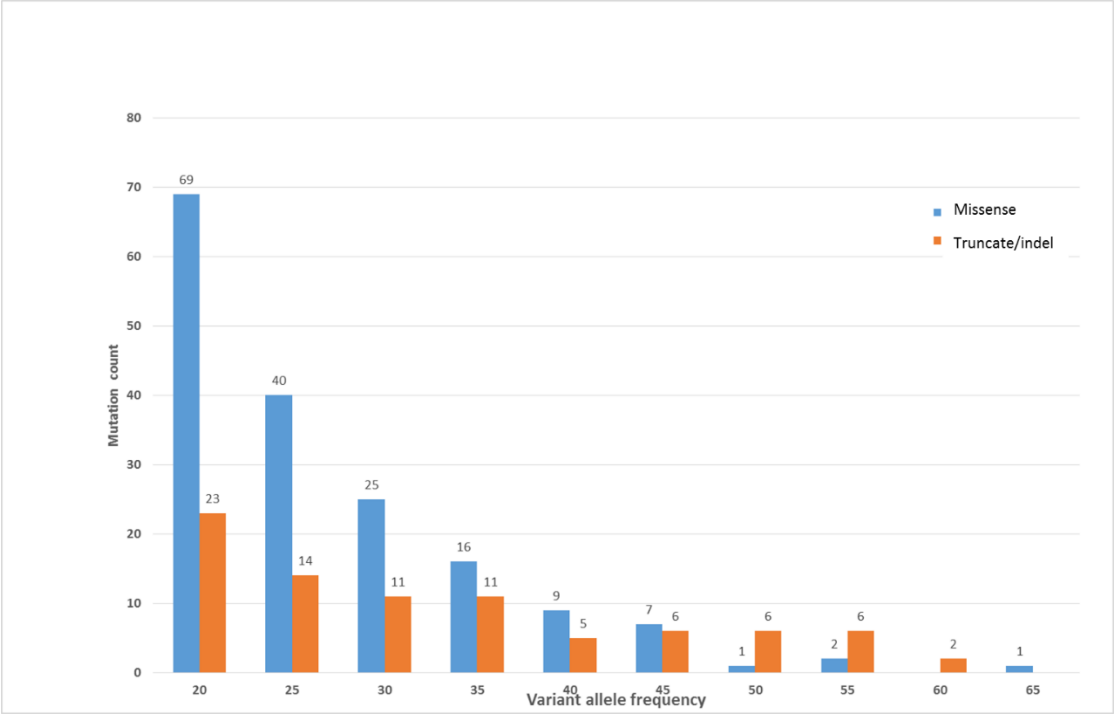


Figure S7. Distribution of significant somatic alterations in patients' cysts samples. (a) Distribution of missense (CADD≥15) and truncation/inframe indels in each cyst by mutation count (a), and (b) mutation count variant allele frequency (VAF). Only mutation with VAF ≥20% are shown. Missesne and truncation/indel alterations are colored in blue and orange, accordingly.

SUPPLEMENTAL TABLES

Supplemental Table 1. Summary of constitutional mutations in study cohort (n=9)

Case ID	Gene	Exon	Constitutional mutation	Mutation type	Mutation designation
BS9001424	*PKD1*	Exon 15	c.4745 G>C, p.W1582S (CADD=26.3)	Missense	Probable pathogenic
PJ9001456	*PKD1*	Exon 15	c.6364delG, p.V2122fs*3	Frameshift	Pathogenic
DR9001565	*PKD1*	Exon 27	c.9504C>G, p.F3168L(CADD=27)	Missense	Probable pathogenic
CDS001574	*PKD1*	Exon 31	c.10084delC, p.Q3362fs*35	Frameshift	Pathogenic
BJA001578	*PKD1*	Exon 15	c.3929_3930het_delAC, P.D1310Gfs*120	Frameshift	Pathogenic
CMJ001593	*PKD1*	Exon 43	c.10406_10407insG, p.E3469fs*2	Frameshift	Pathogenic
RP9001591	*PKD1*	Exon 35	c.G10549T, p.E3517X	Nonsense	Pathogenic
JS9001595	*PKD1*	Exon 15	c.6743_6744dupA, p.N2248Kfs*14	Frameshift	Pathogenic
BH9002280	*PKD2*	Exon 4	c.923het_delT, p.F308Sfs*9	Frameshift	Pathogenic

Supplemental Table 2. *PKD* gene sequence analysis summary statistics of cysts analyzed

Patient ID	Mutated gene	Sequence Analysis (Total)	WES	Mutation-positive cysts (WES)	LR-NGS/ Sanger sequencing	Mutation-positive cysts (LR-PCR sequencing)	Overall mutation detection rate
BS9001424	*PKD1*	10	2	1	10	9	90%
PJ9001456	*PKD1*	12	8	3	12	10	83%
DR9001565	*PKD1*	11	9	3	7	7	100%
CDS001574	*PKD1*	8	7	3	5	5	100%
BJA001578	*PKD1*	10	7	2	9	7	78%
CMJ001593	*PKD1*	8	8	4	6	6	100%
RP9001591	*PKD1*	7	7	2	3	3	100%
JS9001595	*PKD1*	8	8	2	2	2	100%
BH9002280	*PKD2*	9	9	9	9	8	89%
	Total	83	65	29	63	57	90%

Supplemental Table 3. Summary of constitutional and somatic mutations in *PKD1/2* genes detected by LR-PCR sequencing and WES in individual renal cysts by subject (N=9)

Case ID/Gene	Cyst ID	WES ID	Cyst diam	Constitutional mutation	Exon	Somatic mutation (LR-PCR Sanger)	Exon/ Intron	Detected by WES (Yes/No)	Cov Depth	VAF
BS9001424	***L1**		**5**	**c.4745 G>C,p.W1582S**	**Exon 15**	**ND**	__	**NT**		
PKD1	*L2		1	c.4745 G>C,p.W1582S	Exon 15	c.4798dup , p.T1600Asnfs*15	Exon 15	NT		
	*L3		2	c.4745 G>C,p.W1582S	Exon 15	c.12216_12217del, p.Thr4073Profs*83	Exon 45	NT		
	L4	A2	2.5	c.4745 G>C,p.W1582S	Exon 15	c.348_352del , p.Asn116Lysfs*2	Exon 3	No		
	*L5		1.5	c.4745 G>C,p.W1582S	Exon 15	c.3225del , p.Pro1076Argfs*28	Exon14	NT		
	*L6		2	c.4745 G>C,p.W1582S	Exon 15	c.348_352del , p.Asn116Lysfs*2	Exon 3	NT		
	R1	A3	3	c.4745 G>C,p.W1582S	Exon 15	c.11888G>A, p.Trp3963*	Exon 43	Yes	18	0.56
	*R2		2	c.4745 G>C,p.W1582S	Exon 15	c.5395C>T, p.Gln1799*	Exon 15	NT		
	*R4		2.5	c.4745 G>C,p.W1582S	Exon 15	c.3162-2A>C	IVS 11	NT		
	*R5		1.5	c.4745 G>C,p.W1582S	Exon 15	c.4745 G>C,p.W1582S (LOH)	Exon 15	NT		
PJ9001456	**L1**		**4**	**c.6364delG:p.V2122fs**	**Exon 15**	**ND**	__	**NT**		
PKD1	L4	A7	4	c.6364delG:p.V2122fs	Exon 15	c.6364delG:p.V2122fs (LOH)	Exon 15	No	^(804)	-0.92
	L5	A8	5.5	c.6364delG:p.V2122fs	Exon 15	c.348_352del, p.Asn116Lysfs*2	Exon 3	No	^(793)	-0.29
	L6	A9	4	c.6364delG:p.V2122fs	Exon 15	c.12006_12010del, p.Gln4004Alafs*151	Exon 44	No		
	L7		3	c.6364delG:p.V2122fs	Exon 15	c.8016+1del	Exon 21	Yes	12 ^(316 x)	0.5 -0.42
	L10	A10	5	c.6364delG:p.V2122fs	Exon 15	c.7655_7658 delinsTTG, p.Ala2552Valfs*68	Exon 19	No	^(779 x)	-0.32
	L11	A11	2.5	c.6364delG:p.V2122fs	Exon 15	c.3745del, p.Asp1249Thrfs*24	Exon 15	No	^(671 x)	-0.23
	L12		2.5	c.6364delG:p.V2122fs	Exon 15	c.6364delG:p.V2122fs (LOH)	Exon 15	NT	^(638 x)	-0.9
	*L15		7	c.6364delG:p.V2122fs	Exon 15	c.1284_1292del, p.Trp429_Gln431del	Exon 6	NT	^(748 x)	-0.3
	R4	B1	3.1	c.6364delG:p.V2122fs	Exon 15	c.3831_3847del, p.Ser1278Glyfs*17	Exon 15	No		
	R7	B2	2.5	c.6364delG:p.V2122fs	Exon 15	c.12004-2_12019del (splice_acceptor)	Exon 44	Yes	193	0.23
	R16	**A12**	**6**	**c.6364delG:p.V2122fs**	**Exon 15**	**ND**	__	**No**		
DR9001565	L1	A14	8	c.9504C>G,p.F3168L	Exon 27	NT	__	No		

PKD1	*L3	A15	4	c.9504C>G,p.F3168L	Exon 27	#c.9504C>G,p.F3168L (LOH)	Exon 27	No		
	L5	B3	3.5	c.9504C>G,p.F3168L	Exon 27	c.8935_8937delTTC, p.Phe2979del	Exon 24	Yes	30	0.27
	L6	B4	5	c.9504C>G,p.F3168L	Exon 27	NT		No		
	L7	B5	2	c.9504C>G,p.F3168L	Exon 27	c.5395C>T, p.Gln1799*	Exon 15	Yes	41	0.34
	L10	B6	3.5	c.9504C>G,p.F3168L	Exon 27	NT		No		
	R8	A16	6	c.9504C>G,p.F3168L	Exon 27	c.2157del, p.His719Glnfs*66	Exon 11	No		
	R9		4	c.9504C>G,p.F3168L	Exon 27	c.1789del, p.Gln597Argfs*188	Exon 9	NT		
					Exon 27	c.4916dup, p.Gly1640Argfs*18	Exon 15			
	R10		3.5	c.9504C>G,p.F3168L	Exon 27	c.5180del, p.Pro1727Argfs*32	Exon 15	NT		
	R13	A17	3	c.9504C>G,p.F3168L	Exon 27	c.12711C>A, p.Tyr4237*	Exon 46	Yes	39	0.28
	R14	A18	2.5	c.9504C>G,p.F3168L	Exon 27	NT		No		
CDS001574	L2	B7	4	PKD1 c.10084del , p.Gln3362Serfs*35	Exon 22	c.10314_10315insGCTGGCA, p.Arg3439Alafs*34	Exon 33	Yes	157	0.22
PKD1	L4	B8	4	PKD1 c.10084del , p.Gln3362Serfs*35	Exon 22	NT	__	No		
	L6	B9	2	PKD1 c.10084del , p.Gln3362Serfs*35	Exon 22	NT	__	No		
	*L9	A20	1.5	PKD1 c.10084del , p.Gln3362Serfs*35	Exon 22	c.348_352del, p.Asn116Lysfs*2	Exon 3	No		
	R6	A21	3	PKD1 c.10084del , p.Gln3362Serfs*35	Exon 22	c.11887G>A, p.Trp3939*	Exon 43	Yes	27	0.56
	R8	B10	1.5	PKD1 c.10084del , p.Gln3362Serfs*35	Exon 22	NT	__	No		
	R9		2.5	PKD1 c.10084del , p.Gln3362Serfs*35	Exon 22	c.11884_11912del, p.Gln3962Alafs*5	Exon 43	NT		
	R10	B12	2.5	PKD1 c.10084del , p.Gln3362Serfs*35	Exon 22	c.10084del, p.Gln3362Serfs*35 (LOH)	Exon 22	Yes		
BJA001578	L3	B13	10	c.3929_3930del, p.Asp1310Glyfs*120	Exon 15	c.6558_6568del, p.Trp2187Serfs*71	Exon 15	No		
PKD1	L4	B14	4	c.3929_3930del, p.Asp1310Glyfs*120	Exon 15	c.10948delC, p.His3650Thrfs*34	Exon 37	Yes	118	0.15
	L7	B15	2	c.3929_3930del, p.Asp1310Glyfs*120	Exon 15	NT	__	No		
	L8	B16	5	c.3929_3930del, p.Asp1310Glyfs*120	Exon 15	c.10319del, p.Gly3440Alafs*33/ CNV*	Exon 33	No		
	R2		**3**	**c.3929_3930del, p.Asp1310Glyfs*120**	**Exon 15**	**ND**	__	**NT**		
	R4	A23	2	c.3929_3930del, p.Asp1310Glyfs*120	Exon 15	c.1551_1560dup, p.Leu521*	Exon 7	Yes	10	0.8
	R10		2.5	c.3929_3930del, p.Asp1310Glyfs*120	Exon 15	c.412C>T, p.ArgR138*	Exon 4	NT		
	R11	A24	3	c.3929_3930del, p.Asp1310Glyfs*120	Exon 15	#c.3929_3930del, p.Asp1310Glyfs*120 (LOH)	Exon 15	Yes	12	1

	R13	**A25**	**3**	**c.3929_3930del, p.Asp1310Glyfs*120**	**Exon 15**	**ND**		**No**		
	R16		3	c.3929_3930del, p.Asp1310Glyfs*120	Exon 15	c.12707T>A, p.Val4236Asp	Exon 46	NT		
CMJ001593	L1	A27	10	c.10406_10407insG, p.Asp3469Glufs*2	Exon 34	NT	__	No		
PKD1	L2	A28	4	c.10406_10407insG, p.Asp3469Glufs*2	Exon 34	c.6994_7000dup, p.Val2334Glyfs*88	Exon 16	No		
	*L3	A29	4	c.10406_10407insG, p.Asp3469Glufs*2	Exon 34	c.6384C>A, p.Asn2128Lys	Exon 15	No		
	L10	A30	3.5	c.10406_10407insG, p.Asp3469Glufs*2	Exon 34	c.10977del, p.Glu3660Lysfs*24	Exon 37	Yes	58	0.22
	L11	A31	3	c.10406_10407insG, p.Asp3469Glufs*2	Exon 34	c.8815G>T, p.Glu2939*	Exon 24	Yes	46	0.22
	R1	A32	8	c.10406_10407insG, p.Asp3469Glufs*2	Exon 34	NT	__	No		
	R3	A33	2	c.10406_10407insG, p.Asp3469Glufs*2	Exon 34	c.11887G>A, p.Trp3939*	Exon 43	Yes	34	0.09
	R9	A34	2	c.10406_10407insG, p.Asp3469Glufs*2	Exon 34	c.11887G>A, p.Trp3939*	Exon 43	Yes	47	0.21
RP9001591	L2	B18	3	c.G10549T, p.E3517X	Exon 35	c.8996_8997insG, p.Phe2999Leufs*70	Exon 25	Yes	64	0.33
PKD1	L9	B19	3	c.G10549T, p.E3517X	Exon 35	NT	__	No		
	L10	B20	2	c.G10549T, p.E3517X	Exon 35	NT	__	No		
	*L11	B21	2.5	c.G10549T, p.E3517X	Exon 35	*c.G10549T, p.Glu3517* (LOH)	Exon 35	Yes	140	0.97
	L15	B22	1	c.G10549T, p.E3517X	Exon 35	NT	__	No		
	R10	B23	10	c.G10549T: p.E3517X	Exon 35	NT	__	No		
	R17	B24	7	c.G10549T , p.E3517X	Exon 35	c.1005delC, p.Val336Cysfs*129	Exon 5	Yes	38	0.21
JS9001595	L1	B26	7	c.6743_6744dup, p.Val2249Metfs*2	Exon 15	NT	__	No		
PKD1	L4	B27	7	c.6743_6744dup, p.Val2249Metfs*2	Exon 15	NT	__	No		
	L8	B28	3	c.6743_6744dup, p.Val2249Metfs*2	Exon 15	NT	__	No		
	L9	B29	1.5	c.6743_6744dup, p.Val2249Metfs*2	Exon 15	NT	__	No		
	R1	B30	5	c.6743_6744dup, p.Val2249Metfs*2	Exon 15	NT	__	No		
	R2	B31	4	c.6743_6744dup, p.Val2249Metfs*2	Exon 15	c.10220+2T>G (splice donor site)	IVS 5	Yes	39	0.46
	R9	B32	5	c.6743_6744dup, p.Val2249Metfs*2	Exon 15	NT	__	No		
	R10	B33	8	c.6743_6744dup, p.Val2249Metfs*2	Exon 15	c.3184C>T, p.Gln1062*	Exon 14	Yes	27	0.63
BH9002280	L1	B34	4	c.923del , p.Phe308Serfs*9	Exon 4	c.2409delA, p.Ser804Valfs*40	Exon 13	Yes	80	0.3
PKD2	L2	L2	5	c.923del , p.Phe308Serfs*9	Exon 4	c.242 C>A, p.Ser81*	Exon 1	Yes	14	0.57
	L5	L5	7	c.923del , p.Phe308Serfs*9	Exon 4	c.962 T>A, p.Ile321Lys	Exon 4	Yes	23	0.17
	L6	B35	4	c.923del , p.Phe308Serfs*9	Exon 4	c.1843G>A, p.Ala615Thr	Exon 8	Yes	22	0.18
	L9	B36	5	c.923del , p.Phe308Serfs*9	Exon 4	c.1258A>T, p.Arg420Trp	Exon 5	Yes	67	0.27

R1	**R1**	**6.5**	**c.923del , p.Phe308Serfs*9**	**Exon 4**	**ND**	__	**No**		
R2	R2	6.5	c.923del , p.Phe308Serfs*9	Exon 4	+c.1392A>G, p.=	Exon 6	Yes	32	0.34
R7	R7	7	c.923del , p.Phe308Serfs*9	Exon 4	c.1366 C>T, p.Gln456*	Exon 6	Yes	146	0.38
R8	R8	5	c.923del , p.Phe308Serfs*9	Exon 4	c.2682del, p.Gly895Valfs*14	Exon 15	Yes	55	0.11

*Tested by LR-PCR Sequencing (Sanger/NGS); NT, not tested; ND, mutation not detected (highlighted in bold);
L, Left kidney; R, Right kidney; Cyst diam, Cyst diameter

^LR-PCR NGS Coverage depth and VAF (patient PJ9001456). VAF, variant allele frequency.

#Flanking genomic regions show LOH (patients DR9001565, cyst L3/A15; BJA001578, cyst R11/A24; RP9001591 cyst L11/B21).

+Mutation (c.1392A>G, p.=) predicted to create a new donor splice site using splice site prediction tools (ESEfinder, NNSplice and Human splicing finder 3.1) with default settings as the following:

5' splicing site donor of human (U2 type); threshold: 6.67
Wt: score =0
Mut: score =6.72

NNSplice:
5' splicing site donor (score between: 0~1); threshold: 0.4
Wt: score =0
Mut: score =0.99

Human splicing finder (no threshold, but Ref score for both wt and mut sequence):
Wt_5' Motif Ref score= 1.02
Mut_5' Motif Ref score= 9.2

Supplemental Table 4. WES analysis quality metrics (n=55)

Patient ID	Sample WES ID	Total Reads	Captured Reads	% Captured Reads	Average Coverage	Fraction Covered >=10X
BS9001424	A2	59288140	46647670	79	79	95
	A3	60948808	51182719	84	81	95
PJ9001456	A7	61112704	51516100	84	81	94
	A8	64692576	52908950	82	86	95
	A9	57059740	48152933	84	76	94
	A10	56696466	48222269	85	77	94
	A11	58105432	49809367	86	79	93
	A12	53511126	44190577	83	73	93
	B1	75218576	61014391	81	100	96
	B2	69718392	56029475	80	92	96
DR9001565	A14	58622018	50119702	86	79	93
	A15	57994028	49533195	85	79	93
	A16	58038740	48101321	83	78	93
	A17	57663748	49069555	85	78	94
	A18	55774588	45270235	81	75	94
	B3	68230676	54114712	79	88	96
	B4	72135280	58102834	81	95	96
	B5	78874860	63768230	81	104	96
	B6	70553906	57460160	81	94	96
CDS001574	A20	55590492	46663285	84	74	94
	A21	60246768	47784210	79	80	95
	B7	72624574	58490167	81	95	96
	B8	74513118	60092508	81	98	96
	B9	68360776	57113523	84	91	96
	B10	69178470	56933333	82	92	96
	B12	74641886	61432923	82	98	96
BJA001578	A23	59382594	49963127	84	79	94
	A24	59782360	46468366	78	80	94
	A25	57531320	48098903	84	76	94
	B13	75934774	59548796	78	99	96
	B14	68692792	52338655	76	88	95
	B15	73866112	59247067	80	97	96
	B16	71212372	56576270	79	93	96
CMJ0001593	A27	60232948	50752932	84	80	95
	A28	65011266	53044127	82	87	94
	A29	69967054	54169683	77	92	95

	A30	66966870	54225024	81	89	95
	A31	64805090	52926697	82	86	94
	A32	71051458	59647035	84	95	95
	A33	66779892	55156803	83	89	94
	A34	67611950	56878603	84	91	95
BH9002280	L2	62389122	50012518	80	81	95
	L5	68866436	57674420	84	90	95
	R1	66089250	55482615	84	87	95
	R2	65830676	53939148	82	85	95
	R7	67064636	55703092	83	88	95
	R8	66508468	55034994	83	86	95
	B34	75648008	61277253	81	101	97
	B35	76221042	61680888	81	102	96
	B36	71463126	58499640	82	96	96
RP9001591	B18	70125512	56105924	80	92	96
	B19	74910468	60072054	80	99	96
	B20	74945990	60396940	81	99	96
	B21	73595282	59072274	80	97	96
	B22	76493664	62258955	81	102	96
	B23	72595400	58484269	81	96	96
	B24	72419496	58365628	81	96	96
JS9001595	B26	74871118	60357216	81	99	96
	B27	75409158	62195918	82	100	96
	B28	75977794	61275216	81	100	96
	B29	59530170	45746169	77	79	95
	B30	77272994	62133223	80	102	96
	B31	72114850	57032207	79	95	96
	B32	77055686	62202623	81	102	96
	B33	73808990	58468279	79	98	96
Average		67529724	55019045	81.6	89.5	95.2
SD		6989380	5241790	2.2	8.9	1.0

Supplemental Table 5. Classification of somatic alterations (SNV/indels) detected by WES in cyst renal epithelia (N=65)

Alteration type	Variant count
Frameshift	58
Nonsense	130
Splice	59
Inframe indel	59
Missense	1942
Synonymous	555
UTR/Flank	119
Intron/IGR	272
RNA	69
Total	3263

Supplemental Table 6. Pathogenic and likely pathogenic mutations by variant allele frequency

Patient-ID	Cyst ID	Missense (5-19% VAF)	Missense (20-29% VAF)	Missense (30-65% VAF)	Truncate/ inframe (5-19% VAF)	Truncate/ inframe (20-29% VAF)	Truncate/ inframe (30-65% VAF)	Total
BH9002280	B34	17	4		3	1	1	26
	B35	9	4	1				14
	B36	14	3	1	1			19
	L2	43	1		5		1	50
	L5	25		1	5	1	1	33
	R1	32	3		6			41
	R2	47			5	2		54
	R7	25	2		7	1		35
	R8	35	1		10		1	47
BJA001578	A23	7		1	4		1	13
	A24	2						2
	A25	2			3			5
	B13	24	3		3		1	31
	B14	27	2	1	6	2		38
	B15	19	3		2		2	26
	B16	7	6	2	1	1	2	19
BS9001424	A2	78	2		18			98
	A3	60	2	11	5		9	87
CDS001574	A20	8		1		1		10
	A21	12			1		2	15
	B10	15	4	1	1	2	2	25
	B12	22	5		1	1	2	31
	B7	11	5	3	2	5		26
	B8	15	5	1	2		1	24
	B9	8	1	1	3	3	1	17
CMJ0001593	A27	6	1		1			8
	A28	35	2		10			47
	A29	41			5			46
	A30	34	2	2	6	1	1	46
	A31	38	2	3	6	2		51
	A32	47	2		6			55
	A33	4		2	5	1		12
	A34	36	2	1	5	1		45
DR9001565	A14	38			3			41
	A15	23	2	1	4	1		31
	A16	11			1		1	13
	A17	16		1	2	2	1	22
	A18	37	1		6			44
	B3	5	1	1				7

	B4	10	1	2	1			14
	B5	13	2	2	4	1		22
	B6	8		1				9
JS9001595	B26	7		1	3			11
	B27	9	1	2			1	13
	B28	14	4					18
	B29	4	1	1	2			8
	B30	8	1		2	1		12
	B31	7	1				2	10
	B32	17	1		2		2	22
	B33	15	2	1	1		1	20
PJ9001456	A10	31	2		7		1	41
	A11	29		1	4		1	35
	A12	22	4		2	1	1	30
	A7	9		1	5	1	1	17
	A8	46	3		7	1		57
	A9	48	1		16		2	67
	B1	6	1	3	2		1	13
	B2	19	1	2	2	2	1	27
RP9001591	B18	2	2	1			1	6
	B19	6	2		2			10
	B20	3	1	2	3	1		10
	B21	6	4	1	2		1	14
	B22	3			2		1	6
	B23	13	1	2	4		1	21
	B24	12	2	3		1		18
Grand Total		1302	109	62	227	37	48	1785

Total (VAF >5%)-1785

Missense-1473

Truncation/inframe indel-312

Total (VAF >20%)-248

Missesne- 175

Truncation/inframe indel- 73

Supplemental Table 7. Significantly pathogenic (truncation/indels) and probably pathogenic (CADD score≥15) gene variations with VAF ≥20% among the renal cyst samples

Patient ID#	Cyst ID	Gene	CHR	Variant classification	HGVSc	HGVSp	Variant coverage	VAF	CADD score(PHRED)	Existing variation
BJA001578	A23	PKD1	chr16	Frame_Shift_Ins	c.1560_1561insTAACACCGAC	p.Leu521Ter	10	0.80	NA	
BJA001578	A23	C4orf21	chr4	Missense_Mutation	c.3919C>A	p.His1307Asn	15	0.40	28.3	COSM145050
BJA001578	B13	B3GNT3	chr19	In_Frame_Ins	c.156_157insCCCCCC	p.Pro52_Pro53insProPro	28	0.61	NA	
BJA001578	B13	ACTR3	chr2	Missense_Mutation	c.433G>T	p.Ala145Ser	20	0.25	24.8	
BJA001578	B13	ARID1A	chr1	Missense_Mutation	c.920G>T	p.Gly307Val	8	0.25	22	
BJA001578	B13	FCHSD2	chr11	Missense_Mutation	c.2158C>A	p.Pro720Thr	26	0.23	29	
BJA001578	B13	LRCH1	chr13	Missense_Mutation	c.711G>T	p.Lys237Asn	51	0.20	27.4	
BJA001578	B14	STK19	chr6	Missense_Mutation	c.328G>T	p.Asp110Tyr	42	0.31	19.46	
BJA001578	B14	GSR	chr8	Splice_Site	c.422+1G>T		22	0.27	27.6	
BJA001578	B14	TIAM2	chr6	Missense_Mutation	c.494C>T	p.Thr165Met	76	0.25	24	rs375863554
BJA001578	B14	HS2ST1	chr1	Nonsense_Mutation	c.997C>T	p.Arg333Ter	9	0.22	40	COSM912858
BJA001578	B14	NMI	chr2	Missense_Mutation	c.194C>A	p.Pro65His	9	0.22	28.4	
BJA001578	B15	KDM6B	chr17	In_Frame_Del	c.2253_2258delCACCAC	p.Thr754_Thr755del	86	0.40	NA	rs377654044 COSM985382
BJA001578	B15	RAB30	chr11	Missense_Mutation	c.203A>C	p.Gln68Pro	20	0.25	26.5	
BJA001578	B15	ABTB1	chr3	Missense_Mutation	c.112A>C	p.Thr38Pro	20	0.25	25.9	
BJA001578	B15	NF1	chr17	Missense_Mutation	c.3245G>T	p.Gly1082Val	44	0.23	29	
BJA001578	B16	SMARCAD1	chr4	Missense_Mutation	c.2572T>C	p.Phe858Leu	66	0.48	23	
BJA001578	B16	PKD1	chr16	Missense_Mutation	c.6485G>A	p.Arg2162Gln	753	0.35	25.8	
BJA001578	B16	KDM6B	chr17	In_Frame_Del	c.2253_2258delCACCAC	p.Thr754_Thr755del	76	0.33	NA	rs377654044 COSM985382
BJA001578	B16	IGSF9B	chr11	Missense_Mutation	c.1427G>A	p.Arg476His	87	0.28	28	
BJA001578	B16	GFPT1	chr2	Splice_Site	c.1010-2A>C		38	0.26	25.2	
BJA001578	B16	GPR1	chr2	Missense_Mutation	c.183G>T	p.Trp61Cys	8	0.25	29.4	
BJA001578	B16	CST2	chr20	Missense_Mutation	c.232G>T	p.Val78Leu	20	0.25	24.2	rs141816898 COSM1202533
BJA001578	B16	DNAH5	chr5	Missense_Mutation	c.7009C>T	p.Leu2337Phe	29	0.24	27.6	
BJA001578	B16	EML3	chr11	Missense_Mutation	c.2246A>C	p.Glu749Ala	52	0.21	27.6	
BJA001578	B16	NF1	chr17	Missense_Mutation	c.3244G>T	p.Gly1082Cys	29	0.21	29.8	

BS9001424	A2	NOX5	chr15	Missense_Mutation	c.844A>C	p.Ser282Arg	24	0.29	23.9	rs150003957 COSM964378
BS9001424	A2	TIGD2	chr4	Missense_Mutation	c.653C>A	p.Thr218Lys	14	0.21	25.2	
BS9001424	A3	USP51	chrX	Frame_Shift_Del	c.663_666delTGGG	p.Ser221ArgfsTer22	32	0.59	NA	
BS9001424	A3	INSIG2	chr2	Missense_Mutation	c.83T>G	p.Leu28Trp	61	0.57	26.5	
BS9001424	A3	NAA15	chr4	Frame_Shift_Del	c.175delA	p.Ile59SerfsTer34	48	0.56	NA	rs375319596
BS9001424	A3	PKD1	chr16	Nonsense_Mutation	c.11888G>A	p.Trp3963Ter	18	0.56	41	
BS9001424	A3	C1orf74	chr1	Nonsense_Mutation	c.23C>A	p.Ser8Ter	101	0.53	36	
BS9001424	A3	BCOR	chrX	Missense_Mutation	c.4690A>G	p.Arg1564Gly	76	0.51	31	
BS9001424	A3	PSME4	chr2	In_Frame_Del	c.4821_4832delCCCAGTGGAAAA	p.Pro1608_Asn1611del	20	0.50	NA	
BS9001424	A3	EMX2	chr10	Missense_Mutation	c.651A>T	p.Glu217Asp	56	0.48	19.56	
BS9001424	A3	ELP3	chr8	Splice_Site	c.1486-1G>T		77	0.48	21.1	
BS9001424	A3	WARS2	chr1	Missense_Mutation	c.404G>T	p.Arg135Leu	46	0.48	35	rs147962776
BS9001424	A3	PAPD7	chr5	In_Frame_Del	c.1371_1373delGTC	p.Met457_Ser458delinsIle	204	0.48	NA	
BS9001424	A3	SIDT1	chr3	Missense_Mutation	c.2269G>A	p.Ala757Thr	17	0.47	34	COSM201721
BS9001424	A3	RAB23	chr6	Missense_Mutation	c.398A>T	p.Asn133Ile	110	0.46	22.8	
BS9001424	A3	ITGA7	chr12	Missense_Mutation	c.386G>A	p.Arg129Gln	91	0.46	19.41	rs376167554
BS9001424	A3	ZBTB40	chr1	Frame_Shift_Del	c.435_436delAG	p.Gln145HisfsTer7	47	0.45	NA	
BS9001424	A3	DMXL1	chr5	Missense_Mutation	c.4099C>A	p.His1367Asn	52	0.44	15.66	
BS9001424	A3	CRYZ	chr1	Frame_Shift_Del	c.411_414delTCGA	p.Tyr137Ter	143	0.40	NA	
BS9001424	A3	NCOR1	chr17	Missense_Mutation	c.5506G>A	p.Val1836Met	66	0.39	24.9	
BS9001424	A3	QRICH2	chr17	Missense_Mutation	c.4226C>T	p.Ala1409Val	43	0.33	21.4	
BS9001424	A3	NOX5	chr15	Missense_Mutation	c.844A>C	p.Ser282Arg	25	0.32	23.9	rs150003957 COSM964378
BS9001424	A3	MTBP	chr8	Missense_Mutation	c.365G>T	p.Gly122Val	13	0.23	16.47	
BS9001424	A3	SIGIRR	chr11	Missense_Mutation	c.1082C>A	p.Pro361His	49	0.22	24.8	
CDS001574	A20	SPTY2D1	chr11	Missense_Mutation	c.2044C>G	p.Leu682Val	46	0.30	20.8	
CDS001574	A20	BCAR3	chr1	Nonsense_Mutation	c.895C>T	p.Arg299Ter	10	0.20	38	
CDS001574	A21	PKD1	chr16	Nonsense_Mutation	c.11817G>A	p.Trp3939Ter	27	0.56	39	
CDS001574	A21	CNDP1	chr18	In_Frame_Ins	c.43_44insTGC	p.Val15_Leu16insLeu	26	0.46	NA	rs10663835 COSM307404
CDS001574	B10	TINAGL1	chr1	Missense_Mutation	c.961C>T	p.Arg321Cys	64	0.38	34	
CDS001574	B10	OXR1	chr8	Splice_Site	c.1960-1G>T		17	0.29	26	

CDS001574	B10	WDFY3	chr4	Missense_Mutation	c.2039A>C	p.Gln680Pro	17	0.29	16.39	
CDS001574	B10	CFH	chr1	Missense_Mutation	c.3029C>T	p.Ala1010Val	92	0.29	17.6	
CDS001574	B10	TRRAP	chr7	Missense_Mutation	c.2440C>G	p.Pro814Ala	67	0.27	24.1	
CDS001574	B10	PPIL6	chr6	Nonsense_Mutation	c.244G>T	p.Glu82Ter	19	0.26	37	
CDS001574	B10	DNAH5	chr5	Missense_Mutation	c.5340G>T	p.Met1780Ile	29	0.21	16.41	
CDS001574	B12	SNX8	chr7	Nonsense_Mutation	c.910C>T	p.Gln304Ter	66	0.44	36	
CDS001574	B12	AKT2	chr19	Missense_Mutation	c.1016T>G	p.Val339Gly	14	0.29	27.1	
CDS001574	B12	INTS9	chr8	Missense_Mutation	c.269T>G	p.Leu90Arg	33	0.24	27.4	
CDS001574	B12	RAB30	chr11	Missense_Mutation	c.203A>C	p.Gln68Pro	25	0.24	26.5	
CDS001574	B12	SLC14A2	chr18	Missense_Mutation	c.2548A>C	p.Asn850His	21	0.24	22.2	
CDS001574	B12	UPF2	chr10	Nonsense_Mutation	c.257C>A	p.Ser86Ter	59	0.20	36	
CDS001574	B12	PCDHA13	chr5	Missense_Mutation	c.88C>A	p.Gln30Lys	10	0.20	23.7	
CDS001574	B7	WDFY3	chr4	Missense_Mutation	c.2039A>C	p.Gln680Pro	13	0.38	16.39	
CDS001574	B7	SON	chr21	Missense_Mutation	c.331C>A	p.His111Asn	32	0.38	23.3	
CDS001574	B7	AKT2	chr19	Missense_Mutation	c.1016T>G	p.Val339Gly	13	0.31	27.1	
CDS001574	B7	CCDC180	chr9	Splice_Site	c.1921-1G>A		27	0.26	24.7	
CDS001574	B7	MMP8	chr11	Nonsense_Mutation	c.880G>T	p.Glu294Ter	28	0.25	41	
CDS001574	B7	ALDH5A1	chr6	Missense_Mutation	c.815G>T	p.Cys272Phe	20	0.25	27.3	
CDS001574	B7	CEP164	chr11	Frame_Shift_Del	c.337delA	p.Lys116ArgfsTer22	25	0.24	NA	rs75301270 COSM1351515
CDS001574	B7	GABRA6	chr5	Missense_Mutation	c.850A>C	p.Thr284Pro	21	0.24	26.9	
CDS001574	B7	DROSHA	chr5	Missense_Mutation	c.3007A>C	p.Ile1003Leu	17	0.24	23	COSM1186750
CDS001574	B7	INTS9	chr8	Missense_Mutation	c.269T>G	p.Leu90Arg	31	0.23	27.4	
CDS001574	B7	PKD1	chr16	Frame_Shift_Ins	c.10314_10315insGCTGGCA	p.Arg3439AlafsTer34	157	0.22	NA	
CDS001574	B7	TFAM	chr10	Frame_Shift_Del	c.432delA	p.Glu148SerfsTer2	28	0.21	NA	rs78912196 COSM1348365
CDS001574	B7	DGAT2	chr11	Missense_Mutation	c.272T>G	p.Leu91Arg	59	0.20	23.1	
CDS001574	B8	PRR12	chr19	Missense_Mutation	c.5284G>A	p.Gly1762Arg	86	0.37	19.09	
CDS001574	B8	CST2	chr20	Missense_Mutation	c.232G>T	p.Val78Leu	17	0.29	24.2	rs141816898 COSM1202533
CDS001574	B8	SEC24D	chr4	Missense_Mutation	c.1735A>C	p.Ile579Leu	31	0.26	20.9	
CDS001574	B8	SLC14A2	chr18	Missense_Mutation	c.2548A>C	p.Asn850His	16	0.25	22.2	
CDS001574	B8	AMBRA1	chr11	Missense_Mutation	c.143A>C	p.Glu48Ala	17	0.24	27	
CDS001574	B8	LRCH1	chr13	Missense_Mutation	c.706G>T	p.Val236Leu	56	0.23	29.1	
CDS001574	B8	LRCH1	chr13	Missense_Mutation	c.705G>T	p.Leu235Phe	56	0.20	28.5	
CDS001574	B9	LRCH1	chr13	Missense_Mutation	c.705G>T	p.Leu235Phe	65	0.31	28.5	
CDS001574	B9	FAM155B	chrX	In_Frame_Del	c.54_56delCTG	p.Cys20del	26	0.27	NA	rs374286243
CDS001574	B9	NUP155	chr5	Missense_Mutation	c.1196C>A	p.Ser399Tyr	14	0.21	29.6	COSM1218072
CDS001574	B9	TP53I11	chr11	Splice_Site	c.335-2A>C		34	0.21	24.7	

CMJ001593	A27	MEDAG	chr13	Missense_Mutation	c.68G>A	p.Arg23His	15	0.27	28.5	rs71436423 COSM432293
CMJ001593	A28	BAI1	chr8	Missense_Mutation	c.1004G>T	p.Arg335Leu	8	0.25	23	
CMJ001593	A28	DNMT3A	chr2	Missense_Mutation	c.1439T>G	p.Val480Gly	50	0.22	27.4	rs200099128
CMJ001593	A30	PARP14	chr3	Missense_Mutation	c.2768C>A	p.Ser923Tyr	79	0.32	26	
CMJ001593	A30	ZG16	chr16	Missense_Mutation	c.157C>T	p.Arg53Trp	64	0.31	30	
CMJ001593	A30	ANKK1	chr11	Nonsense_Mutation	c.754C>T	p.Gln252Ter	52	0.31	26.8	
CMJ001593	A30	ITGB1	chr10	Missense_Mutation	c.1667A>G	p.Asp556Gly	104	0.25	32	
CMJ001593	A30	PKDCC	chr2	Missense_Mutation	c.911C>T	p.Thr304Met	92	0.23	23.4	rs150069795
CMJ001593	A30	PKD1	chr16	Frame_Shift_Del	c.10980delA	p.Ala3661ProfsTer23	58	0.22	NA	
CMJ001593	A31	PNISR	chr6	Missense_Mutation	c.1651T>C	p.Ser551Pro	12	0.67	22.9	
CMJ001593	A31	CCT4	chr2	Missense_Mutation	c.814A>T	p.Met272Leu	27	0.56	25.9	
CMJ001593	A31	EVI5	chr1	Missense_Mutation	c.1327A>T	p.Ile443Phe	41	0.44	25.1	
CMJ001593	A31	PTGER1	chr19	Missense_Mutation	c.571G>T	p.Gly191Cys	8	0.25	26.7	
CMJ001593	A31	PTGER1	chr19	Missense_Mutation	c.596G>T	p.Arg199Leu	8	0.25	22.9	
CMJ001593	A31	MN1	chr22	Nonsense_Mutation	c.3029G>A	p.Trp1010Ter	36	0.22	39	
CMJ001593	A31	PKD1	chr16	Nonsense_Mutation	c.8815G>T	p.Glu2939Ter	46	0.22	39	
CMJ001593	A32	MAGED2	chrX	Missense_Mutation	c.905G>T	p.Arg302Leu	16	0.25	32	COSM191867
CMJ001593	A32	MCM4	chr8	Missense_Mutation	c.2019C>A	p.Ser673Arg	10	0.20	20.9	
CMJ001593	A33	MVP	chr16	Missense_Mutation	c.1807G>A	p.Val603Ile	51	0.45	26	
CMJ001593	A33	CWF19L2	chr11	Missense_Mutation	c.1880G>T	p.Gly627Val	84	0.40	23	
CMJ001593	A33	TSHZ1	chr18	Nonsense_Mutation	c.1564C>T	p.Gln522Ter	70	0.29	36	
CMJ001593	A34	SMARCAD1	chr4	Missense_Mutation	c.2572T>C	p.Phe858Leu	22	0.41	23	
CMJ001593	A34	DNMT3A	chr2	Missense_Mutation	c.1439T>G	p.Val480Gly	42	0.24	27.4	rs200099128
CMJ001593	A34	PKD1	chr16	Nonsense_Mutation	c.11817G>A	p.Trp3939Ter	47	0.21	39	
CMJ001593	A34	TCP1	chr6	Missense_Mutation	c.269C>A	p.Thr90Asn	15	0.20	27.7	
DR9001565	A15	C1QL2	chr2	Missense_Mutation	c.590G>T	p.Cys197Phe	10	0.30	31	
DR9001565	A15	FER	chr5	Missense_Mutation	c.2248C>T	p.Leu750Phe	24	0.29	31	
DR9001565	A15	CEP164	chr11	Frame_Shift_Del	c.337delA	p.Lys116ArgfsTer22	58	0.21	NA	rs75301270 COSM1351515
DR9001565	A15	WIZ	chr19	Missense_Mutation	c.1112G>T	p.Arg371Leu	10	0.20	23.2	
DR9001565	A16	THRAP3	chr1	Nonsense_Mutation	c.2701C>T	p.Arg901Ter	9	0.33	41	
DR9001565	A17	DOCK4	chr7	Frame_Shift_Del	c.4286_4287delAA	p.Lys1429ArgfsTer3	124	0.39	NA	
DR9001565	A17	CASC5	chr15	Missense_Mutation	c.4886C>T	p.Thr1629Ile	29	0.38	17.62	
DR9001565	A17	PKD1	chr16	Nonsense_Mutation	c.12711C>A	p.Tyr4237Ter	39	0.28	38	CM003948
DR9001565	A18	PCDHGB6	chr5	Missense_Mutation	c.1415C>A	p.Ala472Glu	14	0.29	20.8	
DR9001565	B3	ACSS1	chr20	Missense_Mutation	c.500G>A	p.Arg167His	12	0.42	31	
DR9001565	B3	TIA1	chr2	Missense_Mutation	c.199A>C	p.Asn67His	20	0.25	26.5	

DR9001565	B4	KIF17	chr1	Missense_Mutation	c.3002G>C	p.Arg1001Pro	15	0.33	34	COSM182818
DR9001565	B4	PKD1	chr16	Missense_Mutation	c.6282G>T	p.Trp2094Cys	9	0.33	26.8	
DR9001565	B4	SEC24D	chr4	Missense_Mutation	c.1787G>T	p.Arg596Ile	36	0.25	34	
DR9001565	B4	KCNC3	chr19	3'UTR	c.*81A>C		20	0.25	19.57	
DR9001565	B5	WRNIP1	chr6	Missense_Mutation	c.1120G>A	p.Val374Met	80	0.33	32	
DR9001565	B5	PADI4	chr1	Missense_Mutation	c.979G>C	p.Ala327Pro	69	0.30	23.8	rs145819522
DR9001565	B5	ODF3L2	chr19	Frame_Shift_Ins	c.577_578insC	p.Arg193ProfsTer8	31	0.26	NA	
DR9001565	B5	NOD2	chr16	Missense_Mutation	c.1057T>A	p.Cys353Ser	13	0.23	16.44	
DR9001565	B5	RYR3	chr15	Missense_Mutation	c.9831A>T	p.Arg3277Ser	73	0.22	27.2	
DR9001565	B6	UBE3C	chr7	Missense_Mutation	c.1332G>T	p.Arg444Ser	16	0.31	23.2	
JS9001595	B26	LILRB5	chr19	Missense_Mutation	c.1652A>C	p.Gln551Pro	17	0.35	16.26	
JS9001595	B27	ZNF518B	chr4	Missense_Mutation	c.641A>C	p.Glu214Ala	45	0.96	27.7	
JS9001595	B27	PNPLA6	chr19	Splice_Site	c.2966+2T>G		17	0.35	24.9	
JS9001595	B27	MYOM3	chr1	Missense_Mutation	c.3751A>C	p.Lys1251Gln	20	0.30	23.2	
JS9001595	B27	POLR3E	chr16	Missense_Mutation	c.1459C>T	p.Arg487Trp	166	0.20	17.53	
JS9001595	B28	EPG5	chr18	Missense_Mutation	c.1906T>G	p.Tyr636Asp	36	0.28	26.3	
JS9001595	B28	XPNPEP2	chrX	Missense_Mutation	c.1100C>A	p.Ala367Asp	11	0.27	18.56	
JS9001595	B28	SC5D	chr11	Missense_Mutation	c.439T>G	p.Tyr147Asp	48	0.25	31	
JS9001595	B28	UBR7	chr14	Missense_Mutation	c.246T>G	p.Cys82Trp	39	0.23	27.1	
JS9001595	B29	PCSK5	chr9	Missense_Mutation	c.1312G>T	p.Val438Leu	13	0.31	26.8	
JS9001595	B29	PAPSS2	chr10	Missense_Mutation	c.377C>A	p.Ala126Glu	20	0.20	15.35	
JS9001595	B30	CHD8	chr14	Missense_Mutation	c.1478G>A	p.Arg493Gln	10	0.20	22.3	
JS9001595	B31	PKD1	chr16	Splice_Site	c.10220+2T>G		39	0.46	23.2	
JS9001595	B31	KCNC3	chr19	3'UTR	c.*81A>C		16	0.44	19.57	
JS9001595	B31	POTEJ	chr2	Missense_Mutation	c.3103C>T	p.Arg1035Cys	9	0.22	31	
JS9001595	B32	CRCP	chr7	Splice_Site	c.145-1G>T		19	0.32	23.7	
JS9001595	B32	TOX3	chr16	Missense_Mutation	c.1147A>G	p.Ile383Val	289	0.23	20.8	
JS9001595	B33	PKD1	chr16	Nonsense_Mutation	c.3184C>T	p.Gln1062Ter	27	0.63	35	
JS9001595	B33	ANGPTL3	chr1	Missense_Mutation	c.124G>C	p.Asp42His	73	0.40	28.4	rs199772471
JS9001595	B33	LILRB5	chr19	Missense_Mutation	c.1652A>C	p.Gln551Pro	17	0.29	16.26	
JS9001595	B33	PCSK5	chr9	Missense_Mutation	c.1312G>T	p.Val438Leu	23	0.22	26.8	
BH9002280	B34	PKD2	chr4	Frame_Shift_Del	c.2409delA	p.Ser804ValfsTer40	80	0.30	NA	
BH9002280	B34	MYT1	chr20	Silent	c.2538G>A	p.=	78	0.26	15.84	
BH9002280	B34	ZNF142	chr2	Missense_Mutation	c.4499G>A	p.Arg1500Gln	9	0.22	35	COSM214198
BH9002280	B34	MKNK2	chr19	Missense_Mutation	c.434T>C	p.Leu145Pro	36	0.22	27.5	
BH9002280	B34	PRUNE2	chr9	Missense_Mutation	c.9086G>T	p.Ser3029Ile	29	0.21	32	

BH9002280	B34	IGF1R	chr15	Missense_Mutation	c.311C>A	p.Thr104Lys	10	0.20	32	
BH9002280	B35	CEP97	chr3	Missense_Mutation	c.1142A>T	p.Asp381Val	33	0.30	23.2	
BH9002280	B35	MYBPC3	chr11	Missense_Mutation	c.917G>C	p.Arg306Pro	23	0.26	21	rs373204728 COSM1475467
BH9002280	B35	MYO18A	chr17	Missense_Mutation	c.3613C>T	p.Arg1205Cys	9	0.22	35	
BH9002280	B35	PRRC2B	chr9	Missense_Mutation	c.1997A>C	p.Gln666Pro	27	0.22	25.6	
BH9002280	B35	LAMP1	chr13	Missense_Mutation	c.430G>T	p.Asp144Tyr	40	0.20	26.1	
BH9002280	B36	NXNL1	chr19	Missense_Mutation	c.577C>G	p.Arg193Gly	9	0.44	23.2	
BH9002280	B36	PKD2	chr4	Missense_Mutation	c.1258A>T	p.Arg420Trp	67	0.27	27.7	CM044694
BH9002280	B36	WDFY3	chr4	Missense_Mutation	c.2029A>C	p.Asn677His	16	0.25	24.3	
BH9002280	B36	PIP5K1C	chr19	Missense_Mutation	c.1144G>A	p.Ala382Thr	9	0.22	31	
BH9002280	L2	PKD2	chr4	Nonsense_Mutation	c.242C>A	p.Ser81Ter	14	0.57	36	
BH9002280	L2	DYNC2H1	chr11	Missense_Mutation	c.1412C>T	p.Ser471Phe	60	0.25	23.5	
BH9002280	L5	PRKCI	chr3	Missense_Mutation	c.280G>C	p.Glu94Gln	35	0.34	24.3	
BH9002280	L5	SCAF1	chr19	In_Frame_Ins	c.619_620insCCCCCCCCC	p.Ser207_Pro208insProProPro	12	0.33	NA	
BH9002280	L5	MRM1	chr17	Splice_Site	c.543-2A>G		62	0.29	24.7	
BH9002280	R1	AK9	chr6	Missense_Mutation	c.2479G>A	p.Glu827Lys	80	0.23	35	
BH9002280	R1	ZNF862	chr7	Missense_Mutation	c.1852G>A	p.Val618Met	68	0.22	17.02	
BH9002280	R1	SNTB1	chr8	Missense_Mutation	c.937G>A	p.Gly313Arg	53	0.21	23.5	
BH9002280	R2	PKD2	chr4	Silent	c.11887G>A	p.=	32	0.34	NA	
BH9002280	R2	GRID2IP	chr7	In_Frame_Del	c.2259_2264delGCTCAG	p.Leu754_Ser755del	29	0.24	NA	
BH9002280	R2	FAM46A	chr6	In_Frame_Del	c.139_141delAGC	p.Ser47del	52	0.21	NA	
BH9002280	R7	PKD2	chr4	Nonsense_Mutation	c.1366C>T	p.Gln456Ter	98	0.38	42	
BH9002280	R7	OR4C46	chr11	Missense_Mutation	c.493C>A	p.Pro165Thr	23	0.22	22.8	
BH9002280	R7	FAM155B	chrX	In_Frame_Del	c.54_56delCTG	p.Cys20del	28	0.21	NA	rs374286243
BH9002280	R7	KLK15	chr19	Missense_Mutation	c.245G>T	p.Gly82Val	14	0.21	26.4	rs188149275
BH9002280	R8	YBX3	chr12	In_Frame_Del	c.40_42delACC	p.Thr14del	16	0.31	NA	
BH9002280	R8	SMC4	chr3	Missense_Mutation	c.2113C>T	p.Arg705Cys	13	0.23	26.4	
PJ9001456	A10	PKD1	chr16	Frame_Shift_Del	c.7655_7658 delinsTTG	p.Ala2552Valfs*68		0.32		
PJ9001456	A10	XAF1	chr17	Missense_Mutation	c.614C>T	p.Thr205Met	56	0.27	16.55	rs371250443
PJ9001456	A10	KLHL35	chr11	Missense_Mutation	c.920G>T	p.Gly307Val	12	0.25	26.8	
PJ9001456	A11	MIB2	chr1	Missense_Mutation	c.2092G>A	p.Glu698Lys	10	0.30	22.8	

PJ9001456	A11	PKD1	chr16	Frame_Shift_Del	c.3745del	p.Asp1249Thrfs*24		0.23		
PJ9001456	A12	DNAH5	chr5	Missense_Mutation	c.10220G>T	p.Cys3407Phe	13	0.23	25.1	
PJ9001456	A12	CCDC28A	chr6	Missense_Mutation	c.338A>T	p.Asn113Ile	159	0.22	26.3	
PJ9001456	A12	FAM83B	chr6	Missense_Mutation	c.2386G>A	p.Ala796Thr	38	0.21	23.4	
PJ9001456	A12	SCN4A	chr17	Missense_Mutation	c.1244C>T	p.Thr415Ile	53	0.21	21.3	rs34914278
PJ9001456	A12	EP400	chr12	Frame_Shift_Ins	c.102_103insCCCCCCCCCC	p.Ser37ProfsTer31	35	0.20	NA	
PJ9001456	A7	SVIL	chr10	Missense_Mutation	c.4121T>G	p.Leu1374Arg	10	0.30	25.8	rs199726033 COSM146919
PJ9001456	A7	EP400	chr12	Frame_Shift_Ins	c.102_103insCCCCCCCCCC	p.Ser37ProfsTer31	40	0.20	NA	
PJ9001456	A8	PKD1	chr16	Frame_Shift_Del	c.348_352del	p.Asn116Lysfs*2		0.29		
PJ9001456	A8	DHX38	chr16	Splice_Site	c.3477+2T>G		18	0.28	25.8	COSM304954
PJ9001456	A8	ZBTB38	chr3	Missense_Mutation	c.62C>A	p.Ser21Tyr	13	0.23	25.8	
PJ9001456	A8	TCP1	chr6	Missense_Mutation	c.847G>A	p.Ala283Thr	56	0.21	25.8	
PJ9001456	A8	PLCH2	chr1	Missense_Mutation	c.170G>T	p.Arg57Leu	15	0.20	26.8	rs371340812 COSM381226
PJ9001456	A8	FAM83A	chr8	Missense_Mutation	c.619A>G	p.Lys207Glu	87	0.20	23.9	
PJ9001456	A9	PKD1	chr16	Splice_Site	c.8016+1delG		12	0.50	NA	
PJ9001456	A9	TMPRSS6	chr22	Missense_Mutation	c.1477G>T	p.Ala493Ser	15	0.20	23	
PJ9001456	B1	URGCP	chr7	Missense_Mutation	c.173A>C	p.Asn58Thr	14	0.36	26.9	
PJ9001456	B1	DNAH5	chr5	Missense_Mutation	c.5335G>T	p.Val1779Phe	28	0.32	27.9	
PJ9001456	B1	SLC14A2	chr18	Missense_Mutation	c.2548A>C	p.Asn850His	19	0.32	22.2	
PJ9001456	B1	ADAMTS14	chr10	Missense_Mutation	c.1231C>A	p.His411Asn	83	0.25	28.6	
PJ9001456	B2	EIF3A	chr10	Missense_Mutation	c.330G>T	p.Gln110His	33	0.36	23.5	
PJ9001456	B2	RGS1	chr1	Missense_Mutation	c.553G>T	p.Asp185Tyr	59	0.32	33	
PJ9001456	B2	DNAH5	chr5	Missense_Mutation	c.5335G>T	p.Val1779Phe	23	0.26	27.9	
PJ9001456	B2	NKD2	chr5	In_Frame_Del	c.1315_1317delCAC	p.His439del	26	0.23	NA	COSM1291992
PJ9001456	B2	PKD1	chr16	Splice_Site	c.12004-2_12019delAGGCTGCCCAGCAGCTAC		193	0.23	NA	
PJ9001456	B2	SRCIN1	chr17	Missense_Mutation	c.3298A>C	p.Lys1100Gln	41	0.20	26.4	
RP9001591	B18	PKD1	chr16	Frame_Shift_Ins	c.8996_8997insG	p.Phe2999LeufsTer70	64	0.33	NA	
RP9001591	B18	ATP2B3	chrX	Missense_Mutation	c.2866G>A	p.Gly956Arg	92	0.30	27	

RP9001591	B18	KIF13A	chr6	Missense_Mutation	c.3918A>C	p.Glu1306Asp	22	0.23	24.4	
RP9001591	B18	TNRC6B	chr22	Missense_Mutation	c.265C>T	p.Arg89Trp	10	0.20	34	
RP9001591	B19	EEF1D	chr8	Missense_Mutation	c.73C>T	p.Arg25Trp	10	0.20	30	
RP9001591	B19	MYOM3	chr1	Missense_Mutation	c.3751A>C	p.Lys1251Gln	20	0.20	23.2	
RP9001591	B20	CACNA2D1	chr7	Missense_Mutation	c.668G>T	p.Trp223Leu	12	0.42	35	COSM747982
RP9001591	B20	PRRC2B	chr9	Missense_Mutation	c.1997A>C	p.Gln666Pro	11	0.36	25.6	
RP9001591	B20	PRLR	chr5	Nonsense_Mutation	c.713G>A	p.Trp238Ter	14	0.29	38	
RP9001591	B20	KIF13A	chr6	Missense_Mutation	c.3918A>C	p.Glu1306Asp	21	0.24	24.4	
RP9001591	B21	KIF26A	chr14	Missense_Mutation	c.5624C>T	p.Pro1875Leu	75	0.39	22	rs200461988
RP9001591	B21	KISS1R	chr19	Frame_Shift_Del	c.828_832delGGGCC	p.Trp276CysfsTer28	72	0.35	NA	
RP9001591	B21	ACIN1	chr14	Missense_Mutation	c.3499C>T	p.Arg1167Trp	8	0.25	34	
RP9001591	B21	PSAT1	chr9	Missense_Mutation	c.160A>C	p.Asn54His	76	0.22	21.4	
RP9001591	B21	ABCA13	chr7	Missense_Mutation	c.86A>C	p.Glu29Ala	18	0.22	31	
RP9001591	B21	GPR20	chr8	Missense_Mutation	c.709G>A	p.Val237Met	18	0.22	19.88	
RP9001591	B22	SMARCA2	chr9	In_Frame_Del	c.667_675delCAGCAGCAG	p.Gln226_Gln228del	111	0.36	NA	
RP9001591	B23	ATAD2B	chr2	Frame_Shift_Del	c.458_465delATGGGGAC	p.Asp153AlafsTer7	29	0.52	NA	
RP9001591	B23	SELE	chr1	Missense_Mutation	c.922C>T	p.Arg308Cys	76	0.41	23	
RP9001591	B23	STON2	chr14	Missense_Mutation	c.1498C>T	p.Arg500Trp	22	0.36	29.3	rs149119701
RP9001591	B23	NSMAF	chr8	Missense_Mutation	c.1268A>T	p.Tyr423Phe	19	0.21	29.7	
RP9001591	B24	KIF17	chr1	Missense_Mutation	c.3002G>C	p.Arg1001Pro	16	0.38	34	COSM182818
RP9001591	B24	ABCA13	chr7	Missense_Mutation	c.86A>C	p.Glu29Ala	11	0.36	31	
RP9001591	B24	PRRC2B	chr9	Missense_Mutation	c.1997A>C	p.Gln666Pro	16	0.31	25.6	
RP9001591	B24	RSPRY1	chr16	Missense_Mutation	c.703A>C	p.Lys235Gln	25	0.24	15.76	
RP9001591	B24	PKD1	chr16	Frame_Shift_Del	c.1005delC	p.Val336CysfsTer129	38	0.21	NA	
RP9001591	B24	COL9A3	chr20	Missense_Mutation	c.467C>A	p.Pro156His	10	0.20	24.9	

The pathogenic potential of missense variants was evaluated using the computational analysis tool Combined Annotation–Dependent Depletion (CADD), which enables scoring of deleteriousness of SNVs and indels. A CADD value of $\geq$15 suggests the variant is likely pathogenic (http://cadd.gs.washington.edu/).

Supplemental Table 8. List of genes associated with ciliopathy disorders (N=211)

CEP41	BBS5	HYDIN	CE104	CLRN1	DNAAF1
DNAL1	CC28B	CE41B	TM231	LEFTY2	TOPORS
ALMS1	DDX59	DYH11	CCD65	CRX	NODAL
WDR35	WDR60	TM216	CU002	TSC2	GDF1
TTC8	ZMY10	DRC1	C2D2A	TCTN2	PACS1
BBS4	DYHC2	LBN	TM138	NPHP5	TTC21B
BBS2	FRITZ	FTM	DYXC1	DYNC2H1	CEP164
MKS1	F161A	IF172	IFT27	BBS9	EVC2
B9D1	DAAF1	DYH5	C5orf42	ATXN10	7SEP
KIF7	CCNO	UROM	TMEM216	ZNF423	TMEM67
DNAI1	CE41A	CCD39	GPR98	XPNPEP3	PCDH15
NEK8	TRI32	CU059	SCNN1B	SCNN1A	
NPHP4	BBIP1	SDCG8	ACVR2B	WDPCP	
WDR19	PDE6D	CC151	INPP5E	TMEM138	
INVS	SPAG1	IF140	RPE65	RD3	
EVC	RSH4A	RPGR1	SCNN1G	CEP290	
IFT43	POC1A	XPP3	MYO7A	TCTN1	
PKD1	CC103	TT21B	ARL13B	CRELD1	
RSPH9	CE290	CC114	LCA5	CRB1	
OFD1	AR2BP	OCRL	AIPL1	USH1G	
DNAI2	MRE11	TM237	C2orf71	TMEM231	
GLIS2	CE042	ANKS6	NME8	TSC1	
BBS1	TALD3	TILB	NKX2-5	IMPDH1	
IQCB1	K0556	ARMC4	DFNB31	FOXH1	
BBS10	TMM17	TXND3	CDH23	TULP1	
PKD2	AR13B	LZTL1	RDH12	TRIM32	
HYLS1	RSPH1	MCIN	CCDC40	USH1C	
RPGR	CE164	IF122	DNAH11	SPATA7	
PKHD1	KTU	CEP83	RSPH4A	DNAH5	
BBS12	CE120	DAAF3	PTCH1	RPGRIP1	
NPHP3	DAAF5	ATX10	KIF3A	IFT88	
IFT80	CB071	PTHB1	LRAT	USH2A	
B9D2	TECT1	TAPT1	ZIC3	CCDC39	
NEK1	DCDC2	CENPF	CCDC28B	KIF3B	
NPHP1	TECT3	INP5E	TMEM237	GUCY2D	
MKKS	CCD40	C2CD3	UMOD	CFTR	
AHI1	CSPP1	KIF14	BRCC3	VHL	
BBS7	RSPH3	TECT2	CC2D2A	RPGRIP1L	
MKS3	WDR34	GAS8	DNAAF2	KCNJ13	
ARL6	MIPT3	ZN423	SDCCAG8	DNAAF3	

Supplemental Table 9. Gene variations in principal ciliopathy genes

Patient ID	Cyst ID	Gene	Chr	HGVSc	HGVSp	Total coverage	ALT VAF	dbSNP rs/COSMIC	CADD Score (PHRED)
JS9001595	B28	AHI1	chr6	c.1210A>C	p.Met404Leu	39	0.15		20.7
CMJ0001593	A34	BRCC3	chrX	c.286C>A	p.Gln96Lys	74	0.05		24.3
DR9001565	A17	C5orf42	chr5	c.8960C>A	p.Pro2987Gln	48	0.06		23.4
JS9001595	B26	CC2D2A	chr4	c.4735T>G	p.Tyr1579Asp	65	0.14		23.2
JS9001595	B27	CC2D2A	chr4	c.4735T>G	p.Tyr1579Asp	55	0.15		23.2
JS9001595	B29	CC2D2A	chr4	c.4735T>G	p.Tyr1579Asp	49	0.14		23.2
JS9001595	B30	CC2D2A	chr4	c.4735T>G	p.Tyr1579Asp	74	0.15		23.2
JS9001595	B31	CC2D2A	chr4	c.4735T>G	p.Tyr1579Asp	54	0.11		23.2
JS9001595	B32	CC2D2A	chr4	c.4735T>G	p.Tyr1579Asp	75	0.15		23.2
JS9001595	B33	CC2D2A	chr4	c.4735T>G	p.Tyr1579Asp	73	0.12		23.2
DR9001565	A18	CCDC28B	chr1	c.562C>A	p.Leu188Met	77	0.05		28.7
DR9001565	A15	CEP164	chr11	c.337delA	p.Lys116ArgfsTer22	58	0.21	rs75301270 COSM1351515	
CDS001574	B7	CEP164	chr11	c.337delA	p.Lys116ArgfsTer22	25	0.24	rs75301270 COSM1351515	
PJ9001456	A10	CRX	chr19	c.202G>T	p.Ala68Ser	47	0.06		24.4
PJ9001456	A7	CSPP1	chr8	c.853C>A	p.Pro285Thr	28	0.11		22.5
PJ9001456	A10	DNAH11	chr7	c.3976C>A	p.Leu1326Ile	24	0.13	COSM1088396	26
PJ9001456	A12	DNAH5	chr5	c.10220G>T	p.Cys3407Phe	13	0.23		25.1
PJ9001456	B1	DNAH5	chr5	c.5335G>T	p.Val1779Phe	28	0.32		27.9
PJ9001456	B1	DNAH5	chr5	c.5335G>T	p.Val1779Phe	28	0.32		27.9
CDS001574	B10	DNAH5	chr5	c.5340G>T	p.Met1780Ile	29	0.21		16.41
BJA001578	B16	DNAH5	chr5	c.7009C>T	p.Leu2337Phe	29	0.24		27.6
PJ9001456	B2	DNAH5	chr5	c.5335G>T	p.Val1779Phe	23	0.26		27.9
BH9002280	R8	DNAH5	chr5	c.12795C>A	p.Asn4265Lys	28	0.11		25.1
BH9002280	L2	DYNC2H1	chr11	c.1412C>T	p.Ser471Phe	60	0.25		23.5
PJ9001456	A9	GPR98	chr5	c.14135C>A	p.Ala4712Asp	28	0.11		28.6
DR9001565	A14	IFT88	chr13	c.1519G>T	p.Gly507Cys	26	0.12		31
PJ9001456	A8	KIF14	chr1	c.2604G>T	p.Lys868Asn	46	0.07		25.1
BS9001424	A2	LEFTY2	chr1	c.37C>A	p.Leu13Met	30	0.1		17.59
BS9001424	A2	NODAL	chr10	c.1006C>A	p.His336Asn	39	0.08	COSM1675318	28.1
PJ9001456	A10	PACS1	chr11	c.753C>A	p.Tyr251Ter	43	0.07		35
PJ9001456	A9	PCDH15	chr10	c.4916C>A	p.Thr1639Lys	40	0.1	COSM364266	20.5
PJ9001456	A9	7SEP	chr7	c.113C>A	p.Pro38Gln	46	0.07		31
CMJ0001593	A29	7SEP	chr7	c.832G>T	p.Gly278Cys	49	0.06		25.6
BH9002280	R2	TMEM67	chr8	c.1862C>A	p.Ala621Glu	33	0.09		29.6
DR9001565	A18	TSC1	chr9	c.2148C>A	p.Asn716Lys	48	0.06		29.3
DR9001565	A15	TSC2	chr16	c.5010C>A	p.His1670Gln	36	0.08	rs376306544	22.3
BS9001424	A3	TTC8	chr14	c.1224+1G>T		48	0.06		26.1
CMJ0001593	A34	UMOD	chr16	c.757G>T	p.Gly253Cys	36	0.08		34
CMJ0001593	A29	USH2A	chr1	c.9752G>T	p.Cys3251Phe	62	0.06		34
CMJ0001593	A27	WDR19	chr4	c.2659G>T	p.Asp887Tyr	27	0.11		25.8
BH9002280	R1	WDR19	chr4	c.784G>T	p.Gly262Ter	41	0.07		34
BH9002280	L2	WDR34	chr9	c.670G>T	p.Ala224Ser	73	0.05		19.47
PJ9001456	A10	ZIC3	chrX	c.737C>A	p.Pro246His	41	0.07		26.4

Supplemental Table 10. Gene variations in principal cancer genes

Patient ID	Cyst ID	Gene	Chr	HGVSc	HGVSp	Total Cov	ALT VAF	dbSNP ID/COSMIC	CADD Score (PHRED)
BH9002280	R2	ABL1	chr9	c.1870_1872delAAG	p.Lys624del	100	0.07	rs201725154 COSM1645213	
PJ9001456	A8	AFF4	chr5	c.2519C>A	p.Ser840Tyr	46	0.07		24.4
CMJ0001593	A32	AKAP9	chr7	c.6631C>A	p.Gln2211Lys	22	0.18		27
CDS001574	B12	AKT2	chr19	c.1016T>G	p.Val339Gly	14	0.29		27.1
CDS001574	B7	AKT2	chr19	c.1016T>G	p.Val339Gly	13	0.31		27.1
CMJ0001593	A34	ALDH2	chr12	c.541C>A	p.Gln181Lys	44	0.07		33
BJA001578	B13	ARID1A	chr1	c.920G>T	p.Gly307Val	8	0.25		22
BJA001578	B13	ARID2	chr12	c.4673C>A	p.Ala1558Glu	18	0.17		27.5
RP9001591	B18	ATP2B3	chrX	c.2866G>A	p.Gly956Arg	92	0.3		27
BS9001424	A2	BCL3	chr19	c.783G>T	p.Leu261Phe	37	0.08		23.1
BS9001424	A2	BCOR	chrX	c.4572C>A	p.Asn1524Lys	42	0.07		32
BS9001424	A3	BCOR	chrX	c.4690A>G	p.Arg1564Gly	76	0.51		31
BS9001424	A2	BRD4	chr19	c.3650C>A	p.Ala1217Asp	34	0.09		23.9
DR9001565	B5	CANT1	chr17	c.1060G>A	p.Asp354Asn	50	0.06		22.3
JS9001595	B27	CARD11	chr7	c.922G>A	p.Asp308Asn	33	0.09		35
BS9001424	A2	CARS	chr11	c.1396-1C>T		32	0.09	COSM926250	25.8
DR9001565	A17	CASC5	chr15	c.4886C>T	p.Thr1629Ile	29	0.38		17.62
CMJ0001593	A31	CASC5	chr15	c.5858G>T	p.Arg1953Leu	52	0.08	COSM1372707	14.46
CDS001574	B12	CHEK2	chr22	c.-3C>T		32	0.16		19.31
BJA001578	B15	CLTCL1	chr22	c.3533C>A	p.Ala1178Asp	72	0.06		29.6
CDS001574	B12	COL1A1	chr17	c.3783C>A	p.Asp1261Glu	46	0.07		23.8
BS9001424	A2	CREBBP	chr16	c.6340G>T	p.Gly2114Cys	36	0.08	rs139169188	14.95
BH9002280	L5	CRTC1	chr19	c.1899C>A	p.Asp633Glu	47	0.06		28.8
CMJ0001593	A28	DNMT3A	chr2	c.1439T>G	p.Val480Gly	50	0.22	rs200099128	27.4
CMJ0001593	A29	DNMT3A	chr2	c.1439T>G	p.Val480Gly	41	0.15	rs200099128	27.4
CMJ0001593	A34	DNMT3A	chr2	c.1439T>G	p.Val480Gly	42	0.24	rs200099128	27.4
BH9002280	R2	EBF1	chr5	c.42C>A	p.Ser14Arg	30	0.1		21
DR9001565	A15	ECT2L	chr6	c.659C>A	p.Pro220His	32	0.09		22.6
BS9001424	A2	FANCA	chr16	c.2499C>A	p.Cys833Ter	50	0.06		36
BH9002280	R1	FAT1	chr4	c.1063G>A	p.Val355Met	32	0.09		20.8
JS9001595	B32	FBXW7	chr4	c.622A>T	p.Thr208Ser	52	0.13		14.04
PJ9001456	A11	FGFR2	chr10	c.1265G>A	p.Arg422His	40	0.08		34
BH9002280	L2	FGFR4	chr5	c.1391G>T	p.Arg464Leu	36	0.08		34
PJ9001456	A10	FOXL2	chr3	c.315C>A	p.Asn105Lys	48	0.06		29.3
DR9001565	B4	GNAS	chr20	c.1993C>T	p.Arg665Cys	45	0.11		25.6
RP9001591	B23	IDH1	chr2	c.433G>T	p.Val145Phe	57	0.14		34
BH9002280	R7	KAT6B	chr10	c.1075G>T	p.Asp359Tyr	41	0.1		26.5
BJA001578	B13	KDR	chr4	c.3274G>T	p.Gly1092Cys	46	0.07		33
DR9001565	A14	KMT2C	chr7	c.8559C>A	p.Cys2853Ter	37	0.08		35
BH9002280	L2	KMT2C	chr7	c.14274G>T	p.Lys4758Asn	40	0.08		32
CMJ0001593	A30	LEF1	chr4	c.722+1C>T		30	0.1	COSM585200	26.1
BS9001424	A3	MAML2	chr11	c.781G>T	p.Gly261Cys	49	0.06		24.7
BH9002280	R8	MDM2	chr12	c.*2475A>G		62	0.16		
JS9001595	B28	MLH1	chr3	c.2164A>C	p.Lys722Gln	113	0.07		22.4
JS9001595	B28	MLH1	chr3	c.2165A>C	p.Lys722Thr	113	0.12		24.7
BJA001578	B14	MLH1	chr3	c.2165A>C	p.Lys722Thr	85	0.09		24.7
BS9001424	A2	MLLT10	chr10	c.1464G>T	p.Glu488Asp	36	0.08	COSM1286220	23.2

CMJ0001593	A31	MN1	chr22	c.3029G>A	p.Trp1010Ter	36	0.22		39
DR9001565	A18	MSI2	chr17	c.57C>A	p.Asp19Glu	18	0.17		23.1
CMJ0001593	A28	MYC	chr8	c.397G>T	p.Asp133Tyr	49	0.06		31
BS9001424	A3	NCOR1	chr17	c.5506G>A	p.Val1836Met	66	0.39		24.9
CDS001574	B8	NF1	chr17	c.3244G>T	p.Gly1082Cys	48	0.15		29.8
BJA001578	B15	NF1	chr17	c.3245G>T	p.Gly1082Val	44	0.23		29
BJA001578	B16	NF1	chr17	c.3244G>T	p.Gly1082Cys	29	0.21		29.8
PJ9001456	B2	NF1	chr17	c.3244G>T	p.Gly1082Cys	38	0.18		29.8
BH9002280	B34	NFIB	chr9	c.92G>T	p.Trp31Leu	40	0.08		28.1
BJA001578	A24	NSD1	chr5	c.1034C>T	p.Pro345Leu	49	0.06		33
JS9001595	B28	NT5C2	chr10	c.1460A>C	p.Glu487Ala	28	0.11		29.6
BH9002280	L2	NT5C2	chr10	c.926C>A	p.Thr309Asn	46	0.07		23.4
DR9001565	A14	NUMA1	chr11	c.4549G>T	p.Val1517Phe	44	0.07		24.2
CDS001574	B12	P2RY8	chrX	c.815A>C	p.Tyr272Ser	119	0.08		25.1
CDS001574	B8	P2RY8	chrX	c.815A>C	p.Tyr272Ser	114	0.07		25.1
PJ9001456	B2	P2RY8	chrX	c.815A>C	p.Tyr272Ser	132	0.09		25.1
BH9002280	B35	P2RY8	chrX	c.815A>C	p.Tyr272Ser	118	0.07		25.1
CMJ0001593	A29	PAX7	chr1	c.892C>A	p.Pro298Thr	42	0.07		19.04
PJ9001456	A8	PDE4DIP	chr1	c.636+11C>T		55	0.07		5.573
PJ9001456	A8	PHOX2B	chr4	c.224G>T	p.Ser75Ile	65	0.06		18.27
CMJ0001593	A31	PICALM	chr11	c.1602G>T	p.Lys534Asn	44	0.07		24.6
CMJ0001593	A34	PICALM	chr11	c.1804G>T	p.Ala602Ser	46	0.07		16.67
BS9001424	A2	PIK3R1	chr5	c.1274T>A	p.Leu425His	56	0.14		28.1
DR9001565	A14	POU5F1	chr6	c.670G>A	p.Glu224Lys	45	0.07		23.7
CDS001574	B9	PPFIBP1	chr12	c.2515-3C>A		16	0.25		15.42
BJA001578	A23	PRCC	chr1	c.406C>T	p.Pro136Ser	61	0.07	rs11264542	18.1
PJ9001456	A8	PTPN11	chr12	c.349C>A	p.Leu117Ile	26	0.12	COSM467817	24.4
PJ9001456	A10	RAD21	chr8	c.505G>T	p.Glu169Ter	38	0.08		41
PJ9001456	B1	RANBP17	chr5	c.529G>T	p.Ala177Ser	51	0.14	rs80184931 COSM249534	23.8
PJ9001456	B1	RANBP17	chr5	c.529G>T	p.Ala177Ser	51	0.14	rs80184931 COSM249534	23.8
RP9001591	B20	RAP1GDS1	chr4	c.512-2A>T		37	0.14		22.9
PJ9001456	A7	RARA	chr17	c.848C>A	p.Thr283Asn	50	0.06		31
BH9002280	L5	RUNX1	chr21	c.1126C>A	p.Arg376Ser	31	0.1		24.5
PJ9001456	A9	RUNX1T1	chr8	c.121+245C>T		46	0.07		15.59
JS9001595	B27	SETD2	chr3	c.1031G>T	p.Ser344Ile	41	0.07		19.69
BS9001424	A2	SFPQ	chr1	c.1094G>T	p.Arg365Leu	42	0.1		34
BJA001578	B16	SMARCAD1	chr4	c.2572T>C	p.Phe858Leu	66	0.48		23
CMJ001593	A34	SMARCAD1	chr4	c.2572T>C	p.Phe858Leu	22	0.41		23
RP9001591	B22	SMARCA2	chr9	c.667_675delCAGCAGCAG	p.Gln226_Gln228 del	111	0.36		
BH9002280	L2	SPEN	chr1	c.676C>T	p.Arg226Trp	42	0.07		34
BS9001424	A3	SS18	chr18	c.322G>T	p.Gly108Ter	41	0.07		37
CDS001574	B10	STAG2	chrX	c.2188G>T	p.Val730Phe	39	0.18		25.1
RP9001591	B21	TET2	chr4	c.3901G>T	p.Ala1301Ser	86	0.07		28.7
DR9001565	A16	THRAP3	chr1	c.2701C>T	p.Arg901Ter	9	0.33		41
BJA001578	B16	TPM3	chr1	c.567-621T>C		63	0.1		15.12
CDS001574	B10	TRRAP	chr7	c.2440C>G	p.Pro814Ala	67	0.27		24.1
DR9001565	A18	TSC1	chr9	c.2148C>A	p.Asn716Lys	48	0.06		29.3
DR9001565	A15	TSC2	chr16	c.5010C>A	p.His1670Gln	36	0.08	rs376306544	22.3
BJA001578	B13	YWHAE	chr17	c.623C>T	p.Thr208Met	38	0.08		23.5
BJA001578	A23	ZFHX3	chr16	c.5221_5223delCAA	p.Gln1741del	107	0.07	rs372909378 COSM973528	

BH9002280	B36	ZFHX3	chr16	c.5221_5223delCAA	p.Gln1741del	162	0.07	rs372909378 COSM973528	
DR9001565	A18	ZRSR2	chrX	c.684C>A	p.Ser228Arg	22	0.14	rs372992384	25.5

Supplemental Table 11. Copy number alterations (CNAs) in most commonly altered (≥4 CNV) genes among the cyst samples.

Cyst ID	#Chr	Start	End	Size	Log2ratio	Type	Class	Chr arm	p_value	#Covered Genes	Gene(s)
A2	chr9	88967882	88968131	249	-1.6613	deletion	focal	9q	8.90E-16	1	ZCCHC6
A8	chr8	29207565	29207762	197	1.8895	amplification	focal	8p	4.59E-15	1	DUSP4
A9	chr8	29207565	29207760	195	1.6685	amplification	focal	8p	3.68E-10	1	DUSP4
A10	chr17	80048915	80048992	77	2.116	amplification	focal	17q	5.06E-10	1	FASN
A12	chr8	29207565	29207762	197	1.5937	amplification	focal	8p	4.93E-11	1	DUSP4
A12	chr9	34834124	34834503	379	-1.7457	deletion	focal	9p	3.19E-13	1	FAM205B
A14	chr2	54150092	54154655	4563	-0.8578	deletion	focal	2p	1.62E-09	1	PSME4
A14	chr6	152451796	152451986	190	-1.2775	deletion	focal	6q	7.94E-06	1	SYNE1
A14	chr9	140063932	140064192	260	-1.4343	deletion	focal	9q	1.08E-07	1	LRRC26
A14	chr17	17699029	17699140	111	1.891	amplification	focal	17p	3.66E-12	1	RAI1
A15	chr2	109400015	109400282	267	-1.0377	deletion	focal	2q	3.29E-05	1	RANBP2
A15	chr2	179583358	179583585	227	1.1507	amplification	focal	2q	7.54E-17	1	TTN
A15	chr12	57594755	57594906	151	-1.4565	deletion	focal	12q	9.11E-61	1	LRP1
A15	chr17	17699048	17699125	77	1.8025	amplification	focal	17p	4.90E-11	1	RAI1
A16	chr1	228503564	228503856	292	0.9693	amplification	focal	1q	8.46E-16	1	OBSCN
A16	chr2	54152612	54153125	513	-1.1327	deletion	focal	2p	4.43E-08	1	PSME4
A16	chr2	73151446	73151703	257	-1.704	deletion	focal	2p	3.59E-13	1	EMX1
A16	chr2	179452530	179452662	132	-1.351	deletion	focal	2q	8.27E-62	1	TTN
A16	chr5	138729459	138729994	535	-1.0243	deletion	focal	5q	6.95E-110	1	PROB1
A16	chr11	20404467	20404810	343	-1.096	deletion	focal	11p	2.11E-07	1	HTATIP2
A16	chr12	57594755	57595001	246	-1.091	deletion	focal	12q	8.03E-27	1	LRP1
A17	chr12	57594755	57595001	246	-1.2297	deletion	focal	12q	4.68E-12	1	LRP1
A17	chr16	75018837	75033868	15031	0.9517	amplification	focal	16q	8.12E-05	2	ZNRF1;WDR59
A17	chr17	17699034	17699145	111	1.4843	amplification	focal	17p	2.06E-10	1	RAI1
A18	chr3	142775189	142839795	64606	1.0457	amplification	focal	3q	7.94E-31	2	CHST2;U2SURP
A18	chr8	124382010	124383222	1212	-0.8392	deletion	focal	8q	2.49E-95	1	ATAD2
A18	chr12	57594755	57594906	151	-1.391	deletion	focal	12q	3.04E-12	1	LRP1
A18	chr16	74808399	74908179	99780	1.0433	amplification	focal	16q	2.03E-34	2	FA2H;WDR59
A18	chr17	2089896	2090209	313	0.773	amplification	focal	17p	6.48E-58	1	SMG6
A18	chr17	17699029	17699125	96	1.7915	amplification	focal	17p	1.63E-11	1	RAI1
A18	chr22	40058021	40058283	262	1.2817	amplification	focal	22q	3.82E-20	1	CACNA1I
A18	chr22	51158734	51158986	252	1.3375	amplification	focal	22q	1.87E-07	1	SHANK3
A21	chr1	186649287	186649487	200	-1.4627	deletion	focal	1q	3.13E-11	1	PTGS2
A21	chr4	117220797	117221011	214	-1.583	deletion	focal	4q	3.42E-14	1	MIR1973
A23	chr16	2165656	2173558	7902	-1.017	deletion	focal	16p	1.73E-10	1	PKD1
A24	chr4	117220797	117221011	214	-1.39	deletion	focal	4q	8.93E-13	1	MIR1973
A24	chr9	34834370	34834503	133	-2.128	deletion	focal	9p	3.71E-19	1	FAM205B
A24	chr17	28548645	28548761	116	-1.751	deletion	focal	17q	1.37E-11	1	SLC6A4
A24	chr22	37771163	37771232	69	-1.628	deletion	focal	22q	6.29E-10	1	ELFN2

A25	chr8	29207516	29207762	246	1.4793	amplification	focal	8p	7.15E-12	1	DUSP4
A25	chr11	6585470	6585688	218	-1.251	deletion	focal	11p	9.73E-09	1	DNHD1
A27	chr5	176821167	176821225	58	-1.7185	deletion	focal	5q	9.89E-11	1	SLC34A1
A27	chr8	145649607	145649666	59	-2.1955	deletion	focal	8q	8.59E-19	1	VPS28
A28	chr5	176821171	176821225	54	-1.926	deletion	focal	5q	2.72E-11	1	SLC34A1
A28	chr8	145639222	145639276	54	-2.335	deletion	focal	8q	5.74E-17	1	SLC39A4
A28	chr8	145649607	145649666	59	-2.677	deletion	focal	8q	1.65E-27	1	VPS28
A28	chr17	80048906	80049027	121	-2.2185	deletion	focal	17q	1.44E-14	1	FASN
A28	chr19	16435952	16436100	148	-1.982	deletion	focal	19p	3.77E-12	1	KLF2
A28	chr22	37770507	37770863	356	-1.2957	deletion	focal	22q	1.41E-08	1	ELFN2
A29	chr5	176821166	176821225	59	-1.4625	deletion	focal	5q	6.69E-07	1	SLC34A1
A29	chr9	34833951	34834822	871	0.978	amplification	focal	9p	5.64E-14	1	FAM205B
A29	chr10	85981792	85981846	54	-1.522	deletion	focal	10q	1.97E-18	1	LRIT2
A29	chr11	6541070	6541124	54	-1.608	deletion	focal	11p	2.08E-10	1	DNHD1
A29	chr17	80048912	80048966	54	-1.816	deletion	focal	17q	6.12E-12	1	FASN
A30	chr5	132158646	132159102	456	-1.1692	deletion	focal	5q	4.28E-13	1	SHROOM1
A30	chr7	100230963	100238353	7390	-1.593	deletion	focal	7q	4.78E-15	1	TFR2
A30	chr7	156469165	156469217	52	-1.8185	deletion	focal	7q	1.26E-11	1	RNF32
A30	chr8	124381366	124381470	104	-1.6855	deletion	focal	8q	3.55E-10	1	ATAD2
A30	chr8	145639222	145639281	59	-2.034	deletion	focal	8q	2.27E-16	1	SLC39A4
A30	chr17	80048912	80049034	122	-2.1185	deletion	focal	17q	2.72E-17	1	FASN
A31	chr1	186649287	186649472	185	-1.6845	deletion	focal	1q	5.47E-11	1	PTGS2
A31	chr3	46414577	46414709	132	-1.6825	deletion	focal	3p	8.32E-12	1	CCR5
A31	chr3	142839617	142839728	111	-2.1695	deletion	focal	3q	8.61E-18	1	CHST2
A31	chr7	100230941	100238353	7412	-1.312	deletion	focal	7q	2.93E-36	1	TFR2
A32	chr1	186649287	186649382	95	-1.8705	deletion	focal	1q	4.37E-13	1	PTGS2
A32	chr2	73144998	73145197	199	-1.7115	deletion	focal	2p	4.18E-12	1	EMX1
A32	chr2	109335979	109336107	128	-1.622	deletion	focal	2q	1.26E-09	1	RANBP2
A32	chr7	156469165	156469217	52	-1.361	deletion	focal	7q	8.89E-07	1	RNF32
A32	chr8	29207316	29207767	451	-1.1267	deletion	focal	8p	8.67E-13	1	DUSP4
A32	chr14	100625826	100705839	80013	-1.3802	deletion	focal	14q	4.21E-16	2	DEGS2;YY1
A32	chr16	74993396	75018951	25555	-1.1564	deletion	focal	16q	4.88E-10	1	WDR59
A32	chr19	16435952	16436868	916	-1.8797	deletion	focal	19p	1.42E-14	1	KLF2
A33	chr3	45988080	45988218	138	-2.362	deletion	focal	3p	5.09E-23	1	CXCR6
A33	chr4	117220797	117221011	214	-1.7153	deletion	focal	4q	2.40E-17	1	MIR1973
A33	chr7	156469165	156469217	52	-1.636	deletion	focal	7q	1.54E-08	1	RNF32
A33	chr8	29207316	29207762	446	-1.5237	deletion	focal	8p	3.40E-17	1	DUSP4
A33	chr8	145639227	145639281	54	-2.2075	deletion	focal	8q	1.55E-18	1	SLC39A4
A33	chr8	145649607	145649666	59	-2.6625	deletion	focal	8q	5.37E-23	1	VPS28
A33	chr9	34834370	34834822	452	1.5777	amplification	focal	9p	1.10E-13	1	FAM205B
A33	chr10	85981797	85981851	54	-1.868	deletion	focal	10q	1.08E-12	1	LRIT2
A33	chr14	100705589	100705782	193	-1.4067	deletion	focal	14q	3.08E-09	1	YY1
A33	chr16	2141697	2144251	2554	1.1213	amplification	focal	16p	3.85E-47	1	PKD1

A33	chr17	80048912	80048992	80	-2.9085	deletion	focal	17q	8.68E-46	1	FASN
A34	chr1	186649287	186649482	195	-1.855	deletion	focal	1q	1.00E-12	1	PTGS2
A34	chr3	142839617	142839763	146	-1.604	deletion	focal	3q	3.06E-08	1	CHST2
A34	chr5	132158922	132159082	160	-1.69	deletion	focal	5q	4.07E-09	1	SHROOM1
A34	chr7	100230965	100238353	7388	-1.522	deletion	focal	7q	1.37E-11	1	TFR2
A34	chr7	156469165	156469217	52	-1.648	deletion	focal	7q	5.53E-08	1	RNF32
A34	chr8	29207516	29207762	246	-1.7057	deletion	focal	8p	5.37E-15	1	DUSP4
A34	chr8	145639222	145639281	59	-1.637	deletion	focal	8q	1.07E-10	1	SLC39A4
A34	chr8	145649607	145649666	59	-1.8755	deletion	focal	8q	6.42E-14	1	VPS28
A34	chr10	85981792	85981851	59	-1.6955	deletion	focal	10q	3.32E-10	1	LRIT2
A34	chr14	100705689	100705772	83	-1.7135	deletion	focal	14q	9.28E-10	1	YY1
A34	chr16	2141697	2150027	8330	3.5649	amplification	focal	16p	1.89E-15	1	PKD1
A34	chr16	2155274	2159259	3985	0.8213	amplification	focal	16p	4.40E-17	1	PKD1
A34	chr16	2164597	2166657	2060	2.5752	amplification	focal	16p	4.69E-73	1	PKD1
A34	chr17	80048912	80049030	118	-2.3423	deletion	focal	17q	1.58E-25	1	FASN
A34	chr19	16435952	16436100	148	-2.2115	deletion	focal	19p	1.19E-16	1	KLF2
B1	chr5	176825611	176827304	1693	1.1094	amplification	focal	5q	2.44E-08	2	SLC34A1;PFN3
B1	chr6	152776662	152776782	120	-1.877	deletion	focal	6q	2.06E-10	1	SYNE1
B1	chr16	74926407	74927812	1405	-1.4488	deletion	focal	16q	5.33E-09	1	WDR59
B1	chr21	9825799	9826243	444	1.5545	amplification	focal	21p	1.78E-10	2	MIR3648;MIR3687
B2	chr1	228509919	228509955	36	-1.9805	deletion	focal	1q	2.71E-10	1	OBSCN
B2	chr1	228553243	228553356	113	-2.108	deletion	focal	1q	4.41E-12	1	OBSCN
B2	chr3	45988518	45988785	267	-1.4422	deletion	focal	3p	7.58E-08	1	CXCR6
B2	chr6	152776662	152776782	120	-2.4195	deletion	focal	6q	2.23E-15	1	SYNE1
B2	chr7	48965090	48965240	150	-1.8115	deletion	focal	7p	1.69E-08	1	CDC14C
B2	chr7	150490214	150490333	119	-2.3025	deletion	focal	7q	4.50E-13	1	TMEM176B
B2	chr10	43701488	43701586	98	-2.6095	deletion	focal	10q	9.40E-19	1	RASGEF1A
B2	chr14	100625825	100706000	80175	1.2708	amplification	focal	14q	1.22E-09	2	DEGS2;YY1
B2	chr21	9825804	9825862	58	1.91	amplification	focal	21p	4.04E-07	1	MIR3648
B4	chr3	45988520	45988796	276	-1.65	deletion	focal	3p	5.81E-09	1	CXCR6
B4	chr3	46415373	46449287	33914	1.2725	amplification	focal	3p	1.06E-07	2	CCR5;CCRL2
B4	chr5	138729831	138730341	510	-1.614	deletion	focal	5q	5.31E-48	1	PROB1
B4	chr7	100230939	100231088	149	1.4725	amplification	focal	7q	3.03E-59	1	TFR2
B4	chr8	124382259	124382359	100	-2.4455	deletion	focal	8q	2.43E-128	1	ATAD2
B4	chr10	43701488	43701586	98	-2.3825	deletion	focal	10q	3.89E-13	1	RASGEF1A
B4	chr11	47611995	47612271	276	-1.1743	deletion	focal	11p	1.73E-72	1	C1QTNF4
B4	chr12	57600493	57601866	1373	-1.272	deletion	focal	12q	2.26E-76	1	LRP1
B4	chr13	111935393	111935581	188	1.665	amplification	focal	13q	2.35E-09	1	ARHGEF7
B4	chr19	16436032	16436100	68	2.0465	amplification	focal	19p	3.65E-08	1	KLF2
B5	chr1	186649309	186649464	155	1.773	amplification	focal	1q	9.28E-13	1	PTGS2
B5	chr3	45988343	45988796	453	-1.2036	deletion	focal	3p	1.68E-08	1	CXCR6
B5	chr3	46415373	46449681	34308	1.2063	amplification	focal	3p	3.13E-12	2	CCR5;CCRL2
B5	chr13	111935404	111935581	177	1.632	amplification	focal	13q	7.08E-09	1	ARHGEF7

B5	chr19	16436032	16436102	70	2.1625	amplification	focal	19p	3.84E-10	1	KLF2
B5	chr22	40058164	40058349	185	1.3883	amplification	focal	22q	2.36E-06	1	CACNA1I
B6	chr3	46415373	46449912	34539	1.1287	amplification	focal	3p	1.95E-10	2	CCR5;CCRL2
B6	chr7	48965090	48965240	150	-2.249	deletion	focal	7p	1.06E-32	1	CDC14C
B6	chr10	43701488	43701586	98	-2.029	deletion	focal	10q	4.73E-12	1	RASGEF1A
B6	chr13	111935393	111935581	188	1.9473	amplification	focal	13q	1.88E-12	1	ARHGEF7
B6	chr17	2139638	2147991	8353	1.1798	amplification	focal	17p	2.18E-08	1	SMG6
B6	chr19	16436032	16436100	68	2.093	amplification	focal	19p	2.72E-09	1	KLF2
B7	chr7	150490191	150490333	142	-1.997	deletion	focal	7q	1.30E-11	1	TMEM176B
B7	chr12	22354498	22354572	74	-1.728	deletion	focal	12p	2.00E-08	1	ST8SIA1
B7	chr15	65942820	65942902	82	1.974	amplification	focal	15q	2.47E-09	1	SLC24A1
B7	chr17	5307315	5307526	211	-1.5743	deletion	focal	17p	2.03E-08	1	NUP88
B7	chr21	9825827	9825862	35	1.932	amplification	focal	21p	1.97E-08	1	MIR3648
B7	chr22	39966697	39967018	321	1.3755	amplification	focal	22q	2.34E-09	1	CACNA1I
B8	chr7	150490214	150490333	119	-2.882	deletion	focal	7q	3.33E-26	1	TMEM176B
B8	chr12	22354498	22354588	90	-1.9393	deletion	focal	12p	1.28E-15	1	ST8SIA1
B8	chr15	65942801	65942911	110	1.753	amplification	focal	15q	6.07E-10	1	SLC24A1
B8	chr17	2139648	2139911	263	1.3837	amplification	focal	17p	8.22E-07	1	SMG6
B8	chr17	5307315	5307526	211	-1.3473	deletion	focal	17p	3.08E-07	1	NUP88
B8	chr21	9825827	9825862	35	1.8795	amplification	focal	21p	1.14E-07	1	MIR3648
B9	chr2	54164337	54164601	264	-1.0807	deletion	focal	2p	6.08E-12	1	PSME4
B9	chr5	138729829	138730341	512	-1.2277	deletion	focal	5q	1.36E-35	1	PROB1
B9	chr7	48965090	48965240	150	-1.4005	deletion	focal	7p	1.82E-168	1	CDC14C
B9	chr7	127961182	127961515	333	-1.3228	deletion	focal	7q	6.31E-07	1	RBM28
B9	chr8	124381918	124382359	441	-1.4767	deletion	focal	8q	1.26E-10	1	ATAD2
B9	chr13	111935394	111935581	187	1.573	amplification	focal	13q	2.92E-08	1	ARHGEF7
B9	chr15	65942751	65942911	160	1.573	amplification	focal	15q	3.27E-13	1	SLC24A1
B9	chr17	1961193	1962167	974	0.9136	amplification	focal	17p	6.34E-10	1	HIC1
B9	chr17	5307315	5307576	261	-1.5173	deletion	focal	17p	1.14E-11	1	NUP88
B9	chr22	40075617	40075754	137	2.203	amplification	focal	22q	5.86E-47	1	CACNA1I
B10	chr5	82876236	82876333	97	-1.787	deletion	focal	5q	1.35E-11	1	VCAN
B10	chr7	127961182	127961499	317	-1.3065	deletion	focal	7q	2.12E-09	1	RBM28
B10	chr7	150490191	150490333	142	-1.854	deletion	focal	7q	6.22E-10	1	TMEM176B
B10	chr11	720806	721194	388	-1.8205	deletion	focal	11p	8.57E-13	1	EPS8L2
B10	chr12	22354498	22354572	74	-2.456	deletion	focal	12p	3.35E-16	1	ST8SIA1
B10	chr15	65942801	65942911	110	1.7313	amplification	focal	15q	2.22E-10	1	SLC24A1
B10	chr16	58608978	58612656	3678	-1.05	deletion	focal	16q	2.32E-09	1	CNOT1
B10	chr17	2139648	2139911	263	1.4765	amplification	focal	17p	4.90E-10	1	SMG6
B10	chr17	5307315	5307526	211	-1.5467	deletion	focal	17p	3.76E-08	1	NUP88
B10	chr21	9825827	9825862	35	1.883	amplification	focal	21p	2.39E-09	1	MIR3648
B12	chr4	117220749	117221011	262	-1.5763	deletion	focal	4q	1.56E-11	1	MIR1973
B12	chr5	82876236	82876333	97	-1.963	deletion	focal	5q	4.89E-12	1	VCAN
B12	chr5	132161461	132161833	372	-1.2808	deletion	focal	5q	6.15E-10	1	SHROOM1

B12	chr7	150490214	150490333	119	-1.9495	deletion	focal	7q	6.69E-12	1	TMEM176B
B12	chr10	43701420	43701586	166	-1.5267	deletion	focal	10q	1.71E-10	1	RASGEF1A
B12	chr12	22354498	22354572	74	-2.073	deletion	focal	12p	2.70E-13	1	ST8SIA1
B12	chr21	9825827	9825862	35	1.78	amplification	focal	21p	3.78E-08	1	MIR3648
B13	chr1	228553240	228553356	116	-1.917	deletion	focal	1q	1.18E-09	1	OBSCN
B13	chr6	152776662	152776782	120	-2.089	deletion	focal	6q	5.14E-12	1	SYNE1
B13	chr7	48965090	48965240	150	-2.2745	deletion	focal	7p	2.85E-13	1	CDC14C
B13	chr10	43701488	43701586	98	-2.2395	deletion	focal	10q	1.63E-13	1	RASGEF1A
B13	chr17	1960150	1960251	101	-1.8065	deletion	focal	17p	6.73E-07	1	HIC1
B13	chr17	5307315	5307526	211	-1.7193	deletion	focal	17p	4.54E-09	1	NUP88
B14	chr7	150490214	150490333	119	-2.3325	deletion	focal	7q	8.71E-15	1	TMEM176B
B15	chr1	228553240	228553356	116	-1.85	deletion	focal	1q	1.09E-09	1	OBSCN
B15	chr5	82876236	82876333	97	-1.9095	deletion	focal	5q	1.43E-16	1	VCAN
B15	chr6	152776662	152776782	120	-1.854	deletion	focal	6q	2.42E-10	1	SYNE1
B15	chr7	48965090	48965240	150	-2.166	deletion	focal	7p	3.83E-09	1	CDC14C
B15	chr7	50450128	50450270	142	-1.2557	deletion	focal	7p	3.21E-06	1	IKZF1
B15	chr12	22354485	22354583	98	-1.3757	deletion	focal	12p	6.46E-08	1	ST8SIA1
B16	chr5	82876236	82876333	97	-2.0305	deletion	focal	5q	4.19E-11	1	VCAN
B16	chr6	152776662	152776782	120	-2.2005	deletion	focal	6q	2.40E-13	1	SYNE1
B16	chr7	48964824	48965240	416	-1.7197	deletion	focal	7p	7.52E-12	1	CDC14C
B16	chr12	22354485	22354588	103	-1.7763	deletion	focal	12p	2.41E-13	1	ST8SIA1
B16	chr16	2139910	2168152	28242	3.13535	amplification	focal	16p	1.82E-06	2	MIR1225;PKD1
B18	chr2	242743036	242743481	445	-1.6063	deletion	focal	2q	6.53E-20	1	GAL3ST2
B18	chr5	132161561	132161833	272	-1.3735	deletion	focal	5q	9.70E-19	1	SHROOM1
B18	chr13	20716327	20716453	126	-1.807	deletion	focal	13q	4.88E-16	1	GJA3
B18	chr22	51158898	51159277	379	0.8507	amplification	focal	22q	7.65E-05	1	SHANK3
B19	chr2	242742908	242743481	573	-1.8317	deletion	focal	2q	1.05E-22	1	GAL3ST2
B19	chr3	52399006	52399077	71	1.666	amplification	focal	3p	3.07E-14	1	DNAH1
B19	chr11	725632	726206	574	-1.049	deletion	focal	11p	9.71E-11	1	EPS8L2
B19	chr13	20716231	20716803	572	-1.1435	deletion	focal	13q	8.42E-19	1	GJA3
B19	chr17	28548645	28548761	116	-1.3615	deletion	focal	17q	2.82E-09	1	SLC6A4
B19	chr19	45261486	45261686	200	1.6175	amplification	focal	19q	6.62E-13	1	BCL3
B19	chr22	51158561	51159366	805	1.0255	amplification	focal	22q	5.04E-11	1	SHANK3
B20	chr9	140063392	140063522	130	1.4865	amplification	focal	9q	1.45E-11	1	LRRC26
B20	chr20	3641504	3641629	125	1.3345	amplification	focal	20p	1.41E-09	1	GFRA4
B20	chr22	51158561	51159277	716	0.8748	amplification	focal	22q	2.75E-14	1	SHANK3
B21	chr4	117220796	117220996	200	-1.8945	deletion	focal	4q	1.07E-17	1	MIR1973
B21	chr5	132161461	132161833	372	-1.3123	deletion	focal	5q	2.03E-15	1	SHROOM1
B21	chr5	138730521	138730809	288	0.8453	amplification	focal	5q	7.00E-12	1	PROB1
B21	chr7	50467867	50468252	385	1.2358	amplification	focal	7p	2.14E-18	1	IKZF1
B21	chr8	145638556	145639186	630	-0.6606	deletion	focal	8q	5.50E-07	1	SLC39A4
B21	chr9	140063392	140063522	130	1.2487	amplification	focal	9q	3.09E-11	1	LRRC26
B21	chr11	20404467	20409321	4854	-0.7895	deletion	focal	11p	2.69E-06	2	PRMT3;HTATIP2

B21	chr17	1961819	1961905	86	-2.217	deletion	focal	17p	1.24E-25	1	HIC1
B21	chr20	3641404	3641629	225	1.175	amplification	focal	20p	4.43E-10	1	GFRA4
B21	chr22	51158596	51159277	681	1.04	amplification	focal	22q	2.57E-11	1	SHANK3
B22	chr3	52399006	52399077	71	1.4835	amplification	focal	3p	1.39E-11	1	DNAH1
B22	chr5	138730521	138730794	273	0.8583	amplification	focal	5q	1.02E-16	1	PROB1
B22	chr9	140063392	140063523	131	1.137	amplification	focal	9q	3.03E-09	1	LRRC26
B22	chr17	28548645	28548761	116	-1.315	deletion	focal	17q	5.42E-16	1	SLC6A4
B22	chr20	3641404	3641629	225	0.9707	amplification	focal	20p	1.06E-13	1	GFRA4
B22	chr22	51158561	51159277	716	0.9116	amplification	focal	22q	2.03E-07	1	SHANK3
B23	chr1	6531079	6532607	1528	0.7618	amplification	focal	1p	7.33E-08	1	PLEKHG5
B23	chr2	242742822	242743481	659	-1.6527	deletion	focal	2q	2.03E-15	1	GAL3ST2
B23	chr3	52399006	52399077	71	1.635	amplification	focal	3p	4.22E-13	1	DNAH1
B23	chr5	132161561	132161833	272	-1.3883	deletion	focal	5q	3.23E-14	1	SHROOM1
B23	chr7	50467858	50468170	312	1.1407	amplification	focal	7p	9.50E-12	1	IKZF1
B23	chr8	144917966	144918286	320	1.445	amplification	focal	8q	1.73E-08	1	NRBP2
B23	chr13	20716327	20716583	256	-1.4507	deletion	focal	13q	1.63E-14	1	GJA3
B23	chr19	45261486	45261686	200	1.7085	amplification	focal	19q	8.97E-15	1	BCL3
B23	chr20	3641504	3641629	125	1.3705	amplification	focal	20p	2.09E-09	1	GFRA4
B23	chr22	51158561	51159227	666	1.0244	amplification	focal	22q	1.96E-17	1	SHANK3
B24	chr1	6531066	6531923	857	0.9837	amplification	focal	1p	3.76E-15	1	PLEKHG5
B24	chr1	228520472	228520964	492	-0.7784	deletion	focal	1q	8.62E-08	1	OBSCN
B24	chr3	52399006	52399077	71	1.282	amplification	focal	3p	1.66E-08	1	DNAH1
B24	chr7	50467867	50468243	376	1.0012	amplification	focal	7p	2.98E-09	1	IKZF1
B24	chr17	28548645	28548761	116	-1.535	deletion	focal	17q	1.81E-12	1	SLC6A4
B24	chr19	45261486	45261686	200	1.409	amplification	focal	19q	7.47E-10	1	BCL3
B24	chr20	3641404	3641629	225	1.0893	amplification	focal	20p	4.46E-09	1	GFRA4
B24	chr22	51158561	51159277	716	0.8182	amplification	focal	22q	8.46E-08	1	SHANK3
B26	chr2	73151367	73151693	326	-1.2532	deletion	focal	2p	3.03E-16	1	EMX1
B26	chr2	242742828	242743468	640	-1.3116	deletion	focal	2q	2.33E-20	1	GAL3ST2
B26	chr3	9988735	9989235	500	0.8192	amplification	focal	3p	7.14E-10	2	PRRT3-AS1;PRRT3
B26	chr5	132161189	132161561	372	-1.2353	deletion	focal	5q	1.78E-11	1	SHROOM1
B26	chr11	725632	725797	165	-1.539	deletion	focal	11p	6.76E-11	1	EPS8L2
B26	chr22	51158561	51159267	706	0.9688	amplification	focal	22q	1.93E-07	1	SHANK3
B27	chr2	73151469	73151693	224	-1.9695	deletion	focal	2p	1.63E-42	1	EMX1
B27	chr3	9988746	9989170	424	0.9142	amplification	focal	3p	4.65E-12	2	PRRT3-AS1;PRRT3
B27	chr5	132161211	132161837	626	-0.901	deletion	focal	5q	1.58E-12	1	SHROOM1
B27	chr7	50467975	50468336	361	0.9292	amplification	focal	7p	1.89E-08	1	IKZF1
B27	chr11	6592269	6592647	378	0.9815	amplification	focal	11p	2.72E-10	1	DNHD1
B27	chr13	20716324	20717024	700	-1.0808	deletion	focal	13q	6.04E-28	1	GJA3
B27	chr20	3641497	3641627	130	1.2855	amplification	focal	20p	2.96E-09	1	GFRA4
B28	chr1	6531535	6531723	188	1.0777	amplification	focal	1p	6.98E-10	1	PLEKHG5
B28	chr11	725632	725795	163	-1.538	deletion	focal	11p	1.59E-12	1	EPS8L2

B28	chr11	20404467	20404667	200	-1.2905	deletion	focal	11p	8.98E-08	1	HTATIP2
B28	chr11	47611533	47612149	616	1.0485	amplification	focal	11p	1.28E-11	1	C1QTNF4
B28	chr13	20716231	20716684	453	-1.6984	deletion	focal	13q	3.89E-38	1	GJA3
B28	chr16	2140981	2141132	151	1.3995	amplification	focal	16p	1.11E-10	1	PKD1
B28	chr22	51158561	51159267	706	0.9202	amplification	focal	22q	6.36E-09	1	SHANK3
B29	chr11	725632	725797	165	-1.3175	deletion	focal	11p	4.85E-08	1	EPS8L2
B29	chr16	58620511	58620706	195	-1.7075	deletion	focal	16q	1.98E-14	1	CNOT1
B29	chr16	70366776	70366976	200	-1.3285	deletion	focal	16q	4.07E-08	1	DDX19B
B29	chr19	45261486	45261877	391	0.8518	amplification	focal	19q	1.92E-08	1	BCL3
B30	chr2	54152718	54153229	511	-0.8728	deletion	focal	2p	2.36E-09	1	PSME4
B30	chr5	132161208	132161837	629	-1.0965	deletion	focal	5q	6.04E-19	1	SHROOM1
B30	chr7	50467960	50468156	196	1.196	amplification	focal	7p	4.74E-09	1	IKZF1
B30	chr11	47611533	47612149	616	0.7858	amplification	focal	11p	1.09E-11	1	C1QTNF4
B30	chr16	2141010	2141224	214	1.2497	amplification	focal	16p	1.12E-13	1	PKD1
B30	chr16	58620364	58620706	342	-1.159	deletion	focal	16q	3.53E-13	1	CNOT1
B30	chr22	51158561	51159257	696	0.9432	amplification	focal	22q	1.55E-06	1	SHANK3
B31	chr1	6531535	6531723	188	1.314	amplification	focal	1p	6.76E-14	1	PLEKHG5
B31	chr3	9988746	9989146	400	0.8335	amplification	focal	3p	1.70E-07	2	PRRT3-AS1;PRRT3
B31	chr9	140063347	140063522	175	1.021	amplification	focal	9q	8.48E-08	1	LRRC26
B31	chr16	2140994	2141224	230	1.2693	amplification	focal	16p	2.94E-12	1	PKD1
B31	chr16	58620511	58620706	195	-1.9055	deletion	focal	16q	3.45E-19	1	CNOT1
B32	chr1	6531535	6531723	188	1.5887	amplification	focal	1p	4.06E-20	1	PLEKHG5
B32	chr3	9988737	9989137	400	0.799	amplification	focal	3p	1.92E-10	2	PRRT3-AS1;PRRT3
B32	chr9	140063397	140063522	125	1.3035	amplification	focal	9q	1.85E-08	1	LRRC26
B32	chr11	20404467	20404667	200	-1.342	deletion	focal	11p	7.48E-10	1	HTATIP2
B32	chr11	47611533	47612149	616	1.0077	amplification	focal	11p	6.21E-11	1	C1QTNF4
B32	chr17	1953499	1959727	6228	0.8245	amplification	focal	17p	3.01E-07	2	MIR212;HIC1
B32	chr20	3641499	3641713	214	1.0373	amplification	focal	20p	4.68E-08	1	GFRA4
B33	chr3	9988746	9988868	122	1.401	amplification	focal	3p	3.06E-10	1	PRRT3
B33	chr5	132161211	132161837	626	-1.0332	deletion	focal	5q	7.45E-16	1	SHROOM1
B33	chr9	140063362	140063522	160	1.231	amplification	focal	9q	4.21E-12	1	LRRC26
B33	chr11	6592269	6592583	314	1.1078	amplification	focal	11p	2.35E-16	1	DNHD1
B33	chr11	47611533	47611777	244	1.2553	amplification	focal	11p	5.27E-13	1	C1QTNF4
B33	chr16	2141005	2141224	219	1.17	amplification	focal	16p	1.55E-10	1	PKD1
B34	chr1	228561970	228562197	227	-1.417	deletion	focal	1q	3.65E-07	1	OBSCN
B34	chr2	179399126	179399195	69	2.0045	amplification	focal	2q	2.60E-10	1	TTN
B34	chr7	127953217	127953384	167	1.673	amplification	focal	7q	4.60E-07	1	RBM28
B34	chr9	88967881	88968115	234	1.5827	amplification	focal	9q	5.58E-10	1	ZCCHC6
B35	chr2	109380223	109380558	335	1.5542	amplification	focal	2q	4.42E-12	1	RANBP2
B35	chr2	179399126	179399295	169	1.718	amplification	focal	2q	3.04E-11	1	TTN
B35	chr7	127953217	127953384	167	1.972	amplification	focal	7q	2.36E-09	1	RBM28
B35	chr9	88967884	88968115	231	1.8347	amplification	focal	9q	6.87E-13	1	ZCCHC6

B36	chr2	109380223	109380566	343	1.3542	amplification	focal	2q	1.76E-08	1	RANBP2
B36	chr2	179399126	179399295	169	1.5203	amplification	focal	2q	1.39E-08	1	TTN
B36	chr7	127953217	127953384	167	1.885	amplification	focal	7q	1.16E-08	1	RBM28
B36	chr9	88967877	88968115	238	1.5647	amplification	focal	9q	2.51E-09	1	ZCCHC6
B36	chr10	85984601	85984842	241	1.471	amplification	focal	10q	2.16E-08	1	LRIT2
L2	chr8	144919846	144919935	89	1.591	amplification	focal	8q	1.03E-11	1	NRBP2
L5	chr2	54197623	54197858	235	-1.577	deletion	focal	2p	1.59E-07	1	PSME4
L5	chr7	100238479	100238542	63	1.8115	amplification	focal	7q	3.24E-09	1	TFR2
L5	chr8	144919854	144919930	76	2.301	amplification	focal	8q	2.80E-19	1	NRBP2
L5	chr10	7769599	7769737	138	-1.83	deletion	focal	10p	1.93E-07	1	ITIH2
R1	chr8	144919859	144919935	76	1.963	amplification	focal	8q	9.28E-14	1	NRBP2
R1	chr16	70365719	70367074	1355	-1.1927	deletion	focal	16q	3.50E-06	1	DDX19B
R2	chr10	7769599	7769731	132	-2.22	deletion	focal	10p	9.46E-12	1	ITIH2
R2	chr16	70365722	70365878	156	-2.0755	deletion	focal	16q	2.84E-09	1	DDX19B
R2	chr22	37770784	37770863	79	1.5575	amplification	focal	22q	1.21E-06	1	ELFN2
R7	chr2	54197623	54197855	232	-1.9393	deletion	focal	2p	4.32E-14	1	PSME4
R7	chr8	144919859	144919910	51	1.8225	amplification	focal	8q	5.02E-09	1	NRBP2
R7	chr10	7769599	7769736	137	-2.1405	deletion	focal	10p	4.49E-11	1	ITIH2
R7	chr16	70365714	70367558	1844	-1.1529	deletion	focal	16q	7.01E-09	1	DDX19B
R8	chr3	142841136	142841168	32	1.598	amplification	focal	3q	1.12E-07	1	CHST2
R8	chr8	144919859	144919935	76	2.045	amplification	focal	8q	4.19E-16	1	NRBP2
R8	chr10	7769599	7769736	137	-1.8335	deletion	focal	10p	6.79E-08	1	ITIH2
R8	chr22	37770784	37770863	79	1.8855	amplification	focal	22q	1.48E-09	1	ELFN2

Supplemental Table 12. Copy number variation in *PKD* genes by renal cyst

Patient ID	Cyst WES#	Chr	*Log2 Ratio	Type	Chr arm	Size (bp)	P value	Gene	Exon
JS9001595	B28 (L8)	chr16	1.4	Amplification	16p	151	1.11E-10	*PKD1*	Ex43
JS9001595	B30 (R1)	chr16	1.25	amplification	16p	214	1.12E-13	*PKD1*	Ex43
JS9001595	B31 (R2)	chr16	1.27	amplification	16p	230	2.94E-12	*PKD1*	Ex43
JS9001595	B33 (R10)	chr16	1.17	amplification	16p	219	1.55E-10	*PKD1*	Ex43
CM001593	A34 (R9)	chr16	3.57	amplification	16p	8330	1.89E-15	*PKD1*	Ex29~Ex41
CM001593	A34 (R9)	chr16	0.82	amplification	16p	3985	4.40E-17	*PKD1*	Ex15~Ex21
CM001593	A34 (R9)	chr16	2.58	amplification	16p	2060	4.69E-73	*PKD*	Ex8~Ex11
CM001593	A33 (R3)	chr16	1.12	amplification	16p	2554	3.85E-47	*PKD1*	Ex35-Ex41
BJA001578	B16 (L8)	chr16	3.36	amplification	16p	28242	1.68E-29	*PKD1; MIR1225*	EX5~EX46
BJA001578	B16 (L8)	chr4	2.06	amplification	4q	67810	6.76E-169	*PKD2*	EX1-EX15
BJA001578	A23 (R4)	chr16	-1.02	deletion	16p	7902	1.73E-10	*PKD1*	Ex2-Ex10

All CNV changes are focal. Segment with an average read count Log2 ratio >0.6 were designated as gains and segments with a log2 value < -0.6 were categorized as losses.

Supplemental Table 13. WES analysis results of significantly mutated genes (n=53) in renal cyst epithelium by MuSiC

Gene	Indels	SNVs	Tot Muts	Covd Bps	Muts pMbp	FDR	Protein family	Protein Class
PKD1	10	20	30	1107621	27.09	$< 10^{-23}$	Polycystin-1	
RECQL	0	9	9	136458	65.95	$< 10^{-23}$	ATP-dependent DNA helicase Q1	DNA helicase(PC00011)
FAM46A	6	0	6	165776	36.19	6.65E-13	Protein FAM46A	
SEC24D	0	8	8	349918	22.86	4.08E-09	Protein transport protein Sec24D	vesicle coat protein(PC00235)
SGSM1	0	7	7	253079	27.66	1.47E-08	Small G protein signaling modulator 1	G-protein modulator(PC00022);cysteine protease(PC00081)
KIAA1217	0	8	8	518291	15.44	4.49E-08	Sickle tail protein homolog	
PKD2	2	4	6	226448	26.5	1.63E-05	Polycystin-2	G-protein modulator(PC00022);ion channel(PC00133);membrane-bound signaling molecule (PC00152); protease(PC00190)
CC2D2A	0	8	8	589344	13.57	1.63E-07	Coiled-coil and C2 domain-containing protein 2A	
PTH2	3	0	3	19187	156.4	1.10E-07	Tuberoinfundibular peptide of 39 residues	
SEMA4C	0	5	5	172406	29	4.69E-08	Semaphorin-4C	membrane-bound signaling molecule(PC00152)
P2RY8	0	4	4	78641	50.86	2.48E-07	P2Y purinoceptor 8	
MKNK2	0	4	4	105276	38	5.02E-06	MAP kinase-interacting serine/threonine-protein kinase 2	non-motor microtubule binding protein(PC00166);non-receptor serine/threonine protein kinase(PC00167)
SLC14A2	0	5	5	187786	26.63	3.83E-05	Urea transporter 2	
DNAH5	0	9	9	910125	9.89	0.000504	Dynein heavy chain 5, axonemal	hydrolase(PC00121);microtubule binding motor protein(PC00156)
CCDC122	0	3	3	54214	55.34	0.000149	Coiled-coil domain-containing protein 122	
LRCH1	0	5	5	169623	29.48	3.94E-05	Leucine-rich repeat and calponin homology domain-containing protein 1	

TNN	0	4	4	271054	14.76	3.94E-05	Tenascin-N	signaling molecule(PC00207)
SERTAD4	0	4	4	151849	26.34	0.001463	SERTA domain-containing protein 4	
ALS2	0	5	5	596566	8.38	4.70E-05	Alsin	
LPGAT1	0	3	3	88832	33.77	0.000399	Acyl-CoA:lysophosphatidylglycerol acyltransferase 1	
CST2	0	2	2	27452	72.85	0.001211	Cystatin-SA	
FRG1	0	3	3	59621	50.32	0.001463	Protein FRG1	ribonucleoprotein(PC00201);transfer/carrier protein(PC00219)
HRCT1	1	1	2	19005	105.2	0.009061	Histidine-rich carboxyl terminus protein 1	
VPS4B	0	2	2	79449	25.17	0.001384	Vacuolar protein sorting-associated protein 4B	non-motor microtubule binding protein(PC00166)
CACNG7	0	2	2	81648	24.5	0.000915	Voltage-dependent calcium channel gamma-7 subunit	voltage-gated calcium channel(PC00240)
CNPY1	0	2	2	18915	105.7	0.00209	Protein canopy homolog 1	
DCTN4	0	3	3	138712	21.63	0.000936	Dynactin subunit 4	
IQGAP1	0	3	3	351205	8.54	0.004638	Ras GTPase-activating-like protein IQGAP1	G-protein modulator(PC00022)
FAM155B	2	0	2	74222	26.95	0.001651	Transmembrane protein FAM155B	
LAMP1	0	3	3	91360	32.84	0.014356	Lysosome-associated membrane glycoprotein 1	membrane trafficking regulatory protein(PC00151)
FREM1	0	5	5	558999	8.94	0.029635	FRAS1-related extracellular matrix protein 1	
MRM1	0	2	2	69244	28.88	0.025275	rRNA methyltransferase 1, mitochondrial	
PTS	0	2	2	33871	59.05	0.00475	6-pyruvoyl tetrahydrobiopterin synthase	
ESYT3	0	3	3	208710	14.37	0.001546	Extended synaptotagmin-3	
UBR7	0	3	3	185315	16.19	0.001906	Putative E3 ubiquitin-protein ligase UBR7	
CAD	0	4	4	627659	6.37	0.000654	CAD protein	cysteine protease(PC00081);ligase(PC00142);

								metalloprotease(PC00153);transferase(PC00220)
DHRS4	0	2	2	47853	41.79	0.004503	Dehydrogenase/reductase SDR family member 4	
ACTR3	0	3	3	95408	31.44	0.00475	Actin-related protein 3	actin and actin related protein(PC00039)
MAZ	0	3	3	269853	11.12	0.001546	Myc-associated zinc finger protein	
TMC1	0	3	3	210577	14.25	0.002581	Transmembrane channel-like protein 1	
NKAIN2	0	3	3	89860	33.39	0.042416	Sodium/potassium-transporting ATPase subunit beta-1-interacting protein 2	
SMARCA2	2	1	3	395769	7.58	0.014643	Probable global transcription activator SNF2L2	DNA helicase(PC00011)
WDFY3	0	5	5	737275	6.78	0.012448	WD repeat and FYVE domain-containing protein 3	
DNMT3A	0	3	3	303234	9.89	0.002589	DNA (cytosine-5)-methyltransferase 3A	
NEUROD2	0	2	2	68730	29.1	0.073826	Neurogenic differentiation factor 2	basic helix-loop-helix transcription factor(PC00055);nuclease(PC00170)
OR5M1	0	2	2	54979	36.38	0.108772	Olfactory receptor 5M1	
SMARCAD1	0	2	2	223937	8.93	0.008335	SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A containing DEAD/H box 1	DNA helicase(PC00011)
KIAA1377	0	3	3	290782	10.32	0.00732	Centrosomal protein of 126 kDa	
GJC2	1	1	2	55640	35.95	0.125793	Gap junction gamma-2 protein	gap junction(PC00105)
SPG7	0	3	3	347762	8.63	0.003873	Paraplegin	metalloprotease(PC00153)
ZFHX3	2	1	3	701642	4.28	0.015709	Zinc finger homeobox protein 3	
RGS1	0	2	2	41636	48.04	0.036208	Regulator of G-protein signaling 1	G-protein modulator(PC00022)
PTGER1	0	2	2	43242	46.25	0.022244	Prostaglandin E2 receptor EP1 subtype	G-protein coupled receptor(PC00021)

FDR, false discovery rate.

Supplemental Table 14. Constitutional pathogenic mutations in principal ciliopathy genes

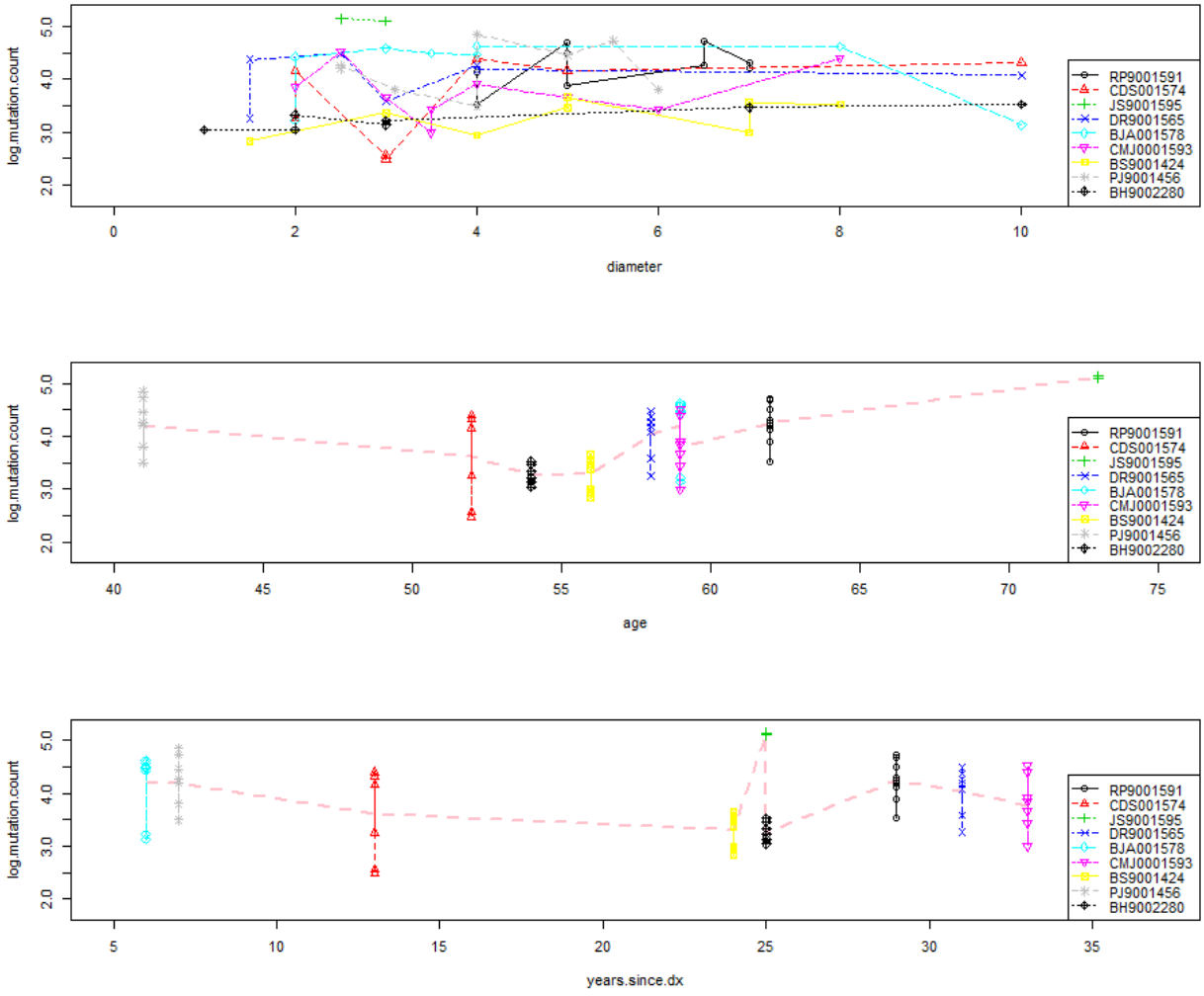
Gene	Category	#Chr	Position	dbSNP ID#	AlleleFreq	SnpEffEffect	Gene	SnpEffHGVS.c	SnpEffHGVS.p
PJ9001456	P.C.	chr1	214822159	None	43/21	frameshift_variant	CENPF	c.7975_7976dupAG	p.Ser2659fs
PJ9001457	P.S	chr11	76912556	None	34/26	frameshift_variant	MYO7A	c.4919delG	p.Gly1640fs
CMJ001593	P.C	chr4	15589551	None	45/28	splice_donor_variant&intron_variant	CC2D2A	c.4179+1delG	
CMJ001595	P.S	chr2	166810195	None	19/74	frameshift_variant&splice_region_variant	TTC21B	c.20_21insCG	p.Lys7fs

P.S., pathogenic inferred from snpEff 'HIGH' impact annotation; P.C., pathogenic inferred from ClinVar.

SUPPLEMENTAL STATISTICAL ANALYSIS

Analysis of somatic variant counts by patient age

I. Analysis of variant counts (N=3,263 variations) in study subjects (N=9)



Below, we fit a linear mixed effects model, where the mixed effects consist of fixed and random effects. The fixed effects are diameter and age. The random effect is a random intercept for each subject. The model is; therefore:

$\text{Log(mutation count}_{ij}) = \beta_0 + \beta_1 * \text{diameter}_{ij} + \beta_2 * \text{age}_i + \gamma_{0i} + \epsilon_{ij},$

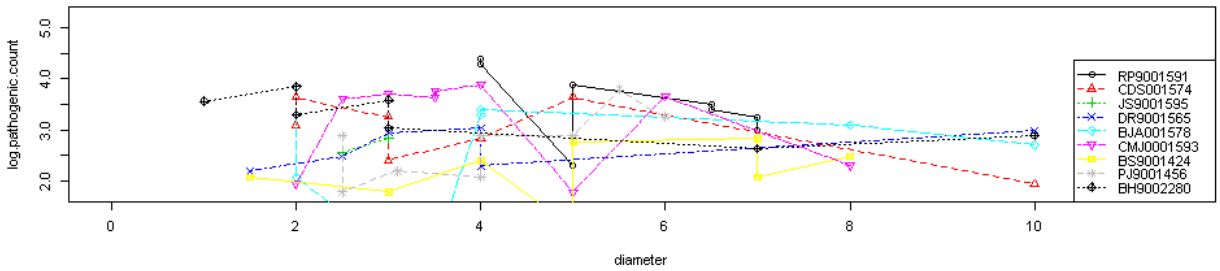
Where $i=1,\ldots,9$ indicates the subject and $j=1,\ldots,m_i$ indicates the # of observations per subject. Here $\gamma_{0i} \sim \text{Normal}(0,\sigma_\gamma)$ is the random effect for subject i, and $\epsilon_{ij} \sim \text{Normal}(0,\sigma_\epsilon)$ is the residual error.

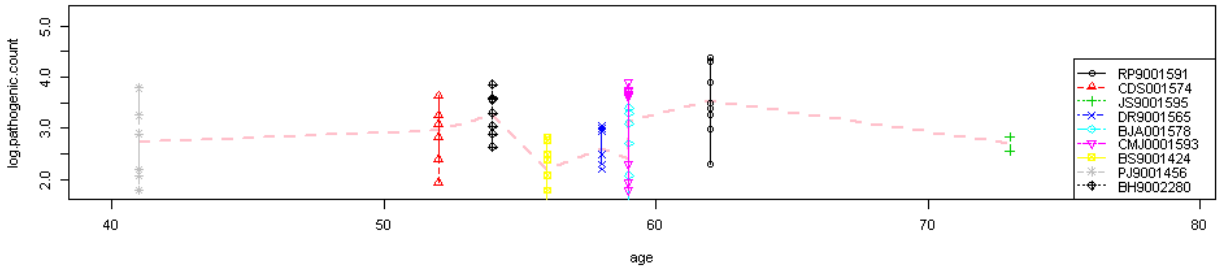
```
lme(log.mutation.count~diameter+age,random=~1|patient)
Linear mixed-effects model fit by REML
Random effects:
 Formula: ~1 | patient
        (Intercept)  Residual
StdDev:    0.477987 0.4896461

Fixed effects: log.mutation.count ~ diameter + age
                Value Std.Error DF  t-value p-value
(Intercept) 1.9914013 1.2904255 55 1.543213  0.1285
diameter    0.0385568 0.0277155 55 1.391165  0.1698
age         0.0314109 0.0224326  7 1.400234  0.2042
 Correlation:
         (Intr) diamtr
diameter -0.111
age      -0.987  0.019

Standardized Within-Group Residuals:
       Min         Q1        Med         Q3        Max
-2.5490576 -0.6135790  0.1578540  0.6405002  1.6287799

Number of Observations: 65
Number of Groups: 9
```

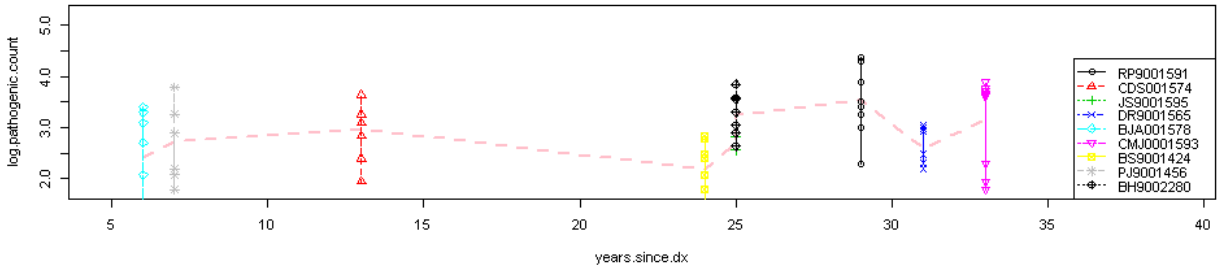
The reason age is not significant (p=0.2042) in the model above is because patient PJ9001456 (grey *) is very young (41) but has a very high mutation count. Therefore we do not see a linear increase in mutation count with age. If we were to restrict the analysis to all subjects over 50, then the effect of age would be very significant (p=0.005; see output below).

```
Linear mixed-effects model fit by REML
 Data: NULL
       AIC      BIC    logLik
  108.0787 118.0236 -49.03933

Random effects:
 Formula: ~1 | patient
        (Intercept)  Residual
StdDev:   0.2104161 0.4903749

Fixed effects: log.mutation.count ~ diameter + age
                 Value Std.Error DF   t-value p-value
(Intercept) -1.4649076 1.2212564 48 -1.199509  0.2362
diameter     0.0387396 0.0279791 48  1.384590  0.1726
age          0.0885528 0.0207249  6  4.272762  0.0052
 Correlation:
         (Intr) diamtr
diameter -0.137
age      -0.992  0.037

Standardized Within-Group Residuals:
        Min          Q1         Med          Q3         Max
-2.37587345 -0.46163074 -0.01423317  0.81118109  1.87578346

Number of Observations: 57
Number of Groups: 8
```

II. Analysis of variant counts (N=1,784 variations classified as pathogenic or likely pathogenic) in study subjects (N=9)








```
> out=lme(log.pathogenic.count~diameter+age,random=reStruct(~1|patient,pdClas
s="pdSymm",REML=FALSE))
> summary(out)
Linear mixed-effects model fit by REML
 Data: NULL
       AIC     BIC    logLik
  170.2983 180.934 -80.14915

Random effects:
 Formula: ~1 | patient
        (Intercept)  Residual
StdDev:   0.3965993 0.7146579

Fixed effects: log.pathogenic.count ~ diameter + age
                 Value Std.Error DF    t-value p-value
(Intercept)  2.5354821 1.2618525 55  2.0093331  0.0494
diameter    -0.0037608 0.0401213 55 -0.0937364  0.9257
```

```
age          0.0058488 0.0219831  7  0.2660608  0.7979
 Correlation:
         (Intr) diamtr
diameter -0.147
age      -0.982  0.010

Standardized Within-Group Residuals:
       Min         Q1        Med         Q3        Max
-2.5909548 -0.6564159  0.2112497  0.7442148  1.4777303

Number of Observations: 65
Number of Groups: 9
```

When we remove patient PJ9001456, age is a significant predictor (higher age implies higher pathogenic count).

```
> out2=lme(log.pathogenic.count~diameter+age,random=reStruct(~1|patient,pdCla
ss="pdSymm",REML=FALSE))
> summary(out2)
Linear mixed-effects model fit by REML
 Data: NULL
       AIC     BIC    logLik
  133.5011 143.446 -61.75055

Random effects:
 Formula: ~1 | patient
         (Intercept)  Residual
StdDev: 2.573239e-05 0.6503021

Fixed effects: log.pathogenic.count ~ diameter + age
                Value Std.Error DF   t-value p-value
(Intercept) -4.004220 1.2008126 48 -3.334592  0.0017
diameter     0.058036 0.0362775 48  1.599769  0.1162
age          0.112998 0.0204946  6  5.513526  0.0015
 Correlation:
         (Intr) diamtr
diameter -0.129
age      -0.988 -0.005

Standardized Within-Group Residuals:
        Min          Q1         Med          Q3         Max
-2.07998196 -0.64887401  0.08380959  0.72471385  1.99506941

Number of Observations: 57
Number of Groups: 8
```

SUPPLEMENTAL METHODS

Study Subjects

Patients enrolled in this study were previously diagnosed with ADPKD and were scheduled for a living donor kidney transplant, and removal of one, or both native kidneys at the NewYork-Presbyterian Hospital/Weill Cornell Medicine campus (NYPH-WCM). Subjects were identified during a preoperative evaluation that occurred 7-10 days before transplant surgery (Supplementary Figure 1). The transplant surgeon (S.K.) determined whether there were clinical indications for nephrectomy prior to enrollment of each subject. If nephrectomy was planned, and the subject was eligible for enrollment, then informed consent was obtained. The protocol was approved by the WCM IRB.

Tissue processing and epithelial cell isolation

Following nephrectomy, the kidney(s) were immediately placed on ice and underwent gross examination (S.S., B.R.). Thereafter, 5-20 cysts per kidney were processed; cyst size and volume were recorded, and cyst epithelial cells were isolated according to standard procedures [1]. Each cyst cavity was washed several times with phosphate buffered solution (PBS) and then incubated with PBS/EDTA to remove epithelial cells from the basement membrane. Epithelial cells were collected by centrifugation and stored at -80°C. DNA was isolated from the cyst epithelial cells and peripheral blood leukocytes (PBL) using the Gentra Puregene DNA extraction kit (Qiagen, Germantown, MD).

Sanger Sequencing

PKD1 (NM_000296.2) and *PKD2* (NM_000297.2) were analyzed by Sanger sequencing as previously described [2]. To avoid amplification of *PKD1* pseudogenes, *PKD1* was amplified using long-range PCR (LR-PCR) primers anchored either in the rare mismatched region within the human homologs, or in the single-copy region of *PKD1* (GeneAmp High Fidelity PCR System, ABI, Foster City, CA). Sanger sequencing data were analyzed by Mutation Surveyor software vs.4.0 (Soft Genetics, State College, PA).

Long-range PCR (LR-PCR) Next Generation Sequencing (NGS)

PKD gene analysis using paired-end NGS was performed by multiplexing individually bar-coded LR-PCR libraries analyzing them in one MiSeq system flow cell (Illumina). Sequencing data were analyzed using a laboratory-developed computational pipeline as described by Tan et al. [3].

Whole Exome Sequencing (WES) and Data Analysis

WES (357,999 exons, >20,000 genes) analyses of renal cyst epithelia and PBL specimens were performed using the HaloPlex Target Enrichment System (Agilent Technologies) and massive parallel sequencing on the Illumina system (San Diego, CA). Somatic and constitutional mutations were analyzed in matched cyst and PBL samples, respectively, and co-analyzed according to established procedures. Briefly, 225 ng of genomic DNA was digested using restriction enzymes, purified and assessed for quality using the Bioanalyzer. The resulting DNA was then hybridized to HaloPlex probes coupled to Illumina sequence motifs and sample barcodes, followed by solid phase capture. Biotinylated DNA-probe hybrids were then ligated and amplified by PCR. The resulting exome DNA library was purified using the Agencourt AMPure XP beads (Beckman Coulter, Inc., Brea, CA) and sequenced on the Illumina HiSeq 2500 platform (100 bp paired-end reads). The total number of reads and captured reads

among these specimens were 67.5 M±7.0 M and 55.0 M±5.2 M (81.6% ± 2.2%), respectively.

WES data analyses of the cyst and matched germline were performed for simultaneous detection of somatic single nucleotide variation (SNV), indels, and copy number variations (CNVs) as previously described [4]. Germline variants were eliminated from the somatic variant list using an FDR corrected Fisher exact test. For identification of somatic mutations, demultiplexed reads from Illumina sequencers were mapped against the GRC37/hg19 human reference genome (vs.19) using Burrows-Wheeler Aligner (BWA 0.7.8) (http://bio-bwa.sourceforge.net/) with the recommended standard settings and preprocessed with SAMtools 0.1.19. GATK (Version 2.8) (https://www.broadinstitute.org/gatk/) for local realignment and base quality score recalibration of the mapped reads. SNVs were called by MuTect (Version 1.1.4) (https://www.broadinstitute.org/cancer/cga/mutect) with the default criteria and filters. Small indels were detected by GATK. Mutations were filtered by variant allele frequency (VAF) where the mutation had to be present in the cyst with minimum total coverage of 8x and a VAF >5% and/or a min of 2 reads. Somatic CNVs were called with VarScan2 (http://varscan.sourceforge.net). Raw copy number regions with chromosome, start position, stop position, and log2 value were processed with DNAcopy package (http://www.bioconductor.org/packages/release/bioc/html/DNAcopy.html) to produce segmented calls delineated by significant change-points of at least three standard deviations (SD). Segments with a log2 value >0.6 were designated as gains and segments with a log2 value < -0.6 were categorized as losses.

Significantly mutated genes and pathway analysis

The pathogenic potential of missense variants was evaluated using the computational analysis tool Combined Annotation–Dependent Depletion (CADD), which enables scoring of deleteriousness of SNVs as well as indel variants. A CADD value of >15 suggests the variant is

potentially pathogenic [5] (http://cadd.gs.washington.edu/). Potential splice-site effects were evaluated using splice site prediction tools ESEfinder 3.0 (http://krainer01.cshl.edu/cgi-bin/tools/ESE3/esefinder.cgi?process=home), Human splicing finder 3.1 (http://www.umd.be/HSF3/) and NNSplice (https://omictools.com/nnsplice-tool) with default settings for all missense, synonymous and intronic changes. Pathogenic and likely pathogenic variants were further filtered by VAF (>30%) and subjected for pathway analysis to identify overrepresented pathways using Reactome (https://reactome.org/) and verified with David (https://david.ncifcrf.gov/). Only significantly overrepresented pathways with low p-values (<0.05); probability that overlap between the queried variant and pathway occur by chance, were reported. Existing variations with a population allele frequency >5% in ExAC (http://exac.broadinstitute.org/) were filtered out as well.

The significance of mutated genes and pathways was analyzed with the Mutational Significance In Cancer (MuSiC) suite of tools (http://gmt.genome.wustl.edu/packages/genome-music/index.html) with the default settings. The MuSiC algorithm calculates the mutation number per gene and compares it to the background mutation rate, applying a Q-score metric and ranking the mutation significance. This algorithm assigns mutations to seven categories: AT transition, AT transversion, CG transition, CG transversion, CpG transition, CpG transversion and indel, and then uses statistical methods based on convolution, the hypergeometric distribution, and likelihood to combine the category-specific binomials to obtain overall P or q values.

Droplet Digital PCR

PKD1 and *PKD2* CNV testing was performed by droplet digital PCR (ddPCR), using 24ng DNA, 1.2 μL of each PrimePCR (Cat#10031276, custom designed *PKD1* and *PKD2* CNV assay) and the Copy Number Reference Assay RPP30 (67 bp, UniqueAssayID: dHsaCP2500350), labeled with FAM and HEX dyes, respectively, 12 μL of the ddPCR™ Supermix (no dUTPs) and 1.2 μL of diluted HaeIII or HingIII enzyme (New England Biolabs, Ipswich, MA) in a total reaction volume of 24 μL, according to the manufacturer's instructions (PrimePCR ddPCR CNV Assay, Bio-Rad, Hercules, CA). Droplets were generated in a QX200 droplet generator (Bio-Rad). PCR was performed in duplicate in a C1000 Touch PCR thermal cycler, and the results were read in a QX200 droplet reader (BioRad).

Statistical Analysis

Each parameter is expressed as the mean ± SD. Two-tailed Student t-test was used to compare normally distributed variables, otherwise, a nonparametric test was applied (i.e., Wilcoxon Rank Sum test). The association between somatic variant count and cyst size was analyzed using linear mixed effects model with log (pathogenic count) as the outcome and age and diameters as predictors. The log transform of pathogenic count was performed in order to satisfy normality assumptions. A random intercept was included for each subject in order to adjust for within subject correlation. These analyses were performed using the "lme" function within the "nlme" package in the R software environment (https://cran.r-project.org/web/packages/nlme/index.html).

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