Supplementary Information

Refining genotype-phenotype correlation in autosomal dominant polycystic kidney disease

Young-Hwan Hwang,* John Conklin,* Winnie Chan, Nicole M. Roslin, Jannel Liu, Ning He, Kairong Wang, Jamie L. Sundsbak, Christina M. Heyer, Masoom Haider, Andrew D. Paterson, Peter C. Harris, and York Pei.

Supplemental Data

Table S1. Characteristics of probands at recruitment

Table S2. *PKD1* protein-truncating mutations in study families

Table S3. *PKD1* non-truncating mutations in study families

Table S4. *PKD1* in-frame insertion/deletions in study families

Table S5. *PKD2* mutations in study families

Table S6. Predicted pathogenic missense mutations in study families

A note on the multivariate Cox proportional hazard model used for the study

Table S1. Characteristics of probands at recruitment (N=220)

Age (years)	38.9 ± 12.7
Male (%)	55.0
Ethnicity (%)	
European	79.5
East Asian	8.2
South Asian	2.7
Black	3.6
Arabian	4.5
Others	1.4
Serum creatinine (mg/dL)	0.90 ± 0.19

Table S2. *PKD1* protein-truncating (PT) mutations in study families

Family No.	Exon	Codon	cDNA change	Protein change	Predicted Effect	PKDB
TOR43	1	56	c.166_167insCGCGGGC	p.Pro56fs59X	Frameshift	novel
TOR2	3	96	c.288_359del*	p.Leu96fs	Large deletion	novel
TOR324	3	97	c.290delA	p.Asp97fs2X	Frameshift	novel
TOR263	3	116	c.348_352delTTTAA	p.Asn116fs1X	Frameshift	1x
TOR198	5	211	c.631_632insTTCAGCCCACAGGC…	p.Ser211fs76X	Frameshift	novel
TOR363	5	231	c.692_693dupT	p.Leu231fs29X	Frameshift	novel
TOR154 & 225	5	286	c.856_862delTCTGGCC	p.Ser286fs1X	Frameshift	3x
TOR379	8	559	c.1674delG	p.Pro559fs24X	Frameshift	novel
TOR329	10	672	c.2016dupG	p.Gly672fs40X	Frameshift	1x
TOR141	10	696	c.2085dupC	p.Ala696fs17X	Frameshift	7x
TOR137	11	705	c.2113C>T	p.Gln705X	Nonsense	1x
TOR242	11	812	c.2433_2434delCT	p.Ser812fs85X	Frameshift	novel
TOR308	11	869	c.2607delC	p.Arg869fs28X	Frameshift	novel
TOR253	11	873	c.2618_2621delTCTG	p.Val873fs23X	Frameshift	1x
TOR300	11	885	c.2652dupC	p.Cys885fs19X	Frameshift	novel
TOR346	12	972	c.2914A>T	p.Lys972X	Nonsense	novel
TOR410	IVS12	995	c.2986-2A>G	p.Ser995fs	Splice site	novel
TOR250	14	1065	c.3194_3209delACCAGTTCCAGCCTCC	p.His1065fs33X	Frameshift	1x
TOR279	15	1210	c.3628G>T	p.Glu1210X	Nonsense	1x

TOR331	15	1347	c.4041_4042delCA	p.His1347fs82X	Frameshift	novel
TOR88	15	1436	c.4306C>T	p.Arg1436X	Nonsense	1x
TOR244	15	1582	c.4746G>A	p.Trp1582X	Nonsense	3x
TOR159	15	1599	c.4797C>G	p.Tyr1599X	Nonsense	novel
TOR314	15	1627	c.4880delA	p.Tyr1627fs6X	Frameshift	novel
TOR196	15	1630	c.4888C>T	p.Gln1630X	Nonsense	1x
TOR192	15	1664	c.4992C>G	p.Tyr1664X	Nonsense	novel
TOR403 & 377	15	1672	c.5014_5015delAG	p.Arg1672fs97X	Frameshift	29x
TOR136	15	1693	c.5079C>A	p.Tyr1693X	Nonsense	2x
TOR139	15	1696	c.5086C>T	p.Gln1696X	Nonsense	3x
TOR189	15	1963	c.5887dupG	p.Val1963fs26X	Frameshift	novel
TOR178	15	2039	c.6115C>T	p.Gln2039X	Nonsense	1x
TOR66 & 248	15	2136	c.6406C>T	p.Gln2136X	Nonsense	3x
TOR316	15	2196	c.6586C>T	p.Gln2196X	Nonsense	1x
TOR392	15	2243	c.6727_6728delCA	p.Gln2243fs17X	Frameshift	2x
TOR12	15	2265	c.6795C>A	p.Tyr2265X	Nonsense	1x
TOR302	16	2354	c.7060C>T	p.Gln2354X	Nonsense	1x
TOR48	17	2402	c.7204C>T	p.Arg2402X	Nonsense	2x
TOR38 & 4	18	2430	c.7288C>T	p.Arg2430X	Nonsense	7x
TOR261	18	2449	c.7346_7347insA	p.Thr2449fs51X	Frameshift	novel
TOR374	18	2474	c.7421_7430delGCTCTTGCCG	p.Gly2474fs142X	Frameshift	novel

TOR388	18	2476	c.7426_7429delTGCC	p.Cys2476fs142X	Frameshift	1x
TOR186	19	2556	c.7666C>T	p.Gln2556X	Nonsense	7x
TOR291	21	2639	c.7915C>T	p.Arg2639X	Nonsense	5x
TOR17	22	2706	c.8116_8125delACCGTGACGC	p.Thr2706fs46X	Frameshift	novel
TOR304	23	2810	c.8428G>T	p.Glu2810X	Nonsense	3x
TOR089	25	3000	c.8998delC	p.Arg3000fs73X	Frameshift	novel
TOR386	IVS27	3196	c.9568+1G>T	p.Leu3196fs	Splice site	novel
TOR361	30	3319	c.9957_9958delCG	p.Ser3319fs69X	Frameshift	1x
TOR412	IVS31	3390	c.10171-1G>C	p.Gln3390fs	Splice site	novel
TOR16	IVS33	3469	c.10405+1G>A	p.Asp3469fs	Splice site	novel
TOR328	35	3509	c.10525_10526delGA	p.Glu3509fs225X	Frameshift	novel
TOR197	36	3550	c.10648_10658delCTGCCGGCCTG	p.L3550fs72X	Frameshift	Novel
TOR404	36	3551	c.10652_10662delCGGCCTGGTGT	p.Pro3551fs111X	Frameshift	Novel
TOR383	IVS36	3607	c.10821+1G>A	p.Lys3607fs	Splice site	novel
TOR126	39	3734	c.11202C>A	p.Tyr3734X	Nonsense	novel
TOR182	40	3773	c.11314_11317dup	p.Ala3773fs43X	Frameshift	novel
TOR254	40	3781	c.11343C>G	p.Tyr3781X	Nonsense	2x
TOR293	40	3793	c.11378delG	p.Gly3793fs32X	Frameshift	novel
TOR303	40	3798	c.11393C>G	p.Ser3798X	Nonsense	novel
TOR229	42	3851	c.11553delC	p.Phe3851fs91X	Frameshift	novel
TOR309	43	3922	c.11766G>A	p.Trp3922X	Nonsense	3x

TOR393	43	3979	c.11935C>T	p.Gln3979X	Nonsense	2x
TOR378	44	4004	c.12010C>T	p.Gln4004X	Nonsense	4x
TOR266 & 270	44	4011	c.12031C>T	p.Gln4011X	Nonsense	4x
TOR354	44	4021	c.12061C>T	p.Arg4021X	Nonsense	5x
TOR195	44	4042	c.12124C>T	p.Gln4042X	Nonsense	8x
TOR296	46	4209	c.12624dupT	p.Glu4209X	Nonsense	novel

Recurrent mutations within the study are highlighted by shaded bars.

Table S3. *PKD1* non-truncating (NT) mutations in study families

Family No.	Exon	Codon	cDNA change	Protein change	Specific Mutation	PKDB
TOR271	5	410	c.1202-9G>A	p.Ala410fs	Atypical splice site	1x
TOR360	6	421	c.1261C>T	p.Arg421Cys	Missense	novel
TOR392	6	429	c.1286G>T	p.Trp429Leu	Missense	1x
TOR385	6	432	c.1295C>T	p.Ala432Val	Missense	2x
TOR241	6	436	c.1306T>C	p.Cys436Arg	Missense	1x
TOR351	6	456	c.1367T>C	p.Leu456Pro	Missense	novel
TOR276	7	466	c.1396G>A	p.Val466Met	Missense	2x
TOR406	7	531	c.1591G>A	p.Glu531Lys	Missense	novel
TOR318	11	727	c.2180T>C	p.Leu727Pro	Missense	7x
TOR395	11	899	c.2696C>G	p.Leu899Val	Missense	novel
TOR356	12	967	c.2899T>C	p.Trp967Arg	Missense	4x
TOR366	13	998	c.2992G>C	p.Ala998Pro	Missense	novel
TOR175	14	1095	c.3284A>G	p.Tyr1095Cys	Missense	novel
TOR335	15	1164	c.3490G>C	p.Gly1164Arg	Missense	novel
TOR342	15	1319	c.3955G>A	p.Gly1319Arg	Missense	novel
TOR323	15	1350	c.4049C>T	p.Thr1350Met	Missense	1x
TOR319	15	1870	c.5609A>G	p.Asn1870Ser	Missense	novel
TOR256	15	1999	c.5995G>A	p.Gly1999Ser	Missense	2x
TOR200	15	2166	c.6496C>T	p.Arg2166Cys	Missense	4x

TOR237	15	2215	c.6643C>T	p.Arg2215Trp	Missense	1x
TOR347	15	2305	c.6916-9G>A	p.Gln2305fs10X	Atypical splice site	2x
TOR307	17	2363	c.7088T>A	p.Val2363Glu	Missense	1x
TOR343	18	2470	c.7409C>T	p.Pro2470Leu	Missense	novel
TOR406	18	2494	c.7480G>A	p.Glu2494Lys	Missense	novel
TOR202	19	2516	c.7546C>T	p.Arg2516Cys	Missense	8x
TOR190	23	2752	c.8255C>A	p.Ala2752Asp	Missense	1x
TOR179*	23	2767	c.8299C>T	p.Arg2767Cys	Missense	3x
TOR227	23	2786	c.8356A>G	p.Lys2786Glu	Missense	novel
TOR368	23	2822	c.8464G>A	p.Val2822Met	Missense	2x
TOR327	23	2835	c.8504C>T	p.Pro2835Leu	Missense	novel
TOR119	23	2920	c.8759T>C	p.Leu2920Pro	Missense	novel
TOR61	23	2931	c.8791+5G>C	p.Gly2931fs	Atypical splice site	1x
TOR285	25	3010	c.9029T>A	p.Leu3010Gln	Missense	novel
TOR371	25	3052	c.9154G>C	p.Gly3052Arg	Missense	novel
TOR240	25	3067	c.9202-16G>A	p.Pro3067fs	Atypical splice site	2x
TOR401	27	3188	c.9563A>C	p.Asn3188Thr	Missense	novel
TOR102	29	3264	c.9791T>C	p.Leu3264Pro	Missense	novel
TOR193	31	3390	c.10167+25_+43delGGCTG GGCTGGGGGTCCTG	p.Gln3390fs	Atypical splice site	4x
TOR288	36	3599	c.10796C>T	p.Ser3599Leu	Missense	1x
TOR235	37	3613	c.10838T>C	p.Leu3613Pro	Missense	novel

TOR249	37	3643	c.10927G>A	p.Val3643Met	Missense	novel
TOR103	37	3657	c.10969G>C	p.Ala3657Asp	Missense	novel
TOR330	37	3658	c.10972A>G	p.Lys3658Glu	Missense	novel
TOR264	39	3753	c.11258G>A	p.Arg3753Gln	Missense	novel
TOR134 & 358	39	3753	c.11257C>T	p.Arg3753Trp	Missense	4x
TOR405	43	3915	c.11744C>A	p.Ala3915Asp	Missense	novel
TOR087*	45	4054	c.12161C>T	p.Ser4054Phe	Missense	1x
TOR18	46	4150	c.12448C>T	p.Arg4150Cys	Missense	2x
TOR118 & 181	46	4155	c.12465T>G	p.Phe4155Leu	Missense	1x
TOR294	46	4211	c.12632A>T	p.Glu4211Val	Missense	novel

*Family with bilineal ADPKD; recurrent mutations are highlighted by shaded bars.

Table S4. *PKD1* in-frame insertion/deletions (IF indels) in study families

Family No.	Exon	Codon	cDNA change	Protein change	Domain	PKDB	PROVEAN	Segregation[‡]
TOR161	15	1661	c.4981_4983delAAC	p.Asn1661del	PKD12	novel	-10.311	++
TOR224	15	1996	c.5986_5994delGTGCAGCGC	p.Val1996_Arg1998del3	PKD16	novel	-11.406	++
TOR411	15	2224	c.6672_6673insGTGGGGCACTACTGC	p.Pro2224_Val2225insVGHYC	REJ	novel	-10.395	+
TOR163	23	2763	c.8287_8289delCTC	p.Leu2763del	REJ	1x	-8.788	++
TOR367	40	3778	c.11332_11340delACCAGCGATinsTGG	p.Thr3778_Asp3780del3insTrp	Extracellular	novel	-9.254	+
TOR338	43	3969	c.11905_11916delGGCCGCCCGCGC	p.Gly3969_Arg3972del4	Extracellular	novel	-6.505	
TOR087*	45	4130	c.12389_12391delTGG	p.Val4130del	C-terminal cytoplasmic	1x	-11.002	++
TOR72	45	4131	c.12391_12393delGAG	p.Glu4131del	C-terminal cytoplasmic	1x	-13.037	+++

[*]Family with bilineal ADPKD; [‡]variant segregated with 1-2 (+), 3-4 (++), and ≥5 disease-informative family members (i.e. affected or unaffected older than age 40 years)

Table S5. *PKD2* mutations in study families

Family No.	Exon	Codon	cDNA change	Protein change	Predicted Effect	PKDB
TOR257 & 223	1~15	1	c.1_2907del*	p.Met1fs	Large del	novel
TOR373 & 408	1	42	c.124_125InsGACCCGGGCCGGC TGATGGCTGGCTGCGCGGCCG TGGGCGCCAGCCTCGCCG	p.Ala42fs66X	Frameshift	2x
TOR213	1	68	c.203dupC	p.Pro68fs23X	Frameshift	11x
TOR380	1	135	c.405delC	p.Gly135fs97X	Frameshift	novel
TOR185	1	180	c.539delT	p.Leu180fs52X	Frameshift	novel
TOR396 & 233	1	189	c.567G>A	p.Trp189X	Nonsense	1x
TOR259	2	201	c.602G>A	p.Trp201X	Nonsense	1x
TOR176 & 413	IVS2	237	c.709+1G>A	p.Leu237fs	Splice site	4x
TOR201	IVS2	237	c.710-2A>G	p.Leu237fs	Splice site	1x
TOR334	IVS2	237	c.710-10T>G	p.Leu237fs	Atypical splice site	novel
TOR187	IVS3	281	c.844-2A>C	p.Lys281fs	Splice site	novel
TOR216	4	320	c.958C>T	p.Arg320X	Nonsense	7x
TOR210, 212 & 232	4	325	c.973C>T	p.Arg325X	Nonsense	6x
TOR29 & 221	4	325	c.974G>A	p.Arg325Gln	Missense	3x
TOR394	IVS4	365	c.1094+1G>A	p.Ala365fs	splice site	1x
TOR105, 107 & 387	IVS4	365	c.1094+3_+6delGTAA	p.Ala365fs	Atypical splice site	4x
TOR290 & 344	5	392	c.1175dupA	p.Trp392X	Nonsense	novel
TOR177, 191, 204, 376, 214 & 215	5	417	c.1249C>T	p.Arg417X	Nonsense	10x
TOR31	IVS5	439	c.1319+1G>A	p.Arg439fs	Splice site	8x
TOR220	6	449	c.1339_1345dup	p.Gly449fs23X	Frameshift	2x
TOR206	IVS6	517	c.1549-2A>G	p.Leu517fs	Splice site	novel

TOR398	7	537	c.1609C>T	p.Gln537X	Nonsense	1x
TOR208	7	569	c.1704dupT	p.Val569fs3X	Frameshift	novel
TOR74	8	632	c.1894T>C	p.Cys632Arg	Missense	1x
TOR101	IVS8	633	c.1898+5G>A	p.Ile633fs	Atypical splice site	4x
TOR209	9	654	c.1960C>T	p.Arg654X	Nonsense	5x
TOR104	9	666	c.1998_2001delCTTT	p.Phe666fs6X	Frameshift	1x
TOR217	IVS10	706	c.2118-2A>G	p.Lys706fs	Splice site	1x
TOR130, 8, 77 & 179*	11	720	c.2159dupA	p.Asn720fs4X	Frameshift	10x
TOR203	IVS11	747	c.2240+1G>C	p.Gly747fs	Splice site	novel
TOR325	IVS12	786	c.2358+1G>A	p.Arg786fs	Splice site	1x
TOR219	13	803	c.2407C>T	p.Arg803X	Nonsense	6x
TOR390	13	812	c.2435_2436delCT	p.Ser812X	Nonsense	novel
TOR218 &375	14	845	c.2533C>T	p.Arg845X	Nonsense	3x
TOR402	14	850	c.2548G>T	p.Glu850X	Nonsense	novel
TOR262 & 350	14	872	c.2614C>T	p.Arg872X	Nonsense	16x
TOR122	15	969	c.2906G>T	p.X969Leu	Nonstop mutation	novel

*Family with bilineal ADPKD; recurrent mutations are highlighted by shaded bars.

Table S6. Predicted pathogenic missense mutations in study families

Family No.	Gene	Exon	Codon	cDNA change	Protein change	Domain[†]	PKDB	Polyphen-2	SIFT	Segregation[‡]
TOR360	PKD1	6	421	c.1261C>T	p.Arg421Cys	C-lectin	novel	0.879	0.02	+++
TOR392	PKD1	6	429	c.1286G>T	p.Trp429Leu	C-lectin	1x	0.985	0	++
TOR385	PKD1	6	432	c.1295C>T	p.Ala432Val	C-lectin	2x	0.991	0	+
TOR241	PKD1	6	436	c.1306T>C	p.Cys436Arg	C-lectin	1x	0.310	0	+
TOR351	PKD1	6	456	c.1367T>C	p.Leu456Pro	C-lectin	novel	0.990	0	
TOR276	PKD1	7	466	c.1396G>A	p.Val466Met	C-lectin	2x	0.961	0.01	++
TOR318	PKD1	11	727	c.2180T>C	p.Leu727Pro	.	7x	0.990	0	+
TOR395	PKD1	11	899	c.2696C>G	p.Leu899Val	PKD3	novel	0.784	0.02	+
TOR356	PKD1	12	967	c.2899T>C	p.Trp967Arg	PKD4	4x	1.000	0	+
TOR366	PKD1	13	998	c.2992G>C	p.Ala998Pro	PKD4	novel	1.000	0	+
TOR175	PKD1	14	1095	c.3284A>G	p.Tyr1095Cys	PKD5	novel	0.994	0	+++
TOR335	PKD1	15	1164	c.3490G>C	p.Gly1164Arg	PKD6	novel	1.000	0	+
TOR342	PKD1	15	1319	c.3955G>A	p.Gly1319Arg	PKD8	novel	1.000	0	+
TOR323	PKD1	15	1350	c.4049C>T	p.Thr1350Met	PKD8	1x	0.971	0.09	++
TOR319	PKD1	15	1870	c.5609A>G	p.Asn1870Ser	PKD14	novel	0.999	0	
TOR256	PKD1	15	1999	c.5995G>A	p.Gly1999Ser	PKD16	2x	0.999	0.3	++
TOR200	PKD1	15	2166	c.6496C>T	p.Arg2166Cys	REJ	4x	0.983	0.03	+
TOR237	PKD1	15	2215	c.6643C>T	p.Arg2215Trp	REJ	1x	0.862	0.01	+
TOR307	PKD1	17	2363	c.7088T>A	p.Val2363Glu	REJ	1x	0.993	0.03	

TOR343	PKD1	18	2470	c.7409C>T	p.Pro2470Leu	REJ	novel	0.998	0.01	+
TOR406	PKD1	18	2494	c.7480G>A	p.Glu2494Lys	REJ	novel	0.939	0.24	+
TOR202	PKD1	19	2516	c.7546C>T	p.Arg2516Cys	REJ	8x	1.000	0.01	++
TOR190	PKD1	23	2752	c.8255C>A	p.Ala2752Asp	REJ	1x	1.000	0	++
TOR179*	PKD1	23	2767	c.8299C>T	p.Arg2767Cys	REJ	3x	1.000	0	+
TOR227	PKD1	23	2786	c.8356A>G	p.Lys2786Glu	REJ	novel	0.998	0.05	+
TOR368	PKD1	23	2822	c.8464G>A	p.Val2822Met	REJ	2x	0.906	0	
TOR327	PKD1	23	2835	c.8504C>T	p.Pro2835Leu	.	novel	1.000	0.01	+
TOR119	PKD1	23	2920	c.8759T>C	p.Leu2920Pro	.	novel	0.987	0.01	+
TOR285	PKD1	25	3010	c.9029T>A	p.Leu3010Gln	.	novel	0.979	0.03	+
TOR371	PKD1	25	3052	c.9154G>C	p.Gly3052Arg	GPS	novel	0.998	0	+++
TOR401	PKD1	27	3188	c.9563A>C	p.Asn3188Thr	PLAT	novel	1.000	0	++
TOR102	PKD1	29	3264	c.9791T>C	p.Leu3264Pro	Cytoplasmic	novel	0.996	0	++
TOR288	PKD1	36	3599	c.10796C>T	p.Ser3599Leu	TM domain	1x	0.999	0	+
TOR235	PKD1	37	3613	c.10838T>C	p.Leu3613Pro	Cytoplasmic	novel	0.987	0.01	
TOR249	PKD1	37	3643	c.10927G>A	p.Val3643Met	Cytoplasmic	novel	0.925	0.18	
TOR103	PKD1	37	3657	c.10969G>C	p.Ala3657Asp	Cytoplasmic	novel	0.935	0.03	+++
TOR330	PKD1	37	3658	c.10972A>G	p.Lys3658Glu	Cytoplasmic	novel	0.214	0.03	
TOR264	PKD1	39	3753	c.11258G>A	p.Arg3753Gln	Extracellular	novel	0.998	0	++
TOR134&358	PKD1	39	3753	c.11257C>T	p.Arg3753Trp	Extracellular	4x	0.994	0	++
TOR405	PKD1	43	3915	c.11744C>A	p.Ala3915Asp	TM domain	novel	0.242	0.02	

TOR087*	PKD1	45	4054	c.12161C>T	p.Ser4054Phe	Extracellular	1x	0.917	0.02	+
TOR18	PKD1	46	4150	c.12448C>T	p.Arg4150Cys	Cytoplasmic C-terminal	2x	1.000	0	
TOR118&181	PKD1	46	4155	c.12465T>G	p.Phe4155Leu	Cytoplasmic C-terminal	1x	0.997	0.01	+
TOR294	PKD1	46	4211	c.12632A>T	p.Glu4211Val	Cytoplasmic C-terminal	novel	0.554	0.01	
TOR29&221	PKD2	4	325	c.974G>A	p.Arg325Gln	Extracellular	3x	0.891	0.01	
TOR74	PKD2	8	632	c.1894T>C	p.Cys632Arg	Extracellular	1x	0.588	0.01	

[†]Domain is annotated according to the UniProtKB (www.uniprot.org); [ǂ]variant segregated with 1-2 (+), 3-4 (++), and ≥5 disease informative family members (i.e. affected or unaffected older than age 40 years)

A note on multivariate Cox proportional hazard model for ESRD and patient death

We performed multivariate Cox proportional hazard analysis with a frailty model to account for random clustering between related subjects from the same family (**Table 4**). The variance of the frailty (i.e. theta) differed significantly from 0, indicating a significant cluster effect (data not shown). Hence, we used the frailty model instead of a standard Cox model.