Supplemental Material

Table of Contents

Supplemental Table 1: Additional coding region genetic variants with MAF <1% by whole exome sequencing in published ADPKD-PCLD genes in *ALG9* loss-of-function carriers.

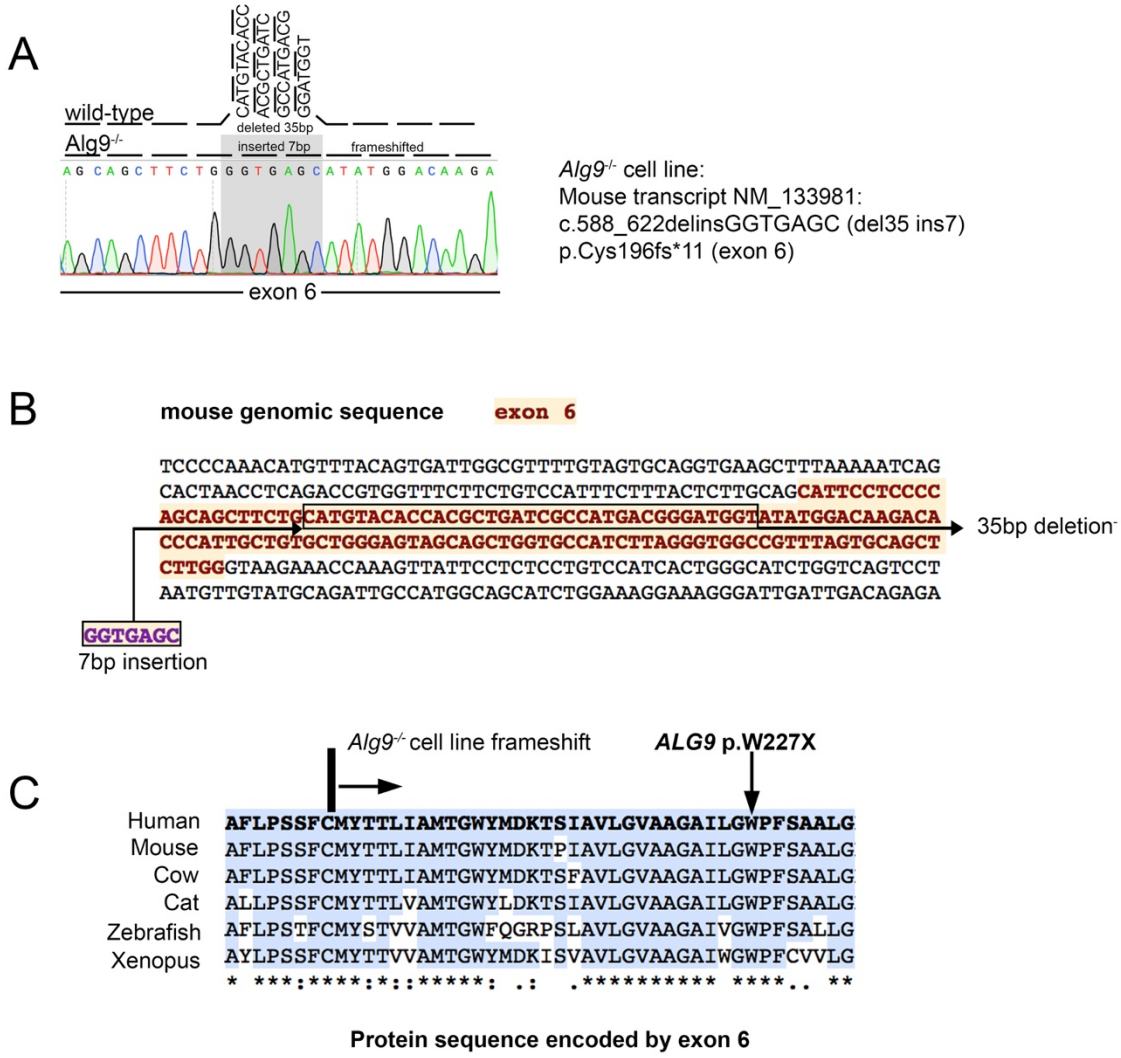
Family ID	Gene	Nucleotide change	Amino Acid Change	MAF Gnomad	MetaSVM [A]	ClinVar/ Database[B]	REVEL[A]
MC2	LRP5[C]	c.3919C>T	p.Arg1307Trp	1.07E-04	D	n/a	0.53
MC5	PKD1	c.9499A>T	p.Ile3167Phe	0.00121	T	Indeterminate	0.459
MC8	PRKCSH	c.962_963insAGA [D]	p.Glu325dup	3.24E-05	-	n/a	-
MC10	PKD1	c.11537+3_11537+5dup	-	0.00975	-	n/a	-
MC12	PKD1	c.3316C>G	p.Leu1106Val	0.00228	T	Likely Neutral	0.057
MC6	PRKCSH	c.628G>A	p.Glu210Lys	4.66E-04	T		0.129
MC13	PKHD1	c.1676G>A	p.Arg559Gln	4.81E-04	T	n.d.	0.279

[A] variant prediction. D: Deleterious, T: Tolerated. REVEL score ranges 0 to 1, with 1 representing all simulations suggest pathogenicity.
[B] ADPKD database (http://pkdb.mayo.edu/) or ARPKD database (http://www.humgen.rwth-aachen.de/index.php), n.d. = not determined, but in silico suggests benign. n/a = not present in database
[C] *LRP5* is in linkage disequilibrium on Chromosome 11 with *GANAB* (1).
[D] Common area of duplication/deletion in Glu repeat region

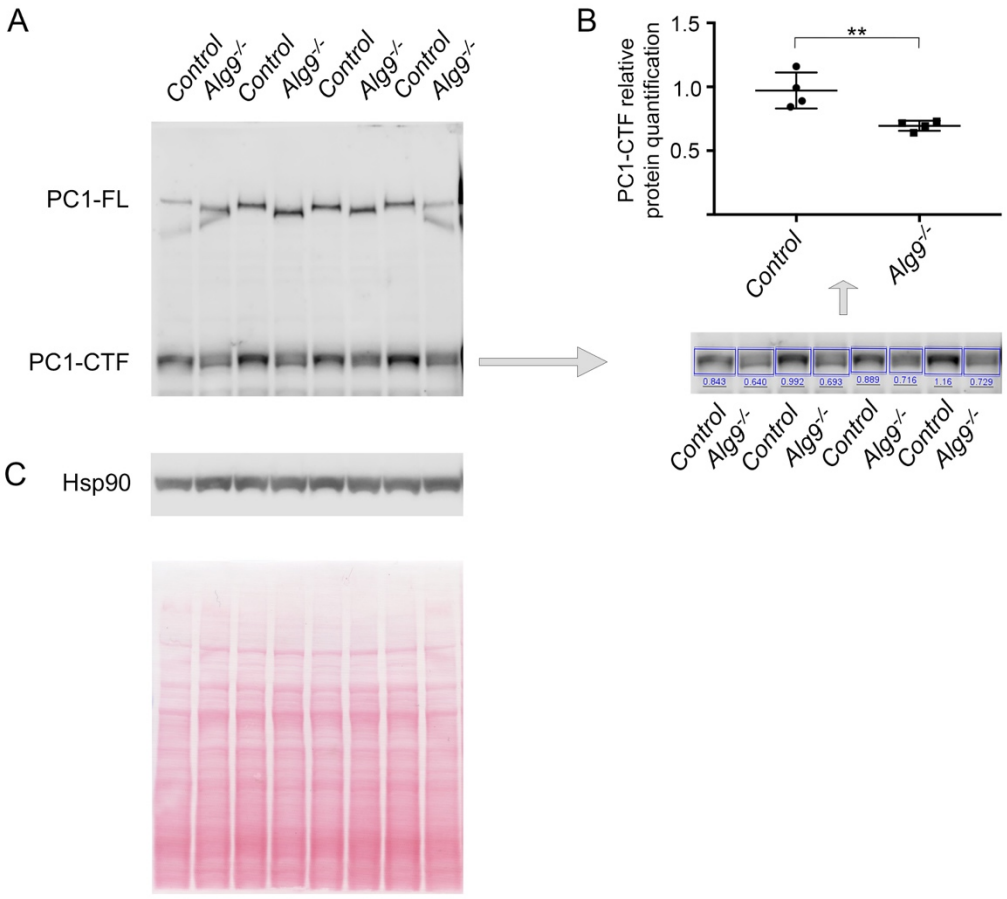
Supplemental Table 2: Matched Control[A] Phenotype Data

Family ID/Gender	Imaging type (age)[B]	Kidney Cysts[C]	TSTC[C]	Nephrolithiasis[D]	eGFR (age)[E]
MC15/F	CT+ (81)	1	3	-	51(83y)
MC16/F	MRI (67)	1	8	-	15(68y)
MC17/F	CT+ (37)	0	0	-	71(43y)
MC18/M	US (74)	0	0	-	34(77y)
MC20/F	MRI+ (36)	0	0	-	111(44y)
MC21/M	CT+ (41)	0	0	-	99(50y)
MC22/F	CT+ (86)	0(1)	3	-	13(97y)
MC23/F	CT+ (86)	0(1)	2	-	30(95y)
MC25/F	MRI (63)	0	0	-	78(63y)
MC27/M	CT+ (69)	2	2	-	58(83y)
MC29/M	CT+ (69)	1	0		66(74y)
MC30/M	CT+ (41)	0	0	-	73(51y)
MC31/F	CT+ (81)	2	2	-	60(83y)
MC32/M	CT+ (69)	0	0	-	60(75y)
MC34/F	US (66)	0	0	Y	90(66y)
MC35/F	CT+ (61)	2	1	-	79(62y)
MC36/F	US (66)	0	0	-	76(68y)
MC38/F	MRI+ (36)	0	0	-	68(44y)
MC39/M	US (74)	0	0	-	27(74y)
MC40/F	CT+ (61)	0	1	-	67(65y)
MC41/F	CT+ (37)	0	0	-	82(47y)
MC42/M	CT+ (69)	2	0	-	73(76y)

[A] Matched controls randomly selected from amongst the MyCode™ cohort participants lacking rare mutations in established ADPKD/PCLD disease genes.
[B] +: with Contrast
[C] Kidney cysts (>8mm) and lesions Too Small To Characterize (TSTC; 4-8mm) as described in Methods and Results. When additional imaging allowed for re-characterization indeterminate masses as cysts, cyst count inclusive of these is noted (#).
[D] Noted during blinded analysis. Y:Yes, +:Nephrolithiasis noted on additional CT scan if available
[E] most recent outpatient estimated Glomerular Filtration Rate (eGFR)



Supplemental Figure 1: Sanger sequencing of *Alg9*$^{-/-}$ cell line. (A) Sanger sequencing of PCR amplicon of *Alg9* exon 6 from *Alg9*$^{-/-}$ cell line genomic DNA shows homozygous sequence with a large insertion/deletion, illustrated on reference sequence **(B)** resulting in a frameshift with termination after 11 erroneous amino acids. **(C)** *Alg9* exon 6 is highly conserved from humans to Xenopus and present and translated in all protein-coding transcripts (2). The location of the truncating mutation in our *Alg9*$^{-/-}$ cell line truncates the protein at the same exon as the human mutation p.W227X in our cohort.



Supplemental Figure 2: Quantification of relative PC1 protein expression level in *Alg9*$^{-/-}$ cells. (A) 110 micrograms of whole cell lysate from four independent biological samples each of wild-type (control) and *Alg9*$^{-/-}$ cell lines were run in parallel for western blot. **(B)** PC1-CTF detected with anti-HA antibody is quantified digitally, subtracting the average local background of sampled from above and below the band. The 4 biological samples for each genotype are plotted with mean and SD indicated. Two-tailed t-test shows a statistically significant difference between the sample means, P=0.009, with mean PC1-CTF intensity from *Alg9*$^{-/-}$ cell 71% that of wild-type. **(C)** Blot for Hsp90 and Ponceau stain of the full membrane demonstrate equal protein loading.

Supplemental Methods

The following primer sequences containing the desired edit and their reverse complements were used to prime the site-directed-mutagenesis PCR:

p.A232P: (5'-GCCATTCAGTGCACCTCTTGGTTTACC-3')

p.A280V: (5'-GAAGTTGGTGATTGTACCACTCAACATTG-3')

p.N315S: (5'-GATTTCTGAATTTCAGTGTAGCCTTTGC-3')

p.R370K : (5'-CACAAAGAGGAGAAATTTCTTTTCCC-3')

p.R517L: (5'-CCTCTGGCCACCCTGATTGTTCCTACTG-3')

p.Y287C: (5'-CAACATTGTTTTGTGTAATATCTTTACTCC-3')

Supplemental Acknowledgements

Regeneron Genetics Center Banner List of Contributors (all contributors are listed in alphabetical order):

RGC Management and Leadership Team:

Goncalo Abecasis, Aris Baras, Michael Cantor, Giovanni Coppola, Aris Economides, John D. Overton, Jeffrey G. Reid, Alan Shuldiner.

Sequencing and Lab Operations:

Christina Beechert, Caitlin Forsythe, Erin D. Fuller, Zhenhua Gu, Michael Lattari, Alexander Lopez, John D. Overton, Thomas D. Schleicher, Maria Sotiropoulos Padilla, Karina Toledo, Louis Widom, Sarah E. Wolf, Manasi Pradhan, Kia Manoochehri, Ricardo H. Ulloa.

Genome Informatics:

Xiaodong Bai, Suganthi Balasubramanian, Leland Barnard, Andrew Blumenfeld, Yating Chai, Gisu Eom, Lukas Habegger, Young Hahn, Alicia Hawes, Shareef Khalid, Jeffrey G. Reid, Evan K. Maxwell, John Penn, Jeffrey C. Staples, Ashish Yadav.

Planning, Strategy, and Operations:

Paloma M. Guzzardo, Marcus B. Jones, Lyndon J. Mitnaul.

Yale CMG (NIH M#UM1HG006504-05) is funded by the National Human Genome Research Institute and the National Heart, Lung, and Blood Institute. The GSP Coordinating Center (U24 HG008956) contributed to cross-program scientific initiatives and provided logistical and general study coordination. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

1. Besse W, Choi J, Ahram D, Mane S, Sanna-Cherchi S, Torres V, and Somlo S. A non-coding variant in GANAB explains isolated polycystic liver disease (PCLD) in a large family. *Human mutation.* 2017.
2. The UniProt C. UniProt: the universal protein knowledgebase. *Nucleic acids research.* 2017;45(D1):D158-D69.