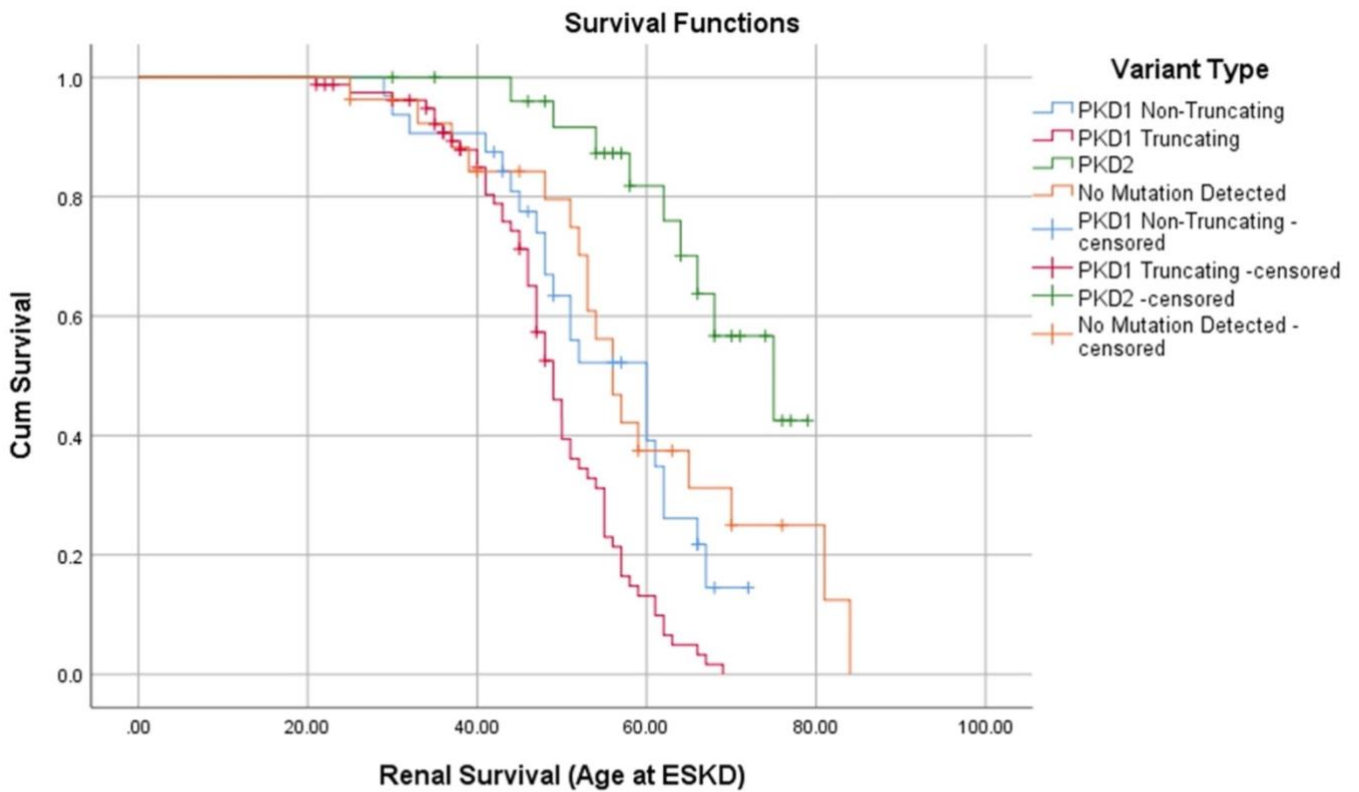


Supplementary Information:

Supplementary Figure 1: Additional survival analyses

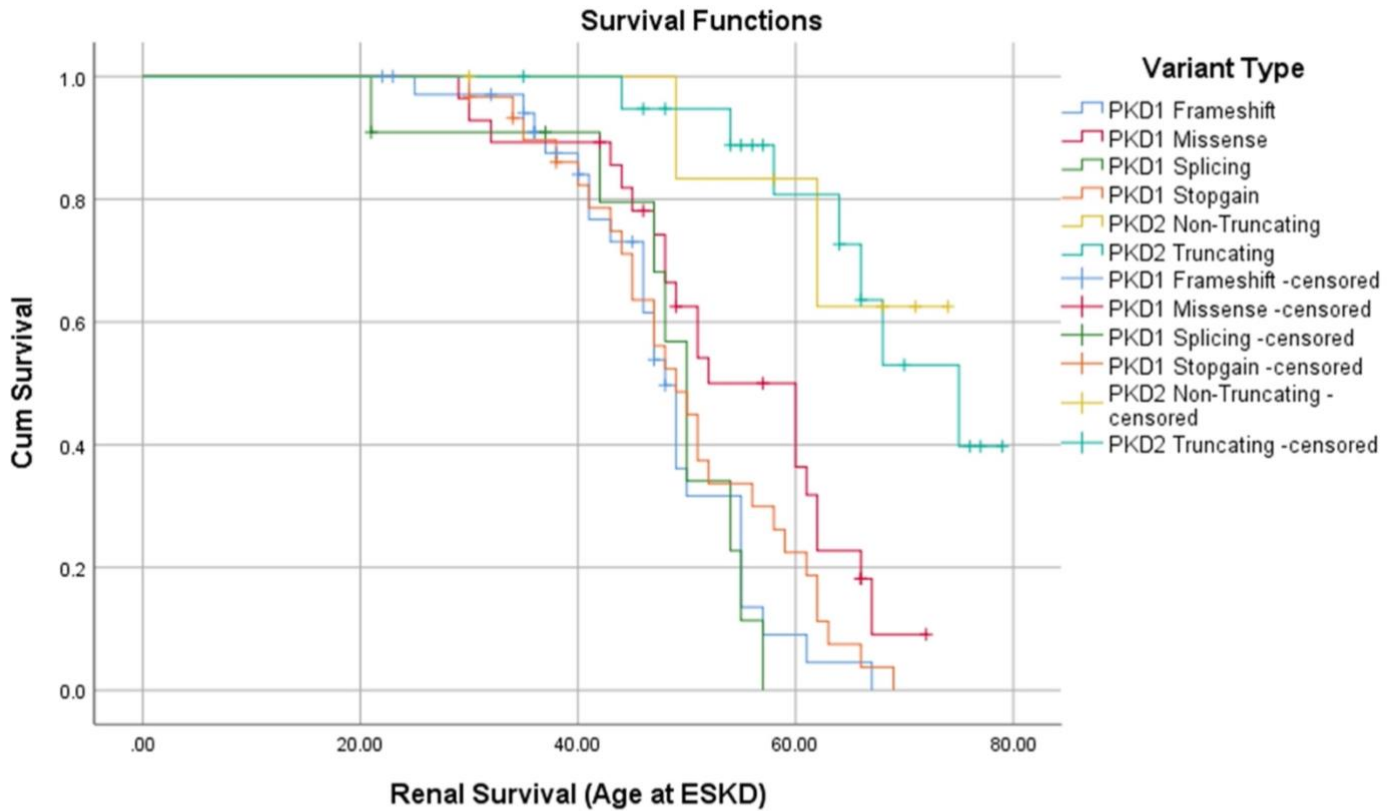
Supplementary Figure 1A: Kaplan-Meier survival curve and results from Log Rank (Mantel-Cox) test for patients with *PKD1* truncating, *PKD1* non-truncating, *PKD2* variants as well as patients where no disease-causing mutation was detected.



Pairwise Comparisons

Variant_Type	PKD1 Non-Truncating		PKD1 Truncating		PKD2		No Mutation Detected	
	Chi-Square	Sig.	Chi-Square	Sig.	Chi-Square	Sig.	Chi-Square	Sig.
Log Rank (Mantel-Cox)								
PKD1 Non-Truncating			9.187	0.002	11.660	0.001	0.371	0.542
PKD1 Truncating	9.187	0.002			41.020	1.507E-10	12.353	0.0004
PKD2	11.660	0.001	41.020	1.507E-10			5.777	0.016
No Mutation Detected	0.371	0.542	12.353	0.0004	5.777	0.016		

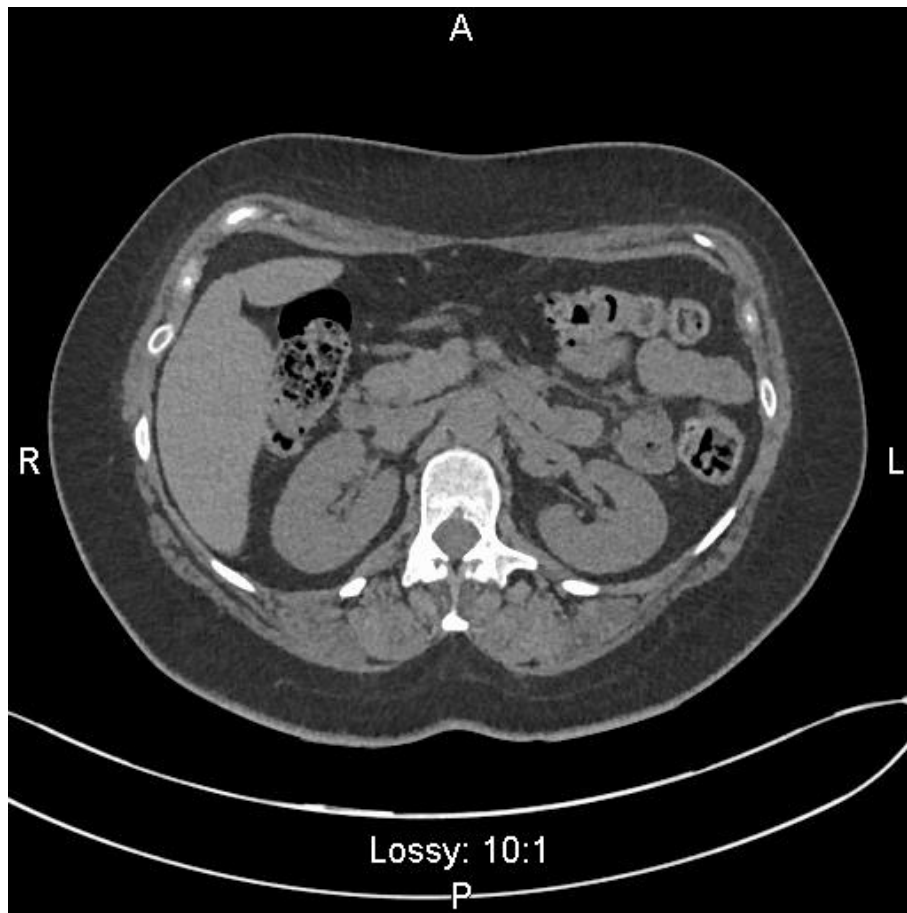
Supplementary Figure 1B: Kaplan-Meier survival curve and results from Log Rank (Mantel-Cox) test for patients with *PKD1* truncating, *PKD1* missense, *PKD1* splicing, *PKD1* stopgain, *PKD2* truncating and *PKD2* non-truncating variants.



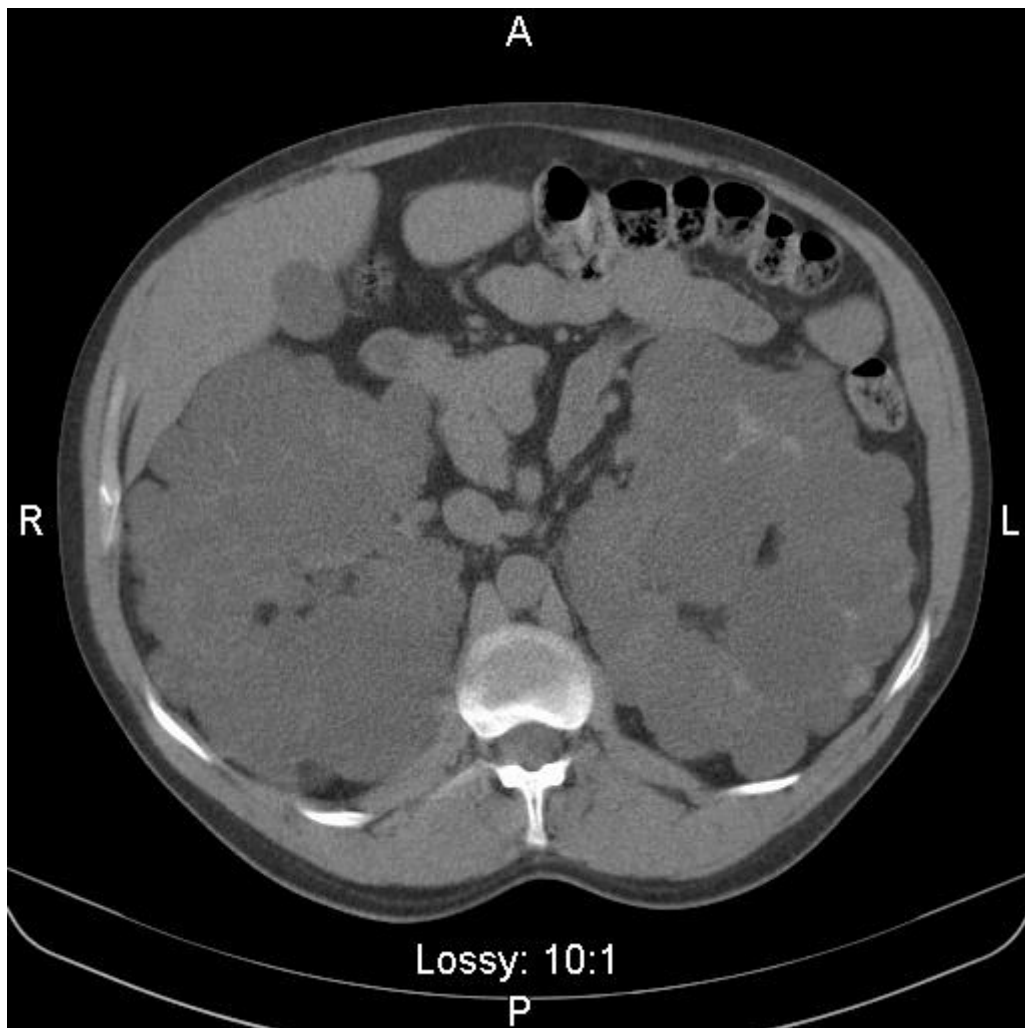
Variant	Pairwise Comparisons											
	PKD1 Frameshift Chi-Square	Sig.	PKD1 Missense Chi-Square	Sig.	PKD1 Splicing Chi-Square	Sig.	PKD1 Stopgain Chi-Square	Sig.	PKD2 Non-Truncating Chi-Square	Sig.	PKD2 Truncating Chi-Square	Sig.
Log Rank (Mantel-Cox)	PKD1 Frameshift		5.763	0.016	0.009	0.925	0.751	0.386	11.402	0.001	26.617	2.481E-07
	PKD1 Missense	5.763	0.016	4.641	0.031	3.140	0.076	4.689	0.030	10.962	0.001	
	PKD1 Splicing	0.009	0.925	4.641	0.031	0.884	0.347	8.985	0.003	23.584	1.196E-06	
	PKD1 Stopgain	0.751	0.386	3.140	0.076	0.884	0.347	9.504	0.002	23.909	1.010E-06	
	PKD2 Non-Truncating	11.402	0.001	4.689	0.030	8.985	0.003	9.504	0.002	0.022	0.882	
	PKD2 Truncating	26.617	2.481E-07	10.962	0.001	23.584	1.196E-06	23.909	1.010E-06	0.022	0.882	

Supplementary Figure 2: Representative kidney imaging

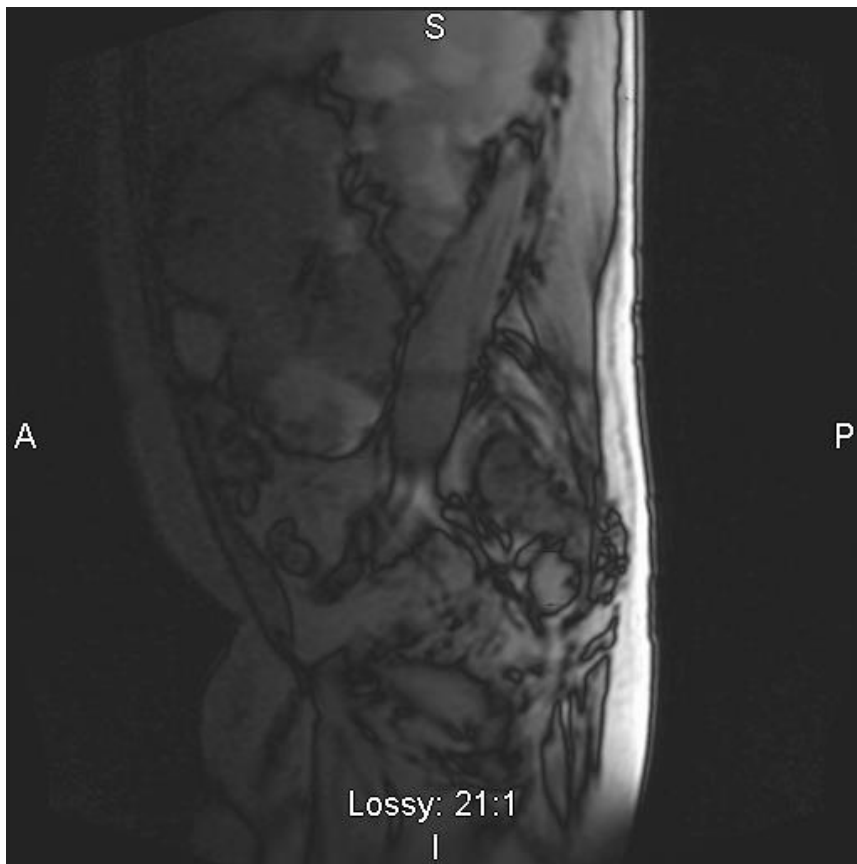
Supplementary Figure 2A: Normal kidney on CT scan



Supplementary Figure 2B: CT scan demonstrating massively enlarged kidneys secondary to truncating *PKD1* stopgain variant in 46-year-old male maintained on haemodialysis (patient 10216).



Supplementary Figure 2C: Enlarged kidney secondary to a *PKD2* missense variant in middle aged male with well preserved kidney function (patient 8124).



Supplementary Methods:

Mayo Clinic Variant Interpretation Guidelines: Variants were assigned a score in each of the nine categories outlined below. The final cumulative variant score determined the classification of the variant (Sum of the other scores: ≥ 13 = Highly Likely Pathogenic, 7 to 12 = Likely Pathogenic, -4 to 6 = Indeterminate, ≤ -5 = Likely Neutral)

GV/GD Score: Assessment of the chemical difference of the residue in orthologs (to fish) (Grantham Variation; GV) and between the residue and the substitution (Grantham Difference; GD): Score +8 to -4 (Rossetti 2007)

Domain Score: Assessment of conservation in a domain: Score 0 to +4

Recurrent AA: Residue that is mutated in ADPKD with substitution different than seen here: Score +1 per incidence

Structure Score: Predicted change in secondary structure due to substitution: Score 0 to +2

gnomAD Score: Score depending on occurrence in gnomAD: 0x = +2, 1x = 0, 2x = -2, 3x = -4 etc.

Previous description: Previous description of this variant: Score up to +2 per occurrence

Segregation Score: Score up to +4 depending on extent of segregation demonstrated

Other variant: No other variant of interest in patient = +2, to truncating variant in patient = -5

Splicing: Score for prediction of altered splicing: no evidence for IVS variant = -5 to strongly predicted +5