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Supplementary Figure 2: Lifetime risk of the development of kidney failure comparing subjects with specific high-risk APOL1 genotypes to low-risk APOL1 genotype. Median time to kidney failure denoted and global Logrank P-value shown.

Supplementary Figure 3: eGFR change over time in subjects by specific APOL1 genotype. eGFR decline rate calculated with covariates held at mean values. Adjusted for primary cause of kidney disease, family history of kidney disease, diabetes mellitus, hypertension, genetic ancestry cluster, and initial measured eGFR.

Supplementary Figure 4: Lifetime risk of developing kidney failure for the interaction between APOL1 high-risk genotype and primary cause of kidney disease. Cox proportional hazard models applied to 1426 CKD patients. Analyses included the main effect of APOL1 risk genotype which remained significant in each model. Cox models were adjusted for family history of kidney disease, sex, ZIP code based median income, genetic ancestry cluster, Elixhauser comorbidity score, diabetes mellitus and hypertension.

Supplementary Figure 5: eGFR change over time in subjects characterized by number of APOL1 risk alleles. eGFR decline rate calculated with covariates held at mean values. Adjusted for primary cause of kidney disease, family history of kidney disease, diabetes mellitus, hypertension, genetic ancestry cluster, and initial measured eGFR.

Supplementary Methods.

Supplementary Table 1: Model characteristic used for gene- and gene-set based collapsing analyses. Max minor allele frequency (MAF) imposed using gnomAD and ExAC as references across six genetic ancestries: African, American, Non-Finnish European, Finnish, East Asian, and South Asian. Internal max MAF uses the full IGM sequence database as reference.

Model Name	Variant Type	max MAF	Internal max MAF	Pathogenicity Filter (Polyphen-2 HumVar)	Regional Intolerance Filter
Dominant Rare Missense	Missense	0.05%	0.10%	Probably, Possibly, Unknown, Benign	None
Dominant Rare Missense MTR	Missense	0.05%	0.10%	Probably, Possibly, Unknown, Benign	MTR ≤50%
Dominant Rare Missense LIMBR	Missense	0.05%	0.10%	Probably, Possibly, Unknown, Benign	LIMBR ≤50%
Dominant Rare Not Benign	PTV + Missense + inframe indel	0.05%	0.10%	Probably, Possibly, Unknown	None
Dominant Rare Not Benign MTR	PTV + Missense + inframe indel	0.05%	0.10%	Probably, Possibly, Unknown	MTR ≤50%
Dominant Rare Not Benign LIMBR	PTV + Missense + inframe indel	0.05%	0.10%	Probably, Possibly, Unknown	LIMBR ≤50%
Dominant Rare PTV	PTV	0.10%	0.10%	NA	NA
Dominant Ultra Rare Deleterious	PTV + Missense + inframe indel	0	0.05%	Probably	None
Dominant Ultra Rare Not Benign	PTV + Missense + inframe indel	0	0.05%	Probably, Possibly, Unknown	None
Dominant Ultra Rare Not Benign MTR	PTV + Missense + inframe indel	0	0.05%	Probably, Possibly, Unknown	MTR ≤50%
Dominant Ultra Rare Not Benign LIMBR	PTV + Missense + inframe indel	0	0.05%	Probably, Possibly, Unknown	LIMBR ≤50%
Recessive Non-synonymous	PTV + Missense + inframe indel	1.00%	1.00%	Probably, Possibly, Unknown, Benign	None
Dominant Synonymous	Synonymous	0.05%	0.10%	NA	None
Recessive Synonymous	Synonymous	1.00%	1.00%	NA	None

Abbreviations: PTV = Protein Truncating Variant, MTR = Missense Tolerance Ratio, LIMBR = Localized Intolerance Model using Bayesian Regression.

Max MAF is applied across the seven genetic ancestries from gnomAD: African, American, Ashkenazi Jewish, East Asian, South Asian, Finnish European, Non-Finnish European; and 6 from ExAC: African, American, Non-Finnish European, Finnish European, East Asian, South Asian.

Supplementary Table 2: Gene names used for gene-set analyses.

Pyroptosis Pathway	Inflammasome Pathway	Autosomal Recessive Kidney Genes (part 1)	Autosomal Recessive Kidney Genes (part 2)	Autosomal Recessive Kidney Genes (part 3)	Autosomal Recessive Kidney Genes (part 4)	Autosomal Recessive Kidney Genes (part 5)
AIM2	*AIM2*	*ABCC6*	*CLDN19*	*FLNB*	*NARS2*	*SCARB2*
APIP	*CARD8*	*ABCD4*	*COL18A1*	*FRAS1*	*NBN*	*SCNN1A*
CASP1	*CASP1*	*ACE*	*COL4A4*	*FREM2*	*NECTIN1*	*SCO1*
CASP4	*CASP4*	*ACP5*	*COQ2*	*G6PC*	*NEK1*	*SDCCAG8*
CASP6	*CASP5*	*ADAMTS13*	*COQ6*	*GALNT3*	*NEK8*	*SERPINH1*
CASP8	*DDX3X*	*AGPAT2*	*COQ7*	*GBA*	*NHP2*	*SI*
DHX9	*DHX33*	*AGT*	*COQ8B*	*GCDH*	*NPHP1*	*SLC12A1*
ELANE	*GSDMD*	*AGTR1*	*COQ9*	*GLB1*	*NPHP3*	*SLC12A3*
GSDMA	*MEFV*	*AGXT*	*COX10*	*GLIS2*	*NPHP4*	*SLC1A1*
GSDMB	*NAIP*	*AHI1*	*COX14*	*GLIS3*	*NPHS1*	*SLC22A12*
GSDMC	*NLRC4*	*ALG8*	*COX20*	*GRHPR*	*NPHS2*	*SLC25A1*
GSDMD	*NLRP1*	*ALG9*	*COX6B1*	*GRIP1*	*NUP107*	*SLC26A4*
GSDME	*NLRP3*	*ALMS1*	*COX8A*	*HBB*	*NUP205*	*SLC2A10*
GZMA	*NLRP6*	*AMN*	*CPT1A*	*HES7*	*NUP93*	*SLC2A2*
GZMB	*NLRP9*	*ANKS6*	*CPT2*	*HGD*	*OCLN*	*SLC34A1*
NAIP	*PYCARD*	*APC2*	*CRB2*	*HOGA1*	*OPLAH*	*SLC34A3*
NLRC4		*APOPT1*	*CRTAP*	*HPS1*	*PAF1*	*SLC37A4*
NLRP1		*APRT*	*CSPP1*	*HPSE2*	*PALB2*	*SLC4A4*
NLRP6		*ARHGDIA*	*CTC1*	*HSD11B2*	*PC*	*SLC7A7*
NLRP9		*ARL13B*	*CTNS*	*HSD17B3*	*PDE6D*	*SLC9A3R1*
TREM2		*ARL6*	*CUBN*	*HSD17B4*	*PDSS1*	*SLX4*
ZBP1		*ARNT2*	*CYP11B1*	*HSD3B2*	*PDSS2*	*SMARCAL1*
		ATP6V0A4	*CYP17A1*	*HSPA9*	*PET100*	*SMOC1*
		ATP6V1B1	*CYP21A2*	*HSPG2*	*PEX1*	*SPINT2*
		ATP7B	*CYP24A1*	*HYLS1*	*PEX10*	*STAR*
		AUH	*DCDC2*	*ICK*	*PEX11B*	*STRA6*
		B3GLCT	*DCHS1*	*IFT122*	*PEX12*	*STRADA*
		B4GAT1	*DDX59*	*IFT140*	*PEX13*	*STUB1*
		B9D1	*DGKE*	*IFT172*	*PEX14*	*SUCLA2*
		B9D2	*DHCR7*	*IFT27*	*PEX16*	*SUGCT*
		BBIP1	*DIS3L2*	*IFT43*	*PEX19*	*TACO1*
		BBS1	*DLL3*	*IFT80*	*PEX2*	*TAPT1*
		BBS10	*DMP1*	*IKBKAP*	*PEX26*	*TBC1D20*
		BBS12	*DNA2*	*INPP5E*	*PEX3*	*TBC1D24*
		BBS2	*DNAAF1*	*INPPL1*	*PEX5*	*TBCE*
		BBS4	*DNASE1L3*	*INSR*	*PEX6*	*TCTN2*
		BBS5	*DNMT3B*	*INVS*	*PGM3*	*TCTN3*
		BBS7	*DPH1*	*IQCB1*	*PHGDH*	*THOC6*
		BBS9	*DYNC2H1*	*ITGA3*	*PIGL*	*TMCO1*
		BCS1L	*EFEMP2*	*ITGA6*	*PIGN*	*TMEM138*
		BMPER	*EGF*	*ITGA8*	*PIGT*	*TMEM216*
		BRIP1	*EIF2AK3*	*ITGB4*	*PKHD1*	*TMEM231*
		BSCL2	*EIF2B4*	*JAM3*	*PLCE1*	*TMEM237*
		BSND	*EMP2*	*KANK1*	*PLG*	*TMEM67*
		BUB1B	*ENPP1*	*KANK2*	*PLOD1*	*TMEM70*
		C1QA	*EPG5*	*KANK4*	*PMM2*	*TRAF3IP1*
		C1QB	*ERBB3*	*KCNJ1*	*PNPLA6*	*TRAIP*
		C1QC	*ERCC4*	*KCNJ10*	*POMC*	*TRAP1*
		C2	*ERCC6*	*KIF14*	*POMT1*	*TRIM32*
		C3	*ERCC8*	*KIF7*	*POR*	*TRMT5*
		C4A	*ESCO2*	*KL*	*PPP1R15B*	*TRNT1*
		C5orf42	*ETFA*	*KYNU*	*PRKCD*	*TRPM6*
		CA2	*ETFB*	*LAMB2*	*PRODH*	*TTC21B*
		CAD	*ETFDH*	*LAMB3*	*PSAP*	*TTC37*
		CC2D2A	*EVC*	*LAMC2*	*PTPRO*	*TTC8*
		CCBE1	*EVC2*	*LARS*	*PYGM*	*TXNL4A*
		CD151	*FAH*	*LCAT*	*RAB18*	*UBE2T*
		CD19	*FAM20A*	*LDHA*	*RAB23*	*UBR1*
		CD81	*FAM20C*	*LFNG*	*RAB3GAP1*	*UMPS*
		CD96	*FAN1*	*LMBRD1*	*RAB3GAP2*	*UPB1*
		CECR1	*FANCA*	*LONP1*	*RAD51C*	*UQCC2*
		CENPF	*FANCC*	*LPIN1*	*RBBP8*	*VIPAS39*
		CEP104	*FANCD2*	*LRIG2*	*RBM8A*	*VPS33B*
		CEP120	*FANCE*	*LRP2*	*RECQL4*	*WDPCP*
		CEP164	*FANCF*	*LRP4*	*RET*	*WDR19*
		CEP290	*FANCG*	*LTBP4*	*RIN2*	*WDR34*
		CEP41	*FANCI*	*LZTFL1*	*RIPK4*	*WDR35*
		CEP83	*FANCL*	*MEFV*	*RIPPLY2*	*WDR60*
		CFH	*FANCM*	*MESP2*	*RMND1*	*WDR73*
		CFI	*FASTKD2*	*MKKS*	*RNU4ATAC*	*WNT3*
		CHRM3	*FAT4*	*MKS1*	*ROR2*	*WNT7A*
		CHST14	*FBLN5*	*MMACHC*	*RPGRIP1L*	*XDH*
		CISD2	*FBXL4*	*MRPS22*	*RRM2B*	*XPNPEP3*
		CLCNKA	*FGF20*	*MUT*	*RTTN*	*XRCC4*
		CLCNKB	*FGFR1*	*MVK*	*SARS2*	*XYLT2*
		CLDN16	*FKBP14*	*MYO1E*	*SBDS*	*ZAP70*
					SC5D	*ZMPSTE24*

Supplementary Table 3: Novel *APOL1* variants identified.

Variant ID	HGVS_c	HGVS_p	*APOL1* Risk Genotype	SRA Domain	Number of Individuals
22-36653390-A-G	c.124A>G	p.Thr42Ala	Low-risk	No	2
22-36653403-A-G	c.137A>G	p.Asp46Gly	Low-risk	No	2
22-36653423-G-A	c.157G>A	p.Gly53Ser	Low-risk	No	2
22-36657720-C-T	c.266C>T	p.Thr89Ile	Low-risk	No	1
22-36661201-G-A	c.319G>A	p.Glu107Lys	Low-risk	No	1
22-36661272-CGA-C	c.391_392delGA	p.Asp131fs	Low-risk	No	1
22-36661274-A-ATTT	c.393_394insTTT	p.Asp131_Lys132insPhe	Low-risk	No	1
22-36661772-C-T	c.890C>T	p.Pro297Leu	Low-risk	No	1
22-36661812-C-G	c.930C>G	p.Ile310Met	Low-risk	No	1
22-36661849-G-C	c.967G>C	p.Glu323Gln	Low-risk	No	1
22-36662017-G-A	c.1135G>A	p.Glu379Lys	Low-risk	Yes	1
22-36662032-A-T	c.1150A>T	p.Ile384Phe	Low-risk	Yes	1
22-36662039-A-G	c.1157A>G	p.Asn386Ser	Low-risk	Yes	1

Supplementary Table 4: Expanded demographics and baseline data of included CKD patients, divided by APOL1 risk genotype, including single risk allele carriers and specific high-risk genotypes.

	Low-Risk Genotype	Single Risk Allele G1 or G2	High-Risk Genotype	G1/G1	G2/G2	G1/G2
Number	1187	336	239	98	32	109
Biologic Sex, Female (%)	564 (48%)	170 (51%)	105 (44%)	47 (48%)	9 (28%)	51 (45%)
Age at recruitment, years median (IQR)	43.7 (27.9 – 57.8)	46.7 (32.1 – 58.6)	43.4 (30.2 – 54.6)	43.0 (32.8 – 52.8)	44.4 (37.1 – 58.2)	43.3 (28.8 – 54.8)
Age at last followup, years median (IQR)	48.4 (32.1 – 62.2)	51.0 (36.5 – 62.2)	48.8 (35.9 – 59.3)	49.4 (37.7 – 56.5)	49.9 (38.6 – 62.6)	47.9 (34.9 – 60.1)
Follow-up time, years median (IQR)	3.7 (0 – 6.1)	3.5 (0 – 6.2)	3.7 (0 – 7.1)	3.1 (0 – 7.1)	3.2 (0-6.7)	4.7 (1.5 – 7.2)
Pediatric at recruitment (%)	149 (13%)	27 (8%)	4 (2%)	3 (3%)	0 (0%)	0 (0%)
Developed Kidney Failure (%)	630 (53%)	198 (59%)	168 (70%)	73 (74%)	21 (66%)	74 (68%)
Age at Kidney Failure, years median (IQR)	43.3 (30.5 – 55.4)	44.8 (30.7 – 55.3)	40.6 (28.0 – 50.2)	40.5 (29.4 – 48.9)	41.5 (28.4 – 53.4)	40.8 (27.9 – 49.9)
Received Kidney Transplant (%)	538 (45%)	163 (49%)	150 (63%)	68 (69%)	18 (56%)	64 (59%)
Family History of Kidney Disease (%)	399 (34%)	108 (32%)	83 (35%)	37 (38%)	12 (38%)	35 (32%)
Initial eGFR, mL/min/1.73m^2 mean (IQR)	57.9 (33.2 – 97.6)	58.7 (34.6 – 86.3)	49.7 (34.5 – 81.7)	53.5 (31.8 – 90.4)	45.0 (19.4 – 67.7)	49.7 (34.7 – 81.7)
Self-Described Race and ethnicity						
Asian, Hispanic or Latinx	3 (0.2%)	1 (0.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Asian, Not Hispanic or Latinx	5 (0.4%)	1 (0.3%)	1 (0.4%)	1 (1%)	0 (0%)	0 (0%)
Black/African American, Hispanic or Latinx	70 (6%)	25 (7%)	14 (6%)	11 (11%)	1 (3%)	2 (2%)
Black/African American, Not Hispanic or Latinx	294 (25%)	148 (44%)	149 (61%)	68 (69%)	20 (63%)	61 (56%)
Black/African American, Unspecified Ethnicity	5 (0.4%)	2 (0.6%)	2 (1%)	1 (1%)	0 (0%)	1 (1%)
Native American, Hispanic or Latinx	3 (0.2%)	1 (0.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Unknown or preferred not to specify, Hispanic or Latinx	265 (22%)	49 (15%)	16 (7%)	4 (4%)	3 (9%)	9 (8%)
Unknown or preferred not to specify, Not Hispanic or Latinx	41 (3%)	14 (4%)	1 (0.4%)	0 (0%)	0 (0%)	1 (1%)
Unknown or preferred not to specify, Unspecified Ethnicity	4 (0.3%)	1 (0.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
White, Hispanic or Latinx	428 (36%)	79 (24%)	41 (17%)	10 (10%)	7 (22%)	24 (22%)
White, Not Hispanic or Latinx	62 (5%)	13 (4%)	15 (6%)	3 (3%)	1 (3%)	11 (10%)
White, Unspecified Ethnicity	7 (0.6%)	2 (0.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Genetic Ancestry Cluster						
Majority Black/African American	364 (31%)	194 (58%)	170 (71%)	79 (81%)	19 (59%)	72 (66%)
Majority Hispanic or Latinx	195 (16%)	17 (5%)	5 (2%)	2 (2%)	0 (0%)	3 (3%)
Admixed connecting cluster	628 (53%)	125 (37%)	64 (27%)	17 (17%)	13 (41%)	34 (31%)
ZIP Code Median Income (by quintile)						
1 (Highest)	33 (3%)	11 (3%)	3 (1%)	0 (0%)	1 (3%)	2 (2%)
2	355 (30%)	108 (32%)	71 (30%)	33 (34%)	10 (31%)	28 (26%)
3	515 (43%)	139 (41%)	102 (43%)	41 (42%)	14 (44%)	47 (43%)
4	218 (18%)	63 (19%)	52 (22%)	19 (19%)	7 (22%)	26 (24%)
5 (lowest)	18 (2%)	5 (1%)	3 (1%)	1 (1%)	0 (0%)	2 (2%)
Missing	48 (4%)	10 (3%)	8 (3%)	4 (4%)	0 (0%)	4 (4%)
Hypertension	452 (38%)	149 (44%)	108 (45%)	39 (40%)	12 (38%)	57 (52%)
Diabetes Mellitus	183 (12%)	55 (16%)	37 (15%)	14 (14%)	2 (6%)	21 (19%)
Elixhauser Comorbidity Score, median (IQR)	5 (0 – 9)	5 (2 – 8)	7 (4 – 8)	7 (2.5 – 8)	8 (4 – 8)	8 (4 – 9.75)
Missing	450 (38%)	134 (40%)	86 (36%)	39 (40%)	12 (38%)	35 (32%)

Supplementary Table 5: Monogenic kidney diseases identified within the study. Includes variant classification, and criteria asserted.

Case	APOL1 Genotype	Gene	Variant	DNA Change	Protein Change	Genotype	ACMG	ACMG Criteria	Genetic Diagnosis	OMIM Number
CKD2_0926	High risk	COL4A5	X-107821341-G-T	c.679G>T	p.Gly227Cys	hemi	LP	PM1, PM2_sup, PM5, PP2, PP3	Alport syndrome 1, X-linked	301050
CKD2_0947	High risk	PKD1	16-2164695-G-A	c.2329C>T	p.Gln777Ter	het	LP	PVS1, PM2_sup	Polycystic kidney disease 1	601313
CKD2_0769	High risk	WT1	11-32450048-G-T	c.779C>A	p.Ser260Ter	het	LP	PVS1, PM2_sup	Denys-Drash syndrome	607102
CKD2_0838	High risk	INF2	14-105167956-C-T	c.254C>T	p.Ser85Leu	het	LP	PM1, PM2_sup, PM5, PP3	Glomerulosclerosis, focal segmental, 5	610982
CKD2_1199	High risk	COL4A4	2-227886805-C-G	c.4175G>C	p.Gly1392Ala	het	LP	PM1, PM2_sup, PP2, PP3, PP4	Alport syndrome, autosomal dominant/recessive; Thin basement membrane disease	203780
CKD2_0452	High risk	CREBBP	16-3779210-TG-T	c.5723del	p.P1908Hfs*30	het	P	PVS1_strong, PS4, PM2_sup,	Rubinstein-Taybi syndrome 1	600140
CKD2_0125	Low risk	PKD1	16-2158353-CGT-C	c.6813_6814delA	p.Arg2272fs	het	LP	PVS1, PM2_sup	Polycystic kidney disease 1	601313
CKD2_1386	Low risk	PKD1	16-2156267-ACACCAGCG	c.7511_7527de	p.Ala2504fs	het	LP	PVS1, PM2_sup	Polycystic kidney disease 1	601313
CKD2_0966	Low risk	COL4A4	2-228009259-AATGAGT-A	c.81_86delACTCA	p.Leu28_Ile29del	het	LP	PM2_sup, PM3_strong, PM4	Alport syndrome, autosomal dominant/recessive; Thin basement membrane disease	203780
CKD2_1299	Low risk	COL4A4	2-227924924-C-T	c.2092G>A	p.Gly698Arg	het	LP	PS4_mod, PM1, PM2_sup, PP2, PP3	Alport syndrome, autosomal dominant/recessive; Thin basement membrane disease	203780
CKD2_1334	Low risk	PKD2	4-88929082-A-AC	c.203dupC	p.Ala69fs	het	LP	PVS1, PM2_sup	Polycystic kidney disease 1	173910
CKD2_1138	Low risk	COL4A4	2-227924284-A-AG	c.2219dupC	p.Val741fs	het	LP	PVS1, PM2_sup	Alport syndrome, autosomal dominant/recessive; Thin basement membrane disease	203780
CKD2_0868	Low risk	TTC21B	2-166785654-A-T	c.1377T>A	p.Cys459Ter	comp het	LP	PVS1, PM2_sup	Nephronophthisis 12	613820
CKD2_0868	Low risk	TTC21B	2-166797621-G-A	c.626C>T	p.Pro209Leu	comp het	P	PS3_sup, PS4, PM2_sup, PM3_strong,	Nephronophthisis 12	613820
CKD2_0021	Low risk	PKD1	16-2161440-C-T	c.3728G>A	p.Trp1243*	het	LP	PVS1, PM2_sup	Polycystic kidney disease 1	601313
CKD2_0241	Low risk	PKHD1	6-51935807-T-C	c.664A>G	p.Ile222Val	comp het	P	PS4, PM1, PM2_sup, PM3_Strong	Polycystic kidney disease 4, with or without hepatic disease	263200
CKD2_0241	Low risk	PKHD1	6-51824680-G-GT	c.5895dupA	p.Leu1966fs	comp het	P	PVS1, PS4, PM2_supporting	Polycystic kidney disease 4, with or without hepatic disease	263200
CKD2_0055	Low risk	PKHD1	6-51909751-CATTCACTCT	c.2711_2715+12	p.Thr904fs	comp het	LP	PVS1, PM2_sup	Polycystic kidney disease 4, with or without hepatic disease	263200
CKD2_0055	Low risk	PKHD1	6-51909784-TA-T	c.2694delT	p.Thr899fs	comp het	LP	PVS1, PM2_sup	Polycystic kidney disease 4, with or without hepatic disease	263200
CKD2_0312	Low risk	COL4A4	2-227967565-C-CT	c.871-2_871-1insA		het	LP	PVS1, PM2_sup	Alport syndrome, autosomal dominant/recessive; Thin basement membrane disease	203780
CKD2_0871	Low risk	MYH9	22-36702030-C-T	c.2105G>A	p.Arg702His	het	P	PS2, PS4, PM2_sup, PM5, PP2, PP3	Macrothrombocytopenia and granulocyte inclusions with or without nephritis or sensorineural hearing loss	155100
CKD2_0634	Low risk	COL4A4	2-227983440-C-T	c.410G>A	p.Gly137Asp	het	LP	PM1, PM2_supporting, PP2, PP3_Strong	Alport syndrome, autosomal dominant/recessive; Thin basement membrane disease	203780
CKD2_0634	Low risk	COL4A5	X-107920806-A-C	c.3885A>C	p.Gln1295His	het	VUS	PM1, PM2_supporting, PP2	Alport syndrome 1, X-linked	301050
CKD2_1140	Low risk	NPHS2	1-179521760-G-A	c.851C>T	p.Ala284Val	hom	P	PS4, PM1, PM2_supporting, PM3_Very	Nephrotic syndrome, type 2	600995
CKD2_1300	Low risk	COL4A4	2-227967475-TCACTGA	c.914_930+29d	p.Phe306fs	het	P	PVS1_strong, PS4, PM2_sup,	Alport syndrome, autosomal dominant/recessive; Thin basement membrane disease	203780
CKD2_0285	Low risk	COL4A4	2-227895270-T-TGA	c.3861_3862insTG	p.Arg1288Serfs*1	het	LP	PVS1, PM2_sup	Alport syndrome, autosomal dominant/recessive; Thin basement membrane disease	203780
CKD2_0014	Low risk	COL4A3	2-228124575-G-A	c.1096G>A	p.Gly366Arg	het	LP	PS4_mod, PM1, PM2_sup, PP2, PP3	Alport syndrome, autosomal dominant/recessive; Thin basement membrane disease	104200
CKD2_0748	Low risk	PKD1	16-2156015-TG-T	c.7713delC	p.Ile2572fs	het	LP	PVS1, PM2_sup	Polycystic kidney disease 1	601313
CKD2_0759	Low risk	PKD1	16-2166120-C-T	c.1723-1G>A		het	LP	PVS1, PM2_sup	Polycystic kidney disease 1	601313
CKD2_1124	Low risk	PKD1	16-2144194-TC-T	c.10516delG	p.Glu3506ArgfsTer	het	LP	PVS1, PM2_sup	Polycystic kidney disease 1	601313
CKD2_0834	Low risk	PKD2	4-88929395-CG-C	c.514delG	p.Asp172fs	het	LP	PVS1, PM2_sup	Polycystic kidney disease 1	173910
CKD2_1142	Low risk	COL4A5	X-107850123-G-C	c.2395+1G>C		het	P	PVS1, PM2_sup, PP4	Alport syndrome 1, X-linked	301050
CKD2_1302	Low risk	PKD1	16-2161213-C-T	c.3955G>A	p.G1319R	het	LP	PS2, PS4_mod, PM2_sup, PP3	Polycystic kidney disease 1	601313
CKD2_0081	Low risk	COL4A3	2-228121078-G-A	c.953G>A	p.Gly318Asp	het	LP	PM1, PM2_sup, PP2, PP3, PP4	Alport syndrome, autosomal dominant/recessive; Thin basement membrane disease	104200
CKD2_0764	Low risk	COL4A5	X-107865942-G-A	c.2804G>A	p.Gly935Asp	het	LP	PS4_mod, PM1, PM2_sup, PP2, PP3, P	Alport syndrome 1, X-linked	301050
CKD2_0249	Low risk	COL4A3	2-228148990-G-A	c.2810G>A	p.G937E	het	LP	PM1, PM2_sup, PP2, PP3, PP4	Alport syndrome, autosomal dominant/recessive; Thin basement membrane disease	104200
CKD2_0179	Low risk	SALL1	16-51175421-G-A	c.3098C>T	p.Thr1033Ile	het	LP	PVS1, PM2_sup	Townes-Brocks syndrome 1	107480
CKD2_0990	Low risk	MC4R	18-58039117-G-A	c.466C>T	p.Q156*	het	P	PVS1, PS4, PM2_supporting	Obesity, Autosomal Dominant	618406
CKD2_1200	Low risk	PKD1	16-2153747-C-T	c.8311G>A	p.Glu2771Lys	het	P	PS4, PM2_sup, PP1_strong	Polycystic kidney disease 1	601313
CKD2_1335	Low risk	MYCN	2-16082413-G-GC	c.228dupC	p.W77Lfs*8	het	LP	PVS1, PM2_sup	Feingold syndrome 1	164280
CKD2_1119	Low risk	HNF1B	deletion of exon 1-9	deletion of exon 1-	deletion of exon 1	het	P		Renal cysts and diabetes syndrome	137920
CKD2_1279	Low risk	COL4A4	2-227906881-C-T	c.3488G>A	p.Gly1163Asp	het	LP	PM1, PM2_sup, PP2, PP3, PP4	Alport syndrome, autosomal dominant/recessive; Thin basement membrane disease	203780
CKD2_1044	Low risk	NPHS2	1-179521760-G-A	c.851C>T	p.Ala284Val	comp het	P	PS3_mod, PS4, PM2_sup, PM3_VerySt	Nephrotic syndrome, type 2	600995
CKD2_1044	Low risk	NPHS2	1-179526214-C-T	c.686G>A	p.Arg229Gln	comp het		PS3_mod, PS4, PM2_sup, PM3_VerySt	Nephrotic syndrome, type 2	600995
CKD2_0800	Low risk	COL4A4	2-228004913-G-T	c.156C>A	p.Cys52Ter	het	LP	PVS1, PM2_sup	Alport syndrome, autosomal dominant/recessive; Thin basement membrane disease	203780
CKD2_1130	Low risk	COL4A5	X-107821308-G-A	c.646G>A	p.Gly216Arg	hemi	LP	PS4_mod, PM1, PM2_sup, PM5, PP2, F	Alport syndrome 1, X-linked	301050
CKD2_0403	Low risk	COL4A5	X-107821308-G-A	c.646G>A	p.Gly216Arg	hemi	LP	PS4_mod, PM1, PM2_sup, PM5, PP2, F	Alport syndrome 1, X-linked	301050
CKD2_0401	Low risk	PKD2	4-88929395-CG-C	c.514delG	p.Asp172fs	het	P	PVS1, PS4_mod, PM2_sup	Polycystic kidney disease 1	173910
CKD2_0777	Low risk	PKD1	16-2140883-A-C	c.12003+2T>G		het	LP	PVS1, PM2_sup	Polycystic kidney disease 1	601313
CKD2_1209	Low risk	COL4A3	2-228121078-G-A	c.953G>A	p.Gly318Asp	homo	P	PVS1, PS4_mod, PM2_sup, PM3_sup,	Alport syndrome, autosomal dominant/recessive; Thin basement membrane disease	104200
CKD2_0383	Low risk	COL4A4	2-227924126-GC-G	c.2377delG	p.Ala793fs	het	LP	PVS1, PM2_sup	Alport syndrome, autosomal dominant/recessive; Thin basement membrane disease	203780
CKD2_0383	Low risk	COL4A4	2-227907873-C-T	c.3317G>A	p.Gly1106Asp	het	LP	PM1, PM2_sup, PP2, PP3, PP4	Alport syndrome, autosomal dominant/recessive; Thin basement membrane disease	203780
CKD2_1054	Low risk	PKD1	16-2142079-TC-T	c.11379delG	p.Thr3794fs	het	LP	PVS1, PPS4_mod, PM2_sup, PP1_stron	Polycystic kidney disease 1	601313
CKD2_1205	Low risk	PAX2	10-102509550-CG-C	c.93delG	p.Leu33fs	het	LP	PVS1, PM2_sup	Glomerulosclerosis, focal segmental, 7	616002
CKD2_1240	Low risk	COL4A3	2-228124575-G-A	c.1096G>A	p.Gly366Arg	het	LP	PS4_mod, PM1, PM2_sup, PP2, PP3	Alport syndrome, autosomal dominant/recessive; Thin basement membrane disease	104200
CKD2_1311	Low risk	KLHL3	5-137045450-G-T	c.230C>A	p.Ala77Glu	het	LP	PS3_mod, PS4_mod, PM2_sup, PP3	Pseudohypoaldosteronism, type IID	614495
CKD2_1061	Low risk	NF1	17-29663492-G-A	c.6147+1G>A		het	P	PVS1_strong, PS4, PM2_sup	Neurofibromatosis type 1	162200
CKD2_0122	Low risk	ACTG2	2-74141962-C-T	c.769C>T	p.Arg257Cys	het	P	PS2_VeryStrong, PS3_sup, PS4, PM2_s	Visceral myopathy 1	155310
CKD2_1098	Low risk	WT1	11-32413566-G-A	c.1399C>T	p.Arg467Trp	het	P	PS4, PM1, PM2_sup, PM5	Denys-Drash syndrome	607102
CKD2_0230	Low risk	CUBN	10-16970304-T-C	c.6125-2A>G		homo	P	PVS1_strong, PM2_sup, PM3_strong	Imerslund-Grasbeck syndrome 1	261100
CKD2_1266	Low risk	SLC34A3	9-140129093-CCT-C	c.1246_1247delCT	p.Leu417fs	comp het	LP	PVS1, PM2_sup	Hypophosphatemic rickets with hypercalciuria	241530
CKD2_1266	Low risk	SLC34A3	9-140130625-T-TC	c.1561dupC	p.Leu521fs	comp het	LP	PVS1, PM2_sup	Hypophosphatemic rickets with hypercalciuria	241530
CKD2_0010	Low risk	HNF1A	12-121416590-C-T	c.19C>T	p.Q7X	het	P	PVS1, PS3_mod, PM2_sup, PP1_mod	MODY, type III	600496
CKD2_1268	Low risk	SLC4A1	17-42333076-G-A	c.1765C>T	p.Arg589Cys	het		PS2, PS3_sup, PS4, PM2_sup, PM5, P	Distal renal tubular acidosis 1	179800
CKD2_0333	Low risk	PAX2	10-102510458-G-T	c.220G>T	p.Glu74*	het	LP	PVS1, PM2_sup	Glomerulosclerosis, focal segmental, 7	616002
CKD2_0632	Low risk	COL4A5	X-107863487-A-G	c.2510-2A>G		het	LP	PVS1_strong, PM2_sup, PP4	Alport syndrome 1, X-linked	301050
CKD2_0155	Low risk	COL4A4	2-227875122-C-A	c.4429G>T	p.Glu1477Ter	het	LP	PVS1, PM2_sup	Alport syndrome, autosomal dominant/recessive; Thin basement membrane disease	203780
CKD2_0033	Low risk	COL4A4	2-227886857-AG-A	c.4122delC	p.C1375Vfs*13	het	LP	PVS1, PM2_sup	Alport syndrome, autosomal dominant/recessive; Thin basement membrane disease	203780
CKD2_0909	Low risk	COL4A5	X-107911629-G-A	c.3685G>A	p.Gly1229Ser	hemi	P	PS4, PM1, PM2_sup, PM5, PP2, PP3,	Alport syndrome 1, X-linked	301050
CKD2_0237	Low risk	NPHS2	1-179521760-G-A	c.851C>T	p.Ala284Val	comp het	P	PS3_mod, PS4, PM2_sup, PM3_VerySt	Nephrotic syndrome, type 2	600995
CKD2_0237	Low risk	NPHS2	1-179526214-C-T	c.686G>A	p.Arg229Gln	comp het		PS3_mod, PS4, PM2_sup, PM3_VerySt	Nephrotic syndrome, type 2	600995
CKD2_1161	Low risk	PKD1	16-2161054-TGAAG-T	c.4110_4113delC	p.Tyr1370fs	het	LP	PVS1, PM2_sup	Polycystic kidney disease 1	601313
CKD2_0009	Low risk	COL4A5	X-107821205-TC-T	c.635delC	p.P212Qfs*9	het	P	PVS1, PS4_mod, PM2_sup	Alport syndrome 1, X-linked	301050
CKD2_0799	Low risk	COL4A3	2-228124575-G-A	c.1096G>A	p.Gly366Arg	het	LP	PS4_mod, PM1, PM2_sup, PP2, PP3	Alport syndrome, autosomal dominant/recessive; Thin basement membrane disease	104200
CKD2_1032	Low risk	COL4A5	X-107911629-G-A	c.3685G>A	p.Gly1229Ser	hemi	LP	PS4, PM1, PM2_sup, PM5, PP2, PP3,	Alport syndrome 1, X-linked	301050
CKD2_1178	Low risk	NPHS2	1-179521760-G-A	c.851C>T	p.Ala284Val	comp het	P	PS3_mod, PS4, PM2_sup, PM3_VerySt	Nephrotic syndrome, type 2	600995
CKD2_1178	Low risk	NPHS2	1-179526214-C-T	c.686G>A	p.Arg229Gln	comp het		PS3_mod, PS4, PM2_sup, PM3_VerySt	Nephrotic syndrome, type 2	600995
CKD2_0329	Low risk	NPHS2	1-179521760-G-A	c.851C>T	p.Ala284Val	homo	P	PS3_mod, PS4, PM2_sup, PM3_VerySt	Nephrotic syndrome, type 2	600995
CKD2_1369	Low risk	PKD2	4-88929395-CG-C	c.514delG	p.Asp172fs	het	P	PVS1, PS4_mod, PM2_sup	Polycystic kidney disease 1	173910
CKD2_1058	Low risk	COL4A5	X-107834398-G-A	c.1276G>A	p.Gly426Arg	hemi	P	PS3_mod, PS4, PM1, PM2_sup, PP2, F	Alport syndrome 1, X-linked	301050
CKD2_0145	Low risk	PKD1	16-2141909-T-G	c.11412-2A>C		het	LP	PVS1_strong, PM2_sup, PP1	Polycystic kidney disease 1	601313
CKD2_0178	Low risk	PKD1	16-2141909-T-G	c.11412-2A>C		het	LP	PVS1_strong, PM2_sup, PP1	Polycystic kidney disease 1	601313
CKD2_1002	Low risk	PKD1	16-2141909-T-G	c.11412-2A>C		het	LP	PVS1_strong, PM2_sup, PP1	Polycystic kidney disease 1	601313
CKD2_0870	Low risk	PAX2	10-102509528-C-CG	c.76dupG	p.Val26fs	het	LP	PVS1, PM2_sup	Glomerulosclerosis, focal segmental, 7	616002
CKD2_1007	Low risk	PKHD1	6-51824680-G-GT	c.5895dupA	p.Leu1966fs	comp het	P	PVS1, PS4, PM2_supporting	Polycystic kidney disease 4, with or without hepatic disease	263200
CKD2_1007	Low risk	PKHD1	6-51935807-T-C	c.664A>G	p.Ile222Val	comp het	P	PS4, PM1, PM2_sup, PM3_Strong	Polycystic kidney disease 4, with or without hepatic disease	263200
CKD2_0459	Low risk	COL4A5	X-107816882-CAAGT-C	c.546+4_546+7de	p.Gln182fs	hemi	LP	PVS1, PM2_sup	Alport syndrome 1, X-linked	301050
CKD2_0405	Low risk	HNF1A	12-121432041-G-A	c.788G>A	p.R263H	het	P	PS3, PS4, PM1, PM2_sup, PM5, PP3	MODY, type III	600496
CKD2_0598	Low risk	COL4A5	X-107863487-A-G	c.2510-2A>G		hemi	LP	PVS1_strong, PM2_sup, PP4	Alport syndrome 1, X-linked	301050
CKD2_1019	Low risk	PAX2	10-102510457-C-G	c.219C>G	p.Y73Ter	het	LP	PVS1, PS4_mod, PM2_sup, PP1	Glomerulosclerosis, focal segmental, 7	616002
CKD2_0767	Low risk	NPHP4	1-5965414-CTGAG-C	c.1889_1892delC	p.Pro630ArgfsTer	comp het	LP	PVS1, PM2_sup	Nephronophthisis 4	606966
CKD2_0767	Low risk	NPHP4	1-5924454-GGTGGCAATC	c.3930_3939del	p.Asp1311fs	comp het	P	PVS1, PM2_sup, PM3_sup	Nephronophthisis 4	606966
CKD2_1090	Low risk	HNF1A	12-121432041-G-A	c.788G>A	p.R263H	het	P	PS3, PS4, PM1, PM2_sup, PM5, PP3	MODY, type III	600496
CKD2_0352	Low risk	COL4A4	2-227872775-G-A	c.4768C>T	p.Gln1590Ter	het	LP	PVS1_strong, PM2_sup, PP4	Alport syndrome, autosomal dominant/recessive; Thin basement membrane disease	203780
CKD2_0352	Low risk	COL4A5	X-107908772-G-T	c.3409G>T	p.Gly1137Cys	het	LP	PM1, PM2_sup, PM5, PP2, PP3	Alport syndrome 1, X-linked	301050
CKD2_1340	Low risk	PKD2	4-88940651-C-T	c.637C>T	p.Arg213Ter	het	P	PVS1, PS4, PM2_sup	Polycystic kidney disease 1	173910
CKD2_0084	Low risk	COL4A3	2-228113210-G-T	c.520G>T	p.Gly174Trp	het	LP	PM1, PM2_sup, PM5, PP2, PP3	Alport syndrome, autosomal dominant/recessive; Thin basement membrane disease	104200

Supplementary Table 6: Top 15 ranked genes across the rare-variant collapsing analysis. Clinical group shows the specific phenotype in which the signal was seen, with the inheritance model showing the specific parameters of included qualifying variants for the signal. For cells with 0 counts, these were replaced with a 1 to calculate a minimum OR, signified by a > sign.

		Best Model			
Gene Name	Phenotype	Inheritance Model/ Collapsing Model	OR (95% CI)	P value (X2 test)	Q value
DHDH	FSGS	Dominant/Rare PTV	38.75 (7.42 – 187)	2.33×10^{-5}	1.00
NLRP1	FSGS	Dominant/Rare Missense MTR50	13 (4.20 – 34.19)	2.33×10^{-5}	1.00
LCTL	Kidney Failure	Dominant/Rare Missense	9.86 (3.42 – 24.98)	3.47×10^{-5}	1.00
DNAJC13	FSGS	Dominant/Rare Not Benign MTR50	16.29 (4.59 – 47.32)	4.18×10^{-5}	1.00
RPL5	FSGS	Dominant/Rare Missense MTR50	68.6 (9.59 – 427)	5.06×10^{-5}	1.00
TIMM8B	All, Kidney Failure	Dominant/Rare Missense MTR50	137 (10.03 – 7176)	5.63×10^{-5}	1.00
ARMC8	All	Dominant/Rare Missense, Missense MTR50	12.24 (3.36 – 41.93)	9.91×10^{-5}	1.00
DMC1	Kidney Failure	Dominant/Rare Missense LIMBR, Missense MTR50	30.51 (5.16 – 180)	1.00×10^{-4}	1.00
DTNB	FSGS	Dominant/ Rare Not Benign MTR50	22.55 (4.90 – 84.41)	1.03×10^{-4}	1.00
CALCR	All	Dominant/Rare Not Benign	11.32 (3.25 – 35.63)	1.13×10^{-4}	1.00
TP53RK	FSGS	Dominant/Rare PTV	>114 (16.00 – >1270)	1.35×10^{-4}	1.00
XRCC5	All	Dominant/Rare Missense MTR50	7.75 (2.65 – 20.15)	1.67×10^{-4}	1.00
CDK15	All	Dominant/Ultra Rare Not Benign LIMBR	137 (6.87 – 9743)	1.88×10^{-4}	1.00
IMMT	All	Dominant/Ultra Rare Not Benign, Not Benign MTR50, Deleterious	137 (6.87 – 9743)	1.88×10^{-4}	1.00
SUCO	Kidney Failure	Dominant/Rare Missense MTR50	9.27 (2.87 – 25.93)	1.91×10^{-4}	1.00

Supplementary Table 7: Top results of the common and rare variant secondary gene-based burden analysis. Gene, functional effect, and maximum minor allele frequency (AF) cut-off compose a single mask, used for calculation of enrichment and P-value using fast Firth approximation.

Gene	Clinical Group	Functional Effect	AF Cutoff	Cases			Controls			Effect (95% CI)	P value	Q value
				Ref/Ref	Ref/Alt	Alt/Alt	Ref/Ref	Ref/Alt	Alt/Alt			
GRAP2	All	Missense	0.05	183	48	1	5133	345	4	2.4 (1.7 - 3.3)	1.82E-06	1.00
PPAT	FSGS	Missense	Singleton	79	3	0	5478	4	0	78.9 (15.7 - 397.3)	5.75E-06	1.00
ESCO2	FSGS	Missense	0.05	67	15	0	5188	291	3	4.2 (2.4 - 7.4)	2.07E-05	1.00
INPP5J	Kidney Failure	Missense	0.05	113	49	6	4669	798	15	2.0 (1.5 - 2.7)	3.87E-05	1.00
SLCO1A2	FSGS	LOF + Missense	Singleton	78	4	0	5465	17	0	23.3 (6.8 - 79.3)	4.26E-05	1.00
SYNRG	FSGS	Missense	Singleton	78	4	0	5446	36	0	18.6 (6.4 - 54.3)	4.55E-05	1.00
KCNIP2	FSGS	Missense	Singleton	79	3	0	5480	2	0	71.4 (9.2 - 552.2)	4.91E-05	1.00
FAM96A	All, Kidney Failure	Missense	0.05	227	5	0	5474	8	0	24.4 (6.0 - 98.8)	6.93E-05	1.00
PRDM16	Kidney Failure	Missense	0.05	138	30	0	5108	374	0	2.6 (1.7 - 4.1)	7.04E-05	1.00
PRR14L	All	Missense	0.1	67	153	12	2848	2520	114	1.7 (1.3 - 2.2)	7.36E-05	1.00

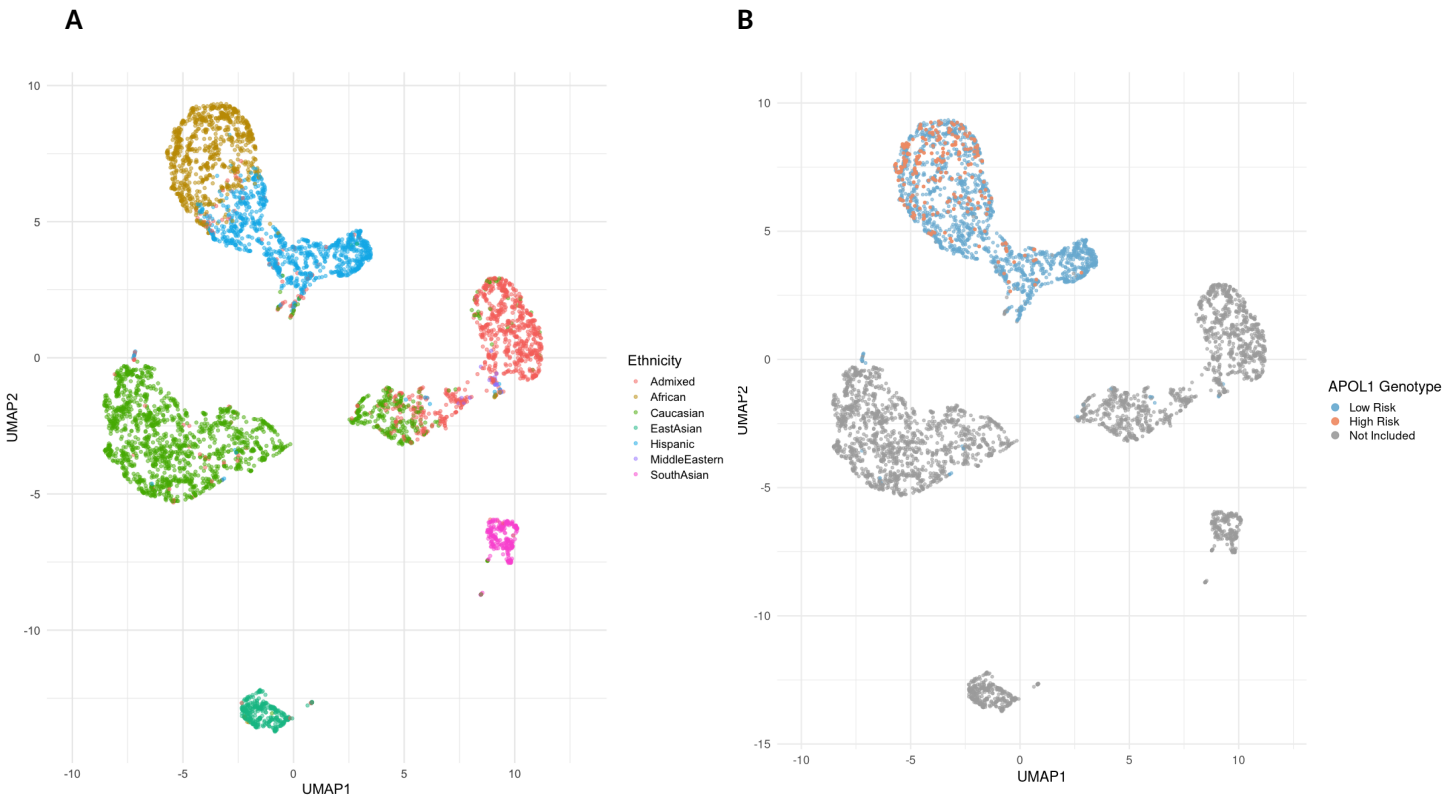
Supplementary Table 8: Results from the gene-set based rare-variant collapsing analysis.

Gene Set	Phenotype	Model	P value	Q value	estimate	conf.low	conf.high	Qualified Case	Unqualified Case	Qualified Ctrl	Unqualified Ctrl	%QV+ Case	%QV+ Ctrl
Inflammasome	All	domRareMissense	0.0005	0.038	1.9	1.31	2.69	45	187	585	4897	19.4	10.7
Inflammasome	HRO	domRareMissense	0.0005	0.038	3.31	1.6	7.4	41	192	11	165	17.6	6.2
Inflammasome	ESKD	domRareMissense	0.0008	0.041	2.03	1.33	3.03	34	134	453	3960	20.2	10.3
Inflammasome	All	domRareMissenseLIMBR	0.0015	0.057	1.92	1.27	2.85	34	198	421	5061	14.7	7.7
Inflammasome	FSGS	domRareMissense	0.0029	0.079	2.43	1.34	4.22	18	61	451	3938	22.8	10.3
Inflammasome	HRO	domRareMissenseLIMBR	0.0031	0.079	3.21	1.39	8.36	30	203	8	168	12.9	4.5
Inflammasome	ESKD	domRareMissenseLIMBR	0.0042	0.091	1.97	1.21	3.1	25	143	338	4075	14.9	7.7
Inflammasome	FSGS	domRareMissenseLIMBR	0.0118	0.224	2.27	1.13	4.21	13	66	337	4052	16.5	7.7
Inflammasome	All	domRareMissenseMTR	0.0221	0.277	1.76	1.07	2.8	23	209	301	5181	9.9	5.5
Inflammasome	APOL1 Het	domRareMissenseMTR	0.0166	0.277	0.46	0.2	0.9	9	330	255	4308	2.7	5.6
Pyroptosis	ESKD	domRareMissense	0.0269	0.277	1.6	1.05	2.4	33	135	535	3878	19.6	12.1
Pyroptosis	FSGS	comphetHR	0.0194	0.277	11.43	1.15	59.41	2	77	8	4381	2.5	0.2
Pyroptosis	FSGS	domRareMissenseLIMBR	0.0208	0.277	2.2	1.1	4.09	13	66	342	4047	16.5	7.8
Pyroptosis	FSGS	domURarenotBenign	0.0273	0.277	3.19	0.98	8.12	5	74	83	4306	6.3	1.9
Inflammasome	HRO	domRareMissenseMTR	0.0256	0.277	2.88	1.09	8.93	21	212	6	170	9	3.4
Inflammasome	ESKD	domRareMissenseMTR	0.0302	0.287	1.82	1.01	3.09	17	151	236	4177	10.1	5.3
Pyroptosis	HRO	domRareMissense	0.0367	0.328	1.97	1.02	3.95	37	196	16	160	15.9	9.1
Pyroptosis	All	domRareMissense	0.0474	0.385	1.43	0.99	2.05	42	190	674	4808	18.1	12.3
Pyroptosis	FSGS	domRarenotBenignMTR	0.0481	0.385	2.25	0.86	4.99	7	72	176	4213	8.9	4
Inflammasome	HRO	domRarenotBenignLIMBR	0.0567	0.431	2.99	0.93	12.62	15	218	4	172	6.4	2.3
Pyroptosis	FSGS	domRareMissense	0.061	0.442	1.73	0.92	3.07	16	63	529	3860	20.3	12.1
Pyroptosis	HRO	domRareMissenseLIMBR	0.0649	0.448	2.21	0.96	5.58	24	209	9	167	10.3	5.1
Pyroptosis	All	domRareMissenseLIMBR	0.0723	0.458	1.46	0.93	2.23	28	204	430	5052	12.1	7.8
Pyroptosis	ESKD	comphetHR	0.071	0.458	5.6	0.55	30.95	2	166	7	4406	1.2	0.2
Inflammasome	APOL1 Het	domRarenotBenignMTR	0.0784	0.477	0.54	0.24	1.07	9	330	218	4345	2.7	4.8
Inflammasome	FSGS	domRareMissenseMTR	0.0881	0.486	1.9	0.78	4.01	8	71	233	4156	10.1	5.3
Pyroptosis	ESKD	domRareMissenseLIMBR	0.0895	0.486	1.54	0.91	2.49	21	147	346	4067	12.5	7.8
Pyroptosis	HRO	domRarenotBenignLIMBR	0.0863	0.486	2.81	0.86	11.99	14	219	4	172	6	2.3
Pyroptosis	FSGS	domRareMissenseMTR	0.0951	0.498	2.03	0.78	4.51	7	72	186	4203	8.9	4.2
Pyroptosis	ESKD	domRareMissenseMTR	0.104	0.527	1.62	0.83	2.95	13	155	194	4219	7.7	4.4
Auto Rec	No Mendelian	domRarenotBenignLIMBR	0.1092	0.535	1.28	0.94	1.75	159	65	3530	1952	71	64.4
Pyroptosis	All	comphetHR	0.1181	0.557	4.05	0.4	21.8	2	230	9	5473	0.9	0.2
Pyroptosis	All	domRareMissenseMTR	0.1209	0.557	1.52	0.85	2.57	17	215	243	5239	7.3	4.4
Pyroptosis	FSGS	domRarenotBenign	0.1465	0.571	1.64	0.74	3.24	10	69	343	4046	12.7	7.8
Pyroptosis	FSGS	domRarenotBenignLIMBR	0.1336	0.571	1.89	0.77	3.99	8	71	243	4146	10.1	5.5
Pyroptosis	APOL1 Het	domRarenotBenignMTR	0.1433	0.571	0.57	0.24	1.17	8	331	186	4377	2.4	4.1
Inflammasome	HRO	domRarenotBenign	0.1437	0.571	2.05	0.79	5.95	18	215	7	169	7.7	4
Pyroptosis	HRO	comphetSynHR	0.1409	0.571	0	0	3.21	0	233	2	174	0	1.1
Auto Rec	No Mendelian	domRarePTV	0.1315	0.571	1.28	0.92	1.76	58	166	1163	4319	25.9	21.2
Pyroptosis	HRO	domRarenotBenign	0.1616	0.614	1.88	0.76	5.1	19	214	8	168	8.2	4.5
Inflammasome	FSGS	comphetHR	0.1674	0.621	2.88	0.33	11.71	2	77	33	4356	2.5	0.8
Inflammasome	APOL1 Het	domRarenotBenign	0.179	0.633	0.69	0.39	1.15	17	322	319	4244	5	7
Pyroptosis	HRO	domRareMissenseMTR	0.1767	0.633	2.03	0.72	6.56	15	218	6	170	6.4	3.4
Pyroptosis	All	domRareSyn	0.1855	0.641	0.63	0.31	1.17	11	221	373	5109	4.7	6.8
Inflammasome	APOL1 Het	domRareMissense	0.1997	0.661	0.76	0.49	1.13	29	310	498	4065	8.6	10.9
Auto Rec	No Mendelian	domRarenotBenignMTR	0.1999	0.661	1.21	0.9	1.64	149	75	3333	2149	66.5	60.8
Auto Rec	No Mendelian	domRarenotBenign	0.2338	0.756	0.79	0.53	1.21	193	31	4818	664	86.2	87.9
Inflammasome	ESKD	domRarePTV	0.3119	0.804	1.68	0.43	4.66	4	164	66	4347	2.4	1.5
Inflammasome	APOL1 Het	comphetSynHR	0.2896	0.804	1.83	0.45	5.45	4	335	23	4540	1.2	0.5
Pyroptosis	ESKD	domRareSyn	0.2809	0.804	0.63	0.27	1.3	8	160	296	4117	4.8	6.7
Pyroptosis	FSGS	domURarenotBenignMTR	0.2946	0.804	1.91	0.22	7.58	2	77	50	4339	2.5	1.1
Pyroptosis	APOL1 Het	comphetSynHR	0.3055	0.804	1.98	0.21	9.4	2	337	11	4552	0.6	0.2
Pyroptosis	APOL1 Het	domRareMissense	0.2658	0.804	1.2	0.85	1.65	49	290	556	4007	14.5	12.2
Pyroptosis	APOL1 Het	domRareMissenseMTR	0.2618	0.804	0.65	0.3	1.25	10	329	198	4365	2.9	4.3
Pyroptosis	APOL1 Het	domRareSyn	0.2664	0.804	1.26	0.81	1.89	29	310	311	4252	8.6	6.8
Pyroptosis	APOL1 Het	domURarenotBenign	0.3118	0.804	1.39	0.61	2.83	9	330	87	4476	2.7	1.9
Inflammasome	HRO	comphetSynHR	0.3036	0.804	0.22	0	2.75	1	232	3	173	0.4	1.7
Inflammasome	HRO	domRarenotBenignMTR	0.2876	0.804	2.07	0.6	9.11	11	222	4	172	4.7	2.3
Auto Rec	No Mendelian	domRareMissenseMTR	0.3077	0.804	1.2	0.86	1.68	172	52	3926	1556	76.8	71.6
Pyroptosis	APOL1 Het	domRarenotBenignLIMBR	0.3175	0.804	0.74	0.39	1.28	14	325	260	4303	4.1	5.7
Inflammasome	APOL1 Het	domRarenotBenignLIMBR	0.3304	0.823	0.74	0.4	1.26	15	324	269	4294	4.4	5.9
Inflammasome	ESKD	domRarenotBenign	0.3595	0.881	1.28	0.68	2.22	15	153	300	4113	8.9	6.8
Pyroptosis	FSGS	domRareSyn	0.3708	0.881	0.52	0.1	1.58	3	76	297	4092	3.8	6.8
Pyroptosis	FSGS	domURarenotBenignLIMBR	0.3705	0.881	1.59	0.18	6.22	2	77	63	4326	2.5	1.4
Pyroptosis	FSGS	domURareDel	0.379	0.886	1.56	0.18	6.09	2	77	65	4324	2.5	1.5
Inflammasome	APOL1 Het	domRareMissenseLIMBR	0.4064	0.915	0.81	0.5	1.26	23	316	376	4187	6.8	8.2
Pyroptosis	HRO	domRarenotBenignMTR	0.4095	0.915	1.9	0.54	8.48	10	223	4	172	4.3	2.3
Auto Rec	No Mendelian	domURareDel	0.4094	0.915	0.87	0.63	1.19	62	162	1711	3771	27.7	31.2
Inflammasome	FSGS	domRarenotBenignMTR	0.4248	0.936	1.36	0.42	3.39	5	74	203	4186	6.3	4.6
Inflammasome	All	comphetHR	0.4794	0.946	1.41	0.27	4.63	3	229	32	5450	1.3	0.6
Inflammasome	ESKD	domRarenotBenignLIMBR	0.498	0.946	1.25	0.62	2.3	12	156	249	4164	7.1	5.6
Inflammasome	FSGS	comphetSynHR	0.4444	0.946	1.77	0.04	11.17	1	78	26	4363	1.3	0.6
Inflammasome	FSGS	domRarenotBenign	0.5033	0.946	1.28	0.49	2.82	7	72	300	4089	8.9	6.8
Inflammasome	FSGS	domRarenotBenignLIMBR	0.4609	0.946	1.35	0.47	3.12	6	73	248	4141	7.6	5.7
Inflammasome	FSGS	domRareSyn	0.4852	0.946	0.57	0.11	1.74	3	76	270	4119	3.8	6.2
Pyroptosis	ESKD	domURareDel	0.5264	0.946	0.34	0.01	2.01	1	167	63	4350	0.6	1.4
Pyroptosis	ESKD	domURarenotBenignLIMBR	0.5253	0.946	0.34	0.01	2.02	1	167	62	4351	0.6	1.4
Pyroptosis	ESKD	domURarenotBenignMTR	0.5139	0.946	0.4	0.01	2.39	1	167	49	4364	0.6	1.1
Pyroptosis	APOL1 Het	domRareMissenseLIMBR	0.5292	0.946	1.14	0.74	1.69	30	309	358	4205	8.8	7.8
Pyroptosis	APOL1 Het	domRarenotBenign	0.5265	0.946	0.85	0.52	1.33	23	316	359	4204	6.8	7.9
Inflammasome	HRO	domURarenotBenign	0.4629	0.946	2.09	0.34	22.3	5	228	2	174	2.1	1.1
Pyroptosis	HRO	comphetHR	0.5271	0.946	Inf	0.11	Inf	2	231	0	176	0.9	0
Pyroptosis	HRO	domRareSyn	0.4971	0.946	0.67	0.25	1.8	10	223	11	165	4.3	6.2
Auto Rec	No Mendelian	domRareMissense	0.4948	0.946	0.75	0.34	1.94	217	7	5324	158	96.9	97.1
Auto Rec	No Mendelian	domURarenotBenign	0.4846	0.946	0.9	0.67	1.2	89	135	2314	3168	39.7	42.2
Inflammasome	All	comphetSynHR	1	1.000	0.53	0.01	3.28	1	231	28	5454	0.4	0.5
Inflammasome	All	domRarenotBenign	0.6937	1.000	1.09	0.62	1.81	18	214	374	5108	7.8	6.8
Inflammasome	All	domRarenotBenignLIMBR	0.6626	1.000	1.13	0.61	1.95	15	217	303	5179	6.5	5.5
Inflammasome	All	domRarenotBenignMTR	1	1.000	0.99	0.48	1.85	11	221	253	5229	4.7	4.6
Inflammasome	All	domRarePTV	0.5793	1.000	1.2	0.31	3.3	4	228	84	5398	1.7	1.5
Inflammasome	All	domRareSyn	0.5865	1.000	0.82	0.42	1.47	13	219	331	5151	5.6	6
Inflammasome	All	domURareDel	0.7794	1.000	1.13	0.29	3.14	4	228	71	5411	1.7	1.3
Inflammasome	All	domURarenotBenign	1	1.000	1.01	0.32	2.52	5	227	102	5380	2.2	1.9
Inflammasome	All	domURarenotBenignLIMBR	0.7996	1.000	0.67	0.13	2.08	3	229	90	5392	1.3	1.6
Inflammasome	All	domURarenotBenignMTR	1	1.000	1	0.26	2.75	4	228	78	5404	1.7	1.4
Inflammasome	ESKD	comphetHR	0.6733	1.000	1.27	0.14	5.12	2	166	32	4381	1.2	0.7
Inflammasome	ESKD	comphetSynHR	0.6334	1.000	0	0	3.02	0	168	26	4387	0	0.6
Inflammasome	ESKD	domRarenotBenignMTR	0.7124	1.000	1.11	0.49	2.22	9	159	206	4207	5.4	4.7
Inflammasome	ESKD	domRareSyn	0.6328	1.000	0.78	0.35	1.55	9	159	270	4143	5.4	6.1
Inflammasome	ESKD	domURareDel	0.7403	1.000	1.19	0.23	3.77	3	165	54	4359	1.8	1.2
Inflammasome	ESKD	domURarenotBenign	0.7806	1.000	1.13	0.29	3.09	4	164	78	4335	2.4	1.8
Inflammasome	ESKD	domURarenotBenignLIMBR	0.7691	1.000	0.61	0.07	2.36	2	166	71	4342	1.2	1.6
Inflammasome	ESKD	domURarenotBenignMTR	0.7646	1.000	1.04	0.2	3.28	3	165	59	4354	1.8	1.3
Inflammasome	FSGS	domRarePTV	1	1.000	0.88	0.02	5.25	1	78	65	4324	1.3	1.5
Inflammasome	FSGS	domURareDel	1	1.000	0.88	0.02	5.3	1	78	57	4332	1.3	1.3
Inflammasome	FSGS	domURarenotBenign	0.6731	1.000	1.27	0.15	4.92	2	77	80	4309	2.5	1.8
Inflammasome	FSGS	domURarenotBenignLIMBR	1	1.000	0.7	0.02	4.17	1	78	71	4318	1.3	1.6
Inflammasome	FSGS	domURarenotBenignMTR	1	1.000	0.8	0.02	4.8	1	78	60	4329	1.3	1.4
Inflammasome	APOL1 Het	comphetHR	0.7221	1.000	0.42	0.01	2.57	1	338	26	4537	0.3	0.6
Inflammasome	APOL1 Het	domRarePTV	1	1.000	0.88	0.28	2.18	5	334	79	4484	1.5	1.7
Inflammasome	APOL1 Het	domRareSyn	0.9079	1.000	1.01	0.61	1.6	22	317	280	4283	6.5	6.1
Inflammasome	APOL1 Het	domURareDel	1	1.000	0.95	0.29	2.37	5	334	67	4496	1.5	1.5
Inflammasome	APOL1 Het	domURarenotBenign	1	1.000	0.87	0.31	2.01	6	333	87	4476	1.8	1.9
Inflammasome	APOL1 Het	domURarenotBenignLIMBR	1	1.000	0.97	0.34	2.25	6	333	78	4485	1.8	1.7
Inflammasome	APOL1 Het	domURarenotBenignMTR	1	1.000	0.92	0.29	2.31	5	334	68	4495	1.5	1.5
Pyroptosis	All	comphetSynHR	1	1.000	0	0	4.65	0	232	15	5467	0	0.3
Pyroptosis	All	domRarenotBenign	0.9025	1.000	1.03	0.61	1.66	20	212	440	5042	8.6	8
Pyroptosis	All	domRarenotBenignLIMBR	0.8845	1.000	1.04	0.55	1.83	14	218	316	5166	6	5.8
Pyroptosis	All	domRarenotBenignMTR	1	1.000	0.99	0.46	1.9	10	222	231	5251	4.3	4.2
Pyroptosis	All	domRarePTV	0.8048	1.000	1.11	0.34	2.75	5	227	103	5379	2.2	1.9
Pyroptosis	All	domURareDel	0.7957	1.000	0.74	0.15	2.32	3	229	83	5399	1.3	1.5
Pyroptosis	All	domURarenotBenign	0.6429	1.000	1.18	0.42	2.75	6	226	111	5371	2.6	2
Pyroptosis	All	domURarenotBenignLIMBR	0.7957	1.000	0.75	0.15	2.33	3	229	83	5399	1.3	1.5
Pyroptosis	All	domURarenotBenignMTR	1	1.000	0.88	0.17	2.77	3	229	66	5416	1.3	1.2
Pyroptosis	ESKD	comphetSynHR	1	1.000	0	0	6.58	0	168	12	4401	0	0.3
Pyroptosis	ESKD	domRarenotBenign	0.7747	1.000	1.08	0.58	1.87	15	153	348	4065	8.9	7.9
Pyroptosis	ESKD	domRarenotBenignLIMBR	0.8657	1.000	1.03	0.48	1.99	10	158	249	4164	6	5.6
Pyroptosis	ESKD	domRarenotBenignMTR	1	1.000	0.95	0.37	2.05	7	161	186	4227	4.2	4.2
Pyroptosis	ESKD	domRarePTV	0.7703	1.000	0.6	0.07	2.31	2	166	79	4334	1.2	1.8
Pyroptosis	ESKD	domURarenotBenign	1	1.000	0.82	0.16	2.55	3	165	81	4332	1.8	1.8
Pyroptosis	FSGS	comphetSynHR	1	1.000	0	0	16.9	0	79	11	4378	0	0.3
Pyroptosis	FSGS	domRarePTV	0.6608	1.000	1.36	0.16	5.27	2	77	78	4311	2.5	1.8
Pyroptosis	APOL1 Het	comphetHR	1	1.000	0	0	7.84	0	339	7	4556	0	0.2
Pyroptosis	APOL1 Het	domRarePTV	0.8317	1.000	0.79	0.25	1.95	5	334	84	4479	1.5	1.8
Pyroptosis	APOL1 Het	domURareDel	0.6423	1.000	1.18	0.41	2.77	6	333	66	4497	1.8	1.4
Pyroptosis	APOL1 Het	domURarenotBenignLIMBR	1	1.000	0.83	0.22	2.27	4	335	64	4499	1.2	1.4
Pyroptosis	APOL1 Het	domURarenotBenignMTR	1	1.000	0.95	0.25	2.63	4	335	54	4509	1.2	1.2
Inflammasome	HRO	comphetHR	0.6321	1.000	2.4	0.19	127.56	3	230	1	175	1.3	0.6
Inflammasome	HRO	domRarePTV	0.6939	1.000	1.65	0.23	18.49	4	229	2	174	1.7	1.1
Inflammasome	HRO	domRareSyn	0.7976	1.000	1.31	0.42	4.48	10	223	6	170	4.3	3.4
Inflammasome	HRO	domURareDel	0.6887	1.000	1.75	0.25	19.68	4	229	2	174	1.7	1.1
Inflammasome	HRO	domURarenotBenignLIMBR	1	1.000	1.3	0.15	15.86	3	230	2	174	1.3	1.1
Inflammasome	HRO	domURarenotBenignMTR	0.6887	1.000	1.75	0.25	19.68	4	229	2	174	1.7	1.1
Pyroptosis	HRO	domRarePTV	1	1.000	1	0.21	5.15	5	228	4	172	2.1	2.3
Pyroptosis	HRO	domURareDel	1	1.000	0.81	0.11	6.18	3	230	3	173	1.3	1.7
Pyroptosis	HRO	domURarenotBenign	1	1.000	1.33	0.25	8.72	5	228	3	173	2.1	1.7
Pyroptosis	HRO	domURarenotBenignLIMBR	1	1.000	1.3	0.15	15.86	3	230	2	174	1.3	1.1
Pyroptosis	HRO	domURarenotBenignMTR	1	1.000	1.3	0.15	15.86	3	230	2	174	1.3	1.1
Auto Rec	No Mendelian	domRareMissenseLIMBR	0.6177	1.000	1.1	0.78	1.57	178	46	4204	1278	79.5	76.7
Auto Rec	No Mendelian	domRareSyn	1	1.000	1.01	0.68	1.54	193	31	4639	843	86.2	84.6
Auto Rec	No Mendelian	domURarenotBenignLIMBR	0.6903	1.000	1.06	0.76	1.45	58	166	1352	4130	25.9	24.7
Auto Rec	No Mendelian	domURarenotBenignMTR	0.8088	1.000	0.95	0.68	1.32	52	172	1303	4179	23.2	23.8

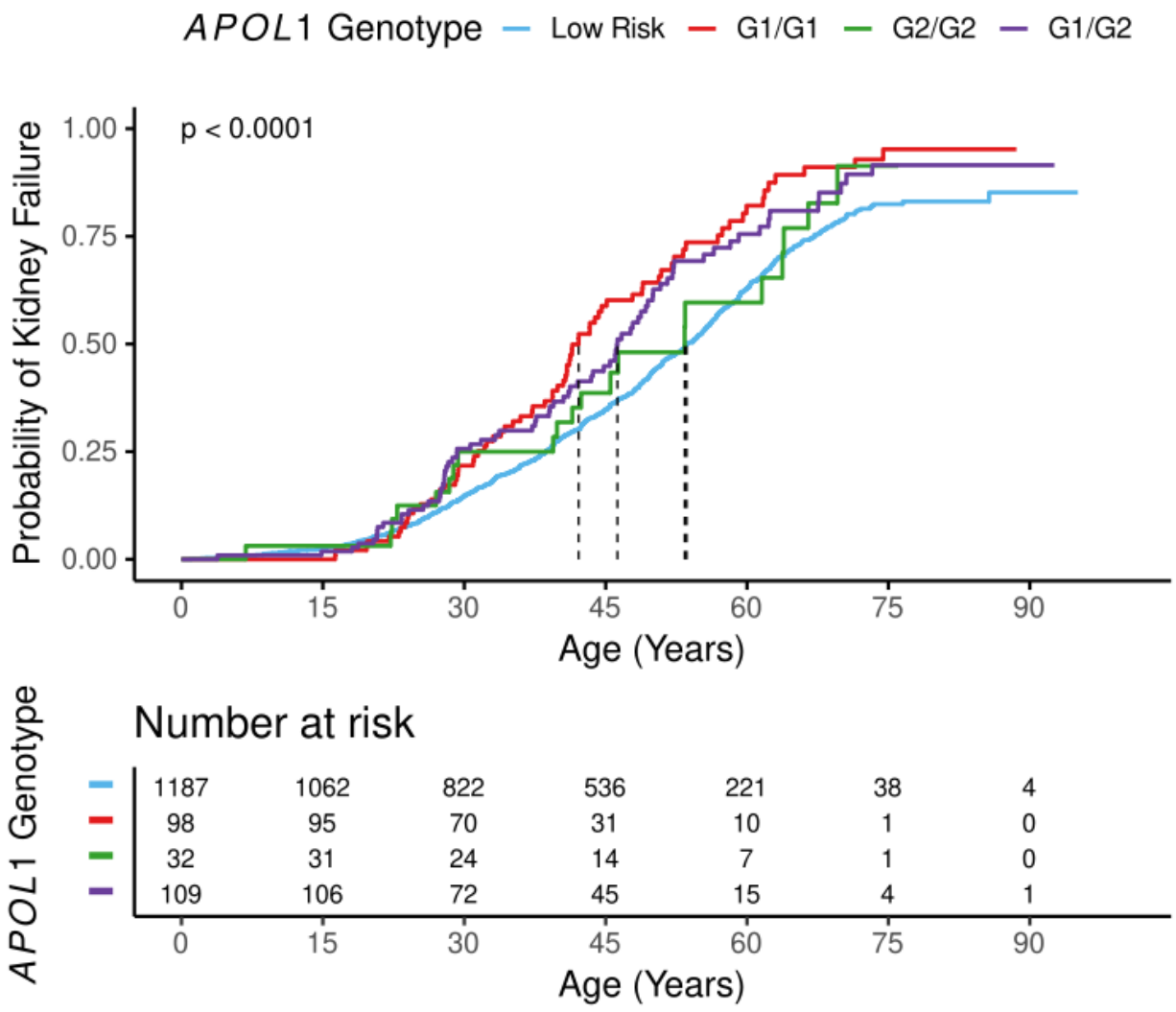
Supplementary Table 9: Qualifying variants identified within the inflammasome gene-set within the dominant rare missense model for the full cohort.

Case	Variant	Gene	Previous disease association
CKD2_1222	1-159036087-T-G	AIM2	No
CKD2_0937	1-247587239-A-G	NLRP3	No
CKD2_0561	1-247587389-A-G	NLRP3	No
CKD2_1041	1-247588420-A-G	NLRP3	No
CKD2_0388	1-247593014-T-C	NLRP3	No
CKD2_0482	11-104900539-T-A	CASP1	No
CKD2_1173	11-104900565-G-A	CASP1	No
CKD2_0495	11-279409-C-T	NLRP6	No
CKD2_1372	11-281097-G-A	NLRP6	No
CKD2_0770	11-281433-G-T	NLRP6	No
CKD2_1397	11-281773-T-C	NLRP6	No
CKD2_0196	11-284626-G-A	NLRP6	No
CKD2_0339	11-285255-C-T	NLRP6	No
CKD2_0112	11-7091547-C-G	NLRP14	No
CKD2_0112	11-7981685-G-A	NLRP10	No
CKD2_0339	11-7981713-C-G	NLRP10	No
CKD2_0423	16-31212939-C-G	PYCARD	No
CKD2_0199	16-31213774-C-G	PYCARD	No
CKD2_0480	16-3293244-A-G	MEFV	No
CKD2_0482	16-3293302-T-C	MEFV	No
CKD2_1249	16-3294028-C-T	MEFV	No
CKD2_1271	16-3299732-C-G	MEFV	No
CKD2_0443	16-3304293-T-C	MEFV	No
CKD2_0731	16-3304653-CT-AC	MEFV	No
CKD2_0809	16-3304659-C-T	MEFV	No
CKD2_1318	17-5347759-C-T	DHX33	No
CKD2_0522	17-5357202-G-A	DHX33	No
CKD2_0457	17-5365850-C-T	DHX33	No
CKD2_0112	17-5418216-C-T	NLRP1	No
CKD2_0618	17-5425000-GT-AA	NLRP1	No
CKD2_0482	17-5437222-C-T	NLRP1	No
CKD2_0678	17-5442786-C-T	NLRP1	No
CKD2_0454	17-5462016-C-G	NLRP1	No
CKD2_0114	17-5462323-C-T	NLRP1	No
CKD2_0692	17-5462748-C-A	NLRP1	No
CKD2_0108	17-5462937-C-T	NLRP1	No
CKD2_1326	17-5487106-C-T	NLRP1	No
CKD2_1238	17-5487114-G-A	NLRP1	No
CKD2_0388	19-15164764-G-A	CASP14	No
CKD2_1006	19-48725055-T-C	CARD8	No
CKD2_1271	19-48734052-G-T	CARD8	No
CKD2_0059	19-48734061-G-A	CARD8	No
CKD2_0515	19-54310857-T-C	NLRP12	No
CKD2_1237	19-56235418-C-G	NLRP9	No
CKD2_1352	19-56235418-C-G	NLRP9	No
CKD2_0127	19-56243626-G-A	NLRP9	No
CKD2_0730	19-56243874-A-C	NLRP9	No
CKD2_0577	19-56244516-C-T	NLRP9	No
CKD2_0515	19-56244672-C-G	NLRP9	No
CKD2_1249	19-56297022-G-A	NLRP11	No
CKD2_0770	19-56423231-G-A	NLRP13	No
CKD2_0108	2-202082453-C-T	CASP10	No
CKD2_0172	2-32475771-G-A	NLRC4	No
CKD2_1128	2-32475819-G-C	NLRC4	No
CKD2_1249	5-70308694-G-T	NAIP	No
CKD2_1343	8-144644980-C-G	GSDMD	No
CKD2_0076	8-144645013-G-C	GSDMD	No

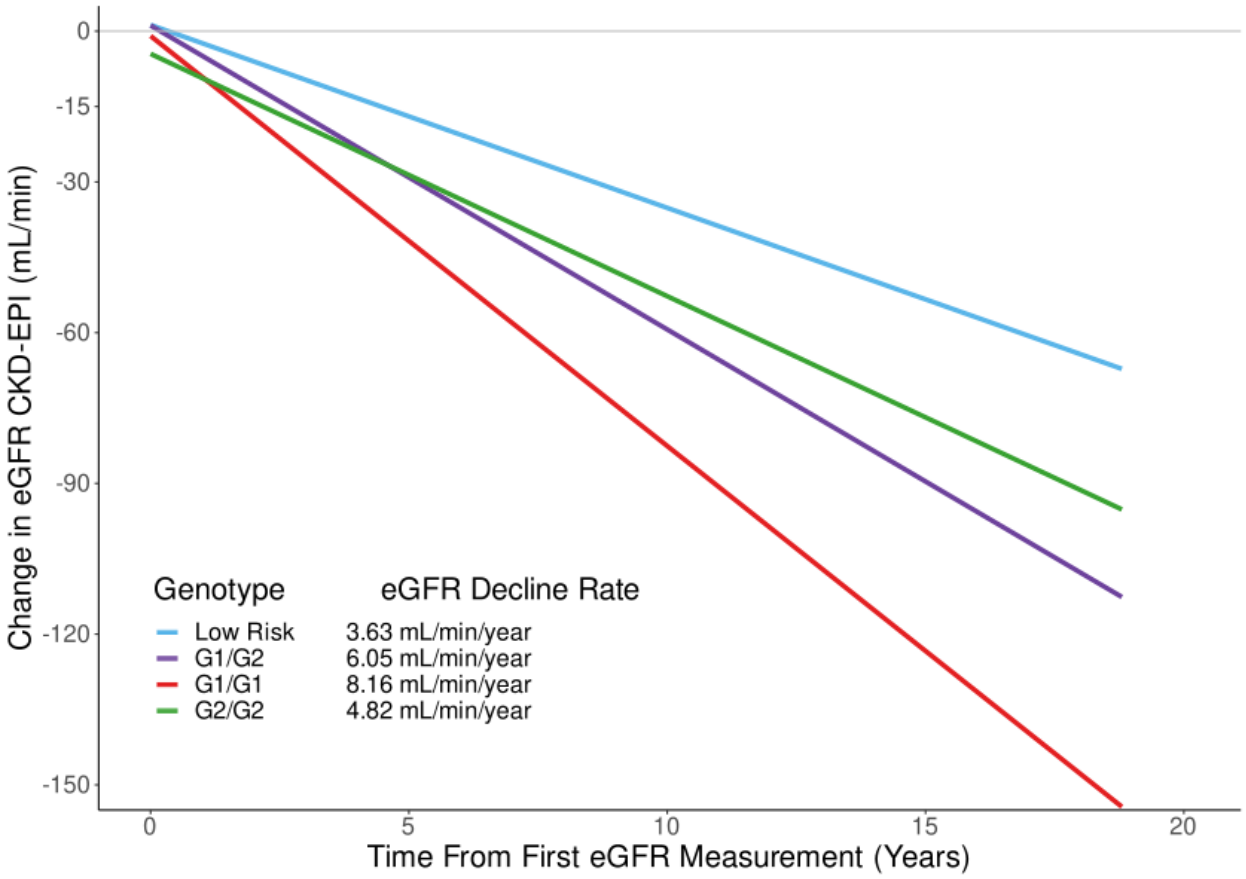
Supplementary Figure 1: Genetic ancestry and clustering using principal components analyses of exome ancestry markers on a UMAP projection. Panel A shows genetic ancestry clusters by predicted ethnicity. Panel B shows the same genetic ancestry clusters by APOL1 risk genotype of included samples and those that were excluded by genetic ancestry-matching. The majority of included samples have a predicted genetic ancestry of African or Hispanic.



Supplementary Figure 2. Lifetime risk of the development of kidney failure comparing subjects with specific high-risk APOL1 genotypes to low-risk APOL1 genotype. Median time to kidney failure denoted and global Logrank P-value shown.

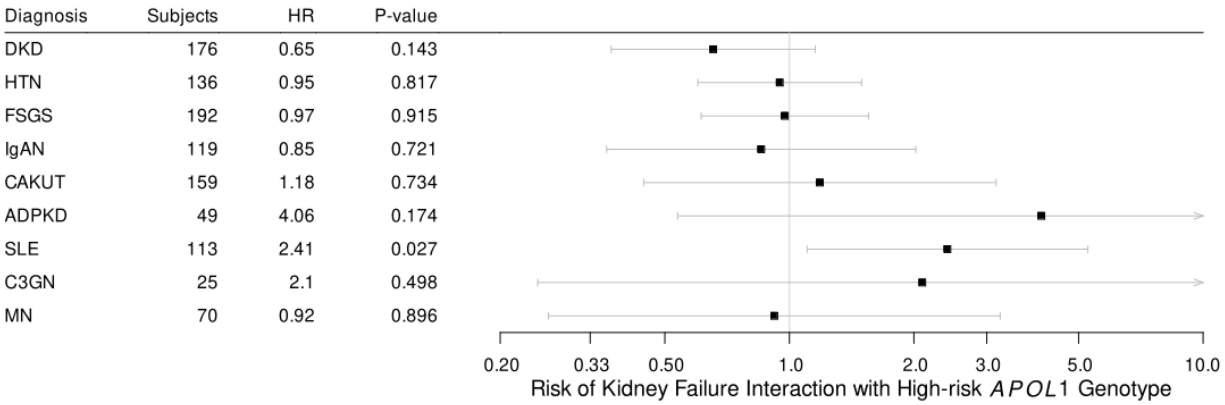


Supplementary Figure 3. eGFR change over time in subjects by specific APOL1 genotype. eGFR decline rate calculated with covariates held at mean values. Adjusted for primary cause of kidney disease, family history of kidney disease, diabetes mellitus, hypertension, genetic ancestry cluster, and initial measured eGFR.

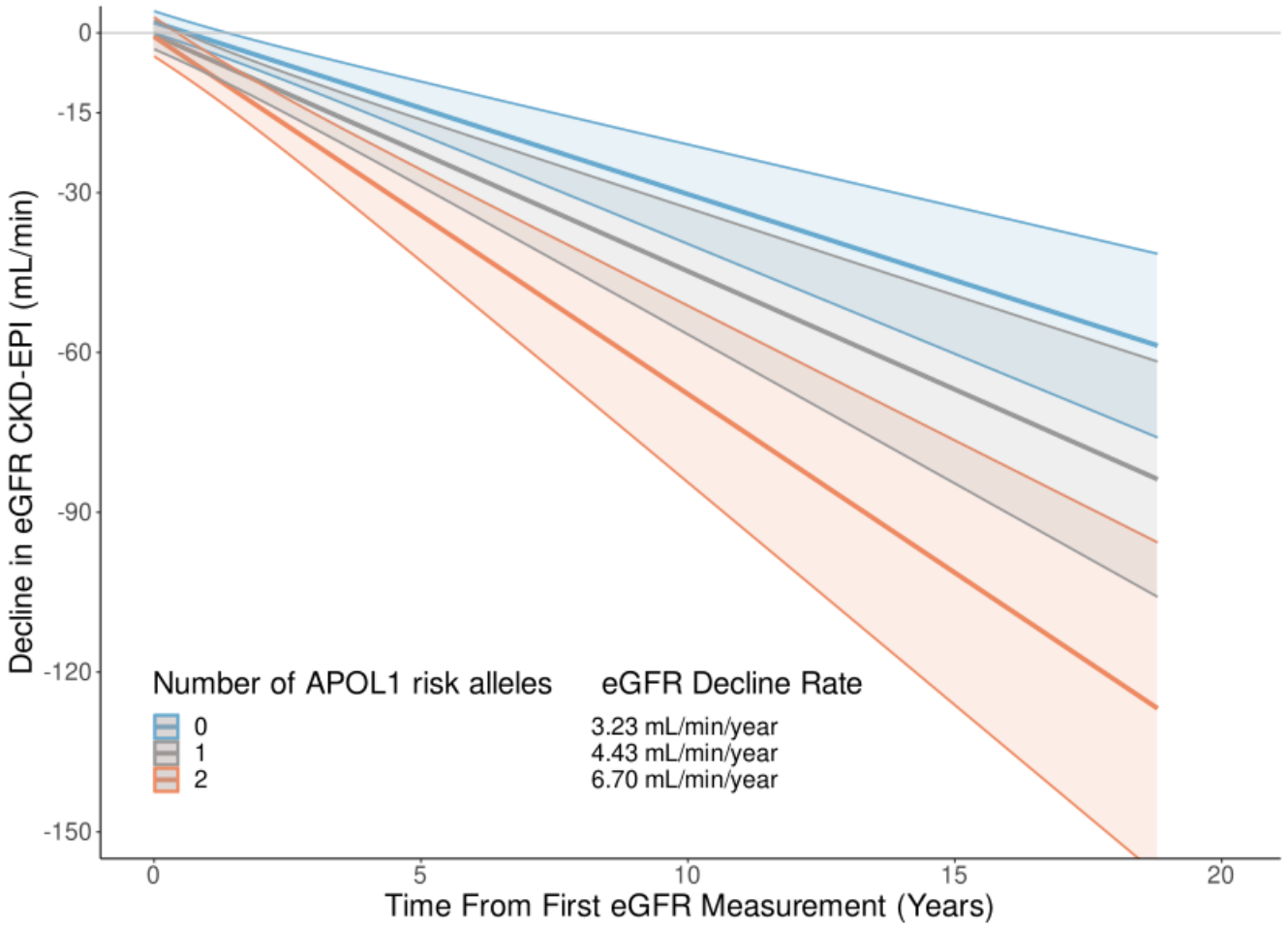


Supplementary Figure 4: Lifetime risk of developing kidney failure for the interaction between APOL1 high-risk genotype and primary cause of kidney disease. Cox proportional hazard models applied to 1426 CKD patients. Analyses included the main effect of APOL1 risk genotype which remained significant in each model. Cox models were adjusted for family history of kidney disease, sex, ZIP code based median income, genetic ancestry cluster, Elixhauser comorbidity score, diabetes mellitus and hypertension.

Abbreviations: C3GN = C3 glomerulopathy, DKD = diabetic kidney disease, FSGS = focal segmental glomerulosclerosis, HTN = hypertension-associated nephropathy, IgAN = IgA nephropathy, MN = membranous nephropathy, SLE = systemic lupus erythematosus, CAKUT = congenital anomalies of the kidney and urinary tract, ADPKD = autosomal dominant polycystic kidney disease.



Supplementary Figure 5: eGFR change over time in subjects characterized by number of *APOL1* risk alleles. eGFR decline rate calculated with covariates held at mean values. Adjusted for primary cause of kidney disease, family history of kidney disease, diabetes mellitus, hypertension, genetic ancestry cluster, and initial measured eGFR.



Supplementary Methods:

Inclusion criteria for CUIMC Genetic Studies of Chronic Kidney Disease biobank (IRB #AAAC7385):

Patients who were seen by the CUIMC Nephrology Division with CKD were eligible for enrolment. CKD was defined by kidney failure defined by the requirement for dialysis or transplantation, Creatinine >1.5 mg/dL in males or >1.3 mg/dL in females with or without proteinuria, and/or the presence of significant proteinuria or hematuria indicative of active glomerular disease.

Exome Sequencing:

Genomic DNA was isolated following standardized protocols. Most were isolated from peripheral blood samples, but other sources were also accepted. Exome sequences were captured using Roche, Agilent, Integrated DNA Technologies (IDT), or Haloplex kits and sequenced on Illumina platforms. FASTQ data were processed and aligned to hg19/GRCh37 using BWA-MEM, and variants were called using the Genome Analysis Toolkit (GATK) v3.6 best practices. (1,2) Variant annotation was performed using ATAV.(3) Variant level QC included a coverage depth ≥10, QD ≥5, Qual ≥50, MQ ≥40, GQ ≥20, Fisher's strand bias score (FS) ≤60 (SNP), ≤200 (indels), strand odds ratio (SOR) ≤3 (SNV), ≤10 (indels), read position rank sum score (RPRS) ≥3, mapping quality rank sum score (MQRS) ≥-10, alternate allele fraction for heterozygous call ≥0.3, VQSLOD ≥-2.632 (SNP), ≥1.262 (indel), random forest true positive probability based on gnomAD ≥0.01 (SNP), ≥0.02 (indel) with known sequencing artifacts excluded.(4)

Clinical Outcomes Genetic Ancestry Matching:

Genetic principle components (PCs) were calculated using flashpca from 12840 ancestry-informative markers. These 10 genetic PCs were used as the input for Louvain clustering to create genetic ancestry clusters. Genetic ancestry clusters with fewer than 5 high risk APOL1 genotype individuals were excluded from the analysis to limit case-control imbalance and bias introduced by genetic ancestry.

Genetic Analysis Cohort Selection Methods:

Individuals included in the control cohort were selected from the ATAV database at the Institute of Genomic Medicine (IGM) who carried a diagnosis of control or healthy blood relative and includes individuals sequenced for the biobank and other projects at the IGM. Individuals were excluded if <85% of the consensus coding sequence bases were adequately covered and if contamination was >2% per VerifyBamID.(5) KING was used to evaluate relatedness between all individuals and we removed one of each pair that showed relatedness of second degree relatives or closer with the inclusion of cases prioritized to controls.(6) Coverage harmonization was then performed per site using a 7% max coverage difference with a depth ≥10. Genetic principle components analysis (PCA) dimensions calculated were again calculated using flashpca from 12840 ancestry-informative markers and the top 10 dimensions were used for Louvain clustering to create genetic ancestry clusters. This dimensionality reduction was checked using uniform manifold approximation and projection (UMAP).(7) Genetic ancestry clusters with fewer than 5 high risk genotype individuals were excluded from the analysis to limit genetic ancestry bias between to cohorts.

Covariate Imputation:

Multiple imputation by chained equations was used to impute missing covariate data which was done using the mice V3.13.0 package in R. 56 individuals had missing zip-code based median income data, and 592 had missing elixhauser comorbidity scores which represented 21% of these data. 30 imputations were performed and combined using Rubin's approach.

ExWAS:

This analysis used sequencing data that was filtered using the above described QC and coverage harmonization. Within this analysis 805,347 variants were identified in the full cohort and following Hardy-Weinberg equilibrium test filtering using a mid-point P cut-off of 1×10^{-35}, 803,539 variants remained. The whole genome regression was performed in regenie using only common SNPs with a minor allele frequency (MAF) >0.01. Variants with less than 5 minor alleles total were excluded as they were unable to reach statistical significance leaving 183,722 variants in the full cohort, 182,699 in the kidney failure subgroup and 181,261 in the FSGS subgroup. Association testing was performed using the approximate Firth likelihood ratio test with leave one chromosome out (LOCO) to account for the case-control imbalance present within this study.

Power Analysis:

Power analyses of the rare dominant gene-based collapsing models show a minimum of 6 QVs in cases per gene were required to reach significance corresponding to a detectable odds ratio of 64.8 for the full cohort, 72 for kidney failure, and 101 for FSGS at 80% power.

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