Supplementary Appendix

Genetic inhibition of APOL1 pore function confers protection against APOL1 mediated kidney disease

Adriana M. Hung, MD, MPH[1,2] , Victoria A. Assimon, PhD[3,†],Hua-Chang Chen, PhD[1,4, †], , Zhihong Yu, MS[1,4†], Caitlyn Vlasschaert, MD[5], Jefferson Triozzi MD[2], Helen Chan, BS[3], Lee Wheless, MD, PhD[6], Otis Wilson, BA[1,2], Shailja Shah, MD, MPH[7], Taralynn Mack, BA[1,8], Trevor Thompson, BA[2], Michael E. Matheny MD, MPH[1,4,9], Saranya Chandrasekar, MS[3], Sahar V Mozaffari, PhD[3], Cecilia P. Chung, MD, MPH[10], Philip Tsao, PhD[14,153], Katalin Susztak, MD, PhD[11], Edward D. Siew, MD MSCI[1,2],Karol Estrada PhD[3], J. Michael Gaziano, MD[12,13], Robert R. Graham, PhD[3], Ran Tao, PhD[1,4], Maarten Hoek, PhD[3], Cassianne Robinson-Cohen, PhD[2], , Eric M. Green, MD, PhD[3¥,] Alexander G Bick, MD, PhD[8,12,*], for the Million Veteran Program.

[1]Nashville VA Medical Center, VA Tennessee Valley Healthcare System, Nashville, TN.
[2]Division of Nephrology & Hypertension, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN.
[3]MAZE Therapeutics, South San Francisco, CA.
[4]Department of Biostatistics, Vanderbilt University Medical Center, Nashville, TN
[5]Department of Dermatology, Vanderbilt University Medical Center, Nashville TN.
[6]VA San Diego Healthcare System and UC San Diego Health, La Jolla CA
[7]Division of Genetic Medicine, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN.
[8]Department of Biomedical Informatics, Vanderbilt University Medical Center, Nashville, TN.
[9]Renal, Electrolyte, and Hypertension Division, Department of Medicine, University of Pennsylvania, Perelman School of Medicine, Philadelphia, Pennsylvania.
[10]VA Cooperative Studies Program, VA Boston Healthcare System, Boston, MA
[11]Department of Medicine, Brigham and Women's Hospital and Harvard School of Medicine, Boston, MA
[+]

[†]Drs. Assimon and Chen contributed equally to this work.
*Drs. Hung, Green and Bick jointly supervised this work

Correspondence to Dr. Hung, 1611 21st Ave S, S3223 MCN, Nashville, TN 37232 or adriana.hung@vumc.org

Table of Contents

Methods used in the mechanistic studies and functional genomics

Maintenance and generation of APOL1 podocyte cell lines utilized in viability assay. The hTERT-immortalized kidney podocyte cell line was procured from the laboratory of Dr. Moin Saleem at the University of Bristol, UK (doi:10.1111/j.1440-1797.2012.01619.x). All cell lines were cultured in RPMI media (Gibco) with 10% Tet System Approved FBS (Takara, 631101) according to a previous report. Cell lines were maintained and engineered at 33˚C. Cell cultures were transferred to 37˚C for at least 10 days to initiate differentiation and subsequently used in viability and protein level (HiBiT assay) experiments (10.1681/ASN.V133630).

Coding sequences of APOL1 G0, G1, G2 with and without the p.N264K variant were cloned into the pLVX-TetOne-Puro vector and verified by sequencing (Genscript Biotech). All constructs were designed to have a C-terminal HiBiT tag. Lentiviral packaging *of vectors was conducted with the Lenti-X Packaging Single Shots (VSVG) system* according to manufacturer instructions (Takara Bio, 631275). Approximately 24 hours before transfection, LentiX293T packaging cells were seeded at a density of 4–5 x 10^6 cells/10-cm plate. After transfection, viral supernatants were collected at 48- and 72-hours and pooled. The pooled viral supernatant was concentrated 10x using a Lenti-X Concentrator (Takara Bio, 631231). A stable cell line was generated by transfecting the podocyte cell line with concentrated virus (300 µL) in media with 5 µg/mL polybrene (Sigma, TR-1003-G). Media was changed the following day. 72-hours post transfection, 2.5 µg/mL puromycin (Gibco, A1113803) was added to the cells and cells were maintained in selection media thereafter. APOL1 stable cellular pools (G0, G1, G2, G0 p.N264K, G1 p.N264K, and G2 p.N264K) were subjected to a stringent limiting dilution to generate pure stable clones. Clones were selected to have similar levels of APOL1 expression.

Viability assay with APOL1 podocyte cell lines. All experiments were performed in 384-well, white, solid bottom, tissue culture treated plates (Greiner, 781080). 30 µL of podocytes (6000 cells/well final) in media were added to each well of an assay ready plate containing a 15-step 2-fold titration of doxycycline. Final concentrations of doxycycline ranged from 0 to 1000 ng/mL. Plates were incubated for 96 hours (humidified, 37˚C with 5% CO_2). After the incubation, the plates were equilibrated at room temperature for 10 minutes and then 15 µL of CellTiter-Gloreagent (Promega, G7570) was added to each well. Plates were placed on an orbital shaker (300 rpm) for 3 minutes to induce cell lysis and then incubated at room temperature for 10 minutes. Luminescence was measured on an Envision plate reader. GraphPad PRISM software (Version 8) was utilized for plotting data as ± SEM. Data in Figure 3C represents toxicity values at a single concentration of doxycycline (500ng/mL) that was determined to have matched APOL1 expression across the clonal cell lines as determined by a HiBiT assay.

Nano-Glo® HiBiT Lytic assay with APOL1 podocyte cell lines to determine APOL1 expression. All experiments were performed in 384-well, white, solid bottom, tissue culture treated plates (Greiner, 781080). 30 µL of podocytes (6000 cells/well final) in media were added to each well of an assay ready plate containing a 15-step 2-fold titration of doxycycline. Final concentrations of doxycycline ranged from 0 to 1000 ng/mL. Plates were incubated for 6 hours (humidified, 37˚C with 5% CO_2). A short induction time was chosen to quantify protein expression while viability was >95% for all cell lines. Afterwards, plates were equilibrated at room temperature for 10 minutes and then 30 µL of NanoGlo HiBiT Lytic reagent (containing Lytic Buffer, LgBiT, and NanoLuc substrate prepared following datasheet instructions) was added to each well. Plates were placed on an orbital shaker (300 rpm) for 3 minutes and then

incubated at room temperature for 10 minutes. Luminescence was measured on an Envision plate reader. GraphPad PRISM® software (Version 8) was utilized for plotting data as relative light units (RLU) ± SEM.

Generation of APOL1 G2 and G2 p.N264K HEK293 cell lines utilized in calcium uptake assay. Coding sequences of APOL1 G2 and APOL1 G2 p.N264K were subcloned into the pcDNA™5/TO T-REx mammalian expression construct and verified by sequencing. The host cell line, HEK-293 T-REx/GCaMP6f K4.1, was stably transfected with these constructs to generate target cell lines that inducibly express APOL1 G2 or APOL1 G2 p.N264K. Gene Pulser Xcell™ Eukaryotic System (Bio-Rad) was used for transfections. Specifically, to 3 x 10^6 cells resuspended in 0.8 mL Opti-MEM was added 10 µg of plasmid DNA. This mixture was subjected to electroporation (square wave protocol: 220 V, 25 ms pulse). After electroporation, cells were diluted in fresh prewarmed complete media and plated in a T75 flask. Antibiotics were added (30 µg/mL Hygromycin B for APOL1 G2 transfected cells and 0.3 mg/mL G418 for APOL1 G2 p.N264K transfected cells) to the appropriate cultures 48 hours after transfection. After antibiotic selection, the stable cellular pools were subjected to a stringent limiting dilution to generate pure stable clones. Cell lines were generated at Axxam S.p.A.

Maintenance of APOL1 G2, G2 p.N264K, and isogenic mock HEK293 cell lines. APOL1 cell lines were maintained in Dulbecco's Modified Eagle Medium (DMEM, BioWhittaker, BE12-614F; 500 mL) supplemented with 10% Performance Plus Serum (Gibco, 16000-044; 50 mL), 1x Penicillin-Streptomycin (BioWhittaker, DE17-602E; 5 mL of 100x solution), Ultraglutamine-1 (BioWhittaker, BE 17-605E/U1; 5 mL of 200 mM solution in 0.85% NaCl), 2.5 µg/mL of Blasticidin (InvivoGen, ant-bl), and 25 µg/mL of Zeocin (InvivoGen, ant-zn). 30 µg/mL of Hygromycin B Gold (InvivoGen, ant-hg-1) or 0.3 mg/mL of G418 (SIGMA, G8168) were also added to complete medium for APOL1 G2 or APOL1 p.N264K cell lines, respectively.

The isogenic mock cell line was maintained in DMEM (500 mL) supplemented with 10% Performance Plus Serum (50 mL), 1x Penicillin-Streptomycin (5 mL of 100x solution), Ultraglutamine-1 (5 mL of 200 mM solution in 0.85% NaCl), 5 µg/mL of Blasticidin, and 50 µg/mL of Zeocin. Note, all the selective agents (except Pen-Strep) were removed from cell culture medium while cell thawing and cell seeding.

Cells were split by gentle wash with PBS, followed by 5 minutes incubation at 37°C with trypsin-EDTA solution. Detached cells were diluted with complete medium, counted, and the desired number of cells was plated into a new flask or used for experiments.

Calcium uptake assay with APOL1 G2, G2 p.N264K, and isogenic mock HEK293 cell lines. Cells were detached from 70-80% confluent flasks and dispensed (20,000 cells/well final) into 384-well, black, clear bottom, poly-D-lysine coated plates in a volume of 25 µL/well. The following day, cells were induced with doxycycline for 6 hours at 37°C (humidified with 5% CO_2) by adding 25 µL/well of 100 ng/mL doxycycline dissolved in fresh complete medium (final concnetration = 50 ng/mL). After doxycycline induction, media was manually removed from all wells, replaced with 10 µL Tyrode's buffer (130 mM NaCl, 5 mM KCl, 10 mM $CaCl_2$, 1 mM $MgCl_2$, 5 mM $NaHCO_3$, 20 mM HEPES, pH 7.4), and incubated at room temperature for 10 minutes. Next, to each well was added 10 µL of a calcium dilution series made using Tyrode's buffer (final top concentration of calcium = 5 mM) via online injection. The fluorescent signal was measured for 3 minutes after injection using a FLIPR^{TETRA} plate reader (λ_{exc} 470-495 nm, λ_{em} 515-575 nm). The instrument settings (exposure time, excitation intensity, and gain) were regulated to obtain a baseline signal of less than 5,000 RFU. FLIPR^{TETRA} measurements were

analyzed with Screenworks© software (Molecular Devices, Version 4.1). Data were exported as Response (F, maximum fluorescence) over Baseline (F0, baseline fluorescence before injection) with the baseline subtraction (ΔF/F0). These data represent averages of two independent experiments performed in quadruplicate. Mean and standard deviations were calculated with Excel software. These values were used to create sigmoidal dose-response curves (variable slope) using GraphPad PRISM software (Version 8). Experimental data was generated at Axxam S.p.A.

qPCR of APOL1 G2, G2 p.N264K, isogenic mock HEK293 cell lines. Total RNA was extracted from 1 x 10^6 cells using the Maxwell® RSC simplyRNA Tissue Kit (Promega, AS1340) according to manufacturer instructions. The extracted RNA was reverse transcribed with the LunaScript RT SuperMix Kit (New England Biolabs, BE3010L). The quality of RNA/cDNA was tested by checking efficiency and signal strength of a "real time" quantification of *Homo sapiens* GAPDH with the following primers: (1) hGAPDH fw exon6 = GTTCGTCATGGGTGTGAACC and (2) hGAPDH rev exon7 = CTAAGCAGTTGGTGGTGCAG. Primers for the amplification of APOL1 were designed to be specific for the codon optimized mRNA sequence of the gene: (1) APOL1 fw = GAGCCTGGACAAGCTGAAAG and (2) APOL1 rev ACAGACTGCAGATTGGCTCT. The expression levels of the target and the housekeeping gene were quantified using SybrGreen technology. Each 20 µL reaction contained cDNA, 0.3 µM of each primer, and 2x qPCRBIO SyGreen Blue Mix Lo-ROX master mix (Resnova, PB20.15-20). A given reaction mixture was then divided into 4 technical replicates of 4 µL each. Non-template control reactions containing master mix, primers, and water (instead of cDNA) where also included in each experiment. Prepared samples where then subjected to the following amplification protocol:

(1) 2 minutes 95°C, 1 cycle
(2) 5 seconds 95°C and 30 seconds 95°C, 40 cycles
(3) 15 seconds 95°C, 1 cycle
(4) 1 minute 60°C, 1 cycle
(5) 15 seconds 95°C, 1 cycle

Acquired data was analyzed using QuantStudio™ Real-Time PCR software. Target-specific (APOL1) signals were normalized to the housekeeping gene, GAPDH, as an indicator of the total cDNA content. Relative Expression Units (REU) were calculated using the ΔCt method according to the following equation: REU = $2^{-\Delta Ct} \times 10^5$; with ΔCt = Ct (target) – Ct (GAPDH). The factor 10^5 was introduced to obtain more intuitive REU values. Experimental data was generated at Axxam S.p.A. and plotted using GraphPad PRISM® software (Version 8).

Cell viability assay with APOL1 G2, G2 p.N264K, isogenic mock HEK293 cell lines. CellTiter-Glo® viability assays were performed in concordance with cellular calcium uptake experiments. Specifically, using the same assay plates, viability measurements were collected immediately after GCaMP6f fluorescence values were recorded from calcium uptake experiments. Reconstituted CellTiter-Glo reagent was added to media present in the wells in a 1:1 volumetric ratio. Plates were incubated for 15 minutes in the dark at room temperature and luminescence was recorded using a FLIPR^{TETRA} plate reader after incubation. These data represent averages of two independent experiments performed in quadruplicate. Mean and standard deviations were calculated with Excel software. Experimental data was generated at Axxam S.p.A. and plotted using GraphPad PRISM software (Version 8).

Supplementary Table 1: BioVU Cohort Characteristics stratified by *APOL1* genotype.

	No *APOL1* p.N264K alleles		**≥1 *APOL1* p.N264K alleles**	
	***APOL1* Low Risk**	***APOL1* High Risk**	***APOL1* Low Risk**	***APOL1* High Risk**
	N=11578	*N=2105*	*N=603*	*N=100*
Age, median [IQR], years	45.0 [31.0;60.0]	45.0 [31.0;59.0]	45.0 [31.0;60.0]	49.0 [32.0;60.0]
Male, n, (%)	4397 (38.0%)	827 (39.3%)	232 (38.5%)	44 (44.0%)
Diabetes, n, (%)	3057 (26.4%)	368 (17.5%)	155 (25.7%)	13 (13.0%)
Body Mass Index, median [IQR]	30.0 [24.7;36.6]	28.5 [23.9;36.3]	34.6 [25.9;39.9]	32.4 [27.2;39.1]
Systolic BP, mmHg, median [IQR]	132 [119;150]	131 [120;151]	132 [117;145]	133 [122;144]
Diastolic BP, mmHg, median [IQR]	77.0 [68.0;86.0]	78.0 [69.0;87.0]	74.0 [63.0;89.0]	79.0 [70.0;92.0]
Baseline eGFR, ml/min/1.73m2, median [IQR]	100.1 [89.1;110.2]	97.3 [90.6;106.9]	95.8 [88.5;108.3]	99.2 [91.6;113.8]

Supplementary Table 2: NIH All of Us Cohort Characteristics stratified by *APOL1* genotype.

	No *APOL1* p.N264K alleles		**≥1 *APOL1* p.N264K alleles**	
	***APOL1* Low Risk**	***APOL1* High Risk**	***APOL1* Low Risk**	***APOL1* High Risk**
	N=12,655	*N=1952*	*N=608*	*N=97*
Age, median [IQR], years	54.8 [41.8–63.8]	53.8 [40.8–61.8]	55.8 [43.8–64.8]	55.8 [41.8–62.8]
Male, n, (%)	4461 (35.2%)	694 (35.6%)	210 (34.5%)	34 (35.0%)
Diabetes, n, (%)	3463 (27.4%)	545 (27.9%)	159 (26.2%)	20 (20.6%)
Body Mass Index, median [IQR]	30.8 [25.9 – 36.9]	31.3 [26.3 – 37.7]	30.3 [25.5 – 36.1]	30.2 [24.8 – 37.4]
Systolic BP, mmHg, median [IQR]	130.0 [119.5-139.0]	130.0 [120.0-140.0]	128.0 [120.0-138.0]	126.0 [117.0-137.0]
Diastolic BP, mmHg, median [IQR]	73.0 [79.0-85.0]	74.0 [79.0-86.0]	78.0 [73.0-84.25]	77.0 [73.0-83]
Median eGFR, ml/min/1.73m^2, median [IQR]	89.1 [73.5–87.8]	86.2 [69.7–101.2]	88.9 [72.1–103.2]	88.9 [76.4 –101.2]

Supplementary Table 3: ESRD definition

Outcome	*Definition*
1. ESRD	
a. eGFR <15 ml/min/1.73m2	An outpatient laboratory measurement of eGFR <15 ml/min/1.73 m^2 with confirmatory eGFR <15 at least 3 months apart
b. dialysis	Either 2 outpatient codes for dialysis or 1 outpatient and 1 inpatient diagnosis code in primary position (at least 3 months apart) Codes are listed in the dialysis codes table (supplemental table 3)
c. transplant	Either an outpatient code for renal transplant or an inpatient code position as the primary diagnosis. In the outpatient setting two codes are require in two different dates. Codes include in the definition table (Table S9.)

Supplementary Table 4. Definitions and procedure codes for dialysis and comorbidities.

Dialysis	
ICD-9 Diagnosis	V45.1, V45.11, V56.0, V56.1, V56.2, V56.8, 585.6, V45.12, V56.31, V56.32, 792.5, 39.95, 39.952, 54.982, 39.953, 54.98, 54.983, 99.78
ICD-10 diagnosis	N18.6 R88.0 Z49.31, Z49.32, Z91.15,3E1M39Z Z49.01, Z49.02, Z99.2
ICD9P C	39.951, 54.981
CPT	90941, 90942, 90943, 90944, G0491, G0492, M0916, M0920, M0931, M0932, 90996, A4690, A4750, A4755, 90935, 90937, 90947, 90999, 90988, 90997, 4054F, 4055F, E1590, G8715, G8727, M0936, 36516, 36901, 36902, 36903, 36904, 36905, 36906, 36516,36901,36902,36903,36904,36905,36906,36907,36908,36909,4052F,4053F,90939, 90940,90963,90964,90965,90966,90967,9 0968,90969,90970,90976,90977,90978,90979,90982,90983, 90984, 90985, 90991, 90994, 99512, 99559, G0257, G0320, G0321, G0322, G0323, G0327, G8075, G8076, G8714, G8956, G9264, G9265, G9266, M0923, M0928, M0937, M0940, M0944, M0945, M0948, M0952, M0956, S9335, S9339, G9240, G9241, 0505F,0507F,9092,90921,90924,90925,90951,90952,90953, 90954, 90955, 90956, 90957, 90958, 90959, 90960, 90961, 90962, 90989, 90990, 90992, 90993,90995, 90998, 4054F, 4055F
ICD-10	E11.00, E11.01, E11.10, E11.11, E11.21, E11.22, E11.29, E11.311, E11.319, E11.321, E11.3211, E11.3212, E11.3213, E11.3219, E11.329, E11.3291, E11.3292, E11.3293, E11.3299, E11.331, E11.3311, E11.3312, E11.3313, E11.3319, E11.339, E11.3391, E11.3392, E11.3393, E11.3399, E11.341, E11.3411, E11.3412, E11.3413, E11.3419, E11.349, E11.3491, E11.3492, E11.3493, E11.3499, E11.351, E11.3511,E11.3512, E11.3513, E11.3519, E11.3521, E11.3522, E11.3523, E11.3529, E11.3531, E11.3532, E11.3533, E11.3539, E11.3541,E11.3542, E11.3543, E11.3549, E11.3551, E11.3552, E11.3553, E11.3559, E11.359, E11.3591, E11.3592, E11.3593, E11.3599, E11.36, E11.37X1, E11.37X2, E11.37X3, E11.37X9, E11.39, E11.40, E11.41, E11.42, E11.43, E11.44, E11.49, E11.51, E11.52, E11.59, E11.610, E11.618, E11.620, E11.621, E11.622,E11.628, E11.630, E11.638, E11.641, E11.649, E11.65, E11.69, E11.8, E11.9, O24.111, O24.112, O24.113, O24.119, O24.12, O24.13
ICD9	250, 250.1, 250.2, 250.3, 250.4, 250.5, 250.6, 250.7, 250.8, 250.9, 357.2, 362.01, 362.02, 362.04, 362.05, 362.06, 362.07, 366.41, 648, 648.01, 648.03, 648.04
Hypertension	

ICD10	I10., O10.011, O10.012, O10.013, O10.019, O10.02, O10.03, O10.911, O10.912, O10.913, O10.919, O10.92, O10.93, O16.1, O16.2, O16.3, O16.4, O16.5, O16.9
ICD-9	401,401.1,401.9,402,402.01,402.1,402.11,402.9,402.91,403,403.01,403.1,403.11, 403.9,403.91,404, 404.01, 404.02, 404.03, 404.1, 404.11, 404.12, 404.13, 404.9, 404.91, 404.92, 404.93, 405.01, 405.09, 405.11, 405.19, 405.91, 405.99, 437.2, 642, 642.01, 642.02, 642.03, 642.04, 642.1, 642.11, 642.12, 642.13, 642.14, 642.2, 642.21, 642.22, 642.23, 642.24, 642.3, 642.31, 642.32, 642.33, 642.34, 642.4, 642.41, 642.42, 642.43, 642.44, 642.5, 642.51, 642.52, 642.53, 642.54, 642.6, 642.61, 642.62, 642.63, 642.64, 642.7, 642.71, 642.72, 642.73, 642.74, 642.9, 642.91, 642.92, 642.93
Nephrotic Syndrome	
ICD10	N04.0, N04.1, N04.2, N04.3, N04.4, N04.5, N04.6, N04.7, N04.8, N04.9
ICD9	581.9
FSGS	
ICD10	N04.1
Diabetes	
ICD10	E11.311, E10.42, E11.319, E11.628, E11.69, E10.618, E10.9, E10.37X3, E10.37X2, E10.11, E10.638, E11.3493, E11.8, E10.319, E11.3592, E11.3391, E10.69, E11.10, E10.29, E10.37X9, E11.9, E10.621, E11.3492, E09.36, E11.3399, E11.11, E11.3591, E11.3299, E10.620, E11.638, E09.42, E10.10, E10.65, E11.3499, E11.01, E11.630, E10.630, E08.36, E10.51, E11.649, E11.621, E11.620, E11.39, E10.21, E10.8, E11.65, E11.51, E10.40, Z46.81, E11.3393, E10.39, E13.42, E11.3593, E10.641, E10.311, E11.36, E11.3292, E10.649, E11.3491, E11.622, E11.3291, E11.618, E11.3599, E10.36, E11.00, E08.42, E13.36, Z96.41, E11.29, E11.3293, E10.628, E11.40, E13.10, E10.622, E11.641, E10.37X1, E11.42, E11.3392, E11.21
ICD9	250.1, 250.12, 250.21, 250.4, 250.41, 250.43, 250.5, 250.51, 250.6, 250.63, 250.72, 250.83, 250.93, 357.2, 362.03, 250, 250.22, 250.23, 250.3, 250.31, 250.53, 250.91, 362.01, 362.04, 362.06, 362.07, V53.91, 250.01, 250.03, 250.13, 250.2, 250.42, 250.52, 250.73, 250.82, 250.9, 250.92, 362.02, 362.05, 366.41, 250.11, 250.32, 250.33, 250.61, 250.62, 250.7, 250.71, 250.8, 250.81, V45.85 250.02
Alport's	
ICD10	Q87.81
ICD9	759.89
ADPKD	
ICD10	Q61.2, Q61.3
ICD9	753.12, 753.13

Cancer	
ICD10	C00.1, C00.2, C00.3, C00.4, C00.5, C00.6, C00.8, C01., C02.0, C02.1, C02.2, C02.3, C02.4, C02.8, C02.9, C03.0, C03.1, C03.9, C04.0, C04.1, C04.8, C04.9, C05.0, C05.1, C05.2, C05.9, C06.0, C06.1, C06.2, C06.89, C06.9, C07., C08.0, C08.1, C08.9, C09.0, C09.1, C09.9, C10.0, C10.1, C10.2, C10.3, C10.4, C10.8, C10.9, C11.0, C11.1, C11.2, C11.3, C11.8, C11.9, C12., C13.0, C13.1, C13.2, C13.8, C13.9, C14.0, C14.2, C14.8, C15.3, C15.4, C15.5, C15.8, C15.9, C16.0, C16.1, C16.2, C16.3, C16.4, C16.5, C16.6, C16.8, C16.9, C17.0, C17.1, C17.2, C17.3, C17.8, C17.9, C18.0, C18.1, C18.2, C18.3, C18.4, C18.5, C18.6, C18.7, C18.8, C18.9, C19., C20., C21.0, C21.1, C21.8, C22.0, C22.1, C22.2, C22.7, C22.8, C22.9, C23., C24.0, C24.1, C24.8, C24.9, C25.0, C25.1, C25.2, C25.3, C25.4, C25.7, C25.8, C25.9, C26.0, C26.1, C26.9, C30.0, C30.1, C31.0, C31.1, C31.2, C31.3, C31.8, C31.9, C32.0, C32.1, C32.2, C32.3, C32.8, C32.9, C33., C34.00, C34.10, C34.2, C34.30, C34.80, C34.90, C37., C38.0, C38.1, C38.2, C38.3, C38.4, C38.8, C39.0, C39.9, C40.00, C40.10, C40.20, C40.30, C41.0, C41.1, C41.2, C41.3, C41.4, C41.9, C43.0, C43.10, C43.20, C43.30, C43.31, C43.39, C43.4, C43.59, C43.60, C43.70, C43.8, C43.9, C46.0, C46.1, C46.2, C46.3, C46.4, C46.50, C46.7, C46.9, C47.8, C48.0, C48.1, C48.2, C48.8, C49.0, C49.10, C49.20, C49.3, C49.4, C49.5, C49.6, C49.8, C49.9, C49.A0, C49.A1, C49.A2, C49.A3, C49.A4, C49.A5, C49.A9, C4A.0, C4A.10, C4A.20, C4A.30, C4A.39, C4A.4, C4A.59, C4A.60, C4A.70, C4A.8, C4A.9, C50.019, C50.029, C50.119, C50.219, C50.319, C50.419, C50.519, C50.619, C50.819, C50.919, C50.929, C51.0, C51.1, C51.2, C51.9, C52., C53.0, C53.1, C53.8, C53.9, C54.0, C54.1, C54.2, C54.3, C54.8, C54.9, C55., C56.9, C57.00, C57.10, C57.20, C57.3, C57.4, C57.7, C57.8, C57.9, C58., C60.0, C60.1, C60.2, C60.8, C60.9, C61., C62.00, C62.10, C62.90, C63.00, C63.10, C63.2, C63.7, C63.8, C63.9, C64.9, C65.9, C66.9, C67.0, C67.1, C67.2, C67.3, C67.4, C67.5, C67.6, C67.7, C67.8, C67.9, C68.0, C68.1, C68.8, C68.9, C69.00, C69.10, C69.20, C69.30, C69.40, C69.50, C69.60, C69.80, C69.90, C70.0, C70.1, C70.9, C71.0, C71.1, C71.2, C71.3, C71.4, C71.5, C71.6, C71.7, C71.8, C71.9, C72.0, C72.1, C72.50, C72.9, C73., C74.90, C75.0, C75.1, C75.2, C75.3, C75.4, C75.5, C75.8, C75.9, C76.0, C76.1, C76.2, C76.3, C76.40, C76.50, C76.8, C77.0, C77.1, C77.2, C77.3, C77.4, C77.5, C77.8, C77.9, C78.00, C78.1, C78.2, C78.39, C78.4, C78.5, C78.6, C78.7, C78.89, C79.00, C79.11, C79.19, C79.2, C79.31, C79.32, C79.49, C79.51, C79.52, C79.60, C79.70, C79.81, C79.82, C79.89, C7A.00, C7A.010, C7A.011, C7A.012, C7A.019, C7A.020, C7A.021, C7A.022, C7A.023, C7A.024, C7A.025, C7A.026, C7A.029, C7A.090, C7A.091, C7A.092, C7A.093, C7A.094, C7A.094, C7A.095, C7A.095, C7A.096, C7A.096, C7A.098, C7A.1, C7B.00, C7B.01, C7B.02, C7B.03, C7B.04, C7B.09, C7B.1, C7B.8, C80.0, C80.1, C80.2, C81.00, C81.01, C81.02, C81.03, C81.04, C81.05, C81.06, C81.07, C81.08, C81.09, C81.10, C81.10, C81.11, C81.11, C81.12, C81.12, C81.13, C81.13, C81.14, C81.14, C81.15, C81.15, C81.16, C81.16, C81.17, C81.17, C81.18, C81.18, C81.19, C81.19, C81.20, C81.20, C81.21, C81.21, C81.22, C81.22, C81.23, C81.23, C81.24, C81.24, C81.25, C81.25, C81.26, C81.26, C81.27, C81.27, C81.28, C81.28, C81.29, C81.29, C81.30, C81.30, C81.31, C81.31, C81.32, C81.32, C81.33, C81.33, C81.34, C81.34, C81.35, C81.35, C81.36, C81.36, C81.37, C81.37, C81.38, C81.38, C81.39, C81.39, C81.40, C81.40, C81.41, C81.41, C81.42, C81.42, C81.43, C81.43, C81.44, C81.44, C81.45, C81.45, C81.46, C81.46, C81.47, C81.47, C81.48, C81.48, C81.49, C81.49, C81.70, C81.70, C81.71, C81.71, C81.72, C81.72, C81.73, C81.73, C81.74, C81.74, C81.75, C81.75, C81.76, C81.76, C81.77, C81.77, C81.78, C81.78, C81.79, C81.79, C81.90, C81.91, C81.92, C81.93, C81.94, C81.95, C81.96, C81.97, C81.98, C81.99, C82.90, C82.91, C82.92, C82.93, C82.94, C82.95, C82.96, C82.97, C82.98, C82.99, C83.10, C83.11, C83.12, C83.13, C83.14, C83.15, C83.16, C83.17, C83.18, C83.19, C83.30, C83.31, C83.32, C83.33, C83.34, C83.35, C83.36, C83.37, C83.38, C83.39, C83.50, C83.51, C83.52, C83.53, C83.54, C83.55, C83.56, C83.57, C83.58, C83.59, C83.70, C83.71, C83.72, C83.73, C83.74,

	C83.75, C83.76, C83.77, C83.78, C83.79, C83.80, C83.81, C83.82, C83.83, C83.84, C83.85, C83.86, C83.87, C83.88, C83.89, C84.00, C84.01, C84.02, C84.03, C84.04, C84.05, C84.06, C84.07, C84.08, C84.09, C84.10, C84.11, C84.12, C84.13, C84.14, C84.15, C84.16, C84.17, C84.18, C84.19, C84.40, C84.41, C84.42, C84.43, C84.44, C84.45, C84.46, C84.47, C84.48, C84.49, C84.60, C84.61, C84.62, C84.63, C84.64, C84.65, C84.66, C84.67, C84.68, C84.69, C84.70, C84.71, C84.72, C84.73, C84.74, C84.75, C84.76, C84.77, C84.78, C84.79, C84.93, C85.80, C85.81, C85.82, C85.83, C85.84, C85.85, C85.86, C85.87, C85.88, C85.89, C88.8, C90.00, C90.01, C90.02, C90.10, C90.11, C90.12, C90.20, C90.21, C90.22, C90.30, C90.31, C90.32, C91.00, C91.01, C91.02, C91.10, C91.11, C91.12, C91.40, C91.41, C91.90, C91.91, C91.92, C91.Z0, C91.Z1, C91.Z2, C92.00, C92.01, C92.02, C92.10, C92.11, C92.12, C92.20, C92.21, C92.22, C92.30, C92.31, C92.32, C92.40, C92.41, C92.42, C92.50, C92.51, C92.52, C92.90, C92.91, C92.92, C92.Z0, C92.Z1, C92.Z2, C93.00, C93.01, C93.02, C93.10, C93.11, C93.12, C93.90, C93.91, C93.92, C93.Z0, C93.Z1, C93.Z2, C94.00, C94.01, C94.02, C94.20, C94.21, C94.22, C94.30, C94.31, C94.32, C94.40, C94.41, C94.42, C94.80, C94.81, C94.82, C95.00, C95.01, C95.02, C95.10, C95.11, C95.12, C95.90, C95.91, C95.92, C96.0, C96.20, C96.21, C96.22, C96.29, C96.4, C96.9, C96.A, C96.Z, D00.00, D00.01, D00.02, D00.03, D00.04, D00.05, D00.06, D00.07, D00.08, D00.1, D00.2, D01.0, D01.1, D01.2, D01.3, D01.40, D01.49, D01.5, D01.7, D01.9, D02.0, D02.1, D02.20, D02.3, D02.4, D03.0, D03.10, D03.11, D03.12, D03.20, D03.21, D03.22, D03.30, D03.39, D03.4, D03.51, D03.52, D03.59, D03.60, D03.61, D03.62, D03.70, D03.71, D03.72, D03.8, D03.9, D05.90, D06.9, D07.0, D07.1, D07.2, D07.30, D07.39, D07.4, D07.5, D07.60, D07.69, D09.0, D09.10, D09.19, D09.20, D09.3, D09.8, D09.9, D22.9, D45., D46.0, D46.1, D46.20, D46.21, D46.22, D46.9, D46.A, D46.B, D46.C, D47.01, D47.02, D47.09, D47.1, D47.3, D47.9, D47.Z1, D47.Z2, D47.Z9, Q85.00, Q85.01, Q85.02, Q85.03, Q85.09

ICD9	140.1, 140.3, 140.4, 140.5, 140.6, 140.8, 140.9, 141, 141.1, 141.2, 141.3, 141.4, 141.5, 141.6, 141.8, 141.9, 142, 142.1, 142.2, 142.8, 142.9, 143, 143.1, 143.8, 143.9, 144, 144.1, 144.8, 144.9, 145, 145.1, 145.2, 145.3, 145.4, 145.5, 145.6, 145.8, 145.9, 146, 146.1, 146.2, 146.3, 146.4, 146.5, 146.6, 146.7, 146.8, 146.9, 147, 147.1, 147.2, 147.3, 147.8, 147.9, 148, 148.1, 148.2, 148.3, 148.8, 148.9, 149, 149.1, 149.8, 149.9, 150, 150.1, 150.2, 150.3, 150.4, 150.5, 150.8, 150.9, 151, 151.1, 151.2, 151.3, 151.4, 151.5, 151.6, 151.8, 151.9, 152, 152.1, 152.2, 152.3, 152.8, 152.9, 153, 153.1, 153.2, 153.3, 153.4, 153.5, 153.6, 153.7, 153.8, 153.9, 154, 154.1, 154.2, 154.3, 154.8, 155, 155.1, 155.2, 156, 156.1, 156.2, 156.8, 156.9, 157, 157.1, 157.2, 157.3, 157.4, 157.8, 157.9, 158, 158.8, 158.9, 159, 159.1, 159.8, 159.9, 160, 160.1, 160.2, 160.3, 160.4, 160.5, 160.8, 160.9, 161, 161.1, 161.2, 161.3, 161.8, 161.9, 162, 162.2, 162.3, 162.4, 162.5, 162.8, 162.9, 163, 163.1, 163.8, 163.9, 164, 164.1, 164.2, 164.3, 164.8, 164.9, 165, 165.8, 165.9, 170, 170.1, 170.2, 170.3, 170.4, 170.5, 170.6, 170.7, 170.8, 170.9, 171, 171.2, 171.3, 171.4, 171.5, 171.6, 171.7, 171.8, 171.9, 172, 172.1, 172.2, 172.3, 172.4, 172.5, 172.6, 172.7, 172.8, 172.9, 174, 174.1, 174.2, 174.3, 174.4, 174.5, 174.6, 174.8, 174.9, 175, 175.9, 176, 176.1, 176.2, 176.3, 176.4, 176.5, 176.8, 176.9, 179, 180, 180.1, 180.8, 180.9, 181, 182, 182.1, 182.8, 183, 183.2, 183.3, 183.4, 183.5, 183.8, 183.9, 184, 184.1, 184.2, 184.3, 184.4, 184.8, 184.9, 185, 186, 186.9, 187.1, 187.2, 187.3, 187.4, 187.5, 187.6, 187.7, 187.8, 187.9, 188, 188.1, 188.2, 188.3, 188.4, 188.5, 188.6, 188.7, 188.8, 188.9, 189, 189.1, 189.2, 189.3, 189.4, 189.8, 189.9, 190, 190.1, 190.2, 190.3, 190.4, 190.5, 190.6, 190.7, 190.8, 190.9, 191, 191.1, 191.2, 191.3, 191.4, 191.5, 191.6, 191.7, 191.8, 191.9, 192, 192.1, 192.2, 192.3, 192.8, 192.9, 193, 194, 194.1, 194.3, 194.4, 194.5, 194.6, 194.8, 194.9, 195, 195.1, 195.2, 195.3, 195.4, 195.5, 195.8, 196, 196.1, 196.2, 196.3, 196.5, 196.6, 196.8, 196.9, 197, 197.1, 197.2, 197.3, 197.4, 197.5, 197.6, 197.7, 197.8, 198, 198.1, 198.2, 198.3, 198.4, 198.5, 198.6, 198.7, 198.81, 198.82, 198.89, 199, 199.1, 199.2, 200, 200.01, 200.02, 200.03, 200.04, 200.05, 200.06, 200.07, 200.08, 200.1, 200.11, 200.12, 200.13, 200.14, 200.15, 200.16, 200.17, 200.18, 200.2, 200.21, 200.22, 200.23, 200.24, 200.25, 200.26, 200.27, 200.28, 200.3, 200.31, 200.32, 200.33, 200.34, 200.35, 200.36, 200.37, 200.38, 200.4, 200.41, 200.42, 200.43, 200.44, 200.45, 200.46, 200.47, 200.48, 200.5, 200.51, 200.52, 200.53, 200.54, 200.55, 200.56, 200.57, 200.58, 200.6, 200.61, 200.62, 200.63, 200.64, 200.65, 200.66, 200.67, 200.68, 200.7, 200.71, 200.72, 200.73, 200.74, 200.75, 200.76, 200.77, 200.78, 200.8, 200.81, 200.82, 200.83, 200.84, 200.85, 200.86, 200.87, 200.88, 201, 201.01, 201.02, 201.03, 201.04, 201.05, 201.06, 201.07, 201.08, 201.1, 201.11, 201.12, 201.13, 201.14, 201.15, 201.16, 201.17, 201.18, 201.2, 201.21, 201.22, 201.23, 201.24, 201.25, 201.26, 201.27, 201.28, 201.4, 201.41, 201.42, 201.43, 201.44, 201.45, 201.46, 201.47, 201.48, 201.5, 201.51, 201.52, 201.53, 201.54, 201.55, 201.56, 201.57, 201.58, 201.6, 201.61, 201.62, 201.63, 201.64, 201.65, 201.66, 201.67, 201.68, 201.7, 201.71, 201.72, 201.73, 201.74, 201.75, 201.76, 201.77, 201.78, 201.9, 201.91, 201.92, 201.93, 201.94, 201.95, 201.96, 201.97, 201.98, 202, 202.01, 202.02, 202.03, 202.04, 202.05, 202.06, 202.07, 202.08, 202.1, 202.11, 202.12, 202.13, 202.14, 202.15, 202.16, 202.17, 202.18, 202.2, 202.21, 202.22, 202.23, 202.24, 202.25, 202.26, 202.27, 202.28, 202.3, 202.31, 202.32, 202.33, 202.34, 202.35, 202.36, 202.37, 202.38, 202.4, 202.41, 202.42, 202.43, 202.44, 202.45, 202.46, 202.47, 202.48, 202.48, 202.5, 202.51, 202.52, 202.53, 202.54, 202.55, 202.56, 202.57, 202.58, 202.6, 202.61, 202.62, 202.63, 202.64, 202.65, 202.66, 202.67, 202.68, 202.7, 202.71, 202.72, 202.73, 202.74, 202.75, 202.76, 202.77, 202.78, 202.8, 202.81, 202.82, 202.83, 202.84, 202.85, 202.86, 202.87, 202.88, 202.9, 202.91, 202.92, 202.93, 202.94, 202.95, 202.96, 202.97, 202.98, 203, 203, 203, 203.01, 203.02, 203.1, 203.1, 203.1, 203.11, 203.12, 203.8, 203.8, 203.8, 203.81, 203.82, 204, 204, 204, 204.01, 204.02, 204.1, 204.1, 204.1,

	204.11, 204.12, 204.2, 204.2, 204.2, 204.21, 204.22, 204.8, 204.8, 204.8, 204.81, 204.82, 204.9, 204.9, 204.9, 204.91, 204.92, 205, 205, 205, 205.01, 205.02, 205.1, 205.1, 205.1, 205.11, 205.12, 205.2, 205.2, 205.2, 205.21, 205.22, 205.3, 205.3, 205.3, 205.31, 205.32, 205.8, 205.8, 205.8, 205.81, 205.82, 205.9, 205.9, 205.9, 205.91, 205.92, 206, 206, 206, 206.01, 206.02, 206.1, 206.1, 206.1, 206.11, 206.12, 206.2, 206.2, 206.2, 206.21, 206.22, 206.8, 206.8, 206.8, 206.81, 206.82, 206.9, 206.9, 206.9, 206.91, 206.92, 207, 207, 207, 207.01, 207.02, 207.1, 207.1, 207.1, 207.11, 207.12, 207.2, 207.2, 207.2, 207.21, 207.22, 207.8, 207.8, 207.8, 207.81, 207.82, 208, 208, 208, 208.01, 208.02, 208.1, 208.1, 208.1, 208.11, 208.12, 208.2, 208.2, 208.2, 208.21, 208.22, 208.8, 208.8, 208.8, 208.81, 208.82, 208.9, 208.9, 208.9, 208.91, 208.92, 209, 209.01, 209.02, 209.03, 209.1, 209.11, 209.12, 209.13, 209.14, 209.15, 209.16, 209.17, 209.2, 209.21, 209.22, 209.23, 209.24, 209.25, 209.26, 209.27, 209.29, 209.3, 209.31, 209.32, 209.33, 209.34, 209.35, 209.36, 209.7, 209.71, 209.72, 209.73, 209.74, 209.75, 209.79, 230, 230.1, 230.2, 230.3, 230.4, 230.5, 230.6, 230.7, 230.8, 230.9, 231, 231.1, 231.2, 231.8, 231.9, 232, 232.1, 232.2, 232.3, 232.4, 232.5, 232.6, 232.7, 232.8, 232.9, 233, 233.1, 233.2, 233.3, 233.3, 233.31, 233.32, 233.39, 233.4, 233.5, 233.6, 233.7, 233.9, 234, 234.8, 234.9, 237.7, 237.7, 237.71, 237.72, 237.73, 237.79, 238.4, 238.71, 238.72, 238.73, 238.74, 238.75, 238.76, 238.77, 238.79

Supplementary Table 5: MVP *APOL1* association with chronic kidney disease. The risk of CKD associate with *APOL1* high risk variants (*APOL1* HR) is not observed in the presence of *APOL1* N264K+ and is comparable to *APOL1* low risk (*APOL1* LR).

	Non-diabetic			Diabetic		
Predictors	*Odds Ratios*	*CI*	*p*	*Odds Ratios*	*CI*	*p*
Model 1						
APOL1 HR, N264K-	1.72	1.60 – 1.84	**<0.001**	1.31	1.22 – 1.41	**<0.001**
APOL1 LR, N264K+	0.86	0.74 – 0.99	0.031	1.02	0.90 – 1.16	0.716
APOL1 HR, N264K+	0.71	0.46 – 1.09	**0.113**	0.75	0.52 – 1.08	**0.125**
Model 2						
APOL1 HR, N264K-	1.73	1.61 – 1.86	**<0.001**	1.31	1.22 – 1.41	**<0.001**
APOL1 LR, N264K+	0.87	0.75 – 1.00	0.052	1.03	0.90 – 1.17	0.704
APOL1 HR, N264K+	0.69	0.45 – 1.07	**0.095**	0.74	0.51 – 1.07	**0.106**
Model 3						
APOL1 HR, N264K-	1.72	1.60 – 1.85	**<0.001**	1.31	1.21 – 1.41	**<0.001**
APOL1 LR, N264K+	0.86	0.75 – 1.00	0.045	1.03	0.91 – 1.18	0.624
APOL1 HR, N264K+	0.70	0.45 – 1.08	**0.102**	0.73	0.51 – 1.06	**0.101**
Model 4						
APOL1 HR, N264K-	1.74	1.62 – 1.87	**<0.001**	1.32	1.22 – 1.42	**<0.001**
APOL1 LR, N264K+	0.86	0.75 – 0.99	0.041	1.04	0.91 – 1.18	0.581
APOL1 HR, N264K+	0.70	0.45 – 1.08	**0.104**	0.74	0.51 – 1.08	**0.116**
Model 5						
APOL1 HR, N264K-	1.72	1.60 – 1.85	**<0.001**	1.32	1.22 – 1.42	**<0.001**
APOL1 LR, N264K+	0.85	0.74 – 0.99	0.033	1.04	0.91 – 1.18	0.559
APOL1 HR, N264K+	0.71	0.46 – 1.10	**0.127**	0.74	0.51 – 1.07	**0.109**
APOL1 HR: N264K Interaction						
Model 1			**0.002**			**0.004**
Model 2			**0.001**			**0.003**
Model 3			**0.001**			**0.003**
Model 4			**0.001**			**0.004**
Model 5			**0.002**			**0.002**

Logistic regression was used to evaluate the association of *APOL1* high-risk and p.N264K allele genotype and CKD. Odds ratios were adjusted for: model 1: age, gender, 10 principal components of ancestry, model 2: Also adjust for body mass index and renin angiotensin aldosterone system inhibition (use of angiotensin converting enzyme or renin angiotensin aldosterone blocker) and model 3: Further adjust for diagnosis of hypertension.
Model 4: adjusted for cancer (excluding non-melanoma skin cancers) and Model 5: adjusted for adult polycystic kidney disease (ADPKD).

All odds ratios are displayed relative to *APOL1* low-risk genotype (LR), and N264K-. *APOL1* high-risk refers to 2 copies of the APOL1 High Risk mutations G1 or G2 or G1 and G2; *APOL1* LR, 0 or 1 total copy of the G1 or G2 High Risk mutation; N264K+, carrying 1 or 2 copies of *APOL1* p.N264K; N264K-, carrying 0 copies of APOL1 N264K.

Supplementary Table 6: MVP *APOL1* association with End Stage Kidney Disease. The risk of ESKD associate with *APOL1* high risk variants (*APOL1* HR) is not observed in the presence of *APOL1* N264K+ and is comparable to *APOL1* low risk (*APOL1* LR).

	Non-diabetic			Diabetic		
Predictors	*Odds Ratios*	*CI*	*p*	*Odds Ratios*	*CI*	*p*
Model 1						
APOL1 HR, N264K-	4.00	3.58 – 4.48	**<0.001**	1.83	1.66 – 2.03	**<0.001**
APOL1 LR, N264K+	0.88	0.63 – 1.22	0.439	1.04	0.84 – 1.28	0.718
APOL1 HR, N264K+	0.74	0.27 – 1.98	**0.548**	0.82	0.43 – 1.55	0.545
Model 2						
APOL1 HR, N264K-	4.03	3.60 – 4.51	**<0.001**	1.85	1.67 – 2.04	**<0.001**
APOL1 LR, N264K+	0.89	0.64 – 1.23	0.482	1.04	0.85 – 1.29	0.688
APOL1 HR, N264K+	0.73	0.27 – 1.95	**0.525**	0.82	0.43 – 1.56	0.55
Model 3						
APOL1 HR, N264K-	3.94	3.52 – 4.41	**<0.001**	1.84	1.66 – 2.04	**<0.001**
APOL1 LR, N264K+	0.88	0.63 – 1.22	0.439	1.05	0.85 – 1.30	0.628
APOL1 HR, N264K+	0.73	0.27 – 1.96	**0.530**	0.82	0.43 – 1.56	0.553
Model 4						
APOL1 HR, N264K-	3.89	3.47 – 4.35	**<0.001**	1.84	1.66 – 2.03	**<0.001**
APOL1 LR, N264K+	0.88	0.64 – 1.23	0.461	1.05	0.85 – 1.30	0.638
APOL1 HR, N264K+	0.73	0.27 – 1.98	**0.540**	0.83	0.44 – 1.57	0.563
Model 5						
APOL1 HR, N264K-	3.88	3.46 – 4.35	**<0.001**	1.83	1.66 – 2.03	**<0.001**
APOL1 LR, N264K+	0.84	0.60 – 1.18	0.322	1.06	0.85 – 1.30	0.619
APOL1 HR, N264K+	0.72	0.26 – 1.96	**0.517**	0.82	0.43 – 1.56	0.546
***APOL1* HR: N264K Interaction**						
Model 1			**0.003**			**0.015**
Model 2			**0.003**			**0.014**
Model 3			**0.003**			**0.014**
Model 4			**0.004**			**0.015**
Model 5			**0.005**			**0.013**

Logistic regression was used to evaluate the association of *APOL1* high-risk and p.N264K allele genotype and ESKD. Odds ratios were adjusted for: model 1: age, gender, 10 principal components of ancestry, model 2: Also adjust for body mass index and renin angiotensin aldosterone system inhibition (use of angiotensin converting enzyme or renin angiotensin aldosterone blocker) and model 3: Further adjust for diagnosis of hypertension. Model 4: adjusted for the diagnosis of cancer (excluding non-melanoma skin cancers) and Model 5: adjusted for adult polycystic kidney disease (ADPKD).

All odds ratios are displayed relative to *APOL1* low-risk genotype (LR), and N264K-. *APOL1* high-risk refers to 2 copies of the *APOL1* High Risk mutations G1 or G2 or G1 and G2; *APOL1* LR, 0 or 1 total copy of the G1 or G2 High Risk mutation; N264K+, carrying 1 or 2 copies of *APOL1* p.N264K; N264K-, carrying 0 copies of *APOL1* N264K.

Supplementary Table 7. MVP Cohort Characteristics stratified by *APOL1* N264K genotype.

	All patients				APOL1 high risk patients			
	[ALL]	N264K-	N264K Heterozygous	N264K Homozygous	[ALL]	N264K-	N264K Heterozygous	N264K Homozygous
	N=121492	*N=116238*	*N=5200*	*N=54*	*N=15604*	*N=15022*	*N=579*	*N=3*
apol1_ht:								
LR_N264K-	101216 (83.3%)	101216 (87.1%)	0 (0.00%)	0 (0.00%)				
HR_N264K-	15022 (12.4%)	15022 (12.9%)	0 (0.00%)	0 (0.00%)	15022 (96.3%)	15022 (100%)	0 (0.00%)	0 (0.00%)
LR_N264K+	4672 (3.85%)	0 (0.00%)	4621 (88.9%)	51 (94.4%)				
HR_N264K+	582 (0.48%)	0 (0.00%)	579 (11.1%)	3 (5.56%)	582 (3.73%)	0 (0.00%)	579 (100%)	3 (100%)
age	59.0	59.0	59.0	62.0	59.0 [51.0;66.0]	59.0 [51.0;66.0]	60.0 [53.0;66.0]	61.0 [50.5;66.5]
sex:								
Males, n(%)	104756	100188	4518 (86.9%)	50 (92.6%)	13431 (86.1%)	12922 (86.0%)	506 (87.4%)	3 (100%)
GFR, ml/min	86.6 [71.3;103]	86.6 [71.2;103]	86.9 [71.9;102]	88.4 [75.2;102]	84.6 [69.2;101]	84.5 [69.0;101]	88.3 [73.1;103]	93.4 [78.2;95.0]
Diabetes, n(%)	40842 (33.6%)	39076 (33.6%)	1747 (33.6%)	19 (35.2%)	5323 (34.1%)	5126 (34.1%)	196 (33.9%)	1 (33.3%)
Hypertension, n(%)	81626 (67.2%)	78099 (67.2%)	3487 (67.1%)	40 (74.1%)	10850 (69.5%)	10447 (69.5%)	401 (69.3%)	2 (66.7%)
SBP, (median [IQR])	130 [120;139]	130 [120;139]	130 [120;140]	130 [124;137]	130 [120;140]	130 [120;140]	131 [120;140]	130 [128;132]
DBP, (median [IQR])	79.0	79.0	79.0	80.0	79.0 [72.0;86.0]	79.0 [72.0;86.0]	79.0 [72.0;86.0]	76.0 [71.5;80.0]
Num_BP_meds, n(%)								
0	48058 (39.6%)	45972 (39.5%)	2069 (39.8%)	17 (31.5%)	5859 (37.5%)	5647 (37.6%)	211 (36.4%)	1 (33.3%)
1 or 2	53693 (44.2%)	51387 (44.2%)	2277 (43.8%)	29 (53.7%)	7024 (45.0%)	6753 (45.0%)	270 (46.6%)	1 (33.3%)
3 or more	19741 (16.2%)	18879 (16.2%)	854 (16.4%)	8 (14.8%)	2721 (17.4%)	2622 (17.5%)	98 (16.9%)	1 (33.3%)
BMI	29.7	29.7	29.5	28.0	29.8 [26.2;34.1]	29.8 [26.2;34.1]	29.4 [25.7;33.4]	27.3 [26.6;31.7]
Nephrotic_Syndrome, n(%)	910 (0.75%)	875 (0.75%)	35 (0.67%)	0 (0.00%)	195 (1.25%)	191 (1.27%)	4 (0.69%)	0 (0.00%)
FSGS, n(%)	140 (0.12%)	136 (0.12%)	4 (0.08%)	0 (0.00%)	54 (0.35%)	53 (0.35%)	1 (0.17%)	0 (0.00%)
CKD, n(%)	18831 (18.7%)	18075 (18.8%)	746 (17.4%)	10 (20.8%)	2967 (23.5%)	2896 (23.8%)	71 (15.6%)	0 (0.00%)
CKD prior to enrollment	16577 (15.7%)	15892 (15.7%)	677 (15.0%)	8 (16.0%)	2740 (20.4%)	2677 (20.7%)	63 (13.0%)	0 (0.00%)
CKD after enrollment	7556 (7.14%)	7256 (7.17%)	296 (6.55%)	4 (8.00%)	1005 (7.49%)	968 (7.49%)	36 (7.44%)	1 (33.3%)
ESRD:	4177 (3.44%)	4027 (3.46%)	149 (2.87%)	1 (1.85%)	1068 (6.84%)	1054 (7.02%)	14 (2.42%)	0 (0.00%)
ESRD prior to enrollment	2196 (1.81%)	2126 (1.83%)	69 (1.33%)	1 (1.85%)	690 (4.42%)	680 (4.53%)	10 (1.73%)	0 (0.00%)
ESRDafter enrollment	1981 (1.63%)	1901 (1.64%)	80 (1.54%)	0 (0.00%)	378 (2.42%)	374 (2.49%)	4 (0.69%)	0 (0.00%)
RAASi, n(%)	48792 (40.2%)	46681 (40.2%)	2091 (40.2%)	20 (37.0%)	6435 (41.2%)	6201 (41.3%)	232 (40.1%)	2 (66.7%)
ADPKD, n(%)	424 (0.35%)	405 (0.35%)	19 (0.37%)	0 (0.00%)	83 (0.53%)	81 (0.54%)	2 (0.35%)	0 (0.00%)
Proteinura, n(%)								
Negative/Trace	67636 (81.1%)	64692 (81.1%)	2916 (81.5%)	28 (70.0%)	8283 (77.1%)	7953 (77.0%)	329 (79.9%)	1 (33.3%)
1+	9094 (10.9%)	8664 (10.9%)	422 (11.8%)	8 (20.0%)	1322 (12.3%)	1263 (12.2%)	57 (13.8%)	2 (66.7%)
>= 2+	6701 (8.03%)	6457 (8.09%)	240 (6.71%)	4 (10.0%)	1143 (10.6%)	1117 (10.8%)	26 (6.31%)	0 (0.00%)

Supplementary Table 8: BioVU *APOL1* association with kidney disease outcomes amongst non-diabetic individuals. The risk of kidney outcomes associate with *APOL1* high risk variants (*APOL1* HR) is not observed in the presence of *APOL1* N264K+ and is comparable to *APOL1* low risk (*APOL1* LR).

***APOL1* genetic variants in BioVU**	*N*	*N with ESKD*	*ESKD Odds Ratio (95% CI)*	*N with CKD*	*CKD Odds Ratio (95% CI)*
APOL1 LR, N264K-	9,348	103	1.0 (ref)	265	1.0 (ref)
***APOL1* HR, N264K-**	1,670	101	5.79 (4.38, 7.68)	112	**2.54** (2.01, 3.20)
APOL1 LR, N264K+	481	4	0.74 (0.27, 2.01)	12	0.85 (0.47, 1.54)
***APOL1* HR, N264K+**	82	0	-	1	**0.36** (0.05, 2.64)

Logistic regression was used to evaluate the association of APOL1 high-risk and p.N264K allele genotype and CKD. Odds ratios were adjusted for age, gender and 10 principal components of ancestry. Interaction is not tested given small sample size.

Supplementary Table 9: All of Us *APOL1* association with kidney disease outcomes amongst non-diabetic individuals**.** The risk of kidney outcomes associate with *APOL1* high risk variants (*APOL1* HR) is not observed in the presence of *APOL1* N264K+ and is comparable to *APOL1* low risk (*APOL1* LR).

***APOL1* genetic variants in All of Us**	*N*	*N with ESKD*	*ESKD Odds Ratio (95% CI)*	*N with CKD*	*CKD Odds Ratio (95% CI)*
APOL1 LR, N264K-	9192	84	1.0 (ref)	760	1.0 (ref)
APOL1 HR, N264K-	1407	58	4.94 (3.48–7.02)	173	**1.81** (1.49–2.20)
APOL1 LR, N264K+	449	3	0.74 (0.23–2.35)	41	0.76 (0.53–1.09)
APOL1 HR, N264K+	77	1	1.36 (0.19–10.05)	6	**0.73** (0.28–1.88)

Logistic regression was used to evaluate the association of APOL1 high-risk and p.N264K allele genotype and CKD. Odds ratios were adjusted for age, gender and 10 principal components of ancestry. Interaction is not tested given small sample size.

Supplementary Table 10. VA Million Veteran Program: Core Acknowledgement for Publications
February 2023

MVP Program Office

- Sumitra Muralidhar, Ph.D., Program Director
  US Department of Veterans Affairs, 810 Vermont Avenue NW, Washington, DC 20420
- Jennifer Moser, Ph.D., Associate Director, Scientific Programs
  US Department of Veterans Affairs, 810 Vermont Avenue NW, Washington, DC 20420
- Jennifer E. Deen, B.S., Associate Director, Cohort & Public Relations
  US Department of Veterans Affairs, 810 Vermont Avenue NW, Washington, DC 20420

MVP Executive Committee

- Co-Chair: Philip S. Tsao, Ph.D.
  VA Palo Alto Health Care System, 3801 Miranda Avenue, Palo Alto, CA 94304
- Co-Chair: Sumitra Muralidhar, Ph.D.
  US Department of Veterans Affairs, 810 Vermont Avenue NW, Washington, DC 20420
- J. Michael Gaziano, M.D., M.P.H.
  VA Boston Healthcare System, 150 S. Huntington Avenue, Boston, MA 02130
- Elizabeth Hauser, Ph.D.
  Durham VA Medical Center, 508 Fulton Street, Durham, NC 27705
- Amy Kilbourne, Ph.D., M.P.H.
  VA HSR&D, 2215 Fuller Road, Ann Arbor, MI 48105
- Shiuh-Wen Luoh, M.D., Ph.D.
  VA Portland Health Care System, 3710 SW US Veterans Hospital Rd, Portland, OR 97239
- Michael Matheny, M.D., M.S., M.P.H.
  VA Tennessee Valley Healthcare System, 1310 24th Ave. South, Nashville, TN 37212
- Dave Oslin, M.D.
  Philadelphia VA Medical Center, 3900 Woodland Avenue, Philadelphia, PA 19104

MVP Co-Principal Investigators

- J. Michael Gaziano, M.D., M.P.H.
  VA Boston Healthcare System, 150 S. Huntington Avenue, Boston, MA 02130
- Philip S. Tsao, Ph.D.
  VA Palo Alto Health Care System, 3801 Miranda Avenue, Palo Alto, CA 94304

MVP Core Operations

- Lori Churby, B.S., Director, MVP Regulatory Affairs
  VA Palo Alto Health Care System, 3801 Miranda Avenue, Palo Alto, CA 94304
- Stacey B. Whitbourne, Ph.D., Director, MVP Cohort Management
  VA Boston Healthcare System, 150 S. Huntington Avenue, Boston, MA 02130
- Jessica V. Brewer, M.P.H., Director, MVP Recruitment & Enrollment

VA Boston Healthcare System, 150 S. Huntington Avenue, Boston, MA 02130
- Shahpoor (Alex) Shayan, M.S., Director, MVP Recruitment and Enrollment Informatics
  VA Boston Healthcare System, 150 S. Huntington Avenue, Boston, MA 02130
- Luis E. Selva, Ph.D., Executive Director, MVP Biorepositories
  VA Boston Healthcare System, 150 S. Huntington Avenue, Boston, MA 02130
- Saiju Pyarajan Ph.D., Director, Data and Computational Sciences
  VA Boston Healthcare System, 150 S. Huntington Avenue, Boston, MA 02130
- Kelly Cho, M.P.H, Ph.D., Director, MVP Phenomics Data Core
  VA Boston Healthcare System, 150 S. Huntington Avenue, Boston, MA 02130
- Scott L. DuVall, Ph.D., Director, VA Informatics and Computing Infrastructure (VINCI)
  VA Salt Lake City Health Care System, 500 Foothill Drive, Salt Lake City, UT 84148
- Mary T. Brophy M.D., M.P.H., Director, VA Central Biorepository
  VA Boston Healthcare System, 150 S. Huntington Avenue, Boston, MA 02130
- MVP Coordinating Centers
    - MVP Coordinating Center, Boston - J. Michael Gaziano, M.D., M.P.H.
      VA Boston Healthcare System, 150 S. Huntington Avenue, Boston, MA 02130
    - MVP Coordinating Center, Palo Alto – Philip S. Tsao, Ph.D.
      VA Palo Alto Health Care System, 3801 Miranda Avenue, Palo Alto, CA 94304
    - MVP Information Center, Canandaigua – Brady Stephens, M.S.
      Canandaigua VA Medical Center, 400 Fort Hill Avenue, Canandaigua, NY 14424
    - Cooperative Studies Program Clinical Research Pharmacy Coordinating Center, Albuquerque – Todd Connor, Pharm.D.; Dean P. Argyres, B.S., M.S.
      New Mexico VA Health Care System, 1501 San Pedro Drive SE, Albuquerque, NM 87108

MVP Publications and Presentations Committee

- Co-Chair: Tim Assimes, M.D.
  VA Palo Alto Health Care System, 3801 Miranda Avenue, Palo Alto, CA 94304
- Co-Chair: Adriana Hung, M.D.
  VA Tennessee Valley Healthcare System, 1310 24th Ave. South, Nashville, TN 37212
- Co-Chair: Henry Kranzler, M.D.
  Philadelphia VA Medical Center, 3900 Woodland Avenue, Philadelphia, PA 19104

MVP Local Site Investigators

- Samuel Aguayo, M.D., Phoenix VA Health Care System
  650 E. Indian School Road, Phoenix, AZ 85012
- Sunil Ahuja, M.D., South Texas Veterans Health Care System
  7400 Merton Minter Boulevard, San Antonio, TX 78229
- Kathrina Alexander, M.D., Veterans Health Care System of the Ozarks
  1100 North College Avenue, Fayetteville, AR 72703
- Xiao M. Androulakis, M.D., Columbia VA Health Care System
  6439 Garners Ferry Road, Columbia, SC 29209
- Prakash Balasubramanian, M.D., William S. Middleton Memorial Veterans Hospital
  2500 Overlook Terrace, Madison, WI 53705

- Zuhair Ballas, M.D., Iowa City VA Health Care System
  601 Highway 6 West, Iowa City, IA 52246-2208
- Jean Beckham, Ph.D., Durham VA Medical Center
  508 Fulton Street, Durham, NC 27705
- Sujata Bhushan, M.D., VA North Texas Health Care System
  4500 S. Lancaster Road, Dallas, TX 75216
- Edward Boyko, M.D., VA Puget Sound Health Care System
  1660 S. Columbian Way, Seattle, WA 98108-1597
- David Cohen, M.D., Portland VA Medical Center
  3710 SW U.S. Veterans Hospital Road, Portland, OR 97239
- Louis Dellitalia, M.D., Birmingham VA Medical Center
  700 S. 19th Street, Birmingham AL 35233
- L. Christine Faulk, M.D., Robert J. Dole VA Medical Center
  5500 East Kellogg Drive, Wichita, KS 67218-1607
- Joseph Fayad, M.D., VA Southern Nevada Healthcare System
  6900 North Pecos Road, North Las Vegas, NV 89086
- Daryl Fujii, Ph.D., VA Pacific Islands Health Care System
  459 Patterson Rd, Honolulu, HI 96819
- Saib Gappy, M.D., John D. Dingell VA Medical Center
  4646 John R Street, Detroit, MI 48201
- Frank Gesek, Ph.D., White River Junction VA Medical Center
  163 Veterans Drive, White River Junction, VT 05009
- Jennifer Greco, M.D., Sioux Falls VA Health Care System
  2501 W 22nd Street, Sioux Falls, SD 57105
- Michael Godschalk, M.D., Richmond VA Medical Center
  1201 Broad Rock Blvd., Richmond, VA 23249
- Todd W. Gress, M.D., Ph.D., Hershel “Woody” Williams VA Medical Center
  1540 Spring Valley Drive, Huntington, WV 25704
- Samir Gupta, M.D., M.S.C.S., VA San Diego Healthcare System
  3350 La Jolla Village Drive, San Diego, CA 92161
- Salvador Gutierrez, M.D., Edward Hines, Jr. VA Medical Center
  5000 South 5th Avenue, Hines, IL 60141
- John Harley, M.D., Ph.D., Cincinnati VA Medical Center
  3200 Vine Street, Cincinnati, OH 45220
- Kimberly Hammer, Ph.D., Fargo VA Health Care System
  2101 N. Elm, Fargo, ND 58102
- Mark Hamner, M.D., Ralph H. Johnson VA Medical Center
  109 Bee Street, Mental Health Research, Charleston, SC 29401
- Adriana Hung, M.D., M.P.H., VA Tennessee Valley Healthcare System
  1310 24th Avenue, South Nashville, TN 37212
- Robin Hurley, M.D., W.G. (Bill) Hefner VA Medical Center
  1601 Brenner Ave, Salisbury, NC 28144
- Pran Iruvanti, D.O., Ph.D., Hampton VA Medical Center
  100 Emancipation Drive, Hampton, VA 23667
- Frank Jacono, M.D., VA Northeast Ohio Healthcare System
  10701 East Boulevard, Cleveland, OH 44106

- Darshana Jhala, M.D., Philadelphia VA Medical Center
  3900 Woodland Avenue, Philadelphia, PA 19104
- Scott Kinlay, M.B.B.S., Ph.D., VA Boston Healthcare System
  150 S. Huntington Avenue, Boston, MA 02130
- Jon Klein, M.D., Ph.D., Louisville VA Medical Center
  800 Zorn Avenue, Louisville, KY 40206
- Michael Landry, Ph.D., Southeast Louisiana Veterans Health Care System
  2400 Canal Street, New Orleans, LA 70119
- Peter Liang, M.D., M.P.H., VA New York Harbor Healthcare System
  423 East 23rd Street, New York, NY 10010
- Suthat Liangpunsakul, M.D., M.P.H., Richard Roudebush VA Medical Center
  1481 West 10th Street, Indianapolis, IN 46202
- Jack Lichy, M.D., Ph.D., Washington DC VA Medical Center
  50 Irving St, Washington, D. C. 20422
- C. Scott Mahan, M.D., Charles George VA Medical Center
  1100 Tunnel Road, Asheville, NC 28805
- Ronnie Marrache, M.D., VA Maine Healthcare System
  1 VA Center, Augusta, ME 04330
- Stephen Mastorides, M.D., James A. Haley Veterans' Hospital
  13000 Bruce B. Downs Blvd, Tampa, FL 33612
- Elisabeth Mates M.D., Ph.D., VA Sierra Nevada Health Care System
  975 Kirman Avenue, Reno, NV 89502
- Kristin Mattocks, Ph.D., M.P.H., Central Western Massachusetts Healthcare System
  421 North Main Street, Leeds, MA 01053
- Paul Meyer, M.D., Ph.D., Southern Arizona VA Health Care System
  3601 S 6th Avenue, Tucson, AZ 85723
- Jonathan Moorman, M.D., Ph.D., James H. Quillen VA Medical Center
  Corner of Lamont & Veterans Way, Mountain Home, TN 37684
- Timothy Morgan, M.D., VA Long Beach Healthcare System
  5901 East 7th Street Long Beach, CA 90822
- Maureen Murdoch, M.D., M.P.H., Minneapolis VA Health Care System
  One Veterans Drive, Minneapolis, MN 55417
- James Norton, Ph.D., VA Health Care Upstate New York
  113 Holland Avenue, Albany, NY 12208
- Olaoluwa Okusaga, M.D., Michael E. DeBakey VA Medical Center
  2002 Holcombe Blvd, Houston, TX 77030
- Kris Ann Oursler, M.D., Salem VA Medical Center
  1970 Roanoke Blvd, Salem, VA 24153
- Ana Palacio, M.D., M.P.H., Miami VA Health Care System
  1201 NW 16th Street, 11 GRC, Miami FL 33125
- Samuel Poon, M.D., Manchester VA Medical Center
  718 Smyth Road, Manchester, NH 03104
- Emily Potter, Pharm.D., VA Eastern Kansas Health Care System
  4101 S 4th Street Trafficway, Leavenworth, KS 66048
- Michael Rauchman, M.D., St. Louis VA Health Care System
  915 North Grand Blvd, St. Louis, MO 63106

- Richard Servatius, Ph.D., Syracuse VA Medical Center
  800 Irving Avenue, Syracuse, NY 13210
- Satish Sharma, M.D., Providence VA Medical Center
  830 Chalkstone Avenue, Providence, RI 02908
- River Smith, Ph.D., Eastern Oklahoma VA Health Care System
  1011 Honor Heights Drive, Muskogee, OK 74401
- Peruvemba Sriram, M.D., N. FL/S. GA Veterans Health System
  1601 SW Archer Road, Gainesville, FL 32608
- Patrick Strollo, Jr., M.D., VA Pittsburgh Health Care System
  University Drive, Pittsburgh, PA 15240
- Neeraj Tandon, M.D., Overton Brooks VA Medical Center
  510 East Stoner Ave, Shreveport, LA 71101
- Philip Tsao, Ph.D., VA Palo Alto Health Care System
  3801 Miranda Avenue, Palo Alto, CA 94304-1290
- Gerardo Villareal, M.D., New Mexico VA Health Care System
  1501 San Pedro Drive, S.E. Albuquerque, NM 87108
- Agnes Wallbom, M.D., M.S., VA Greater Los Angeles Health Care System
  11301 Wilshire Blvd, Los Angeles, CA 90073
- Jessica Walsh, M.D., VA Salt Lake City Health Care System
  500 Foothill Drive, Salt Lake City, UT 84148
- John Wells, Ph.D., Edith Nourse Rogers Memorial Veterans Hospital
  200 Springs Road, Bedford, MA 01730
- Jeffrey Whittle, M.D., M.P.H., Clement J. Zablocki VA Medical Center
  5000 West National Avenue, Milwaukee, WI 53295
- Mary Whooley, M.D., San Francisco VA Health Care System
  4150 Clement Street, San Francisco, CA 94121
- Allison E. Williams, N.D., Ph.D., R.N, Bay Pines VA Healthcare System
  10,000 Bay Pines Blvd Bay Pines, FL 33744
- Peter Wilson, M.D., Atlanta VA Medical Center
  1670 Clairmont Road, Decatur, GA 30033
- Junzhe Xu, M.D., VA Western New York Healthcare System
  3495 Bailey Avenue, Buffalo, NY 14215-1199
- Shing Shing Yeh, Ph.D., M.D., Northport VA Medical Center
  79 Middleville Road, Northport, NY 11768

Supplementary Table 11. Haplotype frequency of APOL1 protein-altering variants in African populations with more than 20 individuals for the haplotype in the Million Veteran Program.

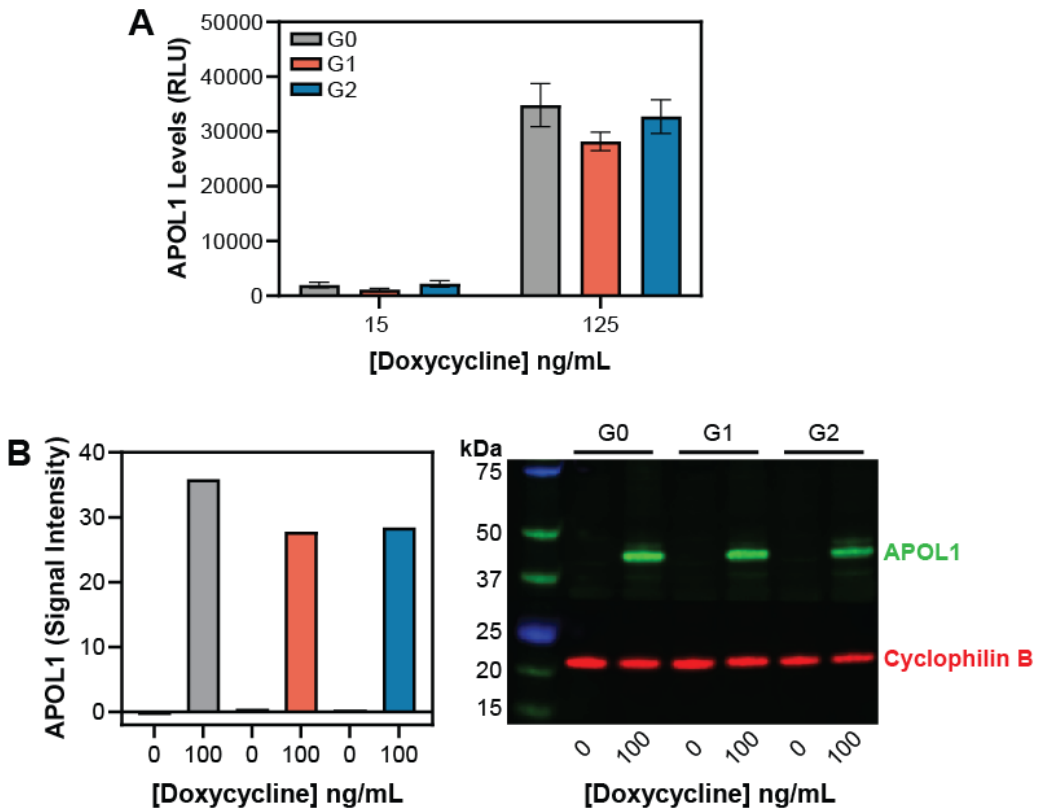
haplotype	G96R	E150K	N176S	I228M	K255R	N264K	G270D	E337N	S342G	I384M	Asn388_Tyr389del	count	freq
	0	1	0	1	1	0	0	0	0	0	0	70375	0.2858
G1	0	0	0	1	1	0	0	0	1	1	0	52918	0.2149
	0	0	0	1	1	0	0	0	0	0	0	33163	0.1347
G2	0	0	0	1	1	0	0	0	0	0	1	30587	0.1242
	0	0	0	0	0	0	0	0	0	0	0	11480	0.0466
	0	0	1	1	1	0	0	1	0	0	0	11018	0.0447
	1	1	0	1	1	0	0	0	0	0	0	10512	0.0427
	0	0	0	1	1	0	0	1	0	0	0	5791	0.0235
N264K	0	1	0	1	1	1	0	0	0	0	0	3627	0.0147
	0	0	0	1	1	0	1	1	0	0	0	1990	0.0081
	0	0	0	0	1	0	0	0	0	0	0	1714	0.007
N264K_G2	0	1	0	1	1	1	0	0	0	0	1	1595	0.0065
G2	0	1	0	1	1	0	0	0	0	0	1	332	0.0013
rsID	rs41297245	rs2239785	rs116136671	rs136175	rs136176	rs73885316	rs73403889	rs16996616	rs73885319	rs60910145	rs71785313		
aa_change	G96R	E150K	N176S	I228M	K255R	N264K	G270D	E337N	S342G	I384M	Asn388_Tyr389del		
pos(GRCh37)	36657740	36661330	36661409	36661566	36661646	36661674	36661691	36661891	36661906	36662034	36662041		
Ref AF	G=0.9552	G=0.6380	A=0.9536	G=0.0557	G=0.0485	C=0.9783	G=0.9902	G=0.9214	A=0.7782	T=0.7806	AATAATT=0.8618		
Alt AF	A=0.0448	A=0.3620	G=0.0464	A=0.9443	A=0.9515	A=0.0217	A=0.0098	A=0.0786	G=0.2218	G=0.2194	A=0.1382		

Supplementary Table 12. Distribution of N264K genotypes in APOL1 low-risk and high-risk genotypes.

n264k	G0/G0	G0/G1	G0/G2	G1/G1	G1/G2	G2/G2	na	All
0	47549	33718	20015	6057	7027	1945	1072	117383
1	2310	825	1488		**381**	**198**	29	5231
2	27		24			**3**		54
na	58	14	236		87	54	3	452
All	49944	34557	21763	6057	7495	2200	1104	123120

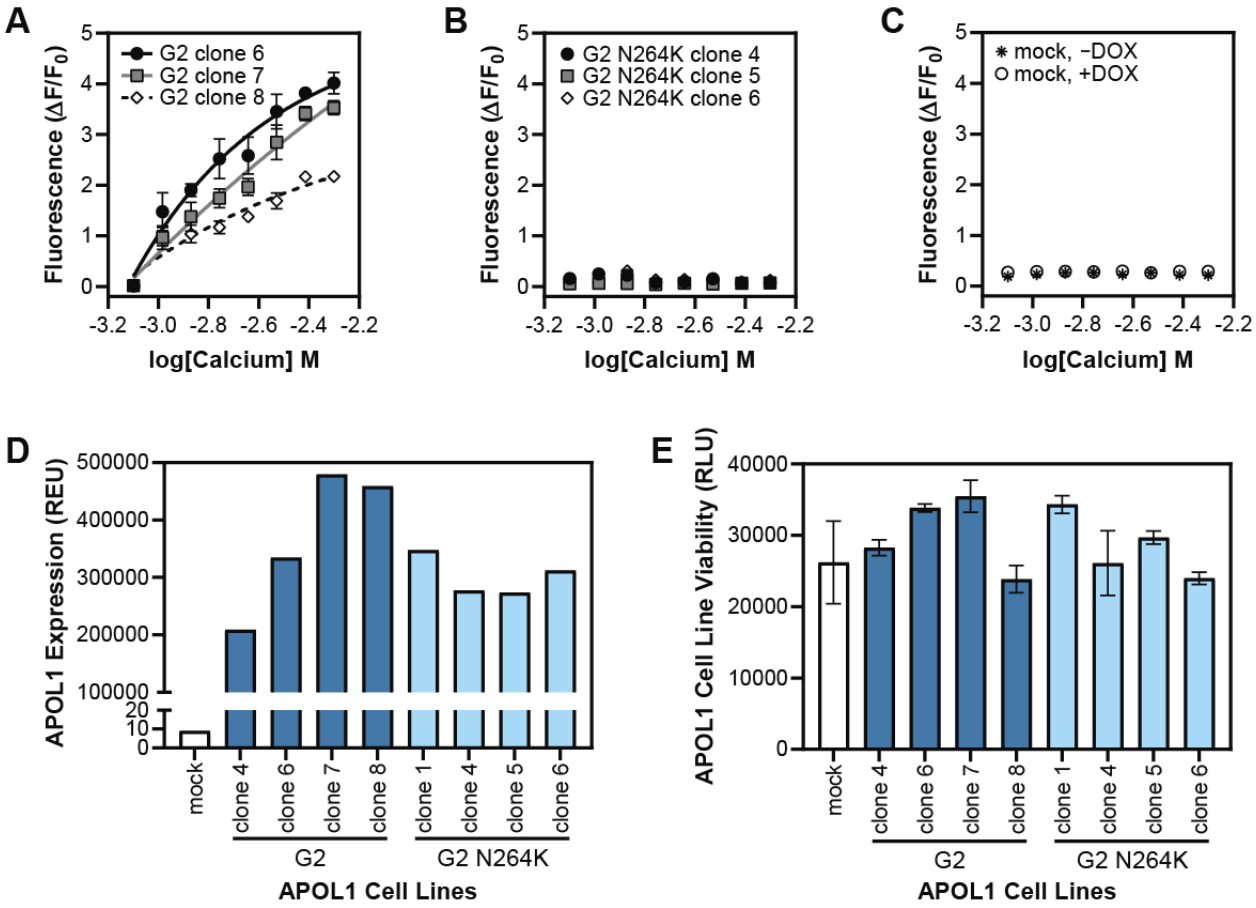
Heterozygous N264K are observed in high risk APOL1 G1/G2 G2/G2
Homozygous N264K are observed in high risk APOL1 G2/G2

Supplementary Figure 1. APOL1 protein expression in G0, G1, and G2 podocyte cell lines.



Equivalent protein expression of APOL1 G0, G1, and G2 was observed in human immortalized podocyte cell lines as measured by a (A) HitBit assay and a (B) Western blot.

Supplementary Figure 2. Additional characterization of APOL1 cell lines utilized in the calcium uptake assay.



Panel A & B show the ion conductance of additional APOL1 G2 and G2 p.N264K cell lines in the presence and absence of doxycycline. Panel C shows the ion conductance of a negative control isogenic cell line, lacking the APOL1 gene, in the presence and absence of doxycycline. Panel D shows qPCR mRNA expression of APOL1 in cell lines utilized in the calcium uptake assay. Panel E shows viability of APOL1 G2 and G2 p.N264K cell lines at the time ion conductance was quantified.