Supplementary Data

Supplementary Table 1: *NPHS1* exome sequencing results (missense variants, dominant model, admixture adjusted)

SNP	CHR	Position (hg19)	Amino Acid Change	Protein Position	OR	CI - L95	CI - U95	P Value	MAF**	Genotype Count Cases[†]	Genotype Count Controls[†]
rs35238405	19	36340467	THR,ALA	233/1241	2.89	1.041	8.028	0.04165	0.0096	0/15/506	0/5/513
var_19_36336287	19	36336287	TYR,CYS	638/1241	5.05	0.5858	43.54	0.1407	0.0029	0/5/516	0/1/517
rs4806213	19	36322601	ASN, SER	1077/1241	1.26	0.9256	1.72	0.1413	0.14	10/105/301	6/95/333
var_19_36340212	19	36340212	ARG,TRP	256/1241	4.27	0.4741	38.47	0.1955	0.0024	0/4/515	0/1/515
rs113825926	19	36340009	THR,ILE	294/1241	0.39	0.07452	2.006	0.2579	0.0034	0/2/519	0/5/513
var_19_36322018	19	36322018	ARG,CYS	1140/1241	1.62	0.7009	3.74	0.2593	0.012	0/15/506	0/9/509
rs116700257	19	36321778	ALA, THR	1188/1241	0.53	0.1764	1.596	0.2594	0.0067	0/5/516	0/9/509
rs35240811	19	36317544	PRO,SER	1200/1241	1.53	0.708	3.3	0.2799	0.013	0/17/504	0/11/507
rs33950747	19	36339247	ARG,GLN	408/1241	1.36	0.6431	2.882	0.4201	0.014	0/16/505	0/13/505
rs3814995	19	36342212	GLU,LYS	117/1241	1.15	0.8128	1.625	0.4312	0.077	2/78/441	5/67/445
var_19_36341302	19	36341302	SER,TYR	191/1241	0.48	0.04369	5.379	0.5554	0.0014	0/1/520	0/2/516
rs34736717	19	36330277	VAL,LEU	991/1241	0.92	0.6985	1.221	0.5771	0.14	9/121/391	9/127/382
rs34320609	19	36339295	LEU,PRO	392/1241	0.91	0.5864	1.401	0.6588	0.045	4/39/478	1/45/472
rs140626538	19	36342505	VAL,ALA	43/1241	1.19	0.5074	2.773	0.6935	0.011	0/12/509	0/10/507
rs114112112	19	36339558	MET,THR	382/1241	1.4	0.2315	8.399	0.7166	0.0024	0/3/518	0/2/516
rs34982899	19	36340187	PRO,ARG	264/1241	0.95	0.5292	1.71	0.8671	0.023	0/23/497	1/23/493
var_19_36341311	19	36341311	ASN, ILE	188/1241	1.14	0.1592	8.213	0.8939	0.0019	0/2/519	0/2/516
var_19_36326622	19	36326622	THR,ALA	1051/1241	1.17	0.07268	18.9	0.9109	0.00096	0/1/520	0/1/517
rs115489112	19	36321820	HIS,TYR	1174/1241	0.96	0.1916	4.779	0.9572	0.0029	0/3/518	0/3/515
var_19_36336581	19	36336581	GLU,LYS	583/1241	0.93	0.05797	14.93	0.9594	0.00097	0/1/517	0/1/517
var_19_36335305	19	36335305	GLU,LYS	663/1241	1	0.06242	16.09	0.9987	0.001	0/1/488	0/1/507
var_19_36336918	19	36336918	ALA,GLU	540/1241	6.46E-10	0	Inf	0.999	0.0016	0/0/307	0/2/325
var_19_36326643	19	36326643	GLU,LYS	1044/1241	7.80E-10	0	Inf	0.9993	0.00048	0/0/521	0/1/517
var_19_36332686	19	36332686	ALA,SER	916/1241	7.35E-10	0	Inf	0.9993	0.00048	0/0/521	0/1/517
var_19_36334400	19	36334400	PRO,THR	770/1241	1.40E+09	0	Inf	0.9993	0.00048	0/1/520	0/0/518

var_19_36335035	19	36335035	ALA,SER	728/1241	6.05E-10	0	Inf	0.9993	0.00048	0/0/521	0/1/517
var_19_36335107	19	36335107	LEU,VAL	704/1241	1.85E+09	0	Inf	0.9993	0.00048	0/1/520	0/0/518
var_19_36335326	19	36335326	VAL,LEU	656/1241	1.61E+09	0	Inf	0.9993	0.00056	0/1/433	0/0/460
var_19_36336411	19	36336411	ALA,PRO	597/1241	1.99E+09	0	Inf	0.9993	0.00048	0/1/517	0/0/517
var_19_36338980	19	36338980	ILE,THR	468/1241	5.77E-10	0	Inf	0.9993	0.00048	0/0/521	0/1/517
var_19_36339202	19	36339202	ALA,GLY	423/1241	6.10E-10	0	Inf	0.9993	0.00048	0/0/521	0/1/517
var_19_36339233	19	36339233	LEU,VAL	413/1241	6.40E-10	0	Inf	0.9993	0.00048	0/0/521	0/1/517
var_19_36339298	19	36339298	GLY,GLU	391/1241	1.45E+09	0	Inf	0.9993	0.00048	0/1/520	0/0/518
var_19_36339634	19	36339634	LEU,VAL	359/1241	1.53E+09	0	Inf	0.9993	0.00048	0/1/520	0/0/518
var_19_36339636	19	36339636	THR,ILE	358/1241	5.20E-10	0	Inf	0.9993	0.00048	0/0/521	0/1/517
var_19_36339923	19	36339923	VAL,MET	323/1241	1.64E+09	0	Inf	0.9993	0.00048	0/1/520	0/0/518
rs115308424	19	36340175	ARG,GLN	268/1241	1.51E+09	0	Inf	0.9993	0.00048	0/1/520	0/0/518
var_19_36340545	19	36340545	ARG,TRP	207/1241	2.00E+09	0	Inf	0.9993	0.00048	0/1/520	0/0/518
var_19_36342518	19	36342518	GLU,LYS	39/1241	7.80E-10	0	Inf	0.9993	0.00048	0/0/521	0/1/517
var_19_36342539	19	36342539	ARG,TRP	32/1241	7.28E-10	0	Inf	0.9993	0.00048	0/0/521	0/1/516

*Dominant model; **reflects combined case and control MAF

ᵗreflects counts (number of observations) of “homozygous minor / heterozygotes / homozygous major” alleles, respectively.

Supplementary Table 2. *NPHS1* Locus-Wide Analysis

SNP	Chr	Position	PolyPhen2	Amino Acid Δ	Protein Pos.	Alleles
rs35238405	19	36340467	probably-damaging	ALA,THR	233/1241	C/T
rs4806213	19	36322601	probably-damaging	SER,ASN	1077/1241	C/T
rs141141839	19	36336287	probably-damaging	CYS,TYR	638/1241	C/T
C19:36340212	19	36340212	probably-damaging	TRP,ARG	256/1241	A/G
rs148104086	19	36342539	probably-damaging	TRP,ARG	32/1241	A/G
rs138173172	19	36332686	possibly-damaging	SER,ALA	916/1241	A/C
rs33950747	19	36339247	probably-damaging	GLN,ARG	408/1241	T/C
rs3814995	19	36342212	possibly-damaging	LYS,GLU	117/1241	T/C
rs115308424	19	36340175	possibly-damaging	GLN,ARG	268/1241	T/C
rs115489112	19	36321820	possibly-damaging	TYR,HIS	1174/1241	A/G
rs140673499	19	36326622	possibly-damaging	ALA,THR	1051/1241	C/T
rs147641617	19	36336581	probably-damaging	LYS,GLU	583/1241	T/C
rs112624813	19	36340499	probably-damaging	LEU,PRO	222/1241	A/G
rs115333628	19	36340506	possibly-damaging	ALA,SER	220/1241	C/A
rs139472106	19	36341989	possibly-damaging	ALA,PRO	134/1241	C/G
rs143649022	19	36332704	probably-damaging	PRO,SER	910/1241	G/A
rs143986233	19	36333098	probably-damaging	HIS,ARG	864/1241	T/C
rs144203682	19	36322556	probably-damaging	HIS,ARG	1092/1241	T/C
rs146400394	19	36333388	probably-damaging	HIS,ARG	800/1241	T/C
rs146858871	19	36322629	possibly-damaging	THR,ALA	1068/1241	T/C
rs149649169	19	36340211	probably-damaging	GLN,ARG	256/1241	T/C
rs150623032	19	36333180	possibly-damaging	SER,ALA	837/1241	A/C
rs151121915	19	36317420	probably-damaging	ALA,VAL	1241/1241	G/A
C19:36337051	19	36337051	probably-damaging	SER,ARG	496/1241	T/G
C19:36339181	19	36339181	possibly-damaging	ARG,LYS	430/1241	C/T
C19:36339287	19	36339287	probably-damaging	SER,GLY	395/1241	T/C
C19:36340454	19	36340454	probably-damaging	GLN,LEU	237/1241	T/A
C19:36342559	19	36342559	possibly-damaging	VAL,ALA	25/1241	A/G
rs34982899	19	36340187	possibly-damaging	PRO,ARG	264/1241	G/C

rs116620503	19	36342451	N/A	ALA,VAL	61/1241	A/G
rs73928330	19	36342697	benign	GLY,ARG	15/1241	C/G
rs34320609	19	36339295	benign	LEU,PRO	392/1241	A/G

Supplementary Table 3. T233A characteristics within all ESKD cases.

	African Ancestry	Sex (%)	Age	*APOL1* G1/G2 (2 risk alleles)	BMI	Family History of ESKD (%)	Age of ESKD
T233A (+) ESKD Cases	0.83 ± 0.11	62.4 (F)	55.9 ± 14.4	0.33 ± 0.47	29.62 ± 7.4	38.6	51.8 ± 14.8
T233A (-) ESKD Cases	0.80 ± 0.12	51.3 (F)	56.1 ± 14.3	0.25 ± 0.43	28.93 ± 7.2	28.9	53.5 ± 14.3
P-Value*	0.020	0.043	0.89	0.090	0.40	0.16	0.30

Categoric data are expressed as percentage; continuous data as mean ± SD.

*P-values were computed using a two tailed T-test at a significance threshold of α=0.05

Supplementary Table 4.

Reported rs35238405 (T233A) minor allele frequencies

Source		MAF*
dbsnp		0.006
EVS (Af. American)		0.012
1000 Genomes		
	All	0.006
	AFR	0.024
	LWK	0.041
	YRI	0.017
	ASW	0.008
	EUR	0
	AMR	0
	CLM	0.008

*MAF: minor allele frequency

Supplementary Table 5. Rs35238405 (T233A) Single-SNP association testing (Dominant Model) in T2D-only, non-nephropathy cases, adjusted for admixture only.

Study	N Case / Control	MAF Case / Control	P	OR	95% CI
T2D-Only (vs. controls)	502 / 1280	0.0070 / 0.0043	0.28	1.7	0.65, 4.41

Supplementary Table 6. Breakdown of variants identified in T2D-GENES exome sequencing "Discovery" study (genome wide)

Effect	Frequency (N)	Proportion
Nonsynonymous Coding	237,989	0.34
$p < 0.0001$	4	
$0.0001 \leq p < 0.001$	23	
$0.001 \leq p < 0.01$	358	
$0.01 \leq p < 0.05$	1968	
Start Gained	2,166	0.0031
Stop Gained	4,254	0.0060
Stop Lost	263	0.00040

Supplementary Table 7: *NPHS1* variants included in SKAT analysis

Chr	SNP	BP (hg19)	Notes	Source
19	rs151121915	36317420	-	Exome Variant Server
19	rs115489112	36321820	-	Exome Variant Server
19	rs144203682	36322556	monomorphic	Exome Variant Server
19	rs4806213	36322601	-	Exome Variant Server
19	rs146858871	36322629	-	Exome Variant Server
19	rs140673499	36326622	-	Exome Variant Server
19	rs138173172	36332686	-	Exome Variant Server
19	rs143649022	36332704	-	Exome Variant Server
19	rs150623032	36333180	monomorphic	Exome Variant Server
19	rs146400394	36333388	-	Exome Variant Server
19	rs147641617	36336581	-	Exome Variant Server
19	19:36337051	36337051	-	1000 Genomes
19	19:36339181	36339181	monomorphic	1000 Genomes
19	19:36339287	36339287	-	1000 Genomes
19	rs34320609	36339295	-	Exome Variant Server
19	rs149649169	36340211	monomorphic	Exome Variant Server
19	rs35238405	36340467	-	T2D-GENES
19	rs112624813	36340499	monomorphic	Exome Variant Server
19	rs139472106	36341989	monomorphic	Exome Variant Server
19	rs3814995	36342212	-	Exome Variant Server
19	rs116620503	36342451	monomorphic	Exome Variant Server
19	rs148104086	36342539	monomorphic	Exome Variant Server
19	19:36342559	36342559	-	1000 Genomes

Supplementary Table 8: Missense variants identified in *NPHS2* in T2D-GENES exome-sequencing Discovery study (Dominant Model, Admixture adjusted).

SNP	Function	Gene	Chr	BP (HG19)	MAF*	P Value**	OR	L95 CI	U95 CI
1:179523626	MISSENSE	NPHS2	1	179523626	0.0009625	0.9909	0.984	0.06138	15.78
rs61747727	MISSENSE	NPHS2	1	179526175	0.07811	0.31	1.194	0.848	1.681
rs61747728	MISSENSE	NPHS2	1	179526214	0.006737	0.7222	0.8231	0.2815	2.407
rs116512679	MISSENSE	NPHS2	1	179544818	0.01359	0.3154	1.491	0.6837	3.251
1:179544824	MISSENSE	NPHS2	1	179544824	0.000499	0.9993	Inf	0	Inf

*Combined case/control MAF; **Dominant model