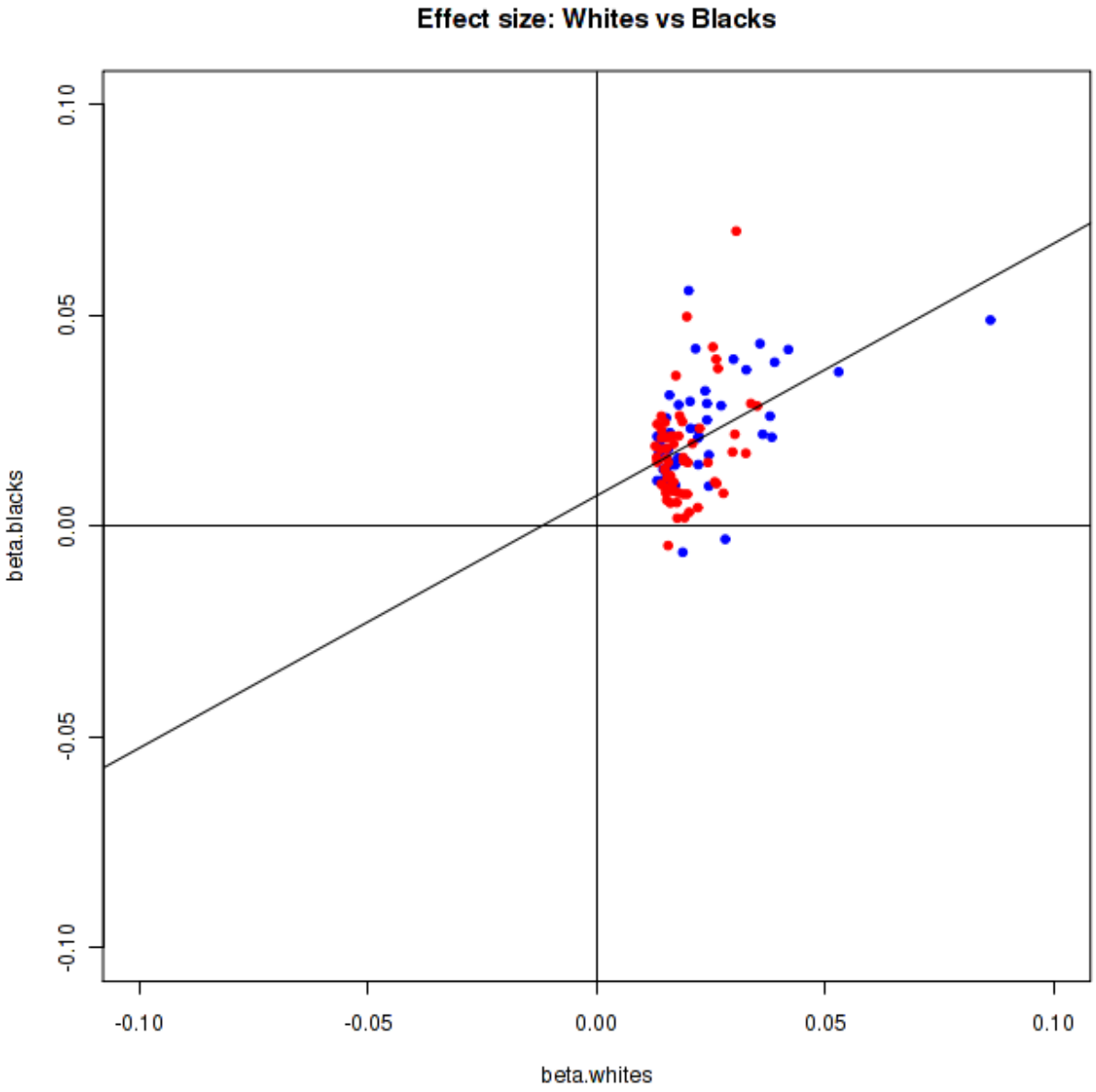
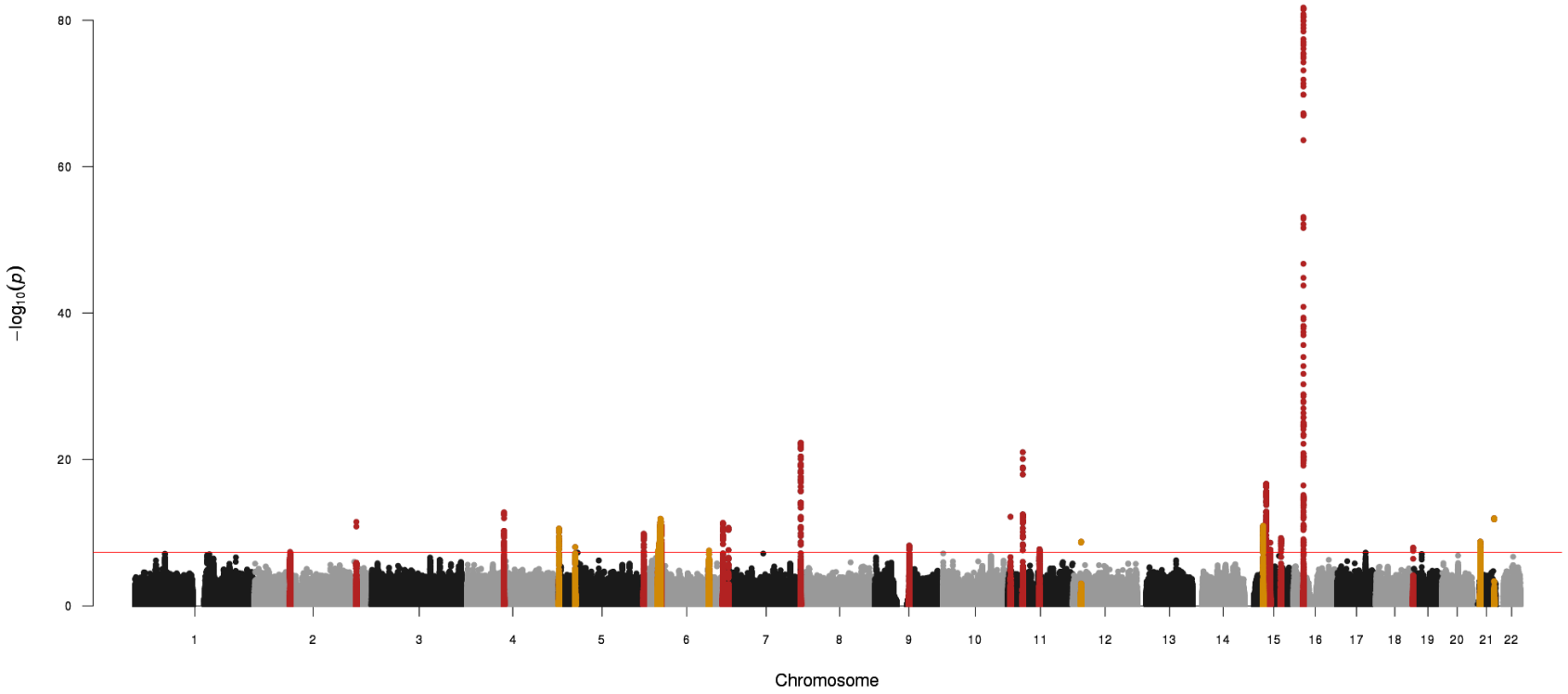
Supplementary Figures



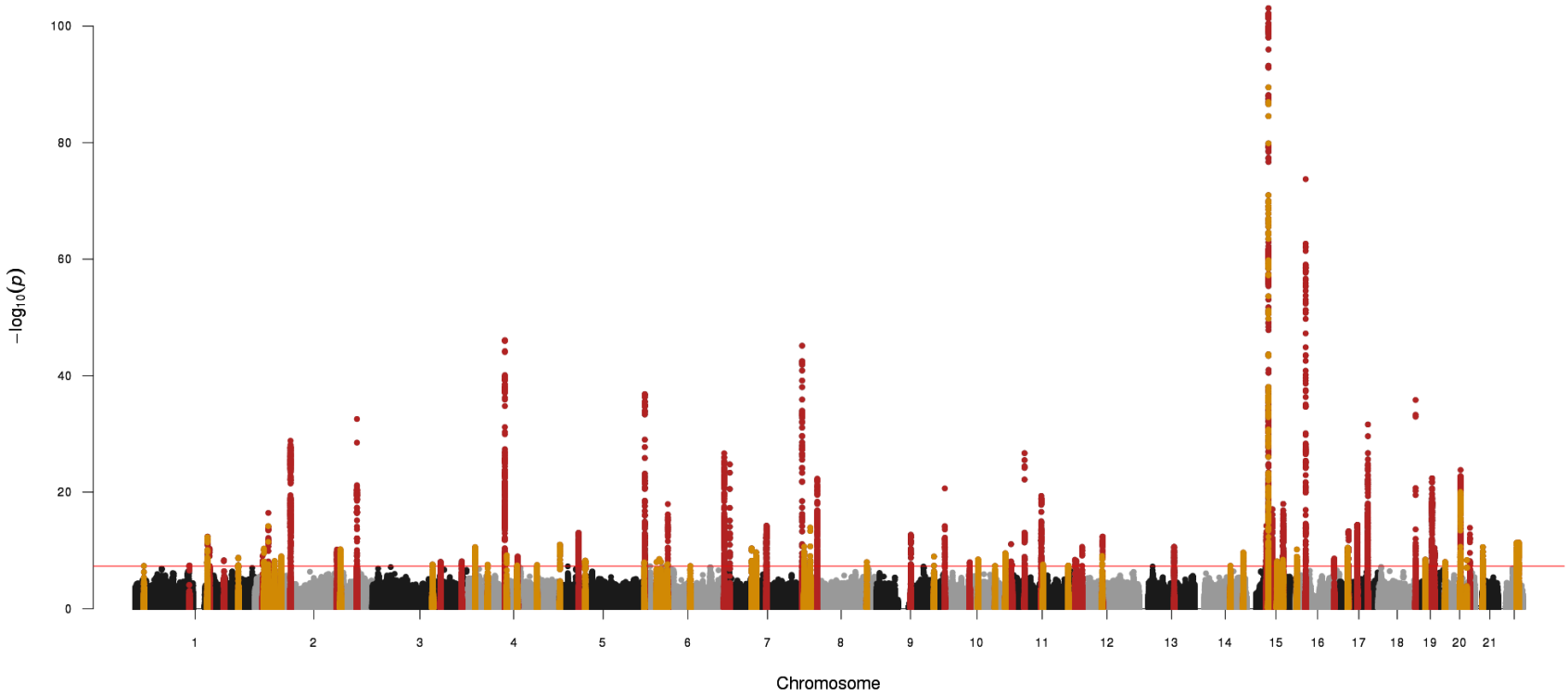
Supplementary Figure 1. Comparison of effect sizes for known and novel SNPs identified with eGFR across non-Hispanic whites and non-Hispanic blacks.

Sentinel SNPs from transethnic discovery meta-analysis were compared for consistency between MVP non-Hispanic blacks (y-axis) and MVP non-Hispanic whites (x-axis). Blue dots denote sentinel SNPs from known loci and red dots denote from novel loci.



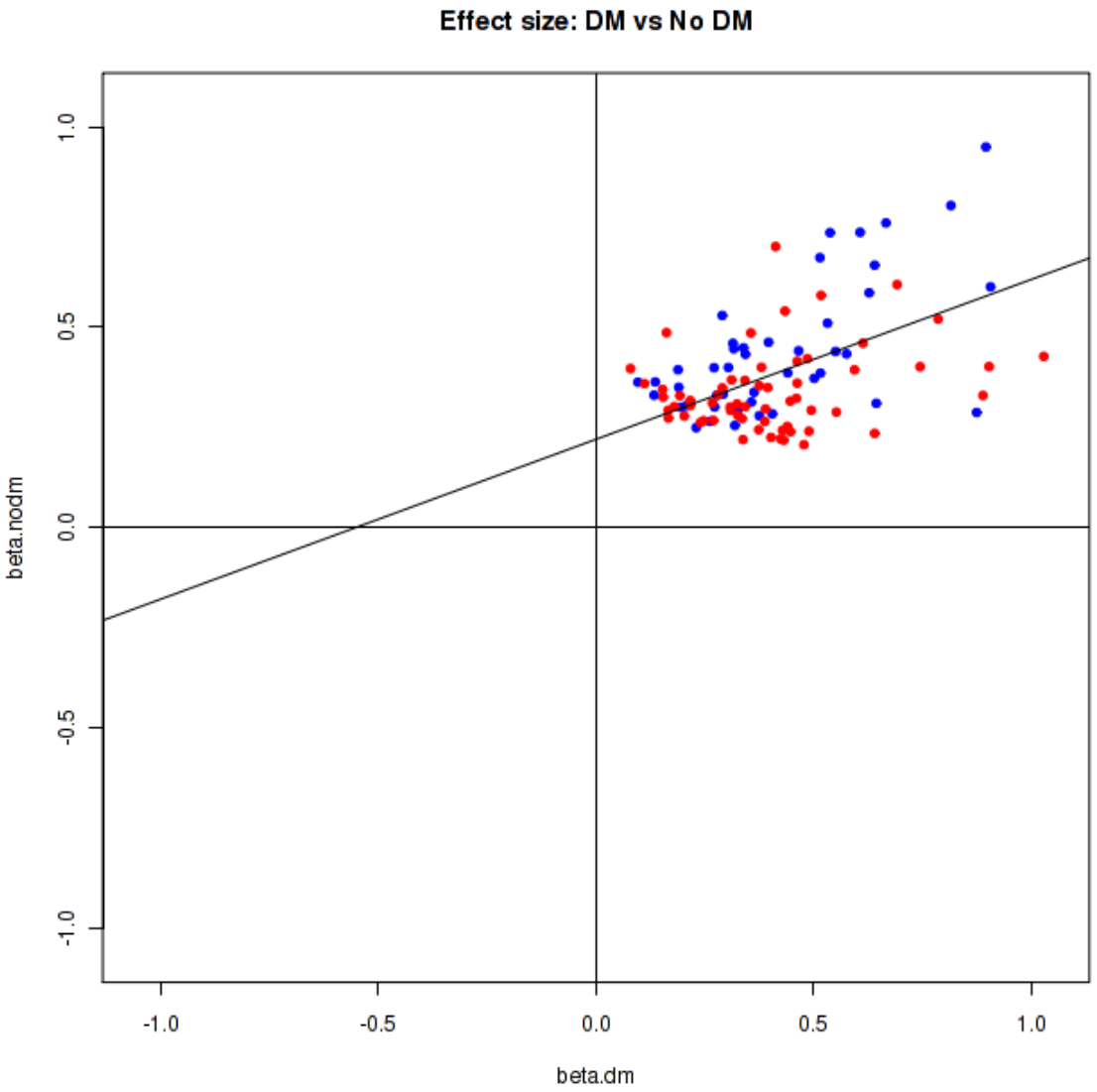
Supplementary Figure 2. Manhattan plot summarizing trans-ethnic discovery meta-analysis of eGFR in diabetic subjects.

The y axis shows the –log10 P-values and the x axis shows the chromosomal positions. The horizontal red line represents the thresholds of P-value = 5 x10-8 for genome-wide significance. SNPs in red are in previously-identified loci, whereas SNPs in orange are in novel loci.



Supplementary Figure 3. Manhattan plot summarizing trans-ethnic discovery meta-analysis of eGFR in non-diabetic subjects.

The y axis shows the –log10 P-values and the x axis shows the chromosomal positions. The horizontal red line represents the thresholds of P-value = 5 x10-8 for genome-wide significance. SNPs in red are in previously-identified loci, whereas SNPs in orange are in novel loci.



Supplementary Figure 4. Comparison of eGFR SNP effect sizes between diabetic and non-diabetic subjects for known and novel SNPs identified across all subjects.

Sentinel SNPs from transethnic discovery meta-analysis were compared for consistency between MVP diabetic subjects (x-axis) and MVP non-diabetic subjects (y-axis). Blue dots denote sentinel SNPs from known loci and red dots denote from novel loci.

Supplementary Tables

Supplementary Table 1. Conditional association results for all jointly conditional SNPs.

Index SNP						Discovery Results				Conditional Results						
rsID	CHR:BP	Nearest Gene	Distance	Location	Effect Allele	EAF_{disc}	$Effect_{disc}$	SE_{disc}	$P\text{-value}_{disc}$	Lead SNP(s)	Novel/Known	Nearest Gene(s)	R^2	$Effect_{cond}$	SE_{cond}	$P\text{-value}_{cond}$
rs2048371	2:54870908	SPTBN1		intron	T	0.717	-0.291	0.049	4.24E-09	rs10865282	novel	C2orf73	0.000	-0.276	0.049	2.45E-08
rs1532783	15:76190906	UBE2Q2		intron	T	0.949	-1.066	0.123	4.52E-18	rs11072567	known	NRG4	0.015	-0.783	0.125	3.30E-10
rs199688956	15:76235871	NRG4		untranslated-3	T	0.029	-1.193	0.166	5.72E-13	rs11072567	known	NRG4	0.030	-0.969	0.167	6.09E-09
rs79091515	1:185026908	RNF2		intron	A	0.022	-1.225	0.186	4.65E-11	rs115276619	known	FAM129A	0.443	-1.179	0.186	2.45E-10
rs2102577	4:77287791	CCDC158		intron	A	0.577	0.490	0.046	3.45E-26	rs13146355	known	SHROOM3	0.006	0.453	0.046	1.31E-22
rs35790011	17:19463591	SLC47A1		missense	A	0.058	-1.588	0.250	2.04E-10	rs2252281	known	SLC47A1	*	-1.582	0.250	2.43E-10
rs316020	6:160669081	SLC22A2		intron	A	0.108	0.707	0.072	5.73E-23	rs2279463	known	SLC22A2	0.016	0.670	0.073	3.23E-20
rs11638272	15:39266793	.-.		unknown	C	0.465	0.265	0.045	5.58E-09	rs28833881	novel	.-.	0.003	0.272	0.045	2.18E-09
rs1545715	7:155668309	SHH	63342		A	0.462	-0.264	0.045	3.00E-09	rs288762	novel	SHH	0.002	-0.280	0.045	3.32E-10
rs6976242	7:156125204	LOC285889	105278		A	0.835	-0.346	0.063	3.57E-08	rs288762	novel	SHH	0.000	-0.359	0.063	1.12E-08
rs2762943	20:52790786	CYP24A1	270	near-gene-5	T	0.076	0.495	0.087	1.14E-08	rs35870583	known	BCAS1 -CYP24A1	0.000	0.528	0.087	1.22E-09
rs537808693	6:31396347	MICA	13257		T	0.349	0.342	0.052	5.72E-11	rs532086	known	C2	0.023	0.317	0.053	2.30E-09
rs1136201	17:37879588	ERBB2		missense	A	0.772	0.401	0.054	1.74E-13	rs541524196	known	.-.	0.028	0.332	0.056	2.55E-09
rs34224335	1:150766085	CTSK	2597		A	0.733	-0.409	0.054	4.08E-14	rs543179	novel	MRPS21	0.016	-1.150	0.088	3.90E-39
rs111285796	16:20361087	UMOD		intron	T	0.832	-1.430	0.061	1.42E-121	rs77924615	known	PDILT	0.348	-0.846	0.072	8.29E-32
rs73543348	16:20388957	PDILT		intron	T	0.122	-0.752	0.070	5.23E-27	rs77924615	known	PDILT	0.032	-0.480	0.071	1.19E-11
rs369062552	11:30749169	DCDC5	102756		T	0.963	1.155	0.152	2.97E-14	rs963837	known	MPPED2 -DCDC5	0.055	1.465	0.153	1.24E-21
rs6504021	17:59240473	BCAS3		intron	T	0.764	-0.448	0.058	8.48E-15	rs9895661	known	BCAS3	0.001	-0.348	0.060	6.63E-09
rs11350775	17:59241456	BCAS3		intron	CT	0.122	0.787	0.104	3.84E-14	rs9895661	known	BCAS3	0.001	0.616	0.108	1.21E-08
rs34091020	17:59486437	TBX2		untranslated-3	G	0.493	-0.571	0.056	2.83E-24	rs9895661	known	BCAS3	0.089	-0.418	0.058	5.87E-13

SNPs are ordered by chromosome and position. rsID - dbSNP accession number; CHR:BP - chromosome and build 37 position; CHR:BP - chromosome and build 37 position; Nearest Gene - most proximal gene within 250kb of index SNP; Distance - distance in base pairs from index SNP to nearest gene; Location - location of index SNP relative to nearest gene; Effect allele - allele corresponding to measured effect on the outcome; EAF_{disc} - effect allele frequency in the combined discovery and replication meta-analysis; $Effect_{disc}$ - measured effect in the discovery meta-analysis; SE_{disc} - standard error of the measured effect in the discovery meta-analysis; $P\text{-value}_{disc}$ - association p-value for the measured effect in the discovery meta-analysis; Lead SNP(s) - SNP(s) with most significant association p-value for the measured effect in the discovery meta-analysis on which the SNP in the rsID column was conditioned; Novel/Known - indicator of whether lead SNP locus was previously reported or novel in our analyses; Nearest Gene(s) - most proximal gene within 500kb of Lead SNP(s); R^2 - linkage disequilibrium correlation between SNP in rsID column and Lead SNP(s); $Effect_{cond}$ - measured effect of SNP in the rsID column in the genome-wide joint conditional analysis; SE_{cond} - standard error of the measured effect of SNP in the rsID column in the genome-wide joint conditional analysis; $P\text{-value}_{cond}$ - association p-value for the measured effect of SNP in the rsID column in the genome-wide joint conditional analysis. *rs35790011 monomorphic in 1KG EU

Supplementary Table 2. **Association results for all significant eGFR variants from blacks-only MVP analysis.**

Index SNP										Discovery Meta-analysis Results			
rsID	**CHR:BP**	**CHR**	**BP**	**Nearest Gene**	**Distance**	**Location**	**Effect Allele**	**Other Allele**	**Novelty eGFR**	**$EAF_{Discovery}$**	**$Effect_{disc}$**	**SE_{disc}**	**$P\text{-}value_{comb}$**
rs6676150	1:155123837	1	155123837	DPM3	10841		C	G	known	0.303	-0.036	0.006	4.06E-09
rs2279463	6:160668389	6	160668389	SLC22A2			A	G	known	0.807	0.042	0.007	7.50E-10
rs13230509	7:1286192	7	1286192	UNCX	9579		C	G	known	0.283	-0.040	0.006	9.29E-11
rs10265221	7:151414329	7	151414329	PRKAG2			T	C	known	0.824	0.043	0.008	3.78E-08
rs334	11:5248232	11	5248232	HBB			A	T	known	0.057	-0.119	0.014	1.54E-18
rs75113983	11:6156162	11	6156162	OLFR690	16750		A	T	novel	0.976	0.111	0.020	2.25E-08
rs200950799	12:17157119	12	17157119	.-.			T	C	novel	0.011	-1.394	0.232	1.71E-09
rs144803907	15:45158662	15	45158662	C15orf43	90240		A	G	novel	0.119	-0.051	0.009	4.50E-09
rs2486272	15:45672253	15	45672253	GATM			T	C	known	0.225	0.083	0.006	2.02E-39
rs1532783	15:76190906	15	76190906	UBE2Q2			T	C	known	0.904	-0.054	0.009	5.12E-09
rs35790011	17:19463591	17	19463591	SLC47A1			A	G	known	0.058	-0.072	0.012	3.92E-10
rs7212621	17:37527911	17	37527911	FBXL20			T	G	known	0.664	-0.038	0.006	7.51E-11
rs56376587	18:77160235	18	77160235	NFATC1			A	C	known	0.792	0.037	0.007	4.03E-08
rs10084572	21:45412872	21	45412872	AGPAT3	5397		T	C	novel	0.014	-1.378	0.193	1.07E-12

SNPs are ordered by chromosome and position. rsID - dbSNP accession number; CHR:BP - chromosome and build 37 position; Nearest Gene - most proximal gene within 250kb of index SNP; Distance - distance in base pairs from index SNP to nearest gene; Location - location of index SNP relative to nearest gene; Effect allele - allele corresponding to measured effect on the outcome; Other allele - allele not corresponding to measured effect on the outcome; Novelty eGFR – annotation of whether locus is novel or previously identified in a GWAS of eGFR; EAF_{disc} - effect allele frequency in the combined discovery and replication meta-analysis; $Effect_{disc}$ - measured effect in the discovery meta-analysis; SE_{disc} - standard error of the measured effect in the discovery meta-analysis; $P\text{-}value_{disc}$ - association p-value for the measured effect in the discovery meta-analysis.

Supplementary Table 3. Summary statistics for regression of effect estimates between MVP race/ethnic groups at known and novel SNPs.

Variable	SNP Group	slope	r2
Effect size	All	0.598	0.212
	Novel	0.786	0.132
	Known	0.485	0.254
Frequency	All	0.988	0.611
	Novel	1.011	0.666
	Known	0.943	0.518
Variance	All	0.186	0.121
	Novel	-0.827	0.153
	Known	0.14	0.104

Variable – parameter being compared across races; SNP group – all SNPs, novel only, or known only; slope – slope of the best-fit regression line for comparison of parameters between non-Hispanic whites and non-Hispanic Blacks; r2 - denotes correlation between effect estimates calculated from a linear regression model.

Supplementary Table 4. LD Score Regression results for each contributing analysis set.

Race Group	Phenotype group	N Samples	Lambda	LD Intercept (SE)	H2 (SE)	N SNPs
	DM+ HTN+	64,389	1.1113	1.0242 (0.0078)	0.0939 (0.0104)	1164108
	DM- HTN+	89,838	1.1619	1.04 (0.0087)	0.1118 (0.0103)	1164794
	DM- HTN-	56,146	1.1459	1.028 (0.0096)	0.1523 (0.0172)	1169086
Whites	DM+ HTN-	6,212	1.0105	0.9909 (0.0062)	0.1279 (0.0687)	1174082
	DM+ HTN+	19,428	1.0255	1.0086 (0.0033)	0.0556 (0.0204)	11565520
	DM- HTN+	23,066	1.0315	1.0189 (0.0039)	0.0546 (0.0245)	11560578
	DM- HTN-	12,265	1.0165	0.999 (0.0034)	0.1249 (0.0365)	11572037
Blacks	DM+ HTN-	1,494	0.9927	0.9975 (0.0034)	Not calculated	11588764

Results presented by Race Group (Non-Hispanic whites, non-Hispanic blacks) and phenotype group (diabetes y/n and hypertension y/n). Lambda – inflation factor of GWAS in each strata: median(chi^2)/0.4549; LD intercept (SE) – intercept from LD score regression analysis with standard error; H2 (SE) – heritability and standard error as computed from LD score regression; N SNPs – number of SNPs included in analysis after merging with race-specific LD reference data.

Supplementary Table 5. **Expression from single-cell RNA sequencing of murine kidney cell types of mouse homologs of colocalized genes associated with eGFR.**

Gene	Endo	Podo	PT	LOH	DCT	CD-PC	CD-IC	Fib	Macro	Neutro	B lymph	T lymph	NK
Bst2	1.395	-0.625	-0.648	-0.536	-0.544	-0.562	-0.455	2.736	1.488	-0.580	0.245	-0.214	-0.366
Nars2	-0.364	2.611	0.337	0.467	0.774	0.249	0.087	-1.141	-0.162	0.268	0.077	0.050	-0.486
Arnt	0.618	2.096	0.271	0.545	0.805	0.589	0.085	-0.939	0.041	-0.120	0.477	-1.020	-0.894
Shroom3	-0.487	1.512	0.087	0.715	0.719	1.305	0.354	-1.059	-0.410	0.083	-0.510	-0.986	-0.891
Mettl10	0.570	1.441	0.177	1.586	1.287	0.517	0.989	-1.572	-0.896	-0.157	-1.028	-1.318	-0.829
Tprkb	0.278	-0.308	2.080	-0.341	-0.252	-0.507	-0.534	-0.765	0.036	0.583	-0.660	-0.647	-0.474
Arl16	0.496	0.131	0.810	0.826	1.419	0.932	0.375	-1.145	-0.108	0.778	-0.590	-0.741	-1.061
Angptl3	-0.293	0.063	0.964	0.935	1.257	0.452	0.511	-1.138	-0.069	1.034	-0.243	-0.917	-0.716
Spire2	-0.375	0.044	0.472	0.601	1.109	1.075	0.920	-1.186	-0.075	0.747	-0.311	-0.890	-0.785
Ube2q2	-0.001	-0.210	0.588	0.750	0.852	0.844	0.651	-1.184	-0.194	0.290	-0.623	-0.491	0.043
Klhdc7a	-0.481	-0.475	0.188	0.555	0.714	1.682	0.529	-0.877	-0.157	0.259	-0.626	-0.877	-0.818
Nrip1	-0.277	-0.442	0.043	0.161	-0.028	1.388	-0.199	-1.249	0.927	-1.107	-1.576	0.448	0.643
Usp24	-0.444	-0.403	0.681	0.950	1.008	1.359	0.033	-1.816	-1.014	0.797	-0.025	-0.783	-0.942
Manba	-0.595	0.260	0.812	0.478	0.868	1.223	0.165	-1.201	0.490	-0.143	-0.698	-0.636	-1.118
Rnf152	-0.423	-0.437	-0.068	-0.307	0.082	-0.279	2.094	-0.586	-0.334	-0.356	-0.381	-0.640	-0.635
Gbas	-0.241	0.047	-0.526	1.143	0.820	1.305	1.440	-0.896	-0.553	-0.079	-1.010	-0.790	-0.738
Whamm	-0.157	0.457	0.308	0.649	1.012	0.198	0.332	-1.338	1.393	0.033	0.002	-0.103	-0.602
Rgs14	-0.967	-0.409	0.242	0.426	1.123	0.082	-0.214	-0.662	0.277	1.966	-0.017	0.079	1.594
Rnaseh2c	-0.376	-0.663	-0.350	-0.622	-1.049	-0.808	-0.963	0.152	0.093	-0.010	0.049	0.877	0.887
Sf3b2	0.488	-0.490	-0.913	-0.632	-0.816	-0.364	-0.359	0.183	-0.075	-0.872	0.353	0.556	0.478

Gene - mouse homolog of significant gene identified in kidney tissue (see ST7a). Endo - endothelial; Podo - podocyte; PT - proximal tubule; LOH - Loop of Henle; DCT - distal convoluted tubule; CD-PC - collecting duct principal cell; CD-IC - collecting duct intercalated cell; Fib - fibroblast; Macro - macrophage; Neutro - neutrophil; B lymph - B lymphocyte; T lymph - T lymphocyte; NK - natural killer cell.

Supplementary Table 6. **Expression of genes from mouse scRNA-seq in human kidney from the Human Protein Atlas.**

Gene	Glomeruli expression[a]	Tubule Expression[a]
BST2	High	Medium
NARS2	Medium	High
ARNT	Medium	Low
SHROOM3	Low	Medium
METTL10	Medium	Medium
TPRKB	Low	Medium
ARL16	Not detected	High
ANTPTL3	Not detected	Not detected
SPIRE2	High	Medium
UBE2Q2	NA[b]	NA[b]
KLHDC7A	NA[c]	NA[c]
NRIP1	Medium	Medium
USP24	Not detected	Medium
MANBA	Not detected	Medium
RNF152	NA[b]	NA[b]
GBAS	Medium	High
WHAMM	Medium	Medium
RGS14	Not detected	Medium
RNASEH2C	NA[b]	NA[b]
SF3B2	Medium	High

Expression in glomeruli and tubule cells categorized as high, medium, or low. [a]Expression profiles for proteins in human kidney based on immunohistochemisty using tissue micro arrays. [b]Pending normal tissue annotation. [c]Estimation of protein expression could not be performed. View primary data.

Supplementary Table 7: 63 SNPs included in w-GRS construction using only previously-published CKDgen results.

SNP	Chr	Position (bp)	Index Gene	Effect allele	Other Allele	Effect	SE	P-value	Index
rs7546668	1	15855123	CASP9	C	G	-0.0063	0.001	1.14E-09	Gorski
rs10127790	1	109891133	SYPL2	T	C	0.0061	0.001	7.58E-09	Gorski
rs267738	1	150940625	ANXA9	T	G	-0.0091	0.0011	1.48E-14	Gorski
rs3850625	1	201016296	CACNA1S	A	G	0.0078	0.0013	5.53E-10	Pattaro
rs807601	2	15793014	DDX1	T	G	0.0064	0.0009	6.60E-12	Pattaro
rs780093	2	27742603	GCKR	T	C	0.0081	0.0009	1.57E-16	Gorski
rs6546838	2	73679280	ALMS1	A	G	-0.0093	0.001	7.72E-20	Pattaro
rs7422339 (now rs1047891)	2	211540507	CPS1	A	C	-0.0106	0.001	2.18E-23	Pattaro
rs2861422	3	141724644	TFDP2	T	C	0.0074	0.001	9.12E-14	Pattaro
rs10513801	3	185822353	ETV5	T	G	0.007	0.0012	2.47E-09	Pattaro
rs17319721	4	77368847	SHROOM3	A	G	-0.0114	0.0009	1.32E-37	Pattaro
rs11959928	5	39397132	DAB2	A	T	-0.0083	0.0009	1.66E-20	Pattaro
rs6420094	5	176817636	SLC34A1	A	G	0.0096	0.001	4.92E-22	Pattaro
rs9472135	6	43809802	VEGFA	T	C	-0.008	0.001	3.34E-15	Pattaro
rs316009	6	160675764	SLC22A2	T	C	0.0131	0.0014	4.38E-19	Pattaro
rs10277115	7	1285195	UNCX	A	T	0.009	0.0012	8.72E-14	Pattaro
rs848490	7	77555005	TMEM60	C	G	0.0073	0.001	7.80E-13	Pattaro
rs7805747	7	151407801	PRKAG2	A	G	-0.013	0.0011	7.96E-29	Pattaro
rs36071802	8	23715871	STC1	T	C	0.0079	0.0009	1.16E-15	Gorski
rs10746942	9	71434465	PIP5K1B	A	G	0.0086	0.0009	3.56E-18	Gorski
rs80282103	10	899071	WDR37	A	T	0.0123	0.0017	1.12E-11	Gorski
rs10994860	10	52645424	A1CF	T	C	0.0071	0.001	1.66E-12	Pattaro
rs163160	11	2789955	KCNQ1	A	G	0.0064	0.001	1.72E-10	Pattaro
rs963837	11	30749090	MPPED2	T	C	-0.0078	0.0009	5.69E-18	Pattaro
rs4014195	11	65506822	AP5B1	C	G	0.0055	0.0008	1.10E-11	Pattaro
rs10774021	12	349298	SLC6A13	T	C	-0.0063	0.0009	4.77E-12	Pattaro
rs10491967	12	3368093	TSPAN9	A	G	-0.0095	0.0013	5.18E-14	Pattaro
rs9529913	13	72345089	DACH1	T	C	-0.0066	0.0009	2.51E-11	Gorski
rs2453533	15	45641225	GATM	A	C	-0.0135	0.0009	2.65E-43	Gorski
rs491567	15	53946593	WDR72	A	C	-0.0084	0.001	2.86E-15	Pattaro
rs1394125	15	76158983	UBE2Q2	A	G	-0.0073	0.001	5.47E-14	Pattaro
rs13329952	16	20366507	UMOD	T	C	-0.0158	0.0011	9.47E-43	Pattaro
rs894680	17	19440538	SLC47A1	A	G	-0.0074	0.001	5.46E-12	Gorski
rs12451586	17	37633835	CDK12	A	T	-0.0092	0.0011	2.78E-15	Gorski
rs11657044	17	59450105	BCAS3	T	C	-0.0115	0.0012	7.89E-22	Pattaro
rs71359461	18	77156103	NFATC1	C	G	-0.0086	0.0013	3.67E-10	Gorski
rs12460876	19	33356891	SLC7A9	T	C	-0.0066	0.0009	1.86E-13	Pattaro
rs6058093	20	33213196	TP53INP2	A	C	-0.0074	0.001	2.26E-13	Gorski
rs6127099	20	52731402	BCAS1	A	T	-0.0095	0.0011	2.91E-17	Gorski
rs10874312	1	82944571	LPHN2	A	G	-0.0057	0.0011	2.20E-08	Gorski
rs12144044	1	113248791	RHOC	A	C	-0.0061	0.0011	2.87E-08	Gorski

rs187355703	2	176993583	HOXD8	C	G	0.0182	0.003	5.15E-10	Gorski
rs111366116	5	53295546	ARL15	T	C	0.0094	0.0015	6.27E-10	Gorski
rs113246091	5	67739274	PIK3R1	A	G	-0.0095	0.0016	1.98E-09	Gorski
rs7764488	6	133812872	EYA4	A	G	0.0061	0.0011	4.08E-09	Gorski
rs13298297	9	119264108	ASTN2	A	G	-0.0075	0.0014	1.53E-08	Gorski
rs1111571	16	68363181	SLC7A6	A	G	0.0061	0.0011	6.20E-09	Gorski
rs9962915	18	5593171	EPB41L3	T	C	-0.0055	0.001	7.19E-09	Gorski
rs12458009	18	59350507	RNF152	T	G	-0.0064	0.0012	2.90E-08	Gorski
rs2802729	1	243501763	SDCCAG8	A	C	-0.0046	0.0008	2.20E-08	Pattaro
rs2712184	2	217682779	IGFBP5	A	C	-0.0048	0.0008	3.02E-09	Pattaro
rs6795744	3	13906850	WNT7A	A	G	0.006	0.0011	3.33E-08	Pattaro
rs228611	4	103561709	NFKB1	A	G	-0.0056	0.0008	3.58E-12	Pattaro
rs3750082	7	32919927	KBTBD2	A	T	0.0045	0.0008	3.22E-08	Pattaro
rs6459680	7	156258568	RNF32	T	G	-0.0055	0.0009	1.07E-09	Pattaro
rs1106766	12	57809456	INHBC	T	C	0.0061	0.001	2.41E-09	Pattaro
rs476633	15	41392134	INO80	C	G	0.0051	0.0009	8.90E-09	Pattaro
rs164748	16	89708292	DPEP1	C	G	0.0046	0.0008	1.95E-08	Pattaro NDM only
rs11666497	19	38464262	SIPA1L3	T	C	-0.0058	0.0011	4.25E-08	Pattaro
rs4667594	2	170008506	LRP2	A	T	-0.0044	0.0008	3.52E-08	Pattaro
rs9682041	3	170091902	SKIL	T	C	-0.0068	0.0012	2.58E-08	Pattaro NDM only
rs7759001	6	27341409	ZNF204	A	G	-0.0051	0.0009	1.75E-08	Pattaro
rs7956634	12	15321194	PTPRO	T	C	-0.0068	0.001	7.17E-12	Pattaro

SNP – dbSNP accession number; Chr – chromosome; Position (bp) – build 37 position of each SNP; Index Gene – Gene annotation from publication; Effect allele - - allele corresponding to measured effect on the outcome; Other allele - allele not corresponding to measured effect on the outcome; Effect - measured effect in the published paper; SE - standard error of the measured effect in the published paper; P-value - association p-value for the measured effect in the published paper; Index – Manuscript reporting associations for which summary statistics are derived, Gorski = Gorski M et al, Scientific Reports, 2017 Apr 28, PMID 28452372 [1]; Pattaro = Pattaro C et al, Nature Communications, 2016 Jan 21, PMID 26831199[2]

Supplementary Table 8. Suggestive phenome-wide associations of previously published CKDgen-weighted eGFR genetic risk score (GRS) in unrelated white individuals in MVP.

PheCode	Description	Phenotype Group	N_{Total}	N_{Cases}	$N_{Controls}$	OR	SE	P-value
585.3	Chronic renal failure [CKD]	genitourinary	167997	16305	151692	0.876	0.008	**3.55E-57**
585	Renal failure	genitourinary	173079	21387	151692	0.893	0.007	**6.32E-53**
585.33	Chronic Kidney Disease, Stage III	genitourinary	158973	7281	151692	0.885	0.012	**6.13E-24**
401.22	Hypertensive chronic kidney disease	circulatory system	55004	8490	46514	0.917	0.012	**5.19E-13**
594	Urinary calculus	genitourinary	186563	13178	173385	1.062	0.009	**2.75E-11**
594.1	Calculus of kidney	genitourinary	184433	11048	173385	1.064	0.010	**3.12E-10**
401.2	Hypertensive heart and/or renal disease	circulatory system	56739	10225	46514	0.939	0.011	**1.72E-08**
586	Other disorders of the kidney and ureters	genitourinary	160917	9225	151692	0.949	0.011	**1.11E-06**
594.3	Calculus of ureter	genitourinary	176071	2686	173385	1.088	0.020	**1.59E-05**

Table is sorted by p-value. PheCode - PheWAS code, a hierarchical grouping of International Classification of Disease, 9th edition (ICD9) codes applied to EMR data, which loosely follow the 3-digit (category) and section groupings defined with the ICD9 code system itself, and have been revised based on statistical co-occurrence, code frequency, and human review; Description - full name of PheCode grouping; Phenotype Group - physiological system to which the PheCode is assigned; N_{Total} - total number of individuals not excluded in analysis of PheCode; N_{Cases} -number of individuals with one or more diagnosis codes corresponding to the PheCode; $N_{controls}$ -number of individuals lacking diagnosis codes or exclusion criteria corresponding to the PheCode; OR -measured odds ratio per standard deviation of w-GRS (standard deviation for all three analyses = 0.0377) for association between the weighted GRS and PheCode; SE - standard error of the measured effect; P-value - p-value for association of the weighted GRS and the PheCode.

Supplementary Note 1.

Relationship between t-statistic, chi-square and R^2

$$t = r \times \sqrt{\frac{n-2}{1-r^2}} \qquad (1)$$

Rearranging the equation in terms of r^2

$$r^2 = \frac{t^2}{(n-2)+t^2} \qquad (2)$$

When n is large enough (n > 20) t-distribution approximates the z distribution

$$r^2 \approx \frac{z^2}{(n-2)+z^2} \qquad (3)$$

The square of a z distribution is the Chi-square distribution

$$r^2 \approx \frac{\chi^2}{(n-2)+\chi^2} \qquad (4)$$

Supplementary Equation 1 describes the relationship between a student's t statistic, correlation coefficient r, and r^2. Supplementary Equation 4 describes the transformed equation that describes r^2 in terms of the chi-square.

As n → ∞

$$r^2 \approx \frac{\chi^2}{n} \qquad (5)$$

When the sample size is sufficiently large enough, the variance explained by each SNP can then be well approximated by Supplementary Equation 5.

$$R^2 \approx \sum_{i=1}^{m} \frac{{\chi_i}^2}{n_i} \qquad (6)$$

Where m = total number of independent SNPs in the study, R^2 is the total variance explained by independent SNPs, n_i and ${\chi_i}^2$ represent the number individuals in the analysis and the square of the Wald z-statistic for the given SNP, respectively.

Supplementary Methods

Enrichment analyses in DEPICT[3] were conducted using significant GWAS sentinel SNPs from three separate analyses as input: 1) transethnic analyses of all MVP subjects, 2) transethnic analyses of MVP subjects with DM, and 3) transethnic analyses of MVP subjects without DM. DEPICT is based on predefined phenotypic gene sets from multiple databases and Affymetrix

HGU133a2.0 expression microarray data from more than >37k subjects to build highly-expressed gene sets for Medical Subject Heading (MeSH) tissue and cell type annotations. Output includes a p-value for enrichment and a yes/no indicator of whether the FDR q-value is <0.05. Tissue level and gene-set enrichment features are considered.

Supplementary Discussion

We conducted tissue-specific and pathway gene enrichment analyses using DEPICT software[3] using the significant GWAS sentinel SNPs identified from transethnic analyses of all subjects, diabetics participants, and non-diabetic participants, respectively, (Supplementary Data 6–7 and 8–9). Enrichment analyses of GWAS SNPs from transethnic two-stage analyses of diabetic participants failed due to an insufficient number of independent loci annotated by DEPICT gene sets. No significant (FDR < 5%) tissue-specific or pathway gene set enrichment was detected. The two most significant tissue-specific gene set enrichments were observed in the urinary tract and the kidney in all subjects ($p = 4.96x10^{-3}$ and $p = 6.49x10^{-3}$, respectively) and non-diabetics participants ($p = 8.90x10^{-4}$ and $1.14x10^{-3}$, respectively). The most significant pathway gene set enrichment was observed in abnormal placental labyrinth vasculature morphology for all subjects (MP:0008803; $p = 3.02x10^{-6}$) and in abnormal liver morphology for non-diabetic participants (MP:0000598; $p = 1.51x10^{-5}$).

Supplementary Note 2.

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Supplementary Note 3.

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