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ORIGINAL ARTICLE

Genome-Wide Association of Kidney Traits in Hispanics/Latinos Using Dense Imputed Whole-Genome Sequencing Data

The Hispanic Community Health Study/Study of Latinos

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BACKGROUND: Genetic factors that influence kidney traits have been understudied for low-frequency and ancestry-specific variants.

METHODS: This study used imputed whole-genome sequencing from the Trans-Omics for Precision Medicine project to identify novel loci for estimated glomerular filtration rate and urine albumin-to-creatinine ratio in up to 12 207 Hispanics/Latinos. Replication was performed in the Women's Health Initiative and the UK Biobank when variants were available.

RESULTS: Two low-frequency intronic variants were associated with estimated glomerular filtration rate (rs58720902 at *AQR*, minor allele frequency=0.01, $P=1.6\times10^{-8}$) or urine albumin-to-creatinine ratio (rs527493184 at *ZBTB16*, minor allele frequency=0.002, $P=1.1\times10^{-8}$). An additional variant at *PRNT* (rs2422935, minor allele frequency=0.54, $P=2.89\times10^{-8}$) was significantly associated with estimated glomerular filtration rate in meta-analysis with replication samples. We also identified 2 known loci for urine albumin-to-creatinine ratio (*BCL2L11* rs116907128, $P=5.6\times10^{-8}$ and *HBB* rs344, $P=9.3\times10^{-11}$) and validated 8 loci for urine albumin-to-creatinine ratio previously identified in the UK Biobank.

CONCLUSIONS: Our study shows gains in gene discovery when using dense imputation from multi-ethnic whole-genome sequencing data in admixed Hispanics/Latinos. It also highlights limitations in genetic research of kidney traits, including the lack of suitable replication samples for variants that are more common in non-European ancestry and those at low frequency in populations.

Key Words: genes ■ genetic variation ■ genetics ■ genome-wide association study ■ kidney ■ population

Urine albumin-to-creatinine ratio (ACR) and decreased estimated glomerular filtration rate (eGFR) reflect different dimensions of chronic kidney disease, that is, kidney damage and reduced kidney function, respectively. Hispanics/Latinos have increased age-adjusted prevalence of chronic kidney disease demonstrated by increased ACR and decreased eGFR compared to non-Hispanic US Whites based on recent data from the HCHS/SOL (Hispanic Community Health Study/Study of Latinos).[1] In HCHS/SOL, the prevalence of albuminuria and reduced eGFR was 14% and 3%, respectively, among individuals who were on average 41 years old.

Genome-wide association studies (GWAS) have uncovered novel loci for ACR and eGFR, although the number of identified loci for ACR is modest compared to other complex traits. Few studies have included Hispanics/Latinos for these chronic kidney disease traits. In our recent work using GWAS approaches, we identified

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Nonstandard Abbreviations and Acronyms

ACR	urine albumin-to-creatinine ratio
eGFR	estimated glomerular filtration rate
GWAS	genome-wide association studies
HCHS/SOL	Hispanic Community Health Study/ Study of Latinos
SNV	single-nucleotide variant
WGS	whole-genome sequencing
WHI	Women's Health Initiative

significant associations of ACR at the *CUBN* and the *HBB* genes, the later related to associations for the sickle cell variant rs334, which is present in Hispanics with African admixture.[2] Additional research using admixture mapping identified an Amerindian variant at *BCL2L11* associated with ACR in HCHS/SOL Hispanics/Latinos.[3] For eGFR, 93 loci have been recently described in multi-ethnic GWAS meta-analyses that included ≈23 000 Hispanics/Latinos.[4] Interestingly, there has been little overlap in loci identified for ACR and eGFR in both Hispanics/Latinos and in studies of individuals of European ancestry.[5]

Prior GWAS have assessed imputed genotypes using references from the 1000 Genome Project. The National Heart, Lung, and Blood Institute Trans-Omics for Precision Medicine project recently generated deep-coverage (mean depth 30×) whole-genome sequencing (WGS) on over 50 000 individuals from multi-ethnic studies, including 7.5% Hispanic/Latinos. This resource provides a large reference of common and low-frequency genetic variants in diverse populations for high-quality imputation in Hispanics/Latinos. We used the Trans-Omics for Precision Medicine WGS haplotypes for a dense imputation of single-nucleotide variants (SNVs) and small deletion/insertions (indels) in the HCHS/SOL study.[6] This study reports findings from GWAS of eGFR and ACR in Hispanics/Latinos using this data. We attempted to validate associations from a recently published GWAS of ACR in the UK Biobank white British, which identified 32 novel loci that have not yet been validated.[7]

METHODS

HCHS/SOL[8] genotype and phenotype data are publicly available at the Database of Genotypes and Phenotypes (dbGaP) and can be accessed at https://www.ncbi.nlm.nih.gov/gap, study accession phs000810. The freeze 5b Trans-Omics for Precision Medicine data used for imputation of WGS data is available at the dbGap, study accession phs001395. To minimize the possibility of unintentionally sharing information that can be used to re-identify private information in this single study, summary data of this study are available from the corresponding author upon reasonable request.

The study was approved by the institutional review boards at each field center, where all participants gave written informed consent, and by the Non-Biomedical institutional review board at the University of North Carolina at Chapel Hill.

Methods are included in the Data Supplement.

RESULTS

Data were available in 12 207 participants for eGFR and 11 688 for ACR. The mean age of participants was 46.1 years (SD 13.9), 58.7% were women, 20.0% had diabetes mellitus, and 28.0% had hypertension treated with medications. Mean eGFR was 96.6 (SD 18.9) mL/min/1.73 m^2 and median ACR was 6.5 (interquartile 4.5–12.2) mg/g creatinine.

GWAS Results

GWAS of eGFR and ACR showed little evidence for genomic inflation (λ=1009 and λ=1005, respectively). Quantile-quantile plots are shown in Figure I in the Data Supplement, and Manhattan plots for eGFR and ACR are shown in Figure II in the Data Supplement. GWAS of eGFR identified 15 loci at $P<10^{-7}$ (Table 1), including a significant association for a low-frequency intronic SNV at the *AQR* gene (rs58720902, minor allele frequency=0.01, $P=1.6\times10^{-8}$; Figure [A]). Most of the SNVs/indels shown in Table 1 were low-frequency variants and showed a large effect on eGFR. These variants were more commonly seen in non-European ancestry populations. For ACR, we identified twelve loci at $P<10^{-7}$ including 2 loci previously identified in admixture mapping (*BCL2L11* rs116907128, $P=3.5\times10^{-8}$) and in a GWAS in HCHS/SOL (*HBB* rs344, $P=8.4\times10^{-11}$), in addition to a novel loci at *ZBTB16* ($P=1.1\times10^{-8}$; Table 2 and Figure [B]). The *HBB* rs344 was also nominally associated with eGFR ($P=5.0\times10^{-3}$).

Replication of HCHS/SOL GWAS Findings

We attempted replication of the SNVs independently associated with eGFR at $P<10^{-7}$ in the Women's Health Initiative (WHI) African Americans and Hispanics/Latinos guided by the allele frequency in ancestry-specific data sets.[9,10] Most of the low frequency/rare SNVs were not available for replication given the studies were imputed to the 1000 Genome Project reference panels. The significantly associated eGFR SNV at the *AQR* locus nominally replicated in WHI Hispanics (minor allele frequency=0.01, $P=0.03$). This SNV was more common in African ancestry (minor allele frequency=0.08), but the association was not significant ($P=0.86$) in WHI African Americans. Although the direction of effect was concordant among discovery and replication samples, there was significant heterogeneity in meta-analysis ($P=1.4\times10^{-5}$; Table 1). The SNV at the *PRNT* gene, rs2422935, was

Table 1. Main Findings for Association With eGFR at $P<10^{-7}$ Using TOPMed Reference Imputation in the HCHS/SOL (n=12 207)

Chr	Position (hg38)	SNPID	Coded Allele	Noncoded	AF Coded	B	*P* Value	Nearby Gene	Function	1000 Genome Project Allele Frequencies			Replication WHI AA (n=8224)	Replication WHI HA (n=3549)
										AFR	AMR	EUR	β (SE), *P* Value	β (SE), *P* Value
2	191304743	rs566396416	A	G	0.002	−12.801 (2.523)	3.8×10^{-7}	*MYO1B*	Intronic	NA	NA	NA	NA	NA
5	113371933	rs17379925	T	C	0.02	3.159 (0.645)	9.0×10^{-7}	*MCC*	Intronic	0.005	0.02	0.05	NA	1.135 (1.143), 0.32
5	171905787	rs77109276	G	A	0.01	−4.179 (0.847)	8.2×10^{-7}	*FBXW11*	Intronic	NA	0.006	0.03	NA	2.600 (1.408), 0.06
6	34250388	rs10080749	G	A	0.33	−0.987 (0.200)	8.0×10^{-7}	*C6orf1*	Intergenic	0.52	0.37	0.12	NA	−0.249 (0.357), 0.49
6	54013111	NA	AT	A	0.001	−20.946 (4.233)	7.5×10^{-7}	*MLIP*	Intergenic	NA	NA	NA	NA	NA
7	128864667	rs537479423	T	C	0.002	−12.396 (2.282)	5.6×10^{-8}	*ATP6V1F*	Intronic	0.01	0.003	NA	NA	NA
7	151442610	rs145127841	A	G	0.006	−6.862 (1.3890)	7.8×10^{-7}	*CRYGN*	Intergenic	0.03	0.006	NA	NA	NA
10	25871827	rs150486305	T	G	0.003	9.716 (1.934)	5.0×10^{-7}	*LOC101929073*	Intergenic	NA	0.001	0.001	NA	NA
11	57930162	NA	T	C	0.001	−17.786 (2.283)	6.0×10^{-8}	*OR9Q1*	Intergenic	NA	NA	NA	NA	NA
11	58498757	NA	G	A	0.001	−17.028 (3.223)	1.3×10^{-7}	*OR5B21*	Intergenic	NA	NA	NA	NA	NA
13	88310365	rs530730032	G	A	0.002	−12.862 (2.555)	4.8×10^{-7}	*LINC00433*	Intergenic	0.005	NA	NA	NA	NA
13	112853280	rs560559296	G	A	0.001	−14.559 (2.730)	9.6×10^{-8}	*ATP11A*	Intronic	NA	0.001	0.005	NA	NA
15	32721018	rs11857586	A	T	0.02	3.527 (0.706)	5.9×10^{-7}	*GREM1*	Intronic	0.15	0.01	0.002	−0.865 (0.498), 0.08	−0.401 (1.229), 0.74
15	34926038	rs58720902	T	G	0.01	4.791 (0.847)	1.6×10^{-8}	*AQR*	Intronic	0.11	0.01	0.00	0.086 (0.523), 0.86	1.97 (6.49), 0.03
20	4739670	rs2422935	A	G	0.54	−0.965 (0.188)	3.0×10^{-7}	*PRNT*	ncRNA intronic	0.53	0.54	0.55	−0.346 (0.278), 0.21	−0.877 (0.314), 0.005

AA indicates African American; AF, allele frequency; AFR, African; AMR, Admixed Americans; Chr, chromosome; EUR, European; HA, Hispanics; and HCHS/SOL, Hispanic Community Health Study/Study of Latinos.

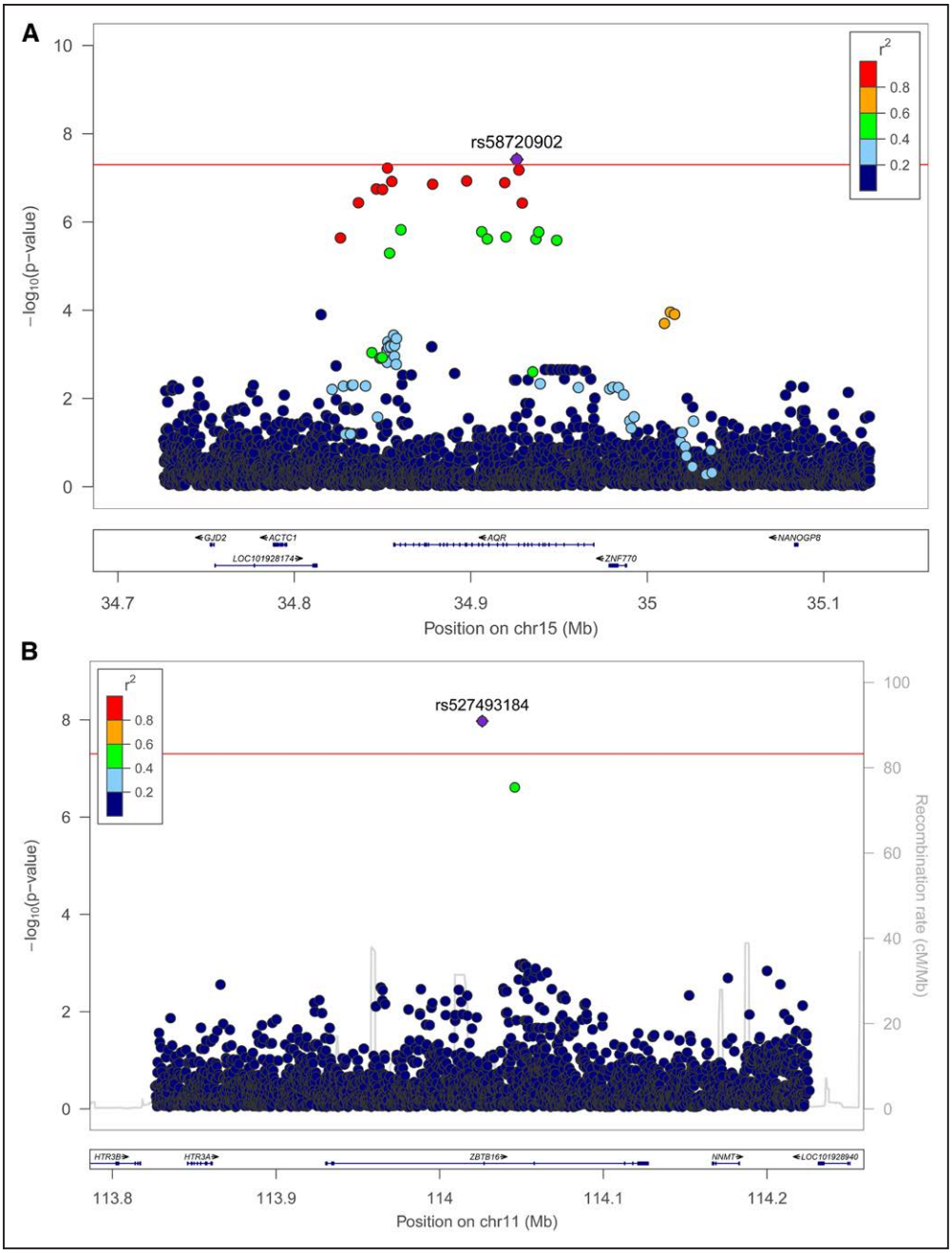

Figure. Main genome-wide association findings for eGFR and ACR.
A, Regional plot for associations at the AQR gene on chromosome 15 for estimated glomerular filtration rate (eGFR) and (**B**) association at the ZBTB16 gene for urine albumin-to-creatinine ratio (ACR) in the HCHS/SOL (Hispanic Community Health Study/Study of Latinos) discovery samples. *X*-axis shows the chromosome position and underlying genes in the region. The *Y*-axis is the −log (*P* values). Each dot is a single-nucleotide variant (SNV) and the color indicates linkage disequilibrium (r^2) with the best variant (in purple). Red horizontal line is the genome-wide association threshold.

nominally associated with eGFR in WHI Hispanics/Latinos but not in African Americans. However, the effect estimates were concordant in direction among HCHS/SOL, WHI Hispanics/Latinos, and African Americans. In meta-analysis across HCHS/SOL and WHI samples, the association reached genome-wide significance ($P=1.4\times10^{-8}$, *P* for heterogeneity=0.18). Among remaining SNVs present in at least one replication sample, meta-analyses of discovery and replication samples showed significant heterogeneity ($P<0.05$), and *P* values were higher than those observed in the discovery sample.

For ACR, because there is no available GWAS summary data in Hispanics or individuals of African ancestry, we attempted replication for SNVs at $P<10^{-7}$ using summary statistics from UK Biobank white British.[7] Five SNVs were available including 2 that were rare in the UK

Table 2. Main Findings for Association With ACR at $P<10^{-7}$ Using TOPMed Reference Imputation in the HCHS/SOL (n=11 688)

Chr	Position (hg38)	SNPID	Coded Allele	Noncoded	AF Coded	B	*P* Value	Nearby Gene	Function	1000 Genome Project Allele Frequencies			Replication UK Biobank *P* Value
										AFR	AMR	EUR	
2	27346004	rs10205592	C	T	0.56	−0.075 (0.014)	1.1×10^{-7}	*GTF3C2*	Intronic	0.87	0.51	0.41	NA
2	108390209	rs13021399	T	A	0.56	−0.081 (0.015)	9.9×10^{-8}	*SULT1C4*	Intergenic	0.02	0.53	0.26	0.36
2	108897145	rs3827760	G	A	0.29	0.097 (0.019)	1.6×10^{-7}	*EDAR*	Missense	0.003	0.39	0.01	0.10
2	109624640	rs919942	A	C	0.63	0.071 (0.014)	8.2×10^{-7}	*SOWAHC*	Intergenic	0.33	0.69	0.54	0.52
2	111121122	rs116907128	A	C	0.14	0.120 (0.022)	3.5×10^{-8}	*BCL2L11*	UTR5	0.002	0.17	0.001	NA
3	196146539	rs540878340	A	G	0.002	0.914 (0.176)	2.0×10^{-7}	*LINC00885*	ncRNA_ intronic	0.02	0.001	NA	NA
11	5227002	rs334	A	T	0.01	0.530 (0.082)	8.4×10^{-11}	*HBB*	Missense			NA	NA
11	103974051	rs7103465	A	G	0.03	0.248 (0.049)	3.7×10^{-7}	*PDGFD*	Intronic	0.11	0.02	0.02	0.41
11	114155245	rs527493184	A	G	0.002	1.029 (0.180)	1.1×10^{-8}	*ZBTB16*	Intronic	0.01	0.003	NA	NA
16	86734887	rs11117207	C	T	0.08	−0.128 (0.025)	3.6×10^{-7}	*FOXL1*	Intergenic	0.27	0.08	0.04	0.62
17	54416610	rs115573116	T	C	0.002	0.756 (0.145)	1.7×10^{-7}	*TOM1L1*	Intergenic	0.03	0.001	NA	NA
22	16823805	rs1032642268	A	G	0.002	0.873 (0.176)	7.1×10^{-7}	*XKR3*	Intergenic	NA	NA	NA	NA

AA indicates African American; AF, allele frequency; AFR, African; AMR, Admixed Americans; Chr, chromosome; EUR, European; HA, Hispanics; HCHS/SOL, Hispanic Community Health Study/Study of Latinos; and UKB, UK Biobank.

Biobank white British data set. None of the SNVs replicated at nominal level and just 3 SNVs had concordant direction of effect between HCHS/SOL and the UK Biobank data.

Secondary analyses showed no differences in effect estimates within diabetes mellitus strata for SNVs that replicated for eGFR or ACR (Table I in the Data Supplement).

Validation of Previously Reported ACR Loci Identified in the UK Biobank

We next examined the association for 46 loci recently reported in the UK Biobank by Haas et al[7] and additional 32 loci reported by Teumer et al[11] (both included the UK Biobank data), which have not been validated in independent studies. Replication criteria consider a nominal association ($P<0.05$) and consistency in direction of effects between our data and the UK Biobank. Six SNVs (5 at novel loci) described by Haas et al[7] replicated: *SNX17* ($P=1.7\times10^{-7}$), *HOTTIP* ($P=0.001$); *WIPF3* ($P=0.003$); *CUBN* ($P=0.005$); *C10orf11* ($P=0.002$), and *ACTN1* ($P=0.002$; Table 3). The most significant SNV at the known *CUBN* locus in our data was rs144250387 ($P=1.9\times10^{-6}$). Only 3 loci replicated from Teumer et al[11] (*KCNK5*, rs1544935, $P=0.003$; *OAF*, rs508205, $P=0.02$; *DPEP1* rs2460448, $P=0.04$; Table II in the Data Supplement).

DISCUSSION

In this genetic study of Hispanics/Latinos using multiethnic dense imputed WGS genotypes, we identified 2 novel loci for eGFR, a novel locus for ACR and replicated additional 8 ACR loci identified in GWAS using the UK Biobank white British samples. Overall, the imputation of Trans-Omics for Precision Medicine SNVs allowed for identification of several associations for low-frequency variants and those that are more common in non-European ancestry. However, our results also underscore the limitations of current genetic studies, including the lack of suitable replication samples for variants that are more common in non-European ancestry or are low frequency.

For eGFR, the *AQR* locus finding was driven by an intronic variant that is rare in European and Admixed Americans, but it is a common variant in African Americans (Table 1). The association replicated in WHI Hispanics but not in African Americans. However, there was significant heterogeneity in meta-analysis, with a larger effect on eGFR in Hispanics/Latinos than African

Table 3. Replication of Associated SNVs From the UK Biobank for ACR in Hispanics/Latinos of the HCHS/SOL Study

SNV	Chr	Position (hg38)	Coded Allele	Other Allele	Coded Allele Frequency	Coded Allele Count	N	β	SE	*P* Value	Gene
rs12032996	1	33454985	A	G	0.19	4380	11688	−0.001	0.018	0.97	*ZSCAN20*
rs10157710	1	47496019	T	C	0.70	16357	11688	0.017	0.015	0.27	*FOXD2*
rs11162351	1	77479047	G	C	0.32	7576	11688	−0.001	0.015	0.95	*AK5*
rs11264327	1	155122631	A	G	0.51	12027	11688	−0.011	0.014	0.44	*EFNA1*
rs12727104	1	171454028	A	G	0.17	3973	11688	−0.005	0.019	0.78	*PRRC2C*
rs12727980	1	200289967	T	C	0.58	13624	11688	0.018	0.014	0.21	*LINC00862*
rs4665972	2	27375230	C	T	0.67	15758	11688	−0.078	0.015	1.7×10^{-7}	*SNX17*
rs6750228	2	51084986	A	T	0.06	1462	11688	0.040	0.030	0.18	*NRXN1*
rs13394343	2	85527219	A	C	0.40	9464	11688	0.004	0.014	0.78	*LOC100630918*
rs10207567	2	202850250	C	G	0.77	18089	11688	0.025	0.016	0.13	*ICA1L*
rs1047891	2	210675783	A	C	0.31	7307	11688	−0.024	0.015	0.11	*CPS1*
rs35483183	2	227011971	A	G	0.07	1698	11688	0.037	0.027	0.17	*COL4A4*
rs6768627	3	46853886	T	C	0.10	2388	11688	0.014	0.023	0.55	*MYL3*
rs112607182	3	170309619	T	C	0.03	654	11688	0.046	0.046	0.32	*PRKCI*
rs3805382	4	55605384	G	A	0.40	9288	11688	0.014	0.015	0.34	*NMU*
rs7654754	4	76488642	A	G	0.48	11204	11688	−0.003	0.014	0.84	*SHROOM3*
rs6535594	4	148211605	A	G	0.57	13421	11688	0.024	0.014	0.08	*NR3C2*
rs702634	5	53975590	A	G	0.79	18513	11688	0.022	0.017	0.21	*ARL15*
rs7731168	5	65000644	C	G	0.20	4761	11688	0.019	0.017	0.27	*CWC27*
rs4410790	7	17244953	C	T	0.38	8913	11688	−0.006	0.015	0.66	*AHR*
rs2023844	7	27203619	A	G	0.88	20613	11688	0.072	0.022	0.001	*HOTTIP*
rs17158386	7	29765745	A	G	0.15	3583	11688	0.057	0.020	0.003	*WIPF3*
rs55798132	8	2808621	A	G	0.008	193	11687	−0.076	0.078	0.33	*LOC101927815*
rs28601761	8	125487789	G	C	0.32	7553	11687	−0.012	0.015	0.40	*TRIB1*
rs45551835	10	16890385	A	G	0.017	405	11688	0.149	0.054	0.005	*CUBN*
rs144360241	10	16925418	C	T	0.005	122	11688	0.087	0.109	0.43	*CUBN*
rs1276720	10	16929427	T	C	0.57	13251	11688	0.014	0.014	0.33	*CUBN*
rs10995311	10	62805174	G	C	0.27	6208	11688	0.001	0.016	0.94	*ADO*
rs67339103	10	76133928	A	G	0.30	7106	11688	0.047	0.015	0.002	*C10orf11*
rs17368443	11	10275289	C	G	0.04	1027	11688	0.043	0.035	0.22	*SBF2*
rs1124694	11	11077129	G	A	0.30	6916	11688	0.001	0.015	0.96	*GALNT18*
rs2601006	12	69585737	T	C	0.44	10299	11688	0.011	0.014	0.42	*CCT2*
rs4288924	14	68835682	A	G	0.56	12993	11688	−0.044	0.014	0.002	*ACTN1*
rs8035855	15	41785763	A	G	0.60	14121	11688	0.004	0.014	0.80	*MAPKBP1*
rs1145074	15	45411626	A	T	0.55	12930	11688	−0.011	0.015	0.47	*SPATA5L1*
rs146311723	15	63512308	C	T	0.096	2261	11688	−0.014	0.023	0.55	*USP3*
rs2472297	15	74735539	T	C	0.095	2232	11688	0.003	0.024	0.89	*CYP1A1*
rs2338796	17	39399374	G	A	0.28	6471	11688	−0.027	0.015	0.08	*FBXL20*
rs35572189	17	81451999	A	G	0.35	8126	11688	−0.004	0.014	0.78	*BAHCC1*
rs784257	18	55729968	C	T	0.90	20951	11688	−0.025	0.024	0.29	*TCF4*
rs838142	19	48748894	G	A	0.40	9448	11688	−0.003	0.014	0.84	*FUT1*

SNVs rs183131780 (*MIR548AR*), rs35924503 (*SPHKAP*), rs189107782 (*FRG1*), rs144994089 (*AQP7*), and rs141640975 (*CUBN*) were not available. ACR indicates urine albumin-to-creatinine ratio; Chr, Chr, chromosome; HCHS/SOL, Hispanic Community Health Study/Study of Latinos; and SNV, single-nucleotide variants.

Americans, suggesting potential differences by ancestry background. A recent study identified a SNV 1 kb downstream of AQR (rs3743121) associated with type 2 diabetes mellitus in East Asians, although the sample size was very small.[12] Experimental knockdown of *AQR* in immortalized cells (HepG2) showed improved glucose uptake and insulin sensitivity with additional effects on glycogen synthesis and gluconeogenesis.[12] In our data, there was no difference in effect estimates by diabetes mellitus status at the *AQR* locus (Table I in the Data

Supplement). However, the identified SNV was associated with a protective effect on eGFR, which mechanisms may include improvement in glucose metabolism. Further studies are needed to validate the association in Hispanics/Latinos. At the *PRNT* locus, an intronic variant was significantly associated with decreased eGFR in the combined discovery and replication samples. This variant is common across all populations, and there is little knowledge on the function of the gene and its relation to kidney traits. The *AQR* and *PRNT* SNVs had little evidence for any regulatory function in our *in silico* analysis.

Our GWAS of ACR identified a new locus at *ZBTB16* driven by a rare variant that was not available in the UK Biobank for replication. We confirmed associations at the *HBB* gene (rs344 related to hemoglobin S or sickle cell trait) and the *BCL2L11* gene, which we have been previously reported in this cohort.[2] We have shown that rs344 is associated with eGFR variation in our data, although at modest *P* values. We also replicated 8 loci initially reported in the UK Biobank for white British, including 5 that were novel: *SNX17* (intronic), *HOTTIP* (ncRNA intronic), *WIPF3* (intergenic), *C10orf11* (intronic), and *ACTN1* (intergenic).[7] At the *SNX17* locus, the SNV is an expression quantitative trait loci for *SNX17* in GTEx muscle skeletal tissue. This gene has no known function related to kidney traits. *HOTTIP* produces a long RNA in antisense to the *HOXA* gene cluster and regulates expression of *HOXA* genes. This locus has been identified in GWAS of blood pressure in individuals of African ancestry and in Hispanics/Latinos,[13,14] but its relation to kidney disease is unknown. The intergenic SNV at *WIPF3* is an expression quantitative trait loci for *WIPF3* in GTEx left ventricle. At least 6 SNVs identified in the UK Biobank were rare in our data and did not replicate in our study: rs189107782 (*FRG1*), rs55798132 (*LOC101927815*), rs144994089 (*AQP7*), and rs45551835, rs144360241, and rs141640975 (*CUBN*). Three additional loci from a recent GWAS of ACR that included the UK Biobank replicated at modest *P* values.[11] Overall, the number of ACR loci that we were able to validate from these previous studies was small.

Both albuminuria and eGFR are independently associated with cardiovascular mortality and progression to end-stage kidney disease.[15–17] Understanding their genetic determinants may offer opportunities for more targeted interventions to reduce these outcomes. Most GWAS studies of eGFR and ACR have included large number of individuals of European ancestry, and findings are driven by European populations. This may explain the lack of replication of some of the ACR findings from the UK Biobank, although Hispanics/Latinos have European ancestry admixture. Transethnic studies with large samples of diverse populations and studies within a single diverse population such as this report are still needed to better characterize disease risk across and within populations. We and others have already shown that the study of admixed populations can identify population-specific SNVs[2,18] or loci driven by SNVs with a higher allele frequency in one population.[14] In addition, we have successfully fine-mapped loci to SNVs with evidence of functionality. For example, the SNV at the *BCL2L11* locus, rs116907128, identified in our study of Hispanics/Latinos, is located within the promoter region of the gene in a region enriched for regulatory markers (DNAse I hypersensitive sites in human kidney cells and histone modification binding sites) which are strong evidence for its regulatory function. This locus replicated in recent analyses of the UK Biobank for ACR. However, the most significant SNVs at the region were either a low-frequency SNV (rs183131780)[7] or an intronic variant to *ACOXL* (rs2880119),[11] and none of these variants showed evidence for functional regulation of nearby genes.

In summary, our GWAS of Hispanics/Latinos using multi-ethnic WGS imputed genotypes identified novel loci for eGFR and replicated published associations for ACR. This study provides evidence for gains in gene discovery and for identifying variants with regulatory function in a study of Hispanics/Latinos and when using dense imputed variant panels.

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Disclosures

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