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Genetic Associations with Metabolic Syndrome and Its Quantitative Traits by Race/Ethnicity in the United States

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Abstract

Background: Elevated insulin resistance (IR), triglycerides (TG), body mass index (BMI), and waist circumference (WC) are features of the metabolic syndrome. Although several single-nucleotide polymorphisms (SNPs) associated with these traits have been reported, no study has reported their risk allele frequencies and effect sizes among the major U.S. race/ethnic groups in a nationally representative sample.
Methods: We compared the risk allele frequencies of eight SNPs previously associated with IR, TG, BMI, or WC by race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American) in 3,030 participants of the National Health and Nutrition Examination Study III (NHANES III). In regression models predicting IR, TG, BMI, WC, and metabolic syndrome, we tested whether the SNP effect sizes on these traits varied by race/ethnicity.
Results: Risk allele frequencies varied by race/ethnicity for all eight loci ($P < 0.0001$). The directionality of effects of the variants on IR, TG, WC, and BMI was generally consistent with previous observations and did not differ by race/ethnicity ($P > 0.001$), although our study had low power for this test. No SNP predicted metabolic syndrome in any of the three groups ($P > 0.05$).
Conclusions: The significance of racial/ethnic differences in risk allele frequencies merits consideration if genetic discoveries are to have clinical and public health applicability.

Introduction

The metabolic syndrome and its components are significant cardiovascular risk factors[1–3] and occur disproportionately in racial/ethnic minorities in the United States.[4] Although the definition of the metabolic syndrome may be clinically useful,[5] its genetic architecture remains unclear. Genome-wide association studies (GWAS) have uncovered single-nucleotide polymorphisms (SNPs) associated with each component of the metabolic syndrome [hypertension,[6] obesity and central adiposity,[7–11] insulin resistance,[12] hypertriglyceridemia, and low levels of high-density lipoprotein cholesterol (HDL-C)[13]], and some of these variants are associated with more than one component.[10–12,14–16] Such pleiotropic associations may give evidence for a common genetic architecture underlying these traits.

The discovery cohorts of large GWAS consortia, such as the Diabetes Genetics Replication and Meta-analysis (DIAGRAM),[17,18] the Genetic Investigation of Anthropometric Traits (GIANT),[8–10,19] the Meta-analysis of Glucose and Insulin Consortium (MAGIC),[12,20] the Global Blood Pressure Genetics (Global BPgen) Consortium,[6] and a recent meta-analysis of blood lipid levels,[13] consisted entirely of subjects of European ancestry. As a result, any findings from these GWAS consortia may not be generalizable to all race/ethnic groups. The International HapMap Project (http://

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hapmap.ncbi.nlm.nih.gov) has shown that that the frequencies of some risk variants vary significantly by ancestry, but no study has confirmed that HapMap risk allele frequencies (RAF) correspond to race/ethnic RAF differences in a nationally representative U.S. population sample. Moreover, few studies have confirmed the associations between these variants and metabolic traits in racial/ethnic groups other than those in which they were first identified.

Here, we used nationally representative data from the National Health and Nutrition Examination Survey (NHANES) to examine the effects of certain SNPs associated with metabolic syndrome traits [specifically insulin resistance, triglyceride (TG) levels, and two measures of adiposity] among three different race/ethnic groups in the United States. We compared the RAF of these SNPs among the three groups and tested the hypotheses that their effects on multiple traits related to the metabolic syndrome do not differ among the three groups.

Methods

Study Population

The NHANES series of studies has been described previously.[21] Briefly, NHANES III (1988–1994) was a large-scale nationally representative cross-sectional study of 33,994 noninstitutionalized U.S. civilians with oversampling of African Americans and Hispanic Americans. Each survey participant underwent a household interview and a physical examination, and fasting blood samples were obtained from a subset of individuals. For the present study, we limited our analyses to NHANES III Phase II (1991–1994) participants aged 20 years or older who had blood samples collected after a fast of at least 8 h. The survey asked each subject to categorize his/her race as "white," "black," or "other" and his/her ethnicity as "Mexican American," "other Hispanic," or "not Hispanic." Due to small sample sizes, we excluded participants who identified their race as "other" and did not self-identify as Mexican American. We categorized our race/ethnic groups into "non-Hispanic white," "non-Hispanic black," and "Mexican American." These self-reported race/ethnic group categories in NHANES III correspond well to the three similar race/ethnicity clusters formed by 128 ancestry informative markers described by Kosoy et al.[22] (Dana Crawford, Ph.D., personal communication). All study subjects provided written informed consent. The National Center for Health Statistics (NCHS) Ethics Review Board approved this study.

Body mass index (BMI) and waist circumference (WC) were measured by standardized protocols.[23] Glucose was measured by hexokinase (COBAS MIRA; Roche Diagnostics Corporation, Montclair, NJ) and insulin levels by radioimmunoassay (Pharmacia Diagnostics, Uppsala, Sweden). We calculated homeostasis model assessment of insulin resistance (HOMA-IR), a surrogate measure of IR, as insulin (μIU/mL)/(22.5e$^{-\ln\text{glucose (mmol/L)}}$).[24] For these analyses, we excluded participants with diabetes, identified by self-reported diagnosis or treatment, a fasting glucose level $\geq$126 mg/dL, or a 2-h oral glucose tolerance test (OGTT) $\geq$200 mg/dL. Of 3,359 eligible participants, 3,030 did not have diabetes at the time of the examination by this definition. Metabolic syndrome was defined by National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria as any three of the following: WC > 88 cm in women or > 102 cm in men, TG $\geq$ 150 mg/dL, HDL-C < 40 mg/dL in men or < 50 mg/dL in women, blood pressure $\geq$ 130/$\geq$ 85 or on blood pressure medication, and fasting glucose $\geq$ 100 mg/dL.[25]

Choice of SNPs and genotyping

NHANES III Phase II collected blood specimens from participants aged 12 or older. DNA lysates were created from cell lines generated using Epstein–Barr–transformed lymphocytes from these specimens. From published meta-analyses,[12,17,20] we selected eight major SNPs associated with metabolic syndrome–related quantitative traits: IR, TG, and BMI or WC (Table 1). Whereas most type 2 diabetes–associated SNPs are associated with defects in insulin secretion (including the strongest known association at *TCF7L2*), we limited the present analyses to SNPs associated with insulin resistance (7 SNPs) and/or at least two other components of the metabolic syndrome (7 SNPs). We used the web-based SNP Annotation and Proxy Search (SNAP) tool to determine R^2 values between loci from HapMap release 22 and to identify proxy SNPs when data for the index SNP were not available (www.broadinstitute.org/mpg/snap/index.php).[26] The seven SNPs previously shown to be associated with IR are rs1260326 near *GCKR*, rs7578326 and rs4675095 near *IRS1*, rs35767 near *IGF1*, rs6926728 near *ENPP1*, rs9939609 near *FTO*, and rs11152213 near *MCR4*. We identified rs6926728 near *ENPP1* as a proxy for the index rs1044498 [$R^2 = 1.0$ in the Centre d'Etude du Polymorphisme Humain Utah (CEU) population and 0.342 in the Yoruba in Ibadan (YRI) population]. The two SNPs near *IRS1* (rs7578326 and rs4675095) are not in linkage disequilibrium (LD) ($R^2 < 0.0001$). Even though large consortia meta-analyses have not reported variants near *ENPP1*, we included it in our analysis because of strong prior associations of rs1044498 with IR.[27–29] The C allele at rs1260326 near *GCKR* is associated with higher IR and lower TG levels[30]; we therefore used the T alleles at this locus as the risk alleles in analyses of TG levels. Two of the seven SNPs associated with IR are also associated with increased BMI (rs9939609 near *FTO* and rs11152213 near *MCR4*). We chose an additional SNP associated with TG (rs174550 near *FADS1*),[13] which has also been associated with higher fasting glucose.[12] Similar to the *GCKR* locus, the C variant at rs174550 is associated with higher TG levels, and the T variant is associated with higher fasting glucose. Genotyping was performed with the iPLEX assay on the MassARRAY platform (Sequenom, San Diego, CA).[31] The minimum call rate was 98.1%, and all SNPs were in Hardy–Weinberg equilibrium (HWE) according to the NCHS criterion for weighted data (HWE is rejected if $P < 0.01$ in at least two of the three race/ethnic groups).

Statistical analyses

We calculated sample-weighted allele frequencies for each risk allele overall and by race/ethnic group and then compared the frequencies across the three groups with chi-squared testing. We recalculated sample weights using previously described methods to avoid nonresponse bias from the collection of DNA only in a subset of NHANES III participants.[32] For comparison, we reported the corresponding allele frequencies from the CEU, YRI, and Mexican (MEX) populations from the International HapMap Project Phase II + III (http://hapmap.ncbi.nlm.nih.gov/cgi-perl/gbrowse/

Table 1. Eight Loci Associated with Metabolic Syndrome Traits in Prior Studies

Nearest gene and chromosome		*SNP*	*Risk allele*	*Direction of effect*	*Traits*	*Reported P value*	*Sample size*
GCKR	2	rs1260326	C	−	TG[37]*	1×10^{-15}	2,931
				−	CRP[38]	3.6×10^{-14}	6,345
				+	T2D[39]*	0.01	8,769
				+	IR[12]*	3.0×10^{-24}	94,636
				+	FG[30]	3×10^{-56}	46,549
IRS1	2	rs7578326	A	+	CAD[40]**	1.2×10^{-5}	2,801
				+	T2D[41]***	9.3×10^{-12}	14,051
				+	IR[41]***	0.007	14,358
		rs4675095	T	+	FI[12]	0.0039	91,210
ENPP1	6	rs6926728	G	+	BMI[27]†	0.01	6,147
				+	T2D[27]†	2×10^{-5}	6,147
				+	FG[28]††	0.01	2,511
				+	IR[28]††	0.006	2,511
FADS1	11	rs174550	T	−	FG[12]	1.7×10^{-15}	118,908
				+	TG[13]†††	2×10^{-14}	38,846
				−	HDL[13]†††	2×10^{-12}	40,330
IGF1	12	rs35767	G	+	IR[12]	2.2×10^{-9}	93,141
FTO	16	rs9939609	A	+	BMI[7]	3×10^{-35}	30,081
				+	T2D[7]	9×10^{-6}	9,103
				−	TG[16]	0.025	17,037
				+	HDL[16]	0.009	17,037
				+	FG[16]	0.044	17,037
				+	FI[16]	0.003	17,037
				+	WC[16]	9×10^{-15}	17,037
				+	CAD[42]	2×10^{-4}	4,897
MCR4	18	rs11152213	C	+	BMI[8]	2.8×10^{-15}	16,876
				+	IR[15]§	3.2×10^{-6}	11,955
				+	MetS[15]§	2.3×10^{-4}	11,955
				+	TG[15]§	0.05	11,955
				−	HDL[15]§	0.002	11,955
				+	WC[15]§§	1.7×10^{-9}	14,639

Previous associations are shown with reported *P* values and sample sizes.
*Association reported for rs780094 ($R^2=0.932$ with rs1260326 in CEU).
**Association reported for rs2943634 (R^2 0.93 with rs7578326 in CEU).
***Association reported for rs2943641 (R^2 0.74 with rs7578326 in CEU).
†Association reported for risk haplotype containing three variants.
††Association reported for rs1044498 (R^2 1.0 with rs6926728 in CEU).
†††Association reported for rs174547 (R^2 1.0 with rs174550 in CEU).
§Association reported for rs12970134 (R^2 0.81 with rs11152213 in CEU).
§§Association reported for rs2229616 (R^2 0.004 with rs11152213 in CEU).
BMI, body-mass index; CAD, coronary artery disease; CRP, C-reactive protein; FG, fasting glucose; FI, fasting insulin; HDL, high-density lipoprotein; IR, insulin resistance; TG, triglycerides; T2D, type 2 diabetes; WC, waist circumference; CEU, Centre d'Etude du Polymorphisme Humain Utah population.

hapmap28_B36/#search). We used linear regression analysis with adjustment for age and sex to model the effect of each risk allele on BMI, WC, log-transformed HOMA-IR, and log-transformed TG level, depending on the trait(s) with which each had been previously associated. For modeling, we assumed an additive relationship (allelic model) between the risk alleles from prior reports and the trait of interest. We then used age- and sex-adjusted logistic regression to model the association between each risk allele and the odds of metabolic syndrome in all subjects. We modeled the effect sizes of each SNP in each race/ethnic group individually and then, to test for effect modification by race/ethnic group, in the total population. To evaluate the possibility of non-observed traits underlying the aggregation of observed metabolic syndrome traits, we performed principal components analysis on the four traits of interest (logHOMA-IR, logTG, BMI, and WC) using an eigenvalue of 1 as the extraction method and varimax rotation. Only one principal component had an eigenvalue greater than 1 and had loading for WC, BMI, logHOMA-IR, and logTG of 0.92, 0.90, 0.80, and 0.49, respectively.

Similar to the analyses of metabolic syndrome traits, we used linear regression to model the effect of each SNP on the first principal component (a continuous outcome), in addition to any interaction by race/ethnic group. Statistical tests in linear and logistic regression models were based on Satterthwaite-adjusted *F* statistics. We used SUDAAN v.10.0 (RTI, Research Triangle Park, NC) and SAS v. 9.2 (SAS Institute Inc, Cary, NC) software for these analyses. For the four quantitative traits, within-race SNP effects were considered significant at $P<0.001$ (0.05/48, where 48 is the product of the 16 trait-SNP associations and the 3 race/ethnic groups) and SNP-race/ethnic interactions at $P<0.0016$ (0.05/32, where 32 is the product of the 16 trait-SNP associations and the 2 race/ethnic groups other than the reference non-Hispanic white group). SNP-race/ethnic

interactions for metabolic syndrome were considered significant at $P < 0.0031$ (0.05/16, where 16 is the product of the 8 SNPs and the 2 nonreference race/ethnic groups). In principal component analysis, main SNP effects were considered significant at $P < 0.0021$ (0.05/24, where 24 is the product of 8 SNPs in 3 race/ethnic groups) and SNP-race/ethnic group interactions were considered significant at $P < 0.0031$ (0.05/16, where 16 is the product of 8 SNPs and 2 nonwhite race/ethnic groups).

Results

Of 3,030 nondiabetic NHANES III participants, 24% met criteria for metabolic syndrome. Table 2 shows the metabolic characteristics of subjects stratified by race/ethnic group. The prevalences of the eight risk alleles are shown in Table 3. Each varied significantly by race/ethnicity ($P < 0.0001$ for all chi-squared analyses). The risk allele frequencies in non-Hispanic whites, non-Hispanic blacks, and Mexican Americans were largely similar to those from the CEU, YRI, and MEX populations in HapMap Phase II+III, respectively. If the C allele at rs1260326 near *GCKR* (higher IR) and the C allele at rs174550 near *FADS1* (higher TG) are considered the risk alleles, then three of the eight risk alleles were the major alleles in non-Hispanic whites, whereas four were the major alleles in non-Hispanic blacks and Mexican Americans. We observed particularly large between-group differences in the allele frequencies of rs6926728 near *ENPP1*, rs4675095 near *IRS1*, and rs174550 near *FADS1*, with non-Hispanic blacks typically being the most discordant.

Within each race/ethnic group, none of the eight SNPs was associated with any of the four quantitative traits at the $P < 0.0001$ level (Table 4). Overall, however, the directionality of the SNP effects within each race/ethnic group was consistent with their previously reported associations; that is, each copy of a given risk allele from previous reports increased IR, TG, WC, and/or BMI. There are three notable observations. First, there was little evidence for the effects of IR-associated variants in non-Hispanic blacks. Second, the two main risk alleles for TG levels (rs1260326 and rs174550) seemed to have particularly strong effects in Mexican Americans, the group with the lowest mean TG level. Both allelic associations had $P < 0.05$ but did not meet our corrected threshold for significance. Third, the effects of obesity-associated variants rs9939609 near *FTO* and rs11152213 near *MCR4* seemed to have much stronger effects in non-Hispanic whites than in the other two race/ethnic groups. Still, no between-group differences were significant.

In age- and sex-adjusted logistic regression models, none of the individual risk alleles was associated with a significant increase of the odds of metabolic syndrome (all $P > 0.05$), in the overall population or in individual race/ethnic groups, and no SNP-race/ethnic group interaction was significant at the prespecified $P < 0.0031$ level for metabolic syndrome. In principal components analysis, the first principal component had an eigenvalue of 2.53 and explained 63% of the variance in logHOMA-IR, logTG, BMI, and WC. In additive linear regression models, no SNP was significantly associated with this first principal component, and no SNP-race/ethnic group interaction was significant (Supplementary Table S1 available online at www.liebertonline.com/met).

Discussion

In the present study, we have reported the U.S. nationally representative prevalences and allelic effects of eight risk alleles associated with traits of the metabolic syndrome: IR, TG levels, BMI, and WC. We confirmed that the RAFs at these eight loci vary significantly between non-Hispanic whites, non-Hispanic blacks, and Mexican Americans but are similar to corresponding HapMap populations. With a few exceptions, we observed directionality of effects consistent with results from previous GWAS consortia. We did not find conclusive evidence that these effects vary by race/ethnic group, although we observed the greatest consistency in non-Hispanic whites, the group who is most ancestrally similar to the populations in which these variants were discovered. Our data suggest that rs1260326 near *GCKR* and rs174550 near *FADS1* may be more strongly associated with TG levels in Mexican Americans and non-Hispanic blacks than in non-Hispanic whites. The A allele at rs9939609 in *FTO* may be more strongly associated with BMI in non-Hispanic whites than in the non-Hispanic blacks or Mexican Americans. No one SNP predicted metabolic syndrome in any race/ethnic group.

Table 2. Phenotypic Traits by Race in National Health and Nutrition Examination Survey III

	Non-Hispanic Whites n = *1,226*	*Non-Hispanic Blacks* n = *898*	*Mexican Americans* n = *906*
Sex (% female)	51.4% (47.9%–55.0%)	55.9% (52.4%–59.5%)	46.7% (43.0%–50.4%)
Age (years)	44 (43–45)	40 (39–41)	36 (35–37)
Prevalence of metabolic syndrome	24.8% (21.9%–27.7%)	17.7% (15.1%–20.3%)	25.7% (22.4%–29.0%)
Body mass index (kg/m^2)	26.4 (26.0–26.8)	27.9 (27.5–28.4)	27.5 (27.2–27.9)
Waist circumference (cm)	91.2 (90.2–92.2)	92.2 (91.2–93.3)	91.9 (91.0–92.9)
Fasting glucose (mg/dL)	93 (93–94)	92 (91–93)	94 (94–95)
Fasting insulin (μU/mL)	9.5 (9.0–10.0)	11.7 (11.06–12.24)	11.9 (11.1–12.7)
HOMA-IR (mg/dL)(μU/mL)	2.2 (2.1–2.3)	2.7 (2.5–2.9)	2.8 (2.6–3.0)
Triglycerides (mg/dL)	161 (131–191)	186 (127–245)	160 (137–184)

Sample-weighted phenotypic traits [mean or proportion and 95% confidence interval (CI)] by race in 3,030 nondiabetic participants of the National Health and Nutrition Examination Survey (NHANES III). Metabolic syndrome is defined as any of the following criteria: Waist circumference > 88 cm in women or > 102 cm in men, serum triglycerides ≥ 150 mg/dL, HDL < 40 mg/dL in men or < 50 mg/dL in women, blood pressure ≥ 130/ ≥ 85 or antihypertensive medications, and fasting glucose ≥ 100 mg/dL.

HOMA-IR, homeostasis model of assessment of insulin resistance.

Table 3. National Health and Nutrition Examination Survey III Risk Allele Frequencies of Eight Loci Associated with Metabolic Syndrome Traits

SNP, nearest gene, chromosome, and risk allele				Risk allele frequencies: Non-Hispanic whites n = 1,226	CEU	Non-Hispanic blacks n = 898	YRI	Mexican Americans n = 906	MEX	P value
rs1260326	*GCKR*	2	C	57% (55%–59%)	58%	84% (82%–86%)	90%	65% (62%–68%)	66%	< 0.0001
rs7578326	*IRS1*	2	A	62% (60%–65%)	65%	57% (55%–60%)	60%	73% (70%–75%)	76%	< 0.0001
rs4675095	*IRS1*	2	T	5.9% (4.9%–7.0%)	6.7%	2.1% (1.4%–2.9%)	0%	19% (17%–21%)	17%	< 0.0001
rs6926728	*ENPP1*	6	G	13% (12%–15%)	12%	65% (62%–67%)	81%	17% (15%–19%)	NA	< 0.0001
rs174550	*FADS1*	11	T	33% (31%–36%)	35%	10% (9%–12%)	2%	61% (58%–64%)	NA	< 0.0001
rs35767	*IGF1*	12	G	85% (83%–86%)	86%	57% (55%–60%)	55%	77% (75%–79%)	69%	< 0.0001
rs9939609	*FTO*	16	A	40% (37%–42%)	46%	47% (45%–50%)	50%	25 (23%–28%)	23%	< 0.0001
rs11152213	*MCR4*	18	C	24% (22%–26%)	29%	28% (25%–30%)	32%	12% (10%–13%)	NA	< 0.0001

Risk allele frequencies [95% confidence interval (CI)] in 3,030 nondiabetic participants of the National Health and Nutrition Examination Survey III (NHANES III), presented with corresponding frequencies from CEU, YRI, and MEX populations from Phase II + III of the International HapMap Project for comparison (http://hapmap.ncbi.nlm.nih.gov/cgi-perl/gbrowse/hapmap28_B36/#search). *P* values correspond to chi-squared comparisons across three race/ethnic groups in NHANES III.

SNP, single-nucleotide polymorphism; NA, not available; CEU, Centre d'Etude du Polymorphisme Humain Utah; YRI, Yoruba in Ibadan; MEX, Mexican population.

Other work has detected such variation by race/ethnic group. Variants in the *FTO* gene, for example, have been shown to have strong effects on adiposity and type 2 diabetes (T2D) risk in whites in the Atherosclerosis Risk in Communities (ARIC) Study but less so in blacks.[33] Consistent with the ARIC study, we do note that the A allele of rs9939609 in *FTO* seems most strongly associated with BMI in non-Hispanic whites and less so in non-Hispanic blacks and Mexican Americans. Our observations of rs1260326 near *GCKR* are also consistent with previous work by the Diabetes Genetics Initiative (DGI) showing that the C alleles at rs780094 and rs1260326 are associated with higher IR, whereas the T alleles at these loci are associated with higher TG levels.[30] The DGI has shown that the associations between these two *GCKR* loci and metabolic traits are similar across GWAS from populations of different race/ethnicity,

Table 4. Effect Modification by Race/Ethnic Group on Genetic Associations Between Metabolic Syndrome Qualitative Traits and Eight Risk Loci in the National Health and Nutrition Examination Survey III

SNP, risk allele, and nearest gene			Non-Hispanic whites: Effect size	$P_{main\ effect}$	Non-Hispanic blacks: Effect size	$P_{main\ effect}$	$P_{interaction}$	Mexican American: Effect size	$P_{main\ effect}$	$P_{interaction}$
Log HOMA-IR										
rs1260326	C	*GCKR*	0.056	0.051	0.060	0.11	0.73	0.053	0.13	0.98
rs7578326	A	*IRS1*	0.032	0.24	−0.017	0.61	0.36	0.091	0.013	0.15
rs4675095	T	*IRS1*	0.086	0.19	−0.055	0.41	0.11	0.0046	0.91	0.29
rs6926728	G	*ENPP1*	0.033	0.39	−0.039	0.26	0.13	−0.028	0.49	0.28
rs35767	G	*IGF1*	−0.0089	0.83	0.031	0.34	0.49	0.043	0.29	0.39
rs9939609	A	*FTO*	0.062	0.033	−0.010	0.77	0.16	−0.043	0.26	0.040
rs11152213	C	*MCR4*	0.0085	0.81	0.012	0.71	0.93	−0.058	0.23	0.34
Log triglycerides										
rs1260326	T	*GCKR*	0.0028	0.93	0.080	0.088	0.12	0.075	0.026	0.075
rs174550	C	*FADS1*	0.049	0.12	0.073	0.15	0.64	0.084	0.0029	0.46
rs9939609	A	*FTO*	−0.012	0.71	−0.0050	0.89	0.99	−0.038	0.37	0.40
rs11152213	C	*MCR4*	0.024	0.53	0.027	0.42	0.99	−0.0025	0.96	0.73
BMI										
rs6926728	G	*ENPP1*	0.42	0.34	−0.28	0.40	0.18	0.017	0.96	0.46
rs9939609	A	*FTO*	0.52	0.060	0.012	0.97	0.32	−0.039	0.90	0.22
rs11152213	C	*MCR4*	0.31	0.34	0.015	0.97	0.51	−0.57	0.16	0.12
Waist circumference										
rs9939609	A	*FTO*	1.17	0.078	−0.32	0.70	0.25	−0.070	0.93	0.29
rs11152213	C	*MCR4*	0.89	0.28	0.18	0.83	0.56	−0.14	0.89	0.56

Effect modification by race/ethnic group of eight risk single-nucleotide polymorphisms (SNPs) on log homeostasis model assessment of insulin resistance (logHOMA-IR), log triglycerides (logTG), body mass index (BMI), and waist circumference. Effects sizes are presented as beta coefficients for each SNP in age/sex-adjusted allelic linear regression models performed separately in each race/ethnic group. *P* values correspond to those beta coefficients ($P_{\text{main effect}}$) and race/ethnic group–SNP interaction terms from models run in the entire multiethnic sample with whites as the referent group ($P_{\text{interaction}}$).

although these associations seem most robust in white populations. Although not statistically significant, our results are consistent with the T allele of rs1260326 having the strongest association with higher TG levels in Mexican Americans and non-Hispanic blacks compared to non-Hispanic whites. This allele is most prevalent in non-Hispanic blacks, whereas the C risk allele for TG levels at rs174550 is most prevalent in Mexican Americans. Of note, a recent report of other loci associated with TG levels found no differences in effect sizes among the three race/ethnic groups in NHANES III.[34]

That no one SNP in our study predicted metabolic syndrome is consistent with previous work. Sjögren et al. examined whether 17 variants associated with T2D and 10 variants associated with at least two components of metabolic syndrome (including *FTO* rs9939609, *GCKR* rs1260326, and *ENPP1* rs1044498) predicted incident metabolic syndrome in the longitudinal Malmö Preventive Project with more than 16,000 participants.[35] Of these 27 variants, only rs7903146 in *TCF7L2* predicted metabolic syndrome after correction for multiple testing, although rs9939609 in *FTO* had an odds ratio for metabolic syndrome of 1.02–1.14 ($P = 0.0065$), mediated predominantly through its effects in BMI.

The present study is the first report of the associations between these risk alleles and metabolic syndrome–related traits in a multiethnic U.S. nationally representative sample. Undertakings such as the present analyses will have increasing importance as new genetic discoveries find clinical and public health application. Although each discovery of a variant associated with metabolic syndrome–related traits might uncover new pathogenic molecular pathways, the applicability of those findings rests on their prevalence and generalizability in the wider population. GWAS are generally conducted in ethnically homogeneous population samples, in which the risk of population stratification is minimized.[36] As a result, any findings from these GWAS consortia may not be generalizable to all racial groups. Because the metabolic syndrome particularly burdens racial/ethnic minorities, it is important to examine genetic associations in these groups as well.

The ongoing efforts in cataloging the genotypes of more race/ethnic groups will further contribute to our understanding of how genetic risk is distributed in diverse populations. This will be particularly important for African populations, whose older age has resulted in greater genetic diversity that will only be fully captured with larger genotyping efforts. The same can be said for Mexican Americans and other genetically heterogeneous Latino groups. Cataloging the frequencies of risk alleles in different race/ethnic groups may not be sufficient, however, if those alleles carry different levels of risk in those groups. The present study and others give evidence that differences exist in the frequencies and effects of risk alleles for metabolic syndrome-related traits among race/ethnic groups. Although not tested here, these race/ethnic differences in the genetic architecture of the metabolic syndrome may in part explain the tendency of African Americans to have greater insulin resistance and risk for T2D and coronary disease relative to their adiposity, HDL-C, and triglyceride levels.[37–39]

Our study has certain limitations of note. Our limited sample size likely did not allow sufficient power to detect the small effect sizes of these variants on quantitative metabolic traits in each of the three race/ethnic groups. As a result, no SNP effect or race/ethnic difference, if present, met our prespecified levels of statistical significance, corrected *a priori* for multiple testing to minimize the risk of false-positive associations. The directionality of our results in non-Hispanic whites is largely consistent with previous GWAS consortia, but less so in non-Hispanic blacks and Mexican Americans. Nonetheless, our findings must be considered hypothesis generating only. Second, as with many studies of race and ethnicity, operationalized definitions can appear artificial. While we used the NHANES definitions of non-Hispanic white, non-Hispanic black, and Mexican American for the present analysis, we recognize that this categorization belies the genetic differences within racial groups (particularly African-Americans and Hispanics) and the genetic similarity between them. Moreover, self-reported race/ethnicity in NHANES III corresponds well, but not perfectly, to genetic assessment of ancestry. Until we have a more nuanced understanding of the genetic diversity of the American population, however, such designations remain useful for the study and improvement of public health. Third, the cross-sectional design of NHANES limits our ability to distinguish those participants who went on to develop IR, overweight, elevated TG levels, or metabolic syndrome after the study. If anything, this limitation would cause an underestimation of the disease burden in the population and an attenuation of the observed effect size of each SNP. Fourth, we only examined the SNPs discovered in European populations, which may not represent the causal variants. Differences in LD across the various ethnic groups may have prevented us from detecting the true association signal at each locus, tagged by the index SNP in Europeans but not in other ethnic groups. More detailed fine mapping across each region is necessary before a comparable effect can be detected or excluded in non-European populations.

The genetic architecture of the metabolic syndrome and its components is not yet widely applicable to the clinical setting, but the scientific community should aim to evaluate the generalizability of such discoveries to all race/ethnic groups. The present study contributes to that effort. As genomic information accumulates a large enough evidence base to be introduced into the clinic, it will be important to know whether that information applies uniformly to all patients, regardless of race/ethnicity. Beyond the clinic, if national guidelines for prevention, diagnosis, and treatment are to genomic discoveries, it will be similarly important that these guidelines are applied to the appropriate subpopulations, if applicable.

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Author Disclosure Statement

No competing financial interests exist for any of the authors.

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