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ORIGINAL ARTICLE

Generalization of adiposity genetic loci to US Hispanic women

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BACKGROUND: Obesity is a public health concern. Yet the identification of adiposity-related genetic variants among United States (US) Hispanics, which is the largest US minority group, remains largely unknown.
OBJECTIVE: To interrogate an *a priori* list of 47 (32 overall body mass and 15 central adiposity) index single-nucleotide polymorphisms (SNPs) previously studied in individuals of European descent among 3494 US Hispanic women in the Women's Health Initiative SNP Health Association Resource (WHI SHARe).
DESIGN: Cross-sectional analysis of measured body mass index (BMI), waist circumference (WC) and waist-to-hip ratio (WHR) were inverse normally transformed after adjusting for age, smoking, center and global ancestry. WC and WHR models were also adjusted for BMI. Genotyping was performed using the Affymetrix 6.0 array. In the absence of an *a priori* selected SNP, a proxy was selected ($r^2 \geqslant 0.8$ in CEU).
RESULTS: Six BMI loci (*TMEM18, NUDT3/HMGA1, FAIM2, FTO, MC4R* and *KCTD15*) and two WC/WHR loci (*VEGFA* and *ITPR2-SSPN*) were nominally significant ($P < 0.05$) at the index or proxy SNP in the corresponding BMI and WC/WHR models. To account for distinct linkage disequilibrium patterns in Hispanics and further assess generalization of genetic effects at each locus, we interrogated the evidence for association at the 47 surrounding loci within 1 Mb region of the index or proxy SNP. Three additional BMI loci (*FANCL, TFAP2B* and *ETV5*) and five WC/WHR loci (*DNM3-PIGC, GRB14, ADAMTS9, LY86* and *MSRA)* displayed Bonferroni-corrected significant associations with BMI and WC/WHR. Conditional analyses of each index SNP (or its proxy) and the most significant SNP within the 1 Mb region supported the possible presence of index-independent signals at each of these eight loci as well as at *KCTD15*.
CONCLUSION: This study provides evidence for the generalization of nine BMI and seven central adiposity loci in Hispanic women. This study expands the current knowledge of common adiposity-related genetic loci to Hispanic women.

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INTRODUCTION

Little is known about the etiologic factors underlying the high prevalence of obesity, particularly among United States (US) minority populations. Concurrent with the obesity epidemic, US demographics have dramatically shifted. As of 2010, US Hispanics represented approximately 16% of the nation to become its largest minority group.[1] Between 2009 and 2010, 41% of US Hispanic women were overweight or obese as compared with 32% of their non-Hispanic White counterparts,[2] with the most notable ethnic disparities occurring among Puerto Rican and Dominican women.[3] Thus, there is a rising impetus to investigate the underlying determinants of obesity among these populations.

In the past 5 years, genome-wide association studies (GWAS) have identified nearly 50 common genetic loci associated with body mass index (BMI)[4–6] and anthropometric measures of central adiposity (that is, waist circumference (WC) and waist-to-hip ratio (WHR))[7,8] in European middle-aged adult populations from Europe, Australia, and the US recent GWAS in non-European ancestry populations have identified additional novel loci, including four new BMI-associated loci among East Asians, of which at least two loci do not show association in individuals of European descent[3,7,9] and possibly three novel loci in a GWAS of BMI in individuals of African descent completed recently.[9–13] Targeted genotyping studies of selected variants have been undertaken in Hispanic Americans.[14] However, to date the contribution of genetic variants to adiposity traits in this diverse ethnic group remain largely unknown.

We investigated the associations of adiposity measures with previously identified European descent established genetic loci for BMI, WC and WHR among 3587 self-identified Hispanic women from the Women's Health Initiative (WHI) SNP (single-nucleotide polymorphism) Health Association Resource (SHARe).

MATERIALS AND METHODS

WHI SHARe participants

WHI consists of multiple components including an observational study and clinical trial cohorts of postmenopausal women in the US;[15] detailed

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recruitment and exclusion criteria have been described previously.[16] Medical histories were updated annually or semi-annually by questionnaire or by phone. All participating institutions obtained Institutional Review Board approval. WHI SHARe included a total sample of 3642 self-identified Hispanic subjects from WHI, who had consented to genetic research.

Phenotypes

All phenotypic information (for example, covariate and outcome variables) was obtained during the WHI baseline questionnaires and clinic examination. Weight was measured after removing shoes, heavy clothing and pocket contents using a calibrated digital scale and recorded to the nearest one-tenth of a kilogram. Height was taken using a wall-mounted stadiometer and recorded to nearest one-tenth of a centimeter. BMI was calculated from measured height and weight ($kg\,m^{-2}$) and was missing for 26 of the participants in our sample. WC was measured at the level of natural waist (narrowest part of torso, $n=14$ missing) and hips at top of the iliac crest with extra layers of clothes removed ($n=13$ missing) and recorded to nearest half-centimeter. WHR was then calculated as the ratio of waist to hip circumference ($n=16$ missing).

Genotypes

As described previously,[17] DNA was extracted by the Specimen Processing Laboratory at the Fred Hutchinson Cancer Research Center (FHCRC) using white blood cells that were collected at the time of enrollment of the subjects in WHI. Specimens were stored at a central biorepository at $-80\,^{\circ}C$ until analysis. Genotyping was done at Affymetrix, Inc. on the Affymetrix 6.0 array (Santa Clara, CA, USA), using $2\,\mu g$ DNA at a concentration of $100\,ng\,\mu l^{-1}$.

Quality control

Of the 3642 women in WHI SHARe who self-identified as Hispanic and consented for genetic testing, approximately 1% of their genetic samples could not be genotyped ($n=36$). We excluded samples that had call rates below 95%, which were duplicates of subjects other than their monozygotic twins, or that appeared to include a Y chromosome (that is, representing possible sample contamination, genotyping errors or an inconsistent genotypic sex; $n=19$). Furthermore, SNPs that were located on the Y chromosome or were Affymetrix QC probes (that is, not intended for analysis) were excluded ($n=3280$). SNPs with a call rate below 95% or concordance rate below 98% were flagged and excluded leaving 871 309 SNPs. These quality control measures left us with 3587 Hispanics and an average call rate of 99.8% across the 871 309 unflagged SNPs. We also excluded one person from identified relative pairs, prioritizing for complete genotype data ($n=93$), leading to a final analytic sample of 3494 self-identified Hispanic women.

Two hundred thirty-eight (2%) additional samples were genotyped as blind duplicates. We analyzed 188 pairs of blind duplicate samples. The overall concordance rate was 99.8% (range 95–100% over all samples, 98–100% across 871 309 SNPs that were included after genotype cleaning).

Admixture

Eigenvectors were computed in Eigenstrat[18,19] to account for global ancestry based on 178 101 markers, excluding mitochondria and sex chromosome markers, that were in common between WHI Hispanics samples and HapMap[20,21] and HGDP[22] reference panels. In particular, we excluded SNPs that were A/T or C/G, on the sex chromosomes, or in the mitochondria. Individuals included from HGDP panels were 225 East Asians and 63 Native Americans, specifically 8 Surui, 22 Mayans, 13 Karitiana, 14 Pima and 6 Colombian. We also estimated proportions of European, Native American and African ancestry (Supplementary Figure 1) in the unrelated WHI SHARe sample ($n=3494$) using Admixture 1.22 (http://www.genetics.ucla.edu/software/admixture).

Adiposity SNP selection

One SNP from each established adiposity locus (described as of 1 July 2012 with BMI WC or WHR in GWAS of European descent individuals) was selected. A total of 47 loci were selected; 32 loci previously associated with BMI and 15 loci previously associated with WC or WHR (Tables 2a and 3a). All selected SNPs from the original publications were those that had the lowest *P*-value and that met genome-wide significance within a predefined locus (typically defined as 1 Mb and $r^2<0.1$).

Generalization

We assessed generalization of previously established GWAS loci using a tiered approach. All SNPs analyzed here were originally reported in populations of European descent, so we define 'generalization' of a genetic effect when a SNP displays a direction of effect consistent with the original report and/or in terms of statistical significance as defined below.

First we interrogated the exact SNP from the published literature, which we defined as an 'index SNP'. All selected index SNPs met genome-wide significance level in prior publications. To assess the consistency of effects in our study, we accessed genome-wide publically available data from the Genetic Investigation of ANthropometric Traits (GIANT) Consortium on the risk allele and its frequency in their large sample of individuals of European descent. Loci previously described with overall or central adiposity were queried in the BMI and WHR adjusted for BMI GWAS results files, respectively. If this information was missing, then we supplemented it with the relevant publication to determine directional consistency. If the previously reported adiposity SNP was not genotyped as part of WHI SHARe, the WHI SHARe SNP in highest linkage disequilibrium (LD) with the previous reported SNP ($r^2\geqslant 0.8$ in Hap Map CEU phase II) was selected as a proxy of the index signal. Generalization of the index or proxy SNPs was declared when directional consistency and nominal statistical significance ($P<0.05$) were observed.

Owing to the extensive admixture in populations of self-identified Hispanic ancestry,[23,24] we also hypothesized that even if a SNP originally identified in European or East Asian ancestry populations is not associated with BMI in those within our cohort of women who report Hispanic ancestry, the locus may still show association with a different variant in the same chromosomal region. Therefore, we searched for common variants within the established loci that better captured the association of the index SNP reported in the European and Asian populations. We identified SNPs as potentially better markers of the index signal, 'index-dependent signals', if they were (1) within 1 Mb of the index SNP, (2) were dependent on the index SNP in the referent population ($r^2\geqslant 0.2$) and (3) were associated with the anthropometric traits in our data at a significance level that was at least one order of magnitude greater than the index SNP or its proxy. In contrast, we also interrogated the evidence for possible 'index-independent signals' by visual inspection of all *P*-values of SNP–anthropometric trait associations for 'SNPs of interest' with $r^2<0.2$ and within the 1 Mb region of the index SNP. Index-independent signals were deemed statistically significant if they displayed nominal significance after correcting for the total number of regions interrogated for each phenotype of interest (BMI: $P=0.05/32$ and WC/WHR: $P=0.05/15$). Conditional analyses were also conducted to confirm signal dependence. If adjustment for the index SNP decreased the *P*-value for the candidate index-independent signal, the SNP–phenotype association was considered suggestive evidence for an index-independent signal, without overwhelming proof that the signal was indeed independent. Certainly these signals need to be further interrogated with much larger sample sizes and/or fine mapping and within the different sub-populations of US Hispanic ancestry. In contrast, if the conditional *P*-value did not change or increased less than one order of magnitude in comparison with the unconditional *P*-value, then we declared this a possible index-independent signal. All conditional analyses were modeled in Stata 12 (StataCorp LP, College Station, TX, USA).

Statistical models

After adjusting for age, smoking status and clinical center, BMI residuals were inverse normally transformed. WC and WHR were adjusted for age, smoking status, clinical center as well as BMI, and then the residuals were inverse normally transformed. Inverse normal transformations entail creating a modified rank variable and then computing a new transformed value for the phenotype per subject such that the distribution of the phenotype is normalized with a mean of 0 and an s.d. of 1. For each of the three inverse normalized phenotypes (that is, BMI, WC adjusted for BMI and WHR adjusted for BMI) single marker linear associations further adjusted for the top 10 principal components assuming an additive model, were run using PLINK software v1.07.[25] Estimated *P*-values below 5×10^{-8} were considered to be genome-wide significant.

LD assessment

We considered signals independent if their LD was $r^2<0.2$ in a sample of 9345 individuals of European descent (primarily non-Hispanic Whites) from the Atherosclerosis Risk in Communities Study (ARIC). If information was

not available from ARIC then HapMap CEU data (phase II or III) were used to represent the LD structure of individuals of European descent and are specifically noted in Tables 2b and 3b. In addition, estimates of LD were calculated in WHI SHARe Hispanics. LD estimates for both ARIC and WHI SHARe were calculated using the PLINK software v1.07.[25]

Table 1. Characteristics of self-identified Hispanics in the WHI SHARe

	Full sample (N = 3587)		*Analytic sample (N = 3494)*	
	Number/ range	*%*	*Number/ range*	*%*
Gender				
Women	3587	100.0%	3494	100.0%
Men				
Age at assessment				
50–59 years	1803	50.3%	1751	50.1%
60–69 years	1415	39.4%	1387	39.7%
70–79 years	369	10.3%	356	10.2%
Missing				
Hispanic ethnic subgroup[a]				
Mexican, Chicano, Mexican-American	1541	43.0%	1485	42.5%
Puerto Rican	369	10.3%	361	10.3%
Cuban	255	7.1%	252	7.2%
Other	814	22.7%	806	23.1%
No subgroup indicated	162	4.5%	159	4.6%
Missing	446	12.4%	431	12.3%
Study participation				
Observational study only	1729	48.2%	1681	48.1%
Clinical trial	1858	51.8%	1813	51.9%
Hormone replacement trial	980	27.3%	953	27.3%
Control arm	472	13.2%	463	13.3%
Dietary modification trial	1202	33.5%	1175	33.6%
Control arm	730	20.4%	715	20.5%
Calcium/vitamin D trial	1057	29.5%	1025	29.3%
Control arm	495	13.8%	479	13.7%
Missing				
US region				
Northeast	448	12.5%	441	12.6%
South	1459	40.7%	1422	40.7%
Midwest	136	3.8%	133	3.8%
West	1544	43.0%	1498	42.9%
Missing				
Marital status				
Never married	153	4.3%	149	4.3%
Divorced or separated	750	20.9%	735	21.0%
Widowed	478	13.3%	463	13.3%
Presently married	2076	57.9%	2020	57.8%
Marriage-like relationship	85	2.4%	82	2.3%
Missing	45		45	
Education				
No formal to incomplete high school	816	22.7%	802	23.0%
High school diploma or equivalent	1914	53.4%	1857	53.1%
College or higher degree	802	22.4%	781	22.4%
Missing	55		54	
Body mass index[b]				
Mean (s.d.)	28.88 (5.59)		28.87 (5.59)	
Underweight ($<18.5\,kg\,m^{-2}$)	7	0.2%	7	0.2%
Normal ($18.5–24.9\,kg\,m^{-2}$)	889	24.8%	871	24.9%
Overweight ($25–29.9\,kg\,m^{-2}$)	1387	38.7%	1344	38.5%
Obesity ($30–34.9\,kg\,m^{-2}$)	828	23.1%	806	23.1%
Obesity II ($35–39.9\,kg\,m^{-2}$)	300	8.4%	294	8.4%
Extreme obesity ($\geqslant 40\,kg\,m^{-2}$)	150	4.2%	146	4.2%
Missing	26		26	
Waist circumference (cm)				
Mean (s.d.)	86.60 (12.30)		86.58 (12.31)	
1st quartile	62–78		62–78	
2nd quartile	79–85		79–85	
3rd quartile	86–94		86–94	
4th quartile	95–125		95–125	
Missing	14		14	

Power

We calculated estimates of power to detect associations of similar magnitude among Hispanics as those previously described in European populations across a range of common minor allele frequencies. These calculations assumed an additive genetic model, an independent sample of 3494 women, the same Bonferroni corrections and phenotype distribution as observed in our sample of US Hispanic women. Based on effect sizes published in European populations, power to detect associations was less among measures of overall (BMI) than for central adiposity (WC and WHR; Supplementary Figure 2). For example, at the minor allele frequency and previously reported effect size of *FTO* (32% and beta = $0.39\,kg\,m^{-2}$ change per T allele)[4] we would at best have 40% statistical power to detect this effect in our study. Similarly, power to detect associations of all other BMI loci was below 80%. Moderately common WC variants (>20%) would be expected to have >80% power at mid-sized effects, which was approximately 1 cm change in WC per effect allele; whereas, most common WHR variants (>5%) frequent would be expected to have >80% power at far smaller effect sizes (approximately 0.011 WHR units). Power calculations were calculated using QUANTO v1.2.4 (http://hydra.usc.edu/gxe/).

RESULTS

The final analytic sample of self-identified Hispanic women included in this sample was 3494. As shown in Table 1, the largest percentage of the women in this sample were between 50 and 59 years of age with a high school diploma or equivalent, were married, of Mexican ancestry, overweight in the absence of abdominal obesity as defined by the World Health Organization[26–28] and were participants in a clinical trial from one of the Western or Southern WHI study centers.

Adiposity SNP generalization

Although no SNPs reached genome-wide significance in this study, we were able to investigate the associations at 47 established obesity loci previously identified in European populations with BMI, WC and WHR in our sample of Hispanic women (Tables 2b and 3b). As summarized in Figure 1, among 16 loci with

Table 1. (Continued)

	Full sample (N = 3587)		*Analytic sample (N = 3494)*	
	Number/ range	*%*	*Number/ range*	*%*
Hip circumference (cm)				
Mean (s.d.)	105.84 (11.14)		105.83 (11.13)	
1st quartile	85–98		85–98	
2nd quartile	99–104		99–104	
3rd quartile	105–112		105–112	
4th quartile	113–144		113–144	
Missing	13		13	
WHR[a]				
Mean (s.d.)	0.82 (0.07)		0.82 (0.07)	
No abdominal obesity (WHR $\leqslant$ 0.85)	2476	69.0%	2413	69.1%
Abdominal obesity (WHR $\geqslant$ 0.85)	1095	30.5%	1065	30.5%
Missing	16		16	

Abbreviations: WHO, World Health Organization; WHR, waist-to-hip ratio; WHI SHARe, Women's Health Initiative SNP Health Association Resource. [a]The other category may include. [b]Overweight and obesity as defined by the WHO expert consultation. Appropriate body mass index for Asian populations and its implications for policy and intervention strategies. The Lancet, 2004; 157–163. Waist Circumference and Waist-Hip Ratio, Report of a WHO Expert Consultation". World Health Organization. 8–11 December 2008. Retrieved 21 March 2012.

Table 2a. Significance level of loci associated with BMI and/or weight from published GWAS studies in European descent men and women and the GIANT consortium

Index or proxy SNP	*In/near gene*	*Chr*	*BP position*	*Phenotype*	*GWAS P-value*		*Risk allele*	*Risk allele frequency HapMap CEU*	*GIANT P-value*
rs2815752	*NEGR1*	1	72524461	BMI	1.61E–22	[6]	A	0.62	1.17E–14
rs1514175	*TNNI3K*	1	74764232	BMI	8.16E–14	[6]	A	0.57	1.41E–09
rs1555543	*PTBP2*	1	96717385	BMI	3.68E–10	[6]	C	0.58	7.81E–07
rs543874	*SEC16B*	1	176156103	BMI	3.56E–23	[6]	G	0.19	1.66E–13
rs6548238	*TMEM18*	2	624905	BMI	3.20E–26	[2]	C	0.88	1.02E–20
rs713586	*RBJ/ADCY3/POMC*	2	25011512	BMI	6.17E–22	[6]	C	0.52	2.51E–07
rs759250[a]	*FANCL*	2	59182657	BMI	1.79E–12	[6]	A	0.32	5.34E–06
rs2121279[b]	*LRP1B*	2	142759755	BMI	1.35E–10	[6]	T	0.12	1.37E–06
rs13098327[c]	*CADM2*	3	85902871	BMI	3.94E–11	[6]	A	0.18	1.14E–07
rs1516728[d]	*ETV5/SFRS10/DGKG*	3	187312585	BMI and weight	7.20E–11	[1]	A	0.78	9.50E–11
rs12641981[e]	Gene desert; *GNPDA2*	4	44874640	BMI	3.78E–31	[6]	T	0.43	7.34E–17
rs3797580[f]	*FLJ35779/HMGCR*	5	75038812	BMI	2.17E–13	[6]	A	0.64	1.92E–07
rs6864049[g]	*ZNF608*	5	124358421	BMI	1.97E–09	[6]	G	0.43	3.73E–06
rs987237[h]	*PRL*	6	50911009	BMI and obesity	1.40E–05	[5]	G	0.09	5.97E–16
rs9366426	*TFAP2B*	6	22172618	BMI	2.90E–20	[6]	C	0.60	6.00E–01
rs3798560[i]	*NUDT3/HMGA1*	6	34451544	BMI	3.02E–08	[6]	C	0.17	5.25E–06
rs10508503	*PTER*	10	16339957	BMI and obesity	2.10E–07	[5]	C	0.93	6.40E–01
rs10840083[j]	*RPL27A/ TUB*	11	8565212	BMI	2.80E–09	[6]	A	0.6	1.92E–07
rs10501087	*BDNF/LGR4/LIN7C*	11	27626684	BMI and weight	8.70E–11	[1]	T	0.8	1.41E–12
rs3817334	*MTCH2*	11	47607569	BMI	1.59E–12	[6]	T	0.45	4.79E–11
rs7138803	*FAIM2* (and *BCDIN3D*)	12	48533735	BMI and weight	1.82E–17	[6]	A	0.44	3.96E–11
rs7988412[k]	*MTIF3*	13	26898282	BMI	9.48E–10	[6]	T	0.23	2.57E–06
rs10151686[l]	*PRKD1*	14	29536217	BMI	5.76E–11	[6]	A	0.03	6.62E–08
rs17109221[m]	*NRXN3*	14	78979872	BMI	2.75E–11	[6]	T	0.27	2.31E–07
rs8054079[n]	*GPRC5B/IQCK*	16	19882908	BMI	2.91E–21	[6]††	C	0.13	2.91E–21
rs8049439	*SH2B1*	16	28745016	BMI and weight	1.40E–09	[1]	C	0.37	1.48E–09
rs9939609	*FTO*	16	52378028	BMI	4.90E–74	[2]	A	0.45	9.94E–60
rs9921354[o]	*MAF*	16	78240951	BMI and obesity	3.80E–13	[5]	T	0.51	2.57E–01
rs1652376[p]	*NPC1*	18	19363464	BMI and obesity	2.90E–07	[5]	G	0.51	9.14E–04
rs571312	*MC4R*	18	55990749	BMI	6.43E–42	[6]	A	0.28	2.14E–22
rs11084753	*KCTD15*	19	39013977	BMI	4.50E–12	[2]	G	0.63	3.62E–09
rs8101149[q]	*TMEM160/ZC3H4*	19	52292281	BMI	1.64E–12	[6]	A	0.68	2.48E–06

Abbreviations: BMI, body mass index; BP, base pair; Chr, chromosome; GIANT, Genetic Investigation of ANthropometric Traits Consortium; GWAS, genome-wide association study; SNP, single-nucleotide polymorphism. ††As data were missing for rs8054079 in the publically available sources, information on rs12444979 was extracted from Speliotes *et al.* In this case, because of the tight linkage disequilibrium between the two variants we inferred that the lowester frequent allele at rs80504079 would increase BMI. [a]Proxy SNP for rs887912, $r^2 = 1$; [b]Proxy SNP for rs2890652, $r^2 = 0.8$; [c]Proxy SNP for rs13078807, $r^2 = 1$; [d]Proxy SNP for rs7647305, $r^2 = 0.8$; [e]Proxy SNP for rs1093897, $r^2 = 1$; [f]Proxy SNP for rs2112347, $r^2 = 0.9$; [g]Proxy SNP for rs4836133, $r^2 = 1$; [h]Proxy SNP for rs4712652, $r^2 = 0.9$; [i]Proxy SNP for rs206936, $r^2 = 1$; [j]Proxy SNP for rs4929949, $r^2 2 = 0.9$; [k]Proxy SNP for rs4771122, $r^2 = 0.9$; [l]Proxy SNP for rs11847697, $r^2 = 0.8$; [m]Proxy SNP for rs10150332, $r^2 = 1$; [n]Proxy SNP for rs12444979, $r^2 = 0.9$; [o]Proxy SNP for rs1424233, $r^2 = 1$; [p]Proxy SNP for rs1805081, $r^2 = 0.9$; [q]Proxy SNP for rs3810291, $r^2 = 0.9$. Published results from studies of individuals of European decent: [1] Thorleifsson *et al.*; [2] Willer *et al.*; [3] Lindgren *et al.*; [4] Heard-Costa *et al.*; [5] Meyre *et al.*; [6] Speliotes *et al.*; [7] Heid *et al.*

evidence of generalization 7 were defined as 'index-dependent signals'. Of these seven, five loci were best represented by the index SNP (or its proxy) and two by a better marker in the region (defined as 'other index-dependent signal'). A total of nine loci displayed, at least, suggestive evidence for index-independent signals as the SNP in these loci with the lowest *P*-value were in low LD with the index signals previously described among European descent individuals and remained nominally significant after adjustment for the index SNP (or its proxy) in conditional analyses.

Among the 32 BMI index signals interrogated in this study, 25 had consistent directions of association as compared with publically available GIANT BMI results, which is more than expected by chance (binomial $P = 2.4 \times 10^{-3}$). The five loci (reported above) with either evidence of generalization at the index or proxy SNP, or evidence of a better marker displayed consistent directions of effect with BMI. Among the 15 central adiposity index signals interrogated in this study, 13 had consistent directions of effects at the WC index SNP or their proxies (more than expected by chance, binomial $P = 3.2 \times 10^{-3}$) and all had consistent directions of effect at the WHR index SNP or its proxy (binomial $P = 3.1 \times 10^{-5}$), as compared with publically available GIANT WHR adjusted for BMI results. WC/WHR loci with either evidence of generalization at the index or proxy SNP, or evidence of a better marker displayed consistent direction of effects with the central adiposity phenotype, for which they were previously reported.

Among index or proxy SNPs selected, the BMI phenotype showed the strongest association with rs9939609 in the *FTO* locus (beta (s.e.) = 0.085 (0.026); $P = 0.001$), followed rs11084753 in the *KCT615* locus (beta (s.e.) = −0.070 (0.025); $P = 0.006$). Other nominally significant ($P < 0.05$) loci were found for *MC4R* (rs571312), *NUDT3/HMGA1* (rs378560), *FAIM2* (rs7139903) and *TMEM18* (rs6548238). Again, among the index or proxy SNPs selected, the strongest association with WC and WHR was found with rs60905288 near *VEGFA* (WC: beta (s.e.) = −0.075 (0.024); WHR: beta (s.e.) = −0.072 (0.024); $P = 0.002$ for both). A locus near *ITPR2-SSPN* showed a nominal association with WHR (rs12814794, beta (s.e.) = 0.050 (0.025); $P = 0.04$).

For 11 adiposity loci (6 BMI and 5 WC/WHR), we observed a 'SNP of interest' with at least one order of magnitude smaller *P*-value than the index SNP or its proxy. These loci are displayed in Supplementary Figures 3–6. SNPs at two loci previously associated with BMI, *NUDT3/HMGA1* (rs6925243, $P = 7.84 \times 10^{-4}$), and *MC4R* (rs1942867; $P = 1.95 \times 10^{-5}$) were dependent on their respective

Table 2b. Results in Hispanic women for published loci from European descent individuals associated with BMI and/or weight

Index or proxy SNP	*In/near nene*	*Most significant SNP***	*Chr*	*BP position*	*Strand*	*Minor/ major allele*	*MAF*	N	*Effect estimate*	*S.e.*	P-*value**	*Estimated effect in kg m^{-2}*	*r^2 with index SNP (in ARIC Whites)*	*r^2 with index SNP (in WHI SHARe Hispanic women)*
rs2815752	*NEGR1*	rs17589316	1	72391927	−	G/A	0.21	3450	0.081	0.030	6.83E−03	0.45	0.130	0.174
rs1514175	*TNNI3K*	rs17095822	1	74948453	−	A/G	0.01	3467	0.403	0.144	5.03E−03	2.25	<0.001	0.004
rs1555543	*PTBP2*	rs17115529	1	96848822	−	G/T	0.28	3465	0.059	0.027	2.94E−02	0.33	0.205	0.167
rs543874	*SEC16B*	rs16852325	1	176235862	+	G/A	0.10	3466	0.090	0.040	2.57E−02	0.50	0.003	0.002
rs6548238	*TMEM18*	rs10205204	2	827100	−	C/T	0.06	3457	0.147	0.052	4.75E−03	0.82	0.005†	0.000
rs713586	*RBJ/ADCY3/POMC*	rs2384061	2	24989124	−	T/C	0.32	3445	0.073	0.025	4.20E−03	0.41	0.699	0.631
rs759250[a]	*FANCL*	rs4672266	2	58978503	−	G/A	0.34	3467	0.093	0.025	**2.30E−04**	0.52	<0.001	0.002
rs2121279[b]	*LRP1B*	rs4595913	2	142910831	+	G/T	0.20	3468	0.095	0.030	1.90E−03	0.53	0.009	0.014
rs13098327[c]	*CADM2*	rs2875492	3	86088900	−	G/A	0.04	3458	−0.189	0.065	3.89E−03	−1.05	0.002	0.008
rs1516728[d]	*ETV5/SFRS10/DGKG*	rs7648336	3	187431942	+	A/C	0.26	3465	−0.091	0.028	**1.14E−03**	−0.51	0.001†	0.011
rs12641981[e]	Gene desert; *GNPDA2*	rs348551	4	44924340	+	A/G	0.01	3464	0.492	0.160	2.08E−03	2.75	<0.001	<0.001
rs3797580[f]	*FLJ35779/HMGCR*	rs16872770	5	75020375	+	A/G	0.08	3360	−0.133	0.044	2.57E−03	−0.75	0.145†	0.149
rs6864049[g]	*ZNF608*	rs17517907	5	124554764	+	G/A	0.18	3468	−0.068	0.031	2.88E−02	−0.38	<0.001	0.017
rs987237[h]	*PRL*	rs2857506	6	50908267	−	T/C	0.09	3461	0.076	0.042	7.09E−02	0.42	0.033	0.047
rs9366426	*TFAP2B*	rs2876611	6	22108317	+	A/G	0.01	3467	−0.400	0.120	**8.54E−04**	−2.24	<0.001	0.001
rs3798560[i]	*NUDT3/HMGA1*	rs6925243	6	34489915	+	G/A	0.33	3468	0.088	0.026	**7.84E−04**	0.49	0.358	0.745
rs10508503	*PTER*	rs4748237	10	16091103	+	G/C	0.49	3468	0.068	0.024	4.23E−03	0.38	<0.001	0.001
rs10840083[j]	*RPL27A/ TUB*	rs11041928	11	8430591	−	G/C	0.04	3457	−0.193	0.061	1.60E−03	−1.08	0.019	0.026
rs10501087	*BDNF/LGR4/LIN7C*	rs10501089	11	27745435	−	A/G	0.05	3439	0.104	0.056	6.32E−02	0.58	<0.001	0.002
rs3817334	*MTCH2*	rs10838774	11	47812690	+	G/A	0.35	3466	−0.081	0.026	1.71E−03	−0.45	0.515	0.316
rs7138803	*FAIM2* (and *BCDIN3D*)	rs17199026	12	48341609	−	A/G	0.07	3468	0.135	0.045	3.08E−03	0.75	0.012	<0.001
rs7988412[k]	*MTIF3*	rs10492484	13	27130706	+	G/A	0.03	3464	0.229	0.073	1.78E−03	1.28	0.001	0.004
rs10151686[l]	*PRKD1*	rs10483379	14	29749214	−	T/C	0.22	3460	0.090	0.029	2.17E−03	0.50	0.028†	0.001
rs17109221[m]	*NRXN3*	rs8020312	14	79223674	+	A/T	0.01	3467	0.299	0.142	3.56E−02	1.67	<0.001	0.000
rs8054079[n]	*GPRC5B/IQCK*	rs12447655	16	20132853	+	G/A	0.09	3463	−0.131	0.042	1.97E−03	−0.73	<0.001	0.006
rs8049439	*SH2B1*	rs10521145	16	28504385	+	A/G	0.09	3458	−0.097	0.041	1.71E−02	−0.54	0.076	0.069
rs9939609	*FTO*	rs9941349	16	52382989	−	A/G	0.32	3467	0.089	0.026	**5.85E−04**	0.50	0.871†	0.456
rs9921354[o]	*MAF*	rs9939361	16	78220241	+	C/G	0.01	3462	0.358	0.147	1.50E−02	2.00	<0.001	0.006
rs1652376[p]	*NPC1*	rs9952592	18	19428220	+	A/G	0.00	3468	−0.526	0.179	3.34E−03	−2.94	<0.001	0.007
rs571312	*MC4R*	rs1942867	18	55887250	−	T/C	0.20	3454	0.111	0.030	**1.95E−04**	0.62	0.744†	0.534
rs11084753	*KCTD15*	rs8104262	19	38895287	+	A/G	0.01	3466	0.424	0.112	**1.65E−04**	2.37	<0.001	<0.001
rs8101149[q]	*TMEM160/ZC3H4*	rs8105312	19	52277204	−	G/A	0.02	3467	0.205	0.085	1.64E−02	1.15	0.005	0.037

Abbreviations: ARIC, Atherosclerosis Risk in Communities Study; BMI, body mass index; BP, base pair; Chr, chromosome; GIANT, Genetic Investigation of ANthropometric Traits Consortium; GWAS, genome-wide association study; LD, linkage disequilibrium; MAF, minor allele frequency; SNP, single-nucleotide polymorphism. *P-values in bold indidicate evidence of association below nominal significance ($P<0.05$) for index or proxy SNPs (reference), and below a Bonferroni threshold for the number of most significant SNPs tested ($P<0.05/32$). **Most significant SNP within 500 kb of the index or proxy SNP (reference). †If pairwise LD information was unavailable in ARIC Whites then HapMap 2 release 22 or HapMap 3 (at *MC4R* only) data in CEU were used instead. ††As data were missing for rs8054079 in the publically available sources, information on rs12444979 was extracted from Speliotes *et al*. In this case, because of the tight linkage disequilibrium between the two variants we inferred that the lowester frequent allele at rs80504079 would increase BMI. [a]Proxy SNP for rs887912, $r^2=1$; [b]Proxy SNP for rs2890652, $r^2=0.8$; [c]Proxy SNP for rs13078807, $r^2=1$; [d]Proxy SNP for rs7647305, $r^2=0.8$; [e]Proxy SNP for rs1093897, $r^2=1$; [f]Proxy SNP for rs2112347, $r^2=0.9$; [g]Proxy SNP for rs4836133, $r^2=1$; [h]Proxy SNP for rs4712652, $r^2=0.9$; [i]Proxy SNP for rs206936, $r^2=1$; [j]Proxy SNP for rs4929949, $r^2=0.9$; [k]Proxy SNP for rs4771122, $r^2=0.9$; [l]Proxy SNP for rs11847697, $r^2 2=0.8$; [m]Proxy SNP for rs10150332, $r^2=1$; [n]Proxy SNP for rs12444979, $r^2=0.9$; [o]Proxy SNP for rs1424233, $r^2=1$; [p]Proxy SNP for rs1805081, $r^2=0.9$; [q]Proxy SNP for rs3810291, $r^2=0.9$.

Table 3a. Significance level of loci associated with with WC and WHR, after adjustment for BMI from published GWAS studies in European descent men and women and the GIANT consortium

Index or proxy SNP	*In/near gene*	*Chr*	*BP position*	*Phenotype*	*GWAS P-value*	*Risk allele*	*Risk allele frequency HapMap CEU*	*GIANT P-value*
rs2301453[a]	*DNM3-PIGC*	1	170624790	WHR	9.51E–18 [7]	G	0.42	2.79E–10
rs2605100[b]	*LYPLAL1*	1	217710847	WC and WHR	2.55E–08, 6.89E–21 [3,7]	G	0.69	2.19E–09
rs6717858[c]	*GRB14*	2	165247907	WHR	2.09E–24 [7]	T	0.54	5.68E–10
rs6784615	*NISCH-STAB1*	3	52481466	WHR	3.84E–10 [7]	T	0.95	3.18E–07
rs6795735	*ADAMTS9*	3	64680405	WHR	9.79E–14 [7]	C	0.54	2.47E–07
rs17695092[d]	*CPEB4*	5	173270459	WHR	1.91E–09 [7]	G	0.29	8.27E–07
rs1294421	*LY86*	6	6688148	WHR	1.75E–17 [7]	G	0.6	6.31E–09
rs6905288	*VEGFA*	6	43866851	WHR	5.88E–25 [7]	A	0.58	4.72E–10
rs987237	*TFAP2B*	6	50911009	WC and BMI	1.87E–11 [3]	G	0.09	0.096
rs1936805[e]	*RSPO3*	6	127493809	WHR	1.84E–40 [7]	T	0.55	1.28E–14
rs1055144	*NFE2L3*	7	25837634	WHR	9.97E–25 [7]	T	0.18	1.49E–08
rs545854[††]	*MSRA*	8	9897490	WC	8.89E–09 [3]	G	0.18[††]	0.64
rs12814794[f]	*ITPR2-SSPN*	12	26331965	WHR	1.14E–17 [7]	G	0.18	3.25E–07
rs1822438[g]	*HOXC13*	12	52628593	WHR	6.38E–17 [7]	A	0.2	4.70E–08
rs4823006	*ZNRF3-KREMEN1*	22	27781671	WHR	1.10E–11 [7]	A	0.53	4.47E–08

Abbreviations: BMI, body mass index; BP, base pair; Chr, chromosome; GIANT, Genetic Investigation of ANthropometric Traits Consortium; GWAS, genome-wide association study; SNP, single-nucleotide polymorphism; WC, waist circumference; WHR, waist-to-hip ratio. [††]rs7826222 was renamed rs545854 in HapMap Build 36 and thus is not present in Build 36 imputations based on that release of HapMap (release 22). As publically available information was not available for this SNP, information on the minor allele was supplemented from Lindgren *et al.* [a]Proxy SNP for rs1011731, $r^2 = 1$; [b]Index SNP from Lindgren *et al*., but proxy SNP for rs4846567 from Heid et al. at $r^2 = 0.6$; [c]Proxy SNP for rs1095252, $r^2 = 0.9$; [d]Proxy SNP for rs6861681, $r^2 = 1$; [e]Proxy SNP for rs9491696, $r^2 = 0.9$; [f]Proxy SNP for rs12814794, $r^2 = 1$; [g]Proxy SNP for rs1822438, $r^2 = 1$. Published results from studies of individuals of European decent: [1] Thorleifsson *et al.*; [2] Willer *et al.*; [3] Lindgren *et al.*; [4] Heard-Costa *et al.*; [5] Meyre *et al.*; [6] Speliotes *et al.*; [7] Heid *et al.*

index or proxy SNPs in CEU ($r^2 \geqslant 0.2$), and therefore were considered to represent a better marker for Hispanics at the index signal (Table 2b, Supplementary Figures 6a and b).

Four BMI loci (*FANCL, ETV5, TFAP2B* and *KCTD15*; Supplementary Figures 3a–d), and five WC or WHR loci (*DNM3-PIGC, GRB14, ADAMTS9, LY86 and MSRA*; Supplementary Figures 4a–d and 5a–c) had low LD in HapMap CEU populations ($r^2 < 0.2$; Tables 2b and 3b) and were therefore considered as possible index-independent signals. All conditional *P*-values for the 'SNP of interest'–phenotype association remained nominally significant after adjustment for the index SNP or its proxy ($P < 0.05$). One BMI locus (*TFAP2B*) appeared to have suggestive evidence of an index-independent signal as the *P*-value decreased from the unconditional analysis for the association between the 'SNP of interest' and BMI (Table 4). However, the evidence for association at three BMI loci (near *FANCL, ETV5* and *KCTD15*) for the 'SNP of interest'–BMI association became weaker on adjustment for the index SNP or its proxy. *KCTD15* was the only locus of these nine loci to have significant evidence of both generalization at both the index signal ($P = 0.006$) and an independent signal ($r^2 < 0.2$; Tables 2a and 2b). At two central adiposity loci (near *DNM3-PIGC* and *MSRA*), there was suggestive evidence of index-independent signals for WC (Table 4). In contrast, at three previously described WHR loci (*GRB14, ADAMTS9* and *LY86*) there was inconsistent evidence across the central adiposity phenotypes tested (WC and WHR models adjusted for BMI).

DISCUSSION

In this study of postmenopausal Hispanic women, we found that the majority of the 47 SNPs interrogated showed consistent direction of effect. Specifically, 25 of 32 SNPs for BMI (binomial test: $P < 7.8E{-}04$), and 13 and 15 of 15 SNPs for WC and WHR (binomial test: $P < 3.2E{-}03$ and $P < 3.1E{-}05$), respectively. Further, we found associations of nine loci with BMI and seven loci with waist phenotypes (WC or WHR) previously shown to be associated with these traits in European populations from Europe, Australia and the United States. In addition, we present possible evidence for independent signals among Hispanics at nine of these loci, three of which became stronger after conditioning (locus near *TFAP2B* with BMI, and loci near *DNM3-PIGC* and *MSRA* with WC or WHR). As verification for the associations of these possible independent signals identified in the Hispanic women in samples of European descent individuals, we looked up the *P*-value in the original published results (Heid and Speliotes references) for seven of the nine SNPs that were available. None of the seven SNPs were even nominally significant (all $P > 0.05$).

Certainly the analyses conducted here needs to be independently verified in an additional Hispanic ancestry sample. Although the exact functional variants underlying these signals still remain to be identified, it is interesting to note that *TFAP2B* encodes a transcription factor that has previously been associated with both BMI and type 2 diabetes in primarily non-Hispanic populations.[29–31] *MSRA* encodes a protein that is thought to repair of oxidative damage to proteins to restore biological activity.[32] Deletion of this gene has been associated with insulin resistance in mice.[33] Dynamin 3 (*DNM3*), a member of the dynamin family of enzymes, and phosphatidylinositol glycan anchor biosynthesis, class C (*PIGC*), are involved in cell membrane interactions and adhesion of proteins to the cell membrane.[34–36] Functional roles of some of the loci with possibly independent signals among Hispanics may include energy homeostasis for *KCTD15* and *ETV5* loci that are highly expressed in the hypothalamus,[37] and insulin signaling from *ADAMTS9,* and *GRB14* loci, particularly in muscle tissue.[38–41]

Although the possibility of multiple signals at established GWAS loci needs to be confirmed in additional, larger samples of Hispanic ancestry, these findings add to the growing literature that indicates multiple variants for BMI, lipids and other complex traits. Moreover, these study findings also add to the growing literature that demonstrates suggestive generalizability of genetic loci across ancestrally distinct populations for some but not all loci. For example, for the SNPs associated with BMI in our Hispanic

Table 3b. Results in Hispanic women for published loci from European descent individuals for loci associated with WC and WHR, after adjustment for BMI

Index or proxy SNP	*In/near gene*	*Chr*	*Phenotype*	*Most significant SNP***	*Chr*	*BP position*	*Strand*	*Minor/ major Allele*	*MAF*	N	*Effect estimate*	*S.e.*	P-*value**	*Estimated effect in cm (WC) or unitless (WHR)*	r^2 *with index SNP (in ARIC Whites)*	r^2*with index SNP (in Hispanic women)*
rs2301453[a]	*DNM3-PIGC*	1	WC adj BMI	rs6698987	1	170635590	−	G/A	0.10	3401	0.131	0.041	**1.47E–03**	1.613	0.057	0.181
			WHR adj BMI	rs6698987	1	170635590	−	G/A	0.10	3399	0.108	0.041	8.24E–03	0.008	0.057	0.181
rs2605100[b]	*LYPLAL1*	1	WC adj BMI	rs4472763	1	217887690	+	C/T	0.19	3453	0.087	0.031	5.00E − 03	1.065	<0.001	0.007
			WHR adj BMI	rs2785990	1	217754055	+	C/T	0.44	3449	−0.073	0.025	3.37E–03	−0.005	0.536	0.435
rs6717858[c]	*GRB14*	2	WC adj BMI	rs6748091	2	165327216	+	G/A	0.07	3454	−0.130	0.048	6.09E–03	−1.605	0.105	0.134
			WHR adj BMI	rs6748091	2	165327216	+	G/A	0.07	3452	−0.155	0.047	**9.56E–04**	−0.011	0.105	0.134
rs6784615	*NISCH-STAB1*	3	WC adj BMI	rs4687612	3	52342972	−	C/T	0.14	3452	−0.080	0.035	2.27E–02	−0.989	0.008	0.009
			WHR adj BMI	rs4687612	3	52342972	−	C/T	0.14	3450	−0.088	0.035	1.19E–02	−0.006	0.008	0.009
rs6795735	*ADAMTS9*	3	WC adj BMI	rs17071048	3	64522218	+	C/T	0.13	3453	0.110	0.037	**3.05E–03**	1.357	<0.001	0.083
			WHR adj BMI	rs4688486	3	64557121	−	A/G	0.34	3452	−0.086	0.026	**9.14E–04**	−0.006	0.020	0.081
rs17695092[d]	*CPEB4*	5	WC adj BMI	rs17750318	5	173194190	+	A/G	0.31	3443	−0.062	0.027	2.18E–02	−0.757	<0.001	0.006
			WHR adj BMI	rs2973894	5	173187427	+	G/A	0.31	3445	0.073	0.026	4.78E–03	0.005	0.058	0.025
rs1294421	*LY86*	6	WC adj BMI	rs2768997	6	6862258	−	C/A	0.14	3451	0.117	0.034	**6.63E–04**	1.443	<0.001	<0.001
			WHR adj BMI	rs17142557	6	6728239	−	A/T	0.01	3451	−0.320	0.106	**2.55E–03**	−0.022	0.005	0.001
rs6905288	*VEGFA*	6	WC adj BMI	rs6905288	6	43866851	−	C/T	0.40	3446	−0.075	0.024	**1.97E–03**	−0.919	1.000	
			WHR adj BMI	rs1358980	6	43872529	−	G/A	0.50	3451	−0.079	0.024	**1.02E–03**	−0.006	0.646	0.583
rs987237	*TFAP2B*	6	WC adj BMI	rs2744498	6	50862810	−	C/A	0.40	3442	−0.055	0.025	2.58E–02	−0.683	0.035	0.139
			WHR adj BMI	rs9473902	6	50795305	−	T/C	0.00	3452	−0.335	0.179	6.12E–02	−0.023	<0.001	0.003
rs1936805[e]	*RSPO3*	6	WC adj BMI	rs17054204	6	127271958	−	T/C	0.05	3424	0.134	0.053	1.16E–02	1.647	0.064†	0.033
			WHR adj BMI	rs1930952	6	127275973	+	A/T	0.41	3415	0.058	0.025	2.01E–02	0.004	0.124	0.121
rs1055144	*NFE2L3*	7	WC adj BMI	rs12533343	7	25642845	+	G/A	0.16	3453	−0.075	0.033	2.45E–02	−0.923	0.011	0.002
			WHR adj BMI	rs17152367	7	25721303	+	C/T	0.01	3441	0.331	0.125	8.35E–03	0.023	<0.001	<0.001
rs545854††	*MSRA*	8	WC adj BMI	rs2409601	8	9771474	+	G/C	0.11	3453	0.117	0.038	**2.43E–03**	1.438	<0.001	0.008
			WHR adj BMI	rs4841248	8	9758513	+	T/C	0.01	3451	0.320	0.142	2.42E–02	0.022	<0.001	0.002
rs12814794[f]	*ITPR2-SSPN*	12	WC adj BMI	rs2170980	12	26513365	−	A/T	0.41	3449	−0.057	0.025	2.21E–02	−0.697	0.007	0.013
			WHR adj BMI	rs1513221	12	26330993	−	A/G	0.12	3443	−0.091	0.037	1.35E–02	−0.006	0.046	0.061
rs1822438[g]	*HOXC13*	12	WC adj BMI	rs17101993	12	52389169	−	C/T	0.12	3453	0.087	0.038	2.23E–02	1.071	0.005	<0.001
			WHR adj BMI	rs17101993	12	52389169	−	C/T	0.12	3451	0.106	0.038	4.94E–03	0.007	0.005	<0.001
rs4823006	*ZNRF3–KREMEN1*	22	WC adj BMI	rs469983	22	27884183	+	C/A	0.12	3454	−0.100	0.036	5.91E–03	−1.227	<0.001	0.003
			WHR adj BMI	rs3788410	22	28000939	−	G/A	0.44	3447	−0.060	0.024	1.25E–02	−0.004	<0.001	0.002

Abbreviations: ARIC, Atherosclerosis Risk in Communities Study; BMI, body mass index; BP, base pair; Chr, chromosome; LD, linkage disequilibrium; MAF, minor allele frequency; SNP, single-nucleotide polymorphism; WC, waist circumference; WHR, waist-to-hip ratio. **P*-values in bold indidicate evidence of association below nominal significance ($P<0.05$) for index or proxy SNPs (reference), and below a Bonferroni threshold for the number of most significant SNPs tested ($P<0.05/15$). **Most significant SNP within 500 kb of the index or proxy SNP (reference). †If pairwise LD information was unavailable in ARIC Whites then HapMap 2 release 22 for data in CEU were used instead. Of note, rs17071048 is monomorphic in CEU HapMap populations; however, in ARIC Whites there was calculatable LD with rs6795735. ††rs7826222 was renamed rs545854 in HapMap Build 36 and thus is not present in Build 36 imputations based on that release of HapMap (release 22). As publically available information was not available for this SNP, information on the minor allele was supplemented from Lindgren *et al*. [a]Proxy SNP for rs1011731, $r^2=1$; [b]Index SNP from Lindgren *et al*., but proxy SNP for rs4846567 from Heid *et al*. at $r^2=0.6$; [c]Proxy SNP for rs1095252, $r^2=0.9$; [d]Proxy SNP for rs6861681, $r^2=1$; [e]Proxy SNP for rs9491696, $r^2=0.9$; [f]Proxy SNP for rs12814794, $r^2=1$; [g]Proxy SNP for rs1822438, $r^2=1$.

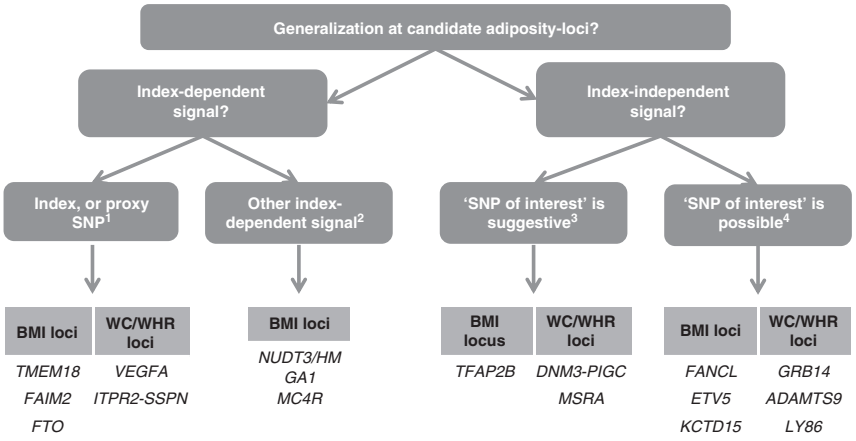

Figure 1. Evidence for generalization of 16 previously identified obesity loci with BMI, WC and WHR in the WHI SHARe sample of Hispanic women. [1]In CEU, index SNPs or proxy SNPs in LD ($r^2 \geqslant 0.8$) below significance threshold of $P < 0.05$. [2]Identified 'SNP of interest' in 1 Mb region is in LD at $r^2 \geqslant 0.2$ in CEU. *P*-value is Bonferroni-corrected significant and was at least one order of magnitude smaller than the *P*-value of the index SNP (or its proxy). [3]Identified 'SNP of interest' in 1 Mb region is in LD at $r^2 < 0.2$ in CEU. After adjustment for the index SNP (or its proxy), the *P*-value decreased for the 'SNP of interest.' [4]Identified 'SNP of interest' in 1 Mb region is in LD at $r^2 < 0.2$ in CEU. After adjustment for the index SNP (or its proxy), the *P*-value for the 'SNP of interest' did not increase more than one order of magnitude. Abbreviations: BMI, body mass index; SNP, single nucleotide polymorphism; WC, waist circumference; WHR, waist-hip ratio.

population, using the index SNP (or proxy SNP in LD, $r^2 > 0.5$) identified in European descent populations, six loci *(TFAP2B, ETV5, TMEM18, FAIM2, FTO* and *MC4R)* also displayed directionally consistent and statistically significant associations with BMI in two large GWAS studies of BMI in African Americans and Asians.[11,13] In addition, two other BMI loci displayed directionally consistent effect estimates for BMI in Hispanics (*NUDT3* and *KCTD15*), but did not display statistical significance. These study findings demonstrate, for the first time, a general relevance of these BMI loci across multiple ancestrally diverse US minority populations. Although we provide some evidence for generalization, our sample size is small and further verification of these findings is necessary. Further, of note, our data demonstrate often substantial differences in allele frequencies between the reference HapMap CEU population and the female participants form the WHI SHARE study. Although this study only summarizes data from a single group of Hispanics, 43% with Mexican origins and, on average, 33% Native American ancestry (Supplementary Figure 1), these data do demonstrate the extensive diversity of the Hispanic population and the critical need for a greater focus on the genetic architecture in ethnic minority populations.

It is of interest to note that *FANCL* did not display any evidence for generalization in African and Asian ancestry populations. In Hispanics, we detected evidence for the proxy SNP and also for a possible independent signal, suggesting distinctions at this locus across ancestral populations.

There have been fewer genetic epidemiological studies of WC and WHR in ancestrally diverse populations—perhaps because waist traits are collected less frequently in large cohorts. One study in a sample of South Asian descent found that SNPs in LD with the identified index SNP (rs1095252) near the *GRB14* loci were associated with WHR and type 2 diabetes.[42] In Hispanic women, we identified a possible index-dependent signal at this locus supporting the relevance of this locus across populations.

In this study, we were able to generalize or find evidence of association at 9 of 32 BMI loci (28%) and 7 of 15 WC/WHR loci (47%). Even among those loci that did not generalize in this study, the majority exhibited consistent directions of effect. The greater proportion of findings at central adiposity loci may likely be due to the greater power to detect associations. As shown in Supplementary Figures 2a–c, power calculations revealed disparate curves for overall (BMI) versus central adiposity measures (WC or WHR), wherein we were underpowered (<80% power) to detect effects for BMI. Between WC and WHR, we were most powered to detect effects on WHR. Of note, these calculations were based on a range of allele frequencies and effect sizes, as well as the distribution of the phenotype in WHI SHARe. Among the three measurements, BMI had the highest level of variability (*z*-score = 5.2), followed by WC (*z*-score = 7.0) and WHR (*z*-score = 11.7), respectively. Similarly, the BMI findings were subjected to a higher penalty of Bonferroni correction (that is, lower alpha), because of the greater number of variants tested. We may also have had greater power to detect waist-related traits as WHI comprises women only, and we have recently established a stronger magnitude of genetic effects in women for many of the established waist variants.[43]

National estimates from 1982 to 1984 from the Hispanic Health and Nutritional Examination Survey[44] were among the first to show that the burden of obesity may not be similar across all adult US Hispanics. More recent data from a diverse cohort study of four US communities strongly supports the possibility that there may be disparities in obesity among this ethic group by country of origin, with Puerto Rican women have the highest prevalence of obesity (51%) followed closely by Dominican (42%), Central American (42%) and Mexican women (42%).[3] Unfortunately, although the WHI Hispanic sample included in WHI SHARe roughly corresponds to the distribution of US Hispanics recorded in the 2010 Census (63% of Hispanics of Mexican descent),[30] it likely does not capture the true diversity that constitutes this ethnicity nor does it imply that these results can be generalized to all US Hispanics. Moreover, the small sample size limited our ability to assess heterogeneity of effect size by population of origin. Future research should be designed and powered to investigate genetic effects across diverse Hispanic backgrounds.

Finally, our sample of primarily postmenopausal women may have been a limitation as there is evidence that genetic effects on adiposity vary substantially across the life course.[45–47]

In turn, this study is strengthened by a number of factors. First, obesity-related racial/ethnic- and gender disparities exist among the largest US minority group—Hispanics[48–51] and progress in the obesity field will only be made when all US populations are successfully interrogated. Therefore, our interrogation of established BMI and WC/WHR loci in an ancestrally diverse population with heightened disparities in disease risk is timely and of great public health significance. Second, to our knowledge this study constitutes

Table 4. Results for conditional analyses of the most significant SNP associated with BMI, WC and WHR, after adjustment for BMI, in Hispanic women before and after conditioning on the index SNP published in European descent populations or a proxy SNP thereof[a]

Phenotype	*In/near gene*	*Chr*	*Index or proxy SNP conditioned on*	*BP position*	*Minor/ major allele*	*MAF*	*Most significant SNP*[b]	*Position (in base pairs)*	*Minor/ major Allele*	*MAF*	N	*Beta*	*S.e.*	P-*value*	N	*Beta*	*S.e.*	P-*value*	*Type*[c]
BMI	*FANCL*	2	rs759250	59182657	A/G	0.18	rs4672266	58978503	G/A	0.34	3452	0.091	0.025	2.92E–04	3452	0.091	0.025	3.02E–04	*Possible*
BMI	*ETV5*	3	rs1516728	187312585	A/T	0.37	rs7648336	187431942	A/C	0.26	3465	–0.091	0.028	1.14E–03	3465	–0.090	0.028	1.22E–03	*Possible*
BM	*TFAP2B*	6	rs9366426	22172618	C/T	0.39	rs2876611	22108317	A/G	0.01	3464	–0.400	0.120	8.49E–04	3464	–0.401	0.120	8.31E–04	*Suggestive*
BMI	*KCTD15*	19	rs11084753	39013977	A/G	0.34	rs8104262	38895287	A/G	0.01	3466	0.424	0.112	1.65E–04	3466	0.424	0.112	1.67E–04	*Possible*
WC adj BMI	*DNM3-PIGC*	1	rs2301453	170624790	G/A	0.38	rs6698987	170635590	G/A	0.10	3394	0.109	0.041	7.76E–03	3394	0.124	0.045	5.96E–03	*Suggestive*
WHR adj BMI	*GRB14*	2	rs6717858	165247907	C/T	0.31	rs6748091	165327216	G/A	0.07	3447	–0.156	0.047	9.06E–04	3447	–0.150	0.050	2.88E–03	*Possible*
WC adj BMI	*ADAMTS9*	3	rs6795735	64680405	C/T	0.34	rs17071048[d]	64522218	C/T	0.13	3453	0.110	0.037	3.05E–03	3453	0.117	0.038	2.19E–03	*Possible*
WHR adj BMI							rs4688486	64557121	A/G	0.34	3452	–0.086	0.026	9.14E–04	3452	–0.088	0.027	9.59E–04	
WC adj BMI	*LY86*	6	rs1294421	6688148	A/C	0.49	rs2768997	6862258	C/A	0.14	3451	0.117	0.034	6.63E–04	3451	0.117	0.034	6.75E–04	*Possible*
WHR adj BMI							rs17142557	6728239	A/T	0.01	3451	–0.320	0.106	2.55E–03	3451	–0.320	0.106	2.52E–03	
WC adj BMI	*MSRA*	8	rs545854	9897490	C/G	0.23	rs2409601	9771474	G/C	0.11	3439	0.118	0.038	2.22E–03	3439	0.120	0.039	1.89E–03	*Suggestive*

Abbreviations: ARIC, Atherosclerosis Risk in Communities; BMI, body mass index; Chr, chromosome; SNP, single-nucleotide polymorphisms; MAF, minor allele frequency; WC, waist circumference; WHR, waist-to-hip ratio. [a]Index (or proxy) SNP and most significant SNP were considered independent per $r^2 < 0.2$ between WHI SHARe Hispanic women and ARIC Study Whites (or CEU HapMap populations, when appropriate). [b]Most significant SNP within 500 kb of the index or proxy SNP (reference). [c]No loci showed more than one order of magnitude increase in *P*-value after adjustment for the index or proxy SNP and therefore none are categorized as being unlikely to have a secondary signal. [d]rs17071048 is monomorphic in CEU HapMap populations; however, in ARIC Whites there was low linkage disequilibrium ($r^2 < 0.001$) with rs6795735.

the first attempt in the scientific literature to perform a large comprehensive study of multiple adiposity phenotypes among a sample of Hispanic individuals. Although previous generalization studies have been published among Hispanics, they were largely conducted in the context of candidate gene studies and did not evaluate well established GWAS variants.

In summary, our findings suggest similar genetic influences on body size and shape across non-Hispanic and Hispanic descent populations, by illustrating associations at nine BMI loci and seven WC/WHR loci previously reported in European descent populations. We also provide tentative evidence that several of the BMI and WC loci harbor multiple independent signals, which has been shown to increase the heritability explained for complex traits across populations. Nonetheless, replication of these signals in larger Hispanic studies is required, as well as GWAS studies to determine if novel obesity loci can be mapped in Hispanic populations.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

MG, LF-R, KM and KEN defined the study approach and aims; MG, LF-R and KM completed the data analysis; MG, LF-R and KEN contributed to the interpretation and presentation of the study findings; all other authors reviewed the manuscript and provided their critical feedback and approval.

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