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Authors

Gong, J

Nishimura, KK

Fernandez-Rhodes, L

et al.

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Trans-Ethnic Analysis of Metabochip Data Identifies Two New Loci Associated with BMI

Jian Gong[1,*], **Katherine K. Nishimura**[1,*], **Lindsay Fernandez-Rhodes**[2], **Jeffery Haessler**[1], **Stephanie Bien**[1], **Misa Graff**[2], **Unhee Lim**[3], **Yingchang Lu**[4,5,6], **Myron Gross**[7], **Myriam Fornage**[8], **Sachiko Yoneyama**[2], **Carmen R. Isasi**[9], **Petra Buzkova**[10], **Martha Daviglus**[11], **Dan-Yu Lin**[12], **Ran Tao**[12], **Robert Goodloe**[13], **William S. Bush**[14], **Eric Farber-Eger**[13], **Jonathan Boston**[13], **Holli H. Dilks**[15], **Georg Ehret**[16,17], **C. Charles Gu**[18], **Cora E. Lewis**[19], **Khanh-Dung H. Nguyen**[16], **Richard Cooper**[20], **Mark Leppert**[21], **Marguerite R. Irvin**[22], **Erwin P. Bottinger**[4], **Lynne R. Wilkens**[3], **Christopher A. Haiman**[23], **Lani Park**[3], **Kristine R. Monroe**[23], **Iona Cheng**[24], **Daniel O. Stram**[23], **Christopher S. Carlson**[1], **Rebecca Jackson**[25], **Lew Kuller**[26], **Denise Houston**[27], **Charles Kooperberg**[1], **Steven Buyske**[28,29], **Lucia A. Hindorff**[30], **Dana C. Crawford**[13], **Ruth J.F. Loos**[4,5,31], **Loic Le Marchand**[3], **Tara C. Matise**[28], **Kari E. North**[2], and **Ulrike Peters**[1,**]

[1]Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington, United States of America [2]Department of Epidemiology, School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States of America [3]Cancer Research Center, University of Hawaii, Honolulu, Hawaii, United States of America [4]The Charles Bronfman Institute for Personalized Medicine, Icahn School of Medicine at Mount Sinai, New York, New York, United States of America [5]The Genetics of Obesity and Related Metabolic Traits Program, Icahn School of Medicine at Mount Sinai, New York, New York, United States of America [6]Division of Epidemiology, Department of Medicine, Vanderbilt-Ingram Cancer Center, Vanderbilt Epidemiology Center, Vanderbilt University School of Medicine, Nashville, Tennessee, United States of America [7]Masonic Cancer Center, University of Minnesota, Minneapolis, Minnesota, United States of America [8]Health Science Center, University of Texas, Austin, Texas, United States of America [9]Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, New York, United States of America [10]Department of Biostatistics, University of Washington, Seattle, Washington, United States of America [11]Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois, U United States of America SA [12]Department of Biostatistics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States of America [13]Center for Human Genetics Research, Vanderbilt University Medical Center, Nashville, Tennessee, United States of America

**Corresponding author: upeters@fredhutch.org (UP).

*Shared first authors

Jian Gong and Katherine K. Nishimura are shared first authors, contributing equally to this manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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[14]Department of Epidemiology and Biostatistics, Institute for Computational Biology, Case Western Reserve University, Cleveland, Ohio, United States of America [15]Sarah Cannon Research Institute, Nashville, Tennessee, United States of America [16]Center for Complex Disease Genomics, McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, United States of America [17]Division of Cardiology, Geneva University Hospital, Geneva, Switzerland [18]Department of Biostatistics, Washington University, St. Louis, Missouri, United States of America [19]Department of Medicine, University of Alabama, Birmingham, Alabama, United States of America [20]Preventive Medicine and Epidemiology, Loyola University, Chicago, Illinois, United States of America [21]Department of Human Genetics, University of Utah, Salt Lake City, Utah, United States of America [22]Department of Epidemiology, University of Alabama, Birmingham, Alabama, United States of America [23]Keck School of Medicine, University of Southern California, Los Angeles, California, United States of America [24]Cancer Prevention Institute of California, Fremont, California, United States of America [25]Department of Internal Medicine, Ohio State Medical Center, Columbus, Ohio, United States of America [26]Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America [27]Wake Forest University School of Medicine, Winston-Salem, North Carolina, United States of America [28]Department of Genetics, Rutgers University, Piscataway, New Jersey, United States of America [29]Department of Statistics and Biostatistics, Rutgers University, Piscataway, New Jersey, United States of America [30]Division of Genomic Medicine, National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland, United States of America [31]The Mindich Child Health and Development Institute, Icahn School of Medicine at Mount Sinai, New York, New York, United States of America

Abstract

Objective—Body mass index (BMI) is commonly used to assess obesity, which is associated with numerous diseases and negative health outcomes. BMI has been shown to be a heritable, polygenic trait, with close to 100 loci previously identified and replicated in multiple populations. We aim to replicate known BMI loci and identify novel associations in a trans-ethnic study population.

Subjects—Using eligible participants from the Population Architecture using Genomics and Epidemiology (PAGE) consortium, we conducted a trans-ethnic meta-analysis of 102,514 African Americans, Hispanics, Asian/Native Hawaiian, Native Americans and European Americans. Participants were genotyped on over 200,000 SNPs on the Illumina Metabochip custom array, or imputed into the 1000 Genomes Project (Phase I). Linear regression of the natural log of BMI, adjusting for age, sex, study site (if applicable), and ancestry principal components, was conducted for each race/ethnicity within each study cohort. Race/ethnicity-specific, and combined meta-analyses using fixed-effects models.

Results—We replicated 15 of 21 BMI loci included in the Metabochip, and identified two novel BMI loci at 1q41 (rs2820436) and 2q31.1 (rs10930502) at the Metabochip-wide significance threshold ($p<2.5x10^{-7}$). Bioinformatic functional investigation of SNPs at these loci suggests a possible impact on pathways that regulate metabolism and adipose tissue.

Conclusion—Conducting studies in genetically diverse populations continues to be a valuable strategy for replicating known loci and uncovering novel BMI associations.

Introduction

Obesity is a heritable risk factor for a large number of serious health conditions(1–4). It already imposes an enormous burden on the public health system and will continue to impact the cost of medical care through the predicted rise in diseases linked to chronic obesity(5–7). In US ethnicities, obesity rates vary in African Americans (36.2%), Hispanics/Latinos (31.5%), Native Americans (41.2%), European Americans (27.9%), and Asians (9.9%)(8). Body mass index (BMI) heritability studies estimate that up to 70% of BMI variability may be attributed to genetic factors(9–11). While this might suggest that genetic traits contribute to racial/ethnic differences in rates of obesity, the relative importance of genetics compared with diet, behavior, and socioeconomic factors is under continued investigation(12). However, it is indisputable that many minority groups have been disproportionately affected by the obesity epidemic and obesity research in minorities must remain a public health priority.

Genome-wide association studies (GWAS) in European ancestry populations have successfully identified numerous genetic variants associated with BMI, firmly establishing the importance of genetic factors on obesity(13–15). However, examining genetic associations in minority groups may reveal previously unidentified BMI loci and help to pinpoint causal variants. Conducting analyses in underrepresented minority populations has been shown to improve the statistical power to detect novel loci by increasing allele frequency and the variance of allele counts for some genetic variants(16–18). A recent fine-mapping study in African Americans benefitted from the lower linkage disequilibrium (LD) patterns when identifying independent signals in known BMI loci, and also found two novel loci, presumably aided by the gain in power due to the higher minor allele frequencies of these variants in those with African genetic ancestry(16). GWAS restricted to minority populations have had similar successes, uncovering additional BMI loci previously unidentified in studies of exclusively European ancestry(19–23). To date, the largest and most comprehensive BMI GWAS included individuals of both European and non-European descent, confirmed 41 known and found 56 novel BMI-associated loci(24). The results from these studies highlights the feasibility and benefits of using diverse human populations as a strategy to broaden our knowledge of BMI genetics.

To identify additional BMI loci, we leveraged the multi-ethnic design of the Population Architecture using Genomics and Epidemiology (PAGE) consortium to conduct a discovery meta-analysis in up to 102,514 individuals. Using this approach, we identified two novel BMI-associated loci, rs2820436 (1q41) and rs10930502 (2q31.1).

Materials and Methods

Study Population

The Population Architecture using Genomics and Epidemiology (PAGE) consortium is funded by the National Human Genome Research Institute to investigate the epidemiologic

architecture of well-replicated genetic variants associated with human diseases or traits(25). The PAGE-I study, initiated in 2008, consists of a coordinating center and four consortia, each with access to large, diverse population-based studies. The four consortia are: Epidemiologic Architecture for Genes Linked to Environment (EAGLE), which is based on data from Vanderbilt University Medical Center's biorepository linked to de-identified electronic health records (EAGLE-BioVU); the Multiethnic Cohort Study (MEC); the Women's Health Initiative (WHI); and Causal Variants Across the Life Course (CALiCO), a consortium of five cohort studies: the Atherosclerosis Risk in Communities (ARIC) study, Coronary Artery Risk Development in Young Adults (CARDIA), the Cardiovascular Health Study (CHS), the Hispanic Community Health Study/Study of Latinos (SOL), and the Strong Heart Study(25). The PAGE-II study, initiated in 2013, added the Charles Bronfman Institute for Personalized Medicine at Mount Sinai Medical Center, BioMe™ BioBank (MSSM). For specific analyses in this paper, PAGE reached out to additional studies, including GenNet and the Hypertension Genetic Epidemiology Network (HyperGen) to increase the African American sample size. The Supporting Information includes detailed descriptions of each study.

African American, Hispanic, Asian/Native Hawaiian, Native American and European participants from the ARIC, EAGLE-BioVU, CHS, CARDIA, MEC, SOL, WHI, GenNet, and HyperGen were eligible for inclusion in this study (S1 Table). Race/ethnicity was self-reported in most studies except for EAGLE-BioVU, where race/ethnicity was administratively-reported and recorded in the electronic health record(26, 27). All studies were approved by Institutional Review Boards at their respective sites, and all study participants save EAGLE-BioVU provided informed consent. The Vanderbilt University Internal Review Board has determined that data contained within EAGLE-BioVU are considered limited datasets as defined by the Health Insurance Portability and Accountability Act (HIPAA) and are in accordance with provisions of Title 45, Code of Federal Regulations, part 46 (45 CFR 46) that define criteria for "non-human subjects" research.

The final sample of minorities from PAGE included 35,606 African American, 26,048 Hispanic/Latino, 22,466 Asian/Native Hawaiian, 17,859 European American, and 535 Native American participants (S1 Table).

Anthropometric measurements

BMI was calculated by taking the ratio of the weight (kg) and height squared (m^2). For ARIC, CHS, CARDIA, HyperGEN, GenNet and WHI, BMI was calculated from height and weight measured at the time of study enrollment. In EAGLE-BioVU and MSSM, the median height and weight was calculated across all complete medical histories. MEC used self-reported height and weight. A validation study within MEC was conducted to assess the validity of these measures and showed that self-reported BMI was sometimes underestimated, but the difference was small (<1 BMI unit) compared to the findings from national surveys(28). To reduce the influence of outliers on the analysis, individuals who were underweight (BMI<18.5 kg/m^2) and extremely overweight (BMI>70 kg/m^2) were

excluded, and BMI values were natural log transformed to correct for the right-skewed distribution of BMI.

Genotyping and Imputation

Genotyping was performed using the Metabochip, whose design has been described elsewhere(29). In brief, the Metabochip is a custom Illumina iSelect genotyping array of nearly 200,000 SNP markers and was designed to cost-effectively analyze putative association signals identified through GWAS meta-analyses of many obesity-related metabolic and cardiovascular traits. Imputation of Metabochip SNPs was conducted in MEC African Americans and Hispanics, MSSM African Americans and Hispanics, and WHI African Americans (SHARe) and Europeans. Study-specific reference samples(30), or reference samples from 1000 Genomes Phase I(31) were used. The programs MaCH and minimac were used for phasing and imputation, respectively(32–34). A summary of genotyping and imputation performance for each participating study has been published previously (35) and reproduced in S2 Table.

Within each race/ethnicity, related participants were identified within and between studies using PLINK(36). Identity by descent was estimated and when apparent first-degree relative pairs were identified, the member with the lower call rate was excluded from further analyses, with the exception of GenNet, SOL, and HyperGen. These studies accounted for family structure using linear mixed models (GenNet, HyperGen) or with generalized estimated equations which incorporate clusters of first degree relative pairs/household members (SOL)(37). In the remaining studies, participants with an inbreeding coefficient $F>0.15$ were excluded. Ancestry principal components were generated using the Eigensoft software(38, 39) using either an unrelated subset, or in the 1000 Genomes reference populations, which were then projected into the study sample. Ancestral outliers were excluded from further analyses, as described previously(40). Additional information is included in the Supporting Information.

A total of 88,505 individuals were genotyped with the Metabochip, and an additional 14,009 with GWAS data were imputed into the 1000 Genomes Project(31) or study-specific reference samples(30). For individuals with imputed data, only the Metabochip genetic variants were included. Genotype data was cleaned by standard quality control procedures as described in the Supporting Information.

Analysis

As has been done in previous publications (16, 41), BMI values were natural log transformed to account for the right-skewed distribution. Extreme BMI values less than 18.5 kg/m^2 or greater than 70 kg/m^2 were excluded from the analysis, with the assumption that these outliers could be attributable to data coding errors or an underlying rare condition outside the scope of this investigation. Given that CARDIA participants were generally younger, and young adults may have naturally low BMI measurements, the 18.5 kg/m^2 exclusion criteria was waived for this cohort. The analyses were restricted to adults 20 years or older.

The population was stratified by study and self-identified race/ethnicity, with each subgroup analyzed separately. Multivariable linear regressions for each study-specific minority group were adjusted for age, sex, study site (if applicable), and ancestry principal components (S2 Table). A sex*age interaction term was included in all models (except WHI, which only includes women) to account for possible effect modification by sex. The sex*age interaction term was intended to account for potential sex-specific effects on BMI that vary by age, given that obesity risk and body composition are known to vary by age, and our study population includes both elderly participants and young adults older than 20 years of age. The results from each ethnicity, and for all ethnicities combined, were meta-analyzed using an inverse-variance weighted fixed-effects model in METAL(42). No inflation was observed in this meta-analysis (inflation factor λ=0.97).

The SNP with the smallest p-value within a locus was considered the lead SNP. BMI associations were considered statistically significant if the p-value surpassed the Bonferroni corrected threshold of significance ($p<2.5\times10^{-7}$), correcting for approximately 200,000 SNPs included on the Metabochip array. The locus was considered novel if the lead SNP was not in LD ($r^2<0.1$ in any 1000 Genomes population) of a previously published known BMI loci. The list of known BMI loci was obtained by extracting records from the GWAS Catalog of the National Human Genome Research Institute (http://www.ebi.ac.uk/gwas/, accessed 4/26/2016), and through a literature search (April 2017) identifying publications based on high-throughput genotyping arrays that are not genome-wide (and thus, excluded from the GWAS Catalog)(16), BMI studies examining GxE associations(43, 44), and internal publications from collaborators that we expect to be published within the next year (Turcot V, in progress). Bioinformatic functional follow-up was performed for the most significant index SNP and all SNPs in high LD with the index ($r^2>=0.8$ in African 1000 Genomes Population) at the four loci. HaploReg v4(45) and the UCSC Genome Browser from the Roadmap epigenomics project were used to assess whether variants in each of these loci were positioned in a putative enhancer or promoter specific to adipose tissue. GTEx expression data was also used to assess whether any of the loci overlapped eQTL results.

Results

The Metabochip array contains high density genetic variants at 21 previously published GWAS-identified BMI loci. We first assessed these known loci to evaluate the reproducibility of these loci in a multi-ethnic study population. Our study confirmed 15 of the 21 previously known BMI loci, significant at $p<5.8\times10^{-5}$, an approximate Bonferroni multiple testing correction for the average 866 SNPs at each BMI locus (S3 Table). Among the Metabochip previously known BMI loci that failed to replicate, the meta-analysis p-values approached significance, with most in the 10^{-4} range.

When we examined the remaining Metabochip content, we found an additional 14 loci associated with BMI, which achieved a Metabochip-wide significance level of $p<2.5\times10^{-7}$, correcting for approximately 200,000 SNPs on the Metabochip array (S4 Table). Eleven of these loci (or SNPs in high LD, $r^2>0.8$, with these loci) were in LD ($r^2>0.1$ in any 1000 Genomes population) with BMI loci previously identified since the development of the Metabochip (14, 21–24, 46–49). A twelfth SNP (rs11927381) no longer achieved

Metabochip-wide significance after conditioning on a nearby SNP (rs1516725) that had previously been associated with BMI (24). Thus, we discovered two novel BMI-associated loci: 1q41 (rs2820436) and 2q31.1 (rs10930502) (Table 1). No evidence of heterogeneity was observed across studies at these two loci, with Cochran's Q heterogeneity p-values of 0.65 and 0.94, for rs2820436 and rs10930502, respectively (Table 1, Fig 1).

The minor allele frequencies of these SNPs differed across the different ethnic groups (Table 1). rs2820436 was most frequent among PAGE African Americans (CAF=0.48), and least frequent in Asians (CAF=0.20), with the strongest association seen in the African Americans (p=8.34E-04) and Hispanic/Latinos (p=1.61E-04). While rs10930502 was also most frequent among African Americans (CAF=0.70) and European Americans (CAF=0.70), and least frequent among Asians (CAF=0.33), the association was strongest among the Asians (p=1.45E-03) and European Americans (p=8.89E-03). Generally, the observed allele frequencies in our own study population were similar to those from the same ethnic groups in the 1000 Genomes populations. Both of these SNPs were analyzed in the most recent and largest BMI GWAS study to date ($p_{(rs2820436)}$=1.02E-02; $p_{(rs10930502)}$=2.91E-04) (24), and were directionally consistent with our own results, providing additional support for these variants.

The variant rs10930502 was included on the Metabochip to follow-up on significant and suggestive signals from the largest available GWAS meta-analysis on BMI, while rs2820436 was included on the array for fine-mapping regions associated with waist-to-hip ratio (WHR). Given that rs2820436 was included on the Metabochip due to its previously published association with a non-BMI trait, we evaluated whether the associations with BMI were independent using individuals where WHR data was available (n=53,481). When the association between rs2820436 and BMI was adjusted by WHR, the overall association did not noticeably change. Conversely, when the association between rs2820436 and WHR was examined, adjusting for BMI, this p-value also achieved Metabochip-wide Bonferroni significance (p=3.09E-10). These findings suggest that this loci may influence multiple phenotypes related to body composition.

Functional investigation of the SNPs supports their likely involvement in lipid metabolism. We found that rs2820436 strongly tagged (r^2=0.94 in 1000 Genomes Phase I Africans) a putative enhancer variant, rs2605096, positioned in an eQTL for the gene lysophospholipase-like 1 (*LYPLAL1)* previously associated with adiponectin(50), adiposity(51), cholesterol, T2D, and WHR(52).

Although rs10930502 was positioned in an eQTL for a lincRNA in adipose tissue, it did not strongly tag a putative regulatory variant. However, it was in moderate LD (r^2=0.48, D′=0.85 in 1000 Genomes Phase I Africans) with variant rs34636594 at 2q31.1, which was positioned in a transcription factor binding enhancer in adipose tissue. LincRNAs are highly tissue specific and typically co-expressed with neighboring genes and thus we hypothesize that the 2q31.1 association may exert its effects on the candidate gene *SLC25A12*, through regulation of lincRNA.

Discussion

This trans-ethnic meta-analysis replicated 15 of 21 previously known BMI loci included on the Metabochip. Of the six loci that did not reach statistical significance in our own study, two of these had lead SNPs that were very rare, with CAF<0.01 in 1000 Genomes populations and PAGE racial/ethnic subgroups. Since most of these loci were originally discovered in GWAS studies with much larger sample sizes (13–15, 24, 53–55), our smaller study was likely insufficiently powered to replicate the rarer variants (Supporting Information). Other loci that we failed to replicate had lead SNPs that were more frequent in Europeans than in non-Europeans. Given that only 17% of our study sample consisted of those with European ancestry, insufficient power may also have contributed to our inability to replicate some of these loci, especially if these were European-specific associations.

Interestingly, both of the novel loci we identified, rs2820436 (1q41) and rs10930502 (2q31.1), are common in those with European ancestry, with a frequency of 0.68 and 0.31 in 1000 Genomes Europeans, respectively. Previous large, European-based BMI GWAS studies may have failed to detect these associations due to population-specific GxG interactions, or GxE interactions linked to cultural, socioeconomic, or behavior risk factors, resulting in a more pronounced effect on BMI in minority groups compared to Europeans. For both novel SNPs reported here, the largest betas in our study occurred in a non-European subgroup, suggesting that the genotypes might have a greater effect on BMI among non-Europeans. Should non-European population-specific effects exist, our large sample of minority subjects may have yielded more power to detect those associations compared to previous GWAS studies that may have been underpowered to detect population-specific effects related to a certain minority group.

Another possible explanation for why these associations were not detected in previous GWAS efforts is that these SNPs may be a poor proxy for the underlying causal SNP in European populations, but are a better proxy for the causal SNP in non-European populations. LD patterns are known to differ by genetic ancestry. It is possible that these SNP are in poor LD with the causal SNP in those with European ancestry, but in high LD with the causal SNPs in those with non-European ancestry. This would cause the association to be weaker or non-significant in Europeans due to exposure misclassification, where the tag SNP is an inaccurate indicator for the presence of the causal SNP. Given that the Metabochip was designed to facilitate fine-mapping in non-Europeans, it is not surprising that some of the Metabochip tag SNPs may perform better at estimating causal genotype-phenotype associations in a predominantly non-European study population.

Our findings demonstrate the value of conducting GWAS in non-European populations, both when replicating findings previously discovered in large, often European-centric GWAS, and for discovering novel associations which may be population-specific, or have stronger effects in those with non-European ancestry. Finally, the functional findings provide additional evidence for the biological relevance of these new loci in the BMI phenotype, which warrant further investigation. While these results are intriguing, additional replication is needed, especially using study populations that include underrepresented individuals. Both

of these SNPs are most frequent in those with African ancestry, and our association in rs10930502 appears to be the strong in those with Asian ancestry.

Many genetic studies of BMI with larger sample sizes have been published and comparatively, we were underpowered to detect and replicate weaker associations, especially in less frequent variants. It is possible that additional novel, or population-specific loci may be found in a larger, trans-ethnic study population. However, we assembled one of the largest and most diverse non-European study populations and were still able to confirm 15 of the 21 known BMI loci included on the Metabochip. While the Metabochip was designed to replicate and fine-map loci known to be associated with 23 disease-related traits, its content is not genome-wide and non-Metabochip loci were not evaluated in this study. Yet, the inclusion of strong and well-established metabolically-related loci allowed us to identify a potential pleiotropic association with WHR. Studies that replicate our findings are advised to isolate the association that contributes specifically to BMI, given that our associations with BMI remain significant after adjusting for WHR. Through accompanying research efforts, we will benefit from the Metabochip's increased marker density to fine-map these associations and further describe the relationship between these loci, BMI, and related phenotypes(35).

Certainly there are challenges associated with multi-ethnic genetic studies, but there are also legitimate benefits which may help explain more of the BMI heritability. The dearth of studies that include underrepresented populations only sustains disparities in genetic research, inhibits our ability to identify population-specific genetic risk factors, and hinders the development and application of genetic findings in real-world clinical settings(56–58). Our findings are promising and perhaps more importantly, demonstrate the need to conduct additional genetic studies of complex traits in non-European individuals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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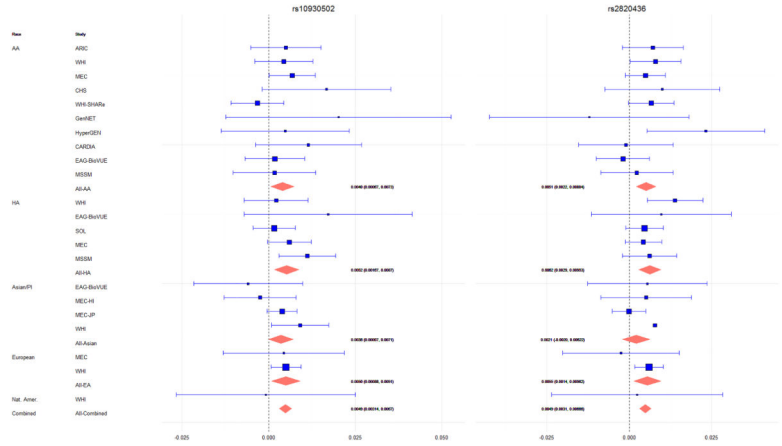

Figure 1. Combined and Study-Specific Associations in Novel BMI-Associated Loci

AA=African American, HA=Hispanic American, PI=Pacific Islander, ARIC=Atherosclerosis Risk in Communities Study, WHI=Women's Health Initiative, MEC=Multiethnic Cohort, CHS=Cardiovascular Health Study, SHARe=WHI SNP Health Association Resource, GenNET=GenNet study, HyperGEN=Hypertension Genetic Epidemiology Network, CARDIA=Coronary Artery Risk Development in Young Adults study, EAG-BioVUE=Epidemiologic Architecture for Genes Linked to Environment accessing Vanderbilt University Medical Center BioVU, MSSM= The Charles Bronfman Institute for Personalized Medicine at Mount Sinai Medical Center, BioMe™ BioBank, SOL= The Hispanic Community Health Study / Study of Latinos.

Table 1

Novel BMI-Associated Loci

Metabochip Loci	Chr:BP	Gene	A1/A2	Population	N	CAF	Beta	SE	P-value	HetP
rs2820436 (1q41)	1:219640680	LYPLAL1/ZC3H11B	A/C	Combined	94255	0.3876	0.0049	0.0009	3.79E-08	0.65
				AA	35606	0.4782	0.0051	0.0015	8.34E-04	NA
				HA	26046	0.4395	0.0062	0.0017	1.61E-04	NA
				AS	14210	0.1952	0.0021	0.0021	3.20E-01	NA
				EA	17859	0.3446	0.0024	0.0132	8.56E-01	NA
				NA	534	0.3446	0.0024	0.0132	8.56E-01	NA
rs10930502 (2q31.1)	2:172890588	METAP1D	A/G	Combined	94256	0.6794	0.0048	0.0009	1.35E-07	0.94
				AA	35599	0.7000	0.004	0.0017	1.70E-02	NA
				HA	26043	0.6555	0.0043	0.0018	1.40E-02	NA
				AS	14220	0.3327	0.0056	0.0018	1.45E-03	NA
				EA	17859	0.6971	0.0056	0.0021	8.89E-03	NA
				NA	535	0.6794	0.0102	0.0137	4.56E-01	NA

Chr: chromosome, BP: base pair position hg19/GRCh37, A1: coded allele, A2: non-coded allele, CAF: coded allele frequency, StdErr=Standard Error, AS=Asian, AA=African American, HA=Hispanic American, EA=European American, NA=Native American, HetP: heterogeneity p-value,

*fine-mapping regions for other traits (HDL, T2D, WHR).