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Title

Ancestral diversity improves discovery and fine-mapping of genetic loci for anthropometric traits - the Hispanic/Latino Anthropometry Consortium

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ABSTRACT

Hispanic/Latinos have been underrepresented in genome-wide association studies (GWAS) for anthropometric traits despite notable anthropometric variability with ancestry proportions, and a high burden of growth stunting and overweight/obesity in Hispanic/Latino populations. This address this knowledge gap, we analyzed densely-imputed genetic data in a sample of Hispanic/Latino adults, to identify and fine-map common genetic variants associated with body mass index (BMI), height, and BMI-adjusted waist-to-hip ratio (WHRadjBMI). We conducted a GWAS of 18 adult studies/consortia as part of the Hispanic/Latino Anthropometry (HISLA) Consortium (Stage 1, n=59,769) and validated our findings in 9 additional studies (HISLA Stage 2, n=9,336). We conducted a trans-ethnic GWAS with summary statistics from HISLA Stage 1 and existing consortia of European and African ancestries. In our HISLA Stage 1+2 analyses, we discovered one novel BMI locus, two novel signals in established loci for BMI, and one secondary signal in an established locus for height. In our trans-ethnic meta-analysis, we identified three additional novel BMI loci, one novel height locus, and one novel WHRadjBMI locus. We also identified three secondary signals for BMI, 29 for height, and two for WHRadjBMI. We replicated 64 established anthropometric loci in Hispanic/Latino populations at genome-wide significance (28% of previously-reported index SNP anthropometric associations). Trans-ethnic meta-analysis of the three ancestries showed a small-to-moderate impact of uncorrected population stratification on the resulting effect size estimates. Our novel findings demonstrate that future studies may also benefit from leveraging differences in linkage disequilibrium patterns to discover novel loci and additional signals with less residual population stratification.

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INTRODUCTION

A complex interplay between political, social, and economic factors has led to an increasing obesogenic global environment. In this modern context, many low- to middle- income nations have experienced a rapid transition from under-nutrition and growth stunting to over-nutrition and obesity.[1] Moreover, population-based surveys from 1975-2002 show that there is an inverse ecologic relationship between the prevalence of growth stunting and the prevalence of overweight seen among preschool children (0-5 years of age) in Latin America.[2] Growth stunting of preschool children ranges from relatively rare (7%) in the Caribbean to notably common (20%) in Central America. Moreover, it is a risk factor for overweight/obesity independent of a child's socioeconomic status.

In Latin America, 35% of the total population was overweight and another 23% was living with obesity by 2016.[3] In Mexico, more than 71% of adults are currently overweight;[4] it is projected that by 2050 only 12% of men and 9% of women will have a healthy weight. And, in a recent study in Argentina, Chile, and Uruguay, the prevalence of obesity was 36%, but when using waist circumference as a measure of central obesity, it was far higher (53%).[5] Within each of these populations, there are also disparities by sex and education.

Race, ethnicity, and ancestry may play a role in anthropometric-related health disparities in Latin American. Previous studies have described the historical contexts leading to admixture in Latin American populations[6; 7] as characterized by highly diverse (variable) ancestral proportions[8-10] from any of the following regions: the Americas, Europe, Africa and East Asia.[11-16] In fact, proportion of Native American ancestry is associated with numerous biomedical traits, like obesity-related traits, and is most strongly associated with height.[17; 18] Height is inversely associated with proportion of Native American ancestry, even after taking into account the fact that globally over time populations have become taller due to mainly non-genetic nutritional factors.[16] The ultimate drivers of this association remain to be elucidated; it is possible that genetic factors and/or socio-economic factors strongly associated with Native American ancestry could be responsible for these findings. Recent studies are starting to provide relevant insights on this topic. As an example, a recent genome-wide association study in Peru[19] identified a missense variant in the *FBN1* gene (rs200342067) that has the largest effect size so far described for common height-associated variants in human populations (each copy of the minor allele reduces height by 2.2 cm). In the 1000 Genomes Project samples, rs200342067 is only present in two American samples (MXL: 0.78% and PEL: 4.12%), and yet the authors reported that this missense variant shows subtle evidence of positive selection in the Peruvian population.[19]

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Obesity in Latin America has quickly surpassed the levels previously seen only among adults of high-income nations, like Canada and the United States (US). In Canada the number of people reporting Latin American origins grew by 83% from the 2001 census[20] relative to the 2016 census,[21] representing 1.3% of the total Canadian population. In the US, both the population size and diversity in national origins (backgrounds) of US Hispanic/Latinos have been increasing over the past several decades.[22] If past demographic trends continue, 24% of the US adult population will identify as Hispanic/Latino by 2065.[22] Obesity-related financial costs in the US are projected to double every decade to ~$900 billion by 2030.[23; 24] US Hispanic/Latino adults and their children/adolescents face a greater burden of obesity than their non-Hispanic white counterparts.[25-28] There is a need to study Hispanic/Latino populations in order to address these disparities.[28; 29]

Given the unique historical and recent demographic shifts occurring across the Americas, there is a clear need to also understand the role that Native American or other under-studied components of admixture have on the genetic architecture of anthropometric traits in Hispanic/Latinos, and its relationship with risk of downstream poor health outcomes. Yet, to date no large-scale genome-wide association studies of anthropometric traits have been conducted among Hispanic/Latino populations. Here, we perform the largest genomic study to date of anthropometric traits, including body mass index (BMI), height, and waist-to-hip ratio adjusted for BMI (WHRadjBMI) in Hispanic/Latino populations to describe what might be novel loci or signals in established loci in this population by sex and life stage.

MATERIALS AND METHODS

Hispanic/Latino Study Samples

The Hispanic/Latino Anthropometry (HISLA) Consortium is comprised of 27 studies/ consortia of adult samples. First, HISLA Stage 1 includes 17 studies and one consortium (Consortium for the Analysis of the Diversity and Evolution of Latin America, CANDELA[18]) collectively representing up to 59,771 adults, depending on the trait, from Brazil, Chile, Colombia, Mexico, Peru, or the US with self-reported heritage from across Spanish-speaking Latin America, or Native American heritage, primarily Pima and Zuni[30] (**Table S1**). HISLA Stage 2 includes nine studies with up to 10,538 adults from across Spanish-speaking Latin America or with related heritage and living in the US (**Table S1**).

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This study was approved by the Institutional Review Boards of the University of North Carolina at Chapel Hill, and all contributing studies had received prior Institutional Review Boards approval for each study's activities.

Anthropometric Traits

BMI is a commonly derived index of obesity risk and is calculated as the ratio of body weight to height squared (kg/m^2). Adult height was measured in or converted to meters. Waist-to-hip ratio (WHR) is used to capture central fat deposition, and it is derived from the circumference of the waist at the umbilicus compared to the circumference of the hip at the maximum protrusion of the gluteal muscles.

Residuals were calculated by sex and/or case status, adjusting for age, age^2, and study-specific covariates (e.g. center, principal components of ancestry, PCA). For WHR, BMI was also adjusted for when creating the residuals to isolate the central deposition of fat from overall body mass. Residuals were then used to create inverse normalizations of BMI and WHRadjBMI, and z-scores of height (=residual/standard deviation for all residuals). In family-based studies the residuals were calculated in women and men together, adjusting for age and sex and other study covariates including PCs. Descriptive statistics on the covariates and anthropometric measures are provided by study in **Table S2** for adults aged up to 98 years. Only one family-based study in Stage 1 (San Antonio Mexican American Family Study or SAMAFS, with <5% being <18 years of age) and two non-family based studies in Stage 2 (the Genetics of Latino Diabetic Retinopathy Study, 0.3%; and the Mapping the Genes for Hypertension, Insulin Resistance, and Salt Sensitivity Study or HTN-IR, 3.9%) included a small subset of adolescents aged 15-17 years, each less than 5% of the total sample.

Childhood/Adolescence Study Samples, Anthropometric Traits, and Obesity

We assembled an independent sample of children/adolescents with anthropometrics, from three studies from the US, Mexico and Chile (**Table S3**). The distribution of covariates and anthropometrics of the samples of children/adolescents in each analysis are described in **Table S4.** First, childhood/adolescent obesity was defined as having a ≥95th BMI-for-age percentile versus ≤50th BMI-for-age percentiles, based on the Centers for Disease Control and Prevention growth curves,[31] as done in previous analyses of childhood obesity.[32] We used these two analyses to look up novel BMI and height findings from our adult HISLA meta-analysis and our trans-ethnic analyses. This resulted in 1,814 children/adolescents aged 2-18 years old for this case-control analysis (**Tables S3-4**). Second, BMI and height-for-age z-scores were calculated

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in children/adolescents from the US and Chile for 5-18 years of age (**Table S4**) based on the more international reference growth curves from the World Health Organization.[33] In Viva la Familia, a family-based study,[34] these residuals were calculated adjusting for sex in the combined sample. The resulting BMI and height-for-age z-scores were available in 1,914 and 1,945 children/adolescents, respectively.

SNP Imputation and Statistical Analyses

We generated autosomal genome-wide imputed data based on 1000 Genomes Phase 1 and 3 references, with the exception of two studies that contributed Exomechip and MetaboChip (Illumina, Inc.; San Diego, CA) genotypes and one study that blended genotypes from multiple platforms (**Tables S5-6**). PCA analyses were conducted in each study to capture the main components of genetic ancestry from the Americas, Europe, Africa, and Asia. Studies with related samples accommodated this non-independence by projecting their principal component analysis from the reference to the study sample, and by accounting for relatedness using either generalized estimating equations[35] or mixed linear models.[10; 36] Assuming an additive genetic model, we tested the association of over 20 million autosomal variants on our traits, accounting for all trait or study-specific covariates (e.g. center; principal components, PCs).

Meta-Analyses of HISLA Stage 1+2

The studies of the HISLA Consortium were meta-analyzed in two stages, including discovery (Stage 1) and validation (Stage 2). Stage 1 included a total sample of 59,771 individuals with data on BMI, 56,161 with height, and 42,455 with WHRadjBMI. All Stage 1 studies/consortia provided full genome-wide analysis results. All SNPs that met our significance criteria were brought forward for validation in Stage 2, which included 10,538 individuals with data on BMI, 8,110 with height, and 4,393 with WHRadjBMI. All reported association results passed our quality control criteria; i.e. variants with low quality (info score <0.4 or Rsq<0.3), minor allele count (MAC) <5, or sample size <100 were removed. We meta-analyzed effects across all studies using a fixed-effect inverse variance weighted meta-analysis in METAL.[37] Genomic control was applied to the HISLA and trans-ethnic meta-analysis, but not applied to the child/adolescent lookups. Given the unique patterns of admixture and ancestry represented by the Brazilian or Native American samples, we conducted sensitivity analyses in Stage 1 studies (i.e. comparing the inclusion and exclusion of the Baependi Heart Study, 1982 Pelotas Birth Cohort Study, and Family Investigation of Nephropathy and Diabetes substudy of individuals of Pima and Zuni heritage) to assess the influence of the three studies on the meta-

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analysis results. CANDELA was retained in all analyses as <10% of the consortium's samples came from Brazil, primarily originating from the South of Brazil with wide-spread European heritage to a lesser extent Native American or African admixture.[18]

Regional plots of all GWAS-significant HISLA Stage 1 findings were plotted using LocusZoom (https://locuszoom.org). From Stage 1, we selected lead variants that met genome-wide significance ($P<5x10^{-8}$) that were independent of each other for replication. In cases where Stage 2 studies did not have the lead variant, we selected two proxies per lead variant with an $r^2 \geq 0.9$ using 1000 Genomes AMR linkage disequilibrium (LD). Stage 2 studies provided a list of the requested lead variants and/or their proxies from Stage 1 for validation. Stage 2 studies were meta-analyzed and subsequently combined with Stage 1 using METAL[25]. Effect heterogeneity was assessed through I^2 across all 27 HISLA adult studies/consortia by entering each study separately into the meta-analysis, irrespective of stage. The characteristics of the final SNP array data used in the HISLA adult studies and the children/adolescent Hispanic/Latino studies are summarized separately in **Tables S5-6.**

Meta-Analyses of HISLA Stage 1 with Other Ancestral Consortia

In addition to a Hispanic/Latino only meta-analysis, we combined the HISLA Stage 1 meta-analysis with data from previous large-scale GWAS meta-analyses from European (the Genetic Investigation of Anthropometric Traits, GIANT, Consortium[38-40], N ~ 300,000) and/or African (the African Ancestry Anthropometry Genetics Consortium, AAAGC[41], N ~ 50,000) descent populations. We used fixed-effect inverse variance weighted meta-analytic techniques in METAL to generate our trans-ethnic meta-analysis.[37] We validated our potentially novel BMI, height[42] and WHRadjBMI[43] findings from this trans-ethnic meta-analysis in either our independent sample of Hispanic/Latino children/adolescents or the British subsample GWAS of the United Kingdom Biobank (UKBB). Regional plots of these analyses of all potentially novel trans-ethnic findings are shown in the supplement (**Figures S7-52**).

Thresholds for Conditional Signals, Discovery, Validation and Transferability

We conducted approximate conditional analyses using the Genome-wide Complex Trait Analysis (GCTA, version 1.93.1) software. For the HISLA analyses, we used our Stage 1 discovery results with the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) as the LD reference dataset. For the approximate conditional trans-ethnic analyses, we used our trans-ethnic results from HISLA Stage 1, AAAGC, or GIANT and a trans-ethnic LD reference dataset of Europeans and Africans from the Atherosclerosis Risk in Communities (ARIC) cohort,

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and Hispanic/Latinos from HCHS/SOL, which was representative of the ancestry distribution of our meta-analysis. In both conditional analyses (HISLA only and trans-ethnic results), we first identified all independent SNPs using the --cojo-slct command. Then, we conditioned each of these independent SNPs on all known SNPs up through December 2019 (BMI[38; 41; 42; 44-59], Height[39; 42; 51; 54; 59; 60], WHRadjBMI[40; 41; 43; 48; 50; 58; 59; 61-65]) within 10Mb of the index SNP. The trans-ethnic meta-analysis results with a *P-value*<5x10^{-8} after conditioning on known SNPs were taken forward for validation in the British subsample of the UKBB.

SNP associations were then defined as either newly discovered or established, depending on their location. An established locus was defined as a SNP association within ±500 kb of at least one previously identified index SNP, otherwise the association was considered a newly-discovered locus.

We designated our Hispanic/Latino SNP-associations within either newly-discovered or established loci as novel if they met the following criteria: 1) were associated at *P-value*<5x10^{-8} in HISLA Stage 1 and directionally consistent in Stage 2 and 2) the addition of Stage 2 samples improved the estimated Stage 1+2 meta-analysis. For the trans-ethnic analyses these criteria were as follows: 1) were associated at *P-value*<5x10^{-8} in the combined HISLA, AAAGC and GIANT meta-analysis, and 2) were both directionally consistent and associated at *P-value*<5x10^{-2} in the subsample of Hispanic/Latino children/adolescents or in the British subsample GWAS from the UKBB.

Novel Hispanic/Latino SNP effects were considered to transfer to Hispanic/Latino children/adolescents, or to African or European ancestry adults, if they were 1) directionally consistent, 2) associated at *P-value*<5x10^{-2}, and 3) had a heterogeneity of I^2<75% in either the Hispanic/Latino children/adolescent lookups, or either 1) the AAAGC or 2) the GIANT adult GWAS results. Conversely, SNP effects of variants previously associated with anthropometric traits in non-Hispanic/Latino populations (i.e. index published SNPs) were considered to be transferable (generalizable) to Hispanic/Latinos if they were 1) directionally consistent, 2) displayed a *P-value*<5x10^{-2} and 3) had little to moderate effect heterogeneity (I^2<75%) in Stage 1.

Fine-Mapping Methods

We used FINEMAP[66] for fine-mapping analyses of the newly-discovered loci identified as part of the HISLA Stage 1 meta-analysis or trans-ethnic meta-analysis, and in established loci. For the established loci, we included index SNP-associations published as of April 2018 (BMI[38; 41; 44; 46-48; 50; 52; 55-58], Height[39; 54; 60], WHRadjBMI[40; 41; 48; 50; 67]) prior to the publications with the UKBB

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results.[42; 43] We used a 1Mb region subset of the summary statistics from the Stage 1 meta-analyses and HCHS/SOL[10] unrelated sample set (N ~ 7,670)to calculate the LD for each locus.

For trans-ethnic fine-mapping of the novel loci and signals identified in the trans-ethnic meta-analysis of HISLA, AAAGC, and GIANT, we used a 1Mb region defining each locus using the summary statistics of the given meta-analysis. We calculated the LD for Hispanic/Latino samples using the HCHS/SOL[10] unrelated sample (N ~ 7,670). For African and European ancestry samples, we calculated the LD using the ARIC unrelated sample that included self-reported African ancestry (N ~ 2,800) and European ancestry (N ~ 9,700). We weighted the LD matrices by the GWAS sample sizes for each trait (HISLA range: ~42,400-56,100; AAAGC: 20,300-42,700; GIANT: 210,000-330,000).

All regions allowed up to a maximum of 10 causal variants. The cumulative 95th% credible set was calculated from the estimated posterior probabilities. Convergence failed for three regions (lead SNPs: rs2902635, rs6900530, and rs4425978, all in known height loci) using the stochastic approach. For these three regions, we used the conditional approach to determine number of causal variants.

Bioinformatics Analyses

To gain further insight into the possible functional role of the identified variants and to assess their relevance to other phenotypes, we conducted bioinformatics queries of our potentially novel loci and novel signals within known loci in multiple publicly available databases, including PhenoScanner,[68] RegulomeDB,[69] Haploreg,[70] UCSC GenomeBrowser,[71] and GTEx.[72]

Trans-Ethnic Findings to Account for Population Structure in Previous GWAS

To quantify the impact of population stratification, we computed the correlation between PC loadings and beta effects estimated from GWAS. We first conducted PCA analysis on the four European populations (CEU, GBR, IBS, and TSI) from 1000 Genomes. We excluded the FIN (Finnish in Finland) population because of its known unique demographic history.[38] We only used biallelic SNPs with minor allele frequency (MAF) > 5% in the four European populations, and then pruned them by both distance and LD using PLINK 1.9.[73] Specifically, we pruned the dataset such that no two SNPs were closer than 2 kb, and then pruned using a 50 SNP LD window (moving in steps of 5 SNPs), such that no SNPs had r^2>0.2. We further removed SNPs in regions of long-range LD.[74] PCA was performed on the remaining SNPs using Eigensoft version 7.2.1(https://github.com/DReichLab/EIG/archive/v7.2.1.tar.gz).

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We performed linear regressions of individual PC values on the allelic genotype count for each polymorphic variant in the four European populations from 1000 Genomes and used the resulting regression coefficients as the estimate of the variant's PC loading. For each PC, we then computed Pearson correlation coefficients of PC loadings and effect sizes (of variants with MAF>1%) from each GWAS summary statistics. We estimated *P-values* based on Jackknife standard errors, by splitting the genome into 1,000 blocks with an equal number of variants. If there was significant correlation in either the GIANT dataset or the HISLA Stage 1, AAAGC and GIANT trans-ethnic meta-analysis, we then further evaluated the improvement of bias due to stratification in trans-ethnic meta-analysis by comparing the correlation coefficients in the trans-ethnic meta-analysis with those in GIANT. Restricting to variants shared between GIANT and the trans-ethnic meta-analysis, we computed their difference in correlation coefficients of PC loadings and effect sizes, and estimated *P-values* again based on Jackknife standard errors from 1,000 equal sized blocks.

RESULTS

One Novel BMI Locus Discovered and Validated in Hispanic/Latino Adults

The first goal of this study was to conduct a genome-wide meta-analysis of anthropometric traits in Hispanic/Latino adults to identify novel loci in an under-studied population (**Figure 1**). All regional plots of all GWAS-significant HISLA Stage 1 findings are shown in the supplement **(Figures S1-6).** No novel loci were identified in all samples combined. Yet, when excluding the Brazilian or Native American samples from Stage 1, we discovered one locus for adult BMI at *PAX3* on chromosome 2 in the HISLA Stage 1 sample (**Table S7**), and we validated this locus in HISLA Stage 2 (**Table 1**). The lead SNP*,* rs994108*,* is in moderate LD (rs7559271, r^2=0.46, D'=1.0 in 1000 Genomes phase 3 AMR) (**Figure 2**) and lies on the same haplotype as a SNP reported to influence facial morphology, including position of the nasion (the deepest point on the nasal bridge where the nose meets the forehead) in Europeans[75] and Hispanic/Latino[76] descent individuals. Other *PAX3* variants in lower LD with the lead SNP have also been associated with nasion position,[77] monobrow, and male-pattern baldness.[78; 79] *PAX3* is a well-known transcription factor in normal embryonic neural crest development and differentiation.[80] Neural crest cells can give rise to mesenchymal stem cells,[81] which can in turn give rise to adipocytes;[81-83] thus, the possible role of *PAX3* in adipogenesis may at least partially explain the association signal with BMI near this gene. Another BMI SNP (rs1505851) near

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ARRDC3 on chromosome 5 at GWAS significance in HISLA Stage 1 (**Table S7, Figure S1**) did not validate in Stage 2 (**Table 1**).

We identified two WHRadjBMI loci at *DOCK2* and *TAOK3* at GWAS significance in HISLA Stage 1 after excluding the Brazilian and Native American samples (**Table S7, Figures S2-S3**), and neither met the p-value threshold for replication and in HISLA Stage 2. The *DOCK2* association for WHRadjBMI was observed among women in Stage 1was however directionally consistent among women in Stage 2. The *TAOK3* association was led by a low frequency variant (rs115981023) that was not directionally consistent across Stages. rs115981023 exhibited moderate heterogeneity across Stage 1 samples after excluding Brazilian and Native American samples (I^2=45%), and this heterogeneity remained (I^2=52%) in the combined meta-analysis of HISLA Stage 1 and 2 samples (**Table 1**).

No potentially novel loci were identified for height in HISLA Stage 1, and the exclusion of the Brazilian and Native American samples did not reveal additional novel height or WHRadjBMI loci.

Three Novel Signals in Established Loci for BMI and Height Discovered and Validated in Hispanic/Latino Adults

At two established loci for BMI, we identified new signals at *ADCY5* and near *C6orf106* (**Table S7**), which were independent of any published findings (**Table S8, Figures S4-5**). We validated these signals in Stage 2 with directional consistency and the combined Stage 1+2 meta-analysis at GWAS significance (**Table 1**). We also identified one new signal for height in an established height locus, *B4GALNT3,* which was independent of the previously reported SNPs for height (**Tables S7-8, Figure S6**). We validated this signal in our Stage 2 with directional consistency and a Stage 1+2 meta-analysis that was GWAS significant (**Table 1**).

Fine-Mapping of Four Novel Adult Hispanic/Latino Anthropometric Findings

We fine-mapped using 1MB regions, the novel *PAX3* locus for BMI and three new signals in known loci discovered and replicated in Stages 1+2 (BMI: *ADCY5* and *C6orf106*; height: *B4GALNT3*; **Table S9**). For the three BMI loci, FINEMAP revealed one potential causal set for each locus at *PAX3, ADCY5,* and *C6orf106* locus. For the *PAX3* locus, only one causal set was proposed and the 95th% credible contained only nine plausibly causal SNPs, with lead SNP rs994108 having a very high posterior probability of being causal (0.89). However, functional annotation of this SNP was unremarkable (**Table S20**). In contrast, For *ADCY5* and *C6orf106,* FINEMAP revealed one causal configuration for each locus but with much greater

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uncertainty with respect to the likely functional variant given the size of the credible sets, 14 and 22 SNPs in the credible region for *ADCY5* and *C6orf106*, respectively. The posterior probability of the best lead SNP at these loci had relatively low posterior probabilities of being the causal SNP, with the best posterior probabilities of 0.23 for rs17361324 (*ADCY5*), and 0.11 for rs73420913 (*C6orf106*), respectively. Interestingly, however, the best candidate for causality at *PAX3* and *ADCY5* loci were the lead SNPs from the HISLA meta-analysis and for *C6orf106* , the FINEMAP and HISLA SNPs were in tight LD (rs73420913 had an r^2=0.96 with the lead HISLA SNP rs148899910), providing greater support for the prioritization of these SNPs for functional interrogation. For the *B4GALNT3* locus for height, FINEMAP revealed six causal configurations. Four of the variants (rs11063185, rs215230, rs7303572, and rs11063184 with each configuration each had a posterior probability >0.99 and contained only itself in the 95% credible set. One variant (rs215223) had a posterior probability of 0.93 and thus included two variants in the 95% credible set. The sixth 95% credible set had a lead variant with a posterior probability of 45%, but contained a total of 1621 additional variants with all very small posterior probabilities (e.g. ≤0.05).

Transferability of Adult Novel Loci/Signals from Hispanic/Latinos to Consortia of Other Ancestral Backgrounds

To assess how well the effect estimates are transferable (generalizable) to other populations, we looked up the novel BMI and height findings from Hispanic/Latinos in the AAAGC and GIANT meta-analysis results (**Table 1**). Keeping limitations with respect to sample size, linkage disequilibrium, allele frequency, and effect size heterogeneity in mind, we did observe directionally consistent -BMI effects at the *PAX3* locus in the other consortia, although without observing nominal significance. The new BMI signals at the *ADCY5* locus (rs17361324) transferred to both AAAGC and GIANT with directional consistency (betas=0.13-0.23) and nominal significance (*P-values*<$5x10^{-2}$). The BMI lead SNP (rs148899910) representing a novel signal near *C6orf106* was available in AAAGC, the signal only appeared to be transferable to GIANT at a proxy SNP (rs1573905, r^2=0.96-1 in 1000 Genomes AMR and EUR**; Table 1**).

The new signal for height in *B4GALNT3* (rs215226) was directionally consistent and nominally significant in AAAGC. In all cases the effect sizes observed in GIANT and AAAGC were attenuated compared to the effect sizes from HISLA Stage 1.

Relevance of Novel Hispanic/Latino Anthropometric Loci/Signals from Adults to Childhood/Adolescence

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We looked up our novel HISLA findings in Hispanic/Latino children/adolescents using BMI-for-age and height-for-age z-scores, as well as a case-control study of childhood obesity. Two of the three novel BMI signals were directionally consistent with the anticipated effect on the odds of obesity during childhood/adolescence, one of which was nominally significant (rs17361324 at *ADCY5*; *P-value*=2.2×10^{-2}). None of the novel HISLA findings generalized at nominal significance with the BMI/height-for-age z-score, but were directionally consistent with the corresponding effect in adulthood (**Table S10**). This may have been due to the small available sample size of Hispanic/Latino children/adolescents.

Transferability of Established Anthropometric Loci to Hispanic/Latino Adults

Using HISLA Stage 1 results, we assessed how many established anthropometric loci, discovered in predominantly non-Hispanic/Latino samples, could be transferred to Hispanic/Latino adults, given the current sample size. As shown in **Table S11**, the index SNPs at 332 of 1280 (25.9%) previously reported BMI loci were transferred to Hispanic/Latinos. Of these BMI loci, 13 SNPs in the HISLA Stage 1 genome-wide data displayed genome-wide significant associations with the SNP reported in the literature (**Table S7**). **Table S12** shows that a slightly higher percentage of known height loci (1177 of 3925, or 30.0%) were transferred to Hispanic/Latinos. Forty-nine height loci displayed a genome wide significant association with height in the surrounding 1 MB interval in HISLA Stage 1 (**Table S7**), with 44 of 49 SNPs being the exact index SNP from the literature (**Table S11**). Lastly, **Tables S13-15** show that 143 of 754 (19.0%) known WHRadjBMI in both sexes combined, 103 of 504 (20.4%) in women only, and 28 of 186 (15.1%) in men only loci were transferable to Hispanic/Latino. However, none of the index SNPs from the previous literature for WHRadjBMI reached genome-wide significance. We did observe genome wide significant evidence for association of a SNP with WHRadjBMI in the 1 MB interval of one known region, although not replicating the exact previously reported index SNP (**Table S7**).

Five Novel Loci and Thirty-Four New Signals in Established Loci for Adult Anthropometric Traits Discovered and Replicated in a Trans-Ethnic Meta-Analytic Context

As shown in **Figure 1,** we pursued a secondary goal of assembling a trans-ethnic meta-analysis of HISLA Stage 1 with the AAAGC and GIANT consortia results to attempt to further leverage differences in allele frequencies across populations to identify additional novel loci and fine-map established loci. As anticipated, this trans-ethnic meta-analysis revealed eight new loci

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and 38 new signals in established loci that were associated at GWAS significance in the combined HISLA, AAAGC and GIANT meta-analysis (**Table S16, Figures S7-S52**), and independent of established SNPs within a 10Mb region (**Table 2**). Of this set, five new loci (3 BMI, 1 height, and 1 WHRadjBMI) and 34 new signals in established loci (3 BMI, 29 Height, and 2 WHRadjBMI) were validated using the adult British subsample of the UKBB. In some cases, the significance in the trans-ethnic results had additional signal driven more by the AAAGC and/or HISLA consortia, which could explain the lack of association in the UKBB British subsample (**Table S16, Figure S53**). An example is rs12636352 (*IGF2BP2* locus), associated with BMI, with HISLA and AAAGC *P-values*$<5\times10^{-5}$ and GIANT *P-value*$=2.0\times10^{-3}$, compared to the UKBB *P-value* $=1.5\times10^{-1}$. We looked up the potentially novel findings from our trans-ethnic meta-analyses in the sample of Hispanic/Latino children/adolescents (**Table S17)**. Five SNPs were associated at nominal significance in the child/adolescent sample, each having been already replicated in UKBB (Table S16). Four of these five loci were directionally consistent in the childhood/adolescence results with the trans-ethnic adult findings (**Table S17**). In summary, we found that two of the potentially new trans-ethnic loci and 19 of the new trans-ethnic signals in established loci were directionally consistent between their trans-ethnic adult effect and their effect on BMI or height-for-age z-scores in Hispanic/Latino children/adolescents. However, this directional consistency was not more than what would have been expected by chance alone ($P\text{-}values_{binomial}>0.10$).

Fine-Mapping of Trans-Ethnic Anthropometric Findings

We also fine-mapped the novel trans-ethnic findings (**Table S18**) using FINEMAP. Seven of the eight novel loci (three for BMI, three for height and one for WHRadjBMI) had one causal variant in the locus, while the novel height locus near *ANKRD36BP1* had two causal variants. In all eight loci, the SNP with the highest posterior probability from each of these credible sets was either the exact SNP with the strongest GWAS evidence or in high LD (r^2 between 0.75 and 0.99 in each ancestry) with the lead GWAS SNP. Two of these seven regions had even stronger supportive evidence, with potential casual SNPs with relatively high posterior probabilities and small 95th% credible sets. For BMI, the *CTD-2007H13.3* credible set spanned three SNPs, including a posterior probability of 0.88 for rs150992, an intergenic SNP associated with enhancer histone marks in 11 tissues including Fat and Brain, three binding motifs, and several eQTL and sQTLs mostly strongly in Whole blood and skeletal muscle, respectively (**Tables S21-22**). For height, the *ANKRS36BP1* region had a total of five SNPs in the credible set, but had a high posterior probability of 0.93 for rs10737541, an intergenic SNP located within

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8 binding motifs. For the other loci the posterior probabilities were lower, between 0.09 and 0.42. Yet, four loci (rs9860730, rs17375290, rs4324883, and rs9463108) still had relatively few SNPs (<15) in the 95th% credible sets. For one height locus (*KCNQ5* region), the SNP with the highest posterior probability (0.26) was not in LD with the lead GWAS SNP (r^2<0.1 in each ancestry) and is thus potentially an additional signal in this region. The lead GWAS SNP for this signal, rs4618485, is an intronic SNP with enhancer histone marks in Heart and Muscle tissue, and is associated with changes in 14 binding motifs.

Within the 38 novel signals in known loci, 36 had configurations with more than one causal SNP (e.g. more than one credible set), and 26 of the putative causal SNPs identified by FINEMAP had a posterior probability higher than 0.8 (**Table S18**). For 18 of 38 regions, the SNP with the highest posterior probability was either the lead GWAS SNP or a SNP in moderate to high LD across the three ancestries (r^2 between 0.6 and 0.99). For 15 of these 18 regions, the 95th % credible set around each of the SNPs with the highest posterior probability contained <10 SNPs and for six regions (by locus name: *KIAA1486, NKX2-2, DEF6, PTK7, SH3PXD2A, C15orf55)*, the credible sets around all causal SNPs for each region were <25 SNPs total. Overall, across all eight novel loci FINEMAP revealed several 95th% credible sets with a small number of SNPs (e.g. 5 credit sets with <10 SNPs) or at least one putative causal variant within a set that had high posterior probabilities (e.g. 2 sets led by a SNP with >0.8 posterior probability). Similar trends were observed for many of new trans-ethnic signals in established loci (**Table S18**), thus demonstrating the utility of trans-ethnic approaches to fine-mapping GWAS loci even in the presence of allelic heterogeneity.

Trans-Ethnic Findings to Account for Population Structure in Previous GWAS

The first two PCs in the PCA (**Figure S54**) reflect geographical or population structure in Europe, corresponding to the North-South and Southeast-Southwest axes of variation, respectively. We found that the bias in effect size estimates due to stratification is most obvious for height as the phenotype is known to be differentiated across Europe.[84-86] Effect sizes on height estimated from the GIANT and our trans-ethnic meta-analysis were both highly correlated with the loadings of the first PCA (rho = 0.125, *P-value*= 3.2x10^{-94} in GIANT; rho = 0.105, *P-value*= 3.4x10^{-70} in meta-analysis). The correlation was much lower in AAAGC and HISLA (rho = 0.012, *P-value*= 2.17x10^{-4} in AAAGC; rho = 0.007, *P-value*= 9.2x10^{-2} in HISLA; **Figure 4A**). Importantly, the magnitude of correlation was lessened in meta-analysis compared with GIANT (*P-value*= 6.6x10^{-9}). Other traits were not *a priori* known to be as differentiated across Europe

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as height, and thus the degree of correlation between effect sizes and PC loadings are much lower in GIANT (e.g. rho = -0.025 for BMI; **Figure 4B-E**).

DISCUSSION

Hispanic/Latinos are a unique population with continental admixture from the Americas, Africa and Europe[11-15] and population of great interest for anthropometric studies. Here, we present results from a large-scale meta-analysis of anthropometric traits in Hispanics/Latinos. As the first of its kind, we have assembled a large sample of Hispanics/Latinos to map a total of 43 novel signals using both a Hispanic/Latino and trans-ethnic discovery effort (**Figure 1**). We transferred (or generalized) more than 1,500 anthropometric-SNP associations to Hispanics/Latinos, 63 of which displayed genome-wide significance, and established that four of seven of our novel HISLA findings transferred to other ancestral populations at nominal significance. Moreover, we note that even though these findings provide additional evidence for transferability of common loci for anthropometrics,[87] still a number of previously-reported anthropometric loci may not have transferred to this population in part due to variability in allele frequencies or effect sizes across ancestral populations.[59]

Our conditional analyses revealed 37 novel signals in established anthropometric loci, which independently replicated in HISLA Stage 2 or the UKBB British subsample. In addition, our lead SNPs for two of our newly discovered BMI signals at *ADCY5* (from the HISLA meta-analysis) and *ADAMTS9-AS2* (from the trans-ethnic meta-analysis) are nominally associated with childhood/adolescent obesity between 2-18 years of age. Four of our new trans-ethnic signals in established height loci also displayed association with height-for-age z-scores in children between 5-18 years of age. These observations support our premise that diverse and trans-ethnic studies represent a valuable tool for identifying multiple signals and fine-mapping in established association regions. This was done with the overarching goal of identifying putative variants that will account for some of the missing heritability of complex diseases and reveal candidate genes and SNPs for functional follow-up.

In light of the notable ancestral, geographical or environmental diversity of the studies analyzed in our meta-analyses, we observed evidence of allele frequency differences for many of our novel discoveries (**Figure 3** and **Figure S53**). Similar to reports from other diverse genome-wide analyses,[59] in some cases this allele frequency heterogeneity may drive the apparent heterogeneity effect across consortia in our HISLA, AAAGC, and GIANT meta-analysis (e.g. *IGF2BP2* I^2=78.7; *MY06* with I^2=84.4, **Tables 2 and S16**). These observations reinforce how studies of one predominant ancestry group, such as Europeans, may fail to

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identify novel loci or, more likely, new signals in known loci (given how many known loci there are currently) with allele frequency differences across ancestral populations.

Residual uncorrected stratification in GWAS could result in biased estimates of effect sizes.[39] For example, effect sizes on height from GIANT were reported to be significantly correlated with North-South axis of variation in Europe suggesting residual uncorrected stratification,[86; 88; 89] which we also observe here. Note that the residual stratification effect is subtle, and while the effect sizes may be biased, this does not imply the identified associations are spurious. For example, compared with effect sizes on height from UKBB, which is based on a single homogeneous population and results in better control of population stratification, the genetic correlation between GIANT and UKBB was 0.94.[86]

Of the three traits studied here, height is the most stratified in Europe. The correlation coefficient between effect sizes on height and PC loadings reached 0.125 in the GIANT only for PC1, while it was much smaller for other traits (e.g. the maximum |*rho*| = 0.042 in GIANT on WHR using only males on PC1). The decrease in bias in trans-ethnic meta-analysis was also obvious in height. The correlation with PC1 was non-significant in HISLA (*rho* = 0.007) and statistically significant but weak in AAAGC (*rho* = 0.012), consistent with a decreased impact of European population stratification on the estimate of effect size in AAAGC and HISLA. This decreased correlation could be due to large non-European ancestries known in these populations (Africans and Native Americans, respectively) that are less affected by population stratification in Europe; it could also be that by using European ancestry based loadings we are less likely to detect non-European based population stratification patterns or that smaller sample sizes in these cohorts resulting in greater noise in effect size estimates. Regardless of the reason, compared to GIANT alone, trans-ethnic meta-analysis of the three cohorts showed less impact of uncorrected stratification in effect size estimates, even though the sample size in AAAGC and HISLA are comparably small. For other traits, the conclusions are qualitatively similar: that trans-ethnic meta-analysis lessened the bias due to stratification, even though the bias in GIANT was not as strong in the first place.

As described above, in this study we were able to 1) discover six novel loci with a notably smaller analytic size than other anthropometric consortia (e.g. GIANT), 2) describe 37 new signals in established loci in HISLA or our trans-ethnic meta-analysis, and 3) generate trans-ethnic effect estimates with better control for population structure. Taken together, these findings indicate the added value of building large, more diverse GWAS in the near future.

Bioinformatic analyses of our population-specific (**Table S19-S20**) and trans-ethnic findings in newly discovered loci give us important insights into the underlying biology of obesity,

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bone development and growth (**Tables S21-S22**). We described any previously reported associations with other phenotypes, consequences on gene expression, and metabolites in publicly available data, as well as any eQTLs or sQTLs. Lead SNPs from our HISLA only meta-analyses appear relatively benign based on CADD and FATHMM-XF scores (**Table S20**). All SNPs potentially change motifs. Both rs17361324 (*ADCY5*) and rs215226 (*B4GALNT3*) have enhancer and promoter histone marks and eQTLs in the respective genes in relevant tissues. For BMI, there is an eQTL for rs17361324-ADCY5 in thyroid, and *ADCY5* has been previously associated with type 2 diabetes,[90] BMI,[91] central obesity traits,[43] height,[51] birth outcomes,[92-94] and a number of other phenotypes. Additionally, rs17361324 is proximate to an *ADCY5* intronic variant (rs1093467, r^2=0.3 in 1000 Genomes AMR) that is highly conserved across species (Haploreg v4.1). For height, there is an eQTL for rs215226-B4GALNT3 in tibial, aortic, and coronary arteries, and tibial nerve. The lead SNP for the height signal in *B4GALNT3*, rs215226, has enhancer histone marks in bone and muscle, and promoter marks in muscle tissue. In addition, the variant rs215226 (B4GALNT3) has a posterior probability of 1 for causality in FINEMAP analyses (see **Table S9**). Other interesting information about these regions is provided in **Table S19.**

The lead SNPs at our newly discovered trans-ethnic loci were mainly located in intronic and intergenic regions (**Table S21**) and were benign. One exception was the novel locus *C11orf63* associated with height led by rs11605693, which showed pathogenic scores for CADD and FATHMM-XF (CADD score=17.1 and FATHMM-XF score=0.87). This lead SNP has an eQTL in *C11orf63* for adipose, tibial nerve, and testis. *C11orf63*, junctional cadherin complex regulator, is responsible for ependymal cells that line the brain and spinal cord.

Among the trans-ethnic findings, a new signal at a known locus for BMI, rs10540 at *RNH1*, has a posterior probability of 0.82 as one of two causal variants (see **Table S18**) in the locus, and is an eQTL for a wide range of tissues and genes (see **Table S22**), potentially making it relevant to body mass. A new signal in a known locus for height, led by rs12918773 that has a posterior probability of 0.98 and is one of four casual variants suggested from fine-mapping in the locus (see **Table S18**), has an eQTL (in lung, thyroid, tibial nerve and artery, breast, testis) with *CDK10*, a gene also associated with growth retardation.[95] In addition, rs1342330, another new signal in a known height locus, has a low regulomeDB score at 2b and several enhancer and promoter histone marks in relevant tissues (**Tables S21**). As an intronic variant, it is an eQTL in the pancreas with *PHACTR2* (**Tables S22**), a gene associated with body dysmorphic disorder.[96] While many of the novel loci/signals appeared to be benign based on CADD and FATHMM-XF scores, they still show enhancer and promoter histone marks in trait

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relevant tissues such as adipose, bone, and muscle, thymus, brain, and adrenal gland. Other information and references about the trans-ethnic findings are provided in **Table S21-22.**

Large-scale analyses of diverse populations hold great potential for advancing the field of genetic epidemiology.[59] This study illustrates how studying admixed populations, like Hispanic/Latinos, and leveraging them in trans-ethnic epidemiologic investigations, can yield additional insights into the genetic architecture of anthropometric traits. Future discovery efforts in Hispanic/Latino populations and with other diverse populations will address the research gap between who is studied and who is affected by conditions like obesity, to the benefit of both public health and precision medicine.

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Supplemental Data

Supplemental Data include 22 tables and 54 figures.

Declaration of Interests

SMG and AMS receive funding from Seven Bridges Genomics to develop tools for the NHLBI BioData Catalyst consortium. All others authors declare no competing interests.

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Figure Titles and Legends

Figure 1. Flowchart of the design and discovery of 43 novel loci in the Hispanic/Latino Anthropometry Consortium (HISLA) Meta-Analysis and the Trans-Ethnic Meta-Analysis of HISLA and Consortia of Other Ancestral Heritages

*Stage 1 maximum sample sizes varied between and 59,771 for BMI, 56,161 for height, and 42,455 for WHRadjBMI (sex combined). **Stage 2 sample sizes varied between 10,538 for BMI, 8,110 for height, and 4,393 for WHRadjBMI (sex combined). Actual sample sizes may vary by SNP. ***The BMI and height-for-age z-score models were conducted using up to 1,914 and 1,945 of children/adolescents, respectively. In contrast, the obesity case-control study compared up to 1,814 children/adolescents who were either ≥95th versus ≤50th BMI-for-age percentiles

Figure 2. PAX3 novel locus (lead SNP rs994108) associated with BMI in the 27 studies/consortia included in Stages 1 and 2 of the Hispanic/Latino Anthropometry Consortium, excluding Brazilian and Native American studies. Linkage disequilibrium is based on 1000 Genomes phase 3 AMR reference.

Figure 3. Variability in HISLA Stage 1+2 (blue), GIANT (red), and AAAGC (green) P-values, Effect Sizes and Risk Allele Frequencies (Asterisks indicating that for GIANT they were marked at proxies r2>0.90 in 1000 Genomes AMR) for the 3 novel body mass index (black) and 3 novel height (gray) loci/signals from the Hispanic/Latino Anthropometry Consortium.

Figure 4. Correlations (rho) between effect estimates and the loadings of the principal components 1-5 in each consortia (HISLA, AAAGC, GIANT) and the meta-analysis of all 3 consortia (Meta) by trait. (A) height, (B) BMI, (C) Waist-to-hip ratio adjusted for BMI (WHRadjBMI) for men and women combined, (D) WHRadjBMI for women only, (E) WHRadjBMI for men only.

Hispanic/Latino Anthropometry Consortium (HISLA); African American Anthropometry Genetics Consortium AAAGC; Genetic Investigation of ANthropometric Traits (GIANT); WHRadjBMI - waist to hip ratio adjusted for BMI

Table Titles and Legends

Table 1. Potential novel loci and new signals in known loci from the Stage 1: Adult HISLA Discovery combined with results from the Stage 2: Adult HISLA Validation.[1] In addition, lookup of results of each locus from the AAAGC and GIANT.
Abbreviations: Chr - chromosome; EAF - effect allele frequency; HetIsq - heterogeneity I-square; N - sample size; WHRadjBMI - waist to hip ratio adjusted for BMI; Hispanic/Latino Anthropometry Consortium (HISLA); African American Anthropometry Genetics Consortium AAAGC; Genetic Investigation of ANthropometric Traits (GIANT)
[1] All studies were meta-analyzed using METAL[37], with each study entered individuals into Stage 1+2 analyses.
[2] BMI and WHRadjBMI analyses did not include Brazilians or Native Americans.

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[3] New loci or signals are those that were validated by HISLA stage 2 results that are directionally consistent with Stage 1 (Table S7) and remaining genome-wide significant after meta-analysis with stage 1.
[4] Proxy GIANT rs1573905 (r2= 0.96 AMR)

Table 2. Novel loci and new signals in established loci by trait from a meta-analyses of HISLA, AAAGC, and GIANT.
Abbreviations: Chr - chromosome; EAF - effect allele frequency; HetIsq - heterogeneity I-square; N - sample size; WHRadjBMI - waist to hip ratio adjusted for BMI; Hispanic/Latino Anthropometry Consortium (HISLA); African American Anthropometry Genetics Consortium AAAGC; Genetic Investigation of ANthropometric Traits (GIANT)
[1] Novel locus defined by no known published variants within 1Mb (+/-500 Kb) of the lead SNP.
[2] Known locus defined by a 1Mb region with previously identified signal(s) for the indicated trait

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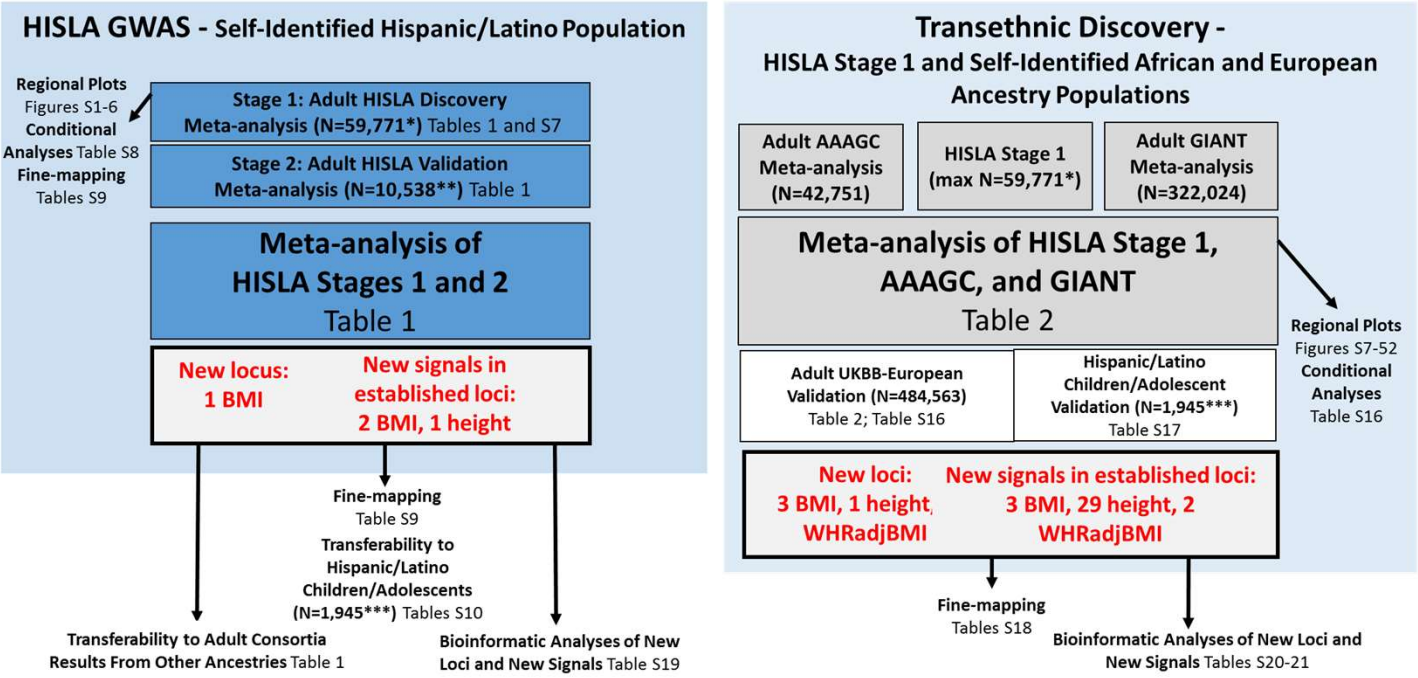

Figure 1. Flowchart of the design and discovery of 44 novel loci in the Hispanic/Latino Anthropometry Consortium (HISLA) Meta-Analysis and the Trans-Ethnic Meta-Analysis of HISLA and Consortia of Other Ancestral Heritages

*Stage 1 maximum sample sizes varied between and 59,771 for BMI, 56,161 for height, and 42,455 for WHRadjBMI (sex combined). **Stage 2 sample sizes varied between 10,538 for BMI, 8,110 for height, and 4,393 for WHRadjBMI (sex combined). Actual sample sizes may vary by SNP. ***The BMI and height-for-age z-score models were conducted using up to 1,914 and 1,945 of children/adolescents, respectively. In contrast, the obesity case-control study compared up to 1,814 children/adolescents who were either ≥95th versus ≤50th BMI-for-age percentiles.

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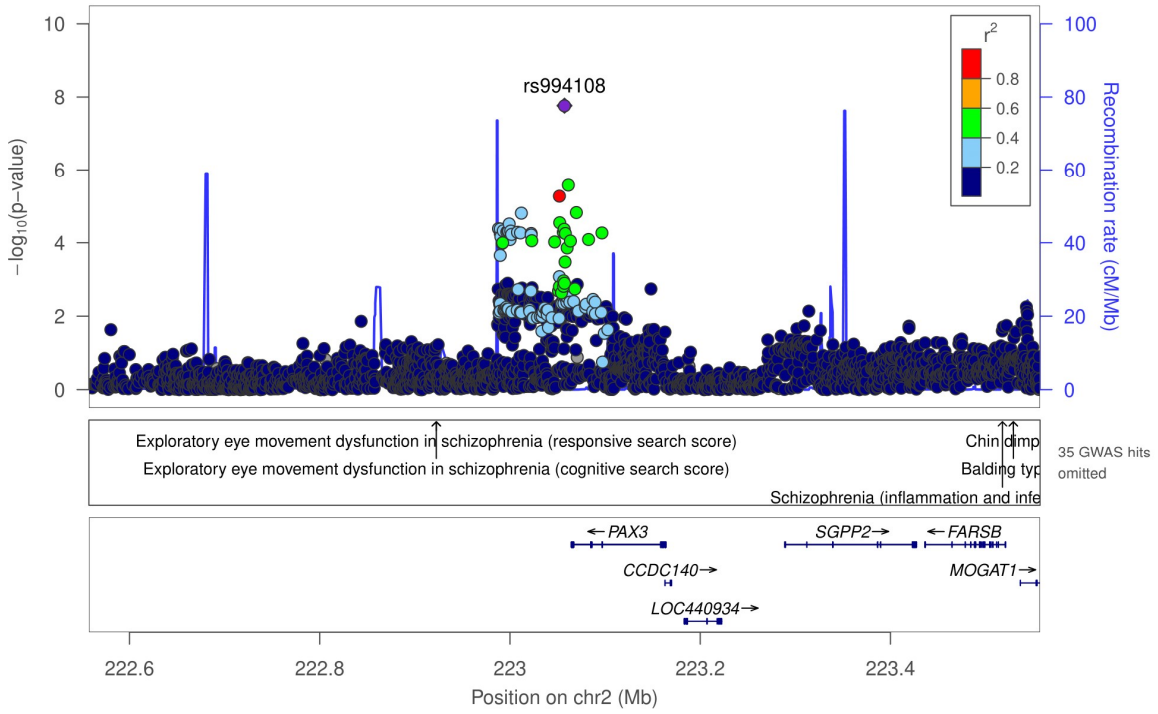
A. *PAX3* locus associated with BMI



B.

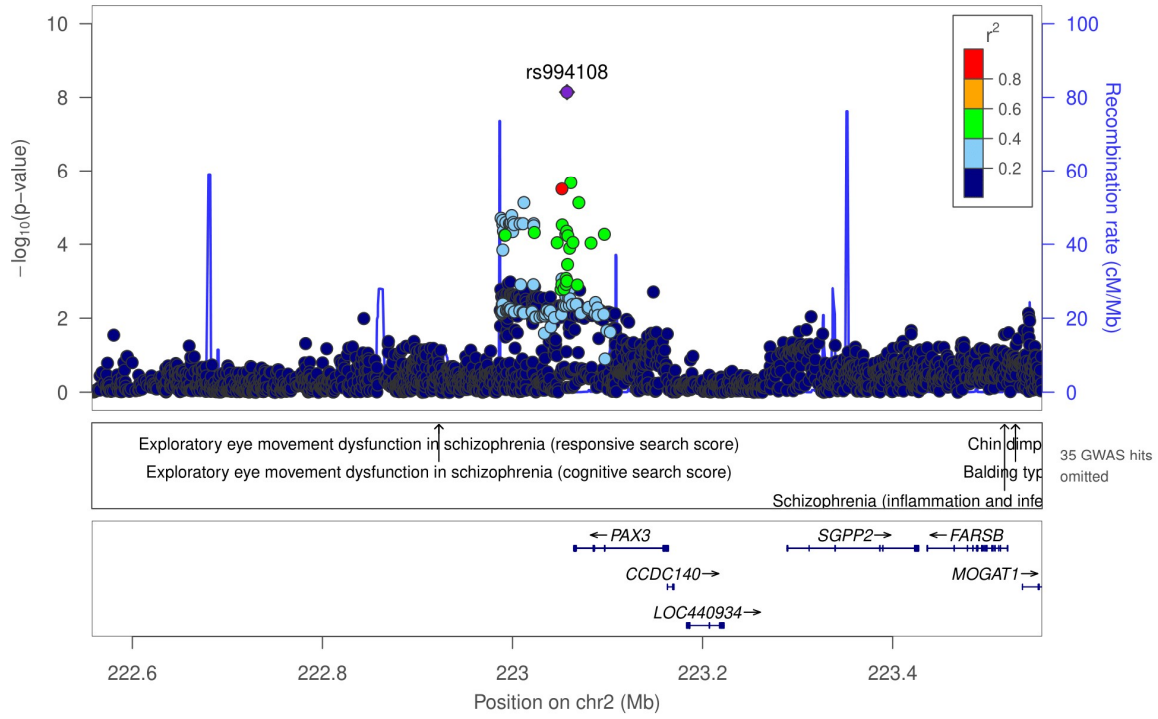


Figure 2. Regional plot, unconditioned (A) and conditioned (B), of the novel *PAX3* locus associated with body mass index (BMI) in the Hispanic/Latino Anthropometry Consortium (HISLA), excluding Brazilian and Native American samples. Linkage disequilibrium patterns are based on rs994108 (shown by the purple triangle) from the Hispanic Communities in Health Study/Study of Latinos.

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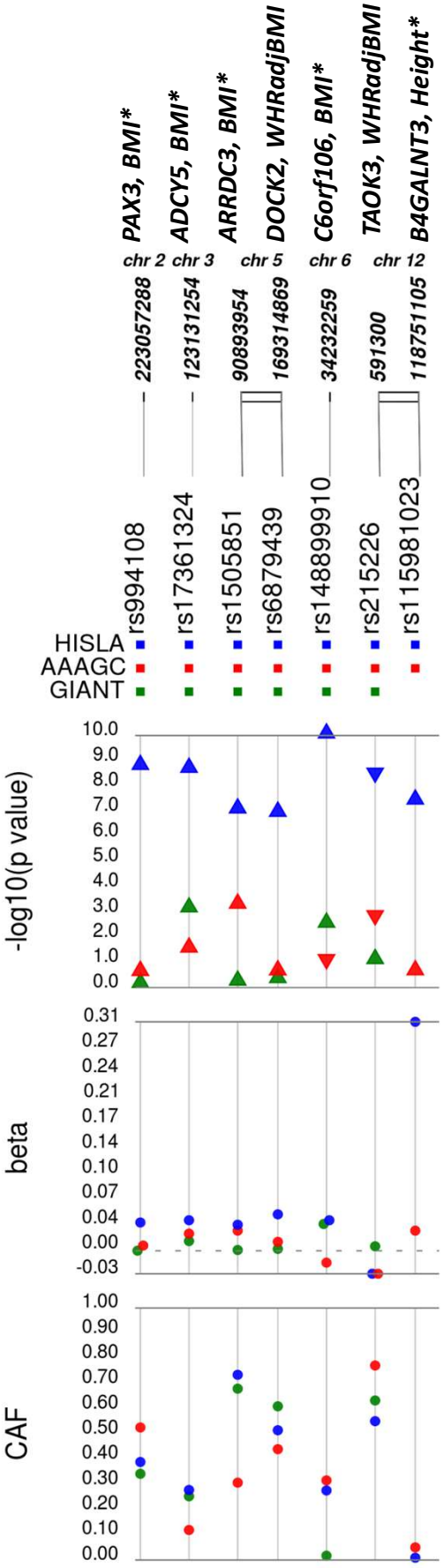

Figure 3. Variability in HISLA Stage 1+2 (blue), AAAGC (red), and GIANT (green) P-values, Effect Sizes and Coded Allele Frequencies for Genome-Wide Significant Anthropometric Loci from HISLA Stage 1.

Hispanic/Latino Anthropometry Consortium (HISLA); African American Anthropometry Genetics Consortium AAAGC; Genetic Investigation of ANthropometric Traits (GIANT); WHRadjBMI - waist to hip ratio adjusted for BMI

*Asterisks indicating a SNPs that were significant either as a novel locus or new signals in a known locus.

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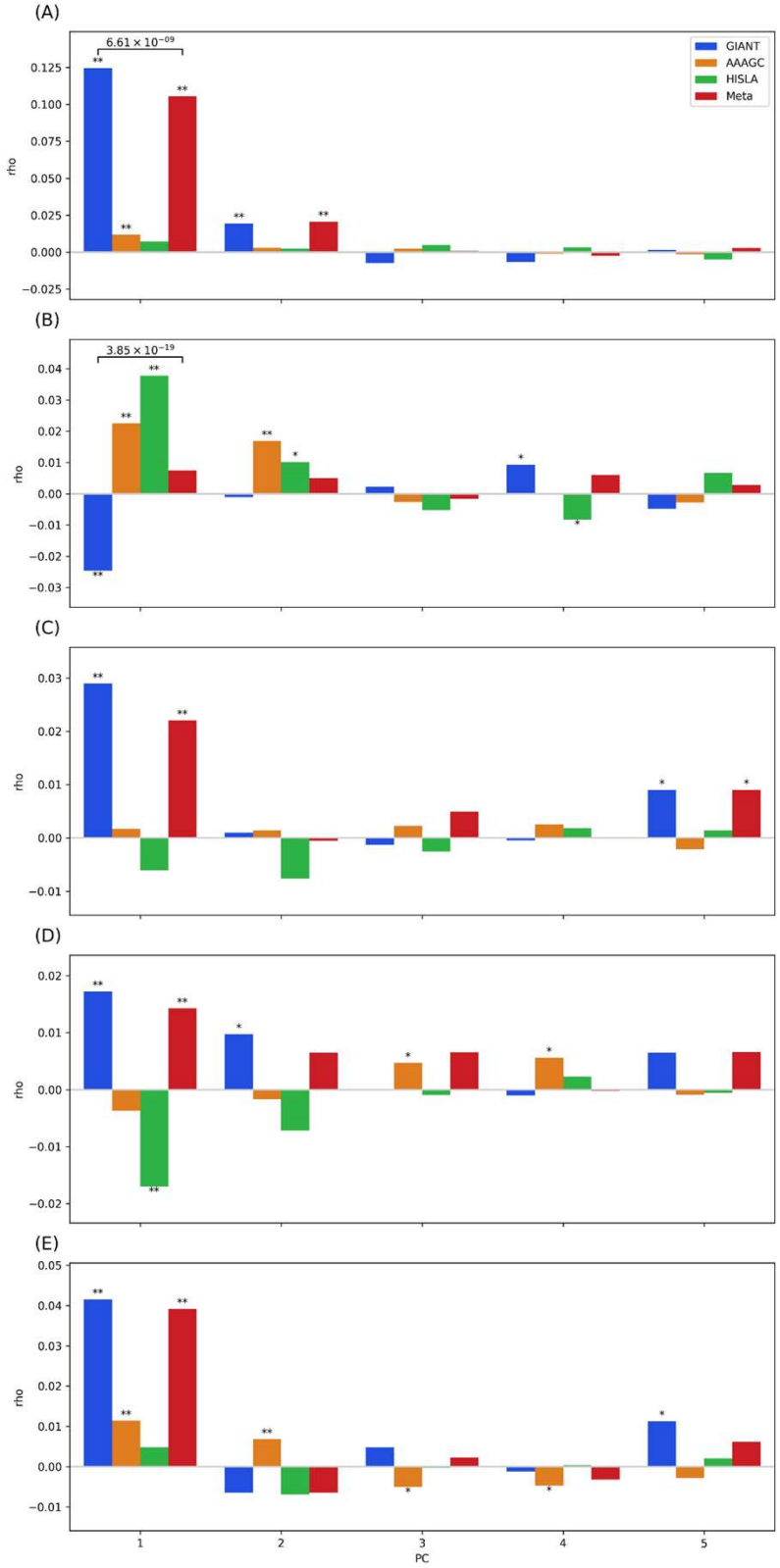

Figure 4. Correlations (rho) between effect estimates and the loadings of the principal components 1-5 in each consortia and the meta-analysis of all 3 consortia by trait. (A) height, (B) BMI, (C) Waist-to-hip ratio adjusted for BMI (WHRadjBMI) for men and women combined, (D) WHRadjBMI for women only, (E) WHRadjBMI for men only.

Hispanic/Latino Anthropometry Consortium (HISLA); African American Anthropometry Genetics Consortium AAAGC; Genetic Investigation of ANthropometric Traits (GIANT); WHRadjBMI - waist to hip ratio adjusted for BMI

Table 1. Potential novel loci and new signals in known loci from the Stage 1: Adult HISLA Discovery combined with results from the Stage 2: Adult HISLA Validation.[1] In addition, lookup of results of each locus from the AAAGC and GIANT.

Trait	Locus Name	SNP rsid	Genomic region	Chr	Position (hg19)	Effect/Other Alleles	Stage	EAF	Beta	SE	P-value	HetISq	N	Yes/No
Novel loci														
BMI[2]	*PAX3*	rs994108	intergenic	2	223057288	C/A	Stage 1: Discovery	0.390	0.041	0.007	**1.62E-08**	0	43048	**Yes**
							Stage 2: Validation	0.394	0.030	0.016	5.65E-02	8	9336	
							Stage 1 + 2	0.389	0.038	0.006	**2.19E-09**	0	52384	
							AAAGC	0.526	0.007	0.007	3.26E-01	0	42751	
							GIANT	0.342	0.0001	0.004	9.81E-01	-	233955	
BMI	*ARRDC3*	rs1505851	intronic	5	90893954	T/C	Stage 1: Discovery	0.741	0.041	0.007	**2.29E-08**	0	52365	No
							Stage 2: Validation	0.709	0.005	0.017	7.62E-01	33.3	9336	
							Stage 1 + 2	0.735	0.035	0.007	1.16E-07	14.1	61701	
							AAAGC	0.307	0.027	0.008	7.00E-04	46.6	42752	
							GIANT	0.680	0	0.004	7.90E-01	-	233999	
WHRadjBMI - Women only[2]	*DOCK2*	rs6879439	intronic	5	169314869	C/T	Stage 1: Discovery	0.520	0.060	0.010	**1.02E-08**	0	18591	No
							Stage 2: Validation	0.526	0.013	0.028	6.54E-01	28.7	2747	
							Stage 1 + 2	0.515	0.049	0.0093	1.57E-07	1.9	23382	
							AAAGC	0.440	0.012	0.012	3.09E-01	0	15600	
							GIANT	0.610	0.0025	0.005	6.30E-01	-	86317	
WHRadjBMI - Sex combined	*TAOK3*	rs115981023	intronic	12	118751105	A/G	Stage 1: Discovery	0.009	0.328	0.057	**1.08E-08**	44.8	19640	No
							Stage 2: Validation	0.004	-0.339	0.687	6.22E-01	0	1340	
							Stage 1 + 2	0.009	0.308	0.057	5.18E-08	52	20980	
							AAAGC	0.050	0.027	0.027	3.07E-01	0	15601	
							GIANT	0.002	no proxy					
New signals in known loci														
BMI	*ADCY5*	rs17361324	intronic	3	123131254	T/C	Stage 1: Discovery	0.280	0.042	0.008	**2.60E-08**	0	43333	**Yes**
							Stage 2: Validation	0.269	0.035	0.018	4.70E-02	0	9035	
							Stage 1 + 2	0.278	0.041	0.007	**2.84E-09**	0	52368	
							AAAGC	0.119	0.023	0.011	3.85E-02	0	42682	
							GIANT	0.253	0.013	0.004	9.90E-04	-	320704	
	C6orf106	rs148899910	intergenic	6	34232259	C/G	Stage 1: Discovery	0.275	0.040	0.007	**9.03E-09**	0	54105	**Yes**
							Stage 2: Validation	0.282	0.049	0.017	4.43E-03	0	9035	
							Stage 1 + 2	0.276	0.041	0.006	**1.24E-10**	0	63140	
							AAAGC	0.316	-0.016	0.008	5.02E-02	30	42750	
							GIANT[4]	0.017	0.036	0.012	3.99E-03	-	216522	
Height	*B4GALNT3*	rs215226	intronic	12	591300	A/G	Stage 1: Discovery	**0.550**	**-0.032**	**0.005**	**5.53E-09**	22.1	52156	**Yes**
							Stage 2: Validation	0.565	-0.020	0.017	2.37E-01	19.3	6906	
							Stage 1 + 2	0.551	-0.031	0.005	**1.98E-09**	21.8	59062	
							AAAGC	0.772	-0.031	0.009	8.99E-04	24	41327	
							GIANT	0.633	0.006	0.004	1.10E-01	-	220370	

Abbreviations: Chr - chromosome; EAF - effect allele frequency; HetIsq - heterogeneity I-square; N - sample size; WHRadjBMI - waist to hip ratio adjusted for BMI; African American Anthropometry Genetics Consotrium AAAGC; Genetic Investigation of ANthropometric Traits (GIANT)

1 All studies were meta-analyzed using METAL (Willer et al 2010 PMID 20616382), with each study entered individuals into Stage 1+2 analyses.

2 These BMI and WHRadjBMI analyses did not include Brazilian and/or Native American samples.

3 New loci or signals are those that were validated by HISLA stage 2 results that are directionally consistent with Stage 1 and remaining genome-wide significant after meta-analysis with Stage 1.

4 Proxy GIANT, rs1573905 (r2= 0.96 AMR)

Table 2. Novel loci and new signals in established loci by trait from a meta-analyses of HISLA, AAAGC, and GIANT.

					Alleles					Unconditioned meta-analysis results				EAF in LD	Results after conditioning on all known SNPs within 10Mb region			UKBB (Validation results)				
Trait	SNP rsid	Chr	Position (hg19)	Locus Name	Effect	Other	Known SNPs (P<5e-8 for trait) within 1MB region	EAF	N	Beta	SE	P-value	HetISq	data	Beta	SE	P-value	EAF	N	Beta	SE	P-value
Novel loci [1]																						
BMI	rs4675117	2	227769794	*RHBDD1*	T	C	None	0.374	343628	0.017	0.003	8.56E-08	0	0.348	0.019	0.003	2.23E-09	0.383	336107	0.006	0.002	1.82E-02
BMI	rs9860730	3	64701146	*ADAMTS9-AS2*	A	G	None	0.642	428763	-0.016	0.003	1.67E-08	0	0.596	-0.015	0.003	3.80E-08	0.712	336107	-0.008	0.003	4.54E-03
BMI	rs150992	5	98275197	*CTD-2007H13.3*	A	G	None	0.702	439077	0.018	0.003	5.40E-10	0	0.709	0.017	0.003	1.02E-08	0.693	336107	0.005	0.003	3.74E-02
Height	rs17375290	1	61334177	*NFIA*	A	G	None	0.806	364636	0.017	0.003	3.47E-08	0	0.801	0.017	0.003	3.00E-08	0.794	336474	0.002	0.002	4.58E-01
Height	rs10737541	1	168214098	*ANKRD36BP1*	T	G	None	0.286	319809	-0.018	0.003	1.60E-09	0	0.320	-0.018	0.003	3.16E-10	0.226	336474	-0.004	0.002	4.37E-02
Height	rs4618485	6	73555917	*KCNQ5*	A	G	None	0.634	348626	0.014	0.003	4.72E-08	39.20	0.637	0.018	0.003	4.34E-12	0.604	336474	0.003	0.002	7.02E-02
Height	rs17493997	8	82044302	*PAG1*	C	G	None	0.360	325906	-0.015	0.003	3.42E-08	0	0.273	-0.017	0.003	2.73E-10	0.299	336474	-0.0003	0.002	8.56E-01
WHRadjBMI sex-combined	rs16873543	6	45577134	*RUNX2*	T	C	None	0.703	209552	-0.018	0.004	3.20E-06	0	0.684	-0.022	0.004	9.65E-09	0.724	484563	-0.008	0.002	5.50E-04
New signals in established loci [2]																						
BMI	rs2943633	2	227054881	*KIAA1486*	A	C	rs4072096,rs2176040	0.511	457848	0.016	0.003	1.23E-09	43.70	0.508	0.015	0.003	6.24E-09	0.540	336107	-0.002	0.002	4.19E-01
BMI	rs12636352	3	185469678	*IGF2BP2*	A	G	81,rs1516725,rs73052033,r	0.411	292895	0.020	0.003	3.44E-09	78.70	0.341	0.019	0.003	1.62E-08	0.347	336107	0.004	0.003	1.46E-01
BMI	rs10540	11	494662	*RNH1*	A	G	rs7126805,rs7952102	0.116	470714	-0.021	0.004	1.01E-07	0	0.131	-0.023	0.004	5.75E-09	0.135	336107	-0.007	0.004	4.16E-02
BMI	rs4807179	19	1956035	*CSNK1G2*	A	G	96359,rs12974458,rs45521	0.484	309507	0.020	0.003	2.75E-10	0	0.523	0.018	0.003	1.52E-08	0.632	336107	0.014	0.002	1.06E-08
BMI	rs4813428	20	21451848	*NKX2-2*	T	C	rs8124896	0.132	321797	0.029	0.005	2.89E-10	0	0.095	0.029	0.005	1.46E-10	0.093	336107	0.013	0.004	2.47E-03
Height	rs4912122	1	19876438	*NKX2-2*	A	G	561719,rs1472565,rs12408	0.413	334951	-0.015	0.003	6.33E-09	0	0.423	-0.019	0.003	1.45E-13	0.350	336474	-0.012	0.002	1.58E-11
Height	rs4425978	1	42243878	*HIVEP3*	T	C	0857,rs731862,rs349427,rs	0.516	351587	0.014	0.003	2.14E-08	0	0.472	0.016	0.003	3.63E-10	0.533	336474	0.008	0.002	5.41E-06
Height	rs618555	1	86481084	*COL24A1*	T	C	84,rs1842579,rs568532609,	0.323	320239	0.019	0.003	5.47E-12	0	0.258	0.016	0.003	2.90E-08	0.311	336474	0.008	0.002	1.67E-05
Height	rs6545538	2	56217900	*MIR216A*	A	G	070,rs1346789,rs3791679,r	0.308	305704	0.022	0.003	1.23E-13	0	0.309	0.019	0.003	2.59E-11	0.266	336474	0.011	0.002	1.25E-08
Height	rs2741311	2	233239743	*ALPP*	T	C	.03274,rs882098,rs7587745	0.054	463609	0.046	0.005	1.41E-21	49.6	0.064	0.030	0.005	4.78E-10	0.080	336474	0.033	0.003	2.39E-24
Height	rs7661148	4	17973217	*LCORL*	A	G	16895971,rs2724475,rs682	0.112	139789	-0.064	0.006	2.57E-24	73.6	0.023	-0.035	0.006	2.55E-08	0.135	336474	-0.061	0.003	2.55E-130
Height	rs6935954	6	26255451	*HIST1H2BH*	A	G	06794,rs3799378,rs122137	0.374	345378	0.042	0.003	3.06E-59	46.5	0.359	0.018	0.003	3.29E-12	0.425	336474	-0.027	0.002	1.10E-54
Height	rs6900530	6	35280971	*DEF6*	T	C	404,rs115453475,rs732594	0.207	123137	-0.057	0.005	3.09E-28	79	0.088	-0.036	0.005	6.75E-12	0.027	336474	-0.073	0.005	1.03E-42
Height	rs9472006	6	43067487	*PTK7*	A	G	62731,rs145629243,rs2125	0.141	212931	-0.027	0.005	4.37E-09	0	0.081	-0.034	0.005	7.04E-14	0.041	336474	-0.013	0.004	2.86E-03
Height	rs3822957	6	76607280	*MYO6*	A	G	23,rs12211255,rs2133193,r	0.235	279818	-0.023	0.003	4.88E-12	84.4	0.197	-0.023	0.003	3.44E-12	0.142	336474	-0.015	0.002	1.98E-09
Height	rs1342330	6	144065685	*PHACTR2*	A	T	rs223604	0.547	353259	0.014	0.003	1.70E-08	0	0.565	0.017	0.003	6.95E-12	0.520	336474	0.006	0.002	8.84E-04
Height	rs6936615	6	154355100	*OPRM1*	A	G	rs2275337	0.859	415248	-0.018	0.003	2.47E-08	0	0.834	-0.020	0.003	2.33E-09	0.830	336474	-0.003	0.002	1.73E-01
Height	rs991946	6	166329862	*RP11-252P19.3*	T	C	002433,rs7768382,rs93480	0.495	379912	-0.019	0.002	1.28E-14	36.7	0.481	-0.019	0.002	9.96E-15	0.479	336474	-0.013	0.002	3.92E-13
Height	rs7816300	8	109787856	*TMEM74*	T	C	rs9969501	0.253	397735	-0.015	0.003	2.24E-08	0	0.264	-0.016	0.003	5.47E-09	0.299	336474	-0.002	0.002	3.94E-01
Height	rs4520250	9	88924057	*ZCCHC6*	A	C	187136,rs1854948,rs37401	0.387	295945	0.015	0.003	3.80E-08	55.9	0.322	0.016	0.003	1.48E-08	0.339	336474	0.010	0.002	4.36E-08
Height	rs7029157	9	97000863	*snoU13*	T	C	3346517,rs13283037,rs940	0.138	262808	0.028	0.004	5.85E-11	16.8	0.115	0.026	0.004	1.00E-09	0.088	336474	0.030	0.003	4.55E-22
Height	rs12347744	9	97575273	*C9orf3*	T	C	8,rs10993370,rs563290728,	0.053	454111	-0.032	0.005	6.55E-11	65.8	0.056	-0.030	0.005	6.06E-10	0.061	336474	-0.031	0.004	1.04E-17
Height	rs7024254	9	109498129	*ZNF462*	A	G	027110,rs4743033,rs70336	0.280	324351	0.017	0.003	1.04E-08	23.7	0.278	0.036	0.003	6.10E-35	0.204	336474	0.010	0.002	6.50E-06
Height	rs10119624	9	118305438	*DEC1*	A	G	84,rs12002061,rs12344818,	0.640	353374	0.021	0.003	2.56E-16	31.1	0.635	0.022	0.003	8.02E-17	0.671	336474	0.012	0.002	3.20E-10
Height	rs2902635	10	105476045	*SH3PXD2A*	T	G	148021,rs10883887,rs1119	0.729	308782	-0.021	0.003	1.59E-12	0	0.739	-0.017	0.003	1.62E-08	0.805	336474	-0.015	0.002	7.65E-12
Height	rs17659078	11	2284590	*ASCL2*	A	C	41514,rs35506085,rs43209	0.241	354931	0.019	0.003	1.78E-10	9	0.243	0.016	0.003	3.45E-08	0.273	336474	0.004	0.002	2.24E-02
Height	rs11605693	11	122837037	*C11orf63*	T	C	rs7107012,rs7107560	0.470	380447	-0.017	0.002	3.44E-12	0	0.449	-0.018	0.002	3.07E-14	0.447	336474	-0.013	0.002	4.45E-13
Height	rs621794	11	125849462	*CDON*	A	G	s608251,rs511987,rs23221	0.475	380049	-0.014	0.002	1.46E-08	0	0.438	-0.014	0.002	7.29E-09	0.429	336474	-0.009	0.002	1.76E-07
Height	rs11221442	11	128577624	*FLI1*	C	G	8566,rs654723,rs531236,rs	0.202	352360	-0.022	0.003	2.03E-12	78.8	0.207	-0.023	0.003	2.03E-13	0.252	336474	-0.008	0.002	2.59E-05
Height	rs12300112	12	103147575	*LINC00485*	C	G	6,rs703593,rs833718,rs107	0.126	154014	0.041	0.006	4.31E-13	45.2	0.063	0.038	0.006	3.11E-11	0.027	336474	0.038	0.005	4.61E-12
Height	rs11616067	12	116393174	*MED13L*	A	G	2460488,rs780886,rs23927	0.775	327941	0.021	0.003	6.38E-12	21	0.802	0.018	0.003	2.80E-09	0.768	336474	0.012	0.002	6.01E-09
Height	rs17197170	14	21977962	*METTL3*	A	G	7,rs8016099,rs17792659,rs	0.856	310344	-0.026	0.004	5.40E-12	64.9	0.858	-0.025	0.004	3.74E-11	0.828	336474	-0.018	0.002	3.07E-14
Height	rs11076551	16	51109492	*RP11-883G14.4*	A	G	,rs8046199,rs138937927,rs	0.289	434688	0.014	0.003	2.14E-08	21.6	0.370	0.015	0.003	5.87E-09	0.376	336474	0.009	0.002	2.51E-07
Height	rs12918773	16	89741403	*C16orf55*	A	G	74,rs2056309,rs57856222,r	0.138	279104	-0.024	0.004	7.45E-09	46.1	0.100	-0.024	0.004	3.50E-09	0.112	336474	-0.024	0.003	4.71E-19
Height	rs1346490	19	7244233	*INSR*	A	C	1549616,rs34840745,rs891	0.521	333896	0.015	0.003	3.99E-09	12.3	0.617	0.014	0.003	4.86E-08	0.620	336474	0.009	0.002	1.67E-07
Height	rs17457472	19	17493610	*PLVAP*	A	C	5,rs2279008,rs2303745,rs7	0.035	356712	-0.051	0.007	5.70E-14	0	0.039	-0.042	0.007	9.89E-10	0.040	336474	-0.019	0.004	1.12E-05
WHRadjBMI sex-combined	rs17099388	5	142095250	*FGF1*	A	G	rs10477191	0.165	105460	0.039	0.007	3.14E-09	0	0.074	0.037	0.007	2.47E-08	0.041	484563	0.025	0.005	2.00E-07
WHRadjBMI sex-combined	rs7975017	12	26428793	*SSPN*	T	C	rs10842707	0.243	267044	-0.021	0.004	7.57E-09	5.50	0.263	-0.021	0.004	1.05E-08	0.239	484563	-0.014	0.002	2.00E-09

Abbreviations: Chr - chromosome; EAF - effect allele frequency; HetIsq - heterogeneity I-square; N - sample size; WHRadjBMI - waist to hip ratio adjusted for BMI; African American Anthropometry Genetics Consortium AAAGC; Genetic Investigation of ANthropometric Traits (GIANT)

1 Novel locus defined by no known published variants within 1Mb (+/-500 Kb) of the lead SNP.

2 Known locus defined by a 1Mb region with previously identified signal(s) for the indicated trait