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Trans-ethnic fine-mapping of genetic loci for body mass index in the diverse ancestral populations of the Population Architecture using Genomics and Epidemiology (PAGE) Study reveals evidence for multiple signals at established loci

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Abstract

Most body mass index (BMI) genetic loci have been identified in studies of primarily European ancestries. The effect of these loci in other racial/ethnic groups is less clear. Thus, we aimed to characterize the generalizability of 170 established BMI variants, or their proxies, to diverse US populations and trans-ethnically fine-map 36 BMI loci using a sample of >102,000 adults of African, Hispanic/Latino, Asian, European and American Indian/Alaskan Native descent from the Population Architecture using Genomics and Epidemiology Study.

We performed linear regression of the natural log of BMI (18.5–70kg/m^2) on the additive single nucleotide polymorphisms (SNPs) at BMI loci on the MetaboChip (Illumina, Inc.), adjusting for age, sex, population stratification, study site or relatedness. We then performed fixed-effect meta-analyses and a Bayesian trans-ethnic meta-analysis to empirically cluster by allele frequency differences. Lastly, we approximated conditional and joint associations to test for the presence of secondary signals.

We noted directional consistency with the previously reported risk alleles beyond what would have been expected by chance (binomial p<0.05). Nearly a quarter of the previously described BMI index SNPs and 29 of 36 densely-genotyped BMI loci on the MetaboChip replicated/generalized in trans-ethnic analyses. We observed multiple signals at 9 loci, including the description of seven loci with novel multiple signals.

This study supports the generalization of most common genetic loci to diverse ancestral populations and emphasizes the importance of dense multi-ethnic genomic data in refining the functional variation at genetic loci of interest and describing several loci with multiple underlying genetic variants.

Keywords

Fine-mapping; Body Mass Index; Allele Frequency Heterogeneity

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ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

CONFLICTS OF INTEREST

On behalf of all authors, the corresponding author states that there is no conflict of interest.

INTRODUCTION

Obesity is a global epidemic and has become a top public health concern given its downstream effects on cardiovascular disease, diabetes, cancer, and other diseases (Popkin 2009). In the United States (US), there are marked racial/ethnic differences in obesity prevalence among adults (Flegal et al. 2012). For example, the US National Health and Nutrition Examination Survey estimated that in 2009–2010, non-Hispanic/Latino African descent (50%) and Hispanic/Latino (39%) adults had the highest burden of obesity; whereas adults of non-Hispanic/Latino European descent had the lowest (34%). Studies of Asian descent subpopulations indicate that they may have an even lower prevalence of obesity between 4–10% (Oza-Frank et al. 2009). Given that non-European ancestries and Hispanic/Latinos collectively make up more than one third of the US population and are experiencing some of the fastest population growth (Humes et al. 2011), future public health research on the determinants of obesity in US must be relevant to these racial/ethnic minorities.

Body mass index (BMI, kg/m^2) is commonly used to classify obesity in epidemiologic studies and is a polygenic trait with heritability estimates ranging between 40–70% (Hjelmborg et al. 2008; Maes et al. 1997). As numerous genome-wide association studies (GWAS) of predominantly European descent populations have identified more than 100 BMI loci (Berndt et al. 2013; Locke et al. 2015; Okada et al. 2012; Speliotes et al. 2010; Wen et al. 2012; Wen et al. 2014; Willer et al. 2009; Winkler et al. 2015), little is known about the effect of these loci in non-European ancestries. Therefore, the study of diverse populations can inform the generalizability and diversity of alleles at established loci and aid the identification of underlying causal variants through trans-ethnic fine-mapping.

To this aim the Population Architecture using Genomics and Epidemiology (PAGE) Study was designed to extend the current body of knowledge on the genetic determinants of complex chronic diseases from studies of primarily European descent populations to African, Hispanic/Latino, Asian and American Indian/Alaskan Native ancestries (Matise et al. 2011), which within the US are differentially affected by the obesity epidemic (Flegal and Troiano 2000; Oza-Frank et al. 2009). In this study of approximately 102,000 adults from diverse ancestries, we aimed to generalize a total of 170 previously described BMI index single nucleotide polymorphisms (SNPs), or their available proxies, located within 166 loci and to fine-map 36 of these BMI loci with dense genotyping on the MetaboChip (Illumina, Inc.) using trans-ethnic meta-analytic methods to narrow the putative interval for future biologic study.

METHODS

Study Population

The Population Architecture using Genomics and Epidemiology (PAGE) Study is comprised of several large study sites/consortia and a coordinating center bringing together samples of diverse populations including those included in this analysis: the Atherosclerosis Risk in Communities (ARIC) Study, the Epidemiologic Architecture for Genes Linked to Environment study accessing BioVU (EAGLE BioVU), Coronary Artery Risk Development in Young Adults (CARDIA), Cardiovascular Health Study (CHS), the Hispanic Community Health Study/Study of Latinos (HCHS/SOL), Multiethnic Cohort (MEC), the Women's Health Initiative (WHI) (Matise et al. 2011). Additional studies collaborating in this analysis also included: the GenNet Network (GenNet), the Hypertension Genetic Epidemiology Network (HyperGEN) Study, the MEC-Slim Initiative in Genomic Medicine for the Americas Type 2 Diabetes Consortium (MEC-SIGMA), the Mount Sinai School of Medicine BioBank (BioME), and the Taiwan-MetaboChip Study for Cardiovascular Disease (TaiChi) study. A detailed description of each study can be found in our Supplemental Materials.

Racial/ethnicity was self-reported in most studies except for EAGLE BioVU where racial/ethnicity is observer-reported (Dumitrescu et al. 2010; Hall et al. 2014). MEC-SIGMA sample included Type 2 Diabetes cases and controls from Los Angeles, CA (Consortium et al. 2014). The TaiChi Consortium substudies were conducted in Taiwan, the San Francisco Bay Area, and Hawaii and represent East Asian ancestry (Assimes et al. 2016). The PAGE MEC and WHI Hispanic/Latino samples predominantly represent individuals of Mexican origin (Carty et al. 2013), whereas the HCHS/SOL (Daviglus et al. 2012) and BioME Hispanic/Latino samples were more diverse with respect to Hispanic/Latino backgrounds and admixture (e.g. African, European and American Indian) (Tayo et al. 2011). The majority of WHI Asian American samples were of Chinese and Japanese descent, but also included smaller samples of other backgrounds (e.g. Hawaiian, Filipino, Korean, and Vietnamese). MEC represents both Japanese and Hawaiian ancestries, which were analyzed separately based on their self-reported Asian background. Only WHI recruited American Indians/Alaskan Natives.

The PAGE datasets generated during and/or analyzed during the current study are available in the dbGaP repository (http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000356.v1.p1). These non-PAGE datasets are either available on dbGaP or if not funded by the National Institutes of Health are available from the corresponding author by request. Each study obtained approval from their Institutional Review Boards and written consent from all participants with the exception of EAGLE BioVU, which followed an opt-out program (Pulley et al. 2010; Roden et al. 2008).

Genotyping and Imputation

The MetaboChip was a custom Illumina iSELECT array that contained approximately 195,000 SNPs and was designed to support large scale follow up of putative associations for cardiovascular and metabolic traits, including BMI (Voight et al. 2012). Approximately 33% of the MetaboChip SNPs were included as replication targets and 62% were included for fine-mapping within 257 targeted densely-genotyped loci, which included 21 loci associated with BMI as of 2009 (Voight et al. 2012) and 15 additional loci (i.e. originally included on the MetaboChip for other cardiometabolic traits) associated with BMI since 2009 (Locke et al. 2015; Okada et al. 2012; Speliotes et al. 2010; Wen et al. 2012; Wen et al. 2014; Winkler et al. 2015). Collectively, these 36 densely-genotyped BMI MetaboChip loci include 37,900 SNPs (Supplemental Table 1), represent 20% of all BMI loci identified as of June 2016. Across the entire MetaboChip more than a third of all BMI loci are represented by either at least one index SNPs, or at leats one proxy SNP. We define a locus as was done as part of the design of the MetaboChip (Voight et al. 2012). Therefore as shown in Supplemental Table 1 the number of SNPs per locus, which varied widely as a function of the base pair range of the putative region of interest (133 to 3,494 SNPs across 38 kb to 1.9Mb, respectively) and the tiered-prioritization of 11 dense-genotyping for cardiometabolic phenotypes of interest (e.g. BMI) (Voight et al. 2012).

As part of the PAGE Study, the genotyping of the MetaboChip was performed at research genomics laboratories: the Human Genetics Center of the University of Texas-Houston (Houston, TX), the Vanderbilt University Center for Human Genetics Research (CHGR) DNA Resources Core (Nashville, TN), University of Southern California Genomics Core (Los Angeles, CA), and the Translational Genomics Research Institute (Phoenix, AZ) (Buyske et al. 2012). Each genotyping center genotyped the same 90 HapMap YRI (Yoruba in Ibadan, Nigeria) samples and 2–3% study-specific blinded replicates to facilitate genotyping quality control. The study-specific SNP- and person-level quality control measures are summarized in Supplemental Table 2.

Imputation of MetaboChip SNPs was conducted in MEC-SIGMA (Hispanic/Latinos only), BioME (African and Hispanic/Latino ancestries), and WHI (representing 54% of WHI African descent women, and all of the WHI European descent women) using 1000 Genomes phase 1 reference populations, or in the case of WHI using study-specific reference samples (Liu et al. 2012), and then filtered on imputation quality (Supplemental Table 2). Less than a third of the final analytic sample genotypes were imputed.

In family- and household-based studies, the family structure was either accounted for using a linear mixed models (GenNet, HyperGen) or a generalized estimating equation incorporating clusters of 1st degree relative pairs/household members (HCHS/SOL) (Lin et al. 2014). Within each racial/ethnic group, related participants within the remaining studies and across the PAGE studies were identified using PLINK (Purcell et al. 2007). When apparent first-degree relative pairs or individuals with high inbreeding coefficients ($F>0.15$) (Weale 2010) were identified by non-PAGE study investigators or by the PAGE Coordinating Center, these individuals or the member from each pair with the lower call rate was excluded from further analysis. Principal components of ancestry were calculated using the Eigensoft software (Patterson et al. 2006; Price et al. 2006) and determined either among the unrelated subset, or in the 1000 Genomes reference populations, and then projected to the study and racial/ethnic sample (Lin et al. 2014). Within each race/ethnic group in each study, ancestral outliers of the resulting principal components were excluded by each study's investigators or the PAGE Coordinating Center from further analysis (Buyske et al. 2012).

Ascertainment of BMI

Weight and height were measured by trained clinic staff in the ARIC, CARDIA, CHS, GenNet, HCHS/SOL, HyperGen, WHI and TaiChi studies. In EAGLE BioVU, weight and height were calculated across the complete medical histories (Crawford et al. 2015) following a published protocol (Goodloe et al. in press). For BioMe, height and weight measures were obtained from participants' medical records at the time of enrollment (Locke et al. 2015; Monda et al. 2013). In MEC weight and height were self-reported by questionnaire with good validity (Lim et al. 2011; Lim et al. 2012).

BMI was then calculated as the ratio of weight to height squared. Following previous PAGE study recommendations to remove extreme outliers (Fesinmeyer et al. 2012; Gong et al. 2013), BMI values <18.5 or >70 kg/m^2 are excluded due to the potential for these extremes to be coding errors, reflect underlying illnesses or rare genetic mutations. However, due to the young average age of CARDIA participants, additional data cleaning was performed in CARDIA and individuals <18.5kg/m^2 were retained in the final analytic sample. To reduce the influence of variation in growth and development on quantitative variation in BMI, we limited our analytic samples to adults >19 years of age in EAGLE BioVU, CARDIA, and BioME, and >20 years of age in HCHS/SOL. Across the PAGE studies (Supplemental Table 3) we had genotype and BMI information available on a resulting analytic sample of 35,606 African, 26,048 Hispanic/Latino, 22,466 Asian and 535 American Indian/Alaskan Native descent adults.

Statistical Analysis

As described previously (Fesinmeyer et al. 2012; Gong et al. 2013) the distribution of BMI was naturally log (ln) transformed to minimize the influence of outliers. All regression models were adjusted for age, sex, the top 2 to top 10 principal components, and study site, as appropriate for the racial/ethnic group and study (Supplemental Table 2). Study- and racial/ethnic-specific linear regression models were implemented in PLINK (Purcell et al. 2007), R (WHI, https://cran.r-project.org), SNPTEST (BioME), GWAF (GenNet, HyperGen) (Chen and Yang 2010), or a weighted version of a generalized estimating equation in SUGEN (HCHS/SOL) (Lin et al. 2014).

Generalization of Established SNP-Associations with BMI in Diverse Populations

We created a Bonferroni corrected threshold of significance for the 170 index SNPs (or if unavailable on the MetaboChip, their highest LD proxy, $r^2 \geq 0.8$ in the discovery population 1000 Genomes pilot CEU, YRI, or CHB+JPT) from previous GWAS or MetaboChip-wide studies (Supplemental Table 4) after accounting for the four loci with more than one racial/ethnic specific finding in strong linkage disequilibrium (LD, $r^2 \geq 0.8$ in CEU, YRI and CHB +JPT). Replication (i.e. in the same population of discovery) or generalization (i.e. to another racial/ethnic group) was declared if an index SNP was: 1) Bonferroni significant for 166 independent tests (p-value$<3.0\times10^{-4}$) and 2) had a consistent direction of effect as the previous report. These same criteria were applied to any index SNP within the 36 densely-genotyped BMI loci. Strong evidence of effect heterogeneity was defined as less than a Bonferroni p-value (i.e. 0.05/166 for index SNPs, or a locus-specific threshold described below). Using a binomial distribution, we tested if the number of observed SNPs with directional consistency between the risk allele observed in this study and prior studies was greater than would be expected by chance (50% expected allele consistency by chance, $p<0.05$ significant).

Replication/Generalization of 36 Densely-Genotyped BMI Loci in Diverse Populations

To identify independent signals in the fine-mapped regions, we generated a locus-specific Bonferroni correction for multiple comparisons based on the number of independent SNPs ($r^2 \leq 0.2$, pruned in PLINK using a 50-SNP window that was shifted by five SNPs each iteration) in the African descent samples with MetaboChip data from the ARIC Study (n=3,399). This served as a worst-case scenario of the maximum number of independent tests in the present study's populations with the least LD. The resulting p-value thresholds for statistical significance ranged from 6.31×10^{-5} to 1.39×10^{-3} (Supplemental Table 1).

Among the subset of the 28,573 SNPs passing quality control and located in the 36 densely-genotyped loci (range per locus: 110 to 2,785; Supplemental Table 1), we conducted inverse variance fixed-effect meta-analysis across studies (>100 observations each) in METAL (version 2011-03-25) (Willer et al. 2010) when the SNP was >0.1% minor allele frequency (MAF) in the racial/ethnic group and was informed by more than half of the maximum racial/ethnic-specific sample size.

Trans-Ethnic Meta-Analyses to Narrow the Putative Interval

Similarly, we generated trans-ethnic meta-analyses for SNPs >0.1% MAF in each racial/ethnic group and informed by at least two populations and more than half of the maximum trans-ethnic sample size (n=101,979). We excluded American Indians/Alaskan Natives from our trans-ethnic fixed-effect estimates due to their small sample size and possible within group heterogeneity due to their recruitment across all nation-wide WHI recruitment centers (n=535).

Linkage Disequilibrium—Finally the fine-mapping of causal variants was informed by estimates of population-specific allele frequencies and LD correlation (r^2, 500 Kb sliding windows) in PLINK (Purcell et al. 2007) using genotypes from the ARIC (African descent), HCHS/SOL (Hispanic/Latino), and WHI studies (Asian, European, and American Indian/Alaskan Native ancestries). As done in a previous large meta-analysis of BMI (Justice et al. in press), trans-ethnic LD estimates were generated from a sample of 17,437 individuals from 1000 Genomes YRI (pilot), ARIC, MEC, HCHS/SOL and WHI, which was both closely proportionate to the racial/ethnic groups of our trans-ethnic meta-analysis (37% African, 26% Hispanic/Latino, 20% Asian, 17% European descent; compared to 35%, 26%, 22%, 18%, respectively, in the full trans-ethnic sample) and also representative of the PAGE studies with the greatest amount of within racial/ethnic group diversity (e.g. HCHS/SOL for Hispanic/Latinos, WHI for Asian Americans; see section on *Study Population* for more information). Regional plots were generated using LocusZoom to visualize trans-ethnic association differences as well as across the LD of various racial/ethnic groups (Pruim et al. 2010).

Bayesian Trans-Ethnic Meta-Analysis—Lastly, the assumption of fixed-effects across racial/ethnic groups was relaxed in a Bayesian trans-ethnic meta-analysis in MANTRA, which allows for the empirical estimation of mean allele frequency differences between racial/ethnic groups as prior information in the clustering of the observed genetic effects across defined racial/ethnic groups (Morris 2011)—in our case African, Hispanic/Latino, Asian and European ancestries. We adjusted for multiple comparisons in this Bayesian analysis by defining very strong evidence in favor of association as having a Bayes Factor (BF)>5, or strong evidence in favor for effect heterogeneity after applying MANTRA as having a posterior probability of effect heterogeneity above a Bonferroni correction for the number of independent index tests (e.g. posterior probability>1–0.05/166) or above the Bonferroni correction for the number of independents tests per locus, both described above. Furthermore, we also calculated the posterior probability ϕ_j that the .th SNP in the .th independent signal is causal as:

$$\varphi_j = \frac{BF_j}{\sum_k BF_k}$$

We then ranked all SNPs by their BFs and summed their cumulative posterior probabilities until it exceeded 99%. The resulting set of SNPs constitutes the 99% credible set and defines a genomic region where there is a 99% probability of containing the causal SNP, if the assumption holds that each region of interest contained only one causal variant.

Established and Novel Secondary Signals at Known Loci—We further investigated our trans-ethnic fixed-effect meta-analysis results at the 36 densely-genotyped loci for second independent signals using Genome-wide Complex Trait Analysis (GCTA, version 64) (Yang et al. 2012; Yang et al. 2011). To inform our approximations we used the same trans-ethnic genotypes of 17,437 individuals from 1000 Genomes YRI (pilot), ARIC, MEC, HCHS/SOL, and WHI, which were used to calculate trans-ethnic LD above and were proportionate to the racial/ethnic groups of our trans-ethnic meta-analysis. We first filtered out SNPs with high trans-ethnic heterogeneity (heterogeneity p-value<1.66×10^{-6}) and then adjusted for the 'lead SNPs' (i.e. the marker with the smallest p-value within each region) of the densely-genotyped regions in an approximate conditional model. We contrasted the conditional effect estimates and p-values of the surrounding SNPs with their unconditional estimates to ascertain if any additional SNPs that were associated unconditionally with BMI at p-value<0.1 then arose as significantly 'independent' after we adjusted for the lead SNPs of these regions and took the number of independent tests in the region into account (see locus-specific threshold above). We repeated this approach to ensure that no additional significant lead conditional SNPs arose in subsequent rounds of adjustments.

Then we entered these potentially independent SNP markers into an approximate joint model in GCTA, which included all of the lead SNPs in the 36 densely-genotyped loci as well as the 170 index SNPs for BMI outside of these regions to account for any potential long-range LD with BMI loci not densely-mapped on the MetaboChip. Joint analyses were repeated dropping out the SNPs with non-significant joint p-values (p-value<0.05/166 for index SNPs; or p-value less than the locus-specific threshold for lead or secondary SNPs in densely-genotyped regions), until a final joint model included only significant joint SNP associations. As a sensitivity analysis of a subset of 6 loci with evidence of independent signals from the approximate GCTA analyses, we performed a single round of exact conditional analyses using the same statistical analysis and meta-analysis software as described above for the unconditional analyses. In this round we adjusted for the lead fixed-effect trans-ethnic SNP and queried the significance of the remaining SNPs within the densely-genotyped region. We also ran the approximate conditional analyses within each race/ethnic group, meta-analyzing conditional results across race/ethnic groups, and compared this approach to the exact and approximate conditional approaches, described above. Additionally these jointly significant SNPs were queried for functional annotation in HaploReg (version 4.1) (Ward and Kellis 2012). Both GERP and SiPhy conservation, as well as GENCODE and RefSeq genetic annotations were queried on each lead SNP.

Statistical Power

To aid with the interpretation of null study findings, *post hoc* we calculated statistical power in Quanto version 1.2.4 (Gauderman and Morrison 2006) to detect BMI genetic effects. Previous PAGE meta-analyses using this transformation have estimated that genetic effects for risk variants at *FTO* could be as much as 1% change in BMI per risk allele (or 0.0119 on the natural ln scale) (Gong et al. 2013). Using information available on the worst-case locus-specific Bonferroni correction from Supplemental Table 1 (6.31×10^{-5}), the varying BMI distributions and sample sizes of the race/ethnic specific and trans-ethnic meta-analyses (Supplemental Table 3) we calculated power to detect effects up to as large as 1% change in BMI per risk allele.

As shown in Supplemental Figure 1, power was expected to be greatest in the trans-ethnic meta-analysis, which would allow for the identification of moderate genetic effects (>0.6% change per risk allele) at ≥80% power for low frequency variants (≥1%). Despite the smaller size of the Asian descent sample, we estimated that we generally would have better power in the analysis than in the African and Hispanic/Latino (>13,000 and >3,000 samples larger, respectively) descent analyses, which would allow us to describe large genetic effects at ≥80% for both low frequency and common variants (≥1%). In contrast, the African, Hispanic/Latino, and European descent analyses were expected not have sufficient power (<80%) to describe low frequency variants (e.g. ≤1%), and only had sufficient power (≥80%) to describe moderate effects (>0.6% change per risk allele) that were common (≥5%) in that specific race/ethnic group.

RESULTS

Our study was comprised of 102,514 individuals from five racial/ethnic groups, with a mean age spanning from 27 years old (range: 20–37 years) in CARDIA to 73 years (65–93 years) in CHS (Supplemental Table 3). The biobank studies (EAGLE BioVU, BioME), as well as HCHS/SOL, HyperGen, and TaiChi represented ages across more than 5 decades of the life course. Women comprised the majority (or entirety, as in the WHI) of all studies, except for the TaiChi sample, which was only 39% female. Within sex obesity prevalence varied substantially across studies (26–64% of females and 19–46% of males were obese at the time of assessment). Yet obesity prevalence appeared to be generally higher in women and men of African, Hispanic/Latino and American Indian/Alaskan Native ancestry compared to women and men of Asian and European ancestry.

Generalization of Established SNP-Associations with BMI in Diverse Populations

Overall, 135 of 165 SNPs, or their proxies ($r^2 \geq 0.8$), were previously shown to associate with BMI, passed quality control filters in at least two racial/ethnic groups, and displayed consistent directions of effect in the trans-ethnic fixed-effect meta-analysis (Supplemental Table 4). This is more concordant than would be expected by chance (binomial p, p_{bin} $=1.63\times10^{-17}$). Of all 170 index SNPs, or their proxies, that passed quality control filters in at least one racial/ethnic group, 42 were significantly associated with BMI in either the trans-ethnic analyses or in at least one racial/ethnic group. For example, we replicated two African descent-specific associations at *GALNT10* (rs4569924 $p=4.79\times10^{-5}$ (Monda et al. 2013). and *DHX34* (rs4802349, $p=3.79\times10^{-8}$ (Gong et al. 2013)), and demonstrated generalization of associations from previous studies of European descent populations for two SNPs at 8p12 (rs7844647, $r^2=0.96$ in CEU, $p=2.03\times10^{-4}$ (Winkler et al. 2015)) at *AGBL4* (rs657452, $p=5.52\times10^{-6}$ (Locke et al. 2015)) to African and Hispanic/Latino descent individuals, respectively.

Eighteen of the 42 significant index SNP associations were only significant in the trans-ethnic sample, perhaps due to its larger sample size (Supplemental Table 4). Three SNPs exhibited significant heterogeneity across the racial/ethnic groups in the trans-ethnic fixed effect meta-analysis, yet only one of these SNPs (rs116612809, the index SNP at *BRE* and the most significant ('top') SNP in the African descent and trans-ethnic fixed-effect analyses) persisted to have evidence in favor of association after accounting for the ancestral heterogeneity in a Bayesian meta-analysis. One index SNP at *TRAF3* (rs7143963; (Winkler et al. 2015)) was nominally significant and directionally consistent in both the African descent and trans-ethnic analyses, but only exhibited significant heterogeneity across the studies of African descent individuals (Supplemental Figure 2), wherein the effect estimates from two studies with <1,200 individuals were the most extreme (HyperGen n=1171, Risk allele frequency=66.9; MEC pilot n=433, 59.2%).

Replication/Generalization of 36 Densely-Genotyped BMI Loci in Diverse Populations

In 35,606 African descent individuals, 31 of 35 index SNPs (or their proxies) that passed quality controls and were located within one of the 36 densely-genotyped BMI loci showed an association that was directionally consistent with the previously reported risk allele ($p_{bin}=1.52\times10^{-6}$). We observed no significant effect heterogeneity within the studies contributing samples of African descent individuals at either the index or lead SNPs (Supplemental Table 5). Our analysis of the dense genotypes of African descent individuals led to the generalization of 14 BMI loci (Table 1), including six loci (*COBLL1*, *POC5, SLC22A3, TCF7L2, MAP2K5, ATP2A1)* not previously associated in African descent populations, and eight loci that were previously generalized to African descent individuals (Gong et al. 2013): *SEC16B, ETV5, TFAP2B, FTO* and *MC4R* with the same lead SNP and *TMEM18, GNPDA2, and BDNF-AS1/BDNF* with a different lead marker (r^2 of 0.86, 0.98, 0.11, respectively). Additionally as described previously (Gong et al. 2013), rs116612809 at *BRE* replicated as the most significant SNP for BMI in our expanded African descent sample (Table 1). Thus our findings resulted in a total of 15 BMI loci with significant evidence of association in African descent individuals, six of which were best represented by the index SNP from GWAS of European (Locke et al. 2015; Speliotes et al. 2010), and non-European populations (Gong et al. 2013; Monda et al. 2013; Pei et al. 2014).

In a sample of 26,048 Hispanic/Latinos, 32 of 36 index SNPs in the densely-genotyped BMI loci had associations that were directionally consistent with previous reports (p_{bin}=8.57×10^{-7}). We also observed no significant heterogeneity within the Hispanic/Latinos studies at either the index or lead SNPs (Supplemental Table 6). Using the dense-genotyping at 36 BMI loci, we were able to generalize 13 BMI loci to Hispanic/Latinos (Table 2), including 8 loci that were generalized to African descent individuals (*SEC16B TMEM18, COBLL1*, *GNPDA2, TCF7L2, MAP2K5, FTO* and *MC4R*) plus an additional 5 loci (*LYPLAL1, IGF2BP2, SLC39A8, KCNQ1, MTCH2*) that only generalized to Hispanic/Latinos.

In the entire Asian descent sample (n= 22,466), 29 of 34 available index SNPs were directionally consistent (Supplemental Table 7; p_{bin}=4.76×10^{-6}). At *MAP2K5* we did observe evidence of heterogeneity across the Asian descent studies at one nominally significant SNP (rs182297248) (Supplemental Figure 3). Excluding the Hawaiian sample from the MEC (n=2,586) did diminish the effect heterogeneity and decreased the p-value, but not enough to become Bonferroni significant (Supplemental Table 7). When we included the Hawaiian samples from the MEC we were able to generalize to Asian descent adults at eight BMI loci, including loci that were previously generalized to African descent individuals (*POC5, TFAP2B, BDNF-AS1*/*BDNF)*, Hispanic/Latinos (*MTCH2)*, or both racial/ethnic groups (*GNPDA2, TCF7L2, FTO, MC4R)* (Table 3). The lead SNP at *MC4R* was the index SNP from GWAS of European/trans-ethnic populations (Pei et al. 2014; Speliotes et al. 2010). In addition, we replicated three loci (*CDKAL1, KCNQ1, GIPR*) that were previously described in only Asian populations using lead SNPs that were in strong LD (r2>0.8) with the previously reported index SNPs (Wen et al. 2012; Wen et al. 2014), or were the Asian index SNP itself (Okada et al. 2012; Wen et al. 2012; Wen et al. 2014). In summary, a total of 11 BMI loci replicated or generalized to our sample of Asian Americans. We noted that *MTCH2 and MC4R* were no longer Bonferroni significant when we excluded the Hawaiian samples from the MEC in our exploratory analyses (Supplemental Table 7). Thus we carried forward the full Asian American sample in our trans-ethnic meta-analyses, below.

In the European descent sample (n=17,859), 30 of 35 available index SNPs were directionally consistent (p_{bin}=9.45×10^{-6}). We observed no significant heterogeneity across studies at either the index or lead SNPs (Supplemental Table 8). Additionally, we replicated associations at nine BMI loci, including five loci that previously had not been associated with any other racial/ethnic group (*NEGR1, LINGO2, PRKD1, KCNJ2, KCTD15).*

Lastly, in the small sample of 535 American Indian/Alaskan Native women 22 of 35 available BMI index SNPs were directionally consistent (Supplemental Table 9; p_{bin}=4.30×10^{-2}). We were able to generalize the lead SNP (rs73012297) at *SLC22A3* to American Indian/Alaskan Native women, at a different lead SNP than had generalized to African descent individuals (rs116859471, in ARIC r^2<0.01 with top American Indian/Alaskan Native SNP).

Trans-Ethnic Meta-Analyses to Narrow the Putative Interval

Across the ancestries carried forward to trans-ethnic analyses (African, Hispanic/Latino, Asian and European descent), we saw greater variability in risk allele frequencies than effect sizes at index BMI SNPs of the densely-genotyped BMI regions on the MetaboChip (Figure 1). Trans-ethnic fixed-effect meta-analysis in up to 101,979 individuals generalized 29 of 36 BMI loci (Table 4). Most of these loci were already replicated/generalized to at least one racial/ethnic group (Figure 2).

The Bayesian trans-ethnic meta-analysis did not reveal additional loci strongly associated with BMI, as defined as log10 Bayes Factor>5 (Table 4). However, after accounting for ancestral heterogeneity 22 loci had strong evidence in favor of association and only three of these were noted to have a different lead SNP than seen in the fixed-effect analysis. For example, at *BRE* the Bayesian approach resulted in a top/index SNP, which had significant heterogeneity across the African descent studies (Table 1) and across the racial/ethnic groups (Table 4). Whereas, the fixed-effect meta-analysis resulted in a lead SNP that was located ~300kb towards *FOSL2* (Supplemental Figure 4). The other two loci (*IGF2BP2, GIPR)* with top significant SNPs that differed between the two trans-ethnic approaches appeared to be capturing the same signal across the range of LD (e.g. African to European descent) represented in our trans-ethnic meta-analysis.

Using the physical location of the top fixed-effect racial/ethnic specific results, we compared our results to the base pair range defined by the bounds of each MetaboChip densely-genotyped region (Supplemental Table 1) and calculated a percentage reduction of our putative interval of interest (Table 5). Across the 29 loci with significant trans-ethnic fixed-effect estimates the reduction in base pairs and percentage narrowed ranged from 14,099 (37% of region) to 930,200 (72%).

Using a Bayesian approach to account for ancestral heterogeneity, we used the physical bounds of the 99% credible set to reduce the putative interval by 52,690 base pairs (bp) at *ETV5* (46% of region) to 764,979 bp at *CDKAL1* (96% of region; Table 5). Figures 3–4 illustrate the trans-ethnic fixed-effect estimates of 12 loci where the Bayesian approach narrowed the putative interval to ≤ 2 SNPs. The remaining 24 fine-mapped regions are plotted in the Supplement (Supplemental Figures 4–7). At three of these loci (*SEC16B, TFAP2B, MC4R*) the 99% credible set reduced the interval of interest by between from 182,749–566,266 bp to a single SNP (Figure 3).

Established and Novel Secondary Signals at Known Loci

We first performed conditional analyses of the trans-ethnic fixed-effect estimates in the 36 densely-genotyped BMI loci after adjusting for the top trans-ethnic fixed-effect SNP. Then we entered these potential independent signals and index SNPs outside of the densely-mapped BMI regions into an approximate joint analysis, keeping only the significant associations in the final joint model. As previously noted in European descent populations (Locke et al. 2015), we observed that the *SBK1* association (index SNP rs2650492, $p_c = 3.5\times10^{-2}$) was dependent on our lead trans-ethnic SNP at *ATP2A1* (rs8061590), and the presence of Bonferroni-significant secondary signals at *BDNF-AS1* and *MC4R* (Table 6) in weak LD with our top trans-ethnic findings (r^2<0.3). Interestingly, we noted that rs2331841 at *MC4R*, originally reported in Asian populations (Okada et al. 2012), was also nominally independent of our top finding in the region ($p_c = 4.10\times10^{-2}$). Additionally, we confirmed the observation that our association signal located between *GPRC5B* and *GPR139* (lead SNP, rs67501351; joint p, $p_j = 7.70\times10^{-19}$) was independent of the signal at *GP2* (index SNP, rs11074446; $p_j = 1.69\times10^{-7}$).

We also noted a secondary signal at *FTO* in our trans-ethnic sample with BMI in joint analyses (Table 6), which was in moderate LD in our trans-ethnic sample with our lead SNP (r^2=0.41). We also observed evidence for 6 additional novel secondary signals at *LYPLAL1, COBLL1, IRS1, SLC39A8, TFAP2B, STK33/TRIM66* (Table 6). Incidentally most of the 99% credible intervals for the 9 loci with evidence of secondary signals not well refined and included ≥15 SNPs (Table 5); however, *TFAP2B* and *FTO* had 99% credible intervals that included 1–6 SNPs (Figures 1–2). Collectively 10 of 18 SNPs representing multiple signals (6 for primary and 4 for secondary signals) within 9 densely-genotyped regions varied in risk allele frequencies by more than 20% across the racial/ethnic groups (Supplemental Figure 8).

Interestingly the top/index SNP at *BRE* was significant in the single-variant model, but was not significant in the joint model of the most significant SNPs representing each signal, which included a variant >3 Mb upstream at *ADCY3* (rs10182181, $p_j = 2.42\times10^{-10}$). Conditional analyses adjusting for rs10182181 at *ADCY3* confirmed that the top fixed-effect and Bayesian SNPs in the region were no longer Bonferroni significant ($p_c = 2.02\times10^{-3}$ and 9.94×10^{-3}, respectively), suggesting that this association may in part be related to long-range LD patterns.

We also conducted a trans-ethnic exact conditional sensitivity analysis of African, Hispanic, Asian and European descent populations in a subset of densely-genotyped BMI loci, which had evidence of two independent signals in the conditional and joint GCTA analyses. At three of the six loci included in the sensitivity analysis we noted Bonferroni significant evidence for secondary signals (*COBLL1, BDNF-AS1/BDNF, MC4R;* $p_{c\ exact} < 9.5\times10^{-5}$) and at three loci, nominally significant evidence for secondary signals (*LYPLAL1*, *SLC39A8, TFAP2B*; $4.5\times10^{-5} \le p_{c\ exact} \le 1.4\times10^{-2}$; Supplemental Table 10). Additionally, we ran a race/ethnic group-stratified approximate conditional analysis. Although this approach had greater missingness in the meta-analyzed trans-ethnic results, it did confirm the Bonferroni significant exact conditional findings at *COBLL1, BDNF-AS1/BDNF, MC4R*, and also yielded significant evidence of a secondary signal at *IRS1.* Although all secondary signals were supported at nominally significance by all methods, Bonferroni significance was only seen at *LYPLAL1*, *SLC39A8, TFAP2B*, *STK33/TRIM66*, and *FTO* in the approximate conditional (Supplemental Table 10) and joint analyses (Table 6) using a mixed reference population.

DISCUSSION

Trans-ethnic fine-mapping has been called for as an important next step in describing the genetic architecture of BMI (Locke et al. 2015). This work expands on previous fine-mapping efforts conducted by the PAGE Study, which generalized 8 of 21 then known BMI loci to African American individuals (Gong et al. 2013), by including several under-studied populations in genetic epidemiology (Bustamante et al. 2011) with distinct burdens of obesity (Flegal et al. 2012; Oza-Frank et al. 2009). We also incorporate BMI index SNPs from African, Asian, and trans-ethnic GWAS (Monda et al. 2013; Okada et al. 2012; Pei et al. 2014; Wen et al. 2012; Wen et al. 2014), and harness the dense genotypes at 36 BMI loci in a trans-ethnic sample to generalize, or fine-map, more than a third of currently known BMI loci to diverse populations.

The trans-ethnic meta-analyses are better powered than racial/ethnic specific analyses (Supplemental Figure 1) for genetic loci that are shared across ancestral groups (Wang et al. 2013). We find that nearly a quarter of the previously described BMI index SNPs and even more (81%) of the densely-genotyped BMI loci available on the MetaboChip met our definition for generalization in a trans-ethnic sample of 101,979 adults. These results help demonstrate the transferability of common genetic loci to diverse populations and how effect dilution can be avoided using fine-mapping techniques (Carlson et al. 2013).

However, some of the BMI loci assessed in this study (7 of 36) were not significant in our trans-ethnic fixed-effect meta-analysis. Three of these loci replicated in European Americans only (*NEGR1, PRKD1, KCNJ2*). One locus (*SLC22A3*) generalized to individuals of African and American Indian/Alaskan Native descent. Two more loci were significant in at least one subgroup, but the risk alleles were directionally inconsistent at the index SNPs and the lead trans-ethnic SNPs in the regions were in weak LD in WHI European women (*KCNJ11* and *BRAP*/*TRAFD1*, $r^2<0.01$; Supplemental Tables 6–7), suggesting that there may be distinct ancestral haplotypes at these loci. Our results are consistent with the hypothesis that the majority of common genetic loci for complex traits like BMI will generalize to diverse populations given sufficient statistical power (a function of allele frequency, effect size and sample size, etc.) (Carlson et al. 2013), and the importance of considering directional consistency and LD when multiple underlying causal variants may be present across populations.

At 6 loci (e.g. *SEC16B, IRS1, SLC39A8, FAIM2, TCF7L2, MC4R*) we noted the same lead SNP using a Bayesian trans-ethnic fine-mapping approach (Morris 2011) as previously reported in European descent individuals using an approximate Bayesian fine-mapping approach (Locke et al. 2015; Wakefield 2007). Of note, the lead SNP at one of these loci, *SLC39A8*, was a non-synonymous SNP that was conserved across species (Supplemental Table 11). We were also able to narrow the putative regions of interest (in base pairs) at 9 of the 20 loci assessed either at least as well or better than in previous studies (*SEC16B, TMEM18, IRS1, TFAP2B, NT5C2, TCF7L2, BDNF-AS1*/*BDNF, MC4R, GIPR*).

The assumption of one underlying signal appeared to hold for five of these fine-mapped loci (e.g. *SEC16B, TMEM18, NT5C2, TCF7L2, GIPR*), which gives us further confidence to interpret the credible intervals of these five loci as representing the interval where there is a 99% probability of capturing the underlying functional variant. Among these loci, there were several interesting functional consequences (Supplemental Table 11) of our lead SNPs. For example, the lead/index SNP 8.8kb 3′ of *SEC16B* and 3.6kb 3′ of RP4-798P15.2 was the only SNP in our Bayesian 99% credible set and was conserved across species and from histone modification assessment was predicted to be an enhancer in muscle tissue (rs543874). The lead SNP (rs6731872), 43kb 3′ of *TMEM18*, was predicted to change BCL and TR4 motifs, and was identified as an eQTL for C10orf32-AS3MT. The lead/index SNP within *TCF7L2* (rs7903146) was found to be a promoter in pancreas; an enhancer in fat, muscle, and five other tissues; and changed several binding motifs. Interestingly a non-synonymous lead SNP at *GIPR* (rs1800437) lies within a CMYC binding motif, and was predicted to be an enhancer, promoter, and an eQTL with *FBXO46/VASP* in whole blood; a DNAse sensitive region in several tissues including fat, muscle, and pancreas; and found to change a CTCF binding motif.

Due to allelic diversity of our sample, we were able to describe secondary signals for BMI at 9 loci, 7 of which for the first time with BMI (*LYPLAL1, COBLL1, IRS1, SLC39A8, TRAP2B, STK33*/*TRIM66*, and *FTO*). SNPs representing four of these 7 new BMI secondary signals had larger risk-allele frequencies (>20%) across the African, Hispanic/Latino, Asian and European ancestries of our trans-ethnic sample (Supplemental Figure 8), further indicating the potential for remarkable variability in the frequency of underlying causal variants at established BMI loci across diverse populations. A sensitivity analysis comparing exact and approximate conditional p-values supported our approximate conditional findings at nominal significane, or in the case of *COBLL1, IRS1, BDNF-AS1*/*BDNF, MC4R*, at Bonferroni significance.

Using our approximate conditional approach we replicated previously-reported independent BMI signals at *BDNF-AS1*/*BDNF, MC4R* and *GPRC5B/GP2* (Locke et al. 2015). Both the independent lead SNPs for the *BDNF-AS1* (rs1519480) and *BDNF* (rs190666912) signals were conserved across species, predicted to be enhancer in brain and other tissues, and lied in DNAse sensitive regions (Supplemental Table 11). The primary signal (rs1519480) was intronic to *BDNF-AS1* and an eQTL for *BDNF* antisense RNA, which binds to GATA2 and YY1. The SNP for the primary signal (rs6567160, located 209kb 3′ of *MC4R* and 1.7kb 5′ of U4, a small nucleor RNA) was both conserved across species and in a DNAse sensitive region in muscle. In contrast the SNP representing the secondary signal (rs77901086) was 44kb 5′ of *MC4R* and was in high LD (r2>0.8 in 1000 Genomes AFR) with a highly conserved non-synonymous SNP (rs2229616) 44kb upstream within *MC4R*, which alters a GATA binding motif and has histone marks consistent with being a promoter and enhancer in brain. However, only rs6567160 remained in our 99% credible set.

Moreover, our observation of novel secondary signals is supported in the literature at three loci. First, with waist-hip ratio *COBLL1* has been described to have as many as five independent signals (Shungin et al. 2015). Interestingly, we observe stronger LD patterns between our primary BMI signal (rs10184004) and their primary-quaternary waist-hip ratio signals (r^2=0.30–0.97 in 1000 Genomes pilot CEU), and stronger LD between our secondary signal (rs17244444) and their quinary signal (r^2=0.44). Whereas the SNP representing the primary signal at 1.7kb 3′ of *COBLL1* (rs10184004) alters several binding sites including Nrf-2 and Maf for MAFK, is DNAase sensitive in skin and is an eQTL with *SLC38A11* in muscle, the SNP for the secondary signal (rs17244444) was intronic to *COBLL1* and also alters a Nrf-2 binding site (Supplemental Table 11). Second, we have previously noted a possible secondary signal at *TRAP2B* in the Hispanic/Latino women from WHI (Graff et al. 2013). The SNPs representing two signals at the *TFAP2B* region were located on either side of this gene and predicted to modify several binding motifs including TATA and GAGA (rs2744475, rs2397016), but only rs2744475 was retained in our 99% credible set.

Third, even though previous studies of BMI have not previously observed strong evidence for a *FTO* secondary signals (Akiyama et al. 2014; Gong et al. 2013; Locke et al. 2015; Peters et al. 2013; Yang et al. 2012), one study of Type 2 Diabetes has noted a secondary signal at *FTO* in European descent individuals (Maller et al. 2012). The independent signals seen in our study (rs3751812; rs9936385, which is r^2=1.0 with rs9939609 in 1000 Genomes YRI pilot) lie in two distinct clusters of SNPs that define two African ancestral haplotypes (Akiyama et al. 2014). Both of our *FTO* signals (rs3751812, rs9936385) lie within the physical bounds of the putative interval of interest from our earlier PAGE fine-mapping work with African Americans only (Peters et al. 2013). Lastly both signals at *FTO* were intronic and predicted to be enhancers in muscle as well as either fat or brain and DNAse sensitive in brain and several other tissues (rs3751812, rs9936385; Supplemental Table 11). The SNP representing the primary signal at *FTO* (rs3751812) was conserved across species, but interestingly the SNP for the secondary signal (rs9936385) was associated with Type 2 Diabetes in a trans-ethnic sample (Mahajan et al. 2014).

At four loci with novel multiple signals for BMI and no president in the literature, we noted interesting functional consequences of the implicated SNPs (Supplemental Table 11). For example, both independent SNPs (rs2820436, 254kb 3′ of *LYPLAL1*; and rs4445477, 287kb 5′ of *RNU5F*) were predicted to be enhancers in fat and a number of other tissues, as well as modify motifs of a number of binding factors. At the *IRS1* locus, both SNPs (rs2176040, rs2673147) were both located between AC068138.1 (>40kb 5′) and *IRS1* (>400kb 3′), predicted to alter binding motifs and be eQTLs with *IRS1* and *RP11-395N3.2* in adipose tissue, but only the SNP for the secondary signal (rs2673147) was predicted to be an enhancer in brain tissue. In contrast to the non-synonymous SNP for the primary signal at *SLC39A8* (rs13107325), the secondary signal (rs28392891) was located 38kb 3′ of *SLC39A8* and predicted to alter a number of binding motifs. The SNPs representing the region's secondary signal (rs76633799) at *STK33* and the primary signals (rs76876925) at *TRIM66* were predicted to change several binding motifs including HDAC2 sites. The variant at *STK33* (rs76633799) was also conserved across species and an enhancer in fat and skin. Yet a key limitation of this work is that independent effect estimation and replication using exact conditional methods are needed to accurately pinpoint the exact underlying genetic variants and describe the variance explained by them in similarly diverse populations.

Although our study does allow for interesting insights on the genetic architecture of BMI across diverse samples, several additional limitations should be noted. First, fine-mapping resolutions depend on many factors, such as the extent of LD within the locus, allele frequencies and sample sizes of populations. Therefore, not surprisingly in this study the narrowing of the interval in trans-ethnic meta-analyses varied from one locus to another (Table 5). Second, in order to relax the strong assumption of fixed genetic effects in all of the racial/ethnic groups, we have also performed a trans-ethnic Bayesian analysis to apply empirical estimates of the mean allele frequency differences, appropriately cluster the racial/ethnic groups and construct credible intervals of confidence that the causal SNP lies within its bounds. Yet the relative improvement in fine-mapping resolution offered by this Bayesian trans-ethnic meta-analysis related to the ancestral heterogeneity at a given locus, the extent to which the estimated allele frequency differences across populations captured this heterogeneity, the number of independent signals, and their allele frequencies, and it comes at the cost of assuming one underlying signals. Even though approximate conditional and joint analyses helped us rule out the presence of statistically significant secondary signals at 27 densely-genotyped loci, future methodologic work should describe the impact of multiple signals on trans-ethnic fine-mapping techniques.

This study represents another step towards prioritizing candidates for future etiologic study and targeted functional follow-up. The genetic architecture of a complex trait like BMI and disparities in obesity emphasize the need for future obesity interventions to consider both determinants of individual and population-level variation. This study expands our understanding of allele frequency heterogeneity in the genetic architecture of BMI, while emphasizing the importance of diverse ancestral populations and high-dimensional genetic data in the fine-mapping of complex traits.

Supplementary Material

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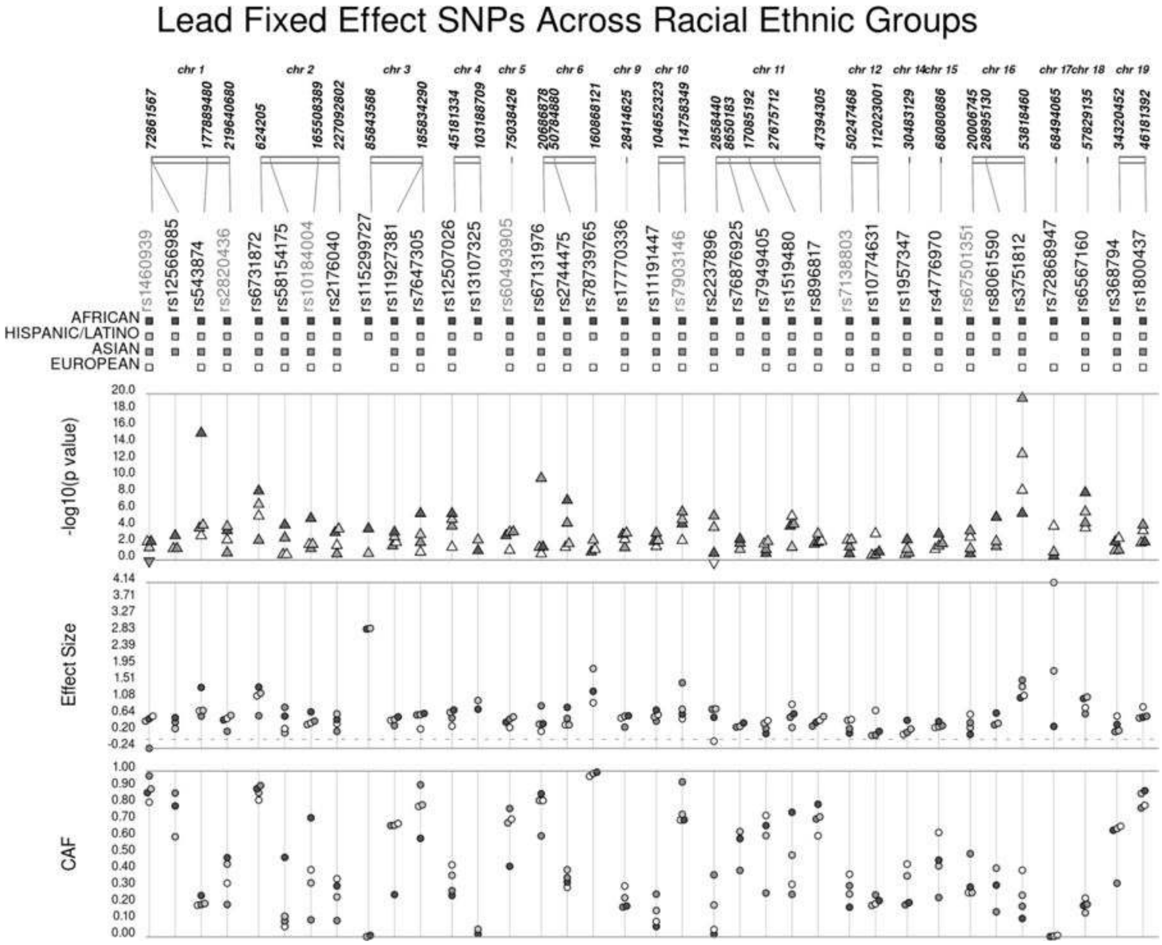

Figure 1.

The comparison of the statistical significance (-log10 of the p-value), effect size (% change in BMI per risk allele) and coded allele frequencies (oriented to the risk allele in the trans-ethnic meta-analysis) across African, Hispanic/Latino, Asian and European ancestries for the lead SNPs (position noted for build 36) within the 36 densely-genotyped BMI regions on the MetaboChip with either locus-specific Bonferroni significant associations (rsid in black) or non-significant (rsid in gray).

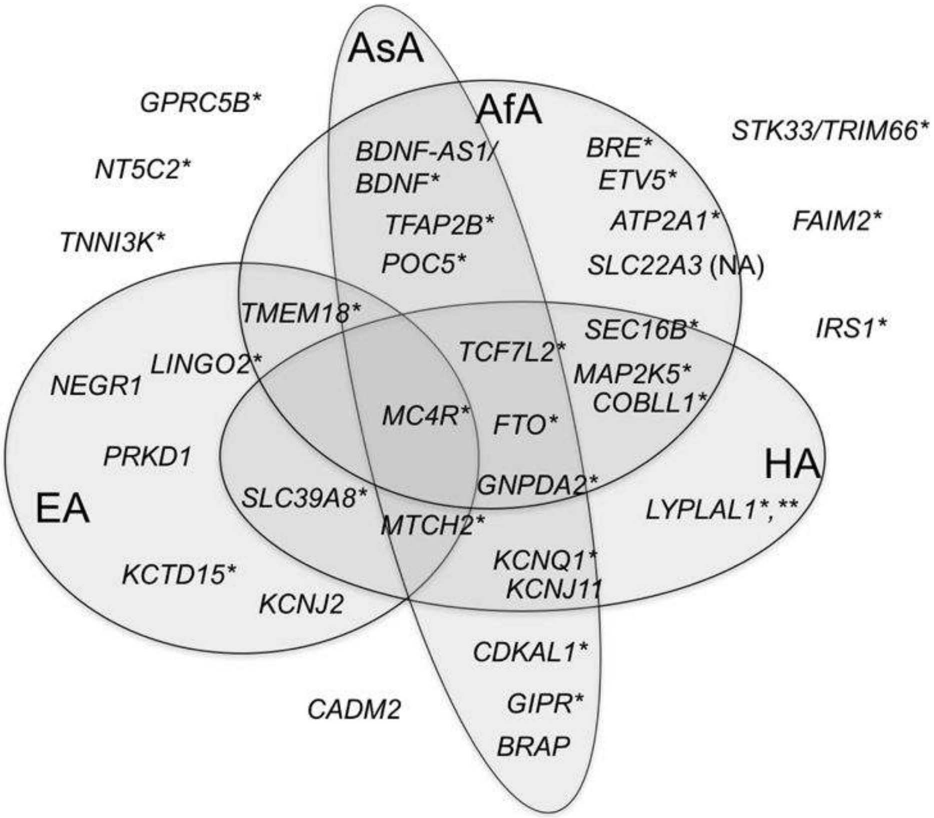

Figure 2.

Venn diagram of overlap in significant lead SNP findings at each of 36 densely-genotyped BMI loci across the racial/ethnic populations [African (AfA), Hispanic/Latino (HA), Asian (AsA), European (EA), American Indian/Alaskan Native descent (NA, in parentheses)] and in the trans-ethnic fixed-effect meta-analysis of African, Hispanic/Latino, Asian and European descent adults (noted with asterisk).

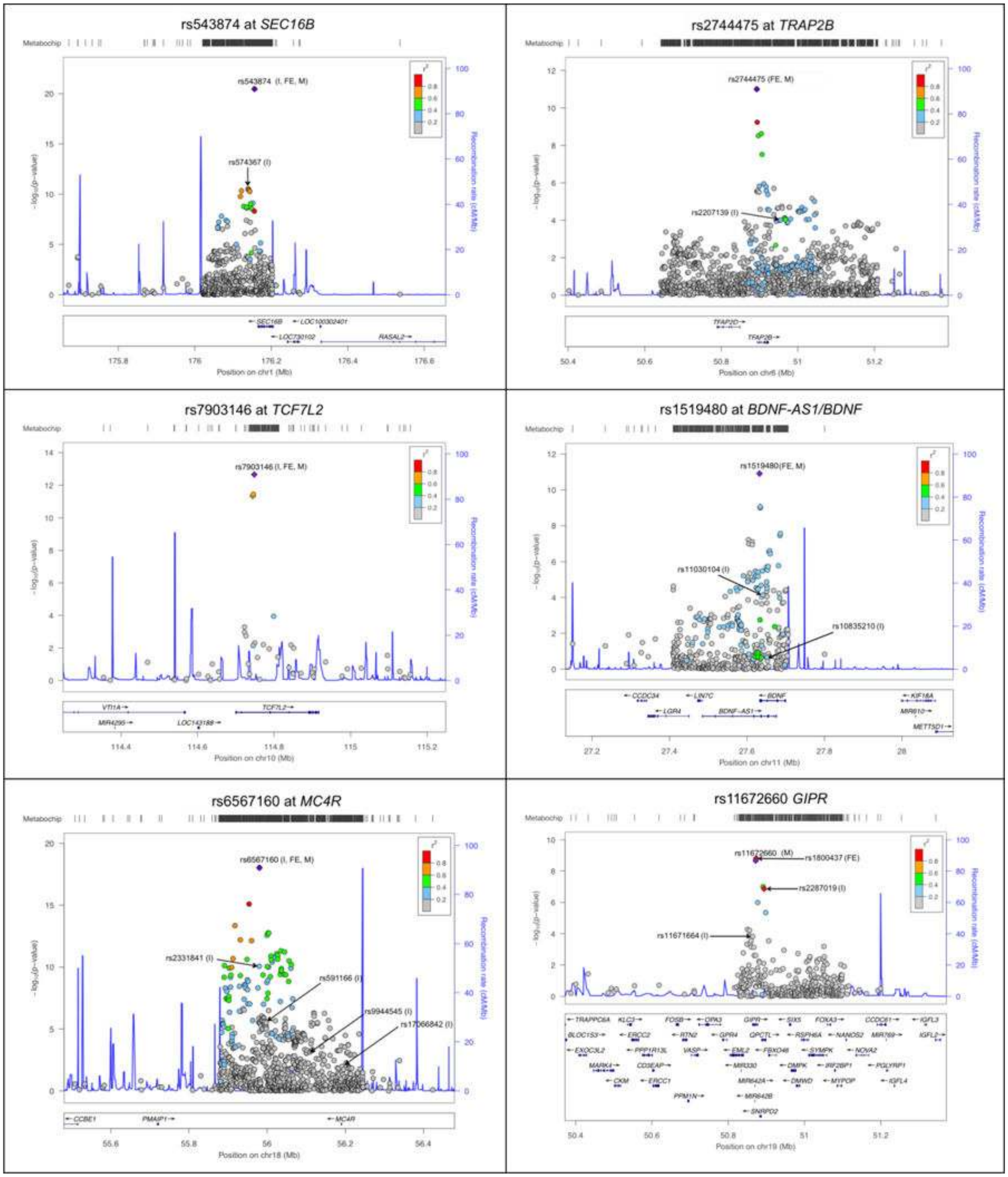

Figure 3.

Regional plots of trans-ethnic fixed-effect estimates (I, index SNPs; FE, top finding) and Bayesian fine-mapping of 6 significant BMI loci to select the SNP with the highest posterior probability (M, shown in purple and reference for trans-ethnic linkage disequilibrium) and narrow the putative interval of interest to <4 SNPs (SNPs in 99% credible interval shown in diamonds) in a sample of up to 101,979 individuals

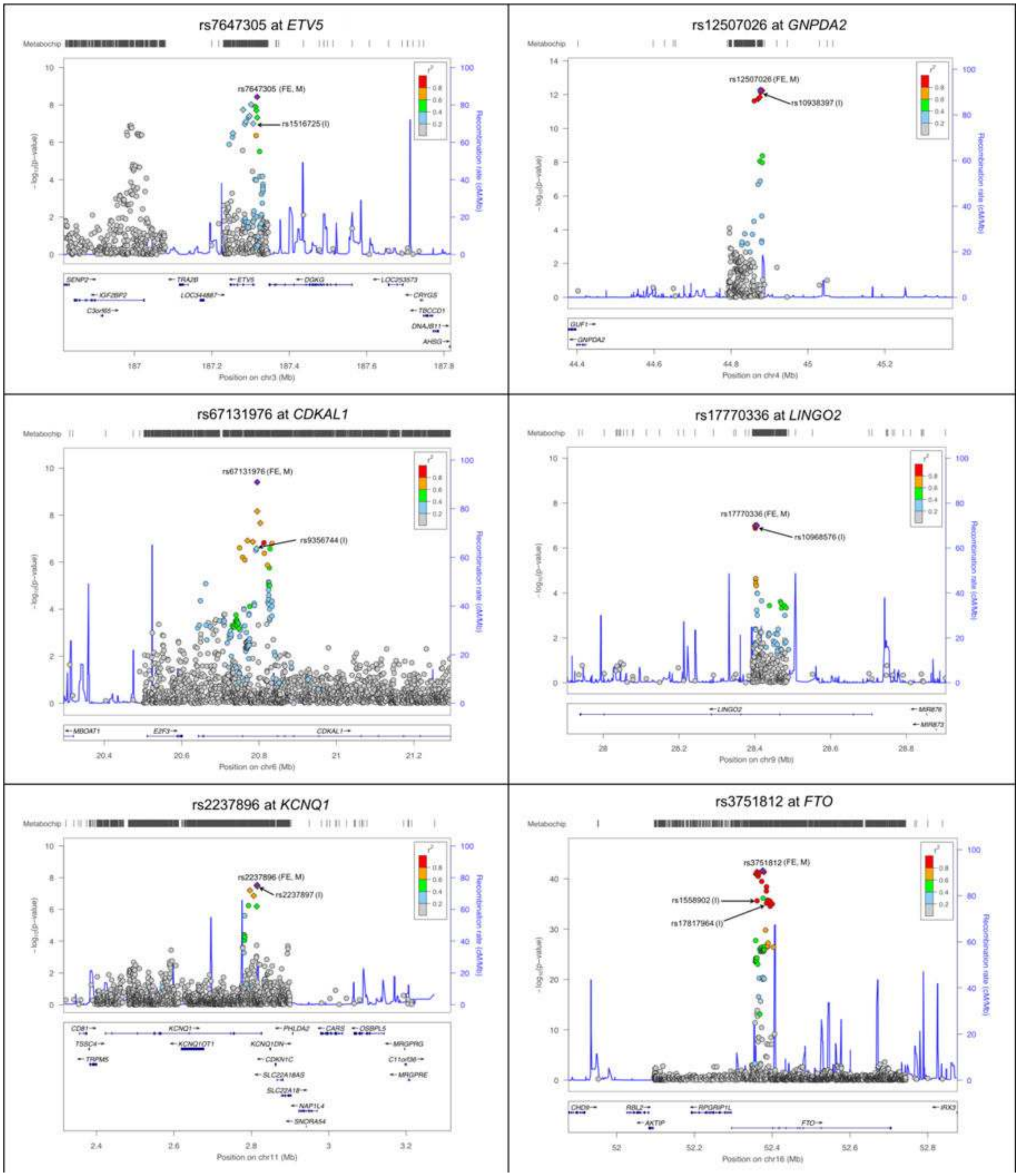

Figure 4.

Regional plots of trans-ethnic fixed-effect estimates (I, index SNPs in black; FE, top finding) and Bayesian fine-mapping of 6 significant BMI loci to select the SNP with the highest posterior probability (M, shown in purple and reference for trans-ethnic linkage disequilibrium) and narrow the putative interval of interest to 4–12 SNPs (SNPs in 99% credible interval shown in diamonds) in a sample of up to 101,979 individuals

Table 1

Replication or generalization of 15 of the fine-mapped 36 BMI loci on the MetaboChip to 35,606 African Americans

														Index-Lead SNPS r2 range****	
Gene	**Chr**	**Marker Type**	**rsID**	**Bp37**	**A1**	**A2**	**Freq**	**Effect (%)**	**StdErr (%)**	**p*****	**I2**	**HetP**	**N**	**In ARIC**	**In WHI EA**
SEC16B	1	Index, Lead	rs543874	177,889,480	g	a	0.249	1.37	0.17	6.0E-15	44.5	4.2E-02	35,604	0.32–1 (same)	0.96–1 (same)
TMEM18	2	Index	rs13021737	632,348	g	a	0.883	1.36	0.23	8.9E-09	26.8	1.7E-01	35,541	0.42–1.00	1.00
		Lead	rs10865549	631,759	a	g	0.883	1.52	0.24	6.4E-10	0	5.0E-01	33,352		
BRE*,**	2	Index, Lead	rs116612809	28,301,171	g	a	0.097	1.39	0.25	6.4E-08	0	6.3E-01	35,583	1 (same)	1 (same)
COBLL1*	2	Index, Lead	rs10184004	165,508,389	t	c	0.719	0.72	0.17	2.1E-05	32.2	1.2E-01	35,598	1 (same)	1 (same)
ETV5	3	Index	rs1516725	185,824,004	c	t	0.817	0.64	0.20	1.2E-03	6.9	3.8E-01	35,485	0.18	0.57
		Lead	rs7647305	185,834,290	c	t	0.594	0.68	0.15	1.1E-05	0	5.3E-01	35,602		
GNPDA2	4	Index	rs10938397	45,182,527	g	a	0.250	0.77	0.17	8.4E-06	51.9	1.5E-02	35,517	0.22–0.98	–
		Lead	rs181153926	45,165,656	t	c	0.249	0.87	0.18	1.6E-06	44.5	4.8E-02	32,146		
POC5	5	Index	rs2112347	75,015,242	t	g	0.495	0.09	0.15	5.5E-01	0	8.9E-01	35,604	0.09	0.36
		Lead	rs984976	74,910,870	a	g	0.150	0.88	0.22	5.4E-05	0	5.2E-01	35,595		
TFAP2B	6	Index	rs2207139	50,845,490	g	a	0.096	0.79	0.26	2.0E-03	44.7	4.1E-02	35,605	0.19	0.47
		Lead	rs2744475	50,784,880	g	c	0.331	0.84	0.16	2.0E-07	7.5	3.7E-01	35,513		
SLC22A3*	6	Index	rs3127574	160,791,370	c	g	0.587	0.03	0.15	8.3E-01	4	4.1E-01	35,597	<0.01	<0.01
		Lead	rs116859471	160,736,564	t	a	0.002	7.37	1.95	2.4E-04	53.3	1.8E-02	33,916		
TCF7L2*	10	Index, Lead	rs7903146	114,758,349	c	t	0.706	0.66	0.17	6.1E-05	26.7	1.8E-01	35,604	1 (same)	1 (same)
BDNF-AS1/BDNF	11	Index	rs11030104	27,684,517	a	g	0.951	1.28	0.36	3.8E-04	14.6	3.0E-01	35,606	0.02–0.05	<0.01
		Lead	rs7929344	27,743,495	a	g	0.245	0.78	0.18	1.1E-05	28.5	1.6E-01	35,586		
MAP2K5	15	Index	rs16951275	68,077,168	t	c	0.610	0.57	0.15	2.7E-04	0	5.7E-01	35,605	0.52–0.93	0.53–0.99
		Lead	rs3784718	68,098,004	c	t	0.630	0.61	0.16	1.2E-04	0	5.9E-01	34,268		
ATP2A1	16	Index	rs2650492	28,333,411	a	g	0.064	0.70	0.33	3.5E-02	0	5.3E-01	35,590	0.82	1.00
		Lead	rs8061590	28,895,130	g	a	0.312	0.69	0.16	2.5E-05	29.8	1.5E-01	35,592		
FTO	16	Index	rs17817964	53,828,066	t	c	0.118	1.05	0.24	1.2E-05	33	1.2E-01	35,606	0.91–0.98	0.94–1.00
		Lead	rs62048402	53,803,223	a	g	0.114	1.19	0.24	1.1E-06	23	2.1E-01	35,603		
MC4R	18	Index, Lead	rs6567160	57,829,135	c	t	0.189	1.08	0.19	2.8E-08	58.9	3.7E-03	35,599	<0.01–1 (same)	<0.01–1 (same)

Abbreviations: ARIC=Atherosclerosis Risk in Communities Study, Bp37=base pair Build 37, Chr=chromosome, EA=European American women, Freq=Frequency of A1, SNPs=single nucleotide polymorphisms, WHI=Women’s Health Initiative.

[*] Note: Starred genes represent fine-mapped loci, which were associated with BMI after the design of the Metabochip in 2009.

[**] Replication of African descent signal (Gong et al. 2013).

[***] For GWAS SNPs a Bonferroni correction for multiple tests reflected the number of independent GWAS signals tested (=0.05/166; Supplemental Table 3). For all other SNPs in the fine-mapped BMI regions, we performed a Bonferroni correction for the number of independent SNPs per region (r2<0.2 in ARIC African-Americans; Supplemental Table 1).

[****] The range of linkage disequilibrium captures any SNP within the fine-mapped loci (Supplemental Table 3) that represents the index BMI signal or secondary signal (described in European descent populations), or race/ethnic population specific marker. ARIC and WHI samples were used to represent the linkage disequilibrium for the PAGE African and European descent samples.

Table 2

Generalization of 13 of the fine-mapped 36 BMI loci on the MetaboChip to 26,048 Hispanic/Latino Americans

													Index-Lead SNPS r2 range****		
Gene	**Chr**	**Marker Type**	**rsID**	**Bp37**	**A1**	**A2**	**Freq**	**Effect (%)**	**StdErr (%)**	**p*****	**ISq**	**HetP**	**N**	**In HCHS/SOL**	**In WHI EA**
SEC16B	1	Index, Lead	rs543874	177,889,480	g	a	0.202	0.76	0.20	1.8E-04	0	4.4E-01	26,045	0.81–1 (same)	0.96–1 (same)
*LYPLAL1***	1	Index	rs2820436	219,640,680	a	c	0.439	0.63	0.17	1.6E-04	0	4.8E-01	26,046	0.33	0.55
		Lead	rs2820446	219,748,818	g	c	0.414	0.89	0.17	1.3E-07	50.8	5.8E-02	25,991		
TMEM18	2	Index	rs13021737	632,348	g	a	0.867	1.14	0.24	3.6E-06	29.5	2.0E-01	26,016	0.82–0.88	1.00
		Lead	rs6744653	628,524	g	a	0.849	1.25	0.23	8.5E-08	43.9	9.8E-02	26,047		
*COBLL1**	2	Index	rs10184004	165,508,389	t	c	0.326	0.39	0.18	3.2E-02	44	9.7E-02	26,045	0.67	0.45
		Lead	rs12692738	165,558,252	c	t	0.252	0.77	0.20	1.1E-04	33	1.8E-01	26,045		
*IGF2BP2***	3	Index	rs11927381	185,508,591	t	c	0.673	0.52	0.18	3.9E-03	23.6	2.5E-01	25,976	0.14	0.05
		Lead	rs6778126	185,405,781	g	a	0.515	0.63	0.17	1.5E-04	43.9	9.8E-02	26,043		
GNPDA2	4	Index	rs10938397	45,182,527	g	a	0.372	0.70	0.17	4.7E-05	49.1	6.7E-02	26,020	0.45–0.99	0.55–0.99
		Lead	rs10938398	45,186,139	a	g	0.371	0.72	0.17	2.9E-05	44.5	9.4E-02	26,048		
*SLC39A8**	4	Index	rs13107325	103,188,709	t	c	0.046	1.03	0.39	9.5E-03	55.2	3.7E-02	26,048	0.29	0.26
		Lead	rs63519	103,202,914	a	c	0.142	0.85	0.24	3.4E-04	31.6	1.9E-01	26,048		
*TCF7L2**	10	Index, Lead	rs7903146	114,758,349	c	t	0.739	0.79	0.19	3.3E-05	63.8	1.1E-02	26,047	1 (same)	1 (same)
*KCNQ1**	11	Index	rs2237897	2,858,546	t	c	0.200	0.82	0.22	1.4E-04	0	9.1E-01	26,044	0.83	0.60
		Lead	rs60808706	2,857,233	a	g	0.217	0.90	0.21	1.6E-05	0	6.2E-01	26,045		
MTCH2	11	Index	rs3817334	47,650,993	t	c	0.397	0.51	0.17	2.5E-03	0	6.1E-01	26,040	0.25	0.47
		Lead	rs11039448	47,918,416	t	g	0.653	0.88	0.17	4.0E-07	0	4.7E-01	26,048		
MAP2K5	15	Index	rs16951275	68,077,168	t	c	0.531	0.37	0.17	3.4E-02	25.4	2.4E-01	26,046	<0.01	<0.01
		Lead	rs76616765	68,003,745	g	c	0.010	3.95	0.91	1.9E-05	0	6.4E-01	24,207		
FTO	16	Index	rs17817964	53,828,066	t	c	0.253	1.37	0.19	2.1E-12	47.2	7.8E-02	26,046	0.69–0.73	0.94–0.98
		Lead	rs7187250	53,810,546	a	c	0.300	1.34	0.18	2.6E-13	47.8	7.4E-02	26,044		
MC4R	18	Index	rs6567160	57,829,135	c	t	0.146	1.12	0.24	3.3E-06	53	4.7E-02	26,047	<0.01–0.79	<0.01–0.75
		Lead	rs72982988	57,802,714	a	g	0.151	1.22	0.24	2.8E-07	16.8	3.0E-01	26,048		

Abbreviations: Bp37=base pair Build 37, Chr=chromosome, EA=European American women, Freq=Frequency of A1, HCHS/SOL=Hispanic Community Health Study/Study of Latinos, SNPs=single nucleotide polymorphisms, WHI=Women's Health Initiative.

[*] Note: Starred genes represent fine-mapped loci, which were associated with BMI after the design of the Metabochip in 2009.

[**] Genome-wide significant findings under review (Gong et al., under review at *Nature Comm*).

[***] For GWAS SNPs a Bonferroni correction for multiple tests reflected the number of independent GWAS signals tested (=0.05/166; Supplemental Table 3). For all other SNPs in the fine-mapped BMI regions, we performed a Bonferroni correction for the number of independent SNPs per region (r2<0.2 in ARIC African-Americans; Supplemental Table 1).

[****] The range of linkage disequilibrium captures any SNP within the fine-mapped loci (Supplemental Table 3) that represents the index BMI signal or secondary signal (described in European descent populations), or race/ethnic population specific marker. HCHS/SOL and WHI European American women were used to represent the linkage disequilibrium of the entire PAGE Hispanic/Latino and European descent samples.

Table 3

Replication or generalization of 11 of the fine-mapped 36 BMI loci on the MetaboChip to 22,465 Asian Americans

														Index-Lead SNPS r2 range****	
Gene	**Chr**	**Marker Type**	**rsID**	**Bp37**	**A1**	**A2**	**Freq**	**Effect (%)**	**StdErr (%)**	**p*****	**ISq**	**HetP**	**N**	**In WHI AA**	**In WHI EA**
GNPDA2	4	Index	rs10938397	45,182,527	g	a	0.279	0.55	0.15	2.6E-04	24	2.3E-01	22,386	0.69–0.96	0.55–0.99
		Lead	rs10938398	45,186,139	a	g	0.281	0.57	0.15	1.6E-04	21	2.6E-01	22,464		
		Lead (No NA)	rs10938398	45,186,139	a	g	0.281	0.54	0.16	5.3E-04	0	4.4E-01	19,878		
POC5	5	Index	rs2112347	75,015,242	t	g	0.443	0.45	0.14	9.0E-04	10	3.5E-01	22,464	0.62, 0.16 (No NA)	0.68, 0.64 (No NA)
		Lead	rs56912706	75,037,086	a	g	0.517	0.57	0.13	2.2E-05	0.4	4.3E-01	22,464		
		Lead (No NA)	rs60423072	75,006,113	t	a	0.825	0.74	0.19	7.1E-05	0	6.9E-01	19,880		
CDKAL1^{*,**}	6	Index	rs9356744	20,685,486	t	c	0.595	0.86	0.14	5.3E-10	43	8.4E-02	22,461	0.94	0.80
		Lead	rs9368222	20,686,996	c	a	0.597	0.88	0.14	2.0E-10	39	1.1E-01	22,393		
		Lead (No NA)	rs9368222	20,686,996	c	a	0.603	0.90	0.14	3.7E-10	57	4.2E-02	19,814		
TFAP2B	6	Index	rs2207139	50,845,490	g	a	0.210	0.29	0.17	8.5E-02	0	6.0E-01	22,464	0.45	0.88
		Lead	rs2076308	50,791,640	c	g	0.270	0.61	0.15	6.3E-05	0	8.0E-01	22,461		
		Lead (No NA)	rs2076308	50,791,640	c	g	0.276	0.63	0.16	5.6E-05	0	5.4E-01	19,875		
TCF7L2[*]	10	Index	rs7903146	114,758,349	c	t	0.934	1.49	0.32	4.6E-06	51	4.0E-02	22,465	0.95	0.89
		Lead	rs4506565	114,756,041	a	t	0.931	1.50	0.32	3.7E-06	50	4.5E-02	22,465		
		Lead (No NA)	rs4506565	114,756,041	a	t	0.954	1.60	0.36	1.2E-05	45	1.0E-01	19,880		
KCNQ1[*]	11	Index	rs2237897	2,858,546	t	c	0.353	0.73	0.18	3.5E-05	62	9.9E-03	14,181	0.83	0.83
		Lead	rs2299620	2,858,295	t	c	0.389	0.85	0.17	6.8E-07	43	9.3E-02	14,182		
		Lead (No NA)	rs2299620	2,858,295	t	c	0.403	0.83	0.18	3.7E-06	59	4.7E-02	11,604		
BDNF-AS1/BDNF	11	Index	rs11030104	27,684,517	a	g	0.566	0.10	0.14	4.5E-01	62	7.2E-03	22,465	0.30–0.92	0.20–0.98
		Lead	rs11030100	27,677,586	g	t	0.570	0.53	0.14	1.1E-04	50	4.3E-02	22,465		
		Lead (No NA)	rs11030100	27,677,586	g	t	0.563	0.52	0.14	3.0E-04	68	8.1E-03	19,879		
MTCH2	11	Index	rs3817334	47,650,993	t	c	0.312	0.23	0.14	1.2E-01	0	8.7E-01	22,447	0.03, 0.03 (No NA)	<0.01, 0.01 (No NA)
		Lead	rs76229852	47,258,369	g	a	0.958	1.48	0.34	2.0E-05	21	2.6E-01	22,465		
		Lead (No NA)	rs10838721	47,509,017	a	g	0.934	1.08	0.28	1.5E-04	0	6.0E-01	19,866		
FTO	16	Index	rs17817964	53,828,066	t	c	0.223	1.28	0.17	2.2E-14	0	4.9E-01	22,465	0.81–0.98	0.95–0.99

Gene	Chr	Marker Type	rsID	Bp37	A1	A2	Freq	Effect (%)	StdErr (%)	p***	ISq	HetP	N	Index-Lead SNPS r2 range**** In WHI AA	Index-Lead SNPS r2 range**** In WHI EA
		Lead	rs3751812	53,818,460	t	g	0.185	1.56	0.17	5.5E-19	0	5.4E-01	22,463		
		Lead (No NA)	rs3751812	53,818,460	t	g	0.180	1.52	0.18	1.4E-16	18	2.9E-01	19,877		
MC4R	18	Index, Lead	rs6567160	57,829,135	c	t	0.197	0.67	0.17	9.0E-05	0	5.8E-01	22,461	<0.01–1 (same)	0.42
		Lead (No NA)	rs6567160	57,829,135	c	t	0.201	0.64	0.17	2.3E-04	0	4.4E-01	19,875		
*GIPR**	19	Index, Lead	rs11671664	46,172,278	g	a	0.531	0.57	0.14	4.2E-05	0	8.4E-01	22,460	0.02–1 (same)	0.34–1 (same)
		Lead (No NA)	rs11671664	46,172,278	g	a	0.517	0.59	0.14	3.6E-05	0	6.2E-01	19,874		

Abbreviations: AA=Asian American, Bp37=base pair Build 37, Chr=chromosome, EA=European American women, Freq=Frequency of A1, NA=Native Haiwaiians, SNPs=single nucleotide polymorphisms, WHI=Women's Health Initiative.

[*] Note: Starred genes represent fine-mapped loci, which were associated with BMI after the design of the Metabochip in 2009.

[**] Replication of Asian descent signal (Okada et al 2012, Wen et al. 2012).

[***] For GWAS SNPs a Bonferroni correction for multiple tests reflected the number of independent GWAS signals tested (=0.05/166; Supplemental Table 3). For all other SNPs in the fine-mapped BMI regions, we performed a Bonferroni correction for the number of independent SNPs per region (r2<0.2 in ARIC African-Americans; Supplemental Table 1).

[****] The range of linkage disequilibrium captures any SNP within the fine-mapped loci (Supplemental Table 3) that represents the index BMI signal or secondary signal (described in European descent populations), or race/ethnic population specific marker. WHI Asian and European American women were used to represent the linkage disequilibrium of the entire PAGE Asian and European descent samples.

Table 4

Trans-ethnic fixed-effect meta-analysis of 36 BMI loci and Bayesian fine-mapping in up to 101,979 individuals

		FE SNP estimates											MANTRA Lead SNP estimates			Index-Lead SNPS r2 range*****	
Gene	Chr	FE Marker Type	rsID	Bp37	Risk Allele	RAF	Effect (%)	StdErr (%)	P***	Isq	HetP****	N	log10BF	HetProb	N	In TE sample	In WHI EA
NEGR1	1	Index	rs3101336	72,751,185	C	0.655	0.17	0.09	6.8E-02	69.4	2.0E-02	101,969				0.18	0.30
		Lead	rs1460939	72,861,567	T	0.868	0.47	0.13	4.3E-04	0.6	3.9E-01	101,976	2.3	0.022	101,976		
TNNI3K	1	Index, Lead	rs12566985	75,002,193	G	0.719	0.42	0.11	2.8E-04	0	5.2E-01	75,627				1 (same), <0.01 (MANTRA)	1 (same), <0.01 (MANTRA)
		–	rs76514352	75,011,423									2.1	0.107	51,874		
SEC16B	1	Index, Lead	rs543874	177,889,480	G	0.213	0.90	0.10	3.5E-21	72.9	1.1E-02	101,972	19.1	0.252	101,972	0.62–1 (same)	0.96–1 (same)
*LYPLAL1***	1	Index, Lead	rs2820436	219,640,680	A	0.388	0.50	0.09	3.2E-08	0	4.7E-01	93,721	6.0	0.006	93,721	1 (same)	1 (same)
TMEM18	2	Index	rs13021737	632,348	G	0.873	1.05	0.12	3.0E-18	42	1.6E-01	101,832				0.61–0.92	0.95
		Lead	rs6731872	624,205	G	0.877	1.09	0.12	8.3E-19	45.3	1.4E-01	101,832	16.6	0.037	101,832		
*BRE**	2	Index	rs116612809	28,301,171	G	0.088	1.05	0.23	8.8E-06	87.9	*2.6E-04*	68,016	5.1	0.937	68,016	0.07	<0.01
		Lead	rs58154175	28,604,833	T	0.315	0.53	0.12	8.8E-06	12.6	3.3E-01	93,669					
*COBLL1**	2	Index, Lead	rs10184004	165,508,389	T	0.452	0.52	0.10	1.3E-07	0	5.5E-01	93,726	5.6	0.011	93,726	1 (same)	1 (same)
*IRS1**	2	Index, Lead	rs2176040	227092802	A	0.275	0.50	0.10	4.0E-07	0	5.5E-01	93,732	5.1	0.006	93,732	1 (same)	1 (same)
CADM2	3	Index	rs13078960	85,807,590	G	0.857	0.00	0.15	9.8E-01	0	8.2E-01	101,976				<0.01	–
		Lead	rs115299727	85,843,586	G	0.009	2.91	0.79	2.6E-04	0	1.0E+00	51,162	2.5	0.049	51,162		
*IGF2BP2***	3	Index, Lead	rs11927381	185,508,591	T	0.563	0.49	0.09	1.3E-07	0	8.4E-01	93,626				1 (same), 0.81 (MANTRA)	1 (same), 0.99 (MANTRA)
		–	rs4481184	185,505,787									5.6	0.005	93,647		
ETV5	3	Index	rs1516725	185,824,004	C	0.864	0.69	0.13	1.0E-07	0	8.7E-01	101,811				0.34	0.57
		Lead	rs7647305	185,834,290	C	0.720	0.59	0.10	3.7E-09	0	5.2E-01	101,974	7.0	0.017	101,974		
GNPDA2	4	Index	rs10938397	45,182,527	G	0.325	0.60	0.08	7.3E-13	1.7	3.8E-01	101,782				0.38–0.98	0.55–1.00
		Lead	rs12507026	45,181,334	T	0.325	0.61	0.08	5.3E-13	6.7	3.6E-01	101,974	10.8	0.011	101,974		
*SLC39A8**	4	Index, Lead	rs13107325	103,188,709	T	0.053	1.05	0.25	3.4E-05	0	8.7E-01	79,090	3.2	0.015	79,090	1 (same)	1 (same)
POC5	5	Index	rs2112347	75,015,242	T	0.531	0.28	0.08	4.3E-04	3.3	3.8E-01	101,972				0.17	0.57
		Lead	rs60493905	75,038,426	C	0.630	0.48	0.09	1.9E-08	0	7.8E-01	101,968	6.4	0.008	101,968		
*CDKAL1**	6	Index	rs9356744	20,685,486	T	0.562	0.42	0.08	2.6E-07	81.2	1.2E-03	101,966				0.24	0.48
		Lead	rs67131976	20,686,878	C	0.729	0.60	0.10	4.0E-10	61.6	5.0E-02	101,973	8.1	0.092	101,973		
TFAP2B	6	Index	rs2207139	50,845,490	G	0.211	0.41	0.10	1.0E-04	2	3.8E-01	101,973				0.33	0.47
		Lead	rs2744475	50,784,880	G	0.352	0.56	0.08	9.9E-12	39.1	1.8E-01	101,763	9.7	0.015	101,763		
*SLC22A3**	6	Index	rs3127574	160,791,370	C	0.497	0.13	0.08	1.2E-01	51.7	1.0E-01	93,727				0.01, 0.03 (MANTRA)	<0.01, <0.01 (MANTRA)
		Lead	rs78739765	160,868,121	G	0.979	1.34	0.43	1.9E-03	0	6.4E-01	72,083					
		-	rs73589298	160,804,090									1.9	0.952	57,992		

		FE SNP estimates											MANTRA Lead SNP estimates			Index-Lead SNPS r2 range*****	
Gene	Chr	FE Marker Type	rsID	Bp37	Risk Allele	RAF	Effect (%)	StdErr (%)	P^{***}	Isq	$HetP^{****}$	N	log10BF	HetProb	N	In TE sample	In WHI EA
LINGO2	9	Index	rs10968576	28,414,339	G	0.217	0.52	0.10	1.1E-07	0	5.9E-01	101,976				0.95	1.00
		Lead	rs17770336	28,414,625	T	0.223	0.52	0.10	9.6E-08	0	6.3E-01	101,930	5.8	0.013	101,930		
NT5C2*	10	Index	rs11191560	104,869,038	C	0.204	0.54	0.11	1.8E-06	0	7.8E-01	101,966				0.86	0.95
		Lead	rs11191447	104,652,323	T	0.193	0.56	0.11	3.8E-07	0	8.4E-01	101,919	5.2	0.008	101,919		
TCF7L2*	10	Index, Lead	rs7903146	114,758,349	C	0.739	0.75	0.10	2.2E-13	54	8.9E-02	101,975	11.2	0.063	101,975	1 (same)	1 (same)
KCNQ1*	11	Index	rs2237897	2,858,546	T	0.237	0.66	0.12	3.3E-08	0	4.0E-01	93,516				0.76	0.97
		Lead	rs2237896	2,858,440	A	0.272	0.73	0.13	3.0E-08	0	4.6E-01	93,196	6.2	0.014	93,196		
STK33/TRIM66	11	Index	rs4256980	8,673,939	G	0.509	0.22	0.08	5.2E-03	0	5.4E-01	101,492				0.80	–
		Lead	rs76876925	8,650,183	G	0.512	0.36	0.10	1.4E-04	0	8.7E-01	72,292	2.7	0.008	72,292		
KCNJ11*	11	Index	rs1557765	17,403,639	T	0.686	0.31	0.10	1.5E-03	0	5.0E-01	93,268				0.08–0.09, 0.20–0.21 (MANTRA)	0.26–0.27, 0.39–0.41 (MANTRA)
		Lead	rs7949405	17,085,192	A	0.568	0.32	0.09	4.8E-04	0	5.8E-01	86,446					
		–	rs214933	17,194,584									2.2	0.005	93,270		
BDNF-AS1/BDNF	11	Index	rs11030104	27,684,517	A	0.694	0.40	0.10	7.3E-05	79.5	2.2E-03	101,516				0.28–0.40	0.13–0.35
		Lead	rs1519480	27,675,712	C	0.444	0.59	0.09	1.2E-11	44.3	1.5E-01	101,510	9.5	0.006	101,510		
MTCH2	11	Index	rs3817334	47,650,993	T	0.338	0.28	0.08	6.3E-04	0	5.0E-01	101,940				0.03	0.09
		Lead	rs896817	47,394,305	C	0.713	0.46	0.09	4.3E-07	0	7.9E-01	101,965	5.1	0.006	101,965		
FAIM2	12	Index, Lead	rs7138803	50,247,468	A	0.285	0.35	0.09	9.0E-05	0	4.8E-01	101,969	2.9	0.003	101,969	1 (same)	1 (same)
BRAP*	12	Index	rs11065987	112,072,424	A	0.716	0.21	0.12	8.8E-02	17.8	3.0E-01	93,730				<0.01–0.06	0.17–0.18
		Lead	rs10774631	112,023,001	A	0.219	0.25	0.10	1.2E-02	46.6	1.3E-01	93,498	0.9	0.024	93,498		
PRKD1	14	Index	rs11847697	30,515,112	T	0.258	0.01	0.14	9.3E-01	0	9.5E-01	93,490				0.02	0.04
		Lead	rs1957347	30,483,129	T	0.303	0.27	0.09	3.4E-03	0	5.4E-01	101,505	1.4	0.016	101,505		
MAP2K5	15	Index	rs16951275	68,077,168	T	0.542	0.35	0.08	2.5E-05	27.3	2.5E-01	101,972				0.56–1 (same)	0.54–1 (same)
		Lead	rs4776970	68,080,886	A	0.422	0.38	0.08	6.1E-06	0	9.0E-01	101,972	4.1	0.004	101,972		
GPRC5B	16	Index	rs12446632	19,935,389	G											0.02, 0.03 (MANTRA)	0.03, 0.05 (MANTRA)
		Lead	rs67501351	20,006,745	G	0.372	0.36	0.08	1.5E-05	28.8	2.4E-01	101,506					
		-	rs28461566	19,998,311									3.5	0.021	101,498		
ATP2A1	16	Index	rs2650492	28,333,411	A	0.146	0.54	0.14	9.5E-05	26.1	2.5E-01	99,770				0.92	0.38–1.00
		Lead	rs8061590	28,895,130	G	0.307	0.52	0.10	2.9E-07	0	3.7E-01	84,081	5.2	0.011	84,081		
FTO	16	Index	rs17817964	53,828,066	T	0.256	1.23	0.10	7.1E-36	0	7.1E-01	101,976				0.94–0.95	0.95–0.99
		Lead	rs3751812	53,818,460	T	0.242	1.34	0.10	2.3E-42	15.6	3.1E-01	101,974	39.9	0.010	101,974		
KCNJ2*	17	Index	rs312750	68,343,539	A	0.638	0.09	0.09	3.4E-01	0	8.9E-01	93,734				<0.01	<0.01
		Lead	rs72868947	68,494,065	T	0.007	2.60	0.78	9.2E-04	52.5	1.2E-01	74,163	1.7	0.105	74,163		
MC4R	18	Index, Lead	rs6567160	57,829,135	C	0.193	0.89	0.10	9.4E-19	13.8	3.2E-01	101,966	16.2	0.011	101,966	0.01–1 (same)	<0.01–1 (same)

		FE SNP estimates											MANTRA Lead SNP estimates			Index-Lead SNPS r2 range*****	
Gene	**Chr**	**FE Marker Type**	**rsID**	**Bp37**	**Risk Allele**	**RAF**	**Effect (%)**	**StdErr (%)**	**P*** **	**Isq**	**HetP******	**N**	**log10BF**	**HetProb**	**N**	**In TE sample**	**In WHI EA**
KCTD15	19	Index	rs29941	34,309,532	G	0.562	0.26	0.09	3.9E-03	0	6.2E-01	101,951				0.49	0.60
		Lead	rs368794	34,320,452	A	0.537	0.32	0.08	1.4E-04	0	4.0E-01	99,796	2.7	0.012	99,796		
*GIPR**	19	Index	rs11671664	46,172,278	G	0.688	0.40	0.11	1.5E-04	79.9	1.9E-03	101,500				0.09–0.88, 0.09–0.88 (MANTRA)	0.42–0.90, 0.42–0.90 (MANTRA)
		Lead	rs1800437	46,181,392	G	0.817	0.64	0.11	1.6E-09	0	8.2E-01	101,488					
		-	rs11672660	46,180,184									7.0	0.007	101,501		

Abbreviations: Bp37=base pair Build 37, BF=Bayes Factor, Chr=chromosome, EA=European American women, FE=Fixed-Effect, HetProb=The posterior probability of heterogeneity, MANTRA=Meta-ANalysis of Trans-Ethnic Association studies, RAF=Risk Allele Frequency, RAF=risk allele frequency, SNPs=single nucleotide polymorphisms, TE=Transethnic.

[*] Note: Starred genes represent fine-mapped loci, which were associated with BMI after the design of the Metabochip in 2009.

[**] Genome-wide significant findings under review (Gong et al., under review at *Nature Comm*).

[***] For GWAS SNPs a Bonferroni correction for multiple tests reflected the number of independent GWAS signals tested (=0.05/166; Supplemental Table 3). For all other SNPs in the fine-mapped BMI regions, we performed a Bonferroni correction for the number of independent SNPs per region (r2<0.2 in ARIC African-Americans; Supplemental Table 1).

[****] Locus-specific Bonferroni significant heterogeneity p-values shown in italics.

[*****] The range of linkage disequilibrium captures any SNP within the fine-mapped loci (Supplemental Table 3) that represents the index BMI signal or secondary signal (described in European descent populations), or race/ethnic population specific marker. ARIC, HCHS/SOL, and WHI samples were used to represent the linkage disequilibrium for the PAGE trans-ethnic and European descent samples.

Table 5

Trans-ethnic meta-analyses to narrow the putative interval of interest at 36 BMI loci

	Stratified Lead FE SNPS			Transethnic Lead SNPs				MANTRA 99% credible interval			
Gene	**Range (Bp37)**	**Reduction (Bp37) %**	**Reduction**	**FE rsID**	**FE Bp37**	**MANTRA rsID**	**MANTRABp37**	**N SNPs**	**Range (Bp37)**	**Reduction (Bp37)**	**% Reduction**
NEGR1	290,988	154,230	35	rs1460939	72,861,567	rs1460939	72,861,567	791	445,217	1	0
TNNI3K	101,051	16,107	14	rs12566985	75,002,193	rs76514352	75,011,423	224	117,158	0	0
SEC16B	16,575	166,174	91	rs543874	177,889,480	rs543874	177,889,480	1	0	182,749	100
*LYPLAL1***	167,016	107,141	39	rs2820436	219,640,680	rs2820436	219,640,680	30	128,966	145,191	53
TMEM18	43,013	205,740	83	rs6731872	624,205	rs6731872	624,205	21	16,729	232,024	93
*BRE**	353,982	930,200	72	rs58154175	28,604,833	rs116612809	28,301,171	26	879,946	404,236	31
*COBLL1**	126,262	106,608	46	rs10184004	165,508,389	rs10184004	165,508,389	15	56,403	176,467	76
*IRS1**	54,967	128,106	70	rs2176040	227,092,802	rs2176040	227,092,802	32	87,419	95,654	52
CADM2	179,274	219,755	55	rs115299727	85,843,586	rs115299727	85,843,586	445	398,619	410	0
*IGF2BP2***	204,453	53,206	21	rs11927381	185,508,591	rs4481184	185,505,787	13	38,588	219,071	85
ETV5	48,250	67,301	58	rs7647305	185,834,290	rs7647305	185,834,290	12	62,861	52,690	46
GNPDA2	22,002	66,280	75	rs12507026	45,181,334	rs12507026	45,181,334	5	10,448	77,834	88
*SLC39A8**	78,859	17,861	18	rs13107325	103,188,709	rs13107325	103,188,709	141	94,766	1,954	2
POC5	260,885	299,794	53	rs60493905	75,038,426	rs60493905	75,038,426	29	372,409	188,270	34
*CDKAL1**	221,440	576,581	72	rs67131976	20,686,878	rs67131976	20,686,878	6	33,042	764,979	96
TFAP2B	272,303	293,963	52	rs2744475	50,784,880	rs2744475	50,784,880	1	0	566,266	100
*SLC22A3**	238,014	32,672	12	rs78739765	160,868,121	rs73589298	160,804,090	720	270,605	81	0
LINGO2	28,519	67,137	70	rs17770336	28,414,625	rs17770336	28,414,625	4	3,722	91,934	96
*NT5C2**	418,829	362,996	46	rs11191447	104,652,323	rs11191447	104,652,323	22	261,330	520,495	67
*TCF7L2**	52,861	23,298	31	rs7903146	114,758,349	rs7903146	114,758,349	2	4,261	71,898	94
*KCNQ1**	331,607	167,414	34	rs2237896	2,858,440	rs2237896	2,858,440	7	18,885	480,136	96
STK33/TRIM66	190,703	122,255	39	rs76876925	8,650,183	rs76876925	8,650,183	368	312,450	508	0
*KCNJ11**	235,612	149,042	39	rs7949405	17,085,192	rs214933	17,194,584	295	383,901	753	0
BDNF-AS1/BDNF	71,243	225,776	76	rs1519480	27,675,712	rs1519480	27,675,712	2	1,874	295,145	99
MTCH2	753,051	420,187	36	rs896817	47,394,305	rs896817	47,394,305	88	543,139	630,099	54
FAIM2	42,290	79,577	65	rs7138803	50,247,468	rs7138803	50,247,468	152	121,090	777	1
*BRAP**	1,332,934	582,773	30	rs10774631	112,023,001	rs10774631	112,023,001	93	1,889,612	26,095	1
PRKD1	30,716	76,520	71	rs1957347	30,483,129	rs1957347	30,483,129	168	106,079	1,157	1
MAP2K5	408,882	156,440	28	rs4776970	68,080,886	rs4776970	68,080,886	122	493,712	71,610	13

	Stratified Lead FE SNPS			Transethnic Lead SNPs				MANTRA 99% credible interval			
Gene	**Range (Bp37)**	**Reduction (Bp37) %**	**Reduction**	**FE rsID**	**FE Bp37**	**MANTRA rsID**	**MANTRABp37**	**N SNPs**	**Range (Bp37)**	**Reduction (Bp37)**	**% Reduction**
GPRC5B	118,750	196,458	62	rs67501351	20,006,745	rs28461566	19,998,311	155	315,118	90	0
ATP2A1	431,490	262,983	38	rs8061590	28,895,130	rs8061590	28,895,130	74	413,702	280,771	40
FTO	15,237	631,041	98	rs3751812	53,818,460	rs3751812	53,818,460	6	20,171	626,107	97
KCNJ2[*]	149,440	107,131	42	rs72868947	68,494,065	rs72868947	68,494,065	790	256,456	115	0
MC4R	73,513	293,976	80	rs6567160	57,829,135	rs6567160	57,829,135	1	0	367,489	100
KCTD15	24,124	14,099	37	rs368794	34,320,452	rs368794	34,320,452	70	38,223	0	0
GIPR[*]	197,022	73,189	27	rs1800437	46,181,392	rs11672660	46,180,184	3	21,988	248,223	92

Abbreviations: Bp37=base pair Build 37, Chr=chromosome, FE=Fixed-Effect, MANTRA=Meta-ANalysis of Trans-Ethnic Association studies, SNPs=single nucleotide polymorphisms.

[*] Note: Starred genes represent fine-mapped loci, which were associated with BMI after the design of the Metabochip in 2009.

[**] Genome-wide significant findings under review (Gong et al., under review at *Nature Comm*).

Table 6

Single variant and joint trans-ethnic fixed-effect estimates for the Bonferroni significant joint signals at the 36 densely-genotyped BMI loci, after accounting for index SNPs (r2<0.9 with each other, included in the trans-ethnic analyses) outside of these regions

	Top SNPS (single variant model)										Top SNPS (joint model)						GWAS-top joint SNPS
Gene	rsID	A1	A2	Freq	Effect (%)	StdErr (%)	P***	Isq	HetP****	Actual n	Aprrox Freq	Effect j (%)	StdErr j (%)	Pj***	Effective n %	VarExp	r2 range**** in transethnic sample
TNNI3K	rs12566985	g	a	0.719	0.42	0.11	2.8E-04	0	5.2E-01	75,627	0.697	0.42	0.11	1.4E-04	85,877	0.0007	1 (same)
SEC16B	rs543874	g	a	0.213	0.90	0.10	3.5E-21	72.9	1.1E-02	101,972	0.217	0.90	0.10	2.3E-19	125,180	0.0028	0.62–1 (same)
*LYPLAL1***	rs2820436	a	c	0.388	0.50	0.09	3.2E-08	0	4.7E-01	93,721	0.387	0.50	0.09	3.5E-08	109,170	0.0012	1 (same)
*LYPLAL1***	rs4445477	a	g	0.621	0.38	0.10	2.5E-04	0	6.3E-01	89,078	0.639	0.37	0.10	1.8E-04	89,156	0.0006	<0.01
TMEM18	rs6731872	g	t	0.877	1.09	0.12	8.3E-19	45.3	1.4E-01	101,832	0.877	1.09	0.12	2.3E-19	135,002	0.0025	0.61–0.92
*COBLL1**	rs10184004	t	c	0.452	0.52	0.10	1.3E-07	0	5.5E-01	93,726	0.444	0.53	0.11	4.0E-07	84,752	0.0014	1 (same)
*COBLL1**	rs17244444	g	a	0.911	0.41	0.16	1.3E-02	58.6	6.4E-02	93,731	0.927	0.64	0.17	1.0E-04	101,259	0.0006	0.07
*IRS1**	rs2176040	a	g	0.275	0.50	0.10	4.0E-07	0	5.5E-01	93,732	0.259	0.75	0.11	5.2E-11	105,388	0.0021	1 (same)
*IRS1**	rs2673147	c	g	0.466	0.15	0.09	9.9E-02	0	8.6E-01	93,727	0.418	0.47	0.10	4.9E-06	104,177	0.0011	0.23
*IGF2BP2***	rs11927381	t	c	0.563	0.49	0.09	1.3E-07	0	8.4E-01	93,626	0.523	0.38	0.09	4.6E-05	105,325	0.0007	1 (same)
ETV5	rs7647305	c	t	0.720	0.59	0.10	3.7E-09	0	5.2E-01	101,974	0.744	0.48	0.10	3.1E-06	104,120	0.0009	0.34
GNPDA2	rs12507026	t	a	0.325	0.61	0.08	5.3E-13	6.7	3.6E-01	101,974	0.317	0.61	0.08	2.5E-14	149,522	0.0016	0.38–0.98
*SLC39A8**	rs28392891	a	t	0.891	0.52	0.15	4.8E-04	62.3	4.7E-02	95,585	0.913	0.51	0.15	6.9E-04	95,771	0.0004	<0.01
*SLC39A8**	rs13107325	t	c	0.053	1.05	0.25	3.4E-05	0	8.7E-01	79,090	0.030	1.03	0.25	4.2E-05	67,039	0.0006	1 (same)
POC5	rs60493905	c	t	0.630	0.48	0.09	1.9E-08	0	7.8E-01	101,968	0.606	0.48	0.09	9.7E-08	111,182	0.0011	0.17
*CDKAL1**	rs67131976	c	t	0.729	0.60	0.10	4.0E-10	61.6	5.0E-02	101,973	0.798	0.60	0.10	2.0E-09	106,176	0.0012	0.24
TFAP2B	rs2744475	g	c	0.352	0.56	0.08	9.9E-12	39.1	1.8E-01	101,763	0.349	0.54	0.08	2.1E-11	143,714	0.0013	0.33
TFAP2B	rs2397016	a	g	0.806	0.76	0.17	6.8E-06	39.6	1.9E-01	79,510	0.909	0.68	0.17	6.8E-05	46,410	0.0008	0.04
LINGO2	rs17770336	t	c	0.223	0.52	0.10	9.6E-08	0	6.3E-01	101,930	0.217	0.52	0.10	2.0E-07	121,118	0.0009	0.95
*NT5C2**	rs11191447	t	c	0.193	0.56	0.11	3.8E-07	0	8.4E-01	101,919	0.127	0.56	0.11	3.6E-07	111,260	0.0007	0.86
*TCF7L2**	rs7903146	c	t	0.739	0.75	0.10	2.2E-13	54	8.9E-02	101,975	0.765	0.75	0.10	6.5E-14	108,781	0.0020	1 (same)
*KCNQ1**	rs2237896	a	g	0.272	0.73	0.13	3.0E-08	0	4.6E-01	93,196	0.133	0.82	0.13	5.5E-10	62,758	0.0015	0.76
STK33	rs76633799	a	g	0.037	1.38	0.37	2.6E-04	0	7.1E-01	57,988	0.017	1.45	0.37	1.1E-04	42,922	0.0007	<0.01
TRIM66	rs76876925	g	a	0.512	0.36	0.10	1.4E-04	0	8.7E-01	72,292	0.556	0.41	0.10	5.7E-05	84,029	0.0008	0.80
BDNF-AS1	rs1519480	c	t	0.444	0.59	0.09	1.2E-11	44.3	1.5E-01	101,510	0.513	0.64	0.09	1.6E-12	104,967	0.0020	0.28–0.40
BDNF	rs190666912	g	c	0.496	0.35	0.09	1.9E-04	16.9	3.0E-01	72,303	0.502	0.43	0.09	2.6E-06	103,685	0.0009	0.17–0.27
MTCH2	rs896817	c	t	0.713	0.46	0.09	4.3E-07	0	7.9E-01	101,965	0.735	0.46	0.09	3.2E-07	126,735	0.0008	0.03

	Top SNPS (single variant model)										Top SNPS (joint model)						GWAS-top joint SNPS
Gene	**rsID**	**A1**	**A2**	**Freq**	**Effect (%)**	**StdErr (%)**	**P*****	**Isq**	**HetP******	**Actual n**	**Aprrox Freq**	**Effect j (%)**	**StdErr j (%)**	**Pj*****	**Effective n %**	**VarExp**	**r2 range****** in transethnic sample**
FAIM2	rs7138803	a	g	0.285	0.35	0.09	9.0E-05	0	4.8E-01	101,969	0.254	0.35	0.09	1.0E-04	127,226	0.0005	1 (same)
MAP2K5	rs4776970	a	t	0.422	0.38	0.08	6.1E-06	0	9.0E-01	101,972	0.440	0.38	0.08	2.0E-06	134,469	0.0007	0.56–1 (same)
GPRC5B	rs67501351	g	c	0.372	0.36	0.08	1.5E-05	28.8	2.4E-01	101,506	0.327	0.40	0.08	4.8E-07	140,434	0.0007	0.02
ATP2A1	rs8061590	g	a	0.307	0.52	0.10	2.9E-07	0	3.7E-01	84,081	0.318	0.56	0.10	3.2E-08	98,598	0.0013	0.92
FTO	rs3751812	t	g	0.242	1.34	0.10	2.4E-42	15.6	3.1E-01	101,974	0.213	1.31	0.13	1.8E-24	114,260	0.0057	0.94–0.95
FTO	rs9936385	c	t	0.289	1.34	0.11	7.5E-37	6.9	3.4E-01	66,366	0.366	1.51	0.16	1.2E-20	84,239	0.0104	0.38–0.39
MC4R	rs6567160	c	t	0.193	0.89	0.10	9.4E-19	13.8	3.2E-01	101,966	0.184	0.89	0.10	7.7E-19	134,789	0.0024	0.01–1 (same)
MC4R	rs77901086	a	c	0.985	1.84	0.43	2.6E-05	0	4.5E-01	88,060	0.989	1.81	0.43	3.2E-05	77,866	0.0007	0.11
KCTD15	rs368794	a	t	0.537	0.32	0.08	1.4E-04	0	4.0E-01	99,796	0.581	0.32	0.08	6.3E-05	131,938	0.0005	0.49
GIPR[*]	rs1800437	g	c	0.817	0.64	0.11	1.6E-09	0	8.2E-01	101,488	0.842	0.64	0.11	6.0E-09	116,182	0.0011	0.09–0.88

Abbreviations: Bp37=base pair Build 37, Chr=chromosome, FE=Fixed-Effect, MANTRA=Meta-ANalysis of Trans-Ethnic Association studies, SNPs=single nucleotide polymorphisms.

[*] Note: Starred genes represent fine-mapped loci, which were associated with BMI after the design of the Metabochip in 2009.

[**] Genome-wide significant findings under review (Gong et al., under reivew at *Nature Comm*).

[***] For GWAS SNPs a Bonferroni correction for multiple tests reflected the number of independent GWAS signals tested (=0.05/166; Supplemental Table 3). For all other SNPs in the fine-mapped BMI regions, we performed a Bonferroni correction for the number of independent SNPs per region (r2<0.2 in ARIC African-Americans; Supplemental Table 1).

[****] The range of linkage disequilibrium captures any SNP within the fine-mapped loci (Supplemental Table 3) that represents the index BMI signal or secondary signal (described in European descent populations), or race/ethnic population specific marker. ARIC, HCHS/SOL, and WHI samples were used to represent the linkage disequilibrium for the PAGE trans-ethnic and European descent samples.