HHS Public Access

Author manuscript

Ann Hum Genet. Author manuscript; available in PMC 2017 September 01.

Published in final edited form as:

Ann Hum Genet. 2016 September ; 80(5): 294–305. doi:10.1111/ahg.12165.

Evidence for association between *SH2B1* gene variants and glycated hemoglobin in non-diabetic European American young adults: The Add Health study

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SUMMARY

Glycated hemoglobin (HbA1c) is used to classify glycaemia and Type 2 diabetes (T2D). Body mass index (BMI) is a predictor of HbA1c levels and T2D. We tested 43 established BMI and obesity loci for association with HbA1c in a nationally-representative multiethnic sample of young adults from the National Longitudinal Study of Adolescent to Adult Health (Add Health: age 24–34 years; n = 5,641 EA; 1,740 AA; 1,444 HA) without T2D, using two levels of covariate adjustment (Model 1: age, sex, smoking, and geographic region; Model 2: Model 1 covariates plus BMI). Bonferroni adjustment was made for 43 SNPs and we considered $P < 0.0011$ statistically significant. Means (SD) for HbA1c were 5.4%(0.3) in European Americans (EA), 5.7%(0.4) in African Americans (AA), and 5.5%(0.3) in Hispanic Americans (HA). We observed significant evidence for association with HbA1c for two variants near *SH2B1* in EA (rs4788102, P =

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Conflict of Interest

There were no potential or real conflicts of financial or personal interest with the financial sponsors of the research project.

2.2×10^{-4}; rs7359397, P = 9.8×10^{-4}) for Model 1. Both results were attenuated after adjustment for BMI (rs4788102, P = 1.7×10^{-3}; rs7359397, P = 4.6×10^{-3}). No variant reached Bonferroni-corrected significance in AA or HA. These results suggest that *SH2B1* polymorphisms are associated with HbA1c, largely independent of BMI, in EA young adults.

Keywords

obesity; diabetes; HBA1c

INTRODUCTION

Diabetes prevalence has risen substantially over the last few decades, disproportionately affecting race/ethnic minorities (Cowie *et al.* 2009, Cowie *et al.* 2010). In 2012, 29 million Americans had diabetes; over 8 million were undiagnosed (Centers for Disease Control and Prevention 2014). The total cost of diabetes in 2007 was estimated to be $245 billion (Centers for Disease Control and Prevention 2014) and this economic burden is likely to escalate over time. The adverse health and economic consequences, combined with significant race/ethnic disparities and high rates of undiagnosed diabetes, emphasize the critical need to address this disease.

Glycated hemoglobin (HbA1c) is a marker of long-term glycemic control and is a diagnostic measure to classify glycaemia and type 2 diabetes (T2D) (American Diabetes Association 2013). HbA1c has been shown to have a substantial genetic component, with heritability estimated at 75% (Simonis-Bik *et al.* 2008). Body mass index (BMI) is a strong predictor of HbA1c and T2D (The *et al.* 2013), especially in younger age groups (Awa *et al.* 2012; Schienkiewitz *et al.* 2006; Abdul-Ghani *et al.* 2005; Hillier and Pedula 2001). Large-scale genome wide association studies (GWAS) for BMI have identified multiple loci that have been widely replicated (Liu *et al.* 2014; Yoneyama *et al.* 2014; Graff *et al.* 2013; Monda *et al.* 2013; Speliotes *et al.* 2010; Thorleifsson *et al.* 2009; Willer *et al.* 2009; Heard-Costa *et al.* 2009; Loos *et al.* 2008; Frayling *et al.* 2007). Some of the genetic loci identified for BMI, including *SH2B1*, have also later been found to be associated with HbA1c (Sandholt *et al.* 2011; Fall *et al.* 2012; Mutombo *et al.* 2014). The majority of genetic studies of BMI and other metabolic traits, however, have focused on adult populations. Much less is known about how genetic loci are associated with metabolic traits such as HbA1c in young adulthood, a life period which may be particularly sensitive with respect to the development of T2D given that substantial decreases in insulin sensitivity occur during pubertal development (Moran *et al.* 1999). An interesting question is whether variants associated with BMI in adults are associated with HbA1c levels in young adults, and whether these effects are independent of BMI.

In the current study, we evaluated the associations between 43 single nucleotide polymorphisms (SNPs) from 41 well-established BMI- and obesity-associated gene regions and HbA1c in the National Longitudinal Study of Adolescent Health (Add Health), a nationally representative sample of European-American (EA), African-American (AA) and

Hispanic-American (HA) young adults (24 – 34 years of age at time of HbA1c measurement). We further tested whether any observed associations were mediated by BMI.

METHODS

Study Sample

The National Longitudinal Study of Adolescent Health (Add Health) study is a national, prospective cohort study of adolescents representative of the U.S. school-based population in grades 7 to 12 (11–22 years of age) in 1994–95 (wave I, n = 20,745) who are followed over three waves into adulthood (wave II: 1996, 12–21 years (n = 14,738); wave III: 2001–2002, 18–27 years (n = 15,197); wave IV: 2008–2009, 23–32 years (n = 15,701). DNA was first collected from all respondents at wave IV, and consent given for banking and use in future genetic studies (n = 12,234). Add Health included a core sample plus subsamples of selected minorities, related adolescents (n = 5,524), and other groups, including well-educated AAs, collected under protocols approved by the Institutional Review Board at the University of North Carolina at Chapel Hill. The survey design and sampling strategy have been described previously (Resnick *et al.* 1997; Miller *et al.* 2004; Harris 2010).

Analytic Sample

At wave IV, 58% (n = 12,066) of wave I (n = 20,745) respondents provided DNA samples with consent for banking and use in future genetic studies. To be eligible for the current study, each individual had to have at least 80% of their SNPs genotyped and have measures of HbA1c (n = 10,943). We excluded the participants meeting one or more of the following: the monozygotic twin with fewer genotyped loci within each twin pair (n = 310), pregnant (n = 313) or disabled (n = 27) individuals, those reporting Native American (n = 56), Asian (n = 519), or ‘other’ race (n = 90), those with a self-reported diagnosis of diabetes (n = 332), taking diabetic medications (n = 33) or with HbA1c ≥ 6.5% (n = 318), and those with missing data for: geographic region (n = 65), BMI (n = 18), race (n = 39), or current smoking (n = 25). The final analytic sample was n = 8,825 from 8,083 households (7,383 singletons, 659 sibling pairs, 40 sibling trios and 1 family with four siblings).

Race/ethnicity

Because genetic biomarkers to determine ancestry were unavailable, we used a race/ethnicity variable constructed from respondent and parental survey items on ancestral background and family relationship status, creating a race/ethnicity variable with priority for agreement between participant and parental report. We used a three-category classification: non-Hispanic EA, non-Hispanic AA and HA with indicators for subpopulation (e.g. Mexican, Cuban) and immigrant status (e.g. US and non-US born).

Anthropometry

Height and weight were measured via standardized protocol, with body mass index (BMI) derived using weight in kg/height in meters squared.

HbA1c Measurement

At wave IV, diabetes was identified using self-reported previous diagnosis and HbA1c from whole blood spot assays collected from finger pricks that were assayed at University of Washington Department of Laboratory Medicine (UW Lab Med, Mark H. Wener, M.D., Director, Seattle, WA). Finger prick measures have achieved the same level of precision and reproducibility as other standard methods of collecting blood such as venipuncture (Tamborlane *et al.* 2005). Diagnosed diabetes (type 1 or type 2) was defined as a "yes" response to the question "Has a doctor, nurse or other health provider ever told you that you have or had high blood sugar or diabetes [if female, when you were not pregnant]?" Undiagnosed diabetes was defined in Add Health as a "no" response to the previous question and an HbA1c≥6.5%, as previously described (The *et al.* 2013; Attard *et al.* 2013).

SNP Selection

SNPs were selected based on BMI and obesity results from the Genome-wide Investigation of ANThropometric measures (GIANT) consortium and other studies in European adults (Speliotes *et al.* 2010; Thorleifsson *et al.* 2009; Willer *et al.* 2009; Heard-Costa *et al.* 2009; Frayling *et al.* 2007). We pruned SNPs using an r^2 criterion of 0.80 (using HapMap CEU, YRI and CHB data). Based on this pruning, we selected a set of 43 SNPs representing 41 EA established regions in or near genes. For AA, we excluded 16 of 43 SNPs (indicated with NA in Table 2) that did not show evidence of association at $P < 0.20$ and consistent direction of effect for BMI in a large AA GWAS meta-analysis of adults (Monda *et al.* 2013; Kang *et al.* 2010). Given the lack of a large GWAS in Hispanics, and the observation that 75% of GWAS SNPs for complex traits were replicated in Hispanics, all 43 SNPs were considered for HA (Carlson *et al.* 2013).

Genotyping

DNA from saliva was used for genotyping. Forty-three established BMI and obesity SNPs were genotyped using TaqMan, using procedures described previously (Graff *et al.* 2012). SNPs were measured from the following 41 regions: *ADCY9, BDNF, CADM2, ETV5, FAIM2, FANCL, FLJ3577, FTO, GNPDA2, GPRC5B, KCTD15, LMX1B, LRP1B, LRRN6C, LYPLAL1, LZTR2, MAF, MAP2K5, MC4RI* (2), *MSRA, MTCH2, MTIF3, NCR3/BAT2, NEGR1, NPC1, NRXN3, NUDT3, POMC, PRKD1, PRL, PTBP2, PTER, QPCTL, RPL27A, SEC16B, SH2B1/APOB* (2), *SLC39A8, TFAP2B, TMEM160, TMEM18, TNNI3K.* The overall discordance rate across SNPs was 0.3%, and the average call-rate was 97.9%.

Statistical Analysis

Race-stratified linear mixed models, including two non-nested random effects for school and family, were used to test for associations with HbA1c. We first tested whether BMI was associated with HbA1c, by ancestry group, after adjusting for age, sex, smoking status and geographic region. Given prior reports, we also tested whether the effect of BMI on HbA1c differed by age by testing a BMI × age interaction. We then tested for evidence of association between each SNP and HbA1c in models stratified by race/ethnicity. Genotype was modeled as an additive effect. Two levels of covariate adjustment were used: Model 1

included adjustment for age, sex, smoking, and geographic region and Model 2 further included BMI. Covariates are from the same visit as HbA1c, which was measured at wave IV. Additional covariate adjustments in AA models (an indicator variable for the oversampling of highly educated AAs (n = 355)) and in HA models (indicator variables for Cuban (n= 193), Puerto Rican (*n* = 224), Central/South American (n =120), Mexican (*n* = 660), or other Hispanic (*n* = 103) ancestry; an indicator variable for being foreign born (n =268)). Bonferroni adjustment was made for 43 SNPs; P < 0.0011 was considered statistically significant.

RESULTS

The analysis sample included 5,641 EA, 1,444 HA and 1,740 AA Add Health participants with genotype and HbA1C data. Sample descriptives are given in Table 1. BMI was significantly positively associated with HbA1c in all three ethnic groups (EA: P = 2.8×10^{-89}; HA: P = 5.2×10^{-28}; AA: P = 1.3×10^{-31}). There was a trend supporting stronger effects of BMI on HbA1c in younger age groups in EAs ($P_{interaction}$= 0.054) and AAs ($P_{interaction}$ = 0.094) (data not shown). Genetic effect alleles and effect allele frequencies for each ethnic group are given in Table 2 and genetic association test results are given in Table 3.

For Model 1 adjustment, two of the 43 SNPs tested were significantly associated with HbA1c in EAs after multiple test correction (P < 0.0011). Both variants are near the *SH2B1/APOB* locus: rs4788102 (P = 2.2×10^{-4}) and rs7359397 (P = 9.8×10^{-4}). SNPs in *CADM2* (rs13078807; P = 0.03), *MTCH2* (rs3817334; P = 0.02) and *NEGR1* (rs2568958; P = 0.01) were nominally associated (P < 0.05) with HbA1c in EAs. After additional adjustment for BMI (Model 2), all associations with HbA1c were attenuated and no variants remained significantly associated with HbA1c after multiple test correction. Three variants were nominally significant after Model 2 adjustment in EAs: *SH2B1/APOB* rs4788102 (P = 0.0017) and rs7359397 (P = 0.0046), and *NEGR1* rs2568958 (P = 0.04). The two *SH2B1/APOB* SNPs, rs4788102 and rs7359397, are highly correlated in EAs (R^2 = 0.97 using 1000 Genomes CEU).

No variants were significantly associated with HbA1c for either Model 1 or Model 2 adjustment, after multiple test correction, for either the HAs or AAs. Three SNPs were nominally significantly associated with HbA1c in HAs: *ADCY9* rs2444217 (P = 0.013), *LMX1B* rs867559 (P = 0.0056), and *NPC1* rs1805081 (P = 0.010). P-values remained similar for all three SNPs after additional adjustment for BMI. One variant was nominally associated with HbA1c in AAs: *SEC16B* rs10913469 (P = 0.02). This variant became slightly more significant (P = 0.0068) after additional adjustment for BMI in Model 2. In addition, *SH2B1/APOB* variant rs4788102 was nominally associated with HbA1c (P = 0.02) *after* BMI adjustment, in AAs. We note, however, that the estimated direction of effect of this SNP for AAs was opposite of that observed in the EAs. There was no evidence for association between either of the *SH2B1/APOB* SNPs and HbA1c in HAs or for *SH2B1/APOB* SNP rs7359397 in AAs (all P > 0.4). There also was no evidence for association between variants that were nominally significant in one ethnicity (EAs: *CADM2* rs13078807, *MTCH2* rs3817334 and *NEGR1* rs2568958; HAs: *ADCY9* rs2444217,

LMX1B rs867559 and *NPC1* rs1805081; AAs: *SEC16B* rs10913469) and HbA1c in any of the other ethnicities (all P > 0.1).

DISCUSSION

HbA1c is a quantitative measure of glucose control. The American Diabetes Association (2013) has included HbA1c ≥ 6.5% as a criterion for the diagnosis of T2D. BMI is a major predictor of glucose levels and T2D (Felber & Golay 2002; Hekimsoy & Oktem 2003; Everhart 1992; Wanamethee & Shaper 1999; Sakurai *et al.* 1999; Pontiroli & Galli 1998; Schienkiewitz *et al.* 2006; Kahn *et al.* 2006). The incidence rate of T2D in young adults has risen dramatically during the past couple of decades and much of that increase is directly attributed to the growing obesity epidemic in young people (Kaufman 2002). Previously, we reported the generalization of EA identified genetic effects for 43 obesity related variants with BMI in our multi-ethic population of young adults participating in Add Health (Graff *et al.* 2012). Herein, we assessed the association of these same variants with HbA1c, both before and after controlling for BMI. We identified significant associations for two variants in *SH2B1* in EAs (rs4788102, $\beta = 0.021$, $P = 2.2\times10^{-4}$; rs7359397, $\beta = 0.018$, $P = 9.8\times10^{-4}$) before adjustment of BMI. After adjustment for BMI, the statistical significance and estimated beta coefficients (for each additional effect allele – see Table 2) were modestly attenuated (rs4788102, $\beta = 0.017$, $P = 1.7\times10^{-3}$; rs7359397, $\beta = 0.015$, $P = 4.6\times10^{-3}$). Of note, both rs4788102 (P = 0.014) and rs7359397 (P = 0.034) were nominally associated with BMI in the EA analytic Wave IV sample. Effect estimates for these two SNPs on BMI were similar to EAs in both HAs and AAs (rs4788102: $\beta = 0.33$ in EAs, $\beta = 0.25$ in HAs and $\beta = 0.29$ in AAs; rs7359397: $\beta = 0.28$ in EAs, $\beta = 0.20$ in HAs and $\beta = 0.24$ in AAs), but the results were not statistically significant.

SH2B1, or SH2B Adaptor Protein 1, has been a strong candidate for metabolic disorders due to its involvement in leptin and insulin signaling (Maures *et al.* 2007). SH2B gene −/− knockout mice have been shown to develop age-dependent hyperinsulinemia, hyperglycemia, and glucose intolerance, where insulin resistance was more severe in older mice (Duan *et al.* 2004). A more recent study identified SH2B1 as a regulator of insulin expression in mice. Chen *et al.* (2014) observed that leptin-deficient ob/ob mice with a heterozygous deletion of *SH2B1* were characterized by decreased pancreatic insulin content and plasma insulin levels, thus exacerbating hyperglycemia and glucose intolerance. In humans, rare *SH2B1* deletions and mutations have been observed in obese individuals with extremely high insulin resistance. *SH2B1* is one of a set of genes that is disrupted in patients with a syndrome defined by a 220-kb deletion of chromosome 16p11.2 and characterized by obesity and severe insulin resistance disproportionate for the degree of obesity (Bochukova *et al.* 2010).

Association results between common *SH2B1* variants and measures of insulin resistance and glucose tolerance in epidemiologic studies have been mixed. In a study of 15 previously identified overweight and obesity genes conducted in ~18K Danish adults, Sandholt *et al.* (2011) reported a nominally significant BMI-independent association between missense *SH2B1* SNP, rs7498665 (Thr484Ala), and risk of T2D ($P = 7.8 \times 10^{-4}$). Rs7498665 is in strong linkage disequilibrium (LD) with our two studied variants in EAs ($R^2 = 1$, D' = 1

with rs4788102; R^2 = 0.97, D' = 1 with rs7359397) based on HapMap CEU data. A two-stage study initially evaluated 32 obesity variants in n = 926 non-diabetic 71 year-old men from Sweden for association with insulin index. The authors found evidence for association at *SH2B1* rs7359397 (P = 0.01). They then followed up this result by testing and finding an association between this SNP and a homeostasis model assessment of insulin resistance in the Meta-Analyses of Glucose and Insulin-related traits (MAGIC) Consortium (n = 37,037; P = 0.0039) (Fall *et al.* 2012). A separate 2013 European meta-analysis of over 93,000 adults, however, found no evidence for an association between *SH2B1* rs4788102 genotype and abnormal glucose homeostasis, defined by impaired fasting glucose, impaired glucose tolerance or T2D (odds ratio = 1.01; 95% confidence interval: 0.98 – 1.05) (Prudente *et al.* 2013). There were considerable differences across cohorts with respect to the measure of hyperglycemia used in this meta-analysis and the authors found considerable heterogeneity of the association results across studies. Further complicating the interpretation of their results, in the context of our own findings, glucose homeostasis was analyzed as a dichotomous trait and included both diabetics and non-diabetics. The authors noted the association between *SH2B1* genotype and hyperglycemia appeared to be stronger in individuals with lower BMI, which would be consistent with younger populations. It is important to note that all studies to date have largely focused on older adults and results may not reflect the relationship between glucose homeostasis and *SH2B1* variants in younger adults. Evidence suggests that elevated BMI is a particularly important risk factor for early T2D (Awa *et al.* 2012; Abdul-Ghani *et al.* 2005; Hillier and Pedula 2001); hence, study of BMI associated *SH2B1* SNPs in younger adults could provide important new insight into the etiological role of SH2B1, or nearby coded proteins, in T2D.

Rs4788102 is an intergenic SNP that maps ~2Kb 5′ of *SH2B1* while rs7359397 is an intergenic SNP that maps just outside the 3′UTR of *SH2B1*. In our study, the two SNPs have highly correlated genotypes in EAs (R^2 = 0.97) and HAs (R^2 = 0.91), but much weaker correlation in AAs (R^2 = 0.25). Both SNPs are in the same wide LD block with reported missense variant rs7498665 in populations of European and Hispanic descent (only rs4788102 is in the same LD block with rs7498665 in AAs) and neither SNP has a known function. While we found evidence for association between these SNPs and Hb1Ac in 5,641 EA young adults, we did not find any such evidence in HAs (n = 1,373). We observed nominal evidence for an association with rs4788102 in AAs (n = 1,641, P = 0.02 after adjustment for BMI), but the effect was in the opposite direction as in EAs. Rs7359397 is not polymorphic in YRI HapMap participants, while rs4788102 and rs7498665 are in perfect LD in YRI HapMap participants (R^2 = 1, D' = 1). Of note, based on HapMap CEU and YRI data, a relatively common haplotype carrying the minor alleles at rs4788102 and rs7359397 in CEU is completely absent in YRI. Thus, the observed nominal association at rs4788102 with a different direction of effect in AAs could be due to different haplotype structures in EAs and AAs tagging a common unknown causal variant(s), rs4788102 tagging a different causal variant(s) in AAs or a type I error (e.g. due to uncorrected population stratification). It should be noted that SNPs were selected for this study based on GWAS for BMI performed in populations of European ancestry and some SNP associations with BMI may not be generalizable to non-European populations. Further, our considerably smaller sample sizes

for HAs and AAs resulted in lower power to detect true effects in these populations relative to our power in EAs.

In summary, we identified a significant association between common *SH2B1* SNPs rs4788102 and rs7359397 and HbA1c in 5,641 EA young adults. These associations were only partially mediated by BMI. These same *SH2B1* common variants have been established to be associated with BMI in older populations of European descent. The relationship between *SH2B1* and glycated hemoglobin related traits has been widely studied, with animal models and human studies of rare functional mutations showing a clear role for *SH2B1*. Results from previous human epidemiological studies of common variants in or near *SH2B1* have been less conclusive. A wide range of human studies has provided conflicting evidence regarding the association between these variants and glycated hemoglobin traits. Our study is unique in that is focuses entirely on young adults, a population understudied for metabolic related traits. Given the observed heterogeneity of effects of *SH2B1* genotypes on glycated hemoglobin traits in the literature, future follow-up studies of young adults would be ideal for replication of our findings.

Acknowledgments

We thank Amy Perou of the BioSpecimen Processing facility and Jason Luo of the Mammalian Genotyping Core at the University of North Carolina at Chapel Hill. This work was funded by National Institutes of Health grant R01HD057194. This research uses data from Add Health, a program project directed by Kathleen Mullan Harris and designed by J. Richard Udry, Peter S. Bearman, and Kathleen Mullan Harris at the University of North Carolina at Chapel Hill, and funded by grant P01-HD31921 from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, with cooperative funding from 23 other federal agencies and foundations. Special acknowledgement is due to Ronald R. Rindfuss and Barbara Entwistle for assistance in the original design. Information on how to obtain Add Health data files is available on the Add Health website (http://www.cpc.unc.edu/addhealth). No direct support was received from grant P01-HD31921 for this analysis. We are grateful to the Carolina Population Center for general support.

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Table 1

Sample characteristics for Add Health participants.

	EA (N=5,641)		HA (N=1,444)		AA (N=1,740)	
	Mean (SD) or %	**Range**	**Mean (SD) or %**	**Range**	**Mean (SD) or %**	**Range**
Gender (female)	52%	NA	50%	NA	55%	NA
Current smoking	40%	NA	25%	NA	29%	NA
Age (years)	28.4 (1.8)	24.0 – 34.0	28.8 (1.8)	24.0 – 34.0	28.4 (1.8)	24.0 – 33.0
BMI	28.4 (7.0)	14.4 – 79.2	29.6 (7.0)	14.3 – 67.9	30.1 (8.0)	16.5 – 71.7
HbA1c (%)	5.4 (0.3)	3.8 – 6.4	5.5 (0.3)	4.1 – 6.4	5.7 (0.4)	4.2 – 6.4
Pre-diabetic *	14%	NA	23%	NA	40%	NA

* Defined as HbA1c between 5.7%–6.4%

Ann Hum Genet. Author manuscript; available in PMC 2017 September 01.

Table 2

Variants used in the present analysis.

					Effect Allele Frequency		
SNP	***Nearest Gene***	**Chr**	**Effect allele**	**Other allele**	**EA**	**HA**	**AA**
rs2444217	*ADCY9*	16	A	G	0.57	0.43	0.76
rs10767664	*BDNF*	11	A	T	0.79	0.81	0.93
rs13078807	*CADM2*	3	G	A	0.20	0.15	NA
rs7647305	*ETV5*	3	C	T	0.79	0.81	0.60
rs7138803	*FAIM2*	12	A	G	0.38	0.27	0.17
rs887912	*FANCL*	2	T	C	0.28	0.19	NA
rs2112347	*FLJ3577*	5	T	G	0.63	0.63	NA
rs9939609	*FTO*	16	A	T	0.39	0.33	0.47
rs10938397	*GNPDA2*	4	G	A	0.43	0.37	0.24
rs12444979	*GPRC5B*	16	C	T	0.86	0.91	NA
rs29941	*KCTD15*	19	G	A	0.68	0.64	NA
rs867559	*LMX1B*	9	G	A	0.19	0.33	0.30
rs2890652	*LRP1B*	2	C	T	0.16	0.13	0.17
rs10968576	*LRRN6C*	9	G	A	0.31	0.24	NA
rs2605100	*LYPLAL1*	1	A	G	0.29	0.32	0.12
rs543874	*LZTR2*	1	G	A	0.20	0.19	0.24
rs1424233	*MAF*	16	T	C	0.48	0.63	0.68
rs2241423	*MAP2K5*	15	G	A	0.77	0.58	0.62
rs12970134	*MC4R*	18	A	G	0.26	0.17	NA
rs571312	*MC4R*	18	A	C	0.23	0.16	NA
rs545854	*MSRA*	8	G	C	0.16	0.23	0.05
rs3817334	*MTCH2*	11	T	C	0.40	0.39	0.26
rs4771122	*MTIF3*	13	G	A	0.22	0.20	NA
rs1077393	*NCR3/BAT2*	6	G	A	0.49	0.49	0.35
rs2568958	*NEGR1*	1	A	G	0.63	0.69	NA
rs1805081	*NPC1*	18	T	C	0.60	0.73	0.92
rs10146997	*NRXN3*	14	G	A	0.79	0.79	0.64

SNP	Nearest Gene	Chr	Effect allele	Other allele	Effect Allele Frequency		
					EA	HA	AA
rs206936	*NUDT3*	6	G	A	0.21	0.40	0.54
rs713586	*POMC*	2	C	T	0.48	0.43	0.84
rs11847697	*PRKD1*	14	T	C	0.05	0.07	NA
rs4712652	*PRL*	6	G	A	0.42	0.38	0.29
rs1555543	*PTBP2*	1	C	A	0.59	0.57	NA
rs10508503	*PTER*	10	C	T	0.92	0.94	0.98
rs2287019	*QPCTL*	19	C	T	0.82	0.87	NA
rs4929949	*RPL27A*	11	C	T	0.51	0.49	NA
rs10913469	*SEC16B*	1	C	T	0.20	0.19	0.30
rs4788102	*SH2B1*	16	A	G	0.39	0.40	0.28
rs7359397	*SH2B1/APOB48*	16	T	C	0.39	0.38	0.08
rs13107325	*SLC39A8*	4	T	C	0.08	0.04	NA
rs987237	*TFAP2B*	6	G	A	0.18	0.27	0.10
rs3810291	*TMEM160*	19	A	G	0.67	0.56	0.21
rs6548238	*TMEM18*	2	C	T	0.83	0.87	0.89
rs1514175	*TNNI3K*	1	A	G	0.44	0.53	NA

"NA" indicates that variant was not tested in African Americans.

Table 3

Association results by ethnic group.

SNP	Nearest Gene	European Americans				Hispanic Americans				African Americans			
		Model 1		Model 2		Model 1		Model 2		Model 1		Model 2	
		beta (SE)	p	beta (SE)	p	beta (SE)	p	beta (SE)	p	beta (SE)	p	beta (SE)	p
rs2444217	*ADCY9*	−0.004 (0.006)	0.51	−0.003 (0.005)	0.60	−0.030 (0.012)	1.26E-02	−0.028 (0.011)	1.29E-02	−4.00E-03 (0.015)	0.77	−0.005 (0.014)	0.71
rs10767664	*BDNF*	0.003 (0.007)	0.65	−0.001 (0.007)	0.91	−0.015 (0.015)	0.32	−0.020 (0.014)	0.15	0.032 (0.025)	0.19	0.032 (0.025)	0.20
rs13078807	*CADM2*	0.015 (0.007)	0.03	0.011 (0.007)	0.11	−0.014 (0.016)	0.40	−0.015 (0.016)	0.33				
rs7647305	*ETV5*	−0.008 (0.007)	0.26	−0.009 (0.007)	0.18	−0.018 (0.015)	0.23	−0.020 (0.014)	0.17	0.004 (0.013)	0.77	−0.002 (0.012)	0.85
rs7138803	*FAIM2*	0.006 (0.006)	0.26	0.004 (0.006)	0.52	−0.016 (0.013)	0.22	−0.016 (0.013)	0.21	0.002 (0.017)	0.93	−0.003 (0.016)	0.84
rs887912	*FANCL*	−0.003 (0.006)	0.65	−0.006 (0.006)	0.32	−0.010 (0.015)	0.53	−0.012 (0.015)	0.42				
rs2112347	*FLJ3577*	−0.003 (0.006)	0.55	−0.005 (0.006)	0.41	−0.008 (0.012)	0.52	−0.011 (0.012)	0.35				
rs9939609	*FTO*	0.004 (0.006)	0.50	−0.007 (0.006)	0.20	0.008 (0.012)	0.54	−0.005 (0.012)	0.66	0.005 (0.012)	0.68	0.004 (0.012)	0.76
rs10938397	*GNPDA2*	0.005 (0.006)	0.37	0.003 (0.005)	0.55	0.005 (0.012)	0.71	0.005 (0.012)	0.68	0.006 (0.015)	0.67	−0.003 (0.014)	0.83
rs12444979	*GPRC5B*	−0.004 (0.008)	0.58	−0.007 (0.008)	0.36	0.030 (0.020)	0.12	0.017 (0.019)	0.36				
rs29941	*KCTD15*	−0.004 (0.006)	0.54	−0.005 (0.006)	0.34	0.017 (0.012)	0.17	0.013 (0.012)	0.28				
rs867559	*LMX1B*	0.005 (0.007)	0.48	0.001 (0.007)	0.86	0.033 (0.012)	5.62E-03	0.028 (0.011)	1.33E-02	−0.001 (0.014)	0.93	−1.00E-04 (0.013)	0.99
rs2890652	*LRP1B*	0.011 (0.008)	0.15	0.008 (0.007)	0.26	0.029 (0.017)	0.09	0.027 (0.016)	0.09	−0.003 (0.016)	0.86	−0.012 (0.016)	0.45
rs10968576	*LRRN6C*	0.006 (0.006)	0.33	0.001 (0.006)	0.85	−0.010 (0.014)	0.45	−0.014 (0.013)	0.30				
rs2605100	*LYPLAL1*	−0.002 (0.006)	0.72	−0.003 (0.006)	0.66	0.0077 (0.012)	0.54	0.005 (0.012)	0.69	0.002 (0.019)	0.91	0.009 (0.019)	0.65
rs543874	*LZTR2*	0.009 (0.007)	0.21	0.002 (0.007)	0.78	−0.009 (0.015)	0.54	−0.016 (0.014)	0.27	−0.022 (0.015)	0.13	−0.028 (0.014)	0.05

SNP	Nearest Gene	European Americans				Hispanic Americans				African Americans			
		Model 1		Model 2		Model 1		Model 2		Model 1		Model 2	
		beta (SE)	p	beta (SE)	p	beta (SE)	p	beta (SE)	p	beta (SE)	p	beta (SE)	p
rs1424233	*MAF*	0.011 (0.006)	0.05	0.009 (0.005)	0.09	0.002 (0.012)	0.88	0.003 (0.012)	0.81	−0.026 (0.013)	0.05	−0.024 (0.013)	0.06
rs2241423	*MAP2K5*	0.006 (0.006)	0.37	0.002 (0.006)	0.79	−0.011 (0.012)	0.34	−0.009 (0.011)	0.43	0.012 (0.013)	0.36	0.006 (0.012)	0.62
rs12970134	*MC4R*	0.004 (0.006)	0.55	−0.004 (0.006)	0.55	0.013 (0.015)	0.40	0.007 (0.015)	0.64				
rs571312	*MC4R*	0.001 (0.006)	0.89	−0.007 (0.006)	0.23	0.007 (0.016)	0.66	−0.003 (0.015)	0.86				
rs545854	*MSRA*	0.005 (0.007)	0.47	0.002 (0.007)	0.75	−0.001 (0.014)	0.92	−0.002 (0.013)	0.90	−0.022 (0.029)	0.44	−0.027 (0.028)	0.34
rs3817334	*MTCH2*	0.013 (0.006)	0.02	0.008 (0.005)	0.13	−0.003 (0.012)	0.77	−0.009 (0.011)	0.43	0.003 (0.014)	0.82	0.001 (0.014)	0.96
rs4771122	*MTIF3*	−0.002 (0.007)	0.79	−0.004 (0.006)	0.50	0.016 (0.015)	0.28	0.010 (0.014)	0.49				
rs1077393	*NCR3/BAT2*	−0.001 (0.005)	0.81	−0.002 (0.005)	0.70	−0.004 (0.012)	0.71	−0.001 (0.011)	0.90	−0.016 (0.013)	0.22	−0.017 (0.013)	0.18
rs2568958	*NEGR1*	0.015 (0.006)	0.01	0.011 (0.006)	0.04	0.002 (0.013)	0.90	0.004 (0.012)	0.74				
rs1805081	*NPC1*	0.001 (0.006)	0.84	−0.002 (0.005)	0.65	0.034 (0.013)	1.00E-02	0.027 (0.013)	0.03	−0.002 (0.022)	0.92	0.009 (0.022)	0.68
rs10146997	*NRXN3*	−0.003 (0.007)	0.63	−0.001 (0.007)	0.82	−0.006 (0.014)	0.66	−0.001 (0.014)	0.93	0.002 (0.013)	0.87	−0.003 (0.013)	0.81
rs206936	*NUDT3*	0.004 (0.007)	0.55	0.001 (0.007)	0.92	0.013 (0.012)	0.25	0.012 (0.011)	0.30	0.013 (0.013)	0.30	0.011 (0.012)	0.38
rs713586	*POMC*	0.004 (0.006)	0.44	−0.001 (0.005)	0.89	−0.001 (0.012)	0.94	−0.001 (0.011)	0.95	−0.025 (0.017)	0.14	−0.023 (0.016)	0.16
rs11847697	*PRKD1*	−0.016 (0.012)	0.21	−0.024 (0.012)	0.05	0.038 (0.022)	0.08	0.031 (0.021)	0.14				
rs4712652	*PRL*	0.003 (0.006)	0.61	−0.001 (0.007)	0.89	−0.015 (0.012)	0.20	−0.017 (0.011)	0.14	0.014 (0.013)	0.30	0.016 (0.013)	0.23
rs1555543	*PTBP2*	0.007 (0.006)	0.18	0.003 (0.005)	0.58	−0.011 (0.012)	0.37	−0.014 (0.011)	0.22				
rs10508503	*PTER*	0.002 (0.010)	0.86	−0.004 (0.010)	0.67	0.013 (0.025)	0.60	0.017 (0.024)	0.47	0.018 (0.051)	0.73	0.027 (0.050)	0.58

SNP	Nearest Gene	European Americans				Hispanic Americans				African Americans			
		Model 1		Model 2		Model 1		Model 2		Model 1		Model 2	
		beta (SE)	p	beta (SE)	p	beta (SE)	p	beta (SE)	p	beta (SE)	p	beta (SE)	p
rs2287019	*QPCTL*	0.001 (0.007)	0.89	−0.004 (0.007)	0.56	0.019 (0.018)	0.28	0.018 (0.017)	0.28				
rs4929949	*RPL27A*	0.007 (0.005)	0.21	0.006 (0.005)	0.29	0.004 (0.012)	0.71	0.005 (0.011)	0.67				
rs10913469	*SEC16B*	0.009 (0.007)	0.17	0.004 (0.007)	0.57	−0.018 (0.015)	0.23	−0.023 (0.014)	0.10	−0.032 (0.014)	0.02	−0.036 (0.013)	6.81E-03
rs4788102	*SH2B1*	0.021 (0.006)	2.24E-04	0.017 (0.005)	1.66E-03	−0.002 (0.012)	0.88	−0.004 (0.011)	0.70	−0.027 (0.014)	0.05	−0.031 (0.013)	0.02
rs7359397	*SH2B1/APOB48*	0.018 (0.006)	9.77E-04	0.015 (0.005)	4.57E-03	−0.002 (0.012)	0.85	−0.002 (0.011)	0.71	−0.013 (0.022)	0.56	−0.018 (0.021)	0.41
rs13107325	*SLC39A8*	−0.003 (0.010)	0.79	−0.008 (0.010)	0.44	0.011 (0.030)	0.72	0.006 (0.029)	0.84				
rs987237	*TFAP2B*	0.010 (0.007)	0.18	0.001 (0.007)	0.84	0.006 (0.013)	0.62	0.001 (0.012)	0.97	−0.005 (0.020)	0.80	−0.004 (0.020)	0.86
rs3810291	*TMEM160*	−0.004 (0.006)	0.45	−0.005 (0.006)	0.36	−0.005 (0.012)	0.69	−0.007 (0.011)	0.55	0.002 (0.015)	0.90	0.003 (0.015)	0.87
rs6548238	*TMEM18*	0.009 (0.007)	0.20	−0.001 (0.007)	0.86	−0.012 (0.017)	0.48	−0.020 (0.016)	0.23	−0.025 (0.020)	0.21	−0.031 (0.020)	0.11
rs1514175	*TNNI3K*	0.000 (0.006)	0.97	−0.003 (0.005)	0.54	0.019 (0.012)	0.11	0.016 (0.011)	0.14				