Published in final edited form as:
Surg Obes Relat Dis. 2013 ; 9(3): 436–441. doi:10.1016/j.soard.2012.04.004.

Frequencies of obesity susceptibility alleles among ethnically and racially diverse bariatric patient populations

Manish Parikh, M.D.[a,*], **Jessica Hetherington, M.D.**[a], **Sheetal Sheth, M.A.**[a], **Jamie Seiler, P.A.-C.**[b], **Harry Ostrer, M.D.**[c], **Glenn Gerhard, M.D.**[b], **Craig Wood, M.S.**[d], and **Christopher Still, D.O.**[d]

[a]Department of Surgery, New York University Medical Center/Bellevue Hospital Center, New York, New York

[b]Weis Center for Research, Geisinger Clinic, Danville, Pennsylvania

[c]Departmens of Pediatrics and Pathology, New York University Medical Center, New York, New York

[d]Geisinger Obesity Research Institute, Geisinger Clinic, Danville, Pennsylvania

Abstract

Background—Genetic factors likely play a role in obesity and the outcomes after bariatric surgery. Single nucleotide polymorphisms in or near the insulin-induced gene 2 (*INSIG-2*), fat mass and obesity-associated gene (*FTO*), melanocortin 4 receptor gene (*MC4R*), and proprotein convertase subtilisn/kexin type 1 gene (*PCSK-1*) have been associated with class III obesity in whites. Minimal data are available regarding the genetic susceptibility to obesity in class III obese nonwhites, especially Hispanics. Our objective was to perform a comparative analysis of 4 common genetic variants (*INSIG-2, FTO, MC4R,* and *PCSK-1*) associated with obesity in a diverse population of bariatric surgery patients to determine whether a difference exists by ethnicity (white versus Hispanic). The setting of the study was 2 university hospitals in the United States.

Methods—Bariatric surgery patients from 2 different institutions were enrolled prospectively, and genotyping was performed. Differences in the distribution of *INSIG-2, FTO, MC4R,* and *PCSK-1* single nucleotide polymorphisms among the different ethnicities (whites and Hispanics) were compared using an additive model (0, 1, or 2 risk alleles). A propensity-matched analysis was used to account for cohort differences.

Results—A total of 1276 bariatric patients were genotyped for the *INSIG-2, FTO, MC4R,* and *PCSK-1* obesity single nucleotide polymorphisms. Statistically significant differences in *FTO, INSIG-2, MC4R, and PCSK-1* were seen using an additive model. *FTO, PCSK-1,* and *MC4R* (test for trend) remained significantly different in the propensity analysis.

Conclusion—Significant differences in the frequencies of several common obesity susceptibility variants in or near *FTO, PCSK-1,* and *MC4R* were found in white and Hispanic patients with class III obesity undergoing bariatric surgery. Larger studies in more class III obese Hispanics of different nationalities are needed.

*Correspondence: Manish Parikh, M.D., Department of Surgery, New York University School of Medicine, Laparoscopic and Bariatric Surgery, Bellevue Hospital Center, 550 First Avenue, NBV 15, South 7, New York, NY 10016. parikm01@med.nyu.edu.

Disclosures
The authors have no commercial associations that might be a conflict of interest in relation to this article.

Keywords

Obesity; Genes; Genetics; Hispanics; Genotyping; Alleles; Frequency; Bariatric surgery

Significant differences exist in the prevalence of obesity among ethnic groups. According to data from the Behavioral Risk Factor Surveillance System surveys conducted from 2006 to 2008, non-Hispanic blacks had a 51% greater prevalence of obesity (37.5%) and Hispanics a 21% greater prevalence of obesity (28.7%) compared with non-Hispanic whites (23.7%) [1]. Although the causes of obesity are multifactorial, genetic susceptibility likely influences a patient's risk of obesity and potential long-term success after intervention, such as bariatric surgery [2].

Several single nucleotide polymorphisms (SNPs) have been found to be associated with obesity through previous genome-wide association and linkage studies. For instance, SNPs in or near the insulin-induced gene 2 (*INSIG-2*), fat mass and obesity-associated gene (*FTO*), melanocortin 4 receptor gene (*MC4R*), and proprotein convertase subtilisn/kexin type 1 gene (*PCSK-1*) have all been found to be associated with class III obesity, primarily in whites [3]. However, a paucity of studies have been published associating these SNPs and obesity in nonwhite patients, particularly Hispanics with severe obesity (body mass index [BMI] >35 kg/m^2).

We compared an inner-city public hospital-based bariatric surgery program (serving primarily Hispanics) and a rural hospital-based bariatric surgery program (serving primarily whites) for the frequency of several obesity alleles by analyzing the 4 common genetic variants in or near the *INSIG-2*, *FTO*, *MC4R,* and *PCSK-1* genes to determine whether a difference in genetic susceptibility to obesity exists between whites and Hispanics.

Methods

Bariatric surgery patients from 2 different institutions (1 an urban public hospital-based bariatric surgery program with a high concentration of Hispanics and 1 a rural hospital-based bariatric surgery program with a primarily white patient population) were enrolled prospectively into an institutional review board–approved clinical study to compare phenotype and genotype between different ethnicities. Each participant provided informed consent. Blood samples were collected at the routine clinical visit, at which venous blood samples were already being drawn as standard of care (e.g., nutritional monitoring). At the blood sampling, an extra sample of venous blood was obtained for genetic analysis. In addition, phenotypic measures were routinely collected at each visit, including race/ethnicity, insurance status, weight, height, type of surgery, and medical co-morbidities determined from the electronic medical record analysis and analysis of questionnaires completed by each patient. The phenotypic data were then separated by ethnicity (categorized as white, Hispanic, black, or "other"). Because of the low number of blacks, this group was subsequently excluded from the statistical analysis. Also, data categorized as "other" were also excluded from the analysis.

Genetic analysis of the patients' blood samples was performed as previously described [2]. In brief, DNA was extracted from ethylenediaminetetraacetic acid-anticoagulated whole blood using the Qiagen MagAttract DNA Blood Midi M48 Kit and Qiagen BioRobot M48 Workstation (Qiagen, Valencia, CA) according to the manufacturer's directions. SNP genotyping was performed using an Applied Biosystems 7500 Real-Time Polymerase Chain Reaction System (Applied Biosystems, Foster City, CA) using the manufacturer's reagents (INSIG2, rs7566605, Assay, ID: C__29404113_20; FTO, rs9939609, Assay, ID:

C__30090620_10; MC4R, rs17782313, C__32667060_10; PCSK1, rs6235, C___2841942_10) and protocol. The thermocycler conditions were as follows: 50°C for 2 minutes, 95°C for 10 minutes, and 40 cycles at 95°C for 15 seconds and at 60°C for 60 seconds. The reaction was then analyzed using Applied Biosystems Sequence Detection Software.

Patients were categorized as obesity SNP homozygous if they were homozygous for an obesity SNP risk allele, obesity SNP heterozygous if they were carriers of the obesity risk allele, and homozygous nonobese if they were homozygous for the low-risk allele. Differences in the distribution of the genotypes for the *INSIG-2*, *FTO*, *MC4R* and *PCSK-1* SNPs among the different ethnicities were compared using an additive model (0, 1, or 2 risk alleles).

For the comparisons of patient characteristics between the different ethnicities, chi-square tests were used for categorical data, 2-sample *t* tests were used to compare the mean values, and Wilcoxon rank sum tests were used to compare the median values. To compare the distribution of genotypes between the different ethnicities, chi-square tests were used to evaluate association assuming independence between the genotypes. Additionally, Wilcoxon rank sum tests were used to evaluate the trend between ethnicity and the number of risk alleles.

To account for the potential effect of bias from cohort differences in BMI and the prevalence of co-morbidities, propensity score matching (with a 3:1 match) was used to select subgroups of patients from within the white and Hispanic groups. The propensity model included age, gender, BMI, and each of 4 co-morbidities (hypertension, diabetes mellitus, hyperlipidemia, and sleep disorder). The caliper method was used for selecting matches with a caliper size of .20. Chi-square tests and Wilcoxon rank sum tests were used to evaluate the association assuming independence and for the evaluation of trend between ethnicity and the number of risk alleles. SAS, version 9.2 (SAS Institute, Cary, NC) was used for statistical analysis.

Results

A total of 1335 bariatric patients from the 2 bariatric surgery programs combined were initially enrolled in the present study and were genotyped for the obesity-associated SNPs in or near the *INSIG-2*, *FTO*, *MC4R,* and *PCSK-1* genes. After excluding blacks (n = 48) and other ethnicities, 1276 patients remained for analysis (1117 white and 159 Hispanic).

The basic demographic and co-morbidity data by ethnicity are listed in Table 1. The mean age was 44 years, although the Hispanic cohort was slightly younger than the white cohort (41.8 versus 46.1 yr; $P = .0001$). The mean preoperative BMI was greater for the whites (50.2 versus 44.7 kg/m^2; $P < .0001$). The frequencies of several co-morbidities were greater for the white population, particularly hypertension, diabetes, hyperlipidemia, and sleep disorder (i.e., sleep apnea). Minor clinical differences were found in the preoperative laboratory profiles among the population. More Hispanics were publicly insured (e.g., Medicaid, managed Medicaid) than whites (75% versus 22%, $P < .0001$).

We then focused on a comparison of whites and Hispanics using a propensity analysis; a 3:1 match was found for 148 of the 159 Hispanic patients (93%). For the propensity-matched subgroups, age, gender, BMI, and co-morbidities were not significantly different between the ethnic/racial groups (Table 2).

Differences in the distribution of genotypes among the different ethnic groups were determined using an additive model (0, 1, or 2 risk alleles). Statistically significant

differences were seen for the *FTO*, *INSIG-2, MC4R*, and *PCSK-1* genotypes between whites and Hispanics in the overall population (Table 3 and Fig. 1A).

For the propensity-matched populations, the frequencies of the *FTO* and *PCSK-1* obesity susceptibility alleles remained significantly different using both the chi-square and the trend test and, thus, were independent of phenotypic bias (Table 3 and Fig. 1B). The frequency of the SNP near the *MC4R* gene was significantly different in the trend test but not for the chi-square test. In contrast, *INSIG-2* was not significant using either test.

Discussion

Genetic factors can contribute ≤40%–70% to the inter-individual variation in obesity [2,4]. Multiple genome-wide association analyses in primarily white populations with class I–II obesity have discovered a number of loci associated with obesity-related traits, including *INSIG-2*, *FTO*, *MC4R*, and *PCSK-1* [5–8]. Given the rapid population growth and increased prevalence of obesity in Hispanics and non-Hispanic blacks, it is important to gain a better understanding of the genetic factors in these patient populations. We found a significant racial/ethnic variation in the frequency of obesity-associated SNPs in or near the *FTO*, *PCSK-1*, and *MC4R* genes (based on a trend in risk alleles between ethnicities) in a diverse cohort of class III obesity patients, and we found that an INSIG-2 SNP might be associated with ≥1 obesity-related co-morbidities.

Of all the loci studied, *FTO* is perhaps the most robustly associated with obesity. Genetic variation in the *FTO* gene has been shown to have the greatest effect on BMI in whites (each risk allele increased the BMI by .26–.66 kg/m^2), increasing the risk of obesity by 1.25–1.32-fold, for each additional risk allele [2]. A recent study focusing on morbidly obese whites also found a correlation between the increased BMI and *FTO* and *INSIG-2* SNPs [9]. The *FTO* gene is a DNA/RNA demethylase, and the mechanism for mediating obesity is unclear but thought to be mediated by way of altered *FTO* demethylase activity causing increased fat mass [10].

FTO polymorphisms have also been strongly associated with obesity in Hispanics. One study of 788 Mexicans found that *FTO* was a major risk factor for obesity, especially class III obesity, in the Mexican-Mestizo population and was upregulated in subcutaneous adipose tissue of class III obese individuals [11]. Another report attempted to identify genetic loci influencing obesity in non-Mexican Hispanics, which was 1 of the first detailed analyses of obesity-related quantitative traits in Caribbean Hispanics [12]. Their report confirmed the association of *FTO* with obesity-related traits and also found that both body weight and BMI mapped to 1 region on chromosome 1q43. However, the average BMI was 28.7 kg/m^2 in that study. Our finding of significant variations in SNP frequency in *FTO* between whites and Hispanics, along with the aforementioned data showing upregulated *FTO* expression in Mexicans, warrants additional studies with larger populations of class III obese Hispanics, including both Caribbean and Mexican Hispanics.

Several studies have also confirmed the link between altered *MC4R* function and obesity, also mediated through increased fat mass [7]. *MC4R* is expressed in the central nervous system and plays a key role in the regulation of food intake and energy homeostasis [13,14]. Other studies have shown common SNPs near the *MC4R* gene are associated with high intakes of energy, especially from dietary fat, and increased diabetes risk, independent of BMI and waist circumference [15]. We also found a significant difference in the distribution of *MCR4* SNP genotypes between whites and Hispanics. The *MC4R* SNP we analyzed is a common SNP near the *MC4R* gene. We have not examined the frequency of rare protein-

coding mutations in *MC4R,* which are known to be associated with monogenic extreme obesity [16].

The 2 other loci studied (*PCSK-1* and *INSIG-2*) have been associated with obesity; however, the data are less robust. Mutations in *PCSK-1* have been shown to cause monogenic obesity, and variants have been shown to contribute to polygenic obesity [8]. The *PCSK-1* SNP is linked to glucose-stimulated pro-insulin conversion [16]. It is, therefore, possible that medication usage to treat diabetes and insulin resistance might have confounded the effects. In our study, we did found a difference in *PCSK-1* SNP expression (in the overall and matched cohorts). Additional studies are needed to substantiate this finding.

A recent meta-analysis of the association between *IN-SIG-2* and obesity revealed there might be an association between *INSIG-2* and extreme obesity and that the heterogeneous results from the varying study designs might have concealed a true association [17]. We found a difference by ethnicity in *INSIG-2* in the overall population ($P = .012$) but not in the propensity-matched population ($P = .07$). However, because *INSIG-2* is involved in cholesterol and triglyceride metabolism [18]; medications used to treat hyperlipidemia (especially common in severely obese patient populations) could confound the results. Furthermore, in our study, the rate of hyperlipidemia varied significantly from 26% in Hispanics to 40% in whites, and this could have confounded the analysis.

Our study had several limitations. The number of non-Hispanic blacks was low (n = 48); therefore, we excluded this population from the present analysis. Also, significant baseline differences were present between the white and Hispanic cohorts; to address this issue, we used propensity score matching (with a 3:1 match) to select subgroups of patients from within the white and Hispanic groups to offset the potential bias from co-morbidities and other factors. The subset analysis still revealed significant racial/ethnic variation in the frequency of obesity SNPs associated with *FTO*, *PCSK-1*, and *MC4R*. We did not differentiate among Hispanics of different nationalities, particularly Mexican versus Caribbean, which is an important issue because Hispanics have a racially diverse ancestry. Follow-up studies of larger Hispanic populations of varying nationalities will be useful to replicate these results.

Ultimately, the value of identifying the genetic susceptibility to obesity in certain patient populations might assist in identifying which patients would be at risk of a poor weight loss outcome after bariatric surgery. An abundance of evidence has shown that genetic factors affect dietary intake, as well as physical activity, smoking, and so forth. This has important implications for improving interventions that address unhealthy behaviors. This also has implications for the predictors of success after bariatric surgery. For instance, Still et al. [2] recently found that common obesity susceptibility variants (including *INSIG-2*, *FTO*, *MC4R,* and PCSK1) were associated with poorer weight loss outcomes after gastric bypass surgery in patients with a BMI <50 kg/m^2 [2]. As the genetic susceptibilities to obesity are better elucidated, clinicians will have a better decision-making tool by using genetic variability to potentially match a patient with the optimal intervention.

Conclusion

Significant differences in the frequencies of several common obesity susceptibility variants, *FTO*, *PCSK-1*, and *MC4R* were found in white and Hispanic patients with class III obesity undergoing bariatric surgery. Larger studies of more class III obese Hispanics of different nationalities and blacks are needed.

Acknowledgments

This study was supported by a New York University Langone Medical Center/Geisinger Seed Grant.

References

1. CDC. Differences in prevalence of obesity among black, white, and Hispanic adults—United States, 2006–2008. MMWR Morb Mortal Wkly Rep. 2009; 58:740–4. [PubMed: 19609247]
2. Still CD, Wood GC, Chu X, et al. High allelic burden of four obesity SNPs is associated with poorer weight loss outcomes following gastric bypass surgery. Obesity. 2011; 19:1676–83. [PubMed: 21311511]
3. Loos RJ. Recent progress in the genetics of common obesity. Br J Clin Pharmacol. 2009; 68:811–29. [PubMed: 20002076]
4. Maes HH, Neale MC, Eaves LJ. Genetic and environmental factors in relative body weight and human adiposity. Behav Genet. 1997; 27:325–51. [PubMed: 9519560]
5. Herbert A, Gerry NP, McQueen MB, et al. A common genetic variant is associated with adult and childhood obesity. Science. 2006; 312:279–83. [PubMed: 16614226]
6. Frayling TM, Timpson NJ, Weedon MN, et al. A common variant in the *FTO* gene is associated with body mass index and predisposes to childhood and adult obesity. Science. 2007; 316:889–94. [PubMed: 17434869]
7. Loos RJ, Lindgren CM, Li S, et al. Common variants near MC4R are associated with fat mass, weight and risk of obesity. Nat Genet. 2008; 40:768–75. [PubMed: 18454148]
8. Benzinou M, Creemers JW, Choquet H, et al. Common nonsynonymous variants in *PCSK1* confer risk of obesity. Nat Genet. 2008; 40:943–5. [PubMed: 18604207]
9. Chu X, Erdman R, Susek M, et al. Association of morbid obesity with *FTO* and *INSIG2* allelic variants. Arch Surg. 2008; 143:235–20. [PubMed: 18347269]
10. Gerken T, Girard CA, Tung YC, et al. The obesity-associated *FTO* gene encodes a 2-oxoglutarate-dependent nucleic acid demethylase. Science. 2007; 318:1469–72. [PubMed: 17991826]
11. Villalobos M, Flores-Dorantes M, Villarrea-Molina M, et al. The *FTO* gene is associated with adulthood obesity in the Mexican population. Obesity. 2008; 16:2296–301. [PubMed: 18719664]
12. Dong C, Beecham A, Slifer S, et al. Genome-wide linkage and peak-wide association study of obesity related quantitative traits in Caribbean Hispanics. Hum Genet. 2011; 129:209–19. [PubMed: 21104097]
13. Loos RJ. Recent progress in the genetics of common obesity. Br J Clin Pharmacol. 2009; 68:811–29. [PubMed: 20002076]
14. Huszar D, Lynch CA, Fairchild-Huntress V, et al. Targeted disruption of the melanocortin-4 receptor results in obesity in mice. Cell. 1997; 88:131–41. [PubMed: 9019399]
15. Qu L, Kraft P, Hunter DJ, Hu FB. The common obesity variant near MC4R gene is associated with higher intakes of total energy and dietary fat, weight change and diabetes risk in women. Hum Mol Genet. 2008; 17:3502–8. [PubMed: 18697794]
16. Loos RJ. The genetic epidemiology of melanocortin 4 receptor variants. Eur J Pharmacol. 2011; 660:156–64. [PubMed: 21295023]
17. Heni M, Haupt A, Schäfer SA, et al. Association of obesity risk SNPs in *PCSK1* with insulin sensitivity and proinsulin conversion. BMC Med Genet. 2010; 11:86. [PubMed: 20534142]
18. Yabe D, Brown MS, Goldstein JL. INSIG-2, a second endoplasmic reticulum protein that binds SCAP and blocks export of sterol regulatory element binding roteins. Proc Natl Acad Sci USA. 2002; 99:12753–8. [PubMed: 12242332]

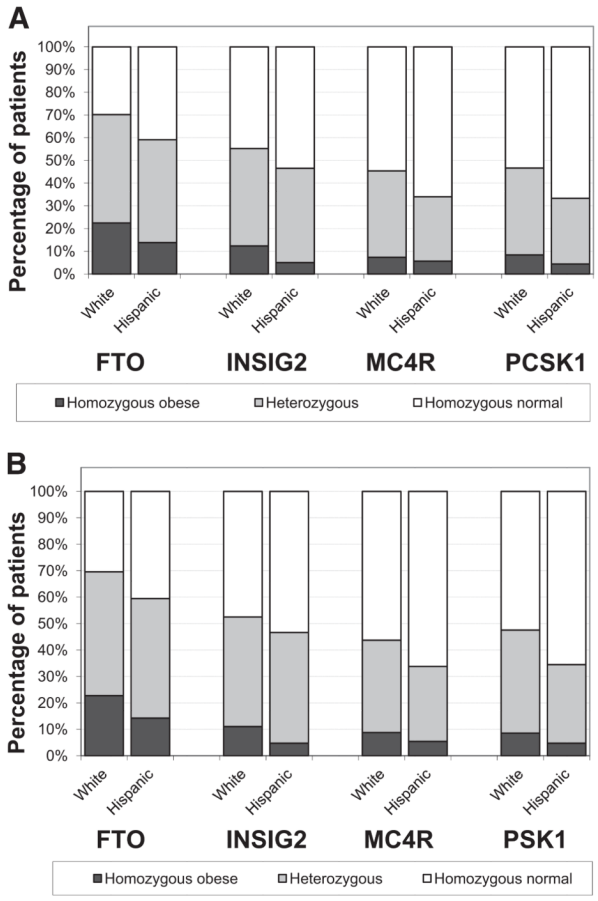

Fig. 1.
(A) Frequency of SNPs by ethnicity for overall population. (B) Frequency of SNPs by ethnicity for propensity-matched population.

Table 1

Phenotypic data by ethnicity and race for overall population

Variable	White (n = 1117)	Hispanic (n = 159)	*P* value
Gender			
Female	894 (80)	142 (89)	.0051
Male	223 (20)	17 (11)	
Age (yr)	46.1 ± 11.1	41.8 ± 14.8	<.0001
Preoperative BMI (kg/m^2)	50.2 ± 8.8	44.7 ± 6.4	<.0001
Co-morbidities			
Hypertension	579 (52)	64 (40)	.0063
Diabetes	450 (40)	51 (32)	.047
Hyperlipidemia	443 (40)	41 (26)	.0007
Sleep disorder	390 (35)	23 (14)	<.0001
Laboratory results			
Glucose	93 [84, 109]	96 [84, 111]	.462
Blood urea nitrogen	14 [1218]	14 [12, 17]	.190
Creatinine	.8 [.7, .9]	.7 [.7, .8]	<.0001
White blood cell count	7.9 [6.6, 9.4]	7.5 [6.4, 8.9]	.027
Red blood cell count	4.6 [4.3, 4.9]	4.5 [4.2, 4.7]	<.0001
Hemoglobin	13.7 [13.0, 14.5]	12.8 [12.1, 13.6]	<.0001
Platelets	284 [243, 330]	259 [223, 302.5]	.0001
Thyroid-stimulating hormone	1.90 [1.29, 2.81]	1.90 [1.45, 2.76]	.703
Alanine aminotransferase	25 [20, 36]	23 [18, 35]	.038
Aspartate aminotransferase	23 [19, 30]	22 [17, 28]	.036
Alkaline phosphate	78 [66, 94]	86 [71, 101]	.0004
Total bilirubin	.4 [.3, .5]	.4 [.3, .5]	.236
Insurance			<.0001
Private	747 (67)	12 (8)	
Government	248 (22)	119 (75)	
Self-pay	122 (11)	24 (15)	
Other/unknown	0 (0)	4 (3)	

BMI = body mass index.

Data presented as numbers, with percentages (column percentages) in parentheses, mean ± standard deviation, or median and interquartile range in brackets.

P values from chi-square test for categorical data, 2-sample *t* tests for mean values, and Wilcoxon rank sum tests for median values.

Table 2

Phenotypic data by ethnicity (white versus Hispanic) for the propensity-matched populations

Variable	Propensity matched population		
	White (n = 444)	Hispanic (n = 148)	*P* value
Gender			
Female	393 (89)	131 (89)	.999
Male	51 (11)	17 (11)	
Age (yr)	43.3 ± 10.6	43.2 ± 11.0	.944
Body mass index (kg/m^2)	46.2 ± 6.0	45.3 ± 6.2	.115
Co-morbidities			
Hypertension	197 (44)	61 (41)	.503
Diabetes	143 (32)	49 (33)	.839
Hyperlipidemia	119 (27)	41 (28)	.831
Sleep disorder	73 (16)	23 (16)	.797

Data presented as numbers, with percentages (column percentages) in parentheses, or mean ± standard deviation.

P values from chi-square test for categorical data, 2-sample *t* test for mean values, and Wilcoxon rank-sum test for median values.

Table 3

Comparative analysis of obesity alleles by ethnicity and race

	Overall population			Propensity matched population		
	White (n = 1117)	**Hispanic (n = 159)**	***P* value**	**White (n = 444)**	**Hispanic (n = 148)**	***P* value**
FTO						
AA	251 (22)	22 (14)	.0053 *	101 (23)	21 (14)	.0239 *
TA	533 (48)	72 (45)	.0012 †	208 (47)	67 (45)	.0066 †
TT	333 (30)	65 (41)		135 (30)	60 (41)	
INSIG-2						
CC	138 (12)	8 (5)	.012 *	49 (11)	7 (5)	.0656 *
GC	479 (43)	66 (42)	.0087 †	184 (41)	62 (42)	.0844 †
GG	500 (45)	85 (53)		211 (48)	79 (53)	
MC4R						
CC	82 (7)	9 (6)	.025 *	39 (9)	8 (5)	.0875 *
TC	425 (38)	45 (28)	.0084 †	155 (35)	42 (28)	.0282 †
TT	610 (55)	105 (66)		250 (56)	98 (66)	
PCSK-1						
GG	94 (8)	7 (4)	.0051 *	38 (9)	7 (5)	.0172 *
CG	427 (38)	46 (29)	.0012 †	173 (39)	44 (30)	.0046 †
CC	596 (53)	106 (67)		233 (52)	97 (66)	

FTO = fat mass and obesity-associated gene; *INSIG-2* = insulin-induced gene 2; *MC4R* = melanocortin 4 receptor gene; PCSK-1 = proprotein convertase subtilisn/kexin type 1 gene.

Data presented as numbers, with percentages (column percentages) in parentheses.

* Chi-square tests (i.e., test for association between ethnicity and genotype groups).

† Wilcoxon rank sum tests (i.e., test for trend between ethnicity and number of risk alleles).