Published in final edited form as:

Obesity (Silver Spring). 2011 October ; 19(10): 2102–2106. doi:10.1038/oby.2011.178.

A Genome-Wide Association Study of BMI in American Indians

Alka Malhotra¹, Sayuko Kobes¹, William C. Knowler¹, Leslie J. Baier¹, Clifton Bogardus¹, Robert L. Hanson¹

¹Phoenix Epidemiology and Clinical Research Branch, National Institute of Diabetes and Digestive and Kidney Diseases, Phoenix, Arizona, USA.

Abstract

Numerous studies have been done to understand genetic contributors to BMI, but only a limited number of studies have been done in nonwhite groups such as American Indians. A genome-wide association study (GWAS) for BMI was therefore performed in Pima Indians. BMI measurements from a longitudinal study of 1,120 Pima Indians and 454,194 single-nucleotide polymorphisms (SNPs) from the 1 million Affymetrix SNP panel were used (35% of SNPs were excluded due to minor allele frequency <0.05). Data included BMI measured at multiple examinations collected from 1965 to 2004, as well as the maximum BMI at one of these visits. General and within-family tests were performed using a maximum-likelihood based mixed model procedure. No SNP reached a genome-wide significance level (estimated at $P < 4.94 \times 10^{-7}$). For repeated measures analyses, the strongest associations for general and within-family tests mapped to two different regions on chromosome 6 (rs9342220 ($P = 1.39 \times 10^{-6}$) and rs7758764 ($P = 2.51 \times 10^{-6}$), respectively). For maximum BMI, the strongest association for the general tests mapped to chromosome 4 (rs17612333; $P = 1.98 \times 10^{-6}$) and to chromosome 3 (rs11127958; $P = 1.53 \times 10^{-6}$) for the within-family tests. Further analysis is important because only a few of these regions have been previously implicated in a GWAS and genetic susceptibility may differ by ethnicity.

Obesity is an increasing health problem worldwide. In the United States, there has been a threefold increase in prevalence of obesity over the past 5 decades, with most of the rise occurring in more recent years (1,2). Both lifestyle and genetic factors contribute to obesity.

Numerous genome-wide association and candidate gene studies have led to the identification of variants that are associated with BMI, a widely used measure of obesity (3–6). Most of these studies have been conducted in white populations, while the genetic architecture of obesity may differ across populations. American Indians, in particular, have a high prevalence of obesity (7), but only a few linkage studies have been performed in this population (8,9). No genome-wide association study (GWAS) for BMI in American Indians has been reported.

Correspondence: Alka Malhotra (alka@niddk.nih.gov).

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at <http://www.nature.com/oby>

DISCLOSURE

The authors declared no conflict of interest.

© 2011 The Obesity Society

We, therefore, performed a GWAS of BMI in Pima Indians. In this population, BMI is highly heritable (7,10). In addition, longitudinal data (collected from 1965 to 2004) are available, and analysis of the repeated measures can provide additional information in identifying variants associated with BMI.

RESEARCH DESIGN AND PROCEDURES

Study participants and phenotypes

Full-heritage American Indians ($n = 1,120$; age 15 years) were selected for the GWAS from participants in a longitudinal study (Table 1). Criteria for inclusion in the GWAS included: (i) membership in a family potentially informative for association with young-onset type 2 diabetes (11) or (ii) participation in detailed studies of metabolic and anthropometric phenotypes in nondiabetic healthy individuals (12). Although 436 individuals were singletons, the remainder were derived from 247 sibships. Size of sibships ranged from two to eight individuals. As individuals were selected in sibships, this was taken into account in the analysis, but we did not attempt to account for other family relationships.

Of the 1,120 participants, 508 were male and 612 were female. Informed consent was obtained for all participants and this study was approved by the institutional review board of the National Institute of Diabetes and Digestive and Kidney Diseases.

Data included BMI at multiple examinations (range: 1–17 examinations for a given individual) collected from 1965 to 2004. Exams were excluded if an individual was pregnant. Average BMI from all 5,904 exams in these individuals was 33.5 kg/m^2 . Table 1 provides details of BMI measurements for both longitudinal BMI (i.e., all examinations) and maximum BMI measurements.

Genotyping and quality control

Individuals were genotyped according to the manufacturer's protocol with the Genome-Wide Human SNP Array 6.0 (Affymetrix, Santa Clara, CA), which contains 909,508 single-nucleotide polymorphisms (SNPs) with known positions in the human genome. Genotypes were generated using the BIRDSEED algorithm. Details on the quality control procedures are given in the Supplementary Methods and Procedures online. A total of 454,194 SNPs passed these quality control procedures and allele frequency limitations (35% of SNPs were removed due to minor allele frequency <0.05).

Association analysis

Genome-wide association tests (done separately for general and within-family) of maximum BMI and longitudinal BMI were performed using the Statistical Analysis System (SAS, Cary, NC) software. An additive model was used (i.e., the number of alleles was included as a fixed effect). Other variables (including age, gender, individual admixture, birth year, diabetes status, and diabetes duration) were included as covariates. See Supplementary Methods and Procedures online for more details.

Genomic control and multiple testing correction

All P values were adjusted by genomic control (13) to account for inflation from population stratification or unspecified relatedness. Briefly, an inflation factor (λ) was calculated as the mean χ^2 overall markers. The χ^2 values for each SNP were corrected by dividing by the inflation factor. An F -test was then used to estimate the corrected P values from the corrected χ^2 values (13).

To account for the multiple statistical tests performed in this GWAS, the method proposed by Duggal *et al.* was used (14). Details can be found in the Supplementary Methods and Procedures online. Using this method, we estimated 101,156 independent tests among the 454,194 SNPs. Using a Bonferroni correction, nominal $P < 4.94 \times 10^{-7}$ was thus considered to be genome-wide significance at $P < 0.05$. We use the term “strong evidence of association” for P values that did not meet this criterion, but had a nominal $P < 10^{-3}$.

RESULTS

For repeated measures analyses, λ was 1.06 and 1.20 for within-family and general tests, respectively. For maximum BMI, λ was 1.05 and 1.20 for within-family and general tests, respectively. The modest inflation in the general tests may, in part, reflect distant relationships that are not taken into account in the present analytical approach.

No SNP had a $P < 4.94 \times 10^{-7}$ which corresponds to a genome-wide significance of $P < 0.05$ by the method of Duggal *et al.* (14). However, for such a stringent P value, power of the present study is low; we estimate that a SNP needs to account for at least 3.65% of the variance to achieve >80% power. For a SNP that explains 1% of the variance, we estimate 41% power at $P < 10^{-3}$.

For the general tests for the repeated measures analysis, the smallest 10 P values ranged from 1.39×10^{-6} to 1.37×10^{-5} , which were observed on chromosomes 3, 4, and 6. These included four highly concordant ($r^2 > 0.95$ for all pairs of SNPs) adjacent SNPs on chromosome 4 (located at 169562461–169570412bp). In addition, SNPs on chromosomes 17 and 20 showed strong evidence for association (Table 2). Of these top SNPs, 50% of them also showed nominal evidence for association ($P < 0.05$) in the within-family tests.

The strongest evidence for association using the within-family test in the longitudinal data was observed on chromosome 6 among six highly concordant SNPs ($P = 2.51 \times 10^{-6}$ to 6.60×10^{-6}). In addition, three SNPs on chromosome 4 ($r^2 > 0.95$ for two of the three SNPs; located at 20863634–20881374bp) and one chromosome 2 SNP (rs10928206) had associations with BMI of similar magnitude (Table 3). Supplementary Figures S1 and S2 online show the results for the repeated measures analysis. In addition, Supplementary Tables S1 and S2 online list the top 500 SNPs for these analyses.

For maximum BMI, the strongest evidence for association came from the within-family tests on chromosome 3 (rs11127958; Table 3; Supplementary Figure S3 and Supplementary Table S3 online). P values for the top SNPs ranged from 1.53×10^{-6} to 2.94×10^{-5} (Supplementary Table S3 online). For the general tests, there were five SNPs on

chromosome 4 and two SNPs each on chromosomes 17 and 20 among the top 10 showing evidence of association with maximum BMI (Table 2; Supplementary Figure S4 and Supplementary Table S4).

We further investigated SNPs located in genes previously identified in GWAS and candidate gene studies of obesity and/or BMI (3–6,15–17). Of the SNPs located within each gene interval, the SNP showing the lowest P value was identified. SNPs at nine genes showed $P < 0.05$ (Table 4).

DISCUSSION

Our GWAS in Pima Indians used both general and within-family analyses of association with BMI. General tests have more power than within-family tests, but within-family tests are not affected by population stratification. To make optimal use of the longitudinal data, two different analytical approaches were used. The analysis of maximum BMI may capture an individual's overall predisposition toward obesity, whereas analysis of all repeated measures makes optimal use of an individual's overall BMI during the course of the study.

For the general tests for maximum BMI, two chromosomes 17 SNPs were associated (P ranging from 7.18×10^{-6} to 2.21×10^{-5}). This same location was also identified in the general tests of analyses using longitudinal BMI measurements (Table 2). In addition, there was good overlap between SNPs on chromosome 4 identified for the general tests of maximum BMI and the repeated measures analyses (Supplementary Tables S1–S4).

SNPs identified in the GWAS regions are undergoing validation in larger samples of Pima Indians. Initially, these are analyzed in a larger group of full-heritage Pimas who were not in the GWAS ($N = 2,133$). Nine of the top ten regions identified in the GWAS general tests (Table 2) have been successfully genotyped. Of these, five have a P value < 0.05 for association in the same direction as in the GWAS (Table 5), with SNPs on chromosome 6 (rs9381282; longitudinal BMI data $P = 0.0008$) and 4 (rs17612333; longitudinal BMI data $P = 0.0014$) showing the lowest P values. Although the number of showing $P < 0.05$ is more than would be expected by chance, further validation studies are important to distinguish reproducible associations. Therefore, variants of interest are being genotyped in an additional set of Pimas ($N = 2,706$) to further examine their effect on BMI. To date, these studies have implicated *MAP2K3* on chromosome 17 and *A2BPI* on chromosome 16 as potential obesity genes (18,19).

Numerous genome-wide and candidate gene studies have been done for BMI and obesity (3–6,15–17). We, therefore, examined SNPs from the current GWAS within genes previously identified. From 23 previously identified candidate genes, 20 had SNPs genotyped in the current GWAS; nine of these had at least one SNP with $P < 0.05$ (Table 4). The *MC4R* SNP previously implicated in a GWAS for BMI (6) is monomorphic for the nonrisk allele in Pima Indians. Furthermore, no SNPs were present for two genes (*MAF* and *SH2B1*). Most signals identified in previous studies are not well captured in the current SNP array; based on genotyping of these candidate SNPs in this population, only seven genes had a SNP with $r^2 > 0.8$ with the sentinel SNP identified from European-GWAS (Table 4). Use

of different genotyping platforms was the main reason for this discrepancy; SNPs were typed using the Illumina platform for most of studies that identified the genes in Table 4 (5,6), while the Affymetrix chip was used in the present study. Given these results and the small sample size of the present study, larger follow-up studies are needed to fully characterize variants in these genes. Several of these genes have been analyzed in a large population-based study with 3,250 Pima Indians and *FTO* has emerged as a significant gene for BMI in the Pima Indian population (ref. 20; Table 4).

In summary, a GWAS in Pima Indians identified SNPs associated with BMI in regions that have not previously been implicated in other ethnic groups. Further analysis of novel regions is important because a majority of previous studies have been done in white populations, whereas genetic susceptibility factors may differ by ethnicity. Future work will include replication studies to confirm the associations of the SNPs identified in the GWAS in a larger group of Pima Indians. In addition, genotyping more SNPs in areas of association will be used for fine-mapping. Information presented in Supplementary Tables S1–S4 can also be used by other studies to see if their results replicate those from the current GWAS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

The authors thank the study participants and staff of the Diabetes Epidemiology and Clinical Research Section and of the Diabetes Molecular Genetics Section for performing the studies generating these data. This research was supported by the Intramural Research Program of the National Institute of Diabetes and Digestive and Kidney Diseases.

REFERENCES

1. Ogden CL, Yanovski SZ, Carroll MD, Flegal KM. The epidemiology of obesity. *Gastroenterology* 2007;132:2087–2102. [PubMed: 17498505]
2. Parikh NI, Pencina MJ, Wang TJ et al. Increasing trends in incidence of overweight and obesity over 5 decades. *Am J Med* 2007;120:242–250. [PubMed: 17349447]
3. Hofker M, Wijmenga C. A supersized list of obesity genes. *Nat Genet* 2009;41:139–140. [PubMed: 19174833]
4. Meyre D, Delplanque J, Chèvre JC et al. Genome-wide association study for early-onset and morbid adult obesity identifies three new risk loci in European populations. *Nat Genet* 2009;41:157–159. [PubMed: 19151714]
5. Thorleifsson G, Walters GB, Gudbjartsson DF et al. Genome-wide association yields new sequence variants at seven loci that associate with measures of obesity. *Nat Genet* 2009;41:18–24. [PubMed: 19079260]
6. Willer CJ, Speliotes EK, Loos RJ et al.; Wellcome Trust Case Control Consortium; Genetic Investigation of ANthropometric Traits Consortium. Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. *Nat Genet* 2009;41:25–34. [PubMed: 19079261]
7. Knowler WC, Pettitt DJ, Saad MF et al. Obesity in the Pima Indians: its magnitude and relationship with diabetes. *Am J Clin Nutr* 1991;53: 1543S–1551S. [PubMed: 2031485]
8. Franceschini N, Almasy L, MacCluer JW et al. Diabetes-specific genetic effects on obesity traits in American Indian populations: the Strong Heart Family Study. *BMC Med Genet* 2008;9:90. [PubMed: 18854016]

9. Hanson RL, Ehm MG, Pettitt DJ et al. An autosomal genomic scan for loci linked to type II diabetes mellitus and body-mass index in Pima Indians. *Am J Hum Genet* 1998;63:1130–1138. [PubMed: 9758619]
10. Baier LJ, Hanson RL. Genetic studies of the etiology of type 2 diabetes in Pima Indians: hunting for pieces to a complicated puzzle. *Diabetes* 2004;53:1181–1186. [PubMed: 15111484]
11. Hanson RL, Bogardus C, Duggan D et al. A search for variants associated with young-onset type 2 diabetes in American Indians in a 100K genotyping array. *Diabetes* 2007;56:3045–3052. [PubMed: 17846125]
12. Traurig M, Mack J, Hanson RL et al. Common variation in SIM1 is reproducibly associated with BMI in Pima Indians. *Diabetes* 2009;58: 1682–1689. [PubMed: 19401419]
13. Devlin B, Bacanu SA, Roeder K. Genomic Control to the extreme. *Nat Genet* 2004;36:1129–1130; author reply 1131. [PubMed: 15514657]
14. Duggal P, Gillanders EM, Holmes TN, Bailey-Wilson JE. Establishing an adjusted p-value threshold to control the family-wide type 1 error in genome wide association studies. *BMC Genomics* 2008;9:516. [PubMed: 18976480]
15. Cotsapas C, Speliotes EK, Hatoum IJ et al.; GIANT Consortium. Common body mass index-associated variants confer risk of extreme obesity. *Hum Mol Genet* 2009;18:3502–3507. [PubMed: 19553259]
16. Kalnina I, Kapa I, Pirags V et al. Association between a rare SNP in the second intron of human Agouti related protein gene and increased BMI. *BMC Med Genet* 2009;10:63. [PubMed: 19602223]
17. van den Berg SW, Dollé ME, Imholz S et al. Genetic variations in regulatory pathways of fatty acid and glucose metabolism are associated with obesity phenotypes: a population-based cohort study. *Int J Obes (Lond)* 2009;33:1143–1152. [PubMed: 19652658]
18. Ma L, Hanson RL, Traurig MT et al. Evaluation of A2BP1 as an obesity gene. *Diabetes* 2010;59:2837–2845. [PubMed: 20724578]
19. Bian L, Mack J, Kobes S et al. MAP2K3 variation is reproducibly associated with body mass index in Pima Indians (abstract# 588) Presented at the 59th Annual Meeting of The American Society of Human Genetics, 21 10 2009, Honolulu, HI.
20. Rong R, Hanson RL, Ortiz D et al. Association analysis of variation in/near FTO, CDKAL1, SLC30A8, HHEX, EXT2, IGF2BP2, LOC387761, and CDKN2B with type 2 diabetes and related quantitative traits in Pima Indians. *Diabetes* 2009;58:478–488. [PubMed: 19008344]

Table 1Characteristics of participants ($N = 1,120$)

	Males	Females
Number	508	612
Average age for all exams (years)	33.7 ± 13.6	34.6 ± 13.8
Age range (years)	15–78	15–88
Age at maximum BMI (years)	34.2 ± 13.0	36.5 ± 13.7
Number of exams (range)	1–16	1–17
Mean BMI ^a (kg/m ²) for all exams	32.1 ± 7.8	34.4 ± 8.5
N with diabetes at first exam	70	103
N with diabetes at last exam	194	305
Mean BMI* (kg/m ²) at maximum	35.6 ± 8.3	38.7 ± 8.7

For each trait the mean $\pm$ s.d. is shown.^aBMI (kg/m²).

Table 2

Top SNPs for general tests for either maximum and/or multiple BMI measurements

Chromosome	SNP name (location (bp) ^a)	Alleles (frequency of allele 1)	Average BMI ^b by genotype (mean ± s.d.)			General	
			1/1 (N)	1/2 (N)	2/2 (N)	Multiple BMI <i>P</i> value (<i>P</i> ^c)	Maximum BMI <i>P</i> value (<i>P</i> ^c)
3 ^d	rs6441552 (101979305)	A/G (0.75)	38.29 ± 8.84 (608)	36.53 ± 8.63 (433)	34.56 ± 7.67 (76)	3.66 × 10 ⁻⁶ (0.0494)	9.94 × 10 ⁻⁵ (0.0467)
4 ^d	rs17612333 ^e (169566959)	A/C (0.37)	40.02 ± 9.56 (152)	37.98 ± 8.93 (484)	35.92 ± 8.01 (484)	7.64 × 10 ⁻⁶ (0.0434)	1.98 × 10 ⁻⁶ (0.0514)
6	rs4711689 ^e (41800790)	C/T (0.29)	39.67 ± 8.99 (99)	38.22 ± 8.90 (440)	36.33 ± 8.47 (579)	1.37 × 10 ⁻⁵ (0.0447)	3.82 × 10 ⁻⁵ (0.0476)
6	rs9381282 ^e (44116303)	G/T (0.46)	35.63 ± 7.52 (227)	36.97 ± 8.20 (574)	39.38 ± 10.12 (315)	1.39 × 10 ⁻⁴ (-0.0368)	8.89 × 10 ⁻⁶ (-0.0481)
6	rs2670134 (52669733)	A/G (0.34)	39.35 ± 8.87 (134)	38.20 ± 8.79 (472)	36.07 ± 8.50 (510)	8.91 × 10 ⁻⁶ (0.0445)	5.64 × 10 ⁻⁵ (0.0452)
6	rs9342220 ^e (90828533)	A/G (0.28)	39.63 ± 10.31 (90)	38.08 ± 9.00 (465)	36.40 ± 8.15 (562)	1.39 × 10 ⁻⁶ (0.0497)	3.22 × 10 ⁻⁵ (0.0481)
17 ^d	rs11652094 (21112882)	C/G (0.75)	38.58 ± 8.77 (578)	36.45 ± 8.80 (458)	34.13 ± 6.50 (83)	3.22 × 10 ⁻⁵ (0.0443)	2.21 × 10 ⁻⁵ (0.0507)
17	rs9890304 ^e (67604910)	C/T (0.42)	39.24 ± 9.51 (215)	37.71 ± 8.83 (517)	35.83 ± 8.09 (347)	1.03 × 10 ⁻⁴ (0.0365)	7.18 × 10 ⁻⁶ (0.0477)
20	rs1418029 ^e (2008151)	C/T (0.11)	43.97 ± 7.84 (17)	38.75 ± 8.97 (213)	36.90 ± 8.66 (880)	2.40 × 10 ⁻⁵ (0.0639)	2.13 × 10 ⁻⁴ (0.0631)
20	rs4811346 (50456516)	G/T (0.19)	40.40 ± 7.91 (26)	38.80 ± 9.24 (360)	36.46 ± 8.39 (720)	1.54 × 10 ⁻⁴ (0.0464)	1.63 × 10 ⁻⁵ (0.0597)

bp, base pairs; SNPs, single-nucleotide polymorphisms.

^aBase pairs based on Build 36.

^bAverage BMI was calculated from the maximum value for each person.

^cRegression coefficient per copy of allele 1 (in log (BMI) units).

^dEvidence for association was seen for at least 2 SNPs in high LD within this region; SNPs with the lowest *P* value are presented.

^eThese SNPs also showed nominal evidence for association (i.e., *P* < 0.05) in the within-family tests.

Table 3

Top SNPs for within-family tests for either maximum and/or multiple BMI measurements

Chromosome	SNP name (location (bp ^a))	Alleles(frequency of allele 1)	Average BMI ^b by genotype (mean ± s.d.)			Within-family	
			1/1 (N)	1/2 (N)	2/2 (N)	Multiple BMI <i>P</i> value (<i>P</i> ^f)	Maximum BMI <i>P</i> value (<i>P</i> ^f)
2 ^d	rs10928206 ^e (144681706)	C/G (0.83)	37.56 ± 8.84 (754)	37.11 ± 8.67 (327)	35.64 ± 7.51 (36)	3.89 × 10 ⁻⁶ (0.0875)	2.40 × 10 ⁻⁶ (0.1044)
3 ^d	rs11127958 ^e (86908290)	A/T (0.83)	38.06 ± 9.05 (677)	36.48 ± 8.12 (312)	34.44 ± 5.91 (24)	2.64 × 10 ⁻⁵ (0.0932)	1.53 × 10 ⁻⁶ (0.1255)
4 ^d	rs11936275 ^e (20881374)	G/T (0.32)	40.00 ± 9.73 (87)	37.67 ± 8.92 (480)	36.84 ± 8.58 (495)	4.73 × 10 ⁻⁶ (0.0823)	5.78 × 10 ⁻⁴ (0.0728)
6 ^d	rs7758764 ^e (53504121)	A/G (0.69)	36.87 ± 8.55 (532)	38.42 ± 9.06 (445)	35.42 ± 7.80 (122)	2.51 × 10 ⁻⁶ (-0.0792)	6.70 × 10 ⁻⁵ (-0.0799)
7	rs6965510 ^e (95067784)	C/T (0.95)	37.18 ± 8.76 (945)	39.36 ± 8.59 (114)	— ^f	2.40 × 10 ⁻⁴ (-0.1452)	3.57 × 10 ⁻⁶ (-0.2136)
10	rs7095572 (14158090)	C/T (0.61)	37.48 ± 9.43 (431)	37.27 ± 7.86 (524)	37.29 ± 9.52 (164)	1.76 × 10 ⁻⁵ (-0.0679)	2.51 × 10 ⁻³ (-0.0564)
11	rs10833444 ^e (21029035)	A/G (0.41)	36.69 ± 8.37 (191)	37.94 ± 9.06 (523)	36.81 ± 8.43 (393)	2.12 × 10 ⁻⁵ (0.0638)	1.13 × 10 ⁻⁴ (0.0694)
11 ^d	rs4399316 ^e (44628470)	C/T (0.42)	38.21 ± 9.30 (179)	37.28 ± 8.69 (573)	37.07 ± 8.57 (365)	7.40 × 10 ⁻⁵ (0.0618)	1.25 × 10 ⁻⁵ (0.0800)
13	rs4772832 ^e (106409598)	C/T (0.43)	37.30 ± 8.48 (203)	37.82 ± 8.71 (532)	36.84 ± 8.93 (374)	1.14 × 10 ⁻⁴ (0.0614)	2.12 × 10 ⁻⁵ (0.0792)
21	rs2836489 (38832550)	C/T (0.75)	37.51 ± 8.61 (648)	36.80 ± 8.69 (394)	38.60 ± 9.76 (76)	4.07 × 10 ⁻⁴ (-0.0616)	1.15 × 10 ⁻⁵ (-0.0901)

bp, base pairs; SNPs, single-nucleotide polymorphisms.

^aBase pairs based on Build 36.

^bAverage BMI was calculated from the maximum value for each person.

^cRegression coefficient per copy of allele 1 (in log (BMI) units).

^dEvidence for association was seen for at least 2 SNPs in high LD within this region; SNPs with the lowest *P* value are presented.

^eThese SNPs also showed nominal evidence for association (i.e., *P* < 0.05) in the within-family tests.

^fNo individual had this genotype.

Table 4

P values (corrected for genomic control) for SNPs located in intervals of previously identified candidate genes (refs. 3–6)

Gene	Chromosome (location in bp)	SNP showing evidence for association in a previously published study	Number of SNPs genotyped in the present GWAS study in the interval	SNP with lowest <i>P</i> value in gene location from current study	<i>P</i> value	Trait (test)	Highest r^2 between candidate SNP (column 3) and those genotyped in the present study (column 4)
NEGR1	1 (71,441,214–72,720,865) ^a	rs2815752	146	rs11209873	0.0031	Maximum BMI (within)	1
RASAL2	1 (176,330,253–176,710,178)	rs10913469 ^b	25	rs2902237	0.0022	Multiple BMI (within)	0.217
SEC16B	1 (176,164,865–176,205,673)	rs10913469 ^b	12	rs2902210	0.0093	Multiple BMI (within)	0.798
TMEM18	2 (657,975–667,439)	rs6548238	1	rs17042334	0.6762	Maximum BMI (general)	0.021
INSIG2	2 (118,562,520–118,584,066)	rs7566605	3	rs10490625	0.1538	Maximum BMI (within)	0.405
SFRS10	3 (187,117,236–187,138,450)	rs7647305 ^b	1	rs6802503	0.5684	Multiple BMI (general)	0.006
ETV5	3 (187,246,805–187,309,571)	rs7647305 ^b	7	rs4686729	0.0776	Maximum BMI (general)	0.134
DGKG	3 (187,347,684–187,562,717)	rs7647305 ^b	36	rs2193587	0.0251	Maximum BMI (general)	0.102
GNPDA2	4 (44,398,926–44,423,369)	rs10938397	2	rs1547525	0.3067	Maximum BMI (within)	0.033
PCSK1	5 (95,751,875–95,794,708)	rs6232	11	rs271924	0.0742	Maximum BMI (general)	0.002
PRL	6 (22,395,459–22,405,709)	rs4712652	3	rs849886	0.1501	Multiple BMI (within)	— ^c
PTER	10 (16,518,973–16,595,742)	rs10508503	26	rs11818351	0.0234	Maximum BMI (general)	— ^c
BDNF	11 (27,623,018–27,699,872)	rs4074134	14	rs12273539	0.0159	Multiple BMI (within)	0.953
MTCH2	11 (47,595,444–47,620,640)	rs10838738	2	rs3817334	0.0427	Multiple BMI (general)	0.985
BCDIN3D	12 (48,317,823–48,723,142) ^a	rs7138803 ^b	41	rs378943	0.0757	Maximum BMI (within)	1
FAIM2	12 (48,346,947–48,783,987) ^a	rs7138803 ^b	48	rs36172	0.0964	Multiple BMI (general)	1
FTO	16 (52,295,376–52,705,882)	rs7193144	92	rs1421085 ^d	0.0462	Multiple BMI (within)	1
NPC1	18 (19,365,463–19,420,426)	rs1805081	15	rs3745023	0.1649	Maximum BMI (within)	0.072
CHST8	19 (38,867,274–38,956,253)	rs29941 ^b	16	rs284690	0.1091	Multiple BMI (general)	— ^c
KCTD15	19 (38,779,607–39,196,984) ^a	rs11084753	61	rs736239	0.0258	Maximum BMI (within)	1

bp, base pairs; SNPs, single-nucleotide polymorphisms.

^aThe sentinel SNP is outside the gene so the interval has been increased by 200 kb on either side to include it.

Author Manuscript

^b SNP is near two candidate genes.
^c SNP was not genotyped in Pima Indians.
^d Same SNP has been identified in previous studies.

Author Manuscript

Author Manuscript

Author Manuscript

Table 5
Replication results of the top nine regions identified in the GWAS for the general tests of association

SNP name	Chromosome (location in bp)	Alleles (frequency of allele 1)	Multiple BMI P value in the replication sample (β^1)	Maximum BMI P value in the replication sample (β^1)
rs6441552	3 (101979305)	A/G (0.74)	0.0650 (0.0139)	0.8959 (0.0010)
rs17612333	4 (169566959)	A/C (0.35)	0.0014 (0.0220)	0.0580 (0.0134)
rs4711689	6 (41800790)	C/T (0.31)	0.5346 (–0.0044)	0.5284 (–0.0045)
rs9381282	6 (44116303)	G/T (0.46)	0.0008 (–0.0223)	0.0912 (–0.0114)
rs2670134	6 (52669733)	A/G (0.33)	0.0533 (0.0134)	0.2206 (0.0086)
rs9342220	6 (90828533)	A/G (0.29)	0.1488 (0.0108)	0.2485 (0.0088)
rs11652094	17 (21112882)	C/G (0.73)	0.0120 (0.0183)	0.1320 (0.0113)
rs1418029	20 (2008151)	C/T (0.12)	0.0059 (0.0295)	0.0526 (0.0217)
rs4811346	20 (50456516)	G/T (0.19)	0.0061 (0.0224)	0.8697 (–0.0014)

bp, base pairs; GWAS, genome-wide association study; SNPs, single-nucleotide polymorphisms.

^aRegression coefficient per copy of allele 1 (in log (BMI) units).