Analyses of shared genetic factors between asthma and obesity in children

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Background: Epidemiologic studies consistently show associations between asthma and obesity. Shared genetics might account for this association.
Objective: We sought to identify genetic variants associated with both asthma and obesity.
Methods: On the basis of a literature search, we identified genes from (1) genome-wide association studies (GWASs) of body mass index (BMI; n = 17 genes), (2) GWASs of asthma (n = 14), and (3) candidate gene studies of BMI and asthma (n = 7). We used GWAS data from the Childhood Asthma Management Program to analyze associations between single nucleotide polymorphisms (SNPs) in these genes and asthma (n = 359 subjects) and BMI (n = 537).
Results: One top BMI GWAS SNP from the literature, rs10938397 near glucosamine-6-phosphate deaminase 2 *(GNPDA2)*, was associated with both BMI ($P = 4 \times 10^{-4}$) and asthma ($P = .03$). Of the top asthma GWAS SNPs and the candidate gene SNPs, none was found to be associated with both BMI and asthma. Gene-based analyses that included all available SNPs in each gene found associations ($P < .05$) with both phenotypes for several genes: neuronal growth regulator 1 *(NEGR1)*; roundabout, axon guidance receptor, homolog 1 *(ROBO1)*; diacylglycerol kinase, gamma *(DGKG)*; Fas apoptotic inhibitory molecule 2 *(FAIM2)*; fat mass and obesity associated *(FTO)*; and carbohydrate (N-acetylgalactosamine 4-0) sulfotransferase 8 *(CHST8)* among the BMI GWAS genes; interleukin 1 receptor-like 1 / interleukin 18 receptor 1 *(IL1RL1/IL18R1)*, dipeptidyl-peptidase 10 *(DPP10)*, phosphodiesterase 4D *(PDE4D)*, V-myb myeloblastosis viral oncogene homolog *(MYB)*, *PDE10A*, *IL33*, and especially protein tyrosine phosphatase, receptor type D *(PTPRD)* among the asthma GWAS genes; and protein kinase C, alpha *(PRKCA)* among the BMI and asthma candidate genes.
Conclusions: SNPs within several genes showed associations to BMI and asthma at a genetic level, but none of these associations were significant after correction for multiple testing. Our analysis of known candidate genes reveals some evidence for shared genetics between asthma and obesity, but other shared genetic determinants are likely to be identified in novel loci. (J Allergy Clin Immunol 2010;126:631-7.)

Key words: *Association, asthma, body mass index, children, genetics, genome-wide association study, obesity, polymorphism, single nucleotide polymorphism*

Asthma and obesity are complex disorders that are influenced by environmental and genetic factors. During the past decades, the prevalence of both traits has markedly increased in children and adults, contributing substantially to morbidity and health costs worldwide.[1] Epidemiologic studies have consistently shown an association between asthma and obesity, and longitudinal studies suggest that obesity precedes asthma.[1-3] Twin studies indicate that shared genetic pathways for asthma and obesity might partly account for the observed associations between these conditions.[4,5] Asthma and obesity are believed to have a strong genetic background, and numerous genetic variants have been associated with both phenotypes.[6-8] Individual studies that have focused on either asthma or obesity have identified genes, including angiotensin I–converting enzyme *(ACE)*, adrenergic receptor B2 *(ADRB2)*, and vitamin D (1,25-dihydroxyvitamin D3) receptor *(VDR)*,[6,7] that might influence both diseases. Genes such as leptin *(LEP)*; protein kinase C, alpha *(PRKCA)*; and tumor necrosis factor *(TNF)* have also been evaluated for pleiotropic effects that influence both asthma and obesity simultaneously.[9-11] Recent genome-wide association studies (GWASs) have identified variants at several loci that are associated with body mass index (BMI), obesity, or both.[12-20] It is unclear whether these loci contribute only to BMI/obesity or whether they also influence asthma risk. Likewise, it is unclear whether variants identified through recent asthma GWASs also contribute to BMI/obesity.[21-26] The aim of this project is to identify common genetic variants that are associated with asthma and obesity. We used GWAS data from the Childhood Asthma Management Program (CAMP) to study associations between single nucleotide polymorphisms (SNPs) in genes previously associated with BMI, asthma, or both. All SNPs identified in GWASs for BMI/obesity and asthma published to date were evaluated systematically, as well as SNPs from candidate gene studies that have been associated with both asthma and obesity.

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Abbreviations used

ACE: Angiotensin I–converting enzyme
ADR: Adrenergic receptor
BMI: Body mass index
CAMP: Childhood Asthma Management Program
CHST8: Carbohydrate (N-acetylgalactosamine 4-0) sulfotransferase 8
DENND1B: DENN/MADD domain containing 1B
DGKG: Diacylglycerol kinase, gamma
DPP10: Dipeptidyl-peptidase 10
FAIM2: Fas apoptotic inhibitory molecule 2
FTO: Fat mass and obesity associated
GBE1: Glucan (1,4-alpha-), branching enzyme 1
GNPDA2: Glucosamine-6-phosphate deaminase 2
GSDML (alias GSDMB): Gasdermin B
GWAS: Genome-wide association study
IL: Interleukin
INSIG2: Insulin-induced gene 2
KCTD15: Potassium channel tetramerization domain containing 15
LEP: Leptin
MYB: V-myb myeloblastosis viral oncogene homolog
NEGR1: Neuronal growth regulator 1
ORMDL3: ORM1-like 3
QC: Quality control
PDE: Phosphodiesterase
PRKCA: Protein kinase C, alpha
PRNP: Prion protein
PTP: Protein tyrosine phosphatase
ROBO1: Roundabout, axon guidance receptor, homolog 1
SNP: Single nucleotide polymorphism
TSLP: Thymic stromal lymphopoietin
VDR: Vitamin D (1,25-dihydroxyvitamin D3) receptor
WDR36: WD repeat domain 36

METHODS

Study design

CAMP was a multicenter clinical trial in children with mild-to-moderate asthma.[27] All recruited children had asthma as defined by having 2 or more symptoms per week, using an inhaled bronchodilator at least twice weekly or asthma medication daily, and airway responsiveness to methacholine of 12.5 mg/mL or less. Children with severe asthma or other clinically significant conditions were excluded. Of the 1,041 children enrolled in the original clinical trial, 968 children and 1,518 of their parents contributed DNA samples. At randomization, baseline data, including measurements of BMI, were collected. Overweight was defined as an age- and sex-adjusted BMI between the 85th and 95th percentiles and obesity as an age- and sex-adjusted BMI equal to or greater than the 95th percentile.[28] Written informed consent was obtained from parents of participating children. The CAMP study was approved by the Institutional Review Boards of Brigham and Women's Hospital and the other participating centers.

Genotyping

A subset of 422 white (non-Hispanic) CAMP probands were genotyped on Illumina's Human-Hap550 Genotyping BeadChip (Illumina, Inc, San Diego, Calif) and used as cases in a case-control study design with white population control subjects (n = 1,533 adults) obtained from Illumina's iControlDB public repository. As reported previously, strict quality control (QC) procedures, including implementation of the genetic matching algorithm to reduce population stratification, reduced the case-control asthma GWAS to 1,205 subjects (359 cases and 846 control subjects) and 518,230 SNPs.[23] For the BMI GWAS, data from an additional 211 CAMP probands obtained with the Illumina Infinium HD Human610-Quad BeadChip were available, and a merged HumanHap550/Human610-Quad dataset composed of 633 CAMP children was created. After QC, 537 asthma cases and 511,782 SNPs remained in the BMI dataset. Because matched Illumina iControlDB control subjects were not available for the merged dataset, only genetic association with BMI was estimated in this dataset. Please see the Methods section of this article's Online Repository at www.jacionline.org for further genotyping and QC details.

Literature search

The online GWAS Catalog[29] was accessed on December 30, 2009, and used to search for published BMI and asthma GWASs. Inclusion of SNP-based associations was limited to those with P values of less than 1.0×10^{-5} (with the exception of 2 asthma GWAS SNPs in V-myb myeloblastosis viral oncogene homolog *[MYB]* and WD repeat domain 36 *[WDR36]*/thymic stromal lymphopoietin *[TSLP]* and 1 BMI GWAS SNP in insulin-induced gene 2 *[INSIG2]*, which were included despite higher P values because they are widely studied and biologically plausible candidates). In addition, a PubMed (www.ncbi.nlm.nih.gov/pubmed) search was performed on December 30, 2009, by using the terms (1) "asthma" together with (2) "body mass index", "BMI," or "obesity" and (3) "association" or "genetic association." Genes with previous evidence of association with both BMI and asthma in candidate gene studies were included by using less stringent criteria (any SNP or other variant associated at $P < .05$). Thus we used the gene as the unit of association and the same SNP or variant needed not to be associated to both phenotypes for inclusion. Some genes have been evaluated for association individually with asthma or BMI/obesity in multiple populations, as summarized in reviews by Ober and Hoffjan,[6] Rankinen et al,[7] and Rogers et al.[8] In the current study we refer to these reviews when referencing most known associations rather than the original studies. For identified genes not included in these reviews, we reference original publications.

Statistical analyses

Genes indentified through the literature search were evaluated for associations with asthma and BMI in CAMP. For asthma, CAMP/Illumina case-control associations (allelic tests) were measured in PLINK,[30] as previously described.[23] BMI was analyzed as a continuous trait with linear regression in PLINK by using an additive genetic model adjusted for age, sex, and informative principal components (to adjust for potential population substructure). PLINK output files were exported to the WGAViewer software,[31] which was used for gene-based and SNP-specific analyses. This software's annotation results are based on the latest Ensembl Core, Variation, and Gene Ontology databases. The annotation span for gene-based analyses was 10,000 bp beyond the 5′ and 3′ gene ends. A total of 2,583 SNPs were identified as being within the span of the 38 identified genes of interest. With a conservative Bonferroni correction, an adjusted P value for significance was estimated to be 1.9×10^{-5} (= .05/2,583). All reported P values are 2-sided.

RESULTS

Baseline characteristics of the CAMP children are presented in Table I. No differences were observed between the asthma and BMI subjects. Thirteen percent of the children met the criteria for obesity and a further 16% for overweight. This is in agreement with recent national figures from the Centers for Disease Control and Prevention.[28] Based on the systematic literature search in PubMed and the online GWAS Catalog,[29] SNPs and genes were classified as (1) 29 SNPs in 17 genes identified in previous BMI GWASs (Table II),[12-20] (2) 14 SNPs in 14 genes identified in previous asthma GWASs (Table III),[21-26] and (3) multiple SNPs in 7

TABLE I. Baseline characteristics of subjects in CAMP

	Asthma GWAS	BMI GWAS
Asthmatic patients	359	537
Age (y)*	8.8 (5.2-13.2)	8.9 (5.2-13.2)
Female sex	38.3%	40.4%
BMI*	17.8 (13.0-29.1)	18.0 (13.0-29.4)
Overweight children†	16.5%	16.2%
Obese children†	13.4%	13.2%

*Numbers represent mean values and ranges (in parentheses).
†Overweight was defined as an age- and sex-adjusted BMI between the 85th and 95th percentiles and obesity as an age- and sex-adjusted BMI equal to or above the 95th percentile.

genes associated with both BMI and asthma in candidate gene studies (Table IV).[6-11,32,33]

BMI GWAS genes

Table II summarizes the top association hits, original *P* values, and source populations from published BMI GWASs to date. Of the 29 top SNPs, which are in or near 17 genes (or gene regions), 17 SNPs were available in the dataset used in this study. For the remaining 12 SNPs, association with a genotyped proxy SNP with high linkage disequilibrium to the original SNP was reported. Only 1 SNP, rs10938397 near glucosamine-6-phosphate deaminase 2 *(GNPDA2)*, was associated with BMI in CAMP ($P = 4 \times 10^{-4}$), and this SNP was also associated with asthma ($P = .03$, Table II). We extended our search for association by considering other SNPs within all identified genes. Using the WGAViewer,[31] we obtained all annotated SNPs in each gene (range, 1-878 SNPs per gene; see Tables E1-E6 in this article's Online Repository at www.jacionline.org) and tested for association with a "gene-based" approach. A few SNPs (0-7 per gene) of this larger BMI GWAS "gene-based" set had nominal *P* values of less than .05 for BMI or asthma (Tables E1 and E2). Associations with both asthma and BMI were not seen for any single SNP in this set, although different SNPs in neuronal growth regulator 1 *(NEGR1)*; roundabout, axon guidance receptor, homolog 1 *(ROBO1)*; diacylglycerol kinase, gamma *(DGKG)*; Fas apoptotic inhibitory molecule 2 *(FAIM2)*; fat mass and obesity associated *(FTO)*; and carbohydrate (N-acetylgalactosamine 4-0) sulfotransferase 8 *(CHST8)* were associated with both asthma and BMI.

Asthma GWAS genes

None of the 14 top SNPs in 14 asthma GWAS genes were associated with BMI, and only the top SNPs in *PDE4D* and ORM1-like 3 *(ORMDL3)* were associated with asthma, as previously reported (Table III).[23] Gene-based analyses showed that *IL1RL1/IL18R1*, dipeptidyl-peptidase 10 *(DPP10)*, *PDE4D*, *MYB*, *PDE10A*, protein tyrosine phosphatase, receptor type D *(PTPRD)*, and *IL33* were nominally associated with both asthma and BMI (see Tables E3 and E4). Two specific SNPs showed association with both phenotypes: rs13431828 in *IL1RL1/IL18R1*, with a *P* value of 8×10^{-4} for asthma and a *P* value of .05 for BMI, and rs10758982 in *PTPRD*, with a *P* value of 4×10^{-3} for asthma and a *P* value of .03 for BMI.

Candidate genes for asthma and BMI

Of the reported top SNPs in candidate genes previously associated with both BMI and asthma, *PRKCA* was associated with BMI only and *ACE* with asthma only (Table IV). Gene-based analyses showed that additional SNPs in *PRKCA* were nominally associated with both asthma and BMI and that SNPs in *LEP* were associated with BMI only (see Tables E5 and E6). No associations with asthma or BMI were seen for SNPs in the other 4 candidate genes.

DISCUSSION

In the past few years, GWASs have implicated a number of new loci in BMI/obesity. These loci were evaluated in this study but were not convincingly associated with BMI in CAMP asthmatic patients apart from a SNP near *GNPDA2*. This suggests that other unknown genes might be of importance for BMI in the presence of asthma. Although several asthma and BMI GWAS genes showed an association with both BMI and asthma in CAMP, different SNPs in each gene were associated with each phenotype, and no associations survived adjustment for multiple testing. Despite evidence of shared genetic pathways for asthma and BMI/obesity in epidemiologic studies, our results do not provide strong evidence for common genetic links in the candidate genes that were studied. This suggests that shared genetic determinants between BMI and asthma are likely to be in unidentified loci.

Several different explanations for the observed epidemiologic obesity-asthma link have been proposed: direct effects of obesity on mechanical functioning of the lung; proinflammatory effects of adipose tissue; hormonal effects, possibly sex specific; fetal programming and epigenetics; and shared genetic effects.[2] A recent Dutch study shows that in children with at least 1 parent with asthma, the risk of asthma in children at 8 years of age increases if the mother was overweight before pregnancy.[34] No association was observed in children without a hereditary predisposition. This study supports the fetal programming and shared genetics hypotheses, although mechanisms are not clear. The shared genetics component is believed to be substantial yet of moderate effect size; estimates from twin studies indicate that 8% of the genetic component of obesity is shared with asthma.[4] Cross-twin, cross-trait risks for obesity and asthma are also reported to be higher in identical than fraternal twins, supporting a common genetic source.[5] This finding was restricted to female subjects, which is in agreement with epidemiologic data being more consistent in women than men.[2] In children the sex-specific association is not observed in most studies until after puberty.[3]

Given that there are common pathophysiologic pathways in asthma and obesity, it is biologically plausible that genes, such as *TNF* and *ADRB2*, could have pleiotropic effects. However, the literature is sparse, with reports of convincing examples of shared genetics between asthma and obesity. Only *LEP*, *PRKCA*, and *TNF* have been evaluated for pleiotropic effects in the same population, and all 3 reports were published in 2009.[9-11] Different variants in each of these genes have been associated with asthma and obesity, and no study has identified an allele that actually associates with the 2 traits. For both *LEP* −2549T/G and *TNF* -308G/A, opposite allelic effects have been observed: *LEP* −2549T has been associated with asthma risk, whereas *LEP* −2549G has been associated with higher BMI,[11] and *TNF* -308A has been associated with asthma risk and being underweight.[9] *PRKCA* was identified as a candidate gene for BMI

TABLE II. Top hits from published BMI GWASs and association with BMI and asthma in CAMP

Position	Nearby gene(s)	SNP	Original *P* value	Population	Children included	Reference no.	Association in CAMP: *P* value, BMI*	Association in CAMP: *P* value, asthma†
1p21.3	*Intergenic*	rs10783050	4×10^{-6}	White, African American	No	19	.41	.71
1p31.1	*NEGR1*	rs2568958	1×10^{-11}	White, African American	No	19	.97	.50
1p31.1	*NEGR1*	rs2815752‡	6×10^{-8}	White	Yes	20	.97	.50
1q25.2	*SEC16B/RASAL2*	rs10913469	6×10^{-8}	White, African American	No	19	.95	.30
2p25.3	*TMEM18*	rs6548238‡	1×10^{-18}	White	Yes	20	.16	.62
2p25.3	*TMEM18*	rs7561317	4×10^{-17}	White, African American	No	19	.15	.63
2q14.1	*INSIG2*	rs7566605‡	8×10^{-3}	White, African American	Yes	14	.96	.04
3p12	*ROBO1*	rs1455824‡	4×10^{-9}§	White (including Costa Rican)	Yes	15	.51	.47
3q27.2	*SFRS10/ETV5/DGKG*	rs7647305	7×10^{-11}	White, African American	No	19	.93	.52
4p13	*GNPDA2*	rs10938397‡	3×10^{-16}	White	Yes	20	4×10^{-4}	.03
7q32.3	*Intergenic*	rs1106683‡	1×10^{-7}	White	No	12	.71	.62
11p11.2	*MTCH2*	rs10838738	5×10^{-9}	White	Yes	20	.59	.08
11p14.1	*BDNF*	rs6265	5×10^{-10}	White, African American	No	19	.91	.89
11p14.1	*BDNF*	rs925946	9×10^{-10}	White, African American	No	19	.92	.87
11p14.1	*BDNF*	rs7481311	8×10^{-6}	White, African American	No	19	.80	.25
11p15.4	*STK33*	rs10769908‡	1×10^{-6}	White	Yes	20	.59	.52
12q13.13	*BCDIN3D/FAIM2*	rs7138803	1×10^{-7}	White, African American	No	19	.47	.29
13q21.32	*Intergenic*	rs1333026	8×10^{-6}	White	No	12	.11	.46
16p11.2	*SH2B1*	rs7498665‡	5×10^{-11}	White, African American	Yes/No	19, 20	.95	.79
16q12.2	*FTO*	rs8050136	1×10^{-47}	White, African American	No	19	.09	.49
16q12.2	*FTO*	rs6499640	4×10^{-13}	White, African American	No	19	.24	.60
16q12.2	*FTO*	rs9939609‡	4×10^{-51}	White	Yes	13, 18, 20	.09	.49
16q12.2	*FTO*	rs1121980‡	4×10^{-8}	White	Yes	17	.18	.38
18q21.32	*MC4R*	rs12970134	1×10^{-12}	White, African American	No	19	.15	.85
18q21.32	*MC4R*	rs17782313‡	5×10^{-18}	White	Yes	17, 20	.14	.54
19q13.11	*KCTD15*	rs11084753	2×10^{-8}	White	Yes	20	NA	NA
19q13.11	*KCTD15/CHST8*	rs29941	7×10^{-12}	White, African American	No	19	.06	.75
20q11.23	*CTNNBL1*	rs6020712	8×10^{-7}	White	No	16	.61	.63
20p12.3	*BMP2*	rs2145270‡	6×10^{-6}	White	Yes	20	.45	.42

BCDIN3D, BCDIN3 domain containing; *BDNF*, brain-derived neurotrophic factor; *BMP2*, bone morphogenetic protein 2; *CTNNBL1*, catenin, beta like 1; *ETV5*, Ets variant 5; *KCTD15*, potassium channel tetramerization domain containing 15; *MC4R*, melanocortin 4 receptor; *MTCH2*, mitochondrial carrier homolog 2; *NA*, not available; *RASAL2*, RAS protein activator like 2; *SEC16B*, SEC16 homolog B; *SFRS10* (alias TRA2B), transformer 2 beta homolog; *SH2B1*, SH2B adaptor protein 1; *STK33*, serine/threonine kinase 33; *TMEM18*, transmembrane protein 18.

*Linear regression in asthmatic patients using PLINK.

†Case-control association using PLINK.

‡Not genotyped in CAMP. Association with a proxy SNP was reported ($r^2 > 0.85$ for all proxy SNPs). Original SNP-proxy SNP: rs2815752-rs3101336, rs6548238-rs2867125, rs7566605-rs17047697, rs1455824-rs6786179, rs10938397-rs13130484, rs1106683-rs12534413, rs10769908-rs725502, rs7498665-rs8049439, rs9939609-rs8050136, rs1121980-rs9930333, rs17782313-rs571312, and rs2145270-rs979012.

§Combined genotype-age interaction *P* value from 5 studies.

through positional cloning in a Costa Rican population ascertained on asthma affection status.[10] Association with asthma was also demonstrated in the same population with replication in an independent population (CAMP), although not to the same SNPs that were associated with BMI. Because CAMP was included as a replication dataset in the original study, our current *PRKCA* findings are not novel.[10]

Our study does not find convincing evidence for shared genetic factors based on analysis of known BMI/obesity genes. *NEGR1*, *ROBO1*, *DGKG*, *FAIM2*, *FTO*, and *CHST8* showed nominal associations (any SNP at $P < .05$) with both BMI and asthma. For most of these genes, only 1 or 2 SNPs were associated with modest *P* values, which does not support a true pleiotropic effect. One SNP near *GNPDA2*, rs10938397, showed evidence of pleiotropic effects on both asthma and BMI. Three other *GNPDA2* SNPs were identified by using WGAViewer, but the only one of these that was available in our dataset was not associated with either phenotype.

ROBO1 was recently identified in a 100,000-SNP GWAS in which strong age-gene interaction effects on obesity were observed.[15] CAMP was included as a replication dataset for the top SNP and confirmed the age-varying association in that the effect was seen only after the age of 10 years. Here we used BMI at randomization (mean age, 8.8 years) as the outcome, which likely explains why only 2 of 149 *ROBO1* SNPs were significantly associated with BMI. Association with *ROBO1* was also seen for asthma (7/149 SNPs at $P < .05$). In the most recent asthma GWAS, *ROBO1* showed suggestive, although not genome-wide significant, associations with asthma.[26]

Of the BMI GWAS top hits, 16 of 29 loci were originally identified in adult studies (Table II). Most of these loci have shown associations with BMI also in children, supporting a role for these genes in BMI across age groups.[35] Surprisingly, only 1 of the top BMI GWAS SNPs and a few other SNPs in these genes, including *FTO*, were associated with BMI in CAMP. This suggests that other unknown genes might be of importance for BMI in asthmatic patients. To our knowledge, differences between the genetics of BMI in healthy subjects and the genetics of BMI in an ascertained asthmatic population are poorly studied. Lack of power is also a possible explanation for why reported associations with BMI did not replicate in this study, and a larger

TABLE III. Top hits from published asthma GWASs and association with BMI and asthma in CAMP

Position	Nearby gene(s)	SNP	Original *P* value	Population	Children included	Reference no.	Association in CAMP: *P* value, BMI*	Association in CAMP: *P* value, asthma†
1q31	*DENND1B/CRB1*	rs2786098	9×10^{-11}	White	Yes	26	.14	.96
2q12	*IL1RL1/IL18R1*	rs1420101	6×10^{-12}	White, East Asian	Yes	21	.81	.23
2q12.3	*DPP10*	rs1435879	3×10^{-6}	African ancestry	Yes	25	.72	.18
3p12	*ROBO1/GBE1*	rs275358	4×10^{-6}	White	Yes	26	.10	.54
5q12	*PDE4D*	rs1588265	4×10^{-7}	White	Yes	23	.28	4×10^{-7}
5q22	*WDR36/TSLP*	rs2416257	1×10^{-4}	White, East Asian	Yes	21	.27	.82
5q33	*ADRA1B*	rs10515807	4×10^{-6}	African ancestry	Yes	25	.99	NA
6q23	*MYB*	rs9494145	4×10^{-3}	White, East Asian	Yes	21	.21	.79
6q27	*PDE10A*	rs1358786‡	8×10^{-8}	White	Yes	26	.75	.57
9q21.31	*TLE4*	rs2378383	7×10^{-7}	Hispanic/Mexican	Yes	22	.38	.59
9p23	*PTPRD*	rs1326772	8×10^{-7}	White	Yes	26	.57	.54
9q24	*IL33*	rs3939286	5×10^{-6}	White, East Asian	Yes	21	.07	.26
17q21	*ORMDL3/GSDML*	rs7216389	9×10^{-11}	White	Yes	24	.81	.002
20q12	*PRNP*	rs6052761	2×10^{-6}	African ancestry	Yes	25	.64	.82

CRB1, Crumbs homolog 1; *GBE1*, glucan (1,4-alpha-), branching enzyme 1; *NA*, not available (excluded after QC); *TLE4*, transducin-like enhancer of split 4.
*Linear regression in asthmatic patients using PLINK.
†Case-control association using PLINK.
‡Not genotyped in CAMP. Association with a proxy SNP, rs1033700 ($r^2 = 0.86$ with rs1358786) was reported.

TABLE IV. Candidate genes for both BMI/obesity and asthma and association with BMI and asthma in CAMP

Position	Gene	SNP	Original association with asthma: *P* value	Original association with asthma: Children included	Original association with asthma: Refrence no.	Original association with BMI/obesity: *P* value	Original association with BMI/obesity: Children included	Original association with BMI/obesity: Referecne no.	Association in CAMP: Analyzed SNP in CAMP	Association in CAMP: *P* value, BMI*	Association in CAMP: *P* value, asthma†
2p25	*ACP1*	A/B/C genotypes§	<.01	No	32	.008	No	33	rs12714402	.25	.80
5q32-34	*ADRB2*‡	rs1042714‖	<.05	Yes	6, 8	<.05	Yes	7	rs2082382	.41	.77
		rs1042713	<.05			<.05			rs1042713	.74	.90
6p21.3	*TNF*‡	rs1800629‖	<.05	Yes	6, 8, 9	<.05	No	7	rs2857595	.89	.15
7q31.3	*LEP*	rs2167270‖	<.05	Yes	11	<.05	Yes	11	rs10249476	.17	.29
12q13.11	*VDR*‡	Multiple SNPs	<.05	Yes	6	<.05	No	7	rs7967152	.19	.64
17q22	*PRKCA*	rs11079657	3×10^{-5}	Yes	10	6×10^{-5}	Yes	10	rs11079657	.88¶	.07¶
		rs228883							rs228883	.05¶	.98¶
17q23.3	*ACE*‡	In/del§	<.05	Yes	6	<.05	No	7	rs4343	.71	.006

ACP1, Acid phosphatase 1.
*Linear regression in asthmatic patients using PLINK.
†Case-control association using PLINK.
‡Several associations have been reported with asthma and BMI, as reviewed in Ober and Hoffjan,[6] Rankinen et al,[7] and Rogers et al.[8]
§Not genotyped in CAMP. The SNP with the smallest *P* value for BMI or asthma in CAMP was reported.
‖Not genotyped in CAMP. Association with a proxy SNP in linkage disequilibrium with the original SNP was reported ($r^2 > 0.85$ for all proxy SNPs).
¶Recessive model as in Murphy et al.[10]

dataset would be ideal for confirmation of our results. In CAMP we cannot estimate the epidemiologic link between BMI and asthma *per se* because all children were ascertained on the basis of asthma. Previous analyses in CAMP show that lower forced expiratory volume/forced vital capacity ratios are correlated with increasing BMI, whereas BMI was not strongly associated with asthma symptoms or atopy.[36] It is possible that other intermediate phenotypes of asthma have a stronger genetic overlap with BMI/obesity than asthma *per se*. Another limitation with the present study is the inclusion of SNPs in the gene-based analyses in WGAViewer. Here we used a rather narrow annotation span (ie, ± 10,000 bp around the 5′ and 3′ ends), which means that SNPs further upstream or downstream of this span were not included in the analyses. Furthermore, SNPs not annotated to a specific gene by the Ensembl database were also missed.

Since 2007, 6 GWASs on asthma have been published, and 14 new loci have been identified. Despite rather limited study power, we could replicate several of these associations with asthma. We found strong associations between *PDE4D* SNPs and asthma, as well as between *ORMDL3*/gasdermin B *(GSDML)* SNPs and asthma, as previously reported.[23] In addition, the *IL1RL1/IL18R1* locus was convincingly associated with asthma (7/21 SNPs were associated, lowest $P = 8 \times 10^{-4}$ for rs13431828 in the 5′ untranslated region), as was *DPP10* (35/260 SNPs were associated, lowest $P = 9 \times 10^{-5}$ for the intronic rs1914973). In addition to *DPP10*, *ADRA1B* and prion protein *(PRNP)* were identified as asthma candidate genes in a recent GWAS on subjects with African ancestry.[25] The findings could not be replicated in additional African American or European datasets, which is in agreement with our results on *ADRA1B* and *PRNP*. *IL33* was

recently identified in an Icelandic GWAS for sequence variants affecting eosinophil counts and asthma.[21] Three of 20 *IL33* SNPs had *P* values of less than .05 for asthma in our study. Additionally, we could not replicate associations between DENN/MADD domain containing 1B *(DENND1B)* SNPs and asthma in our study.[26]

IL1RL1/IL18R1, *DPP10*, *PDE4D*, *MYB*, *PDE10A*, *PTPRD*, and *IL33* showed evidence of association with both asthma and BMI, although associations with BMI were modest ($P = .01$-$.05$) and not significant after correction for multiple comparisons. The only exception is *PTPRD*, with 3 SNPs with *P* values of approximately 3×10^{-4} and a total of 66 of 878 SNPs associated with BMI at $P < .05$. Association was also seen between *PTPRD* SNPs and asthma (lowest $P = 2 \times 10^{-3}$). The PTPRD protein is a member of the protein tyrosine phosphatase family involved in a variety of cellular processes, including cell growth, differentiation, and oncogenic transformation.[37] *PTPRD* showed suggestive association with asthma in the most recent GWAS,[26] as well as in a previous asthma study.[38] Association with BMI or obesity has, to our knowledge, not been reported previously, although other members of the protein tyrosine phosphatase family, such as *PTPRF*, have been associated with BMI and insulin resistance.[37,39] In total, 2 SNPs in asthma GWAS genes showed association with both phenotypes, rs13431828 in *IL1RL1/IL18R1* and rs10758982 in *PTPRD*.

A few studies have associated *ACE* polymorphisms with asthma, especially the insertion/deletion variant in intron 16, although other studies have not done so.[6] Few studies have actually evaluated other *ACE* variants. Association between the *ACE* −262 A/T polymorphism and aspirin-intolerant asthma has been reported, although not with asthma *per se*.[40] In this study 7 of 14 *ACE* SNPs had *P* values of less than .05 for asthma (lowest $P = 6 \times 10^{-3}$).

In conclusion, we have systematically identified genes found to be associated with asthma and BMI in previous GWASs and tested whether these associations hold in a well-characterized study of asthmatic children. We did not find convincing evidence from analyses of known candidate genes that asthma and obesity share genetic determinants, which is consistent with a thorough literature review. However, our results suggest that *GNPDA2*, *PTPRD*, and *ROBO1* deserve further study for a potential role in influencing both conditions. Because epidemiologic studies, including twin studies, show strong evidence that asthma and obesity share common genetic determinants, combined large-scale GWASs of asthma and obesity will likely uncover new genetic loci that underlie both of these conditions.

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Key messages

- **Shared genetics might account for the link between obesity and asthma.**
- **Association analyses of known asthma and BMI genes show some evidence for a shared genetic predisposition to asthma and obesity in children.**
- **Other shared genetic determinants for obesity and asthma are likely to be identified in novel loci.**

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METHODS

Genotyping

Genome-wide SNP genotyping for CAMP subjects and publically available Illumina iControlDB white control subjects (n = 1,533) was performed on Illumina's Human-Hap550 Genotyping BeadChip (Illumina, Inc). The genotyping and QC procedures have been described in detail elsewhere.[E1] In brief, SNPs were dropped from analysis for the following QC reasons: (1) low clustering scores, (2) flanking sequences did not map to a unique position on the HG17 reference genome sequence, (3) monomorphic status, (4) 5 or more Mendelian errors, 5) missing in more than 5% of subjects, (6) minor allele frequency of less than 0.01, (7) Hardy-Weinberg equilibrium *P* values among control subjects of less than 0.001, or (8) significantly different missing rate in cases and control subjects, as determined by a *P* value of less than 10^{-5}. After QC, 518,230 SNPs were included in the analyses. CAMP subjects were dropped from the analysis because they were siblings of other subjects (23 cases) or had more than 5% of genotype data missing (19 cases). Evidence of identity by descent with *P*i-hat of greater than .01 was seen in 57 control subjects (removed), and there was discordance between reported and observed sex differences in 3 control subjects (removed). In addition, 21 cases and 687 control subjects were removed during implementation of the genetic matching algorithm to reduce population stratification, which left 359 asthma cases and 846 control subjects for GWAS analysis published previously.[E1]

For the BMI GWAS analysis, data from an additional 211 CAMP probands obtained with the Illumina Infinium HD Human610-Quad BeadChip were available, and a merged HumanHap550/Human610-Quad dataset composed of 633 CAMP children was created. Four subjects had genotyping performed on both the Infinium HumanHap550 BeadChip and the Infinium HD Human610-Quad BeadChip for QC. Concordance among these replicates was excellent, with an average concordance of 99.99% for all pairwise comparisons and a minimum concordance of 99.89%. Each subject's genotypic sex, as determined by the sexcheck algorithm in PLINK,[E2] agreed with the phenotypic sex. The Mendelian error rate was checked in nuclear families by using PLINK, and an average error rate of only 0.008% was observed in the final set of subjects.

Of 592,532 SNP markers present on the 610 chip, 9,022 were failed for 1 or more of the following reasons: (1) probe sequences do not map uniquely to the HG18 genome build; (2) poor cluster separation, as manually reviewed in Illumina BeadStudio software; (3) −log10(*P* value) for Hardy-Weinberg equilibrium test of 8 or greater; and (4) completion rate of less than 95%. Of 561,466 SNPs present on the 550 chip, 16,419 were failed for 1 or more of the above reasons, for either a Mendelian error count of 5 or greater or monomorphic status, or for both. Only markers that passed QC on both chips were included in the final dataset. An additional 1,819 markers were then excluded based on discordance among the replicates run on both chips. The final number of passing markers in the merged dataset is 528,890. To use the same QC criteria as for the asthma dataset, another 550 markers were excluded based on a Hardy-Weinberg equilibrium test *P* value of less than .001 and 16,594 based on an minor allele frequency of less than 0.01, leaving 511,782 SNPs for BMI association analyses. CAMP subjects were excluded on the basis of similar QC criteria as for the asthma dataset, leaving 555 subjects for analyses. In addition, 18 subjects were excluded because of missing information about BMI or other covariates, leaving 537 subjects for the final analyses. Matched Illumina iControlDB control subjects were not available for the merged dataset, and thus genetic association with BMI was only estimated by using the 537 CAMP probands.

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TABLE E1. Screening of BMI GWAS genes in CAMP: Significant SNP-based association with BMI ($P < .05$)

Gene and SNP	Chromosomal location	Association with BMI (*P* value)*	Total no. of SNPs tested in gene
NEGR1	1p31.1		
rs12058282		5×10^{-3}	122
rs12131309		.03	
rs1506457		.04	
rs7550923		.04	
rs12729554		<.05	
SEC16B	1q25.2	All NS	48
RASAL2	1q25.2	All NS	22
TMEM18	2p25.3	All NS	10
INSIG2	2q14.1	All NS	12
ROBO1	3p12		
rs7622139		3×10^{-3}	152
rs4362686		.02	
ETV5	3q27.2	All NS	10
DGKG	3q27.2		
rs7618021		4×10^{-3}	78
rs6798931		6×10^{-3}	
GNPDA2	4p13	All NS	1
MTCH2	11p11.2	All NS	3
BDNF	11p14.1	All NS	11
STK33	11p15.4		
rs12282398		.02	25
BCDIN3D/ KIAA1602/ NCK-associated protein 5-like	12q13.13	All NS	8
FAIM2	12q13.13		
rs4898541		.01	19
SH2B1	16p11.2	All NS	1
FTO	16q12.2		
rs9931164		.03	97
MC4R	18q21.32		
rs1943226		<.05	2
KCTD15	19q13.11		
rs285676		2×10^{-3}	9
rs29944		.04	
CHST8	19q13.11		
rs16968313		<.05	45
CTNNBL1	20q11.23	All NS	17
BMP2	20p12.3	All NS	11

BCDIN3D, BCDIN3 domain containing; *BDNF*, brain-derived neurotrophic factor; *BMP2*, bone morphogenetic protein 2; *CTNNBL1*, catenin, beta like 1; *ETV5*, Ets variant 5; *KCTD15*, potassium channel tetramerization domain containing 15; *MC4R*, melanocortin 4 receptor; *MTCH2*, mitochondrial carrier homolog 2; *NS*, not significant; *RASAL2*, RAS protein activator like 2; *SEC16B*, SEC16 homolog B; *SH2B1*, SH2B adaptor protein 1; *STK33*, serine/threonine kinase 33; *TMEM18*, transmembrane protein 18.

*Linear regression in asthmatic patients using PLINK.

TABLE E2. Screening of BMI GWAS genes in CAMP: Significant SNP-based association with asthma ($P < .05$)

Gene and SNP	Chromosomal location	Association with asthma (*P* value)*	Total no. of SNPs tested in gene
NEGR1	1p31.1		121
rs17575184		4×10^{-3}	
rs17091873		.01	
SEC16B	1q25.2	All NS	48
RASAL2	1q25.2	All NS	22
TMEM18	2p25.3		10
rs11673780		<.05	
INSIG2	2q14.1	All NS	12
ROBO1	3p12		149
rs6548651		6×10^{-3}	
rs11925648		.02	
rs1865862		.02	
rs3773201		.04	
rs331142		.04	
rs331146		.04	
rs7429525		<.05	
ETV5	3q27.2	All NS	10
DGKG	3q27.2		75
rs11706414		8×10^{-3}	
rs888383		.04	
GNPDA2	4p13	All NS	1
MTCH2	11p11.2	All NS	3
BDNF	11p14.1	All NS	11
STK33	11p15.4	All NS	21
BCDIN3D/ KIAA1602/ NCK-associated protein 5-like	12q13.13	All NS	4
FAIM2	12q13.13		19
rs766977		8×10^{-3}	
rs836959		.02	
SH2B1	16p11.2	All NS	1
FTO	16q12.2		97
rs8062891		.04	
MC4R	18q21.32	All NS	2
KCTD15	19q13.11	All NS	9
CHST8	19q13.11		43
rs8112967		4×10^{-3}	
rs10520203		9×10^{-3}	
rs2115374		.02	
rs16968399		.03	
CTNNBL1	20q11.23		17
rs6020251		.03	
BMP2	20p12.3	All NS	11

BCDIN3D, BCDIN3 domain containing; *BDNF*, brain-derived neurotrophic factor; *BMP2*, bone morphogenetic protein 2; *CTNNBL1*, catenin, beta like 1; *ETV5*, Ets variant 5; *KCTD15*, potassium channel tetramerization domain containing 15; *MC4R*, melanocortin 4 receptor; *MTCH2*, mitochondrial carrier homolog 2; *NS*, not significant; *RASAL2*, RAS protein activator like 2; *SEC16B*, SEC16 homolog B; *SH2B1*, SH2B adaptor protein 1; *STK33*, serine/threonine kinase 33; *TMEM18*, transmembrane protein 18.

*Case-control association using PLINK.

TABLE E3. Screening of asthma GWAS genes in CAMP: Significant SNP-based association with BMI ($P < .05$)

Gene and SNP	Chromosomal position	Association with BMI (P value)*	Total no. of SNPs tested in gene
DENND1B	1q31	All NS	31
CRB1	1q31	All NS	24
IL1RL1/IL18R1	2q12		21
rs13431828		<.05	
DPP10	2q12.3		264
rs2420815		.03	
rs2420819		.03	
ROBO1	3p12	See Table E1	
GBE1	3p12	All NS	25
PDE4D	5q12		238
rs154224		.04	
rs9292198		.04	
rs27727		.04	
rs7714708		<.05	
rs244570		<.05	
WDR36	5q22	All NS	12
TSLP	5q22	All NS	9
ADRA1B	5q33	All NS	17
MYB	6q23	All NS	9
rs9321496		.02	
rs7760247		.03	
PDE10A	6q27		142
rs9457084		.02	
rs9347080		.03	
rs537694		.03	
rs220809		.04	
rs3008032		.04	
rs16897948		.04	
rs454165		<.05	
rs1022180		<.05	
TLE4	9q21.31	All NS	31
PTPRD	9q23		878
rs7860014		3×10^{-4}	
rs2382017		3×10^{-4}	
rs294814		4×10^{-4}	
rs13297654		.01	
rs10815977		.01	
rs10977821		.01	
rs904781		.01	
rs1885431		.01	
rs7036240		.01	
rs1570267		.01	
rs10124689		.01	
rs4742605		.01	
rs10491909		.01	
rs10114268		.01	
rs368381		.02	
rs2031214		.02	
rs7875273		.02	
rs1500327		.02	
rs10977060		.02	
rs10977022		.02	
rs1865343		.02	
rs7856797		.02	
rs867980		.02	
rs989814		.02	
rs1500334		.02	
rs4742502		.02	
rs1331660		.02	
rs324519		.02	
rs10977546		.02	
rs10816057		.02	
rs12344079		.02	
rs3901934		.02	
rs294854		.02	
rs1535675		.02	
rs1865341		.02	
rs17587734		.03	
rs1407913		.03	
rs10511494		.03	
rs7848626		.03	
rs10758982		.03	
rs12348476		.03	
rs6477314		.03	
rs150409		.03	
rs1322136		.03	
rs13285004		.03	
rs11792302		.03	
rs3818346		.04	
rs2498598		.04	
rs4237177		.04	
rs294856		.04	
rs2821505		.04	
rs7023008		.04	
rs291296		.04	
rs4740990		.04	
rs364297		.04	
rs11791447		.04	
rs1353983		.05	
rs2814717		.05	
rs10977555		.05	
rs10978074		.05	
rs2498609		.05	
rs2890870		.05	
rs7031287		.05	
rs1889820		.05	
rs12339036		.05	
rs410601		.05	
IL33	9q24		20
rs1929994		.02	
rs928413		.04	
ORMDL3/GSDMB	17q21	All NS	8
PRNP	20p12		10
rs6037938		.04	

(Continued)

TABLE E3. *(Continued)*

CRB1, Crumbs homolog 1; *GBE1*, glucan (1,4-alpha-), branching enzyme 1; *NS*, not significant; *TLE4*, transducin-like enhancer of split 4.
*Linear regression in asthmatic patients using PLINK.

TABLE E4. Screening of asthma GWAS genes in CAMP: Significant SNP-based association with asthma ($P < .05$)

Gene and SNP	Chromosomal position	Association with asthma (*P* value)*	Total no. of SNPs tested in gene
DENND1B	1q31		31
rs10494755		.03	
CRB1	1q31		24
rs10754220		.04	
IL1RL1/IL18R1	2q12		21
rs13431828		8×10^{-4}	
rs3213733		3×10^{-3}	
rs10204137		.02	
rs10192157		.02	
rs10206753		.02	
rs3771166		.02	
rs1041973		.04	
DPP10	2q12.3		260
rs1914973		9×10^{-5}	
rs10496488		2×10^{-4}	
rs12464801		3×10^{-3}	
rs921211		3×10^{-3}	
rs17452458		3×10^{-3}	
rs10496487		3×10^{-3}	
rs11123313		3×10^{-3}	
rs10195710		3×10^{-3}	
rs2036779		4×10^{-3}	
rs6736340		.01	
rs10187644		.01	
rs9308710		.01	
rs1430101		.01	
rs1545396		.01	
rs11685217		.01	
rs843408		.02	
rs11693826		.02	
rs17452616		.02	
rs1965088		.02	
rs17043916		.02	
rs17043949		.03	
rs11695180		.03	
rs1820924		.03	
rs12994269		.03	
rs1550985		.03	
rs10496481		.03	
rs17043899		.03	
rs6738130		.03	
rs10496469		.04	
rs6542217		.04	
rs11123279		.04	
rs10864934		.04	
rs13030450		.04	
rs6750402		.04	
rs13032069		<.05	
ROBO1	3p12	See Table E2	
GBE1	3p12	All NS	25
PDE4D	5q12		239
rs2548659†		2×10^{-7}	
rs1588265†		4×10^{-7}	
rs983280†		5×10^{-7}	
rs1544791†		1×10^{-6}	
rs6450521		1×10^{-3}	
rs1870077		1×10^{-3}	
rs2938784		2×10^{-3}	
rs905834		2×10^{-3}	
rs296410		8×10^{-3}	
rs6869459		2×10^{-3}	
rs17782238		.01	
rs7712329		.01	
rs7728286		.01	
rs4551023		.02	
rs2702373		.03	
rs4326095		.03	
rs7717802		.03	
rs35289		.04	
rs12186707		.04	
rs17783275		<.05	
WDR	5q22	All NS	12
TSLP	5q22		9
rs1837253		9×10^{-3}	
ADRA1B	5q33		16
rs7718362		.04	
MYB	6q23		9
rs12663543		.01	
PDE10A	6q27		140
rs713084		5×10^{-3}	
rs12525763		.01	
rs7753004		.01	
rs2983496		.02	
rs3008014		.02	
rs2983500		.02	
rs4709946		.03	
rs7772901		.03	
rs520349		.04	
rs6924284		.04	
TLE4	9q21.31	All NS	31
PTPRD	9q23		858
rs11794550		2×10^{-3}	
rs10958998		2×10^{-3}	
rs10758982		4×10^{-3}	
rs833455		.01	
rs7856850		.01	
rs1500336		.01	
rs7035431		.01	
rs10758979		.01	
rs10977210		.01	
rs7027702		.02	
rs2784592		.02	
rs1999850		.02	
rs13294631		.03	
rs16929628		.03	
rs1217003		.03	
rs1579564		.03	
rs1537812		.03	
rs1008981		.03	
rs17585256		.03	
rs3903826		.04	
rs10511491		.04	
rs7020647		.04	
rs7032880		.04	
rs2784609		.04	
rs13288779		<.05	
rs1335999		<.05	
IL33	9q24		20
rs12551256		.03	
rs16924159		.04	
rs7025417		.04	

(Continued)

TABLE E4. *(Continued)*

Gene and SNP	Chromosomal position	Association with asthma (*P* value)*	Total no. of SNPs tested in gene
ORMDL3/ *GSDML*	17q21		5
rs4795405		7×10^{-4}	
rs7216389		2×10^{-3}	
rs8079416		.01	
PRNP	20p12	All NS	

CRB1, Crumbs homolog 1; *GBE1*, glucan (1,4-alpha-), branching enzyme 1; *NS*, not significant; *TLE4*, transducin-like enhancer of split 4.

*Case-control association using PLINK.

†The 4 top SNPs identified in Himes et al[E1] were not annotated to *PDE4D* according to the WGAViewer but were still included here because they are located within the gene according to a thorough sequence of the *PDE4D* gene.[E3]

TABLE E5. Screening of candidate genes for both asthma and BMI/obesity in CAMP: Significant SNP-based association with BMI ($P < .05$)

Gene and SNP	Chromosomal position	Association with BMI (*P* value)*	Total no. of SNPs tested in gene
ACP1	2p25	All NS	3
ADRB2	5q32-34	All NS	12
TNF	6p21.3	All NS	8
LEP	7q31.3		7
rs791608		.02	
rs2122627		.02	
VDR	12q13.11	All NS	29
PRKCA	17q22-q23.2		126
rs7211269		3×10^{-3}	
rs12452826		3×10^{-3}	
rs3848423		8×10^{-3}	
rs12232511		.02	
rs4791036		.03	
rs9896134		.03	
rs11656279		<.04	
ACE	17q23.3	All NS	14

ACP1, Acid phosphatase 1; *NS*, not significant.
*Linear regression in asthmatic patients using PLINK.

TABLE E6. Screening of candidate genes for both asthma and BMI/obesity in CAMP: Significant SNP-based association with asthma ($P < .05$)

Gene and SNP	Chromosomal position	Association with asthma (*P* value)*	Total no. of SNPs tested in gene
ACP1	2p25	All NS	3
ADRB2	5q32-34	All NS	12
TNF	6p21.3	All NS	10
LEP	7q31.3	All NS	6
VDR	12q13.11	All NS	29
PRKCA	17q22-q23.2		123
rs9892651		2×10^{-3}	
rs9901804		9×10^{-3}	
rs11871468		.02	
rs11869197		.03	
rs4791036		<.05	
ACE	17q23.3		14
rs4343		6×10^{-3}	
rs4311		9×10^{-3}	
rs4329		.01	
rs4353		.01	
rs4461142		.01	
rs4362		.02	
rs4305		.02	

ACP1, Acid phosphatase 1; *NS*, not significant.
*Case-control association using PLINK.