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Analyses of shared genetic factors between asthma and obesity in children

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Abstract

Background—Epidemiological studies consistently show associations between asthma and obesity. Shared genetics may account for this association.

Objective—To identify genetic variants associated with both asthma and obesity.

Methods—Based on a literature search, we identified genes from: 1) Genome-wide association studies (GWAS) of Body Mass Index (BMI) (n=17 genes), 2) GWAS 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 (CAMP) 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 *GNPDA2*, was associated with both BMI ($p=4 \times 10^{-4}$) and asthma (p=0.03). 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 ($p<0.05$) with both phenotypes for several genes: *NEGR1*, *ROBO1*, *DGKG*, *FAIM2*, *FTO* and *CHST8* among the BMI GWAS genes; *ILRL1/IL18R1*, *DPP10*, *PDE4D*, *MYB*, *PDE10A*, *IL33* and especially *PTPRD* among the asthma GWAS genes; and *PRKCA* among the BMI and asthma candidate genes.

Conclusions—SNPs within several genes showed associations to BMI and asthma at a gene 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.

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Keywords

Association; Asthma; BMI; Children; Genetics; GWAS; Obesity; Polymorphism; SNP

Introduction

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] Epidemiological 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 may 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 *ACE*, *ADRB2* and *VDR*[6, 7], that may influence both diseases. Genes such as *LEP*, *PRKCA* and *TNF* have also been evaluated for pleiotrophic effects that influence both asthma and obesity simultaneously.[9–11] Recent genome-wide association studies (GWAS) have identified variants at several loci that are associated with BMI and/or obesity.[12–20] It is unclear if these loci contribute only to BMI/obesity, or if they also influence asthma risk. Likewise, it is unclear if variants identified through recent asthma GWAS 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 to BMI and/or asthma. All SNPs identified in GWAS 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.

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 < 12.5 mg/ml. 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 percentile and obesity as an age and sex adjusted BMI equal to or above 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, CA) and used as cases in a case-control study design with white population controls (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 (GEM) algorithm to reduce population stratification, reduced the case-control asthma GWAS to 1,205 subjects (359 cases, 846 controls) 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 controls were not available for the merged dataset, only genetic association to BMI was estimated in this dataset. Please see Online Repository Material 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 GWAS. Inclusion of SNP-based associations was limited to those with p-values $< 1.0 \times 10^{-5}$ (with the exception of two asthma GWAS SNPs in *MYB* and *WDR36/TSLP* and one BMI GWAS SNP in *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 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 using less stringent criteria (any SNP or other variant associated at $p<0.05$ level). 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 to asthma or BMI/obesity in multiple populations as summarized in reviews by Ober et al[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, using an additive genetic model adjusted for age, gender 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 GO databases. The annotation span for gene-based analyses was 10K base pairs 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} (=0.05/2,583). All reported p-values are two-sided.

Results

Baseline characteristics of the CAMP children are presented in Table 1. 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 agreement with recent national figures from the Center for Disease Control.[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 GWAS [Table 2], 2) 14 SNPs in 14 genes identified in previous asthma GWAS [Table 3], and 3) multiple SNPs in 7 genes associated with both BMI and asthma in candidate gene studies [Table 4].

BMI GWAS genes

Table 2 summarizes the top association hits, original p-values and source population from published BMI GWAS 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 to a genotyped proxy SNP with high LD to the original SNP was reported. Only one SNP, rs10938397 near *GNPDA2*, was associated with BMI in CAMP ($p=4 \times 10^{-4}$), and this SNP was also associated with asthma (p=0.03) [Table 2]. 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) [Tables E1-E6] 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 <0.05 for BMI or asthma [Table E1 and E2].

Associations to both asthma and BMI were not seen for any single SNP in this set, although different SNPs in *NEGR1, ROBO1, DGKG, FAIM2, FTO* and *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 *ORMDL3* were associated with asthma as previously reported[23] [Table 3]. Gene-based analyses showed that *ILRL1/IL18R1, DPP10, PDE4D, MYB, PDE10A, PTPRD* and *IL33* were nominally associated with both asthma and BMI [Tables E3 and E4]. Two specific SNPs showed association to both phenotypes; rs13431828 in *ILRL1/IL18R1*, with $p=8 \times 10^{-4}$ for asthma and p<0.05 for BMI, and rs10758982 in *PTPRD*, with $p=4 \times 10^{-3}$ for asthma and p=0.03 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 4]. Gene-based analyses showed that additional SNPs in *PRKCA* were nominally associated with both asthma and BMI, and SNPs in *LEP* with BMI only [Tables E5 and E6]. No associations to asthma or BMI were seen for SNPs in the other four candidate genes.

Discussion

In the past few years, GWAS 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 asthmatics apart from a SNP near *GNPDA2*. This suggests that other unknown genes may 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 epidemiological 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 to the observed epidemiological 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 one parent with asthma, the risk of asthma in children at 8 years of age increases if the mother was overweight before pregnancy.[32] 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 but 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 in fraternal twins, supporting a common genetic source.[5] This finding was restricted to females, which is in agreement with epidemiological 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 pathophysiological pathways in asthma and obesity, it is biologically plausible that genes such as *TNF* and *ADRB2* could have pleiotrophic effects. The literature is, however, sparse with reports of convincing examples of shared genetics between asthma and obesity. Only *LEP*, *PRKCA* and *TNF* have been evaluated for pleiotrophic effects in the same population, and all three 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 two traits. For both *LEP* -2549T/G and *TNF* -308G/A, opposite allelic effects have been observed: *LEP* -2549T has been associated with asthma risk, while *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 via positional cloning in a Costa Rican population ascertained on asthma affection status.[10] Association to asthma was also demonstrated in the same population with replication in an independent population (CAMP), but 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 with $p<0.05$) with both BMI and asthma. For most of these genes, only one or two SNPs were associated with modest p-values, which does not support a true pleiotrophic effect. One SNP near *GNPDA2*, rs10938397, showed evidence of pleiotrophic effects on both asthma and BMI. Three other *GNPDA2* SNPs were identified by 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 100K SNP GWAS where 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. Here, we used BMI at randomization (mean age 8.8 years) as outcome, which likely explains why only 2/149 *ROBO1* SNPs were significantly associated with BMI. Association to *ROBO1* was also seen for asthma (7/149 SNPs with $p<0.05$). In the most recent asthma GWAS, *ROBO1* showed suggestive, but not genome-wide significant, associations to asthma.[26]

Of the BMI GWAS top hits, 16/29 loci were originally identified in adult studies [Table 2]. Most of these loci have shown associations with BMI also in children, supporting a role for these genes in BMI across age groups.[33] Surprisingly, only one of the top BMI GWAS SNPs and few other SNPs in these genes, including *FTO*, were associated with BMI in CAMP. This suggests that other unknown genes may be of importance for BMI in asthmatics. To our knowledge, differences between the genetics of BMI in healthy individuals and genetics of BMI in an ascertained asthma population are, however, poorly studied. Lack of power is also a possible explanation why reported associations to BMI did not replicate in this study, and a larger dataset would be ideal for confirmation of our results. In CAMP, we cannot estimate the epidemiological 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, while BMI was not strongly associated with asthma symptoms or atopy.[34] 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, +/− 10K 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, six GWAS 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/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′ UTR region), as well as *DPP10* (35/260 SNPs were associated, lowest $p= 9 \times 10^{-5}$ for the intronic rs1914973). In addition to *DPP10, ADRA1B* and *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 out of twenty *IL33* SNPs had $p<0.05$ for asthma in our study. Additionally, we could not replicate associations between *DENND1B* SNPs and asthma in our study.[26]

ILRL1/IL18R1, DPP10, PDE4D, MYB, PDE10A, PTPRD and *IL33* showed evidence of association with both asthma and BMI, although associations to BMI were modest (p-values 0.01–0.05) and not significant after correction for multiple comparisons. The only exception is *PTPRD* with three SNPs with p-value around 3×10^{-4} and a total of 66 SNPs associated with BMI out of 878. 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 (PTP) family involved in a variety of cellular processes including cell growth, differentiation and oncogenic transformation.[35] *PTPRD* showed suggestive association to asthma in the most recent GWAS[26] as well as in a previous asthma study.[36] Association with BMI or obesity has to our knowledge not been reported previously, although other members of the PTP family, such as *LAR/PTPRF*, have been associated with BMI and insulin resistance.[35, 37] In total, two SNPs in asthma GWAS genes showed association with both phenotypes, rs13431828 in *ILRL1/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 failed to do 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, but not with asthma per se.[38] In this study, 7/14 *ACE* SNPs had $p<0.05$ 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 GWAS 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 epidemiological studies, including twin studies, show strong evidence that asthma and obesity share common genetic determinants, combined large-scale GWAS studies of asthma and obesity will likely uncover new genetic loci that underlie both of these conditions.

Key messages

- Shared genetics may 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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Abbreviations used

ACE	Angiotensin I converting enzyme
ADR	Adrenergic receptor
ACP1	acid phosphatase 1
BMI	Body mass index
BDNF	Brain-derived neurotrophic factor
BCDIN3D	BCDIN3 domain containing
BMP2	Bone morphogenetic protein 2
CAMP	Childhood Asthma Management Program
CHST8	Carbohydrate (N-acetylgalactosamine 4-0) sulfotransferase 8
CRB1	Crumbs homolog 1
CTNNBL1	Catenin, beta like 1
DENND1B	DENN/MADD domain containing 1B
DGKG	Diacylglycerol kinase, gamma
DPP10	Dipeptidyl-peptidase 10
ETV5	Ets variant 5
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 tetramerisation domain containing 15
LD	Linkage disequilibrium
LEP	Leptin
MC4R	Melanocortin 4 receptor
MTCH2	Mitochondrial carrier homolog 2
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
RASAL2	RAS protein activator like 2
ROBO1	Roundabout, axon guidance receptor, homolog 1
SEC16B	SEC16 homolog B
SFRS10 (alias TRA2B)	Transformer 2 beta homolog
SH2B1	SH2B adaptor protein 1
STK33	Serine/threonine kinase 33
SNP	Single nucleotide polymorphism
TLE4	Transducin-like enhancer of split 4
TMEM18	Transmembrane protein 18
TNF	Tumor necrosis factor
TSLP	Thymic stromal lymphopoietin
VDR	Vitamin D (1,25- dihydroxyvitamin D3) receptor
WDR36	WD repeat domain 36

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Table 1

Baseline Characteristics of Subjects in CAMP

	Asthma GWAS	BMI GWAS
Asthmatics	359	537
Age, years*	8.8 (5.2–13.2)	8.9 (5.2–13.2)
Gender, female	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 value and range (in brackets).

†Overweight was defined as an age and sex adjusted BMI between the 85th and 95th percentile and obesity as an age and sex adjusted BMI equal to or above the 95th percentile.

Table 2

Top hits from published BMI GWAS and association to BMI and asthma in CAMP

Position	Nearby gene(s)	SNP	Original p-value	Population	Children included	Ref	Association in CAMP	
							p-value BMI*	p-value asthma†
1p21.3	*Intergenic*	rs10783050	4×10^{-6}	Caucasian, African American	No	19	0.41	0.71
1p31.1	*NEGR1*	rs2568958	1×10^{-11}	Caucasian, African American	No	19	0.97	0.50
1p31.1	*NEGR1*	rs2815752‡	6×10^{-8}	Caucasian	Yes	20	0.97	0.50
1q25.2	*SEC16B/RASAL2*	rs10913469	6×10^{-8}	Caucasian, African American	No	19	0.95	0.30
2p25.3	*TMEM18*	rs6548238‡	1×10^{-18}	Caucasian	Yes	20	0.16	0.62
2p25.3	*TMEM18*	rs7561317	4×10^{-17}	Caucasian, African American	No	19	0.15	0.63
2q14.1	*INSIG2*	rs7566605‡	8×10^{-3}	Caucasian, African American	Yes	14	0.96	0.04
3p12	*ROBO1*	rs1455824‡	4×10^{-9}§	Caucasian (incl. Costa Rica)	Yes	15	0.51	0.47
3q27.2	*SFRS10/ETV5/DGKG*	rs7647305	7×10^{-11}	Caucasian, African American	No	19	0.93	0.52
4p13	*GNPDA2*	rs10938397‡	3×10^{-16}	Caucasian	Yes	20	4×10^{-4}	0.03
7q32.3	*Intergenic*	rs1106683‡	1×10^{-7}	Caucasian	No	12	0.71	0.62
11p11.2	*MTCH2*	rs10838738	5×10^{-9}	Caucasian	Yes	20	0.59	0.08
11p14.1	*BDNF*	rs6265	5×10^{-10}	Caucasian, African American	No	19	0.91	0.89
11p14.1	*BDNF*	rs925946	9×10^{-10}	Caucasian, African American	No	19	0.92	0.87
11p14.1	*BDNF*	rs7481311	8×10^{-6}	Caucasian, African American	No	19	0.80	0.25
11p15.4	*STK33*	rs10769908‡	1×10^{-6}	Caucasian	Yes	20	0.59	0.52
12q13.13	*BCDIN3D/FAIM2*	rs7138803	1×10^{-7}	Caucasian, African American	No	19	0.47	0.29
13q21.32	*Intergenic*	rs1333026	8×10^{-6}	Caucasian	No	12	0.11	0.46
16p11.2	*SH2B1*	rs7498665‡	5×10^{-11}	Caucasian, African American	Yes/No	19, 20	0.95	0.79
16q12.2	*FTO*	rs8050136	1×10^{-47}	Caucasian, African American	No	19	0.09	0.49
16q12.2	*FTO*	rs6499640	4×10^{-13}	Caucasian, African American	No	19	0.24	0.60
16q12.2	*FTO*	rs9939609‡	4×10^{-51}	Caucasian	Yes	13, 18, 20	0.09	0.49

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Position	Nearby gene(s)	SNP	Original p-value	Population	Children included	Ref	Association in CAMP	
							p-value BMI*	p-value asthma†
16q12.2	*FTO*	rs1121980‡	4×10^{-8}	Caucasian	Yes	17	0.18	0.38
18q21.32	*MC4R*	rs12970134	1×10^{-12}	Caucasian, African American	No	19	0.15	0.85
18q21.32	*MC4R*	rs17782313‡	5×10^{-18}	Caucasian	Yes	17, 20	0.14	0.54
19q13.11	*KCTD15*	rs11084753	2×10^{-8}	Caucasian	Yes	20	NA	NA
19q13.11	*KCTD15/CHST8*	rs29941	7×10^{-12}	Caucasian, African American	No	19	0.06	0.75
20q11.23	*CTNNBL1*	rs6020712	8×10^{-7}	Caucasian	No	16	0.61	0.63
20p12.3	*BMP2*	rs2145270‡	6×10^{-6}	Caucasian	Yes	20	0.45	0.42

*Linear regression in asthmatics using PLINK.

†Case-control association using PLINK.

‡Not genotyped in CAMP. Association to 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, rs2145270 - rs979012.

§Combined genotype-age interaction p-value from 5 studies.

Table 3

Top hits from published asthma GWAS and association to BMI and asthma in CAMP

Position	Nearby gene(s)	SNP	Original p-value	Population	Children included	Ref	Association in CAMP	
							p-value BMI*	p-value asthma†
1q31	*DENND1B/CRB1*	rs2786098	9×10^{-11}	Caucasian	Yes	26	0.14	0.96
2q12	*IL1RL1/IL18R1*	rs1420101	6×10^{-12}	Caucasian, East Asian	Yes	21	0.81	0.23
2q12.3	*DPP10*	rs1435879	3×10^{-6}	African ancestry	Yes	25	0.72	0.18
3p12	*ROBO1/GBE1*	rs275358	4×10^{-6}	Caucasian	Yes	26	0.10	0.54
5q12	*PDE4D*	rs1588265	4×10^{-7}	Caucasian	Yes	23	0.28	4×10^{-7}
5q22	*WDR36/TSLP*	rs2416257	1×10^{-4}	Caucasian, East Asian	Yes	21	0.27	0.82
5q33	*ADRA1B*	rs10515807	4×10^{-6}	African ancestry	Yes	25	0.99	NA
6q23	*MYB*	rs9494145	4×10^{-3}	Caucasian, East Asian	Yes	21	0.21	0.79
6q27	*PDE10A*	rs1358786‡	8×10^{-8}	Caucasian	Yes	26	0.75	0.57
9q21.31	*TLE4*	rs2378383	7×10^{-7}	Hispanic/Mexican	Yes	22	0.38	0.59
9p23	*PTPRD*	rs1326772	8×10^{-7}	Caucasian	Yes	26	0.57	0.54
9q24	*IL33*	rs3939286	5×10^{-6}	Caucasian, East Asian	Yes	21	0.07	0.26
17q21	*ORMDL3/GSDML*	rs7216389	9×10^{-11}	Caucasian	Yes	24	0.81	0.002
20q12	*PRNP*	rs6052761	2×10^{-6}	African ancestry	Yes	25	0.64	0.82

*Linear regression in asthmatics using PLINK.

†Case-control association using PLINK.

‡Not genotyped in CAMP. Association to a proxy SNP, rs1033700 ($r^2 = 0.86$ with rs1358786) was reported.

NA = not available (excluded after QC).

Table 4

Candidate genes for both BMI/obesity and asthma and association to BMI and asthma in CAMP

			Original association to asthma			Original association to BMI/obesity			Association in CAMP		
Position	**Gene**	**SNP**	**p-value**	**Children included**	**Ref**	**p-value**	**Children included**	**Ref**	**Analyzed SNP in CAMP**	**p-value BMI***	**p-value asthma†**
2p25	*ACP1*	A/B/C genotypes§	<0.01	No	39	0.008	No	40	rs12714402	0.25	0.80
5q32-34	*ADRB2*‡	rs1042714‖	<0.05	Yes	6, 8	<0.05	Yes	7	rs2082382	0.41	0.77
		rs1042713	<0.05			<0.05			rs1042713	0.74	0.90
6p21.3	*TNF*‡	rs1800629‖	<0.05	Yes	6, 8, 9	<0.05	No	7	rs2857595	0.89	0.15
7q31.3	*LEP*	rs2167270‖	<0.05	Yes	11	<0.05	Yes	11	rs10249476	0.17	0.29
12q13.11	*VDR*‡	Multiple SNPs	<0.05	Yes	6	<0.05	No	7	rs7967152	0.19	0.64
17q22	*PRKCA*	rs11079657	3×10^{-5}	Yes	10				rs11079657	0.88¶	0.07¶
		rs228883				6×10^{-5}	Yes	10	rs228883	0.05¶	0.98¶
17q23.3	*ACE*‡	In/del§	<0.05	Yes	6	<0.05	No	7	rs4343	0.71	0.006

*Linear regression in asthmatics using PLINK.

†Case-control association using PLINK

‡Several associations have been reported to asthma and BMI as reviewed in[6–8]

§Not genotyped in CAMP. The SNP with smallest p-value for BMI or asthma in CAMP was reported.

‖Not genotyped in CAMP. Association to a proxy SNP in LD with the original SNP was reported (r^2>0.85 for all proxy SNPs)

¶Recessive model as in original publication[10]