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Genome-wide association study of body mass index in 23,000 individuals with and without asthma

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Abstract

Background—Both asthma and obesity are complex disorders that are influenced by environmental and genetic factors. Shared genetic factors between asthma and obesity have been proposed to partly explain epidemiological findings of co-morbidity between these conditions.

Objective—To identify genetic variants that are associated with body mass index (BMI) in asthmatic children and adults, and to evaluate if there are differences between the genetics of BMI in asthmatics and healthy individuals.

Methods—In total, 19 studies contributed with genome-wide analysis study (GWAS) data from more than 23,000 individuals with predominantly European descent, of whom 8,165 are asthmatics.

Results—We report associations between several *DENND1B* variants ($p=2.2\times10^{-7}$ for rs4915551) on chromosome 1q31 and BMI from a meta-analysis of GWAS data using 2,691 asthmatic children (screening data). The top *DENND1B* SNPs were next evaluated in seven independent replication data sets comprising 2,014 asthmatics, and rs4915551 was nominally replicated ($p<0.05$) in two of the seven studies and of borderline significance in one ($p=0.059$). However, strong evidence of effect heterogeneity was observed and overall, the association between rs4915551 and BMI was not significant in the total replication data set, $p=0.71$. Using a random effects model, BMI was overall estimated to increase by 0.30 kg/m^2 ($p=0.01$ for combined screening and replication data sets, N=4,705) per additional G allele of this *DENND1B* SNP. *FTO* was confirmed as an important gene for adult and childhood BMI regardless of asthma status.

Conclusions and Clinical Relevance—*DENND1B* was recently identified as an asthma susceptibility gene in a GWAS on children, and here we find evidence that *DENND1B* variants may also be associated with BMI in asthmatic children. However, the association was overall not replicated in the independent data sets and the heterogeneous effect of *DENND1B* points to complex associations with the studied diseases that deserve further study.

Keywords

Association; Asthma; BMI; Genetics; Genome-wide; Obesity

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Conflict of interest statement

No author has declared any relevant conflict of interest for this manuscript.

Introduction

During the past decades, the prevalence of asthma and obesity/overweight has markedly increased in children and adults, contributing substantially to morbidity and health costs worldwide.[1] Both asthma and obesity are complex disorders that are influenced by environmental and genetic factors. Twin studies have shown that genetic factors account for around 60–70% of the population variation in body mass index (BMI) and similar numbers have been presented for the heritability of asthma.[2–4] Numerous genetic variants have also been associated with each phenotype.[5–7]

Shared genetic factors between asthma and obesity have been proposed to partly explain epidemiological findings of co-morbidity between these conditions[8, 9], and longitudinal studies show that obesity seems to precede asthma.[1, 10, 11] Association analyses of known asthma and BMI genes show some evidence for a shared genetic predisposition to asthma and obesity, although other shared genetic determinants are likely to be identified.[12]

Recent genome-wide association studies (GWAS) have identified variants at several loci that are associated with BMI and/or obesity, with the strongest association to *FTO*, *TMEM18* and *MC4R*.[13–23] Of the BMI top GWAS hits published to date, the majority of loci were originally identified in adult populations, although many of these loci have also shown associations with BMI or obesity in children.[23, 24]

While the genetics of BMI in the general adult population has been rather extensively studied, few candidate gene studies and no GWAS have been performed to evaluate the influence of genetics on BMI in asthmatics. Thus, it is currently not known if there are any differences between the genetics of BMI in healthy individuals and in an ascertained asthmatic population. Association analyses of genetic markers and BMI in asthmatics can give valuable insights in the complex interplay between genes, asthma and obesity.

The aim of this project was to identify common genetic variants associated with BMI in asthmatic children and adults, and to evaluate if there are differences between the genetics of BMI in healthy individuals and asthmatics.

Methods

Ethics statement

Written informed consent was obtained from all participants or their parents and all studies were approved by the local ethics committees.

Subjects

All study subjects (totaling 23,562 individuals) were derived from existing studies (cohort, case-control and family based studies) on asthma and respiratory diseases from Australia, Canada, Central America, Europe, and the US (Table 1 and Supplement data). ALSPAC, BAMSE, Busselton Health Study, B58C (partly), CAPPS, ECHRS, EGEA, GABRIELA, MAGICS/ISAAC, MAS, PIAMA, SAGE, SAPALDIA and TOMSK are part of the

GABRIEL consortium and described in detail elsewhere.[25] In the GABRIEL studies, doctor's diagnosis of asthma (ever) was used to define cases (subjects who reported to ever have had asthma were also included as cases in ECRHS and SAPALDIA) and non-asthmatics were used as controls. Established definitions for asthma were used in the other studies (CAMP, GACRS, GINI/LISA, Hartford/Puerto Rico and CAG) as described in the Supporting information.

Separate analyses were run in children (< 18 years) and adults, and some studies contributed samples to both age groups. BMI was measured at a clinical visit in each study and we used the measurement closest in time to the diagnosis of asthma. BMI values were not available for all individuals listed in Table 1, and somewhat lower figures are therefore presented in respective tables and figures with BMI results. Detailed information about each participating study is given in the Supporting information (Information S1).

Genotyping

All genotyping in the GABRIEL studies were carried out at Centre National de Génotypage (Evry, France) using the Illumina Human610 Quad BeadChip (Illumina, Inc., San Diego, CA)[25], except for the MAGICS/ISAAC data set (Illumina HumanHap300 BeadChip, thus contributing with 300K SNPs in the analysis).[26] As reported previously, strict quality control (QC) procedures were applied to all genotyped data sets.[25, 26] 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 1,205 population controls obtained from Illumina's iControlDB public repository.[27] The SNP selected for replication in GACRS (rs4915551) was genotyped using the Sequenom MassArray platform with iPlex chemistry. In CAG[28], GINI/LISA and Puerto Rican participants genotype information for the replication SNPs were extracted from existing imputed GWAS data. Detailed information about genotyping procedure in each participating study is given in the Supporting information (Information S1).

Statistical analyses

The ancestry analysis was carried out in all studies with GWAS data using EIGENSTRAT 2.0[29], and outliers were flagged and eliminated from subsequent analyses.[25, 27] Separate association analyses were performed in each study and the GWAS results were then subject to meta-analysis (for asthmatic children; screening and replication data sets separately and finally combined). BMI was analyzed as a continuous trait, in asthmatics and non-asthmatics separately, with linear regression in PLINK[30], using an additive genetic model adjusted for age, gender and informative principal components (to adjust for potential population substructure). BMI standard deviation score (or equivalent such as z score) analyses were also performed in a subset of the child studies. The CAPPS, EGEA, and SAGE data sets comprised a mixture of unrelated and related cases and controls, and regression models adjusting for clustering of family genotypes was used in Stata Statistical Software (College Station, TX). In the family based studies CAMP and TOMSK, only probands were included in BMI analyses (siblings excluded). SNPs passing the following quality control criteria in each study were later included in the meta-analysis: 1) genotype missing rate<3 % in both cases and controls; 2) minor allele frequency ≥ 1% in controls; 3)

Hardy-Weinberg equilibrium p-value >0.0001 in controls. Combined meta-analysis and tests for heterogeneity between studies were carried out in Metal, using a weighted z-score method (fixed effects) that accounts for the direction of association relative to a consistent reference allele (http://www.sph.umich.edu/csg/abecasis/metal/index.html).[21] A minimum of 1500 subjects were used as a cut off in each analysis. The weights are proportional to the square-root of sample size in each study and the squared weights sum to 1.0. Quantile-quantile plots (Q-Q plots), Manhattan plots and annotations were created in the WGAViewer software, which is based on the latest Ensembl Core, Variation, and GO databases.[31] Funnel plots and random effects models were done in Stata Statistical Software (College Station, Tx). Plots of the regional association results were created using LocusZoom.[31] At individual study level, logistic regression analysis, adjusted for informative principal components (in PLINK or Stata), was used to estimate the association between specific *DENND1B* SNPs and asthma (followed by meta-analysis across studies using Metal). Power calculations based on reported effects of one of the major BMI genes, *FTO* [21] show that at least 2,500 individuals are required for robust association analyses (80% power based on Beta = 0.33, MAF 0.41 and significance level 0.05, one-sided p-value).

Results

Table 1 shows the descriptive statistics of the child (screening and replication data sets) and adult studies and subjects included in this analysis after QC. The mean BMI values varied somewhat between studies, from 15.8 to 19.1 in children (age range 3.5–18 years) and from 24.3 to 28.4 in adults, but no large differences were seen between BMI in asthmatics and non-asthmatics. Figure 1 shows the QQ-plot based on 536,451 SNPs from the meta-analysis results on BMI in 2,691 asthmatic children using the screening data set (observed p-values on the y-axis to those expected on the x-axis for a null distribution). The tail marginally deviates from what is expected by chance without evidence of population stratification (genomic inflation factor 1.01), which suggests that true associations between some SNPs and BMI in asthmatic children exist in the data. We identified associations between several SNPs in *DENND1B* on chromosome 1q31 and BMI in asthmatic children (top SNP rs4915551, p-value=2.2×10^{-7}, Figure 2a and Table 2), and a locus on chromosome 7 containing *SLC12A9* was also indicated. A regional plot of association results for SNPs in the *DENND1B* loci on chromosome 1q31 is presented in Figure S1, where linkage disequilibrium values (r^2 0.4–0.8 between rs4915551 and the other top SNPs) are also indicated. The top 10 SNPs from the screening analysis, including *DENND1B* SNPs, were next analyzed in seven independent replication data sets comprising 2,014 asthmatic children from Europe, Central and North America (Table 1). One of the *DENND1B* SNPs was nominally significant also in the combined replication data sets (rs10737692, p= 0.04). The association for the top *DENND1B* SNP rs4915551 was nominally replicated (p<0.05) in two of the studies (Figure 3), GACRS and CAPPS, and of borderline significance in GINI/LISA (p=0.059). However, signs of heterogeneity were found for rs4915551, which indicate large inter-study variations and overall, the association was not significant in the replication data set, p=0.71 (Table 3). Combined analyses of both screening and replication data (N=4,705) confirmed highly significant tests for heterogeneity for all top *DENND1B* SNPs

(p-value = 5.8×10^{-3} to 4.5×10^{-5} (Table 3). The forest plot of rs4915551 in the combined analyses (Figure 3) also shows that BMI was estimated to change from −1.4 units in the Canadian study CAPPS (p=0.01) to +1.7 units in the Russian study Tomsk (p=0.003). Using a random effects model, BMI was overall estimated to increase by 0.30 kg/m^2 (p=0.01) per additional G allele of this *DENND1B* SNP. Minor allele frequencies for this SNP varied between 0.17 (Russia) and 0.37 (Puerto Rico), but showed no correlation with the direction of the effect on BMI (p>0.68).

Because BMI changes with age in children, standard deviation (sds) BMI scores analyses (e.g. Z-scores, iso-BMI or specific cut-off such as above 85th or 95th percentile) are often suggested and we therefore compared our age and sex adjusted BMI results with sds BMI score results in studies with these data available (9 studies, N asthmatics = 3,696). Figure 4 shows that the sds score analyses are very consistent with the age and sex adjusted BMI results within each study and the pattern of clear heterogeneity is essentially unchanged (p<0.0001 for heterogeneity, p-value for association =0.008 fixed effects and p=0.12 random effects).

No association between *DENND1B* SNPs and asthma in children (case-control analysis, N=11,956) or adults (N=11,575) were seen (Table S1).

For BMI in non-asthmatic children (n=6,019 from data available in 8 studies), the top SNP on chromosome 9 (p-value =2.2×10^{-7}) is located in *DENND1A* (rs10818854), respectively (Figure 2b, Supporting Figure S2 and Table S2). A handful of additional SNPs in *DENND1A* were associated with BMI in non-asthmatic children (p-value ≈ 10^{-4} to 10^{-6}, Figure S3), but all SNPs had MAF around 0.03–0.04. *DENND1B* SNPs showed nominal p-values between 0.02–0.08 for BMI in non-asthmatic children, e.g. p=0.03 for rs4915551 (Figure 2b and Table S1), but the direction was generally in the opposite direction as in asthmatics. No association was found between rs4915551 and BMI in asthmatic or non-asthmatic adults (p=0.53 and 0.87). *DENND1A* rs10818854 was not associated with BMI in asthmatic children (p-value = 0.47, screening data set).

The meta-analysis of GWAS results on BMI in asthmatic adults (n=3,242) showed little evidence of strong genetic determinants (Figure 2c, Figure S4 and Table S3). The top SNP, rs643507 (p-value =8.0×10^{-9}), resides in a reasonable candidate gene for BMI, *LPIN2*, but has a minor allele frequency below 1% in 4 of the 7 adult studies. SNPs in *STARD13*, *PRKCQ* and *SLC24A2* with a p-value in the range of 10^{-6} were also observed.

Only 3 SNPs were associated at p-values ≤10^{-6} with BMI in non-asthmatic adults (n=7,679), all being intergenic SNPs (Figure 2d, Figure S5 and Table S4). The top SNP, rs7775861 on chromosome 6, was however close to genome wide significant at p=8.6×10^{-8}. Since *FTO* has been implicated as an important gene for BMI in several other GWAS, we tested the top *FTO* SNP reported in the literature (rs9939609 represented by rs8050136)[21] to evaluate if this SNP was associated with BMI in our data and found nominally significant associations (p-values=4.5×10^{-4} and 1.2×10^{-3} in non-asthmatic and asthmatic adults, p-values=6.1×10^{-3} and 2.6×10^{-4} in non-asthmatic and asthmatic children, respectively).

Discussion

Herein we report the results from unbiased GWAS analyses on BMI in a large collection of asthmatics and healthy individuals. Associations were found between several SNPs in *DENND1B* on chromosome 1q31 and BMI in 2,691 asthmatic children and also replicated in independent data sets; however, the effect estimates were very heterogeneous across studies from different geographical locations and overall not significant in the total replication data set. Only weak associations were found between *DENND1B* SNPs and BMI in non-asthmatic children and no associations were seen in asthmatic/non-asthmatic adults. A recent GWAS study identified *DENND1B* as a new susceptibility gene for asthma[32], and it is intriguing that we now find some evidence for association with another phenotype, BMI in asthmatic children. Given the overall lack of replication of the BMI results and the fact that the association did not reach genome-wide significance, we cannot completely rule out that other factors such as environmental exposures, other genetic variants or chance may have contributed to our findings. Additional replication of the association is necessary to validate our results.

Epidemiological studies have consistently found associations between asthma, particularly non-atopic asthma[33], and BMI/obesity, although temporal aspects of the asthma–obesity link seems to be rather complex in children.[34, 35] The shared genetic component between the two phenotypes 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.[8] The literature is, however, sparse with examples of shared genetics between asthma and obesity. *LEP, PRKCA* and *TNF* genes have been evaluated for pleiotrophic effects in the same population [36–38], as well as candidate genes from recent GWAS, including *GNPDA2, PTPRD* and *ROBO1*.[12] Our findings do not support the notion that *DENND1B* variants contribute to an increase in risk of either asthma or BMI in the general population, but rather that the identified variants affect BMI conditional on the child's asthma affection status. The association signal in asthmatics seemed to be restricted to *DENND1B* and not extend beyond the recombination hot spots up- and downstream of the gene.

Body mass index in children is known to change substantially with age.[39] Consequently, the definitions of overweight and obesity are age and sex specific. Cut-offs for these conditions have been established in certain reference populations, e.g. in the US [40], as well as Europe and Asia.[39] Similar to many other genetic studies in children [14, 37, 41], we used age and sex adjusted BMI as a continuous trait in the screening and replication data analyses. This maximized power by using a large number of cohorts and hence large overall sample sizes. However, the age and sex adjusted results were compared with z-score analyses (or equivalent sds BMI scores) for the top *DENND1B* SNP in 3,700 asthmatics, and the results were found to be very similar in respective cohort.

DENND1B (also known as DENN/MADD) is expressed in a wide range of tissues and cells, including adipocytes, but most predominantly in natural killer cells and dendritic cells.[32] *DENND1B* is predicted to exert its effects through the *TNF*-pathway via binding to the TNFR1, whereby MAP kinase activation and arachidonic acid release take place.[42]

DENND1B has been proposed to have dual activities under normal and stress conditions such as hypoxia or macrophage invasion.[43] The TNF-pathway has been suggested to have a key role in both asthma and obesity, which makes the finding in our study biologically plausible. Children with asthma may be considered to suffer from chronic, inflammatory stress, and there is increasing evidence that overweight/obesity is a proinflammatory state with chronic stress.[44] The link between DENND1B and the TNF-pathway has, however, been questioned and there is evidence that proteins in the DENN domain–containing family are involved in guanine–nucleotide exchange and endosomal-membrane trafficking.[45, 46] Further research is needed to determine potential interaction between DENND1B and TNF-related proteins. Recent meta-analyses of large GWAS implicate involvement of *DENND1B* also in the pathogenesis of Crohn's disease and primary biliary cirrhosis, which supports its role in inflammatory diseases.[47, 48]

In the original asthma GWAS, *DENND1B* variants were associated with decreased risk (e.g. the minor allele of the top hit, rs2786098) of asthma in children with European ancestry, while increased risk were seen in children with African ancestry.[32] Strong evidence of heterogeneity was found also in our study (especially for rs4915551) despite the fact that all cohort members in this study were predominantly of European descent, which is likely explained by the large geographical differences among the cohorts (Australia, Europe, Central and North America), as well as different exposure patterns (e.g. farm exposure as in GABRIELA[49]). A tendency towards a West-East gradient in the effect estimate of the top *DENND1B* SNP (rs4915551) was also seen ranging from significantly negative effect in a Canadian study to positive effect on BMI in the Russian study. In most of the included studies, a rather liberal asthma definition was used (doctor's diagnosis ever), similar to the GABRIEL study.[25] Other studies have used more stringent criteria, e.g. CAMP and the replication study GACRS (Supporting data for details), and different asthma criteria could also influence heterogeneity of effect. The top *DENND1B* SNP in our study (rs4915551), had $p=3.12\times10^{-5}$ in the original asthma GWAS with OR = 0.73 (G vs A) in Europeans.[32] Similar to the results from the main GABRIEL study[25] , the American EVE consortium[28] and an Australian study [50], we did not find any association between *DENND1B* and asthma per se.

Interestingly, *DENND1A* on chromosome 9q33 showed evidence of association in non-asthmatic children, albeit not at a genome-wide significant level and the top SNPs had a minor allele frequency of around 3–4%. Associations with polycystic ovary syndrome have also been reported for one of the SNPs, rs10818854 in Han Chinese.[51] *DENND1A* encodes for Connecdenn, which binds to Clathrin that mediates internalization of proteins and lipids through endocytosis.[46] Connecdenn shows 38% overall identity with the DENND1B encoded protein, which has also been named Connecdenn-2.

Analyses of genetic determinants for BMI in adults did not reveal any strong candidate genes. Two SNPs in *STARD13* (chromosome 13q12) were associated at $p=3\times10^{-6}$ and 1×10^{-5} in asthmatics. *STARD13* has previously been associated with intracranial aneurysm[52], and it is unclear if this gene has any relevance also for BMI levels based solely on our data. Several SNPs on chromosome 6 showed associations to BMI in adult non-asthmatics, but these were intergenic and have not been associated with BMI or obesity

before. SNPs in *FTO* did not reach genome wide significance in any of the groups, but were nominally associated with BMI in both adults and children regardless of asthma status. Although the data sets were rather large with adequate power to detect associations to common SNPs with the largest effect sizes on BMI, it is likely that an even larger study population would yield clearer results.

In summary, we find evidence that *DENND1B* variants identified using a GWAS approach may be associated with BMI in asthmatic children. Overall, the results were however not replicated in the independent data sets, and our results should therefore be interpreted with caution. The heterogeneous effect of *DENND1B* on BMI, as well as on BMI sds scores, in our study and on asthma in a previous GWAS[32], point to complex associations with the studied diseases that deserve further study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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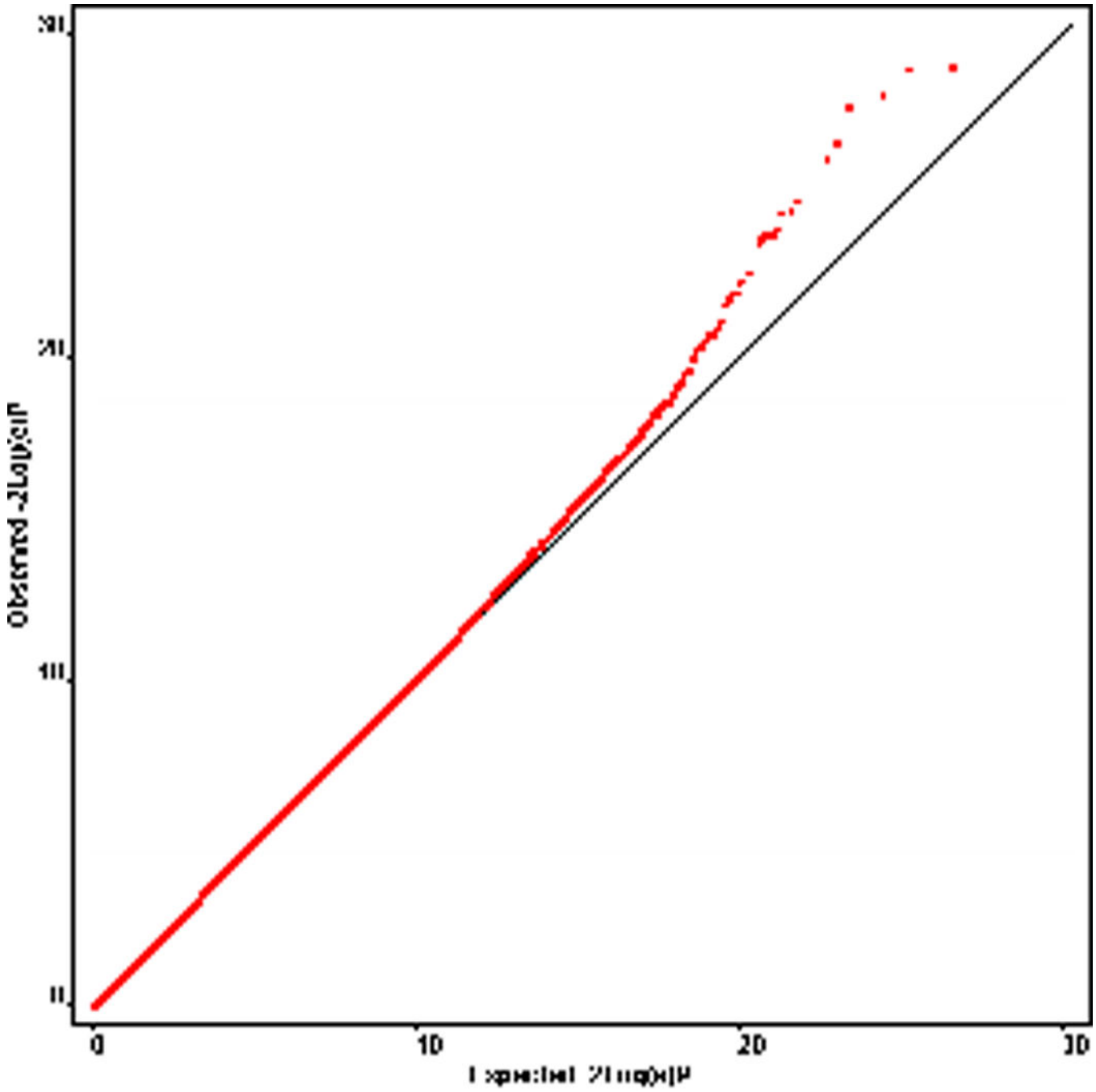

Figure 1.

Quantile-quantile (QQ) plot of SNPs after meta-analysis for association to BMI in the screening data set consisting of 2,691 *asthmatic children* (observed p-values on the y-axis to those expected on the x-axis for a null distribution; i.e. no overall association between SNPs and BMI). Deviation of measures at the tail (upper right corner) may indicate true associations between some SNPs and BMI in asthmatic children.

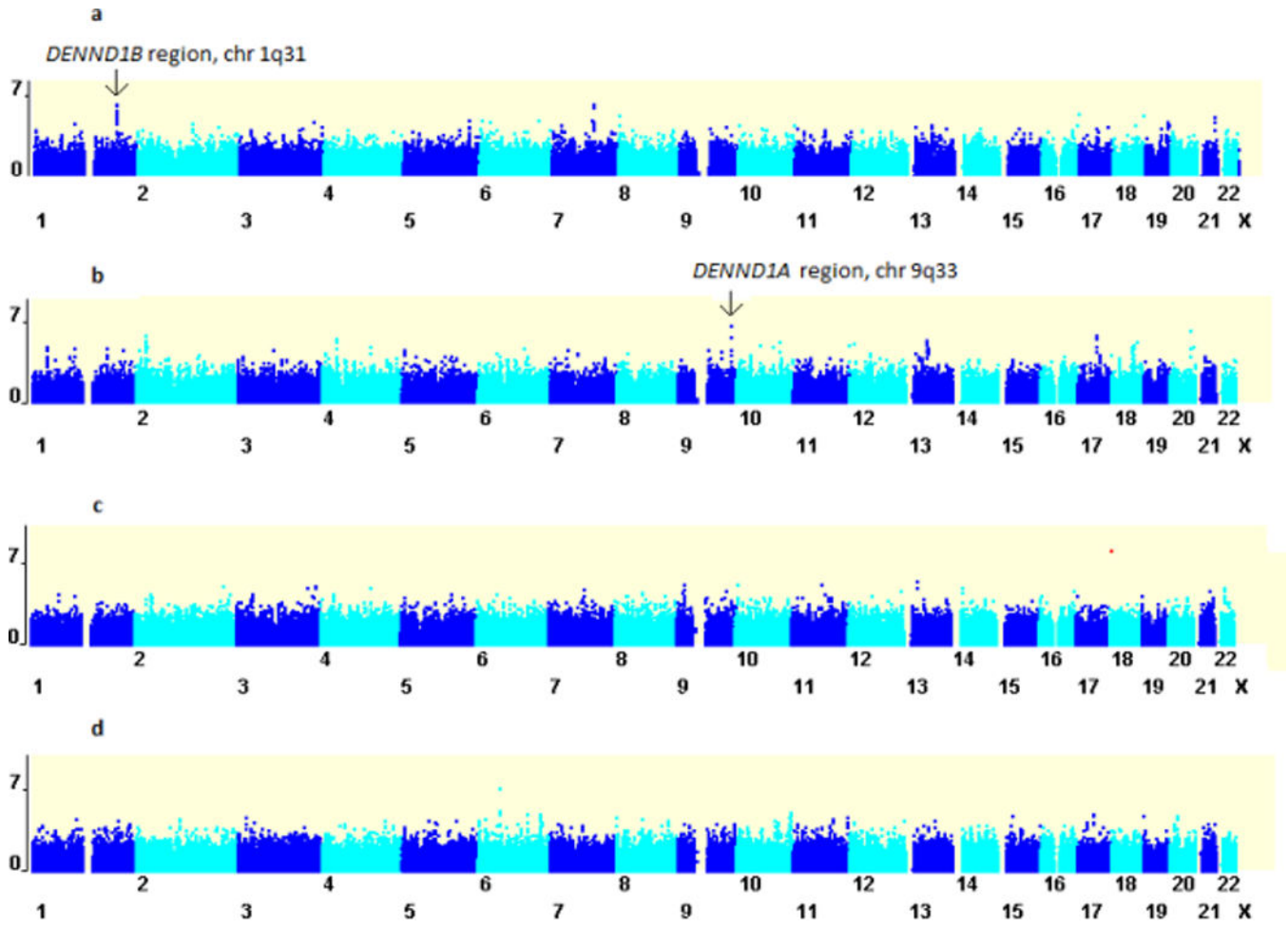

Figure 2.

a. Manhattan plot showing the significance of association of all SNPs (n=536,451) across chromosomes 1–22 and × in the meta-analysis with BMI in *asthmatic children* (screening data set, n=2,691 individuals). SNPs are plotted on the × axis according to their position on each chromosome and association with BMI is indicated on the y axis (as −log10 P value). The region containing *DENND1B* on chromosome 1q31 is indicated with an arrow.

b. Manhattan plot showing the significance of association of all SNPs (n=527,642) across chromosomes 1–22 and × in the meta-analysis with BMI in *non-asthmatic children* (n=6,019 individuals).

c. Manhattan plot showing the significance of association of all SNPs (n=532,694) across chromosomes 1–22 and × in the meta-analysis with BMI in *asthmatic adults* (n=3,242 individuals).

d. Manhattan plot showing the significance of association of all SNPs (n=512,478) across chromosomes 1–22 and × in the meta-analysis with BMI in *non-asthmatic adults* (n=7,679 individuals).

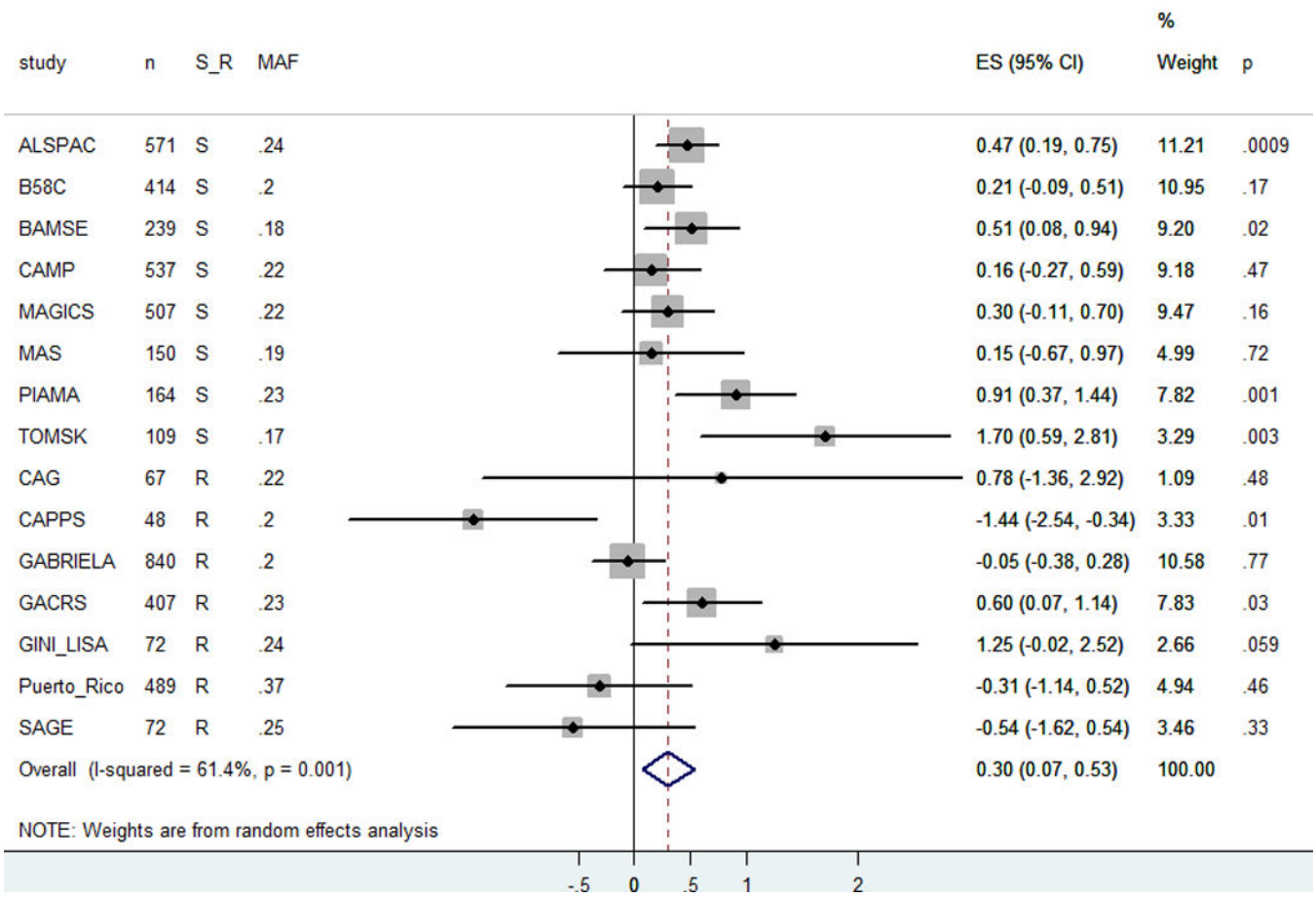

Figure 3.

Forest plot from the meta-analysis results of *DENND1B* rs4915551 G/A effects on BMI in asthmatic children (n children = 4,705 from both screening (S) and replication (R) studies. The X-axis represents the beta values (ES) for association with BMI. Evidence of heterogeneity was found (p=0.001) and random effects analysis was therefore used. The diamond represents the overall estimate (i.e. beta-coefficient, also represented by the dotted line) with 95% confidence intervals, which corresponds to the per-allele change in BMI (minor allele G as effect allele, additive genetic model). Sample size (n), beta-coefficient (ES) and p-values for the association to BMI, and study weight in the meta-analysis are given for each study. The grey box around each study's beta-coefficient is proportional to the weight (using the inverse variance method).

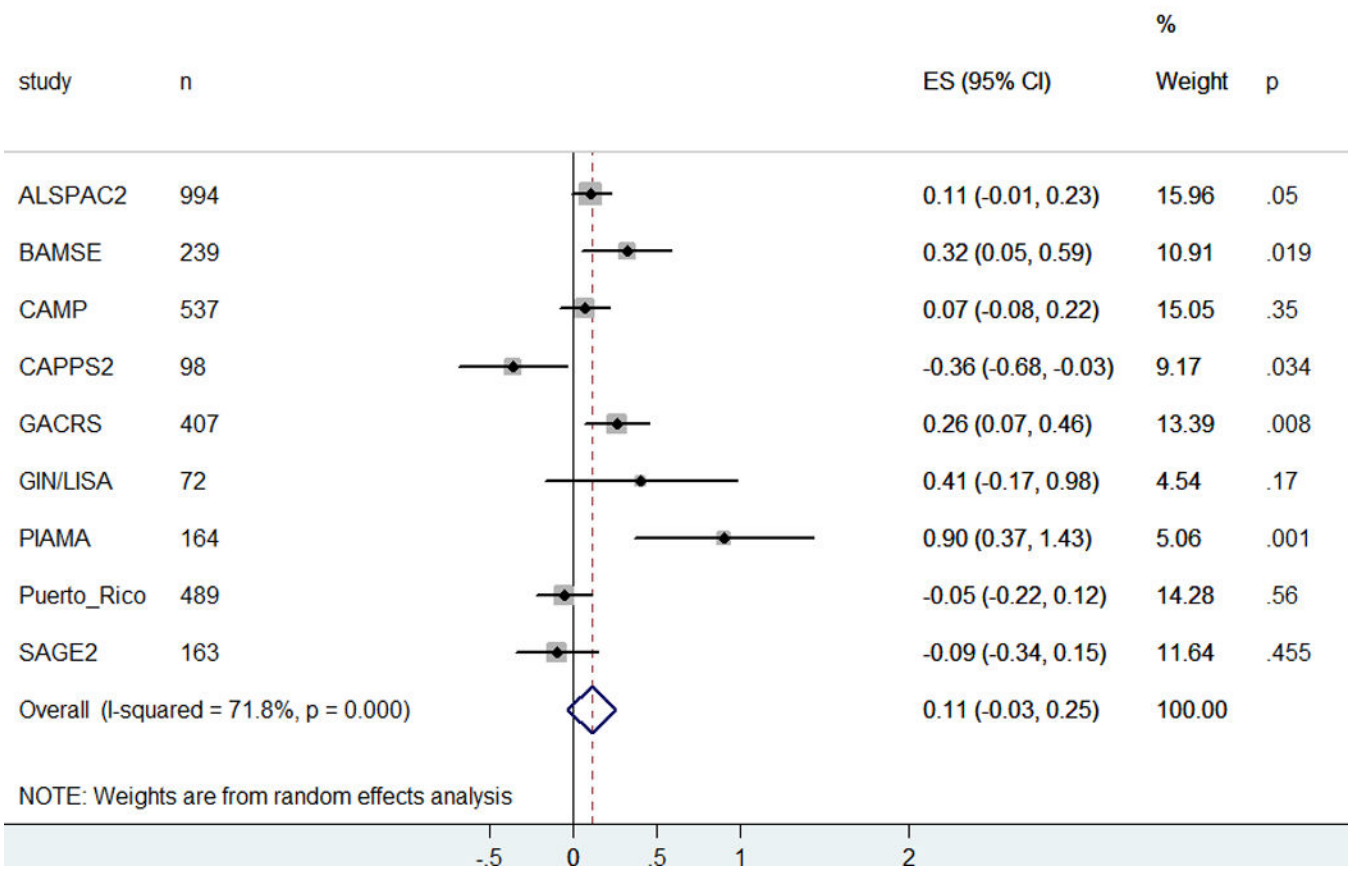

Figure 4.

Forest plot from the meta-analysis results of *DENND1B* rs4915551 G/A effects on BMI standard deviation (sds) / z scores in asthmatic children (n children = 3,696) from studies with these data available. ALSPAC, CAPPS and SAGE had some additional cases available for these analyses (compared with age and sex adjusted analyses), and these studies are therefore labeled ALSPAC2, CAPPS2 and SAGE2, respectively. The X-axis represents the beta values (ES) for association with BMI. Evidence of heterogeneity was found ($p<0.001$) and random effects analysis was therefore used. The diamond represents the overall estimate (i.e. beta-coefficient, also represented by the dotted line) with 95% confidence intervals, which corresponds to the per-allele change in BMI sds / z score (minor allele G as effect allele, additive genetic model). Sample size (n), beta-coefficient (ES) and p-values for the association, and study weight in the meta-analysis are given for each study. The grey box around each study's beta-coefficient is proportional to the weight (using the inverse variance method).

Table 1

Baseline Characteristics of Subjects in the Study Cohorts

Study name	Study design	Platform	Country	Asthma	Non-asthma	Age, years	Gender, female	BMI, asthmatics	BMI, non-astmatics
Childhood onset - Screening data sets						***Mean (min-max)***	***n, %***	***Mean (min-max)***	***Mean (min-max)***
ALSPAC	BC; Nested Ca-Co	Illumina 610-Quad	United Kingdom	571	573	7.5 (7.1–9.2)	510 (44.5)	16.3 (12.8–25.7)	16.2 (13.0–27.3)
BAMSE	BC;Ca-Co	Illumina 610-Quad	Sweden	239	246	8.3 (7.3–10.4)	216 (44.5)	17.3 (13.3–25.3)	17.0 (13.5–24.6)
British 1958 Cohort									
- B58C GABRIEL	Nested Ca-Co	Illumina 610-Quad	United Kingdom	197	723	7.3 (7.0–8.0)	390 (54.0%)	15.8 (11.5–23.9)	15.8 (10.7–25.2)
- B58C WTCCC	Pop-based cohort	Illumina 550K	United Kingdom	80	1204	7.3 (7.0–8.0)	589 (48.9%)	15.9 (9.5–21.9)	15.8 (9.3–23.6)
- B58C T1DGC	Pop-based cohort	Illumina 550K	United Kingdom	137	2092	7.3 (7.0–8.3)	994 (50.8%)	15.9 (12.5–23.9)	15.9 (10-5–25.7)
CAMP*	Fam.; Ca-Co	Illumina 550K and 610K	USA	537	-	8.8 (5.2–13.2)	205 (38.2)	17.9 (13.0–29.4)	-
MAGICS / ISAAC	Ca-Co	Illumina 330K	Germany	507	346	10.3 (4–17)	357 (42)	18.6 (10.6–31.6)	17.8 (11.6–29.0)
MAS	BC; Ca-Co	Illumina 610-Quad	Germany	150	-	9.6 (7–13)	65 (43)	17.5 (12.2–27.0)	-
PIAMA	BC;Ca-Co	Illumina 610-Quad	Holland	164	186	8.2 (7.4–9.7)	167 (47.7)	16.8 (13.0–24.6)	16.5 (13.0–23.2)
TOMSK Children	Fam.	Illumina 610-Quad	Russia	109	-	14.9 (3.5–51)	41 (37.2)	19.1 (10.0–69.3)	-
Replication data sets									
CAPPS†	Trio / Cohort	Illumina 610-Quad	Canada	181 / 48	236	24.8 (6.2–49.7)	205 (49.2)	16.6 (13.4–25.3)	16.6 (12.7–24.2)
GABRIELA	Ca-Co	Illumina 610-Quad	Germany	840	841	8.7 (5–14)	803 (47.8%)	17.1 (10.0–37.3)	17.0 (12.0–27.7)
GACRS	Fam.	Sequenom	Costa Rica	407	-	8.7 (6.0–13.3)	171 (42.0)	16.8 (11.3–30.1)	-

Study name	Study design	Platform	Country	Asthma	Non-asthma	Age, years	Gender, female	BMI, asthmatics	BMI, non-astmatics
Childhood onset - Screening data sets						***Mean (min-max)***	***n, %***	***Mean (min-max)***	***Mean (min-max)***
GINI/LISA	Pop-based BC	Affymetrix 5.0 / 6.0	Germany	72	-	10.2 (9.9–11.1)	27 (37.5%)	17.2 (11.4–26.4)	-
Hartford/ Puerto Rico	Ca-Co	Illumina Human Omni2.5	Puerto Rico / USA	514	421	10.0 (6–14)	451 (47.8)	21.1 (12.9–58.4)	19.9 (11.8–39.6)
SAGE children†	Trio / Cohort	Illumina 610-Quad	Canada	72	145	9.0 (7.7–10.2)	93 (42.9)	17.6 (13.6–29.0)	17.5 (11.2–30.3)
CAG†	Fam; Ca-Co	Illumina 1Mv1	USA	67	-	28.2 (6–74)	21 (31.3)	24.4 (14.9–39.5)	-
Adult studies									
British 1958 Cohort, B58C									
- B58C GABRIEL	Nested Ca-Co	Illumina 610-Quad	United Kingdom	445	425	45.2 (44.3–46.0)	466 (53.6%)	27.6 (17.0–46.6)	27.2 (17.0–54.7)
- B58C WTCCC	Pop-based cohort	Illumina 550K	United Kingdom	180	1,249	44.9 (44.5–46.0)	709 (49.6%)	28.2 (18.4–56.3)	27.3 (17.1–49.5)
- B58C T1DGC	Pop-based cohort	Illumina 550K	United Kingdom	339	2,248	45.3 (44.5–46.0)	1,328 (51.3%)	28.0 (17.3–53.1)	27.4 (17.4–50.5)
Busselton Health Study	Pop. based	Illumina 610-Quad	Australia	509	703	53.4 (17.3–91.4)	704 (58.1)	25.9 (18.7–40.8)	26.0 (15.8–40.7)
ECHRS	Pop. Based	Illumina 610-Quad	Multiple European	678	1,527	33.9 (19.7–48.1)	1181 (53.6)	24.8 (15.5–44.8)	24.8 (16.7–54.1)
EGEA	Fam.;Ca-Co	Illumina 610-Quad	France	821	831	42.4 (15.1–79.5)	675 (40.9)	24.3 (15.8–44.0)	24.3 (16.7–53.7)
SAPALDIA	Pop. Based	Illumina 610-Quad	Switzer-land	349	878	42.1 (18.3 – 61.8)	572 (46.6)	24.4 (16.7–39.3)	23.9 (16.9 – 45.5)
SAGE Parents†	Trio / Cohort	Illumina 610-Quad	Canada	77	192	44.6 (12.3–68.1)	148 (54.6)	28.4 (20.3–43.3)	27.2 (19.8–37.7)
TOMSK adults	Fam.	Illumina 610-Quad	Russia	62	331	39.4 (19–78)	203 (61.3)	25.2 (16.9–44.4)	26.1 (13.6–52.9)
Total sample size, child studies‡				4,705	7,013				
Total sample size, adult studies				3,460	8,384				
Total sample size, all				8,165	15,397				

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[*] In CAMP, 359 asthmatics included in GWAS analyses on asthma and 537 asthmatics included in GWAS analyses on BMI. 1205 Illumina controls did not contribute with BMI data. 205 were girls of the asthmatic children.

[†] In CAPPS, asthma in children and adults were analyzed together for power reasons. Out of 181 asthmatics, 48 were children. BMI was only available in CAPPS children. In SAGE, association to asthma in children and adults were analyzed together for power reasons. Association to BMI was analyzed separately in children and adults. In CAG, both children and adults were included in the BMI analyses (*DENND1B* replication only).

[‡] Children with childhood onset of asthma were included in analyses of childhood asthma even if individuals were older (>18 years) at the time of enrollment, except for EGEA where individuals > 15 years were considered adults. Association to BMI was analyzed separately in children (<18 years) and adults. BMI values were not available for all individuals listed in this table, and somewhat lower are therefore presented in respective tables and figures with BMI results.

BC = Birth cohort, Ca-Co = Case-control, Fam = Family based, Pop. based = Population based

Table 2

Top 10 SNPs from meta-analysis of GWAS on BMI in asthmatic children, screening data set (n=2,691)

SNP	Chr.	Position	Min. allele	MAF*	Nearby gene	Distance to gene	p-value† association	Test and Direction‡	p-value heterogeneity
rs4915551	1	197508901	G	0.24	*DENND1B*	0	2.2×10^{-7}	A vs G --------	0.07
rs7803865	7	100505792	G	0.44	*AC011895.1*	−1595	5.9×10^{-7}	A vs G ---??---	0.35
rs1775454	1	197727298	T	0.22	*DENND1B*	0	8.6×10^{-7}	T vs C ++++?-++	0.09
rs314376	7	100457356	G	0.45	*SLC12A9*	0	1.0×10^{-6}	A vs G ---??---	0.29
rs13232524	7	100512824	T	0.47	*AC011895.1*	−8627	1.0×10^{-6}	T vs C +++-++++	0.03
rs1775456	1	197733055	G	0.22	*DENND1B*	0	1.7×10^{-6}	A vs G -----+--	0.09
rs2111931	1	195795841	C	0.23	*DENND1B*	0	1.8×10^{-6}	T vs C -----+--	0.09
rs10737692	1	197548933	A	0.23	*DENND1B*	0	1.8×10^{-6}	A vs G ++++?-++	0.08
rs1775444	1	196007313	T	0.22	*DENND1B*	0	2.1×10^{-6}	T vs C +++++-++	0.12
rs1924518	1	197738327	A	0.22	*DENND1B*	0	2.4×10^{-6}	A vs G ++++?-++	0.11

*MAF = Minor allele frequency was estimated in the ALSPAC study (n=1,144 children; asthma cases and controls combined).

†P-values for combined meta-analysis using a fixed effects model since the heterogeneity test was non-significant (except rs13232524, p=0.03)

‡Direction reflects the effect (positive or negative on BMI-values) of the effect allele vs reference allele as indicated in the “Test and Direction” column.

“?” reflects missing data from that particular study. Study order corresponding to +/− position (alphabetical order) ALSPAC, BAMSE, B58C (sub-studies pooled), CAMP, MAGICS/ISAAC, MAS, PIAMA, and TOMSK. A total of 536,451 markers were analyzed (minimum number of children in the GWAS analysis, n=1500)

Table 3

Top 10 SNPs from meta-analysis of GWAS on BMI in asthmatic children identified in the screening data set and association in replication data set and combined

		Replication studies			Screening and replication studies combined		
SNP	**Nearby gene**	**N**	**p-value* association**	**p-value heterogeneity**	**N**	**p-value* association**	**p-value heterogeneity**
rs4915551	*DENND1B*	2014	0.71	0.01	4705	2.8×10^{-5}	3.6×10^{-4}
rs7803865	*AC011895.1*	1460	0.52	0.89	3107	4.2×10^{-5}	0.10
rs1775454	*DENND1B*	1460	0.12	0.73	3644	4.4×10^{-3}	6.6×10^{-4}
rs314376	*SLC12A9*	952	0.62	0.76	2599	2.5×10^{-5}	0.11
rs13232524	*AC011895.1*	886	0.70	0.41	3577	5.3×10^{-5}	5.2×10^{-3}
rs1775456	*DENND1B*	957	0.20	0.58	3648	5.2×10^{-4}	3.8×10^{-3}
rs2111931	*DENND1B*	1368	0.63	0.02	4058	2.9×10^{-4}	5.5×10^{-4}
rs10737692	*DENND1B*	1461	0.04	0.19	3645	1.7×10^{-2}	4.5×10^{-5}
rs1775444	*DENND1B*	959	0.21	0.58	3650	5.8×10^{-4}	5.8×10^{-3}
rs1924518	*DENND1B*	1355	0.87	0.15	3539	2.9×10^{-4}	5.6×10^{-3}

*P-values for combined meta-analysis using a fixed effects model

Replication studies - CAPPS, SAGE, GACRS, GABRIELA, GINI/LISA, Hartford/Puerto Rico and Chicago. Combined: ALSPAC, BAMSE, B58C (sub-studies pooled), CAMP, MAGICS/ISAAC, MAS, PIAMA, TOMSK, CAPPS, SAGE, GACRS, GABRIELA, GINI/LISA, Hartford / Puerto Rico and CAG.