Published in final edited form as:
Clin Endocrinol (Oxf). 2014 November ; 81(5): 702–710. doi:10.1111/cen.12428.

Associations of genetic variants in/near BMI-associated genes with type 2 diabetes: A systematic meta-analysis

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Declaration of interest
None of the authors has any potential conflicts of interest to declare.

Financial disclosure
None of the authors have received any financial benefit for their participation in the research nor the writing of this article.

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ICMJE criteria for authorship read and met: BX, DZ, FT, AM, APM, NK, JCC, YSC, WZ, KLM, JSK, XOS, HP, EST, HP, JYW, GRC
Agree with manuscript results and conclusions: BX, DZ, FT, AM, APM, NK, JCC, YSC, WZ, KLM, JSK, XOS, HP, EST, HP, JYW, GRC
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Summary

Objective—Genome-wide association studies have identified many obesity/body mass index (BMI)-associated loci in Europeans and East Asians. Since then, a large number of studies have investigated the role of BMI-associated loci in the development of type 2 diabetes (T2D). However, the results have been inconsistent. The objective of this study was to investigate the associations of 11 obesity/BMI with T2D risk and explore how BMI influences this risk.

Methods—We retrieved published literature from PubMed and Embase. The pooled odds ratios (OR) with 95% confidence intervals (CI) were calculated using fixed- or random- effect model.

Results—In the meta-analysis of 42 studies for 11 obesity/BMI-associated loci, we observed a statistically significant association of *FTO* rs9939609 polymorphism (66,425 T2D cases/239,689 normoglycemic subjects; $p=1.00\times10^{-41}$) and six other variants with T2D risk (17,915 T2D cases/ 27,531 normoglycemic individuals: n=40,629 to 130,001; all $p<0.001$ for *SH2B1* rs7498665, *FAIM2* rs7138803, *TMEM18* rs7561317, *GNPDA2* rs10938397, *BDNF* rs925946 and *NEGR1* rs2568958). After adjustment for BMI, the association remained statistically significant for four of the seven variants (all $p<0.05$ for *FTO* rs9939609, *SH2B1* rs7498665, *FAIM2* rs7138803, *GNPDA2* rs10938397). Subgroup analysis by ethnicity demonstrated similar results.

Conclusions—This meta-analysis indicates that several BMI-associated variants are significantly associated with T2D risk. Some variants increase the T2D risk independent of obesity, while others mediate this risk through obesity.

Keywords

Type 2 diabetes; Obesity; *FTO*; Variants; Meta-analysis

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Introduction

Obesity is an established risk factor for development of type 2 diabetes (T2D). Many studies have investigated the role of obesity/ body mass index (BMI)-associated loci in predicting risk of T2D. In 2007, a variant (rs9939609) in the fat mass and obesity-associated (*FTO*) gene was first reported to be statistically significantly associated with obesity [odds ratio (OR)=1.32, 95% confidence interval (CI)=1.26-1.39] and with T2D in individuals of European descent (OR=1.15, 95%CI=1.09-1.23). 1 However, after adjustment for BMI, a surrogate measure of obesity, the significance of association was completely abolished (OR=1.03, 95%CI=0.96-1.10), suggesting that the effect of *FTO* gene polymorphism on T2D was mediated through obesity among Europeans. 1 At the same time, Scuteri et al. also reported that common variants in the *FTO* gene were associated with obesity related traits. 2 Since then, many studies have investigated the *FTO*-T2D association among different ethnic populations and obtained inconsistent results. Following the initial evidence of the BMI-independent association of *FTO* variant with T2D in Asians,3 a recent large meta-analysis including 96,551 East and South Asians confirmed this observation (crude OR=1.15, 95%CI=1.09-1.21; after adjustment for BMI: OR=1.10, 95%CI=1.05-1.16).4 However, the BMI-independent role of *FTO* in risk of T2D among Europeans still remains a matter of debate;1, 5–20 some studies indicated a significant association with T2D after correction for BMI, 5, 15, 17 while others reported a marginal or null association. 1, 5–14, 16, 18–20

Subsequently, many other loci associated with obesity or BMI have been identified 12,21 but their association with T2D is also controversial,12,13,18–20,22–24. This may be due to insufficient statistical power and/or inter-population heterogeneity. In this study, we performed a systematic meta-analysis to investigate 11 of the most commonly studied BMI-associated variants (*FTO* rs9939609, *SH2B1* rs7498665, *FAIM2* rs7138803, *TMEM18* rs7561317, *GNPDA2* rs10938397, *BDNF* rs925946, *NEGR1* rs2568958, *SEC16B1* rs10913469, *KCTD15* rs29941, *ETV5* rs7647305 and *MTCH2* rs10838738) for their role in predicting risk of T2D.

Materials and methods

Literature and search strategy

To date, more than 50 BMI-associated variants or their proxies have been reportedly associated with various metabolic traits, we could use only 11 variants in the present meta-analysis due to limited data for other variants in the published studies and/or lack of response from the authors. 25 We searched the literature databases including PubMed and Embase. The search strategy was to identify all possible studies that involved the use of

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following key words: (*FTO* or *SH2B1* or *FAIM2* or *TMEM18* or *NEGR1* or *GNPDA2* or *SEC16B* or *KCTD15* or *BDNF* or *ETV5* or *MTCH2* or fat mass and obesity associated gene or Src-homology-2 *(SH2)* domain containing putative adaptor protein 1 or fas apoptotic inhibitory molecule 2 or transmembrane protein 18 or neuronal growth regulator 1 or glucosamine-6-phosphate deaminase 2 or SEC16 homolog B (S. cervisiae) or potassium channel tetramerization domain containing 15 or brain derived neurotrophic factor or ets variant gene 5 or mitochondrial carrier homolog 2) and (polymorphism or variant or variation) and (type 2 diabetes or T2D). The language of publication was restricted to English. The reference lists of retrieved articles were curated manually. If more than one article was published using the same case series, only the study with the largest sample size was included in the meta-analysis. The literature search was last updated on June 20, 2013.

Inclusion criteria and data extraction

We included a study in the meta-analysis if it met all the following inclusion criteria: (1) investigated the association of BMI-associated gene variant(s) with T2D; (2) used case-control or cohort design and (3) provided OR with 95% CI under an additive model or sufficient data for calculation of this estimate. Following information was extracted from each study: (1) name of the first author, (2) year of publication, (3) country of origin, (4) ethnicity of the studied population, (5) study design, (6) number of cases and controls or total subjects, (7) sex distribution and the mean ages, (8) mean BMI, and (9) studied single nucleotide polymorphisms (SNPs). All articles were independently accessed by two authors (BX and DZ) to ensure their compliance with the inclusion/exclusion criteria. Any disagreements were resolved through discussion and a consensus decision was reached. All included studies had informed consent from all the participants and were approved by the appropriate Ethics Committees.

Statistical analysis

We calculated the summary estimate under an additive genetic model in this meta-analysis because majority of the included studies only provided OR with 95%CI under this model.4 We analyzed the associations of 11 BMI-associated gene variants with T2D by calculating pooled ORs and 95% CIs. The significance of the OR was determined by a Z test ($p<0.05$ was considered statistically significant) and Cochrane's Q test was performed to test the between-study heterogeneity using a cut-off of $p<0.10$ as statistically significant. We used a random- (DerSimonian-Laird method) or fixed- (Mantel-Haenszel method) effects model to calculate pooled OR in the presence ($p<=0.10$) or absence ($p>0.10$) of heterogeneity, respectively. We used Begg's test and Egger's test ($p<0.05$ was considered statistically significant) to examine any publication bias. To evaluate the stability of the results, we performed sensitivity analysis by removing one study at a time. Statistical analyses for meta-analyses were performed using STATA version 11.0 (StataCorp LP, College Station, TX, USA). The associations were not corrected for multiple testing sine the used loci for association testing have strong priors.

Results

Characteristics of the studies on FTO variant and 10 other BMI associated loci

Details of the process of inclusion/exclusion of various studies in the meta-analysis are described in Figure 1. We identified a total of 195 potential relevant articles from the literature search. Of these, 146 were excluded at the outset because of obvious irrelevance as observed from the title or the abstract (e.g. those articles that evaluated the association of *FTO* gene variant with obesity only, metabolic syndrome, type 1 diabetes, gestational diabetes, cardiovascular disease, polycystic ovary syndrome or cancer). In addition, three review articles and two meta-analyses were also excluded. Six articles were further excluded on account of duplicated publications 22, 26–29 or unavailability of OR with 95% CI values. 25 Therefore, a total of 38 articles met the inclusion criteria 1,3–21, 23,24, 30–45.

Since more than one study on *FTO* variant was included in each of the articles by Scott et al. 5 and by Hertel et al., 17 they were considered as separate studies in the meta-analysis. Thus, the final meta-analysis included a total of 42 studies (21 studies for Europeans, 15 studies for East Asians and 6 studies for South Asians) from 35 articles 1, 3–21,23,24,30–45 that had data on rs9939609 (or proxy [r^2>0.85]) variant in *FTO* gene. Out of 21 studies in Europeans, 12 had data on rs9939609, 5 on rs8050136, 2 on rs1121980 and 2 on rs1421085. Only one variant was selected if any study analyzed more than one variant, and we used the *FTO* variant rs9939609 to represent other polymorphisms because they are in strong linkage disequilibrium (LD) with each other (r^2>0.85). All studies provided the crude (except the study by Webster et al 16) and BMI-adjusted (except the study by Scott et al 5) ORs with 95% CIs for *FTO*-T2D association. Characteristics of the included studies for *FTO* variant(s) in Europeans are listed in Supplementary Table 1.

For 10 other BMI-associated gene variants included in the meta-analysis, the data on specific SNPs (or proxies) in specific genes was available in variable number of studies. All the variants and their proxies were in strong LD with each other (all r^2>0.85 in Hapmap-CEU, CHB and JPT for each SNP). All studies provided the crude and BMI-adjusted ORs with 95%CIs for the association of specific variants with T2D. Characteristics of the included studies for these ten loci are listed in Supplementary Table 2. The genotypes of all 11 BMI-associated variants were in Hardy-Weinberg equilibrium in controls of all included studies (all p>0.05).

Meta-analysis results for FTO variant

A total of 66,425 T2D cases and 239,689 normoglycemic controls for *FTO* rs9939609 (or proxy) were identified from all the included studies. We observed a statistically significant association of rs9939609 variant with the risk of T2D [(OR=1.14, 95%CI=1.12-1.16, p(z-test)=1.00×10^{-41}), I^2=0.0%, p for heterogeneity=0.386, Table 1]. Interestingly, the association remained statistically significant after adjustment for BMI [(OR=1.07, 95%CI=1.05-1.09, p(z-test)=6.42×10^{-41}, I^2=0.0%, p for heterogeneity=0.576)]. In the subgroup analysis by ethnicity, similar results were found in Europeans (Table 1 and Figure 2A and 2B), East Asians and South Asians without or with adjustment for BMI (Table 1).

Meta-analysis results for 10 other BMI-associated loci

We had a variable number of subjects for association analysis of each BMI-associated gene variant with T2D. The sample size in T2D cases ranged from 17,915 to 27,531, and from 40,629 to 130,001 for normoglycemic controls. We observed a statistically significant association of six BMI-associated gene variants with the risk of T2D (*SH2B1* rs7498665: OR=1.08, 95%CI=1.05-1.12, p(z-test)=2.28×10^{-7}; *FAIM2* rs7138803: OR=1.08, 95%CI=1.05-1.11, p(z-test)=1.35×10^{-7}; *TMEM18* rs7561317: OR=1.13, 95%CI=1.06-1.21, p(z-test)=4.47×10^{-4}; *GNPDA2* rs10938397: OR=1.07, 95%CI=1.03-1.10, p(z-test)=5.86×10^{-5}; *BDNF* rs925946: OR=1.06, 95%CI=1.03-1.10, p(z-test)=1.08×10^{-4}, *NEGR1* rs2568958: OR=1.04, 95%CI=1.01-1.08, p(z-test)=0.015 (Table 1). After adjustment for BMI, the associations remained statistically significant for three variants (*SH2B1* rs7498665: OR=1.06, 95%CI=1.02-1.09, p(z-test)=8.71×10^{-4}; *FAIM2* rs7138803: OR=1.05, 95%CI=1.02-1.08, p(z-test)=0.001; *GNPDA2* rs10938397: OR=1.04, 95%CI=1.01-1.08, p(z-test)=0.021) but was abolished for three other variants (*TMEM18* rs7561317, *BDNF* rs925946 and *NEGR1* rs2568958) (Table 1). However, we did not observe statistically significant associations of four other BMI-associated gene variants (*SEC16B* rs10913469, *KCTD15* rs29941, *ETV5* rs7647305, *MTCH2* rs10838738) with T2D without or with adjustment for BMI (Table 1).

In the Europeans, five BMI-associated gene variants (*SH2B1* rs7498665, *FAIM2* rs7138803, *TMEM18* rs7561317, *GNPDA2* rs10938397 and *NEGR1* rs2568958) were significantly associated with the risk of T2D. However, the associations remained statistically significant for only two variants (*SH2B1* rs7498665 and *FAIM2* rs7138803) after adjustment for BMI (Table 1). In the East Asians, three BMI-associated gene variants (*FAIM2* rs7138803, *GNPDA2* rs10938397 and *BDNF* rs925946) were significantly associated with the risk of T2D without or with adjustment for BMI (Table 1). The overall sample size was adequately powered (>90%) to detect the association.

Sensitivity analysis and publication bias

We performed sensitivity analysis by excluding one study at a time. The results confirmed the statistically significant association between 11 BMI-associated variants and the risk of T2D without or with adjustment for BMI (data not shown). There was no evidence of any publication bias for all the variants (p>0.05 for Begg's test and Egger's test).

Discussion

In this study, we performed an extensive review and meta-analysis to investigate the role of BMI-associated gene variants in predicting risk of T2D. Our study indicates that in addition to *FTO*, polymorphisms in six other BMI associated genes (*SH2B1*, *FAIM2*, *TMEM18* *GNPDA2*, *BDNF* and *NEGR1*) were statistically significantly associated with an increased risk of T2D in Europeans and East Asians. Associations of variants in four genes including *FTO*, *SH2B1*, *FAIM2* and *GNPDA2* with T2D may not be entirely mediated via obesity (BMI).

The *FTO* gene on chromosome 16q12.2 was first identified as a susceptibility locus for T2D in Europeans by genome-wide association study (GWAS). 1 However, based on complete abolition of the *FTO* variant-T2D association on adjustment for BMI, the study concluded that the effect of the *FTO* variant on T2D was fully mediated through adiposity. 1 Subsequently, many individual studies have reported inconsistent results. 1, 5–20 A recent meta-analysis of the association between *FTO* variant and incident T2D in three cohorts showed influence of the *FTO* variant on the risk of T2D independent of BMI. 17 In the present study, we also found that BMI had no substantial impact on the association between *FTO* rs9939609 variant and risk of T2D and the association was observed irrespective of ethnicity. Our meta-analysis includes probably the largest sample size to date investigating this association and hence the results are highly convincing. In addition, we observed a similar effect size among Europeans and Asians with or without adjustment for BMI, suggesting a global role for *FTO* variants in predicting an independent risk for T2D.

Two recent GWAS studies initially designed to identify obesity susceptibility loci reported 10 other BMI-associated gene variants. 12, 21 Although several studies have investigated the associations of these reported variants with T2D, results have not been replicated. Since obesity is one of the main risk factors for T2D, exploration of obesity-associated genes in the development of T2D has important implications. We have recently established the association of BMI-associated variant in *MC4R* with risk of T2D and demonstrated no influence of BMI on the strength of association. 46 Our present observations provide evidence of possible existence of two types of obesity-associated genetic variants that could explain the link between obesity and T2D; most increase risk of T2D through obesity, while some have independent association with T2D. To our knowledge, no meta-analysis on this aspect has been performed and our results might shed light on the underlying mechanism on how obesity increases the risk of T2D.

It is still not clear how variants in the BMI associated genes could independently influence the risk of T2D. As is known, the FTO protein is highly expressed in the central nervous system (CNS) and regulates energy metabolism. 21 Many studies have also indicated that variants in *FTO* influences energy-dense food intake rather than regulation of energy expenditure. 47 In addition, *FTO* variants are reported to be associated with diabetes-related metabolic traits (including higher fasting insulin, glucose and triglycerides, and lower HDL cholesterol), although the associations disappeared after adjustment for BMI.48 Furthermore, the FTO is also highly expressed in muscle, and a recent study supported an important role of FTO in oxidative metabolism, lipogenesis and oxidative stress in muscle, 49 which suggests its potential involvement in the muscle defects that characterize T2D. Similar to FTO, SH2B1, FAIM2, TMEM18, NEGR1, GNPDA2 and BDNF are also highly expressed in the CNS and thus may play influence the above mentioned traits.21 SH2B1 is specifically implicated in the insulin signaling pathway and *Sh2b1*-null mice tend to have high-fat diet-induced hyperglycemia, hyperinsulinemia, and glucose intolerance.50 NEGR1 plays an important role in neuronal outgrowth.51 BDNF is suggested to regulate blood glucose homeostasis and insulin sensitivity peripherally.52 The potential role of FAIM2, TMEM18, and GNPDA2 proteins in T2D associated pathophysiological processes needs to be investigated further.

Our data shows that although the association of several of BMI-associated variants with type 2 diabetes is statistically significant, their effect size is small. 53 This suggests that globally BMI-associated SNPs may play relatively small role in the pathophysiology of T2D. However, majority of the T2D-associated variants identified to date influence beta-cell function rather than insulin resistance and hence it may not be unreasonable to assume that BMI-associated variants might have more of an effect on insulin resistance than on beta-cell dysfunction.54 This may also explain why majority of these variants do not predict strong risk for T2D.

Our meta-analysis is subject to several limitations. First, BMI is not the ideal measure of obesity and adjustment for BMI may not fully consider the effect of obesity on variant-T2D association. Other measures of obesity such as waist circumference and waist-hip ratio should be taken into account in future studies. Second, the diabetic status and subsequent anti-diabetic treatment or life-style intervention may influence adiposity and BMI. Third, we cannot rule out the well-known reporting biases that have been identified after the onset of diseases like T2D, and thus prospective studies will be superior to cross-sectional designs for answering such questions with reasonable confidence. Fourth, since most of the studies included in this meta-analysis did not provide data on diet, physical activity and other metabolic variables, we could not address their influence on the effect of *FTO* variant on obesity and obesity comorbidity. Fifth, to date only three studies 13, 18, 20 have examined the cumulative risk of several obesity-associated loci (some in the form of genetic risk score) on T2D, which impeded our attempts of pooled analysis. Finally, in this meta-analysis, we only included published studies, thus, the exclusion of unpublished data may bias the results. To overcome these limitations, a nested T2D case-control (matched for ethnicity, sex, age, adiposity) recruited from a multi-ethnic prospective study seems to be an optimal design to properly assess the association of obesity-related variants with T2D risk.

In conclusion, our meta-analysis with sufficient statistical power has confirmed the statistically significant associations of seven BMI-associated genes (*FTO*, *SH2B1*, *FAIM2*, *TMEM18*, *BDNF*, *GNPDA2*, *NEGR1*) with risk of T2D in Europeans or East Asians, and several variants seem to predict risk of T2D, independent of BMI. However, observations on several other BMI-associated genes in the development of T2D could not be replicated. The findings suggest that it will be important to dissect the pathways that separate the roles of these variants in the risk of T2D.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This study was partially supported by Council of Scientific and Industrial Research (CSIR), and Ministry of Science of Technology, Govt. of India, India through their XII FYP titled “CARDIOMED”. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. We thank Dr Mark I McCarthy (Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK), Dr Michael Boehnke and Dr Heather M. Stringham (Department of Biostatistics and Center for Statistical Genetics, University of Michigan, Ann Arbor, USA) for providing data.

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Abbreviations

BMI	body mass index
CI	confidence interval
FTO	fat mass and obesity-associated
OR	odds ratio
T2D	type 2 diabetes

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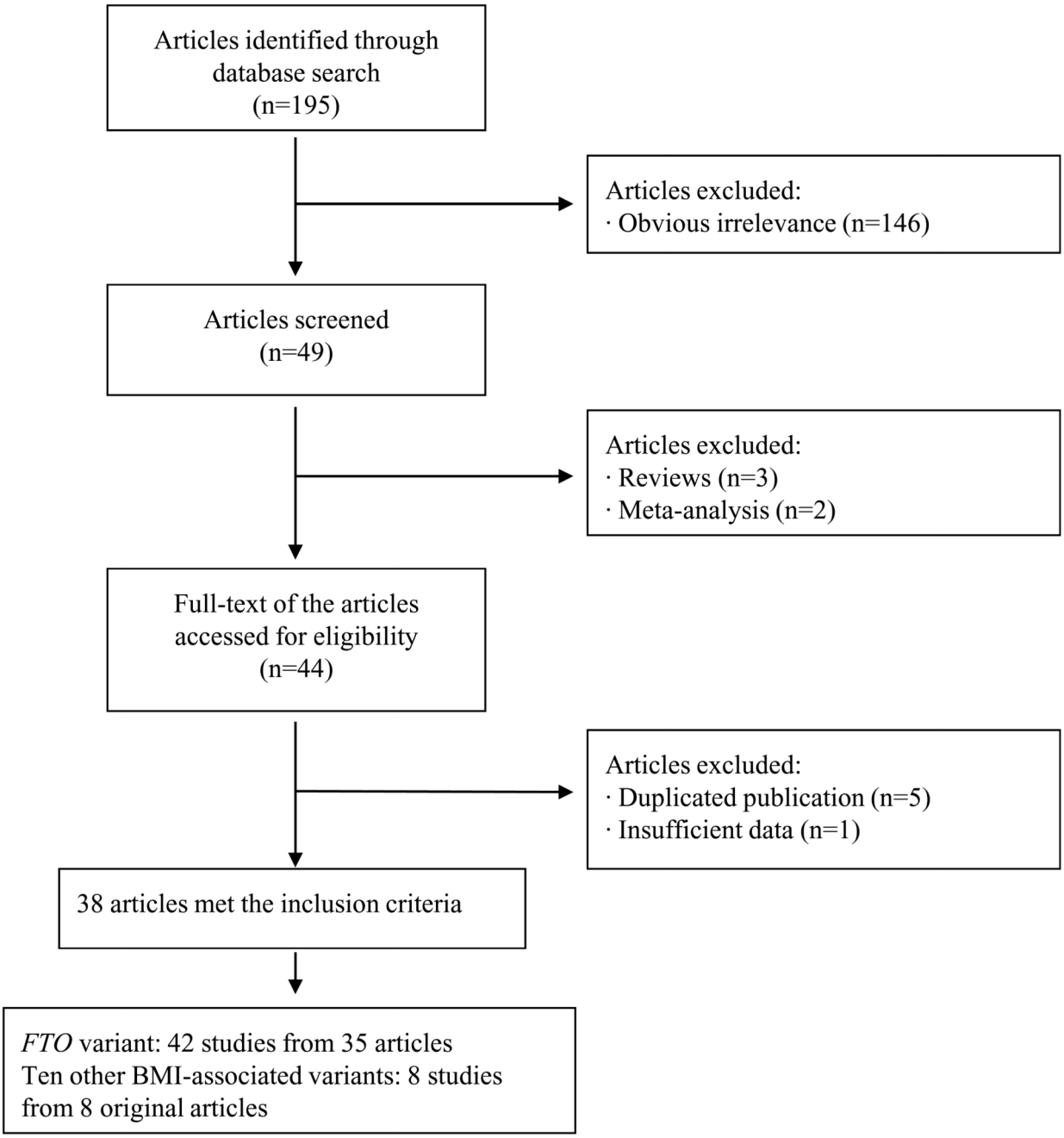

Figure 1.
Flow chart of exclusion/inclusion of individual articles (or studies) for meta-analysis

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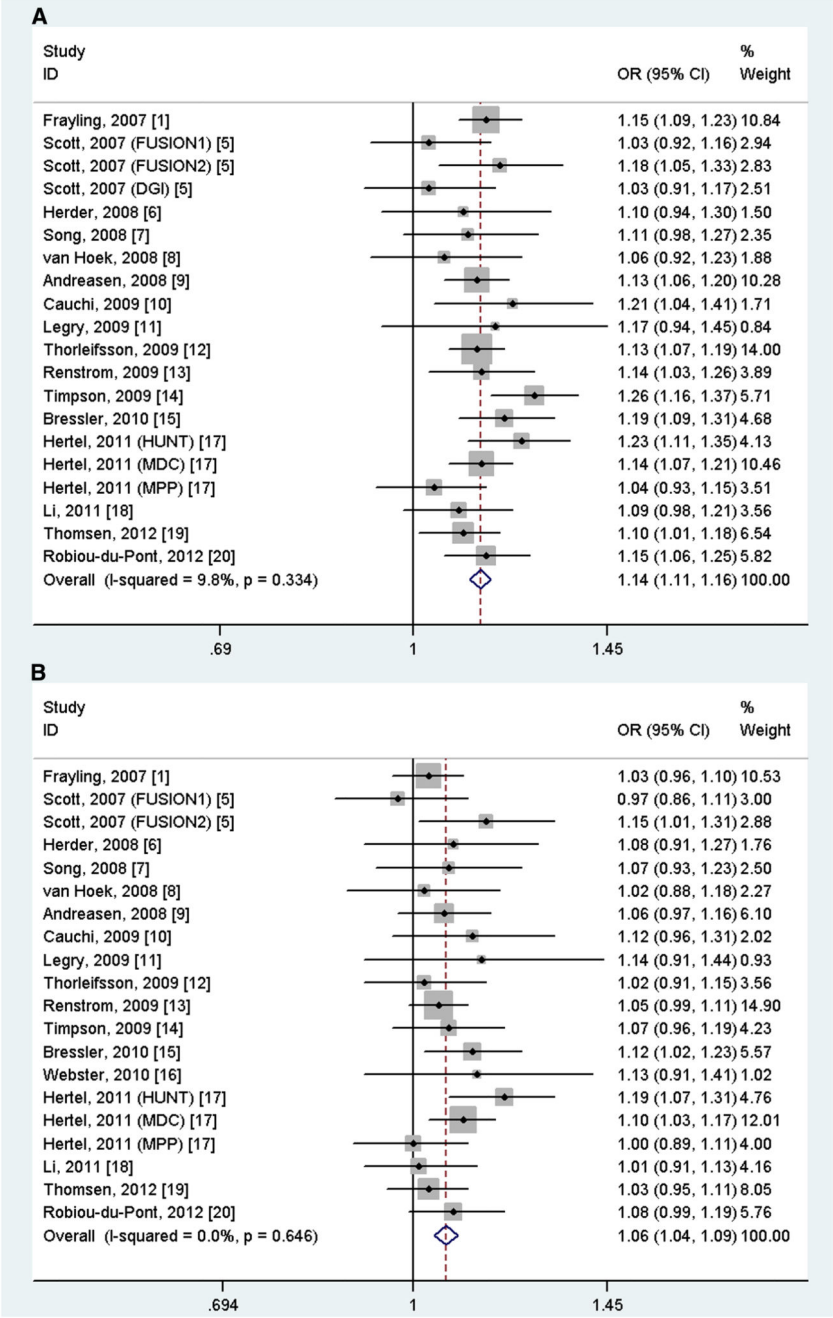

Figure 2.

Meta-analysis of the association between *FTO* rs9939609 variant and type 2 diabetes (A) without and (B) with adjustment for body mass index

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Table 1

Meta-analysis of BMI-associated gene variants and type 2 diabetes risk based on ethnicity

Gene/SNP	No. of studies (cases/ controls)	OR (95%CI) without BMI adjustment	P_z [a]	Effect model	I^2 (%)	P_H [b]	OR (95%CI) with BMI adjustment	P_z [a]	Effect model	I^2 (%)	P_H [b]
All											
FTO rs9939609	42 (66,425/239,689)	1.14 (1.12-1.16)	1.00×10^{-41}	Fixed	5.7	0.386	1.07 (1.05-1.09)	6.42×10^{-41}	Fixed	0.0	0.576
SH2B1 rs7498665	7 (24,063/68,660)	1.08 (1.05-1.12)	2.28×10^{-7}	Fixed	43.5	0.101	1.06 (1.02-1.09)	8.71×10^{-4}	Fixed	24.1	0.245
FAIM2 rs7138803	6 (23,025/64,775)	1.08 (1.05-1.11)	1.35×10^{-7}	Fixed	0.0	0.723	1.05 (1.02-1.08)	0.001	Fixed	0.0	0.728
TMEM18 rs7561317	8 (27,531/130,001)	1.13 (1.06-1.21)	4.47×10^{-4}	Random	62.4	0.009	1.08 (1.00-1.17)	0.051	Random	68.2	0.003
GNPDA2 rs10938397	6 (20,187/40,629)	1.07 (1.03-1.10)	5.86×10^{-5}	Fixed	5.8	0.379	1.04 (1.01-1.08)	0.021	Fixed	40.5	0.136
BDNF rs925946	6 (23,025/64,775)	1.06 (1.03-1.10)	1.08×10^{-4}	Fixed	28.1	0.224	1.02 (0.97-1.07)	0.525	Random	50.7	0.071
NEGR1 rs2568958	7 (18,953/67,646)	1.04 (1.01-1.08)	0.015	Fixed	43.3	0.102	1.03 (0.94-1.06)	0.158	Fixed	2.1	0.409
SEC16B rs10913469	6 (23,025/64,775)	1.00 (0.97-1.04)	0.938	Fixed	0.0	0.468	0.97 (0.93-1.00)	0.062	Fixed	38.7	0.147
KCTD15 rs29941	7 (24,063/68,660)	1.02 (0.99-1.05)	0.245	Fixed	0.0	0.754	1.01 (0.97-1.04)	0.738	Fixed	0.0	0.988
ETV5 rs7647305	6 (17,915/63,761)	1.05 (0.98-1.12)	0.202	Random	56.5	0.042	1.02 (0.95-1.10)	0.544	Random	55.8	0.046
MTCH2 rs10838738	6 (20,187/40,629)	1.00 (0.97-1.16)	0.999	Fixed	19.3	0.288	1.00 (0.95-1.05)	0.883	Random	46.5	0.096
Europeans											
FTO rs9939609	21 (32,681/196,140)	1.14 (1.11-1.16)	1.36×10^{-36}	Fixed	9.8	0.334	1.06 (1.04-1.09)	3.51×10^{-8}	Fixed	0.0	0.646
SH2B1 rs7498665	5 (11,269/59,661)	1.09 (1.05-1.13)	2.45×10^{-6}	Fixed	38.9	0.162	1.06 (1.02-1.10)	0.003	Fixed	32.1	0.207
FAIM2 rs7138803	4 (10,231/55,776)	1.08 (1.05-1.13)	1.69×10^{-5}	Fixed	0.0	0.557	1.05 (1.01-1.10)	0.008	Fixed	0.0	0.452
TMEM18 rs7561317	6 (14,737/121,002)	1.14 (1.05-1.24)	0.003	Random	66.8	0.010	1.08 (0.98-1.18)	0.133	Random	69.2	0.006
GNPDA2 rs10938397	4 (7,393/31,630)	1.06 (1.01-1.11)	0.020	Fixed	35.4	0.200	1.03 (0.95-1.12)	0.414	Random	56.6	0.075
BDNF rs925946	4 (10,231/55,776)	1.04 (1.00-1.09)	0.065	Fixed	37.7	0.186	1.00 (0.96-1.04)	0.903	Fixed	43.2	0.152
NEGR1 rs2568958	5 (11,269/59,661)	1.06 (1.02-1.10)	0.002	Fixed	0.0	0.787	1.03 (1.00-1.07)	0.072	Fixed	0.0	0.740
SEC16B rs10913469	4 (10,231/55,776)	0.97 (0.93-1.02)	0.225	Fixed	0.0	0.807	0.93 (0.88-0.97)	0.002	Fixed	0.0	0.566
KCTD15 rs29941	5 (11,269/59,661)	1.01 (0.97-1.05)	0.597	Fixed	0.0	0.866	1.00 (0.96-1.04)	0.998	Fixed	0.0	0.954
ETV5 rs7647305	4 (10,231/55,776)	1.03 (0.94-1.13)	0.483	Random	69.6	0.020	1.00 (0.92-1.08)	0.910	Random	54.7	0.085
MTCH2 rs10838738	4 (7,393/31,630)	1.03 (0.99-1.08)	0.174	Fixed	0.0	0.845	1.02 (0.96-1.07)	0.557	Fixed	12.1	0.332
East Asians											
FTO rs9939609	15 (27,401/31,708)	1.15 (1.09-1.22)	2.43×10^{-7}	Fixed	40.0	NA	1.11 (1.05-1.17)	3.0×10^{-4}	Fixed	35.9	NA
SH2B1 rs7498665	2 (12,794/8,999)	1.11 (0.95-1.30)	0.179	Random	74.6	0.049	1.05 (0.99-1.12)	0.130	Fixed	50.0	0.157

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Gene/SNP	No. of studies (cases/ controls)	OR (95%CI) without BMI adjustment	P_z [a]	Effect model	I^2 (%)	P_H [b]	OR (95%CI) with BMI adjustment	P_z [a]	Effect model	I^2 (%)	P_H [b]
FAIM2 rs7138803	2 (12,794/8,999)	1.07 (1.02-1.11)	0.002	Fixed	0.0	0.479	1.05 (1.00-1.09)	0.058	Fixed	0.0	0.733
TMEM18 rs7561317	2 (12,794/8,999)	1.11 (0.95-1.29)	0.175	Random	66.1	0.086	1.10 (0.97-1.26)	0.133	Random	52.5	0.147
GNPDA2 rs10938397	2 (12,794/8,999)	1.08 (1.03-1.13)	0.001	Fixed	0.0	0.589	1.06 (1.01-1.12)	0.015	Fixed	0.0	0.617
BDNF rs925946	2 (12,794/8,999)	1.09 (1.04-1.14)	0.001	Fixed	0.0	0.633	1.07 (1.01-1.12)	0.006	Fixed	0.0	0.481
NEGR1 rs2568958	2 (7,684/7,985)	0.92 (0.83-1.02)	0.106	Fixed	54.8	0.137	0.95 (0.85-1.06)	0.351	Fixed	51.1	0.153
SEC16B rs10913469	2 (12,794/8,999)	1.04 (0.99-1.09)	0.154	Fixed	0.0	0.733	1.01 (0.96-1.07)	0.610	Fixed	0.0	0.791
KCTD15 rs29941	2 (12,794/8,999)	1.03 (0.98-1.08)	0.223	Fixed	42.6	0.187	1.01 (0.96-1.07)	0.593	Fixed	0.0	0.761
ETV5 rs7647305	2 (7,684/7,985)	1.10 (0.98-1.24)	0.116	Fixed	4.0	0.307	1.15 (1.01-1.30)	0.039	Fixed	20.5	0.262
MTCH2 rs10838738	2 (12,794/8,999)	0.97 (0.93-1.02)	0.196	Fixed	45.9	0.174	0.98 (0.88-1.08)	0.627	Random	64.1	0.095
South Asians											
FTO rs9939609	6 (6,271/11,841)	1.13 (1.03-1.24)	0.01	Random	54.6	NA	1.10 (1.00-1.21)	0.05	Random	55.6	NA

Notes : OR, odds ratio; CI, confidence interval; NA, not available

[a] *P* value for Z test

[b] *P* value for x^2-based Q test (If *P*<=0.10, the random effect model was used; otherwise, the fixed effect model was applied)