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The effect of rs9930506 FTO gene polymorphism on obesity risk: a meta-analysis

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Abstract: Obesity is associated with polymorphisms of the fat mass and obesity associated gene (FTO). This meta-analysis aimed to investigate the association of the rs9930506 FTO gene polymorphism and obesity. To the best of our knowledge, this study is the first meta-analysis to evaluate the relation between FTO rs9930506 polymorphism and obesity.

We searched PubMed, Web of Science, and Embase to identify studies investigating the relations between the rs9930506 FTO gene polymorphism and obesity risk. We pooled adjusted odds ratios (OR) as overall and in continent subgroups. A Fixed-effects model was used to analyze the results of these studies in dominant and recessive models.

By examining 3337 obesity cases and 3159 healthy controls, we identified 8 eligible case-control studies. Considering the dominant model of inheritance, there was a relationship between the rs9939506 polymorphism and obesity (OR=1.34 [1.03- 1.74]). The association remained significant in the European subgroup (OR=1.68 [1.2-2.36]), but not in the Asian subgroup. Using the recessive model, we also found a significant relationship when the overall association was investigated (OR=2.47; 95% CI 1.56-3.91). In conclusion, this study identified that the carriers of the risk allele of FTO rs9930506 polymorphism are at higher risk for obesity.

Keywords: Obesity, FTO, polymorphism, rs9930506

Abbreviations

FTO: Fat mass and Obesity gene
BMI: Body mass index
HWE: Hardy-Weinberg Equilibrium
IRX3: Iroquois-related homeobox 3

Introduction

Prevalence of obesity is rising around the world and presently obesity is a worldwide health-related problem [1]. More than one-third of adults (34.9 %) and 16.9 % of 2 to 19 year-olds in the United States are obese [2]. Obesity *may increase the risk of many diseases,* such as cardiovascular disease, type 2 diabetes, cancers, hypertension, and dyslipidemia. Various factors have been implemented in the formation and progression of obesity [3]. Genetics, behavioral and environmental effects are among the most important factors associated with the risk of obesity [3, 4]. Several studies have identified a relationship between the Fat mass and obesity gene (FTO) and obesity, highlighting it as a gene of interest for obesity research [5-6]. The FTO gene is highly expressed in the hypothalamus, visceral fat and liver. It contributes to an inflammatory state, food intake and appetite [6, 7].

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Several polymorphisms of the FTO gene including rs178117449, rs9939609, rs3751812, rs1421085, rs9930506, and rs7202116 have been associated with obesity [8]. FTO rs9930506 polymorphism is reported to have a strong effect on body weight, BMI, and body composition [6, 7].

The expression of the FTO gene is related to the regulation of food intake [8] and carriers of the obesity risk allele of FTO had higher food intake and appetite for high- calorie foods [9]. Moreover, in carriers of obesity risk allele of FTO, fat cell lipolysis is reduced, indicating the possible primary role of FTO gene in fat metabolism [10]

Until recently, only a few studies have investigated the association between FTO rs9930506 and obesity, which reported inconsistent results. For example, one study found that variants in FTO gene were not associated with obesity in a Chinese Han population [18]. Therefore, we carried out a systematic review and meta-analysis to investigate the association of FTO rs9930506 polymorphism with obesity.

Methods

Publication search

We systematically searched literatures in PubMed, Embase, and Web of Science databases up to February 2019 for studies concerning the association between rs9930506 FTO polymorphism and obesity (or obesity-related traits including body weight, fat mass, and BMI). The search was not limited by language. Our search strategy consisted of terms related to polymorphism (Mesh term "Polymorphism, Single Nucleotide") combined with specific terms for obesity (Mesh term "obesity"). The keywords including (FTO OR fat mass and obesity-associated gene OR rs9930506) AND ((obesity associated gene) OR (FTO) OR (rs9930506)) AND ((Polymorphism) OR (variant) OR (variation) OR (genotype)) AND (obesity) were used to search. Further assessment was performed with hand search of references of eligible studies and meta-analyses.

Inclusion and exclusion criteria

Studies included in this meta-analysis comprised the following criteria: 1) studies investigating the relations between obesity risk and rs9930506 polymorphism. 2) Studies with case-control design, 3) the cases were obese and the controls were healthy subject, 3) Sufficient data available to calculate odds ratio (OR) with a confidence interval (CI) of 95%. Exclusion criteria were: 1) Studies with no control group, 2) all type of letters to editors, commentary, and editorial, animal studies, case reports, and case series, 3) studies in which the control subjects violated the Hardy-Weinberg Equilibrium (HWE).

Data extraction

Two reviewers (SD and MGh) independently searched the databases and extracted the required data using a standardized form. Information on author name, country, ethnicity, year of publication, mean age, mean BMI, source of controls (population based or hospital based) and odds ratios (OR) and their reported 95% confidence interval for homozygote, heterozygote, recessive and dominant models were retrieved. P-values of the HWE were calculated from the above genotype data. The search results were then evaluated by four reviewers (SAMJ, GAT, ASM, MB) and disagreements were resolved by discussions among the reviewers. For adults, subjects with BMI ≥30 kg/m^2 were defined as case subjects of obesity, and individuals with BMI <30 kg/m^2 were considered control subjects. For children, the WHO criteria for childhood obesity was adopted [11].

Quality assessment

Four methodological components which may bias the association between FTO gene polymorphism and risk of obesity were assessed: (1) source of control group, (2) ethnicity, (3) Hardy-Weinberg Equilibrium among controls, and (4) sample size.

Statistical analysis

The overall effects were calculated in dominant and recessive genetic models in this meta-analysis. The effect sizes were calculated by both fixed and random-effect models. Heterogeneity across studies was assessed using Q and I^2 statistics. An I^2 value above 75% at a significance level of <0.1 was considered a statistically significant heterogeneity. Publication bias and small study effect were assessed with the Egger's test and contour-enhanced funnel plot. The contour-enhanced funnel plot makes it easier to assess the statistical significance of the hypothetical missing studies. We assessed the measure of association for GG vs A/G+A/A (recessive), and G/G+A/G vs A/A (dominant)).

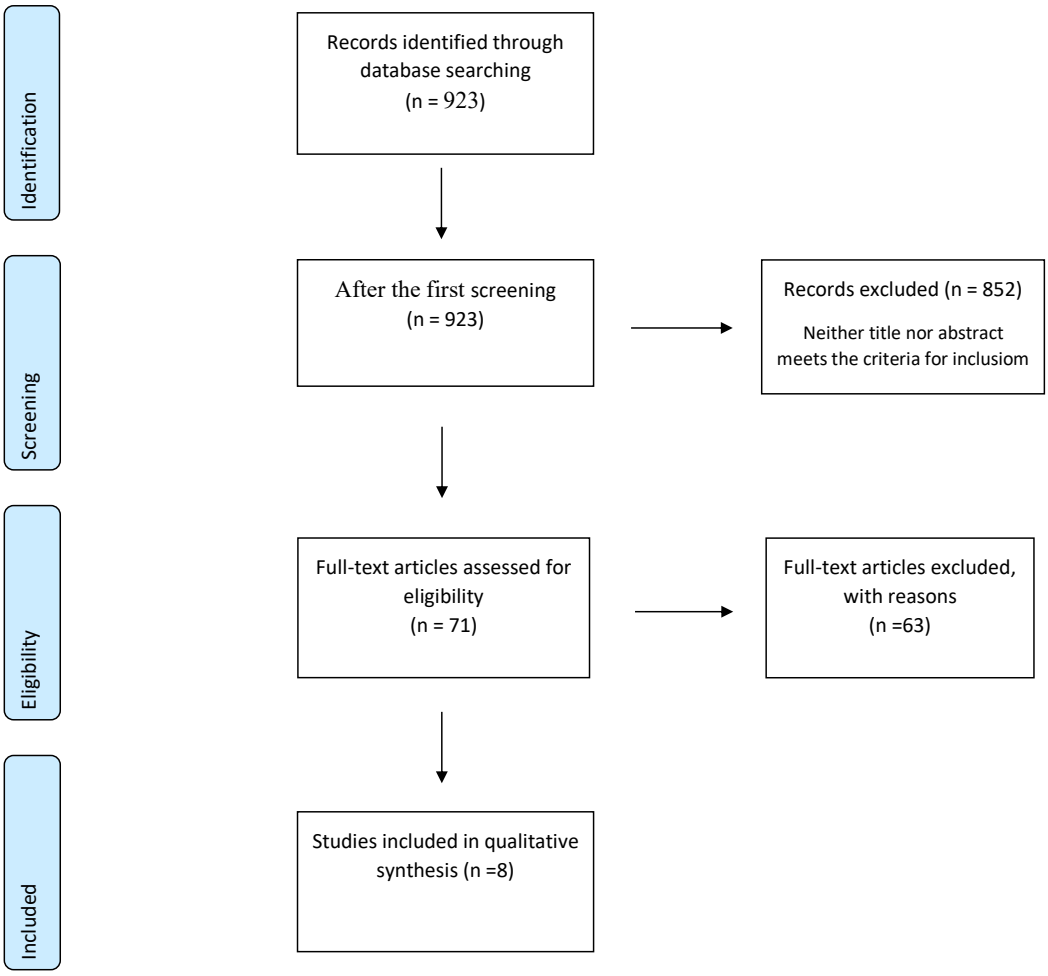

Figure 1: Flow diagram. Literature selection flow diagram according PRISMA guideline

In addition to overall analysis (where all groups were combined), subgroup analysis was performed for continent subgroups (Asian and European). All analyses were performed using Stata version 13 (Stata Corp LP, College Station, TX, USA).

Results

Characteristics of the included studies

According to the search strategy, a total of 923 articles were retrieved from databases. After the first screening, in which the titles and abstracts were reviewed for relevance, 852 articles were excluded. After reviewing full text of these articles, 63 additional articles were excluded, which left total of 8 articles for inclusion in this meta-analysis (3337 obesity cases and 3159 healthy controls) according to the PRISMA guidelines [12], the flow diagram is shown in Figure 1.

Dominant model

Considering the dominant model of inheritance, there was a relationship between the rs9930506 polymorphism and obesity (OR 1.34 [1.03- 1.74]). There was observable heterogeneity (I^2: 74.8%, P=.001) and small study effect (b=2.87, P=.01) in this analysis. The association remained significant in European subgroup (OR 1.68 [1.2-2.36]), but not in Asian subgroup (Figure 2, 3).

Recessive model

Regarding the recessive model, five studies reported adjusted or there was observable heterogeneity (I^2:

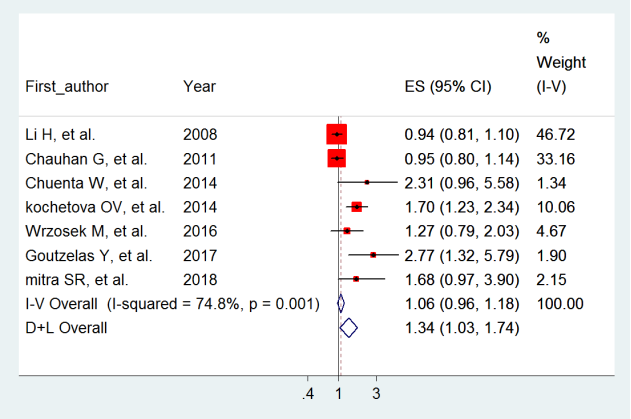

Figure 2: Forest plot of association between FTO rs9930506 polymorphism and the risk of obesity [dominant model GG + AG vs AA]

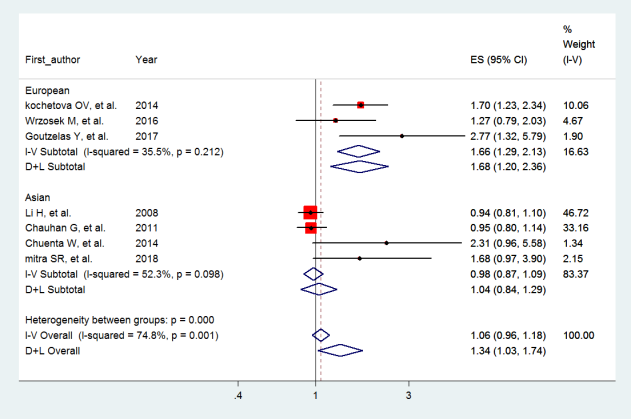

Figure 3: Forest plot of association between FTO rs9930506 polymorphism and the risk of obesity in Asian and European subgroups [dominant model GG + AG vs AA].

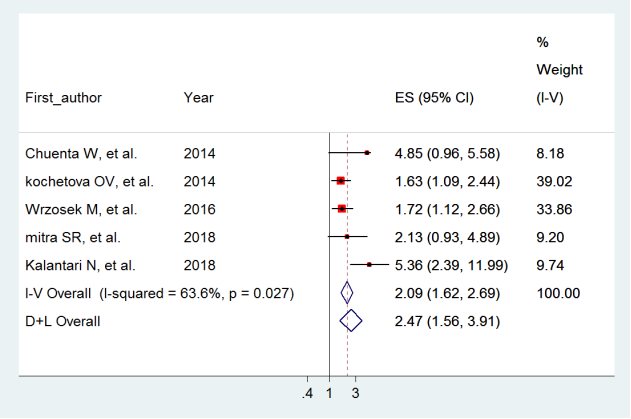

Figure 4: Forest plot of association between FTO rs9930506 polymorphism and the risk of obesity [recessive model GG vs AG + AA].

63.6%, P=.027), but Egger's test provided no evidence of publication bias (b=3.82, P=.062) in the analysis of this model. Overall, a significant association was seen in the recessive model (OR 2.47 [1.56-3.91]) (Figure 4).

Discussion

To our knowledge, this is the first meta-analysis to investigate the association between rs9930506 FTO polymorphism and obesity risk. This meta-analysis investigated the associations between FTO rs9930506 polymorphism and obesity risk in 3337 cases and 3159 controls. We found significant evidence for a modest increase in the risk allele carriers in various ethnic populations. Some studies have reported that FTO polymorphisms plays a key role in regulating body weight and BMI [13-19]. The FTO rs9930506 polymorphism is located in intron 1 and carriers of G allele are at higher risk of obesity [20-21]. Some Studies reported that FTO polymorphisms play a critical role in food intake and energy expenditure [22-24]. However, it seems that the effects of FTO gene on body weight, body fat and body composition can be independent of food intake and energy expenditure, since this association remained significant after adjustments for physical activity and food intake [25].

Several meta-analyses have been conducted on the FTO polymorphisms and obesity risk [26-28]. Quan et al reported that homozygous risk allele carrier's rs9939609 polymorphism increased obesity risk in children and adolescents [28]. Wardle et al found that FTO variants could impair satiety control thus have influence on appetite and adiposity [29]. Another meta-analysis was found that FTO polymorphisms are associated with obesity in the Chinese population [30].

The exact molecular mechanism of FTO on obesity, body weight and BMI is not clear yet. Recently, it is reported that FTO genotype had a strong association with obesity through changing the expression level of Iroquois-related homeobox 3 (IRX3) gene [31]. IRX3 is a member of the Iroquois homeobox gene family and it was known to play an important role in the early step of neural development [32, 33]. The expression level of IRX3 in hypothalamus could be related to energy intake. It has been demonstrated that the IRX3 gene is controlled by a sequence of intron 1 of the FTO gene and polymorphisms in this intron can influence the expression level of IRX3 [26].

Limitations

Our results may demonstrate a relationship between FTO rs9930506 polymorphism and obesity risk. However, the exact pathways by which FTO rs9930506 polymorphism is associated with obesity are not specified yet and require further investigations.

Conclusion

This meta-analysis demonstrated that the FTO gene is associated with the risk of obesity. FTO rs9930506 polymorphism has a strong relation to obesity. Further studies are needed to increase our understanding of the association between FTO rs9930506 polymorphism and obesity.

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Ethics approval: The conducted research is not related to either human or animals use.

Availability of data and material: Not applicable

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