FTO Polymorphisms Are Associated with Obesity But Not with Diabetes in East Asian Populations: A Meta-analysis

BO XI[#,+] AND JIE MI[+]

[#]*Graduate School, Peking Union Medical College, Beijing 100730, China*; [+]*Department of Epidemiology, Capital Institute of Pediatrics, Beijing 100020, China*

Objective To clarify the contradictory findings in patients with obesity and type 2 diabetes by meta-analysis. **Methods** PubMed and Embase were searched for articles published up to March 2009. All studies on the association of FTO polymorphisms with obesity and type 2 diabetes were included. Pooled odds ratio was calculated using the model of fixed or random effects. Sensitivity analysis was performed to evaluate the stability of meta-analytic results. **Results** Meta-analysis suggested that rs9939609 A allele was more significantly associated with obesity risk than T allele (3 studies / 2 004 cases and 4 544 control subjects): random effect odds ratio (OR)=1.28, 95%CI=1.05 and 1.55, $P_{\text{heterogeneity}}$ =0.05, I^2=66.6%. Similar results were observed in rs8050136 polymorphism (3 studies/2 404 cases and 5 713 control subjects): fixed effect OR =1.25, 95%CI=1.13, 1.37, $P_{\text{heterogeneity}}$=0.12, I^2=51.9%. However, no significant association was found between genetics and risk of type 2 diabetes after control of potential confounders (at least for BMI) either for rs9939609 (fixed effect OR=1.05, 95% CI=0.97,1.13) or for rs8050136 polymorphism (fixed effect OR =1.07, 95%CI: 0.99, 1.16). Furthermore, the sensitivity analysis strengthened our confidence in validity of the association. **Conclusion** FTO polymorphisms are associated with obesity but not with type 2 diabetes in East Asian populations. Further large-scale studies are required to conclusively establish the association.

Key words: FTO; Polymorphism; Obesity; Type 2 diabetes; Meta-analysis

INTRODUCTION

Human obesity and type 2 diabetes (T2D) place significant and growing burdens on society through their impact on morbidity and mortality[1]. Genome-wide association (GWA) studies have improved our understanding of the genetic basis of common and complex diseases, such as obesity and T2D. The FTO gene on chromosome 16q12.2 has been identified as a susceptible locus for obesity and type 2 diabetes. The association of FTO polymorphisms with T2D has been fully explained by linking FTO polymorphisms with BMI[2-3]. However, the association needs to be confirmed by further replicable studies, particularly in other ethnic populations. Up to date, the findings are somewhat inconsistent in East Asians[4-6]. Given the lower allele frequency risk and the relatively leaner body build of T2D patients in East Asian populations, a larger sample size is needed to detect the association of FTO polymorphisms with T2D[7]. It has been demonstrated that meta-analysis could pool samples from several studies and produce a greater power. Furthermore, it can identify the causative genes and quantify the genetic risks. Therefore, meta-analysis of all available published studies on the association of FTO polymorphisms with obesity and T2D in East Asian populations was performed.

MATERIALS AND METHODS

Search Strategy

All studies on the association of FTO polymorphisms with obesity or T2D in East Asian populations published before March 2009 were included in meta-analysis. The studies were searched from PubMed and Embase. As a search criterion, various combinations of terms, including FTO, polymorphism*, variant*, BMI, obesity, T2D, and Asians, were used. References in the retrieved articles were screened. There were no language restrictions. Abstracts, case reports, editorials, and reviews were excluded. Studies included in the

Correspondence should be addressed to: Dr. Jie MI, Department of Epidemiology, Capital Institute of Pediatrics, No. 2 Yabao Road, Chaoyang District, Beijing 100020, China. Tel: 86-10-8569-5591; Fax: 86-10-8563-2799; E-mail: jiemi@vip.163.com

Biographical note of the first author: Bo XI, male, born in 1980, Doctor of Public Health at Peking Union Medical College, majoring in epidemiology. E-mail: swei006@163.com

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current meta-analysis must meet the following criteria: using case-control design; giving information about the distribution of FTO genotypes in both obese and T2D cases and corresponding controls, in Hardy-Weinberg equilibrium (HWE) of controls; providing odds ratio or sufficient data for calculation in East Asian populations.

Data Extraction

Data were independently abstracted in duplicate by two investigators using a standard protocol and data-collection form. From each study, the following information was extracted, which included: first author's last name, year of publication, country and ethnicity of the population studied, characteristics/ selection criteria of the subjects and their number, odds ratio (OR) and 95% confidence interval, control of confounding factors by matching or adjustment. Information was not always provided for all the named categories. Disagreements were solved in consensus meetings.

Statistical Analysis

For each study, OR of the most adjusted model was used to estimate a pooled OR obtained by combinations of study-specific ORs using the model of fixed effects (Mantel-Hasnszel) or the model of random effects (Der Simonian and Laird). Random effect model is more appropriate when heterogeneity appears. Significance of the pooled OR was determined by Z test (P<0.05). Chi-square based Q statistic test was performed to assess the inter-study heterogeneity, which was considered significant when P was less than 0.10. Heterogeneity was quantified with the I^2 statistic, which is independent of the number of studies in meta-analysis. I^2 takes a value of 0%-100% with a higher value denoting a greater degree of heterogeneity.

Publication bias was investigated by funnel plot, in which the standard error of log (OR) of each study was plotted against its OR. An asymmetric plot suggested possible publication bias. Sensitivity analysis was performed to evaluate the stability of meta-analytic results. In this analysis, the overall homogeneity and effect size were calculated after some studies were removed. All analyses were carried out with Review Manager software version 4.2 (Cochrane Collaboration, Copenhagen, Denmark).

RESULTS

Eligible Studies

Publications were retrieved based on the searching criteria for obesity susceptibility related to FTO polymorphisms, and four articles met our inclusion criteria, two of which[5,8] did not provide detailed characteristics of case and control subjects. Of the four articles, two in Chinese[5,7], one in both Chinese and Korean[8], and the other one in Japanese[9] (Table 1).

Regarding T2D related to FTO polymorphisms, seven articles met our inclusion criteria. Of these articles, one did not provide detailed characteristics of case and control subjects[5]; three were in Japanese[4, 10-11], two in Chinese[5,7], one in Korean[6]; and one in both Chinese and Korean[8], five claimed that T2D was diagnosed according to World Health Organization (WHO) criteria[4-5, 8, 10-11] and two claimed that T2D was diagnosed following the guidelines of the American Diabetes Association[6-7]. Data extracted from the seven articles included in meta-analysis are presented in Table 2.

Meta-analysis

The present meta-analysis included three studies on rs9939609 polymorphism with 2004 obese cases and 4544 control subjects, and three studies on rs8050136 polymorphism with 2404 cases and 5713 control subjects. In investigating the association of rs9939609 A allele with risk of obesity (but not with T allele), meta-analysis showed strong evidence for inter-study heterogeneity ($P_{\text{heterogeneity}}$=0.05, I^2=66.6 %) in the three studies[5,7,9]. Therefore, the random effect model was used to pool the results (Fig. 1A). The pooled OR was 1.28 (95%CI=1.05, 1.55), indicating that rs9939609 A allele was responsible for obesity in East Asian populations. Similarly, a rs8050136 A/C polymorphism was significantly associated with obesity risk in these populations: fix effect OR=1.25 (95%CI=1.13, 1.37) (Fig. 1B), and heterogeneity between studies was not significant ($P_{\text{heterogeneity}}$=0.12, I^2=51.9%)[5, 8-9].

Analysis of five studies comprising 5517 T2D cases and 6186 control subjects showed that rs9939609 A allele was not associated with T2D risk compared with T allele: fixed effects OR=1.05, 95% CI:0.97, 1.13. There was no evidence of inter-study heterogeneity ($P_{\text{heterogeneity}}$=0.69, I^2=0%)[4-5,7,10-11] (Fig. 2A). Similar result was observed for rs8050136 polymorphism, consisting of five studies (6 824 T2D and 8 007 control subjects), fixed effects OR=1.07, 95%CI: (0.99, 1.16); $P_{\text{heterogeneity}}$=0.18, I^2=36.3%[4-6,8,10] (Fig. 2B). Sensitivity analysis was performed by omitting some studies to evaluate the stability of meta-analytic results. In meta-analysis of the studies for rs9939609 polymorphisms, (when the study of Chang *et al.*[7] was exduded,) the inter-study homogeneity ($P_{\text{heterogeneity}}$=0.52, I^2=0%) remained and

TABLE 1

Background Information Concerning the Studies on Obesity

Study	SNPs	Country	Racial Descent	Selection/Characteristics of Cases	Selection/Characteristics of Controls	Adjustment for Confounders
Li, 2008[5]	rs9939609 rs8050136	China	Chinese	Obesity Was Defined as BMI ⩾28 kg/m^2 According to the Chinese Criteria *N.A.*	Normal Weight was Defined as BMI<24 kg/m^2 According to the Chinese Criteria *N.A.*	1,2,3
Chang, 2008[7]	rs9939609	China	Chinese	Obesity Was Defined as BMI⩾30kg/m^2. 638 Patients (M/F=219 /419); Age: 37.00±0.56 Years; BMI: 38.86±8.19 kg/m^2	Non-obesity Was Defined as BMI<30kg/m^2 1 610 Controls (M/F=822 /788); Age: 61.08 ± 0.33 Years; BMI: 24.04± 2.89 kg/m^2	1,2
Ng, 2008[8]	rs8050136	China and Korea	Chinese & Korean	Obesity Was Defined as BMI⩾25 kg/m^2 *N.A.*	Normal Weight was Defined as BMI<25 kg/m^2 *N.A.*	1,2
Hotta, 2008[9]	rs9939609 rs8050136	Japan	Japanese	Severe Adult Obesity Was Defined as BMI ⩾30 kg/m^2 927 Patients (M/F= 419/508); Age: 48.7±14.2 Years; BMI 34.2±5.4 kg/m^2	Normal-weight Controls Was Defined as BMI<25 kg/m^2 1 527 Controls (M/F= 685/842); Age: 48.1 ±16.5 Years; BMI 21.7 ± 2.1 kg/m^2	1,2

Note. *N.A.* information was not available; 1 age; 2 sex; 3 region; 4 BMI; 5 study population.

TABLE 2

Background Information Concerning the Studies on Type 2 Diabetes

Study	SNPs	Country	Racial Descent	Selection/Characteristics of Cases	Selection/Characteristics of Controls	Adjustment for Confounders
Horikoshi, 2007[4]	rs9939609 rs8050136	Japan	Japanese	T2D Was Diagnosed with WHO Criteria.	The Inclusion Criteria for Control Subjects Were as Follows: (1) >60 Years of Age; (2) HbA_{1c} Values <5.6%; and (3) No Family History of Type 2 Diabetes in First- and Second-degree Relatives	1,2,4
				864 Patients (M/F=535/329);	864 Controls (M/F=386/478)	
				Age: 63.1±9.5 Years	Age: 69.5±6.8 Years	
				BMI: 24.3±3.9 kg/m^2	BMI: 23.8±3.7 kg/m^2	
				FPG: *N.A.*	FPG: 5.13±0.74 mmol/L	
Li, 2008[5]	rs9939609 rs8050136	China	Chinese	T2D Was Diagnosed with WHO Criteria or Self-report of Being Previously Diagnosed as Diabetic or Treated with Medication for Diabetes Confirmed by Medical Record Review	Control Subjects Were Normal Fasting Glucose, Which Was Defined as Fasting Glucose <5.6 mmol/L (100 mg/dL)	1, 2, 3, 4
				N.A.	*N.A.*	
Lee, 2008[6]	rs8050136	Korea	Korean	T2D Was Diagnosed with the Criteria of the American Diabetes Association. Patients Were Excluded if They Were Positive for the Glutamic acid Decarboxylase Antibody	The Control Subjects Comprised of the Population with Normal Glycemia from Subjects Receiving physical Check-ups and Non-diabetic Patients Receiving Regular Follow ups	1, 2, 4
				908 Patients (M/F=439/469);	502 Controls (M/F=269/233)	
				Age: 58.2±11.1 Years	Age: 55.0±9.4 Years	
				BMI: 24.3±3.2 kg/m^2	BMI: 22.1±3.0 kg/m^2	
				FPG: 7.5±2.2 mmol/L	FPG: 5.1±1.0 mmol/L	

(to be continued)

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Study	SNPs	Country	Racial Descent	Selection/Characteristics of Cases	Selection/Characteristics of Controls	Adjustment for Confounders
Chang, 2008[7]	rs9939609	China	Chinese	Type 2 Diabetes Was Diagnosed with the Criteria of the American Diabetes Association. T2D Patients with Ages of Onset <35 Years Were Excluded.	Control Subjects Were Normal Glucose Tolerance, Which Was Confirmed with a 75-g Oral Glucose Tolerance Test.	1,2,4
				759 Cases (M/F=381/378);	784 Controls (M/F= 438/346);	
				Age: 60.03±11.85 Years;	Age: 63.37±14.0 Years;	
				BMI: 24.66±3.40 kg/m^2;	BMI: 23.63±3.08 kg/m^2;	
				FPG: *N. A.*	FPG: *N. A.*	
Ng, 2008[8]	rs8050136	China and Korea	Chinese & Korean	Hong Kong	Hong Kong	1,2,4,5
				T2D Was Diagnosed with WHO Criteria	Control Subjects Defined as Normal Glucose Tolerance (Fasting Plasma Glucose [FPG] <6.1 mmol/L)	
				Korea SNUH and Korea KHGS:	Korea SNUH:	
				T2D Was Diagnosed with WHO Criteria	The Inclusion Criteria for Control Subjects Were as Follows: (1) ⩾60 Years Old; (2) No History of Diabetes; (3) No First-degree Relatives with Diabetes; (4) FPG <6.1 mmol/L, and (5) A1C <5.8%.	
					Korea KHGS:	
					Control Subjects Were Sex- and Age-matched with Cases without Family History of Diabetes and with Normal Glucose Level at OGTT (FPG <7 mmol/L and 2-h Plasma Glucose <7.8 mmol/L)	
				Hong Kong:	Hong Kong:	
				1 481 Cases (M/F=598/883);	1 530 Controls (M/F= 703/827);	
				Age: 49.7±13.7 years;	Age: 25.3±14.4 Years;	
				BMI: 25.1±4.2 kg/m^2;	BMI: 21.0±3.7 kg/m^2;	
				FPG: *N.A.*	FPG: 4.8±0.4 mmol/L	
				Korea SNUH:	Korea SNUH:	
				761 Cases (M/F=761/632);	632 Controls (M/F= 287/345);	

(to be continued)

(continued)

Study	SNPs	Country	Racial Descent	Selection/Characteristics of Cases	Selection/Characteristics of Controls	Adjustment for Confounders
				Age: 59.2± 9.9 Years; BMI: 24.5±2.9 kg/m^2; FPG: *N.A.* Korea KHGS: 799 Cases (M/F= 428/371); Age: 56.1±8.6 Years; BMI: 25.5±3.3 kg/m^2; FPG: *N.A.*	Age: 64.7±3.6 Years; BMI: 23.6±3.1 kg/m^2; FPG: 4.9±0.5 mmol/L. Korea KHGS: 1 516 Controls (M/F= 805/711); Age: 55.8± 8.7 Years; BMI: 24.2±3.2 kg/m^2; FPG: 4.6±0.4 mmol/L.	
Omori, 2008[10]	rs9939609 rs8050136	Japan	Japanese	T2D Was Diagnosed with the WHO Criteria. 1 630 patients (M/F= 978/652); Age: 61.5 ±11.6 years; BMI: 23.7± 3.9 kg/m^2; FPG: 9.1±3.5 mmol/L.	Control Subjects Were Enrolled from an Annual Physical Check up. 1 064 Controls (M/F=638/426); Age:45.5 ±9.5 Years; BMI: 22.9±3.0 kg/m^2; FPG: 5.1±0.5 mmol/L.	1,2,4
Horikawa, 2008[11]	rs9939609	Japan	Japanese	T2D Was Diagnosed with the WHO Criteria. 1 921 patients (M/F=1093/828); age: 61.7 ± 9.9 years; BMI: 23.7 ± 3.6 kg/m^2; FPG: *N.A.*	The Inclusion Criteria for Normal, Control Subjects Were as Follows: (1) Older Than 60 yr; (2) Glycosylated Hemoglobin A_{1c} Values Less Than 5.8%; and (3) No Past History of type 2 diabetes. 1 622 Controls (M/F=709/913); Age: 70.0 ± 7.5 Years; BMI:22.5 ± 3.1 kg/m^2; FPG: *N.A.*	1,2,4

Note. *N.A.* information was not available; 1 age; 2 sex; 3 region; 4 BMI; 5 study population.

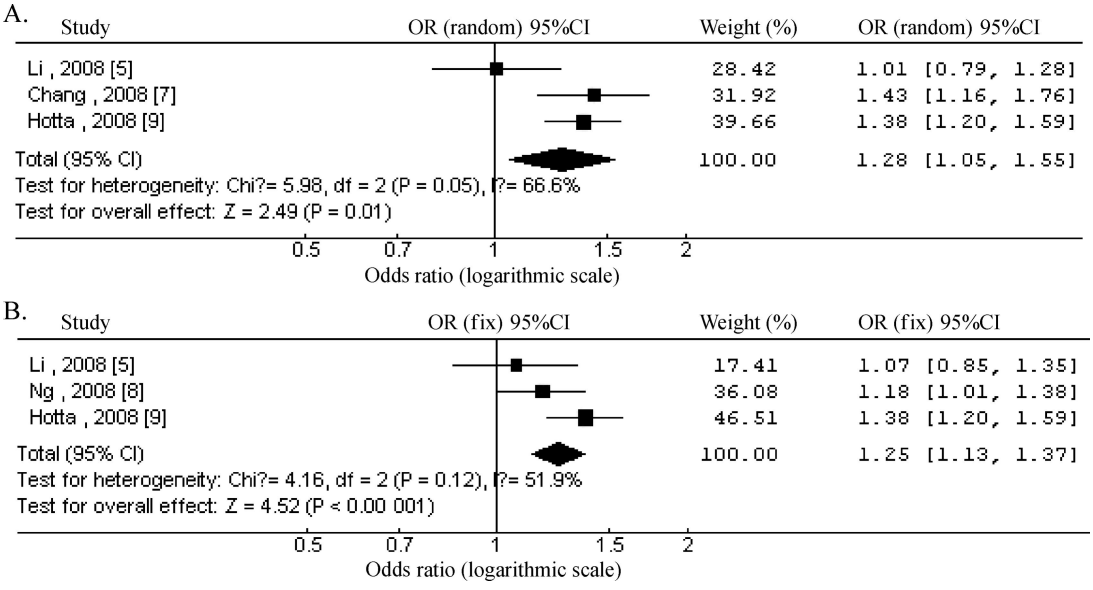

FIG. 1. Meta-analysis of the association of FTO polymorphisms with obesity in East Asian populations Each comparison is presented by the name of the first author and the year of publication. The studies are shown by a point estimate of the OR and the accompanying 95% CI displayed on a logarithmic scale. **A.** Association of rs9939609 A/T polymorphisms with obesity, including 3 studies (2004 cases and 4544 control subjects), using a random-effect model and an additive model of inheritance. **B.** Association of FTO rs8050136 A/C polymorphisms with obesity, including 3 studies (2404 case and 5713 control subjects)**,** using a fix-effect model and an additive model of inheritance. The studies are categorized according to the weight measured by contribution to the pooled OR estimate with the between-study heterogeneity tested using the X^2-based Q-statistic and its impact quantified using I^2 ranging 0%-100%.

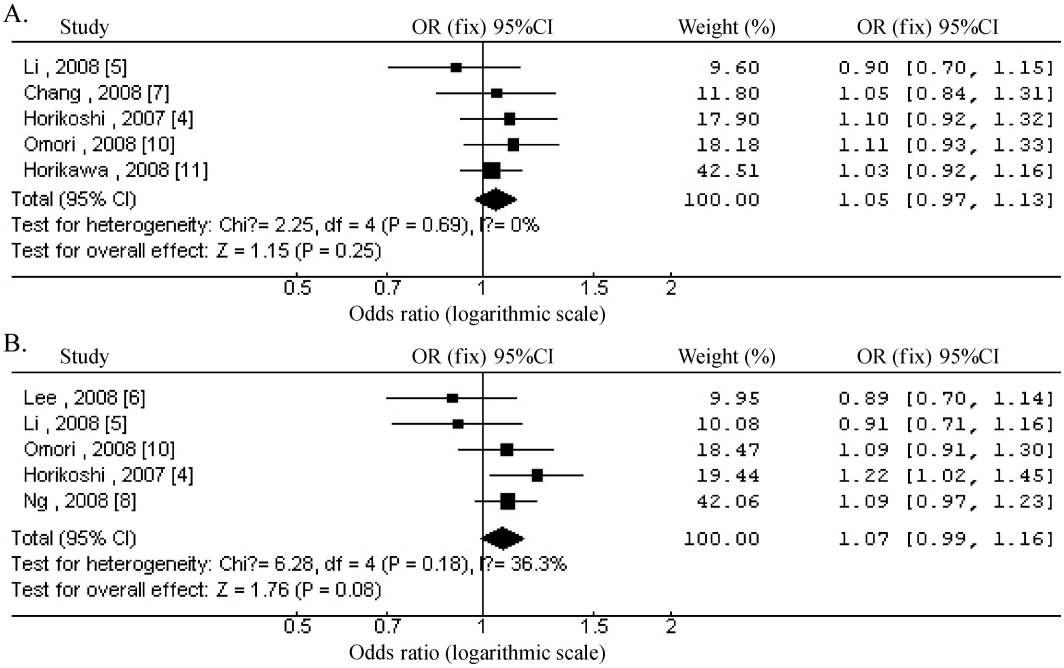

FIG. 2. Meta-analysis of the association of FTO polymorphisms with T2D in East Asian population Each comparison is presented by the name of the first author and the year of publication. The studies are shown by point estimate of the OR and the accompanying 95% CI displayed on a logarithmic scale. **A.** Association of rs9939609 A/T polymorphisms with T2D, including 5 studies (5517 cases and 6186 control subjects), using a fix-effect model and an additive model of inheritance. **B.** Association of FTO rs8050136 A/C polymorphisms with T2D, including 5 studies (6824 cases and 8007 control subjects), using a fix-effect model and an additive model of inheritance. The studies are categorized according to the weight measured by contribution to the pooled OR estimate, with the between-study heterogeneity tested using X^2-based Q-statistic and its impact quantified using I^2 ranging 0%-100%.

the pooled OR (95% CI) was 1.05 (0.96, 1.13) in fixed effect model. Similarly, in meta-analysis of the studies for rs8050136 polymorphism, the inter-study homogeneity remaining after the study of Lee *et al*.[6] was excluded, which used the guidelines of the American Diabetes Association ($P_{heterogeneity}$=0.28, I^2=21.2%), and no change was observed in the pooled OR (fixed effect OR=1.09, 95% CI=0.99, 1.20). In addition, the constructed funnel plots showed a symmetrical distribution, suggesting that there was no apparent publication bias concerning the rs9939609 and rs8050136 polymorphisms with T2D risk (Fig. 3).

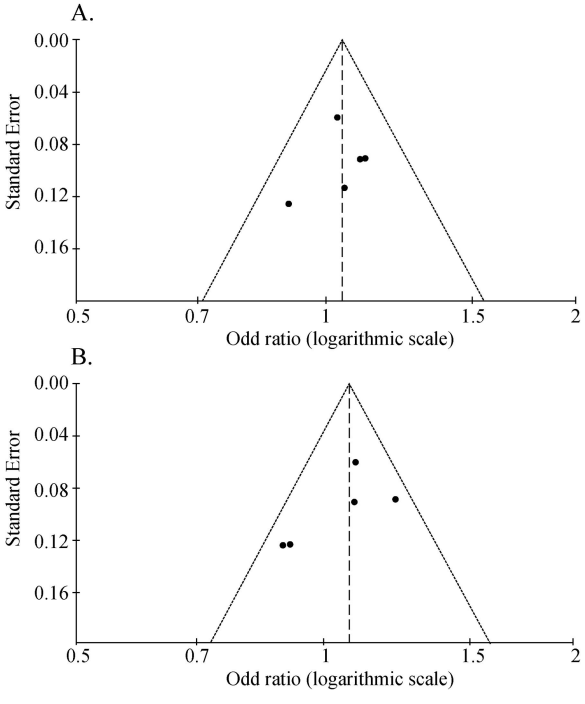

FIG. 3. Funnel plot of the risk of rs9939609 (**A**) and rs8050136 (**B**) for T2D according to the standard error for all studies (black rounds) with odds ratio displayed on a logarithmic scale.

DISCUSSION

There have been conflicting results in putative association of common rs9939609 or rs8050136 polymorphisms of the FTO gene with obesity and T2D in East Asian populations. We assume that not only environmental factors such as dietary habits and physical activity may modify or confound the association of FTO polymorphisms with obesity and T2D but also the insufficient sample size may decrease the statistical power. In the present meta-analysis, a better power was achieved to identify the effect of the minor allele on obesity and T2D, showing that rs9939609 A allele is significantly associated with obesity risk rather than with T allele: OR=1.28 (95%CI=1.05, 1.55). Similar results were observed in rs8050136 polymorphisms: OR=1.25 (95%CI=1.13, 1.37). However, genetics was not significantly associated with type 2 diabetes risk after potential confounders (at least of BMI) were controlled, either for rs9939609 or rs8050136 polymorphisms.

The possible mechanism underlying the association of FTO gene variants with obesity and T2D risk remains unclear. It has been found that the common variants of the FTO gene are strongly associated with BMI, obesity, and T2D in white European adults and children[2-3]. The association of FTO polymorphisms with T2D could be fully explained by linking FTO polymorphisms with BMI. Ng *et al*.[8] reported that in combined samples of the Chinese and Korean population, the FTO (rs8050136) variants were not associated with T2D after adjustment of the covariates, such as age, sex, BMI, study population, which is consistent with our meta-analysis results. FTO protein was found to be highly expressed in brain, particularly in hypothalamus, which is consistent with an important role of the central nervous system (CNS) in regulating weight[12]. The experimental data suggest that FTO is functionally involved in energy homeostasis by controlling energy expenditure[13]. However, in human beings, the study showed that FTO variant conferring a predisposition to obesity was not involved in the regulation of energy expenditure, but played a role in the control of food intake and choice[14].

Andreasen *et al*.[15] have reported that fasting serum leptin levels are significantly higher in rs9939609 A allele carriers. Others have supported that FTO plays a central role through its effect on cerebrocortical insulin sensitivity as individuals homozygous to allele risk have a reduced insulin response in the brain[16]. Future studies focusing on this phenotype may help determine the mechanisms underlying the association of common variants at the FTO gene and T2D.

Some potential limitations should also be considered in our study. First, meta-analysis was based on estimates of adjusted partial confounders. More precise analysis should be performed if confounders such as gender, age, dietary habits, and lifestyle were adjusted. In contrast, overcorrection may have occurred in T2D studies. It may be true that most studies are adjusted for intermediate rather than confounding factors, such as BMI, which may lead to underestimation of the pooled OR. Secondly, meta-analysis of FTO variants with obesity is based

on few studies and a limited sample size. Additionally, since the obese cases and control subjects are defined in different ways among different studies, the results need to be interpreted with caution. Thirdly, gene-gene and gene-environmental interactions are not addressed. Moreover, though the funnel plot has shown symmetry, publication bias may appear as Revman software cannot provide Begg's test and the Egger's test for the degree of asymmetry.

In conclusion, FTO polymorphisms are associated with obesity but not with type 2 diabetes, which may be of important clinical and public health implications in East Asian populations[17]. However, the association of FTO polymorphisms with obesity due to bias or confounding cannot be ruled out. More epidemiological and mechanistic studies are needed to further clarify the association of FTO variants with the risk of obesity and T2D.

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