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RESEARCH ARTICLE

Association of the fatty acid-binding protein 2 gene Ala54Thr polymorphism with insulin resistance and blood glucose: a meta-analysis in 13451 subjects

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Abstract

Background The results from the published studies on the association of fatty acid-binding protein 2 (FABP2) Ala54Thr polymorphism with insulin resistance and blood glucose are conflicting. In this meta-analysis, we investigated the association of the FABP2 Ala54Thr polymorphism with insulin resistance and blood glucose.

Methods We collected data on fasting blood glucose and fasting insulin, 2-h blood glucose (2-h BG) and 2-h insulin (2-h insulin), and homeostasis model assessment insulin resistance index. A dominant model was used for this meta-analysis.

Results Thirty-one studies with 13 451 subjects were included in this meta-analysis. The carriers of Thr54 allele have significantly higher homeostasis model assessment insulin resistance index and marginally higher fasting insulin than the non-carriers: standardized mean difference (SMD) = 0.07, 95% confidence interval (CI, 0.02, 0.12), $p = 0.007$, $p_{\text{heterogeneity}} = 0.19$ and SMD = 0.08, 95% CI (−0.01, 0.17), $p = 0.07$, $p_{\text{heterogeneity}} < 0.00001$, respectively. A borderline significant association between the FABP2 Ala54Thr polymorphism and an increased 2-h BG was also detected under the dominant model: SMD = 0.10, 95% CI (0.00, 0.20), $p = 0.05$, $p_{\text{heterogeneity}} = 0.09$. In addition, a borderline association between this polymorphism and an increased fasting blood glucose in populations of other ethnic origins was detected under the dominant model: SMD = 0.11, 95% CI (−0.00, 0.23), $p = 0.06$, $p_{\text{heterogeneity}} = 0.03$.

Conclusions Our meta-analysis suggests that the Thr54 allele of the FABP2 Ala54Thr is weakly associated with a higher degree of insulin resistance, higher level of fasting insulin and higher level of 2-h BG. Our meta-analysis also suggests a weak association between this polymorphism and an increased fasting blood glucose in populations of other ethnic origins under the dominant model.

Keywords blood glucose; fatty acid-binding protein 2; insulin resistance; meta-analysis; polymorphism

Introduction

Type 2 diabetes has become a major health problem in modern societies [1,2]. The exact pathogenesis underlying the development and progression

of type 2 diabetes has not been fully elucidated yet. Insulin resistance, which is both regulated environmentally and genetically, is a major risk for the development of type 2 diabetes [3]. Observational evidence and intervention studies indicate that the quantity and quality of dietary fats influence insulin resistance [4,5]. An increased intake of dietary fats can worsen insulin resistance, and insulin sensitivity has been shown to decrease in experimental animals fed a high-fat diet [5]. Genetic factors also play a key role in the development of insulin resistance [6]. Evidences from twin and family studies have strongly suggested that genetic factors are involved in the development of insulin resistance [6]. In recent years, much has been learned about specific genes that influence insulin resistance [7]. However, due to various reasons, the identification of susceptibility genes is difficult and most associations have not been replicated [7].

Fatty acid-binding protein 2 (FABP2) is an intracellular protein expressed exclusively in the enterocytes of proximal small intestine [8]. FABP2 has a high affinity for saturated and unsaturated long-chain fatty acids and is believed to be involved in the absorption and transport of dietary fatty acids [9]. The association between fatty acid metabolism and insulin resistance is well known, and the FABP2 gene has been suggested as a possible candidate gene in the development of insulin resistance and type 2 diabetes [4,5,10,11]. In 1995, Baier *et al*. reported a G/A mutation (rs1799883). A transition from G to A at codon 54 in exon 2 of the FABP2 gene results in a substitution of threonine for alanine (Ala54Thr) [12]. This polymorphism is very common, with a Thr54 allelic frequency of about 30% in most populations [13]. Studies suggest that the amino acid substitution is a functional mutation and influences small intestinal lipid absorption [14,15]. Carriers of the Thr54-containing protein have a twofold greater affinity for long-chain fatty acids than those with the Ala54-containing protein [14,15]. Furthermore, triglycerides excretion was enhanced in Caco-2 cells transfected with a gene with Thr54 mutants as compared to Ala54 wild type [14]. It has been shown that subjects with the Thr54 allele may increase intestinal absorption of dietary fatty acids and a resulting increased flux of dietary fatty acids in the circulation may lead to an impairment of sensitivity of glucose metabolism to insulin, supporting the role of the FABP2 Ala54Thr polymorphism in the aetiology of insulin resistance and type 2 diabetes [12,15]. A study by Baier has shown that the FABP2 Ala54Thr polymorphism is associated with insulin resistance and higher levels of plasma free fatty acid in Pima Indians, a population with a high prevalence of obesity and type 2 diabetes [12]. Based on these findings, a number of investigators studied the possible association of the FABP2 Ala54Thr polymorphism with insulin resistance and blood glucose, but the results are conflicting and inconclusive [8–13,16–40]. In this article, a meta-analysis was performed on previous reports to investigate the association of this polymorphism with insulin resistance and blood glucose.

Subjects and methods

Identification and eligibility of relevant studies

We identified all articles published before June 2009 on the FABP2 Ala54Thr polymorphism and its association with insulin resistance-related traits and blood glucose. We carried out a systematic search of the literature by using electronic databases including PubMed, HugeNavigator and China National Knowledge Internet. The languages were limited to English and Chinese. The keywords used for this search were 'fatty acid-binding protein 2 (FABP2)' concatenated with 'polymorphism or variant or SNP or mutation'. Data on fasting blood glucose (FBG) and fasting insulin (F-insulin) levels, 2-h blood glucose (2-h BG) and 2-h insulin (2-h insulin) levels (both of them were measured 2 h after consumption of 75 g glucose), and homeostasis model assessment insulin resistance index (HOMA-IR) were collected. The selection criteria for studies to be considered for this meta-analysis were as follows: (1) data were reported on at least one of the five variables; (2) we only included studies in which means of these variables and their standard deviations (SD) or standard errors by genotype were available; (3) in the case of interventional studies, we used pre-intervention baseline data; (4) subjects were confined to adults who were at least 18 years old. All references cited in the studies were also reviewed to find other published work that was not indexed by PubMed, HugeNavigator and China National Knowledge Internet. Animal studies, case reports, review articles, abstracts, editorials, reports with incomplete data and studies based on pedigree data were excluded.

Data extraction

Two investigators independently reviewed the articles to exclude irrelevant and overlapping studies. The results were compared, and disagreements between the investigators were discussed and resolved by consensus. When overlapping articles were found, we only included the publication that reported the most extensive information. From each study, the following information was extracted: journal, year of publication, first author, racial background of the study population, demographics, sample size, means and SDs or standard errors by genotypes, health condition, gender, age, genotyping methods, assay methods and units of the variables that were included in the meta-analysis.

Statistical analysis

Review Manager 5.0 software (The Cochrane Collaboration, Oxford, UK) was used for the meta-analysis. On the basis of previous reports and comparability, a dominant

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model may be the genetic model determining the difference in insulin resistance and blood glucose, we used a dominant model [(AlaThr + ThrThr) *versus* AlaAla] for this meta-analysis [8–13,16–40]. All data in this analysis were presented as mean ± SD. When the standard error was reported in the original article, the value of the SD was calculated. When information was reported for more than one subpopulation (e.g. subjects with type 2 diabetes and controls, male subjects or female subjects, subjects from different geographical areas or different ethnicity) in one study, each subpopulation was treated as a separate comparison in our meta-analysis. All populations described in the included studies were tested for Hardy–Weinberg equilibrium [41]. We conducted subgroup analyses stratified by ethnicity and gender. Ethnic subgroups were defined as European descendents, East Asian or populations of other ethnic origins. Subgroup analysis in subjects with obesity and in healthy subjects was also performed separately. In addition, we performed subgroup analysis including only the non-diabetic subjects. To ensure adequate statistical power, we only performed the meta-analysis on the subgroup with at least four studies.

A pooled standardized mean difference (SMD), together with 95% confidence interval (CI), was used for the meta-analysis. If the significant Q statistic ($p < 0.1$) indicated heterogeneity across studies, the random effects model was used [42]. Otherwise, the fixed effects model was selected. In addition, the random effects model was used for sensitivity analysis [42]. As the random effects model provides a more conservative evaluation of the significance of the association than one based on the fixed effects model, the significant pooled SMD estimated with the fixed effects model was subjected to sensitivity analysis (estimated with the random effects model again) [43].

Funnel plots were performed to look for evidence of publication bias. The funnel plots should be asymmetric when there is publication bias and symmetric in the case of no publication bias. Egger's test, estimated by MIX 1.7 software was performed to measure the funnel plot asymmetry [44]. A significance level of 0.1 was used as an indication for the presence of potential publication bias [44].

Results

Selection and characteristics of studies

Figure S1, Supporting Information, describes the flow of candidate and eligible articles. Initial search of the literature yielded 782 publications. We excluded 699 irrelevant articles on the basis of title and abstract. The original articles were retrieved and evaluated for compliance with the inclusion criteria. Fifty-two articles were ineligible for the following reasons: 37 articles did not provide complete data for this meta-analysis, 4 articles had subjects overlap with other publications, 7 articles involved subjects younger than 18 years, 2 studies were based on pedigree data and 2 articles were review articles. There was concordance between the two investigators in selecting the studies (κ-value = 93.0%).

The selected study characteristics were summarized in Table S1, Supporting Information. A total of 31 studies were included in the meta-analysis. Of these 28, 24, 14, 4, and 4 studies separately presented the data on FBG, F-insulin, HOMA-IR, 2-h BG and 2-h insulin. In all 31 studies, there were 13 studies of European descendents, 8 studies of East Asians and 10 studies of other ethnic origins. In 3 studies, all the subjects were female, and in 6 studies, all the subjects were male, whereas in the remaining 22 studies, the subjects consisted of both male and female and among the 22 studies, 2 studies provided the data on male and female subjects, respectively. In the eligible studies, 5 studies involved subjects with obesity (body mass index $\geq$30), 6 studies involved healthy subjects, 20 studies involved non-diabetic subjects, and 7 studies separately provided the information on more than one subpopulation. Each subpopulation was treated as a separate comparison. The genotype frequencies of all populations described in the eligible studies were consistent with the Hardy–Weinberg equilibrium. The complete data by genotypes can be found in Table S2, Supporting Information.

Summary statistics

Overall, 13 451 subjects were enrolled in this meta-analysis. Among them, 6894 subjects (51%) had the genotype AlaAla, and 6557 (49%) were Thr54 carriers (Table S1, Supporting Information). We distinguished 40 comparisons on the basis of categories such as ethnicity, gender and health condition. Of these 34, 31, 20, 6 and 7 comparisons were included for comparing the difference in FBG, F-insulin, HOMA-IR, 2-h BG and 2-h insulin, respectively (Table 1; Supporting Information Table S2).

Association between the FABP2 Ala54Thr polymorphism and FBG

A marginally significant association between the FABP2 Ala54Thr polymorphism and an increased FBG in populations of other ethnic origins was detected under dominant model: SMD = 0.11, 95% CI (−0.00, 0.23), $p = 0.06$, $p_{\text{heterogeneity}} = 0.03$ (Table 1). The other pooled SMDs were not significant ($p > 0.05$) (Table 1, Figure 1).

Association between the FABP2 Ala54Thr polymorphism and F-insulin

The result on all 31 comparisons showed that the FABP2 Ala54Thr polymorphism was marginally associated with a higher level of F-insulin under dominant model: SMD = 0.08, 95% CI (−0.01, 0.17), $p = 0.07$, $p_{\text{heterogeneity}} <$ 0.00001 (Table 1, Figure 1). The subgroup analyses by ethnicity suggested a significant association between

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Table 1. Meta-analysis of the fatty acid-binding protein 2 Ala54Thr polymorphism and FBG, F-insulin, HOMA-IR, 2-h BG, and 2-h insulin association

Group and subgroups under analysis	Comparisons (*n*)	Q test (*p*-value)	Model selected	SMD (95% CI)	*p*
FBG					
All	34	0.16	Fixed	0.03 (−0.01, 0.07)	0.10
Non-diabetic	21	0.04	Random	0.05 (−0.04, 0.13)	0.29
European	14	0.58	Fixed	−0.00 (−0.06, 0.06)	0.98
East Asian	10	0.76	Fixed	0.00 (−0.08, 0.08)	0.99
Other	10	0.03	Random	0.11 (−0.00, 0.23)	0.06
Male	10	0.58	Fixed	0.01 (−0.05, 0.08)	0.70
Female	4	0.51	Fixed	0.02 (−0.09, 0.14)	0.68
Healthy	5	0.78	Fixed	0.09 (−0.12, 0.31)	0.40
F-insulin					
All	31	<0.00001	Random	0.08 (−0.01, 0.17)	0.07
Non-diabetic	20	<0.00001	Random	0.12 (−0.03, 0.28)	0.13
European	13	0.85	Fixed	−0.02 (−0.08, 0.05)	0.64
East Asian	7	0.17	Fixed	0.15 (0.04, 0.26)	0.009
East Asian sensitivity analysis	–	–	Random	0.14 (−0.00, 0.28)	0.06
Other	11	<0.00001	Random	0.19 (−0.04, 0.41)	0.10
Male	8	0.04	Random	0.04 (−0.09, 0.17)	0.53
Female	4	0.99	Fixed	0.09 (−0.03, 0.20)	0.16
Obese	6	0.79	Fixed	0.02 (−0.14, 0.19)	0.79
Healthy	6	0.22	Fixed	0.14 (−0.09, 0.37)	0.22
HOMA-IR					
All	20	0.19	Fixed	0.07 (0.02, 0.12)	0.007
All sensitivity analysis	–	–	Random	0.07 (0.00, 0.14)	0.04
Non-diabetic	14	0.06	Random	0.03 (−0.09, 0.16)	0.60
European	4	0.99	Fixed	0.10 (−0.07, 0.28)	0.25
East Asian	6	0.20	Fixed	0.12 (0.01, 0.24)	0.03
East Asian sensitivity analysis	–	–	Random	0.12 (−0.02, 0.26)	0.09
Other	10	0.08	Random	0.03 (−0.08, 0.13)	0.60
Male	4	0.04	Random	−0.05 (−0.28,0.18)	0.69
Obese	5	1.00	Fixed	0.11 (−0.09, 0.31)	0.29
2-h BG					
All	6	0.09	Random	0.10 (0.00, 0.20)	0.05
2-h insulin					
All	7	0.04	Random	0.04 (−0.07, 0.16)	0.44

FBG, fasting blood glucose; F-insulin, fasting insulin; 2-h BG, 2-h blood glucose; HOMA-IR, homeostasis model assessment insulin resistance index; 2-h insulin, 2-h insulin, SMD, standardized mean difference; CI, confidence interval.

the FABP2 Ala54Thr polymorphism and higher level of F-insulin in East Asians under dominant model: SMD = 0.15, 95% CI (0.04, 0.26), $p = 0.009$, $p_{\text{heterogeneity}} = 0.17$ (Table 1). However, the pooled SMD for this association from sensitivity analysis was borderline significant: SMD = 0.14, 95% CI (−0.00, 0.28), $p = 0.06$ (Table 1).

Association between the FABP2 Ala54Thr polymorphism and HOMA-IR

The result on all 20 comparisons showed that the carriers of Thr54 allele had significantly higher HOMA-IR than the non-carriers: SMD = 0.07, 95% CI (0.02, 0.12), $p = 0.007$, $p_{\text{heterogeneity}} = 0.19$ (Table 1, Figure 2). This significant association was also observed in sensitivity analysis: SMD = 0.07, 95% CI (0.00, 0.14), $p = 0.04$ (Table 1, Figure 2). To evaluate the gender- and race-specific effect on HOMA-IR, we conducted the subgroup analyses by ethnicity and gender. A significant association of the FABP2 Ala54Thr polymorphism with higher HOMA-IR in East Asians was detected under dominant model: SMD = 0.12, 95% CI (0.01, 0.24), $p = 0.03$, $p_{\text{heterogeneity}} = 0.20$ (Table 1). However, the pooled SMD for this association from sensitivity analysis was not significant: SMD = 0.12, 95% CI (−0.02, 0.26), $p = 0.09$ (Table 1).

Association of the FABP2 Ala54Thr polymorphism with 2-h BG and 2-h insulin

A borderline significant association between the FABP2 Ala54Thr polymorphism and an increased 2-h BG was detected under dominant model in this meta-analysis: SMD = 0.10, 95% CI (0.00, 0.20), $p = 0.05$, $p_{\text{heterogeneity}} = 0.09$ (Table 1, Figure 3). The result for dominant comparison showed no evidence that the FABP2 Ala54Thr polymorphism was associated with 2-h insulin: SMD = 0.04, 95% CI (−0.07, 0.16), $p = 0.44$, $p_{\text{heterogeneity}} = 0.04$ (Table 1, Figure 3).

Publication bias

Publication bias was assayed by funnel plot and Egger's test. The funnel plots comparing the differences in FBG, F-insulin and HOMA-IR were all basically symmetric (Figure S2A–C, Supporting Information) and Egger's

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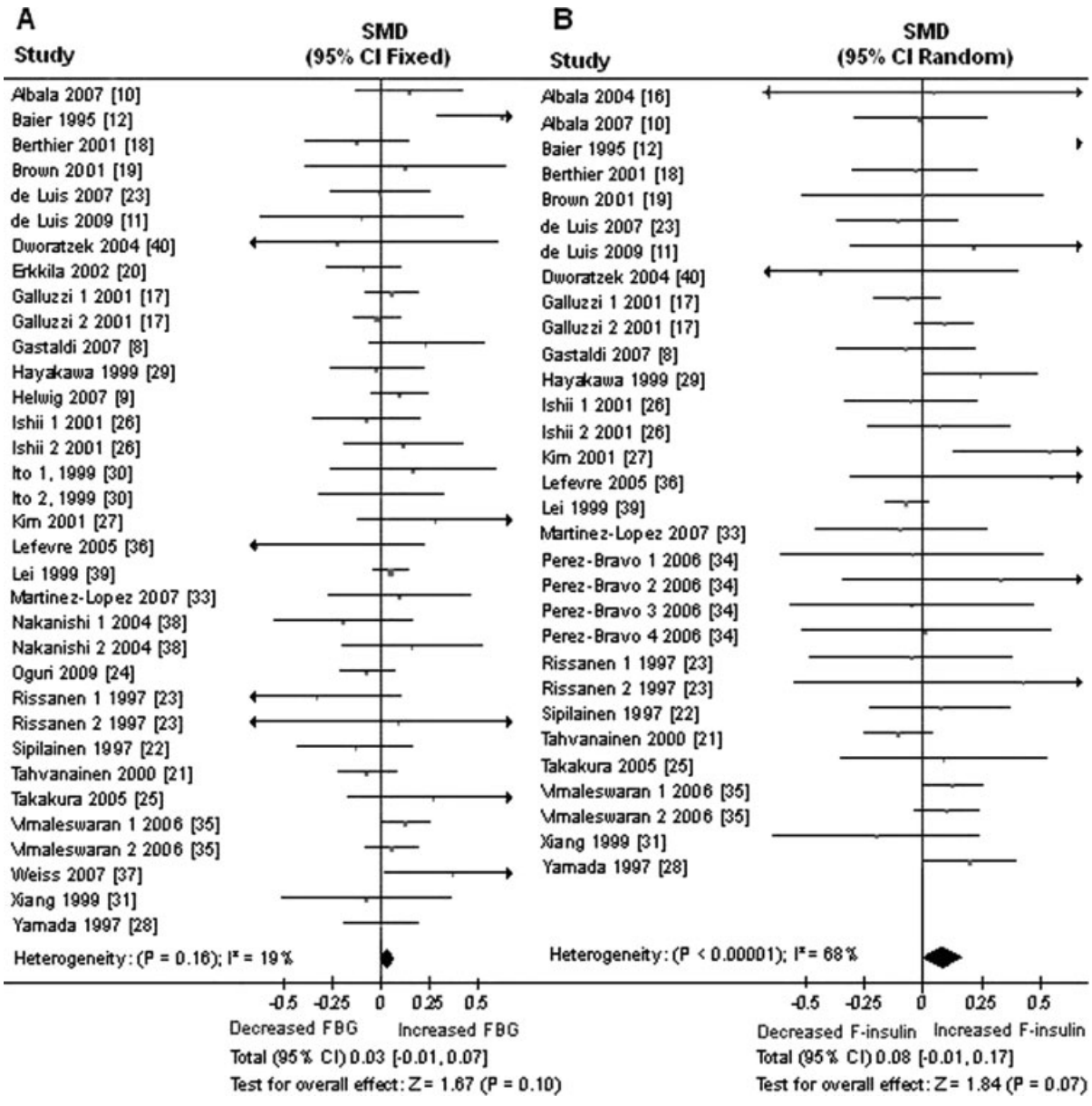

Figure 1. Forest plot of the association of the FABP2 Ala54Thr polymorphism with fasting blood glucose and fasting insulin. (A) Fasting blood glucose: result from the analysis on all 34 comparisons; (B) fasting insulin: result from the analysis on all 31 comparisons

test did not indicate asymmetry of the plots: intercept $= -0.1524$, 95% CI $(-2.1396, 1.8349)$, $p = 0.8769$, intercept $= 0.7293$, 95% CI $(-0.4485, 1.9072)$, $p = 0.2154$ and intercept $= -0.1893$, 95% CI $(-1.0327, 0.6649)$, $p = 0.6545$, respectively.

Discussion

The FABP2 Ala54Thr gene polymorphism has been suggested as a possible genetic factor associated with insulin resistance and type 2 diabetes [10,11]. However, the results from the published studies on the association of the FABP2 Ala54Thr polymorphism with insulin resistance and blood glucose are conflicting and inconclusive [8–13, 16–40]. The lack of concordance across many of these studies reflects limitation in the studies, such as small sample sizes, ethnic difference and research methodology. Meta-analysis is a powerful tool for summarizing the results from different studies by producing a single estimate of the major effect with enhanced precision [45]. It can overcome the problem of small sample size and inadequate statistical power of genetic studies of complex traits, and provide more reliable results than a single case–control study [45].

In this meta-analysis, we investigated the association of the FABP2 Ala54Thr polymorphism with insulin resistance and blood glucose. The results show that the FABP2 Ala54Thr polymorphism can influence the degree of insulin resistance and the level of blood glucose. The carriers of Thr54 allele have significantly higher HOMA-IR and marginally higher F-insulin than the

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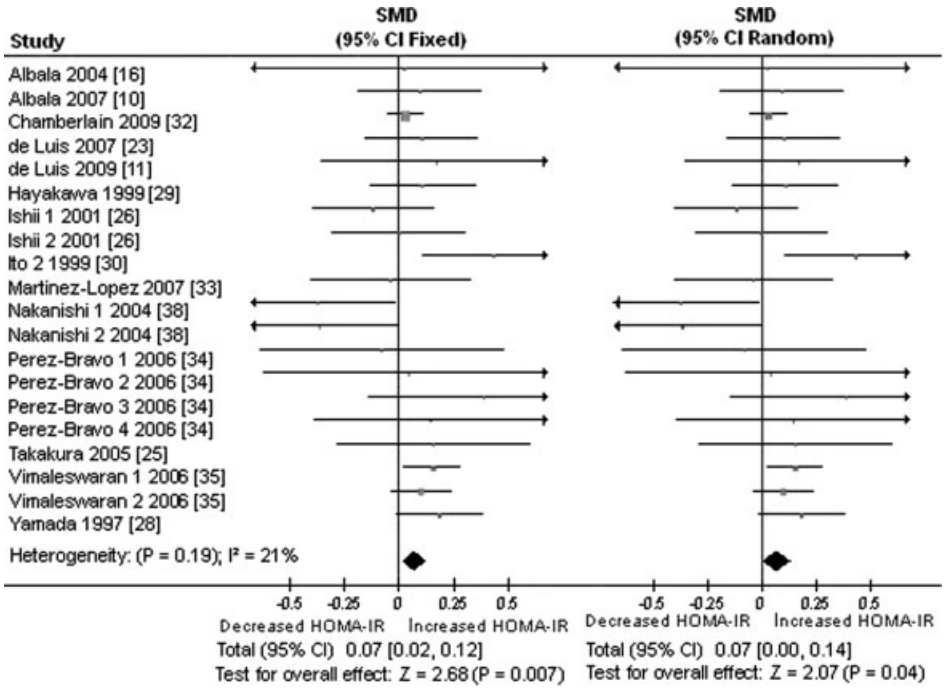

Figure 2. Forest plot of the association of the FABP2 Ala54Thr polymorphism with homeostasis model assessment insulin resistance index. Result from the analysis on all 20 comparisons. There was not significant heterogeneity among the studies. The pooled SMD estimated with the fixed effects model was significant. The meta-analysis was performed again by using the random effects model

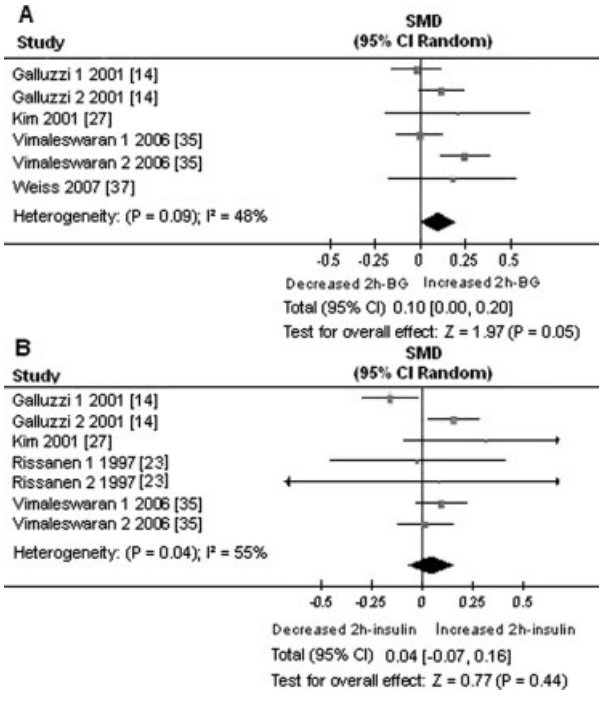

Figure 3. Forest plot of the association of the FABP2 Ala54Thr polymorphism with 2-h blood glucose and 2-h insulin. (A) 2-h blood glucose: result from the analysis on all six comparisons; (B) 2-h insulin: result from the analysis on all seven comparisons

non-carriers. A borderline significant association between the FABP2 Ala54Thr polymorphism and an increased 2-h BG was also detected under the dominant model. As gender and ethnicity probably were important variables in determining associative risk with insulin resistance and type 2 diabetes, we performed subgroup analyses of gender and ethnicity. The significant association of the FABP2 Ala54Thr polymorphism with F-insulin and HOMA-IR was detected in East Asians applying the dominant model. However, the sensitivity analysis in East Asians only suggests a marginal association of the FABP2 Ala54Thr polymorphism with F-insulin, and does not suggest the significant association of this polymorphism with HOMA-IR, which indicates that the association of the Ala54Thr polymorphism with F-insulin and HOMA-IR in East Asians is not very robust. Based on these findings, our meta-analysis suggests that the FABP2 Ala54Thr polymorphism is weakly associated with a higher degree of insulin resistance, higher level of F-insulin and higher level of 2-h BG. The weak effects of this polymorphism on insulin resistance and F-insulin particularly exist in East Asians. In addition, our meta-analysis suggests a weak association between the FABP2 Ala54Thr polymorphism and an increased FBG in populations of other ethnic origins under dominant model.

The association of the FABP2 Ala54Thr polymorphism with insulin resistance and blood glucose is not likely to be due to type I errors (false-positive results). First, because a random effects model considers both between- and within-study heterogeneity, it provides a more conservative evaluation of the significance of the association than the one based on fixed effects [42,43]. The random effects model was used for sensitivity analysis in our meta-analysis. Here, the significant pooled SMD estimated with the fixed effects model was estimated with the random effects model a second time. Thus, the results from our meta-analysis were based on a more conservative evaluation, which was expected to

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avoid false-positive results. Second, many investigators generally preferred to publish the statistically significant results rather than negative findings. If the meta-analysis was based on such selectively published reports, pooled effect would be overestimated. However, we did not detect publication bias in our meta-analysis, indicating that the pooled results were unbiased. Third, insulin resistance is a major risk factor for type 2 diabetes, and a higher degree of insulin resistance would lead to impaired glucose tolerance and increased levels of blood glucose [3]. Our meta-analysis showed a similarly positive association and ethic effect for F-insulin and HOMA-IR. It also showed significant association of the FABP2 Ala54Thr polymorphism with blood glucose in all ethnicities (for 2-h BG) or in populations of other ethnic origins (for FBG). Because the significant association of the FABP2 Ala54Thr polymorphism with several indices was observed, the results from our meta-analysis showed theoretical consistency. Thus, the findings in our meta-analysis are not likely to be due to type I errors. Fourth, the FABP2 Ala54Thr polymorphism is very common, with the Thr54 allelic frequency of about 30% in most populations [13]. Among the subjects included in our meta-analysis, 49% of them were Thr54 carriers. If the incidence of the Thr54 carriers was sufficiently high, this may have prevented the type I error.

Potential mechanisms behind these findings have been reported. Studies suggest that lipids and glucose compete as oxidative fuel sources in muscle. Increased concentrations of fatty acids in plasma would inhibit glucose uptake in muscle and lead to insulin resistance and the occurrence of type 2 diabetes [12]. Studies have shown that the amino acid substitution from Ala to Thr is in fact a functional mutation, and results in greater affinity of the protein for long-chain fatty acids [14,15]. Subjects with the Thr54 allele may increase intestinal absorption of dietary fatty acids, which would elevate plasma lipid concentrations and thereby increase the rate of fat oxidation, which are known to cause an impairment of sensitivity of glucose metabolism to insulin [12,14,15]. Experimental evidences suggest that the FABP2 Ala54Thr polymorphism affects metabolic interaction that involve lipids and carbohydrates, which leads to changes in essential metabolites that are associated with insulin resistance and type 2 diabetes [12,46]. Due to the excessive absorption of fatty acids which are attributed to the Thr54 variant, skeletal muscles preferentially use fatty acids for energy rather than glucose, resulting in increased insulin resistance and blood glucose levels [12,46].

The current meta-analysis has several limitations which should be noted. First, insulin resistance and type 2 diabetes are highly heritable and originate from the interactions of multiple genes, environmental factors, and behaviour. Lacking of the original data of the included studies limited our further evaluation of potential interactions because the interactions among gene–gene, gene–environment and even different polymorphic loci of the same gene may modulate insulin resistance and the blood glucose levels. A more precise analysis could be conducted if more detailed individual data were available, which would allow for an adjusted estimate. Second, because of data limitation, we did not perform additional analyses in different clinical subgroups, such as comparison of patients with and without hypertension, comparison of patients with and without hyperlipidemia. Third, we did not perform the meta-analysis on the association of the FABP2 Ala54Thr polymorphism with risk of type 2 diabetes because few studies on this association were reported. Fourth, because it was very difficult to get the full articles published in various languages, we only included the studies published in English and Chinese. Thus, the limitations mentioned may affect our final conclusions.

In conclusion, our meta-analysis suggests that the Thr54 allele of the FABP2 Ala54Thr is weakly associated with a higher degree of insulin resistance, higher level of F-insulin and higher level of 2-h BG. The effects of this polymorphism on insulin resistance and F-insulin particularly exist in East Asians. Our meta-analysis also suggests a weak association between this polymorphism and an increased FBG in populations of other ethnic origins under dominant model.

Supporting information

Supporting information may be found in the online version of this article.

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Conflict of interest

None declared.

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