Association between GNB3 c.825C>T polymorphism and the risk of overweight and obesity: A meta-analysis

Hui-Lan Li a,b, Yan-Jiao Zhang c,d, Xiao-Ping Chen c,d, Jian-Quan Luoc,d, Si-Yun Liue, Zan-Lin Zhang a,*

a Department of Pharmacy, Xiangya Hospital, Central South University, Changsha 410008, Hunan, PR China
b School of Pharmaceutical Science, Central South University, Changsha 410013, Hunan, PR China
c Institute of Clinical Pharmacology, Central South University, Hunan Key Laboratory of Pharmacogenetics, Changsha 410078, PR China
d School of Public Health, Central South University, Changsha 410078, Hunan, PR China

Abstract

Background: The association between G protein β-polypeptide 3 gene (GNB3) c.825C>T polymorphism (rs5443) and the risk of overweight/obesity has been investigated in many published studies, but the results were conflicting and inconclusive. A meta-analysis was performed to make a more accurate assessment of the relationship.

Methods: The PubMed, ProQuest Health & Medical Complete, Web of Science, Chinese Biomedical Medical databases (CBM), Chinese National Knowledge Infrastructure (CNKI), and Wan Fang databases were searched to identify eligible literatures. Pooled odds ratios (ORs) with the corresponding 95% confidence intervals (CIs) were used to assess the strength of association between GNB3 c.825C>T polymorphism and overweight/obesity.

Results: Eleven articles including 15 case-control studies with a total of 10,396 subjects (3,171 cases of overweight/obesity and 7,225 controls) were enrolled in the meta-analysis. The GNB3 c.825C>T was significantly associated with overweight/obesity under a recessive model (OR = 1.22, 95% CI: 1.04–1.44, P = 0.015). Moreover, the GNB3 825T allele was obviously associated with overweight alone in all inheritable models (P < 0.05) except in a recessive model (P = 0.084). In the stratification analysis by potential confounding variables, a significant association was observed between GNB3 c.825C>T polymorphism and overweight/obesity risk in males under an allelic model (P = 0.008), a homozygous model (P = 0.014), a recessive model (P = 0.005), and a dominant model (P = 0.049). And the results also showed that GNB3 c.825C>T polymorphism was significantly associated with overweight/obesity in subgroups of mean age less than 30 years, consistent with HWE, and high-quality studies (P = 0.027, P = 0.043, P = 0.040, respectively) under a recessive model, but not in other subgroups. Meta-regression also revealed that P value of HWE, publication year, and the quality scores of studies were the sources of heterogeneity in a recessive model and an allelic model. "Leave one out" sensitivity analyses indicated that the association was more significant after excluding some studies. The funnel plot and Egger's linear regression test and Begg's test revealed no apparent publication bias.

Conclusion: This meta-analysis suggests that the presence of TT homozygote might be one of the genetic factors susceptible to overweight/obesity and that males or aged under 30 years increase the genetic susceptibility.

1. Introduction

The prevalence of overweight and obesity has been rapidly increasing in the world. According to World Health Organization (WHO), more than 1.9 billion adults aged above 18 years and 42 million children under the age of 5 were overweight or obese globally in 2014. Obesity is characterized by abnormal or excessive body fat accumulation, which is a risk factor for type 2 diabetes, hypertension, cardiovascular diseases, cancers, and cognitive dysfunction (Mitchell et al., 2011). Therefore, obesity has become a major public health challenge. It is generally accepted that obesity is attributed to a shift in dietary and physical activity habits (El-Sayed Moustafa and Froguel, 2013). In addition to the unhealthy lifestyle, genetic factors are assumed to play an important role in obesity susceptibility, which hereditability has been estimated about 61%–80% (Nan et al., 2012). Numerous genes related to obesity have been found by candidate gene and genome-wide association approaches (Rao et al., 2014).
One commonly studied candidate gene for obesity is G protein β3-polypeptide 3 gene (GNB3). Heterotrimeric G proteins are composed of an alpha, a beta, and a gamma subunit encoded by families of related genes, which are critical to translate signals from the cell surface into a cellular response in all cells of the body (Downes and Gautam, 1999). A study by Wang HY et al. showed a critical role in adipogenesis played by G proteins (Wang and Malbon, 1996). Elevation expression of Gi alpha 2 subunit or expression of constitutively active Gi alpha 2 promotes lipid accumulation and adipogenic conversion of cells (Su et al., 1993). In addition, transgenic mice lacking the Gi alpha 2 subunit are lean and deficient in fat mass (Moxham et al., 1993). G protein beta subunits are important regulators of alpha subunits and of certain signal transduction. A recent study by Goldlust IS et al. reported that the duplication of the GNB3 gene has been linked to an obesity phenotype not only in humans but also in the transgenic mouse model (Goldlust et al., 2013). A single-nucleotide polymorphism (c.825C>T, rs5443) in exon 10 of GNB3 has been reported that associated with the occurrence of a splice variant Gi33s (Siffert et al., 1998). Despite a deletion of 41 amino acids and one WD repeat domain of the G beta subunit, splice variant Gi33s is proved to be a biologically active protein and can ultimately enhance signal transduction via pertussis toxin-sensitive G proteins (Siffert et al., 1999; Rosskopf et al., 2000). GNB3 c.825C>T polymorphism influences G protein receptor mediated signal transduction, including lipolysis. Functional studies have established that GNB3 825TT homozygote has lowered Gi3 protein and impaired the function of adrenoreceptors, thus reducing lipolysis in human fat cells (Rydén et al., 2002; Hauner et al., 2002).

The first study on the relationship between overweight/obesity and GNB3 c.825C>T polymorphism was conducted in 1999 by Siffert W et al. They found a significant association between the 825T allele and overweight and obesity with odds ratios between 2 and 3 in Germans, Chinese, and black South Africans (Siffert et al., 1999). Since then, much research has focused on the association between GNB3 c.825C>T polymorphism and overweight/obesity. However, the results were inconsistent and conflicting. Therefore, we performed a meta-analysis of previous studies to comprehensively evaluate the relationship between GNB3 c.825C>T polymorphism and overweight/obesity susceptibility.

2. Methods

2.1. Search strategy

We searched the PubMed, ProQuest Health & Medical Complete, Web of Science, Chinese Biomedical Medical databases (CBM), Chinese National Knowledge Infrastructure (CNKI), and Wan Fang (Chinese) databases for all publications on the association between GNB3 c.825C>T polymorphism and the risk of overweight and obesity, using the following search terms: (‘G protein beta 3 polypeptide’ or ‘GNB3’) and (‘obesity’ or ‘obese’ or ‘overweight’ or ‘body mass index’ or ‘BMI’) and (‘polymorphism’ or ‘variant’). All studies were published from 1999, when the first study of the topic was reported, to 20 May, 2015. There were no language limitations on the search. “Related articles” option in PubMed was examined. Reference lists from the retrieved articles were also screened.

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows: 1) the study had a case control design for the association between the GNB3 c.825C>T and the risk of overweight and obesity. 2) Complete information of allelic frequencies and genotypic frequencies was available in cases and controls for calculating the odds ratio (OR) with 95% CI directly and indirectly. 3) The criteria for diagnosis was established using body mass index (BMI) cut-off points for obesity. We have excluded studies for 1) review articles, case reports, editorials, or animal research, and 2) overlapping and insufficient data.

2.3. Quality assessment and data extraction

The quality of the studies was critically assessed using the Newcastle–Ottawa Quality Assessment Scale (NOS) by two authors (Li HL and Zhang YJ). The following aspects of each study were appraised: selection of cases and controls, comparability, and outcome or exposure. Quality scores ranged from 0 to 9. In addition, we assessed the quality of included studies by P value of Hardy–Weinberg equilibrium (HWE) for the control genotype. Studies only consistent with HWE were scored in part of “selection of control” (Table 2). The study that scored seven or more stars was considered as a high-quality study, otherwise, the low-quality study. Guidelines from meta-analysis of observational studies in epidemiology (MOOSE) group were followed to extract the following data: first author, publication year, country and ethnicity, source of control, sample size and mean age of cases and controls, genotyping method, P value for HWE, BMI cut-off points, number of gender (males/females), and the genotypic and allelic frequencies in cases and controls. The studies were reviewed by two authors respectively. The results were compared and disagreements were solved with consensus.

2.4. Statistical analysis

The STATA 12.0 software (StataCorp, College Station, TX, USA) was used for all statistical analyses. The association between GNB3 c.825C>T polymorphism and overweight/obesity was assessed using crude odds ratio (OR) with 95% confidence interval (CI). The pooled ORs were determined for allelic model (T versus C), homozygous model (TT versus CC), heterozygous model (CT versus CC), recessive model (TT versus CT/CC), and dominant model (CT/TT versus CC). The pooled OR was calculated using the Z test with the significance set at P<0.05. HWE was assessed using the Chi-square test. The heterogeneity between studies was evaluated using the I² test and Q statistic test. The value of I² lies between 0% and 100%, and the larger value indicates increasing heterogeneity (Higgins et al., 2003). If heterogeneity was observed between studies (I² >50% or P<0.05), the DerSimonian and Laird method for random-effects model was used to calculate the pooled OR and 95% CI. Otherwise, the Mantel–Haenszel method for fixed-effects model was adopted for the meta-analysis. Stratification analysis according to the P value of HWE, ethnicity, mean age, gender, and quality scores of studies were also performed to evaluate the association. Meta-regression was applied to explore the sources of between-study heterogeneity. The study publication year, ethnicity, BMI cut-off points, number of cases and controls, quality scores of studies and the P value of HWE were regarded as the potential confounding factors. Sensitivity analysis was performed to evaluate the effect of individual study on pooled results and assess the stability of results. The potential publication bias was graphically represented by funnel plots, and the funnel plot asymmetry was evaluated with Egger’s linear regression test and Begg’s test (Egger et al., 1997; Begg and Mazumdar, 1994).

3. Results

3.1. Study characteristics

A total of 780 studies were identified by searching databases. After carefully screening titles and abstracts, 26 articles were chosen after removing duplicates, animal research, and not significantly relevant papers. Finally, 11 articles including 15 case–control studies with a total of 3171 cases of overweight/obesity and 7225 controls were included after detailed evaluation in the present meta-analysis (Fig. 1). And the main characteristics of included studies are presented in Table 1. Two studies used polymerase chain reaction–restriction fragment length polymorphism (PCR–RFLP) as genotyping methods (Lee et al., 2015; Hsiao et al., 2013), whereas thirteen studies used Taqman assay (Siffert et al., 1999; Wang et al., 2008; Chen et al., 2006; Zhou et al., 2005; Lee et al., 2005; Suwazono et al., 2004; Benjaffel et al., 2001;
Table 1

Characteristics of studies of overweight/obesity and GNB3 c.825C>T polymorphism.

| Author      | Year | Country | Ethnicity | Source of control | Genotyping method | BMIs cut-off points | Group | Number | Case | Mean age (y) | Gender | PHWE
|-------------|------|---------|-----------|-------------------|-------------------|---------------------|-------|--------|------|-------------|---------|-------
| Lee et al.  | 2015 | Korea   | Asian     | PB                | TaqMan            | 85th                | Case  | 394    | 379/409 | 85 209 | 100 | 8–9 | 231/163 | 0.023
|             |      |         |           |                   | Control           |                     | Control | 1769   | 1746/192 | 407 932 | 430 | 8–9 | 875/894 |
| Hsiao et al.| 2013 | China   | Asian     | PB                | TaqMan            | 24                  | Case  | 467    | 402/532 | 87 228 | 152 | About 40 | 333/144 | 0.188
| Wang et al. | 2008 | China   | Asian     | PB                | PCR-RFLP          | 25                  | Case  | 129    | 137/121 | 38 61 | 30 55 | 10   | 85/44   | 0.495
| Chen et al. | 2006 | China   | Asian     | PCR-RFLP         | 23                |                     | Case  | 161    | 149/173 | 38 73 | 50   | NA    | 58/103  | 0.001
| Zhou et al. | 2005 | China   | Asian     | PB                | PCR-RFLP          | 25                  | Case  | 142    | 154/130 | 43 68 | 31 55 | 10   | NA      | 0.584
| Lee et al.  | 2005 | Korea   | Asian     | PCR-RFLP         | 25                |                     | Case  | 130    | 132/128 | 32 68 | 30 25 | 3   | 130/0   | 0.082
| Suwazono et al. | 2004 | Japan   | Asian     | PB                | PCR-RFLP          | 25                  | Case  | 183    | 195/171 | 52 91 | 40 42 | 9    | 0/183   | <0.001
| Suwazono et al. | 2004 | Japan   | Asian     | PCR-RFLP         | 25                |                     | Case  | 322    | 322/322 | 80 162 | 80 40 | 9    | 322/0   | 0.179
| Benjafeld et al. | 2001 | Britain | Caucasian | PCR-RFLP        | 25                |                     | Case  | 1131   | 1144/1148 | 278 588 | 265 38 | 11  | 1144/0  | 0.054
| Hinney et al.| 2001 | Germany | Caucasian | PCR-RFLP        | 90th              |                     | Case  | 491    | 695/287 | 251 193 | 47 24 | About 20 | 225/296 | 0.957
| Ohshiro et al. | 2001 | Japan   | Asian     | PCR-RFLP        | 30                |                     | Case  | 110    | 144/76 | 47 50 | 13 25 | 3   | 110/0   | 0.837
| Siffert et al.| 1999 | Germany | Caucasian | PCR-RFLP        | 25                |                     | Case  | 92     | 108/76 | 32 44 | 16    | About 20 | 92/0   | 0.753
| Siffert et al.| 1999 | China   | Asian     | PCR-RFLP        | 25                |                     | Case  | 207    | 292/122 | 102 88 | 17    | About 20 | 207/0  | 0.700
| Siffert et al.| 1999 | South Africa | Black African | PCR-RFLP   | 25            |                     | Case  | 186    | 166/206 | 33 100 | 53    | About 20 | 186/0  | 0.903
| Siffert et al.| 1999 | Zimbabwe| Black African | PCR-RFLP     | 25            |                     | Case  | 82     | 86/18    | About 20 | 82/0 | About 20 | 201/0  | 0.706

Abbreviations: BMI, body mass index; PB, population based; HB, hospital based; HWE, Hardy–Weinberg equilibrium. PHWE indicates the P value of Hardy–Weinberg equilibrium.
association in the recessive model (OR = 1.19, 95% CI: 1.00–1.43, P = 0.055) in the Asian subgroup (Table 5). In the subgroup analysis by mean age (categorized as mean age less than 30 years and mean age more than 30 years), we found only significant association in the recessive model (OR = 1.26, 95% CI: 1.04–1.55, P = 0.029) in the mean age less than 30 years subgroup (Table 5, and Fig. 3). Stratified analyses by gender (categorized as all, male and female) showed a significant association between GNB3 c.825C>T polymorphism and overweight/obesity in the male subgroup under an allelic model (OR = 1.27, 95% CI: 1.06–1.51, P = 0.008), a homozygous model (OR = 1.68, 95% CI: 1.11–2.54, P = 0.014), a recessive model (OR = 1.30, 95% CI: 1.08–1.56, P = 0.005) and a dominant model (OR = 1.38, 95% CI: 1.00–1.88, P = 0.049) (Table 5, and Fig. 4). In addition, we stratified the studies by quality scores, and found that an obvious association was found in a high-quality study under the recessive model (OR = 1.30, 95% CI: 1.01–1.66, P = 0.040) (Table 5).

3.3. Heterogeneity analysis

The subgroup analysis revealed that heterogeneity was removed in the analysis of mean age above 30 years, and black African subgroup. Moreover, the heterogeneity consistent with the HWE subgroup was obviously removed with an I² value of 4.5% in the recessive model. In the allelic model, meta-regression showed that the P value of HWE, publication year, and study quality scores were the sources of heterogeneity between studies (P = 0.043, P = 0.055, P = 0.047, respectively), as well
as in the homozygous model (P = 0.013, P = 0.013, P = 0.013, respectively). Furthermore, in the recessive model, meta-regression also revealed that the P value of HWE, publication year, and study quality scores were the sources of heterogeneity (P = 0.008, P = 0.009, P = 0.021, respectively), those three covariates were able to explain 86.47% of between-study variance, which was consistent with the subgroup analysis. In addition, meta-regression revealed that the study quality score was the source of heterogeneity in the dominant model (P = 0.080), which also was in agreement with the subgroup analysis.

3.4. Sensitivity analysis and publication bias

Sensitivity analysis was performed to evaluate the stability of results by excluding individual study each time. The analysis results

Table 5
Pooled ORs and 95% CIs of subgroup analysis.

| Subgroups                  | T vs. C OR (95% CI) | T vs. C P | T vs. C I² (%) | TT vs. CC OR (95% CI) | TT vs. CC P | TT vs. CC I² (%) | (TT + CT) vs. CC OR (95% CI) | (TT + CT) P | (TT + CT) I² (%) |
|----------------------------|---------------------|----------|----------------|-----------------------|------------|-----------------|-----------------------------|------------|------------------|
| HWE                       |                     |          |                |                       |            |                 |                             |            |                  |
| Yes (n = 12)              | 1.09 (0.96–1.23)    | 0.184    | 49.7           | 1.18 (0.91–1.54)      | 0.213      | 47.3            | 1.15 (1.00–1.32)             | 0.043      | 4.5              |
| No (n = 3)                | 1.14 (0.89–1.46)    | 0.289    | 75.0           | 1.37 (0.79–2.35)      | 0.259      | 78.5            | 1.46 (0.84–2.52)             | 0.178      | 85.6             |
| Ethnicity                 |                     |          |                |                       |            |                 |                             |            |                  |
| Asian (n = 10)            | 1.08 (0.97–1.19)    | 0.174    | 48.9           | 1.18 (0.94–1.48)      | 0.165      | 56.1            | 1.19 (1.00–1.43)             | 0.055      | 54.2             |
| Caucasian (n = 3)         | 1.18 (0.72–1.92)    | 0.517    | 80.6           | 1.64 (0.52–5.15)      | 0.399      | 76.4            | 1.50 (0.64–3.55)             | 0.355      | 0                |
| Black African (n = 2)     | 1.36 (0.92–2.01)    | 0.129    | 0              | 2.05 (0.49–14.18)     | 0.256      | 0               | 1.33 (0.86–2.06)             | 0.202      | 62.6             |
| Mean age                  |                     |          |                |                       |            |                 |                             |            |                  |
| Less than 30 (n = 7)      | 1.19 (0.99–1.44)    | 0.067    | 60.9           | 1.48 (0.99–2.21)      | 0.057      | 54.7            | 1.26 (1.04–1.55)             | 0.029      | 22.9             |
| More than 30 (n = 7)      | 0.99 (0.90–1.09)    | 0.852    | 0              | 0.97 (0.80–1.17)      | 0.759      | 0               | 1.06 (0.91–1.23)             | 0.478      | 0                |
| NA (n = 1)                | 1.55 (1.18–2.03)    | 0.001    | 0              | 2.69 (1.54–4.70)      | 0.000      | 0               | 2.83 (1.78–4.50)             | 0.000      | 0                |
| Gender                    |                     |          |                |                       |            |                 |                             |            |                  |
| All (n = 8)               | 1.03 (0.89–1.18)    | 0.702    | 53.6           | 1.08 (0.80–1.46)      | 0.631      | 56.2            | 1.15 (0.87–1.51)             | 0.332      | 64.1             |
| Male (n = 6)              | 1.27 (1.06–1.51)    | 0.008    | 44.8           | 1.68 (1.11–2.54)      | 0.014      | 46.9            | 1.31 (1.08–1.57)             | 0.005      | 0.9              |
| Female (n = 1)            | 0.96 (0.77–1.20)    | 0.711    | 0              | 0.94 (0.60–1.48)      | 0.790      | 0               | 1.12 (0.76–1.64)             | 0.570      | 0.82             |
| Study quality             |                     |          |                |                       |            |                 |                             |            |                  |
| High (n = 8)              | 1.20 (0.97–1.50)    | 0.093    | 59.7           | 1.56 (0.94–2.60)      | 0.087      | 54.4            | 1.30 (1.01–1.66)             | 0.040      | 17.5             |
| Low (n = 7)               | 1.05 (0.94–1.17)    | 0.388    | 41.8           | 1.11 (0.88–1.41)      | 0.372      | 49.7            | 1.19 (0.96–1.47)             | 0.118      | 61.0             |

n is the number of studies.

as in the homozygous model (P = 0.013, P = 0.013, P = 0.013, respectively). Furthermore, in the recessive model, meta-regression also revealed that the P value of HWE, publication year, and study quality scores were the sources of heterogeneity (P = 0.008, P = 0.009, P = 0.021, respectively), those three covariates were able to explain 86.47% of between-study variance, which was consistent with the subgroup analysis. In addition, meta-regression revealed that the study quality score was the source of heterogeneity in the dominant model (P = 0.080), which also was in agreement with the subgroup analysis.

Sensitivity analysis was performed to evaluate the stability of results by excluding individual study each time. The analysis results

Fig. 2. Forest plot of overweight/obesity associated with GNB3 c.825C>T polymorphism in the recessive model (TT versus CT/CC) stratified by the P value of Hardy–Weinberg equilibrium.

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demonstrated that the association was more significant after excluding the study by Hinney et al. under an allelic model (OR = 1.12, 95% CI: 1.01–1.24, $P = 0.027$), a homozygous model (OR = 1.28, 95% CI: 1.01–1.61, $P = 0.040$), and a recessive model (OR = 1.25, 95% CI: 1.06–1.47, $P = 0.009$), and the study by Zhou et al. under an allelic model (OR = 1.12, 95% CI: 1.01–1.24, $P = 0.041$), a homozygous model (OR = 1.27, 95% CI: 1.00–1.60 $P = 0.042$), and a recessive model (OR = 1.24, 95% CI: 1.05–1.47, $P = 0.010$). Moreover, the inter-study heterogeneity was completely removed after excluding the study by Chen et al. in recessive model. Deleting other individual study make little difference in corresponding pooled effects of all models (data not shown), which suggesting that our results are statistically robust. The funnel in all models revealed no obvious publication bias. Fig. 5 showed the funnel plots of the recessive model. The results were confirmed by Egger’s linear regression test and Begg’s test (Table 4).

3.5. Association between GNB3 c.825C>T polymorphism with overweight or extremely obese

Of 11 articles, five studies were separately analyzed the relationship between overweight and GNB3 c.825C>T polymorphism. We evaluated the relationship between overweight and GNB3 c.825C>T polymorphism alone. The results revealed a significant association between overweight and GNB3 c.825C>T polymorphism in all inherited models ($P < 0.05$) except a recessive model ($P = 0.084$) (Table 6). As noted, two studies were individually analyzed the association between extremely obese and GNB3 c.825C>T polymorphism. In contrast, no significant association was found in all inherited models ($P > 0.05$) between extremely obese and GNB3 c.825C>T polymorphism (Table 6).
the pooled effect of high quality studies was closer to the overall pooled effect in all inherited model.

Currently, there are several different definitions for overweight and obesity. BMI is the most widely used measures, which provide a useful population-level measure of overweight and obesity. However, BMI cut-off points for overweight and obesity differ in different regions. And in children and adolescents, BMI 85th and 95th percentiles was defined as overweight (Must et al., 1991; Himes and Dietz, 1994). We separately analyzed the association of the GNB3 c.825C>T polymorphism with overweight or extremely obese alone and the results indicated the impact by the genetic factor of GNB3 c.825C>T polymorphism was greater in overweight than extremely obese. The potential reasons maybe that the extremely obese could be affected more significantly than other factors or other genetic factors.

Heterogeneity between included studies is a common problem in meta-analysis. In present meta-analysis, moderate heterogeneity was found in four inherited models. To investigate this problem in greater depth, subgroup analysis and meta-regression analysis showed that quality scores of included studies were the sources of heterogeneity in the four inherited model. And the P value of HWE and publication year were the sources of heterogeneity in the allelic model, homozygous model, and recessive model. Furthermore, the funnel plot and Egger’s linear regression test and Begg’s test indicate no apparent publication bias in the present meta-analysis. "Leave one out" sensitivity analyses indicated that the association was more significant after excluding some studies.

Table 6

| Inherited model | Overweight OR (95% CI) | P | I² (%) | Extremely obese OR (95% CI) | P | I² (%) |
|-----------------|------------------------|---|--------|----------------------------|---|--------|
| T vs. C         | 1.21 (0.98–1.51)       | 0.084 | 0.005  | 1.42 (1.11–1.81)            | 0.005 | 0.005  |
| TT vs. CC       | 1.36 (1.05–1.75)       | 0.006 | 0.007  | 0.81 (0.55–1.19)            | 0.280 | 26.3   |
| CT vs. CC       | 1.36 (1.05–1.75)       | 0.006 | 0.007  | 0.81 (0.55–1.19)            | 0.280 | 26.3   |
| TT vs. (CT + CC)| 1.21 (0.98–1.51)       | 0.084 | 0.005  | 1.42 (1.11–1.81)            | 0.005 | 0.005  |
| (TT + CT) vs. CC| 1.11–1.81              | 0.005 | 0.005  | 1.10–1.81                   | 0.005 | 0.005  |


A previous meta-analysis by Souza et al. showed a trend ($P = 0.053$) associating CC and lower BMI under a fixed model (Souza et al., 2008). This suggests that the $GNB3$ c.825C$\rightarrow$T polymorphism was thought to play a key role in overweight/obesity. Our analysis confirmed the association of the $GNB3$ c.825C$\rightarrow$T polymorphism with overweight/obesity. More recently, a meta-analysis involving 10 studies by Tang et al. failed to observe association of $GNB3$ c.825C$\rightarrow$T polymorphism and overweight/obesity in a fixed effect model under a homogenous model (TT versus CC) (Tang et al., 2014). Their results were inconsistent with the present meta-analysis. The difference could be explained by that they included a review published in 2000 by Siffert et al. (2000), of which data overlapped with the study published in 1999 by Siffert et al. (1999). Moreover, they did not assess the association under other inherited models and perform the stratification analysis by the potential confounding variables. Several limitations in the current meta-analysis should be mentioned. Firstly, some included studies do not comply with HWE due to the fact that a very limited amount of studies reported the association between $GNB3$ c.825C$\rightarrow$T and the overweight/obesity, which may influence the cause-effect relationship. Fortunately, the overall pooled effects were in line with the subgroup analysis consistent with the $P$ value of HWE, which illustrates that our results were stable. Secondly, we had insufficient information regarding genotypes and allelic frequency by different sex. In addition, some authors were contacted via email with respect to missing information, but data was not available.

In conclusion, our results suggested that the presence of $GNB3$ 825TT homozygote might be one of the genetic factors susceptible to overweight/obesity and that male or aged less than 30 years increases the genetic susceptibility. We also demonstrated that $GNB3$ 825TT and overweight alone were significantly associated. Additional large sample size and well-studied association studies are needed to provide powerful evidence to the conclusions.

Conflict of interest

The authors declare that they have no conflict of interest.

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