The Association between GNB3 Gene Polymorphism and Obesity: A Systematic Review and Meta-Analysis

Narges Faramarziyan[1], Masoud Rahmati[1*], Rahim Mirnasouri[1], Mostafa Bahrami[1]

1. Department of Physical Education and Sport Sciences, Faculty of Literature and Human Sciences, Lorestan University, Khoramabad, Iran.

***Correspondence:**
Masoud Rahmati PhD, Department of Physical Education and Sport Sciences, Faculty of Humanities, Lorestan University, Khorramābād, Iran.
Tel: (98) 663 322 3253
Email: rahmati.mas@lu.ac.ir

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Abstract

The association between Guanine Nucleotide Binding protein β protein polypeptide 3(GNB3) C825T polymorphism and obesity has recently been reported. However, the findings remain inconclusive. The aim of this systematic review and meta-analysis was to detect the relationship between GNB3 C825T polymorphism and obesity.

Materials and Methods: Six electronic databases including Embase, Medline, science direct and SID were investigated and searched for English articles, published before February 2016, which referred to the association between GNB3 C825T polymorphism and obesity. Pooled odds ratios (OR) with a 95% confidence interval (CI) were calculated in allele, recessive, dominant and additive genetic models to assess this association.

Results: The findings demonstrated that GNB3 TT homozygote status was significantly associated with an increased risk of obesity compared with CC wild-type homozygote (TT vs. CC: OR= 1.237, 95% CI: 1.040- 1.472, P-value:0.016), while one mutation allele (TC) could not significantly increase the risk of obesity (TC vs. CC: OR= 0.91, 95% CI: 0.79- 1.05, P-value:0.207).

Conclusion: Our meta-analysis suggested a significant association between the TT genotype of the GNB3 gene polymorphism and obesity risk. Thus, targeted healthcare should be strengthened with regard to this gene carrier in order to prevent obesity.

Keywords: polymorphism, GNB3 gene, obesity, meta-analysis.

Introduction

Obesity is characterized as excess fat storage in adipose tissue and abnormality in lipid metabolism (1) and it may be influenced by genetic, environmental factors and their interactions (2). It is an important clinical and public health problem which is rapidly growing all over the world so that about 300 million people around the world are considered obese (3,4). Moreover, it is estimated that 1.12 billion people will be obese around the world in 2030 (4). The social and economic costs of obesity are tremendously high as obesity elevates the risk of several medical complications, such as type 2 diabetes mellitus (T2DM), hypertension, dyslipidemia, and cardiovascular diseases (3,4). The Guanine Nucleotide Binding protein β protein polypeptide 3 (GNB3) gene is one of the five genes coding for a G-protein b subunit that have been identified in the human genome (5,6). The functional C825T polymorphism [rs5443] in

exon 10 of the human GNB3 gene, which encodes the G β 3 subunit of G proteins was recognized (7). In this polymorphism, the 825T allele, rather than the 825C allele, is associated with a splice site in exon 9, leading to the deletion of 41 amino acids in the Gβ3 subunit of G proteins. Evidence suggests that this short isoform marked by the 825T allele is biologically active and associated with enhanced G protein activation (8). All three known b-adrenergic receptors (bARs) are expressed in human adipocytes where they can regulate energy expenditure by stimulating lipolysis and thermogenesis through increased adenylyl cyclase activity. Several functional polymorphisms occur within the coding region of the bAR receptor genes and their G-protein coupled receptors and some have been associated with alterations in lipolysis and thermogenesis (9). The T allele of the GNB3 rs5443 SNP has been shown to cause augmented G-protein activation and thus increased in vitro cell proliferation. The T allele of the GNB3 rs5443 SNP was identified to be associated with obesity, hypertension, and atherosclerosis (10). However, evidence for relevance of GNB3 rs5443 to obesity is currently inconsistent. The T allele of GNB3 rs5443 SNP has been reported to predispose to obesity in German (11-13), Chinese, and South African populations (13). On the other hand, this association with obesity has not been replicated in white Danish subjects (14) and also in a Japanese study (15). In addition, data from a study supports this fact that there was statistically significant association between SNP and total cholesterol levels in a Japanese population (indicating higher levels of cholesterol in subjects with the T allele) (16); even though there are some conflicting results in another Japanese studies showing no association with cholesterol (17). Moreover, previous pharmacogenetics studies (18-20) have revealed that the GNB3 rs5443 polymorphism was associated with weight reduction with sibutramine treatment in overweight or obese participants, suggesting either the T allele (18,20) or the C allele (19) with greater weight loss (10). In general, aforementioned studies results showed that in some of these studies, existence of polymorphism leads to developing obesity, while some other studies showed conflicting results. Therefore, the aim of this research was to achieve solid evidence to answer this critical question: whether there is a relationship between GNB3 gene Polymorphism and obesity or not?

Materials and Methods

Search strategy

In this study medline and Embase databases searched in order to find relevant sources. Source indices used in all relevant articles and reports appeared in electronic search were evaluated to find other probable useful sources. Therefore, we formulated the following PICO (participants of interest, intervention, control and primary outcome of interest) question: Which SNPs of GNB3 rs5443 reported in literature is related to obesity? Key Words used for searching databases selected from medical topical headings MeSH were: "G protein beta 3 polypeptide" or "GNB3" in combination with "polymorphism" or "mutation" or "variant", and in combinations with "obesity" or "overweight". All English-language studies that were published till February 28, 2016, were studied.

Selection Criteria

The inclusion criteria was : 1) original scientific articles 2) studies examining the relationship between GNB3 gene Polymorphism and obesity in adults 3) studies reporting allele and genotype multiplicity for obese individuals and control group 4) articles describing clearly the parameters for diagnosis of obesity 5) studies considering GNB3 gene Polymorphism as the main independent variables. Accordingly, the following exclusion criteria were also used: 1) review articles 2) articles with lack of control group 3) articles associating obesity with diseases 4) articles with no reports about allele and

genotype 5) articles with samples which were pregnant women or postmenopausal 6) articles with samples who had undergone weight loss surgery 7) articles in which individuals were treated with medications 8) the unavailability of full-text articles and articles which were published in a language other than English.

Data extraction

Information regarding guidelines from meta-analysis of observational studies in epidemiology (MOOSE) group were followed to extract the following data: the name of the first author, year of publication, country in which the study conducted, sample size, age, allele and genotype frequency in sample and control groups, measurement methods of GNB3 gene polymorphism and the relationship between GNB3 gene polymorphism and obesity were extracted from the articles.

Quality assessment

Methodological quality of the included studies was independently assessed by two authors using the Newcastle–Ottawa Quality Assessment Scale (NOS) criteria (21). Using this method, each study was judged on standard criteria by two authors (Rahmati M and Mirnasouri R) and subsequently categorized based on three factors: (1) subject selection: 0–4 points; (2) comparability of subject: 0–2 points; (3) clinical outcome: 0–3 points. Studies that were awarded 5 stars or more can be considered as of medium to high quality (22). Moreover, the P-value of Hardy-Weinberg equilibrium (HWE) was assessed with the χ^2 test among the control genotypes (23).

Statistical analysis

In this meta-analysis the association between obesity and GNB3 gene Polymorphism was examined using different genetic models including allelic model (T vs C), additive model (TT vs CC), mutation allele (TC vs cc), dominant model (TT + CT vs CC) and recessive model (TT vs CT + CC) (24). Examining Alleles and genotypes between obese individuals and control group took place by using odds ratios (OR) with confidence coefficient of 95%. To determine heterogeneity of studies; pooled ORs, chi-square and I- square tests were used (evidence for heterogeneity I^2> 50%, %, P<0/1). Heterogeneity in studies using Random-effects model was used (25). Hardy-Weinberg equilibrium (HWE) is an application of the binomial theorem to population genetics and stating that the genetic variation in a population will remain constant from one generation to the next in the absence of disturbing factors. The assessment of departure from HWE is performed by chi-square test in the controls because a deviation from HWE in the cases might indicate a genetic association, and the difference of HWE between the cases and the controls can be used to test for association (26). Sensitivity Analysis used to evaluate whether the results of the meta-analysis is under influence of specific study or studies. Furthermore, the funnel plot graphs were used to assess the bias in publication of the articles. Evaluation of asymmetrical funnel plot was done using Egger's regression asymmetrical test and Begg's tests. Analysis of data was conducted utilizing statistical software STATA (Version 12) the level of significance was considered P<0/05 (27).

Results

As a result of our searching methodology among electronic databases of articles, 1650 studies have been found. After carefully screening the titles and abstracts, 47 articles have been selected after removing duplicates, animal research, and not highly pertinent articles. Studies which had below characteristics were removed from the present meta-analysis: 1) studies carried out in review approach (28-31,2) some cases in which their samples chosen from pregnant or post-menopausal women (32-34,3) obese individuals that their obesity associated with other diseases like diabetes, acute myocardial

infarction, ischemia, hypertension and metabolic syndrome (9,11,14,15,35-39,4) studies that obese individual treated with medications (18-20,40-42,5) studies which did not report allele or genotype frequency (43-45,6) Studies with no control group (46-56,7) individuals undergone weight loss surgery (57,58,8) inaccessibility of full-text articles (59,9) articles which were published in a language other than English (60,61). It should be noted that to access data in studies published in non-English language, the authors of them were requested via email if they are pleased to provide their data. The authors of 2 articles in Chinese language which full text of their articles were not available, did not response to our request and the author of another article which was published in English refused to give us access to full text of his article. Therefore, these three articles were kept out from this study. As a result, 6 papers (10,13,62-65) including 1007 obese patients and 4305 normal weight control were chosen to enter the meta-analysis (Figure 1, Table 1). Information regarding distribution of genotypes, HWE *P*-values in the controls, and obesity is provided in Table 1. In a study published by Siffert et al. (1999), samples were selected from three different races of people; each of them considered as a separate work in this meta-analysis (13). Classification of body mass index (BMI) in this study was considered as following according to the study carried out by Siffert et al. (1999): BMI < 25 as normal weight, BMI ≥ 25 as overweight and BMI > 27 as obese.

Meta-analysis

In the meta-analysis of all involved studies, no significant heterogeneity was detected between the GNB3 C825T polymorphism and obesity risk (*P* for heterogeneity= 0.33, I^2=12.8%) in the addictive genetic model (TT vs. CC). The results showed that GNB3 TT homozygote status was significantly associated with an increased risk of obesity compared with CC wild-type homozygote (Figure 2), while one mutation allele (TC) could not significantly increase the risk of obesity (TT vs. CC: OR=1.237, 95% CI:1.040-1.472, P-value:0.016, Figure 3; TC vs. CC: OR=0.91, 95% CI:0.79-1.05, *P*-value:0.207, *P* for heterogeneity= 0.025, I^2= 52.2%). A significant association was also observed in the recessive model (TT vs. CT+CC: OR= 0.808, 95% CI:0.680-0.961, *P*-value:0.016, *P* for heterogeneity=0. 330, I^2=12.8%), but not in the dominant model (TT+CT vs. CC: OR=1.060, 95% CI:0.902-1.246, *P*=0.480, *P* for heterogeneity=0.005, I^2=65.2%) or allele comparison (T vs. C: OR=1.096, 95% CI: 0.949- 1.267, *P*-value: 0.213, *P* for heterogeneity= 0.318, I^2=14.3%) (Figures 4-6). All the six studies were assessed for the quality according to the Newcastle-Ottawa Scale and most studies scored 5 stars or more, suggesting a moderate to good quality (Table 2). A sensitivity analysis was conducted to assess the influence of each individual study on the pooled OR by removing each study in turn. The results demonstrated no evidence of any individual study having excessive influence on the pooled OR under the dominant and recessive model.

There is no evidence of publication bias for studies that examine the relationship between GNB3gene polymorphism and obesity. Begg's funnel plot and Egger's test was performed to assess the publication bias of the eligible literatures in this meta-analysis. The shapes of the funnel plots in all genetic models did not reveal any evidence of obvious asymmetry. The Egger's test further confirmed the absence of publication bias for any of the genetic models in this meta-analysis (*P*-value:0.218 for additive model, *P*-value:0.394 for mutation model, *P*-value:0.218 for recessive model, *P*-value: 0.254 for dominant model, and *P*-value: 0.081 for allelic model). In addition, Beggs test results were not significant in all genetic models (*P*-value:0.685 for additive model, *P*-value:0.271 for mutation model, *P*-value:0.685 for recessive model, *P*-value: 0.385 for dominant model, and *P*-value:0.351 for allelic model).

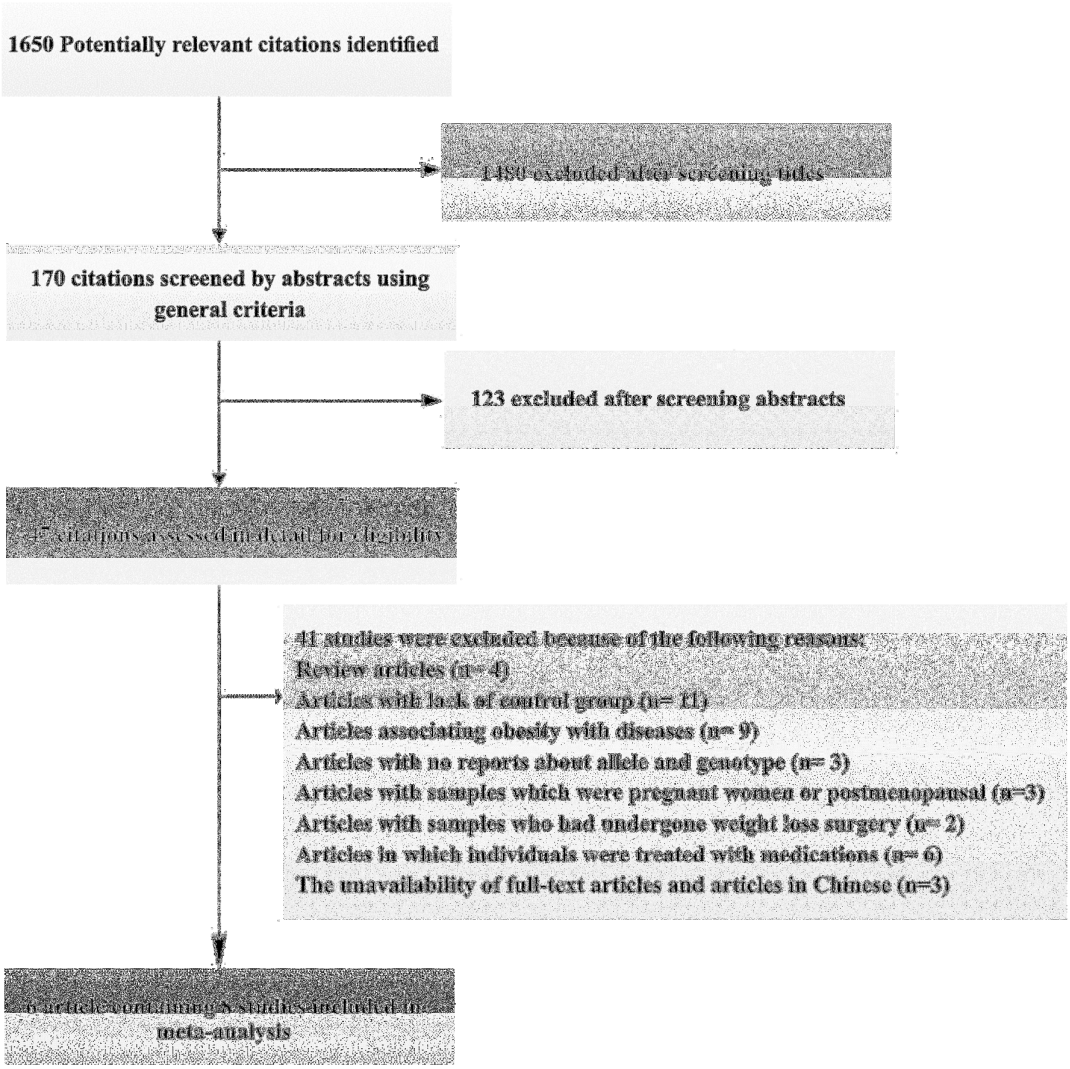

Figure 1. Flow diagram of the included studies

Discussion

The present meta-analysis indicated that the GNB3 C825T polymorphism was associated with obesity in overall populations (TT vs. CC, OR= 1.237, 95% CI: 1.040- 1.472, *P*-value: 0.016), although one mutation allele (TC) could not significantly increase the risk of obesity (TC vs. CC: OR= 0.91, 95% CI: 0.79- 1.05, *P*-value: 0.207). In general, the current meta-analysis includes 1007 obese subjects without symptoms of diseases such as diabetes, metabolic syndrome, hypertension and heart disease and 4345 controls with normal weight from Germany, China, South Africa, Taiwan, Kyrgyzstan and Australia.

Genetic factors are likely to modify the risk of most prevalent diseases. Genetic factors are the main causes of death in adults such as cardiovascular diseases, different types of cancers and its risk factors including hypertension, dyslipidemia, obesity, and

Table 2. Quality assessment conducted according to the Newcastle-Ottawa criteria for all the included studies in this meta-analysis.

First author	Year	Quality indicators		
		Selection	Comparability	Outcome
Siffert	1999	****	**	**
Benjafield	2001	****	**	**
Hinney	2001	****	*	***
Suwazono	2004	**	*	**
Hsiao	2013	****	*	**
Erkin	2013	****	**	**

insulin resistance (66). Gene and environment interactions and lifestyle factors, particularly physical activity can also modify the risk of having the abovementioned diseases. Studies on risk of obesity have identified polymorphism and environmental factors as risk factors. The results of these studies showed that genetic factors may be responsible of 40% to 70% of obesity prevalence (43). The search for genes that increase the susceptibility to develop obesity has become important and one such candidate genes is the GNB gene (43). G protein is one of the most important members of cell receptors closely related to mitosis and cellular growth. GNB3 gene is essential for the synthesis of G protein β3 subunit. A splice variant could be induced by the C825T polymorphism of GNB3 gene, which can lead to a deletion of 41 amino acids of the β3 subunit (67). There is enough evidence that the b3-subunit of heterotrimeric G-proteins (located on chromosome 12p13) is implicated in adipogenesis, adipose distribution and body weight. In particular, the 825T mutation in exon 10 has been found to be positively associated with overweight and post pregnancy weight retention (32).

Several review studies regarding relationship between GNB3 gene polymorphism and different factors including cardiovascular diseases, risk of hypertension, obesity, depression, diabetic and nephropathy have been conducted (29,31,68). Also, several meta-analysis on the relationship of the polymorphism with the diseases including hypertension, cancer, stroke, irritable bowel

Table 1. The data extracted from the articles

Author	Year	Country	Ethnicity	BMI	Sample size		TT		CT		CC		T frequency		Genotyping Method	P_{HWE}
					Case	control	Case	Control	Case	Control	Case	Control	Case	Control		
Siffert (13)	1999	Germany	Caucasian	BMI>27	22	207	5	17	11	88	6	102	10	61	PCR-RFLP	0.753
Siffert (13)	1999	China	Asian	BMI>27	58	832	19	181	30	416	9	235	34	389	PCR-RFLP	0.903
Siffert (13)	1999	South Africa	Black African	BMI>27	22	201	18	138	4	58	0	5	20	167	PCR-RFLP	0.706
Benjafield (63)	2001	Australia	Caucasian	29±5	84	105	4	2	38	44	42	59	23	24	PCR-RFLP	0.504
Hinney (65)	2001	Germany	Caucasian	29.5±4.1	51	254	3	24	23	121	25	109	14	84	PCR-RFLP	0.957
Suwazono (64)	2004	Japan	Asian	27.3	505	2120	120	463	253	1137	132	520	246	1031	PCR-RFLP	0.105
Hsiao (10)	2013	Taiwan	Asian	BMI≥27	176	505	63	153	73	263	40	89	100	285	PCR-RFLP	0.188
Erkin (62)	2013	Kyrgyz	Asian	BMI≥30	89	121	4	5	60	58	25	58	34	34	PCR-RFLP	0.215

Abbreviations: BMI, body mass index; P_{HWE}, the *P*-value of Hardy-Weinberg equilibrium

syndrome were conducted (27,67,69-72). For example, in several studies, there was a significant relationship between GNB3 gene and blood pressure (69,72). But in other studies a significant association between GNB3 gene, stroke, irritable bowel syndrome, hypertension was not (27,70,71). In a Meta-analysis conducted by Zhang et al. (2015), significant relationship between this gene and cancer was not found, but a significant relationship between the GNB3 polymorphism and breast cancer was observed (67).

Guanine nucleotide-binding proteins (G proteins) are key determinants of specific and temporal characteristics of many signaling processes and are expressed in all cells in human body to primarily transduce signals from the cell surface into a cellular response. G proteins consist of α, β, and ɤ subunits and different genes encode for 18 α subunits, 5 β subunits, and 12 ɤ subunits, which enable formation of highly variable heterotrimers (28). Activation of a G protein-coupled receptor results in an exchange of guanosine triphosphate for guanosine diphosphate which will be followed by dissociation of the α subunit from the βɤ complex (31). Subsequently, both α- and βγ-subunits can activate a plethora of effectors e.g. ion channels, phospholipase C, the MAP-kinase pathway, the adenylyl cyclase system, which ultimately results in a cellular response, e.g. hormone secretion, contraction, proliferation, etc (29). G protein activation is terminated through the intrinsic GTPase activity of the *α*-subunit which hydrolyzes bounded GTP to GDP. Following this step, G protein *α*- and *βγ*-subunits re-associate and are available for a new activation cycle through a G protein-coupled receptor (29). As reported the α, β, ɤ subunit composition of G proteins determines the receptor and effector specificities of particular heterotrimers. Thus, alterations in G protein signaling can cause multiple disorders and likely malfunctionality (71).

Possible mechanisms of obesity in 825T allele carriers may be due to the reduction in lipolytic activity in fat cells in response to catecholamines and increased adipogenesis through excessive stimulation through pertussis toxin sensitive (PTX) – receptors (62). Lipolysis is controlled by several hormones, among which catecholamines are the most important in human beings. They act via G-protein-coupled adrenergic receptors (50). Catecholamines have pronounced lipolytic properties, and catecholamine-induced lipolysis is markedly dependent on body regions (i.e., subcutaneous vs. Visceral). Catecholamine-induced lipolysis in visceral adipose tissue is increased, especially in obese individuals, whereas there is lipolytic resistance to catecholamines in subcutaneous adipose tissue (47).

Furthermore, it has been reported that the GNB3 825T polymorphism is possibly associated with blunted lipolytic response due to reduced function of Gprotein-coupled adrenergic receptors (47). Although mechanisms by which the GNB3 C825T polymorphism affects lipid metabolism is not fully understood.

Besides, conflicting results among studies on the relationship of GNB3 C825T gene polymorphism with obesity have been reported. Considering these conflicting results, we could not have clear conclusion to show whether there is a significant relationship between obesity and GNB3 C825T gene polymorphism or not. Suwazano et al. (2004) showed that GNB3 C825T polymorphism was a significant factor for overweight of Japanese people (64). Moreover, Hinney et al. (2001) showed that 825TGNB3 allele does not have a major role in weight of children, adolescents and youth (65). While, Siffert et al. (1999) showed that the 825T allele frequency was significantly higher in overweight and obese individuals compared to individuals with normal weight (13). Furthermore, Kumosani et al. (2014) showed that the presence of the T allele had a major role in obesity since higher amount of TT genotype was observed in obese individuals (43). But, in general, the outcomes of this meta-analysis presented a significant correlation between TT genotype of GNB3

polymorphism and obesity. Therefore, more research is needed to show whether there is a relationship between GNB3 gene and obesity in other different races or not. The results of this meta-analysis showed that there is a significant relationship between GNB3 polymorphism and obesity. However, more resources are needed on obesity to confirm these results.

Conclusions

This meta-analysis indicates that the TT genotype of the GNB3 gene polymorphism is associated with increased risk of obesity.

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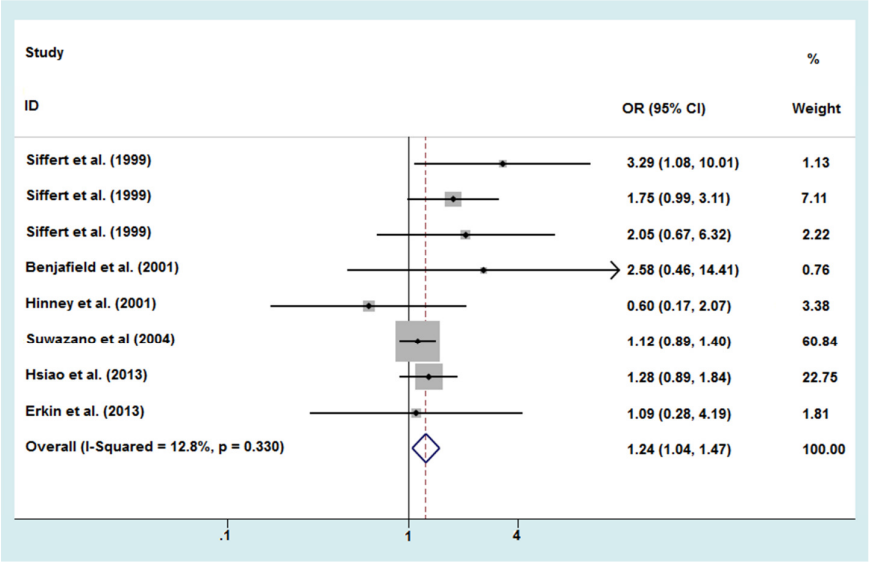

Figure 2. The forest plot of TT versus CC of GNB3 C825T polymorphism and obesity

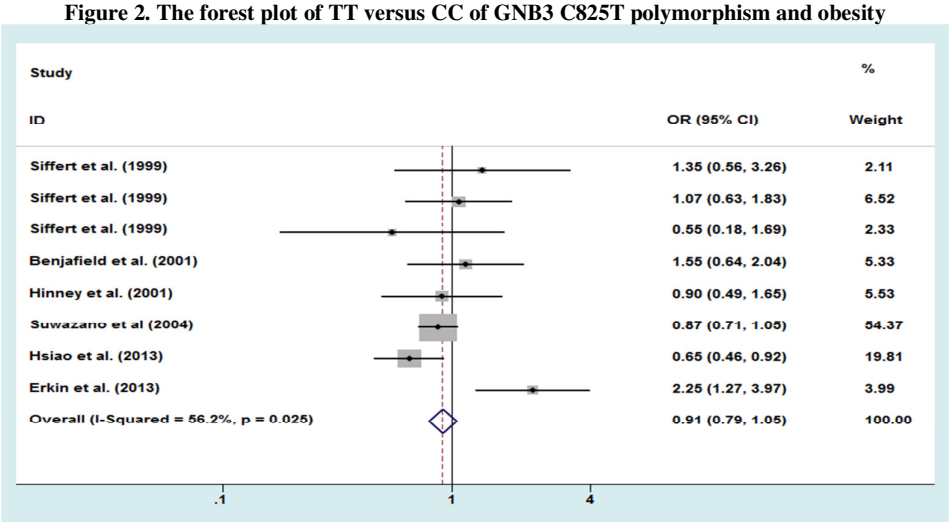

Figure 3. The forest plot of TC versus CC of GNB3 C825T polymorphism and obesity

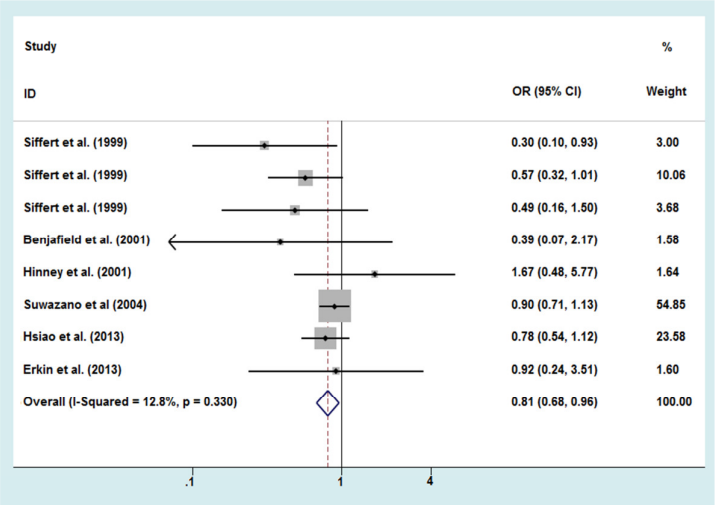

Figure 4. The forest plot of TT versus CT+ CC of GNB3 C825T polymorphism and obesity

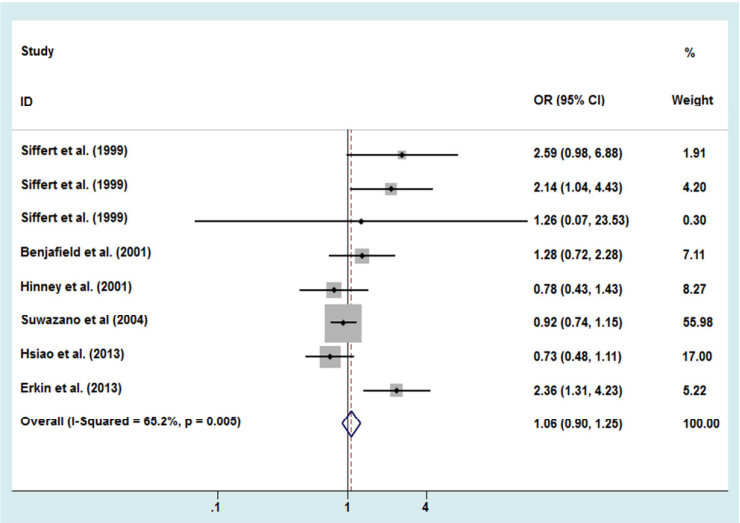

Figure 5. The forest plot of TT+ CT versus CC of GNB3 C825T polymorphism and obesity

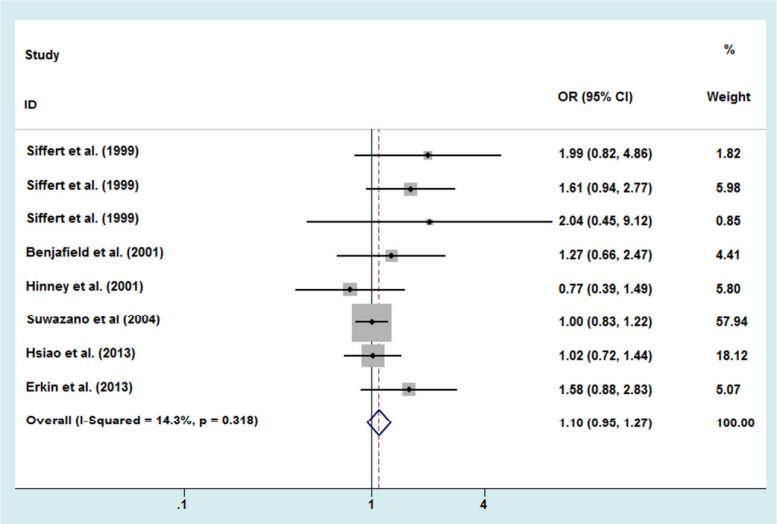

Figure 6. The forest plot of T versus C of GNB3 C825T polymorphism and obesity.

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