The C825T Polymorphism of the G-Protein β3 Gene as a Risk Factor for Depression: A Meta-Analysis

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Abstract

Background

The G-protein β3 gene (GNβ3) has been implicated in psychiatric illness through its effects upon intracellular transduction of several neurotransmitter receptors. Multiple studies have investigated the relationship of the C825T polymorphism of the GNβ3 gene (GNβ3 C825T) to depression and antidepressant response. However, the relationship between GNβ3 C825T and depression remains inconsistent. Therefore, here we performed a meta-analysis to investigate the role of GNβ3 C825T in depression risk.

Methods

Published case-control studies examining the association between GNβ3 C825T and depression were systematically searched for through several electronic databases (PubMed, Scopus, Science Direct, Springer, Embase, psyINFO, and CNKI). The association between GNβ3 C825T and depression risk were assessed by odd ratios (ORs) and their 95% confidence intervals (CIs) for each study. Pooled ORs were constructed for allele contrast (C versus T), homozygote (CC versus TT) model, heterozygote (CC versus CT) model, dominant model (CC + CT versus TT), and recessive (CC versus TT + CT) model. In order to evaluate possible biases, a sensitivity analysis was conducted by sequential deletion of individual studies in an attempt to assess the contribution of each individual dataset to the pooled OR.

Results

Nine studies, including 1055 depressed patients and 1325 healthy controls, were included. A significant association between GNβ3 C825T and depression was found to exist, suggesting that the T-allele of GNβ3 C825T can increase susceptibility to depression. After stratification by ethnicity, the same association was found in the Asian subpopulation, but not the Caucasian subpopulation.
Conclusions
This is the first meta-analysis to reveal a relationship between GNβ3 C825T and depression. Asian T-allele carriers of GNβ3 C825T appear to be more susceptible to depression.

Introduction
Major depressive disorder (MDD) is a prevalent psychiatric disorder characterized by persistent depressed mood and anhedonia [1]. According to clinical and animal model research, different aspects of human physiology are altered in depression, including the neurotransmitter and neuropeptide systems, neurotropic factors, the hypothalamic-pituitary-adrenal (HPA) axis, and hippocampal neurogenesis [2–4].

In particular, reduced G-protein function has been identified in the peripheral blood cells of patients with depression [5], and altered levels of G-proteins have been found in two regions of the prefrontal cortex of depressed human subjects, which were attenuated by antidepressant therapy [6,7]. G-proteins play key roles in molecular signaling following neurotransmitter receptor activation, leading to an increase of intracellular calcium ion (Ca^{2+}) concentrations [8–10]. On this basis of modulating neurotransmitter receptor activation, G-proteins may be one of the keys to understanding the underlying mechanism(s) of depression [11].

In recent years, several genome-wide association studies (GWAS) have discovered statistically significant genetic variations relevant to the etiology of depression, yielding novel insights into genetic risk factors underlying depression [12,13]. Several genetic polymorphisms, such as BDNF Val66Met and 5-HTR2A T102C, have been identified as potential risk factors for depression [14,15]. Another such polymorphism—the C825T polymorphism within the G-protein β3 gene (GNβ3 C825T)—has been increasingly linked to depression. The T-allele of GNβ3 C825T can result in the deletion of 41 amino acids, leading to alterations in cellular signal transduction and ion transport [16]. The association between GNβ3 C825T and depression was first identified through a polymerase chain reaction (PCR)-based method [17], which has been followed by additional GNβ3 genotyping studies across different countries worldwide.

However, results from these genotyping studies have been contradictory. While some studies have found that the frequency of the T-allele of GNβ3 C825T is significantly higher in depressed patients, several other studies have shown no associations between depression and GNβ3 gene polymorphisms. Therefore, here we performed a meta-analysis to assess the relationship between depression and GNβ3 C825T.

Methods
Search Strategy and Inclusion Criteria
All published studies examining the association between GNβ3 C825T and depression were systematically searched for through several electronic databases (PubMed, Scopus, Science Direct, Springer, Embase, psyINFO, and CNKI) from January 1990 to September 2014 using the following search terms: (“G protein-β-3” OR GNβ3) AND C825T AND (“mood disorders” OR “major depressive disorder” OR MDD OR “depressive episode” OR “depression”).

Only full-length articles meeting the following criteria were included: (i) a case-control design; (ii) evaluating GNβ3 C825T and depression risk; (iii) an adequate description of the diagnostic criteria for patient inclusion and exclusion; and (iv) sufficient reported data for estimating odds ratios (ORs) and their 95% confidence intervals (95% CIs). Abstracts, conference
proceedings, case studies, family-based designs, population-based studies of healthy subjects, reviews, and duplicate cohorts were excluded.

Data Extraction
Three authors independently extracted data to avoid extraction errors with discrepancies resolved by discussion. The following parameters were extracted from each eligible article: first author, publication year, country of origin, ethnicity (defined as either Asian or Caucasian), diagnostic system, number of cases and controls (male/female), antidepressant therapy, Hardy-Weinberg equilibrium, the available genotype, and allele frequency information for the C825T polymorphism.

Statistical Methods
All statistical analyses were conducted using Rev Man 5.0.1 and STATA software (version 12.1; Stata Corporation, College Station, Texas, USA). All P-values were two-sided with a P<0.05 considered statistically significant. The association between GNB3 C825T and depression risk were assessed by ORs (and their 95% CIs) for each study. Pooled ORs were constructed for allele contrast (C versus T), homozygote (CC versus TT) model, heterozygote (CC versus CT) model, dominant model (CC + CT versus TT), and recessive (CC versus CT+TT) model. A chi-squared-based Q-statistic test was used to detect the heterogeneity among studies. If the P-value of the Q-test exceeded 0.05 (indicating a lack of heterogeneity among the studies), a fixed-effect model was used; otherwise, a random-effects model was used. We used a Z-test to determine the significance of the pooled ORs with a P<0.05 considered statistically significant.

In order to evaluate possible biases, a sensitivity analysis was conducted by sequential deletion of individual studies in an attempt to assess the contribution of each individual dataset to the pooled OR. Finally, we estimated publication bias by Egger’s test with a P<0.05 considered statistically significant.

Results

Literature Search Results
The study selection procedure is shown in Fig 1. The literature search identified 230 potentially relevant records. After screening titles and abstracts, 29 full-text articles were reviewed, of which 20 were excluded for the following reasons: (i) four studies were systematic reviews or meta-analyses on G-protein function [6,11,18,19]; (ii) seven studies assessed SNP effects in other psychiatric disorders [20–26]; (iii) three studies did not use a case-control design [27–29]; (iv) three studies did not assess GNB3 C825T but measured G-protein expression [5,30,31]; and (v) three studies assessed GNB3 C825T and the antidepressant response [16,32,33]. There were no previously published GWAS concerning GNB3 C825T in depression, so no GWAS was included in this meta-analysis.

Hence, nine studies were ultimately included in this meta-analysis based on our inclusion criteria [34–42]. The study characteristics are displayed in Tables 1 and 2. Of these nine included studies, three were on Caucasians and the other six were on Asians. The genotype distributions were in agreement with the Hardy-Weinberg equilibrium for each individual study.

Overall Meta-Analysis
The nine case-control studies, consisting of 1055 depressed cases and 1325 controls, were pooled together to assess the association between depression and GNB3 C825T. On the basis of the random effects model, the pooled OR for the T-allele of GNB3 C825T showed a significant
correlation with depression risk under the allele model (C-allele versus T-allele: OR = 1.39, 95% CI = 1.13–1.72, Z = 3.10, P = 0.002; Fig 2). When we calculated the pooled OR for TT homozygosity relative to CC homozygosity, the OR increased to 1.84 (95% CI = 1.20–2.83, Z = 2.81, P = 0.005; Fig 3). Significant associations between the T-allele of GNβ3 C825T and depression risk were also observed under the dominant model (CC + CT versus TT: OR = 1.54, 95% CI = 1.08–2.18, P = 0.02), the recessive model (CC versus CT+TT: OR = 1.53, 95% CI = 1.15–2.04, P = 0.02), and the heterozygote model (CC versus CT: OR = 1.32, 95% CI = 1.08–1.62, P = 0.03; Figs 2 and 3).

Subgroup Analysis

A subgroup analysis was performed based on ethnicity. The ethnicity-stratified analysis indicated that GNβ3 C825T is strongly related to depression risk in the Asian subpopulation under all genetic models except for the heterozygote model (CC versus CT: OR = 1.35, 95% CI = 1.13–1.62, Z = 2.81, P = 0.005; Fig 3).
CI = 0.87–2.08, \( P = 0.18 \); Table 3). However, no relationship between GNβ3 C825T and depression was found in Caucasian subpopulation under any genetic model (Figs 2 and 3).

**Heterogeneity Analysis**

Significant heterogeneity was found among ORs in overall comparisons (\( I^2 = 64\% \), \( \tau^2 = 0.06 \) for allele model; \( I^2 = 61\% \), \( \tau^2 = 0.26 \) for homozygote model; \( I^2 = 61\% \), \( \tau^2 = 0.17 \) for dominant model), while no heterogeneity was found under the heterozygote model (\( I^2 = 37\% \), \( \tau^2 = 12.76 \)). To determine the origins of the heterogeneity, subgroup analysis on ethnicity

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**Table 2. Genotyping Characteristics of Included Studies.**

| Author   | Diagnosis | Cases | Genotype distribution (%) | Allele frequency (%) | HWE |
|----------|-----------|-------|---------------------------|----------------------|-----|
|          |           |       | CC | CT | TT | C   | T   | HWE |
| Alessandro | Control  | 76    | 36(47) | 31(41) | 9(12) | 103(68.0) | 49(32.0) | Yes |
|          | MDD       | 222   | 86(39) | 115(52) | 21(9) | 287(65.0) | 157(35.0) |     |
| Anttila  | Control   | 392   | 218 (55.6) | 144 (36.7) | 30 (7.7) | 580(74.0) | 204(26.0) | Yes |
|          | Depression | 119 | 63 (52.9) | 46 (38.7) | 10 (8.4) | 172(72.3) | 66(27.7) |     |
| Cao      | Control   | 156   | 44(28.2) | 72(46.2) | 40(25.6) | 160(51.3) | 152(48.7) | Yes |
|          | Depression | 180 | 20(11.1) | 76(42.2) | 84(46.7) | 116(32.2) | 244(67.8) |     |
| Chen     | Controls  | 106   | 29 (27.4) | 41 (38.7) | 36 (34.0) | 99(46.7) | 113(53.3) | Yes |
|          | PSD       | 53    | 8(15.1) | 22 (41.5) | 23 (43.4) | 38 (35.8) | 68 (64.2) |     |
| Kunugi   | Control   | 198   | 49 (24.7) | 90 (45.5) | 59 (29.8) | 188 (47.5) | 208 (52.5) | Yes |
|          | Depression | 68   | 16 (23.5) | 32 (47.1) | 20 (29.4) | 64 (47.1) | 72 (52.9) |     |
| Lee      | Control   | 133   | 43 (32.3) | 62 (46.6) | 28 (21.1) | 148 (56.0) | 118 (44.0) | Yes |
|          | MDD       | 106   | 19 (17.9) | 60 (56.6) | 27 (25.5) | 98 (46.0) | 114 (54.0) |     |
| Lin      | Control   | 153   | 31 (20.0) | 90 (59.0) | 32 (21.0) | 152 (52.0) | 154 (48.0) | Yes |
|          | Depression | 65   | 16 (25.0) | 36 (55.0) | 13 (20.0) | 68 (52.3) | 62 (47.7) |     |
| Peter    | Control   | 111   | 57 (52.0) | 46 (41.0) | 8 (7.0) | 160 (72.0) | 62 (28.0) | Yes |
|          | Depression | 88   | 33 (38.0) | 36 (41.0) | 19 (21.0) | 102 (58.0) | 74 (42.0) |     |
| Xiao     | Control   | 100   | 27 (27.0) | 51 (51.0) | 22 (22.0) | 105 (52.5) | 95 (47.5) | Yes |
|          | Depression | 154 | 35 (22.7) | 49 (31.8) | 70 (44.8) | 119 (38.6) | 189 (61.4) |     |

HWE: Hardy-Weinberg equilibrium; MDD: major depressive disorder; PSD: post-stroke depression.

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**Fig 2. Meta-Analyses for the Association between the GNβ3 C825T Polymorphism and Depression.**

Overall and subgroup forest plots showing the summary effect sizes and heterogeneity findings for (A) C-allele versus T-allele and (B) the recessive model (CC versus CT+TT).

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was carried out as described above. However, significant heterogeneity remained among the Asian and Caucasian subpopulations.

Sensitivity and Publication Bias Analysis

Sensitivity analyses were conducted with the leave-one-out method to assess the degree to which each individual study influenced the results of the overall analysis. The results of the sensitivity analysis confirmed that no single study influenced the pooled ORs (S1–S5 Tables). No strong statistical evidence for publication bias was observed in Egger’s test (all P>0.05) (S1–S5 Figs).

Discussion

To our knowledge, this is the first meta-analysis to demonstrate a relationship between GNB3 C825T and depression. We used 5 models to estimate the relationship between G protein-β-3 gene C825T polymorphism and depression. A significant association between T-allele within GNB3 C825T and depression were found both in the homozygote and heterozygote genotype variation. The results of the dominant model and the recessive model supported CT genotype and TT genotype respectively could increase the risk of depression. Notably, compared with cohorts without the variation, the frequency of the GNB3 C825T TT genotypes in depressed patients was significantly higher than that of healthy controls with an increase of depression by 84 percent; the heterozygote variation (CT) caused an increase of depression by 32 percent as well. The results of our meta-analysis among all the 5 models showed that GNB3 C825T polymorphism increased a risk of depression and the sensitivity analyses further confirmed the stability of the results, suggesting that GNB3 C825T may be an important heritable factor.
underlying the genetic mechanism of depression. Our results also show a significant association between the T-allele of GNB3 C825T and depression risk in Asians, but not in Caucasians.

GNB3 C825T has been shown to be predictive of depressive mood in a young, healthy Western population [29], and previous German studies [17,29,41] report that T-allele carriers of GNB3 C825T are more prone to depression. In contrast to these previous studies, our results show that the C825T polymorphism does not show any relationship with depression risk in Caucasians. In accordance with our findings, a previous meta-analysis performed by Hu et al. [19] found that GNB3 C825T has no effect on the antidepressant response to MDD in Caucasians. Rosskopf et al.’s analysis of GNB3 gene polymorphisms in Caucasians, Africans, and Asians [43] found that the prevalence of GNB3 haplotypes in these various ethnic populations differs. Notably, the two key GNB3 polymorphisms, termed ‘C-haplotype’ and ‘T-haplotype’, were restricted to one or two major ethnic populations. As higher T-allele frequencies of GNB3 C825T are found in Asians over Caucasians, we speculate that ethnogenetic heterogeneity in T-allele frequencies may underlie these observed discrepancies between Asians and Caucasians.

Thus far, the majority of psychiatric studies have focused on investigating the function and expression of G-proteins in affective disorders. G-proteins are composed of three subunits, which can dissociate into Gα and Gβγ units after receptor activation. The Gβ subunit is further subdivided into three subtypes: 1, 2, and 3 [44,45]. Significant elevations in the stimulatory Gα subunit (Gαs) have been observed in peripheral blood cells and post-mortem brain tissue from bipolar depressed patients [46]. Moreover, peripheral blood cells demonstrate elevated platelet levels of Gα in patients with unipolar major depression [30].

Ever since Siffert et al. first identified a genetic variant (C825T) in exon 10 of the G-protein gene [47], GNB3 C825T has become one of the most investigated genetic variations in bipolar depression and major depression [20,37]. Previous studies have attempted to determine the association between GNB3 C825T and antidepressant response in MDD patients. Since disparate conclusions exist from these studies, Hu et al. performed a meta-analysis, including seven studies composed of 1047 depressed patients, to assess this question [19]. His research group showed that GNB3 C825T may influence antidepressant response to MDD among Asians. Accordingly, our meta-analysis demonstrates that GNB3 C825T may be a possible risk factor for depression in Asians. As GNB3 C825T has been previously associated with monoamine neurotransmitter receptor activation [48], the altered signal transduction produced by the T-allele of GNB3 C825 may underlie the findings from Hu et al.’s and our meta-analyses. These findings may provide genetic target(s) to explore the underlying mechanism of depression and aid in the development of more effective antidepressants.

Significant heterogeneity was found among ORs in the allele model, homozygote model, and dominant model. Possible factors underlying this high heterogeneity may include age, gender, and ethnicity. However, no differences were detected after an ethnicity-based subgroup analysis. Gender differences were also considered; however, due to the lack of reported data, we could not perform this analysis. Notably, Anttila et al. has previously identified an association between GNB3 C825T and depression risk in females but an opposing trend in males [34]. Clearly, larger clinical studies on GNB3 C825T and depression risk with age-based, gender-based, and ethnicity-based subgroups are necessary to analyze these factors.

Several limitations should be mentioned with respect to our findings. Firstly, the number of included studies was not sufficient for a comprehensive analysis of GNB3 C825T and depression risk in the Caucasian subpopulation. Thus, more studies are needed to explore the relationship between GNB3 C825T and depression in Caucasians. Secondly, only English studies were included in the meta-analysis. This may have been a source of publication bias although no such publication bias was found in our meta-analysis. Thirdly, we did not analyze the possible impact of gender differences, which may explain the observed heterogeneity. Finally, one
study by Chen et al., which mainly targeted PSD patients, was not excluded from this study, as it could be classified into depression. The sensitivity analyses indicated that this study did not influence the effect size or conclusions.

In conclusion, this is the first meta-analysis to reveal a relationship between GNβ3 C825T and depression. We found that Asian T-allele carriers of GNβ3 C825T are more susceptible to depression. In contrast, no significant association between T-allele carriers of GNβ3 C825T and depression risk was found in Caucasians. These results may provide clinicians and public health administrators with an important screening tool for assessing depression. As many factors have been associated with depression risk, additional factors (such as gender, age, ethnicity, and environmental factors) should be taken into consideration in future studies on this topic.

Supporting Information

S1 Fig. Egger’s Test for C-Allele versus T-Allele.
(TIF)

S2 Fig. Egger’s Test for CC versus CT+TT.
(TIF)

S3 Fig. Egger’s Test for CC versus TT.
(TIF)

S4 Fig. Egger’s Test for CC versus CT.
(TIF)

S5 Fig. Egger’s Test for CC+CT versus TT.
(TIF)

S1 File. PRISMA 2009 Flow Diagram.
(DOC)

S2 File. PRISMA 2009 Checklist.
(DOC)

S3 File. Meta-analysis-on-genetic-association-studies-form.
(DOCX)

S1 Table. Sensitivity Analyses for C-Allele versus T-Allele.
(DOCX)

S2 Table. Sensitivity Analyses for CC vs. CT+TT.
(DOCX)

S3 Table. Sensitivity Analyses for CC vs. TT.
(DOCX)

S4 Table. Sensitivity Analyses for CC vs. CT.
(DOCX)

S5 Table. Sensitivity Analyses for CC+CT vs. TT.
(DOCX)

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Author Contributions
Conceived and designed the experiments: CZ LF. Performed the experiments: SB CH. Analyzed the data: JP XW LW LS. Contributed reagents/materials/analysis tools: QM. Wrote the paper: LF PX.

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