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The polymorphism of G protein β3 subunit C825T and cancer risk: A Meta-analysis

Yaxuan Zhang, Dongfeng Han, Wenjin Wei, Xiupeng Xu, Rui Zhang, Qingsheng Dong, Xiefeng Wang, Junxia Zhang, Yingyi Wang, Ning Liu

ABSTRACT

Aims: In previous studies, G protein β3 subunit (GNB3) C825T polymorphism was reported to have association with various cancers. However, the results were inconclusive, this meta-analysis was performed to investigate the association between GNB3 gene polymorphism C825T and cancer risk. Methods: A comprehensive search in PubMed database was conducted for studies by March, 2014. Meta-analysis was performed using the STATA 11.0 software. Cancer risk associated with GNB3 C825T was estimated by pooled odds ratios (ORs) and 95% confidence intervals (95% CIs). Results: Nine independent studies including 2246 cancers and 3851 controls were included in our meta-analysis. Our results indicated that GNB3 C825T was not associated with the risk of cancer for alleles T vs C [odd ratio (OR) = 1.03, 95% confidence interval (95%CI): 0.95–1.12], TT vs CC (OR = 1.10, 95%CI: 0.91-1.33), CT vs CC (OR = 1.03, 95%CI: 0.91–1.16), CT/TT vs CC (OR = 1.04, 95%CI : 0.93–1.17), and TT vs. CC/CT (OR = 1.01, 95%CI : 0.78-1.31). In stratified analysis, however, we found a significant association between GNB3 C825T and increased breast cancer risk in Caucasian (TT vs CC OR=1.44, 95% CI=1.02–2.04; TT vs CT/CC OR=1.49, 95% CI=1.07–2.09). Conclusion: The GNB3 C825T polymorphism was not associated with the risk of cancers as a whole, but there was a significant association between the polymorphism and breast cancer in Caucasian.

Keywords: Cancer, GNB3, C825T, Meta-analysis, Polymorphism

Yaxuan Zhang[1], Dongfeng Han[1], Wenjin Wei[1], Xiupeng Xu[1], Rui Zhang[1], Qingsheng Dong[1], Xiefeng Wang[1], Junxia Zhang[2], Yingyi Wang[2], Ning Liu[3]

Affiliation: [1]Marster, Department of Neurosurgery, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu Province, PR China; [2]Doctor, Department of Neurosurgery, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu Province, PR China; [3]Professor, Department of Neurosurgery, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu Province, PR China.

Corresponding Author: Ning Liu, 300 Guangzhou Road, NanJing City, JiangSu province, PR, China. 210029; Email: liuning0853@126.com

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INTRODUCTION

G protein, operation as a molecular transducer, was necessary for different biological signals outside of a cell transmit into the inside of the cell. G protein was composed by α, β, and γ subunits, and β and γ subunits forming a functional monomer [1]. The beta-3 subunit is one of the most important components of intracellular

signal transduction in cells and was encoded by G protein β-3 gene (GNB3) [2]. Once activated, α and β subunits dissociated from the receptor and the state of serious intracellular effecter systems changed [3, 4]. Therefore, G protein plays an important role in intracellular signal transduction, and once hurt may induce cells out of control, which could be one of the mechanisms of tumorigenesis.

The GNB3 gene, consists of 12 exons, located on chromosome 12p13 [5]. The polymorphism C825T of GNB3 located in exon 10. In previous studies, polymorphism of GNB3 C825T has been reported to have association of variety disease such as obesity, heart disease [6–8], hypertension and lately It is reported that the polymorphism was correlated with the cerebrovascular risk independent of blood pressure [9]. However, the GNB3 C825T allele, was reported to have association with G protein activation, which could resulting in increased cell proliferation [10, 11]. Some researchers indicated that the polymorphism C825T of GNB3 could be a potential candidate biological marker of cancer risk [12], for that the wrong synthesis of G protein was associated with signaling processes inside of cells, as well as cell growth and replication control [2, 13–15]. In recent years, the association between C825T polymorphism of GNB3 and cancers, including breast cancer [16, 17], prostate cancer [18], thyroid carcinomas [19], bladder cancer [20], gastric cancer [21], cholangiocarcinoma [22], glioma [23], and even lymphocytic leukemia [24] has been studied, however, the results were inconsistent.

Therefore, to determine whether the GNB3 C825T polymorphism was associated with different cancers and whether the polymorphism could proved to be one potential cancer marker, we preformed this meta-analysis, which may be important for the previous diagnosis of cancers and may helpful for researchers who interested in the association between GNB3 gene and cancer.

MATERIALS AND METHODS

Publication search

To acquire all the studies that have association of the GNB3 C825T polymorphism with cancer risk, we searched the PubMed, Wanfang, CNKI (China National Knowledge Infrastructure) database, using the terms "GNB3 polymorphism" and "G Protein β3 polymorphism" and "cancer" up to March 31, 2014 without language restrictions. The searching work were performed by two reviewers independently to ensure the correctness of our work.The retrieved literatures was scrutinized to ensure whether data on the topic of interest were included.

Inclusion criteria

Studies included in our meta-analysis had to fit the following criteria: (1) studies that evaluated the relationship between the GNB3 C825T polymorphism and cancer; (2) a case-control study; (3) the available allele frequency of the GNB3 C825T allele; (4) providing sufficient data of GNB3 C825T polymorphism to calculate the odds ratio (OR) with 95% confidence interval (95% CI). Accordingly, case-only studies, reviews, or studies without usable data were all excluded.

Data extraction

The following information from each eligible study was extracted carefully for our analysis: first author's name, year of publication, cancer type, country of origin, ethnicity, total number of cases and controls, number of cases and controls with the GNB3 C825T polymorphism (CC genotype with CT and TT genotypes). We examined the extracted information by two authors independently to ensure that the job compiled without man-made faults.

Statistical analysis

We used χ2 test to test whether genotype frequencies of control groups were in Hardy–Weinberg equilibrium (HWE). Then, we employed the odds ratios (OR) and 95% confidence intervals (95% CIs) of the recessive genetic model (TT vs CT/TT), dominant genetic model (CT/TT vs CC), and homozygote comparison (TT vs CC), heterozygote comparison (CT vs CC) as well as allele T vs. allele C in cases and controls to assess the association between the GNB3 C825T polymorphism and cancer risk. Stratified analysis were performed in the subgroups of the same cancer type or the same race which consisting of more than two studies. We employed the Q-statistic and I-squared statistic to determine the degree of heterogeneity, $p<0.05$ in Q-statistic or I-squared statistic >50% was regarded as significant heterogeneity. When there was no statistical heterogeneity, we used the fixed-effect model and when there was a statistical heterogeneity, we used the random-effect model. All statistical analyses were performed with the STATA package version 11.0 (Stata Corporation, USA).

To conduct sensitivity analysis, we deleting a single study each time involved in the meta-analysis to identify the potential influence of the individual dataset on the pooled ORs. We employed the Begg's funnel plots and Egger's test to assess the potential publication bias and the asymmetry of the funnel plot, respectively [25, 26].

RESULTS

Study characteristics

A total of 20 studies were retrieved in Pubmed by the keywords mentioned earlier. Among these studies, we extracted 6097 subjects involving 2246 cases and 3851 controls in nine available literatures [12, 16–19, 21, 22, 27, 28], and we excluded the other literatures for that two studies have no data we wanted [20, 29], four were not case-control studies [23, 24, 30, 31], and five

paid no attention to the relationship between GNB3 polymorphism and cancers [32–36]. To amplify the sample size, we included the two studies which were not in agreement with HWE [12, 22] in our meta-analysis, and the results were not changed compared to the results that excluded the two studies. In the nine studies, there were six case-control studies of Caucasian, two of Asians, and one of Latino. The characteristics of each case-control study are summarized in Table 1.

Quantitative synthesis

In the meta-analysis of all involved studies, the Q-test showed there was no heterogeneity in all genetic models of the nine studies except the genetic model TT versus CC/CT, therefore we used random effects model in the TT versus CC/TT model and the fixed effects model in the rest of genetic models to calculate the combined effects. Finally, the OR (95% CI) values of the genetic models in whole samples were: T versus C: 1.03(0.95–1.12) P=0.29 (for heterogeneity); TT versus CC: 1.10 (0.91–1.33) P=0.14; TC versus CC: 1.03(0.91–1.12) P=0.13; CT/TT versus CC: 1.04 (0.95–1.12) P=0.87; TT versus CC/CT: 1.01(0.78–1.31) P = 0.03. These results indicated in a certain extent that the individuals with TT homozygote have an increased risk of cancer compared with those the CC homozygote and TC heterozygote carriers, but there was no statistical significance.

Then we performed a stratified analysis, as the results given in Table 2, no statistical association between GNB3 C825T polymorphism and cancer risk was observed either by ethnicity or by cancer type. When we preformed the stratified analysis by breast cancer in Caucasian, however, we come to a conclusion that the homozygote genotype TT was associated with significantly increased breast cancer risk compared with the homozygote genotype CC (OR=1.44, 95% CI: 1.02–2.04), and CT/CC (recessive model OR=1.49, 95% CI: 1.07–2.09), but no statistical significance was observed when we compared CT versus CC (OR=0.93, 95% CI: 0.75–1.15) and TT/TC versus CC (dominant model, OR=1.01, 95% CI: 0.83–1.23).

Sensitivity analysis and Publication bias

We performed a sensitivity analysis to ensure the confidence for the results, although there was no significant heterogeneity in most genetic models except the genetic model CT/TT versus TT. After exclusion of either individual study, there was little modification of the estimates with pooled ORs ranging from 0.95 to 1.12 (Figure 1), this showed clearly that the results of our meta-analysis was believable.

We employed Begg's test and a funnel plot to estimate the publication bias of the studies included in our meta-analysis. And the result showed that there was no significant publication bias for GNB3 C825T polymorphism, and the funnel plot showed a symmetrical distribution of the studies (Figure 2).

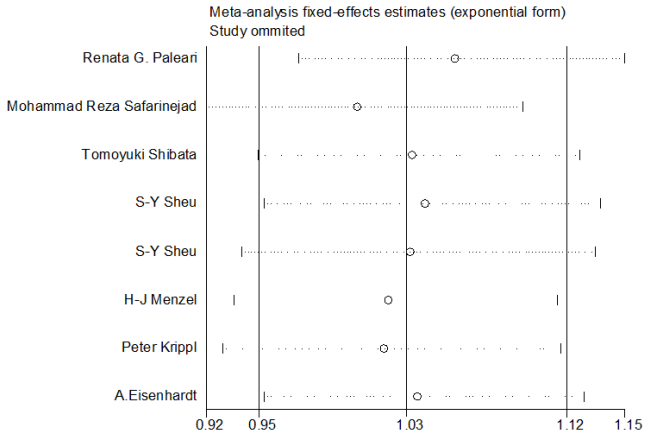

Figure 1: Sensitivity analysis of included studies.

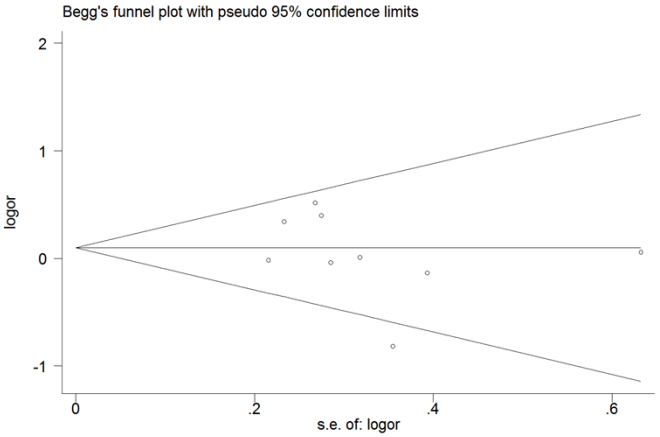

Figure 2: Begg's funnel plot for publication bias test, TT versus CC; each point represents a separate study for the indicated association. Log (OR): natural logarithm of OR. Horizontal line represents size of effect.

DISCUSSION

G protein is one of the most important members of cell receptors, was closely related to mitosis and cellular growth [37]. 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 [2]. In the previous studies, researchers had concerned about the association between GNB3 C825T polymorphism and other diseases such as obesity [38], hypertension [2, 39], cardiovascular disease [40]. However, in the past decade, increasing researchers were attracted by the potential relationship between the GNB3 C825T polymorphism and cancer, so that the association between GNB3 with its genetic polymorphism and risk of cancer has been widely studied.

From previous studies, we cannot obtain a clear conclusion that whether the GNB3 C825T polymorphism was associated with cancer risks, even the same type of

Table 1: Characteristics of studies included in the meta-analysis

Firstau	Year	Cancer	Country	Race	Case	Control	caseCC	caseCT	caseTT	conCC	conCT	conTT	HWE
Renata G. Paleari	2011	breast cancer	Brazil	Latino	134	129	43	71	20	37	53	39	0.04
Mohammad Reza Safarinejad	2012	Prostate Cancer	Iran	Asian	172	344	44	87	41	113	168	63	0.97
Tomoyuki Shibata	2010	gastric cancer	Japan	Asian	161	183	33	90	38	42	84	48	0.66
Christian Dominik Fingas	2010	Cholangiocellular carcinoma	Germany	Caucasian	40	40	17	16	7	18	15	7	0.00
S-Y Sheu	2007	thyroid tumour	Germany	Caucasian	431	321	209	189	33	152	144	25	0.25
S-Y Sheu	2005	thyroid tumour	Germany	Caucasian	361	1859	171	160	30	906	791	162	0.56
H-J Menzel	2004	breast cancer	Austria	Caucasian	215	371	102	82	31	176	159	36	0.99
Peter Krippl	2004	breast cancer	Austria	Caucasian	497	493	247	198	52	247	209	37	0.43
A. Eisenhardt	2011	prostate cancer	Germany	Caucasian	235	111	114	98	23	52	47	12	0.78

Table 2: Meta-analysis of the GNB3 polymorphism and cancer risk association in total and race

	Sample size		OR (95% CI)		P		
	Case	Control	T vs. C	TT vs. CC	CT vs. CC	CTTT vs. CC	TT vs. CCCT
Total	2246	3851	1.03(0.95–1.12) 0.30	1.10(0.91–1.33) 0.14	1.03(0.91–1.16) 0.86	1.04(0.93–1.17) 0.87	1.01(0.78–1.31) 0.03
Ethnicity							
Asian	333	527	1.16(0.95–1.41) 0.19	1.35(1.90–2.02) 0.22	1.34(0.96–1.89) 0.94	1.35(0.98–1.86) 0.67	1.09(0.78–1.51) 0.11
Caucasian	1779	3195	1.03(0.94–1.14) 0.95	1.14(0.91–1.43) 0.69	0.98(0.86–1.12) 0.96	1.01(0.89–1.15) 0.99	1.15(0.93–1.43) 0.54
Cancer type							
breast cancer	846	993	1.01(0.88–1.17) 0.05	1.02(0.52–1.99) 0.01	0.95(0.78–1.16) 0.75	0.99(0.82–1.19) 0.83	0.99(0.45–2.17) 0.00
prostate cancer	407	455	1.15(0.94–1.42) 0.15	1.36(0.88–2.10) 0.17	1.14(0.83–1.58) 0.31	1.18(0.87–1.60) 0.18	1.24(0.84–1.82) 0.31
thyroid tumor	792	2180	1.00(0.87–1.15) 0.71	0.97(0.70–1.36) 0.95	1.03(0.85–1.24) 0.55	1.02(0.85–1.22) 0.59	0.96(0.69–1.33) 0.92
breast cancer in Caucasian	712	864	1.10(0.94–1.28) 0.87	1.44(1.02–2.04) 0.88	0.93(0.75–1.15) 0.78	1.01(0.83–1.23) 0.94	1.49(1.07–2.09) 0.81

cancer. For instance, Safarinejad et al. indicated that the frequency of the GNB3 825T allele in patients with prostate cancer was significantly higher than in controls, for that patients with prostate cancer who had the TT genotype were at 2.52 times higher risk for prostate cancer than the CC genotype referent group (OR 2.22, 95% CI: 1.18–4.22, p=0.008)[18], however, Eisenhardt et al. suggested that there was no association between prostate cancer and the polymorphism of the GNB3 C825T [21]. So a meta-analysis was needed to certify the association between this polymorphism and cancer risk.

In our meta-analysis, we involved a total of nine case-control studies in Caucasians, Asians, and Latinos including five different types of cancer. To investigate the role of GNB3 C825T polymorphism in cancer, we calculated the effect of different genetic models involving T vs C, TT vs CC, TC vs CC, CT/TT vs CC (dominant genetic model) and TT vs CT/TT (recessive genetic model). Finally, our study suggested that there was no association existed between the GNB3 C825T polymorphism and cancer risk in the overall population. Since the studies involved in our meta-analysis including just one from Latinos, when performed a stratified analysis by ethnicity, we only calculated the samples from Caucasians and Asians. However, the results were also indicated that there were no significant association between the polymorphism and cancer risk in Caucasians and Asians. Then we performed a stratified analysis by the types of cancer, including breast cancer, prostate cancer, and thyroid tumor, and no significant results were obtained, too. But when we performed an analysis of breast cancer in Caucasians, a significant association was observed under the genetic models homozygote comparison (TT vs CC) and recessive genetic model (TT vs TT/CC), the results indicated that the homozygote TT may increase the risk of breast cancer among Caucasians.

Limitations of the meta-analysis existed and should be discussed. First, some relevant studies did not including in our analysis because the raw data were incomplete. Second, Siffert et al. analyzed the distribution frequencies of GNB3 C825T and indicated an existence of different genotypic frequencies among different ethnic group [2], since seven of the nine studies in our analysis were performed in Caucasian, when to assess the whole effects between the GNB3 polymorphism and cancer risk, more studies are needed in other ethnic population to exclude the effect of different genotypic frequencies among different ethnic groups. Third, to expanding the sample size, two studies which were not in HWE were not excluded, although the results were not changed. Even though the above limitations, however, this meta-analysis we performed had some advantages. First, to the best of our knowledge, this is the first meta-analysis which comprehensively assessed the association between the GNB3 gene C825T polymorphism and cancer risk. Second, the substantial data we used in this analysis were select strictly from different studies which could increase the statistical power of the analysis significantly. Third, we indicated that there existed no publication bias suggesting that the whole pooled result should be unbiased.

CONCLUSION

In conclusion, this meta-analysis indicating that the GNB3 C825T polymorphism was not associated with cancer risk in whole population, but could increase the risk of breast cancer in Caucasian. Bounded by the sample size and source of the ethnic group, more information is needed in the future to ensure our results.

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Author Contributions
Yaxuan Zhang – Conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Critical revision of the article, Final approval of the version to be published
Dongfeng Han – Conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Critical revision of the article, Final approval of the version to be published
Wenjin Wei – Conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Critical revision of the article, Final approval of the version to be published
Xiupeng Xu – Conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Critical revision of the article
Rui Zhang – Conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Critical revision of the article
Qingsheng Dong – Conception and design, Drafting the article, Critical revision of the article, Final approval of the version to be published

Xiefeng Wang – Conception and design, Drafting the article, Critical revision of the article, Final approval of the version to be published
Junxia Zhang – Conception and design, Drafting the article, Critical revision of the article, Final approval of the version to be published
Yingyi Wang – Conception and design, Drafting the article, Critical revision of the article, Final approval of the version to be published
Ning Liu – Conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Critical revision of the article, Final approval of the version to be published

Guarantor
The corresponding author is the guarantor of submission.

Conflict of Interest
Authors declare no conflict of interest.

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ABOUT THE AUTHORS

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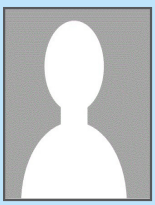
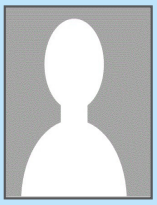
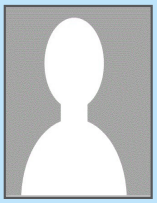


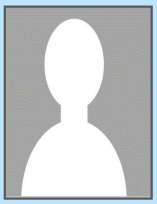
Yaxuan Zhang is a postgraduate at neurosurgery of The First Affiliated Hospital of Nanjing Medical University. He earned undergraduate degree from Shanxi Medical University.
Email: yyaj2013@163.com



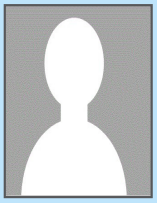
Dongfeng Han is Department of Neurosurgery, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu Province, PR China



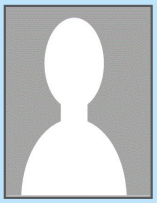
Wenjin Wei is Department of Neurosurgery, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu Province, PR China



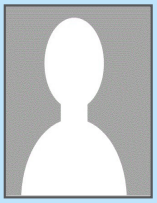
Xiupeng Xu is Department of Neurosurgery, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu Province, PR China



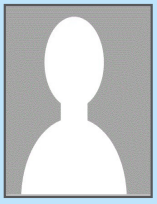
Rui Zhang is Department of Neurosurgery, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu Province, PR China



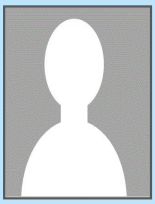
Qingsheng Dong is Department of Neurosurgery, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu Province, PR China



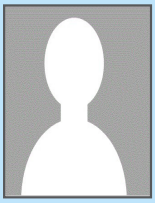
Xiefeng Wang is Department of Neurosurgery, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu Province, PR China



Junxia Zhang is Department of Neurosurgery, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu Province, PR China



Yingyi Wang is Department of Neurosurgery, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu Province, PR China



Ning Liu is Department of Neurosurgery, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu Province, PR China.