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ORIGINAL ARTICLE

Quantitative assessment of the association between *GNB3* C825T polymorphism and cancer risk

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Summary

Purpose: *The association between GNB3 C825T polymorphism and cancer risk has been investigated. However, results remain inconclusive. In this study we aimed to obtain a more precise estimation of this association.*

Methods: *A meta-analysis of 8 eligible studies including 1,812 cancer cases and 3,731 controls was conducted with odds ratios (ORs) and the corresponding 95% confidence interval (95% CI).*

Results: *The results demonstrated a borderline association between the GNB3 C825T polymorphism and the risk of overall cancer in the dominant model (TT+TC vs CC, OR=1.13, 95% CI=1.00-1.28, P_H=0.71, p=0.05). In the stratified analysis by cancer type, significant association of cancer risk was observed in thyroid carcinoma (TC vs CC, OR=1.26, 95% CI=1.02-1.54, P_H=0.63, p=0.03; TT+TC vs CC, OR=1.24, 95% CI=1.02-1.51, P_H=0.70, p=0.04). After further stratified analysis based on country, the GNB3 C825T polymorphism showed statistically significant association with increased risk of cancer in Austria (TT vs CC, OR=1.44, 95% CI=1.01-2.04, P_H=0.88, p=0.04; TT vs TT+TC, OR=1.49, 95% CI=1.07-2.64, P_H=0.87, p=0.02) and Germany (TC vs CC, OR=1.25, 95% CI=1.02-1.53; P_H=0.87, p=0.03; TT+TC vs CC, OR=1.23, 95% CI=1.02-1.49, P_H=0.90, p=0.04).*

Conclusion: *The current meta-analysis suggested that the GNB3 C825T polymorphism may contribute to increased risk of cancer, especially of thyroid carcinoma.*

Key words: *cancer, GNB3, meta-analysis, polymorphism*

Introduction

The high incidence of cancer leads to high mortality rates, with one in every four individuals being potential cancer patients [1]. Although the etiology of cancer remains largely unknown, increasing evidence suggests the susceptibility to cancer is influenced by hereditary factors.

Guanine nucleotide-binding proteins (G-proteins) are composed of an alpha, beta and gamma subunit and control a broad range of biological processes through transmitting signals between the cell surface receptor and intracellular signalling pathway [2]. G-protein β3 (*GNB3*) gene is located on chromosome 12p13 and encodes a heterotrimeric protein, which plays an important role in cell growth and mitosis [3,4].

A common polymorphism at position 825 (C825T) in exon 10 of the *GNB3* gene was identified, and it has since been associated with G-protein activation [4]. In addition, the association between *GNB3* C825T polymorphism and cancer risk has been investigated. However, to the best of our knowledge, results remain inconclusive. Considering that evidence from the independent studies regarding the association is relatively powerless, we conducted a meta-analysis to assess this relationship more precisely.

Methods

Identification of eligible studies

A comprehensive search was undertaken using the

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PubMed database for papers concerning cancer risk in relation to *GNB3* C825T polymorphism. In addition, studies were identified by a manual search from reference of original studies or review articles on this topic. The last search date was May 2, 2014.

Inclusion and exclusion criteria

Criteria for study inclusion were as follows: (1) an independent case-control study based on human subjects; (2) examining the association between *GNB3* C825T polymorphism and cancer risk; (3) including detailed genotype distribution of the polymorphism in cancer cases and controls. Major reasons for exclusion of studies were as follows: (1) not for cancer research; (2) only case population; (3) not associated with the polymorphism.

Data extraction

Information was carefully extracted from all eligible studies independently by two investigators. The following data were collected from each study: first author's name, year of publication, country, numbers of genotyped cases and controls, and genotype distributions of cases and controls.

Statistics

ORs together with their corresponding 95% CI were used to assess the strength of association between the *GNB3* C825T polymorphism and the risk of cancer. Between-study heterogeneity was assessed by using Q-statistics (heterogeneity was considered statistically significant if PH< 0.05). If the results were heterogeneous, the pooled ORs were calculated by the random-effect model. Otherwise, a fixed-effect model was used. The pooled ORs were performed for the recessive model (TT vs TC+CC), the dominant model (TT+TC vs CC), the co-dominant model (TT vs CC; TC vs CC) and the additive model (T vs C), respectively. Subgroup analyses were also performed to test the effects of cancer type and country. Publication bias was investigated by the Begg's funnel plot, and an asymmetric plot suggested possible publication bias. The Begg's funnel plot asymmetry was assessed by the Egger's test. The t-test was performed to determine the significance of the asymmetry, and a PE value of <0.05 was considered a significant publication bias. All analyses were done with STATA 12.0 software (Stata Corporation, College Station, TX).

Results

Characteristics of studies

The detailed process of identifying eligible studies is shown in Figure 1. A total of 20 publications from PubMed was reviewed using the specified key words. After a review of title, abstracts and articles, 8 studies with 1,812 cancer cases and 3,731 controls met the inclusion criteria and were included in this meta-analysis. The characteristics of the selected studies are shown in Table 1. The meta-analysis comprised case-control studies only, including 3 breast cancers, 2 thyroid carcinomas and 3 other cancers. Two of the eligible studies included individuals from Austria, 3 from Germany and 3 from other countries.

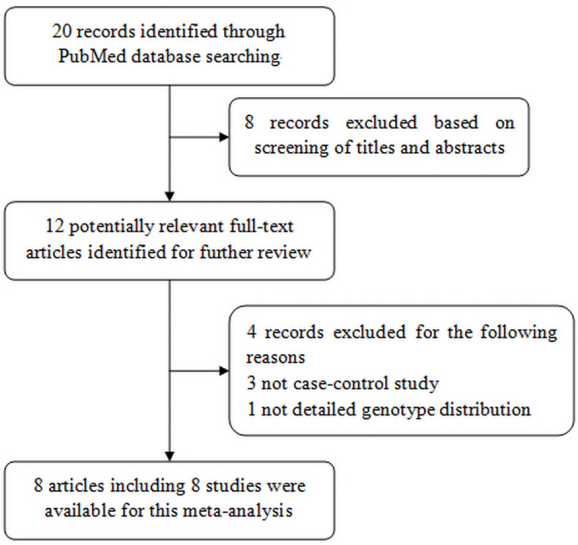

Figure 1. The flow diagram of the literature search and the study select.

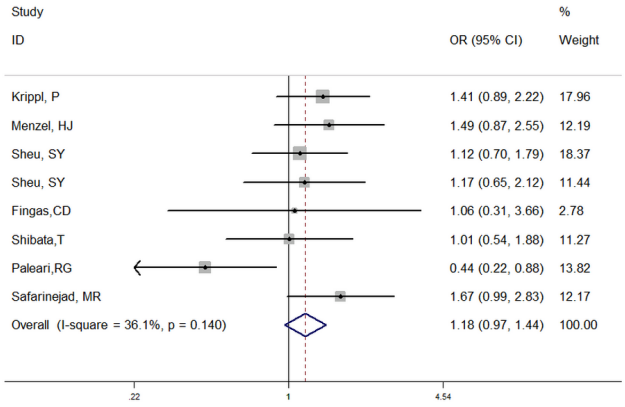

Figure 2. Forest plot for association of *GNB3* C825T polymorphism and cancer risk (co-dominant model, TT vs CC).

Meta-analysis results

As shown in Table 2, a borderline association between the *GNB3* C825T polymorphism and cancer risk were observed in the dominant model

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

First author [Ref]	*Year*	*Country*	*Cancer type*	*Number of cases/controls*	*Case*			*Control*		
					CC	*CT*	*TT*	*CC*	*CT*	*TT*
Krippl [5]	2004	Austria	Breast cancer	497/493	247	198	52	247	209	37
Menzel [6]	2004	Austria	Breast cancer	215/371	102	82	31	176	159	36
Sheu [7]	2005	Germany	Thyroid carcinoma	281/1859	120	137	24	906	791	162
Sheu [8]	2007	Germany	Thyroid carcinoma	312/321	135	151	26	152	144	25
Fingas [9]	2010	Germany	CCA	40/40	17	16	7	18	15	7
Shibata [10]	2010	Japan	Gastric cancer	161/174	33	90	38	42	84	48
Paleari [11]	2011	Brazil	Breast cancer	134/129	43	71	20	37	53	39
Safarinejad [12]	2012	Iran	Prostate cancer	172/344	44	87	41	113	168	63

CCA: cholangiocarcinoma, CC: cytosine and cytosine, CT: cytosine and thymine, TT: thymine and thymine

Table 2. Pooled ORs and 95% CI of the *GNB3* C825T polymorphism and cancer risk in all genetic models

Variables	*TT vs CC*		*TC vs CC*		*(TT+TC) vs CC*		*TT vs (TC+CC)*		*T vs C*	
	OR (95 % CI)	P_H	*OR (95 % CI)*	P_H	*OR (95 % CI)*	P_H	*OR (95 % CI)*	P_H	*OR (95 % CI)*	P_H
Total	1.18(0.97-1.44)	0.14	1.12(0.99-1.28)	0.58	1.13(1.00-1.28)	0.71	1.04(0.78-1.39)	0.02	1.09 (0.99-1.19)	0.23
Cancer type										
Breast cancer	1.01(0.52-2.00)	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	1.01(0.88-1.16)	0.05
Thyroid carcinoma	1.14 (0.79-1.65)	0.91	1.26(1.02-1.54)	0.63	1.24(1.02-1.51)	0.70	1.01(0.71-1.44)	0.80	1.13(0.98-1.31)	0.89
Other cancer	1.32(0.90-1.93)	0.45	1.32(0.96-1.81)	0.94	1.32(0.98-1.78)	0.84	1.08(0.79-1.49)	0.27	1.15(0.95-1.39)	0.26
Country										
Austria	1.44(1.01-2.04)	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	1.09(0.94-1.28)	0.87
Germany	1.13(0.80-1.61)	0.99	1.25(1.02-1.53)	0.87	1.23(1.02-1.49)	0.90	1.01(0.72-1.42)	0.97	1.13(0.98-1.30)	0.96
Other country	0.93(0.44-1.97)	0.01	1.29(0.96-1.73)	0.90	1.19(0.91-1.56)	0.32	0.79(0.40-1.56)	0.01	0.97(0.68-1.39)	0.02

P_H: p value for heterogeneity. For other abbreviations see footnote of Table 1

(TT+TC vs CC, OR=1.13, 95% CI=1.00-1.28, P_H=0.71, p=0.05). In the stratified analysis by cancer type, significant associations were observed in thyroid carcinoma (TC vs CC, OR=1.26, 95% CI=1.02-1.54, P_H=0.63, p=0.03; TT+TC vs CC, OR=1.24, 95% CI=1.02-1.51, P_H=0.70, p=0.04). In addition, stratified analysis based on country showed that the *GNB3* C825T polymorphism was associated with cancer risk not only in Austria (TT vs CC OR=1.44, 95% CI=1.01-2.04, P_H=0.88, p=0.04; TT vs TT+TC, OR=1.49, 95% CI=1.07-2.09, P_H=0.94, p=0.02), but also in Germany (TC vs CC, OR=1.25, 95% CI=1.02-1.53; P_H=0.87, p=0.03; TT+TC vs CC, OR=1.23, 95% CI=1.02-1.49, P_H=0.90, p=0.04).

The Begg's funnel plot and Egger's test were performed to assess publication bias. The shapes of the funnel plots did not reveal any evidence of obvious asymmetry (data not shown). Then, the Egger's test provided statistical evidence of funnel plot symmetry. The results still did not show any evidence of publication bias (recessive model, P_E=0.48; dominant model, P_E=0.88; co-dominant model, TT vs CC, P_E=0.68, TC vs CC, P_E=0.85; additive model, P_E=0.70).

Discussion

To our knowledge, this is the first comprehensive meta-analysis concerning the effect of the *GNB3* C825T polymorphism on cancer risk. By analyzing the data extracted from 8 studies, we revealed that *GNB3* C825T polymorphism might be associated with increased cancer risk, especially for thyroid carcinoma. Further stratified analysis based on country, statistically significant associations with increased risk of cancer were found in Austria and Germany.

Several limitations of this meta-analysis should be addressed. Firstly, the sample size was not sufficiently large for subgroup analyses for *GNB3* C825T polymorphism, with possible insufficient statistical power to investigate the real

relationship. Secondly, all the included studies in the present meta-analysis were published in English, therefore publication bias might exist although the statistical test did not indicate it. Thirdly, our results were based on unadjusted estimates, whereas a more precise analysis should be conducted if raw data from each individual study were available.

In conclusion, this meta-analysis indicated that *GNB3* C825T polymorphism was associated with cancer risk. However, larger, better studies are needed to further assess the association between this polymorphism and cancer risk.

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