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Association between polymorphism of the G-protein β3 subunit C825T and essential hypertension: an updated meta-analysis involving 36,802 subjects

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ABSTRACT

Purpose: The G-protein β3-subunit gene C825T polymorphism (*GNB3*-C825T) has been reported to be associated with essential hypertension (EH), but results from previous studies are conflicting. The present study aimed at investigating the association between this polymorphism and risk of EH using a meta-analysis on the published studies.
Materials and Methods: PubMed, Embase, CBM (China Biological Medicine Database), Wanfang and VIP databases were searched to identify eligible studies published in English and Chinese before March 2013. Data were extracted using standardized methods. The association was assessed by the odds ratio (OR) with 95% confidence intervals (CI). Begg's test was used to measure publication bias.
Results: A total of 40 case-control studies containing 16,518 EH patients and 20,284 controls were involved in this meta-analysis. Overall, a significant association was found between *GNB3* C825T polymorphism and risk of EH when all studies were pooled with a random-effects model for T versus C (OR=1.09, 95% CI: 1.04-1.19). In the subgroup analysis, the same association was found in overall Caucasian (T versus C, OR=1.16, 95% CI 1.08-1.24) and Chinese populations (TT versus CC, OR=1.23, 95% CI 1.06-1.57). No associations were detected between *GNB3*-C825T and the risk of EH overall in Asian and Japanese people.
Conclusions: Meta-analysis results suggest that the *GNB3*-C825T polymorphism is associated with risk of EH in the overall population, the Caucasians and the Chinese. The effect of the variants on the expression levels and the possible functional role of the variants in EH should be addressed in further studies.

Key words: GTP-Binding Proteins, Polymorphism, Genetic hypertension, Meta-Analysis

INTRODUCTION

Essential hypertension (EH), a complex disease which accounts for ~95% of hypertensive cases, is an increasingly serious worldwide public-health challenge and is generally considered as a paradigmatic multi-factorial disease that is determined by a combination of genetic factors, environmental stimuli and their interaction (O'Shaughnessy, 2001) . It was estimated that 20–60% of the inter-individual variation in blood pressure (BP) is genetically controlled (Kurtz and Spence, 1993). Accordingly, the discovery of many potential hypertension-susceptibility genes has allowed for a better understanding of the disease etiology. Candidate polymorphisms of the genes involved in the pathways of Na^+/H^+ exchange, the renin-angiotensin-aldosterone system and the autonomic nervous system such as G-protein β3-subunit (*GNB3*)-C825T, angiotensin-converting enzyme insertion/deletion, and β2-adrenergic receptor A46G have been investigated in different ethnic populations (Puddu et al., 2007).

G-proteins are hetero-trimers composed of α, β, and γ subunits, which act as switches for signal transduction from the extracellular space into the cell via their interaction with G-protein-coupled receptors. The β-subunit plays an important role in regulation of the α-subunit and several signal transduction receptors and effectors (Downes and Gantam, 1999). A previous study demonstrated that enhanced signal transduction and cell proliferation were abnormalities in a certain group of patients with EH and revealed that enhanced G protein activation led to this common disorder (Siffert et al., 1995). The *GNB3* gene is one of the five genes coding for a G-protein β-subunit that have been identified in the human genome (Elefsinioti et al., 2004). One widely-studied polymorphism of the *GNB3* gene is the C825T polymorphism, which consists of a substitution of C by T at position 825 in exon 10. Siffert et al. (1998) first found that the *GNB3*-825T allele was associated with EH. Since then, many researchers have studied the relationship between the *GNB3*-C825T polymorphism and EH in different populations with controversial results (Snapir et al., 2001; Huang et al., 2003; Potoczna et al., 2004). To estimate fully and comprehensively the association between this gene polymorphism and EH risk across different ethnic populations we conducted an updated meta-analysis, including more studies in the Asian population than the meta-analysis of Bagos et al. carried out in 2007, to derive a more precise estimation of the association.

MATERIALS AND METHODS

Literature search

To search for all the studies that examined the association of the *GNB3*-C825T polymorphism with essential hypertension risk we conducted a computerized literature search from PubMed, Embase, CBM (China Biological Medicine Database), Wanfang

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and VIP databases, using the following keywords and subject terms: (hypertension or blood pressure or essential hypertension) AND (*GNB3*-C825T or G-protein beta3) AND (allele or genotype or polymorphism or variant or variation). The full text of the retrieved articles was scrutinized to inspect whether data on the topic of interest were included. We systematically searched eligible studies reported before March 1, 2013.

Eligible publications had to be written in either Chinese or English. The references of all retrieved articles were also screened. To prevent data duplication, when a report overlapped with another study, only the more detailed study was included. If an article reported results on different ethnic sub-populations, each sub-population was treated as a separate study.

Inclusion/exclusion criteria

Studies included in the meta-analysis had to meet all the following criteria: (1) the evaluation of the relationship between the *GNB3*-C825T polymorphism and essential hypertension; (2) the use of case-control study design or cross-sectional study design; (3) the available genotype/allele frequency of the *GNB3*-C825T allele between cases and controls; (4) all subjects were well ethnicity-matched; (5) hypertension was defined as systolic BP equal to or above 140 mmHg or diastolic BP equal to or above 90 mmHg or treatment with antihypertensive medication; however, studies evaluating secondary hypertension or other types of monogenic hypertension were excluded from the present investigation. If the genotype frequency was not reported, we contacted the original authors by e-mail to obtain the missing data.

Data extraction

To minimize the selection bias, the data were independently gathered in duplicate by two investigators on the basis of a standard protocol. The data extracted from the studies included such details as the first author, the year of publication, study population (region, ethnicity and sex), total number of cases and controls and genotype information. The excluded studies were comprised of studies of poor research quality, providing little or insufficient data, violating the inclusion criteria, and repeated publications. If the same research result appeared in different articles, the result was only adopted once in the present meta-analysis. If there was discrepancy between them, it was settled by discussion until a consensus was reached.

Statistical Analysis

As case-control or cross-sectional studies were used, odds ratios (ORs) corresponding to a 95% confidence interval (CI) were implemented to assess the intensity of the association between the GNB3-C825T polymorphism and EH; the ORs were calculated according to the method described by Woolf (WOOLF 1955). We examined the contrast of the T vs. C, TT vs. CC, TC vs. CC, and also examined the dominant genetic model TT+TC vs. CC and the recessive model TT vs. TC+CC.

We applied two models of meta-analysis for dichotomous outcomes in Review-Manager 5.0 software (The Cochrane Collaboration, Oxford, UK): the fixed-effects model and the random-effects model. When there was inter-study heterogeneity a pooled OR was estimated by the random-effects model (DerSimonian and Laird's method) (DerSimonian and Laird, 1986); otherwise the fixed-effects model (Mantel-Haenszel method) was used (Mantel and Haenszel, 1959). The fixed-effects model assumes homogeneity among study estimates and is used when there is no evidence for heterogeneity. Conversely, when heterogeneity exists a random-effects model is usually more appropriate because it takes into account the inter-study variability. We used a χ^2-based Q statistic to assess the inter-study heterogeneity (Lau et al.,1997), which is considered to be significant for $P < 0.10$ because of the low power of the statistic, as well as the I^2 statistic for estimation of inconsistency in meta-analysis (Trikalinos et al., 2006). Heterogeneity was assessed by the I^2 statistic, which was documented for the percentage of the observed inter-study variability due to heterogeneity rather than chance; it ranges from 0 to 100%, where a value of 0% indicates no observed heterogeneity, and larger values indicate an increasing degree of heterogeneity (roughly suggested cut-off points include: I^2=0–25%, no heterogeneity; I^2=25–50%, moderate heterogeneity; I^2=50–75%, large heterogeneity; I^2=75–100%, extreme heterogeneity (Higgins et al., 2003). The fixed-effects model (if $P \geq 0.10$) or the random-effects model (if $P<0.10$) was used to pool the results. The significance of the pooled ORs was determined by the Z-test, and $P<0.05$ was considered significantly different.

Sensitivity analyses were conducted by deleting a single study each time involved in the meta-analysis to identify the potential influence of the individual dataset on the pooled ORs.

A funnel plot was used to estimate the potential publication bias. The asymmetry of the funnel plot was assessed by Egger's linear regression test (Song and Gilbody, 1998).

RESULTS

Studies included in the meta-analysis

A total of forty relevant studies concerning the association between *GNB3*-C825T and the risk of EH were identified. These studies involved 16,518 patients and 20,284 controls, containing the studies of fourteen Caucasian populations, twenty-four Asian populations and two African-American populations. Because the sample population in the African-American group was inadequate, ethnicity-specific meta-analysis was conducted on Caucasian and Asian populations. In the subgroup analysis, eight studies in Japanese populations and fifteen studies in Chinese populations were included in Asian-specific groups. Among those forty studies there were four that contained information about distinct independent populations and thus they were considered as different studies that should be counted twice (Brand et al., 1999; Kunugi et al., 2002; Ishikawa et al., 2000; Dai et al., 2002 . Out of all those studies, we found that the control groups were in Hardy-Weinberg equilibrium (HWE) except for four studies (Benjafield et al.,1998; Andersen et al., 2006; Yamamoto et al., 2004; Suwazono et al., 2004).The main characteristics of included studies are listed in Table 1.

Frequency of the GNB3-825T Allele in Different Ethnic Groups

There was no significant heterogeneity among the fourteen Caucasian population studies for a mixed company (χ^2=19.47,

TABLE 1

Characteristics of the studies included in meta-analysis

Study	Year	Region	Ethnicity	Sex	Sample Size Control/Case	Genotype Frequency						HWE
						Control			EH patients			
						CC	CT	TT	CC	CT	TT	
Siffert et al.	1998	Germany	C	ALL	427/426	239	162	26	200	187	39	Yes
Benjafield et al.	1998	Australia	C	ALL	189/110	101	82	6	27	71	12	No
Brand et al.	1999	France	C	ALL	308/681	148	127	33	292	302	87	Yes
Brand et al.	1999	Ireland	C	M	159/206	78	70	11	98	92	16	Yes
Beige et al.	1999	Germany	C	ALL	1000/476	514	412	74	201	224	51	Yes
Hengstenberg et al.	2000	Germany	C	ALL	1126/926	526	485	115	407	407	112	Yes
Hengstenberg et al.	2000	Germany	C	ALL	383/223	179	165	39	99	101	23	Yes
Buchmayer et al.	2000	Australia	C	ALL	174/174	72	85	17	85	70	19	Yes
Zychma et al.	2000	Poland	C	ALL	157/245	68	77	12	109	144	22	Yes
Potoczna et al.	2004	Switzerland	C	ALL	112/192	57	40	15	86	82	24	Yes
Martin et al.	2005	Spain	C	ALL	78/76	29	36	13	25	42	9	Yes
Mahmood et al.	2005	United Arabian Emirates	C	ALL	211/145	43	118	50	25	81	39	Yes
Andersen et al.	2005	Denmak	C	ALL	4193/3139	2022	1744	427	1545	1288	306	No
Kedzierska et al.	2006	Poland	C	M	18/26	15	2	1	9	12	5	Yes
Alioğlu et al.	2008	Turkish	C	ALL	82/209	27	40	15	37	124	48	Yes
Cabadak et al.	2011	Turkish	C	ALL	106/101	47	37	22	35	31	35	Yes
Kato et al	1998	Japan	A	ALL	515/718	128	263	124	187	359	172	Yes
Kario et al.	1999	Japan	A	ALL	106/161	22	51	33	29	93	39	Yes
Ishikawa et al.	2000	Japan	A	ALL	422/304	96	204	122	67	161	76	Yes
Ishikawa et al.	2000	Japan	A	ALL	165/181	37	85	43	43	90	48	Yes
Tsai et al.	2000	Taiwan, China	A	ALL	199/302	43	96	60	57	149	96	Yes
You et al	2000	China	A	ALL	100/98	31	52	27	25	47	26	Yes
Tozawa et al.	2001	Japan	A	ALL	180/179	39	82	59	32	68	79	Yes
Dai et al.	2002	China	A	ALL	257/133	70	127	60	28	73	32	Yes
Dai et al.	2002	China	A	ALL	110/98	31	52	27	25	47	26	Yes
Wang et al.	2003	China	A	ALL	140/408	39	66	35	131	182	95	Yes
Izawa et al.	2003	Japan	A	M	533/574	159	261	113	138	291	145	Yes
Huang et al.	2003	China	A	ALL	580/585	126	303	151	134	290	161	Yes
Tan et al.	2003	China	A	ALL	112/112	66	40	6	38	60	14	Yes
Yamamoto et al.	2004	Japan	A	ALL	540/266	162	239	139	70	120	76	No
Wang et al.	2004	China	A	ALL	244/290	67	119	58	82	144	64	Yes
Suwazono et al.	2004	Japan	A	ALL	2289/332	574	1216	499	78	171	83	No
Shioji et al.	2004	Japan	A	ALL	1105/775	287	536	282	177	385	213	Yes
Li et al.	2005	China	A	ALL	503/501	137	259	107	142	256	103	Yes
Zhang et al.	2005	China	A	ALL	150/110	51	72	27	32	52	27	Yes
Dong et al.	2006	China	A	ALL	87/97	27	46	14	25	47	25	Yes
Li et al.	2006	China	A	ALL	151/310	42	70	39	89	161	60	Yes
Zhang et al.	2006	China	A	ALL	100/100	32	53	15	19	46	35	Yes
Bae et al.	2007	Korea	A	ALL	924/688	217	469	238	193	139	175	Yes
Huang et al.	2007	China	A	ALL	495/256	104	262	129	51	133	72	Yes
Gai et al.	2007	China	A	ALL	197/136	54	95	48	31	73	32	Yes
Zhao et al.	2009	China	A	ALL	293/331	52	137	104	117	179	35	Yes
Nejatizadeh et al.	2011	Iran	A	ALL	345/449	192	144	9	185	211	53	Yes
Dong et al.	1999	United Kingdom	African	ALL	243/185	14	83	146	3	61	121	Yes
Larson et al.	2000	United States of America	African	ALL	432/472	25	170	237	29	190	253	Yes

HWE: Hardy-Weinberg equilibrium.

df=15, *P*=0.21). The pooled *GNB3*-825T allele frequency using the fixed-effects model was 37.75% (95% CI: 35.39-39.14%).

The pooled *GNB3*-825T frequencies were 48.37% (95% CI: 46.94-52.27%) for Asians (χ^2=27.63, *P*<0.001; random-effects model) and 76.28% (95% CI: 71.03-82.46%) for African-Americans.

Results of Meta-analysis

In the meta-analysis of all involved studies, the Q test showed heterogeneity in the 40 studies – we therefore used the random effects model to calculate the combined effects in the following genetic models. The OR (95% CI) values (Fig. 1) were: T versus C: 1.09 (1.04-1.19) *P*=0.012; TT versus CC: 1.02 (0.88-1.26)

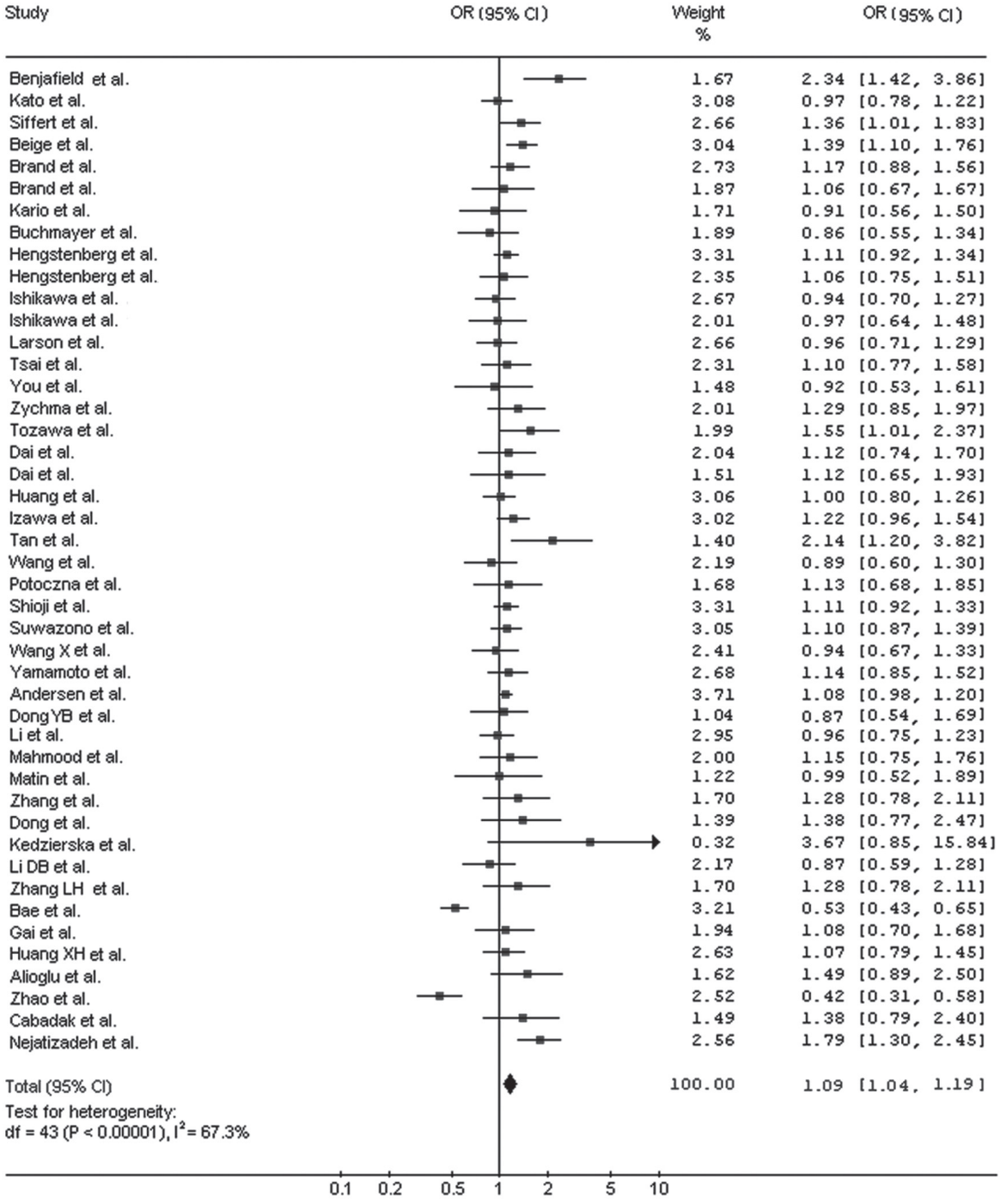

Figure1: Pooled OR (T versus C) and 95% CI of individual studies and pooled data for the association between polymorphism of GNB3 C825T and EH in the overall population

P=0.005; TC versus CC: 1.11 (0.72-1.54) *P*=0.132. However, no significant association was identified in the dominant model or in the recessive model (Table 2). Heterogeneity among studies was identified in all the comparisons (*P* for heterogeneity *Q* test <0.1). Furthermore, the I^2 statistics suggested the existence of moderate heterogeneity for all comparisons in all studies. Therefore, a sub-group analysis of the studies by ethnicity grouping was suggested.

We found a significant association when all Caucasian population studies were pooled with the fixed-effects model for T versus C (OR=1.16, 95% CI 1.08-1.24; *P*=0.216 for heterogeneity, Fig. 2), TT+TC versus CC (OR=1.33, 95% CI 1.13-1.56; *P*=0.324 for heterogeneity), TT versus TC + CC (OR=1.13, 95% CI 1.02-1.20; *P*=0.152 for heterogeneity). The same association was found in the Chinese population when all studies were pooled with the random-effects model for TT vs. CC (OR=1.23, 95% CI 1.06-1.57; *P*<0.001 for heterogeneity, Fig. 3). No associations were detected between *GNB3*-C825T and the risk of EH in Asians or the Japanese (Table 2).

Sensitivity Analysis

We removed the studies by Benjafield AV et al. (in the Caucasian population) and Yamamoto M et al. (in the Asian population) in the meta-analysis, since the genotype distribution in the control groups of the study deviated slightly from HWE. We found that the corresponding pooled ORs were not substantially altered (Table 3), which indicated the reliability of our results.

Publication Bias

Begg's test and a funnel plot were performed to access the publication bias of the studies. In this study there was no significant publication bias for *GNB3*-C825T polymorphism (T versus C: overall population, *P*=0.106; Caucasian population, *P*=0.472; Asian population, *P*=0.645). The funnel plot showed a symmetrical distribution of the studies (funnel plot of *GNB3*-

TABLE 2

The results of meta-analysis between GNB3-C825T polymorphism and EH

Groups	Genetic model	Sample size Control/Case	Test of heterogeneity		OR(95%CI)	*Z(P)* value for overall effect test
			P	I^2(%)		
Overall	T vs.C	20,284/16,518	<0.001	67.3	1.09(1.04-1.19)	1.91(0.012)
	TT vs. CC		0.003	34.8	1.02(0.88-1.26)	2.13(0.005)
	TC vs. CC		0.053	32.9	1.10(0.72-1.54)	2.21(0.132)
	TT+TC vs. CC		0.103	25.1	1.04(0.79-1.34)	1.96(0.038)
	TT vs. TC+CC		<0.001	51.4	1.01(0.84-1.24)	1.90(0.024)
Caucasian-overall	T vs.C	8723/7355	0.216	21.2	1.16(1.08-1.24)	4.20(<0.001)
	TT vs. CC		0.135	39.8	1.02(0.75-1.37)	2.82(0.084)
	TC vs. CC		0.118	26.4	1.01(0.84-1.24)	3.37(0.139)
	TT+TC vs. CC		0.324	12.6	1.33(1.13-1.56)	3.40(0.007)
	TT vs. TC+CC		0.152	27.6	1.13(1.02-1.25)	2.29(0.026)
Asian-overall	T vs.C	10,886/8,504	<0.001	64.2	0.99(0.93-1.05)	0.30(0.562)
	TT vs. CC		0.093	53.6	0.86(0.67-1.19)	1.58(0.081)
	TC vs. CC		0.262	37.1	1.14(0.84-1.55)	0.62(0.006)
	TT+TC vs. CC		0.053	49.5	1.16(0.89-1.51)	1.08(0.279)
	TT vs. TC+CC		0.006	44.8	0.94(0.72-1.21)	0.49(0.184)
Japanese-overall	T vs.C	5849/3490	0.62	0.00	1.09(1.00-1.19)	1.87(0.059)
	TT vs. CC		0.271	23.4	1.01(0.76-1.38)	1.48(0.259)
	TC vs. CC		0.324	13.7	0.77(0.56-1.33)	0.73(0.008)
	TT+TC vs. CC		<0.001	68.6	1.12(0.81-1.55)	0.67(0.531)
	TT vs. TC+CC		0.236	24.2	1.10(0.99-1.21)	1.74(0.044)
Chinese-overall	T vs.C	3768/3877	<0.001	57.4	1.12(0.86-1.46)	0.67(0.421)
	TT vs. CC		<0.001	64.1	1.23(1.06-1.57)	1.26(0.032)
	TC vs. CC		<0.001	70.3	0.84(0.62-1.27)	1.35(0.102)
	TT+TC vs. CC		<0.001	52.9	1.09(0.89-1.34)	0.29(0.837)
	TT vs. TC+CC		<0.001	62.8	0.96(0.65-1.42)	0.84(0.328)

825T versus C and susceptibility of EH in overall population is shown in Fig. 4).

DISCUSSION

Our results indicated that the prevalence of the *GNB3*-825T allele varied from 37.75-76.28% in different ethnic groups, the lowest being demonstrated for Caucasians and the highest for African-Americans. Furthermore, meta-analysis results showed that an association existed between the *GNB3*-C825T allele frequency and risk of EH in the overall population (T versus C, OR=1.09, 95% CI 1.04-1.19), and the Caucasian (T versus C, OR=1.16, 95% CI 1.08-1.24; TT+TC versus CC, OR=1.33, 95% CI 1.13-1.56; TT versus TC + CC, OR=1.13, 95% CI 1.02-1.20) and Chinese populations (TT vs. CC, OR=1.23, 95% CI 1.06-1.57). Conversely, no associations were detected in Asian or Japanese people.

G-proteins comprise a family of ubiquitously distributed signal-transduction proteins. Most membrane receptors rely on heterotrimeric G-proteins to activate or inhibit intracellular signaling cascades. G-proteins are influenced by hormones

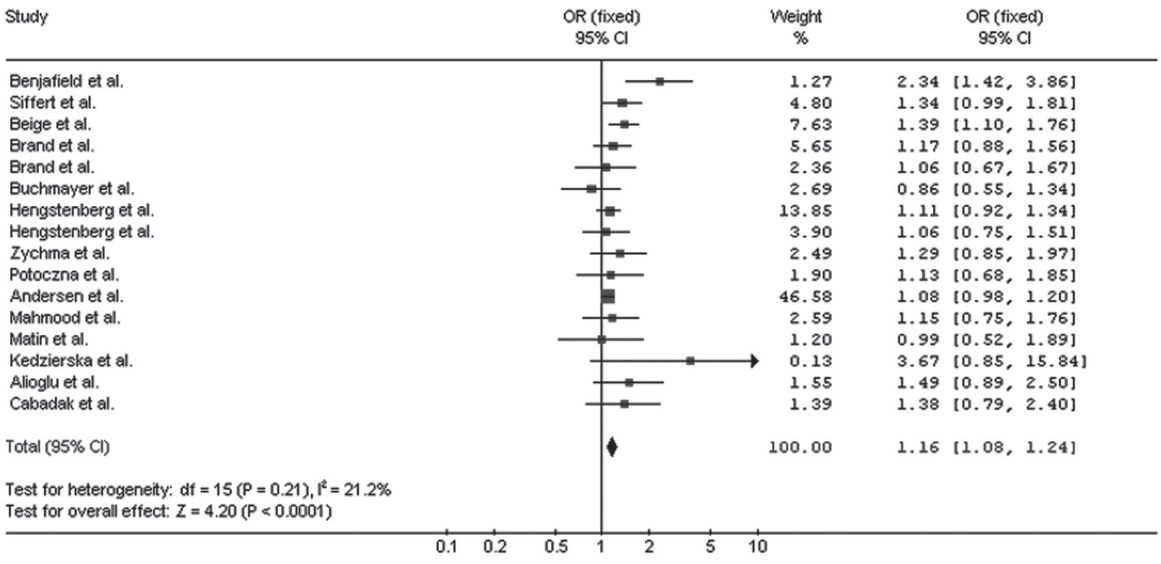

Figure 2: Pooled OR (T versus C) and 95% CI of individual studies and pooled data for the association between polymorphism of GNB3-C825T and EH in Caucasian population

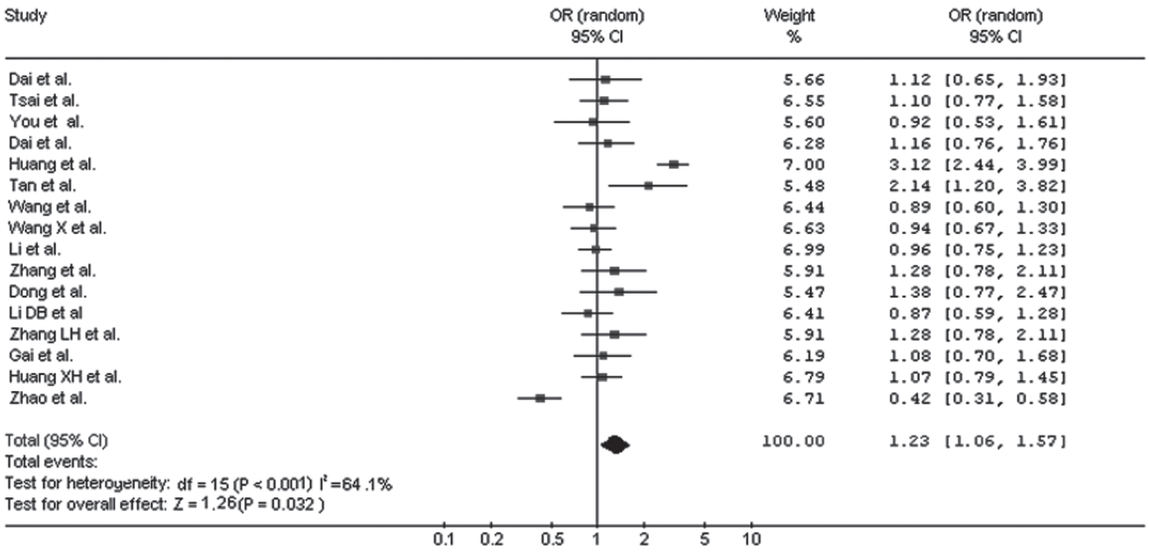

Figure 3: Pooled OR (TT versus CC) and 95% CI of individual studies and pooled data for the association between polymorphism of GNB3-C825T and EH in Chinese population.

TABLE 3

Main results of the pooled OR in sensitivity analysis

Groups	Genetic model	Sample Size Control/Case	Test of heterogeneity		OR(95%CI)	*Z(P)* value for overall effect test
			P	I^2		
Caucasian-overall	T vs.C	8,544/7,245	0.211	20.9	1.17(1.07-1.25)	4.18(<0.001)
	TT vs. CC		0.134	39.3	1.02(0.75-1.37)	2.81(0.084)
	TC vs. CC		0.137	27.0	1.01(0.84-1.24)	3.41(0.138)
	TT+TC vs. CC		0.175	13.4	1.33(1.12-1.56)	3.42(0.007)
	TT vs. TC+CC		0.184	25.3	1.13(1.02-1.25)	2.28(0.031)
Asian-overall	T vs.C	10,336/8,238	<0.001	64.2	0.97(0.92-1.05)	0.28(0.558)
	TT vs. CC		0.089	52.7	0.86(0.67-1.10)	1.61(0.089)
	TC vs. CC		0.264	36.8	1.14(0.82-1.56)	0.62(0.025)
	TT+TC vs. CC		0.053	50.1	1.15(0.89-1.51)	1.06(0.264)
	TT vs. TC+CC		0.005	43.7	0.93(0.72-1.21)	0.51(0.182)

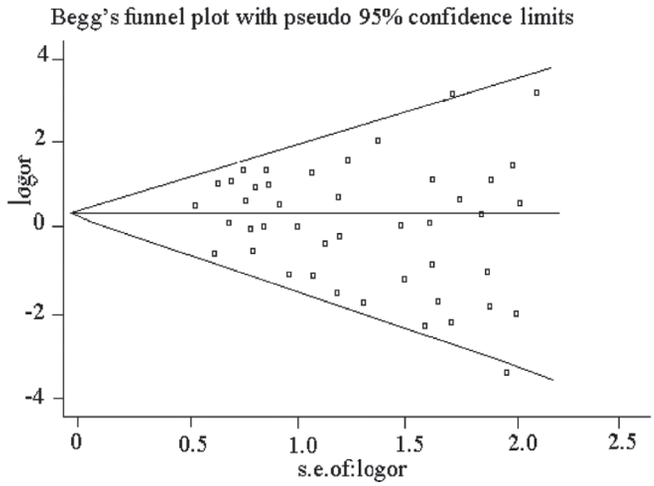

Figure 4: Funnel plot for detecting publication bias among all studies for allele comparison (GNB3-825T versus C) in the overall population. Logor (y axis) the log of OR,s.e. of logor (x axis) the standard error of lor(OR). OR: odds ratio.

and neurotransmitters and act to regulate blood pressure. Polymorphisms of the *GNB3* gene have received considerable attention as candidate genes for EH. The *GNB3*-C825T allele was demonstrated to lack 41 amino acids in the β3 subunit of trimeric G-proteins (Siffert et al., 1998). This allele has also been associated with enhanced G-protein signaling (Siffert et al., 1998; Sun et al., 2005), presumably through abnormal stability or functional interactions of the shortened G-proteins.

In recent years many studies have reported a correlation between *GNB3*-C825T and EH in Caucasian, African, South American and Asian populations. Our analysis showed that the *GNB3*-C825T allele was associated with EH in the overall population, which is in agreement with the results of a previous multi-ethnic population meta-analysis (Bagos et al., 2007). These authors reported that TT versus CC + CT: OR=1.08, 95% CI: 1.01–1.15, P<0.001 and TT + CT versus CC: OR=1.17, 95% CI: 1.06–1.29, P<0.001. Further subgroup analysis led to a similar result, i.e., significant associations from studies in the Caucasian population and no associations from studies in Asians. However, we did observe that the *GNB3*-825T allele (TT vs. CC, OR=1.23, 95% CI 1.06-1.57) was a risk factor for EH in Chinese people. Our studies of the Chinese population involving *GNB3*-C825T and EH risk include not only the mainland investigations but also Taiwanese ones.

In addition, we calculated the average frequency of the T allele in different ethnic people, which was lowest in Caucasians, intermediate in Asian, and the highest in Africans. Siffert et al. analyzed the distribution frequencies of *GNB3*-C825T from a German cohort, and Chinese and African populations, and found that T allele frequencies differed significantly among different ethnic groups and were the lowest in Germans (31.9%), intermediate in Chinese (47.7%) and highest in Africans (81.4–84.1%) (Siffert et al., 1998). The different genotypic frequencies of *GNB3*-825T allele might influence the phenotypes related to hypertension such as salt sensitivity in different ethnic populations (Franco et al., 2006), which may contribute to different correlations between Chinese and other populations. It is worth noting that the number of studies from the African population was much lower than for other races. More studies from African people are needed to re-estimate the frequency.

Some limitations of this meta-analysis should be discussed. First, this meta-analysis focused only on papers published in the English and Chinese languages and the ones that reported in other languages may bias the present results, even though publication bias was not detected with Begg's test. Additionally, there may be other eligible studies that were not published and indexed by electronic databases. Third, significant between-study heterogeneity was observed. Although we used the random-effects model to pool ORs, it may affect the precision of results. Finally, lack of individual participants' data restricted the further adjustments by other co-variables such as smoking, body mass index, hyperlipidemia, etc.

CONCLUSIONS

The results of the meta-analysis suggest that the *GNB3*-825T allele is associated with increased risk of EH in the overall population, as well as the Caucasian and Chinese populations. The T allele frequency is the lowest in Caucasians, intermediate in Asians, and highest in Africans. The effect of the variants on the expression levels and the possible functional role of the variants of EH should be addressed in further studies.

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