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Title page

Association between the G-protein β3 subunit C825T polymorphism with essential hypertension: a meta-analysis in Han Chinese population

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Concise and informative title: association of GNB3-C825T with hypertension

Abstract

Objective: We aimed to evaluate the contribution of the G-protein β3 subunit C825T (GNB3-C825T) polymorphism to essential hypertension (EH) in Han Chinese population by performing the meta-analysis. **Materials/Methods:** A meta-analysis was performed in 12 case-control genetic association studies including 3,020 hypertension patients and 2,790 controls from MEDLINE (PubMed) and the China National Knowledge Infrastructure (CNKI) platforms. The STATA 10.0 software was used in analysis. **Results:** Overall, there was no significant association between the GNB3-C825T polymorphism and EH in neither additive [TT vs. CC: OR(95%CI)=1.11(0.74–1.69), P=0.61; TC vs. CC: OR(95%CI)=1.08 (0.89–1.31), P=0.42], nor dominant [TT+TC vs. CC: OR(95%CI)=1.11 (0.86–1.42), P=0.43] and nor recessive [TT vs. TC+CC: OR(95%CI)=1.04 (0.75–1.44), P=0.81] genetic models. Although futher subgroup analysis found statistically significant results [T vs. C: OR (95%CI) = 1.50 (1.05–2.15), P=0.03] in the southern population, but after exclusion one particular study, the significant association was disappeared. No significant result was found in the northern population. **Conclusions:** there was no significant association identified between GNB3-C825T polymorphism and EH in Han Chinese population. Further larger sample and well-designed studies are needed to assess the genetic association particularly in the southern Han Chinese population.

Keywords: Hypertension, Genetic association study, Systematic review, Han Chinese, Meta-analysis.

Introduction

Hypertension is an important worldwide public-health challenge due to the high prevalence and is a leading risk factor for mortality (1, 2). An international collaborative study reported that 27.2% of the Chinese population aged from 35 to 74 years old have hypertension, indicating that hypertension is highly prevalent in Chinese (3). Essential hypertension (EH) is one of the most common complex diseases that accounts for 95% of all cases of hypertension(4) and is likely to be the consequence of interaction between genetic and environmental factors(5). The correlation between high blood pressure phenotypes is stronger between parents and children than that between spouses, suggesting genetic factors are more crucial than environmental ones(6). To investigate genetic mechanisms of hypertension, candidate polymorphisms of the genes involved in the pathways of rennin-angiotensin-aldosterone system, autonomic nervous system and Na+/H+ exchanger such as G-protein β3 subunit (GNB3)-C825T, angiotensin converting enzyme (ACE)-Insertion/Deletion, angiotensinogen (AGT)-M235T and aldosterone synthase (CYP11B2)-C344T have been investigated in different ethnic populations(7).

The GNB3 gene (12p13) (OMIM 139130) encodes the β -3 subunit of heterotrimeric G-proteins, composing of three subunits (α, β and γ). (Pls confirm : β -3 subunit of heterotrimeric G-proteins, composing of three subunits (α, β and γ). Not logical to me?!!!)The β-subunit plays an important role on regulation of the α-subunit and several signal transduction receptors and effectors(8). Enhanced GNB3 activation influences specific signal transduction pathways, cell proliferation, even immortalized lymphoblast and fibroblastsin in patients with EH, together with elevated Na^+/H^+ exchange activity(9, 10). It has been reported that 30–50% of essential hypertensive patients have an increase in the activity of Na+/H+ exchanger in their blood cells(11). Therefore, levels and activity of

GNB3 could become a candidate marker for predicting the susceptibility to EH. In 1998, Siffert et al. first identified a C825T polymorphism at position 825 in exon 10 of the gene encoding GNB3 and found GNB3-825T allele was associated with EH(10). Since then, many researchers have studied the relationship between GNB3-C825T polymorphism and EH in different population with controversial results (12-14). A meta-analysis including 34 studies observed a significant association between C825T polymorphism and hypertension in Caucasians but a non-significant association in Asian populations(14). In China, association studies between GNB3-C825T polymorphism and EH have been extensively pursued with inconsistent results. Different population structure, latitude distribution, ethnic difference and limited statistical power may be the possible contributors to the observed inconsistency.

In this study, we performed a meta-analysis to confirm whether GNB3-C825T polymorphism was associated with EH in Han Chinese population and further stratified by geographical locations the publications including data published in Chinese to increase statistical power and more effectively clarify the role of GNB3 polymorphisms in the susceptibility of EH.

Materials and methods

Literature search

We searched MEDLINE (PubMed) and the China National Knowledge Infrastructure (CNKI) by employed the following keywords: GNB3-C825T, G-protein beta3, polymorphism, hypertension, blood pressure, essential hypertension, China and Chinese. The following criteria were established for the study selection: 1) Case-control studies concerning the association of GNB3-C825T polymorphism with EH in Chinese

populations in China; 2) Having demographic data of subjects, such as Chinese ethnicity and geographical locations; and 3) Data on genotype distributions. Hypertension was defined as cases if patients had a systolic blood pressure (SBP) ≥ 140 mmHg or a diastolic blood pressure (DBP) ≥ 90 mmHg, or they were undergoing antihypertensive treatments. Controls were defined as indivdules with a SBP lower than 140 mmHg, or DBP lower than 90 mmHg, and they were not receiving any antihypertensive therapies. Studies on secondary hypertension or with other serious diseases were excluded. In addition, studies were excluded from the consideration if: 1) The studies were not designed as case-control studies; 2) The source of cases and controls and other essential information was not presented; 3) Reviews and duplication of the publications; 4) The control group in studies deviated from the Hardy-Weinberg equilibrium; and 5) Subjects of the studies were not Han Chinese.

We separated the selected studies into the Northern studies and the Southern studies according to the following criteria. The Huai River-Qinling Mountains line is generally regarded as the geographical dividing line between South and North China. If the location of the subjects was on the North of the Huai River-Qinling Mountains line, the studies were assigned to the Northern studies, otherwise Southern studies.

Data extraction

Two investigators extracted standard information from each independent study. From each study, the following information was obtained: first author, year of publication, geographical location/province, ethnical background of the study population, demographics, validity of the genotyping method and numbers of the cases and controls for each genotype and allelic frequency of GNB3-C825T polymorphism. To make sure the accuracy of the data, extractions were performed by two reviewers independently.

Meta analysis

Statistical analysis was performed with STATA 10.0 software (STATA Corp., College Station, Texas, USA; version 10.0). To measure the strength of genetic association between GNB3-C825T polymorphism and EH, the odds ratios (OR) and 95% confidence interval (95%CI) were calculated. In addition to the investigations using all of the studies, comparisons between studies by categorizing subjects into different subgroups according to geographical location were also carried out. Heterogeneity among the studies was analyzed using the heterogeneity Q statistic test. The inconsistency index I^2 (ranging from 0 to 100%) was also calculated, where higher values of the index indicated the existence of heterogeneity(15). If the significant Q statistic (P<0.1) indicated the existing of heterogeneity across studies, the DerSimonian and Laird method in the random effects model was used for meta-analysis. Otherwise, the Mantel-Haenszel method in the fixed effect model was used. Sensitivity analyses were performed by sequentially omitting one study each time to assess each potential influence of the individual study on the pooled estimate. We also performed Egger's test to examine publication bias. A goodness-of-fit χ^2 test was used to check whether the frequencies of genotypes deviation from the Hardy-Weinberg Equilibrium (HWE) (http://ihg2.helmholtz-muenchen.de/cgi-bin/hw/hwa1.pl). P<0.05 was considered statistically significant.

Results

Characteristics of studies

The initial search with the keywords identified a total of 27 studies. Of the 27 studies, three studies were excluded because the study population was not the Han Chinese

population (13, 16, 17) and two articles were excluded since they were pedigree-based research(18, 19). Among the other excluded studies, two studies were duplicate publications (20, 21) and three studies were reviews(22-24). Furthermore, four studies were excluded due to the deviation from the Hardy-Weinberg equilibrium in the control groups (25-28). Thus, 12 case-control studies including a total of 5,810 individuals (3,020 unrelated hypertensive patients and 2,790 normotensive controls) were included in the present investigation. Seven case and control studies were selected from hospital (12, 30, 33-35, 37, 38), while four community-based cases and controls were used (31, 32, 36, 39). In one study, samples were selected from both hospital and community (29). The WHO criteria for hypertension diagnosis were used in all included studies. The method of genotyping test was PCR-RFLP in all included studies.

The characteristics of all included studies are shown in Table 1. Among the eligible studies, three of which investigated Southern Han Chinese populations including Shenzhen city (Guangdong), Henan and Chongqing City (Sichuan) provinces (29-31). Other subjects came from Northern Han Chinese populations including Beijing City, Heilongjiang, Jilin, Liaoning, Shandong and Shanxi provinces(12, 32-39). According to the data of all studies, the frequency of GNB3-825T allele was 47.3% for hypertension and 48.2% for normotensive control. In the Northern population, the frequency of the GNB3-825T allele was 48.7% (47.5% for cases and 50.0% for controls), while the GNB3-825T allele frequency was 40.6% (45.5% for cases and 36.1% for controls) in Southern studies. There was a significant difference between the Southern and the Northern populations (χ^2=31.017, P<0.001). After exclusion the study from Chongqing study, the significant difference of T allele frequency was not found between northern and southern populations (45.2% for southern population and 48.7% for northern population, χ^2 = 3.762, P = 0.052).

Meta analysis in all investigated studies

In the meta-analysis of all involved studies, there was no significant association between GNB3-C825T polymorphism and EH in the Chinese Han population (Table 2). The Q test showed heterogeneity in the 12 studies. We therefore used the random effects model to calculate the combined effects in three genetic models. The OR (95% CI) were TT *vs.* CC: 1.11 (0.74–1.69), *P*=0.61; TC *vs.* CC: 1.08 (0.89–1.31), *P*=0.42 in additive model; similarly, no significant association was identified neither in the dominant model (OR=1.11; 95% CI: 0.86–1.42, *P*=0.43) nor in the recessive model (OR=1.04; 95% CI: 0.75–1.44, *P*=0.81). Heterogeneity between studies was identified in the all comparisons (*P* for heterogeneity Q test < 0.1). Furthermore, the I^2 statistics suggested an existence of extreme heterogeneity for all comparisons in all studies.

Subgroup analysis

Heterogeneity was found between each of the studies (Table 2). Therefore, a sub-group analysis of the studies by geography grouping of Northern and Southern China was suggested. With no further evidence of heterogeneity in each sub-group, we used the fixed effects model to evaluate the pooled OR of three Southern population studies (Figure 1). We observed that the presence of GNB3-825T allele was significantly associated with higher risk of EH than that of GNB3-825C allele carriers (T *vs*. C: OR=1.50, 95% CI: 1.05–2.14, *P*=0.026) in Southern Han Chinese population. However, there was no statistically significant association in Northern Han Chinese population (T *vs*. C: OR=0.98, 95% CI: 0.79–1.21, *P*=0.829). The same results were observed in all three genetic models (detailed data was not shown). Between-study heterogeneity was found in the Northern studies (*P* for heterogeneity Q test < 0.001), but not in the Southern studies (*P* for

heterogeneity Q test=0.101).

Sensitivity analysis

To further strengthen the confidence for the results, we conducted a sensitivity analysis and the result showed that there was little modification of the estimates after exclusion of an individual study, with pooled ORs ranging from 0.89 to 1.07. Similarly, exclusion of individual Northern studies did not modify the estimates much, with pooled ORs ranging from 0.91 to 1.05. However, among the South studies, Chongqing study from Sichuan province influenced the combined effects with distinct modification. Since the T allele frequency of Chongqing province was 23.2% in controls, which was significantly lower than other studies as we discussed above (Table 1). After exclusion of this Chongqing study, no significant association was found between GNB3-C825T polymorphism and EH in the Southern studies (OR=1.26, 95%CI: 0.94-1.68, P = 0.123). There was no difference in the Northern data analyzed by either fixed effect model or random effect model. The results from fixed effect model was OR (95%): 0.92 (0.85-1.00), and from random effect model was OR (95%): 0.98 (0.79-1.21), respectively.

Publication bias

Publication bias, i.e., the manuscripts can be accepted and published easier if they contain positive results. This is an important consideration in estimating the reliability of meta-analysis. In this study, there was no publication bias for GNB3-C825T polymorphism by Egger's test (t=0.49, P = 0.631). However, the funnel plot showed the asymmetrical distribution of the studies (Figure 2).

Discussion

GNB3-C825T polymorphism was demonstrated to result in the lack of 41 amino acids in β3 subunit of trimeric G-proteins and was shown to be associated with hypertension (10). This polymorphism has also been associated with enhanced G-protein signaling(10, 40, 41), presumably through abnormal stability or functional interactions of the shortened G-proteins as the polymorphism does not affect GNB3 mRNA levels(40). A case-control study found that GNB3-C825T polymorphism influenced plasma sodium and potassium concentrations in essential hypertension patients, evidenced by an increased activity of the Na+/H+ exchanger(42). Thus, GNB3-C825T polymorphisms could be a valuable marker for predicting the susceptibility to hypertension and/or salt sensitivity (9, 10).

In recent years, many studies have reported a correlation between GNB3-C825T and EH in Caucasian, African, South American and Asian populations, respectively (43, 44). However, there were also discrepant conclusions in the other investigations (45, 46). Bogos *et al*.(14) carried out a meta-analysis of total 34 studies with 14,094 hypertensive patients and 17,760 controls from Caucasian, African and Asian populations, and confirmed that GNB3-825T allele was correlated with EH (TT vs. CC + CT: OR=1.08; 95% CI: 1.01-1.15, P<0.001 and TT + CT vs. CC: OR=1.17; 95% CI: 1.06-1.29, P<0.001). But further subgroup analysis failed to identify significant associations from studies in Asian populations. Our meta-analysis showed that the GNB3-C825T polymorphism was not associated with EH in Han Chinese populations, which is in agreement with the result of the above multiethnic population meta-analysis(14). When stratifying for the geographical location, we observed that GNB3-825T allele (OR = 1.50, 95% CI: 1.05-2.15, P=0.026) was a risk factor for EH in Southern Han Chinese populations. However, only three investigations on the Southern Han Chinese populations were eligible and selected for the meta-analysis, and thus less EH patients and normotensive individuals were in this study.

False-positive result, therefore, is not negligible. Furthermore, in the sensitivity analysis, we found that the allelic frequency of GNB3-C825T from the study of Chongqing study from Sichuan province significantly influenced the combined effects in studies conducted in Southern China. After excluding of this study, the significant association in South studies disappeared. Therefore, it should be very cautious to draw a conclusion on a significant association between GNB3-C825T polymorphism and EH in Southern Han Chinese population.

It should be taken into consideration that the GNB3-825T allele was thought to be a 'thrifty genotype', similar with AGT-M235T polymorphism, due to the high frequency in original ethnicities and significant correlation with obesity(47). On the other hand, GNB3-825T, AGT-235T and cytochrome P450 3A5 (CYP3A5)-**1* alleles contribute to the susceptibility to salt sensitivity(48), suggesting that these polymorphisms may present the same distributions under the same selective pressure. It has been reported that the frequencies of AGT-235M and CYP3A5-**3* allele increase with distance from the equator (r=0.712, $P < 0.001$ and r=0.612, $P < 0.001$) (49), meanwhile indicating that GNB3-825T allele decreases with the distance from the equator. In addition, an increase in latitude associated with lower frequency of GNB3-825T allele was confirmed by the Human Genome Diversity Project (HGDP) (50). In the current study, we calculated the frequency of GNB3-825T allele of all the studies included in the meta-analysis, and further analyzed the association of the frequency with latitude of geographical regions. We failed to observe the correlation between GNB3-825T allele and latitude (r=0.469, P=0.106), and similar result was obtained after removing the Chongqing study (r=0.322, P=0.307). It is worth noting that less number of the studies from Southern population may reduce the statistical analysis power and lead to failure of detecting the association between the frequency of

GNB3-825T allele and latitude in Han Chinese population. Although we were not able to identify the problems in the study design and SNP genotyping methods, the rather low frequency of GNB3-825T allele in the Chongqing is attributable to the sample selection bias or lack of quality control for the genotyping analysis. More studies from South of China are needed to re-estimate the frequency.

The negative result in the Chinese Han population might be caused by interethnic differences. Siffert *et al.* (51) analyzed the distribution frequencies of GNB3-C825T from a German cohort, Chinese and African populations, and founded that T allele frequencies differed significantly between different ethnic groups and were the lowest in Germans (31.9%), intermediate in Chinese (47.7%) and the highest in Africans (81.4 to 84.1%). In our study, the average frequency of T allele, similar to their reports, was 47.7% in Han Chinese population. In addition, two studies in Japanese populations reported the frequencies of GNB3-825T allele 49.2% and 50.1%, respectively, and the study did not observe any significant associations between GNB3-C825T polymorphism and EH either (45, 52). The different genotypic frequencies of GNB3-825T allele might influence the phenotypes related to hypertension, such as salt sensitivity, in different ethnic population (53), which may contribute to different correlations between Chinese Han and other populations. Therefore, the genetic background and heterogeneity of the study populations might influence the results of association studies between genetic polymorphisms and EH.

Several potential limitations in this study are worth noting. Firstly, although the Egger's test is not significant, an asymmetric funnel plot suggests the existence of bias. Except for publication bias, possible reasons for asymmetry in funnel plots in this meta-analysis may be genotype testing, poor study design, heterogeneity and chance findings (54). Secondly, the number of investigations is not large enough to confirm or

reject a genetic association reliably, especially given there are only three eligible studies with the Southern populations. Therefore, the effect of possible false-negative findings of the individual studies due to low statistical power could affect the overall results of this meta-analysis. Thirdly, as a research method, meta-analysis has some limitations, e.g. meta-analysis cannot neither eliminate the between-study heterogeneity nor improve the quality of original studies. Therefore, well-designed large-scale studies are needed for providing sufficient statistical power to detect the associations. Based on the current meta-analysis, some limitations of the eligibility of the studies should also be considered. These limitations are common in genetic epidemiology studies and are propagated in a meta-analysis. Among the 12 eligible studies, only eight studies' controls were matched for age and gender to the cases. The selection bias of controls from inpatient, outpatient or random samples was another potential source of variation in different studies. Furthermore, there were not enough information on the various potential confounders in the some of these original publications, such as age, gender, BMI, SBP and DBP.

Conclusions

Our results of the meta-analysis suggested that GNB3-825T allele is not associated with the increased risk of EH in Chinese Han population. Larger and well-designed studies including different regional Han Chinese populations should be considered in future studies.

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