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WJH covers topics concerning atherosclerosis, atrial fibrillation, blood pressure measurement, cerebrovascular diseases, clinical aspects and trials for hypertension, community cardiovascular practice, diabetes, hypertension education programs, endocrine hypertension, epidemiology of hypertension and metabolic disorders, experimental hypertension, renal hypertension; and hypertension-related heart failure, hemodynamics, imaging procedures, implementation of guidelines, lifestyle changes, microcirculation, molecular biology, neural mechanisms, new therapeutic development, obesity and metabolic syndrome, organ damage, pharmacoeconomics, public health, renin-angiotensin system, sleep apnea, therapeutics and clinical pharmacology. Priority publication will be given to articles concerning diagnosis and treatment of hypertensive disease. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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ORIGINAL ARTICLE

Observational Study

Association between G-protein β3 subunit gene and isolated systolic blood pressure elevation of greater than 130 mmHg: A large-scale cross-sectional study in the Japanese population

Masahiko Eto, Taro Takeshima, Masanori Harada, Shinji Fujiwara, Maki Kumada, Toyomi Kamesaki, Kazuhiro Takamura, Tsuneaki Kenzaka, Yoshikazu Nakamura, Takanori Aonuma, Masanobu Okayama, Eiji Kajii

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Yoshikazu Nakamura, Department of Public Health, Jichi Medical University, Shimotsuke 329-0498, Tochigi, Japan

Takanori Aonuma, Department of Surgery, Wakuya Medical and Welfare Center, Wakuya 987-0121, Miyagi, Japan

Masanobu Okayama, Division of Community Medicine and Medical Education, Kobe University Graduate School of Medicine, Kobe 652-0032, Hyogo, Japan

Author contributions: Eto M, Takeshima T, Harada M, Fujiwara S, Kumada M, Kamesaki T, Takamura K, Kenzaka T, Nakamura Y, Aonuma T, Okayama M and Kajii E contributed to study conception and design; Eto M, Takeshima T, Harada M, Kumada M, Kamesaki T, Takamura K, Kenzaka T and Okayama M contributed to data acquisition, data analysis and interpretation, and writing of article; Eto M, Nakamura Y, Aonuma T, Okayama M and Kajii E contributed to editing, reviewing and final approval of article.

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Correspondence to: Masanobu Okayama, MD, PhD, Division of Community Medicine and Medical Education, Kobe University Graduate School of Medicine, 2-1-5 Arata-sho, Hyogo-ku, Kobe 652-0032, Hyogo, Japan. okayama@jichi.ac.jp
Telephone: +81-78-3826732

Fax: +81-78-3826283

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Abstract

AIM

To investigate whether GNB3 C825T single nucleotide polymorphism (SNP) contributes to systolic blood pressure (SBP) ⩾ 130 mmHg in a large-scale cross-sectional study among the Japanese population with diastolic blood pressure (DBP) < 85 mmHg.

METHODS

We analyzed 11008 Japanese subjects, including 2797 cases (SBP ⩾ 130 and DBP < 85 mmHg) who were not taking anti-hypertensive medication and 8211 controls (SBP < 130 and DBP < 85 mmHg), all of whom enrolled in the genome banking project of the 21st Century COE (Center of Excellence) Program at Jichi Medical University. Subjects were divided into four groups according to gender (male and female) and age (⩽ 49 years and ⩾ 50 years). *GNB3* gene polymorphism was determined using the TaqMan probe method. We compared the frequencies of alleles and genotypes between cases and controls by chi-squared test. The strength of the associations was estimated by odds ratios (ORs) and 95%CI by using logistic regression analysis. The ORs were adjusted for age and body mass index.

RESULTS

Allele and genotype distributions significantly differed between cases and controls only in males aged ⩽ 49 years. Compared to the CC genotype, a significant OR was obtained in the TT genotype among males aged ⩽ 49 years.

CONCLUSION

This study indicates that the TT genotype of the GNB3 C825T SNP may contribute to SBP elevation of greater than 130 mmHg compared to the CC genotype in Japanese males aged ⩽ 49 years.

Key words: Prehypertension; Hypertension; G-protein β3 subunit gene; Single nucleotide polymorphism

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Core tip: The association of *GNB3* gene polymorphism with hypertension has been examined in different populations. Unfortunately, the reported results have been controversial. This large-scale cross-sectional study of the Japanese population clarifies that among males aged ⩽ 49 years, the TT single nucleotide polymorphism of GNB3 C825T is significantly associated with high systolic blood pressure (SBP) (⩾ 130 mmHg). Therapeutic intervention is recommended at this level of SBP to prevent cardiovascular disease and its progression to hypertension. This approach is likely to be more effective for youngsters, compared to the elderly. This study suggests that using genetic information could make this approach more effective.

Eto M, Takeshima T, Harada M, Fujiwara S, Kumada M, Kamesaki T, Takamura K, Kenzaka T, Nakamura Y, Aonuma T, Okayama M, Kajii E. Association between G-protein β3 subunit gene and isolated systolic blood pressure elevation of greater than 130 mmHg: A large-scale cross-sectional study in the Japanese population. *World J Hypertens* 2017; 7(2): 24-31 Available from: URL: http://www.wjgnet.com/2220-3168/full/v7/i2/24.htm DOI: http://dx.doi.org/10.5494/wjh.v7.i2.24

INTRODUCTION

Blood pressure (BP) is a quantitative phenotype and has a continuous distribution[1,2]. Essential hypertension (HT) is the upper part of the distribution. HT is a dichotomous trait and is defined as a BP level ⩾ 140/90 mmHg. HT is one of the most important risk factors for stroke, cardiovascular disease (CVD) and end-stage renal disease (ESRD), and is a leading cause of morbidity and mortality. However, the level at which BP starts causing end-stage organ damage is thought to be lower than 140/90 mmHg. An earlier intervention to reduce BP is beneficial in the absence of cardiovascular disease. Several population-based prospective studies have indicated that a linear and impressive increase in the risk for CVD starts at a BP level ⩾ 120/80 mmHg[3-7]. On the basis of these findings, the seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure (JNC-7 in 2003) introduced the term "prehypertension" as a BP category, which is defined as BP levels of 120 to 139/80 to 89 mmHg. Prehypertension (Pre-HT) includes two different subcategories: Stage 1 pre-HT (120 to 129/80 to 84 mmHg) and stage 2 pre-HT (130 to 139/ 85 to 89 mmHg)[8]. Since the JNC-7 proposal, numerous studies including Multiple Risk Factor Intervention Trial (MRFIT), the Framingham Heart Study, and the TRial of Preventing Hypertension (TROPHY) study have investigated the risk of pre-HT for various types of adverse outcomes. As a result, different effects of two BP ranges in pre-HT patients on future outcomes have been demonstrated[5,6,9-11]. Per the guidelines provided by the Japanese Society of Hypertension (JSH) in 2009, the target level of BP control was less than 130/85 mmHg in young and middle-aged individuals. Nowadays, therapeutic lifestyle interventions such as weight loss, salt restriction, and exercise are recommended, especially at SBP levels ⩾ 130 mmHg to prevent cardiovascular disease and its progression to HT, although drug intervention

is recommended at SBP ⩾ 140 mmHg. HT is a multifactorial disorder caused by the interaction between genetic and environmental factors. Many studies have sought to identify genetic variants linked to HT, but there have been few studies to correlate genetic variants with isolated SBP elevation ⩾ 130 mmHg.

Heterotrimeric G-proteins, which consist of three subunits (α, β and γ), are located on the cytoplasmic side of the cell membrane and relay signals from G protein-coupled receptors (GPCRs) to downstream effectors[12,13]. In humans, there are at least 16, 5, and 12 different genes encoding α, β and γ subunits, respectively[14-17]. The combinations of the three subunits affect the function of G-proteins[18]. The *GNB3* gene is one of the five genes encoding the G-protein β subunit. Although the C825T single nucleotide polymorphism (SNP) within exon 10 of *GNB3* does not change the encoded amino acid (ser275ser), the 825T allele expresses a truncated splice variant of Gβ3, termed Gβ3s, which contains 41 fewer amino acids[16,18-20]. The missing domain is the functionally important region that forms tight binding with γ subunit. Gβ3s effect original downstream transduction by forming a functional heterodimer with Gγ5[16,18-20].

Since the first report by Siffert *et al*[18] showing a significant association between the *GNB3* 825T allele and HT, numerous studies have investigated the role of this SNP in HT. However, some studies have reported conflicting results and controversial conclusions exist[21-31]. An explanation for this discrepancy may be that the effects of *GNB3* SNP on BP are small and require large sample sizes to be detectable. In addition, few association studies have examined the effect of *GNB3* C825T SNP on the risk of SBP elevation ⩾ 130 mmHg. Moreover, because of ethnic divergence of gene SNPs, it is important to construct a database of SNPs related to HT in different ethnic groups. In this study, we used a large-scale population-based database (*n* = 21004) constructed by Jichi Medical University. The aim of this study was to investigate whether the *GNB3* C825T SNP contributes to SBP ⩾ 130 mmHg in a large-scale cross-sectional study among the Japanese population with DBP < 85 mmHg.

MATERIALS AND METHODS

Ethical considerations

This is a large-scale cross-sectional study for the assessment of the association between *GNB3* SNP (C825T, rs6489738) and SBP elevation of greater than 130 mmHg among a Japanese population. Written informed consent was obtained from all individuals before their participation. This study was approved by the Jichi Medical University Epidemiological and Ethical Committee.

Recruitment of participants

This study is based on the data from the genome banking project of the 21st Century COE (Center of Excellence) Program "Development of Frontier Medical Science in the Field of Community Medicine" at Jichi Medical University. In brief, this project recruited a total of 21004 Japanese people aged ⩾ 20 years living in 78 rural and suburban areas of 30 prefectures across Japan from June 2004 to March 2008. Among the 11008 enrolled Japanese subjects, 2797 cases (SBP ⩾ 130, DBP < 85 and not taking anti-hypertensive medication) and 8211 controls (SBP < 130, DBP < 85) participated in this study.

Physical examination

Blood pressure was measured using a standard mercury sphygmomanometer on the right arm after at least 5 min of rest in a sitting position. The first and fifth Korotkoff sounds were considered the SBP and DBP, respectively. In this study, newly diagnosed cases were defined as SBP higher than or equal to 130 mmHg and DBP less than 85 mmHg. The cases currently taking anti-hypertensive medication at the time of the study or with a history of HT were excluded. The controls were defined as SBP less than 130 mmHg and DBP less than 85 mmHg. Height and weight of the subjects were obtained from health-checkup records or medical records. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared: Weight (kg)/[height (m) × height (m)].

Genotyping of SNP

Venous blood was collected in 5-mL tubes containing 50 mmol/L ethylenediaminetetraaceticacid (EDTA) as anticoagulant. Genomic DNA (50-100 μL) was extracted from the peripheral blood mononuclear cells (PBMCs) of centrifuged blood using a Puregene DNA Purification Kit (Gentra Systems, Inc., Minneapolis, MN, United States). Genotyping for the SNP (C825T, rs 6489738) on G-protein β-3 subunit gene (*GNB3*) was carried out by the TaqMan probe method. Probes and primer mixtures were selected from a commercial database for the TaqMan probe system (myScience: Applied Biosystems, Foster City, CA, United States). Genomic DNA (0.5 μg) was applied to a 384-well plate and air-dried for use as templates for the reaction. The polymerase chain reaction (PCR) mixture contained 2.5 μL of probe mix and the same amount of Master Mix solution (Applied Biosystems). The standard thermocycle parameter provided by the manufacturer was used. An ABI 7900HT apparatus (Applied Biosystems) was used for reaction, genotype calling, and data exporting. The procedure for SNP genotyping was carried out at Jichi Medical University.

Statistical analysis

Subjects were divided into four subgroups based on their gender (male and female) and the age (⩽ 49 years and ⩾ 50 years). Statistical analyses were performed for each subgroup. Unless otherwise specified, continuous variables such as age and BMI are expressed as mean ± SD. Allele frequencies were determined by gene counting method. The chi-squared test was used to determine whether the genotype distributions differed from the expected from Hardy-Weinberg equilibrium (HWE). HWE was applied to the control and case population to evaluate the data quality. The differences in genotype

Table 1 Characteristics of the subjects

	Male			Female		
	Cases mean ± SD	Controls mean ± SD	*P*-value[1]	Cases mean ± SD	Controls mean ± SD	*P*-value[1]
Age ⩽ 49 yr	*n* = 390	*n* = 1423		*n* = 256	*n* = 2917	
Age, yr	37.9 ± 7.8	37.6 ± 7.7	0.53	41.4 ± 7.1	36.7 ± 8.0	< 0.001
BMI, kg/m^2	24.4 ± 3.3	23.2 ± 3.1	< 0.001	23.7 ± 4.4	21.5 ± 3.1	< 0.001
SBP, mmHg	135.2 ± 6.9	114.7 ± 8.9	< 0.001	135.3 ± 6.4	109.4 ± 10.1	< 0.001
DBP, mmHg	77.6 ± 5.2	71.1 ± 7.7	< 0.001	76.2 ± 6.5	66.7 ± 8.2	< 0.001
Age ⩾ 50 yr	*n* = 925	*n* = 1675		*n* = 1226	*n* = 2196	
Age, yr	66.9 ± 9.8	63.3 ± 9.7	< 0.001	67.0 ± 9.7	61.8 ± 9.1	< 0.001
BMI, kg/m^2	23.3 ± 3.0	22.7 ± 3.0	< 0.001	23.0 ± 3.4	22.3 ± 2.9	< 0.001
SBP, mmHg	138.7 ± 8.8	115.3 ± 9.5	< 0.001	139.4 ± 9.6	114.1 ± 10.0	< 0.001
DBP, mmHg	76.6 ± 6.1	70.5 ± 7.8	< 0.001	75.2 ± 6.7	68.8 ± 8.0	< 0.001

[1]*t*-test. DBP: Diastolic blood pressure; BMI: Body mass index; SBP: Systolic blood pressure.

frequencies between cases and controls were compared with a χ^2 test or Fisher's test using 2 × 3 tables. Odds ratios (ORs) with 95% confidence intervals (95%CI) were computed to estimate associations between genotypes and SBP ⩾ 130 mmHg using logistic regression analysis with adjustment for age and BMI as covariates. Results were considered to be statistically significant if a *P*-value was less than 0.05 or if a 95%CI did not include unity. All statistical analyses were carried out using IBM SPSS for Windows version 20 (IBM Inc., New York, NY, United States). The prevalence of cases defined as SBP ⩾ 130 and DBP < 85 mmHg was different between subjects ⩽ 49 and ⩾ 50 years in both males and females. Thus, statistical analyses were performed in four subgroups (males ⩽ 49 years, males ⩾ 50 years, females ⩽ 49 years, and females ⩾ 50 years), respectively. The genotype distributions within each subgroup were consistent with Hardy-Weinberg equilibrium.

RESULTS

Table 1 presents demographic characteristics of the study subjects. Subjects were defined as cases if SBP ⩾ 130 and DBP < 85 mmHg and defined as controls if SBP < 130 and DBP < 85 mmHg. The mean age, BMI, SBP, and DBP of the cases were significantly higher than those of the controls in all subgroups stratified by gender and age (⩽ 49 years, ⩾ 50 years), except for the mean age of males aged 49 years or below.

Table 2 shows the distribution of allele and genotype frequencies of the *GNB3* SNP rs 6489738 (C825T). There were no deviations from Hardy-Weinberg equilibrium in all cases and in all controls among the gender/age sub-categories (*P* > 0.18 in all cases, *P* > 0.50 in all controls). Comparison of allele and genotype distributions between cases and controls revealed that *GNB3* C825T SNP was significantly (*P* = 0.008) associated with the prevalence of SBP ⩾ 130 mmHg among males aged 49 years or below, but not in other subgroups.

Table 3 shows the multivariable logistic regression analysis. Compared to the CC genotype, the odds ratio of the TT genotype for SBP ⩾ 130 mmHg was significantly higher in males aged 49 years or younger. Significance was maintained even after adjusting for age and BMI. Significant probability values for the C825T SNP were obtained by a recessive model.

DISCUSSION

In this large-scale cross-sectional study, we confirmed that a C825T SNP on *GNB3* was associated with isolated SBP elevation ⩾ 130 mmHg in Japanese males aged 49 years or younger. Definition of cases was SBP ⩾ 130 and DBP < 85 mmHg and that of controls was SBP < 130 and DBP < 85 mmHg. Our population-based large samples did not include cases undergoing anti-hypertensive treatment or with a history of HT. All cases were newly diagnosed as isolated systolic pre-HT or isolated systolic HT. In this study, statistical analyses were performed in four subgroups (males ⩽ 49 years, males ⩾ 50 years, females ⩽ 49 years, and females ⩾ 50 years). No significant association of this SNP with isolated SBP elevation ⩾ 130 mmHg was detected, except for the subgroup of males ⩽ 49 years, in which individuals homozygous for the T allele had a significantly higher risk for isolated SBP ⩾ 130 mmHg, but individuals heterozygous for the T allele did not show significantly higher risk when compared to the CC genotype. The effect on blood pressure was thought to be influenced by the number of 825T alleles. In other words, this recessive effect of 825T allele suggests that a single copy of 825C allele is sufficient to attenuate BP raising-effect of the 825T allele or that the direct effect of the 825T allele on BP is small, although the shorter product (Gβ3s) of the *GNB3* 825T allele is associated with enhanced activation of heterotrimeric G-proteins compared with the product(Gβ3) of the 825C alleles[18]. Recently, the association of *GNB3* C825T with control, pre-HT, and HT subjects was examined in a Greek population (*n* = 330), but no statistical difference in the genotype frequencies was found among the three groups[32]. We were able to confirm significant association of the 825T allele with isolated SBP ⩾ 130 mmHg by using a large-scale database. The frequencies of the T allele in total subjects among subgroups of males ⩽ 49 years, males

Table 2 Allele and genotype frequencies of *GNB3* in the gender/age sub-categories

	Male			Female		
	Cases *n* (%)	Controls *n* (%)	*P*-value[1]	Cases *n* (%)	Controls *n* (%)	*P*-value[1]
Age ⩽ 49 yr						
Allele						
C825 (wild)	350 (44.9)	1433 (50.4)	0.007	244 (47.7)	2912 (49.9)	0.33
T825 (variant)	430 (55.1)	1413 (49.6)		268 (52.3)	2922 (50.1)	
Genotype						
CC	85 (21.8)	356 (25.0)	0.008	60 (23.4)	718 (24.6)	0.5
CT	180 (46.2)	721 (50.7)		124 (48.4)	1476 (50.6)	
TT	125 (32.1)	346 (24.3)		72 (28.1)	723 (24.8)	
HWE	χ^2 = 1.76, *P* = 0.19	χ^2 = 0.26, *P* = 0.61		χ^2 = 0.22, *P* = 0.64	χ^2 = 0.42, *P* = 0.52	
Age ⩾ 50 yr						
Allele						
C825 (wild)	903 (48.8)	1649 (49.2)	0.78	1229 (50.1)	2175 (49.5)	0.63
T825 (variant)	947 (51.2)	1701 (50.8)		1223 (49.9)	2217 (50.5)	
Genotype						
CC	221 (23.9)	412 (24.6)	0.92	309 (25.2)	537 (24.5)	0.88
CT	461 (49.8)	825 (49.3)		611 (49.8)	1101 (50.1)	
TT	243 (26.3)	438 (26.1)		306 (25.0)	558 (25.4)	
HWE	χ^2 = 0.01, *P* = 0.94	χ^2 = 0.36, *P* = 0.55		χ^2 = 0.01, *P* = 0.91	χ^2 = 0.02, *P* = 0.89	

[1]χ^2 test. HWE: Hardy-Weinberg equilibrium.

Table 3 Associations between genotypes of GNB3 and SBP ⩾ 130 mmHg

	Male		Female	
	Crude OR (95%CI)	Adjusted OR (95%CI)[1]	Crude OR (95%CI)	Adjusted OR (95%CI)[1]
Age ⩽ 49 yr				
CC	1	1	1	1
CT	1.05 (0.78-1.39)	1.09 (0.81-1.45)	1.01 (0.73-1.39)	1.01 (0.73-1.41)
TT	1.51 (1.11-2.07)	1.53 (1.11-2.10)	1.19 (0.83-1.70)	1.13 (0.78-1.63)
Age ⩾ 50 yr				
CC	1	1	1	1
CT	1.04 (0.85-1.27)	1.01 (0.82-1.24)	0.96 (0.81-1.15)	1.02 (0.85-1.22)
TT	1.03 (0.83-1.30)	1.03 (0.81-1.30)	0.95 (0.78-1.16)	1.01 (0.82-1.24)

[1]Logistic regression analysis with adjustment for age and body mass index.

⩾ 50 years, females ⩽ 49 years, and females ⩾ 50 years were 50.8%, 50.9%, 50.3% and 50.3%, respectively. The frequencies of the 825T allele in control subjects were 49.6%, 50.8%, 50.1% and 50.5%, respectively. According to previous reports, the frequencies of the 825T allele differed significantly among different ethnic groups: 25%-31.7% in Germans[18,22,33,34], 30% in Irish (Belfast)[31], 31% in French[31], 45.6%-53.1% in Japanese[2,24-26,28,30,35], 50.1% in Canadian Sandy Lake Oji-Cree[36], 74.5% in African Americans[29], and 79% in Black Africans[37]. The 825T allele frequencies in the Japanese population of the present study were compatible with those in previous reports. The genotype distributions of total subjects (cases plus controls) within each subgroup were consistent with Hardy-Weinberg equilibrium ($P > 0.61$). The possibility of selection bias was low in males ⩽ 49 years of this study. It is of interest that the BP raising-effect of the 825T allele was limited to males ⩽ 49 years.

There have been no reports regarding the associations between *GNB3* C825T and the risk of SBP ⩾ 130 mmHg in a Japanese population. This is the first study demonstrating a significant association between *GNB3* C825T and the risk of SBP ⩾ 130 mmHg in young Japanese males. There have been several studies regarding the associations between *GNB3* C825T and HT in Japanese populations[24-28,30]. In these studies, hypertensive cases were selected as SBP ⩾ 160 and/or DBP ⩾ 95 mmHg[26,28], SBP ⩾ 140 and/or DBP ⩾ 90 mmHg[24,25,30], or SBP ⩾ 134 and/or DBP ⩾ 79 mmHg by ambulatory blood pressure monitoring (ABPM)[26]. The subjects taking anti-hypertensive medication were included as cases. Normotensive controls were defined as SBP < 140 and DBP < 90 mmHg[24-28,30], except in one study in which the criteria of controls were SBP < 134 and DBP < 79 mmHg by ABPM[26]. Although Izawa *et al*[25] demonstrated a significant association between *GNB3* C825T and HT only in males (mean age 56.3 years), the *GNB3* genotype distribution did not significantly differ between cases and controls in the analyses of all subjects. In this study, newly diagnosed cases were defined as SBP higher than or equal to 130 mmHg and DBP less than 85 mmHg. In addition, subjects taking anti-hypertensive medication at the time of

the study or with a history of HT were excluded. Therefore, the different definitions of hypertension might affect the conclusions about the relationship between *GNB3* and HT. The findings in this study were obtained by using a large sample sized genome banking data collected from all over Japan. These results suggest that the *GNB3* C825T SNP is a likely risk factor for pre-HT in Japanese young males.

There was an interesting report (n = 447) regarding the association between *GNB3* 825T allele and SBP values in young adult Canadian Oji-Cree population[36]. The frequency of the 825T allele of the subjects was 50.1%, which is similar to the population in this study. However, the presence of the 825T allele was associated with lower SBP in young males and females, essentially making this a normotensive study sample of aboriginal people. The authors explained that functional impact of the *GNB3* 825T allele may differ according to age and, furthermore, that the impact could be different when HT has become an established phenotype. We hypothesize that there may be an interaction between the 825T allele and subjects' lifestyle, especially with low salt intake. In our population, differences in salt intake among subgroups might affect the onset of isolated SBP $\geqslant$ 130 mmHg. In future studies, the interaction of *GNB3* C825T SNP and lifestyle, such as salt-intake, alcohol habits, and obesity must be explored.

Some limitations need to be noted when considering the results from this study. First, logistic regression analysis was adjusted only for age and BMI as covariates. We need to reassess the interactions in combination with other potential confounding factors (such as environmental factors). Second, the cross-sectional design does not allow us to make any conclusive statements. A significant association between *GNB3* C825T and isolated SBP elevation $\geqslant$ 130 mmHg in males aged $\leqslant$ 49 years needs to be reassessed in a prospective cohort study.

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COMMENTS

Background

Heterotrimeric G-proteins, which consist of three subunits (Gα, Gβ and Gγ), relay signals from G protein-coupled receptors (GPCRs) to downstream effectors. GPCRs activation by agonist-binding induces conformational changes and results in the dissociation of Gαβγ into Gα and Gβγ, both of which initiate distinct downstream signaling cascades. In humans, there are at least 16, 5, and 12 different genes coding α, β, and γ subunits, respectively. The combination of αβγ affects the function of G-protein. Essential hypertension (HT) display enhanced signal transduction through pertussis toxin (PTX)-sensitive G proteins (Gi), of which G-Protein β3 subunit gene (*GNB3*) single nucleotide polymorphism (SNP, C825T) was reported by Siffert *et al* in 1998. The 825T allele is associated with the generation of a short splice variant termed G-βs, which has been proposed to lead to enhanced signal transduction by forming a functional heterodimer with Gγ5. Since first report by Siffert *et al* showing a significant association between the 825T allele and HT, numerous studies have investigated the association between the 825T allele and HT or blood pressure (BP) levels. However, the results have been conflicting to date, especially in non-whites. Moreover, it was unclear whether the 825T allele is associated with earlier blood pressure elevation, especially preHT. In addition, the frequency of the 825T allele showed the ethnic or regional diversity. Thus, it was thought to be important to construct a large-scale database of SNP in different ethnic groups. In this study, the possible effect of *GNB3* SNP (C825T) on the risk of systolic BP of greater than 130 mmHg was examined by using a large-scale Japanese population-based database (n = 21004) constructed by Jichi Medical University.

Research frontiers

A previous study reported that the GNB3-systolic BP associations was more evident among subjects with lower sodium intake/excretion, but not with higher intake/excretion. There was the possibility that higher salt intake masks the potential effect of GNB3 on BP levels. The differences in salt intake should be considered. In addition, the interaction between *GNB3* C825T SNP and other lifestyle, such as alcohol habits, and obesity must be explored. The T allele is in almost complete linkage disequilibrium with other polymorphisms within the *GNB3* gene. The mechanism by which *GNB3* C825T or the "T haplotype" increases renal sodium transport remains to be determined. The 825TT humans expressing the Gβ3-s might show a general increase in cAMP levels in renal tubular cells, due to an enhanced signaling effect, when compared to 825CC individuals. An increase in cAMP levels in the renal tubular cells would have the effect of altering the expression of channels such as aquaporin or epithelial sodium channels (ENaC). A mild alteration in the expression of these channels would lead to alterations in the salt concentrations of blood. Further studies are needed to precisely define the biochemical mechanisms by which enhanced G-protein signaling may contribute to BP elevation.

Innovations and breakthroughs

The frequency of the 825T allele shows the ethnic or regional diversity. In addition, the effect on blood pressure by the 825T alleles is small. If sample size is small, the higher frequency of 825T allele in Japanese may hamper the detection of the potential association. The authors could detect a significant association in M $\leqslant$ 49 by using large scale database. In addition, it is of interest that BP raising-effect by the 825 T allele was limited to M $\leqslant$ 49. The sex and age-specific analyses should be performed when the prevalence of cases are different among subgroups.

Applications

The different definitions of HT might affect the conclusions about the relationship between *GNB3* C825T and HT.

Peer-review

This is an appealing study which emphasize that GNB3 C825T polymorphism may be a useful genetic marker for hypertension.

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