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Combined Action of ACE Gene I/D and GNB3 Gene C825T Polymorphisms on Essential Hypertension in Northern Han Chinese*

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Abstract Essential hypertension (EH), a complex polygenic disease, is considered to the result of the genetic interaction of multiple gene alterations in concert with environmental factors. Evidences showed that angiotensin-converting enzyme (ACE) gene and G protein beta3 subunit (GNB3) gene are both important susceptibility genes for EH, and that there exists putative biological connection between the two genes in developing hypertension. To investigate whether hypertension was affected by gene-gene interaction between the two genes in the northern Chinese Han population, a case-control association study including 502 hypertensive cases and 490 healthy controls was conducted, selecting the ACE gene I/D polymorphism and the GNB3 gene C825T polymorphism. Linkage disequilibrium analysis revealed a significant nonrandom distribution only in male hypertensives, indicating that interaction between ACE gene and GNB3 gene may predispose males to the occurrence of hypertension. Multivariate stepwise logistic regression in single locus analysis, with adjustment for common risk factors for hypertension, demonstrated that the *OR* for DD/ID versus Ⅱ for hypertension among men was significant (*OR* 1.57; 95% CI, 1.09～2.27; $P = 0.016$) in dominant genetic model. In combination analysis stratified with respect to gender, slightly significant ORs were found after adjustment in males: *OR* for TT *vs* CC, 0.11; 95% CI, 0.01～0.99; $P = 0.049$ within ACE DD genotype; *OR* for DD/ID *vs* Ⅱ, 1.52; 95% CI, 1.01～2.29; $P = 0.047$ within GNB3 CC+CT genotype. The results suggest that ACE, or a nearby gene, is a male-specific susceptible gene for hypertension, and that there may exist epistatic gene-gene interaction between ACE D allele and GNB3 825C allele.

Key words angiotensin-converting enzyme, G-protein beta3 subunit, interaction, combination effect, hypertension

Since the genes for many of mendelian diseases have been positioned successfully, now identifying the genes that contribute to or modify complex inherited diseases becomes the focus and major challenge for people. Essential hypertension (EH), a complex disease, is one of the leading health killers and is considered to the result of the genetic interaction of multiple gene alterations in concert with environmental factors, e.g., nutrition and physical activity[1,2]. Although researches showed that genetic factors accounted for 30%～60% of the blood pressure (BP) variation in the population[3,4], until now the genes responsible for susceptibility to EH are mostly unknown. This may be that many susceptibility genes of EH usually apply small genetic effect and are context dependent, so that they could not easily be detected in many genetic backgroup/populations by means of one gene at a time[5,6]. So, multiple candidate genes should be taken into research simultaneously to genetically dissect EH.

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Many studies have showed that angiotensin-converting enzyme (ACE) gene and G protein beta3 subunit (GNB3) gene are both important susceptibility genes for EH and that there exists biological connection between the two genes in developing hypertension. ACE, an important member of the renin-angiotensin system, regulates BP by mediating the conversion of inactive angiotensin Ⅰ into angiotensin Ⅱ (Ang Ⅱ), which is a powerful vasoconstrictor and activates the angiotensin Ⅱ type 1 (AT1) or angiotensin Ⅱ type 2 (AT2) plasma membrane receptor, and by degrading a potent vasodilator, bradykinin[7]. For GNB3, a component of G protein, it mediates the development of hypertension through enhancing the G protein activity, which has a strong impact on the intercellular signal transduction[2]. Ang Ⅱ receptors, AT1 and AT2, are typical G-protein-coupled receptors, thus Ang Ⅱ acts upon the cell *via* metabotropic receptors, and the signal is transmitted inside the cell *via* G proteins[8]. When variants alter in the two genes and the alteration affects the normal working of the connected pathway, hypertension might be caused.

ACE gene insert/deletion (I/D) polymorphism and GNB3 gene C825T polymorphism have been extensively examined in candidate gene association study for hypertension, respectively. For ACE I/D polymorphism, Rigat *et al*.[9] firstly discovered that the polymorphism accounted for 47% of the total phenotypic variance of serum ACE and that ACE activity was related to the I/D genotype, showing a dosage effect of the D allele, with the D/D genotype showing highest ACE activity and the I/I genotype the lowest. A large population-based Framingham Heart study found that ACE I/D polymorphism was associated with BP and hypertension, with male specific effect[10]. However, considerable negative results were gotten on this question[8, 11~14]. There were also no consistent results in association studies for GNB3 C825T polymorphism and hypertension. Since Siffert *et al*.[15] reported that 825T was significant associated with EH, many following studies got conflicting results[8,12]. The causes of these discrepancies are multiple. The most important cause is that hypertension is polygenic disease. Thus, only when a sufficient number of control genes are altered in concert would high BP ensue. Besides many commonly mentioned reasons[16], another important reason may be that there exists gene-gene interaction. However, few studies were conducted to explore a possible gene-gene interaction between the ACE and GNB3 gene polymorphisms and hypertension.

Considering the functional importance of the two related genes in the development of hypertension and the fact that few combination analysis was performed in the world, we carried out a case-control association study with hypertension in northern Chinese Han population with a relatively large sample selecting the ACE gene I/D polymorphism and the GNB3 gene C825T polymorphism, aiming at examining whether there was gene-gene interaction between these polymorphisms on the outcome of hypertension in the northern Chinese Han population.

1 Methods

1.1 Subjects

The International Collaborative Study of Cardiovascular Disease in Asia (InterASIA in China) provided all the DNA samples and clinical data for the present study[17]. The local bioethical committee approved the study protocol and each participant in the study signed the written consent. The samples involved in the present investigation consisted of 992 (502 unrelated hypertensive patients and 490 unrelated normotensive controls) northern Han Chinese from Beijing City, Jilin Province and Shandong Province. All measurement and interviews were taken under standard conditions as previously described[17]. All hypertensive patients were defined as 3 consecutive blood pressure (BP) measurements $\geqslant$160 mmHg (systolic blood pressure, SBP) and/or $\geqslant$100 mmHg (diastolic blood pressure, DBP), and controls had SBP <140 mmHg and DBP <90 mmHg. Blood pressure values of hypertensive patients receiving treatment were adjusted according to the algorithm described in the analyses of Framingham data[3]. None of the subjects had secondary forms of hypertension, coronary heart disease or diabetes.

1.2 Genotyping and statistical analysis

We genotyped ACE I/D polymorphism and GNB3 C825T polymorphism by means of polymerase chain reaction and restriction fragment-length polymorphism methods, as described elsewhere[18, 19].

Statistical analyses were carried out using Stata (Intercooled Stata 8.0 for Windows). Genetic Data Analysis program, GDA, was used to assess single locus Hardy-Weinberg equilibrium (HWE), and to test multilocus linkage disequilibrium (LD), as proposed

by Williams *et al.* [5,14,20]. Continuous variables by hypertension status were presented as $\bar{x} \pm s$. The between-group demographic and blood pressure data were assessed by the *t*-test for continuous variables and by the chi-square test for categorical ones. Allele frequencies were calculated from the genotypes of the subjects. Differences in allele frequencies and genotype distributions between the hypertensives and normotensives were compared using the chi-square test or, where appropriate, the Fisher's exact test. Secondary analyses were carried out to test for dominant, recessive, and additive modes of inheritance. Interaction between genotypes at the ACE locus and GNB3 locus was estimated by stepwise logistic regression analysis for hypertension status and by multiple linear regression analysis for blood pressure. Adjustment was performed by incorporating conventional risk factors. Crude odds ratios (*OR*s) with 95% confidence interval (CI) were computed to estimate the relative risk for hypertension. Gender-specified analyses were conducted. All statistical tests were two sided, and a probability value of less than 0.05 was considered statistically significant.

2 Results

The main baseline characteristics of hypertensive cases and healthy controls in female and male subgroups are shown in Table 1. Neither in females nor in males, there were significant differences between the cases and controls in age and proportions of smokers and drinkers. In females, BP measurement and body mass index (BMI), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) and glucose (Glu) levels were significantly higher in cases than in controls, but not for creatinine (Cr), cholesterol (Cho) and low-density lipoprotein cholesterol (LDL-C). In males, except HDL-C and Glu, other clinical characteristics show significant difference between cases and controls. Within the subjects stratified according to gender and hypertensive status, the genotypic distributions of the ACE2 gene I/D polymorphism and the GNB3 gene C825T polymorphism all were consistent with distribution predicted by the theory of HWE.

Table 1 Demographic characteristics

Parameters	Female		Male	
	NT (233)	EH (240)	NT (257)	EH (262)
Age (years)	55.0±9.1	55.1±9.2	52.2±9.1	52.2±9.3
BMI (kg/m^2)	24.5±3.6	26.8±4.0**	24.2±3.6	25.9±3.6**
SBP (mmHg)	116.0±11.7	184.9±27.9**	118.8±11.5	169.9±26.3**
DBP (mmHg)	73.0±8.1	103.0±12.9**	77.0±7.5	105.6±11.6**
Cr (μmol/L)	63.8±12.1	64.8±14.1	73.6±10.1	76.4±14.1**
TG (mmol/L)	1.44±0.85	1.79±1.07**	1.42±0.88	1.62±1.05*
HDL-C (mmol/L)	1.36±0.33	1.24±0.28**	1.28±0.34	1.27±0.32
Glu (mmol/L)	5.59±1.56	6.12±2.30**	5.60±1.77	5.75±1.09
Cho (mmol/L)	5.22±1.07	5.32±1.01	4.92±1.02	5.15±0.96**
LDL-C (mmol/L)	3.20±0.91	3.25±0.89	2.99±0.81	3.15±0.82*
Drinking (%)	6.9	5.8	57.6	60.7
Smoking (%)	14.2	12.5	69.3	66.4

NT, Normotensive; EH, Essential hypertension; BMI, Body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; Cr, Creatinine; TG, Triglycerides; HDL-C, High-density lipoprotein cholesterol, Glu, Glucose; Cho, Cholesterol; LDL-C, Low density lipoprotein cholesterol. $^*P < 0.05$, $^{**}P \leqslant 0.01$.

No significant differences were found in the frequencies distribution of genotypes and alleles of ACE gene I/D polymorphism and of GNB3 gene C825 polymorphism in overall subjects studied (Table 2). The corresponding *OR*s for hypertension related to the ACE alleles and GNB3 alleles were not significantly different from 1.0 in any of dominant, recessive, and additive modes of inheritance (data not shown). Subsequently a stratified analysis was carried out with respect to gender to study the gender-specific effect. In male subgroup, we observed a different genotype distribution with an increase of DD/ID genotype in hypertensives (*OR* for DD/ID *vs* Ⅱ, 1.49; 95% CI, 1.03 ～2.15; $P = 0.027$) (Table 3). Multivariate

stepwise logistic regression analysis, with adjustment for age, BMI, TG, HDL-C, Glu, Cr, Cho, LDL-C, smoking and drinking, still demonstrated that the OR for hypertension among men was significant (*OR* 1.57; 95% CI, 1.09～2.27; $P = 0.016$) in dominant genetic model. With multiple stepwise linear regression, the mean values of SBP and DBP were compared among/between subjects in any of genetic model, and no statistically significant result was yielded in overall subjects or in gender-specific subjects. In men, adjusted *P* values of SBP and DBP in dominant genetic model were 0.14 and 0.07, respectively.

Table 2 ACE and GNB3 genotype distribution in overall subjects

Phenotype/genotype	Genotype No. (%)					Allele No. (%)			
	II	*ID*	*DD*	χ^2	*P*	*I*	*D*	χ^2	*P*
NT (490)	205 (41.8)	217 (44.3)	68 (13.9)	2.12	0.35	627 (64.0)	353 (36.0)	0.24	0.63
EH (499)	192 (38.5)	244 (48.9)	63 (12.6)			628 (62.9)	370 (37.1)		
	CC	*CT*	*TT*			*C*	*T*		
NT (489)	135 (27.1)	252 (51.5)	102 (20.9)	0.06	0.97	522 (53.4)	456 (46.6)	0.05	0.82
EH (502)	142 (28.3)	257 (51.2)	103 (20.5)			541 (53.9)	463 (46.1)		
	CC	*CT*	*TT*						
ACE II									
NT (204)	59 (28.9)	105 (51.5)	40 (19.6)	0.45	0.80	223 (54.7)	185 (45.3)	0.14	0.71
EH (192)	61 (31.8)	93 (48.4)	38 (19.8)			215 (56.0)	169 (44.0)		
ACE ID									
NT (217)	56 (25.8)	112 (51.6)	49 (22.6)	0.52	0.77	224 (51.6)	210 (48.4)	0.38	0.54
EH (244)	56 (22.9)	130 (53.3)	58 (23.8)			242 (49.6)	246 (50.4)		
ACE DD									
NT (68)	20 (29.4)	35 (51.5)	13 (19.1)	2.11	0.35	75 (55.2)	61 (44.9)	1.89	0.17
EH (63)	24 (38.1)	32 (50.8)	7 (11.1)			80 (63.5)	46 (36.5)		

NT, Normotensive; EH, Essential hypertension.

Table 3 Odds ratios for EH for ACE and GNB3 genotypes in males

Genotypes	*OR*	95% *CI*	*P*
GNB3 TT *vs* CC	1.03	0.61～1.76	0.90
GNB3 TT/TC *vs* CC	0.97	0.65～1.46	0.89
GNB3 TT/TC *vs* CC	0.97	0.65～1.46	0.77
GNB3 CC/CT *vs* TT	0.94	0.60～1.47	0.41
ACE DD *vs* II	1.25	0.71～2.19	0.41
ACE DD/ID *vs* II	1.49	1.03～2.15	0.027
ACE II/ID *vs* DD	1.02	0.61～1.71	0.94
	OR (TT *vs* CC)	*OR* (TT/CT *vs* CC)	*OR* (CC/CT *vs* TT)
ACE II	0.85 (0.35～2.04) *P*=0.69	0.85 (0.35～2.04) *P*=0.69	1.06 (0.49～2.28) *P*=0.88
ACE ID	1.57 (0.69～3.54) *P*=0.24	1.35 (0.70～2.60) *P*=0.33	0.75 (0.39～1.42) *P*=0.35
ACE DD	0.26 (0.35～1.55) *P*=0.08*	0.48 (0.16～1.42) *P*=0.14	2.63 (0.54～16.9) *P*=0.18
ACE II + ID	1.24 (0.70～2.20) *P*=0.43	1.11 (0.71～1.73) *P*=0.64	0.83 (0.52～1.34) *P*=0.43
ACE ID+ DD	1.11 (0.55～2.25) *P*=0.75	1.03 (0.59～1.77) *P*=0.92	0.89 (0.50～1.58) *P*=0.68
	OR (DD *vs* II)	*OR* (DD/ID *vs* II)	*OR* (II/ID *vs* DD)
GNB3 CC	1.83 (0.64～5.48) *P*=0.21	1.28 (0.63～2.63) *P*=0.46	0.57 (0.20～1.53) *P*=0.22
GNB3 CT	1.19 (0.54～2.60) *P*=0.63	1.52 (0.90～2.57) *P*=0.10	1.10 (0.54～2.25) *P*=0.78
GNB3 TT	0.56 (0.08～2.94) *P*=0.44	1.68 (0.71～4.01) *P*=0.20	2.75 (0.58～17.3) *P*=0.15
GNB3 CC+ CT	1.39 (0.75～2.56) *P*=0.26	1.42 (0.94～2.16) *P*=0.08*	0.87 (0.50～1.53) *P*=0.61
GNB3 CT+ TT	1.04 (0.52～2.06) *P*=0.91	1.57(1.01～2.43) *P*=0.36	1.32 (0.71～2.51) *P*=0.35

OR, Odds ratios; CI, Confidence interval. * After adjustment, slightly significant *OR*s were found: *OR* for TT *vs* CC, 0.11; 95% CI, 0.01～0.99; $P = 0.049$ within ACE DD genotype; *OR* for DD/ID *vs* II, 1.52; 95% CI, 1.01～2.29; $P = 0.047$ within GNB3 CC+CT genotype.

Two-locus LD analysis disclosed that the nonrandom distribution of variants of the two genes, located in different chromosome (ACE on chromosome 17 and GNB3 on chromosome 12), is significant only in male hypertensives (P = 0.017). A stratified combination analysis was performed with respect to genotypes in overall subjects (Table 2). The ACE genotype distribution and D allele frequency were not significantly different between two groups within each of the GNB3 genotype, and no significant effect was observed for GNB3 genotype distribution and 825T allele with respect to each of ACE genotype. No significant gender-specific effect was observed in gender-stratified analysis (data no shown). Crude ORs for hypertension were calculated under different combination of ACE I/D and GNB3 C825T polymorphism. Neither for overall sample nor for gender-stratified subgroups disclosed significant effect. The Crude ORs with lowest P value was observed in males (Table 3). After adjustment, slightly significant ORs were found: OR for TT *vs* CC, 0.11; 95% CI, 0.01～0.99; P = 0.049 within ACE DD genotype; OR for DD/ID *vs* Ⅱ, 1.52; 95% CI, 1.01～2.29; P = 0.047 within GNB3 CC + CT genotype. In these two types of genotype combination, no statistically significant result was observed between SBP/or DBP and genetic locus.

3 Discussion

In the present study, single locus analysis revealed that ACE I/D variant showed a significant association in dominant model, with an adjusted OR for hypertension of 1.57 for individuals carrying the D allele. At the same time, the result demonstrated a male-specific effect. Our result is partly consistent with those of Rigat *et al*. and O'Donnell *et al*[9, 10], who both reported that DD genotype was associated with increased risk for hypertension and BP. Our result is different from those of Williams *et al*, Siani *et al*, Wang *et al*, Kedzierska *et al* and Mondry *et al*[8, 11～14], all of whom reported no significant association between ACE I/D polymorphism and hypertension in Ghanaians, Italians, Kazakh in China, Polish Caucasian and Germans, respectively. Through comparison, we observed that the D allele is the major allele either in western populations or in African population, but not in eastern populations. Within the two Eastern populations, the Kazakh population in China has relatively higher DD genotype and D allele frequency. Ethnic difference and geographical difference may be partially responsible for the observed discrepancy. The phenomenon is same for GNB3 C825T polymorphism. Our data yielded no association between C825T variant and EH, which was consistent with Wang *et al*'s result[12], but not with Kedzierska *et al*'s finding[8]. The TT genotype and T allele frequencies in our study are similar as those demonstrated by Wang *et al*[12, 21] and are consistent with the ethnic distribution of C825T variant surveyed by Siffert *et al*, but differ from those reported by Kedzierska *et al*[8]. The mechanism causing hypertension may not be the same among people with different origin and different history of evolution.

Recently, a method of multilocus LD tests was introduced by Williams *et al*[5,14] to evaluate gene-gene interaction between/among genes in hypertension studies. Applying the method in Atrial Fibrillation study, Tsai *et al*[22] also had some interesting finding. Our data revealed a significant nonrandom distribution only in male hypertensives (P = 0.017). Because ACE and GNB3 genes locate in different chromosome, ACE on chromosome 17 and GNB3 on chromosome 12, therefore, it is expected that the variants in the two genes would be in equilibrium according to standard population genetic models. Thus, our result indicates that interactions between ACE and GNB3 genes may predispose males to the occurrence of hypertension.

Joo *et al*[23] used a set-selection method to test the disease association of a set of possibly interacting genetic markers and found that 2-SNP combinations analysis may yield stronger association than single SNP analysis. In practice, Williams *et al*[14] found that 16 out of 120 multilocus comparisons deviated significantly from random in hypertensives, but not in normotensives, in whose study 7 polymorphic sites in 4 genes, including ACE gene, had no significant association with hypertension. Similarly, Siani *et al*[13] reported that the carriers of the MM, AA, CC, DD/ID combination demonstrated a substantially higher probability of being hypertensive, although they detected no significant association in each of single locus analysis. When combination analysis applied, surprising results was also observed in our study. Within ACE DD genotype, GNB3 TT genotype has a higher prevalence in controls than in cases (44% *vs* 17%). GNB3 TT genotype was only associated with a decrease in the risk for hypertension in men (OR for TT *vs* CC, 0.11; 95% CI, 0.01～0.99; P = 0.049). This

is contrast to the studies of Siffert *et al* and Kedzierska *et al*[8, 15], who reported that the presence of T allele of GNB3 C825T polymorphism significantly increased the risk for hypertension. Our finding is also different from that reported by Wang *et al*[12], who reported that no significant *OR* for TT vs CC was found within ACE DD genotype in entire sample (*OR*, 0.9; 95% CI, 0.3～2.8; $P = 0.85$). In male group in our study, another new finding revealed that the carriers with ACE DD/ID combined genotype had an increase of risk of hypertension 1.5-fold compared with the subjects with II genotype within GNB3 CC/CT genotype (*OR*, 1.52; 95% CI, 1.01～2.29; $P = 0.047$). Combined the finding in LD analysis and single locus analysis, our results suggest that there is gene-gene interaction between the ACE and GNB3 genes, which was not found in previous studies of Wang *et al* and Kedzierska *et al*[8, 12].

A common hypothesis, known as "common disease/common variant" (CD/CV), suggests that common, complex diseases, such as EH, is affected by common disease susceptibility variants at disease loci[24, 25]. Theses disease susceptibility genes usually apply modest genetic effect on EH, which make it very difficult to be detected in single locus study. Thus, this might be a possible reason for us no detecting positive association between GNB3 C825T variant with EH in single locus analysis. As reported by Joo *et al*[23], 2-SNP combinations analysis may yield stronger association than single SNP analysis, so that we can detect the slight association of GNB3 CC genotype with an increase in risk for hypertension within ACE DD genotype. The etiology of EH is complex, which implicates that it might be caused by an interaction among multiple intertwined genes or gene-environment interactions, or both. Our findings implicate that there exists epistatic gene-gene interaction. Perhaps GNB3 825C allele might have independent effect on EH, but its independent contribution to EH is relatively weak and it mainly rely on ACE D allele to apply effect on the outcome of EH. Gene-gene interaction means ACE D allele and GNB3 825C allele interplay simultaneously to affect EH through some connected biological pathway. Kedzierska *et al*[8] suspected that both the mutations of ACE and GNB3 genes may lead to the increased activity of sodium-proton antiport Na^+-H^+, which can play an important role in the pathogenesis of hypertension. Naber *et al*[26] discussed the putative connected biological pathway in Myocardial Infarction in German whites. However, the enhanced signaling properties of G proteins might due to the presence of 825C in specific combination of genotypes in the northern Chinese Han population. But the hypothesis needs to be verified in other independent sample from the same geographical region and in biological function experiment.

Single locus analysis, LD analysis and combination analysis all disclosed that statistical significant findings only appeared in male group, which suggest that there existed gender-specific genetic effect for the occurrence of hypertension in the northern Chinese Han population. Our finding is consistent with O'Donnell *et al* and Higaki *et al*[10, 27], both of which reported a unique male-specific role of ACE in EH in large population-based samples. Our data imply that ACE, or a nearby gene that is LD with ACE gene, is a male-specific candidate gene for hypertension. Our result is different from Wang *et al* and Kedzierska *et al*[8, 12]. The relatively small samples might limit their ability in gender-specific stratification analysis.

The study did have some limitations. First, the development of EH is a complex process that is controlled by a network of genes as well as by environmental factors. Thus, many related genes should be included to investigate the relationship among them comprehensively. But, large-scale or even whole-genome association studies would not warrant success in the genetic dissection of complex diseases until many critical theoretical and practical problems have been solved[28～30]. Second, the sample is not large enough. Thus, there might have no enough power to detect the possible positive association after stratification, and at the same time, there may be also potential to yield false positive result. Third, our data only yielded slightly significant results in combination analysis and our data demonstrated significant association only with hypertension status, not with BP. Moreover, there lacks an intuitive relationship between the statistical model and biological reality[31, 32]. Thus, the result should be tested in other independent samples and in biological experiments.

In conclusion, we selected two genes in a putative pathway, ACE and GNB3, to examine whether there was interaction effect between the genes. The present study suggests that the ACE D allele was significantly associated with EH in male group in the Northern

Chinese Han population, and that there is a slightly synergetic effect or gene-gene interaction between the ACE D allele and GNB3 825C allele. Further investigation is warranted to investigate the relationship between the two genes and EH in different independent larger sample and in experiment.

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在中国北方汉族人群中血管紧张素转换酶基因 I/D 多态与 G 蛋白 beta3 亚基基因 C825T 多态对原发性高血压的联合作用 *

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摘要 原发性高血压是一种复杂的多基因疾病，被认为是多个变异了的基因遗传交互以及环境因素共同作用的结果. 证据表明，血管紧张素转换酶基因和 G 蛋白 beta3 亚基基因各自都是重要的原发性高血压的易感基因，并且可能存在共同的通路来导致高血压疾病的发展. 为了探索这两个基因在中国北方汉族人群中是否对高血压有影响，挑选血管紧张素转换酶基因 I/D 多态与 G 蛋白 beta3 亚基基因 C825T 多态，在一个包含 502 个高血压病例和 490 个健康对照的样本中做了关联研究. 连锁不平衡分析揭示，仅仅在男性中有显著性的非随机性分布，表明血管紧张素转换酶基因与 G 蛋白 beta3 亚基基因倾向在男性中造成高血压. 调整了的单位点的多变量逐步回归分析展示，在男性显性模型中 DD/ID 对Ⅱ的比值比达到显著性水平(*OR* 1.57；95% CI，1.09～2.27；$P = 0.016$). 在对性别进行分层后的联合分析中，在男性中经过调整后的比值比具有弱显著性水平：在血管紧张素转换酶基因的 DD 基因型中，TT 对 CC 的比值比是 0.11；95% CI，0.01～0.99；P=0.049；在 G 蛋白 beta3 亚基基因的 CC+CT 基因型中，DD/ID 对Ⅱ的比值比是 1.52；95% CI，1.01～2.29；$P = 0.047$. 结果暗示，血管紧张素转换酶基因或附近的某个基因是具有男性性别倾向的高血压易感侯选基因，同时，在血管紧张素转换酶基因基因的 D 等位基因和 G 蛋白 beta3 亚基基因的 825C 等位基因之间，可能存在具有上位效应的基因 - 基因相互作用.

关键词 血管紧张素转换酶，G 蛋白 beta3 亚基，相互作用，联合效应，高血压
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