Original Article

Association Study between Hypertension and A/G Polymorphism at Codon 637 of the Transporter Associated with Antigen Processing 1 Gene

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To explore the effect of A/G polymorphisms at codon 637 of the transporter associated with antigen processing 1 (TAP1) gene on the risk of hypertension. A case-control study of epidemiology was conducted. The case group included 277 community-based patients (136 males and 141 females; mean age 58.7±12.1 years) diagnosed with hypertension, and the control group consisted of 227 healthy subjects (95 males and 132 females; mean age 51.29±12.16 years) from the same community. The A/G polymorphisms at codon 637 of the TAP1 gene was examined by the polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) method with genomic DNA. The effect of A/G polymorphisms at codon 637 of the TAP1 gene on hypertension was analyzed by using multivariate unconditional logistic regression models. The contribution of TAP1 637 A/G allele frequencies of the control group was consistent with that predicted by the Hardy-Weinberg equilibrium test (x^2=230, p=0.632). There was a significant difference in the frequency of the A/G polymorphisms at codon 637 of the TAP1 gene between hypertensive patients (74.4/25.6%) and controls (82.4%/17.6%), x^2=9.324, p=0.002. Genotype model (AA-AG-GG) analysis showed that there was a significant difference in the frequency of the recessive genotype between cases and controls (AA/AG *vs.* GG: odds ratio [OR]=3.046, 95% confidence interval [CI]=1.138–8.153) after adjustment for the covariates of age, serum total cholesterol, triglycerides, body mass index (BMI) and smoking. But there were no significant differences in the frequency of the genotype for the dominant model (AA *vs.* AG/GG: p=0.293) or additive model (AA *vs.* AG *vs.* GG: p=0.081) after adjustment. One-way ANOVA analysis showed that the systolic blood pressure, diastolic blood pressure, and BMI levels of the GG genotype were significantly higher than those of the AA or AG genotypes. In conclusion, our findings suggest that the A/G polymorphisms at codon 637 of the TAP1 gene contributes to the risk of hypertension, possibly *via* the increases in blood pressure and BMI. (*Hypertens Res* 2007; 30: 683–690)

***Key Words*: hypertension, transporter associated with antigen processing gene, polymorphism**

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Introduction

Hypertension is a complex multifactorial and polygenic disorder that is thought to result from an interaction between an individual's genetic background and various environmental factors (*1*). Recently, several studies confirmed that many genes showed a significant association with both blood pressure variation and hypertension (*2*, *3*) and that these genes play different roles in the pathomechanism of hypertension (*4*).

As an important functional ATP-binding cassette (ABC) transporter, the transporter associated with antigen processing (TAP) transport precedes major histocompatibility complex (MHC) binding histocompatibility antigens and make a significant contribution to epitope selection (*5*). The glycosylation of TAP could severely influence its immune function and also initiate glycosylation-related oxidative stress impairment (*6*, *7*), which maybe correlate to pathomechanism of dysfunction of the artery endothelium in patients with hypertension (*8–10*).

The polymorphisms of TAP gene are thought to play a role in alterations in the peptide processing pathway by selecting the sequence and size of amino acid of peptide (*11*, *12*), and thereby contribute to the dysfunction of the endothelium. Resently, a study reported that elevated couple sharing rates of TAP1B, TAP1C and TAP2B genes might increase the susceptibility to hypertensive disorder complicating pregnancy (*13*).

Biochemical and functional evidence from sequence comparison to P-glycoprotein and cystic fibrosis transmembrane conductance regulator (CFTR), as well as the postulated functional properties of selective amino acids in related ABC transporters, indicated that the TAP1 protein is critical for proper TAP function (*12*, *14*). A/G polymorphisms at codon 637 of the TAP1 gene which can cause a change in amino acids from Asp (GAC) to Gly (GGC), would play an important role in functional alteration of TAP1 (*12*).

Accordingly, we here investigated the possible associations between A/G polymorphism at codon 637 of the TAP1 gene and both blood pressure variation and hypertension.

Methods

Subjects

A total of 277 patients with hypertension (but without any other renal or hepatic disease) were recruited from a community-based population. Hypertension was defined as a systolic blood pressure (SBP) ≥140 mmHg, diastolic blood pressure (DBP) ≥90 mmHg, and/or the current use of antihypertensives. This definition is based on the average of three blood pressure readings measured with patients seated, as prescribed in the "Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure" (JNC 7).

A total of 227 controls were randomly selected from among subjects participating in a community-based survey of cardiovascular risk factors in the same community. The control subjects were judged to be free of hypertension by history and clinical examination.

A detailed medical history was obtained from all participants by standardized questionnaire. The blood pressure, height and weight were obtained using standardized protocols by trained professionals. Smokers were defined as persons who had smoked at least 20 cigarettes per week for at least 3 months at some point in their life. The protocol was approved by the local bioethical committee and informed consent was obtained from each participant. Drinkers were defined as individuals who consumed at least 150 g (for men) or 100 g (for women) per week for at least 3 months at some point in their life.

Table 1 summarizes the demographic data of recruited subjects. Patients showed significantly higher levels of age, body mass index (BMI), SBP, DBP, serum total cholesterol (TC), triglycerides (TG), and glucose (GLU), and higher proportions of diabetics and smokers than controls. No significant differences were found in gender, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, serum C-reactive protein (CRP) or proportion of drinkers between patients and controls. The administration of medication after the patients were informed of their disease might have influenced the clinical characteristics of cases.

Table 1. Comparison of Basic Characteristics between Cases (277) and Controls (227)

Variables	Cases	Controls	*p* value*
Age (years)	58.68±12.10	51.79±12.51	<0.0001
Gender (male (%))	49.1	41.9	0.104
BMI (kg/m^2)	25.25±2.73	24.13±2.83	<0.0001
SBP (mmHg)	145.05±15.40	117.61±9.68	<0.0001
DBP (mmHg)	91.14±10.22	78.44±7.02	<0.0001
HDL-C (mg/dL)	1.25±0.35	1.31±0.46	0.352
LDL-C (mmol/L)	3.43±2.56	3.30±2.47	0.700
TC (mmol/L)	4.83±1.17	4.09±1.66	<0.0001
TG (mmol/L)	1.64±0.71	1.20±0.73	<0.0001
CRP (mg/L)	11.62±41.55	6.76±13.08	0.218
GLU (mmol/L)	6.41±2.25	5.40±1.95	<0.0001
Diabetes (yes (%))	39.4	20.7	<0.0001
Smoker (yes (%))	33.2	23.8	0.023
Drinker (yes (%))	26.5	21.0	0.153

*t-test of means±SD values for continuous variables and χ^2 test for numeration data. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; CRP, C-reactive protein.

Table 2. Multivariate Untraditional Logistic Regression of Hypertension for Screening Covariates of Genotype of TAP1 Gene 637 Polymorphism by Forward Stepwise (Likelihood Ratio) Method

Variable*	β	SEM	Wald	p	OR	95% CI
TAP1 637	0.216	0.205	1.106	0.293	1.241	0.830–1.855
Age	0.029	0.009	10.928	0.001	1.029	1.012–1.047
Smoking	0.568	0.222	6.514	0.011	1.764	1.141–2.729
TG	0.596	0.148	16.158	0.000	1.815	1.357–2.428
BMI	0.115	0.036	10.07	0.002	1.122	1.045–1.204
TC	0.188	0.080	5.529	0.019	1.207	1.032–1.412

*Variable(s) entered on steps 1–5: TG, ages, BMI, smoking and TC. OR, odds ratio; CI, confidence interval; TAP, transport associated with antigen processing; TG, triglycerides; BMI, body mass index; TC, total cholesterol.

Genotyping

Genomic DNAs were prepared by proteinase K/phenol methods from the blood of donors who had provided their informed consent, and were purified using a DNAprep Kit (Shanghai Shenergy Biocolor Bioscience & Technology Co., Ltd., Shanghai, P.R. China). The polymerase chain reaction (PCR)–restriction fragment length polymorphism (RFLP) method was applied to discriminate dimorphic sites of A/G polymorphisms at codon 637 of the TAP1 gene. PCR was carried out as described by Saeki *et al*. (*15*), using the following primers: forward, 5′-CCCTATCCAGCTACAACC-3′; reverse, 5′-AACGCCACTGCCTGTCGCT-3′ (provided by Shanghai Shenergy Biocolor Bioscience & Technology Co., Ltd.). For optimum PCR amplification, a 15 µL reaction mixture containing 1× PCR buffer, 2 mmol/L $MgCl_2$, 10 pmol of each primer, 0.2 mmol/L dNTP, 0.5 units of AmpliTaq polymerase (Shanghai Shenergy Biocolor Bioscience & Technology Co., Ltd.) and 30 ng genomic DNA was used.

The cycling program for PCR of these two polymorphisms consisted of a denaturation step at 95°C for 5 min, followed by 32 cycles of denaturation at 95°C for 50 s, annealing at 52°C for 45 s, and extension at 72°C for 50 s, and then a final extension step at 72°C for 5 min. Amplifications were performed in Perkin-Elmer 9600 thermocyclers, using "optical" reaction plates and caps (PE-Biosystems, Warrington, UK). PCR products were digested overnight at 37°C with XmilI (Fermentas Life Sciences Inc., Baltimore, USA), followed by detection on 3% ethidium bromide–stained agarose gels. The TAP1 637 dimorphic site represents the mutant type G allele and produces two fragments for the GG genotype (51 and 132 bp). The wild-type A allele is not recognized by the XmilI enzyme, and only shows one 183 bp band (for the AA genotype). The AG heterozygote has three bands, with sizes of 183, 132 and 51 bp. In addition, we randomly selected 20 cases and sequenced the PCR product using the above primers to further confirm whether the A/G polymorphisms at codon 637 of the TAP1 gene was present in this Chinese population.

Statistical Analysis

Statistical analysis was carried out by using SPSS version 12.0 for Windows. All measured variables are presented as the means±SD. Comparisons between cases and controls were made using the unpaired Student's *t*-test. Hardy-Weinberg equilibrium was assessed by the χ^2 test. Association analysis of the A/G polymorphisms at codon 637 of the TAP1 gene with hypertension was tested by the χ^2 test. A two-tailed probability value of 0.05 was considered significant. Multiple unconditional logistic regression was applied to investigate the independent role of the TAP1 637 polymorphism and the forward stepwise (likelihood ratio) method was used to screen confounding factors (Table 2). The probability for stepwise entry is 0.05 and that for stepwise removal is 0.1. One-way ANOVA was used to test differences in SBP, DBP, GLU, BMI, TG and TC between cases and controls for each genotype.

Results

Hardy-Weinberg Equilibrium Test

The contribution of TAP1 637 A/G allele frequencies of the control group was consistent with the distribution predicted by the Hardy-Weinberg equilibrium test (x^2=0.230, p=0.632). The TAP1 637 A/G allele and genotype frequencies are shown in Table 3.

Polymorphisms Associated with Hypertension

A multiple unconditional Logistic regression was used to screen covariates by the forward stepwise (likelihood ratio) method. The variables considered were gender, age, HDL, LDL, BMI, TG, TC, diabetes and smoking, and the results are shown in Table 2. TAP1 637 (AG/GG *vs*. AA) entered the model as block 1 and other covariates entered as block 2, the probability for stepwise entry was 0.05 and the probability for stepwise removal was 0.1, the classification cutoff was 0.5 and the maximum number of iterations was 10. Omnibus tests of model coefficients shows no statistical significance

Table 3. Genotype and Allele Frequency Distributions of TAP1 Gene 637 A/G in Cases and Controls

	Group (*n* (%))		*p*	*p**	OR*	95% CI*
	Cases (*n*=277)	Controls (*n*=227)				
Alleles						
A	412 (74.4)	374 (82.4)				
G	142 (25.6)	80 (17.6)	0.002	0.081	1.341	0.964–1.866
Genotypes						
AA	159 (57.4)	153 (67.4)				
Dominant model						
AG/GG	118 (42.6)	74 (32.6)	0.035	0.293	1.241	0.830–1.855
AA/AG	253 (91.3)	221 (97.4)				
Recessive model						
GG	24 (8.7)	6 (2.6)	0.004	0.027	3.046	1.138–8.153
AA	159 (57.4)	153 (67.4)				
Addictive model						
AG	94 (33.9)	68 (30.0)				
GG	24 (8.7)	6 (2.6)	0.008	0.081	1.341	0.964–1.866

*Age, total cholesterol (TC), triglycerides (TG), body mass index (BMI) and smoking were adjusted. OR, odds ratio; CI, confidence interval.

Table 4. Comparing of Clinical Characteristics between AA, AG and GG Genotypes

Variable	AA (*n*=231)	AG (*n*=109)	GG (*n*=12)	*p*
SBP (mmHg)	131.92±19.39	132.35±18.01	142.57±16.95	0.012
DBP (mmHg)	85.06±11.22	84.85±10.26	92.23±9.31	0.002
GLU (mmol/L)	5.89±2.32	6.02±1.93	5.91±1.73	0.861
BMI (kg/m^2)	24.54±2.71	24.88±2.99	26.22±2.67	0.006
TG (mmol/L)	1.42±0.77	1.48±0.73	1.49±0.76	0.692
TC (mmol/L)	4.43±1.51	4.60±1.39	4.59±1.29	0.468

Data are mean±SD. SBP, systolic blood pressure; DBP, diastolic blood pressure; GLU, glucose; BMI, body mass index; TG, triglycerides; TC, total cholesterol.

($p>0.05$). Model summary shows all the values of −2 log likelihood exceed 596.738 and parameter estimates changed by less than 0.001, the Hosmer and Lemeshow tests of steps 1–5 show that goodnesses of models fit were well.

Table 3 shows the genotype and allele frequency distributions of the A/G polymorphisms at codon 637 of the TAP1 gene in cases and controls. There is a significant difference of A/G allele genotypes between hypertension patients (74.4/25.6%) and controls (82.4%/17.6%) ($x^2=9.324$, $p=0.002$). After adjustment by the covariates of age, TC, TG, BMI and smoking (multivariate nonconditional logistic regression), odds ratio (OR)=1.341, 95% confidence interval (CI)=0.964–1.866.

Considering the lower GG genotype frequency (6/2.6%) in controls, G would be a mutative allele type. Genotype (AA-AG-GG) analyses were conducted for three types of genetic model, a dominant model (AA *vs*. AG/GG), a recessive model (AA/AG *vs*. GG) and an additive model (AA *vs*. AG *vs*. GG), and the results showed that there were significant differences between cases (57.4%/33.9% *vs*. 8.7%) and controls (67.4%/30.0% *vs*. 2.6%) for recessive model (OR=3.046, 95% CI=1.138–8.153) upon adjustment by the covariates of age, TC, TG, BMI and smoking. But there was no difference in the dominant model (OR=1.241, 95% CI=0.830–1.855) after adjusting for the covariates described above.

As for the additive model, the different genotype alterations (AA to AG or AG to GG) (null variable method) would not increase the same risk (OR). Logistic regression analyses showed that the risk of hypertension increase remarkably with AA alteration to GG (OR=3.129, 95% CI=1.157–8.465) after adjustment for age, TC, TG, BMI and smoking. Actually, for AG alteration to GG, OR is 2.899 (95% CI=1.045–8.064) whereas for AA alteration to AG, OR is 1.079 (95% CI=0.708–1.643), after adjusting for the covariates described above.

Comparison of Clinical Characteristics among Different Genotypes

Hypertensive patients who had been treated with drugs or

Table 5. Allele and Genotype Frequencies of TAP1 Genes 637 in Chinese and Other Ethnic Groups

Ethnic group	Allele (*n* (%))		Genotype (*n* (%))			
	A	G	AA	AG	GG	AG/GG
Chinese						
Present study (2*n*=454)	374 (82.4)	80 (17.6)	153 (67.4)	68 (30.0)	6 (2.6)	74 (32.6)
HapMap-CHB (2*n*=90)	73 (81.1)	17 (18.9)	28 (62.2)	17 (37.8)		17 (37.8)
Japanese						
Kuwata *et al*. (*39*) (2*n*=208)	178 (86)	30 (14)				
Maruya *et al*. (*24*) (2*n*=212)	183 (86.3)	29 (12.7)				
Takeuchi *et al*. (*23*) (2*n*=190)	162 (85.3)	28 (14.7)				
Ishihara *et al*. (*40*) (2*n*=182)	157 (86.3)	25 (13.7)				
Korean						
Pyo *et al*. (*26*) (2*n*=368)	304 (82.6)	64 (17.4)	124 (67.4)	56 (30.4)	4 (2.2)	60 (32.6)
Lee *et al*. (*41*) (2*n*=368)	305 (82.9)	63 (17.1)				
Whang *et al*. (*25*) (2*n*=360)	304 (84.5)	56 (15.5)				
French						
Zhang *et al*. (*35*) (2*n*=200)	167 (83.5)	33 (16.5)	70 (70.0)	27 (27.0)	3 (3.0)	30 (30.0)
Djilali-Saiah *et al*. (*37*) (2*n*=324)	271 (83.7)	53 (16.3)				
Chevrier *et al*. (*34*) (2*n*=140)	130 (92.8)	10 (7.2)				
Moins-Teisserenc *et al*. (*36*) (2*n*=82)	73 (89.1)	9 (10.9)				
German						
Hohler *et al*. (*27*) (2*n*=202)	175 (82.7)	27 (17.3)				
Caucasian						
Teisserenc *et al*. (*28*) (2*n*=346)	300 (86.7)	46 (13.3)				
USA Caucasian						
Barron *et al*. (*33*) (2*n*=320)	278 (86.9)	42 (13.1)				
Sardinian						
Cucca *et al*. (*29*) (2*n*=158)	131 (82.9)	27 (17.1)				
Kaingang						
Faucz *et al*. (*38*) (2*n*=480)	365 (76.0)	115 (24.0)				
Guanrani						
Faucz *et al*. (*38*) (2*n*=184)	70 (38.0)	114 (62.0)				
Caucasoid						
Faucz *et al*. (*38*) (2*n*=182)	150 (81.9)	32 (18.1)				
Anatolian						
Ozbas-Gerceker *et al*. (*32*) (2*n*=200)	171 (85.5)	29 (14.5)				
Pole						
Witkowska-Tobola *et al*. (*30*) (2*n*=132)	114 (86.4)	18 (13.6)				
Tunisians						
Ismail *et al*. (*31*) (2*n*=162)	139 (85.8)	23 (14.2)				

managed with behavioral or dietary changes (*n*=152) were excluded from the analysis. In the remaining patients with hypertension and controls, the clinical characteristics SBP, DBP, GLU, BMI, TG and TC were compared among the different genotype groups.

One-way ANOVA was used to test the difference in SBP, DBP, GLU, BMI, TG and TC between different genotypes. The test of homogeneity of variances for SBP, DBP, GLU, BMI, TC and TG showed no statistical significance ($p>0.05$). The results showed that the SBP, DBP and BMI of subjects with the GG genotype were significantly higher than those of subjects with the AA or AG genotype (Table 4).

Discussion

TAP consists of two subunits, TAP1 and TAP2. Respectively, human TAP1 gene and TAP2 gene are located in different loci of the chromosome 6 band p21.3 (*16*). TAP gene polymorphism has an influence on peptide selectivity, and mutations in the TAP1 and/or TAP2 genes would produce some nonfunctional proteins that could have a severe impact on the cellular immune system, even leading to genetic diseases, such as the rare bare lymphocyte syndrome (BLS), autoimmune disease and transplantation reaction and tumor (*12*, *17*, *18*).

An A-to-G transition of the TAP1 gene at codon 637 would lead to replacement of Asp-637 by glycine (*19*), and such a replacement may play an important role in the assembly of class I molecules and presentation of endogenous peptides (derived from the nucleus and cytosole) to CD8 (+) T cells. Glycosylation of TAP1 may be involved in pathomechanism of the dysfunction of artery endothelium in patients with hypertension (*6*, *7*, *12*, *13*, *20*). In the present study, we attempted to find an association between the A/G polymorphisms at codon 637 of the TAP1 gene and essential hypertension.

For the request of comparing with other ethnic populations, we calculated TAP1 637 A/G allele frequencies of other ethnic populations from published references. According to the classic names of TAP alleles of WHO Nomenclature Committee for Factors of the HLA System (*21*), TAP1 alleles were named by the combination of TAP1 637 site with TAP1 333 site for the linkage, as well as Powis (*22*) described. TAP1 alleles include TAP1A (TAP1*0101) of Ile-333 and Asp-637, TAP1B (TAP1*020101) of Val-333 and Gly-637, TAP1C (TAP1*0301) of Val-333 and Asp-637, and TAP 1D (TAP1*0401) of Ile-333 and Gly-637. Correspondingly, TAP1 637 A/G allele can be calculated as follows, A allele frequency equals to the frequency of TAP1A add TAP1C, G allele frequency equals to TAP1B add TAP1D (Table 5).

Comparing with other ethnic normal populations, TAP1 637 G allele frequency (17.6%) of controls in the present study was similar to the other normal populations in Asian, such as Japanese (*23*, *24*), 12.7% to 14.7% (the lowest p value of χ^2 test is 0.2), and Koreans (*25*, *26*), 15.5% to 17.4%. Similar results were observed in some European populations, such as German 17.3% (*27*), Caucasian 13.3% (*28*), Sardinian 17.1% (*29*), Pole 13.6% (*30*), Tunisian 14.2% (*31*), Anatolian 14.5% (*32*) and USA Caucasian 13.3% (*33*). Whereas in French populations, TAP1 637 G allele frequencies alters from 7.2% to 16.5% (*34–37*). Remarkably, results from Faucz *et al*. (*38*) indicated that there was a significant difference of G allele frequencies in referred populations, Caucasoid 18.1%, Kaingang 24% and Guanrani 62%.

On the other hand, data searched for the single nucleotide polymorphism (SNP) rs1135216 (the A/G polymorphisms at codon 637 of the TAP1 gene) using the National Center for Biotechnology Information (NCBI) website (http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=1135216) suggested that there was a slight discrepancy of minor allele frequency (MAF) across populations. The TAP1 637 G allele frequency is 18.9% in HapMap-CHB (Han Chinese in Beijing), 12.5% in HapMap-CEU (Utah residents with ancestry from northern and western Europe), 13.6% in HapMap-JPT (Japanese in Tokyo) and 21.2% in HapMap-YRI (Yoruba in Ibadan), and these results were identical to those obtained using the HapMap website (http://www.hapmap.org/cgi-perl/gbrowse/hapmap_B35/). Generally, inequality of genetic effects may be a reasonable explanation for this discrepancy.

Except for genetic heterogeneity, the discrepancy of TAP1 637 A/G allele frequencies between different races and ethnicities may come from the inequalities of sample size and representativeness, and also might be derived from different genotyping methods, since the RFLP-PCR method used in most studies would be more stable than other methods, such as the amplification refractory mutation system (ARMS)-PCR method (*38*).

TAP1 637 G allele frequency in control group (17.6%) in accordance with that in HapMap-CHB (18.9%) and some other ethnic populations, and similar comparative results of genotype frequencies (Table 5) suggests that there is a good representativeness of the control subjects in the present study. And so, the results in the present study is relatively reliable.

In the present study, the χ^2 test showed no statistically significant difference ($p=0.081$) in the genotype distribution between cases and controls adjusted by the covariates of age, TC, TG, BMI and smoking, whereas multivariate logistic regression analysis for additive model showed that the AA alteration to GG resulted in a clear increase in the risk of hypertension, with OR=3.129, 95% CI=1.157–8.465, after adjusting for the covariates described above. Concretely, OR is 1.079 (95% CI=0.708–1.643) for AA to AG and OR is 2.899 (95% CI=1.045–8.064) for AG to GG. Remarkably, comparative results of clinical characteristics of TAP1 637 genotype showed that SBP and DBP of subjects with the GG genotype were higher than those of subjects with the AA or AG genotypes. Accordingly, this evidence suggests that the alteration of genotype AA or AG to GG may play a potential role in blood pressure increase. So, the TAP gene should be considered a potential candidate gene for cause of cardiovascular disease except autoimmune disease, infectious disease and tumors (*6*, *7*, *12*, *13*).

In conclusion, our study suggests for the first time that there is a statistically significant positive association of the A/G polymorphisms at codon 637 of the TAP1 gene with both blood pressure variation and hypertension in a Chinese Han population. However, the exact biological role of TAP1 in the pathophysiology of hypertension is not clear yet. Additional clinical or epidemiological investigations will be needed to confirm this relationship, particularly studies with a large sample size, a prospective design, genome control, and/or a range of different populations. Such investigations could provide powerful new evidence of the relationship between the TAP1 gene and hypertension.

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