Original Article

T1198C Polymorphism of the Angiotensinogen Gene and Antihypertensive Response to Angiotensin-Converting Enzyme Inhibitors

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This study examined the association between T1198C polymorphism of the angiotensinogen (AGT) gene and the blood pressure response to ACE inhibitors in a Chinese hypertensive cohort. After a 2-week single-blind placebo run-in period, benazepril (10–20 mg/day) or imidapril (5–10 mg/day) was administered for 6 weeks to 509 patients with mild-to-moderate essential hypertension. Polymerase chain reaction combined with restriction enzyme digestion was used to detect the polymorphism, and the patients were classified as having the TT, TC, or CC genotype. The achieved changes in systolic and diastolic blood pressure (SBP and DBP) were analyzed to determine their association with genotypes at the AGT gene locus. In the total 509 patients, the TT genotype was observed in 44 patients (8.7%), the TC genotype in 214 patients (42.0%), and the CC genotype in 251 patients (49.3%). The SBP reductions in patients with the TT genotype, TC genotype, and CC genotype were −15.3±12.7 mmHg, −14.0±12.7 mmHg, and −14.4±12.4 mmHg, respectively (p=0.809). The DBP reductions in patients with the TT genotype, TC genotype, and CC genotype were −8.5±8.1 mmHg, −8.3±7.5 mmHg, and −8.9±6.6 mmHg, respectively (p=0.638). There were no significant differences in the changes in SBP or DBP after treatment among the three genotype groups. In conclusion, these results suggest that the AGT genotype does not predict the blood pressure-lowering response to antihypertensive treatment with ACE inhibitors in Chinese hypertensive patients. (*Hypertens Res* 2005; 28: 981–986)

***Key Words*: hypertension, angiotensinogen, treatment, genes**

Introduction

Essential hypertension (EH) is a complex syndrome determined by both genetic and environmental factors. The response of patients to antihypertensive therapy is variable. It has long been suspected that interindividual variation in the efficacy and side effects of medications may be influenced by genetic factors. The renin-angiotensin-aldosterone system (RAAS) plays an important role in the development and extent of EH. The RAAS has drawn substantial attention as a cardinal source of candidate genes for EH (*1–5*). It is reasonable to hypothesize that variation in genes of the system may be predictive of variation in blood pressure (BP) response. Variation in genes of the RAAS has been investigated in relation to antihypertensive response to angiotensin-converting enzyme (ACE) inhibitors, β-blockers, calcium channel blockers, and angiotensin type 1-receptor blockers (ARB). However, previously published studies have had somewhat conflicting results (*6–16*).

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Table 1. Clinical Characteristics of the Benazepril and Imidapril Groups

	Benazepril	Imidapril	*p* value†
Number of patients (n_1/n_2)	250 (71/179)	259 (84/175)	0.323
Sex (male/female)	141/109	165/94	0.092
Age (years)	56.3±10.0	54.8±9.7	0.098
BMI (kg/m^2)	26.2±3.1	26.2±3.2	0.801
Creatinine (mg/dl)	82.1±20.4	85.7±21.2	0.054
Sodium (mmol/l)	141.7±4.1	141.8±3.9	0.657
Potassium (mmol/l)	4.4±0.4	4.4±0.5	0.900
Chloride (mmol/l)	103.5±3.6	103.8±3.6	0.387
Glucose (mmol/l)	5.3±1.0	5.2±1.0	0.494
Uric acid (μmol/l)	298.3±97.9	306.7±99.6	0.340
Total cholesterol (mmol/l)	5.1±1.0	5.1±1.0	0.604
Triglyceride (mmol/l)	1.3±0.4	1.3±0.4	0.913
HDL cholesterol (mmol/l)	1.7±0.8	1.7±0.8	0.870
GPT (U/l)	26.4±14.0	26.7±13.3	0.820
Pretreatment SBP (mmHg)	155.3±12.4	153.9±12.4	0.183
Posttreatment SBP (mmHg)	140.5±12.8*	140.1±13.0*	0.694
Pretreatment DBP (mmHg)	97.1±5.3	96.7±5.3	0.351
Posttreatment DBP (mmHg)	88.3±8.0*	88.3±7.2*	0.961
Pretreatment HR (bpm)	75.0±8.6	75.4±8.5	0.584
Posttreatment HR (bpm)	74.6±8.2	74.8±8.5	0.828
Fall in SBP at 6 weeks (mmHg)	14.8±13.1	13.8±12.0	0.361
Fall in DBP at 6 weeks (mmHg)	8.8±7.4	8.4±6.8	0.457
Change in HR at 6 weeks (bpm)	0.4±9.0	0.6±8.3	0.741

Data are presented as the mean±SD. n_1, number of patients who received benazepril 10 mg/day or imidapril 5 mg/day over the entire 6-week treatment period; n_2, number of patients who received benazepril 20 mg/day or imidapril 10 mg/day during the last 3 weeks of treatment; BMI, body mass index; HDL, high density lipoprotein; GPT, glutamic-pyruvic transaminase; SBP and DBP, systolic and diastolic blood pressure; HR, heart rate. †*p* value calculated by ANOVA for continuous variables and χ^2 test for categorical variables. *$p<0.001$ between pretreatment and posttreatment.

The angiotensinogen (AGT) gene, the source of the RAAS generated mainly in the liver, has been implicated in EH. Polymorphisms within the AGT gene have been linked to hypertension, in particular the T1198C polymorphism in exon 2 (*17–19*). The AGT T1198C variant has not only been shown to be associated with hypertension but is also related to salt-sensitive hypertension and circulating AGT levels; however, these associations remain controversial (*20–23*).

The aim of the present study was to investigate the association between T1198C polymorphism of the AGT gene and the BP response to benazepril or imidapril and the distribution of the polymorphism in Chinese essential hypertensive patients. For this purpose, we employed data from a randomized and double-blind trial which compared the clinical effect of treatment with benazepril and imidapril in Chinese hypertensive patients.

Methods

Study Patients

The material studied comes from the Comparative Study of Hypotensive Efficacy and the Cough Occurrence of Imidapril *versus* Benazepril (*24*), which is a randomized and double-blind trial performed in 20 centers in 12 cities in P.R. China.

Both male and female patients who met the following criteria were included: age, 18–79 years; a history of EH; and diastolic BP (DBP) 90–109 mmHg or systolic BP (SBP) 140–179 mmHg. The exclusion criteria were secondary hypertension or known renal artery stenosis; congestive heart failure, cerebrovascular accident, transient ischemic attacks or myocardial infarction within the past year; a documented history of unstable angina pectoris within the past 6 months; clinically important cardiac arrhythmia; uncontrolled diabetes mellitus (fasting blood glucose [FBG]>180 mg/dl); any clinically important abnormal laboratory finding, such as glutamic-pyruvic transaminase (GPT)/creatinine twice the upper limit of normal; a history or suspicion of alcohol or drug abuse; pregnancy or lactation in females; concomitant use of any agent that may cause an alteration of BP; or known hypersensitivity or contraindication to ACE inhibition. The appropriate ethics committees approved this study. All of the participating patients gave their informed consent.

Study Design

All antihypertensive agents were withdrawn before the start of a 2-week single-blind placebo run-in period. At the end of the placebo period, a total of 640 qualified patients were allocated randomly to groups to receive either 5 mg imidapril or 10 mg benazepril orally once daily for 3 weeks. After that, patients whose BP was <140/90 mmHg continued the same dose regimen for another 3 weeks. In patients whose BP was not adequately controlled (BP≥140/90 mmHg), the dose of either regimen was doubled for the following 3 weeks. Five hundred and sixty-six patients completed the 6-week trial, and their data were used for the present study. The DNA of 509 patients was successfully extracted for further analysis.

BP was measured by trained doctors using a mercury sphygmomanometer after the patient had rested for at least 10 min in a seated position, and was determined as the average of three measurements taken 1 min apart.

Definition of Study Variables

Baseline information on the following variables was included in the analysis: sex, body mass index (weight/height^2), patient history, heart rate (HR), BP, ECG, chest X-ray, and pregnancy test (urine). Laboratory variables included the levels of serum creatinine, sodium, potassium, chloride, glucose, uric acid, total cholesterol, triglyceride, high density lipoprotein, and GPT.

Molecular Analysis of the AGT Gene

Genomic DNA was isolated from peripheral leukocytes separated from the blood. The T1198C polymorphism was investigated by polymerase chain reaction (PCR) amplification of genomic DNA followed by restriction endonuclease digestion by *Tth*111 I (*25*). Amplification yielded a product of 163 bp. In the presence of cytosine at position 1198, cleavage by *Tth*111 I generated a 140-bp fragment. The patients were classified as having the TT, TC, or CC genotype.

Statistical Analysis

The SPSS 11.5 statistical package (SPSS, Chicago, USA) was used for analysis. Allele frequencies were calculated from the genotypes of all subjects. Hardy-Weinberg equilibrium (HWE) was assessed by χ^2 analysis. Continuous data are presented as the mean±SD. Differences between groups were tested by an χ^2 test for qualitative parameters and by one-way analysis of variance (ANOVA) or general linear model (GLM) analysis of variance for quantitative parameters. All tests were two-tailed and values of $p<0.05$ were considered to indicate statistical significance.

Results

At the end of the placebo period, a total of 250 qualified patients were allocated randomly to the benazepril group to receive 10 mg benazepril orally once daily for 3 weeks, after which 71 patients whose BP was <140/ 90 mmHg continued with the same dose regimen for another 3 weeks. In the 179 patients whose BP was not adequately controlled (BP≥140/90 mmHg), the dose of benazepril was doubled (20 mg/day) for the following 3 weeks. A total of 259 qualified patients were allocated randomly to the imidapril group to receive 5 mg imidapril orally once daily for 3 weeks, after which the 84 patients whose BP was <140/90 mmHg continued with the same dose regimen for another 3 weeks. In the 175 patients whose BP was not adequately controlled (BP≥140/90 mmHg), the dose of imidapril was doubled (10 mg/day) for the following 3 weeks.

AGT genotypes were determined for 509 subjects. Since there were no significant differences in clinical characteristics or hemodynamic parameters between the benazepril and imidapril groups (Table 1), we combined the data for these groups when analyzing the relationship between polymorphism of the AGT gene and the BP response to ACE inhibition (Table 2).

The AGT genotype distribution and the clinical characteristics of the patients are shown in Table 2. The TT genotype was observed in 44 patients (8.7%), the TC genotype in 214 patients (42.0%), and the CC genotype in 251 patients (49.3%). Allele frequencies were 29.7% for the T allele and 70.3% for the C allele. The AGT genotype was consistent with HWE in the total 509 subjects ($\chi^2=0.0289$, df=1, $p>0.05$). There were no significant differences in clinical characteristics except sex ($p=0.016$) among the TT, TC, and CC genotype groups. There were also no significant differences among the three genotype groups in HR, SBP, or DBP either before or after treatment. Significant decreases in SBP and DBP occurred after treatment in all genotype groups ($p<0.001$). There were no significant differences in the changes in HR after treatment among the three genotype groups.

The SBP reductions in patients with the TT genotype, TC genotype, and CC genotype were −15.3±12.7 mmHg, −14.0±12.7 mmHg, and −14.4±12.4 mmHg, respectively ($p=0.809$). The DBP reductions in patients with the TT genotype, TC genotype, and CC genotype were −8.5±8.1 mmHg, −8.3±7.5 mmHg, and −8.9±6.6 mmHg, respectively ($p=0.638$). There were no significant differences in the changes in SBP or DBP after treatment among the three genotype groups. There were also no such differences in SBP and DBP changes in the analysis stratified by sex (Table 3). In other subgroup analyses, including by age (a <60 years old group and a ≥60 years old group), family history of hypertension, and previous antihypertensive medications, there were also no significant differences in the changes in SBP or DBP

Table 2. Clinical Characteristics and AGT Genotype Distribution of the Study Population

	TT	TC	CC	*p* value†
Number of patients (n_1/n_2)	44 (23/21)	214 (104/110)	251 (123/128)	0.905
Sex (male/female)	26/18	144/70	136/115	0.016
Age (years)	53.8±9.8	55.2±10.2	56.1±9.6	0.281
BMI (kg/m^2)	26.4±3.5	26.2±2.9	26.2±3.4	0.870
Creatinine (mg/dl)	80.3±25.4	83.8±19.3	84.6±21.2	0.444
Sodium (mmol/l)	141.9±4.0	141.5±3.8	141.9±4.2	0.515
Potassium (mmol/l)	4.4±0.5	4.4±0.4	4.4±0.5	0.952
Chloride (mmol/l)	103.8±3.5	103.6±3.3	103.7±3.8	0.931
Glucose (mmol/l)	5.1±0.9	5.2±0.9	5.3±1.1	0.185
Uric acid (μmol/l)	323.4±117.4	309.9±99.2	292.7±94.0	0.060
Total cholesterol (mmol/l)	5.1±0.8	5.1±1.0	5.1±1.1	0.976
Triglyceride (mmol/l)	1.3±0.3	1.2±0.3	1.3±0.4	0.574
HDL cholesterol (mmol/l)	1.8±0.8	1.7±0.8	1.6±0.8	0.409
GPT (U/l)	25.5±14.3	26.7±13.1	26.6±14.0	0.855
Pretreatment SBP (mmHg)	154.2±11.6	153.9±12.8	155.3±12.2	0.495
Posttreatment SBP (mmHg)	138.9±13.2*	139.9±13.0*	140.9±12.8*	0.540
Pretreatment DBP (mmHg)	97.2±5.4	96.4±5.2	97.2±5.3	0.246
Posttreatment DBP (mmHg)	88.7±8.4*	88.1±8.1*	88.3±7.0*	0.907
Pretreatment HR (bpm)	73.1±8.7	75.1±8.4	75.7±8.6	0.181
Posttreatment HR (bpm)	72.7±8.3	75.5±8.6	74.3±8.1	0.078
Change in HR at 6 weeks (bpm)	0.5±7.5	−0.4±9.4	1.3±8.1	0.093

Data are presented as the mean±SD. AGT, angiotensinogen; n_1, number of patients who received benazepril during the treatment period; n_2, number of patients who received imidapril during the treatment period; BMI, body mass index; HDL, high density lipoprotein; GPT, glutamic-pyruvic transaminase; SBP and DBP, systolic and diastolic blood pressure; HR, heart rate. †*p* value calculated by ANOVA for continuous variables and χ^2 test for categorical variables. *$p<0.001$ between pretreatment and posttreatment.

Table 3. Reduction in SBP (mmHg) and DBP (mmHg) in All Patients and in the Subgroups Stratified by Sex According to the AGT Genotypes

Genotype	All patients			Male			Female		
	n	Fall in SBP	Fall in DBP	*n*	Fall in SBP	Fall in DBP	*n*	Fall in SBP	Fall in DBP
TT	44	15.3±12.7	8.5±8.1	26	16.0±14.7	8.1±8.8	18	14.3±9.3	9.0±7.1
TC	214	14.0±12.7	8.3±7.5	144	13.9±12.3	8.1±7.2	70	14.1±13.7	8.7±8.1
CC	251	14.4±12.4	8.9±6.6	136	13.0±11.7	8.5±6.7	115	16.0±13.0	9.4±6.5
Total	509	14.3±12.5	8.6±7.1	306	13.7±12.2	8.3±7.1	203	15.2±13.0	9.1±7.1
F value		0.211	0.450		0.690	0.112		0.472	0.236
p value		0.809	0.638		0.502	0.894		0.625	0.790

Data are presented as the mean±SD, ANOVA. SBP and DBP, systolic and diastolic blood pressure; AGT, angiotensinogen.

after treatment among the three genotype groups. Because there was a significant difference in sex among the three genotype groups, GLM was used to investigate the intergroup differences in BP and BP reduction after adjusting for sex. GLM analysis of variance indicated that there were also no significant differences among the three genotype groups in pretreatment BP, posttreatment BP, or SBP or DBP reduction even after adjusting for sex.

Discussion

The RAAS plays an important role in the development and extent of EH. AGT, the specific substrate of the RAAS, has been related to EH in a number of molecular genetic association and linkage studies (*26*, *27*). Among different missense mutations at the AGT gene locus, the T1198C single nucleotide polymorphism (SNP), in which the substitution of a thymidine residue (T) to a cytosine residue (C) at nucleotide position 1198 leads to the neutral substitution of the amino

acid methionine for that of threonine at amino acid position 235 in the AGT protein (M235T), has been investigated by a number of studies in various ethnic groups. In the last decade, many reports had examined the association of the T1198C (corresponding to the M235T) polymorphisms with either plasma AGT levels, SBP or DBP, risk of hypertension, or risk of ischemic heart or ischemic cerebrovascular disease. In a meta-analysis of 127 trials published between January 1992 and March 2002, Sethi *et al*. (*28*) found that T1198C genotype was associated with a stepwise increase in AGT levels in white subjects and a significant but moderate increase in risk of hypertension in both white and Asian subjects. Genotype did not predict plasma AGT levels in Asian and black subjects, hypertension in black subjects, or SBP or DBP in either ethnic group. In our study, the pretreatment SBP and DBP were similar in the three genotype groups, which appears to be consistent with the findings of Sethi *et al*. (*28*).

In previous pharmacogenetic studies, among hypertensive patients treated with ACE inhibitors, Hingorani *et al*. (*29*) found that the BP response was dependent on AGT genotype in 102 white subjects (68 treated with captopril, 11 with enalapril, 10 with lisinopril and 13 with perindopril). The BP fall after 4 weeks of ACE inhibitor treatment was higher in subjects bearing one or two copies of the 1198C (235T) allele compared with 1198TT (235MM) homozygotes. But in the present study, analysis of the AGT gene T1198C polymorphism was unable to predict the BP response to the ACE inhibitors (imidapril or benazepril).

There are several explanations for the inconsistent results. First, the RAAS plays a pivotal role in BP regulation. ACE inhibitors can inhibit the RAAS extensively by inhibiting the conversion of angiotensin I to angiotensin II. This leads to a decrease in angiotensin II production and then high angiotensin I levels; an increase in renin production as a result of the negative feedback regulation of renin expression by angiotensin II; and a decrease in AGT levels by the increase in renin (*30*). Angiotensin II, the major effector molecule of the RAAS, acts as a physiologically important regulator of BP. The acute BP response to ACE inhibitors is mainly due to vasodilation induced by reduction of the plasma concentration of angiotensin II (*31*). AGT is the precursor of angiotensin II, and the plasma concentration of AGT may be reflected in differences in the rate of formation of angiotensin II. Increased AGT and angiotensin II plasma levels have been observed in white subjects carrying the 1198C allele, but not in Asian subjects carrying the 1198C allele (*28*, *32*). Consequently, white hypertensive patients, but not Asian hypertensive patients, carrying the 1198C allele exhibited greater BP reduction when treated with ACE inhibitors. Second, pharmacodynamic mechanisms may play the predominant role in determining interindividual variation in blood response to the antihypertensive drugs now in common use, such as the imidapril and benazepril used in our study. The pharmacokinetic mechanisms determine the fate of the drug. The frequency distribution histogram for most measures of response to these drugs is unimodal and normally distributed. Such a frequency distribution is consistent with multifactorial determination by effects of many genetic and environmental factors, with no single factor having a discernibly large effect on response, so it is more difficult to identify the effects of a single gene polymorphism. Third, EH is a polygenic disorder, but not a monogenic trait. As to the antihypertensive response to ACE inhibition, the effect of a single gene polymorphism may be too trivial to be detected. So, a specific multilocus haplotype, rather than any of the single loci that define the haplotype, is more significant in determining the association (*33*). Finally, although Hingorani *et al*. (*29*) found that the BP response to ACE inhibitors is dependent on AGT genotype in 102 white subjects, Mondorf *et al*. (*25*) found no relationship between the polymorphism and BP response to an ACE inhibitor (captopril) in 121 white subjects. The conflicting results among the studies by Hingorani *et al*. (*29*) and Mondorf *et al*. (*25*) and the present findings might be explained in part by the genetic and environmental heterogeneity among different ethnic groups, and differences in the agents used, study protocols, and study durations. For these reasons, consistent associations have been difficult to demonstrate, at least up to the present.

In summary, our results do not suggest a significant role of AGT gene polymorphism in BP regulation, and there was insufficient evidence that the AGT genotype predicts the response to imidapril or benazepril in Chinese patients with EH.

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References

1. Matsubara M, Metoki H, Katsuya T, *et al*: T+31C polymorphism (M235T) of the angiotensinogen gene and home blood pressure in the Japanese general population: the Ohasama Study. *Hypertens Res* 2003; **26**: 37–46.
2. Jin JJ, Nakura J, Wu Z, *et al*: Association of angiotensin II type 2 receptor gene variant with hypertension. *Hypertens Res* 2003; **26**: 547–552.
3. Ono K, Mannami T, Baba S, Yasui N, Ogihara T, Iwai N: Lack of association between angiotensin II type 1 receptor gene polymorphism and hypertension in Japanese. *Hypertens Res* 2003; **26**: 131–134.
4. Kikuya M, Sugimoto K, Katsuya T, *et al*: A/C1166 gene polymorphism of the angiotensin II type 1 receptor (AT1) and ambulatory blood pressure: the Ohasama Study. *Hypertens Res* 2003; **26**: 141–145.
5. Matsubara M, Sato T, Nishimura T, *et al*: *CYP11B2* polymorphisms and home blood pressure in a population-based cohort in Japanese: the Ohasama Study. *Hypertens Res* 2004; **27**: 1–6.
6. Kurland L, Liljedahl U, Karlsson J, *et al*: Angiotensinogen

gene polymorphisms: relationship to blood pressure response to antihypertensive treatment. *Am J Hypertens* 2004; **17**: 8–13.
7. Kurland L, Melhus H, Karlsson J, *et al*: Aldosterone synthase (CYP11B2) −344 C/T is related to antihypertensive response. *Am J Hypertens* 2002; **15**: 387–393.
8. Sasaki M, Oki T, Luchi A, *et al*: Relationship between the angiotensin converting enzyme gene polymorphism and the effects of enalapril on left ventricular hypertrophy and impaired diastolic filling in essential hypertension: M-mode and pulsed Doppler echocardiographic studies. *J Hypertens* 1996; **14**: 1403–1408.
9. Dudley C, Keavney B, Casadei B, Conway J, Bird R, Ratcliffe P: Prediction of patient responses to antihypertensive drugs using genetic polymorphisms: investigation of the renin-angiotensin system genes. *J Hypertens* 1996; **14**: 259–262.
10. Nakano Y, Oshima T, Watanabe M, Matsuura H, Kajiyama G, Kambe M: Angiotensin I-converting enzyme gene polymorphism and acute response to captopril in essential hypertension. *Am J Hypertens* 1997; **10**: 1064–1068.
11. Ueda S, Meredith PA, Morton JJ, Connell JMC, Elliott L: ACE (I/D) genotype as a predictor of the magnitude and duration of the response an ACE inhibitor drug (enalaprilat) in humans. *Criculation* 1998; **98**: 2148–2153.
12. Liljedahl U, Karlsson J, Melhus H, *et al*: A microarray minisequencing system for pharmacogenetic profiling of antihypertensive drug response. *Pharmacogenetics* 2003; **13**: 7–17.
13. Miller JA, Thai K, Scholey JW: Angiotensin II type 1 receptor gene polymorphism predicts response to losartan and angiotensin II. *Kidney Int* 1999; **56**: 2173–2180.
14. Katsuya T, Iwashima Y, Sugimoto K, *et al*: Effects of antihypertensive drugs and gene variants in the renin-angiotensin system. *Hypertens Res* 2001; **24**: 463–467.
15. Nakamura Y, Tamaki S, Uchida Y, *et al*: Angiotensin converting enzyme genotype influences the response to the angiotensin II receptor antagonist losartan in patients with hypertension. *Hypertens Res* 2004; **27**: 137–140.
16. Yu H, Zhang Y, Lu G: Relationship between the polymorphism of the angiotensin converting enzyme gene and the response to angiotensin converting enzyme inhibition in hypertensive patients. *Hypertens Res* 2003; **26**: 881–886.
17. Jeunemaitre X, Soubrier F, Kotelevtsev YV, *et al*: Molecular basis of human hypertension: role of angiotensinogen. *Cell* 1992; **71**: 169–180.
18. Kunz R, Kreutz R, Beige J, Distler A, Sharma AM: Association between the angiotensinogen 235T-variant and essential hypertension in whites: a systematic review and methodological appraisal. *Hypertension* 1997; **30**: 1331–1337.
19. Staessen JA, Kuznetsova T, Wang JG, Emelianov D, Vlietinck R, Fagard R: M235T angiotensinogen gene polymorphism and cardiovascular renal risk. *J Hypertens* 1999; **17**: 9–17.
20. Katsuya T, Ishikawa K, Sugimoto K, Rakugi H, Ogihara T: Salt sensitivity of Japanese from the viewpoint of gene polymorphism. *Hypertens Res* 2003; **26**: 521–525.
21. Poch E, Gonzalez D, Giner V, Bragulat E, Coca A, de la Sierra A: Molecular basis of salt sensitivity in human hypertension. Evaluation of renin-angiotensin-aldosterone system gene polymorphisms. *Hypertension* 2001; **38**: 1204–1209.
22. Rotimi C, Puras A, Cooper R, *et al*: Polymorphism of renin-angiotensin genes among Nigerians, Jamaicans, and African Americans. *Hypertension* 1996; **27**: 558–563.
23. Caufield M, Lavender P, Newell Price J, *et al*: Linkage of the AGT gene to human EH in African Caribbeans. *J Clin Invest* 1995; **96**: 687–692.
24. Imidapril and Benazepril Clinical Study Cooperation Unit: Comparative Study of Hypotensive Efficacy and the Cough Occurrence of Imidapril *versus* Benazepril. *Chin J Cardiol* 2004; **32**: 304–307.
25. Mondorf UF, Russ A, Wiesemann A, Herrero M, Oremek G, Lenz T: Contribution of ACE gene polymorphism and angiotensinogen gene polymorphism to blood pressure reduction in essential hypertension. *Am J Hypertens* 1998; **11**: 174–183.
26. Walker WG, Welton PK, Saito H, Rusell RP, Hermann J: Relation between blood pressure and renin, renin substrate, angiotensin II, aldosterone and urinary sodium and potassium in 574 ambulatory subjects. *Hypertension* 1979; **1**: 287–291.
27. Hegele RA, Brunt JH, Connelly PW: A polymorphism of the angiotensin gene associated with variation in blood pressure in a genetic isolate. *Circulation* 1994; **90**: 2207–2212.
28. Sethi AA, Nordestgaard BG, Tybjærg-Hansen A: Angiotensinogen gene polymorphism, plasma angiotensinogen, and risk of hypertension and ischemic heart disease: a meta-analysis. *Arterioscler Thromb Vasc Biol* 2003; **23**: 1269–1275.
29. Hingorani AD, Jia H, Stevens PA, Hopper R, Dickerson JE, Brown MJ: Renin-angiotensin system gene polymorphisms influence blood pressure and the response to angiotensin converting enzyme inhibition. *J Hypertens* 1995; **13**: 1602–1609.
30. Takahashi N, Hagaman JR, Kim HS, Smithies O: Computer simulations of blood pressure regulation by the renin-angiotensin system. *Endocrinology* 2003; **144**: 2184–2190 (Minireview).
31. Juillerat L, Nussberger J, Menard J, *et al*: Determinants of angiotensin II generation during ACE inhibition. *Hypertension* 1990; **16**: 564–572.
32. Caulfield M, Lavender P, Farrall M, *et al*: Linkage of the angiotensinogen gene to essential hypertension. *N Engl J Med* 1994, **330**: 1629–1633.
33. Martin ER, Lai EH, Gilbert JR, *et al*: SNPing away at complex disease: analysis of singe-nucleotide polymorphisms around APOE in Alzheimer disease. *Am J Hum Genet* 2000; **67**: 383–394.