Blood pressure in relation to three candidate genes in a Chinese population

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Objective **In a prospective analysis of a Caucasian population, we recently found that the genes encoding angiotensin-converting enzyme (ACE, *I/D* polymorphism), α-adducin (Gly460Trp) and aldosterone synthase (−344C/T) jointly influence the incidence of hypertension. We therefore investigated the association between blood pressure and these three genes in a Chinese population.**

Methods **We genotyped 479 Han Chinese from 125 nuclear families recruited in northern China via random sampling (∼75%) and at specialized hypertension clinics (∼25%). We performed population-based and family-based association analyses using generalized estimating equations (GEE) and the quantitative transmission disequilibrium test (QTDT), respectively, while controlling for covariables.**

Results **The participants included 239 (49.9%) women and 132 (27.6%) hypertensive patients, of whom 77 took antihypertensive drugs. The blood pressure, measured at the subjects' homes, averaged 126/80 mmHg. Mean values of urinary sodium, potassium and Na^+/K^+ ratio were 226 mmol/day, 37 mmol/day and 6.31, respectively. In adjusted GEE analyses, systolic blood pressure was 9.3 mmHg (95% confidence interval 3.6–15.0 mmHg; $P = 0.001$) and 14.6 mmHg (95% confidence interval 3.4–25.8 mmHg; $P = 0.01$) higher in the ACE *DD* than *II* subjects among the α-adducin TrpTrp ($n = 141$) and aldosterone synthase *CC* ($n = 33$) homozygotes, respectively ($P \leqslant 0.05$ for interactions of the ACE genotype with the α-adducin and aldosterone synthase polymorphisms). Among 40 informative offspring homozygous for the α-adducin Trp allele, systolic blood pressure was significantly associated with transmission of the ACE *D* allele ($\beta = 5.5$ mmHg; $P = 0.046$).**

Conclusions **The ACE *I/D*, α-adducin Gly460Trp and aldosterone synthase −344C/T polymorphisms interact to influence systolic blood pressure in Chinese, suggesting that these genes might indeed predispose to hypertension, especially in an ecogenetic context characterized by a high salt intake. *J Hypertens* 22:937–944 © 2004 Lippincott Williams & Wilkins.**

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Introduction

In a prospective analysis of a Caucasian population, we recently found that, over a median follow-up of 9 years, the incidence of hypertension was 31% higher in *DD* homozygous carriers of the insertion/deletion polymorphism (*I/D*) of the angiotensin-converting enzyme gene (ACE) than in their *I* allele counterparts. Moreover, in the presence of the mutated α-adducin Trp allele (Gly460Trp polymorphism), the aldosterone-synthase *CC* genotype (−344C/T polymorphism), or both genetic variants combined, the risk of hypertension associated with the ACE *DD* homozygosity increased to 59, 122 and 252%, respectively [1]. In cross-sectional analyses of the same population, the ACE *D* allele and the mutated α-adducin Trp allele were jointly associated with significant increases in the serum concentration of creatinine and the urinary excretion of proteins [2], as well as with greater intima–media thickness of the femoral artery [3] and enhanced stiffness of both the carotid and femoral

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arteries [4]. The hypothesis underlying our previous studies [1–4] was that these three candidate genes and their interactions might lead to structural and/or functional changes in the cardiovascular–renal system, via their influence on sodium reabsorption in the kidney and the circulating fluid volume.

Asians, compared with Caucasians, have lower frequencies of the ACE *D* allele [5] and the aldosterone synthase *CC* genotype [6], but a higher prevalence of the α-adducin Trp allele [7,8]. On balance, the currently available literature suggests that the association between hypertension and the ACE *D* allele might be more pronounced in Chinese [9] than in Caucasians [1,5,10]. Such cross-racial discrepancy in phenotype–genotype associations might be due to disparity in the frequency of risk-carrying alleles [11–13], environmental factors and/or lifestyle. We therefore investigated the associations between blood pressure and the aforementioned three candidate genes in a Chinese population sample, while accounting for covariables and lifestyle factors.

Methods

Study population

We conducted the present study in Gaoping, a city 600 km south of Beijing, China. The study was set up in collaboration with the investigators of the Flemish Study on Environment, Genes and Health Outcomes [1,2] and the European Project on Genes in Hypertension [14], with implementation of the same methods in phenotyping [15] and genotyping [13,16]. To achieve a high degree of standardization, the same study forms, coding rules and manuals of operations were used in these studies. For the purpose of the present study, these documents were translated into Chinese. In addition, the coordinators of the field work in Gaoping and the investigators involved in the construction and analysis of the database took part in the same training programme as their European counterparts.

The Gaoping study was conducted according to the principles outlined in the Helsinki declaration for investigation of human subjects. The Institutional Review Board of the Fuwai Hospital and Cardiovascular Institute approved the study protocol. All subjects gave written informed consent. Using the city registry of addresses and a computerized random number function (SAS RANUNI), nuclear families of Han Chinese were randomly recruited from the population. To increase the number of hypertensive patients, approximately 25% of the families were enrolled via specialized clinics. Nuclear families had to consist of either one parent and at least two offspring or two parents and one or more siblings. Moreover, to make repeated home visits feasible, nuclear families only qualified for participation if all family members resided within 10 km of the local study coordinating centre. The age range for participation was from 18 to 60 years.

In 2001, 125 nuclear families including 513 subjects were enrolled. The participation rate among the subjects contacted was 95.9%. Twenty-three subjects had not been genotyped for all genes and 11 had incomplete anthropometrical measurements ($n = 6$) or other missing information ($n = 5$). Thus, the number of subjects included in the present analysis totalled 479.

Field work

All subjects were visited repeatedly in their homes. Blood pressure was measured five times consecutively during each of two home visits, after 5 min rest in the sitting position. Hypertension was diagnosed if the average of the ten blood pressure readings was at least 140 mmHg systolic or 90 mmHg diastolic pressure, or if the subjects were on antihypertensive medication. We used a validated questionnaire [1,2,14,15] to collect information on medical history, smoking habits, alcohol intake and use of medication. In the interval between home visits, usually 2–3 weeks apart, subjects collected a 24-h urine sample in a wide-neck plastic container for the measurement of creatinine and electrolytes. Venous blood was sampled after an overnight fast, while the subject was in the sitting position, for the measurement of plasma renin activity and total cholesterol and for genotyping. All biochemical measurements were performed in the central laboratory of Fuwai Hospital (Beijing, China), which fulfilled the quality control criteria of the regulatory authority of Beijing.

Determination of genotypes

Genomic DNA was extracted from peripheral blood. The ACE *I*/*D* polymorphism was detected as described by Morgan *et al.* [16]. Allelic discrimination of the α-adducin Gly460Trp polymorphism was carried out as described previously [1], using a 5′ nuclease assay [17] on an ABI Prism 7700 apparatus (Perkin Elmer, Foster City, California, USA). For determination of the −344C/T aldosterone synthase genotypes, we also used the 5′ nuclease detection assay on an ABI PRISM 7700 sequence detection system. The forward and reverse primers and the −344T and −344C probes were 5′ CTAAATCTGTGGTATAAAAATAAAGTCTATTAA AAGA, 5′ TTTCTCCAGGGCTGAGAGGA, 5′ FAM-CAAGGCTCCCTCTCATCTCACGATAAG-TAMRA, and 5′ VIC-AAGGCCCCCTCTCATCTCACGATA-TAMRA. The polymerase chain reaction (PCR) fluid contained 50 ng DNA, 300 nmol primers, 70 nmol FAM-probe and 50 nmol VIC probe per 25 µl. The amplification conditions were 50°C for 2 min and 95°C for 10 min, followed by 40 cycles at 95°C for 15 s and 61°C for 1 min.

Statistical methods

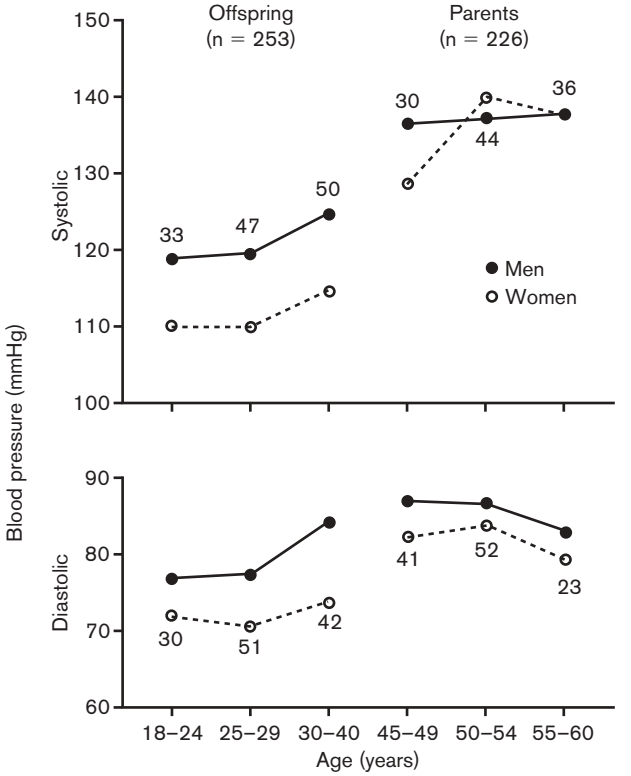
We used SAS version 8.1 (SAS Institute, Cary, North Carolina, USA) for database management and statistical analysis. Comparisons of means and proportions relied on the standard normal z-test and Fisher's exact test, respectively. We studied genetic associations using generalized estimating equations (GEE) to account for the non-independence of the phenotypic measurements within families [18], while controlling for covariables and confounders. To take advantage of the family structure, we also ran the quantitative transmission disequilibrium test as implemented in the QTDT program (version 2.4.2, http://www.well.ox.ac.uk/asthma/QTDT) [19]. With similar adjustments as in the other analyses, we investigated the association between blood pressure and allelic transmission using the orthogonal model in a variance components framework [20].

Results

Characteristics of the participants

The 479 participants consisted of 226 parents and 253 offspring (Table 1). Overall, mean (SD) age and body mass index were 39.6 (12.8) years and 24.2 (3.4) kg/m^2, respectively. In parents and offspring combined, blood pressure averaged 125.8 (18.9) mmHg systolic and 79.8 (11.5) mmHg diastolic. In offspring, both systolic and diastolic blood pressure were higher in men than in women (Fig. 1). In parents, the gender-difference was only significant for diastolic ($P = 0.03$) but not for systolic blood pressure ($P = 0.50$). The study sample included 132 (27.6%) hypertensive patients, of whom 77 took antihypertensive drugs (calcium-channel blockers, $n = 40$; ACE inhibitors, $n = 18$; diuretics, $n = 8$; β-blockers, $n = 5$; and various combination tablets with low doses of hydrochlorothiazide, reserpine and dihydralazine, $n = 23$). Seven (1.5%) women used oral contraceptives but none took hormonal replacement therapy.

Fig. 1



Mean systolic and diastolic blood pressure by sex and age in parents and offspring. For each subgroup the number of subjects is given.

Population-based association analyses

Genotype frequencies in parents and offspring are reported in Table 2. In parents, the frequencies of the ACE *I/D* ($P = 0.85$), α-adducin Gly460Trp ($P = 0.24$) and aldosterone synthase −344C/T ($P = 0.40$) genotypes did not deviate from Hardy–Weinberg equili-

Table 1 Characteristics of the participants

	Parents ($n = 226$)		Offspring ($n = 253$)	
Characteristic*	Fathers ($n = 110$)	Mothers ($n = 116$)	Sons ($n = 130$)	Daughters ($n = 123$)
Age (years)	53.1 ± 4.1	51.6 ± 3.7	28.0 ± 4.5	28.7 ± 5.3
Body mass index (kg/m^2)	24.4 ± 3.1	24.9 ± 4.0	24.1 ± 3.4	23.3 ± 3.2
Systolic pressure (mmHg)†	137.2 ± 19.3	135.4 ± 20.5	121.2 ± 11.2	111.4 ± 10.3
Diastolic pressure (mmHg)†	85.7 ± 11.8	82.5 ± 10.0	79.9 ± 11.6	72.0 ± 7.9
Taking antihypertensive drugs, *n* (%)	33 (30.0)	34 (29.3)	7 (5.4)	3 (2.4)
Current smoking, *n* (%)	63 (57.3)	3 (2.6)	79 (60.8)	0
Alcohol intake, *n* (%)	33 (30.0)	0	58 (44.6)	0
Serum total cholesterol (mmol/l)	4.16 ± 0.85	4.37 ± 1.05	4.14 ± 1.00	4.07 ± 1.01
Plasma renin activity (ng/l per second)	0.36 (0.31–0.43)	0.45 (0.39–0.53)	0.72 (0.64–0.81)	0.71 (0.63–0.80)
Urinary volume (l)	1.70 ± 0.69	1.63 ± 0.56	1.46 ± 0.63	1.37 ± 0.51
Urinary creatinine excretion (mmol/day)	8.7 ± 2.8	6.4 ± 1.7	8.6 ± 3.2	6.9 ± 2.1
Urinary Na^+ excretion (mmol/day)	247 ± 107	218 ± 81	231 ± 100	207 ± 79
Urinary K^+ excretion (mmol/day)	39 ± 17	39 ± 16	37 ± 17	37 ± 13
Urinary Na^+/K^+ ratio	6.63 ± 2.78	6.07 ± 2.11	6.56 ± 2.51	5.96 ± 2.25

*Values are arithmetic means (± SD), geometric means (95% confidence interval), or number of subjects (%). †Mean of 10 blood pressure readings (five at each of two separate home visits).

Table 2 Genotype frequencies in parents and offspring

Genes	Genotypes		
ACE gene	*II*	*ID*	*DD*
Parents	88 (38.9)	105 (46.5)	33 (14.6)
Offspring	94 (37.1)	111 (43.9)	48 (19.0)
α-Adducin gene	GlyGly	GlyTrp	TrpTrp
Parents	50 (22.1)	103 (45.6)	73 (32.3)
Offspring	62 (24.5)	123 (48.6)	68 (26.9)
Aldosterone-synthase gene	*CC*	*CT*	*TT*
Parents	15 (6.6)	96 (42.5)	115 (50.9)
Offspring	18 (7.1)	110 (43.5)	125 (49.4)

ACE, angiotensin-converting enzyme.

brium. In neither parents nor offspring did genotype frequencies differ according to the presence or absence of hypertension ($P \geqslant 0.15$).

In GEE analyses adjusted for sex, age, age^2, body mass index, current smoking, alcohol intake and the use of antihypertensive drugs, systolic and diastolic blood pressure, analysed as continuous traits, were not significantly associated with any of the three genes considered separately (Table 3 and Fig. 2). However, the adjusted GEE analyses revealed significant ($P \leqslant 0.05$) interactions of the ACE *I/D* polymorphism with both the α-adducin and aldosterone synthase genetic variants (Table 4). Indeed, among 141 subjects homozygous for the α-adducin Trp allele, systolic blood pressure was 9.3 mmHg (95% confidence interval 3.6 to 15.0) higher in ACE *DD* than *II* homozygotes. Furthermore, in 33 aldosterone synthase *CC* homozygotes, the corresponding difference between *DD* and *II* subjects was in the same direction, averaging 14.6 mmHg (95% confidence interval 3.4–25.8).

Genotype frequencies were high enough to test interactions between the ACE and α-adducin polymorphisms in parents and offspring separately (Fig. 3). These sensitivity analyses confirmed that among 73 parents and 68 offspring, systolic blood pressure was higher in ACE *DD* than *II* subjects. The differences averaged 18.5 mmHg (95% confidence interval 8.6–28.5) and 6.4 mmHg (95% confidence interval 1.7–11.0), respectively (Fig. 3).

In further analyses of plasma renin activity and urinary sodium excretion, we excluded participants using antihypertensive medications and women taking oral contraceptives because of the potential influence of these drugs on plasma renin activity. After adjustment for sex, age and body mass index, GEE analyses showed that in all untreated subjects plasma renin activity decreased by 8.7% (95% confidence interval −15.2% to −1.7%) for each 100 mmol/day increase in urinary sodium excretion. In the presence of α-adducin TrpTrp homozygosity, this association was significantly dependent on the ACE genotype ($P = 0.02$ for interaction between the ACE genotype and urinary sodium excretion in relation to plasma renin activity; Table 5); for each 100 mmol/day increase in urinary sodium excretion, plasma renin activity did not change in ACE *II* homozygotes, increased by 26.0% (95% confidence interval +2.5% to +54.9%) in *ID* heterozygotes, but decreased by 51.9% (95% confidence interval −73.0% to −14.4%) in *DD* subjects.

Table 3 Systolic and diastolic blood pressures in relation to single genes*

	Systolic pressure (mmHg)		Diastolic pressure (mmHg)	
Genes and genotypes	mean ± SE	*P* (ANOVA)	mean ± SE	*P* (ANOVA)
ACE				
II ($n = 182$)	124.8 ± 1.2		79.4 ± 0.7	
ID ($n = 216$)	126.6 ± 1.1		80.2 ± 0.7	
DD ($n = 81$)	127.8 ± 1.5†	0.27	80.0 ± 1.0	0.76
α-Adducin				
GlyGly ($n = 112$)	126.7 ± 1.6		80.8 ± 1.0	
GlyTrp ($n = 226$)	125.4 ± 1.0		79.4 ± 0.6	
TrpTrp ($n = 141$)	126.7 ± 1.4	0.96	80.0 ± 0.9	0.47
Aldosterone synthase				
CC ($n = 33$)	129.1 ± 3.1		78.5 ± 1.9	
CT ($n = 206$)	126.1 ± 0.9		80.3 ± 0.6	
TT ($n = 240$)	125.7 ± 1.1	0.63	79.7 ± 0.7	0.60

*The analyses were adjusted for sex, age, age^2, body mass index, smoking, alcohol intake and the use of antihypertensive drugs. †$P = 0.09$ versus *II* homozygotes. ACE, angiotensin-converting enzyme.

Family-based QTDT analysis

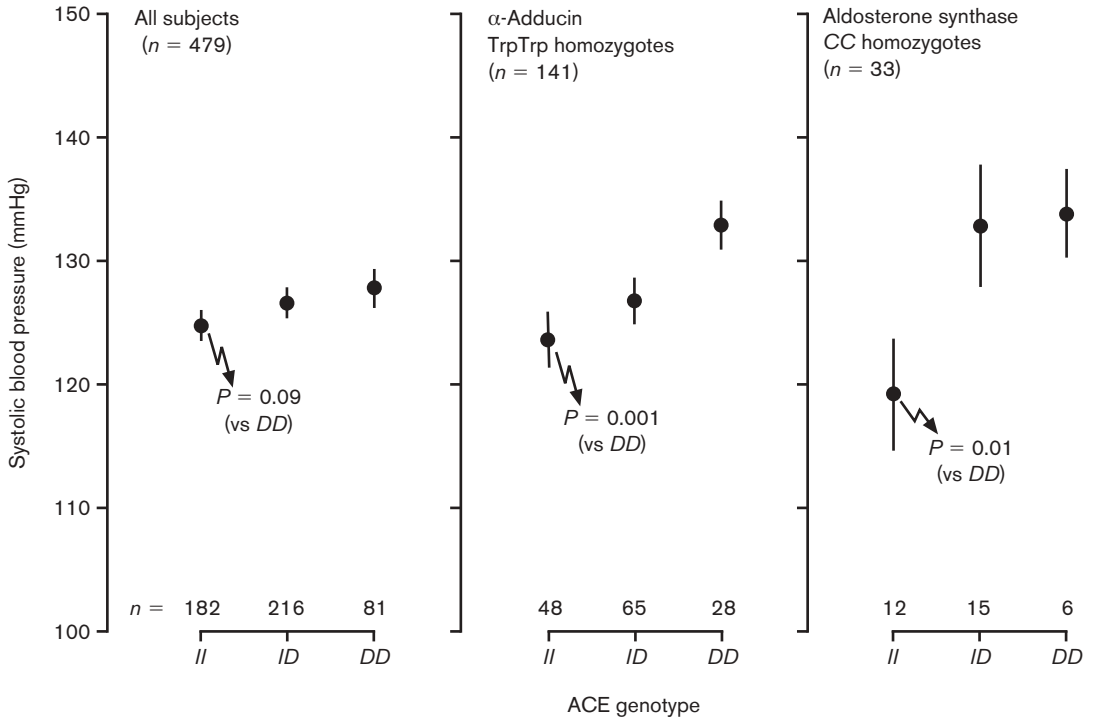
Our study sample included 15 one-parent families with two ($n = 10$) or more ($n = 5$) offspring and 103 two-parent families with one ($n = 11$), two ($n = 81$) or more ($n = 11$) offspring. Among the offspring, we identified Mendelian inheritance errors in 18 subjects. With regard to the three genes under study, the orthogonal model did not reveal significant population stratification ($0.48 < P < 0.99$).

In 169 informative offspring, the orthogonal model, with adjustments applied for the same covariables as before, did not show significant associations between blood pressure and the transmission of the ACE *D* allele ($P > 0.55$). However, the association between systolic blood pressure and transmission of the ACE *D* allele reached statistical significance when the analysis was restricted to 40 informative offspring homozygous for the α-adducin Trp allele [regression coefficient (β) = 5.5 mmHg; $P = 0.046$].

Discussion

Our main finding was that in Han Chinese systolic blood pressure was elevated in the presence of the ACE *D* allele among α-adducin TrpTrp and aldosterone synthase *CC* homozygotes. This association was independent of major blood pressure determinants, such as sex, age, body mass index, current smoking,

Fig. 2



Systolic and diastolic blood pressure by angiotensin-converting enzyme (ACE) genotype in all participants and in subjects homozygous for the α-adducin Trp allele or for the aldosterone synthase *C* allele. Values are adjusted for sex, age, age^2, body mass index, current smoking, alcohol intake and use of antihypertensive drugs. Vertical lines denote SEs. For each genotype the number of subjects is given (bottom).

Table 4 Systolic and diastolic blood pressures in relation to multiple genes

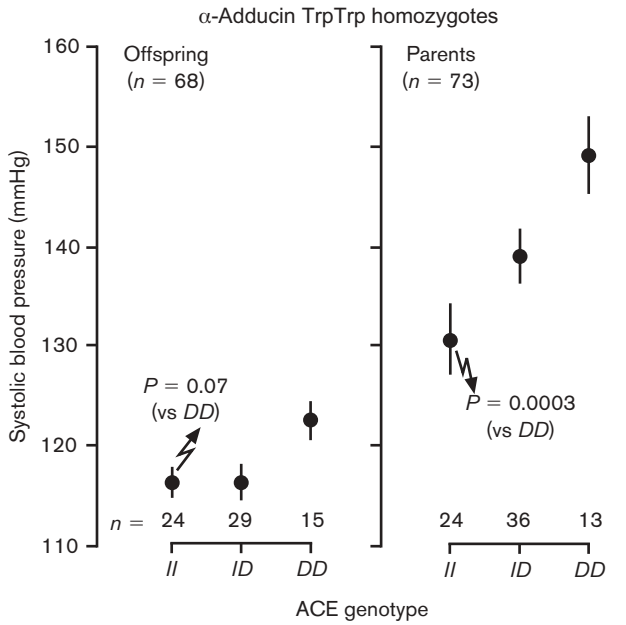
	Systolic pressure (mmHg)		Diastolic pressure (mmHg)	
Genes and genotypes	mean ± SE	$P^{\dagger}$	mean ± SE	$P^{\dagger}$
α-Adducin/ACE				
GlyGly+GlyTrp/*II* ($n = 134$)	124.6 ± 1.3		79.1 ± 0.8	
Gly/Gly+GlyTrp/*ID* ($n = 151$)	126.3 ± 1.3		80.6 ± 0.8	
GlyGly+GlyTrp/*DD* ($n = 53$)	124.2 ± 1.6		77.9 ± 0.9	
TrpTrp/*II* ($n = 48$)	123.6 ± 2.2		79.6 ± 1.3	
TrpTrp/*ID* ($n = 65$)	126.8 ± 1.8		79.4 ± 1.2	
TrpTrp/*DD* ($n = 28$)	132.9 ± 1.9	0.05	82.3 ± 1.4	0.06
Aldosterone synthase/ACE				
CC/II ($n = 12$)	119.2 ± 4.5		75.6 ± 3.5	
CC/ID ($n = 15$)	132.8 ± 4.9		79.5 ± 2.3	
CC/DD ($n = 6$)	133.8 ± 3.5		82.8 ± 3.9	
CT+TT/II ($n = 170$)	124.8 ± 1.1		79.5 ± 0.7	
CT+TT/ID ($n = 206$)	125.9 ± 1.1		80.2 ± 0.7	
CT+TT/DD ($n = 75$)	126.2 ± 1.5	0.046	78.8 ± 0.7	0.41

*The analyses were adjusted for sex, age, age^2, body mass index, smoking, alcohol intake and the use of antihypertensive drugs. †For interactions between the angiotensin-converting enzyme (ACE) genotype and the presence or absence of adducin Gly allele or aldosterone synthase *C* allele.

alcohol intake and the use of antihypertensive drugs. The sensitivity analysis in parents and offspring separately, as well as the QTDT analysis, confirmed the interaction between the ACE and α-adducin polymorphisms. Our null findings in single-gene analyses were in agreement with the results of previous Chinese and Japanese studies [6,8,21]. These genetic polymorphisms might be associated with blood pressure only in homogeneous subgroups, such as the low-renin hypertensive patients [22–24].

Our finding on the combined effect of the three genes

Fig. 3



Systolic and diastolic blood pressure by angiotensin-converting enzyme (ACE) genotype in the parents and offspring who were homozygous for the α-adducin Trp allele. Values are adjusted for sex, age, age^2, body mass index, current smoking, alcohol intake and use of antihypertensive drugs. Vertical lines denote SEs. For each genotype the number of subjects is given (bottom).

on systolic blood pressure was in line with the results of a previous population study in Caucasians [1]. In a prospective analysis of 678 randomly selected subjects, the incidence of hypertension was 31% ($P = 0.005$) higher in ACE *DD* homozygotes than in *I* allele carriers, but the risk increased to 59% in carriers of the α-adducin Trp allele, 122% in aldosterone synthase *CC* homozygotes, and 252% in subjects who had both the α-adducin Trp allele and the aldosterone synthase *CC* genotype [1]. In keeping with carefully standardized laboratory experiments in hypertensive patients [13], we speculate that the enhanced generation of angiotensin II in *DD* homozygotes [25,26], in the presence of the mutated α-adducin gene, may lead to sodium retention and chronic volume expansion [13], and hence to an increase in blood pressure. Indeed, we observed a strong inverse association between plasma renin activity and urinary sodium excretion in ACE *DD* homozygotes, particularly when combined with the α-adducin TrpTrp genotype. It is known that on a high sodium diet plasma renin activity decreases to compensate for sodium retention and volume expansion [27]. Furthermore, the lower innate aldosterone secretion [28–30] in aldosterone synthase *CC* homozygotes may lead to stimulation of the renin–angiotensin system [31] and possibly to overcompensation in ACE *DD* homozygotes, in whom the ACE activity is already systemically enhanced [25,26]. Thus, subjects who have the aldosterone synthase *CC* and ACE *DD* genotypes may, under facilitating environmental conditions, become susceptible to develop high-renin [31] hypertension. Failure to account for genetic interactions might partially explain the inconsistent results of population studies on the association between blood pressure and the ACE gene [10,32–34].

Our population-based study is in line with previous case–control studies in Chinese, which demonstrated significant association between hypertension and the ACE *D* allele [35,36]. A recent meta-analysis of 18 Chinese case–control studies, including 1612 hypertensive cases and 1710 normotensive controls, showed a pooled odds ratio of 1.37 (95% confidence interval

Table 5 Association between plasma renin activity and urinary sodium excretion by ACE and α-adducin genotype*

Genes and genotypes	Plasma renin activity (ng/l per second) Geometric means (95% confidence interval)	Urinary sodium excretion (mmol/day) Arithmetic means ± SE	Plasma renin activity (ng/l per second) in relation to urinary sodium excretion (+ 100 mmol/day) Regression coefficient (95% confidence interval)	*P*	*P*-int†
ACE					
II ($n = 150$)	0.58 (0.51–0.66)	237 ± 10	−5.9% (−14.6% to +3.8%)	0.22	
ID ($n = 178$)	0.55 (0.50–0.62)	219 ± 8	−4.4% (−16.0% to +8.9%)	0.50	
DD ($n = 69$)	0.61 (0.48–0.77)	227 ± 12	−29.3% (−40.2% to −16.5%)	<0.0001	0.22
α-Adducin/ACE					
GlyGly+GlyTrp/*II* ($n = 113$)	0.60 (0.52–0.69)	228 ± 11	−11.7% (−20.4% to −2.0%)	0.02	
Gly/Gly+GlyTrp/*ID* ($n = 123$)	0.54 (0.48–0.61)	216 ± 9	−11.9% (−23.8% to +1.7%)	0.08	
GlyGly+GlyTrp/*DD* ($n = 45$)	0.72 (0.58–0.89)	224 ± 17	−7.0% (−20.6% to +9.0%)	0.37	0.79
TrpTrp/*II* ($n = 37$)	0.53 (0.42–0.66)	267 ± 16	+1.1% (−16.3% to +22.0%)	0.91	
TrpTrp/*ID* ($n = 55$)	0.59 (0.49–0.71)	221 ± 11	+26.0% (+2.5% to +54.9%)	0.03	
TrpTrp/*DD* ($n = 24$)	0.46 (0.28–0.73)	234 ± 16	−51.9% (−73.0% to −14.4%)	0.01	0.02

*After adjustment for sex, age and body mass index, the analyses were performed in 397 subjects who did not take antihypertensive drugs and/or oral contraceptives. †For interactions between the angiotensin-converting enzyme (ACE) genotype and urinary sodium excretion in relation to plasma renin activity.

1.15–1.63; $P = 0.0004$) for the risk of hypertension in ACE *DD* homozygotes versus *I* allele carriers [9].

Angiotensin II [37], which is generated by ACE, and α-adducin [12] modulate sodium homeostasis. Unbalanced dietary intakes of sodium and potassium might therefore play an important role in the ecogenetic pathogenesis of hypertension in Chinese. The Intersalt study included 600 Chinese participants recruited in equal proportions from the cities of Beijing, Nanning and Tianjin [38]. The mean urinary sodium and potassium excretion ranged from 169 to 246 mmol/24 h and from 27 to 35 mmol/24 h, respectively, with urinary Na^+/K^+ ratios of 6.0 up to 7.6. Furthermore, clinical experiments in hypertensive patients of Caucasian extraction showed an enhanced blood pressure increase in response to sodium loading in carriers of the ACE *D* and α-adducin Trp alleles [13]. Moreover, the high frequency of the mutated α-adducin Trp allele in Chinese compared with Caucasians might additionally contribute to their greater propensity to salt-sensitive volume-expanded hypertension.

In conclusion, in spite of its small sample size, the present study in Han Chinese confirmed earlier observations in Caucasians [1]. Our findings are consistent and suggest that the ACE *DD* and α-adducin TrpTrp genotypes, and probably also the aldosterone synthase –344CC genotype, contribute to the risk of hypertension, especially in an ecogenetic context characterized by a high salt intake. When confirmed, our findings may have implications for risk stratification and the management of hypertension in Chinese. If the hypertensive carriers of the ACE *DD* and α-adducin TrpTrp genotypes are salt-sensitive, they might show an enhanced blood pressure response to dietary sodium restriction or diuretics.

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