Hypertension Research (2012) 35, 70–76

www.nature.com/hr

ORIGINAL ARTICLE

Association between the angiotensinogen gene T174M polymorphism and hypertension risk in the Chinese population: a meta-analysis

Wei Gu[1,3], Ya Liu[1,3], Zuoguang Wang[1], Kuo Liu[1], Yuqing Lou[1], Qiuli Niu[1], Hao Wang[1], Jinghua Liu[2] and Shaojun Wen[1,4]

No consensus has been reached on the association between the angiotensinogen gene polymorphism T174M and hypertension risk in the Chinese population. We conducted a meta-analysis to systematically pursue their possible association. Case–control studies in the Chinese and English publications were identified by searching the MEDLINE, EMBASE, CBM, CNKI, Wanfang and VIP databases. The fixed-effects model and the random-effects model were applied for dichotomous outcomes to combine the results of the individual studies. After this, we selected 16 studies that met the inclusion criteria. In total, the selected studies contributed a study population containing 3828 hypertensive patients and 3251 normotensive controls. We found no statistical association between the T174M polymorphism and hypertension risk in all subjects, in a Han Chinese subgroup or in non-Han Chinese minorities. However, a statistically significant association was observed between the T174M polymorphism and a hypertensive group (systolic blood pressure $\geqslant$160 mm Hg and/or diastolic blood pressure $\geqslant$95 mm Hg) in the dominant genetic model (MM+MT *vs.* TT: P=0.03, odds ratio=1.71, 95% confidence interval 1.07–2.74, $P_{heterogeneity}$=0.27, I^2=24%, fixed-effects model). No evidence of publication bias was observed. More studies, especially studies stratified for different stages of hypertension, should be performed in the future to fully examine this question. Studies investigating gene–gene interactions, gene—environment interactions, as well as their mutual interactions will also be important.
Hypertension Research (2012) **35,** 70–76; doi:10.1038/hr.2011.141; published online 1 September 2011

Keywords: angiotensinogen; Chinese; meta-analysis; polymorphism

INTRODUCTION

Essential hypertension (EH), which accounts for ~95% of hypertensive cases, is an increasingly serious health problem in the developed countries. In China, hypertension is one of the fastest growing diseases of the past 30 years. According to a 2002 survey, the prevalence rate of hypertension among Chinese adults was ~18.8%, with a total of 170 million people suffering from hypertension.[1] EH is generally regarded as a paradigmatic multi-factorial disease that is determined by a combination of genetic factors, environmental stimuli and their interaction.[2] It is estimated that ~20–60% of the inter-individual variation of blood pressure (BP) is genetically controlled.[3] Accordingly, the discovery of many potential hypertension-susceptibility genes has allowed for a better understanding of disease etiology.

The rennin–angiotensin–aldosterone system is an important regulator of BP.[4] Angiotensinogen (AGT) is a liver protein that interacts with renin to produce angiotensin I, the prohormone of angiotensin II, which is the major effector molecule of rennin–angiotensin–aldosterone system. *AGT* gene variants can modify the plasma AGT concentration, which has been directly linked with arterial BP.[5] Among these variants, the *AGT* T174M polymorphism (rs4762), a C to T conversion at nucleotide position 521 in exon 2, results in the replacement of threonine by methionine at codon 174. It will be included in the meta-analysis.

In 1992, the *AGT* gene T174M polymorphism was first reported to be related to EH prevalence by Jeunemaitre *et al.*[5] Since then, there has been a great effort to further elucidate their association. For the Chinese population, some studies[6–13] have implied that the T174M polymorphism is associated with EH or BP, whereas other studies[14–21] were unable to replicate these findings. In fact, many studies focusing on the Chinese population provided equivocal or largely negative evidence for the

[1]Department of Hypertension Research, Beijing Anzhen Hospital, Capital Medical University and Beijing Institute of Heart Lung and Blood Vessel Diseases, Beijing, PR China and [2]Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, Beijing, PR China
[3]These authors contributed equally to this work.
[4]Member of the International Society of Hypertension.
Correspondence: Dr S Wen, Department of Hypertension Research, Beijing Anzhen Hospital, Capital Medical University and Beijing Institute of Heart Lung and Blood Vessel Diseases, 2 Anzhen Road, Beijing 100029, PR China.
E-mail: wenshaojun@yahoo.com.cn
or Dr J Liu, Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, 2 Anzhen Road, Beijing 100029, PR China.
E-mail: LiujingHua@vip.sina.com
Received 18 March 2011; revised 19 May 2011; accepted 19 June 2011; published online 1 September 2011

association between the polymorphism and hypertension. To fully elucidate the effect of the T174M polymorphism on EH risk in the Chinese population, we conducted a carefully designed meta-analysis that included all the eligible case–control studies published to date.

METHODS

Identification and eligibility of relevant studies

To search for all the studies that examined the association of the T174M polymorphism with EH risk in the Chinese population, we conducted a computerized literature search of the PubMed, EMBASE, CBM (China Biological Medicine Database), CNKI (China Nation Knowledge Infrastructure Platform), Wanfang and VIP databases, using the following keywords and subject terms: 'AGT', 'polymorphism', 'hypertension' and 'Chinese or China or Taiwanese or Taiwan'. The present meta-analysis eligibility deadline was February 2011. Eligible publications had to be written in either Chinese or English. The references of all retrieved articles were also screened. To prevent data duplication, when a report overlapped with another study, only the most detailed study was included. If an article reported results on different ethnic sub-populations, each sub-population was treated as a separate study in our meta-analysis. Studies included in the meta-analysis had to meet all the following criteria: (i) the presentation of an investigation of the relationship between the *AGT* T174M polymorphism and EH in the Chinese population, (ii) the use of an unrelated case–control design (family-based study design with linkage considerations was excluded), (iii) the available genotype frequency, (iv) the genotype distribution of the control population had to be in Hardy–Weinberg equilibrium (HWE) and (v) the study had to define hypertension as systolic (SBP) $\geqslant$140 mm Hg and/or diastolic (DBP) $\geqslant$90 mm Hg[22,23] and/or treatment with anti-hypertensive medication. If the genotype frequency was not reported, we contacted the original authors by e-mail to obtain the missing data.

Data extraction

To minimize the selection bias, two authors independently extracted the information from each study. Disagreements were resolved by discussion between the authors. The following information was gathered from each study: first author, year of publication, racial background and resident region of study population, genotype detection method of each study, diagnostic standard, matching in sex and age, number of cases and controls, and distribution of genotypes and alleles in both the case and control groups.

Statistical analysis

As case–control studies were used, odds ratios (ORs) corresponding to a 95% confidence interval (CI) were applied to assess the strength of the association between the T174M polymorphism and hypertension, and the OR was calculated according to the method described by Woolf.[24] We tested only the dominant genetic model (MM+MT *vs.* TT) because (i) the low frequency of homozygosity for high-risk alleles would yield a considerable number of studies with zero cell counts, generating unreliable OR estimates and (ii) the combination of MM and MT genotypes into one group was utilized in most primary studies included in our meta-analysis. The current strategy for analysis was consistent with that used in some previous studies.[25–29]

In our study, two models of meta-analysis were applied for dichotomous outcomes in Review-Manager 5.0.25 software (The Cochrane Collaboration, Oxford, UK): the fixed-effects model and the random-effects model. The fixed-effects model, using the Mantel–Haenszel method, assumes that studies are sampled from populations with the same effect size, making an adjustment to the study weights according to the in-study variance. The random-effects model, using DerSimonian and Laird's method, assumes that studies are taken from populations with varying effect sizes, and calculates the study weights both from in-study and between-study variances, considering the extent of variation or heterogeneity. We performed a χ^2-based Q-statistic test to assess the between-study heterogeneity.[30] Heterogeneity was considered significant for $P<0.10$ because of the low power of the statistic. The inconsistency index I^2 was also calculated to evaluate the variation caused by heterogeneity rather than by chance. Higher values of the index indicate the existence of heterogeneity.[31] The fixed-effects model (if $P>0.10$) or the random-effects model (if $P<0.10$) were used to pool the results.[32] The significance of the pooled ORs was determined by the Z-test, and a $P<0.05$ was considered significant.

Subgroup analysis according to racial descent was carried out for the Han Chinese and non-Han Chinese minority populations to estimate ethnic-specific OR. In addition, subgroup analysis according to different diagnostic standards for hypertension was also performed.

Sensitivity analyses were conducted by sequential removal of single studies in an attempt to identify the potential influence of the individual data set on the pooled ORs. Publication bias was investigated by funnel plot, in which the standard error of the log of each study was plotted against its corresponding OR. An asymmetric plot suggested possible publication bias. Funnel-plot asymmetry was assessed by Egger's linear regression test.[33] We performed a t-test to determine the significance of the intercept, and a $P<0.05$ was considered significant. HWE was tested with a χ^2 test for goodness of fit based as applied by a web program (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl). All other statistical analyses were performed using ReviewManager 5.0.25 and the Stata version 10.0 software (Stata Corporation, College Station, Texas, USA). All P-values were two-sided.

RESULTS

Studies included in the meta-analysis

After the literature search and selection applying our inclusion criteria, 22 relevant articles on the relationship between the T174M polymorphism and EH in the Chinese population were identified. Among the 22 eligible articles, a study by Chiang *et al.*[34] was replaced with a later report[21] that included a larger population. Moreover, Fang *et al.*[35] and Niu *et al.*[36–38] were excluded as they were family-based studies. In addition, the genotype data of the control population provided in He *et al.*[39] was excluded, as it deviated from HWE ($P_{HWE}<0.0001$). After exclusion, 16 studies, comprising 3828 hypertensive patients and 3251 controls, were collected as considered appropriate for the meta-analysis.[6–21] An included study by Niu *et al.*[11] was an unpublished thesis that was acquired from a medical doctorate dissertation database. This database is a common sub-database shared by the CNKI and Wanfang databases. Yuan *et al.*[13] provided data on two Chinese minority populations: the Hani and the Yi. The two minorities were treated as separate studies. The characteristics of the selected studies are summarized in Table 1. The populations among these studies were as follows: thirteen studies involved Han Chinese subjects (3051 cases and 2620 controls), and three studies involved non-Han Chinese minority populations (777 cases and 631 controls) including Kazakh, Yi, Hani and Aims populations. Of the 16 studies, 69% (11/16) stated that the age and sex status were well matched between the study case and control population; 75% (12/16) were age-matched and 94% (15/16) were gender-matched. All the studies used a blood sample for genotyping.

Main meta-results and subgroup analysis

The distribution of genotypes and alleles in the individual studies is listed in Table 2. The significance level for HWE testing for controls is also shown in Table 2. We observed a wide variation of the 174M allele frequencies in cases and controls ranging from 0.0463 to 0.234 and 0.0375 to 0.1993, respectively, across different studies. Accordingly, the pooled overall frequency of the 174M allele in the Chinese population was 12.64% in hypertensive cases and 10.78% in normotensive controls. The main results of this meta-analysis and the heterogeneity test are listed in Table 3. For all subjects, the random-effects model was used to pool the results, as the between-study heterogeneity was significant. There was no significant association between the T174M polymorphism and hypertension in the total of the 16 studies using the dominant genetic model (MM+MT *vs.* TT: P=0.24, OR=1.14, 95% CI 0.92–1.41, $P_{heterogeneity}$=0.002, I^2=57%; Figure 1).

Table 1 Detailed characteristics of eligible studies considered in the meta-analysis

First author	*Year*	*Ethnicity*	*Region*	*Diagnostic standard (mm Hg)*	*Matching*	*Source of samples*	*Method*
Zheng[6]	2003	Han	Shanghai	SBP⩾140, DBP⩾90	Yes	Population based	PCR-RFLP
Zhang[7]	2006	Han	Henan	SBP⩾140, DBP⩾90	Yes	Hospital based	PCR-RFLP
Zhou[19]	2005	Kazakh	Xinjiang	SBP⩾140, DBP⩾90	Yes	Population based	PCR-RFLP
Yin[8]	2007	Han	Sichuan	SBP⩾140, DBP⩾90	Yes	Hospital based	PCR-RFLP
Li[9]	1998	Han	Heilongjiang	SBP⩾160, DBP⩾95	Yes[1]	Population based	PCR-RFLP
Kong[14]	2004	Han	Henan	SBP⩾140, DBP⩾90	Yes	Hospital based	PCR-RFLP
Yue[10]	2008	Han	Hebei	SBP⩾140, DBP⩾90	Yes[2]	Population based	PCR-RFLP
Liu[15]	2004	Han	Shanghai	SBP>140, DBP>90	Yes[3]	Hospital based	Sequencing
Zhang[16]	2004	Han	Jiangsu	SBP⩾140, DBP⩾90	Yes	Hospital based	PCR-RFLP
Ye[17]	2000	Han	Fujian	SBP⩾160, DBP⩾95	Yes	Hospital based	PCR-RFLP
Gong[18]	1998	Han	Shandong	SBP⩾160, DBP⩾95	Yes[3]	Population based	PCR-RFLP
Niu[11]	2007	Han	Beijing	SBP⩾140, DBP⩾90	Yes	Population based	PCR-RFLP
Yuan[13]	2009	Hani	Yunnan	SBP⩾140, DBP⩾90	Yes	Population based	PCR-RFLP
Yuan[13]	2009	Yi	Yunnan	SBP⩾140, DBP⩾90	Yes	Population based	PCR-RFLP
Jiang[12]	2009	Han	Jiangsu	SBP⩾140, DBP⩾90	Yes	Population based	TaqMan-PCR
Wang[20]	2002	Aims	Taiwan	SBP⩾140, DBP⩾90	Yes	Hospital based	Sequencing
Tsai[21]	2003	Han	Taiwan	SBP⩾140, DBP⩾90	Yes[3]	Hospital based	PCR-RFLP

Abbreviations: DBP, diastolic blood pressure; PCR-RFLP, polymerase chain reaction and restriction fragment length polymorphism; SBP, systolic blood pressure. Yes, age and gender matched, Yes[1], gender matched, not mention for age matched, Yes[2], age matched, Yes[3], gender matched.

Table 2 Sample size, the distribution of genotypes and allele frequencies of cases and controls, and *P*-values of HWE in controls

	Sample size		*TT (genotype)*		*MT/MM (genotype)*		*M allele frequency (%)*		*HWE* P-*value*[a]
First author	*Cases*	*Controls*	*Cases*	*Controls*	*Cases*	*Controls*	*Cases*	*Controls*	*Controls*
Zheng[6]	59	58	49	38	10	20	0.0847	0.1724	0.1125
Zhang[7]	100	40	66	37	34	3	0.225	0.0375	0.8053
Zhou[19]	399	268	296	209	103	59	0.1353	0.1156	0.7264
Yin[8]	140	40	89	29	51	11	0.1964	0.1375	0.3133
Li[9]	90	109	67	95	23	14	0.1388	0.0688	0.4694
Kong[14]	297	196	262	167	35	29	0.0606	0.0816	0.1065
Yue[10]	78	82	67	60	11	22	0.0705	0.1463	0.8292
Liu[15]	185	185	155	149	30	36	0.0811	0.0973	0.1426
Zhang[16]	43	65	39	58	4	7	0.0465	0.0538	0.6463
Ye[17]	72	85	52	70	20	15	0.14	0.088	0.3722
Gong[18]	54	85	49	75	5	10	0.0463	0.0588	0.5644
Niu[11]	1305	1154	991	886	314	268	0.1383	0.1239	0.9395
Yuan (Hani)[13]	172	133	145	120	27	13	0.0785	0.0488	0.5534
Yuan(Yi)[13]	99	134	82	115	17	19	0.0859	0.0708	0.3770
Jiang[12]	220	235	126	167	94	68	0.234	0.1553	0.7393
Wang[20]	107	96	91	79	16	17	0.0794	0.0937	0.8511
Tsai[21]	408	286	326	231	82	55	0.1151	0.1993	0.5798

Abbreviation: HWE, Hardy–Weinberg equilibrium.
[a]The *P*-value of HWE determined by the χ^2-test.

Table 3 OR (95% CI) of the association of the T174 M polymorphism and hypertension in different subgroups under the dominant genetic contrast

Genotype contrast	*Population*	*Study numbers*	$P_{heterogeneity}$	P-*value*[a]	*OR*	*95% CI*
Dominant model (MM + MT *vs.* TT)	Overall	16	0.002[b]	0.24	1.14	0.92–1.41
	Han Chinese	13	0.0005[b]	0.45	1.11	0.84–1.47
	Non-Han Chinese minorities	3	0.57[c]	0.13	1.23	0.94–1.62
	SBP⩾160 mm Hg, DBP⩾95 mm Hg[d]	3	0.27[c]	0.03	1.71	1.07–2.74

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; OR, odds ratio; SBP, systolic blood pressure.
[a]The *P*-value of OR determined by the *Z*-test.
[b]Random-effects estimate.
[c]Fixed-effect estimate.
[d]SBP⩾160 mm Hg and/or DBP⩾95 mm Hg hypertension population.

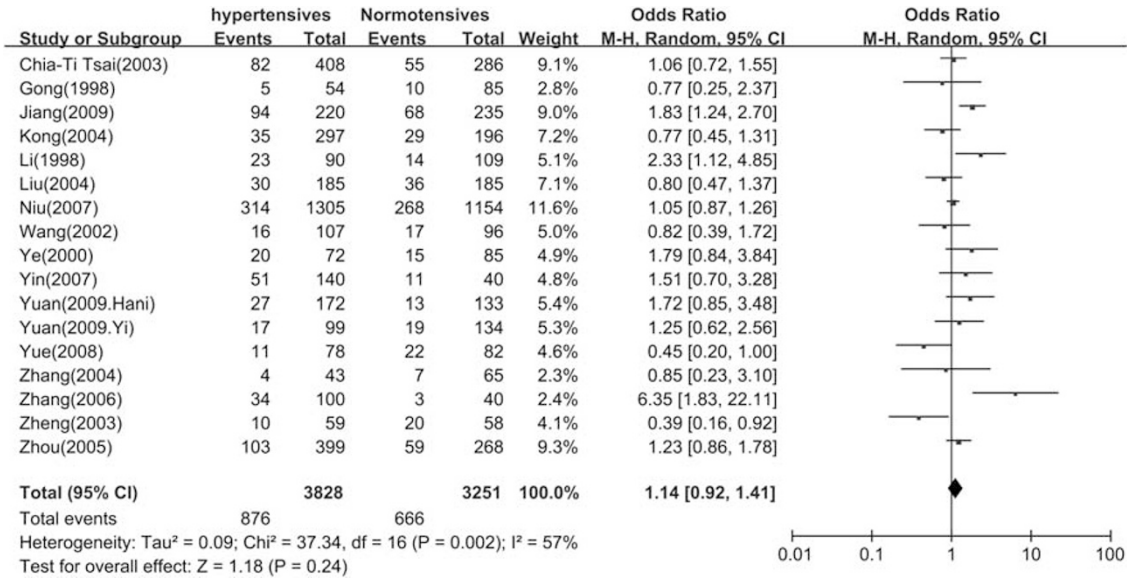

Figure 1 Meta-analysis examining the overall association between the T174M polymorphism and hypertension under the dominant genetic model (MM+MT *vs.* TT). 'Events' indicates the total count of individuals with the MM+MT genotypes. 'Total' indicates the total number of individuals. A full color version of this figure is available at the *Hypertension Research* journal online.

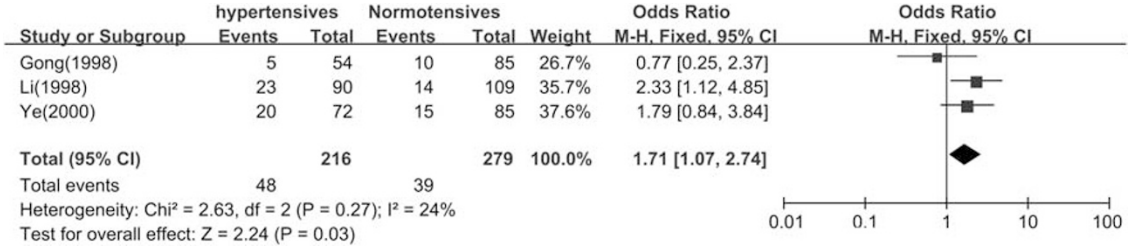

Figure 2 Meta-analysis examining the association between the T174M polymorphism and systolic (SBP) $\geqslant$160 mm Hg and/or diastolic (DBP) $\geqslant$95 mm Hg hypertension under the dominant genetic model (MM+MT *vs.* TT). 'Events' indicates the total number of the MM+MT genotype individuals and 'Total' indicates the total number of the MM+MT genotype plus the TT genotype individuals. A full color version of this figure is available at the *Hypertension Research* journal online.

In the subgroup analysis by ethnicity, all studies were categorized into two groups: Han Chinese and non-Han Chinese minorities. For the latter, there was only one study that considered Kazakh, Yi, Hani and Aims populations. The 174M allele was more common in Han Chinese cases and controls (13.09% and 11.24%, respectively) than in non-Han Chinese minorities (10.88% and 8.87%, respectively). For Han Chinese, no evidence of association between the T174M polymorphism and hypertension in the dominant genetic model could be found (MM+MT *vs.* TT: P=0.45, OR=1.11, 95% CI 0.84–1.47, $P_{\text{heterogeneity}}$=0.0005, I^2=66%, random-effects model; Table 3). For non-Han Chinese minorities, no significant between-study heterogeneity existed ($P_{\text{heterogeneity}}$=0.57), and the fixed-effects model was used to pool the results. As with the Han Chinese, no association was found between the T174M polymorphism and hypertension in the minority populations (Table 3).

For the subgroup analysis based on different diagnostic standards, the data from three studies[9,17,18] were combined to form a hypertensive group (SBP $\geqslant$160 mm Hg and/or DBP $\geqslant$95 mm Hg, 1978 WHO criteria.[40]) In this subgroup, a significant association was found in the dominant genetic model and the between-study heterogeneity was insignificant (MM+MT *vs.* TT: P=0.03, OR=1.71, 95% CI 1.07–2.74, $P_{\text{heterogeneity}}$=0.27. I^2=24%, fixed-effects model; Figure 2).

Sensitivity analysis

To investigate the impact of individual data sets on the pooled OR, we sequentially deleted data from single studies involved in the meta-analysis. No individual study had an undue influence on the pooled ORs, and the between-study heterogeneity still existed for all subjects and the subgroup analysis of Han Chinese when any single study was excluded.

Publication bias

A Begg's funnel plot and Egger's test were performed to assess the publication bias in the literature. As shown in Figure 3, the shape of the funnel plot did not reveal any evidence of obvious asymmetry in the dominant model, and the Egger's test suggested an absence of publication bias among all studies (t=0.26, P=0.800 for MM+MT *vs.* TT).

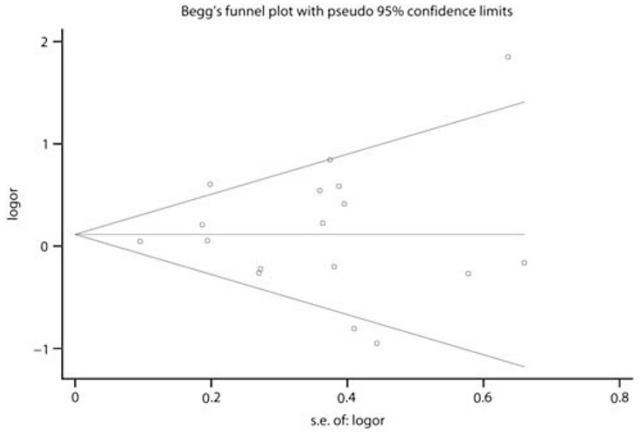

Figure 3 Begg's funnel plot analysis was used to detect publication bias for the dominant model (MM+MT *vs.* TT). No asymmetry was found as indicated by the *P*-value of the Egger's test.

DISCUSSION

The literature examining the relationship between the T174M polymorphism and EH risk in the Chinese population was replete with small studies with conflicting findings. No clear consensus has been reached. Therefore, we performed the present meta-analysis on the Chinese population that included 16 studies from 12 provinces with 3828 cases and 3251 controls. Only the dominant genetic model was selected to reduce the chance of false-positive findings. Unfortunately, we were unable to identify a significant association between the T174M polymorphism and hypertension in all subjects. However, several potential explanations may explain the lack of association between them in the population.

First, it should be noted that hypertension is a complex polygenic disease. A single polymorphism or gene likely has weak effects on the individual's phenotype, as complex traits presumably arise from multiple interacting polymorphisms or genes. A study by Hegele *et al.*[41] showed that the *AGT* T174M polymorphism only accounted for 3.1% of the total variation in SBP in men. Some previous studies revealed that the T174M variant was in tight linkage disequilibrium with other variants such as coding region variants, promoter variants and other yet unknown functional *AGT* polymorphisms.[5,42–44] Therefore, it is necessary to evaluate the combined effect of T174M with other relevant polymorphisms in the *AGT* gene or different genes. The results from Yuan *et al.*[13] suggested there was no evidence of association between T174M polymorphism by itself with hypertension in the Hani minority in China. However, when the T174M polymorphism was analyzed in combination with the M235T variant in the coding region, a significantly elevated risk of hypertension (OR=1.62, 95% CI 1.02–2.59; P=0.043) could be found. A meta-analysis by Ji *et al.*[45] reported that the M235T variant increases the risk of hypertension in the Chinese population (OR=1.54, 95% CI 1.16–2.03, P=0.002), whereas the current meta-analysis has indicated no significant effect of the T174M variant on the incidence of hypertension. Owing to the low frequency of T174M, the statistical power of the research might be limited to detecting differences in OR estimates. Consequently, given that our study focused on the effect of a single polymorphism to determine the genetic determinants of EH, negative findings were not surprising. With a tight linkage disequilibrium between the M235T and T174M polymorphisms, the relationship between M235T and EH might partially be attribute to the effect of T174M. Additional well-designed studies with a larger population, especially studies investigating the combined effect of T174M and other polymorphisms are needed to fully elucidate the relationships between the polymorphisms and EH in the future.

Second, hypertension is an acknowledged multi-factorial disease. Beside genetic background, environmental factors and individual biological characteristics may also influence the occurrence and development of hypertension. The former includes salt intake, smoking and alcohol consumption, and the latter includes race, age, gender, body mass index and BP. For example, in at least one study, age was a determinant attribute of the penetrance of genetic variants, and the age-dependent genetic effects could not be ignored.[46] Hiroyasu *et al.*[47] reported that there was a higher prevalence of the T174M variant among persons with hypertension onset $<$55 years compared with those with later onset. Without comprehensively considering these factors, any analysis may fail in exploring the independent role of suspected polymorphism in hypertension.

China is a very large multi-ethnic country with 56 identified ethnic groups. Among these groups, Han Chinese are the largest ethnic group, making up over 93% of the total population.[48] In the subgroup analysis, we divided all studies into two subgroups: Han Chinese and non-Han Chinese minorities. No significant association between EH and the T174M polymorphism was observed among studies considering Han Chinese. These results were in accordance with the results for the overall population. For non-Han Chinese minorities, a negative result was also obtained. In this subgroup, the genetic background was quite complex and four ethnic minorities were included: Kazakh, Yi, Hani and Aims. Moreover, both the studies and population of non-Han Chinese minorities were limited. Interestingly, a statistically significant association of the T174M polymorphism with the hypertensive group (SBP $\geqslant$160 mm Hg and/or DBP $\geqslant$95 mm Hg) was detected when different diagnostic standards were used (P=0.03, OR=1.71, 95% CI 1.07–2.74). The result might be worth deliberating because the pooled sample size of three studies was relatively small (216 cases and 279 controls). A sampling bias might exist, which would lead to the increase in the probability of a false-positive (type I error). Thus, after considering the possible bias, the positive results must be considered with caution.

In the present meta-analysis, the frequency of the 174M allele varied widely across the populations of Chinese and Han Chinese, which suggested that there was considerable heterogeneity in these populations. The genetic background of the Chinese population was intricate owing to the large number of ethnicities included. Furthermore, some studies[49,50] indicate that the genetic profile of the Han Chinese is mixed, and heterogeneity could exist. Sensitivity analysis was performed to investigate the heterogeneity source in both the overall and the subgroup analyses. The analysis indicated that the corresponding pooled ORs were not materially altered, thus indicating our results were statistically robust. Heterogeneity, however, still existed in the sensitivity analysis. It was possible that differences in diagnostic standards across the studies were a source of heterogeneity. In addition, heterogeneity might also result from specific clinical characteristics.

Our findings on the T174M polymorphism were different from the results from a meta-analysis by Pereira *et al.*,[27] in which a similar population, East Asians, were studied. In that meta-analysis, there was a significant association between the T174M polymorphism and hypertension in the East Asian population (10 studies were included, only 4 of which considered ethnic Chinese subjects). The discrepancy between the Pereira results and the findings of our meta-analysis might be due to the potential publication bias observed in the previous meta-study. In addition, many Chinese studies in local journals were not included in that meta-analysis, potentially leading to a language bias.

To summarize, our meta-analysis failed to provide evidence for the genetic association of the *AGT* gene T174M polymorphism with hypertension risk in the Chinese population. Similar results were found in the subgroup analyses of Han Chinese and non-Han Chinese minorities. However, the T174M polymorphism did present a significant association with the hypertensive group (SBP $\geqslant$160 and/or DBP $\geqslant$95 mm Hg). Additional studies and large case–control studies, especially studies stratified for different stages of hypertension, should be performed to clarify the association between the T174M polymorphism and EH in the Chinese population. Further studies investigating gene–gene, gene–environment and their mutual interactions are certainly important, as well.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

We are very grateful and thank all the participants in this study. This work was financially supported by the National High Technology Research and Development Program (2008AA02Z441) and the National Eleventh Five-year Plan Program (2008BAI52B03) from the Ministry of Science and Technology in People's Republic of China.

1 Kong LZ, Hu SS. *Report on Cardiovascular Disease in China*. Encyclopedia of China Publishing House: Beijing, 2005, pp 86–88.
2 O'Shaughnessy KM. The genetics of essential hypertension. *Br J Clin Pharmacol* 2001; **51**: 5–11.
3 Kurtz TW, Spence MA. Genetics of essential hypertension. *Am J Med* 1993; **94**: 77–84.
4 Perazella MA, Setaro JF. Renin-angiotensin-aldosterone system: fundamental aspects and clinical implications in renal and cardiovascular disorders. *J Nucl Cardiol* 2003; **10**: 184–196.
5 Jeunemaitre X, Soubrier F, Kotelevtsev YV, Lifton RP, Williams CS, Charru A, Hunt SC, Hopkins PN, Williams RR, Lalouel JM, Corvol P. Molecular basis of human hypertension: role of angiotensinogen. *Cell* 1992; **71**: 169–180.
6 Zheng TS, Xiang KS, Sun LQ, Li J, Zhang Y. An analysis of Thr174Met and Met235Thr variants of aniotensinogen gene in Chinese subjects with hypertension, coronary heart disease and/or diabetes mellitus. *Lao Nian Yi Xue Yu Bao Jian* 2003; **9**: 16–19.
7 Zhang Q, Cui TX, Li L, Qiao P. Detection of angiotensinogen gene polymorphism and plasma NO and endothelin in patients with essential hypertension. *J Zhengzhou Med Univ* 2006; **41**: 640–643.
8 Yin SY, Ge LC, Yang SJ. Relationship between angiotensinogen gene T174M polymorphism and essential hypertension. *Xi Bu Yi Xue* 2007; **19**: 1064–1066.
9 Li SY, Li YQ, Wu YD, Luo JB, Wang XY, Ma JH, Lu XS. Correlation between the polymorphism of angiotensinogen gene at position 174 and essential hypertension. *Yi Chuan* 1998; **20**: 18–20.
10 Yue YH, Li ZZ, Wang HI, Yang SH, Cao CF, Wang HJ, Yin J, Zhang JF, Liu H. Relation between M235T and T174M polymorphisms of angiotensinogen gene and cerebral infarction. *Nao Yu Shen Jing Ji Bing Za Zhi* 2008; **16**: 164–167.
11 Niu WQ. *Synergistic Effect of the Renin–Angiotensin–Aldosterone System Genes Polymorphisms with Essential Hypertension Among Han Chinese*. Zhong Guo Xie He Yi Ke Da Xue: Beijing, 2007.
12 Jiang X, Sheng H, Li J, Xun P, Cheng Y, Huang J, Xiao H, Zhan Y. Association between renin–angiotensin system gene polymorphism and essential hypertension: a community-based study. *J Hum Hypertens* 2009; **23**: 176–181.
13 Yuan JL, Tang WR, Chun YN, Ying H, Yang Y, Xiao CJ. Angiotensinogen T174M and M235T variants and hypertension in the Hani and Yi minority groups of China. *Biochem Genet* 2009; **47**: 344–350.
14 Kong XD, Yang YX, Zhang SZ. Haplotypes extending across AGT are associated essential hypertension. *Yi Chuan* 2004; **26**: 797–802.
15 Liu Y, Jin W, Sheng HH, Lu L, Huang W, Yu JD. Angiotensinogen gene polymorphism and essential hypertension. *Shanghai Yi Xue* 2004; **27**: 662–664.
16 Zhang YD, Ce JQ, Shi JP, Qian M, Liu Y. Association of plasma angiotensinogen and angiotensinogen gene polymorphism with ischemic cerebrovascular diseases. *Zhongguo Lin Chuang Shen Jing Ke Xue* 2004; **12**: 230–233.
17 Ye Q, Wu KC, Xie LD, Lin JY, Lin CR. The association between the polymorphism of renin-angiotensinogen genes and essential hypertension. *Zhongguo Xin Xue Guan Bing Za Zhi* 2000; **28**: 169.
18 Gong YQ, Dou XW, Chen BX. Association analysis of angiotensinogen gene variants with essential hypertension. *J Shangdong Med Univ* 1998; **36**: 186–188.
19 Zhou L, Li NF, Wang XL, Zhang DL, Wang J, Ouyang WJ, Zhou KM, Bu KL. Distributer characteristics of angiotensiongen (AGT) gene T17M polymorphism in Kazakans of Xinjiang. *Yi Xue Fen Zi Sheng Wu Xue Za Zhi* 2005; **2**: 162–165.
20 Wang JH, Lin CM, Wang LS, Lai NS, Chen DY, Cherng JM. Association between molecular variants of the angiotensinogen gene and hypertension in Amis tribes of eastern Taiwan. *J Formos Med Assoc* 2002; **101**: 181–188.
21 Tsai CT, Fallin D, Chiang FT, Hwang JJ, Lai LP, Hsu KL, Tseng CD, Liau CS, Tseng YZ. Angiotensinogen gene haplotype and hypertension: interaction with ACE gene I allele. *Hypertension* 2003; **41**: 9–15.
22 Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruilope L, Rynkiewicz A, Schmieder RE, Boudier HA, Zanchetti A, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Erdine S, Kiowski W, Agabiti-Rosei E, Ambrosioni E, Lindholm LH, Viigimaa M, Adamopoulos S, Agabiti-Rosei E, Ambrosioni E, Bertomeu V, Clement D, Erdine S, Farsang C, Gaita D, Lip GJM, Manolis AJ, Nilsson PM, O'Brien E, Ponikowski P, Redon J, Ruschitzka F, Tamargo J, van Zwieten P, Waeber B, Williams B. 2007 Guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2007; **25**: 1105–1187.
23 Ogihara T, Kikuchi K, Matsuoka H, Fujita T, Higaki J, Horiuchi M, Imai Y, Imaizumi T, Ito S, Iwao H, Kario K, Kawano Y, Kim-Mitsuyama S, Kimura G, Matsubara H, Matsuura H, Naruse M, Saito I, Shimada K, Shimamoto K, Suzuki H, Takishita S, Tanahashi N, Tsuchihashi T, Uchiyama M, Ueda S, Ueshima H, Umemura S, Ishimitsu T, Rakugi H. The Japanese society of hypertension guidelines for the management of hypertension (JSH 2009). *Hypertens Res* 2009; **32**: 3–107.
24 Woolf B. On estimating the relation between blood group and disease. *Ann Hum Genet* 1955; **19**: 251–253.
25 Pereira TV, Rudnicki M, Cheung BM, Baum L, Yamada Y, Oliveira PS, Pereira AC, Krieger JE. Three endothelial nitric oxide (NOS3) gene polymorphisms in hypertensive and normotensive individuals: meta-analysis of 53 studies reveals evidence of publication bias. *J Hypertens* 2007; **25**: 1763–1774.
26 Chen Y, Pei J. An assessment of a TNF polymorphic marker for the risk of HCV infection: meta-analysis and a new clinical study design. *Infect Genet Evol* 2009; **9**: 1356–1363.
27 Pereira TV, Nunes AC, Rudnicki M, Yamada Y, Pereira AC, Krieger JE. Meta-Analysis of the association of 4 angiotensinogen polymorphisms with essential hypertension: a role beyond M235T? *Hypertension* 2008; **51**: 778–783.
28 Pereira TV, Rudnicki M, Franco RF, Pereira AC, Krieger JE. Effect of the G-308A polymorphism of the tumor necrosis factor a gene on the risk of ischemic heart disease and ischemic stroke: a meta-analysis. *Am Heart J* 2007; **153**: 821–830.
29 Wang JL, Li X, Hao PP, Feng X, Chen YG, Zhang Y. Angiotensin II type 1 receptor gene A1166C polymorphism and essential hypertension in Chinese: a meta-analysis. *J Renin Angiotensin Aldosterone Syst* 2010; **11**: 127–135.
30 Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. *Ann Intern Med* 1997; **127**: 820–826.
31 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**: 557–560.
32 Petitti D. *Meta-Analysis, Decision Analysis, and Cost-Effectiveness Analysis*. Oxford University Press: New York, 1994, pp 15–20.
33 Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; **315**: 629–634.
34 Chiang FT, Hsu KL, Tseng CD, Hsiao WH, Lo HM, Chern TH, Tseng YZ. Molecular variant M235T of the angiotensinogen gene is associated with essential hypertension in Taiwanese. *J Hypertens* 1997; **15**: 607–611.
35 Fang YJ, Deng HB, Thomas GN, Tzang CH, Li CX, Xu ZL, Yang M, Tomlinson B. Linkage of angiotensinogen gene polymorphisms with hypertension in a sibling study of Hong Kong Chinese. *J Hypertens* 2010; **28**: 1203–1209.
36 Niu T, Chen C, Yang J, Wang B, Wang Z, Schork N, Fang Z, Xu X. Blood pressure and the T174M and M235T polymorphisms of the angiotensinogen gene. *Ann Epidemiol* 1999; **9**: 245–253.
37 Niu T, Yang J, Wang B, Chen W, Wang Z, Laird N, Wei E, Fang Z, Lindpaintner K, Rogus JJ, Xu X. Angiotensinogen gene polymorphisms M235T/T174M: no excess transmission to hypertensive Chinese. *Hypertension* 1999; **33**: 698–702.
38 Niu T, Xu X, Rogus J, Zhou Y, Chen C, Yang J, Fang Z, Schmitz C, Zhao J, Rao VS, Lindpaintner K. Angiotensinogen gene and hypertension in Chinese. *J Clin Invest* 1998; **101**: 188–194.
39 He JL, Yang GA, Sun HY, Wu LE, Zhang CY, Yuan LH, Yang YM. Association between gene polymorphisms of rennin gene G10631A and angiotensinogen gene C521T and cerebral infarction. *Lin Chuang Shen Jing Bing Xue Za Zhi* 2010; **23**: 95–98.
40 World Health Organization. Arterial hypertension: report of a WHO expert committee. *WHO Tech Rep Ser* 1978; **628**: 7–56.
41 Hegele RA, Brunt JH, Connelly PW. A polymorphism of the angiotensinogen gene associated with variation in blood pressure in a genetic isolate. *Circulation* 1994; **90**: 2207–2212.
42 Corvol P, Jeunemaitre X. Molecular genetics of human hypertension: role of angiotensinogen. *Endocr Rev* 1997; **18**: 662–677.
43 Dickson ME, Sigmund CD. Genetic basis of hypertension: revisiting angiotensinogen. *Hypertension* 2006; **48**: 14–20.
44 Cvetkovic B, Keen HL, Zhang X, Davis D, Yang B, Sigmund CD. Physiological significance of two common haplotypes of human angiotensinogen using gene targeting in the mouse. *Physiol Genomics* 2002; **11**: 253–262.
45 Ji LD, Zhang LN, Shen P, Wang P, Zhang YM, Xing WH, Xu J. Association of angiotensinogen gene M235T and angiotensin-converting enzyme gene I/D polymorph-

isms with essential hypertension in Han Chinese population: a meta-analysis. *J Hypertens* 2010; **28**: 419–428.
46 Shi G, Gu CC, Kraja AT, Arnett DK, Myers RH, Pankow JS, Hunt SC, Rao DC. Genetic effect on blood pressure is modulated by age: the hypertension genetic epidemiology network study. *Hypertension* 2009; **53**: 35–41.
47 Iso H, Harada S, Shimamoto T, Sato S, Kitamura A, Sankai T, Tanigawa T, Iida M, Komachi Y. Angiotensinogen T174M and M235T variants, sodium intake and hypertension among non-drinking, lean Japanese men and women. *J Hypertens* 2000; **18**: 1197–1206.
48 Cavalli-Sforza LL. The Chinese human genome diversity project. *Proc Natl Acad Sci USA* 1998; **95**: 11501–11503.
49 Xu S, Yin X, Li S, Jin W, Lou H, Yang L, Gong X, Wang H, Shen Y, Pan X, He Y, Yang Y, Wang Y, Fu W, An Y, Wang J, Tan J, Qian J, Chen X, Zhang X, Sun Y, Zhang X, Wu B, Jin L. Genomic dissection of population substructure of Han Chinese and its implication in association studies. *Am J Hum Genet* 2009; **85**: 762–774.
50 Wen B, Li H, Lu D, Song X, Zhang F, He Y, Li F, Gao Y, Mao X, Zhang L, Qian J, Tan J, Jin J, Huang W, Deka R, Su B, Chakraborty R, Jin L. Genetic evidence supports demic diffusion of Han culture. *Nature* 2004; **431**: 302–305.