Original Article

jraas

Journal of the Renin-Angiotensin-Aldosterone System
January-March 2021: 1–12

DOI: 10.1177/1470320321995074
journals.sagepub.com/home/jra
SAGE

Association between angiotensin converting enzyme gene polymorphism and essential hypertension: A systematic review and meta-analysis

Mingyu Liu[1], Jian Yi[2] and Wenwen Tang[3]

Abstract

Background: The current meta-analytic study explored the relation between ACE gene insertion/deletion (I/D), and the risk of EH by reviewing relevant trials so as to determine the association between Angiotensin Converting Enzyme (ACE) gene polymorphism and essential hypertension (EH) susceptibility.

Methods: Relevant studies published before May 2019 were collected from the PubMed, Cochrane, Embase, CNKI, VANFUN, and VIP databases.

Results: Fifty-seven studies involving a total of 32,862 patients were included. These studies found that ACE gene D allele was associated with higher EH susceptibility in allelic model, homozygote model, dominant model, and regressive model, and that Asian population with ACE gene D allele showed a higher EH susceptibility in all these models. Moreover, ACE gene D allele was found closely related to a higher EH susceptibility in the subgroups of HWE, NO HWE, Caucasian population, and Mixed population, with the majority being males in allelic model, homozygote model, and regressive model and the majority being females in allelic model.

Conclusion: ACE gene D allele is associated with an overall higher EH susceptibility, which is confirmed in the subgroup analysis of Asian population, HWE, NO HWE, Caucasian population, and Mixed population.

Keywords

Angiotensin converting enzyme, gene polymorphism, essential hypertension, meta-analysis

Date received: 30 August 2019; accepted: 21 January 2021

Introduction

Essential hypertension (EH), abbreviated as hypertension, is a common and frequently-occurring disease mainly manifested by elevated blood pressure, and it remains one of the principal causes of death in cardiovascular diseases. With the acceleration of population aging and the growing number of obese people, the prevalence rate of EH shows an increasing trend in both developed and developing countries. Hypertension is a disease prominently featured by family clustering. The incidence rate of hypertension in children whose parents both suffer from the health problem can be as high as 46%, and about 60% of hypertensive patients can be asked about family history.[1–3]

Key gene dominant inheritance and polygene associated inheritance are the two main modes of inheritance of hypertension. In the genetic phenotype of hypertension, occurrence, height, and other factors related to blood pressure complications, such as obesity, are also hereditary, and the incidence of elevated blood pressure can be hereditary. Candidate genes for hypertension include renin–angiotensin system (RAS) genes, sodium system related genes, signal transduction pathway related genes, and endothelin system genes. Angiotensin converting enzyme (ACE) is an important enzyme in the RAS system. The relationship between this gene polymorphism and the genetic

[1]Ninth Hospital of Wuhan, Wuhan City, Hubei Province, China
[2]Department of Endocrinology, Ninth Hospital of Wuhan, Wuhan City, Hubei Province, China
[3]Department of Cardiology, Ninth Hospital of Wuhan, Wuhan City, Hubei Province, China

Corresponding author:
Mingyu Liu, Ninth Hospital of Wuhan, No. 20, Jilin Street, Qingshan District, Wuhan City, Hubei Province 430081, China.
Email: mingyul_liumy@163.com

heterogeneity of hypertension has been extensively researched by scholars around the world.[4,5]

The relation between ACE gene polymorphism and essential hypertension research is currently a research hot spot, and most research results include ACE gene polymorphism and the pathogenesis of EH. Besides, there is a certain relationship between the risk factors of cardiovascular diseases. Therefore, whether the ACE gene I/D polymorphism can be employed as a clinical and subclinical marker for the prognosis observation, diagnosis, and treatment of essential hypertension still needs further research. This meta-analysis was performed with all available literature to obtain updated evidence about the association between ACE gene insertion/deletion (I/D) and EH susceptibility.

Materials and methods

Searching strategy

To identify studies on the association between ACE gene insertion/deletion (I/D) and the risk of EH, relevant studies published before May 2019 were retrieved from the Cochrane, Pubmed, Embase, CNKI, VANFUN, and VIP databases. The references of all the identified articles were also retrieved to identify additional related studies. The search terms were as follows: polymorphism, variant, genotype, gene, angiotensin converting enzyme, ACE, hypertension, essential hypertension, and EH. These terms were searched in combination with "AND" or "OR." The literature review was performed independently by two investigators, with a third resolving any disputes as needed.

Following the PICOS (Participants, Interventions, Comparisons, Outcomes, and Study Design) principle, the key search terms included (P) patients with EH; (I) detection of ACE gene polymorphism; (C/O) comparison of ACE gene polymorphism between the EH group and the control group; (S) case-control trial or cohort study.

Study selection criteria

Included studies met the following criteria: (1) case-control studies or cohort studies; (2) the subjects in the case group were patients with EH; (3) the subjects in the control group were healthy controls or patients without EH; (4) the research factors were ACE gene insertion/deletion (I/D); and (4) articles were written in English or Chinese.

Studies were excluded for meeting the following criteria: (1) repeated articles or results; (2) clear data errors; (3) case reports, case-control studies, theoretical research, conference reports, systematic reviews, meta-analyses, or other forms of research or comment that were not designed in a randomized controlled manner; (4) irrelevant outcomes; and (5) lack of a comparable control group.

Two investigators independently determined whether studies met the inclusion criteria, with a third resolving any disputes as needed.

Data extraction and quality assessment

Two categories of information were extracted from each included study: basic information and primary study outcomes. Basic information relevant to this meta-analysis was as follows: author names, year of publication, country, ethnicity, sample size, age, polymorphism, and genotyping method. Primary clinical outcomes relevant to this analysis were genotype frequencies (ACE gene insertion/deletion (I/D)) in the EH group and control groups. The data extraction was performed independently by two investigators, with a third resolving any disputes as needed.

Statistical analysis

STATA v12.0 (TX, USA) was used for all statistical analyses. Heterogeneity in the study results was assessed using chi-squared and I^2 tests, and appropriate analysis models (fixed-effect or random-effect) were determined. A chi-squared $p \leqslant 0.05$ and an $I^2 > 50\%$ indicated high heterogeneity, and thus a random-effects model was used. A chi-squared $p > 0.05$ and an $I^2 \leqslant 50\%$ indicated acceptable heterogeneity, and thus a fixed-effects model was used instead. Egger's test and Begg's test were performed to determine publication bias. On condition that the Hady Weinberg equilibrium (HWE) genetic balance test was neither provided in the original text nor performed in the control group, Stata v12.0 was used to obtain corresponding results (p value). Five commonly used gene models were selected for this meta-analysis: allelic model (D vs I), homozygote model (DD vs II), heterozygote model (DI vs II), dominant model (DD + DI vs II), and regressive model (DD vs DI + II). All the indexes and statistics were analyzed by OR and 95%CI.

Overview of included studies

A total of 877 articles were screened in the initial key word search, of which 786 were excluded after title/abstract review. The remaining 91 articles were subject to a complete full-text assessment, and as a result, 34 articles were excluded due to the following reasons: (1) theoretical research (11); (2) without clinical outcomes (18); (3) repeated articles (2); and (4) lack of a control group (3). We ultimately identified 57 studies[6–62] that met the inclusion criteria of the current meta-analysis, which incorporated a total of 16,298 EH patients in the EH group and 16,564 healthy controls or patients without EH in the

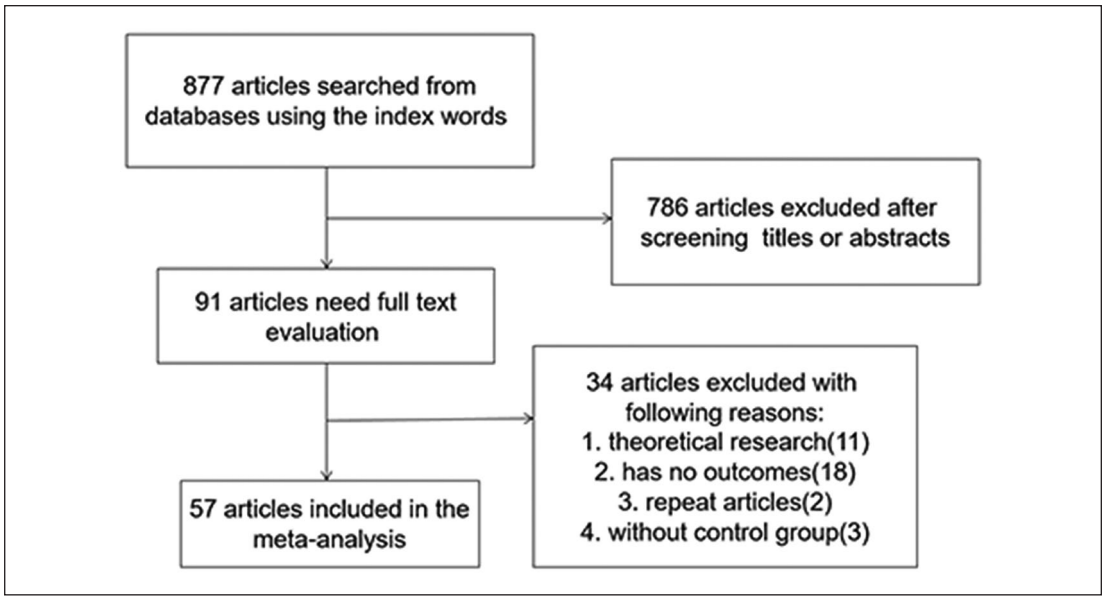

Figure 1. Literature search and selection strategy.

control group. Study selection is outlined in Figure 1. Table 1 summarizes the basic information of each study, including author names, year of publication, country, ethnicity, sample size, age, polymorphism, and genotyping method.

Meta-analysis of ACE gene insertion/deletion (I/D) polymorphism and EH susceptibility

All the included studies reported the association between ACE gene insertion/deletion (I/D) polymorphism and EH susceptibility. In view of the significant heterogeneity between studies (chi-squared $p < 0.05$ and $I^2 > 50\%$), a random-effects model was established to analyze the five gene models in all the subgroup analyses except for allelic model in the subgroup of Caucasian (D vs I) (chi-squared $p > 0.05$ and $I^2 < 50\%$).

The results suggested that ACE gene D allele was associated with a higher EH susceptibility as compared with ACE gene I allele, as evidenced by the following statistics: allelic model (D vs I) (OR: 2.273, 95%CI: 2.068–2.499); homozygote model (DD vs II) (OR: 1.472, 95%CI: 1.247–1.739); dominant model (DD + DI vs II) (OR: 1.178, 95%CI: 1.053–1.319); and regressive model (DD vs DI + II) (OR: 1.422, 95%CI: 1.240–1.630).

The subgroup analysis also indicated that the Asian population with ACE gene D allele was associated with a higher EH susceptibility as compared with those with ACE gene I allele, as demonstrated by the following data: allelic model (D vs I) (OR: 2.199, 95%CI: 1.991–2.430); homozygote model (DD vs II) (OR: 1.545, 95%CI: 1.314–1.817); dominant model (DD + DI vs II) (OR: 1.189, 95%CI: 1.066–1.326); regressive model (DD vs DI + II) (OR: 1.488, 95%CI: 1.298–1.706). Moreover, ACE gene D allele was associated with a higher EH susceptibility in the subgroup of HWE, as evidenced by the statistics below: allelic model (D vs I) (OR: 2.158, 95%CI: 1.976–2.356); homozygote model (DD vs II) (OR: 1.394, 95%CI: 1.182–1.644); regressive model (DD vs DI + II) (OR: 1.372, 95%CI: 1.193–1.578). ACE gene D allele was associated with a higher EH susceptibility in the subgroup of NO HWE, as shown by the following results: allelic model (D vs I) (OR: 3.158, 95%CI: 1.948–5.121); regressive model (DD vs DI + II) (OR: 1.782, 95%CI: 1.070–2.967). The Caucasian population with ACE gene D allele were associated with a higher EH susceptibility, as demonstrated by the following statistics: allelic model (D vs I) (OR: 2.448, 95%CI: 2.021 2.965). The Mixed population with ACE gene D allele was associated with a higher EH susceptibility, as suggested by the data below: allelic model (D vs I) (OR: 2.516, 95%CI: 1.289–4.911). All these results were shown in Figures 2 and 3 and Table 2.

Meta-analysis of ACE gene insertion/deletion (I/D) polymorphism and EH susceptibility in males

Eight studies[9,11,16,23,52,53,55,57] involving a total of 7124 EH patients in the EH group and 6967 healthy controls or patients without EH in the control group reported the association between ACE gene insertion/deletion (I/D) polymorphism and EH susceptibility in males. Studies that were significantly heterogeneous (chi-squared $p < 0.05$ and $I^2 > 50\%$) were analyzed using a random-effects

Table 1. The basic characteristics description of included studies.

Study	Country	Ethnicity	No. of patients		Age		Genotype of EH group			Genotype of control group		
			EH group	Control group	EH group	Control group	II	ID	DD	II	ID	DD
Yi et al.[8]	China	Asian	198	131	50	42	67	95	36	34	69	28
Yi et al.[8]	China	Asian	120	102	53	41	22	74	24	26	50	26
Fan et al.[9]	China	Asian	921	951	—	—	311	427	183	333	454	164
Fan et al.[9]	China	Asian	285	312	—	—	113	126	46	113	156	40
Wang Xiaoyun[10]	China	Asian	81	30	65.85	65.23	38	9	34	18	7	5
Yuan Fengxian[11]	China	Asian	69	99	50.7	—	15	30	24	39	45	14
Xu Xiangjun[18]	China	Asian	28	29	64.43	61.48	12	11	5	10	13	6
Tian Lihong[19]	China	Asian	56	40	66.8	64.9	12	20	24	11	21	8
Dong-Ming et al.[12]	China	Asian	146	108	—	—	58	57	31	50	40	18
Lifang[20]	China	Asian	158	314	46.7	35.1	60	69	28	130	153	54
Shi Zhilin[21]	China	Asian	128	150	—	—	47	67	14	62	78	10
Lv Dongxia[22]	China	Asian	102	107	—	—	44	42	16	42	46	19
Liu et al.[23]	China	Asian	100	100	59.4	54.4	13	43	44	21	50	29
Zhang et al.[24]	China	Asian	115	96	—	—	24	51	40	33	45	18
He Fengrong[25]	China	Asian	209	303	49	48.4	77	111	21	124	134	45
He Fengrong[25]	China	Asian	189	303	48.7	48.4	78	87	24	124	134	45
Yun Meiling[26]	China	Asian	106	97	65.84	74.78	59	30	17	39	43	15
Liang Riming[27]	China	Asian	64	122	62.07	61.08	30	18	16	56	50	16
Song Xin et al.[7]	China	Asian	91	109	56.07	50.36	28	43	20	54	41	14
Jiang et al.[13]	China	Asian	220	235	62.2	61.1	83	108	29	110	112	13
Qi Xiaohua[29]	China	Asian	100	100	—	—	39	41	20	32	54	14
Zhao Yan[30]	China	Asian	200	185	58.2	51.9	62	114	24	89	86	10
Niu et al.[14]	China	Asian	1089	926	50.62	52.99	335	501	253	300	451	175
Zhou Biao[31]	China	Asian	112	103	—	—	31	36	45	38	44	21
Gao Bingfeng[32]	China	Asian	78	62	—	—	21	43	14	25	33	4
Dong et al.[33]	China	Asian	120	30	63.64	60.3	51	43	26	94	13	3
Gong Hongtao[34]	China	Asian	200	192	53.7	51.6	58	46	56	74	94	24
Yao Bingju[15]	China	Asian	125	1100	—	—	42	50	33	34	48	28
Lin Huizhong[35]	China	Asian	1380	888	60.6	59.7	534	621	225	346	421	121
Xue et al.[36]	China	Asian	110	43	—	—	28	44	38	19	19	5

(Continued)

Table 1. (Continued)

Study	Country	Ethnicity	No. of patients		Age		Genotype of EH group			Genotype of control group		
			EH group	Control group	EH group	Control group	II	ID	DD	II	ID	DD
Lai Yanxian[37]	China	Asian	108	102	—	—	27	50	27	42	47	13
Fan et al.[16]	China	Asian	3630	826	—	—	1286	1689	626	268	392	158
Jhawat[17]	India	Asian	510	279	—	—	154	250	106	60	140	70
Bin[6]	China	Asian	486	457	62.65	62.67	167	181	138	159	227	71
Liu Longmei et al.[28]	China	Asian	50	50	52.1	52.1	13	16	21	20	18	12
Krishnan et al.[38]	India	Mixed	280	220	43.6	42.7	59	68	81	118	58	44
Amrani et al.[39]	Algeria	Caucasian	75	70	48.1	43.1	25	40	10	43	25	2
Abbas S et al.[40]	India	Mixed	138	116	41.29	40.03	37	83	18	12	70	34
Heidari F et al.[41]	Malaysia	Asian	72	72	47.22	46.92	4	25	43	18	35	19
Rasyid et al.[42]	Indonesia	Asian	104	99	—	—	21	34	49	21	34	44
Srivastava et al.[43]	India	Mixed	222	252	51.6	49.7	42	106	74	16	98	138
Gupta et al.[44]	India	Mixed	106	110	53.9	51.96	27	49	30	33	50	27
Das et al.[45]	India	Mixed	35	35	—	—	12	4	19	14	18	3
Ramachandran et al.[46]	Malaysia	Asian	65	70	58.48	46.2	24	34	7	40	28	2
Dell'omo et al.[47]	Italy	Caucasian	79	16	48	47	7	36	36	2	8	6
Zapolska-Downar et al.[48]	Poland	Caucasian	40	40	24.1	24.7	6	26	8	13	17	10
Fu et al.[49]	Japan	Asian	275	441	61.7	64.9	117	113	45	195	194	52
Demirel et al.[50]	Italy	Caucasian	129	129	45	35.6	23	63	43	20	51	58
Stankovic et al.[51]	Yugoslavia	Caucasian	105	210	—	—	31	85	59	34	115	61
Morshed et al.[52]	Bangladesh	Asian	44	59	47.3	43.5	5	17	22	19	26	14
Gesang et al.[53]	China	Asian	103	123	49	47	29	47	27	48	60	15
Fu Y et al.[54]	China	Asian	235	510	60.9	64.7	5	68	162	20	158	332
Higaki et al.[55]	Japan	Asian	1200	3814	65.9	57.7	525	529	191	1638	1708	468
Bedir et al.[56]	Turkey	Caucasian	165	143	49.8	58.9	23	77	65	19	82	42
Sugiyama et al.[57]	Japan	Asian	711	532	63.8	55.3	290	322	99	200	247	85
Mondorf et al.[58]	Germany	Caucasian	121	125	46.42	47.3	31	55	35	19	66	40
Maeda et al.[59]	Japan	Asian	41	34	59.3	61.1	13	14	14	16	9	9
Vassilikioti et al.[60]	Greece	Caucasian	98	84	—	—	23	45	30	15	40	29
Maguchi et al.[61]	Japan	Asian	84	84	48	48	40	29	15	28	39	17
Ishigami et al.[62]	Japan	Asian	87	95	59.3	57.4	44	26	17	35	43	17

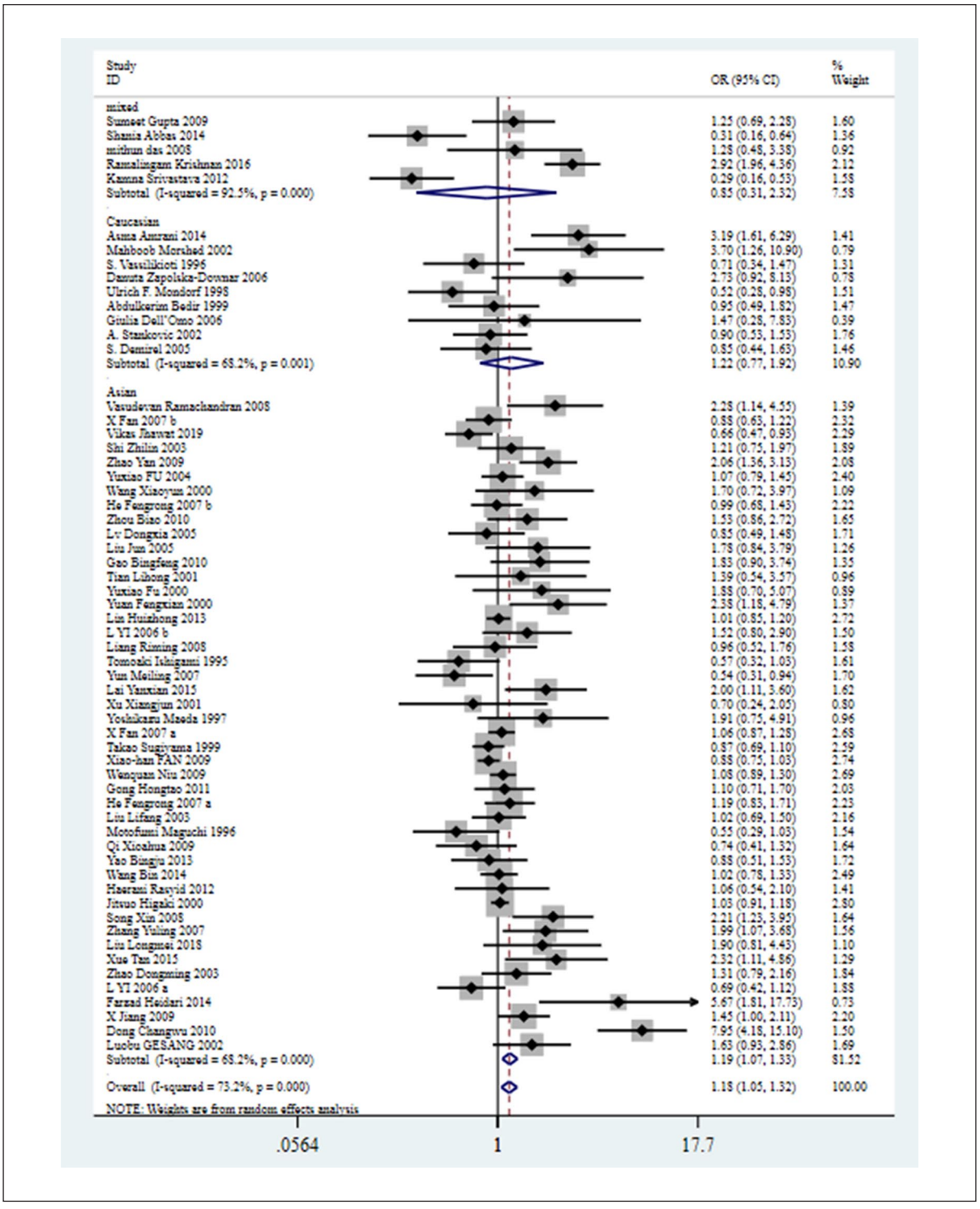

Figure 2. Forest plot of studies evaluating the relationship between ACE I/D polymorphism and EH risk based on dominant model.

model, while the rest studies were analyzed using a fixed-effects model (chi-squared $p > 0.05$ and $I^2 < 50\%$).

The results demonstrated that ACE gene D allele was associated with a higher EH susceptibility in males, as evidenced by the following statistics: allelic model (D vs I) (OR: 1.834, 95%CI: 1.688–1.993); homozygote model (DD vs II) (OR: 1.260, 95%CI: 1.076–1.477); regressive model (DD vs DI + II) (OR: 1.286, 95%CI: 1.117–1.480). All these results were presented in Figure 4 and Table 3.

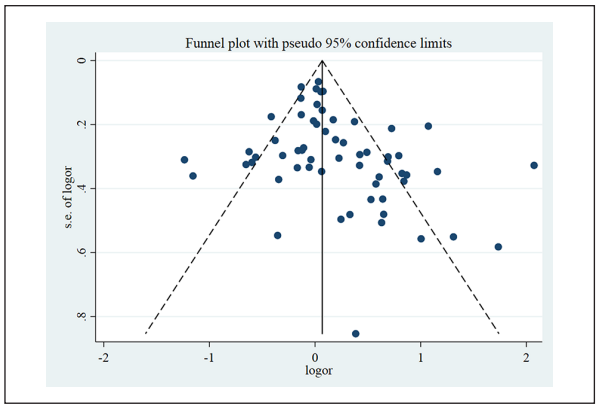

Figure 3. Funnel plot analysis of included studies concerning ACE I/D polymorphism.

Meta-analysis of ACE gene insertion/deletion (I/D) polymorphism and EH susceptibility in females

Eight studies[9,11,16,23,52,53,55,57] involving a total of 7,124 total EH patients in the EH group and 6,967 healthy controls or patients without EH in the control group reported the association between ACE gene insertion/deletion (I/D) polymorphism and EH susceptibility in females. For studies that were significantly heterogeneous (chi-squared $P < 0.05$ and $I^2 > 50\%$), a random-effects model was used to analyze allelic model (D vs I), homozygote model (DD vs II), and regressive model (DD vs DI + II), while for the rest studies (chi-squared $P > 0.05$ and $I^2 < 50\%$), a fixed-effects model was used to analyze the other two models.

Table 2. Meta-analysis of ACE gene insertion/deletion (I/D) polymorphisms and EH susceptibility.

Gene type	Race	*N* (case/control)	OR (95%CI)	*p**	I^2	*p*#	*p* Value	
							Begg	Egger
DD vs II + ID								
	Overall	16,298/16,564	1.422 (1.240, 1.630)	0	75.30%	0	0.005	0.004
	Mixed	781/733	1.274 (0.470, 3.458)	0	93.60%	0.634	0.624	0.477
	Caucasian	856/876	1.185 (0.831, 1.689)	0.011	59.70%	0.349	0.297	0.331
	Asian	14,661/14,955	1.488 (1.298, 1.706)	0	69.50%	0	0.008	0.001
	HWE	15,021/15,507	1.372 (1.193, 1.578)	0	74.00%	0	0.008	0.010
	NO HWE	1277/1057	1.782 (1.070, 2.967)	0	79.90%	0.026	0.404	0.578
DD+ID vs II								
	Overall	16,298/16,564	1.178 (1.053, 1.319)	0	73.20%	0.004	0.021	0.024
	Mixed	781/733	0.850 (0.311, 2.322)	0	92.50%	0.752	0.327	0.274
	Caucasian	856/876	1.219 (0.773, 1.922)	0.001	68.20%	0.394	0.940	0.205
	Asian	14,661/14,955	1.189 (1.066, 1.326)	0	68.20%	0.002	0.004	0.003
	HWE	15,021/15,507	1.109 (0.999, 1.231)	0	64.40%	0.053	0.018	0.031
	NO HWE	1277/1057	1.527 (0.904, 2.578)	0	86.30%	0.114	0.835	0.638
DD vs II								
	Overall	16,298/16,564	1.472 (1.247, 1.739)	0	77.20%	0	0.005	0.008
	Mixed	781/733	1.010 (0.242, 4.212)	0	94.70%	0.989	1.000	0.750
	Caucasian	856/876	1.268 (0.756, 2.127)	0.005	63.90%	0.368	0.211	0.053
	Asian	14,661/14,955	1.545 (1.314, 1.817)	0	71.70%	0	0.003	0.001
	HWE	15,021/15,507	1.394 (1.182, 1.644)	0	73.90%	0	0.006	0.011
	NO HWE	1277/1057	1.920 (0.955, 3.861)	0	85.10%	0.067	0.835	0.813
ID vs II								
	Overall	16,298/16,564	1.037 (0.935, 1.150)	0	61.60%	0.495	0.170	0.169
	Mixed	781/733	0.699 (0.297, 1.644)	0	87.10%	0.411	0.624	0.154
	Caucasian	856/876	1.142 (0.744, 1.755)	0.010	60.10%	0.544	0.144	0.217
	Asian	14,661/14,955	1.039 (0.939, 1.150)	0	56.00%	0.459	0.083	0.074
	HWE	15,021/15,507	0.993 (0.901, 1.094)	0	51.70%	0.881	0.103	0.231
	NO HWE	1277/1057	1.272 (0.786, 2.059)	0	80.10%	0.327	0.404	0.669
D vs I								
	Overall	16,298/16,564	2.273 (2.068, 2.499)	0	80.40%	0	0	0
	Mixed	781/733	2.516 (1.289, 4.911)	0	92.60%	0.007	0.624	0.935
	Caucasian	856/876	2.448 (2.021, 2.965)	0.172	30.80%	0	0.095	0.105
	Asian	14,661/14,955	2.199 (1.991, 2.430)	0	79.60%	0	0	0
	HWE	15,021/15,507	2.158 (1.976, 2.356)	0	74.40%	0	0	0
	NO HWE	1277/1057	3.158 (1.948, 5.121)	0	91.00%	0	0.532	0.228

*p value of Heterogeneity chi-squared.
#p value of Pooled statistic.

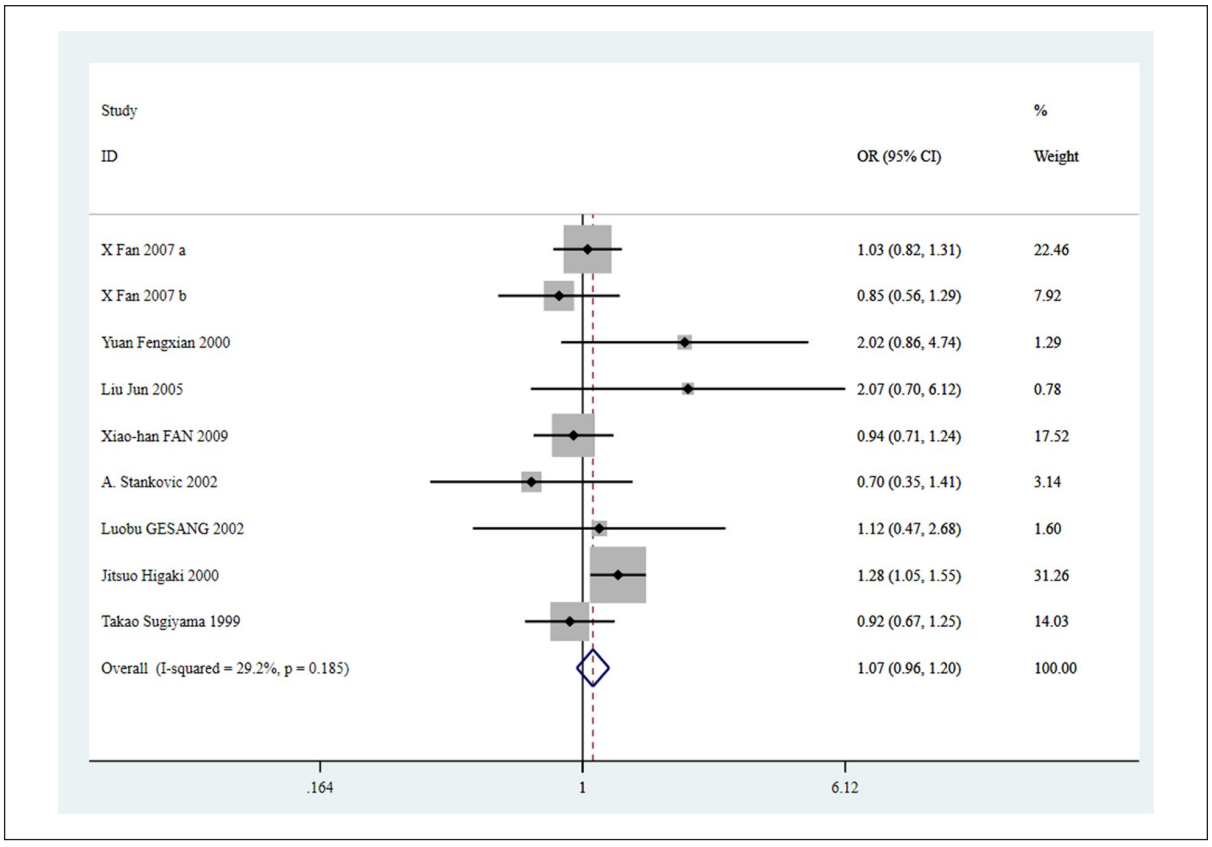

Figure 4. Forest plot of studies evaluating the relationship between ACE I/D polymorphism and EH risk in males based on dominant model.

Table 3. Meta-analysis of ACE gene insertion/deletion (I/D) polymorphisms and EH susceptibility in male.

Gene type	*N* (case/control)	OR (95%CI)	*p**	I^2	*p*#	*p* Value	
						Begg	Egger
DD vs II + ID	7124/6967	1.286 (1.117, 1.480)	0.062	46.20%	0	0.754	0.451
DD+ID vs II	7124/6967	1.254 (0.966, 1.628)	0.185	29.20%	0.211	0.754	0.995
DD vs II	7124/6967	1.260 (1.076, 1.4766)	0.036	51.60%	0.089	0.917	0.7
ID vs II	7124/6967	1.008 (0.896, 1.135)	0.477	0.00%	0.889	1	0.553
D vs I	7124/6967	1.834 (1.688, 1.993)	0.065	45.60%	0	0.348	0.219

**p* value of Heterogeneity chi-squared.
#*p* value of Pooled statistic.

The results showed that ACE gene D allele was associated with a higher EH susceptibility in females, as evidenced by the following statistics: allelic model (D vs I) (OR: 1.840, 95%CI: 1.582-2.141).

All these results were presented in Figure 5 and Table 4.

Discussion

It is generally believed that EH is caused by the interaction between multi-gene heredity and environment, while the true cause of the disease remains unclear. As the most common epidemic disease in modern times, EH seriously endangers human health and can further lead to coronary atherosclerosis. EH is acknowledged as one of the major risk factors for death and serious diseases, including heart disease, stroke, heart failure, and kidney failure. EH is closely related to multiple factors, and statistics from studies at home and abroad shows that the influence of genetic factors on blood pressure accounts for 30%–50% of all their effects on the pathogenesis of EH.[1–3]

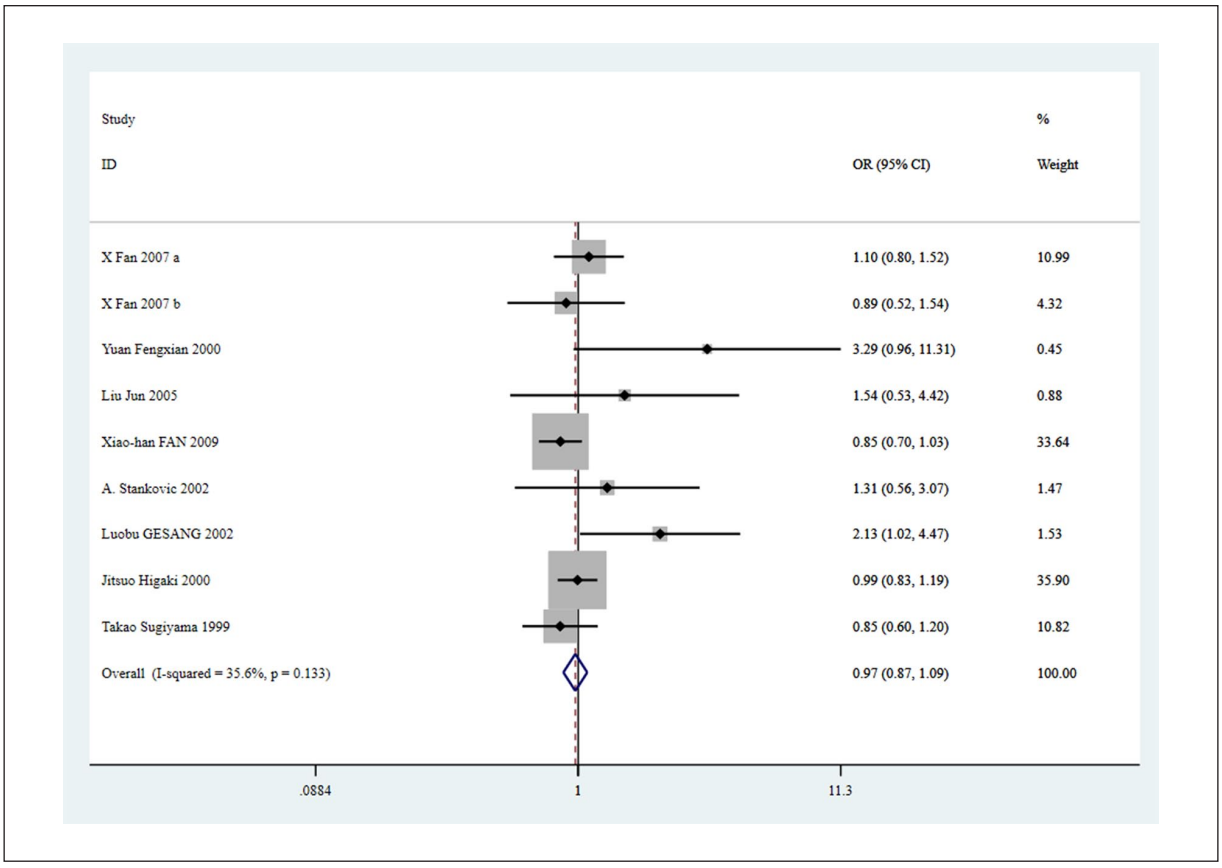

Figure 5. Forest plot of studies evaluating the relationship between ACE I/D polymorphism and EH risk in females based on dominant model.

The renin-angiotensin system (RAS) has significant functions in blood pressure regulation, electrolyte balance, vascular tension, and cardiovascular remodeling. As a membrane binding enzyme, ACE is located in vascular endothelial cells and widely distributed in the body. ACE is a key enzyme of RAS, and it can catalyze angiotensin I into angiotensin II, a strong vasoconstrictor, and slow down inactive shock peptide vasodilation. Given the role of RAS in blood pressure regulation, the ACE gene may be a candidate gene for treating EH.[37–39]

The gene-encoding ACE is an important candidate gene for cardiovascular disease, and its 16 intron insertion/deletion (I/D) polymorphism in the non-coding region can cause the presence or absence of a 287 bp DNA fragment. Studies on high-accutase and Japanese populations demonstrated that ACE insertion/deletion polymorphism accounts for 50% of the variation in plasma ACE levels. Ang II is a powerful vasoconstrictor converted from Ang I by ACE, and it affects the structures of the arterial wall and induces arteriosclerosis by promoting cell growth or extracellular matrix synthesis. ACE inactivates bradykinin and leads to the proliferation of vascular smooth muscle cells.[4–6]

In the present study, we found that ACE gene D allele was associated with a higher EH susceptibility in allelic model, homozygote model, dominant model, and regressive model. The Asian population with ACE gene D allele was related to a higher EH susceptibility in allelic model, homozygote model, dominant model, and regressive model. Moreover, ACE gene D allele was found associated with a higher EH susceptibility in the subgroups of HWE, NO HWE, Caucasian population, and Mixed population. In addition, ACE gene D allele was associated with a higher EH susceptibility in males in allelic model, homozygote model, and regressive model as well as a higher EH susceptibility in females in allelic model.

It should be noted that there were certain limitations in the present analysis, which inevitably precluded more in-depth analyses. First, only articles written in English and Chinese were included. Second, the exclusion/inclusion criteria and the severity of EH differed in various individual studies. Third, environmental factors such as smoking, high-fat diet, antioxidant intake, use of certain lipid-lowering drugs, or hormone varied among the patients. Fourth, only pooled data were analyzed due to the unavailability of individual patient data.

Table 4. Meta-analysis of ACE gene insertion/deletion (I/D) polymorphisms and EH susceptibility in female.

Gene type	*N* (case/control)	OR (95%CI)	*p**	I^2	*p*#	*p* Value	
						Begg	Egger
DD vs II + ID							
	7124/6967	1.206 (0.909, 1.599)	0.004	64.60%	0.194	0.118	0.04
DD + ID vs II							
	7124/6967	0.974 (0.872, 1.087)	0.133	35.60%	0.634	0.076	0.033
DD vs II							
	7124/6967	1.264 (0.903, 1.770)	0.002	67.20%	0.173	0.251	0.033
ID vs II							
	7124/6967	0.953 (0.847, 1.073)	0.749	0.00%	0.427	0.175	0.047
D vs I							
	7124/6967	1.840 (1.582,2.141)	0.026	54.00%	0	0.016	0.017

*p value of Heterogeneity chi-squared.
#p value of Pooled statistic.

Conclusion

Our results indicate that ACE gene D allele is associated with an overall higher EH susceptibility in Asian population, HWE, NO HWE, Caucasian population, and Mixed population in both males and females.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Mingyu Liu https://orcid.org/0000-0001-5317-052X

References

1. Tipnis SR, Hooper NM, Hyde R, et al. A human homolog of angiotensin-converting enzyme. Cloning and functional expression as a captopril-insensitive carboxypeptidase. *J Biol Chem* 2000; 275: 33238–33243.
2. Mengesha HG, Petrucka P, Spence C, et al. Effects of angiotensin converting enzyme gene polymorphism on hypertension in Africa: a meta-analysis and systematic review. *PLoS One* 2019; 14: e0211054.
3. Heidari F, Vasudevan R, Mohd Ali SZ, et al. RAS genetic variants in interaction with ACE inhibitors drugs influences essential hypertension control. *Arch Med Res* 2017; 48: 88–95.
4. Pontremoli R, Sofia A, Tirotta A, et al. The deletion polymorphism of the angiotensin I-converting enzyme gene is associated with target organ damage in essential hypertension. *J Am Soc Nephrol* 1996; 7: 2550–2558.
5. Sasaki M, Oki T, Iuchi 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.
6. Bin W. Relationship between angiotensin converting enzyme and aldosterone synthase gene polymorphisms and essential hypertension in Qiqihar Han population. *J Qiqihar Univ Med* 2014: 2: 2653–2656.
7. Xin S , Xiubo J, Yunjie W, et al. Distribution of ACE gene polymorphism and its high expression in essential hypertension. *Acta Acad Med QingDao Univ* 2008; 44: 209–211.
8. Yi L, Gu YH, Wang XL, et al. Association of ACE, ACE2 and UTS2 polymorphisms with essential hypertension in Han and Dongxiang populations from north-western China. *J Int Med Res* 2006; 34: 272–283.
9. Fan X, Wang Y, Sun K, et al. Polymorphisms of ACE2 gene are associated with essential hypertension and antihypertensive effects of Captopril in women. *Clin Pharmacol Ther* 2007; 82: 187–196.
10. Wang Xiaoyun LK. The relationship between ACE Gene mRNA expression and essential hypertension. *Chin J Prev Control Chronic Dis* 2000; 8: 111–113.
11. Yuan Fengxian GJ. Association between angiotensin 1-converting enzyme gene polymorphism and essential hypertension. *J ChinMed Univ* 2000; 29: 372–373.
12. Dong-Ming Z, Rong-Qiu Z and Wen-Xuan S. ACE gene polymorphism relating to essential hypertension and left ventricular hypertrophy. *Mod Med Health* 2003; 12: 1526–1527.
13. Jiang X, Sheng H, Li J, et al. Association between renin-angiotensin system gene polymorphism and essential hypertension: a community-based study. *J Hum Hypertens* 2009; 23: 176–181.
14. Niu W, Qi Y, Hou S, et al. Haplotype-based association of the renin-angiotensin-aldosterone system genes polymorphisms with essential hypertension among Han Chinese: the Fangshan study. *J Hypertens* 2009; 27: 1384–1391.
15. Yao Bingju LS. Association between angiotensin converting enzyme gene polymorphism and essential hypertension in Hui and Han population of Fujian Province. *China Med* 2013; 8: 1690–1692.
16. Fan XH, Wang YB, Wang H, et al. Polymorphisms of angiotensin-converting enzyme (ACE) and ACE2 are not associated with orthostatic blood pressure dysregulation

in hypertensive patients. *Acta Pharmacol Sin* 2009; 30: 1237–1244.
17. Jhawat V, Gupta S, Agarwal BK, et al. Angiotensin converting enzyme gene insertion/deletion polymorphism is not responsible for antihypertensive therapy induced new onset of type 2 diabetes in essential hypertension. *Clin Med Insights Endocrinol Diabetes* 2019; 12: 1179551418825037.
18. Xu Xiangjun WZ. Study on the relationship between hypertensive cerebral hemorrhage and angiotensin converting enzyme gene polymorphism and serum level. *Stroke Nerv Dis* 2001; 8: 84–87.
19. Tian Lihong TH. Association of angiotensin converting enzyme gene polymorphism with serum level and senile hypertension. *J Postgrad Med* 2001; 5: 15–17.
20. Lifang L. Association of essential hypertension and atherosclerosis with ACE, GNB3, CYP11B2 and alpha-adducin gene polymorphisms in Han population. *Peking Union Med Coll* 2003: 32–105.
21. Shi Zhilin WS. The polymorphism of angiotensin in converting enzyme of essential hypertension patients. *J Clin Intern Med* 2003; 20: 514–516.
22. Lv Dongxia LJ. Association between ACE gene I/D polymorphism and essential hypertension in middle-aged and elderly Han population in Jiamusi area. *Chin J Gerontol* 2005; 5: 531–532.
23. Liu J, Lu FH, Wen PE, et al. The impact of gender factor on the candidate gene study of essential hypertension. *Zhonghua xin xue guan bing za zhi* 2005; 33: 1010–1013.
24. Zhang YL, Zhou SX, Lei J, et al. Association of angiotensin I-converting enzyme gene polymorphism with ACE and PAI-1 levels in Guangdong Chinese Han patients with essential hypertension. *Nan Fang Yi Ke Da Xue Xue Bao* 2007; 27: 1681–1684.
25. He Fengrong CX. Association between ACEI/D gene polymorphism and essential hypertension metabolic syndrome in Wuhan. *J Clin Hematol* 2007; 6: 254–256.
26. Yun Meiling ZJ. Angiotensin converting enzyme gene polymorphism in Hainan Han hypertensive population. *Nat Sci J Hainan Univ* 2007; 25: 265–268.
27. Liang Riming YX. Association between ACE polymorphism and essential hypertension complicated with coronary heart disease. *China Pract Med* 2008; 3: 32–33.
28. Longmei L, Shuangyan Z, Zehua Y, et al. Distribution of ACE gene polymorphism and its high expression in essential hypertension. *Chin J Clin Pathol* 2018; 10: 132–134.
29. Qi Xiaohua CZ. Association between essential hypertension and ACE gene polymorphism in Korean and Han population. *J Jilin Univ* 2009; 35: 906–909.
30. Zhao Yan WF. Insertion/deletion variation in angiotensin converting enzyme gene is associated with susceptibility to essential hypertension in Shanghai Han population. *Mol Cardiol China* 2009; 9: 223–226.
31. Zhou Biao SG. A case-control study on the relationship between ACE gene polymorphism and essential hypertension in Shehan population. *Prev Med* 2010; 22: 1–4.
32. Gao Bingfeng ZY. Association of ACE gene I/D polymorphism with essential hypertension and hypertensive intracerebral hemorrhage. *Shandong Med J* 2010; 50: 39–40.
33. Dong C, Dong M, Xing Q, et al. Relationship between polymorphism of angiotensin converting enzyme gene and different traditional Chinese medicine syndrome in patients with essential hypertension. *Chin J Pathophysiol* 2010; 26: 1545–1548.
34. Gong Hongtao MX. Association between polymorphisms of angiotensin-converting enzyme and aldosterone synthase genes and essential hypertension. *Chin Gen Pract* 2011; 14: 2609–2611.
35. Lin Huizhong CH. Association of ACE, CYP11B2 and alpha-ADDUCIN gene polymorphisms with hypertension in Fujian Han nationality. *Basic Clin Med* 2013; 33: 429–433.
36. Xue T, Shi J, Wang X, et al. Relationship between ACE gene (I/D) polymorphism and familial essential hypertension. *Chin J cardiovasc Rehabil Med* 2015; 24: 127–130.
37. Lai Yanxian GB. Analysis of ACE polymorphism in essential hypertension patients of Uygur and Han nationalities in Xinjiang. *Guanzhou Med J* 2015; 46: 12–15.
38. Krishnan R, Sekar D, Karunanithy S, et al. Association of angiotensin converting enzyme gene insertion/deletion polymorphism with essential hypertension in south Indian population. *Genes Dis* 2016; 3: 159–163.
39. Amrani A, Baba Hamed MB and Mesli Talebbendiab F. Association study between some renin-angiotensin system gene variants and essential hypertension in a sample of Algerian population: case control study. *Ann Biol Clin* 2015; 73: 557–563.
40. Abbas S, Raza ST, Chandra A, et al. Association of ACE, FABP2 and GST genes polymorphism with essential hypertension risk among a North Indian population. *Ann Hum Biol* 2015; 42: 461–469.
41. Heidari F, Vasudevan R, Mohd Ali SZ, et al. Association of insertion/deletion polymorphism of angiotensin-converting enzyme gene among Malay male hypertensive subjects in response to ACE inhibitors. *J Renin Angiotensin Aldosterone Syst* 2015; 16: 872–879.
42. Rasyid H, Bakri S and Yusuf I. Angiotensin-converting enzyme gene polymorphisms, blood pressure and pulse pressure in subjects with essential hypertension in a South Sulawesi Indonesian population. *Acta Med Indones* 2012; 44: 280–283.
43. Srivastava K, Sundriyal R, Meena PC, et al. Association of angiotensin converting enzyme (insertion/deletion) gene polymorphism with essential hypertension in northern Indian subjects. *Genet Test Mol Biomarkers* 2012; 16: 174–177.
44. Gupta S, Agrawal BK, Goel RK, et al. Angiotensin-converting enzyme gene polymorphism in hypertensive rural population of Haryana, India. *J Emerg Trauma Shock* 2009; 2: 150–154.
45. Das M, Pal S and Ghosh A. Angiotensin converting enzyme gene polymorphism (insertion/deletion) and hypertension in adult Asian Indians: a population-based study from Calcutta, India. *Hum Biol* 2008; 80: 303–312.
46. Ramachandran V, Ismail P, Stanslas J, et al. Association of insertion/deletion polymorphism of angiotensin-converting enzyme gene with essential hypertension and type 2 diabetes mellitus in Malaysian subjects. *J Renin Angiotensin Aldosterone Syst* 2008; 9: 208–214.
47. Dell'omo G, Penno G, Pucci L, et al. ACE gene insertion/deletion polymorphism modulates capillary permeability in hypertension. *Clin Sci* 2006; 111: 357–364.

48. Zapolska-Downar D, Siennicka A, Chelstowski K, et al. Is there an association between angiotensin-converting enzyme gene polymorphism and functional activation of monocytes and macrophage in young patients with essential hypertension? *J Hypertens* 2006; 24: 1565–1573.
49. Fu Y, Katsuya T, Matsuo A, et al. Relationship of bradykinin B2 receptor gene polymorphism with essential hypertension and left ventricular hypertrophy. *Hypertens Res* 2004; 27: 933–938.
50. Demirel S, Akkaya V, Cine N, et al. Genetic polymorphisms and endothelial dysfunction in patients with essential hypertension: a cross-sectional case-control study. *Neth Heart J* 2005; 13: 126–131.
51. Stankovic A, Zivkovic M and Alavantic D. Angiotensin I-converting enzyme gene polymorphism in a Serbian population: a gender-specific association with hypertension. *Scand J Clin Lab Invest* 2002; 62: 469–475.
52. Morshed M, Khan H and Akhteruzzaman S. Association between angiotensin I-converting enzyme gene polymorphism and hypertension in selected individuals of the Bangladeshi population. *J Biochem Mol Biol* 2002; 35: 251–254.
53. Gesang L, Liu G, Cen W, et al. Angiotensin-converting enzyme gene polymorphism and its association with essential hypertension in a Tibetan population. *Hypertens Res* 2002; 25: 481–485.
54. Fu Y, Katsuya T, Asai T, et al. Lack of correlation between Mbo I restriction fragment length polymorphism of renin gene and essential hypertension in Japanese. *Hypertens Res* 2001; 24: 295–298.
55. Higaki J, Baba S, Katsuya T, et al. Deletion allele of angiotensin-converting enzyme gene increases risk of essential hypertension in Japanese men: the Suita Study. *Circulation* 2000; 101: 2060–2065.
56. Bedir A, Arik N, Adam B, et al. Angiotensin converting enzyme gene polymorphism and activity in Turkish patients with essential hypertension. *Am J Hypertens* 1999; 12: 1038–1043.
57. Sugiyama T, Morita H, Kato N, et al. Lack of sex-specific effects on the association between angiotensin-converting enzyme gene polymorphism and hypertension in Japanese. *Hypertens Res* 1999; 22: 55–59.
58. Mondorf UF, Russ A, Wiesemann A, et al. Contribution of angiotensin I converting enzyme gene polymorphism and angiotensinogen gene polymorphism to blood pressure regulation in essential hypertension. *Am J Hypertens* 1998; 11: 174–183.
59. Maeda Y, Ikeda U, Ebata H, et al. Angiotensin converting enzyme gene polymorphism in essential hypertension based on ambulatory blood pressure monitoring. *Am J Hypertens* 1997; 10: 786–789.
60. Vassilikioti S, Doumas M, Douma S, et al. Angiotensin converting enzyme gene polymorphism is not related to essential hypertension in a Greek population. *Am J Hypertens* 1996; 9: 700–702.
61. Maguchi M, Kohara K, Okura T, et al. Angiotensin-converting enzyme gene polymorphism in essential hypertensive patients in Japanese population. *Angiology* 1996; 47: 643–648.
62. Ishigami T, Iwamoto T, Tamura K, et al. Angiotensin I converting enzyme (ACE) gene polymorphism and essential hypertension in Japan. Ethnic difference of ACE genotype. *Am J Hypertens* 1995; 8: 95–97.