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The Association of Angiotensin-converting Enzyme I/D and Angiotensinogen M235T Polymorphism Genes with Essential Hypertension: A Meta-analysis

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Abstract

BACKGROUND: Essential or primary hypertension in developing countries has become a major problem. Recent hypertension-related research has revealed susceptibility genes in genome-wide association studies. Several studies have associated angiotensin-converting enzyme (ACE) I/D and angiotensinogen (AGT) M235T polymorphisms with essential hypertension, but results have been inconsistent.

AIM: This meta-analysis aimed to clarify the association of AGT and ACE polymorphisms with the risk of primary hypertension.

METHODS: PubMed, Embase database, Medline, Google Scholar, and Scopus.com, as well portal Garuda (www.garuda.ristekdikti.go.id) and Cochrane were used to retrieve all publications from 2006 to 2020 relating risk factors for hypertension with ACE I/D and AGT M235T polymorphisms. The meta-analysis was conducted from January to April 2020. All association studies were identified and data extracted from each study. Revman 5.3 software was used for meta-analysis to estimate odds ratios (OR) after extracting data and evaluating the quality of the enrolled studies.

RESULTS: Twenty-seven studies (totaling 5105 patients and 5196 controls) were identified. The overall effect suggested ACE I/D was significantly associated with primary hypertension (OR: 95% confidence interval = 1.51 [1.29–1.77], p = 0.004). There was no association between AGT M235T with the risk of essential hypertension.

CONCLUSION: This meta-analysis found a significant association between ACE I/D gene polymorphisms with primary hypertension susceptibility. However, the AGT M235T gene had no association with the risk of primary hypertension. The Adrenoreceptor-beta/Renin-angiotensin System A allele should be considered a risk factor for essential hypertension.

Introduction

Essential or primary hypertension is a treatable disease that involves complex interactions between environmental and genetic factors [1], [2]. In developing countries such as in Asia and Africa, essential hypertension affects 25%–35% of the adult population [3]. In the past decade, many genes have been associated with high blood pressure and hypertension. The most extensively studied candidate genes for essential hypertension are Renin-angiotensin System (RAS) genes, which include angiotensinogen (AGT) and angiotensin-converting enzyme (ACE) genes [4]. Identified in the etiopathogenesis of hypertension, ACE is a key component of RAS [5].

The AGT gene is one of the major structural genes in the RAS pathway and it also regulates AGT expression, particularly the renin substrate. Research showed that the renin substrate is cleaved by renin into angiotensin I and then into vasoactive angiotensin II by ACE [6]. These two genes are the most prominent candidate genes being analyzed for their close association with the development of essential hypertension. However, in some populations, the results were inconclusive. Due to several limitations, the previous meta-analyses were not adequate to determine the actual correlation between ACE and AGT with hypertension because of its complex, multifactorial etiology, and the close but confusing links between Adrenoreceptor-beta/RAS (ADRB/RAS) polymorphisms and ethnicity.

Our present meta-analysis aimed to clarify the association between ACE I/D and AGT M235T gene polymorphisms and the risk of essential hypertension in populations from Asia to Africa, which have almost the same socio-economic conditions as other developing countries. Our meta-analysis results may be able to establish a clearer association in this topic.

Materials and Methods

The PubMed, Embase.com, Medline, Google Scholar, Scopus.com, and Cochrane databases were used to retrieve all publications from 2006 to 2020 relating risk factors for hypertension and single ADRB/ACE polymorphisms. The meta-analysis was conducted from January to April 2020. All association studies were identified and data extracted from each study. The first step in this study involved evaluating the quality of enrolled studies and extracting data. After that, software RevMan 5.3 was used for this meta-analysis to estimate odds ratios (OR). These publications were related to case-control and cross-sectional studies that reported a relation/link between the risk of essential hypertension and ADRB/ACE polymorphisms using the keywords: AGT AND ACE AND polymorphism AND blood pressure OR Hypertension AND Genetic AND Variation to retrieve the related documents. The document retrieval was limited to English-language articles (Figure 1).

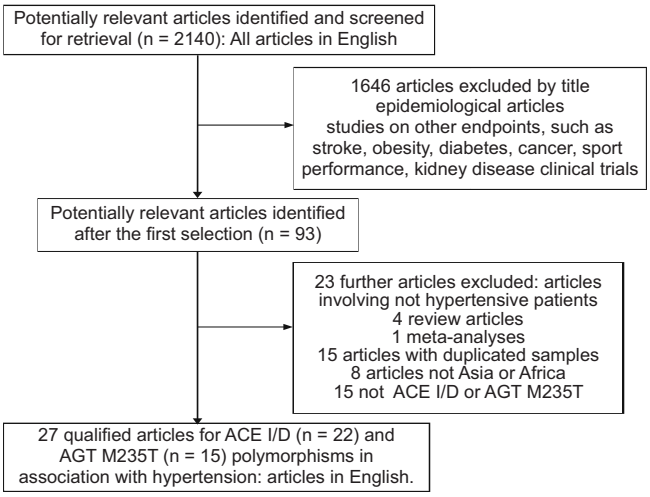

Figure 1: Flowchart of eligibility pathway in our study

Inclusion criteria and data extraction

Inclusion criteria

The following inclusion criteria were used in this meta-analysis: (1) The published articles reported studies of the correlation between ACE I/D or AGT M235T polymorphisms and incidence of essential hypertension; (2) the articles discussed cross-sectional or case-control studies, where the control group included healthy or relatively healthy people without hypertension and the case group was patients with essential hypertension; (3) the articles provided studies of the frequency distribution of the ACE I/D or AGT M235T directly or indirectly in cases and control groups or in the cross-sectional study; (4) genetic polymorphisms of ACE I/D and AGT M235 T were in line with Hardy–Weinberg equilibrium (HWE) or not in equilibrium; and (5) hypertension was defined as the presence of systolic blood pressure measurement of at least 140 mmHg and diastolic blood pressure measurement of at least 90 mmHg. In addition, for ACE and AGT genotypes, there were six ethnic groupings, either from Asia or from Africa (Table 1).

Two investigators (P.H and V.Y.S) extracted data independently and if there were differences, the consensus was reached by discussing or consulting a third party. The following contents were extracted from the studies: The first author's name, year of publication, ethnicity (Asia or Africa) of the study population, the characteristics of each group in cases and controls or cross-sectional study, the genotyping method, controls' source, and sample sizes of cases and controls or cross-sectional study. The allele frequencies and genotypic distributions in both cases and controls or cross-sectional study were calculated. In addition, the HWE status in each group was tested for this study (Table 1).

Exclusion criteria

Articles were excluded if the literature did not provide valid data, was duplicated, or the full text could not be obtained.

Statistical analysis

The pooled OR was calculated to estimate the association between AGT/ACE polymorphisms and essential hypertension and its associated 95% confidence interval (CI). The pooled OR was determined through a Z-test ($p < 0.05$). Heterogeneity was detected by Q test; if an article had an absence of heterogeneity ($I^2 < 50\%$), the Mantel–Haenszel method was used to calculate pooled OR and 95% Cis/fixed effect. A random-effect model was used in meta-analysis when I^2 was greater than 50%. RevMan 5.3 software was used to conduct all analysis in this study. As a visual aid, a funnel plot was used to investigate the publications and possible types of bias. The forest plot was used to show the characteristics of the various findings.

Results

Data synthesis

A total of 27 studies consisting of 22 articles concerning ACE I/D and 15 articles discussing AGT M235T were included in our analysis. The cumulative genotype percentages for DD, ID, and II for ACE were 31.5%, 43.2%, and 2.3%, respectively, and for AGT, there were MM 28.8%, MT 37.7%, and TT 33.6 %, while in the control group, the percentages were 26.9%, 42.2 %, and 30.9% for DD, ID, and II, respectively, and MM 33.3%, MT 36.7%, and TT 33.0%. Overall, our analysis found that the D allele (OR: 95% CI = 1.51 [1.29–1.77], $p < 0.00001$) (Figure 2a) and DD genotype (OR: 95% CI = 1.54 [1.15–2.06], $p = 0.004$) were

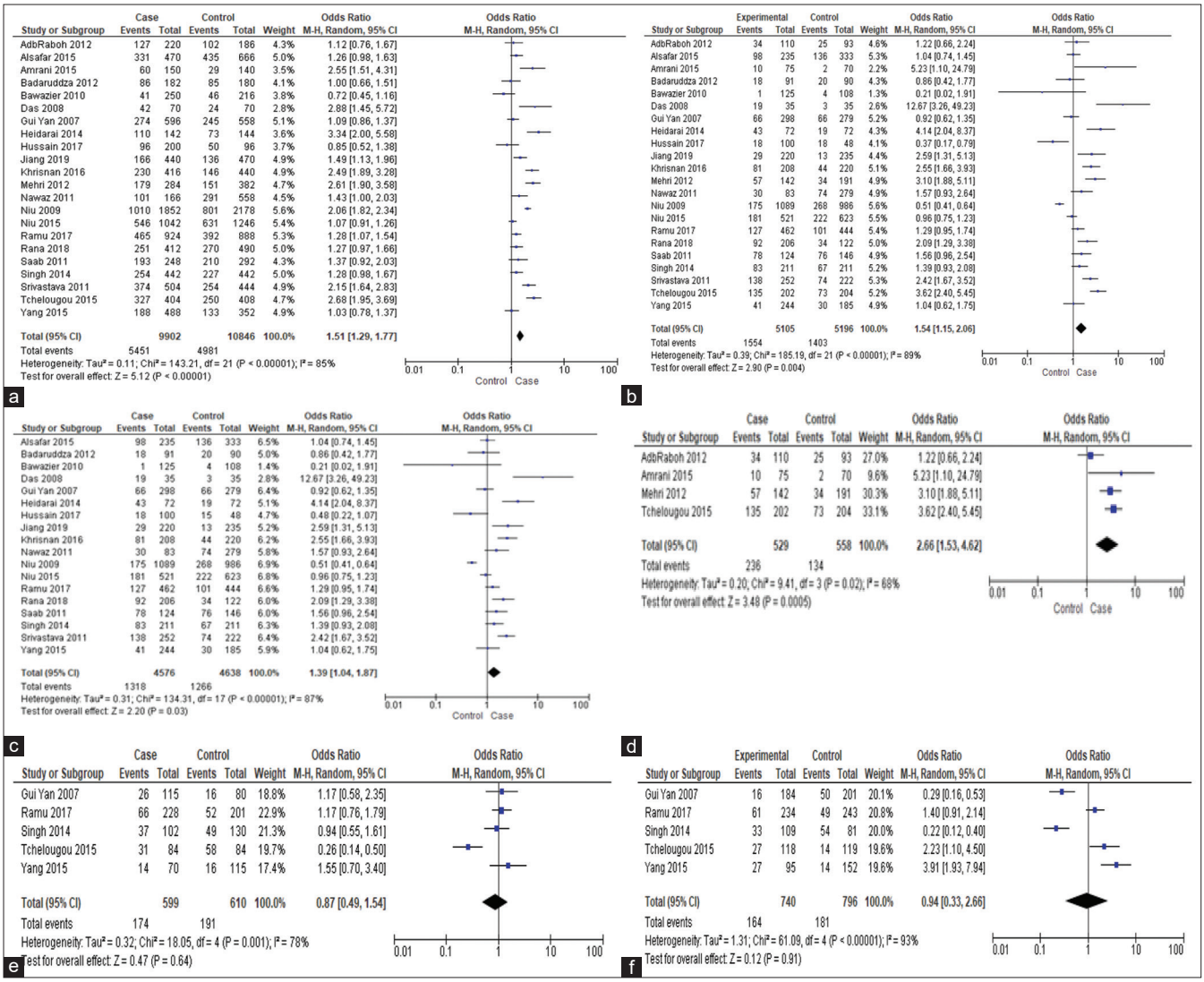

Figure 2: Forest plot for association between angiotensin-converting enzyme I/D gene polymorphism and the risk of essential hypertension: (a) D versus I; (b) DD versus ID + II); (c) Asian sub-group DD versus ID + II; (d) African sub-group DD versus ID + II; (e) Male gender sub-group DD versus ID + II; and (f) Female gender sub-group DD vs. ID + II

significantly associated with increased risk of essential hypertension (Figure 2b) but the TT allele (OR: 95% CI = 1.03 [0.74–1.43], p = 0.86) (Figure 3b) and T allele (OR: 95% CI = 1.20 [0.90–1.61], p = 0.22) were not associated with essential hypertension (Figure 3a). To establish a comprehensive analysis, we also performed a sub-group analysis according to the continent of origin and gender. Continent sub-group analysis consisted of Asian and African sub-groups.

In the Asian sub-group analysis, the genotype percentages were DD 28.0%, ID 45.4%, and II 26.6% and for MM, MT, and TT in patients with essential hypertension, there were 25.5%, 38.0%, and 36.3%, respectively. Meanwhile, in the control group, the percentages were 25.1%, 43.2%, and 31.7% for DD, ID, and II, respectively, and for AGT M235T, there were MM 28.7%, MT 36.8%, and TT 34.5%. In the African continent sub-groups, the percentages were DD 44.6%, ID 41.8%, and II 13.6% and for the AGT 235 gene, the percentages were MM 8.2%, MT 19.2%, and TT 72.5% in patients with essential hypertension. In the control group, the genotype percentages for ACE I/D were DD 24.0%, ID 43.7%, and II 28.7%.

In AGT M235T, there were MM 11.3%, MT 17.2%, and TT 71.4%. In the gender sub-group, the percentages of ACE I/D in males were DD 29.7%, ID 46.4%, and II 23.8% and for the AGT 235 gene, the percentages were MM 10.7%, MT 36.1%, and TT 53.3% in patients with essential hypertension. In the control group, the genotype percentages for ACE I/D in males were DD 29.6%, ID 41.0%, and II 29.4%. In AGT M235T, there were MM 13.7%, MT 33.1%, and TT 53.2%. Moreover, in females, there were DD 31.3%, ID 40.2%, and II 28.5% and for the AGT 235 gene, the percentages were MM 8.7%, MT 33.1%, and TT 58.2% in patients with essential hypertension. In the female control group, the genotype percentages for ACE I/D were DD 23.6%, ID 41.6%, and II 24.8%. In M235T, there were MM 9.7%, MT 33.4%, and TT 56.9%.

Our results found associations between ACE I/D gene polymorphisms and the risk of essential

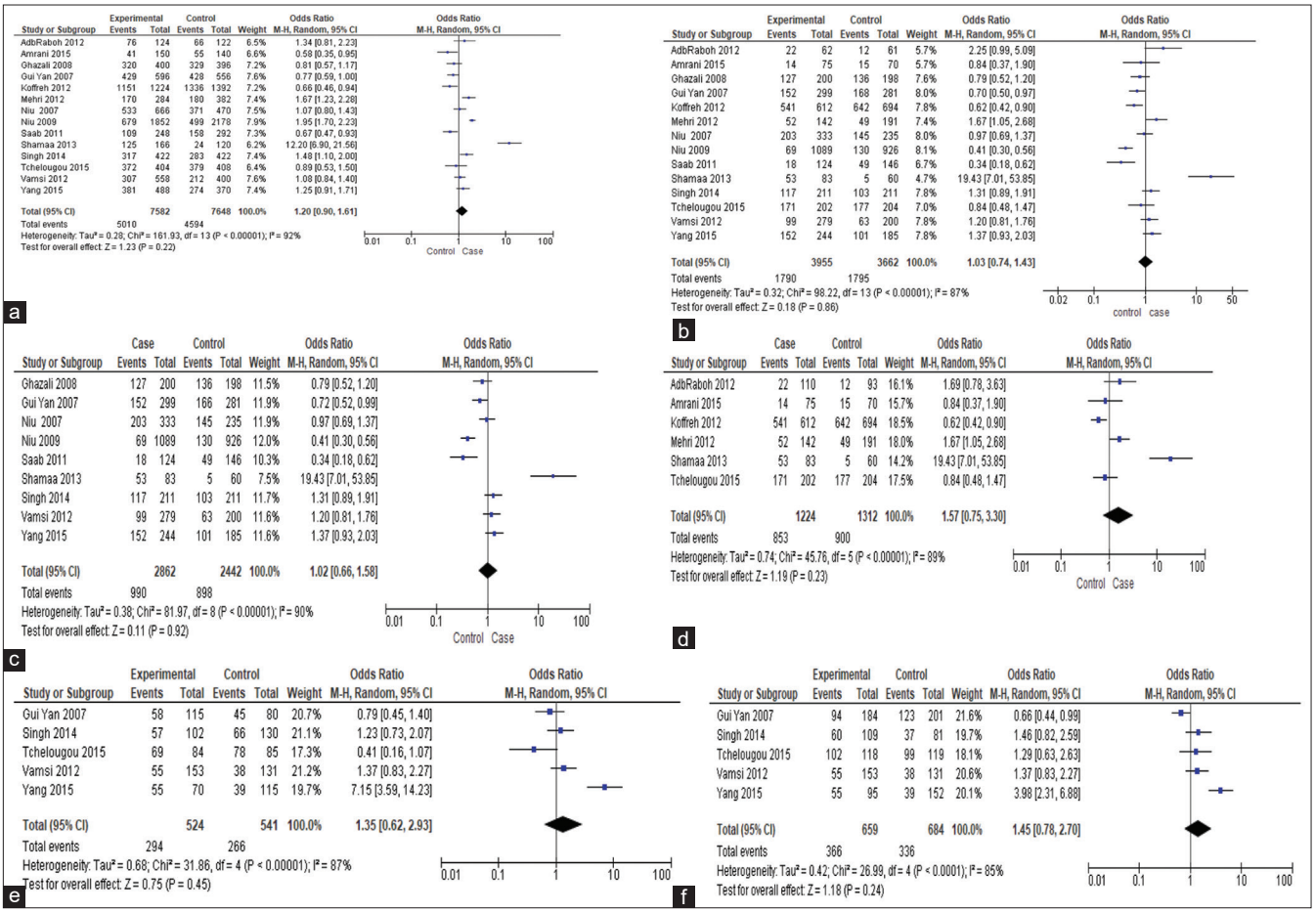

Figure 3: Forest plot for association angiotensinogen M235T gene polymorphism and the risk of essential hypertension: (a) M versus T; (b) TT versus MM+MT; (c) Asian sub-groups (TT vs. MM+MT); (d) African sub-groups (TT vs. MM+MT); (e) Male gender sub-groups (TT vs. MM+MT); and (f) Female gender sub-groups (TT vs. MM+MT)

hypertension in the Asian DD genotype (OR: 95% CI = 1.39 [1.04–1.87], p = 0.03) (Figure 2c) and African continent DD genotype sub-group (OR: 95% CI = 2.66 [1.53–4.62], p = 0.00005) (Figure 2d), while in the gender sub-groups, our results did not find any increased risk of essential hypertension in the DD genotype male sub-groups (OR: 95% CI = 0.87 [0.49–1.54], p = 0.64) nor female sub-groups (OR: 95% CI = 0.94 [0.33–2.66], p = 0.91) (Figure 2e and f).

Oppositely, the results showed some association between the increased risk of essential hypertension and the AGT TT genotype (OR: 95% CI = 1.03 [0.74–1.43], p = 0.86). Our results also found no association between AGT M235T polymorphisms and the risk of essential hypertension in the Asian gender sub-groups (OR: 95% CI = 1.03 [0.66–1.58], p = 0.92), while there were in the African sub-groups (OR: 95% CI = 1.57 [0.75–3.30], p = 0.23), and AGT M235T in males (OR: 95% CI = 1.35 [0.62–2.93], p = 0.45), and in females (OR: 95% CI = 1.45 [0.78–2.70], p = 0.24) (Figure 3).

Sensitivity analysis and publication bias

The Begg's funnel plot and Egger's regression tests were used to perform analysis of sensitivity and publication bias. In this study, these tests were performed to assess the publication bias in dominant comparison (ACE I/D=0.1753). This study did not find that the combined OR values changed significantly, which indicated the meta-analysis was stable and reliable. For the funnel plot analysis (Figure 4), the symmetry of each genotype funnel plot displayed no publication bias. The selected studies were considered more representative due to evaluation of the funnel plot symmetry with Begg's and Egger's tests which showed that there was no significant publication bias in the various publications.

Discussion

Essential hypertension is a complex, multifactorial disease with genetic, and environmental risk factors that contribute to its growing incidence [31], [32], [33]. Hypertension causes significant morbidity and mortality worldwide [34], [33]. Genome-wide association studies have contributed significantly to the present research concerning

Table 1: The baselines characteristics of the study populations in this meta-analysis

Study years	Country	HWE	Method	Polymorphism						Age	SBP	DBP
				ACE I/D			AGT M235T					
				DD	DI	II	MM	MT	TT			
Gui-yan *et al*. 2006 [4]	China	Yes	PCR-RFLP	66	142	90	19	127	152	52.90 ± 11.43	NA	NA
				66	113	100	16	94	168	50.15 ± 9.64	NA	NA
Das *et al*. 2008 [7]	India	No	PCR	19	4	12	NA	NA	NA	NA	NA	NA
				3	18	14	NA	NA	NA	NA	NA	NA
Ghazali *et al*. 2008 [3]	Malaysia	No	PCR-Sequencing		NA	NA	7	66	127	54.8 ± 6.3	153.5 ± 21.8	89.2 ± 13.0
					NA	NA	7	55	136	54.3 ± 6.4	132.8 ± 16.8	78.6 ± 10.2
Bawazier *et al*. 2010 [8]	Indonesia	No	PCR	1	39	85	NA	NA	NA	45.22 ± 7.45	149.8 ± 19.2	95.1 ± 9.8
				4	38	66	NA	NA	NA	41.26 ± 7.55	105.6 ± 6.5	68.2 ± 7.1
Saab *et al*. 2011 [9]	Lebanon	Yes	PCR -RFLP	78	37	9	34	72	18	NA	NA	NA
				76	58	12	38	59	49	NA	NA	NA
Koffreh *et al*. 2012 [10]	Nigeria	Yes	PCR-RFLP	NA	NA	NA	4	67	541	51.3 ± 13.76	161.14 ± 23.247	93.25 ± 13.768
				NA	NA	NA	2	52	642	31.9 ± 10.27	116.76 ± 9.19	72.181 ± 8.41
Vamsi *et al*. 2012 [6]	India	Yes	PCR-RFLP	NA	NA	NA	70	110	99	55.57 ± 9.78	160.53 ± 20.98	98.23 ± 12.87
				NA	NA	NA	53	84	63	47.63 ± 9.65	120.05 ± 0.71	80.0 ± 0.35
Shamaa *et al*. 2013 [11]	Egypt	No	PCR-RFLP	NA	NA	NA	12	18	53	53.5 ± 7.4	145.28 ± 7.0	91.2 ± 2.15
				NA	NA	NA	41	14	5	51.3 ± 8.8	117.33 ± 4.27	79.17 ± 3.46
Singh *et al*. 2014 [12]	India	Yes	PCR-RFLP	83	88	40	13	81	117	54.46 ± 12.65	NA	NA
				67	93	51	30	78	103	43.64 ± 13.87	NA	NA
Heidarai *et al*. 2014 [13]	Malaysia	Yes	PCR	43	24	4	NA	NA	NA	47.22 ± 11.3	152.0 ± 13.0	NA
				19	35	18	NA	NA	NA	46.92 ± 12.7	120 ± 13.3	NA
Yang *et al*. 2015 [14]	China	Yes	PCR-RFLP	41	106	97	14	78	152	61.148 ± 13.491	NA	NA
				30	73	73	13	71	101	59.281 ± 12.828	NA	NA
Alsafar *et al*. 2015 [15]	UAE	Yes	PCR-RFLP	98	135	2	NA	NA	NA	NA	NA	NA
				136	163	34	NA	NA	NA	NA	NA	NA
Tchelougou *et al*. 2015 [16]	Africa	Yes	PCR	135	57	10	2	29	171	51 ± 10.01	160 ± 20.66	95 ± 11.87
				73	104	27	3	24	177	49.50 ± 13.54	120 ± 11.47	70 ± 8.24
Krishnan *et al*. 2016 [17]	India	Yes	PCR	81	68	59	NA	NA	NA	43.6 ± 5.6	151 ± 9.8	92.56 ± 8.7
				44	58	118	NA	NA	NA	42.78 ± 5.7	123.34 ± 1.8	69.89 ± 5.
Ramu *et al*. 2017 [18]	India	No	PCR	127	211	124	NA	NA	NA	45.1 ± 0.4	153.4 ± 0.8	97.3 ± 0.5
				101	190	153	NA	NA	NA	47.4 ± 0.4	117.5 ± 0.4	78.2 ± 0.3
Hussain *et al*. 2017 [19]	Pakistan	Yes	PCR-RFLP	18	61	21	NA	NA	NA	52 ± 11	147 ± 23	90 ± 12
				15	20	13	NA	NA	NA	47 ± 8	111 ± 15	72 ± 10
Nawaz *et al*. 2011 [20]	Pakistan	Yes	PCR	30	41	12	NA	NA	NA	36.88 ± 12.38	NA	NA
				74	143	62	NA	NA	NA	28.23 ± 10.45	NA	NA
Niu *et al*. 2015 [21]	Kazahtan	Yes	PCR-RFLP	181	184	156	NA	NA	NA	52.3 ± 12.4	159.3 ± 23.6	96.6 ± 11.8
				222	187	214	NA	NA	NA	40.2 ± 14.3	117.9 ± 11.6	74.2 ± 8.2
Srivastava *et al*. 2012 [22]	India	Yes	PCR	138	98	16	NA	NA	NA	51.6 ± 7.2	145.5 ± 14.05	120 ± 3.47
				74	106	42	NA	NA	NA	49.7 ± 10.4	93.6 ± 8.09	80.49 ± 2.5
Jiang 2019 [23]	China	No	PCR	29	108	83	NA	NA	NA	62.2 ± 6.1	159.0 ± 12.9	94.8 ± 8.5
				13	112	110	NA	NA	NA	61.1 ± 7.7	119.7 ± 10.1	77.7 ± 6.8
AdbRaboh [24]	Egypt	Yes	PCR-RFLP	34	59	17	8	32	22	45 ± 8.2	147.8 ± 13.5	95.6 ± 6.3
				25	52	16	7	42	12	42 ± 7.3	131.4 ± 13.4	82 ± 7.2
Amrani 2015 [25]	Algeria	Yes	PCR-RFLP	10	40	25	48	13	14	48 ± 1.5	154 ± 10	91 ± 5
				2	25	43	30	25	15	43.1 ± 1.4	112 ± 6	72 ± 7
Badaruddza 2012 [26]	India	Yes	PCR-RFLP	18	49	24	NA	NA	NA	52.30 ± 6.54	147.38 ± 11.49	92.53 ± 10.35
				20	46	24	NA	NA	NA	52.30 ± 5.01	131.46 ± 11.49	79.50 ± 9.05
Mehri 2012 [27]	Tunisia	Yes	PCR-RFLP	57	65	20	23	67	52	61.4	161.6 ± 16.4	100.4 ± 11.2
				34	83	74	60	82	49	60.1	126.8 ± 5.2	82.5 ± 4.3
Niu 2007 [28]	Tibet	Yes	PCR-RFLP	NA	NA	NA	6	124	203	52.27 ± 11.89	176.89 ± 15.52	106.97 ± 11.06
				NA	NA	NA	8	82	145	49.63 ± 10.02	112.60 ± 12.38	75.03 ± 10.25
Niu 2009 [29]	China	Yes	PCR-RFLP	175	451	300	496	361	69	50.62 ± 6.58	160.95 ± 18.07	99.64 ± 10.59
				268	474	347	540	419	130	52.99 ± 7.50	118.64 ± 17.66	77.26 ± 7.83
Rana 2018 [30]	India	No	PCR	92	69	45	NA	NA	NA	NA	NA	NA
				89	93	63	NA	NA	NA	NA	NA	NA

ACE: Angiotensin converting enzyme, AGT: Angiotensinogen, HWE: Hardy–Weinberg equilibrium, NA: Not available, PCR: Polymerase chain reaction, PCR-RFLP: Polymerase chain reaction restriction fragment length polymorphism, SBP: Systole blood pressure, DBP: Diastole blood pressure.

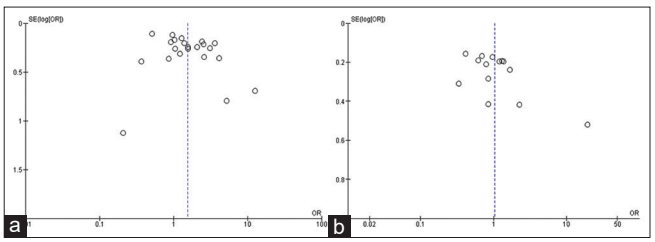

Figure 4: (a) Funnel plot angiotensin-converting enzyme I/D and (b) Funnel plot angiotensinogen M235T

essential hypertension by providing the typology for 100,000s of single nucleotide polymorphisms through extensive cohorts [35] Results showed that as many as 22 genome-wide scans have identified genetic loci for blood pressure [36] The contribution of genetic types to blood pressure variation is estimated to range from 30% to 50%. The identification of genotypical variants can enrich our understanding of the etiology of hypertension while also helping to clarify the biochemical and physiological pathways in the disease pathophysiology [32].

The first candidate genes linked to essential hypertension were AGT and ACE [34]. RAS is an important component of blood pressure regulation and associated with hypertension [37], [38]. The classical pathway of the RAS begins with renin cleaving its substrate, AGT, to produce the inactive peptide, angiotensin I, which is then converted to angiotensin II by endothelial ACE. ACE activation of angiotensin II occurs especially in the lungs [39], [40].

Many studies have investigated the relationship between genetic susceptibility and essential hypertension. Research about AGT M235T and ACE I/D showed some association with essential hypertension in Caucasian populations but not in Asians and Africans. We collected 41 papers that investigated

links between genotypes and essential hypertension. Twenty-seven papers found associations between ACE I/D and the risk of essential hypertension, and eight found no association with hypertension. Six studies showed significant correlations between AGT M235T and essential hypertension while six did not find any association. In the present meta-analysis, our results support the findings of some association of ACE I/D polymorphisms with essential hypertension.

Our meta-analysis results concerning ACE I/D are consistent with the previous studies that found the DD genotype has strong association with essential hypertension. In the sub-group analysis in the Asian population, consistent results were showing that the DD genotype has association with essential hypertension. In addition, in the African sub-groups, the DD genotype was also associated with essential hypertension. However, in the gender sub-group analysis, there was no association in the male or female sub-groups between the DD genotype with essential hypertension. Interestingly, the meta-analysis conducted by Staessen *et al*. [41] found a significant association between allele D with hypertension in female and Asian populations.

Jeunemaitre *et al.* [42] initially identified that AGT M235T was associated with severe hypertension cases compared to controls, and the 235T variant was correlated with increased plasma AGT (20% higher in 235T homozygotes than in 235M homozygotes). Further findings in Caucasian populations in North America, Europe, Australia, Japan, and Taiwan, and in black populations in the Caribbean, United States, and Africa showed contradictory associations between 235T and hypertension [34]. Our results found no association between the genotype TT with essential hypertension in all analysis and ethnic subgroups. The same result was shown by Ghazali *et al*. [3] in the Malaysian population. Meanwhile, different results from the meta-analysis conducted by Staessen *et al*. [43] showed that the T allele was associated with essential hypertension in Caucasian populations but that the association between hypertension and the T allele may be weaker in black and Asian populations.

Several limitations were noted in the present meta-analysis study. First, since only articles published and written in the English language were retrieved for analysis, this might introduce a potential selection bias. Second, this meta-analysis was not based on individual participant data of each qualified study, such as body mass index, level of physical activity, limiting analysis for gene-to-environment interaction, and age of the participant. Third, the analysis was limited to specific genes for only polymorphism I/D in ACE and AGT M235T genes but other functional genes in the promoter region such as A-240T polymorphisms and AT1R A1166C were not analyzed because of the insufficient data and limited availability. In addition, for allele frequency across studies, the ACE I/D polymorphism exhibited wide divergences, indicating the presence of allele heterogeneity. Fourth, some sub-group analyzes may have been lower for power analysis due to the limited number of studies and small sample sizes involved.

Furthermore, in the present meta-analysis of the included studies, deviations from the HWE were also found. These Hardy–Weinberg inconsistencies might be considered as significant limitations, which might drive some of the false-positive findings. The previous studies might be considered to have a low level of evidence due to these limitations to confer strength to the overall association results.

Conclusion

The present meta-analysis suggests that angiotensin converting enzyme (ACE I/D) polymorphisms are associated with increased risks of essential hypertension, especially among Asian and African populations. Some studies with different results showed that AGT M235T has no association in Asian and African populations. These findings seem to show that differences in gene pool at different frequencies for each population have different effects on the onset of disease, but the gender-based sub-groups do not differ in expression between men and women. However, in the future, larger sample size studies conducted in different ethnic populations are required to further evaluate our conclusions.

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