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Angiotensinogen M235T polymorphism and susceptibility to hypertrophic cardiomyopathy in Asian population: A meta analysis

Zhen Zhen[1], Lu Gao[1], Qin Wang[1], Xi Chen[1], Jia Na[1], Xiwei Xu[2] and Yue Yuan[1]

Abstract

Objective: To explore the relationship between the polymorphism of angiotensinogen gene (AGT) M235T and susceptibility to hypertrophic cardiomyopathy (HCM) in Asian population by meta-analysis.

Methods: PubMed, Embase, Web of Science, Cochrane library, CNKI, Wan Fang, and other databases were searched to collect the literature about AGT M235T polymorphism and HCM from the inception to March 1, 2020. The Newcastle-Ottawa Scale (NOS) checklist was uesd to perform independent literature review and study quality assessment. Data was analyzed by Stata 15.0 software.

Results: The results showed that, except for the recessive genetic model (TT vs MT+MM: OR = 1.27, 95%CI: 1.05–1.53), in the other four genetic models, the M235T polymorphism had no significant correlation with the risk of HCM (T vs M: OR = 1.17, 95%CI: 0.88–1.57; TT+MT vs MM: OR = 1.13, 95%CI: 0.55–2.33; TT vs MM: OR = 1.25, 95%CI: 0.60–2.59; TM vs MM: OR = 0.95, 95%CI0.5–1.82). The results of subgroup analysis showed that, except for the heterozygous genetic model, in the other four genetic models, M235T polymorphism was significantly associated with sporadic hypertrophic cardiomyopathy (SHCM), but not with familial hypertrophic cardiomyopathy (FHCM) ($p > 0.05$).

Conclusion: M235T polymorphism in Asians is associated with HCM, especially SHCM. Heterozygotes increase the risk of patients with SHCM.

Keywords

Angiotensinogen, polymorphism, hypertrophic cardiomyopathy, meta-analysis

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Introduction

Hypertrophic cardiomyopathy (HCM) is a primary myocardial disease characterized by myocardial hypertrophy and disorder of myocardial fiber arrangement, which is mainly caused by mutation of myocardial subsection gene. It is a common cause of sudden cardiac death in young patients and athletes with various clinical symptoms. It usually occurs with the rule of familial autosomal dominant inheritance and with genetic heterogeneity.[1,2] In general population, its incidence rate is 0.23%, and the annual mortality rate is about 1% to 2%.[3,4] In patients with HCM, myocardial tissue is hypertrophy below the level of the left ventricular papillary muscle at the apex, and this hypertrophy is abnormal and asymmetric.[5] About two-thirds of patients with HCM show the characteristics of family

[1]Department of Cardiology, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China
[2]Internal Medicine Teaching and Research Department, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China

Corresponding authors:
Xiwei Xu, Internal Medicine Teaching and Research Department, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, 56 South Lishi Road, Beijing 100045, China.
Email: xuxiweibch@163.com

Yue Yuan, Department of Cardiology, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, 56 South Lishi Road, Beijing 100045, China.
Email: yuanyuebj22@sina.com

inheritance, which is called familial hypertrophic cardiomyopathy (FHCM), that is, there are two or more patients with HCM in the same family, while the others are sporadic hypertrophic cardiomyopathy (SHCM).[6] Some studies have shown that women with HCM are older, have more symptoms, and worse clinical results than men.[7]

Renin-angiotensin system (RAS) affects the occurrence and development of left ventricular hypertrophy of the heart mainly through cell proliferation, cell hypertrophy, and partial myocardial hypertrophy.[8] Angiotensinogen (AGT) is a glycoprotein composed of 485 amino acids, which is produced by hepatocytes and released into the circulation. As RAS plays an important role in the occurrence and development of myocardial hypertrophy, the concentration of AGT plays a rate-limiting role in the production of angiotensin I (Ang I), while AGT plays an important regulatory role in the production of angiotensin II (Ang II).[9] AGT is the only precursor of Ang B, and a slight change in its concentration will significantly affect the production of Ang II. It is a precursor peptide of angiotensin converting enzyme II, exerting positive inotropic, hypertrophy, and apoptosis effects on myocardial cells, and is the center involved in the control of hypertrophy and heart failure.[10,11]

AGT gene is located at 1q42.2 position with a total length of 12,068 bp, and its gene coding region consists of five exons and four introns. AGT gene mutation is mainly caused by the change of thymine nucleotide (T) to cytosine nucleotide (C) at position +704 of the second exon of AGT gene, resulting in the change of methionine (Met) encoded by codon 235 to threonine (Thr), namely M235T, thus forming two alleles, 235M (wild type) and 235T (variant type). There are three genotypes in the population: homozygous 235MM, 235TT and heterozygous 235M type.[12] Paillard et al.[13] found that AGT-235 T allele can increase the level of AGT in plasma. At the same time, Lanz et al.[14] speculated that T allele and TT genotype can indirectly increase the level of angiotensin II (AngII) by increasing the level of AGT in plasma. The increase of the level of AGT in plasma not only causes contraction of small artery smooth muscle and proliferation, hypertrophy and lipid deposition of vascular smooth muscle cells, but also excites sympathetic nervous system and increases norepinephrine secretion. This mechanism has been proved to be related to hypertension,[15] coronary heart disease,[14] and coronary atherosclerosis.[16]

There are many studies on ATG gene polymorphism and HCM, but the results in different ethnic groups at home and abroad are not consistent. In the early days, Ishanov et al.[17] in Japan found that the AGT 235T allele was associated with the onset of HCM. Later, López-Haldón et al.[18] also found that an increasing incidence of myocardial hypertrophy and cardiac events in Spanish patients with 235TT genotype. Yang et al.[19] also found that AGT 235T allele T is a risk factor for HCM. AGT T allele, angiotensin (ACE) D allele, TT and DD genotypes have synergistic effects on HCM pathogenesis. However, Rani et al.'s[20] study found that AGT 235T allele T is a protective factor for HCM. Meta-analysis can combine and comprehensively evaluate multiple independent research results with the same research purpose to make up for the deficiency of a single research. Yao et al.[21] in 2015 found that AGT M235T polymorphism and HCM were not correlated in Europeans, but was correlated in Asians. Therefore, meta-analysis was used to further summarize and analyze the related studies on HCM and AGT M235T polymorphism in Asian population, so as to evaluate the relationship between the two more effectively and provide evidence-based medical evidence for clinical medicine.

Data and methods

Search strategy

PubMed, Embase, Web of Science, Cochrane library, CNKI, Wanfang, and other databases were searched to collect the literature on the association of AGT M235T polymorphism and HCM, from the inception to March 1, 2020. The following key words were used: "Angiotensinogen," "AGT," "M235T," "Hypertrophic Cardiomyopathy/HCM," and "polymorphism or mutation." Meanwhile, the references of retrieved articles were also tracked to find the related papers. There is no language restriction for literature.

Screening criteria

Inclusion criteria. (1) Case-control studies on the relationship between AGT M235T polymorphism and HCM in Asian population, such as Indian, Japanese, and Chinese; (2) With complete original data or enough data to calculate the odds ratio (OR) and its 95%CI; (3) The case group were all confirmed patients with HCM, while the control group were non-HCM or healthy people from the same area, and there was no significant difference in gender and age between the groups.

Exclusion criteria. (1) Patients with HCM caused by other diseases (such as hypertension, valvular heart disease) or with these complications were excluded; (2) For the repeated published literature, only the recently published research with the largest sample size was included; (3) The score of Newcastle-Ottawa Scale (NOS) was less than 6.

Data extraction

Two researchers independently screened the literature according to the inclusion and exclusion criteria. Then they extracted and cross-checked the data. The disputes

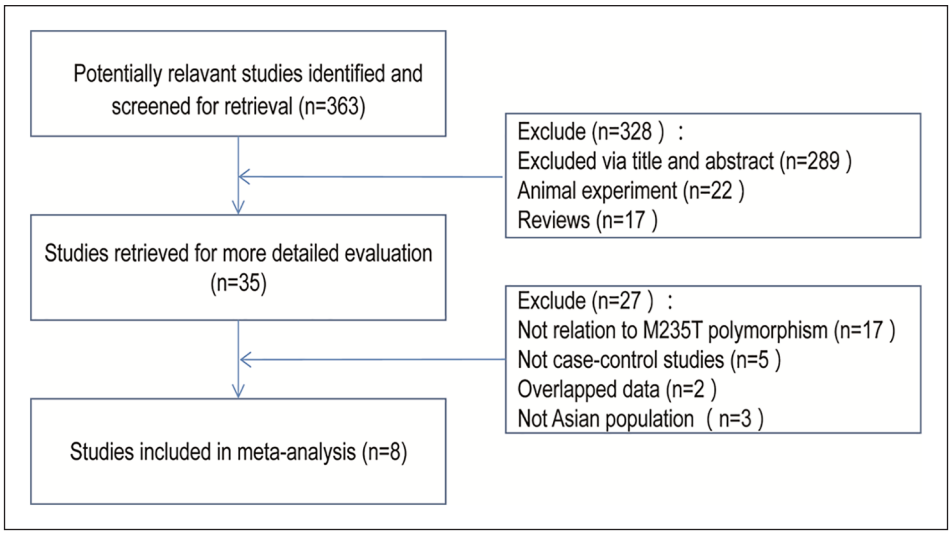

Figure 1. Literature screening procedure.

were settled through discussion or assisted by the third researcher. Data extraction was performed using a standardized data-collection form: first author, publication year, country, control source, sample size, genotype distribution, and frequency.

Literature quality evaluation

The quality evaluation of the included studies was independently evaluated according to the NOS.[22] The evaluation items included: study population selection, comparability, exposure or result evaluation. The total score is 9 points. In this study, the score ⩾6 points was rated as high quality.

Statistical analysis

The statistical analysis was performed using the Stata 15.0 software (StataCrop, College Station, TX). The measurement data used mean difference (MD) as effect size, and the dichotomous variables used odds ratios (ORs) and its 95%CI. The pooled ORs were calculated using five models: allele model (T vs M), dominant model (TT+MT vs MM), recessive model (TT vs MT+MM), homozygous model (TT vs MM) and heterozygous model (TM vs MM). The genotype distribution of the control group was tested with Hardy-Weinberg equilibrium (HWE). The heterogeneity among the included studies was analyzed by the χ^2 test, and the Q test and I^2 statistics were quantitatively judged the heterogeneity. If there was no statistical heterogeneity ($p > 0.05$, or $I^2 < 50\%$), the fixed effects model (FEM) was used for meta analysis. Otherwise, the random effects model (REM) was used. Publication bias was analyzed by funnel plots and quantified by Egger's regression. Obvious clinical heterogeneity was treated by subgroup analysis.

Results

Results and characteristics of literature retrieval

A total of 363 potential articles were initially searched (Figure 1). Then 289 identical and irrelevant articles were excluded via the titles and abstracts, and 22 animal experimental studies and 17 reviews were also excluded. Finally, 35 articles were included. After full-text retrieval, the following articles were excluded: 17 studies not related to M235T mutations, five studies not case-control studies, two duplicate studies, and three non-Asian studies. Therefore, our meta-analysis finally included eight studies[16,17,19,20,23–26] with 773 cases and 1170 controls. All included literature had high quality with an average score of 7.67. The basic characteristics of the included literature were shown in Table 1.

Meta-analysis results

In general, AGT M235T polymorphism was not significantly associated with HCM in the allele model, dominant, homozygous, and heterozygous genetic models, while there was a significant association between the two in the recessive genetic model (TT vs TM+MM) (Table 2). Allele model: OR = 1.17 (95%CI: 0.88–1.57, $p > 0.05$) (Figure 2(a)); dominant genetic model: OR = 1.13 (95%CI: 0.55–2.33, $p > 0.05$) (Figure 2(b)); recessive genetic model: OR = 1.27 (95%CI: 1.05–1.53, $p = 0.012$) (Figure 2(c)); homozygous genetic model: OR = 1.25 (95%CI: 0.60–2.59, $p > 0.05$) (Figure 2(d)); heterozygous genetic model: OR = 0.95 (95%CI: 0.50–1.82, $p > 0.05$) (Figure 2(e)).

The FEM was used in the recessive genetic model with low heterogeneity, while the REM was used in the other genetic models with high heterogeneity. The funnel plots (Figure 3) for testing publication bias were all basically

Table 1. Characteristics of the included literature.

Study	Country	HCM Genotypes			Control Genotypes			HWE (control)	Source of control	*p* for HWE	NOS score
		TT	MT	MM	TT	MT	MM				
Yoshiji et al.[23]	Japan	37	29	5	76	44	2	0.119	Healthy subjects	0.119	8
Ishanov et al.[17]	Japan	67	28	1	94	61	5	0.188	Healthy subjects	0.188	8
Yang et al.[19]	China	42	17	4	45	30	11	0.109	Healthy subjects	0.109	7
Kawaguchi[16]-a	Japan	67	28	1	94	61	5	0.188	Healthy subjects	0.188	8
Kawaguchi[16]-b	Japan	67	28	1	63	38	4	0.554	Relatives of HCM patients	0.554	8
Cai et al.[25]	China	45	22	5	36	30	14	0.092	Healthy subjects	0.092	7
Chen et al.[24]	China	36	42	16	52	50	18	0.304	Hospital-based individuals	0.304	7
Manohar Rao et al.[26]	India	70	68	12	65	85	15	0.084	Healthy subjects	0.084	8
Rani et al.[20]	India	16	72	43	26	126	20	0.000	Healthy subjects	0.000	8

HCM: Hypertrophic cardiomyopathy; HWE: Hardy-Weinberg equilibrium; NOS: Newcastle-Ottawa Scale.

Table 2. Results of meta-analysis.

Genetypes	*n*	OR	95%CI	*p*	I^2	*p* for Heterogeneity	Model	*p* for publication bias
T vs M	8	1.17	0.88~1.57	0.28	75.2	0	REM	0.049
TT + MT vs MM	8	1.13	0.55~2.33	0.746	72.4	0	REM	0.025
TT vs MT + MM	8	1.27	1.05~1.53	0.012	44.8	0.07	FEM	0.881
TT vs MM	8	1.25	0.60~2.59	0.554	68.0	0.002	REM	0.068
TM vs MM	8	0.95	0.50~1.82	0.881	61.9	0.007	REM	0.02

OR: odds ratio; REM: random effect model; FEM: fixed effect model.

symmetrical. The *p* values of Egger's test for the recessive genetic model and homozygous genetic model were more than 0.05, while the *p* values of Egger's test for the allele model, dominant genetic model and heterozygous genetic model were less than 0.05, which indicated that there was certain publication bias.

As the overall comparison showed high heterogeneity, in order to analyze the causes of heterogeneity, subgroup analysis was carried out on HCM typing, country and whether the control groups in accord with HWE (Table 3). The subgroup analysis of HCM subtyes showed that heterogeneity was significantly reduced in FHCM and SHCM. In SHCM subgroup, allele model: OR = 1.87 (95%CI: 1.41–1.57, $p < 0.05$); dominant genetic model: OR = 2.52 (95%CI: 1.10–5.81, $p < 0.05$); recessive genetic model: OR = 2.09 (95%CI: 1.50–2.90, $p < 0.05$); homozygous genetic model: OR = 3.27 (95%CI: 1.40–7.63, $p < 0.05$); heterozygous genetic model: OR = 1.77 (95%CI: 0.74–4.24, $p > 0.05$). Obviously, except for the heterozygous genetic model, the other four genetic models had statistical significance.

The subgroup analysis of the countries showed no significant reduction in heterogeneity, and no statistically significant genetic models in the Chinese, Japanese and Indian populations. The subgroup analysis of the control group in accord with HWE showed that there was statistical significance in the recessive genetic model, but there was no statistical significance in the other fours models, which was consistent with the overall comparison results.

Sensitivity analysis

Since the study of Rani et al.[20] had significantly increased the heterogeneity of the study, the sensitivity analysis was conducted after removing this study. The results (Figure 4) showed that after removing the studies of Yoshiji et al.[23] and Chen et al.,[24] the allele model had statistical significance. After removing the study of Yoshiji et al.,[23] the homozygous genetic model had statistical significance. The results of the other genetic models were stable, with no statistically significant change after removing single literature.

The results of sensitivity analysis of SHCM subgroup (Figure 5) showed that in the allele model, recessive gene model and heterozygous gene model, no statistically significant change occurred in the data after removing single literature, which indicated that the three gene genetic models were robust. The dominant genetic model had no statistical significance after removing these three studies.[16,17,26] The homozygous genetic model had no statistical significance after removing the study of Manohar Rao et al.[26]

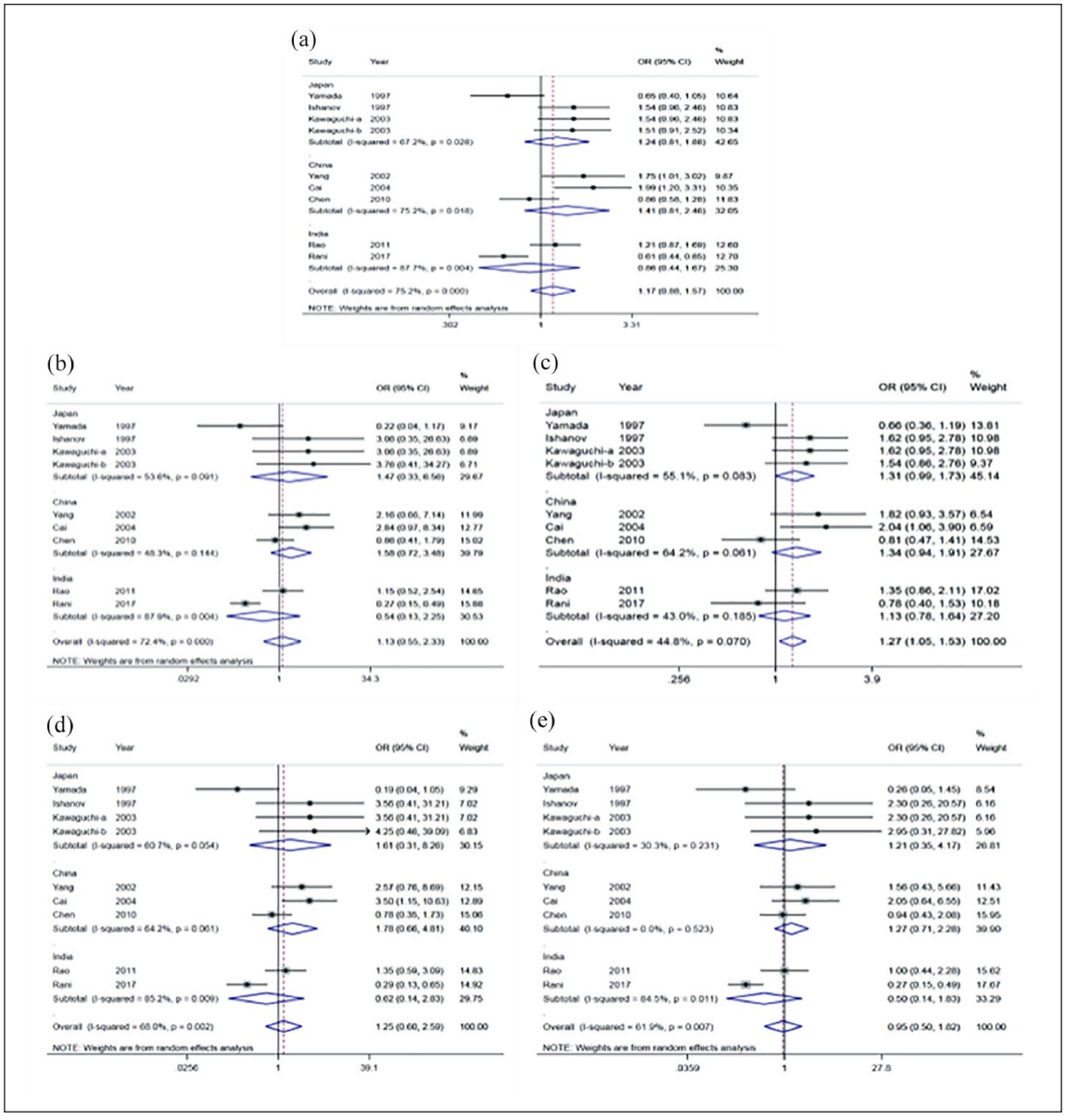

Figure 2. Forest plot for the association between AGT M235T Polymorphism and HCM: (a) Allelic model, (b) Dominant model, (c) Recessive model, (d) Homozygous model, and (e) Heterozygote model.

Discussion

The elevated plasma AGT level increases the generation of AngII in plasma and local myocardial tissue. AngII is an important factor in the occurrence and development of cardiomyopathy, which can induce myocardial cell proliferation, stimulate myocardial protein synthesis, and eventually lead to myocardial hypertrophy.[27] AGT M235T polymorphism may be related to the concentration of AGT in plasma, so M235T polymorphism may be associated with the occurrence and development of HCM.

This meta-analysis included 8 studies with a total of 773 cases and 1170 controls. The overall results showed that in the recessive genetic model (TT vs TM+MM), AGT M235T polymorphism was significantly associated with HCM (OR = 1.27, 95%CI: 1.05–1.53). This indicated that TT genotype is a risk factor for HCM in Asian population, which was also confirmed by the sensitivity analysis. However, AGT M235T polymorphism had no significant correlation with HCM in the allele model, dominant, homozygous, and heterozygous genetic model, and the difference was not statistically significant. But it could not be considered that the allele and homozygous genetic models were not associated with HCM, because the results of sensitivity analysis showed that the allele model and homozygous genetic model were still unstable to some extent, and statistically significant changes had taken place after elimination of some studies, which might be related

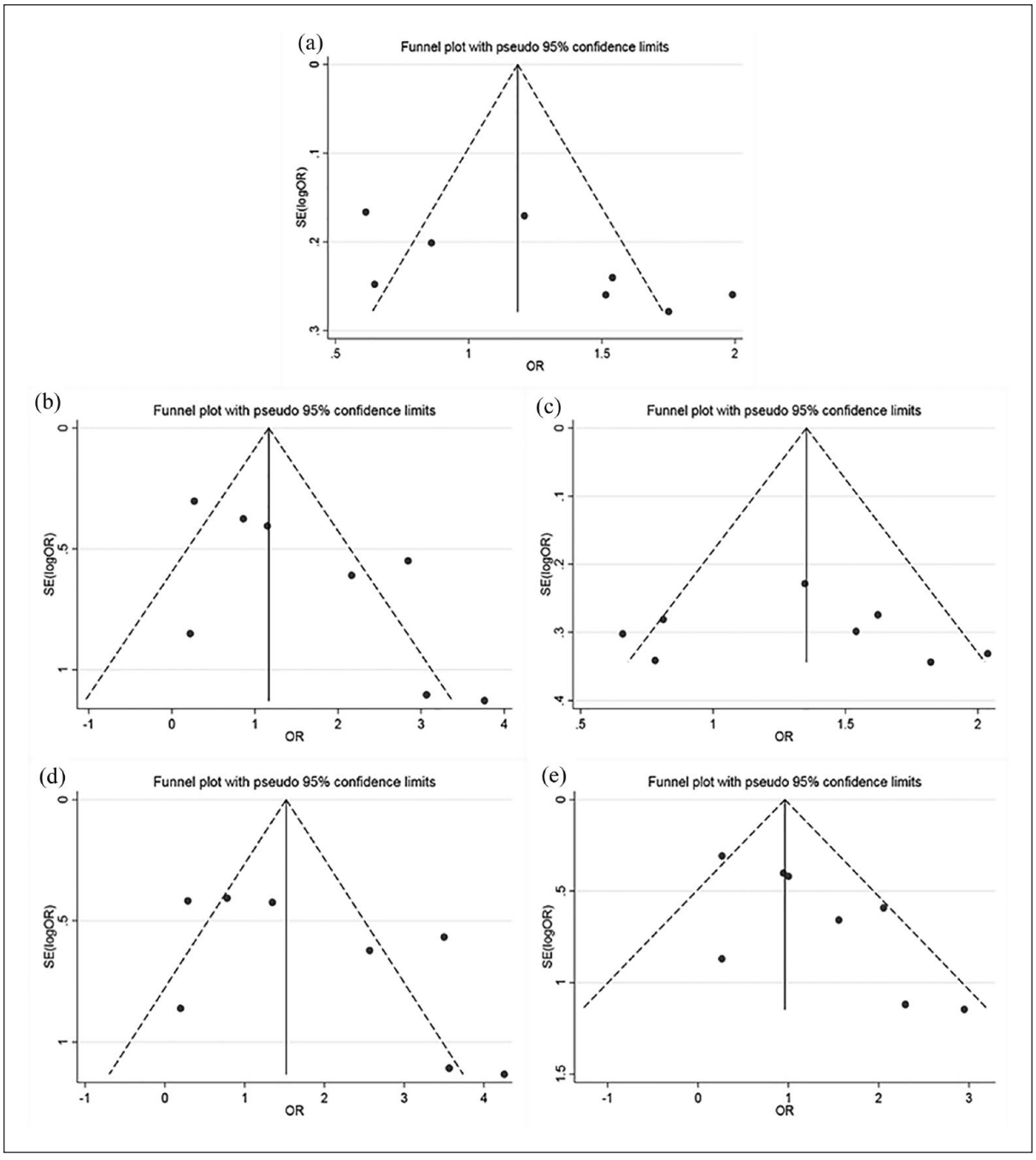

Figure 3. Funnel plots for publication bias: (a) Allelic model, (b) Dominant model, (c) Recessive model, (d) Homozygous model, and (e) Heterozygote model.

to the publication bias and heterogeneity among studies. Study of Luo et al.[28] suggested that AGT M235T polymorphism was not associated with HCM in the genetic model (MM/MT vs TT) (OR = 0.84, 95%CI: 0.67–1.05). However, Yao et al.[21] showed an association between the AGT M235T polymorphism and HCM in Asians. Therefore, we limited the study population to Asian population, and further analyzed the relationship between AGT M235T polymorphism and susceptibility to HCM. Our experimental analysis also confirmed that AGT M235T polymorphism was significantly correlated with HCM in Asian population.

In order to analyze the causes of heterogeneity, subgroup analysis was carried out on HCM typing, country and whether the control groups in accord with HWE. The population in this study mainly from three countries—China, Japan, and India, with three studies in Chinese, three studies in Japanese, and two studies in Indian. After

Table 3. Results of subgroup analysis.

Subgroup	Number	T vs M		TT + MT vs MM		TT vs MT + MM		TT vs MM		TM vs MM	
		OR (95%CI)	*p*	OR (95%CI)	*p*	OR (95%CI)	*p*	OR (95%CI)	*p*	OR (95%CI)	*p*
Substyes											
FHCM	4	1.09 (0.71~1.68)	0.682	0.97 (0.49~1.92)	0.923	1.04 (0.73~1.48)	0.823	0.94 (0.46~1.93)	0.874	0.94 (0.45~1.93)	0.857
SHCM	4	1.87 (1.41~2.47)	0.000	2.52 (1.10~5.81)	0.030	2.09 (1.50~2.90)	0.000	3.27 (1.40~7.63)	0.006	1.77 (0.74~4.24)	0.200
Country											
China	3	1.41 (0.81~2.46)	0.227	1.58 (0.72~3.48)	0.257	1.34 (0.94~1.91)	0.263	1.78 (0.66~4.81)	0.259	1.27 (0.71~2.28)	0.418
Japan	3	1.24 (0.81~1.88)	0.326	1.47 (0.33~6.56)	0.610	1.31 (0.99~1.73)	0.231	1.61 (0.31~8.26)	0.566	1.21 (0.35~4.17)	0.760
India	2	0.86 (0.44~1.67)	0.658	0.54 (0.13~2.25)	0.400	1.13 (0.78~1.64)	0.751	0.62 (0.14~2.83)	0.536	0.50 (0.14~1.83)	0.295
HWE											
Yes	7	1.28 (1.00~1.65)	0.054	1.40 (0.81~2.41)	0.233	1.33 (1.09~1.61)	0.005	1.46 (0.98~2.19)	0.064	1.18 (0.78~1.78)	0.445
No	1	0.61 (0.44~0.85)	0.003	0.27 (0.15~0.49)	0.000	0.87 (0.40~1.53)	0.470	0.29 (0.13~0.65)	0.003	0.27 (0.15~0.49)	0.000

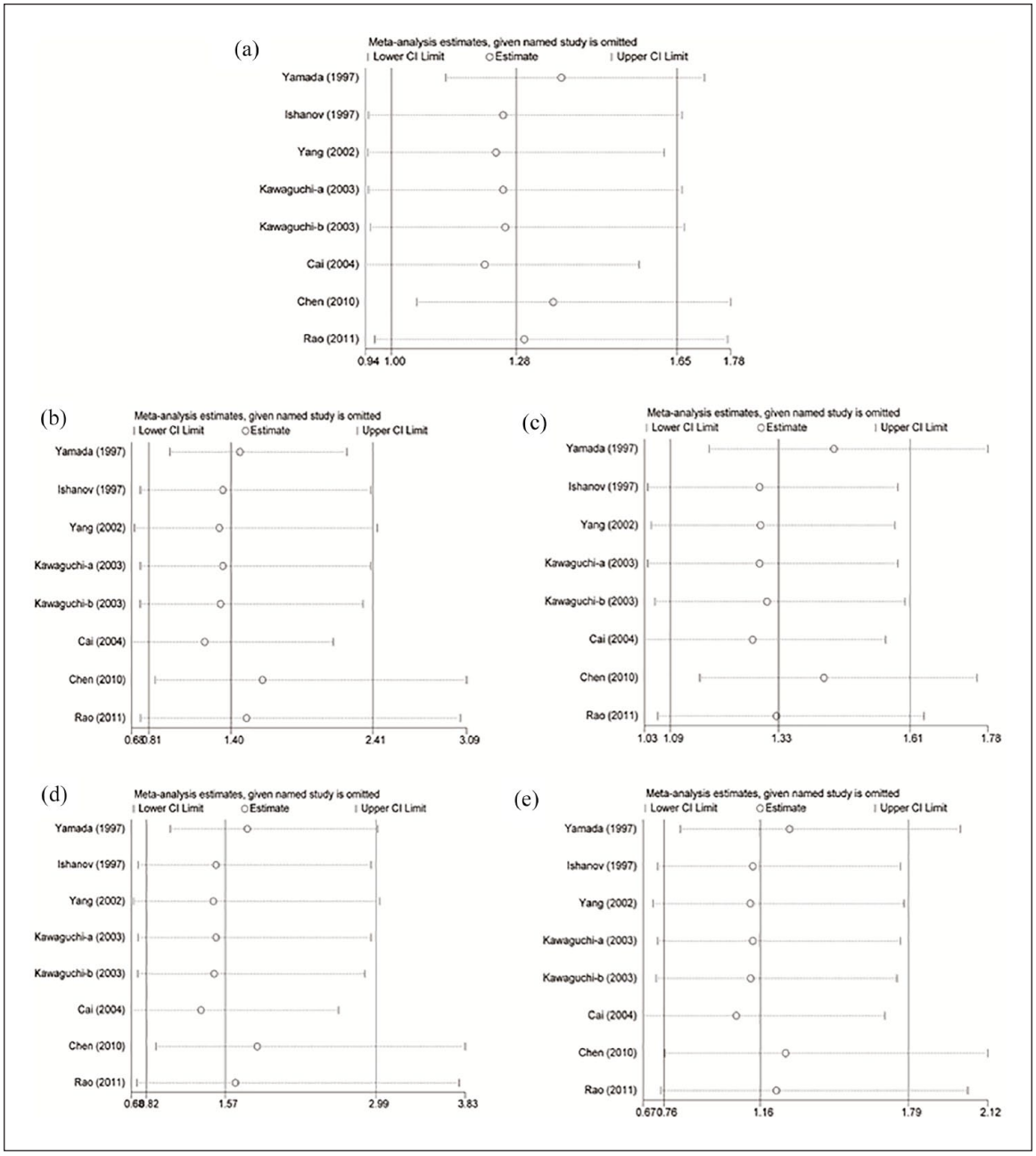

Figure 4. Sensitivity analysis of the studies of HWE satisfaction in the control group: (a) Allelic model, (b) Dominant model, (c) Recessive model, (d) Homozygous model, and (e) Heterozygote model.

grouping the countries, the heterogeneity did not decrease and remained large. The results of combined analysis showed that AGT M235T polymorphism has no significant association with HCM in these three populations. Subgroup analysis on whether the control groups met HWE showed that except for the study by Rani et al.,[20] the control groups in the other studies met the HWE. But due to its high quality, the study by Rani et al. was included in the overall analysis. The results showed that the heterogeneity of each genetic model was significantly reduced after removing this article, which indicated that it was also a source of heterogeneity. Subgroup analysis of the control groups in accordance with HWE showed that only the recessive gene genetic model showed statistically significant changes, while the allele model and other three gene genetic models showed no statistical significance. This result is consistent with the overall comparison.

FHCM and SHCM is the two types of HCM. There are four included studies[16,17,19,26] can extract data to analyze these two types. The results showed that the heterogeneity was significantly reduced in the allele model and the other four genetic models. Except for the slight heterogeneity in

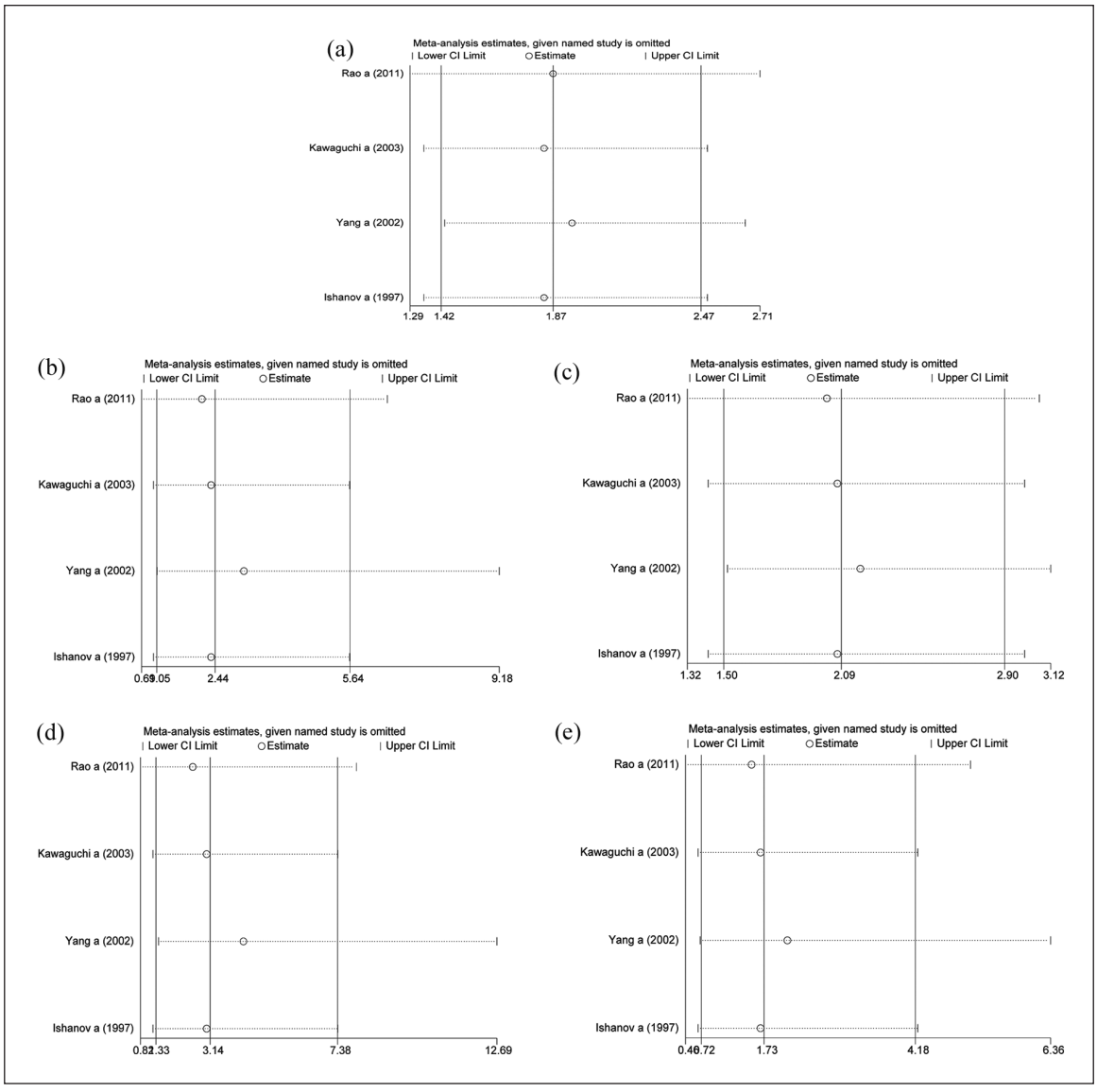

Figure 5. Sensitivity analysis results of SHCM group: (a) Allelic model, (b) Dominant model, (c) Recessive model, (d) Homozygous model, (e) Heterozygote model.

the allele model of FHCM ($I^2 = 53.5\%$), there was no heterogeneity in the other genetic models of FHCM and the five genetic models of SHCM. This indicated that HCM typing was the main heterogeneous source of AGT M235T polymorphism and susceptibility to HCM in Asian population. The results showed that there was no statistically significant difference between the five genetic models of AGT M235T polymorphism and FHCM, while there was no correlation between the heterozygous genetic model and SHCM. Sensitivity analysis also confirmed this result which was consistent with the conclusion of overall comparison. However, the allele model, dominant, recessive, and homozygous genetic model are significantly correlated with HCM. The results of sensitivity analysis show that the results of allele model and recessive gene genetic model are robust. However, the dominant gene genetic model and homozygous genetic model have certain instability. Study of Yao et al.[21] suggests that the AGT M235T recessive gene genetic model is correlated with HCM in the overall comparison of Asian population. After the HCM classification of the whole population, the AGT M235T polymorphism is not correlated with FHCM, but is significantly correlated with SHCM. This study is consistent with its conclusion. This meta-analysis included more studies and confirmed such a correlation to a deeper extent.

This study still has some limitations: (1) there is publication bias. In the allele model, dominant and heterozygous genetic model, the p value of Egger's Test is less than 0.05, which indicates that there is publication bias which may have a potential impact on the conclusion

reached at present; (2) there is some heterogeneity in the overall comparison, and the source of heterogeneity is probably mainly from HCM typing. But only four studies on HCM typing were analyzed currently. The low sample size may have certain limitations on the extrapolation of results; (3) sensitivity analysis shows that there is a certain instability in the allele model, dominant and homozygous genetic models; and (4) The interaction between genes-genes and genes-environment may play a certain role, but due to the lack of relevant data, we cannot conduct further research on it.

In conclusion, there is a significant correlation between AGT M235T polymorphism and HCM in Asian population, and especially in SHCM patients. Heterozygotes significantly increase the disease risk of SHCM patients in Asian population. Our research provides more theoretical basis for understanding the relationship between AGT M235T gene polymorphism and HCM susceptibility in Asian populations, and provides strong evidence for HCM prevention and treatment. However, considering the limitations, further clinical researches with higher quality are still required to confirm our results.

Declaration of conflicting interests

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ORCID iD

Xiwei Xu https://orcid.org/0000-0002-9465-830X

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