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Original Article

Association between angiotensinogen M235T polymorphism and hypertrophic cardiomyopathy

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Abstract: Background: To investigate the relationship between angiotensinogen (AGT) gene M235T polymorphism and hypertrophic cardiomyopathy (HCM) to explore the potential role of the AGT polymorphism in HCM. Methods: PubMed, Embase, OVID, Cochrane library, CNKI, Wan Fang Database were searched to identify the studies involving AGT M235T polymorphism and HCM. Two authors performed independent literature review and study quality assessment using the Newcastle-Ottawa Scale (NOS) checklist. A random-effects model was used to calculate the overall combined risk estimates. Results: Nine studies involving 887 cases and 1407 controls were included in our meta-analysis. No significant associations were found between AGT M235T polymorphism and HCM (allele model T vs M: OR = 1.17, 95% CI = 0.95-1.45; dominant model TT vs (MM/MT): OR = 1.21, 95% CI = 1.00-1.45; recessive model (TT/MT) vs MM: OR = 1.12, 95% CI = 0.87-1.45; heterozygous comparison MT vs MM: OR = 1.07, 95% CI = 0.82-1.41; homozygous comparison TT vs MM OR = 1.19, 95% CI = 0.88-1.61. In subgroup analysis, the significant difference of association between AGT M235T polymorphism and HCM existed in Asian and sporadic hypertrophic cardiomyopathy (SHCM), but no significant difference was found in Europeans and familial hypertrophic cardiomyopathy (FHCM). Conclusions: There is no association between AGT M235T polymorphism and HCM in general populations, but such a relationship exists in Asians and SHCM.

Keywords: Hypertrophic cardiomyopathy, angiotensinogen, gene polymorphism, meta-analysis

Introduction

Hypertrophic cardiomyopathy (HCM) is characterized by left ventricular hypertrophy (LVH) with impaired diastolic function [1]. The prevalence of the disease is about 1 in 500 in general populations [2]. HCM is a primary autosomal dominant inherited disorder affecting heart muscle with heterogeneity in its clinical manifestations, natural history, and prognosis. It has an incidence of about 2.5 per 100,000 per year and its mortality rate is 0.7% per year, which attributes to the common cause of sudden cardiac death in young people and athletes [2, 3]. It is estimated that familial hypertrophic cardiomyopathy (FHCM) accounts for two-thirds cases of HCM with at least two affected close relatives in each family [4]. Therefore, risk stratification and early identification of high-risk patients are important in clinical practice.

Mutations in genes encoding sarcomere protein account for the most important class in HCM. To date, at least 18 gene mutations coding for sarcomere proteins have been identified in patients with HCM [5]. In some cases, although family members have the same identical mutation, some of them do not develop disease. Environment factors, age, sex, and modifier genes may account for the variations. It is reported that renin-angiotensin system (RAS) plays an important role in cellular hypertrophy, blood pressure, cell proliferation, and cardiac function [6]. Angiotensinogen (AGT) gene is the main component of RAS, which is located at chromosome lq42-43, with 12,000 bp in length and five exons and four introns [7]. AGT is produced by the liver and converted to angiotensin I by renin. Angiotensin I is further converted to angiotensin II. The M235T (rs699) polymorphism, altering methionine to threonine at residue 235 of the mature protein, has been associated with high plasma AGT levels among patients with the T allele [8]. It is reported that AGT M235T polymorphism has been associat-

ed with cardiovascular disease risk such as myocardial infarction, LVH and coronary atherosclerosis [5]. However, inconsistent results were observed in literatures.

In order to further evaluate the association between AGT M235T polymorphism and hypertrophic cardiomyopathy risk, we therefore performed a systematic meta-analysis of all available data from case-control studies, aiming to better understand the relationship between AGT M235T polymorphism and hypertrophic cardiomyopathy susceptibility.

Methods

We attempted to follow the proposed MOOSE (Meta-Analysis of Observational Studies in Epidemiology) 10 guidelines to report the present meta-analysis [9].

Literature search strategies

We searched PubMed, Embase, OVID, Cochrane library, CNKI (Chinese National Knowledge Infrastructure), Wanfang Databases through October 2014, and systematically identified case-control studies with the use of a standardized protocol. The following search terms were used: 1) renin-angiotensin-aldosterone system, renin-angiotensin system, angiotensinogen; 2) hypertrophic cardiomyopathy, HCM, familial hypertrophic cardiomyopathy, FHCM, sporadic cardiomyopathy, SHCM; 3) polymorphism, mutation. The search was limited to articles in English and Chinese. Two reviewers (J.-L.Y. and Y.-F.Z.) independently evaluated identified titles and abstracts, and manuscripts were retrieved for any publication that either review considered as potentially relevant. Additional publications were sought using the reference lists of identified papers; published reviews on the topic. The results sections and tables of these studies were then examined to see if data on M235T genotype were reported.

Study selection

Two blinded reviewers re-evaluate all of the abstracts and manuscripts identified as potentially relevant, and publications were selected for this review if both reviewers concluded that they met the following criteria: 1) the study was a case-control study; 2) the study was about the relationship between AGT M235T genotype and cardiovascular risk; 3) the control groups were healthy people; and 4) Odds ratio (OR) and the corresponding 95% confidence interval (CI) (or data to calculate them) were reported; 5) of HWE (Hardy-Weinberg equilibrium) in control ($P > 0.05$); 6) if the same population was studied in more than one study, we included the study with the larger sample size and more comprehensive outcome evaluation. Studies were included in this review if both authors considered relevant. Any discordance between reviewers was resolved by consensus.

Data extraction

Data extraction was then performed using a standardized data-collection form: first author's name; year of publication; country of origin; ethnicity; source of controls; number of genotypes in cases and controls; the *P* value of Hardy-Weinberg equilibrium (HWE) in control. If any data essential to the analysis were not available from a study, best efforts were made to contact the authors to fill in the missing data. Two authors independently conducted the data extraction. Any disagreements were resolved by discussion.

Quality assessment

The quality of studies was independently assessed by two reviewers using the 9-point Newcastel-Ottawa Scale (NOS). The quality of each study was assessed based on three broad perspectives including selection, comparability, and exposure. A total score of seven or greater indicated that one study was of high quality.

Statistical analysis

OR and 95% CIs were calculated to assess the strength of the association between AGT M235T polymorphism and hypertrophic cardiomyopathy. The pooled ORs were calculated using five models: allele model (T allele vs M allele), dominant model (TT + MT vs MM), recessive model (TT vs MM + MT), homozygous comparison (TT vs MM), and heterozygous comparison (MT vs MM). Homogeneity of ORs across studies was tested using the Q statistic (significance level at $P < 0.10$). The I^2 statistic, which is a quantitative measure of inconsistency across studies, was also calculated [10]. If I^2 >50%, the results were pooled using a random effect model; otherwise, the fixed model was used [11].

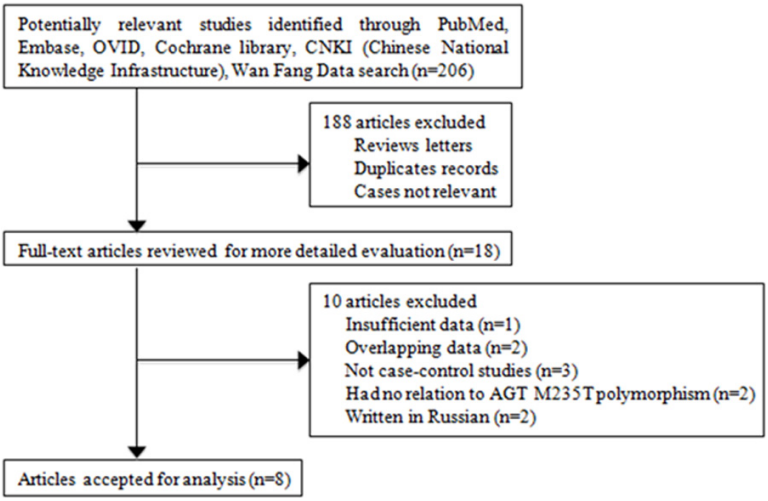

Figure 1. Flow chart of study chart.

HWE was examined in the control group using Pearson's chi square test, and $P < 0.05$ was considered as a significant selective bias. Potential publication bias was assessed by visual inspection of the funnel plots, in which the log ORs were plotted against their SEs. We also performed the Begg rank correlation test and Egger linear regression test at the $P < 0.10$ level of significance [12, 13]. If an asymmetric funnel plot was found, a contour-enhanced funnel plot was used to further explore the source of bias. A P value < 0.05 was considered statistically significant, except where otherwise specified. All analyses were performed using STATA version 12.0 (StataCorp LP, College Station, Texas).

Results

Study selection and characteristics

A total of 206 records were identified by initial search in the selected database (**Figure 1**). After screening the titles and abstracts, 18 studies [14-31] were preliminarily included for further full-text identification. Then, we excluded studies based on the following reasons: two studies [21, 28] written in Russian, 2 studies [23, 31] as duplicated reports, 3 studies [25-27] not the case-control studies, 1 study with no sufficient data [22], 2 studies not related to M235T mutation [17, 24]. Consequently, 8 publications were included in our meta-analysis (details in **Figure 1**). Notably, one publication including two different groups was considered as separate studies. Thus, 9 studies from 8 articles [14-16, 18-20, 29], involving 887 cases and 1,407 controls were identified in total. The baseline characteristics of each study were presented in **Table 1**. Among all the included studies, 4 studies [14, 18, 30] (from 3 articles) analyzed HCM subtype (FHCM and SHCM) Genotypic distribution of studied SNP in controls was in accordance with HWE ($P > 0.05$) and the quality of all studies was considered as high with the average score of about 7.44 per study. The characteristics of all included studies are summarized in **Table 1**.

Statistical results

Overall, no significant association was detected between the AGT M235T polymorphism and hypertrophic cardiomyopathy risk in the four genetic models (allele model: OR = 1.17, 95% CI = 0.95-1.45, $P = 0.147$, **Figure 2**; dominant model: OR = 1.12, 95% CI = 0.87-1.45, $P = 0.374$; homozygous comparison: OR = 1.19, 95% CI = 0.88-1.61, $P = 0.251$; heterozygous comparison: OR = 1.07, 95% CI = 0.82-1.41, $P = 0.611$), except recessive model (OR = 1.21, 95% CI = 1.00-1.45, $P = 0.047$, **Table 3**). There was no evidence of heterogeneity for these outcomes (seen in **Table 2**).

We also performed subgroup analyses by HCM subtypes and ethnicity. As shown in **Figure 3**, we found that the variant homozygotes were significantly associated with increased susceptibility for SHCM (recessive model: OR = 2.06, 95% CI = 1.48-2.87, $P < 0.001$). Similar results were obtained in other three genetic models (allele model: OR = 1.87, 95% CI = 1.41-2.47, $P < 0.001$; dominant model: OR = 2.58, 95% CI = 1.12-5.94, $P = 0.026$; homozygous comparison: OR = 3.33, 95% CI = 1.43-7.77, $P = 0.005$). However, we observed no significant results in subgroup of FHCM. In terms of subgroup of ethnicity, the results suggested that AGT M235T polymorphism may increase the risk of HCM under recessive model (OR = 1.29, 95% CI = 1.04-1.59, $P = 0.019$) in Asians (**Figure 4**). The heterogeneity among the included 9 studies is not significant except the allele model (details in **Table 3**).

Table 1. Characteristics of 8 case-control studies of AGT M235T polymorphism and HCM

Study	Year	Country	Ethnicity	HCM Genotypes			Control Genotypes			Allelic frequency (Case/Control)		Source of control	HWE Y/N (*P*)	Study score
				TT	MT	MM	TT	MT	MM	T	M			
Rao	2011	India	Asian	70	68	12	65	85	15	208/215	92/115	Age and sex matched healthy subjects	Y (0.08)	8
Coto	2010	Spain	European	41	100	64	60	145	95	182/265	228/335	Ethnic matched healthy subjects	Y (0.73)	7
Chen	2010	China	Asian	36	42	16	52	50	18	114/154	74/86	Hospital-based individals did not have symptoms of cardiovascular disease	Y (0.30)	7
Cai	2004	China	Asian	45	22	5	36	30	14	112/102	32/58	Healthy subjects	Y (0.09)	7
Kawaguchi-a	2003	Japan	Asian	67	28	1	94	61	5	162/249	30/71	Healthy subjects	Y (0.19)	8
Kawaguchi-b	2003	Japan	Asian	67	28	1	63	38	4	162/164	30/46	Relatives of HCM patients	Y (0.55)	8
Yang	2002	China	Asian	42	17	4	45	30	11	101/120	25/52	Healthy subjects	Y (0.11)	7
Lopez-Haldon	1999	Spain	European	7	20	13	54	128	87	34/236	46/302	Healthy subjects	Y (0.58)	7
Yamada	1997	Japan	Asian	37	29	5	76	44	2	103/196	39/48	Healthy subjects	Y (0.12)	8

Table 3. Subgroup analysis of different genetic models by ethnicity and disease subtype

Subgroup	Number	T vs M		TT + MT vs MM		TT vs MM + MT		MT vs MM		TT v sMM	
		OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
FHCM	4	1.87 (1.41, 2.47)	< 0.001	2.58 (1.12, 5.94)	0.026	2.06 (1.48, 2.87)	< 0.001	1.82 (0.76, 4.37)	0.177	3.33 (1.43, 7.77)	0.005
SHCM	4	1.09 (0.71, 1.68)	0.699	0.99 (0.50, 1.97)	0.975	1.02 (0.72, 1.46)	0.894	0.96 (0.47, 1.99)	0.919	0.96 (0.47, 1.98)	0.919
Asian	7	1.00 (0.80, 1.24)	0.963	1.02 (0.72, 1.42)	0.933	0.96 (0.65, 1.43)	0.857	1.03 (0.72, 1.47)	0.877	0.98 (0.63, 1.54)	0.933
European	2	1.25 (0.94, 1.67)	0.120	1.30 (0.87, 1.92)	0.207	1.29 (1.04, 1.59)	0.019	1.14 (0.75, 1.75)	0.546	1.48 (0.74, 2.94)	0.107

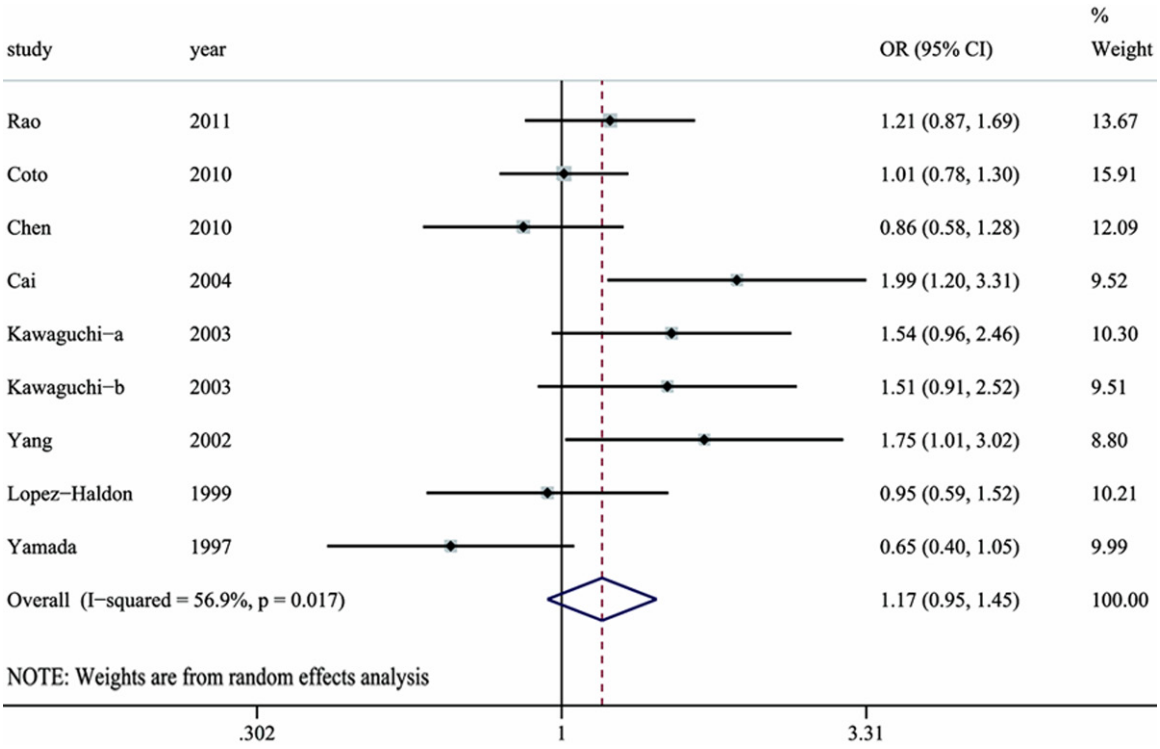

Figure 2. Forest plot of AGT M235T polymorphism and HCM in allelic model.

Table 2. Odds ratio and heterogeneity tests for AGT M235T polymorphism and HCM in different models

HCM vs control	I^2	Model	Odds ratio	95% CI		
				L limit	U limit	*P*-value
T vs M	57%	Random	1.17	0.95	1.45	0.147
TT+MT vs MM	24%	Fixed	1.12	0.87	1.45	0.374
TT vs MM + MT	40%	Fixed	1.21	1.00	1.45	0.047
MT vs MM	0	Fixed	1.07	0.82	1.41	0.611
TT vs MM	42%	Fixed	1.19	0.88	1.61	0.251

Publication bias

Begg's funnel plot and Egger's test were applied to assess the publication bias of studies in this meta-analysis. As shown in **Figure 5**, the funnel plots seemed symmetrical in allele model, and the result of Begg's test ($P = 0.251$ for allele model, $P = 0.348$ for dominant model, $P = 0.602$ for recessive model, $P = 0.348$ for homozygous comparison, $P = 0.251$ for heterozygous comparison) confirmed no significant pub-lication bias existing in our study. Similar results were observed in the Egger's test ($P = 0.321$ for allele model; $P = 0.376$ for dominant model; $P = 0.867$ for recessive model; $P = 0.415$ for homozygous comparison; $P = 0.497$ for heterozygous comparison; respectively).

Discussion

The renin-angiotensin system (RAS) plays an important role in the development of LVH because of its action on cell proliferation, cellular hypertrophy, and in part of the development of cardiac hypertrophy. Angiotensinogen (AGT) is a glycoprotein consisting of 485 amino acids produced by the hepatocytes and released into the circulation. It is the precursor peptide of Ang II, which can exerts inotropic, hypertrophic and apoptotic effects on cardiomyocytes and is the central for any process involving in control of hypertrophy and heart failure [6]. Since the cardiac RAS plays an important role in the development of cardiac hypertrophy, the concentration of angiotensinogen is rate limiting in the production of angiotensin I, which plays a significant role in the regulation of angiotensin II production. AGT gene is located on chromosome Iq42 and comprises five exons and four introns spanning 12 kb [7]. The M235T polymorphism of the

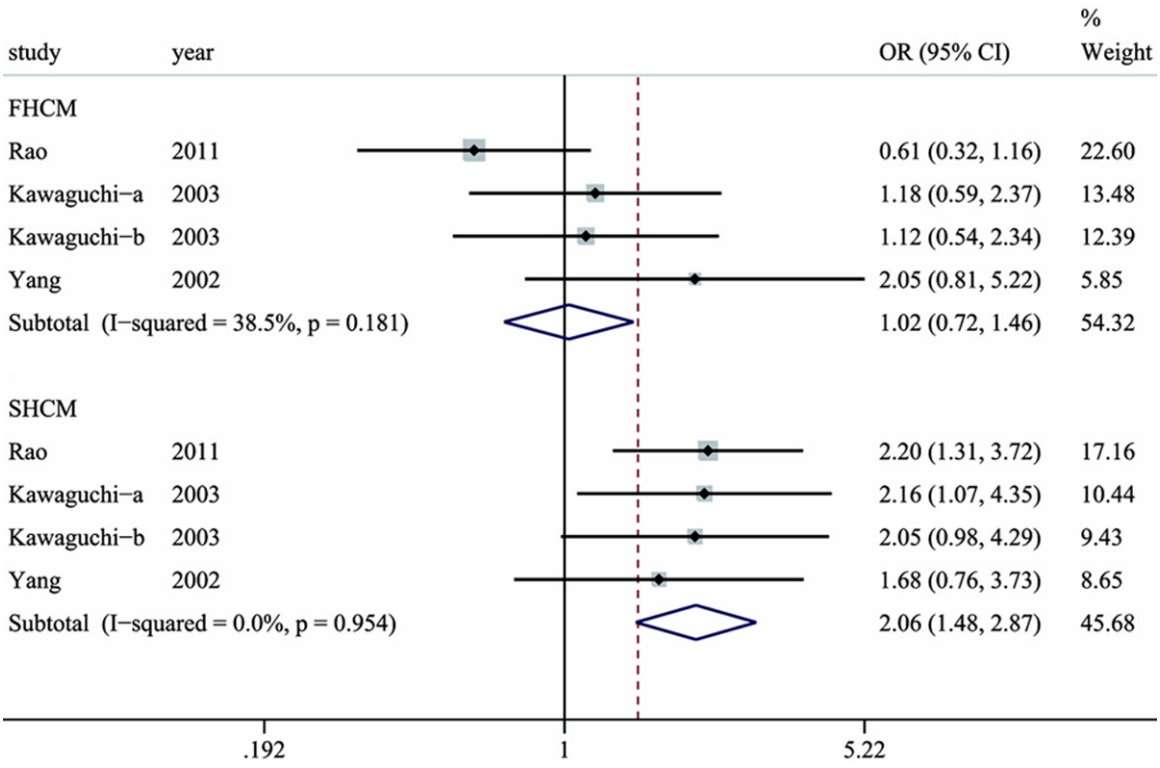

Figure 3. Forest plot of AGT M235T polymorphism and SHCM in recessive model.

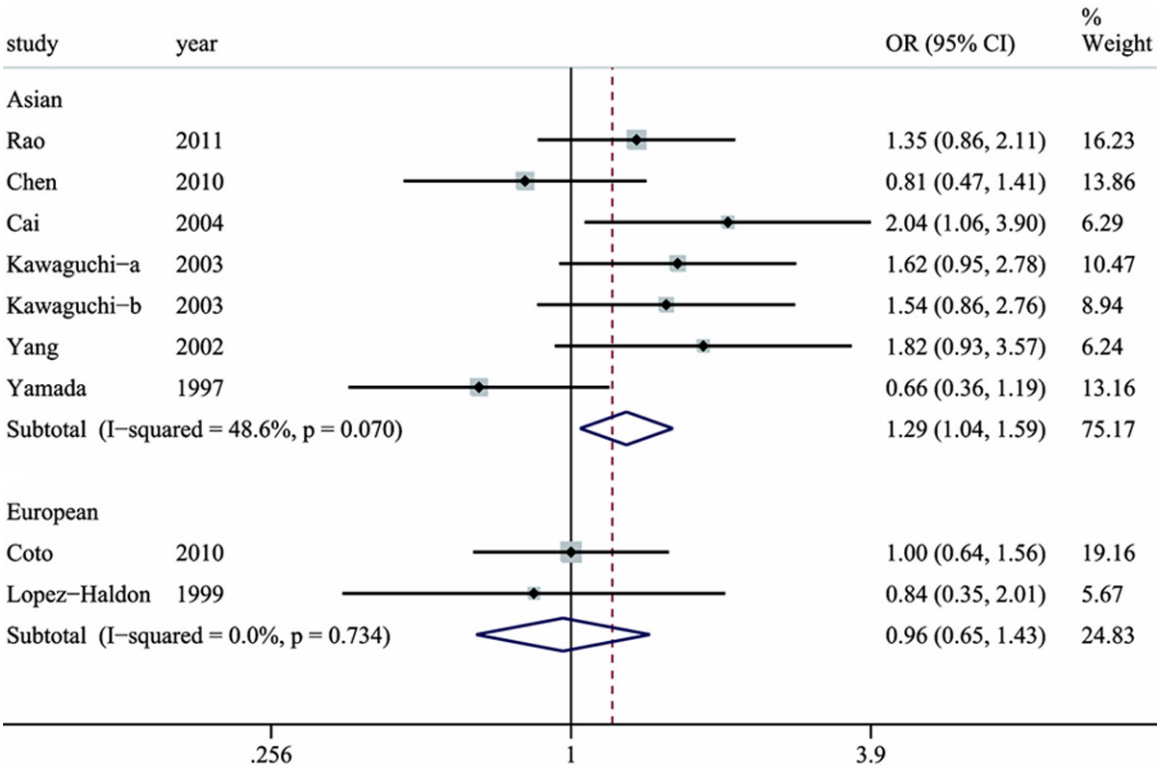

Figure 4. Forest plot of AGT M235T polymorphism and HCM in Asians in recessive model.

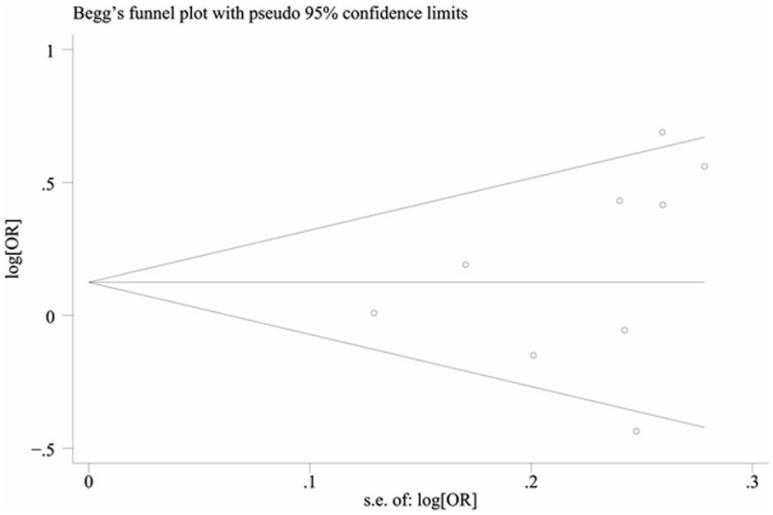

Figure 5. Funnel plot.

AGT gene is associated with increased plasma levels of AGT [32]. Thus, the polymorphism of AGT M235T may have relation to the development of hypertrophic cardiomyopathy. Over the last decade, there were several case-control studies attempting to investigate the relationship, but the results were inconclusive. Some studies [14, 16, 18, 23] have reported a positive association whereas others [19, 20] did not find any association with HCM. Consequently, we conducted the present meta-analysis to further analyze the impact of AGT M235T polymorphism on hypertrophic cardiomyopathy susceptibility.

The present meta-analysis included nine studies with a total of 887 cases and 1,407 controls. Overall, our results found that AGT M235T polymorphism was not directly associated with hypertrophic cardiomyopathy risk. In subgroup analysis of HCM subtype, however, a significant association between AGT M235T polymorphism and SHCM risk was observed. The lack of association of this polymorphism with FHCM shows that this mutation is associated with SHCM rather that FHCM where the mutations in sarcomeric genes have been found to be associated with the disease. The familial and sporadic forms of HCM represent two different parts of the spectrum with the same condition, and have significant implications in relation to risk factor stratification and also genetic counseling. The RAS may also be associated with hypertrophy of FHCM. However, the degree of its contribution is greaterin SHCM than in FHCM, indicating that SHCM is partially determined by genetic disposition.

Given the fact that different racial populations possess different genetic background, we also conducted subgroup analyses in terms of ethnicity for further exploration. The association existed in Asian people. In addition, Cai et al [16] found that TT carriers had more chance to develop HCM than variant allele carriers, indicating this polymorphism might influence the biological characteristics of HCM in Asian populations. To our knowledge, this was the first time to evaluate the association between this polymorphism and HCM risk in Asian ethnicity.

It is known that heterogeneity has a significant influence on the reliability in interpreting the results of meta-analyses. In our study, moderate heterogeneity was found in the overall comparisons. When stratified analysis by HCM subtype, there was no heterogeneity in SHCM, which means that the results regarding HCM subtype were trusted. When stratified analysis by ethnicity, moderate heterogeneity was found in Asians. The reason might be the presence of different genetic backgrounds and environments in different ethnicities and individuals.

It is prudent to acknowledge that several potential limitations are apparent. First of all, we did not receive a response from the corresponding authors of one study. Therefor we did not include it in our meta-analysis. Thus there might be the possibility of publication bias, but the results of statistical tests showed that publication bias is unlikely. In addition, our analysis is based on observational studies. Potential biases may exist. Gene-gene interactions and interactions between genes and other environmental factors may play a role, which could not be included in our meta-analysis due to a lack of relative data. Last but not the least, due to the limited participant data provided by individual studies, we could not make a more precise assessment by ruling out confounding factors which may lead to biased results.

Conclusions

In conclusion, our meta-analysis indicated that the AGT M235T polymorphism might not be directly associated with HCM in general populations. However, such a relationship may exist in SHCM and Asians. More large-scale and well-designed studies are warranted for further verification of our results in the future.

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Disclosure of conflict of interest

None.

Abbreviations

HCM, Hypertrophic cardiomyopathy; SHCM, Sporadic hypertrophic cardiomyopathy; FHCM, Familial hypertrophic cardiomyopathy; OR, Odds ratio; AGT, Angiotensinogen.

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References

[1] Schwartz K, Carrier L, Guicheney P and Komajda M. Molecular basis of familial cardiomyopathies. Circulation 1995; 91: 532-540.

[2] Marian AJ, Mares A Jr, Kelly DP, Yu QT, Abchee AB, Hill R and Roberts R. Sudden cardiac death in hypertrophic cardiomyopathy. Variability in phenotypic expression of beta-myosin heavy chain mutations. Eur Heart J 1995; 16: 368-376.

[3] Marian AJ. Pathogenesis of diverse clinical and pathological phenotypes in hypertrophic cardiomyopathy. Lancet 2000; 355: 58-60.

[4] Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P, Dubourg O, Kuhl U, Maisch B, McKenna WJ, Monserrat L, Pankuweit S, Rapezzi C, Seferovic P, Tavazzi L and Keren A. Classification of the cardiomyopathies: a position statement from the European Society Of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2008; 29: 270-276.

[5] Carrier L, Friedrich FW. Genetics of hypertrophic and dilated cardiomyopathy Curr Pharm Biotechnol 2012; 13: 2467-2476.

[6] Schluter KD and Wenzel S. Angiotensin II: a hormone involved in and contributing to pro-hypertrophic cardiac networks and target of anti-hypertrophic cross-talks. Pharmacol Ther 2008; 119: 311-325.

[7] Jeunemaitre X, Inoue I, Williams C, Charru A, Tichet J, Powers M, Sharma AM, Gimenez-Roqueplo AP, Hata A, Corvol P and Lalouel JM. Haplotypes of angiotensinogen in essential hypertension. Am J Hum Genet 1997; 60: 1448-1460.

[8] Mehri S, Mahjoub S, Farhati A, Bousaada R, Ben Arab S, Baudin B and Hammami M. Angiotensinogen gene polymorphism in acute myocardial infarction patients. J Renin Angiotensin Aldosterone Syst 2011; 12: 42-47.

[9] Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA and Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008-2012.

[10] Higgins JP, Thompson SG, Deeks JJ and Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557-560.

[11] DerSimonian R and Kacker R. Random-effects model for meta-analysis of clinical trials: an update. Contemp Clin Trials 2007; 28: 105-114.

[12] Begg CB and Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994; 50: 1088-1101.

[13] Egger M, Davey Smith G, Schneider M and Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-634.

[14] Polugari Prem Kumar Manohar R, Munshi A, Mullapudi R, Potham Sampath K, Sharath A, Gundala Anil K and Sadhnani M. The M235T polymorphism of the angiotensinogen gene in South Indian patients of hypertrophic cardiomyopathy. J Renin Angiotensin Aldosterone Syst 2011; 12: 238-242.

[15] Coto E, Palacin M, Martin M, Castro MG, Reguero JR, Garcia C, Berrazueta JR, Moris C, Morales B, Ortega F, Corao AI, Diaz M, Tavira B and Alvarez V. Functional polymorphisms in genes of the Angiotensin and Serotonin systems and risk of hypertrophic cardiomyopathy: AT1R as a potential modifier. J Transl Med 2010; 8: 64.

[16] Cai SY, Shi YP, Yu F and Xu G. [Association of angiotensinogen gene M235T variant with hypertrophic cardiomyopathy]. Zhonghua Yi Xue Yi Chuan Xue Za Zhi 2004; 21: 280-282.
[17] Wang S, Wang J, Zou Y, Wang J, Wang H and Hui R. Angiotensinogen gene variations and LV outflow obstruction in hypertrophic cardiomyopathy. Herz 2014; 39: 258-263.
[18] Kawaguchi H. Angiotensin-converting enzyme and angiotensinogen gene polymorphism in hypertrophic cardiomyopathy. Exp Clin Cardiol 2003; 8: 155-159.
[19] Lopez-Haldon J, Garcia-Lozano JR, Martinez Martinez A, Nunez-Roldan A and Burgos Cornejo J. [The effect of polymorphisms of the angiotensin-converting enzyme and angiotensinogen genes on the phenotypic expression of Spanish patients with hypertrophic cardiomyopathy]. Med Clin (Barc) 1999; 113: 161-163.
[20] Yamada Y, Ichihara S, Fujimura T and Yokota M. Lack of association of polymorphisms of the angiotensin converting enzyme and angiotensinogen genes with nonfamilial hypertrophic or dilated cardiomyopathy. Am J Hypertens 1997; 10: 921-928.
[21] Kozhevnikova MV, Kaplunova V, Privalova EV, Khabarova NV and Belenkov Iu N. [Renin-angiotensin-aldosterone system in hypertrophic cardiomyopathy]. Kardiologiia 2014; 54: 23-28.
[22] Zhou Ju FK, Xiao Bai. Association between AGT M235T polymorphism and hypertrophic cardiomyopathy ,hypertension. China Journal of Cardiology 2003; 31: 273.
[23] Ishanov A, Okamoto H, Yoneya K, Watanabe M, Nakagawa I, Machida M, Onozuka H, Mikami T, Kawaguchi H, Hata A, Kondo K and Kitabatake A. Angiotensinogen gene polymorphism in Japanese patients with hypertrophic cardiomyopathy. Am Heart J 1997; 133: 184-189.
[24] Ortlepp JR, Vosberg HP, Reith S, Ohme F, Mahon NG, Schroder D, Klues HG, Hanrath P and McKenna WJ. Genetic polymorphisms in the renin-angiotensin-aldosterone system associated with expression of left ventricular hypertrophy in hypertrophic cardiomyopathy: a study of five polymorphic genes in a family with a disease causing mutation in the myosin binding protein C gene. Heart 2002; 87: 270-275.
[25] Kolder IC, Michels M, Christiaans I, Ten Cate FJ, Majoor-Krakauer D, Danser AH, Lekanne Deprez RH, Tanck M, Wilde AA, Bezzina CR and Dooijes D. The role of renin-angiotensin-aldosterone system polymorphisms in phenotypic expression of MYBPC3-related hypertrophic cardiomyopathy. Eur J Hum Genet 2012; 20: 1071-1077.
[26] Brugada R, Kelsey W, Lechin M, Zhao G, Yu QT, Zoghbi W, Quinones M, Elstein E, Omran A, Rakowski H, Wigle D, Liew CC, Sole M, Roberts R and Marian AJ. Role of candidate modifier genes on the phenotypic expression of hypertrophy in patients with hypertrophic cardiomyopathy. J Investig Med 1997; 45: 542-551.
[27] Kaufman BD, Auerbach S, Reddy S, Manlhiot C, Deng L, Prakash A, Printz BF, Gruber D, Papavassiliou DP, Hsu DT, Sehnert AJ, Chung WK and Mital S. RAAS gene polymorphisms influence progression of pediatric hypertrophic cardiomyopathy. Hum Genet 2007; 122: 515-523.
[28] Belenkov YN, Privalova EV, Kaplunova VY, Stambol'skii DV and Fomin AA. [Analysis of morpho-functional parameters of the heart and polymorphisms of Renin-Angiotensin-aldosterone system genes in patients with different variants of the course of hypertrophic cardiomyopathy]. Kardiologiia 2010; 50: 27-34.
[29] Chen Duoxue WA, Kong Dehua. Angiotensinogen gene M235T polymorphism and hypertrophic cardiomyopathy. Anhui Medical and Pharmoaceutical Hournal 2010; 14: 180-182.
[30] Yang Rong ZF, Ma Wenzhu. Angiotensinogen M235T gene polypmorphisms in hypertrophic cardiomyopathy. China Journal of Modern Medicine 2002; 12: 43-45.
[31] Yang Rong ZF, Ma Wenzhu. Linkage analysis of angiotensin converting enzyme gene insertion/deletion polymorphism of the gene polymorphism and angiotensinogen M235T with hypertrophic cardiomyopathy. Chinal Journal of Cardiology 2001; 29: 231-234.
[32] Campbell CY, Fang BF, Guo X, Peralta CA, Psaty BM, Rich SS, Young JH, Coresh J, Kramer HJ, Rotter JI and Post WS. Associations between genetic variants in the ACE, AGT, AGTR1 and AGTR2 genes and renal function in the Multiethnic Study of Atherosclerosis. Am J Nephrol 2010; 32: 156-162.