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Review Article

Association of Matrix Metalloproteinase-9 Gene -1562C/T Polymorphism with Essential Hypertension: A Systematic Review and Meta-Analysis Article

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Abstract

Background: Matrix metalloproteinase-9 (MMP-9) gene -1562C/T polymorphism could regulate its expression level and thus affected people's predisposition to essential hypertension. However, related studies yielded inconsistent or contradictory results.

Methods: To evaluate the association of MMP-9 -1562C/T polymorphism with essential hypertension, we performed a meta-analysis by combining all available independent case-control studies (n=6).A systematic literature search of PubMed, Web of Science, Scopus and CNKI (Chinese National Knowledge Infrastructure) databases was conducted by two researchers independently for all relevant articles published before March 2015.

Results: MMP-9 -1562C/T polymorphism was associated with essential hypertension under the allelic model (T vs.C, OR=1.36, 95% CI=1.17-1.59, *P*<0.0001). Subsequent sensitivity analysis confirmed the stability of the results. Such association was also observed in the dominant (TT+CT vs. CC, OR=1.30, 95% CI=1.10-1.54, *P*=0.002) and co-dominant (CT vs. TT+CC, OR=1.27, 95% CI=1.05-1.53, *P*=0.01) models but not in the recessive model (TT vs. CT+CC, OR=1.30, 95% CI=0.50-3.36, *P*=0.59).

Conclusion: MMP-9 -1562C/T polymorphism was associated with the risk of essential hypertension.

Keywords: MMP-9, Essential hypertension, Meta-analysis

Introduction

Essential hypertension is considered as one of the most important risk factor forchronic cardiovascular remodeling and dysfunction (1). It has become a major cause of morbidity and mortality worldwide (2, 3). However, the etiology of essential hypertension remains unclear. In recent years, it has been suggested that matrix metalloproteinases (MMPs) may play an important role in the pathogenesis of essential hypertension through the regulation of extracellular matrix (ECM) remodeling (4-6).

Matrix metalloproteinases (MMPs) are a group of zinc-dependent proteolytic enzymes able to degrade various ECM components under bothphysiological and pathological conditions (7-9). Enhanced MMP activity is often found in clinical hypertension (1, 5, 10-14). As an important member of this family, MMP-9 (also called gelatinase B) can degrade gelatine, fragments of collagen degraded by collagenase and type IVcollagen. Increased MMP-9 levels have been reported in hypertensive patients (1, 12, 15).

Gene polymorphisms can potentially affect the expression levels of the corresponding genes. Given the reported involvement of MMP-9 in the development of essential hypertension (1, 15), several polymorphic sites of MMP-9 have been-widely investigated for their potential association with essential hypertension (16-21). Among them, the -1562C/T polymorphism (rs3918242) in the promoter region of MMP-9 has drawn some attention due to its reported ability to influence the expression of MMP-9 (22). Although Huang et al. have reported that MMP-9 -1562C/T polymorphism was significantly associated with essential hypertension (16), such association was not observed in other studies (17-19, 21). Therefore, there was still a controversy over the association of MMP-9 -1562C/T polymorphism with essential hypertension.

To address this issue, we performed a systemic review and a meta-analysis of all available genetic association studies of MMP-9 -1562C/T polymorphism related to essential hypertension to investigate the association of MMP-9 -1562C/T polymorphism with the risk of essential hypertension. This systemic review may help us to understand the role of MMP-9 in the development of essential hypertension better.

Materials and Methods

Literature Search

A systematic literature search of PubMed, Web of Science, Scopus and CNKI (Chinese National Knowledge Infrastructure) databases was conducted by two researchers independently for all relevant articles published before March 2015. The research key words included "primary hypertension", "essential hypertension", "MMP-9", "matrix metalloproteinase-9", "1562", "rs3918242", "variant", "genotype", "SNP", "mutation" and "polymorphism". We also manually searched the reference lists of the included studies to find additional eligible studies. Finally, 2,243 cases and 1,359 controls were included in this meta-analysis.

Inclusion and Exclusion Criteria

Studies included for this meta-analysis should meet the following criteria:1) case-control studies or cohort studies focusing on the association between MMP-9 -1562C/T polymorphism and essential hypertension; 2) patients have been clinically diagnosed with hypertension due to systolic blood pressure (SBP) > 140 mm Hg and/or diastolic blood pressure (DBP) > 90 mm Hg, or taking antihypertensive medications; 3) the numbers of patients and normotensive people with different genotypes were available. The exclusion criteria of the meta-analysis were: 1) animal studies; 2) meta-analyses, reviews, meeting abstracts or editorial comments; 3) studies with duplicate data or incomplete data for odds ratio (OR) calculation.

Data Extraction

Information was extracted from all eligible studies by two authors independently and checked by a third author with disparities resolved by consensus. The collected data included the first author's name, publication date, and country, the distribution of genotypes in cases and controls, genotyping method and the total number of cases and controls.

Statistical Analysis

We used Review Manager 5.2 (Cochrane Collaboration, Oxford, United Kingdom) and Stata (Version 12.0, Stata Corporation, Texas, USA) for all the statistical analysis. The association was evaluated with the use of the allelic model (mutation [M] allele versus wild [W] allele), the dominant model (WM+MM versus WW), the recessive model (MM versus WM+WW) and the co-dominant model (WM versus WW+MM), respectively. We calculated the OR and 95% CI for each study as well as the combined OR and corresponding 95% CI for all the included studies. The heterogeneity between individual studies was assessed using Chi-square-based Q-tests with the significance level set at $P< 0.1$ (23). If the heterogeneity existed among the included studies, we calculated the pooled OR using the random-effect model (the DerSimonian and Laird method) (24). Otherwise, we adopted the fixed-effect model (the Mantel–Haenszel method) (25). The significance of the pooled OR was assessed by Z-test with $P< 0.05$ considered significant. We also performed

sensitivity analysis by omitting an individual study each time to check whether any of these estimates could bias the overall estimate.

For each study, the Hardy–Weinberg equilibrium (HWE) was assessed by Fisher's exact test with P < 0.05 considered significant (26). The potential publication bias was checked by Begg's funnel plot (27) and the funnel plot asymmetry was assessed by Egger's linear regression test with the significance level set at *P*< 0.05 (28).

Results

Literature selection

The literature selection process was illustrated in Fig. 1.

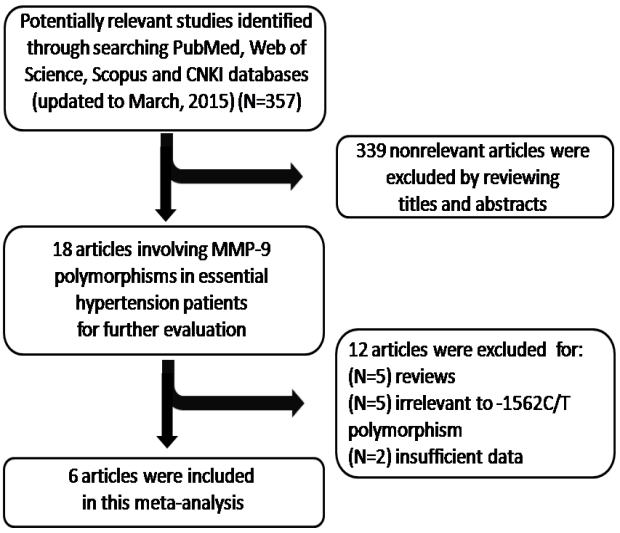

Fig. 1: Flow chart of study selection

Table 1: Characteristics of the six eligible studies included for the investigation of MMP-9 -1562C/T polymorphism's association with essential hypertension

First author	Year	Country	Sample size(case/control)	Method	Hypertension			Control		
					TT	CT	CC	TT	CT	CC
Huang	2013	China	984/244	PCR/LDR	129	168	687	14	45	185
Bayramoglu	2013	Turkey	125/99	PCR-RFLP	0	36	89	0	24	75
Lacchini	2010	Brazil	173/137	PCR-RFLP	0	44	129	2	25	110
Xu	2013	China	53/52	PCR-RFLP	1	14	38	0	11	41
Xing	2009	China	807/509	PCR-RFLP	19	212	576	14	101	394
Ma	2010	China	101/318	PCR-RFLP	NA	NA	87	NA	NA	261

NA, not available

We retrieved 357 articles totally after an initial search from the PubMed, Web of Science, Scopus and CNKI databases.

By reviewing the corresponding titles and abstracts, 339 of them were excluded due to lack of association with the relationship betweenMMP-9 -1562C/T polymorphismand essential hypertension. With reviews, meta-analyses, studies without sufficient data or replication study excluded, six eligible studies were finally analyzed. Thus, six case-control studies/groups involving 2,243 cases and 1,359 controls were included in this meta-analysis to evaluate the relationship between MMP-9 -1562C/T polymorphism and essential hypertension (16-21). Table 1 summarized the main characteristics of these included studies, including sample size, method, genotype distribution etc.

Pooled analysis

From five case-control studies, we recruited a total sample size of 3,183 subjects with 2,142 cases and 1,041 controls included for the evaluation of the relationship between MMP-9 -1562C/T polymorphism and essential hypertension. Under the allelic model (T allele vs.C allele), no obvious heterogeneity existed and therefore the fixed-effect model was adopted to pool the results ($P_{heterogeneity}$=0.76, I^2=0%). The corresponding meta-analysis result showed that MMP-9 -1562C/T polymorphism was associated with the risk of essential hypertension (OR=1.36, 95% CI=1.17-1.59, *P*<0.0001; Fig. 2).

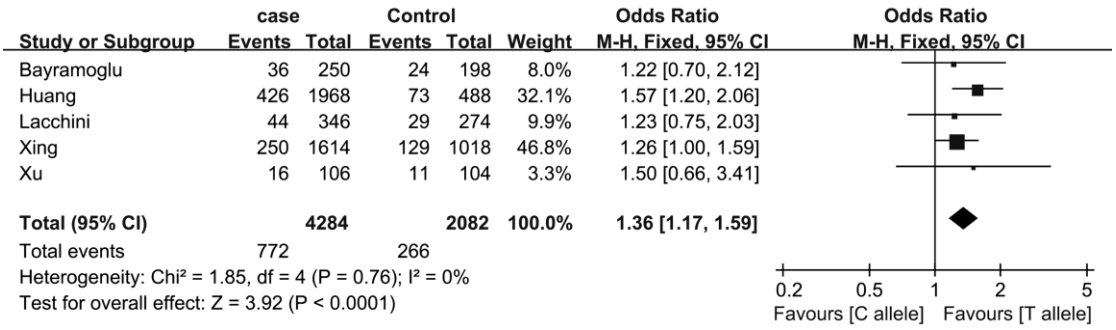

Fig. 2: Forest plot of essential hypertension associated with MMP-9 -1562C/T polymorphism under the allelic model (T allele vs. C allele)

We also performed sensitivity analysis to test the stability of the results. We removed one included study each time and calculated the pooled ORs for the remaining studies to check whether any of these estimates could bias the overall estimate. As Table 2 demonstrated, removal of any included studies still indicated that MMP-9 -1562C/T polymorphism was associated with the risk of essential hypertension. Therefore, the meta-analysis results showed by Fig. 2 were reliable and stable.

Table 2: Sensitivity analysis of the association of MMP-9 -1562C/T polymorphism with the risk of essential hypertension under the allelic model (T allele vs. C allele)

Excluded		OR	95% CI	*P*-value	Heterogeneity
First author	Sample				
Huang	China	1.26	1.05-1.53	0.01	0.98
Bayramoglu	Turkey	1.38	1.17-1.62	0.0001	0.64
Lacchini	Brazil	1.38	1.17-1.62	0.0001	0.64
Xu	China	1.36	1.16-1.59	0.0001	0.62
Xing	China	1.45	1.18-1.79	0.0005	0.77

OR, Odds ratio; CI, Confidence Interval; P-value, Meta-analysis P-value; heterogeneity, heterogeneity *P*-value

To explore further the potential way the T allele affected the risk of essential hypertension, we then evaluated the association under the other three genetic models. Since there was no obvious between-study heterogeneity in the dominant (TT+CT vs. CC, $P_{heterogeneity}$=0.63, I^2=0%) or co-dominant model (CT vs. TT+CC, $P_{heterogeneity}$=0.34, I^2=11%), thefixed-effect model was used for these two genetic models. The random-effect model was usedfor the recessive modeldue to the existence of significant between-studyheterogeneity (TT vs. CT+CC, $P_{heterogeneity}$=0.05, I^2=61%). There was no evident association of MMP-9 -1562C/T polymorphism with essential hypertension under the recessive model (TT vs. CT+CC, OR=1.30, 95% CI=0.50-3.36, *P*=0.59) (Fig. 3A). The TT and CT genotypes were associated with the risk of essential hypertension under the dominant model (TT+CT vs. CC, OR=1.30, 95% CI=1.10-1.54, *P*=0.002)(Fig. 3B). The CT genotype was associated with the risk of essential hypertension under the co-dominant model (CT vs. TT+CC, OR=1.27, 95% CI=1.05-1.53, *P*=0.01) (Fig. 3C). Collectively, it appeared that the CT genotype was the key risk factor for essential hypertension.

Publication bias

We employed Begg's funnel plot and Egger's linear regression test to evaluate the potential publication bias of the included studies. No obvious asymmetry of the funnel plot under the allelic model was observed (*P*=0.462, Fig. 4).

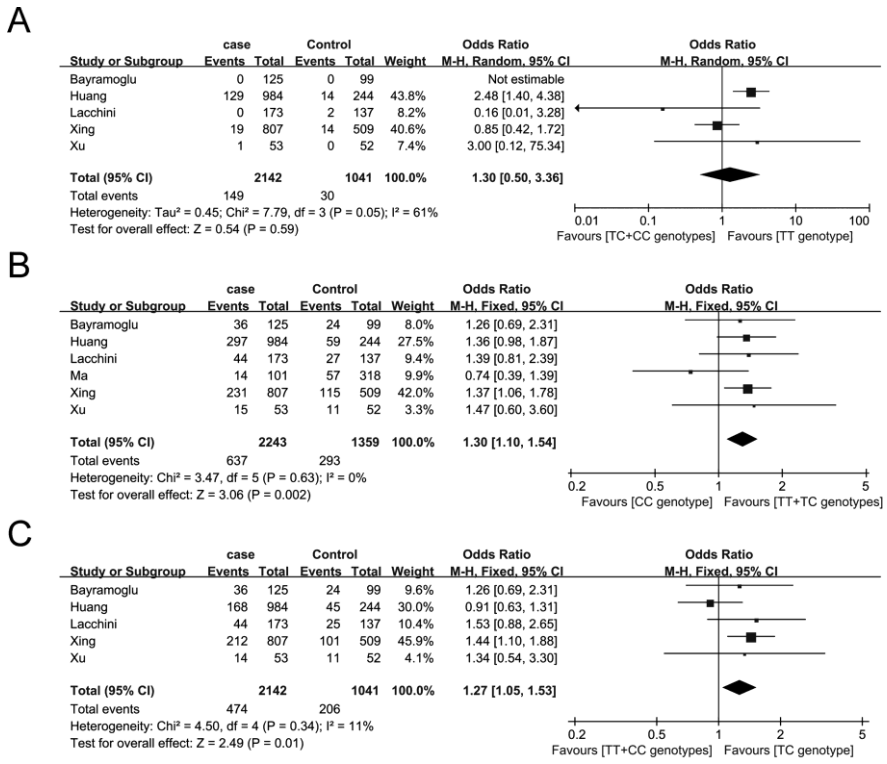

Fig. 3: Forest plot of essential hypertension associated with MMP-9 -1562C/T polymorphism under the recessive (TT vs. CT+CC) (A), dominant (TT+CT vs. CC) (B) and co-dominant (CT vs. TT+CC) (C) model

Egger's linear regression test did not show any significant statistical evidence of publication bias under the allelic model (*P*=0.906), either.

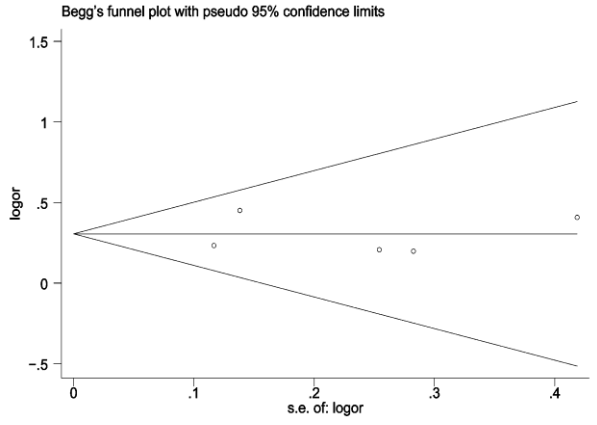

Fig.4: Begg's funnel plot of the meta-analysis ofessential hypertension associated with MMP-9 -1562C/T polymorphism under the allelic model. Each point represents an individual study. Logor: natural logarithm of OR; horizontal line: mean magnitude of the effect; s.e.: standard error

Discussion

Our meta-analysis showed that MMP-9 -1562C/T polymorphism was associated with essential hypertension under the allelic model (T vs.C, OR=1.36, 95% CI=1.17-1.59, *P*<0.0001). Corresponding sensitivity analysis confirmed the stability of such relationship. The association was also observed in the dominant (TT+CT vs. CC, OR=1.30, 95% CI=1.10-1.54, *P*=0.002) and co-dominant(CT vs. TT+CC, OR=1.27, 95% CI=1.05-1.53, *P*=0.01) models but not in the recessive model(TT vs. CT+CC, OR=1.30, 95% CI=0.50-3.36, *P*=0.59).

MMP-9 has attracted some attention due to its reported involvement in the development of essential hypertension (1, 15). Several polymorphic sites of MMP-9 gene have been investigated for their potential relationship with essential hypertension (16, 18, 29, 30). Any genetic polymorphisms affecting its expression level or activity can become a potential biomarker of essential hyper-

tension. Since the -1562 T allele of MMP-9 could lead to increased MMP-9mRNA levels, MMP-9 protein levels and MMP-9 activity, this polymorphic site has been widely investigated (22, 31, 32). MMP-9 -1562C/T polymorphism has been reported to be associated with several cardiovascular diseases like atrial fibrillation (33), atherosclerosis (22), carotid atherosclerosis (34) and coronary artery disease (30, 35). However, there is still a controversy over its association with essential hypertension.

In the current study, our meta-analysis result showed that the -1562T allele of MMP-9 was associated with essential hypertension. This was in consistent with the former report that the carriers of the T-1562 allele had significantly higher brachial systolicand pulse pressure as well as carotid systolic andpulse pressure (31). It was also in accordance with the previous report that -1562 T allele of MMP-9 is associated with gestationalhypertension (36). Besides, it also agreed with the increased MMP-9 expression and activity conferred by the -1562T allele (15, 31, 32, 37), which had been reported to be significantly associated with higher blood pressure (10, 37). Our sensitivity analysis suggested the stability of the association of the -1562T allele of MMP-9 with essential hypertension. The association of this polymorphic site with essential hypertension was also observed in the dominant and co-dominant models but not in the recessive model. The statistical results of these genetic models indicated that the increased risk of essential hypertension was mainly caused by the CT genotype. However, further experiments are badly needed to better elucidate the underlying mechanism.

Several limitations in the present study should be considered. The total number of the included studies was still relatively small. Although our sensitivity analysis indicated the stability of our meta-analysis results, more studies with lager sample size are still called upon to confirmit. Moreover, other clinical factors like age, sex, BMI, family history and environment may result in bias. Further investigation is called upon to determine if these factors affect the results of our meta-analysis.

Conclusion

This meta-analysis involving six relevant studies suggested that MMP-9 -1562C/T polymorphism was associated with the risk of essential hypertension under the allelic, dominant and co-dominant models, respectively. Nevertheless, further studies are essential to validate such association and elucidate the underlying mechanism.

Ethical considerations

Ethical issues (Including plagiarism, Informed Consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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