CEOG Clinical and Experimental Obstetrics & Gynecology

AT1R A1166C polymorphism and risk of pregnancy-induced hypertension: a meta-analysis of case control studies

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Summary

Purpose: The purpose of this study was to perform a quantitative review of previous case control studies examining the association between *AT1R* A1166C polymorphism and pregnancy-induced hypertension (PIH). *Materials and Methods:* Odds ratio (OR) and 95% confidence intervals (CI) were used as measures of effect sizes. Overall effect sizes were derived using a random-effects model or fixed-effects model when appreciated, and stratified by ethnicity. Funnel plots and Egger's regression asymmetry tests were utilized for publication bias detection. *Results:* A total of ten articles (including 920 PIH cases and 1408 controls) were included in this meta-analysis. The overall effect sizes (OR = 2.14, 95% CI: 1.54 - 2.98, $p < 0.00001$) of additive model indicated PIH patients had a significant higher frequency of allele C. Meanwhile, the OR of the dominant model was 2.22 (95% CI: 1.51 - 3.26, $p < 0.00001$) which signified that PIH patients also had a significant higher frequency of AC+CC genotypes. The subgroup analyses were in line with the overall outcomes except the Caucasians PIH patients had a non-significant CA+CC genotypes (OR = 1.37, 95% CI: 0.95 - 1.98, $p > 0.05$). The Egger's test of additive model ($p = 0.451$) and dominant model ($p = 0.623$) revealed no statistical significance for publication bias. *Conclusion:* The meta-analysis suggested that the *AT1R* A1166C polymorphism was significantly associated with the PIH, especially in Asian subjects.

Key words: AT1R; A1166C polymorphism; Meta-analysis; Pregnancy-induced hypertension; Previous case control studies.

Introduction

Pregnancy-induced hypertension (PIH) is a multifactorial disease manifested due to a complex combination of environmental factors and several predisposing genes including factors in the renin angiotensin (RA) system [1]. It is estimated to affect 6% to 8% of US pregnancies [2]. A recent report indicated women with PIH were at increased risk of preeclampsia, cesarean delivery, renal dysfunction, and placental abruption; associated risks to the fetus include intrauterine growth restriction, preterm delivery, low birth weight, and neonatal intensive care unit (NICU) admission [3]. Nonetheless, the pathogenesis of the disease still remains enigmatic.

It has been known that the RA system plays a key role in blood pressure regulation [4]. Therefore, many investigators have postulated and proved that alterations in the RA system play a significant role in the pathophysiology of PIH [5, 6]. As one of the main components of the RA system, human angiotensin II type 1 receptor (AT1R) has been recently cloned and localized to chromosome 3q [7]. Moreover, it might be a plausible candidate for susceptibility to PIH in a previous study [8]. In addition, a polymorphism of the *AT1R* gene which was an adenine/cytosine (A/C) base substitution at position 1166 was identified, and an increased prevalence of the C allele in hypertensive disorders was found [9]. Szombathy *et al.* also confirmed that the A1166C variant of *AT1R* significantly increased the risk of PIH [10]. However, Schmidt *et al.* [11] and Takami *et al.* [12] were against the association that *AT1R* A1166C polymorphism could increase risk of PIH.

It is clearly observed that an inconsistent result of previous studies existed on the association between the *AT1R* A1166C polymorphism and the risk of PIH. This may be resulted from the small sample size of the researched patients and/or the different ethnicity of the patients. To provide the current best evidence, the present authors conducted a meta-analysis of case control studies with the aim to show the relationship of *AT1R* A1166C polymorphism and the risk of PIH explicitly.

Materials and Methods

Search strategy

The authors performed the pre-established search strategies and retrieved literatures in a systematic way from the PubMed, MEDLINE, Springer, China National Knowledge Infrastructure (CNKI) and Wanfang database with the retrieval deadline of January 24th, 2014. The keywords used for all searches were in three aspects: 1) "pregnancy-induced hypertension", "gestational hypertensive disorders"; 2) "AT1R", "Angiotensin-II type 1 receptor", "AGTR1"; AND 3) "polymorphism", "genetic", "variant". There were no language restrictions of the retrieved literatures. In addition, a manual search of print documents and the citations from relevant original studies and review articles was retrieved for any additional studies.

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Revised manuscript accepted for publication July 1, 2014

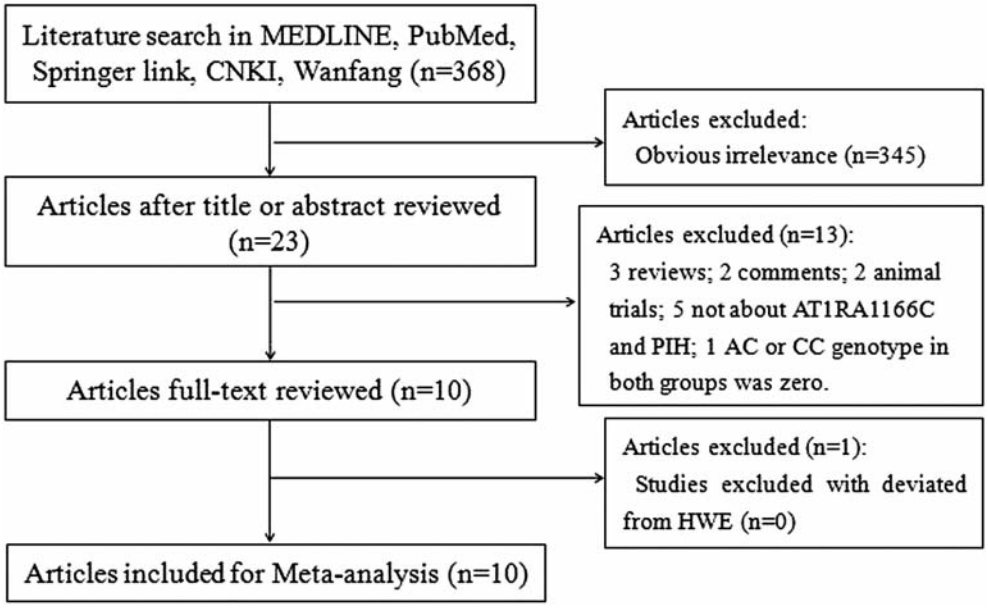

Figure 1. — Literature search and study selection.

Inclusion and exclusion criteria

Studies included in the present meta-analysis should meet the following criteria: 1) research design was case-control study; 2) study object was human beings; 3) the case group were pregnant women with PIH, and the control group were healthy pregnant women or with other kinds of hypertension; 4) the articles were studies of the association between *AT1R* A1166C polymorphism and PIH; 5) the genotype of *AT1R* A1166C should be provided or could be calculated out from the data of the studies, and the data should conform to the Hardy-Weinberg equilibrium (HWE). Besides, references would be excluded when the following conditions appeared: 1) the case and the control were family members or close relatives; 2) article was non-original literature such as review, letters, and comments; 3) paper was re-publication or the literature was used with same population data.

Data abstraction and quality evaluation

Articles were reviewed and filtered out independently by two investigators according to the prior criteria. Then the data were extracted independently in duplicate using a standardized form to assess the eligibility for inclusion. In brief, information were tabulated according to article's first author's name, year of publication, research conducted region, age and gestation of the pregnant women, the sample size of the case, and control group of each study. When completed, the information tables were exchanged and checked. Any discrepancies were resolved by discussion and by referencing to the original publication.

The quality of the articles was evaluated according to the standard of Clark's study [13]. There were ten terms in the standard, and each item was recorded for one score. In this scoring system, the article was regarded high quality literature if the evaluation score was above 5; otherwise, the literature was poor quality and was not suitable for comprehensive evaluation in the meta-analysis [14].

Statistical analysis

This study aimed at investigating whether there were associations between the *AT1R* A1166C polymorphism and risk of PIH of the pregnant women. Of the included researches, the HWE should be firstly calculated and displayed. If the *p*-value of the HWE less than 0.05, there was considered significant imbalance of the studied objects and the study were excluded. Then the effect size of adjusted odds ratio (OR) with 95% CI of the additive model (C *vs.* A) and dominant model (CA + CC *vs.* AA) were pooled in order to assess the relationship between the A1166C polymorphism and PIH.

Heterogeneity among studies was evaluated by the Cochran Q test and the I^2 parameter [15]. In the tests, $p < 0.05$ or $I^2 > 50\%$ was considered to be heterogeneous. When substantial heterogeneity was detected, the authors calculated summary OR and their 95% CI with the random effects model. If not, the pooled estimate was presented based on the fixed effects model.

The authors further conducted subgroup analysis according to ethnicity (Caucasians /Asian/ Chinese) to investigate the impacts on the present outcomes. Publication bias was also assessed by the funnel plot with Egger's regression asymmetry test [16, 17]. In addition, HWE and Egger's regression were performed using Stata 11.0, while the OR (95%CI) and funnel plot were displayed by software RevMan5.1.

Results

Literature retrieval

The procedures and the outcomes of the included literatures are clearly shown in Figure 1. According to the pre-established search strategies, the authors achieved 368 articles from PubMed, MEDLINE, Springer link, CNKI, and Wanfang database. A total of 345 repeated and obvious irrelevance articles were excluded out of the outcomes. Of the rest 23 studies, the authors reviewed the titles, abstracts, and the full texts only in ten articles (three reviews; two comments; two animal trials; five not about *AT1R* A1166C and PIH; one AC or CC genotype in both groups was zero) met the criteria and were included into the meta-analysis [1, 18-26]. Besides, all the ten included studies were consistent with the HWE, and there were no additional articles obtained from the manual search.

Table 1. — *Characteristics of ten studies on AT1R A1166C and pregnancy-induced hypertension.*

Id	Author / year	Quality Score	Country	Ethnicity	Age	Gestation	Case	Control	Case genotype			Control genotype			HWE	
									AA	CA	CC	AA	CA	CC	Chi-square test	*p* value
1	Hu 2000	8	China	Asian	21-37, 20-39	31-40, 32-41	88	136	70	16	2	126	10	0	0.198	0.6562
2	Bai 2002	7	China	Asian	28±4, 28±3	32-42, 36-42	72	185	70	2	0	170	14	1	0.932	0.3342
3	Nalogowska-Glosnicka 2000	7	Poland	Caucasian	20-48, 17-42	NP	122	144	58	49	15	80	57	7	0.639	0.4240
4	Shang 2003	7	China	Asian	28.4±3.4, 29.3±4.6	34.7±2.9, 34.9±1.4	90	96	40	47	3	78	18	0	1.027	0.3108
5	Liu 2004	7	China	Asian	30.5±3.7, 28.7±3.2	35.1±3.9, 36.4±4.1	90	90	74	14	2	96	4	0	0.042	0.8383
6	Kobashi 2004	8	Japan	Asian	29.7±0.5, 29.2±0.3	36.6±0.3, 39.1±0.1	114	291	93	19	2	260	28	3	3.161	0.0754
7	Liao 2007	7	China	Asian	27.8±2.9, 27.7±2.7	38.6±2.7, 39.0±1.9	102	108	71	29	2	96	12	0	0.370	0.5410
8	Jiang 2008	6	China	Asian	26.4±4.1, NP	NP	67	70	56	11	0	66	4	0	0.061	0.8054
9	Li 2008	6	China	Asian	27.0±6.5, NP	NP	87	175	58	28	1	137	38	0	2.596	0.1071
10	Seremak-Mrozikiewicz 2000	6	Poland	Caucasian	NP	NP	88	113	43	35	10	64	46	3	2.806	0.0939

NP: Not provided; HWE: Hardy-Weinberg equilibrium.

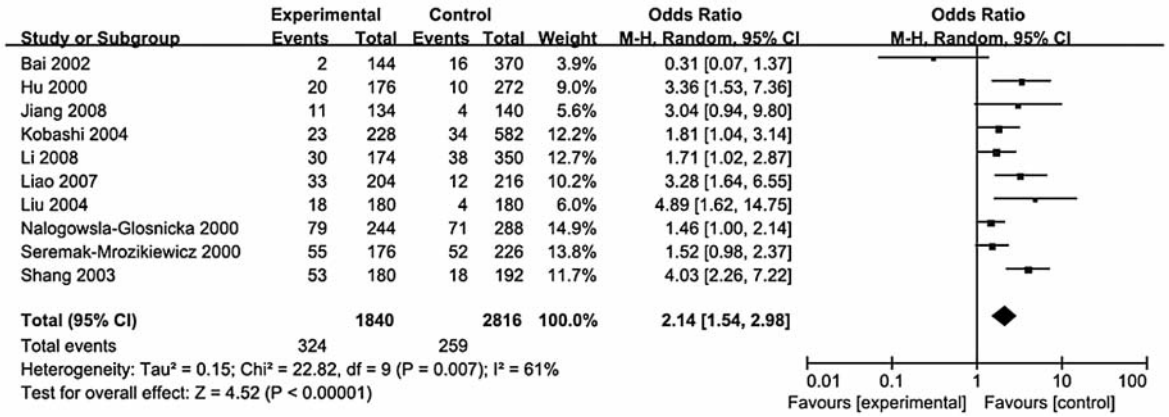

Figure 2. — Forest plots of the frequency of allele C in *AT1R* A1166C in pregnancy-induced hypertension patients *vs.* the controls. Squares represent the effect size for the odds ratio of the frequency of allele C in *AT1R* A1166C in pregnancy-induced hypertension patients *vs.* the controls. Size of the squares is proportional to the size of the cohorts. Error bars represent 95% confidence intervals (CI). The diamond shape represents the pooled estimates within each analysis.

Study characteristics and quality assessment

The characteristics and information of the included studies are shown in Table 1 [1, 18-26]. The ten included articles were all case control studies and were published between 2000 and 2008. A total of eight articles were studied in Asia, and the other two were conducted in Europe. Parts of the studies were lack of the age and the gestation of the pregnant woman. The total samples of the ten articles were 2,328 which included 920 PIH cases and 1,408 controls. Besides, the qualities evaluated of the included articles were arranged from six to eight, which meant all the included studies were high quality researches.

Meta-analysis

In overall analysis of the ten selected studies, the heterogeneity test of the additive model (C *vs.* A) showed that there were significant heterogeneities ($p = 0.007$, $I^2 = 61\%$). Therefore, the random effect model could be applied to analyze the effect sizes. The pooled estimates of OR was 2.14 (95%CI: 1.54 - 2.98, $p < 0.00001$; Figure 2), indicating the

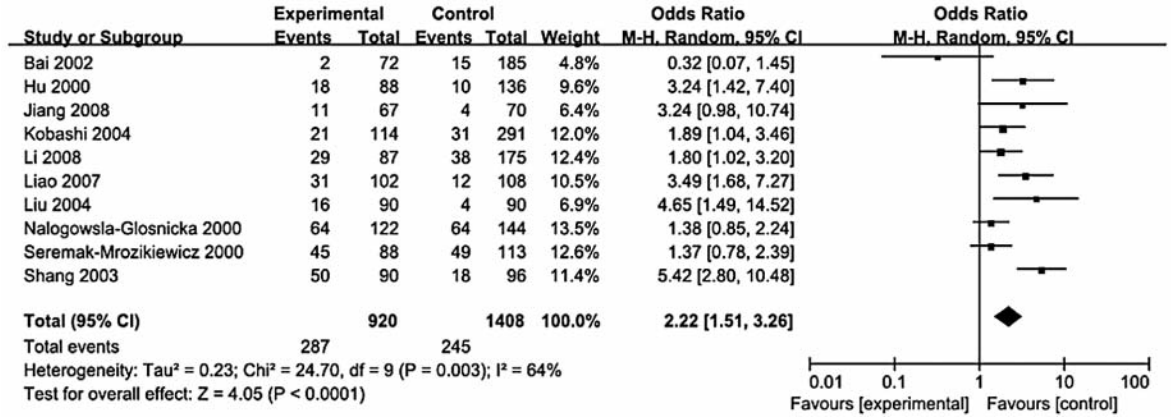

Figure 3. — Forest plots of the frequency of AC+CC genotypes of *AT1R* gene in pregnancy-induced hypertension patients *vs.* the controls. Squares represent the effect size for the odds ratio of the frequency of AC+CC genotypes of *AT1R* gene in pregnancy-induced hypertension patients *vs.* the controls. Size of the squares is proportional to the size of the cohorts. Error bars represent 95% confidence intervals (CI). The diamond shape represents the pooled estimates within each analysis.

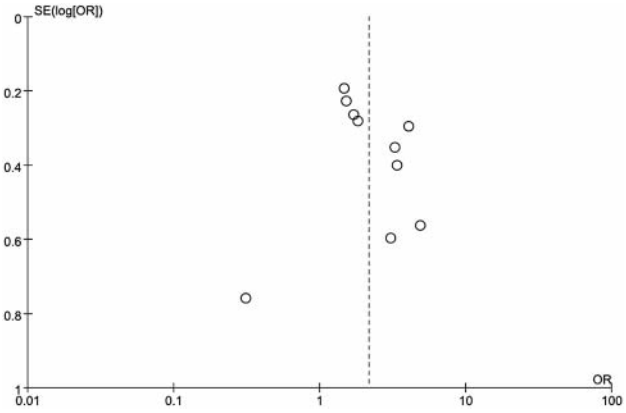

Figure 4. — Funnel plots of the studies of frequency of allele C in *AT1R* A1166C in pregnancy-induced hypertension patients *vs.* the controls. No publication bias was found in this meta-analysis from the funnel plots.

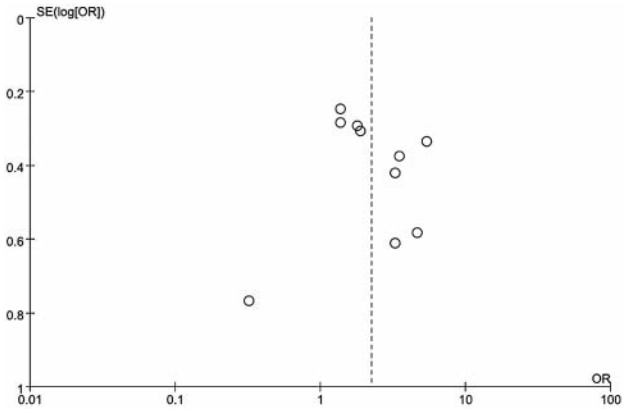

Figure 5. — Funnel plots of the studies of frequency of AC+CC genotypes of *AT1R* gene in pregnancy-induced hypertension patients *vs.* the controls. No publication bias was found in this meta-analysis from the funnel plots.

Table 2. — *Subgroup analysis of the association between AT1R A1166C and pregnancy-induced hypertension.*

Groups		No. of studies	C *vs.* A				CA +CC *vs.* AA			
			OR (95%CI)	P_A	I^2 (%)	P_H	*OR (95%CI)*	P_A	I^2 (%)	P_H
Overall		10	2.14 (1.54,2.98)	<0.00001	61	0.007	2.22 (1.51, 3.26)	<0.0001	64	0.003
Ethnicity	Caucasian	2	1.49 (1.11, 1.98)	0.007	0	0.90	1.37 (0.95, 1.98)	0.09	0	0.98
	Asian	8	2.47 (1.64, 3.73)	<0.0001	57	0.02	2.62 (1.67, 4.11)	<0.0001	58	0.02
	Chinese	7	2.61 (2.62, 4.22)	<0.0001	59	0.02	2.77 (1.64, 4.68)	0.0001	61	0.02

OR: odds ratio; *CI*: confidence interval; P_A: *p* value for test of the association; P_H: *p* value for between-study heterogeneity.

frequencies of allele C were significantly higher in PIH patients than those in control group.

The statistical heterogeneity of the studies of dominant model (CA+CC *vs.* AA) were also significant ($p = 0.003$, $I^2 = 64\%$), thus the random effects model was used for the analysis. Besides, the pooled OR (95% CI) of the dominant model was 2.22 (95% CI: 1.51 - 3.26, $p < 0.0001$, Figure 3) which demonstrated women with AC+CC genotypes were significantly higher in PIH patients.

Subgroup analysis

The subgroup analysis by ethnicity (Caucasians /Asian/Chinese) of additive model and dominant model are presented in Table 2. According to the outcomes, the fre-

quencies of allele C (Caucasians: OR = 1.49, 95% CI, 1.11-1.98; Asian: OR = 2.47, 95% CI, 1.64 - 3.73; Chinese: OR = 2.61, 95%CI, 2.62 - 4.22) and women with AC+CC genotypes (Asian: OR = 2.62, 95% CI, 1.67, 4.11; Chinese: OR = 2.77, 95% CI, 1.64, 4.68) were significantly higher in PIH patients, which were in accordance with the overall analysis above. In addition, the total estimate of the AC+CC genotypes of the Caucasians (OR = 1.37, 95% CI: 0.95 - 1.98, $p > 0.05$) also indicated the PIH patients processed more AC + CC genotypes, but the result was not significant.

Publication bias

The funnel plots of the additive model (C *vs.* A) and dominant model (CA + CC *vs.* AA) in this meta-analysis are shown in Figures 4 and 5. The distribution of the points in the two figures seemed symmetrical which indicated there were no significant publication biases of the included studies. In addition, the Egger's test of also additive model ($p = 0.451$) and dominant model ($p = 0.623$) also revealed no statistical significance for publication bias.

Discussion

Many studies on the association of the *AT1R* A1166C polymorphism and risk of PIH have been published in recent years [9, 27-29]. However these studies have shown mixed results due to small sample sizes or low statistical power. In the present meta-analysis, the authors combined and reanalyzed ten studies which contained 2,328 patients (920 PIH cases and 1408 controls cases) in order to achieve an integrative knowledge of *AT1R* A1166C polymorphism and risk of PIH.

The meta-analysis of the case control studies in present work indicated that PIH patients had higher frequencies of allele C and AC+CC genotypes compared to the controls. It was consistent with previous studies that C1166 of the *AT1R* gene was significantly associated with the risk of PIH in Polish [20] and Caucasian [8] subjects. In addition, a case-control study performed on some PIH patients in France also revealed a statistically significant increase in allelic frequency of C1166 in hypertensive subjects when compared to normotensive ones [9]. Therefore, this analysis confirmed that higher frequencies of allele C and AC+CC genotypes were related to the increasing risk of PIH.

It has been known that genes coding for components of the RA system involved in blood pressure regulation and vascular smooth muscle cell proliferation were considered to be candidate genes for risk factors for PIH as well as essential hypertension. AT1R, as one kind of the main components of the RA system were reported the mediators of vasoconstrictive function and salt distribution due to RA system [30]. Jiang *et al.* confirmed the associations between the C1166 allele of the *AT1R* gene and PIH [28]. Otherwise, the allele C1166 has been reported to be associated with aortic stiffness which might lead to high blood pressure [31], and the polymorphism was found to be associated with salt sensitivity in hypertensive patients [32]. Thus, the *AT1R* A1166C polymorphism might increase the risk of PIH. However, the molecular and biochemical mechanism by which the A1166C variant of the *AT1R* gene was involved in the manifestation of PIH was still obscure as the variable nucleotide was located in the 3' untranslated region [33, 34].

In this meta-analysis, the included articles were all high quality researches which could decrease the selection bias and increase the reliability of our outcomes. Besides, the funnel plots and Egger's tests proved there were no significant biases in the present authors' studies. It signifies that the unpublished and missing retrieved articles would not significantly affect the present results . However some limitations of this study should be discussed. First of all, the articles included in the meta-analysis were few, especially studies of Europe subjects after they were stratified by ethnicity. Thus more high quality researches were needed to verify the stability of the results. Secondly, some information such as the age and gestation of the patient were not provided, and these factors might influence our outcomes. Last but not the least, there was no grey literature retrieved and included, so the study results may overstate the *AT1R* A1166C role on the risk of PIH.

Conclusion

The meta-analysis suggested that *AT1R* A1166C polymorphism may increase the risk of PIH development.

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