Association of ATIR polymorphism with hypertension risk: An update meta-analysis based on 28,952 subjects

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Abstract

Background: Previous studies have shown that angiotensin II ATI receptor gene (*ATIR*) polymorphisms are associated with the risk for hypertension. However, the results remain controversial. In the present study, we performed a metaanalysis to systematically summarize the association between *ATIR* genetic polymorphisms and the risk for hypertension. **Methods:** We searched the literature in PubMed, EMBASE, ISI Web of Science, Wanfang, and Chinese National Knowledge Infrastructure databases (CNKI) to find case-control studies on the associations of ATIR genetic polymorphisms with the risk for hypertension. The meta-analysis was performed by using RevMan 5.0 software. The association of hypertension risk with *ATIR* genetic polymorphism was estimated by pooled odds ratios (ORs) and 95% confidence intervals (95% Cls).

Results: Fifty-six studies involving 28,952 subjects were included in the present meta-analysis. Our results suggest that the polymorphism (A1166C) of ATIR gene is associated with a statistically increased hypertension risk, not only in Asian populations but also in Caucasian populations. We did not find any association in African populations.

Conclusions: This meta-analysis suggests that A1166C polymorphism in the ATIR gene is associated with the risk of hypertension in Asian and Caucasian populations.

Keywords

Genetic polymorphism, hypertension, meta-analysis, angiotensin II AT1 receptor

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Introduction

Hypertension is a major public health problem throughout the world.¹ However, the pathogenesis of hypertension remains unclear. It is considered that hypertension is a complex disease resulting from the interaction between genetic polymorphisms and environmental factors.² Recently, many genes have been identified as candidates for contribution to hypertension.³ Of these, the angiotensin II AT1 receptor (AT1R) plays an important role in normal blood pressure regulation and in the pathophysiological progression of hypertension.^{4–6} The polymorphisms of the *AT1R* gene have been reported to be associated with the pathogenesis of hypertension.^{7–9} In particular, a single nucleotide polymorphism (SNP), A1166C, is the most studied variant being located in the 3' untranslated region of the *AT1R* gene.¹⁰

Several studies have indicated that A1166C polymorphism is associated with hypertension.^{11,12} However, this association has not been confirmed in other reports.^{13,14} In 2010, Wang et al. conducted a meta-analysis assessing the

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Creative Commons CC-BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 3.0 License (http://www.creativecommons.org/licenses/by-nc/3.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access page (http://www.uk.sagepub.com/aboutus/openaccess.htm). association of the *AT1R* gene A1166C polymorphism with hypertension in the Chinese population; this indicated that the *AT1R* C allele carriers have a higher risk for hypertension.¹⁵ Niu and Qi also performed a meta-analysis and found that the *AT1R* C allele conferred an increased risk of hypertension.¹⁶ However, in these two meta-analyses, the number of the included studies was rather small. In recent years, many new large-sample-size case-control studies have been conducted.^{11–14} Therefore, to further assess the relation between *AT1R* gene polymorphism and hypertension, we performed a carefully designed meta-analysis including 56 studies involving 28,952 subjects.

Methods

Selection of studies

We conducted a systematic computerized literature search for studies published before 1 December 2014. We searched the literature in PubMed, EMBASE, ISI Web of Science, Wanfang database in China, and Chinese National Knowledge Infrastructure (CNKI) database with the following search terms: "hypertension" and "angiotensin II type 1 receptor" or "AT1R" and "polymorphism" or "SNP", or "mutation" or "variant", by two independent investigators. The publication date and language were not restricted in the present study. All studies which met to the inclusion criteria were retrieved for further examination and data extraction.

Selection criteria

Studies satisfying the following criteria were included: 1) reported the relation between the *AT1R* genetic polymorphism and susceptibility to hypertension; 2) definition of hypertension as systolic (or diastolic) blood pressure ≥ 140 mmHg (or 90 mmHg) or treatment with antihypertensive medication; 3) in a case-control using either a hospital-based or a population-based design; 4) detailed genotype data were provided for the calculation of odds ratio (OR) and 95% confidence interval (95% CI). Studies that focused on juvenile hypertension or secondary forms of hypertension such as pregnancy-induced hypertension were excluded from this study.

Data extraction

Two researchers performed the data extraction independently. The following information from all eligible studies were obtained: first author's last name, year of publication, ethnicity of the population studied, study design, number of subjects in each category, baseline characteristics of the study population, and the number of persons with different genotypes in cases and controls and the genotyping methods.

Statistical analysis

The RevMan 5.0 software was employed for the present meta-analysis. The Hardy–Weinberg equilibrium was estimated by the χ^2 -test. We performed analyses under the dominant model (CC+AC vs. AA), recessive model (CC vs. AC+AA), and additive model (C vs. A). We utilized Q-test and I² test to examine the heterogeneity between each study. By heterogeneity test, if I² < 50%, we select the fixed effect model to merge OR. If I² > 50%, we selected the random effect model to merge OR. Sensitivity analysis and publication bias analysis were tested using RevMan 5.0 statistical software. The statistical significance of the pooled OR was determined with the *Z* test, and a *p* value of <0.05 was considered significant.

Results

Baseline characteristics

A total of 447 articles concerning the *AT1R* A1166C polymorphism and hypertension were retrieved after first search in PubMed, EMBASE, ISI Web of Science, Wanfang in China, and CNKI databases. As shown in Figure 1, after excluding duplicated publications or those that did not meet the inclusion criteria, we included 56 case-control studies for the final analysis.^{11–14,17–68} The characteristics of each study are summarized in Table 1. These 56 studies involved 28,952 subjects (14,708 hypertensive patients and 14,290 healthy control subjects). There were 39 studies carried out in Asian populations,^{19–22,24–53,57,58,61,63,65} while 15 studies were performed in Caucasian populations.^{11–13,18,23,54–56,59,60,62,64,66–68} Only two studies involved an African population.^{17,18}

Meta-analysis

As shown in Table 2. we found the polymorphism (A1166C) of AT1R gene was associated with a statistically increased hypertension risk ((AC+CC) vs. AA: OR = 1.44 (95% CI: 1.24–1.66, p < 0.001); (AA+AC) vs. CC: OR = 0.61 (95%) CI: 0.46–0.81, p < 0.001); C allele vs. A allele: OR = 1.35 (95% CI: 1.18–1.55, p < 0.001)) in the total population (Figures 2 to 4). In the subgroup analyses, the association was also significant among studies using Asian populations in all genetic models ((AC+CC) vs. AA: OR = 1.41 (95%) CI: 1.19–1.66, p < 0.001; (AA+AC) vs. CC: OR = 0.50 (95% CI: 0.38-0.65, p < 0.001); C allele vs. A allele: OR =1.40 (95% CI: 1.21–1.63, p < 0.001)). However, we only found an association in a dominant model ((AC+CC) vs. AA: OR = 1.37 (95% CI: 0.99-1.89, p = 0.05)), but not in a recessive model ((AA+AC) vs. CC: OR = 0.81 (95% CI: 0.53-1.22, p = 0.32)) or an additive model (C allele vs. A allele: OR = 1.09 (95% CI: 0.79-1.51, p = 0.58)) in

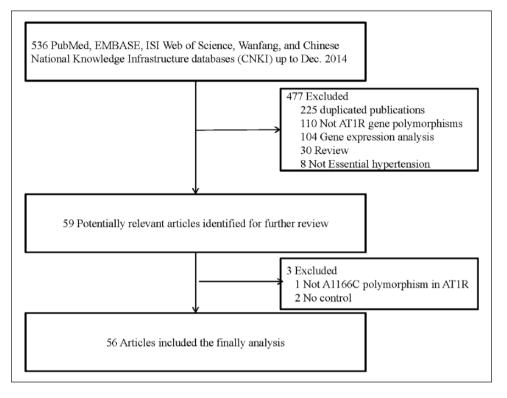


Figure 1. Flow diagram of study identification.

Caucasian populations. We did not found any association in African populations ((AC+CC) vs. AA: OR = 2.53 (95% CI: 0.66–9.70, p = 0.18); C allele vs. A allele: OR = 2.16 (95% CI: 0.93–5.01, p = 0.18)).

Publication bias

The publication bias test of the literature was conducted using a funnel plot and Egger's test. Symmetrical funnel plots were obtained in the SNP tested in all of the models, which displayed no publication bias (Figure 5). Egger's test further confirmed the absence of publication bias in this meta-analysis (all p > 0.05, data not shown).

Sensitivity analysis

We removed one single study from the overall pooled analysis each time to check the influence of the removed data set to the overall ORs. The pooled ORs and 95% CIs were not significantly altered when any part of the study was omitted, which indicated that any single study had little impact on the overall ORs and the results of this metaanalysis were stable.

Discussion

The present study aimed to explore the association of the *AT1R* gene A1166C polymorphism with hypertension

among a total of 28,952 subjects via a meta-analysis. We demonstrated that the AT1R gene 1166C allele carriers have higher risk for hypertension in Asian and Caucasian population, but not in African population.

Meta-analysis is a powerful tool for summarizing results from different studies by producing a single evaluation of the major effect. Genetic association studies have a tendency to lack the power to detect a statistically significant association with complex diseases, especially studies with small sample sizes. To achieve a satisfactory power, meta-analysis of multiple studies clearly has a role in offering an association study with such potentials. In the present study, we collected 56 case-control studies involving 28,952 subjects in this meta-analysis to clarify the relation between AT1R genetic polymorphism and hypertension. We found a significant association between C allele and the increased risk of essential hypertension. In the stratified analysis, we divided these studies into different subgroups by race of the participants. Significant association between hypertension and the A1166C polymorphism was observed in both Asian and Caucasian populations, but not in African populations. Our results were in line with a previous meta-analysis in a Chinese population. However, the mechanism responsible for the association of hypertension risk with A1166C polymorphism remains unclear. A1166C polymorphism is in a non-coding region of AT1R gene, and therefore the amino acid sequence of the AT1 receptor is not altered. The lack

Authors	Year	Country	Ethnicity	Case	Control	H-WE	Genotyping	Genotype	Ъе					Allele			
							methods	Case			Control			Case		Control	
								Ą	AC	U U	AA	AC	S	∢	υ	∢	υ
Bayramoglu et al. ^{II}	2014	Turkey	Caucasian	142	108	Yes	PCR-RFLP	137	ъ	0	94	4	0	279	ъ	202	4
Chandra et al. ¹²	2014	India	Caucasian	250	250	Yes	PCR-RFLP	101	144	35	155	83	12	346	214	393	107
Shahin et al. ¹³	2014	Jordanian	Caucasian	108	102	Yes	PCR-RFLP	67	37	4	64	32	9	171	45	160	44
Kooffreh et al. ¹⁴	2013	Nigeria	West Africa	612	612	Yes	PCR-RFLP	605	7	0	606	9	0	1217	7	1218	9
Mehri et al. ¹⁷	2012	Tunisia	North Africa	142	161	Yes	PCR-RFLP	17	63	62	74	82	35	97	187	230	152
Saab et al. ¹⁸	2011	Lebanon	Caucasian	124	146	Yes	PCR-RFLP	31	64	29	83	52	=	126	122	218	74
Guo et al. ¹⁹	2010	China	Asian	220	220	Yes	PCR	173	47	0	179	4	0	393	47	399	4
Nie et al. ²⁰	2009	China	Asian	510	510	Yes	PCR-RFLP	445	64	_	452	56	7	954	99	096	60
Li et al. ²¹	2009	China	Asian	296	198	Yes	PCR-RFLP	226	70	0	147	51	0	522	70	345	51
Jiang et al. ²²	2009	China	Asian	220	235	Yes	PCR-RFLP	201	61	0	212	23	0	421	61	447	23
Bautista et al. ²³	2008	NSA	Caucasian	256	257	Yes	PCR-RFLP	223	33	0	233	23	_	479	33	489	25
Liu et al. ²⁴	2003	China	Asian	446	302	Yes	PCR-RFLP	420	26	0	277	25	0	866	26	579	25
Ding et al. ²⁵	2008	China	Asian	200	220	Yes	PCR-RFLP	157	43	0	179	4	0	357	43	399	4
Niu et al. ²⁶	2009	China	Asian	1089	926	Yes	PCR-RFLP	734	262	93	629	266	<u>s</u>	1730	448	I 524	328
Fan et al. ²⁷	1998	China	Asian	51	74	Yes	PCR-RFLP	41	01	0	68	9	0	92	0	142	9
Fang et al. ²⁸	2003	China	Asian	104	154	Yes	PCR-RFLP	83	8	m	139	4	_	184	24	292	16
Fang et al. ²⁹	2007	China	Asian	468	233	Yes	PCR-RFLP	411	53	4	198	34	_	565	61	430	36
Guo et al. ³⁰	2007	China	Asian	290	291	Yes	PCR-RFLP	255	35	0	237	53	_	545	35	527	55
Han and Li ³¹	2000	China	Asian	95	80	Yes	PCR-RFLP	85	0	0	72	ø	0	180	0	152	œ
He et al. ³²	2007	China	Asian	148	125	Yes	PCR-RFLP	114	34	0	109	16	0	262	34	234	16
Jiang et al. ³³	2001	China	Asian	125	103	Yes	PCR-RFLP	102	23	0	96	7	0	227	23	661	7
Lin et al. ³⁴	2000	China	Asian	116	86	Yes	PCR-RFLP	95	21	0	8	S	0	211	21	167	ъ
Li et al. ³⁵	2007	China	Asian	104	98	Yes	PCR-RFLP	83	20	_	82	16	0	186	22	180	16
Li et al. ³⁶	2008	China	Asian	321	203	Yes	PCR-RFLP	246	73	7	153	50	0	565	77	356	50
Liu et al. ³⁷	2001	China	Asian	68	186	Yes	PCR-RFLP	63	4	_	171	15	0	130	9	357	15
Peng et al. ³⁸	2006	China	Asian	68	84	Yes	PCR-RFLP	53	13	7	75	ø	_	119	17	I 58	0
Xiang et al. ³⁹	1998	China	Asian	48	67	Yes	PCR-RFLP	43	4	_	64	m	0	90	9	131	m
Xie et al. ⁴⁰	2008	China	Asian	55	80	Yes	PCR-RFLP	45	0	0	76	4	0	001	0	I 56	4
Xu et al. ⁴¹	2002	China	Asian	83	64	Yes	PCR-RFLP	48	32	m	43	61	2	128	38	105	23

Table 1. Characteristics of participants.

Authors	Year	Country	Ethnicity	Case	Control	H-WE	Genotyping	Genotype	ь					Allele			
							methods	Case		Ũ	Control			Case		Control	
								AA	AC		AA	AC	S	∢	υ	∢	υ
Zhang et al. ⁴²	2006	China	Asian	001	40	Yes	PCR-RFLP	85	=	4	38	7	0	8	6	78	5
Yu et al. ⁴³	666 I	China	Asian	137	63	Yes	PCR-RFLP	901	29	2	57	9	0	241	33	120	9
Yuan et al. ⁴⁴	2007	China	Asian	679	616	Yes	PCR-RFLP	590	88	_	505	011	_	1268	90	1120	112
Zhang et al. ⁴⁵	2005	China	Asian	213	200	Yes	PCR-RFLP	164	47	7	148	50	7	375	51	346	54
Zhang et al. ⁴⁶	2007	China	Asian	126	143	Yes	PCR-RFLP	92	34	0	107	36	0	218	34	250	36
Zhang et al. ⁴⁷	2001	China	Asian	87	55	Yes	PCR-RFLP	70	4	m	51	4	0	154	20	901	4
Zhong and Ha ⁴⁸	2000	China	Asian	112	70	Yes	PCR-RFLP	85	26	_	65	S	0	196	28	135	S
Lu et al. ⁴⁹	2005	China	Asian	206	86	Yes	PCR-RFLP	180	24	7	82	4	0	384	28	168	4
Shi et al. ⁵⁰	2004	China	Asian	45	40	Yes	PCR-RFLP	61	26	0	20	20	0	64	26	60	20
Zhao et al. ⁵¹	2006	China	Asian	64	61	Yes	PCR-RFLP	27	35	7	47	n	_	89	39	107	15
Yang et al. ⁵²	2006	China	Asian	328	571	Yes	PCR-RFLP	253	75	0	510	61	0	581	75	1081	61
Pan et al. ⁵³	2010	China	Asian	246	285	Yes	PCR-RFLP	151	77	8	255	26	4	379	113	536	34
Wang et al. ⁵⁴	1997	British	Caucasian	108	84	Yes	PCR-RFLP	45	40	23	39	42	m	130	86	120	48
Schmidt et al. ⁵⁵	1997	German	Caucasian	278	172	Yes	PCR-RFLP	145	113	20	8	76	15	403	153	238	901
Liyou et al. ⁵⁶	666 I	Australian	Caucasian	334	327	Yes	PCR-RFLP	188	115	ЗІ	202	103	22	491	177	507	147
Thomas et al. ⁵⁷	2000	China	Asian	232	174	Yes	PCR-RFLP	203	28	_	152	21	_	434	30	325	23
Kato et al. ⁵⁸	2000	Japan	Asian	839	631	Yes	PCR-RFLP	701	132	9	525	103	m	1534	144	1153	601
Dzida et al. ⁵⁹	2001	Poland	Caucasian	250	150	Yes	PCR-RFLP	131	95	24	96	48	9	357	143	240	60
Agachan et al. ⁶⁰	2003	Turkey	Caucasian	104	81	Yes	PCR-RFLP	63	35	9	60	20	_	161	47	140	22
Ono et al. ⁶¹	2003	Japan	Asian	1492	2326	Yes	PCR-RFLP	1259	224	6	2071	235	20	2742	242	4377	275
Pamies-Andreu et al. ⁶²	2003	Spain	Caucasian	4	61	Yes	PCR-RFLP	8	8	S	31	23	7	54	28	85	37
Tsai et al. ⁶³	2003	China	Asian	408	286	Yes	PCR-RFLP	378	29	_	270	16	0	785	31	556	16
Stankovic et al. ⁶⁴	2003	Serb	Caucasian	001	198	Yes	PCR-RFLP	52	40	œ	601	74	15	144	56	292	104
Sugimoto et al. ⁶⁵	2004	Japan	Asian	576	631	Yes	PCR-RFLP	476	001	0	538	89	4	1052	001	1165	97
Barbalić et al. ⁶⁶	2006	Croatian	Caucasian	95	115	Yes	PCR-RFLP	48	33	4	55	50	0	129	61	160	70
Freitas et al. ⁶⁷	2007	Brazil	Caucasian	82	78	Yes	PCR-RFLP	46	30	9	55	20	m	122	42	130	184
Born et al. ⁶⁸	2006	Netherlands	Caucasian	221	139	Yes	PCR-RFLP	157	60	4	67	35	4	374	68	229	49

Table I. (Continued)

Genetic model	Sample size		Test of association			Test for heterogeneity	
	Case	Control	OR	95% CI	٩	đ	2
Total							
(AC+CC) vs. AA	14,708	14,290	1.44	1.24–1.66	<0.001	<0.001	78%
(AA+AC) vs. CC	14,708	14,290	0.61	0.46-0.81	<0.001	0.005	40%
C vs. A	29,166	28,738	I.35	1.18–1.55	<0.001	<0.001	81%
Caucasian							
(AC+CC) vs. AA	2385	2184	1.37	0.99–1.89	0.05	<0.001	83%
(AA+AC) vs. CC	2385	2184	0.81	0.53-1.22	0.32	0.01	53%
C vs. A	4830	4526	I.09	0.79–1.51	0.58	<0.001	89%
Asian							
(AC+CC) vs. AA	11,461	11,219	1.41	1.19–1.66	<0.001	<0.001	75%
(AA+AC) vs. CC	11,461	11,219	0.50	0.38-0.65	<0.001	0.57	%0
C vs. A	22,612	22,438	I.40	1.21–1.63	<0.001	<0.001	73%
African							
(AC+CC) vs. AA	754	803	2.53	0.66–9.70	0.18	<0.001	78%
(AA+AC) vs. CC	I	I	I	Ι	I	I	Ι
C vs. A	1508	1606	2.16	0.93-5.01	0.07	0.12	%09

ATIR gene and hypertension.
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OR: odds ratio, CI: confidence interval.

	Case		Cont			Odds Ratio	Odds Ratio
Study or Subgroup	Events		Events			M-H, Random, 95% CI	M-H, Random, 95% Cl
Agachan et al.2003	41	104	21	81	1.8%	1.86 [0.99, 3.50]	-
Barbalic et al.2006	47	95	60	115	1.9%	0.90 [0.52, 1.55]	-
Bautista 2008	33	256	24	257	1.9%	1.44 [0.82, 2.51]	
Bayramoglu 2014	5	142	14	108	1.1%	0.25 [0.09, 0.70]	
Born et al. 2006	64	221	42	139	2.1%	0.94 [0.59, 1.50]	+
Chandra 2014	179	250	95	250	2.2%	4.11 [2.83, 5.99]	
Ding YL. 2008	43	200	41	220	2.1%	1.20 [0.74, 1.93]	+
Dzida et al 2001	119	250	54	150	2.2%	1.61 [1.07, 2.45]	
Fan H 1998	10	51	6	74	1.1%	2.76 [0.94, 8.17]	<u> </u>
Fang JR 2007	57	468	35	233	2.1%	0.78 [0.50, 1.24]	-+
Fang M 2003	21	104	15	154	1.6%	2.34 [1.15, 4.80]	
Freitas et al. 2007	36	82	23	78	1.7%	1.87 [0.97, 3.60]	
Guo 2010	47	220	41	220	2.1%	1.19 [0.74, 1.89]	
Guo LF 2007	35	290	54	291	2.1%	0.60 [0.38, 0.95]	
Han XL 2000	10	250	8	80	1.2%		
	34				1.2%	1.06 [0.40, 2.82]	
He QF 2007		148	16	125		2.03 [1.06, 3.89]	
Jiang 2009	19	220	23	235	1.8%	0.87 [0.46, 1.65]	
Jiang ZN 2001	23	125	7	103	1.3%	3.09 [1.27, 7.54]	
Kato et al. 2000	138	839	106	631	2.4%	0.98 [0.74, 1.29]	
Kooffreh 2013	7	612	6	612	1.1%	1.17 [0.39, 3.50]	
Li 2009	70	296	51	198	2.2%	0.89 [0.59, 1.35]	T
Li JM 2007	21	104	16	98	1.6%	1.30 [0.63, 2.66]	
Li T 2008	75	321	50	203	2.2%	0.93 [0.62, 1.41]	+
Lin CR 2000	21	116	5	86	1.2%	3.58 [1.29, 9.92]	
Liu CQ 2001	5	68	15	186	1.1%	0.90 [0.32, 2.59]	
Liu et al. 2002	26	446	25	402	1.9%	0.93 [0.53, 1.64]	
liu Y 2003	26	446	25	302	1.9%	0.69 [0.39, 1.21]	
Liyou et al 1999	146	334	125	327	2.4%	1.25 [0.92, 1.71]	
Lu QS 2005	26	206	4	86	1.1%	2.96 [1.00, 8.76]	
Mehri 2012	125	142	117	191	1.9%	4.65 [2.59, 8.34]	
Nie 2009	65	510	58	510	2.2%	1.14 [0.78, 1.66]	+
Niu WQ 2009	355	1089	297	926	2.5%	1.02 [0.85, 1.24]	+
Ono et al. 2003	233	1492	255	2326	2.5%	1.50 [1.24, 1.82]	-
Pamies-Andreu et al. 2003	233	41	30	61	1.5%	1.32 [0.60, 2.92]	
Pang G 2010	95	246	30	285	2.1%	5.35 [3.39, 8.45]	
	15	68	9	84	1.3%		
Peng S 2006 Seeb 2011	93				2.0%	2.36 [0.96, 5.79]	
Saab 2011		124	63	146		3.95 [2.35, 6.66]	
Schmidt et al.1997	133	278	91	172	2.2%	0.82 [0.56, 1.19]	6 1
Shahin 2014	41	108	38	102	1.9%	1.03 [0.59, 1.80]	
Shi JP 2004	26	45	20	40	1.4%	1.37 [0.58, 3.22]	
Stankovic et al. 2003	48	100	89	198	2.0%	1.13 [0.70, 1.83]	T
Sugimoto et al. 2004	100	576	93	631	2.4%	1.22 [0.89, 1.65]	T
Thomas et al. 2000	29	232	22	174	1.8%	0.99 [0.55, 1.79]	-
Tsai et al. 2003	30	408	16	286	1.8%	1.34 [0.72, 2.51]	
Wang 1997	63	108	45	84	1.9%	1.21 [0.68, 2.16]	
Xiang KS 1998	5	48	3	67	0.7%	2.48 [0.56, 10.93]	
Xie YX 2008	10	55	4	80	0.9%	4.22 [1.25, 14.25]	
Xu W 2002	35	83	21	64	1.7%	1.49 [0.76, 2.95]	+
Yang XL 2006	75	328	61	571	2.3%	2.48 [1.71, 3.59]	-
Yu HZ 1999	31	137	6	63	1.3%	2.78 [1.09, 7.05]	
Yuan H 2007	89	679	111	616	2.4%	0.69 [0.51, 0.93]	
Zhang KX 2005	49	213	52	200	2.1%	0.85 [0.54, 1.33]	-+
Zhang LP 2007	34	126	36	143	1.9%	1.10 [0.64, 1.89]	
	15						
Zhang Q 2006 Zhang V 2001		100	2	40	0.7%	3.35 [0.73, 15.39]	
Zhang Y 2001 Zhao DZ 2006	17	87	4	55	1.0%	3.10 [0.98, 9.75]	
Zhao RZ 2006 Zhang V 2000	37	64	14	61	1.5%	4.60 [2.12, 10.00]	
Zhong Y 2000	27	112	5	70	1.2%	4.13 [1.51, 11.31]	
Total (95% CI)		14708		14290	100.0%	1.44 [1.24, 1.66]	•
Total events	3282		2599			fried used	
Heterogeneity: Tau ² = 0.21; (47. df =		.00001)	I ² = 78%	E	
Test for overall effect: $Z = 4.8$		7751 A. 1995 A. 1997				0.1	01 0.1 1 10 100
	- 1. 0.00						Favours [case] Favours [control]

Figure 2. Forest plot of hypertension associated with *ATIR* genetic polymorphism in a dominant model ((AC+CC) vs. AA). The squares and horizontal lines correspond to the study-specific OR and 95% Cl, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of OR and 95% Cl.

Study or Subgroup	Case Events		Cont		Weight	Odds Ratio M-H, Random, 95% Cl	Odds Ratio M-H, Random, 95% CI
Agachan et al.2003	98	104	80	81	1.5%	0.20 [0.02, 1.73]	
Barbalic et al.2006	81	95	105	115	4.8%	0.55 [0.23, 1.30]	
Bautista 2008	256	256	256	257	0.7%	3.00 [0.12, 73.99]	
Bayramoglu 2014	142	142	108	108	0.1 10	Not estimable	
Born et al. 2006	217	221	132	139	3.2%	2.88 [0.83, 10.02]	
Chandra 2014	245	250	238	250	3.9%	2.47 [0.86, 7.12]	
Ding YL. 2008	200	200	220	220		Not estimable	
Dzida et al 2001	226	250	144	150	4.5%	0.39 [0.16, 0.98]	
Fan H 1998	51	51	74	74		Not estimable	
Fang JR 2007	464	468	232	233	1.4%	0.50 [0.06, 4.50]	
Fang M 2003	101	104	153	154	1.3%	0.22 [0.02, 2.15]	
Freitas et al. 2007	76	82	75	78	2.7%	0.51 [0.12, 2.10]	
Guo 2010	220	220	220	220		Not estimable	
Guo LF 2007	290	290	290	291	0.7%	3.00 [0.12, 73.95]	
Han XL 2000	95	95	80	80	0.1 10	Not estimable	
He QF 2007	148	148	125	125		Not estimable	
Jiang 2009	220	220	235	235		Not estimable	
Jiang ZN 2001	125	125	103	103		Not estimable	
Kato et al. 2000	833	839	628	631	2.8%	0.66 [0.17, 2.66]	
Kooffreh 2013	612	612	612	612	2.0 %	Not estimable	
Li 2009	296	296	198	198		Not estimable	
Li JM 2007	103	104	98	98	0.7%	0.35 [0.01, 8.70]	
Li T 2008	319	321	203	203	0.8%	0.31 [0.01, 6.57]	
Lin CR 2000	116	116	203	203	0.0 %	Not estimable	
Liu CQ 2001	67	68		186	0.7%		
	446		186		0.7%	0.12 [0.00, 3.00]	
Liu et al. 2002		446	402	402		Not estimable	
liu Y 2003	446	446	302	302	C 101	Not estimable	-
Liyou et al 1999	303	334	305	327	6.4%	0.71 [0.40, 1.25]	
Lu QS 2005	204	206	86	86	0.8%	0.47 [0.02, 9.95]	
Mehri 2012	80	142	156	191	6.9%	0.29 [0.18, 0.47]	
Nie 2009	509	510	508	510	1.2%	2.00 [0.18, 22.17]	
Niu WQ 2009	996	1089	895	926	7.3%	0.37 [0.24, 0.56]	
Ono et al. 2003	1483	1492	2306	2326	5.2%	1.43 [0.65, 3.15]	
Pamies-Andreu et al. 2003	36	41	54	61	3.3%	0.93 [0.27, 3.17]	
Pang G 2010	228	246	281	285	3.8%	0.18 [0.06, 0.54]	
Peng S 2006	66	68	83	84	1.2%	0.40 [0.04, 4.48]	
Saab 2011	95	124	135	146	5.4%	0.27 [0.13, 0.56]	
Schmidt et al.1997	258	278	157	172	5.7%	1.23 [0.61, 2.48]	T
Shahin 2014	104	108	96	102	3.1%	1.63 [0.44, 5.93]	
Shi JP 2004	45	45	40	40		Not estimable	
Stankovic et al. 2003	92	100	183	198	4.7%	0.94 [0.39, 2.30]	-
Sugimoto et al. 2004	576	576	627	631	0.8%	8.27 [0.44, 153.91]	
Thomas et al. 2000	231	232	173	174	0.9%	1.34 [0.08, 21.50]	
Tsai et al. 2003	407	408	286	286	0.7%	0.47 [0.02, 11.68]	
Wang 1997	85	108	81	84	3.3%	0.14 [0.04, 0.47]	
Xiang KS 1998	47	48	67	67	0.7%	0.23 [0.01, 5.88]	
Xie YX 2008	55	55	80	80		Not estimable	
Xu W 2002	80	83	62	64	1.9%	0.86 [0.14, 5.31]	
Yang XL 2006	328	328	571	571		Not estimable	
Yu HZ 1999	135	137	63	63	0.8%	0.43 [0.02, 9.02]	
Yuan H 2007	678	679	615	616	0.9%	1.10 [0.07, 17.66]	
Zhang KX 2005	211	213	198	200	1.7%	1.07 [0.15, 7.64]	<u> </u>
Zhang LP 2007	126	126	143	143		Not estimable	
Zhang Q 2006	96	100	40	40	0.8%	0.26 [0.01, 5.03]	
Zhang Y 2001	84	87	55	55	0.8%	0.22 [0.01, 4.29]	
Zhao RZ 2006	62	64	60	61	1.2%	0.52 [0.05, 5.85]	
Zhong Y 2000	111	112	70	70	0.7%	0.53 [0.02, 13.12]	
Total (95% CI)		14708		14290	100.0%	0.61 [0.46, 0.81]	•
Total events	14304		14061				
Heterogeneity: Tau ² = 0.24; C	chi² = 65.13	3, df = 3	9 (P = 0.0	005); l² =	40%		0.002 0.1 1 10 500
Test for overall effect: Z = 3.3			1000	2010			0.002 0.1 1 10 500

Figure 3. Forest plot of hypertension associated with *AT1R* genetic polymorphism in a recessive model ((AA+AC) vs. CC). The squares and horizontal lines correspond to the study-specific OR and 95% CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of OR and 95% CI.

Study or Subgroup	Events		Cont		Weight	Odds Ratio M-H, Random, 95% Cl	Odds Ratio M-H, Random, 95% Cl
Agachan et al.2003	47	208	22	162	1.8%	1.86 [1.07, 3.23]	
Barbalic et al.2006	61	190	70	230	2.1%	1.08 [0.71, 1.64]	
Bautista 2008	33	512	25	514	1.8%	1.35 [0.79, 2.30]	
Bayramoglu 2014	5	284	14	216	1.0%		
						0.26 [0.09, 0.73]	
Born et al. 2006	68	442	49	278	2.1%	0.85 [0.57, 1.27]	
Chandra 2014	214	560	107	500	2.3%	2.27 [1.73, 2.99]	
Ding YL. 2008	43	400	41	440	2.0%	1.17 [0.75, 1.84]	
Dzida et al 2001	143	500	60	300	2.2%	1.60 [1.14, 2.26]	
Fan H 1998	10	102	6	148	1.0%	2.57 [0.90, 7.32]	
Fang JR 2007	61	626	36	466	2.0%	1.29 [0.84, 1.98]	T
Fang M 2003	24	208	16	308	1.6%	2.38 [1.23, 4.60]	
Freitas et al. 2007	42	164	184	314	2.1%	0.24 [0.16, 0.37]	
Guo 2010	47	440	41	440	2.0%	1.16 [0.75, 1.81]	
Guo LF 2007	35	580	55	582	2.0%	0.62 [0.40, 0.96]	-
Han XL 2000	10	190	8	160	1.1%	1.06 [0.41, 2.74]	
He QF 2007	34	296	16	250	1.7%	1.90 [1.02, 3.53]	
Jiang 2009	19	440	23	470	1.7%	0.88 [0.47, 1.63]	_
Jiang ZN 2001	23	250	7	206	1.3%	2.88 [1.21, 6.86]	
Kato et al. 2000	144	1678	109	1262	2.3%	0.99 [0.77, 1.29]	+
Kooffreh 2013	7	1224	6	1224	1.0%	1.17 [0.39, 3.48]	
Li 2009	70	592	51	396	2.1%	0.91 [0.62, 1.33]	
Li JM 2007	22	208	16	196	1.6%	1.33 [0.68, 2.62]	
Li T 2008	77	642	50	406	2.1%	0.97 [0.66, 1.42]	+
Lin CR 2000	21	232	5	172	1.1%	3.32 [1.23, 9.00]	
Liu CQ 2001	6	136	15	372	1.1%	1.10 [0.42, 2.89]	
Liu et al. 2002	26	892	25	804	1.8%	0.94 [0.54, 1.63]	
liu Y 2003	26	892	25	604	1.8%	0.70 [0.40, 1.22]	
Liyou et al 1999	177	668	147	654	2.3%	1.24 [0.97, 1.60]	
Lu QS 2005	28	412	4	172	1.0%	3.06 [1.06, 8.87]	
Mehri 2012	187	284	152	382	2.2%	2.92 [2.12, 4.02]	
Nie 2009	66	1020	60	1020	2.2%	1.11 [0.77, 1.59]	
Niu WQ 2009	448	2178	328	1852	2.5%	1.20 [1.03, 1.41]	-
Ono et al. 2003	242	2984	275	4652	2.4%	1.40 [1.17, 1.68]	-
Pamies-Andreu et al. 2003	28	82	37	122	1.7%	1.19 [0.66, 2.17]	
Pang G 2010	113	492	34	570	2.1%	4.70 [3.13, 7.05]	
Peng S 2006	17	136	10	168	1.3%	2.26 [1.00, 5.11]	
Saab 2011	122	248	74	292	2.2%	2.85 [1.98, 4.10]	
Schmidt et al. 1997	153	556	106	344	2.3%		-
	45					0.85 [0.63, 1.14]	
Shahin 2014		216	44	204	2.0%	0.96 [0.60, 1.53]	
Shi JP 2004	26	90	20	80	1.6%	1.22 [0.62, 2.41]	
Stankovic et al. 2003	56	200	104	396	2.1%	1.09 [0.75, 1.60]	_
Sugimoto et al. 2004	100	1152	97	1262	2.3%	1.14 [0.85, 1.53]	
Thomas et al. 2000	30	464	23	348	1.8%	0.98 [0.56, 1.71]	
Tsai et al. 2003	31	816	16	572	1.7%	1.37 [0.74, 2.53]	
Wang 1997	86	216	48	168	2.0%	1.65 [1.07, 2.55]	
Xiang KS 1998	6	96	3	134	0.7%	2.91 [0.71, 11.94]	
Xie YX 2008	10	110	4	160	0.9%	3.90 [1.19, 12.77]	
Xu W 2002	38	166	23	128	1.8%	1.36 [0.76, 2.42]	
Yang XL 2006	75	656	61	1142	2.2%	2.29 [1.61, 3.25]	
Yu HZ 1999	33	274	6	126	1.2%	2.74 [1.12, 6.72]	
Yuan H 2007	90	1358	112	1232	2.3%	0.71 [0.53, 0.95]	
Zhang 🕅 2005	51	426	54	400	2.1%	0.87 [0.58, 1.31]	-+
Zhang LP 2007	34	252	36	286	1.9%	1.08 [0.66, 1.79]	
Zhang Q 2006	19	200	2	80	0.6%	4.09 [0.93, 18.00]	<u> </u>
Zhang Y 2001	20	174	4	110	1.0%	3.44 [1.14, 10.36]	
Zhao RZ 2006	39	128	15	122	1.6%	3.13 [1.62, 6.04]	
Zhong Y 2000	28	224	5	140	1.1%	3.86 [1.45, 10.24]	· · · · · · · · · · · · · · · · · · ·
and the second se							
Total (95% CI)		29166		28738	100.0%	1.35 [1.18, 1.55]	◆
Total events	3716		2986			and a second	
Heterogeneity: Tau ² = 0.20; (16, df =		.00001)	I ² = 81%		
Test for overall effect: Z = 4.2			51		2		0.05 0.2 1 5 20

Figure 4. Forest plot of hypertension associated with *ATIR* genetic polymorphism in an additive model (C vs. A). The squares and horizontal lines correspond to the study-specific OR and 95% CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of OR and 95% CI.

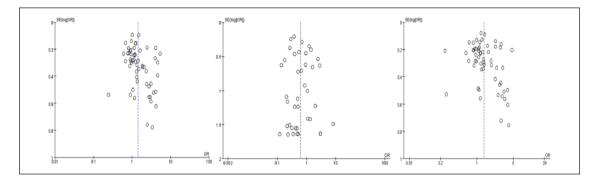


Figure 5. Funnel plot for publication bias test. Each circle denotes an independent study for the indicated association. Log[OR], natural logarithm of OR. Horizontal line stands for mean effect size. A: dominant model; B: recessive model; C: additive model.

of a functional role of the A1166C polymorphism makes this SNP somewhat unappealing as a "true" influence of hypertension susceptibility. However, the A1166C polymorphism might affect mRNA stability and transcription, or alternatively be in linkage disequilibrium with other functional polymorphisms. Therefore, the functional study of this variant was expected in the future.

Furthermore, we did not find the publication bias. Sensitivity analysis also showed that omission of any single study did not have significant impact on the combined ORs. This made the results of this meta-study more reliable to some extent. However, we found significant heterogeneity among all the included studies. This heterogeneity may result from study design of included studies. Two kinds control sourceshospital-based controls and population-based controls were used in the studies. The hospital-based controls might have selection biases and might not be representative of the general population. In addition, three races including Asian, Caucasian, and African populations were involved in the present study. This fact may be another source of heterogeneity.

There were also some limitations in this meta-analysis. Firstly, some clinical factors such as age, sex may affect the hypertension risk. In the present study, we did not adjust these confounders. Determining whether or not these factors influence the results of this meta-analysis would need further investigation. Secondly, this metaanalysis only focused on papers published in the English and Chinese language. Thirdly, the cross-sectional nature of our included studies precludes comments on causality. Finally, in this study, we only focused on the AT1R gene A1166 C polymorphism and did not evaluate other polymorphisms in the AT1R gene, leading to the possibility that the potential role of the A1166 C polymorphism is diluted or masked by other gene–gene or gene–environment interactions.

Conclusion

In conclusion, this meta-analysis clarified the association of A1166C polymorphism in *AT1R* gene of the risk of hypertension. The presence of *AT1R* gene 1166C allele is associated with an increased risk of hypertension in Asian and Caucasian populations.

Conflict of interest

The authors declare that there are no conflicts of interest.

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