

# The APLNR gene polymorphism rs7119375 is associated with an increased risk of development of essential hypertension in the Chinese population

## A meta-analysis

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### Abstract

Hypertension (HT) has recently been defined as a systolic blood pressure (BP) of  $\geq 130$  mm Hg and/or a diastolic BP of  $\geq 80$  mm Hg. It is important to further understand the pathophysiology of essential HT as its proportion is larger among most of the diagnosed HT cases. The apelin and apelin receptor (APLNR) are known to play roles in regulating BP, but the putative associations of single nucleotide polymorphisms in the APLNR gene with the risk of development of essential HT have not yet been fully investigated. Herein, we conducted a meta-analysis to investigate the relationship between single nucleotide polymorphisms in the APLNR gene and the risk of essential HT.

We conducted a search in the PubMed and Web of Science databases for eligible studies. The pooled odds ratios (ORs) with their 95% confidence intervals (CI) were calculated using random-effects models when heterogeneity was expected across the studies. Otherwise, fixed-effect models were used.

Regarding the SNP rs7119375, 5 studies were analyzed, which included a total of 3567 essential HT patients and 3256 healthy controls. Four of the 5 studies were from China and 1 was from Mexico. The meta-analysis showed the existence of a significant association between the AA genotype of rs7119375 and the risk of developing essential HT in the Chinese population, as determined using additive and recessive models (OR, 2.11; 95% CI, 1.12–3.96;  $I^2 = 86\%$  for AA vs GG. OR, 1.53; 95% CI, 1.21–1.94;  $I^2 = 28\%$  for AA vs AG. OR, 1.88; 95% CI, 1.13–3.12;  $I^2 = 79\%$  for AA vs AG + GG).

Our study showed, for the first time, the existence of an association between rs7119375 and the risk of development of essential HT in the Chinese population, although the sample size was small and there was considerable population heterogeneity. The apelin/APLNR system could be a novel therapeutic target for the treatment of essential HT, and more studies are warranted to further investigate the association.

**Abbreviations:** APLNR = apelin receptor, BP = blood pressure, CAD = coronary artery disease, CI = confidence interval, dBP = diastolic BP, ECs = endothelial cells, eNOS = endothelial nitric oxide synthase, HT = hypertension, HWE = Hardy-Weinberg equilibrium, IHD = ischemic heart disease, IL-6 = interleukin-6, NOS = Newcastle-Ottawa scale, OR = odds ratio, SNP = single nucleotide polymorphism.

**Keywords:** apelin, hypertension, single nucleotide polymorphism

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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## 1. Introduction

Previously, hypertension (HT) was defined as a systolic blood pressure (BP) of 140 mm Hg or higher and/or a diastolic BP (dBp) of 90 mm Hg or higher. However, the definition of HT was revised in the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline as a systolic BP of  $\geq 130$  mm Hg and/or a dBp of  $\geq 80$  mm Hg.<sup>[1]</sup> Based on this, it is estimated that almost half of the adult population in the United States of America may have HT.<sup>[1]</sup> Essential HT (also called primary HT or idiopathic HT) is diagnosed when there are no other diseases or disorders that can cause secondary HT, and it is the most common type of HT in clinical practice (approximately 90% of all cases of HT).<sup>[1]</sup> HT complications include cardiovascular diseases, cerebrovascular diseases, and chronic kidney disease, which can be potentially fatal.<sup>[1]</sup> The World Health Organization has reported that ischemic heart disease and stroke are the leading causes of death,<sup>[2]</sup> and that high BP accounts for about 47% of ischemic heart disease cases and 54% of stroke cases worldwide.<sup>[3]</sup> Therefore, it is important to better understand the pathophysiology further and develop more effective treatments for essential HT.

Essential HT is considered a complex disorder that may be caused by multiple factors, including not only environmental factors but also genetic factors. For example, genome-wide association studies and meta-analyses have suggested that single nucleotide polymorphisms (SNPs) in the uromodulin gene<sup>[4]</sup> and the endothelial nitric oxide synthase (eNOS) gene<sup>[5,6]</sup> are associated with the risk of development of essential HT. The apelin and apelin receptor (APLNR) are known to play roles in regulating BP, and several case-control studies have been performed to investigate the associations between SNPs in the apelin and/or APLNR (also known as APJ, APJR, HG11, and AGTRL1) gene and essential HT susceptibility. Recently, a meta-analysis has found no significant correlations between SNPs in the apelin gene and the risk of development of essential HT in the Chinese population.<sup>[7]</sup> To the best of our knowledge, however, the associations between SNPs in the APLNR gene and the risk of development of essential HT have not been investigated. Therefore, we conducted this meta-analysis to determine the association between SNPs in the APLNR gene and the risk of development of essential HT.

## 2. Materials and methods

### 2.1. Search strategy and eligibility criteria

We searched for eligible studies among all papers published before January 8, 2020, without any language restrictions, in PubMed and Web of Science databases, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.<sup>[8]</sup> Two authors (M.Y. and K.A.) performed the database searches independently, and each discrepancy was discussed until a consensus was reached. We used the following terms for the database searches: ((apelin receptor) OR APLNR OR APJ OR APJR OR HG11 OR AGTRL1) AND (polymorphism OR polymorphisms OR variant OR variants) AND (hypertension OR (blood pressure)). We also screened the references of the included studies manually. Our eligibility criteria were as follows:

- (1) studies that focused on the associations between SNPs in the APLNR gene and the risk of development of essential HT;
- (2) studies in which the participants had been classified into an essential HT patients group (systolic BP  $\geq$ 140 mm Hg and/or diastolic BP  $\geq$ 90 mm Hg until the year 2017, excluding secondary HT) and a healthy control group;
- (3) studies that provided sufficient data to calculate the odds ratios (ORs) and 95% confidence intervals (CIs).

Family-based studies were excluded from our study.

### 2.2. Data extraction

From the shortlisted studies, we extracted the following necessary information: the first author's name; publication year; region and country; genotyping method used; SNPs in the APLNR gene; number of cases and controls; allele and genotype frequencies.

### 2.3. Quality assessment of the included studies

The Newcastle-Ottawa scale (NOS)<sup>[9]</sup> was used to assess the quality of the studies selected for inclusion in our meta-analysis. 2 authors (M.Y. and K.A.) evaluated the scores independently, and any discrepancy was discussed until a consensus was reached.

### 2.4. Data analysis and statistics

The Hardy-Weinberg equilibrium (HWE)<sup>[10]</sup> for each study was tested for the control group using the chi-squared ( $\chi^2$ ) test (in Table 1). A *P* value of less than .05 was considered to indicate a statistically significant result in the HWE test. The heterogeneity was estimated using the Cochran *Q* test and the *I*<sup>2</sup> statistic.<sup>[11]</sup> The meta-analyses were conducted using random-effects models when the Cochran *Q* test results were significant (*P* < .10). Otherwise, fixed-effects models were used. The heterogeneity was categorized as low if the *I*<sup>2</sup> was 0% to 25%, as moderate if the *I*<sup>2</sup> was 25% to 75%, or as high if the *I*<sup>2</sup> was 75% to 100%.<sup>[12]</sup> The data on the OR and their 95% CIs were pooled, and forest plots were drawn using Review Manager, version 5.3. Begg<sup>[13]</sup> and Egger<sup>[14]</sup> tests were also conducted, and a funnel plot was drawn using the R software, version 3.4.0, to assess the presence of publication bias, as described previously.<sup>[15]</sup> A *P* value of less than 0.1 was considered as indicative of a statistically significant result in both Begg and Egger tests. We compared the genotype distributions between the case and control groups in each study using the  $\chi^2$  test based on 3  $\times$  2 tables (in Table 2). A *P* value of less than .05 was considered as indicative of a statistically significant result in the  $\chi^2$  test.

### 2.5. Ethical review

Because the present study is a meta-analysis of previously published studies, additional ethical approval and patient consent were not necessary.

### 2.6. Data availability statement

All data analyzed during this study are available on reasonable request to the corresponding author.

**Table 1**

**Characteristics and rs7119375 genotype distributions (expressed in numbers) between the case and control groups in the studies included in our meta-analysis.**

Author year	Region country	Geno-typing	N of cases/controls	Genotypes in HT cases				Genotypes in controls				HWE for controls	NOS
				GG	AG	AA	MAF	GG	AG	AA	MAF		
Huang 2016	Fujian China	TaqMan	556/475	271	220	65	0.315	243	183	49	0.296	<i>P</i> = .10	7
Li 2016	Heilongjiang China	TaqMan	650/645	361	256	33	0.248	415	211	19	0.193	<i>P</i> = .20	8
Liu 2014	Heilongjiang China	PCR-LDR	1009/756	517	403	89	0.283	565	173	18	0.138	<i>P</i> = .28	6
Niu 2010	Shanghai China	PCR-RFLP	969/980	593	312	64	0.227	601	339	40	0.214	<i>P</i> = .36	7
Esteban 2016	Mexico City Mexico	TaqMan	383/400	224	140	19	0.232	205	168	27	0.278	<i>P</i> = .34	6

HT = hypertension, HWE = Hardy-Weinberg equilibrium, MAF = minor allele frequency, N = number, NOS = Newcastle-Ottawa scale, PCR-LDR = polymerase chain reaction-ligase detection reaction, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism.

**Table 2**  
**Genotype distributions (expressed in numbers) of each SNP between the case and control groups.**

SNPs in <i>APLNR</i> gene	Author year (sub-group)	Wild homozygote		Heterozygote		Mutant homozygote		$\chi^2$	P
		Case	Control	Case	Control	Case	Control		
rs10501367	Wu 2018 (male)	232	115	135	72	11	16	7.5209	<b>.0233</b>
	Wu 2018 (female)	143	93	113	59	11	7	1.1278	.569
	Esteban 2016	223	202	139	167	21	31	5.1562	.0759
	Niu 2010 (male)	286	287	175	171	35	31	0.2407	.8866
	Niu 2010 (female)	278	297	150	167	45	27	5.7054	.0577
rs11544374	Wu 2018 (male)	281	132	91	62	6	9	7.5663	<b>.0228</b>
	Wu 2018 (female)	169	117	94	36	4	6	8.9248	<b>.0115</b>
	Liu 2014	548	637	381	110	80	9	180.33	<. <b>001</b>
	Nowzari 2018	13	12	32	37	15	21	0.6369	.7273
rs9943582	Huang 2016 (male)	83	92	65	111	25	22	5.9853	.0502
	Huang 2016 (female)	166	120	176	99	41	31	2.5138	.2845
	Li 2016 (male)	179	222	121	119	22	23	2.0863	.3524
	Li 2016 (female)	175	161	122	105	31	15	3.8172	.1483
	Liu 2014	647	466	319	245	43	45	2.9851	.2248
rs948847	Nowzari 2018	18	26	26	29	16	15	0.8865	.642
	Liu 2014	316	268	493	360	200	128	4.3103	.1159
rs2282623	Liu 2014	339	257	490	368	180	131	0.0855	.9582

P values shown in bold are considered as indicative of statistical significance.

SNP = single nucleotide polymorphism.

### 3. Results

We searched in PubMed and Web of Science databases, and identified a total of 63 articles. After removing 19 duplicates, we reviewed the titles and/or abstracts, and excluded 33 articles. We then assessed the full texts of the remaining 11 articles and excluded 4 more articles. Finally, we selected 7 studies in which the associations between 6 SNPs in the *APLNR* gene, rs7119375, rs10501367, rs11544374, rs9943582, rs948847, and rs2282623 and the risk of developing essential HT had been investigated.<sup>[16–22]</sup>

Rs7119375, rs10501367, and rs9943582 are located upstream of exon 1, rs11544374 and rs948847 are located within exon 1, and rs2282623 is located in intron between exon 1 and exon 2 of the *APLNR* gene.<sup>[23]</sup> A flow diagram showing our search strategy and process is presented in Figure 1.<sup>[24]</sup> However, as there were just a few studies pertaining to SNPs other than rs7119375, we decided to conduct a meta-analysis for rs7119375 alone and to discuss the other SNPs later.

A total of 5 studies, with a total of 3567 essential HT patients and 3256 controls, were included in our meta-analysis for determining the clinical significance of rs7119375 for essential HT.<sup>[16–20]</sup> The profiles of the 5 studies are shown in Table 1. Four of the 5 studies were reported from China<sup>[17–20]</sup> and 1 was conducted in Mexico.<sup>[16]</sup> Although we noticed that 3 of the 4 studies from China had been conducted by the same group or related groups,<sup>[18–20]</sup> we considered that the study populations were different from each other for the following reasons: First, the participants of Niu's study<sup>[20]</sup> were from Shanghai. Second, both, the participants in Li's<sup>[18]</sup> and Liu's<sup>[19]</sup> studies were from Heilongjiang province. But another study,<sup>[25]</sup> in which the participants were the same as those in Liu's study,<sup>[19]</sup> was accepted for publication in July 2013, and the participants of Li's study<sup>[18]</sup> were enrolled between September 2013 and October 2015. Therefore, we considered that there was no overlap in the participants of the 3 studies.<sup>[18–20]</sup> The control groups in all the 5 included studies were in accordance with the HWE ( $P > .05$ ). The NOS scores in the 5 included studies are also shown in Table 1. The quality of 3 of the 4 studies conducted in the Chinese

populations was considered to be high ( $\geq 7$ ). Liu's study<sup>[19]</sup> was thought to introduce a high level of heterogeneity, as described later.

Following extraction of the data on the genotype distributions in each study, we conducted the meta-analysis by combining the OR for the risk of development of essential HT in each study using additive (Fig. 2A, B), dominant (Fig. 2C), recessive (Fig. 2D), and allelic models (Fig. 2E). We found a significant risk of essential HT using the additive model (AA vs AG) (OR, 1.42; 95% CI, 1.14–1.77;  $I^2 = 43\%$  as shown in Fig. 2B) without publication bias ( $P$  values as evaluated by Begg and Egger test were 0.82 and 0.78, respectively), although we could not find any significant risk under the other models. We then performed sub-group analyses by ethnicity, and found that the risk of development of essential HT was significantly higher in the groups with the AA genotype as per the additive and recessive models, in the Chinese population (OR, 2.11; 95% CI, 1.12–3.96;  $I^2 = 86\%$  for AA vs GG [as shown in Fig. 2A]; OR, 1.53; 95% CI, 1.21–1.94;  $I^2 = 28\%$  for AA vs AG [as shown in Fig. 2B]; OR, 1.88; 95% CI, 1.13–3.12;  $I^2 = 79\%$  for AA vs AG+GG [as shown in Fig. 2D]). Both Begg and Egger tests again showed the absence of any publication biases in the sub-group analyses as shown in Figure 2F to J.

The heterogeneity levels across the studies included in our meta-analysis were very high. We performed sensitivity analysis by excluding each of the 4 studies<sup>[17–20]</sup> in our sub-group analysis of the Chinese population using the additive model ( $I^2 = 86\%$  for AA vs GG) and recessive model ( $I^2 = 79\%$ ), and found that when we excluded Liu's study,<sup>[19]</sup> the heterogeneity decreased and the ORs were still significant in both models (OR, 1.50; 95% CI, 1.15–1.94;  $I^2 = 13\%$  for AA vs GG [as shown in Fig. 3A]; OR, 1.45; 95% CI, 1.12–1.86;  $I^2 = 9\%$  for AA vs AG+GG [as shown in Fig. 3B], respectively). Therefore, inclusion of Liu's study<sup>[19]</sup> was thought to increase the heterogeneity in our sub-group analysis conducted for the Chinese population.

As there were only a few studies in which the association of the rs10501367, rs11544374, rs9943582, rs948847, and rs2282623

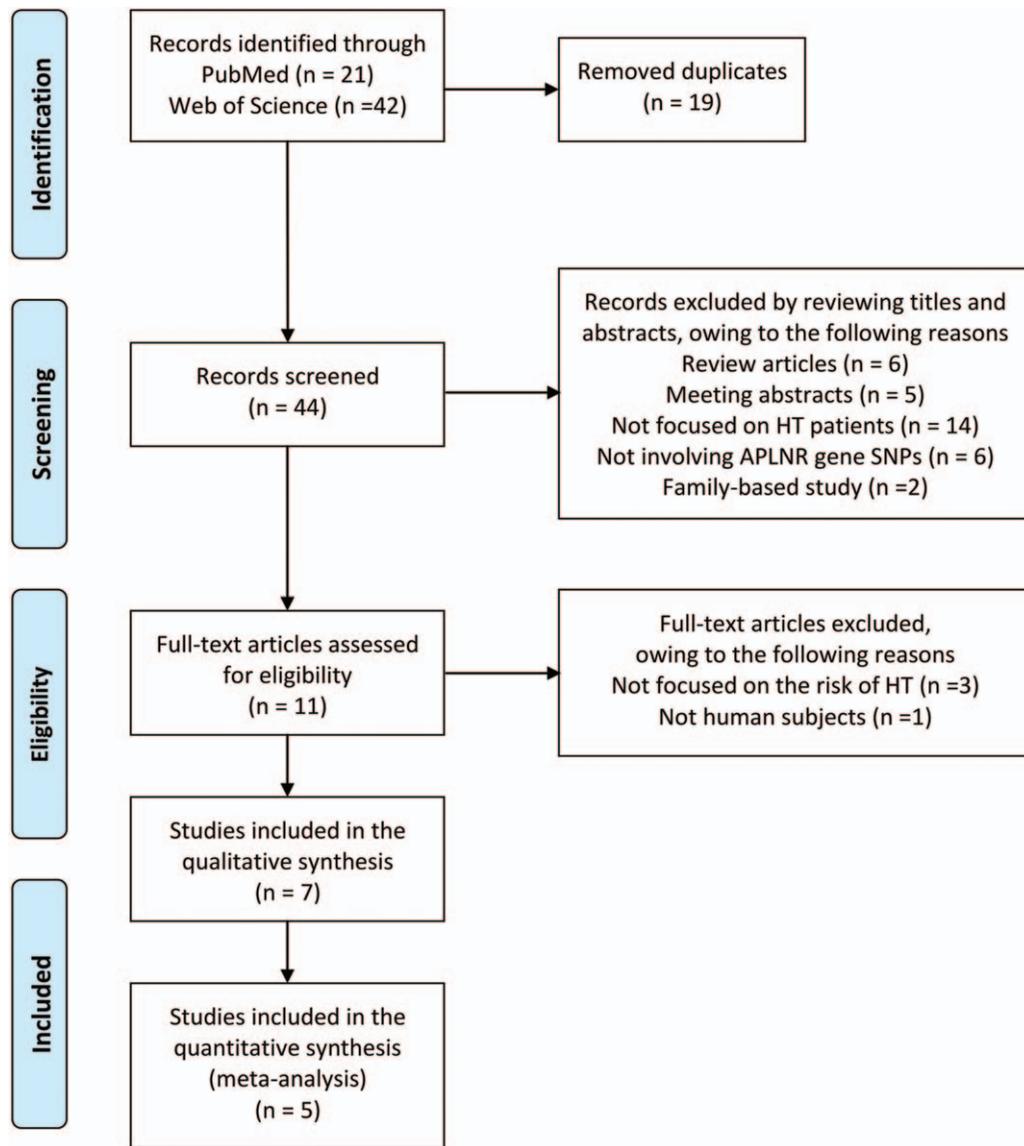


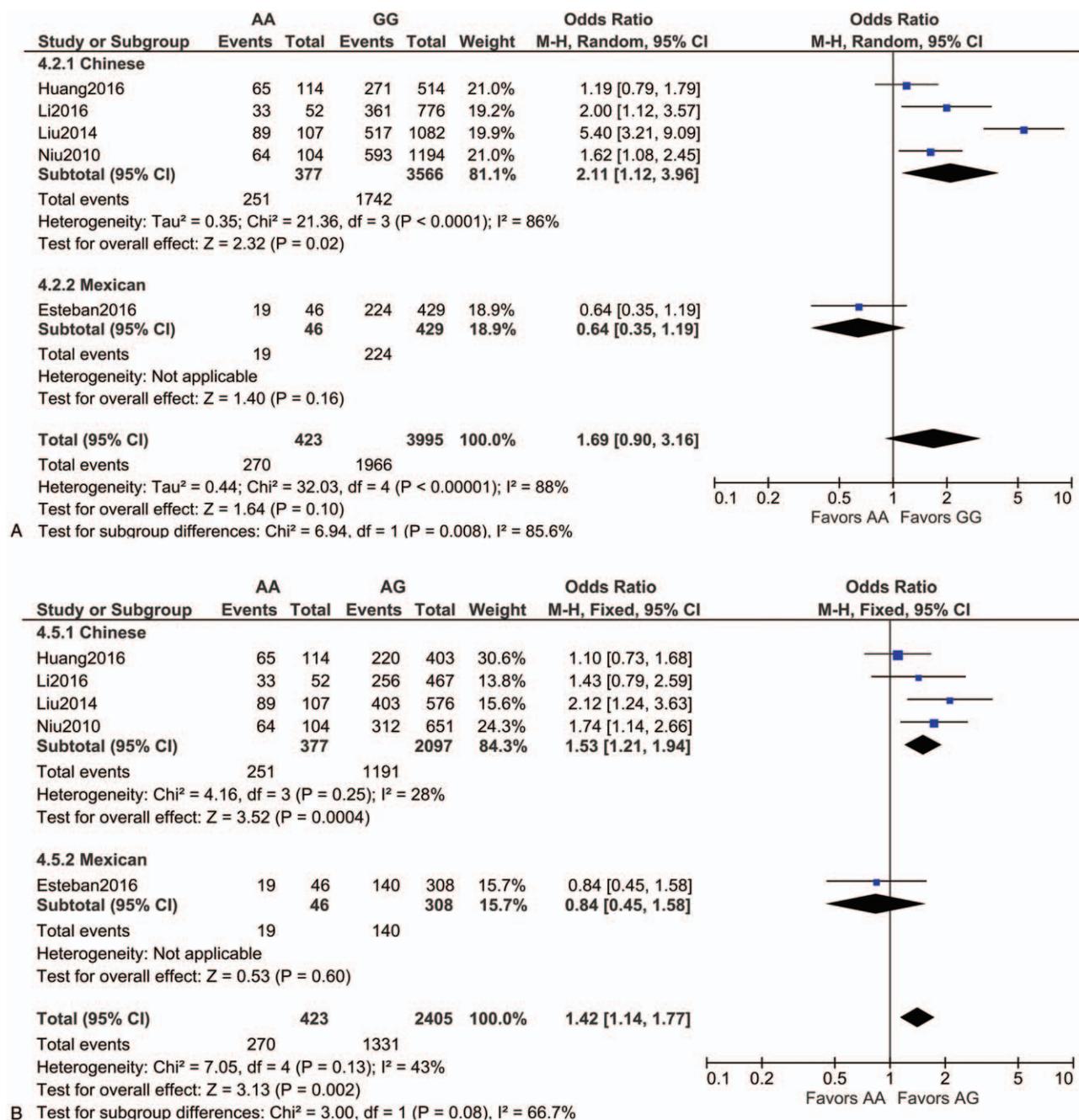
Figure 1. Flow diagram<sup>[24]</sup> of our search strategy and process.

SNPs with the risk of development of essential HT had been investigated, we did not include these 5 SNPs in our meta-analysis. Instead, we compared the genotype distributions between the case and control groups in each study using the  $\chi^2$  tests (Table 2). Among the studies, in Nowzari's study,<sup>[21]</sup> which was based on the Iranian population, the participants were classified into four groups: group 1, consisting of patients with both coronary artery disease (CAD) and HT (systolic BP  $\geq 140$  mm Hg and/or dBP  $\geq 90$  mm Hg); group 2, consisting of patients with CAD but without HT; group 3, consisting of patients without CAD but with HT; group 4, consisting of patients with neither CAD nor HT. We decided to include the data of group 3 as HT cases and those of group 4 as healthy controls (Table 2). Overall, as shown in Table 2, analysis using the  $\chi^2$  test showed that none of these SNP genotypes were significantly associated with the prevalence of essential HT ( $P > .05$ ), except for rs11544374 in 2 Chinese studies (Liu's<sup>[19]</sup> and Wu's<sup>[22]</sup> study).

#### 4. Discussion

To the best of our knowledge, this is the first meta-analysis investigating the association between SNPs in the APLNR gene and the risk of development of essential HT. Although the sample size was small, our meta-analysis showed that the AA genotype of rs7119375, as compared to the AG or the GG genotypes, increased the risk of development of essential HT in the Chinese population. None of the other SNP genotypes seemed to be significantly associated with the prevalence of essential HT, except for rs11544374 as shown in Table 2. However, whether these SNPs are actually associated with the risk of development of essential HT or not is still unclear, because of the small number of related studies.

Our results suggest an important clinical implication of rs7119375 because it is located in the promoter region of the APLNR gene<sup>[23]</sup> and may regulate gene expression.<sup>[17]</sup> Although the included studies in our meta-analysis did not measure circulating apelin levels or expressing APLNR levels, a meta-



**Figure 2.** Forest plot of the risk of development of essential HT associated with the rs7119375 SNP in Chinese and Mexican populations using the (A) additive model (AA vs GG), (B) additive model (AA vs AG), (C) dominant model, (D) recessive model and (E) allelic model. (F–J) Funnel plot, Begg test, and Egger test for (A–E) in the sub-group analysis of the Chinese population. Note that the log (OR) is plotted on the horizontal axis.

analysis showed that circulating apelin levels were significantly lower in patients with CAD.<sup>[26]</sup> The APLNR gene localizes in chromosome 11q12.1<sup>[27]</sup> and encodes for the G protein-coupled receptor for which apelin is an endogenous ligand.<sup>[28]</sup> APLNR is expressed in various organs, such as the blood vessels, heart, and kidneys, and in multiple cell types, such as endothelial cells (ECs), smooth muscle cells, and cardiomyocytes.<sup>[29]</sup> The apelin/APLNR system induces vasodilation via activation of eNOS pathway in intact ECs under physiological conditions whereas the presence of APLNR in smooth muscle cells can cause vasoconstriction

under conditions where ECs are damaged.<sup>[30]</sup> Therefore, although apelin has complex vasomotor effects, the apelin/APLNR system may be clinically recognized as a novel therapeutic target for HT,<sup>[29–31]</sup> especially among patients with SNPs in the promoter region of the APLNR gene after the relationships between the SNPs and apelin/APLNR expressions are investigated in future researches. Actually, when administered intravenously in rats, apelin peptides lowered the mean arterial pressure by approximately 10 to 20 mmHg.<sup>[32]</sup> When infused intra-arterially in healthy volunteers, apelin peptides caused

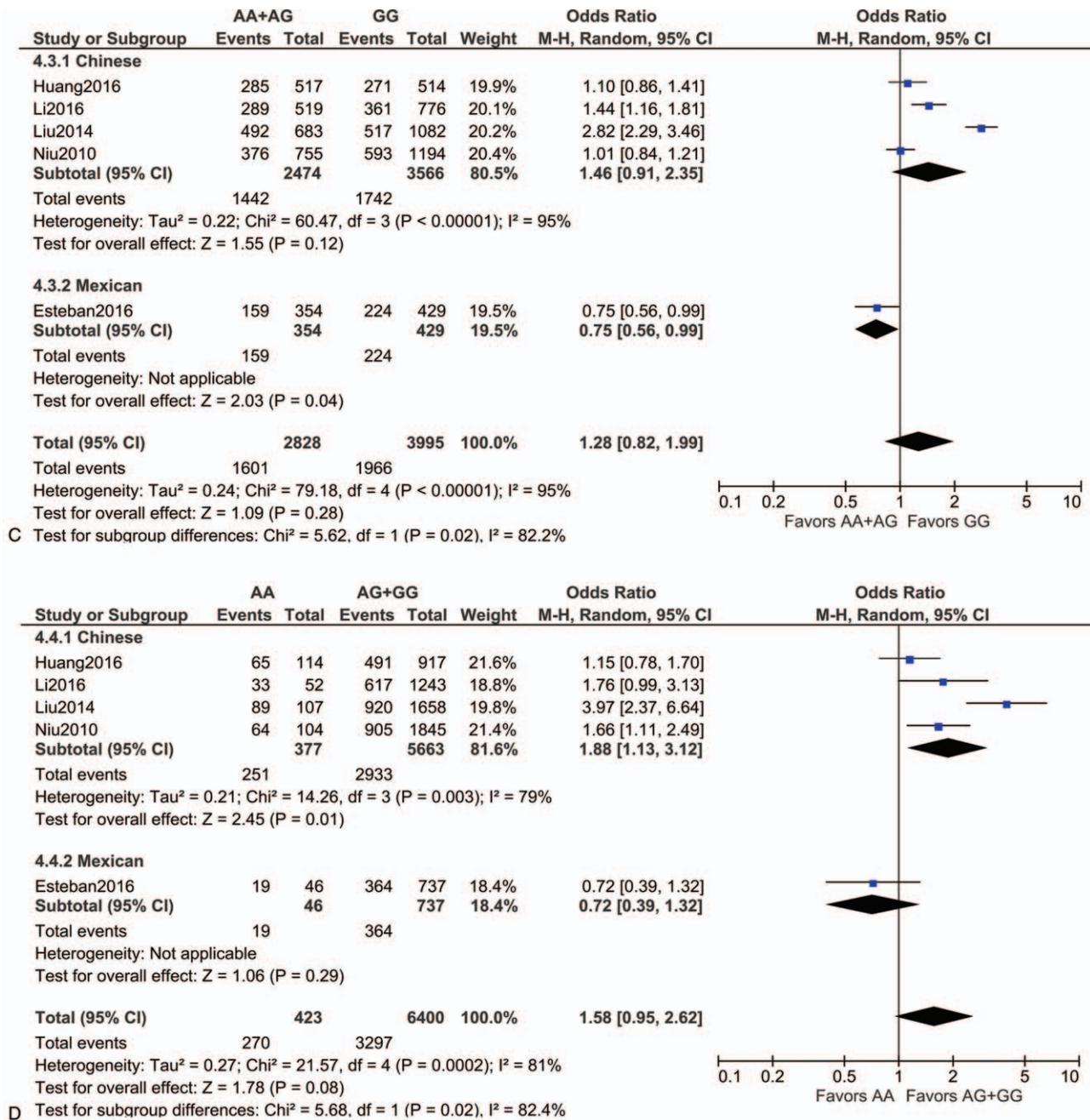


Figure 2. (Continued).

arterial vasodilation in human forearm vessels.<sup>[33]</sup> These effects of apelin peptides were suppressed by nitric oxide inhibitors. Although plasma half-lives of apelin peptides are short (less than 10 minutes),<sup>[31,33]</sup> novel APLNR agonists with longer biological half-lives and higher activities have been developed.<sup>[30]</sup> In addition, angiotensin-converting enzyme inhibitors and angiotensin II type 1 receptor blockers may be effective especially among hypertensive patients with SNPs in the promoter region of the APLNR, because these drugs can also activate eNOS pathway.<sup>[34]</sup> But this hypothesis needs to be verified.

The heterogeneity levels across the studies included in our meta-analysis were very high. The small number of studies could

be the main reason for the high heterogeneity. In addition, inclusion of Liu's study<sup>[19]</sup> was thought to be one of the reasons for the high levels of heterogeneity. In Liu's study,<sup>[19]</sup> the fasting blood glucose levels and body mass index in the essential HT group were relatively higher than those in the other studies (Table 3). Moreover, subjects with diabetes were excluded in Huang's study,<sup>[17]</sup> and both the fasting blood glucose levels and body mass index were comparable between the case and control groups in Li's study.<sup>[18]</sup> Matching of the characteristics between the case and control groups is important in non-randomized studies, as described in the NOS scoring system.<sup>[9]</sup> We hypothesize that the case group in Liu's study<sup>[19]</sup> might not be

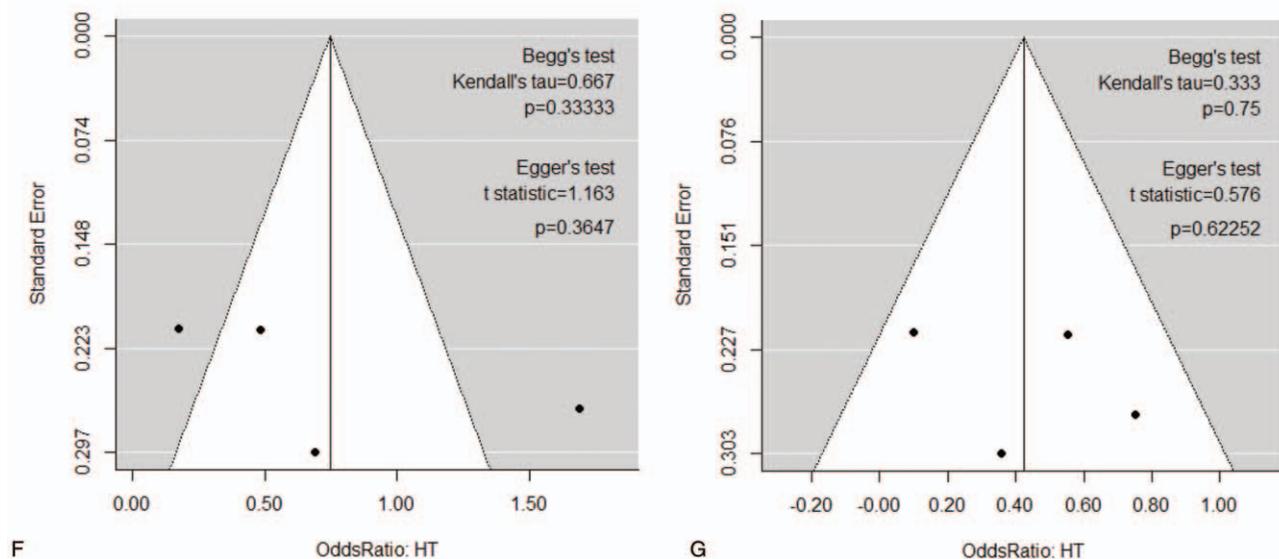
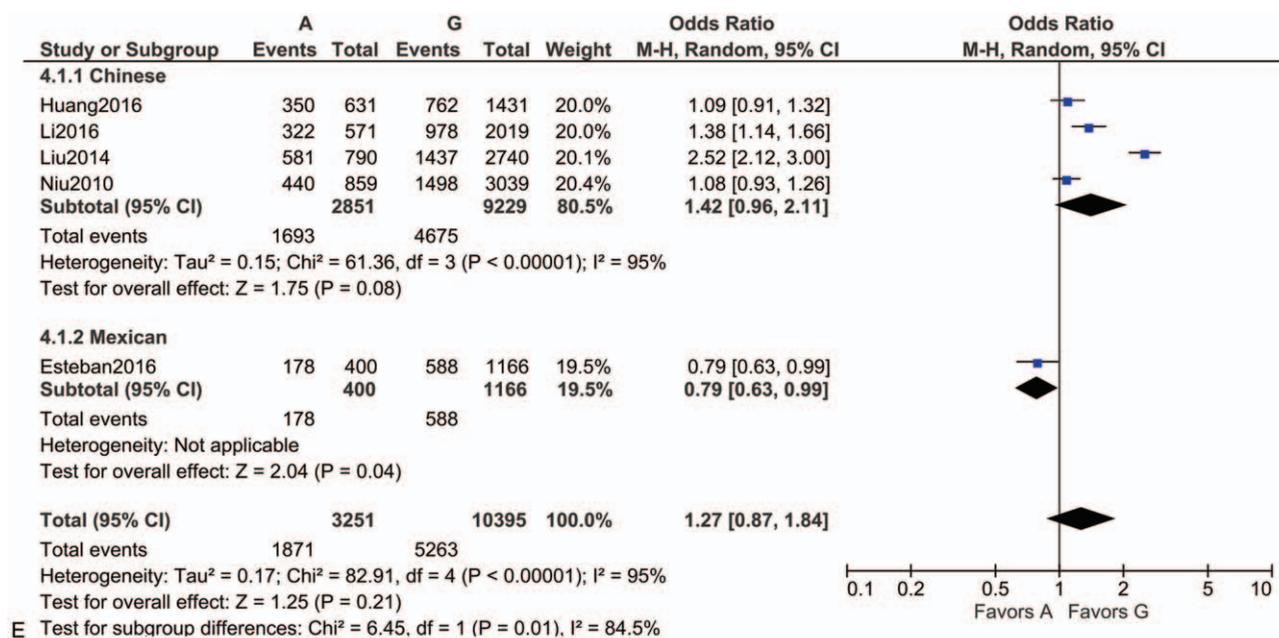


Figure 2. (Continued).

representative of essential HT patients because of the relatively higher number of essential HT patients with underlying diabetes and/or obesity. For example, the apelin/APLNR system could be involved in the glucose uptake via the eNOS and/or PI3K/Akt pathway.<sup>[35-37]</sup> Therefore, we infer that the presence of diabetic patients in the case group might have influenced the allele frequencies of the APLNR gene in Liu's study.<sup>[19]</sup>

The results of Ebbstein's study<sup>[16]</sup> conducted in Mexico were conflicting with the results of the Chinese studies<sup>[17-20]</sup> as shown in Figure 2. The authors inferred that this difference might be because of the heterogeneous genetic background of cases in Mexico City where a lot of immigration has occurred in the last century.<sup>[16]</sup> Otherwise, we infer that this discrepancy may be related to the ethnic differences of daily salt intake between East Asia and Latin America.<sup>[38]</sup> East Asian people have higher salt intake, which can

lead to higher salt sensitivity of BP.<sup>[39]</sup> Consistently, the GenSalt study showed that 2 SNPs in the APLNR gene (rs2282623 and rs746886) were significantly associated with BP response to low salt diet among the Chinese population with daily high dietary salt intake.<sup>[40]</sup> Anyway, it is of great interest to investigate whether our findings in the Chinese population can be generalized to other ethnic groups, especially among East Asian populations because rs671 in ALDH2 gene, for example, is considered to be associated with essential HT among Chinese and Japanese populations<sup>[41,42]</sup> as well as a Korean population.<sup>[43]</sup> Moreover, a meta-analysis has shown that rs9943582 in APLNR gene is associated with a marginally increased risk of CAD among Chinese, Japanese, and Korean populations.<sup>[26]</sup> However, our systematic literature search showed that there were only 7 studies (5 in China, 1 in Mexico, and 1 in Iran) in which the association between SNPs in the APLNR

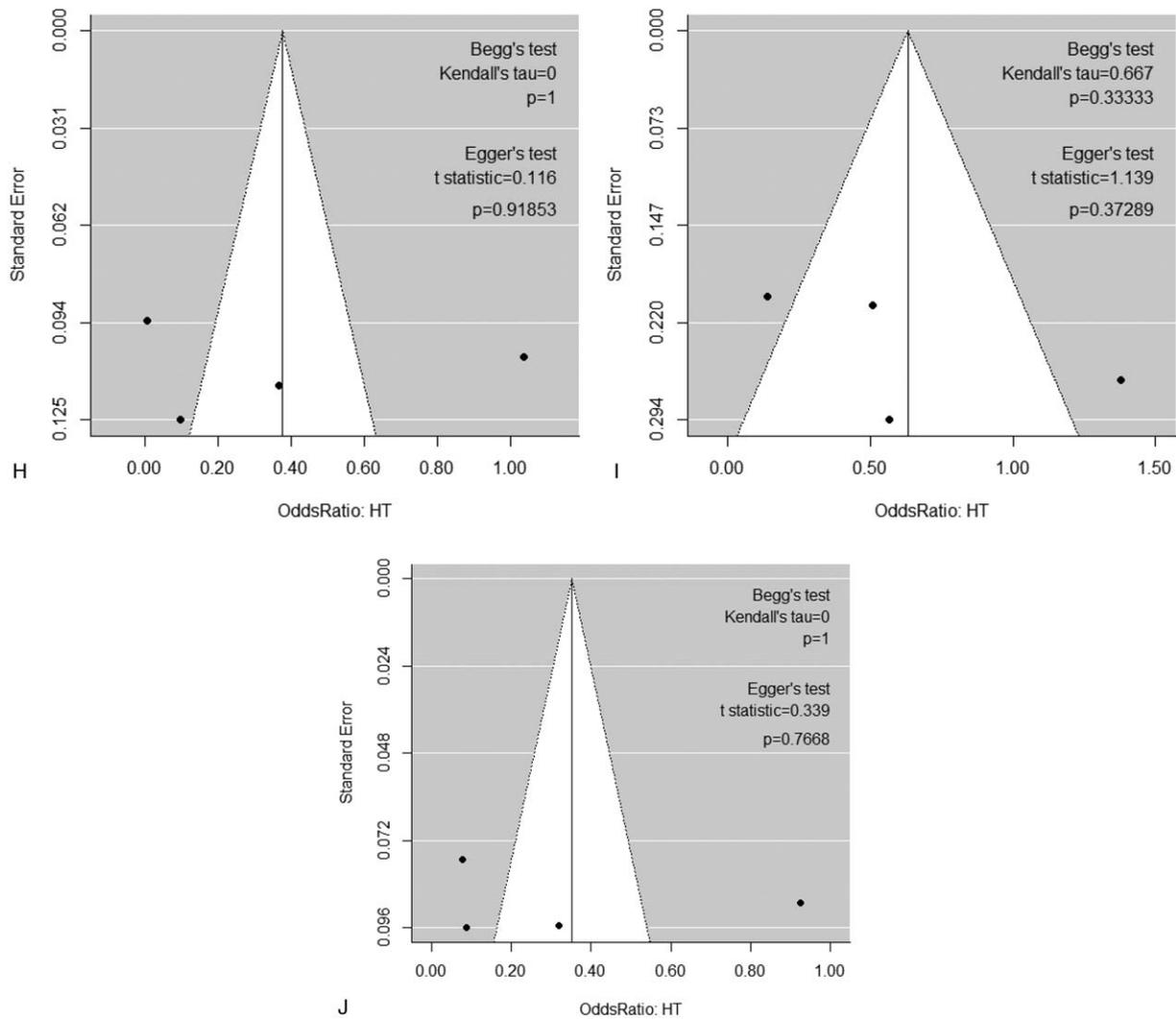


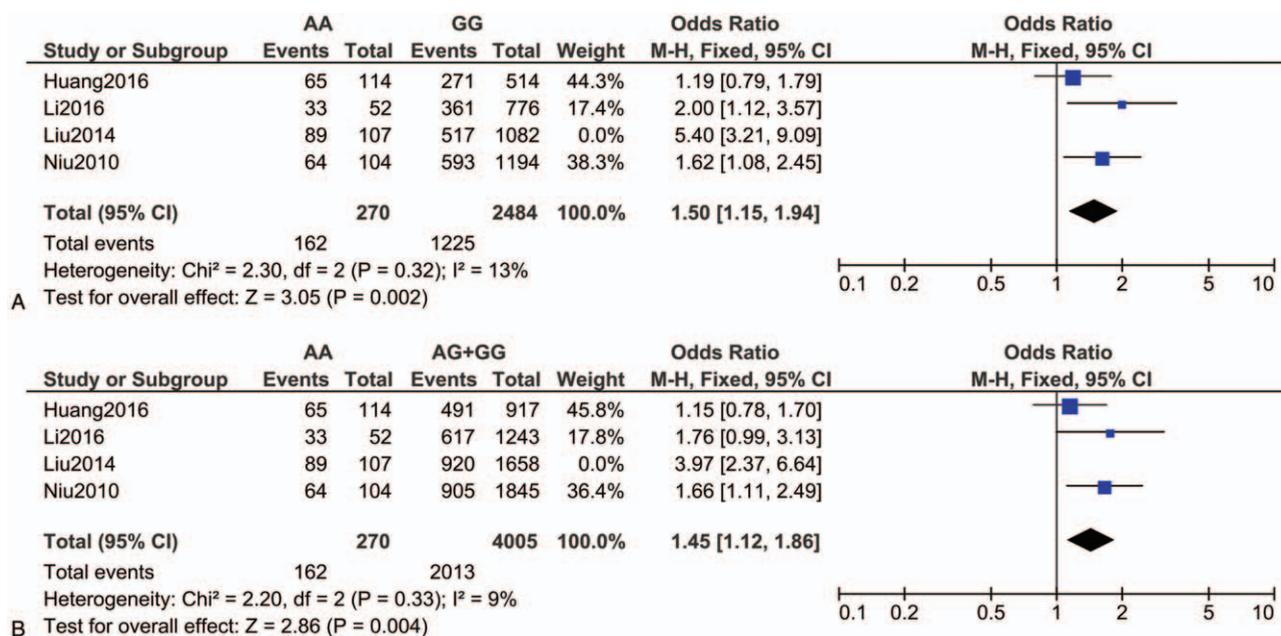
Figure 2. (Continued).

gene and the risk of development of essential HT had been investigated,<sup>[16–22]</sup> and we agree with Liu et al that more studies in other ethnic groups and populations should investigate whether the associations can be generalized to non-Chinese groups.<sup>[19]</sup>

The apelin/APLNR system plays various roles in many physiological processes including cardiovascular functions, fluid homeostasis, and energy metabolism,<sup>[44]</sup> and could also be involved in inflammatory responses. The lipopolysaccharide-induced pro-inflammatory cytokines, interleukin-6 (IL-6), and interferon-gamma, activated enteric apelin expression via the Jak/Stat signaling pathway in the rodent gastrointestinal tract.<sup>[45]</sup> Jak/Stat is also a downstream signaling pathway activated by granulocyte colony stimulating factor.<sup>[46]</sup> In experimental rodents with colitis, administration of exogenous apelin stimulated colonic epithelial proliferation,<sup>[47]</sup> and decreased the expression of pro-inflammatory cytokines including IL-6 by improving intestinal lymphatic drainage function.<sup>[48]</sup> This indicated that the apelin/APLNR system may play regenerative and supportive roles in inflammatory bowel disease.<sup>[49]</sup> In Dahl salt-sensitive rats loaded with high salt, administration of exogenous ELABELA, a novel endogenous

ligand of APLNR, suppressed high salt-induced HT and decreased the expression of pro-inflammatory cytokines including IL-6 and INF- $\gamma$  in the kidney.<sup>[50]</sup> Therefore, although the precise mechanisms are yet to be elucidated, the apelin/APLNR system could be a therapeutic target for inflammatory-related diseases as well.

A major limitation of the present meta-analysis was the small number of studies. Moreover, 4 of the 5 studies were from China, and 3 of the 4 were conducted by the same or related groups, although we considered, as described above, that the participants in the 3 studies were not duplicated. The high heterogeneity of the study populations was also one of the limitations of our study. Therefore, more attention to the risk of bias is needed when interpreting the results of the present meta-analysis. Nevertheless, at least in the Chinese population, our meta-analysis showed, for the first time, a significant association between the AA genotype of the APLNR gene polymorphism rs7119375 and the risk of development of essential HT. More studies with larger sample sizes and in other populations are necessary to further investigate the effects of SNPs in the apelin/APLNR system on the risk of development of essential HT.



**Figure 3.** Forest plot of the risk of development of essential HT associated with the rs7119375 SNP in the sub-group analysis of the Chinese population using the (A) additive model (AA vs GG) and (B) recessive model after excluding Liu’s study.

**Table 3**

**Fasting blood glucose and body mass index in the group with essential HT in each study (data shown as means ± standard deviations).**

Author year sub-group	Fasting Glucose Levels (mmol/L)			
	Male CT group	Female CT group	Male HT group	Female HT group
Huang 2016	4.9 ± 0.5	5.0 ± 0.5	5.1 ± 0.6	5.1 ± 0.6
Li 2016	5.77 ± 1.76	5.77 ± 1.80	5.73 ± 1.84	5.92 ± 1.92
Liu 2014		5.33 ± 1.12		6.14 ± 2.15
Niu 2010	4.94 ± 0.67	4.91 ± 0.60	5.47 ± 1.52	5.54 ± 2.01

Author year sub-group	Body Mass Index (kg/m <sup>2</sup> )			
	Male CT group	Female CT group	Male HT group	Female HT group
Huang 2016	23.0 ± 3.1	22.5 ± 2.9	25.0 ± 4.0	24.9 ± 3.2
Li 2016	25.29 ± 3.02	25.14 ± 3.48	25.41 ± 3.31	24.72 ± 3.40
Liu 2014		23.18 ± 3.77		27.89 ± 6.29
Niu 2010	23.85 ± 3.36	23.21 ± 3.03	25.75 ± 2.83	25.10 ± 3.68

CT = Control, HT = hypertension.

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