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Association between *PRKAA1* rs13361707 T>C polymorphism and gastric cancer risk

Evidence based on a meta-analysis

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Abstract

Background: Recently, several published studies investigating the relationship between protein kinase catalytic subunit alpha-1 gene (*PRKAA1*) rs13361707 T>C polymorphism and gastric cancer (GC) susceptibility reported controversial results. The purpose of this meta-analysis was to estimate the strength of the relationship.

Methods: Qualified studies were identified form a comprehensive search conducted in the Embase, Pubmed, Wangfang, and China National Knowledge Infrastructure (CNKI) databases for studies published before February 12, 2018. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were used to assess the relationship between the *PRKAA1* rs13361707 T>C polymorphism and GC risk.

Results: Fifteen independent case-control studies, which included 14,615 GC patients and 18,143 control subjects, were included in this present meta-analysis. The overall analysis of the 15 studies indicated that the *PRKAA1* rs13361707 T>C polymorphism significantly increased susceptibility for GC in all genetic models. When stratified analysis was carried out by country and source of controls, similar results were found in each subgroup, except for the Hispanic Americans. There was no publication bias in our study. Omitting each study 1 at a time in the sensitivity analysis of the *PRKAA1* rs13361707 T>C polymorphism and GC risk had no noticeable influence on the pooled OR, which identified the reliability of the meta-analysis. False-positive report probability analysis and trial sequential analysis demonstrated that such relationship was confirmed in the present study.

Conclusions: The meta-analysis reveals that the *PRKAA1* rs13361707 T>C polymorphism has a significant relationship with increased GC risk. To confirm the risk identified in the present meta-analysis, well-designed and large-scale case-control studies are warranted to investigate the relationship, especially among non-Asian ethnicity.

Abbreviations: CIs = confidence intervals, CNKI = Chinese National Knowledge Infrastructure, FPRP = false-positive report probability analysis, GC = gastric cancer, GWAS = genome-wide association studies, HWE = Hardy–Weinberg equilibrium, NOS = Newcastle–Ottawa Scale, ORs = odds ratios, *PRKAA1* = protein kinase catalytic subunit alpha-1 gene, SNPs = single-nucleotide polymorphisms, TSA = trial sequential analysis.

Keywords: gastric cancer, meta-analysis, polymorphism, *PRKAA1*, risk

1. Introduction

As 1 of the most frequently encountered malignant tumors, gastric cancer (GC) has become the third main cause of tumor-associated death in the world, with a 5-year survival rate, which is low, especially for advanced GC.[1] More than half of the worldwide GC patients occur in East Asia, where the incidence of GC mortality is the highest in the world.[2] According to cancer statistics, there were about 679,000 new cases of GC diagnosed, and nearly 498,000 died of GC in China in the year 2015. The morbidity and mortality of GC were second only to lung cancer, which was similar to the epidemiological results of GC in Japan and South Korea.[3] There were approximately 26,370 estimated new cases and 10,730 estimated deaths due to GC in the United States in the year 2016.[4] Because of the mechanism of the carcinogenesis of GC is still not fully understood, GC has become a major public health problem. As with other complicated diseases, the development of GC is a complex, multistep, and multifactorial process, with multiple potential risk factors, including diet, tobacco smoke, exposure to *Helicobacter pylori* (*H pylori*), and stomach disease history.[5] Additionally, the development of GC may also be related to genetic susceptibility factors.[6] Currently, genetic factors for GC risk are still not fully recognized.

The 5′-AMP-activated protein kinase (AMPK) is encoded by the AMP-activated protein kinase catalytic subunit alpha-1 gene (*PRKAA1*), which is located on chromosome 5p13.1.[7] AMPK, encoded by 7 genes (α1, α2, β1, β2, γ1, γ2, γ3), is an αβγ heterotrimer and has multiple subunit isoforms. AMPK has up to 12 isoenzyme combinations, each of which has a different

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YJ and WL contributed equally to this study.

The authors declare that there were no conflicts of interest.

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expression in tissue and subcellular fractions.[8] AMPK, which plays a critical role in the biosynthesis of macromolecules and cellular metabolism, is an energy sensor.[9] Activating AMPK can inhibit lipid accumulation in the body, increase the oxidation of fatty acids, and decrease the biosynthesis of cholesterol and fatty acids.[10] Activating AMPK suppresses cell proliferation in both nonmalignant and cancerous cells, which has been verified by many studies. AMPK activation occurs as a result of various mechanisms, which include G1 phase arrest in the cell cycle and the inhibition of protein and fatty acid synthesis that mediate the results of AMPK activation.[11,12] AMPK cell cycle regulation is mediated through activating the p53-p21 axis pathway, activating tumor suppressor liver kinase B1 (LKB1), inhibiting the mammalian target of the rapamycin pathway, and through other similar mechanisms.[13] Based on the above evidence, studies investigating the function of AMPK have focused on its critical role in the development of some cancers and on its potential use as a therapeutic target for some malignant tumors.[14] These studies reveal that AMPK plays a critical role in the occurrence and development of GC, and polymorphisms of the encoding gene could therefore change individual susceptibility to GC.

The most common forms of genetic mutations in the human genome are single-nucleotide polymorphisms (SNPs).[15] There are several polymorphisms that have been confirmed in the *PRKAA1* gene. Among them, the *PRKAA1* rs13361707 T>C polymorphism, which is associated with gastric carcinoma risk, is the most widely investigated. However, the relationship of the *PRKAA1* rs13361707 T>C polymorphism with GC risk is still ambiguous.[16–18] Two previous meta-analyses were conducted in 2015 to clarify the role of the *PRKAA1* rs13361707 T>C polymorphism in GC risk.[19,20] However, the number of case-control studies included in these meta-analyses on the relationship between *PRKAA1* rs13361707 T>C and GC risk was extremely small, and several eligible studies were not identified for inclusion; thus, these studies did not have sufficient statistical power. Since then, some new studies have investigated the association between the *PRKAA1* rs13361707 T>C polymorphism and GC risk, but the results of these studies remain inconclusive. Therefore, to explore the real correlation of the *PRKAA1* rs13361707 T>C polymorphism with GC susceptibility, we conduct this updated meta-analysis.

2. Materials and methods

Ethical approval was not necessary for the present meta-analysis.

2.1. Search strategy

To identify eligible case-control studies, electronic searches were conducted in the PubMed, Embase, Wangfang, and China National Knowledge Infrastructure (CNKI) databases. No language limitation was included in the search (last update: February 12, 2018). The following key terms were searched: ("*PRKAA1*" or "protein kinase catalytic subunit alpha-1"), ("gastric carcinoma" or "gastric cancer") and ("polymorphism" or "mutation" or "variant"). Meanwhile, to find other relevant publications, we also retrieved the references and review articles of the eligible studies. Ethical approval was not necessary for the present meta-analysis.

2.2. Inclusion and exclusion criteria

The eligible studies, included in this meta-analysis, must have met the following criteria: examine the relationship between the *PRKAA1* s13361707 T>C polymorphism and GC risk; use a case-control study design; sufficient data for estimating an odds ratio (OR) and corresponding 95% confidence interval (CI); and clearly describe the sources of cases and controls and GC diagnoses. The exclusion criteria were as follows: duplicate data; insufficient data; and abstracts, meta-analyses, comments, reviews, and editorial letters. When the same or overlapping data were used, we chose the newest or largest-sized published studies.

2.3. Data extraction

Two reviewers (JY and WL) extracted information from all collected studies independently according to the above inclusion criteria. Discrepancies were solved by discussion among all reviewers. In all selected studies, the first author, year of publication, country, ethnicity, sources of controls, number of cases and controls with different genotypes, evidence of Hardy–Weinberg equilibrium (HWE) in the control group, and so on were collected.

2.4. Quality assessment

The Newcastle–Ottawa Scale (NOS) and the Agency for Healthcare Research and Quality (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp; maximum score = 9 points) were used to appraise the quality of the studies collected in this meta-analysis. In short, each study is scored based on the selection of patients, the comparability of the groups, and the quality of the sampling process. Stars are granted for every quality item; studies awarded the maximum of 9 stars, have the highest quality.

2.5. In silico analysis of PRKAA1 expression

To analyze the expression of *PRKAA1* in both GC and paracancerous tissues, the online mini database from the Zhang Lab of Peking University (http://gemini.cancer-pku.cn/) was used.[21] RNA expression profiles of 410 GC samples and 228 normal samples from the corresponding tissues were included in the database.

2.6. Statistical analysis

To assess the strength of the relationship between the *PRKAA1* s13361707 T>C polymorphism and GC risk under the homozygous (CC vs TT), heterozygous (CC vs CT), recessive (CC vs CT + TT), dominant (CT + CC vs TT), and allele contrast (C vs T) models, pooled ORs and 95% CIs were used. The significance of pooled ORs was tested by *Z* test. A difference was considered significant when *P* was less than .05. HWE in the controls was assessed in each study with a goodness-of-fit test (chi-square or Fisher exact test). Subgroup analysis was conducted by country and source of controls. The heterogeneity among eligible studies was assessed by a chi-square-based *Q* test, and the random (DerSimonian–Laird method) effect model was used to calculate the pooled OR when the I^2 value $\geqq$50%, which was considered as representing significant statistical heterogeneity. Otherwise, the fixed (Mantel–Haenszel method) effect model was applied.[22] Sensitivity analysis was conducted by excluding 1 study at a time to examine the stability of the pooled results. Begg funnel plot and Egger linear regression test were applied to assess potential publication bias.[23,24] False-positive report probability

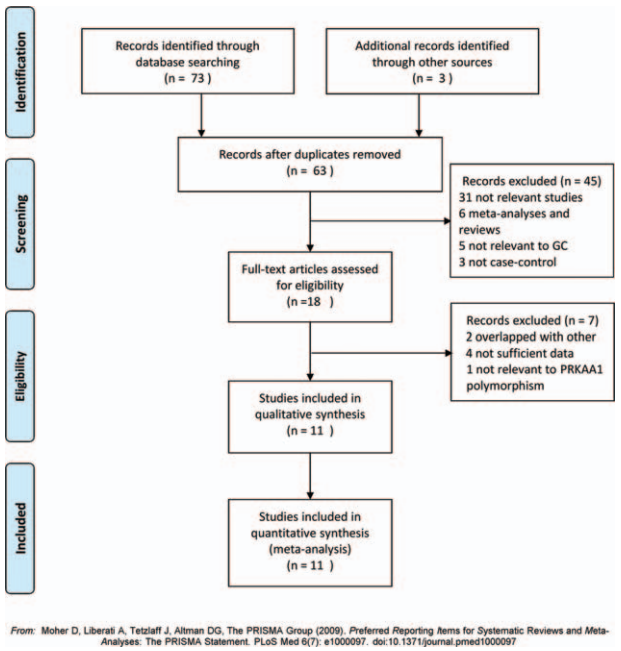

Figure 1. Flow chart of studies selection in this meta-analysis.

(FPRP) analysis and trial sequential analysis (TSA) were performed as described previously.[25] All statistical analyses were conducted by the STATA 12.0 software (STATA Corp. College Station, TX) using 2-sided significance tests, and $P < .05$ was considered statistically significant.

3. Results

3.1. Description of included studies

The process of study selection and exclusion is shown in Fig. 1. A total of 76 studies were retrieved from the Embase, Pubmed, Wangfang, and CNKI databases. Sixty-three publications remained after excluding duplicate studies. Forty-five publications were excluded after reviewing the titles and abstracts of all relevant studies. Of these 45 studies, 31 were clearly irrelevant, 5 were not relevant to GC, 6 were meta-analyses or reviews, and 3 were not case-controls. The full texts of the 18 articles were examined according to the selection criteria. Seven of the full-text studies were excluded for the following reasons: 2 studies had overlapping data, 4 studies did not have sufficient data, and 1 study was not relevant to the *PRKAA1* rs13361707 T>C polymorphism. Eleven eligible articles were included based on the inclusion and exclusion criteria.[16–19,26–32] One publication conducted by Shi et al[29] included 5 different case-control studies. Therefore, 15 case-control studies with a total of 14,615 GC cases and 18,143 control subjects for the *PRKAA1* rs13361707 T>C polymorphism were included in our meta-analysis. There were 11 case-control studies conducted in the Chinese population, 3 were conducted in the Korean population, and only 1 was performed in the Hispanic Americans. All the studies were published between September, 2011 and January, 2017. GC cases in the studies ranged from 60 to 3245. The number of control subjects, mainly blood donors or healthy individuals, ranged from 60 to 3227 in the studies. All the patients from the 15 case-control studies were pathologically or histologically diagnosed as having gastric carcinoma. Seven studies were hospital-based and 8 studies were population-based. The NOS score, which ranged from 6 to 8 points, was applied to assess the quality of the enrolled studies. The methodological quality of the included studies suggested that the studies were reliable (Supplemental Table 1, http://links.lww.com/MD/C181). The genotype distributions in the controls of all eligible studies were consistent with HWE. Table 1 shows the characteristics of the selected studies. Table 2 shows the allele frequency and genotype distribution of the *PRKAA1* rs13361707 T>C polymorphism in cases and controls.

3.2. Quantitative data synthesis

The main results in the present meta-analysis of the relationship between the *PRKAA1* rs13361707 T>C polymorphism and GC risk are described in Table 3. The overall analysis of 15 studies

Table 1

Characteristics of eligible case-control studies included in this meta-analysis.

First author	Year	Country	Ethnicity	Source of controls	Genotyping method	Sample size		NOS score
						Cases	Controls	
Zhang[26]	2016	China	Asian	HB	MALDI-TOF	60	60	7
Wu[27]	2014	China	Asian	HB	Multiplex SNaPshot SNP	217	428	7
Eom[28]	2016	Korea	Asian	HB	GoldenGate assay	846	846	6
Song[16]	2013	Korea	Asian	PB	TaqMan	3245	1700	6
Shi[29]	2011	China	Asian	PB	AGWHSA 6.0 chips	979	2268	8
Shi[29]	2011	China	Asian	PB	AGWHSA 6.0 chips	1873	2076	8
Shi[29]	2011	China	Asian	PB	AGWHSA 6.0 chips	895	3227	8
Shi[29]	2011	China	Asian	PB	AGWHSA 6.0 chips	2404	3227	8
Shi[29]	2011	China	Asian	PB	AGWHSA 6.0 chips	1392	1513	8
Qiu[19]	2015	China	Asian	PB	TaqMan	1124	1194	8
Kim[30]	2014	Korea	Asian	HB	GoldenGate assay	475	473	7
Cai[31]	2017	China	Asian	PB	KASP	473	487	6
Sun[17]	2014	America	Caucasian	HB	Taqman	130	124	6
Dong[18]	2015	China	Asian	HB	iMLDR	167	186	7
Li[32]	2013	China	Asian	HB	Taqman	335	334	7

AGWHSA 6.0 CHIPS = Affymetrix Genome-Wide Human SNP Array 6.4 chips, HB = hospital-based; PB = population-based, HRM-PCR = high-resolution melting–polymerase chain reaction, iMLDR = improved multiplex ligase detection reaction, KASP = kompetitive allele-specific PCR, MALDI-TOF-MS = polymerase chain reaction–matrix-assisted laser desorption/ionization time-of-flight mass spectrometry, NOS = Newcastle–Ottawa Scale.

Table 2

***PRKAA1* rs13361707 polymorphism genotype distribution and allele frequency in cases and controls.**

		Genotype(N)								Allele frequency (N)					
		Case				Control				Case		Control			
First author	Year	Total	TT	CT	CC	Total	TT	CT	CC	T	C	T	C	MAF	HWE
Zhang[26]	2016	60	10	27	23	60	16	34	10	47	73	66	54	0.45	0.26
Wu[27]	2014	217	48	115	54	428	133	209	86	211	223	475	381	0.45	0.81
Eom[28]	2016	846	176	421	249	846	248	424	174	773	919	920	772	0.46	0.77
Song[16]	2013	3245	682	1654	909	1700	477	846	377	3018	3472	1800	1600	0.47	0.96
Shi[29]	2011	979	160	517	302	2268	607	1154	507	837	1121	2368	2168	0.48	0.35
Shi[29]	2011	1873	371	941	561	2076	578	1034	464	1683	2063	2190	1962	0.47	0.97
Shi[29]	2011	895	225	447	223	3227	898	1616	713	897	893	3412	3042	0.47	0.78
Shi[29]	2011	2404	459	1221	724	3227	898	1616	713	2211	2669	3412	3042	0.47	0.78
Shi[29]	2011	1392	237	675	480	1513	392	745	376	1149	1635	1529	1497	0.49	0.56
Qiu[19]	2015	1124	209	571	344	1194	356	565	273	989	1259	1277	1111	0.47	0.09
Kim[30]	2014	475	97	241	137	473	135	242	96	435	515	512	434	0.46	0.51
Cai[31]	2017	473	88	213	172	487	143	246	98	389	557	532	442	0.45	0.68
Sun[17]	2014	130	79	45	6	124	68	48	8	203	57	184	64	0.26	0.90
Dong[18]	2015	167	62	68	37	186	41	91	54	192	142	173	199	0.53	0.82
Li[32]	2013	335	71	167	97	334	102	165	67	309	361	369	299	0.45	0.98

HWE = Hardy–Weinberg equilibrium, MAF = minor allele frequency.

Table 3

Meta-analysis results.

Genetic models	No. of studies	OR (95% CI)	*P*	I^2 (%)	P_{het}	*P* (Begg)	*P* (Egger)
Homozygous (CC vs TT)							
Overall	15	1.76 (1.31–2.35)	<.001	94.1	<.001	.092	.850
China	11	1.81 (1.23–2.67)	.003	95.7	<.001		
Korea	3	1.80 (1.53–2.05)	<.001	0.0	.469		
America	1	0.65 (0.21–1.95)	.438	—	—		
PB	8	1.95 (1.31–2.89)	.001	96.7	<.001		
HB	7	1.52 (1.01–2.29)	.045	78.7	<.001		
Heterozygous (CC vs CT)							
Overall	15	1.36 (1.23–1.50)	<0.001	60.7	.001	.692	.261
China	11	1.37 (1.21–1.57)	<0.001	68.1	.001		
Korea	3	1.38 (1.23–1.54)	<0.001	0.0	.986		
America	1	0.81 (0.48–1.36)	0.419	—	—		
PB	8	1.43 (1.30–1.56)	<0.001	52.4	.040		
HB	7	1.16 (0.88–1.52)	0.293	67.7	.005		
Recessive (CC vs CT + TT)							
Overall	15	1.47 (1.24–1.73)	<0.001	87.8	<.001	.692	.981
China	11	1.49 (1.20–1.84)	<0.001	91.0	<.001		
Korea	3	1.45 (1.30–1.62)	<0.001	0.0	.376		
America	1	0.70 (0.24–2.08)	0.339	—	—		
PB	8	1.52 (1.22–1.88)	<0.001	93.0	<.001		
HB	7	1.40 (1.09–1.80)	0.009	61.1	.017		
Dominant (CT + CC vs TT)							
Overall	15	1.48 (1.32–1.66)	<0.001	73.6	<.001	.767	.398
China	11	1.51 (1.30–1.75)	<0.001	78.1	<.001		
Korea	3	1.50 (1.35–1.67)	<0.001	0.0	.830		
America	1	0.78 (0.48–1.29)	0.523	—	—		
PB	8	1.58 (1.42–1.76)	<0.001	68.1	<.001		
HB	7	1.24 (0.91–1.70)	0.179	78.9	<.001		
Allele (C vs T)							
Overall	15	1.34 (1.24–1.44)	<0.001	76.4	<.001	.843	.574
China	11	1.35 (1.23–1.48)	<0.001	80.6	<.001		
Korea	3	1.34 (1.25–1.43)	<0.001	0.0	.469		
America	1	0.81 (0.54–1.22)	0.305	—	—		
PB	8	1.38 (1.29–1.48)	<0.001	73.6	<.001		
HB	7	1.21 (0.98–1.49)	0.073	81.2	<.001		

CI = confidence interval, OR = odds ratio.

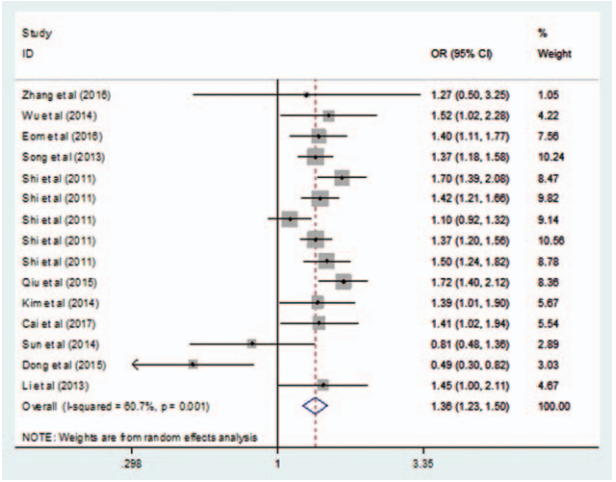

Figure 2. Forest plots of the *PRKAA1* rs13361707 T>C polymorphism and gastric cancer risk (heterozygous: CC vs CT).

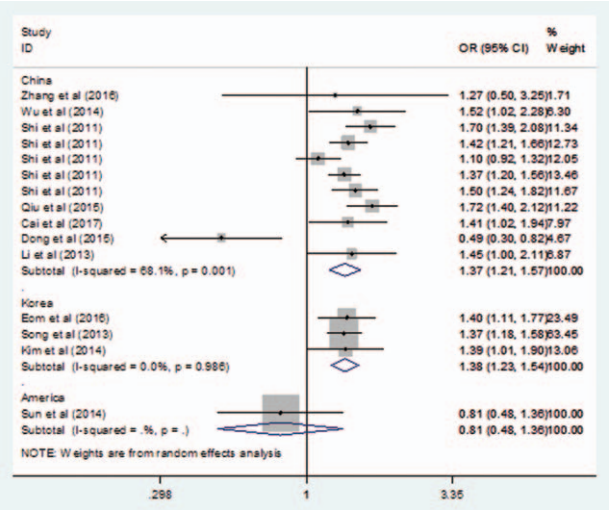

Figure 3. Forest plots of the *PRKAA1* rs13361707 T>C polymorphism and gastric cancer risk in subgroup by country (heterozygous: CC vs CT).

revealed a significant relationship between the *PRKAA1* rs13361707 T>C polymorphism and GC susceptibility under all genetic model (CC vs TT: OR 1.76, 95% CI 1.31–2.35, $P<.001$, $I^2=94.1\%$; CC vs CT: OR 1.36, 95% CI 1.23–1.50, $P<.001$, $I^2=60.7\%$; CC vs CT+TT: OR 1.47, 95% CI 1.24–1.73, $P<.001$, $I^2=87.8\%$; CT+CC vs TT: OR 1.48, 95% CI 1.32–1.66, $P<.001$, $I^2=73.6\%$; C vs T: OR 1.34, 95% CI 1.24–1.44, $P<.001$, $I^2=76.4\%$; Fig. 2).

In the subgroup analysis stratified by country, the results indicated that the *PRKAA1* rs13361707 T>C polymorphism was significantly associated with increased gastric risk in the Chinese population in 5 genetic model (CC vs TT: OR 1.81, 95% CI 1.23–2.67, $P=.003$, $I^2=95.7\%$; CC vs CT: OR 1.37, 95% CI 1.21–1.57, $P<.001$, $I^2=68.1\%$; CC vs CT+TT: OR 1.49, 95% CI 1.20–1.84, $P<.001$, $I^2=91.0\%$; CT+CC vs TT: OR 1.51, 95% CI 1.30–1.75, $P<.001$, $I^2=78.1\%$; C vs T: OR 1.35, 95% CI 1.23–1.48, $P<.001$, $I^2=80.6\%$), and the same results were shown in the Korean population under 5 genetic models (CC vs TT: OR 1.80, 95% CI 1.53–2.05, $P<.001$, $I^2=0.0\%$; CC vs CT: OR 1.38, 95% CI 1.23–1.54, $P<.001$, $I^2=0.0\%$; CC vs CT+TT: OR 1.45, 95% CI 1.30–1.62, $P<.001$, $I^2=0.0\%$; CT+CC vs TT: OR 1.50, 95% CI 1.35–1.67, $P<.001$, $I^2=0.0\%$; C vs T: OR 1.34, 95% CI 1.25–1.43, $P<.001$, $I^2=0.0\%$; Fig. 3).

When stratified by the source of controls, we found that the *PRKAA1* rs13361707 T>C polymorphism was associated with a significantly increased GC risk both in population-based controls (CC vs TT: OR 1.95, 95% CI 1.31–2.89, $P=.001$, $I^2=96.7\%$; CC vs CT: OR 1.43, 95% CI 1.30–1.56, $P<.001$, $I^2=52.4\%$; CC vs CT+TT: OR 1.52, 95% CI 1.22–1.88, $P<.001$, $I^2=93.0\%$; CT+CC vs TT: OR 1.58, 95% CI 1.42–1.76, $P<.001$, $I^2=68.1\%$; C vs T: OR 1.38, 95% CI 1.29–1.48, $P<.001$, $I^2=73.6\%$) and hospital-based controls (CC vs TT: OR 1.52, 95% CI 1.01–2.99, $P=.045$, $I^2=78.7\%$; CC vs CT+TT: OR 1.40, 95% CI 1.09–1.80, $P=.009$, $I^2=61.1\%$; Fig. 4).

3.3. False-positive report probability analysis for significant findings

We conducted a FPRP analysis for all observed significant findings. With the assumption of a prior probability of .1, the FPRP values were all <0.2, indicating that these associations were significant (Table 4).

3.4. In silico analysis of PRKAA1 expression

The results revealed that the expression of *PRKAA1* in GC tissue was higher than that in paracancerous tissue (TPM: Transcripts Per Kilobase Million=55 vs 30, respectively, $P<.01$, Supplemental Fig. 1, http://links.lww.com/MD/C181).

3.5. Heterogeneity and sensitivity analysis

High heterogeneity for the included populations was observed under all genetic models by random-effect analysis, except for in the Korean population under 5 genetic models. Thus, the fixed-effects analysis was carried out for the Korean population under each genetic model. Sensitivity analysis was performed, and there

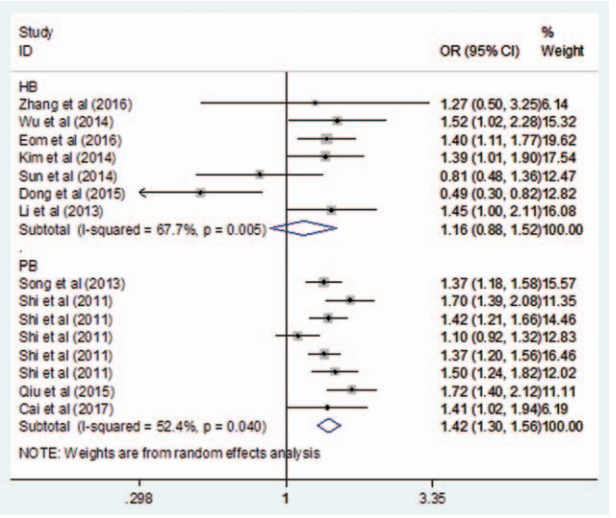

Figure 4. Forest plots of the *PRKAA1* rs13361707 T>C polymorphism and gastric cancer risk in subgroup by source of controls (heterozygous: CC vs CT).

Table 4

False-positive report probability analysis values for the noteworthy findings.

Genotype	Crude OR (95% CI)	P*	Statistical power†	Prior probability				
				.25	.1	.01	.001	.0001
Homozygous (CC vs TT)	1.76 (1.31–2.35)	.000	0.139	.003	.008	.083	.476	.901
Heterozygous (CC vs CT)	1.36 (1.23–1.50)	.000	0.975	.000	.000	.000	.000	.000
Recessive (CC vs CT + TT)	1.47 (1.24–1.73)	.000	0.596	.000	.000	.001	.056	.373
Dominant (CT + CC vs TT)	1.48 (1.32–1.66)	.000	0.591	.000	.000	.000	.000	.000
Allele (C vs T)	1.34 (1.24–1.44)	.000	0.999	.000	.000	.000	.000	.000

CI = confidence interval, OR = odds ratio.

* A chi-square test was used to evaluate the distributions of genotype frequency.

† Statistical power was calculated by use of the number of observations in the subgroup and *P* values in this table.

was no obvious influence on the pooled OR by omitting each study one at a time, which confirmed the robustness of the meta-analysis (Fig. 5).

3.6. Publication bias

There was no asymmetry in the funnel plot when we detected the publication bias of the current meta-analysis. Neither Begg rank correlation method nor Egger regression method showed publication bias. Thus, the above results suggested that no publication bias was observed in the meta-analysis (Table 3, Fig. 6).

3.7. Trial sequential analysis

We performed TSA to minimize random errors and strengthen the robustness of our conclusions. As shown in Supplemental Fig. 2 (http://links.lww.com/MD/C181), we found that the cumulative z-curve crossed the monitoring boundary before reaching the required sample size, indicating that the cumulative evidence is sufficient and no further study was needed to verify the conclusions.

4. Discussion

Previously published studies have indicated that the interactions between genes and environmental factors result in GC. However, by modulating the effects of environmental factors, genetic susceptibility may substantially influence an individual's susceptibility.[33] Genetic risk of various cancers has attracted increasing attention to the research on the gene polymorphisms involved in tumour occurrence. It has been reported in previous studies that there is a significant association between some genetic factors, such as *MUC1*, *PSCA*, and *PRKAA1* polymorphisms, and susceptibility to GC.[34]*PRKAA1*, a subunit of the AMPK pathway, is critical to cellular activity and cancer development, and studies have demonstrated its role in cell differentiation, apoptosis, autophagy, and cancer progression,[35–38] and also in clinical prognosis.[39,40] Recently, targeting *PRKKA1* was reported as a potential method of cancer suppression.[38] The rs13361707 SNP is located in the first intron of *PRKAA1* at 5p13.1and is the most widely investigated. A genome-wide association study (GWAS) of GC in the Han Chinese population showed a significant association between the *PRKAA1* rs13361707 T>C polymorphism and noncardia GC risk.[29] However, subsequent replication studies on the association between *PRKAA1* rs13361707 T > C polymorphism and GC susceptibility were not consistent. To derive a more precise estimation of this relationship, we conducted a systematic meta-analysis.

In 2011, a GWAS conducted by Shi et al[29] in Asian populations, identified the *PRKAA1* rs13361707 T>C polymorphism associated with GC risk; the result was reconfirmed in another GWAS performed in European populations in 2015.[41] However, in the published replication studies conducted in diverse populations, the conclusions about the relationship between the *PRKAA1* rs13361707 T>C polymorphism and GC susceptibility are conflicting. For instance, Hwang et al's[42] study

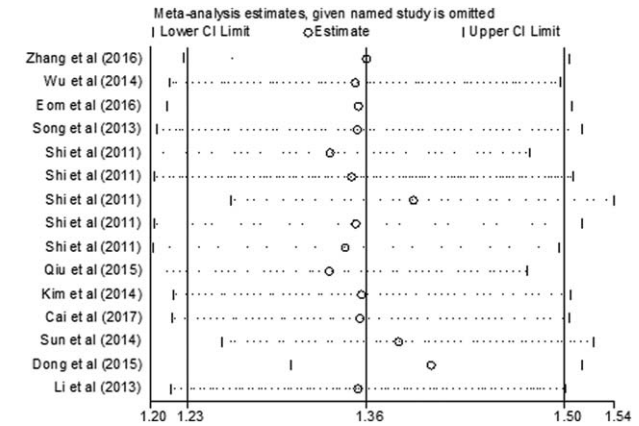

Figure 5. Sensitivity analysis of the *PRKAA1* rs13361707 T>C polymorphism and gastric cancer risk (heterozygous: CC vs CT).

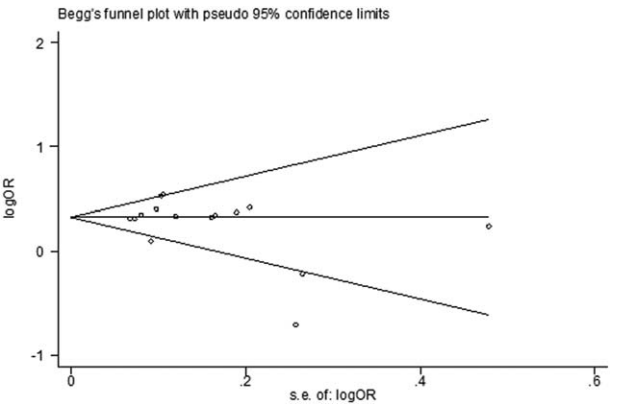

Figure 6. Funnel plot assessing evidence of publication bias (heterozygous: CC vs CT).

indicated that individuals with the rs13361707C allele have significantly increased risk for the development of GC, and Zhang et al[26] revealed no correlation between the *PRKKA1* rs13361707 T>C polymorphism and GC susceptibility; however, Dong et al[18] found that the *PRKAA1* rs13361707 T>C polymorphism may act as a protective factor against gastric carcinomas. In our present study, 15 case-control studies were eventually included, comprising a total of 14,615 cases and 18,143 controls. In the total population, the pooled results of our meta-analysis indicated that there was an obviously significant association between the *PRKAA1* rs13361707 T>C polymorphism and GC susceptibility in all genetic models—a finding consistent with the previously published GWAS. In 2015, two meta-analyses assessed the relationship between the *PRKAA1* rs13361707 T>C polymorphism and GC risk.[19,20] Both results acquired the same conclusion that the *PRKAA1* rs13361707 T>C polymorphism significantly increased the risk of GC. Although these results were consistent with the findings of our meta-analysis, the sample sizes included in these meta-analyses were very small compared with our study. Additionally, all case-control studies included in the above 2 meta-analyses were conducted only in Asian populations. The results of our meta-analysis, which included more case-control studies and more ethnicities, have more sufficient statistical power and are more reliable. We also performed FPRP analysis to confirm that the evidence of our results was reliable and robust, and the result of TSA indicated that sample size in our meta-analysis was sufficient. In addition, in silico analysis of *PRKAA1* expression also indicated that this polymorphism might be associated with *PRKAA1* gene mRNA expression alteration. Our meta-analysis indicated that the *PRKAA1* rs13361707 T>C polymorphism could significantly increase GC risk. The result allowed us to raise a hypothesis that *PRKAA1* rs13361707 T>C might be an independent risk factor, and might be a potential marker for screening and early diagnosis of GC.

Because of significant heterogeneities in the results, subgroup analysis was conducted by country. The results indicated that the *PRKAA1* rs13361707 mutation significantly increased the risk of GC in China and Korea, which is in agreement with previous GWAS and meta-analyses.[19,20,29] There was no statistically significant association between the *PRKAA1* rs13361707 T>C polymorphism and GC risk in America; this result suggests that the differences between diverse ethnic populations might be a potential source of heterogeneity in this relationship. However, this result should be interpreted with caution, not only because the result was inconsistent with the previous GWAS performed with in western population,[41] but also because only one case-control study was included in the American subgroup; therefore, this result needs to be confirmed by more case-control studies, especially in Western populations. When stratified by the source of controls, we found that the *PRKAA1* rs13361707 T>C polymorphism was associated with a significantly increased GC risk both in population based and hospital-based controls. However, the statistical difference was more significant in population-based; this result further confirms that the *PRKAA1* rs13361707 T>C polymorphism is a risk factor for GC susceptibility. Therefore, further functional studies and future investigations should pay more attention to the *PRKAA1* rs13361707 T>C polymorphism and its molecular mechanism involving the occurrence of GC.

Despite our best efforts to explore the association between the *PRKAA1* rs13361707 T>C polymorphism and GC susceptibility in this meta-analysis, there are still several limitations existing in the following aspects. Firstly, our study is a summary of the data. We did not verify our results from the level of basic experiments. Secondly, we included only published studies in our analysis. Some eligible studies were not included in our present analysis because they were not identified using our search criteria. Thirdly, all of the selected papers were conducted in Asian populations except 1 study. The sample size of the study in the non-Asian population was extremely small. The differences in the stages and types of GC were not considered, as there was insufficient data on these factors in the included studies. Excluding these variables may reduce the accuracy of the conclusions. Fourthly, the high heterogeneity among the included studies might weaken the reliability of the conclusions, although the random-effects model was performed in our meta-analysis. More original data from a large sample of diverse ethnicities are needed to confirm the relationship between the *PRKAA1* rs13361707 T>C polymorphism and GC risk.

5. Conclusions

In conclusion, despite the above mentioned limitations, our present meta-analysis indicated that the *PRKAA1* rs13361707 T>C polymorphism could significantly increase GC risk. It is critical that further investigations with larger sample sizes, more ethnic groups, and strict protocols are designed to more precisely examine the relationship between the *PRKAA1* rs13361707 variants and GC risk, especially among non-Asian ethnicity.

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Author contributions

Conceptualization: L. Li.
Methodology: J. Lu.
Software: X. Zhao.
Writing – original draft: Y. Jiang, W.B. Li.

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