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RESEARCH ARTICLE

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CASR rs1801725 polymorphism is associated with the risk and prognosis of colorectal cancer: A case-control study

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Abstract

Background: The extracellular calcium-sensing receptor (CASR) controls body calcium homeostasis. Increased levels of calcium are associated with protecting against colorectal cancer (CRC). This study aimed to determine the relationship between CASR gene rs1801725 polymorphism and CRC risk and prognosis.

Methods: We conducted a hospital-based case-control study and a meta-analysis to evaluate the association of CASR gene rs1801725 polymorphism with CRC susceptibility.

Results: This study proved that CASR rs1801725 polymorphism was associated with a higher risk to develop CRC (TT vs GG: OR 1.92, 95% CI [1.03-3.59], $P = .042$; T vs G: OR 1.30, 95% CI [1.03-1.64], $P = .030$). Subgroup analysis showed that this polymorphism increased the risk of CRC among smokers, and those aged ≥60 years (TT vs GG: OR 3.37, 95% CI [1.12-10.14], $P = .034$). We also found that this polymorphism was associated with the tumor size, TNM stage, and lymph node metastasis of CRC (GT vs GG: OR 2.03, 95% CI [1.32-3.10], $P = .001$). In addition, CASR gene rs1801725 polymorphism correlated with the survival of CRC patients. Further meta-analysis also obtained a significant association between this SNP and CRC risk (TT + GT vs GG: OR 1.28, 95% CI [1.01, 1.63], $P = .041$). Subgroup analyses by ethnicity observed a link between rs1801725 polymorphism and CRC risk in Asians, but not in Caucasians and mixed populations.

Conclusion: In conclusion, this case-control study and meta-analysis showed that CASR rs1801725 polymorphism increased the risk of CRC. Further studies from other races are urgently needed.

KEYWORDS

case-control study, CASR, colorectal cancer, meta-analysis, single nucleotide polymorphism

1 | INTRODUCTION

Colorectal cancer (CRC) is the second leading cause of cancer-related mortality worldwide.[1-3] Approximately 20% of CRC patients were reported to have distant metastasis at the time of presentation.[4] However, the etiology of CRC is still not clearly understood. Many risk factors including diet, smoking status, and alcohol consumption are proved to be significantly associated with the risk

of CRC.[3,5-9] Many studies demonstrated that high calcium intake may help to reduce the risk of CRC.[10,11] Calcium is involved in cell proliferation and differentiation, reducing the rate of colonic epithelial cell proliferation.[12] Calcium-sensing receptor (CASR) and calcium are good tissue controllers for colon cells. Calcium inhibits the normal proliferation of colon cells through CASR signaling.[13] CASR plays a key role in maintaining calcium balance by regulating the parathyroid hormone (PTH) secreted by the parathyroid glands.[14] CASR was reported to be as a tumor suppressor in colon cancer.[15]

The CASR gene, containing seven exons, is located on chromosome 3q13. A single nucleotide polymorphism (SNP) of CASR gene, rs1801725 polymorphism, is associated with higher levels of serum calcium.[16] Recently, some studies have focused on the analysis of association between the CASR gene rs1801725 polymorphism and CRC risk.[17-23] However, no studies exploring the association between CASR rs1801725 polymorphism and CRC risk in Chinese Han populations were reported. Thus, we performed this hospital-based case-control study and meta-analysis to assess evaluate the association of CASR gene rs1801725 polymorphism with CRC risk.

2 | MATERIALS AND METHODS

2.1 | Participants

This hospital-based case-control study included 437 histologically confirmed CRC cases and 490 cancer-free controls. All patients provided written informed consent before their inclusion in the study, according to the Declaration of Helsinki. This study got the approvement from ethical Committee of Nantong Third People's Hospital (Nantong, China). Patients with histologically confirmed CRC newly diagnosed were enrolled in this study. Patients with neuroendocrine carcinoma, malignant melanoma, gastrointestinal stromal tumor, and metastatic colorectal carcinoma did not meet the inclusion criteria. 490 healthy donors were recruited from the hospital physical examination center at the same period. Controls were excluded if they had history of gastrointestinal disease or any chronic diseases. All patients and controls were Chinese and genetically unrelated. We obtained the sociodemographic parameters (age, sex, family history of cancer, body mass index (BMI), dietary calcium, and tumor site) through medical records.

2.2 | DNA extraction and genotyping

Blood samples were collected with EDTA containing tubes. According to the manufacturer's instructions, DNA was extracted from peripheral blood using the QIAamp DNA Blood Mini Kit (Qiagen). The DNA quality was determined by measuring the optical density OD 260/280 ratio. SNP genotyping was performed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLR). The primers were 5'-CTGAGCTTTGATGAGCCTCAGAAGGAC-3' (forward) and 5'-CACTGATGACAAGCTCTGTGAACTGGA-3' (reverse). Polymerase chain reaction amplifications were performed 93°C for 10 minutes and then 35 cycles of 93°C for 45 seconds, then 63°C for 30 seconds, then 72°C for 45 seconds and in the end final extension at 72°C for 10 minutes. The products were run on 3% agarose gel and stained with ethidium bromide for visualization under UV light.

2.3 | Methods

The goodness-of-fit chi-squared test was used to test deviation of the genotype frequencies from Hardy-Weinberg equilibrium (HWE) principle. Differences in the demographic or risk factors were examined by t-test or chi-squared test. Logistic regression was performed to evaluate the association between CASR rs1801725 polymorphism and risk of CRC with odds ratios (ORs) and 95% confidence intervals (CIs). For statistical analyses, we used the SAS software package (ver. 9.1.3; SAS Institute, Cary, NC, USA). Further, we conducted a meta-analysis to fully investigate the role of CASR rs1801725 polymorphism with CRC. This meta-analysis was performed using the Stata 11.0 software (StataCorp, College Station, TX, USA).[24] $P < .05$ was considered statistically significant.[25-27]

3 | RESULTS

3.1 | Characteristics of study population

The baseline characteristics of the study population are shown in Table 1. No significant differences were observed regarding the age, sex, smoking, and alcohol consumption. Other clinical features of CRC are presented in Table 1.

3.2 | Association of CASR gene rs1801725 polymorphism with the risk of CRC

The genotype distribution in the controls conformed to HWE, suggesting these subjects could represent the total population. As shown in Table 2, TT genotype of rs1801725 polymorphism could increase the risk of CRC compare to GG genotype (TT vs GG: OR 1.92, 95% CI [1.03-3.59], $P = .042$). This significant association was also observed in the allelic model.

Next, we conducted the subgroup analysis of sex, smoking, alcohol, and age (Table 3). Data showed that CASR gene rs1801725 polymorphism increased the risk of CRC among smokers, and those aged ≥60 years. Due to the positive findings, cross-over analysis was used to assess the effects of the interaction between genetic factors and smoking or drinking on CRC risk (Table 4). For smokers, however, carrying the TT genotype increased the risk of CRC when compared with non-smokers carrying GG genotype (TT + smoking vs GG + non-smoking: OR, 2.87, 95% CI, 1.08-7.64; $P = .043$),

TABLE 1 Patient demographics and risk factors in colorectal cancer

Variable	Cases (n = 437)	Controls (n = 490)	*P*
Age (years)	55.72 ± 9.68	55.64 ± 10.50	.912
Sex			
Male	317 (72.5%)	352 (71.8%)	.811
Female	120 (27.5%)	138 (28.2%)	
Smoking			
Yes	210 (48.1%)	231 (47.1%)	.792
No	227 (51.9%)	259 (52.9%)	
Alcohol			
Yes	186 (42.6%)	211 (43.1%)	.894
No	251 (57.4%)	279 (56.9%)	
Histological grade			
Well differentiated	96 (22.0%)		
Moderate differentiated	292 (66.8%)		
Poor differentiated	49 (11.2%)		
TNM stage			
I+II	245 (56.1%)		
III+IV	192 (43.9%)		
Tumor size			
>5 cm	195 (44.6%)		
≤5 cm	242 (55.4%)		
Lymph node metastasis			
No	238 (54.5%)		
Yes	199 (45.5%)		
Distant metastasis			
M0	360 (82.4%)		
M1	77 (17.6%)		

Note: Bold values are statistically significant ($P < .05$).
Abbreviation: BMI, Body Mass Index.

indicating that the interaction between genetic factors and smoking in CRC. However, no interaction was obtained between genetic factors and drinking.

And then, we evaluated the link between CASR gene rs1801725 polymorphism and the clinicopathological features of CRC patients (Table 5). We found that CASR gene rs1801725 polymorphism was related with tumor size, TNM stage, and lymph node metastasis in CRC.

3.3 | CASR gene rs1801725 polymorphism with CRC patient prognosis

We made a follow-up of CRC patients to evaluate the effect of CASR gene rs1801725 polymorphism on the risk of CRC prognosis. CRC patients with the GG genotype carriers showed worse overall survival than those TT genotype carriers (Figure 1).

3.4 | Meta-analysis of CASR gene rs1801725 polymorphism with the risk of CRC

In order to overcome the limitations of individual studies and reduce the possibility of false-positive findings, we conducted meta-analysis to analyze the role of CASR rs1801725 polymorphism in the risk of developing CRC. The characteristics of the selected studies are presented in Table 6. Six studies were about Caucasians; 1 were about mixed population; and 1 was about Asians. This meta-analysis consisted of 3 hospital-based studies and 5 population-based studies. The Newcastle-Ottawa Scale (NOS) scores of the included studies ranged from 5 to 7 stars, which proved the high methodological quality of all these studies.

In the overall analysis, CASR rs1801725 polymorphism increased the risk of CRC in the recessive model (TT vs GT + GG: OR 1.28, 95% CI [1.01-1.63], $P = .041$, Figure 2, Table 7). Stratification analysis of different ethnicity proved that rs1801725 polymorphism was not associated with the risk of CRC in Caucasians and other mixed populations (T vs G, Figure 3). No positive results were obtained in stratification analyses by source of control (SOC). We did Egger's and Begg's tests to confirm that no obvious publication bias was found for rs1801725 polymorphism (data not shown).

TABLE 2 Logistic regression analysis of associations between CASR rs1801725 polymorphism and risk of colorectal cancer

	Cases* (n = 437)		Controls* (n = 490)			
Genotype	n	%	n	%	OR (95% CI)	*P*
GT vs GG	125/284	28.6/65.0	128/343	26.1/70.0	1.18 (0.88, 1.58)	.269
TT vs GG	27/284	6.2/65.0	17/343	3.5/70.0	**1.92 (1.03, 3.59)**	**.042**
TT vs GT + GG	27/409	6.2/93.6	17/471	3.5/96.1	1.83 (0.98, 3.40)	.057
TT + GT vs GG	152/284	34.8/65.0	145/343	29.6/70.0	1.27 (0.96, 1.67)	.095
T vs G	179/693	20.5/79.3	162/814	16.5/83.1	**1.30 (1.03, 1.64)**	**.030**

Note: Bold values are statistically significant ($P < .05$).
*The genotyping was successful in 436 cases and 488 controls.

TABLE 3 Stratified analyses between CASR rs1801725 polymorphism and the risk of colorectal cancer

Variable	(case/control) GG	GT	TT	GT vs GG	TT vs GG	GT + TT vs GG	TT vs GG + GT
Sex							
Male	70/81	231/258	15/11	1.04 (0.72-1.49); 0.853	1.58 (0.68-3.66); 0.298	1.06 (0.74-1.52); 0.782	1.54 (0.70-3.40); 0.321
Female	55/47	53/85	12/6	0.60 (0.36-1.02); 0.064	1.71 (0.60-4.91); 0.441	0.69 (0.41-1.14); 0.157	2.26 (0.82-6.23); 0.142
Smoking							
Yes	44/46	148/177	17/6	0.87 (0.55-1.40); 0.633	**2.96 (1.08-8.20); 0.037**	0.94 (0.59-1.50); 0.814	**3.29 (1.27-8.51); 0.017**
No	81/82	136/166	10/11	0.83 (0.57-1.22); 0.381	0.92 (0.37-2.29); 1.000	0.84 (0.57-1.22); 0.386	1.04 (0.43-2.50); 1.000
Alcohol							
Yes	54/58	113/141	18/10	0.86 (0.55-1.34); 0.569	1.93 (0.82-4.56); 0.114	0.93 (0.60-1.44); 0.823	2.15 (0.96-4.77); 0.076
No	71/70	171/202	9/7	0.84 (0.57-1.23); 0.374	1.27 (0.45-3.59); 0.793	0.85 (0.58-1.25); 0.432	1.44 (0.53-3.94); 0.613
Age (years)							
<60	109/99	164/206	14/10	0.72 (0.51-1.02); 0.068	1.27 (0.54-3.41); 0.668	0.76 (0.53-1.05); 0.103	1.56 (0.68-3.58); 0.305
≥60	16/29	120/137	13/7	1.59 (0.82-3.07); 0.195	**3.37 (1.12-10.14); 0.034**	1.67 (0.87-3.22); 0.147	2.27 (0.88-5.84); 0.105

Note: Bold values are statistically significant ($P < .05$).

TABLE 4 Genetic (G) and environmental (E) factors 2*4 fork analysis

G[a]	E[b]	Case	Control	OR (95% CI); P value	Reflecting information
rs1801725					
TT vs GG	Smoking				
+	+	17	6	**2.87 (1.08,7.64); 0.043**	G, E combined effect
+	−	10	11	0.92 (0.37,2.29); 1.000	G alone effect
−	+	44	46	0.97 (0.58,1.62); 1.000	E alone effect
−	−	81	82	1.00 (reference)	Common control
GT vs GG	Smoking				
+	+	148	177	0.85 (0.58,1.23); 0.389	G, E combined effect
+	−	136	166	0.83 (0.57,1.22); 0.381	G alone effect
−	+	44	46	0.97 (0.58,1.62); 1.000	E alone effect
−	−	81	82	1.00 (reference)	Common control
TT vs GG	Drinking				
+	+	18	10	1.78 (0.77,4.11); 0.216	G, E combined effect
+	−	9	7	1.27 (0.45,3.59); 0.793	G alone effect
−	+	54	58	0.92 (0.56,1.51); 0.800	E alone effect
−	−	71	70	1.00 (reference)	Common control
GT vs GG	Drinking				
+	+	113	141	0.79 (0.52,1.19); 0.293	G, E combined effect
+	−	171	202	0.84 (0.57,1.23); 0.374	G alone effect
−	+	54	58	0.92 (0.56,1.51); 0.800	E alone effect
−	−	71	70	1.00 (reference)	Common control

Note: [a]G (+): CASR gene rs1801725 variants (Heterozygous or homozygous); G (−): wild type.

[b]E(+): smoking/non-smoking; E (−): non-smoking/non-drinking. Bold values are statistically significant ($P < 0.05$).

Bold values are statistically significant ($P < .05$).

TABLE 5 The associations between CASR rs1801725 polymorphism and clinical characteristics of colorectal cancer

Characteristics	Genotype distributions			
	GG	GT	TT	GT + TT
Histological grade				
MD/WD	73/32	209/57	10/7	219/64
OR (95% CI); *P*-value	1.0 (reference)	1.61 (0.97-2.67); .079	0.63 (0.22-1.79); .408	1.50 (0.91-2.47); .114
Histological grade				
PD/WD	20/32	18/57	10/7	28/64
OR (95% CI); *P*-value	1.0 (reference)	0.51 (0.23-1.09); .114	2.29 (0.75-6.98); .167	0.70 (0.34-1.43); .360
TNM stage				
III+IV/I+II	59/66	113/171	20/7	133/178
OR (95% CI); *P*-value	1.0 (reference)	1.33 (0.86-2.95); .223	**3.20 (1.26-8.10); .018**	0.84 (0.55-1.27); .455
Tumor size				
>5 cm/≤5 cm	50/75	127/157	18/9	145/166
OR (95% CI); *P*-value	1.0 (reference)	1.21 (0.79-1.86);.375	**3.00 (1.25-7.21); .018**	1.31 (0.86-2.00);.208
Lymph node metastasis				
Yes/No	53/72	170/114	15/12	185/126
OR (95% CI); *P*-value	1.0 (reference)	**2.03 (1.32-3.10); .001**	1.70 (0.74-3.93); .286	**2.00 (1.31-3.04); .001**
Distant metastasis				
M1/M0	20/105	52/232	5/22	57/254
OR (95% CI); *P*-value	1.0 (reference)	1.18 (0.67-2.07); .673	1.19 (0.40-3.52); .776	1.18 (0.67-2.06); .677

Note: Bold values are statistically significant ($P < .05$).

Abbreviations: MD, Moderately differentiation; PD, Poorly differentiation; WD, Well differentiation.

4 | DISCUSSION

In this study, we found that CASR gene rs1801725 polymorphism was associated with increased risk of CRC in a Chinese Han population. Subgroup analysis observed that CASR gene rs1801725 polymorphism increased the risk of CRC among smokers, and those aged ≥60 years. We also found that this polymorphism was associated with the tumor size, TNM stage, and lymph node metastasis of CRC. In addition, CASR gene rs1801725 polymorphism correlated with the survival of CRC patients. Further meta-analysis also obtained a significant association between this SNP and CRC risk. Subgroup analyses by ethnicity observed a link between rs1801725 polymorphism and CRC risk in Asians, but not in Caucasians and mixed populations.

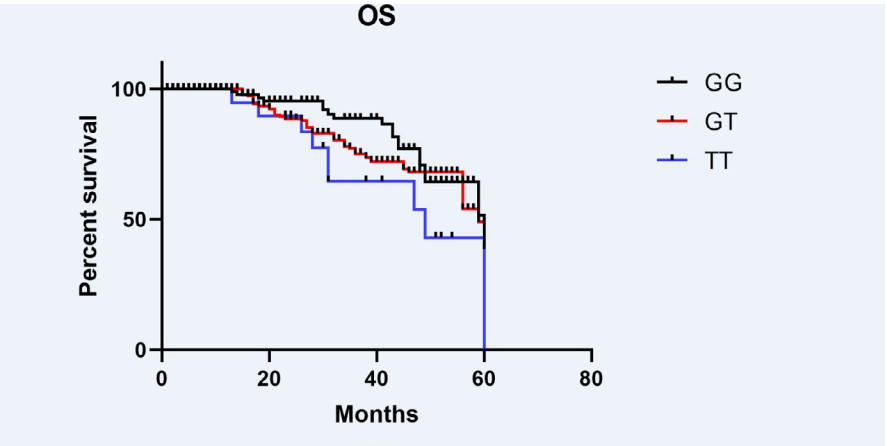

FIGURE 1 Kaplan-Meier analysis of the association of rs1801725 polymorphism with CRC survival

TABLE 6 Characteristics of included studies

Author and year	SOC	Country	Ethnicity	Case			Control			HWE	NOS
				GG	GT	TT	GG	GT	TT		
This study 2020	HB	China	Asian	284	125	27	343	128	17	Y	6
Dabiri 2016	PB	IRAN	Caucasian	181	107	15	215	121	18	Y	7
Mahmoudi 2014	HB	IRAN	Caucasian	210	123	17	302	178	30	Y	6
Jenab 2009	PB	Europe	Caucasian	859	276	25	870	272	18	Y	7
Dong 2008	PB	USA	Mixed	1197	371	27	1476	430	33	Y	6
Basci 2008	PB	Hungary	Caucasian	186	75	17	188	68	4	Y	7
Peters 2004	PB	USA	Caucasian	545	148	17	531	179	16	Y	6
Speer 2002	HB	Europe	Caucasian	36	20	0	81	30	1	Y	7

Abbreviations: HB, hospital-based controls; HWE, Hardy-Weinberg Equilibrium; NOS, Newcastle-Ottawa Scale; PB, population-based controls; SOC, source of controls.

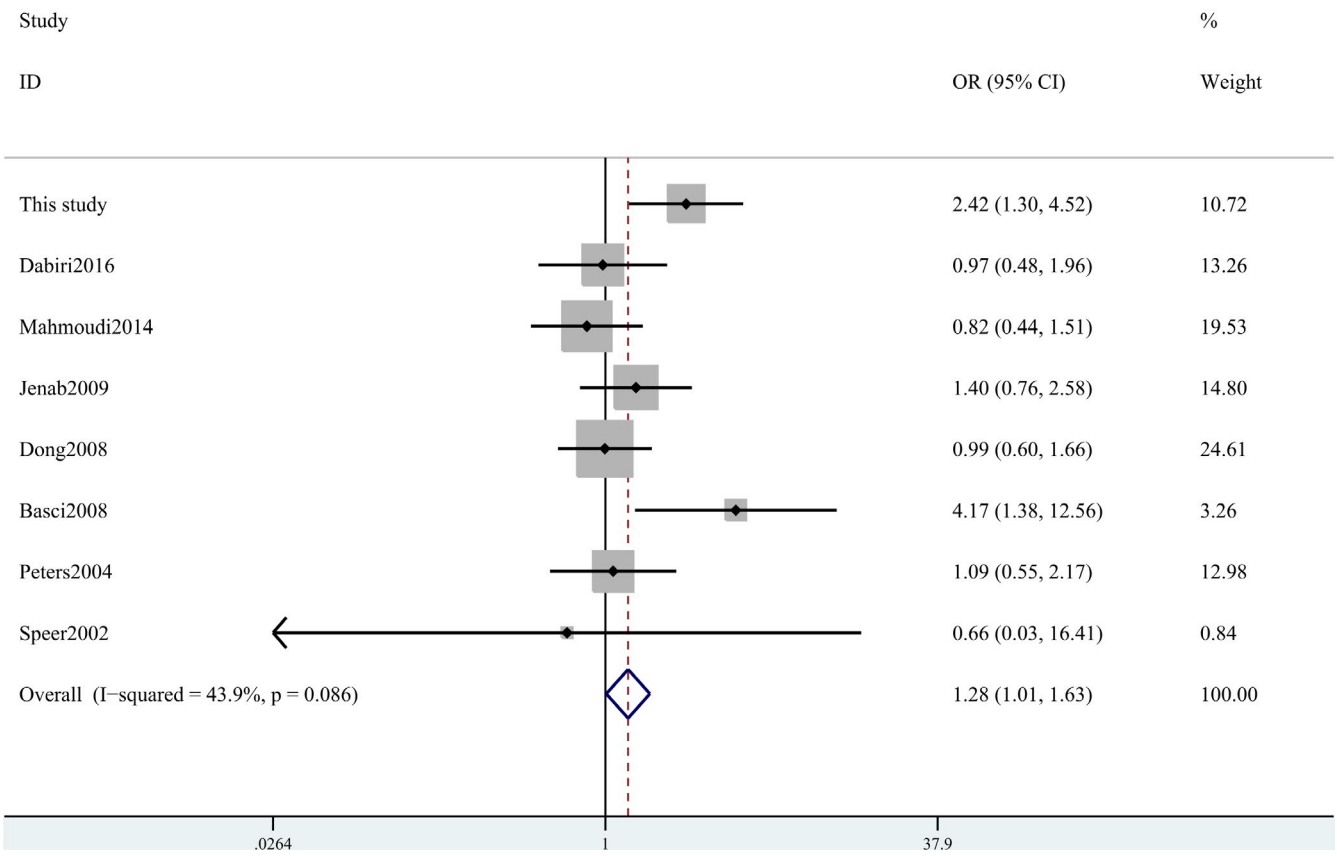

FIGURE 2 Forest plot shows odds ratio for the associations between rs1801725 polymorphism and CRC risk (TT vs GT + GG)

Some studies have indicated that diet is one of the major risk factors of CRC.[28] High calcium intake is significantly associated with the risk of CRC.[29-31] These studies provide support for inverse associations between intakes of calcium and dairy foods and the risk of CRC. Calcium could prevent suppresses dysplasia and protect the colon from malignant transformation.[32,33] CASR is reported to be a potential mediator for these above function.[34] CASR is an important part of the calcium-mediated pathway of calcium's anti-cancer effect on the development of CRC. The expression of CASR is higher in normal colorectal epithelial cells, but it is lower in well-differentiated colon cancer tissues.[35,36]

To date, several studies[17-23] have investigated the association between the CASR gene rs1801725 polymorphism and the risk of CRC. However, these studies reached no consistency. Speer et al first reported that there is no association between rs1801725 gene polymorphism and rectal cancer.[10] However, they proved an

TABLE 7 Summary of the subgroup analyses in this meta-analysis

Comparison	Category	Category	Studies	OR (95% CI)	*P*-value	*P* for heterogeneity
T vs G		Total	8	1.06 (0.98,1.14)	.143	.138
	Ethnicity	Asian	1	**1.30 (1.03,1.64)**	**.030**	N/A
		Caucasian	6	1.03 (0.93,1.13)	.602	.172
		Mixed	1	1.05 (0.91,1.20)	.508	N/A
	SOC	HB	3	1.12 (0.95,1.31)	.168	.155
		PB	5	1.04 (0.96,1.14)	.359	.153
TT + GT vs GG		Total	8	1.05 (0.96,1.14)	.290	.324
	Ethnicity	Asian	1	1.27 (0.96,1.67)	.095	N/A
		Caucasian	6	1.01 (0.90,1.13)	.874	.321
		Mixed	1	1.06 (0.91,1.24)	.459	N/A
	SOC	HB	3	1.13 (0.94,1.36)	.204	.308
		PB	5	1.03 (0.93,1.13)	.592	.292
TT vs GT + GG		Total	8	**1.28 (1.01,1.63)**	**.041**	.086
	Ethnicity	Asian	1	**2.42 (1.30,4.52)**	**.005**	N/A
		Caucasian	6	1.20 (0.89,1.63)	.229	.205
		Mixed	1	1.00 (0.60,1.66)	.983	N/A
	SOC	HB	3	1.37 (0.90,2.07)	.144	.046
		PB	5	1.25 (0.93,1.66)	.139	.191
TT vs GG		Total	8	1.24 (0.98,1.58)	.075	.190
	Ethnicity	Asian	1	**1.92 (1.03,3.59)**	**.042**	N/A
		Caucasian	6	1.21 (0.89,1.63)	.229	.193
		Mixed	1	1.01 (0.60,1.69)	.973	N/A
	SOC	HB	3	1.23 (0.81,1.89)	.336	.156
		PB	5	1.25 (0.93,1.67)	.135	.180
GT vs GG		Total	8	1.03 (0.94,1.13)	.531	.525
	Ethnicity	Asian	1	1.18 (0.88,1.58)	.269	N/A
		Caucasian	6	0.99 (0.88,1.11)	.851	.456
		Mixed	1	1.06 (0.91,1.25)	.444	N/A
	SOC	HB	3	1.11 (0.91,1.35)	.297	.482
		PB	5	1.01 (0.91,1.12)	.863	.415

Note: Bold values are statistically significant ($P < .05$).

Abbreviations: HB, hospital-based controls; PB, population-based controls; SOC, source of controls.

association between rs1801725 gene polymorphism and more advanced rectal tumors.[10] Several subsequent studies also failed to demonstrate an association between rs1801725 polymorphism and CRC risk.[18-22] However, a study from Hungary involving in 278 cases and 260 controls showed that rs1801725 polymorphism was a risky factor for CRC.[23] In this study, we found that CASR rs1801725 polymorphism increased the risk of CRC in a Chinese population. We assumed that CASR rs1801725 polymorphism causing decreased sensing of extracellular calcium might contribute to the development of CRC. The reasons why their conclusions about this SNP and CRC risk were contradictory, but may be partly explained by diversity inheritance of different ethnicities. Additionally, data indicated that CASR rs1801725 polymorphism was related to the tumor size, TNM stage, and lymph node metastasis of CRC. Besides, CASR gene rs1801725 polymorphism was associated with the survival of CRC patients. To the best of our knowledge, this is the first study to observe an association between this SNP and CRC risk in Chinese Han population.

Due to the abovementioned inconsistent findings, we reviewed all eligible studies and conducted a meta-analysis. The results of this meta-analysis proved the association of CASR rs1801725 polymorphism with higher risk of CRC. We also conducted stratification analyses of ethnicity and SOC. Stratification analyses by ethnicity revealed that CASR rs1801725 polymorphism was associated with higher risk of CRC among Asians, but not among Caucasians. These discrepancies may attribute to a difference in allele frequency of the CASR rs1801725 polymorphism among these groups. For Asians, the C allele frequency was 0.203, which was higher than in Caucasians (0.152). We hypothesized that the potential reasons for different findings between Asians and Caucasians might due to

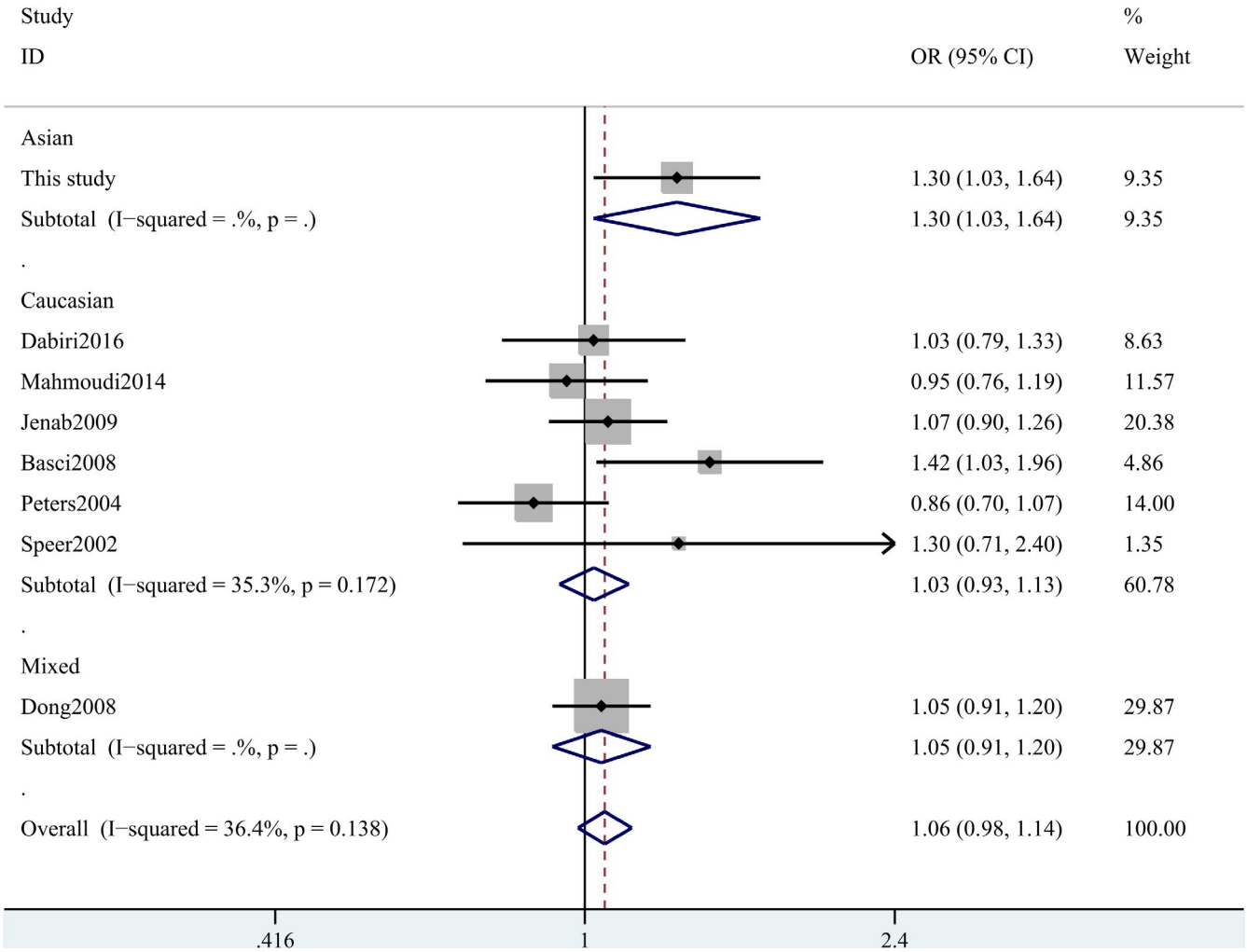

FIGURE 3 Stratification analysis by ethnicity shows odds ratio for the association between rs1801725 polymorphism and CRC risk (T vs G)

genetic heterogeneity, clinical heterogeneity, different methods of genotyping and also random errors. No significant association was observed in the subgroup analysis of SOC. We believe the data of this meta-analysis was robust. Firstly, we did this meta-analysis with larger sample size. Second, sensitivity analysis indicated that our data about rs1801725 polymorphism were reliable and high quality.

This study had potential limitations. First, due to limited data, we were not able to investigate the association between CRC and other potential risk factors. Second, our results were based on unadjusted estimates for confounding factors, which is inevitable but might affect final results. Third, due to the lack of relevant data, we are unable to assess the potential interaction between genes and the genetic environment. Fourth, the sample size of this study and meta-analysis was limited. Fifth, Other functional SNPs of CASR gene should be explored. Sixth, whether CASR gene polymorphism affects the expression of CASR gene and protein should also be investigated. In spite of these limitations, our study is the first study to reveal a significant association between CASR gene polymorphism and CRC risk in Chinese population. Our study protocol was well designed and gained importance to raise the awareness of CASR gene polymorphism on CRC risk.

In conclusion, this study found that CASR gene rs1801725 polymorphism was associated with the risk and prognosis of CRC. Future studies are needed to validate whether CASR gene rs1801725 contributes to CRC susceptibility in other ethnic groups.

AUTHOR CONTRIBUTION

Yu-E Diao and Qing Xu conceived of the study, participated in its design. Yu-E Diao and Qing Xu conducted the systematic literature review. Qing Xu performed data analyses. Yu-E Diao and Qing Xu drafted the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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