

Original Article

A meta-analysis of the associations between the Q141K and Q126X ABCG2 gene variants and gout risk

Rui Li^{1*}, Lei Miao^{1*}, Liyan Qin¹, Yang Xiang¹, Xiaojin Zhang², Hui Peng³, Mailamuguli¹, Yuping Sun⁴, Hua Yao²

¹School of Public Health, Xinjiang Medical University, Urumqi, Xinjiang, China; ²The First Affiliated Hospital of Xinjiang Medical University, Urumqi, Xinjiang, China; ³Clinical Laboratory, Traditional Chinese Medical Hospital of Xinjiang Uygur Autonomous Region, Urumqi, Xinjiang, China; ⁴School of Basic Medical Sciences, Xinjiang Medical University, Urumqi, Xinjiang, China. *Equal contributors.

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Abstract: Background: Gout is an inflammatory disease in which genetic factors play a role. ABCG2 is a urate transporter, and the Q141K and Q126X variants of ABCG2 have been associated with a risk of developing gout, though previous studies of these associations have been inconsistent. Therefore, we conducted a meta-analysis to explore the relationship between these genetic variants and gout. Methods: We examined 8 electronic literature databases. In total, 9 eligible articles on the associations between the Q141K (rs2231142) and Q126X (rs72552713) variants and gout risk, including 11 case-control studies were selected. We used odds ratios (OR) and 95% confidence intervals (CI) to assess the strength of these relationships in dominant, recessive, and co-dominant models. Results: This study included 6652 participants (2499 gout patients and 4153 controls). The Q141K variant was found to significantly increase the risk of gout in Asians (dominant model: OR=2.64, 95% CI=2.04-3.43, P=0.02 for heterogeneity; recessive model: OR=3.19, 95% CI=2.56-3.97, P=0.28 for heterogeneity; co-dominant model: OR=1.37, 95% CI=1.18-1.59, P=0.09 for heterogeneity) and other populations (dominant model: OR=1.85, 95% CI=1.20-2.85, P<0.0001 for heterogeneity; recessive model: OR=3.78, 95% CI=2.28-6.27, P=0.19 for heterogeneity; co-dominant model: OR=1.48, 95% CI=1.26-1.74, P=0.19 for heterogeneity). The Q126X variant also significantly increased the risk of gout in Asians (dominant model: OR=3.87, 95% CI=2.07-7.24, P=0.06 for heterogeneity). Conclusions: These results suggest associations between the rs2231142 and rs72552713 ABCG2 gene polymorphisms and gout risk, which led to unfavorable outcomes. However, studies with larger sample sizes and homogeneous populations should be performed to confirm these results.

Keywords: Gout, Q141K, Q126X, single nucleotide polymorphism, meta-analysis

Introduction

Gout is a recurrent relapsing inflammatory disease, caused by the precipitation of monosodium urate (MSU) crystals in the joints and soft tissues. Gout is characterized by intense pain that typically persists for approximately one week. In recent years, the prevalence and incidence of gout has been increasing. In 2001 [1], the prevalence of gout was only 0.33% in Shanghai. In 2009, Yu-Hong Jia et al. [2] reported an increased prevalence of gout of as high 1.21% in Tangshan. Today, the prevalence of gout has increased to 1.23% [3]. In addition, Edward and colleagues [4] also reviewed the epidemiology of gout and suggested that the disease is becoming more prevalent. As a result

of its increasing prevalence, gout has attracted public attention.

Previous studies demonstrate that environmental exposure and genetic factors play important roles in the development of gout. Jennifer et al. [5] demonstrated that body mass index (BMI), total fat mass, serum triglycerides and serum glucose levels were significantly increased in gout patients. Ling-Qin Li [6] found that hyperuricemia, BMI, high triglycerides, hypertension, a high purine diet, drinking and smoking increase the risk of gout. Previous studies have demonstrated that genetic variations in solute carrier family 2, member 9 (SLC2A9) [7]; solute carrier family 22, member 11 (SLC22A11) [8]; solute carrier family 17, member 1 (SLC17A1)

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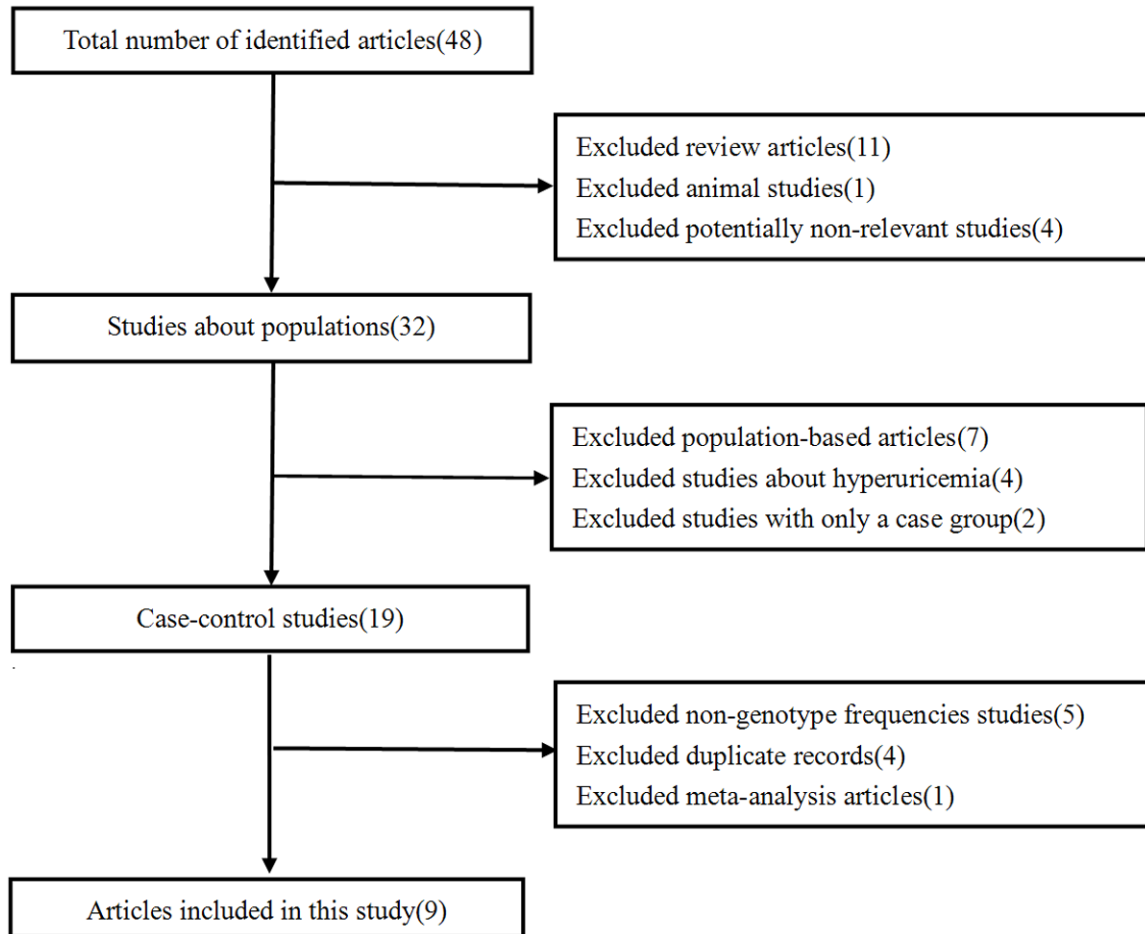


Figure 1. Flow diagram of study selection for meta-analysis.

[9]; coding for PDZ domain containing 1 (PDK-Z1) [10] and ATP-binding cassette, subfamily G, member 2 (ABCG2) [11] might increase the risk of gout.

ABCG2 is a urate transporter that excretes uric acid [12]. According to gene sequencing analysis, ABCG2 contains more than 80 different single-nucleotide polymorphism (SNP) loci. Among these, Q141K and Q126X are the most commonly studied. SNP rs2231142, also referred to as C421A or Q141K in ABCG2, is located in exon 5 [10] and substitutes glutamic acid for diaminocaproic acid. Previous studies have reported a relationship between rs2231142 and gout. SNP rs72552713, also referred to as C376T or Q126X in ABCG2, has also been shown to play a role in gout. However, due to small sample sizes and data quality, inconsistent results have been reported. To address these issues, we performed a meta-

analysis to explore the roles of rs2231142 and rs72552713 in gout.

Methods

Search strategy

We searched for published articles in eight electronic literature databases (Chaoxing Medalink, Wangfang Data, Weipu, Chinese Biomedical Literature Service System, China National Knowledge Infrastructure (CNKI), Chinese Science Citation Database (CSCD), Ebsco Science Direct and Pubmed). No limit was imposed on publication dates, and the last search update was performed on May 30, 2015. The literature search was performed in English and Chinese using the following primary key words: gout, ABCG2, C421A, Q141K, rs2231142, C376T, Q126X, and rs72552713.

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Table 1. Characteristics of the included studies (Q141K)

First author (Ref.)	Year	Ethnicity/country	Diagnostic standard	Study design	Sample size (case/control)	HWE p-value	Genotype distribution (case/control)			Genotype frequency (case/control)		
							CC	CA	AA	CC (%)	CA (%)	AA (%)
Wang Qiong [17]	2014	Asians China	ACR preliminary diagnostic criteria for acute gout (1977)	Case-control	185/311	Yes	64/157	86/126	35/28	34.6/50.5	46.5/40.5	18.9/9.0
Zhang Xin-Lei [28]	2014	Asians China	ACR preliminary diagnostic criteria for acute gout (1977)	Case-control	147/321	Yes	30/167	79/134	38/20	20.4/52.0	53.7/41.7	25.9/6.2
Li Fa-Gui [12]	2011	Asians China	ACR preliminary diagnostic criteria for acute gout (1977)	Case-control	200/235	Yes	64/103	91/112	45/20	32.0/43.8	45.5/47.7	22.5/8.5
Amanda 1 [25]	2010	Maori New Zealand	ACR preliminary diagnostic criteria for acute gout (1977)	Case-control	185/215	Yes	142/172	34/39	2/1	79.8/81.1	19.1/18.4	1.1/0.5
Amanda 2 [25]	2010	Pacific Islander New Zealand	ACR preliminary diagnostic criteria for acute gout (1977)	Case-control	173/109	Yes	58/69	78/36	37/4	33.5/63.3	45.1/33.0	21.4/3.7
Amanda 3 [25]	2010	Caucasian New Zealand	ACR preliminary diagnostic criteria for acute gout (1977)	Case-control	214/562	Yes	122/425	76/125	13/8	57.8/76.2	36.0/22.4	6.2/1.4
Danqiu Zhou [36]	2014	Asians China	ACR preliminary diagnostic criteria for acute gout (1977)	Case-control	352/350	Yes	87/167	181/150	84/33	24.7/47.7	51.4/42.9	23.9/9.4
Klaus [32]	2009	Caucasian German	ACR preliminary diagnostic criteria for acute gout (1977)	Case-control	677/1552	Yes	500/1241	168/299	9/12	73.9/80.0	24.8/19.2	1.3/0.8
Zhang Xiu-Juan [36]	2012	Asians China	ARA diagnostic criteria for acute gout (1997)	Case-control	110/236	Yes	35/120	55/96	20/20	31.8/50.8	50.0/40.7	18.2/8.5
You Yu-Quan [39]	2013	Asians China	ACR preliminary diagnostic criteria for acute gout (1977)	Case-control	154/160	Yes	48/98	78/49	28/13	31.2/60.3	50.6/30.6	18.2/8.1
Ye De-Shao [62]	2012	Asians China	ACR preliminary diagnostic criteria for acute gout (1977)	Case-control	102/102	Yes	23/53	42/40	37/9	22.5/52.0	41.2/39.2	36.3/8.8

Table 2. Characteristics of the included studies (Q126X)

First author (Ref.)	Year	Ethnicity/country	Diagnostic standard	Study design	Sample size (case/control)	HWE p-value	Genotype distribution (case/control)			Genotype frequency (case/control)		
							CC	CT	TT	CC (%)	CT (%)	TT (%)
Zhang Xin-Lei [28]	2014	Asians China	ACR preliminary diagnostic criteria for acute gout (1977)	Case-control	136/321	Yes	127/320	9/1	0/0	93.4/99.7	6.6/0.3	0/0
Danqiu Zhou [36]	2014	Asians China	ACR preliminary diagnostic criteria for acute gout (1977)	Case-control	352/350	Yes	319/338	33/12	0/0	90.6/96.6	9.4/3.4	0/0

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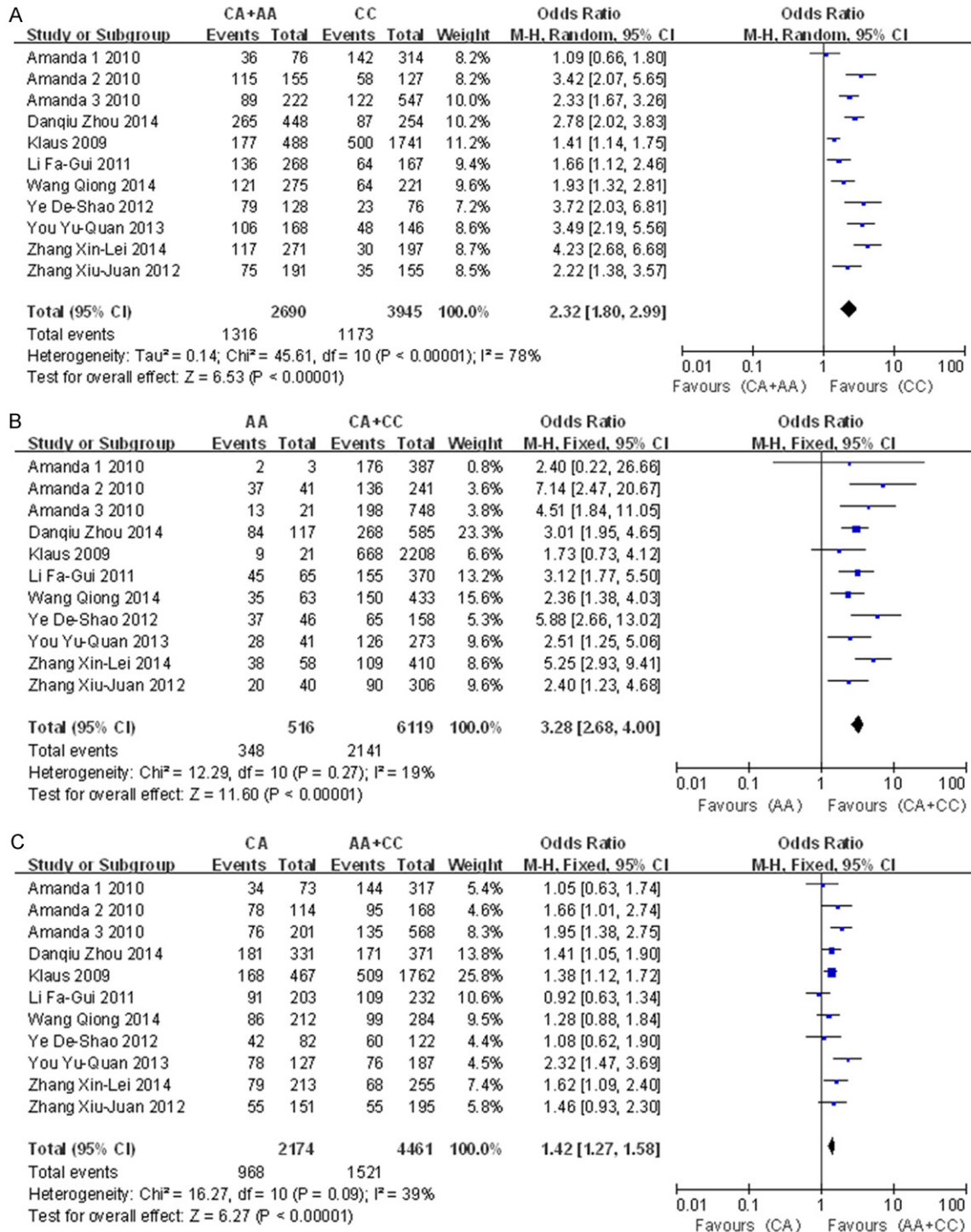


Figure 2. Forest plot of the associations between the Q141K variant and gout risk using the A: Dominant model (CC compared to AC+AA), B: Recessive model (AA compared to CC+AC), and C: Co-dominant model (AC compared to CC+AA).

The following index terms were used: gout and ABCG2, gout and C421A, gout and Q141K, gout and rs2231142, gout and C376T, gout and Q126X, and gout and rs72552713.

Selection criteria

In this meta-analysis, we established the following inclusion criteria: (1) the publication

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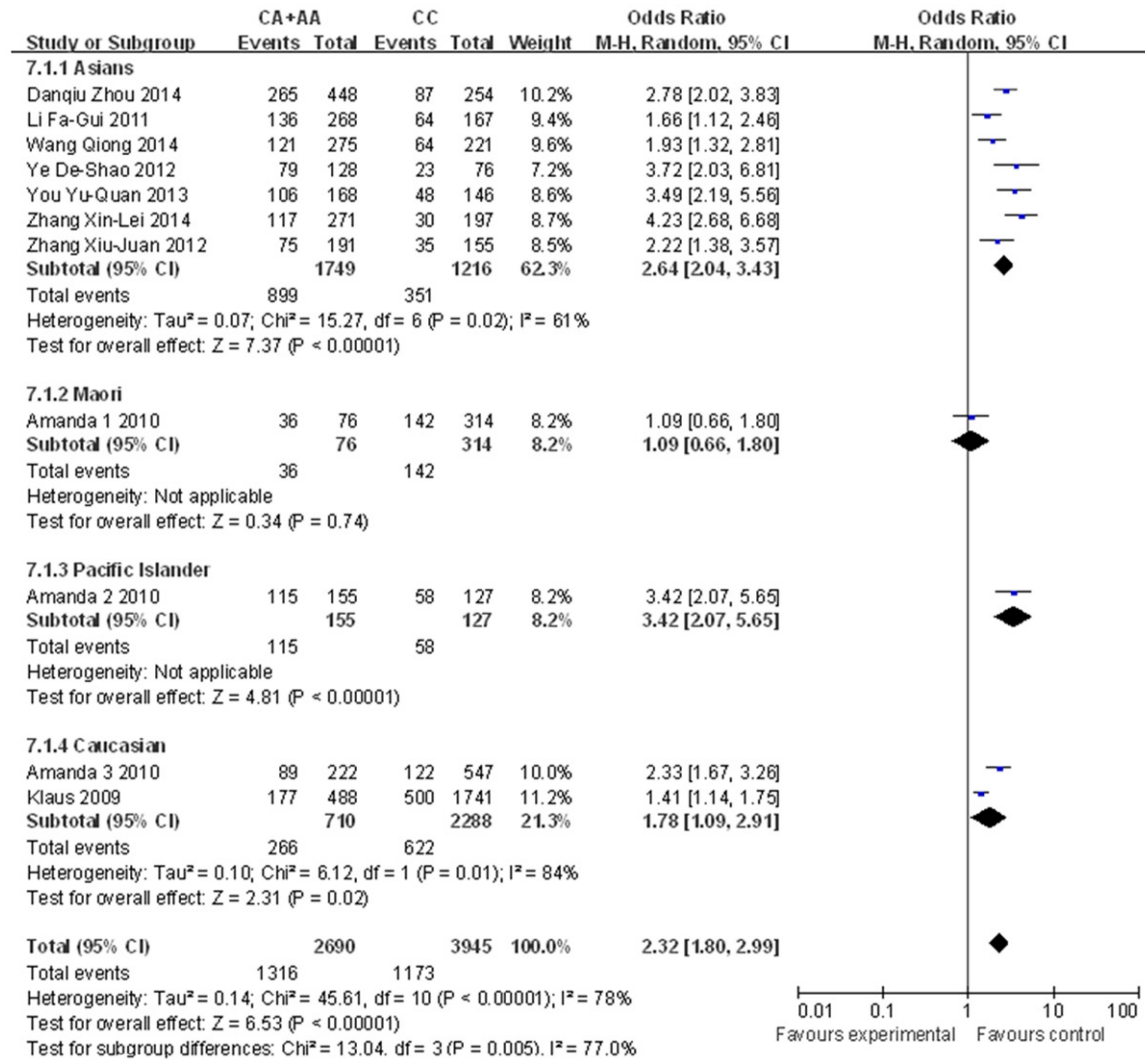


Figure 3. Forest plot describing ethnicity in the dominant model (Q141K).

must be a genetic connectedness study regarding gout and an ABCG2 gene polymorphism; (2) the diagnostic criteria [13] must adhere to the American College of Rheumatology (ACR) preliminary diagnostic criteria for acute gout; (3) the publication must be a case-control study; (4) the participants must not have serious diseases other than gout; (5) the cases and controls must include specific genotype distribution data; (6) the genotype distribution of the control group must satisfy Hardy-Weinberg equilibrium (HWE); and (7) if a study contained more than one more sample, each sample was used for this meta-analysis.

Quality assessment

Two authors selected studies based on the selection criteria described. Disagreements

were resolved by consulting a third author. If more than one article described the same study, we selected the best article and described those with incomplete data. Then, we performed a quality assessment. The assessment criteria were based on the STREGA (STrengthening the Reporting of Genetic Association studies) principle [14], which consists of six requirements. If the included studies fulfilled three or more of those requirements, they were considered to be of good quality. Fortunately, the quality of the included studies was high, and we were able to collect the following data from each study: the first author's name, publication year, country, ethnicity, diagnostic standard of gout, study design, total number of cases and controls, HWE *P*-value, genotype distribution and geno-

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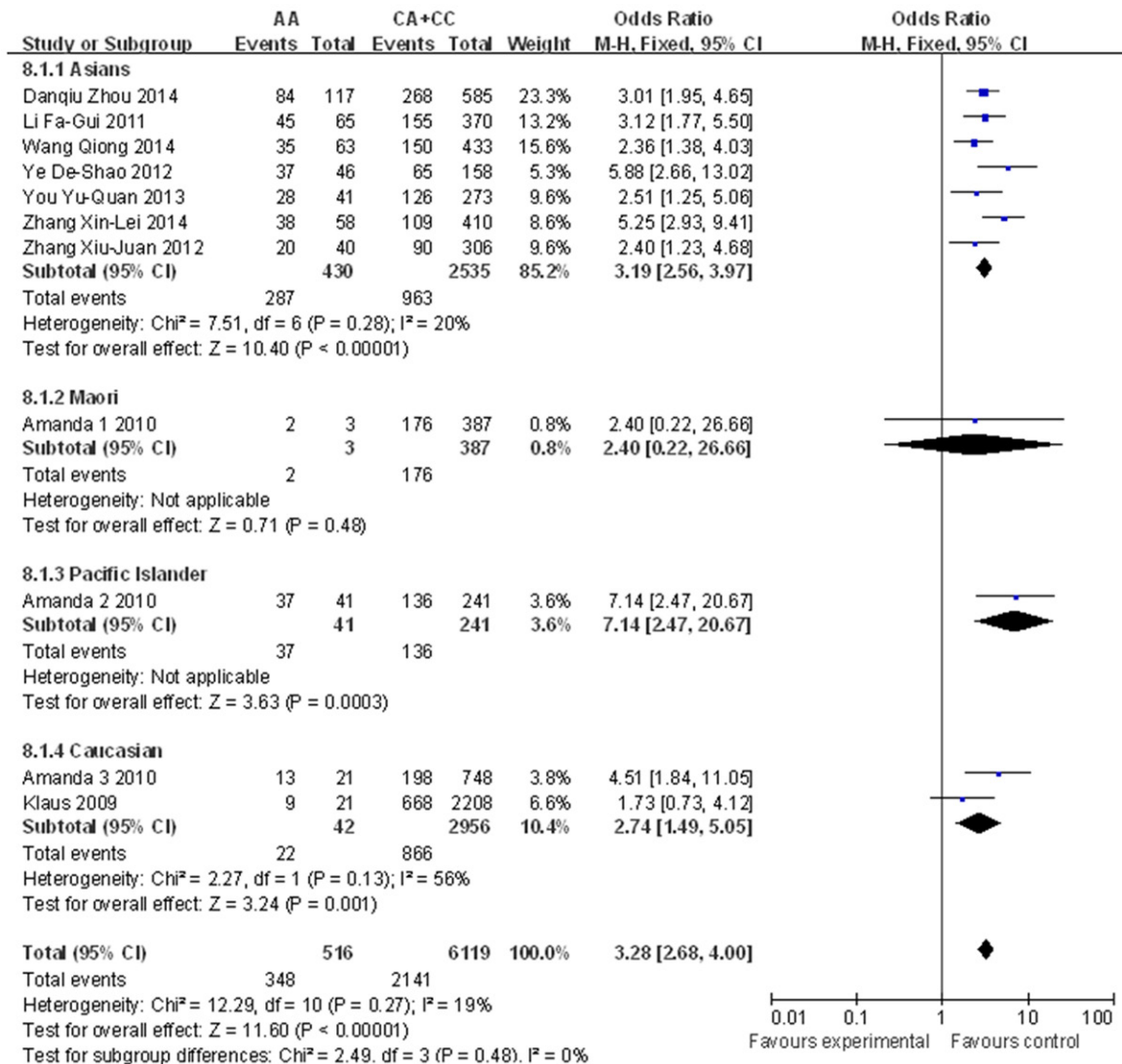


Figure 4. Forest plot describing ethnicity in the recessive model (Q141K).

type frequencies. These data were organized into two tables for analysis.

Statistical analysis

We used Review Manager 5.1 software (The Cochrane Collaboration, Oxford, UK) and Stata software (version 11.0) to perform statistical analyses. Associations between gout susceptibility and the rs2231142 and rs72552713 ABCG2 gene polymorphisms were indicated by the odds ratio (OR) and the corresponding 95% confidence interval (CI). Each relationship was assessed in a dominant model (Q141K: CC compared to AC+AA; Q126X: CC compared to CT+TT), a recessive model (Q141K: AA com-

pared to CC+AC), and a co-dominant model (Q141K: AC compared to CC+AA). We used the I^2 statistic to evaluate heterogeneity between studies, and a fixed effects model (FEM) to calculate the pooled OR and 95% CI if the P -value was greater than 0.05, which indicated no heterogeneity. If heterogeneity was observed, we used a random effects model (REM) to combine eligible data. We examined significant pooled ORs using the Z statistic. To guarantee the stability of the results, we implemented a sensitivity analysis by the sequential removal of individual studies. Publication bias was assessed using funnel plots with Begg's test and Egger's test, in which $P > 0.05$ indicated no publication bias.

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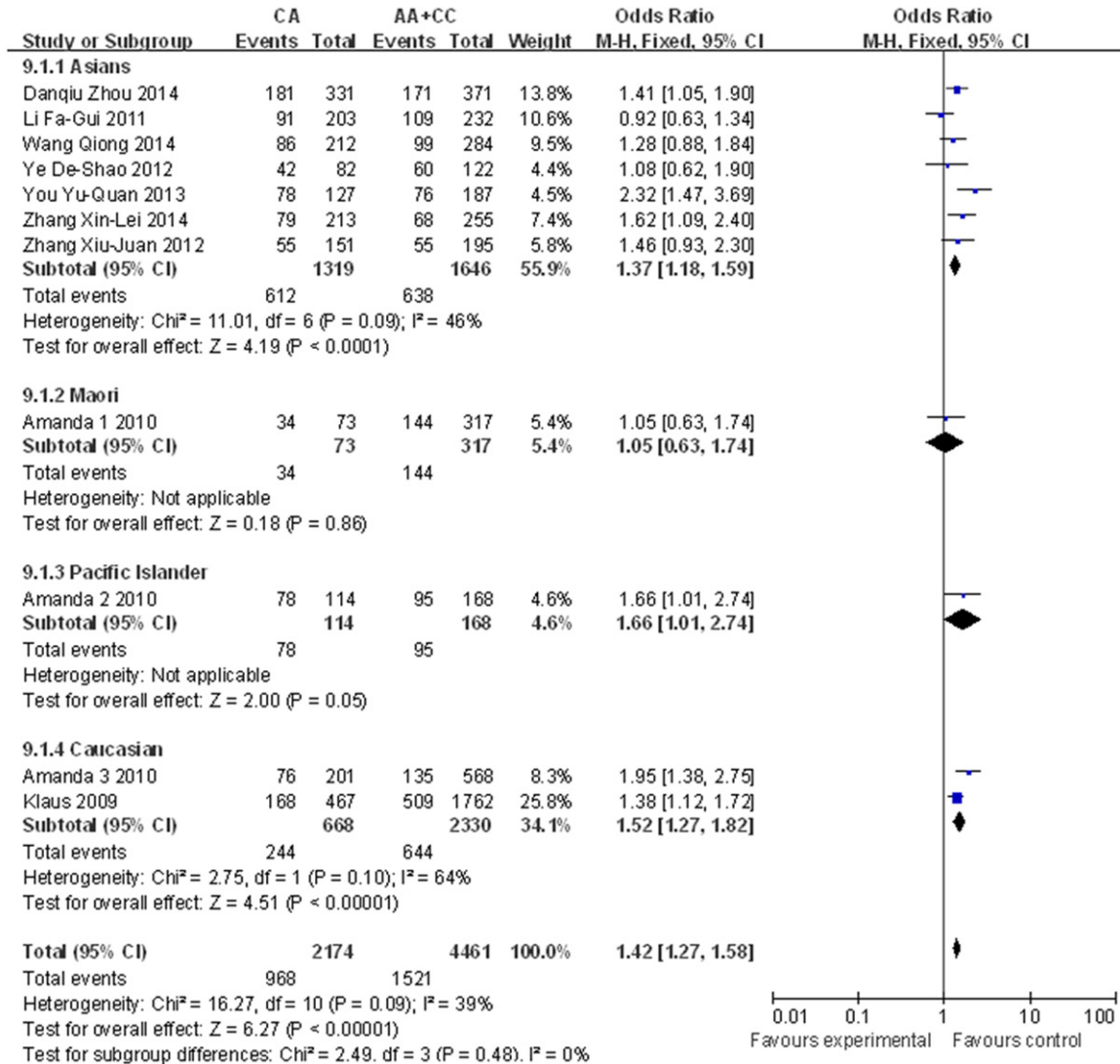


Figure 5. Forest plot describing ethnicity in the co-dominant model (Q141K).

Results

Search results and study characteristics

In total, 48 records were identified that analyzed the associations between ABCG2 polymorphisms and gout risk. The following studies were initially excluded: 11 review articles, an animal-based study and 4 potentially irrelevant studies. Among the remaining 32 studies, 13 additional articles were also excluded: 7 studies were based on specific examined populations, 4 studies did not show a relationship to gout and 2 studies lacked control groups. Thus, 19 total case-control publications were ultimately used. An addition 5 studies was excluded

from our meta-analysis due to the absence of genotype frequencies, and 4 pairs of studies were published using the same data, leading us to exclude those 4 additional studies. In total, 9 studies were included in our meta-analysis following the exclusion of another meta-analysis article. All of these 9 studies involved the Q141K variant, and only 2 studies referred to the Q126X variant. The study search procedure used is outlined in **Figure 1**.

Of these 9 studies, of the Q141K variant, one study contained data for three different ethnicities; therefore, each of these studies was treated separately. Thus, 11 total study populations were pooled for our analyses. These 11 studies

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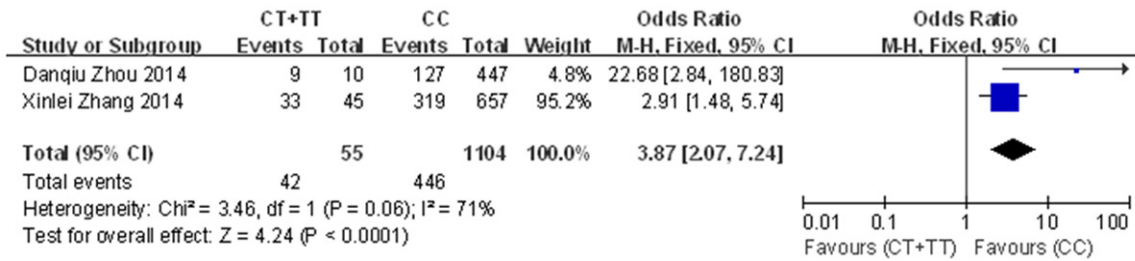


Figure 6. Forest plot for the association between the Q126X variant and gout risk using the dominant model (CT+TT compared to CC).

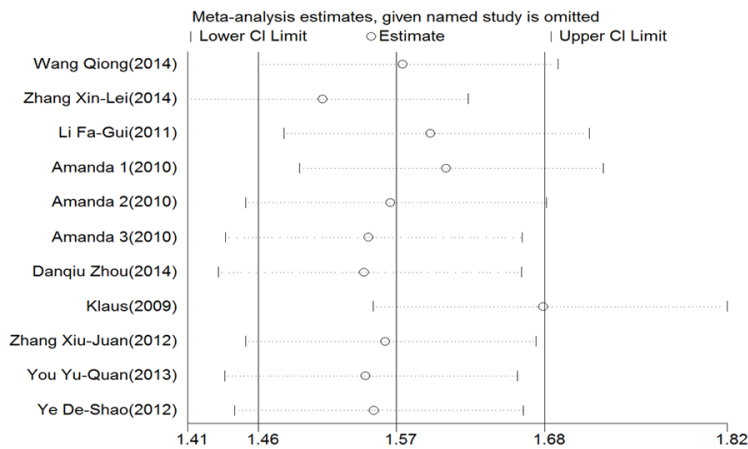


Figure 7. Sensitivity analysis for the association between the Q141K variant and gout risk.

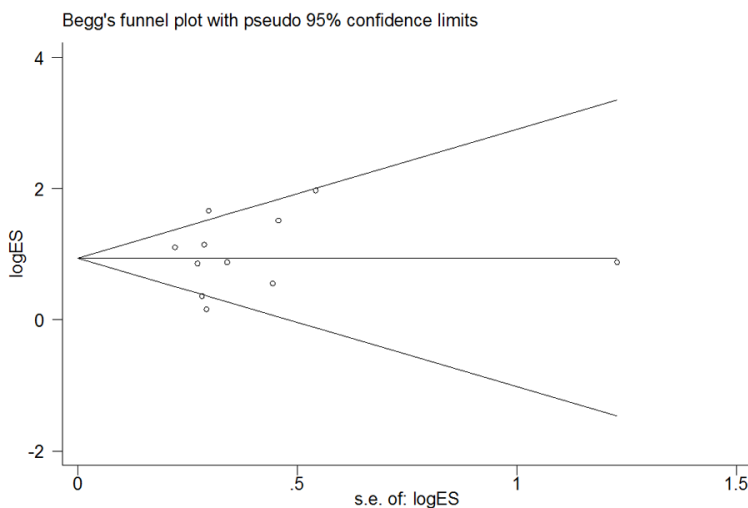


Figure 8. Begg's funnel plot examining the publication bias of studies using the recessive model (Q141K).

included 7 studies from China [15-21], 3 studies from New Zealand [22] and one study from

Germany [23]. A total of 2499 gout patients and 4153 controls were recruited for this analysis from these 11 studies. We extracted the characteristics of these studies, which are summarized in **Tables 1, 2** of Article 9 on the Q126X variant. These characteristics were derived from 499 gout patients and 671 controls, and are summarized in **Table 2**.

Meta-analysis

A significant association was found between the rs2231142 polymorphism and gout risk in the dominant model (OR=2.32, 95% CI=1.80-2.99, P<0.0001 for heterogeneity), the recessive model (OR=3.28, 95% CI=2.68-4.00, P=0.27 for heterogeneity) and the co-dominant model (OR=1.42, 95% CI=1.27-1.58, P=0.09 for heterogeneity) (**Figure 2**). Subgroup analysis by ethnicity also revealed significant associations for both Asians (dominant model: OR=2.64, 95% CI=2.04-3.43, P=0.02 for heterogeneity; recessive model: OR=3.19, 95% CI=2.56-3.97, P=0.28 for heterogeneity; co-dominant model: OR=1.37, 95% CI=1.18-1.59, P=0.09 for heterogeneity) and other populations (dominant model: OR=1.85, 95% CI=1.20-2.85, P<0.0001 for heterogeneity; recessive model: OR=3.78, 95% CI=2.28-

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6.27, $P=0.19$ for heterogeneity; co-dominant model: $OR=1.48$, $95\% CI=1.26-1.74$, $P=0.19$ for heterogeneity) (Figures 3-5). Our results also demonstrated that the rs72552713 polymorphism can increase the risk of gout in the dominant model: $OR=3.87$, $95\% CI=2.07-7.24$, $P=0.06$ for heterogeneity (Figure 6).

Sensitivity analysis and publication bias

To ensure the stability of our results and given the heterogeneity among studies, we performed a sensitivity analysis by removing studies independently. We did not identify any study that significantly influenced the pooled ORs, indicating that the overall OR was stable (Figure 7). We used funnel plots with Begg's and Egger's tests to detect publication bias. The funnel plot was nearly symmetrical, and the Begg's test (dominant model: $P=0.586$; recessive model: $P=0.484$; co-dominant model: $P=0.815$) and Egger's test (dominant model: $P=0.060$, $95\% CI=-0.203-8.08$; recessive model: $P=0.642$, $95\% CI=-2.70-4.16$; co-dominant model: $P=0.998$, $95\% CI=-3.23-3.24$) did not reveal significant publication bias (Figure 8).

Discussion

Subsequent to the development of genetic technologies, numerous studies examining the association between ABCG2 polymorphisms and gout risk have been reported. Among the ABCG2 polymorphisms, Q141K and Q126X are the most commonly studied. Nevertheless, the role of the Q141K variant in gout risk and the potential for the Q126X variant to increase gout risk are controversial. Lili Zhang et al. [24] demonstrated that rs2231142 is significantly associated with gout in Europeans, Americans, African Americans and Mexican Americans. Hirotaka et al. [25], Kazumasa et al. [11] and Xiaofei Lv [26] also showed that the Q141K variant increases the risk of gout. However, Amanda et al. [22] reported no association of rs2231142 with gout in Maori samples. Until now, there has been no meta-analysis demonstrating the role of Q126X in gout. To address these discrepancies, we performed a meta-analysis to explore the relationships between rs2231142 and rs72552713 and gout, and we conducted a subgroup analysis to identify racial differences in rs2231142.

In our meta-analysis, we identified 11 studies involving 4 ethnicities (Asians, Maori, Pacific Islanders and Caucasians) from 3 countries (China, New Zealand and Germany) and including a total of 6652 participants (2499 gout patients and 4153 controls). Our results suggested that the Q141K variant results in increased gout risk in dominant, recessive, and co-dominant models, and in subgroup analyses, Q126X also increased gout risk in a dominant model. However, heterogeneity had a significant effect on both the dominant model and rs2231142 subgroup analysis. This effect might be explained by confounders such as age, gender and inscrutable environmental factors. Previous studies have demonstrated that gout might be more prevalent in men [27] and postmenopausal women [28]. However, because these data were not included in certain studies we analyzed, we did not estimate the adjusted OR. Gene-environment interactions might also play a significant role in gout risk, which represents a limitation of our meta-analysis.

Ethnic differences are always mentioned by researchers not only in discussions of gout [29] but also in the association between the Q141K polymorphism and gout risk [24, 30]. In our meta-analysis, we performed a subgroup analysis based on ethnicity. From this subgroup analysis, we found that regardless of race, the Q141K variant increases the risk of gout. The data indicate that rs2231142 enhances the risk of gout particularly in Pacific Islanders, for whom the OR reached 3.42. However, with respect to the Maori, although the OR revealed a relationship with gout and a tendency toward unfavorable outcomes, the association was not significant as the $95\% CI (0.66-1.80)$ exceeded 1. However, these results might be explained by the critical factor of quantity. Our meta-analysis only included one study of Maori people, one of Pacific Islanders and two of Caucasians; therefore, there might be inconsistencies in our analysis related to sample size. Resolving this issue would require further large-scale analyses.

Gout is caused by hyperuricemia, which manifests as high serum uric acid (SUA) *in vivo*. Previous studies [12] have demonstrated that ABCG2 is a urate transporter and there is a significant association between hyperuricemia

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and gout. Hirota and colleagues [31, 32] divided samples into 4 groups according to ABCG2 function ($\leq 1/4$ function, $1/2$ function, $3/4$ function, and full function) and reported that ABCG2 dysfunction increases gout risk, especially in the group with the lowest ABCG2 function. Abbas et al. [12] found that SLC2A9 and SLC17A3 also increase uric acid concentration and gout risk. Therefore, we should consider gene-gene interactions and linkage disequilibrium to validate our results, the lack of which is a limitation of the current meta-analysis. This meta-analysis did have certain advantages. We identified 9 articles describing 11 studies, ensured the inclusion of an adequate sample size to validate the relationship between the rs2231142 polymorphism and gout risk, and demonstrated the association between rs72552713 polymorphism and gout risk.

Conclusion

Our results suggest that the rs2231142 ABCG2 polymorphism is associated with gout not only in Asians but also in other populations. The rs72552713 ABCG2 polymorphism also plays a role in gout in Asians. Our evidence revealed that Q141K and Q126X are risk factors for the development of gout. Heterogeneity in our model and subgroup analyses and certain limitations of this meta-analysis suggest that additional investigations with large sample sizes using well-designed methods and more homogeneous populations should be performed.

Acknowledgements

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Disclosure of conflict of interest

None.

Abbreviations

ABCG2, ATP-binding cassette, subfamily G, member 2; MSU, monosodium urate; SUA, serum uric acid; SLC2A9, solute carrier family 2, member 9; SLC22A11, solute carrier family 22, member 11; SLC17A1, solute carrier family 17, member 1; PDKZ1, coding for PDZ domain

containing 1; SNP, single-nucleotide polymorphism; ACR, American College of Rheumatology; HWE, Hardy-Weinberg equilibrium; OR, odds ratio; CI, confidence interval; FEM, fixed effects model; REM, random effects model.

Address correspondence to: Dr. Hua Yao, The First Affiliated Hospital of Xinjiang Medical University, Urumqi, Xinjiang, China. E-mail: Yaohua01@sina.com

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