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Research Article

A Meta-Analysis of the Association between the Q141K ABCG2 Gene Variant and Gout Risk

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Abstract

Background: Gout is an inflammatory disease and genetic factors play a role in gout. ABCG2 is a urate transporter, and an association has been reported between the Q141K variant of ABCG2 and gout risk. Previous studies have demonstrated inconsistent results regarding this association. Therefore, we conducted a meta-analysis to explore the relationship between this variant and gout.

Methods: We searched 7 electronic literature databases. In total,9 eligible articles on the association between the Q141K(rs2231142) variant 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 the relationship in a dominant model, a recessive model, and a co-dominant model.

Results: This study includes 6652 participants(2499 gout patients and 4153 controls). The Q141K variant significantly increased 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).

Conclusions: This result suggests associations between the rs2231142 ABCG2 gene polymorphism and gout risk, and this relationship trends to unfavorable outcomes. However, larger samples and homogeneous population's studies should be performed in the future.

Keywords

Gout; Q141K; Single nucleotide polymorphism; Meta-analysis

Introduction

Gout is a series of recurrent relapsing inflammatory disease. Gout is caused by monosodium urate (MSU) crystals that precipitate in 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, as high 1.21% in Tangshan. Today, the prevalence of gout has increased to 1.23% [3]. In addition, Edward and colleagues [4] reviewed the epidemiology of gout and also suggested that gout is becoming more prevalent. As a result of these trends, gout has increasingly attracted public attention.

Various studies demonstrate that environmental exposures and genetic factors play an important role 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. Equally, Ling-Qin Li [6] also found that hyperuricemia, BMI, high triglycerides, hypertension, high purine diet, drinking and smoking may increase the risk of gout. Regarding inherited genetic risk variants, various 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) [9]; coding for PDZ domain containing 1 (PDKZ1) [10] and ATP-binding cassette, subfamily G, member 2 (ABCG2) [11] may increase the risk of gout.

ABCG2 is a urate transporter that excretes uric acid [12]. According to the gene sequencing analysis; ABCG2 contains greater than 80 different single-nucleotide polymorphism (SNP) loci. Among them, Q141K and Q126X are the most studied. SNP rs2231142 also referred to as C421A or Q141K in ABCG2, is located in exon 5 [10] and causes substitution of glutamic acid with diamino caproic acid. Various studies have reported a relationship between rs2231142 and gout. However, due to small sample sizes or quality of data, variable results have been reported. To address these reasons, we performed a meta-analysis to explore the role of rs2231142 in gout.

Methods

Search strategy

We searched published articles in seven electronic literature databases (Chaoxing Medalink, Wangfang Data, Weipu, Chinese Biomedical Literature Service System, China National Knowledge Infrastructure (CNKI), Chinese Science Citation Database (CSCD) and PubMed). No time limitation was imposed, and the last search update was performed on 30 April 2015. The literature was searched in English and Chinese using the following primary key words: gout, ABCG2, C421A, Q141K, rs2231142; In addition, the following index terms were used: gout and ABCG2, gout and C421A, gout and Q141K or gout and rs2231142.

Selection criteria

In this meta-analysis, we first established inclusion criteria: (1) The publication had to be a genetic connectedness study regarding gout and the ABCG2 gene polymorphism; (2) The diagnostic criteria [13] should adhere to the American College of Rheumatology (ACR) preliminary diagnostic criteria for acute gout; (3) The publication was a case-control study design; (4) The participant did not have other serious disease in addition to gout; (5) The case and control should include specific genotype distribution data (6) The genotype distribution of the control group should fulfill Hardy-Weinberg

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equilibrium(HWE); (7) If a study contained more than one more samples, each sample was used for this meta-analysis.

Quality assessment

Two authors selected studies based on the selection criteria. Disagreements were resolved by consulting a third author. Moreover, we selected the best article describing the same studies and discarded those with incomplete data. Then, we performed a quality assessment to ensure the results would be available in this meta-analysis. The assessment criteria were based on the STREGA (Strengthening the Reporting of Genetic Association studies) principle [14], which contains six items. If the included studies fulfill three or more of those items, they were considered good quality. Fortunately, the quality of the included studies was high. Therefore, we collected 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 genotype frequencies. Then, these data were input into one table for analysis.

Statistical analysis

We used Review Manager 5.1 software (The Cochrane Collaboration, Oxford, UK) and Stata software (version 11.0) to perform the statistical analyses. The association between susceptibility of gout and the rs2231142 ABCG2 gene polymorphism was indicated by odds ratio (OR) and the corresponding 95% confidence interval (CI). The relationship was assessed in a dominant model (CC vs. AC+AA), a recessive model (AA vs. CC+AC), and a co-dominant model (AC vs. CC+AA). In addition, we used I^2 statistic to evaluate heterogeneity between studies. Then, we used a fix effects model (FEM) to calculate the pooled OR and 95%CI if the *P*-value>0.05, which indicated no heterogeneity. If heterogeneity was noted, we used a random effects model (REM) to combine eligible data. We examined significant pooled OR using the Z statistic. Next, to guarantee the stability of the results, we implemented a sensitivity analysis by sequential removal of individual studies. In addition, publication bias was assessed by funnel plots with the Begg's test and Egger's test, in which *P*>0.05 indicated no publication bias.

Results

Search results and study characteristics

In total, 48 records were identified from electronic databases that analyzed the association 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 were based on populations, 4 studies did not have relationship with gout and 2 studies were lacked control groups. Thus, 19 total case-control publications were ultimately obtained. In addition, 5studies were excluded from our meta-analysis due to lack of genotype frequencies. Furthermore, 4 pairs of studies were published using the same data; therefore, we excluded 4 additional studies. In total, 9 studies were included in our meta-analysis following exclusion of another meta-analysis article. The study search procedure is outlined in Figure 1.

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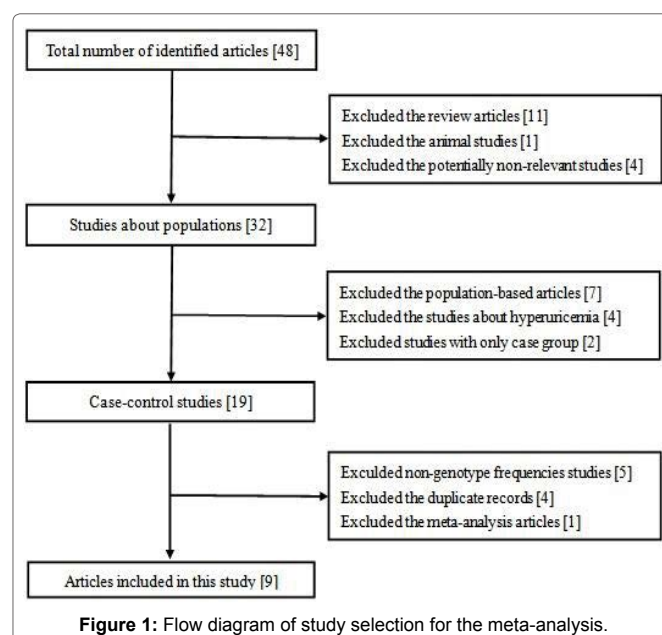

Figure 1: Flow diagram of study selection for the meta-analysis.

and 4153 controls were recruited for this analysis from these 11 studies. We extracted the characteristics of these studies, which are summarized in Table 1.

Meta-analysis

A significant association was noted between the rs2231142 polymorphism and gout risk in a dominant model (OR=2.32, 95%CI=1.80-2.99, *P*<0.0001 for heterogeneity), a recessive model (OR=3.28, 95%CI=2.68-4.00, *P*=0.27 for heterogeneity) and a co-dominant model (OR=1.42, 95%CI=1.27-1.58, *P*=0.09 for heterogeneity) (Figure 2). Similarly, subgroup analysis by ethnicity also revealed the same significant association 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=2.28-6.27, *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).

Sensitivity analysis and publication bias

To ensure the stability of the 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 6). Then, we used funnel plots with the Begg's test 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) also did not reveal significant publication bias (Figure 7).

Discussion

Following the development of genetics technology, numerous studies examining the association between ABCG2 polymorphisms

Table 1: Characteristics of the included studies.

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 [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 [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 [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

and gout risk have been reported. Among ABCG2 polymorphisms, Q141K and Q126X are the most studied. Nevertheless, some controversy about whether the Q141K variant has a role in the risk of gout has been noted. For example, Lili Zhang et al. [24] demonstrated that rs2231142 was significantly associated with gout in Europeans, Americans, African Americans and Mexican Americans. In agreement, Hirotaka et al. [25] and Kazumasa et al. [11] both indicated that the Q141K variant increased the risk of gout. On the contrary, Amanda et al. [22] reported the lack of an association of rs2231142 with gout in Maori samples. To address these discrepancies, we performed a meta-analysis to explore the relationship of rs2231142 and gout, and conducted a subgroup analysis to discuss racial differences.

In our meta-analysis, we identified 11 studies that contained 4 ethnicities (Asians, Maori, Pacific Islander and Caucasian), originating from 3 countries (China, New Zealand and Germany) and including a total of 6652 participants (2499 gout patients and 4153controls). Our results suggested that the Q141K variant has an increased gout risk in a dominant model, a recessive model, a co-dominant model and subgroup analyses. However, heterogeneity had a significant effect on the dominant model and subgroup analysis. The cause of this result may be potential confounders such as age, gender and inscrutable environmental factors. Previous studies demonstrated that men [26] and postmenopausal women [27] may have an increased prevalence of gout. However, due to the lack of these data in certain included studies, we did not estimate the adjusted OR. Regarding environmental factors, we could consider a gene-environment interaction, which represents a limitation in our current meta-analysis.

Ethnicity difference is always mentioned by investigators not only in discussions of gout [28], but also in the association between the Q141K polymorphism and gout risk [24]. In our present meta-analysis, we also performed subgroup analysis based on ethnicity.

From this subgroup analysis, we suggest that regardless of race, the Q141K variant may increase 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 trended to unfavorable outcomes, the association may not have significance as the 95% CI (0.66-1.80) exceeded 1. What may explain this result is the simple critical factor of quantity. Our meta-analysis only selected one study of Maori people, one of Pacific Islanders and two of Caucasians, therefore there may be problems related to sample size. This issue requires more large-scale analyses.

Gout is caused by hyperuricemia, which manifests as high serum uric acid (SUA) in vivo. Previous studies [12] demonstrated that ABCG2 is a urate transporter and that there is a significant association with hyperuricemia and gout. Hirotaka and colleagues [29,30] divided samples into 4 groups according to ABCG2 function (≤1/4 function, 1/2 function, 3/4 function, and full function) and reported that ABCG2 dysfunction increases gout risk especially in the lowest function group. In addition, Abbas et al. [12] found that SLC2A9 and SLC17A3 also increased uric acid concentration and gout risk. Therefore, we should consider gene-gene interactions and linkage disequilibrium to validate our results as this lack of analysis is a limitation to the current meta-analysis. This meta-analysis does have certain advantages. We identified 9 articles describing 11 studies and ensured an adequate sample size to validate the relationship between the rs2231142 polymorphism and gout risk.

Conclusion

Overall, our results suggest that the rs2231142 ABCG2 polymorphism was associated with gout not only in Asians but also in other populations. Our evidence revealed that Q141K is a risk factor for the development of gout. Heterogeneity in subgroup analysis
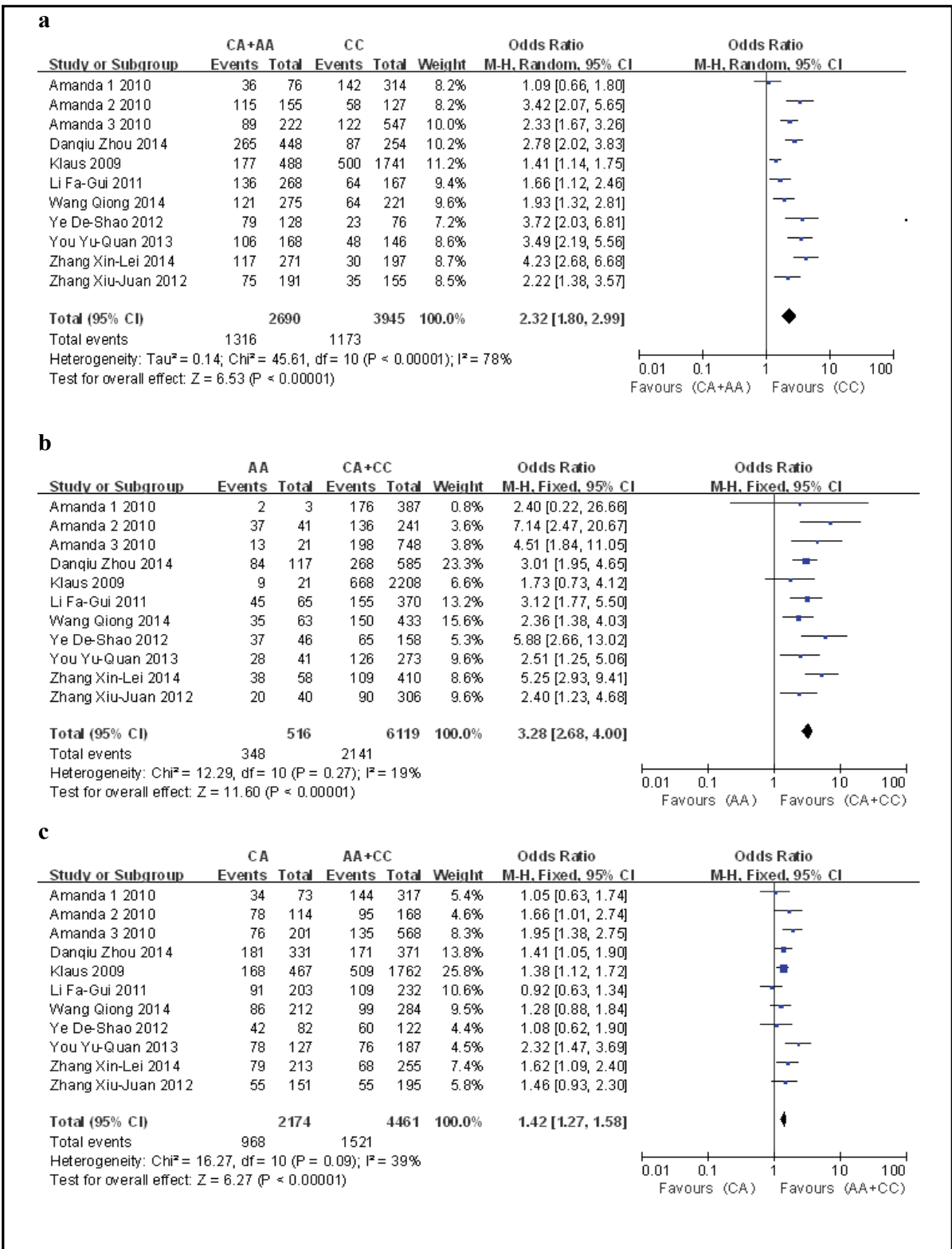
Figure 2: Forest plot for the association between the Q141K variant and gout risk a: dominant model (CC vs. AC+AA), b: recessive model (AA vs. CC+AC), c: co-dominant model (AC vs. CC+AA).
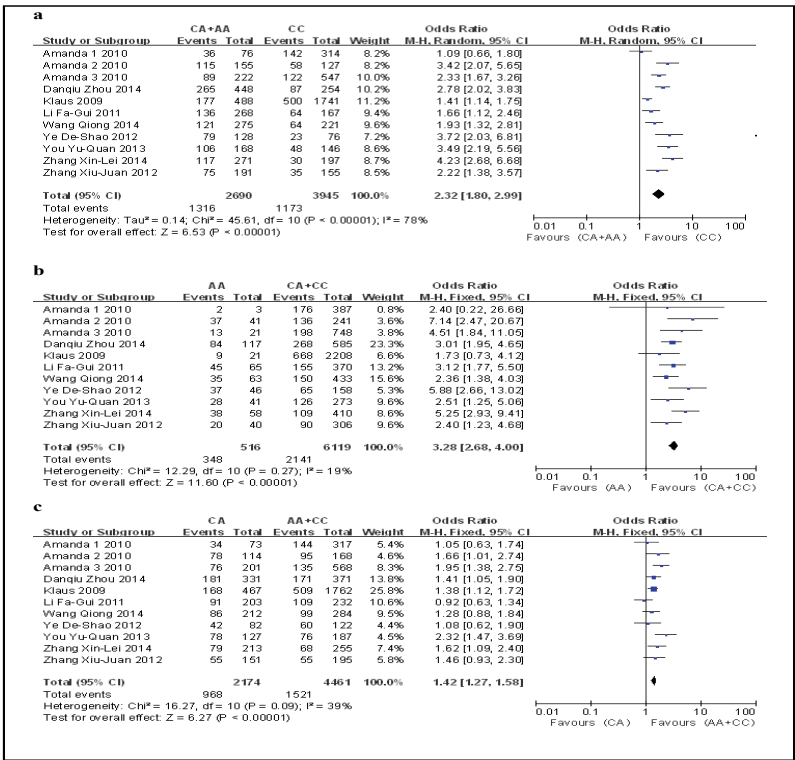
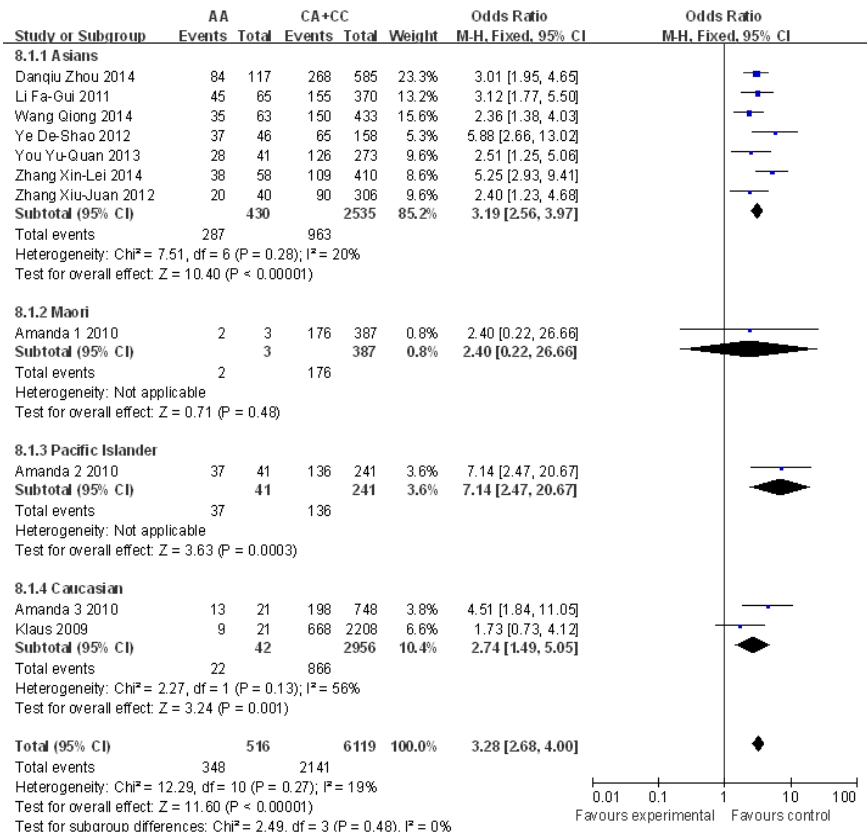**Figure 3:** Forest plot describing ethnicity in the dominant model.

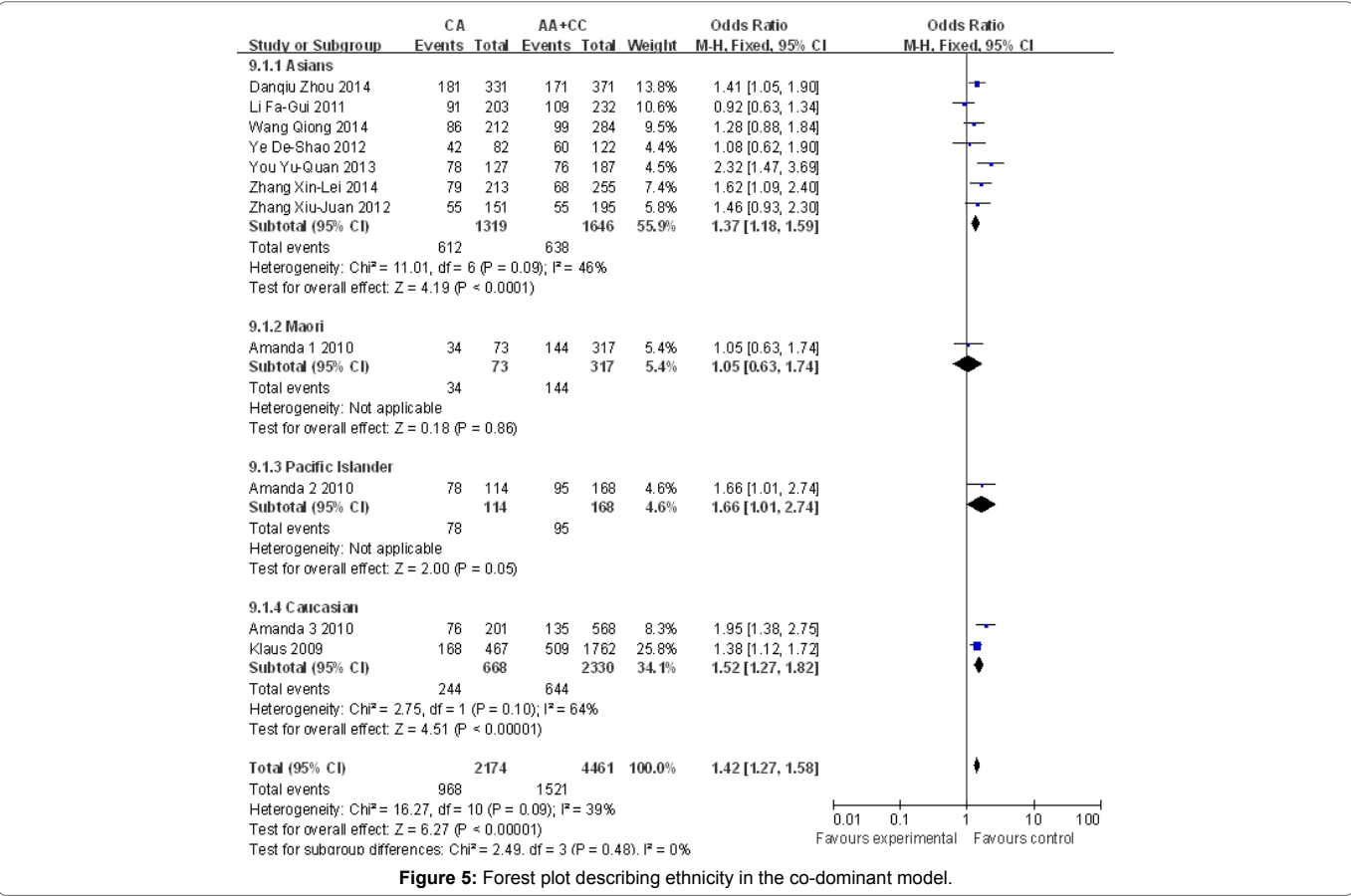**Figure 4:** Forest plot describing ethnicity in the recessive model.

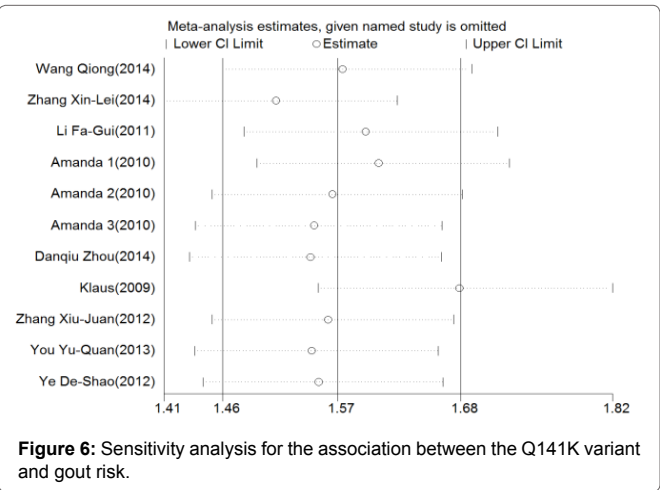**Figure 5:** Forest plot describing ethnicity in the co-dominant model.

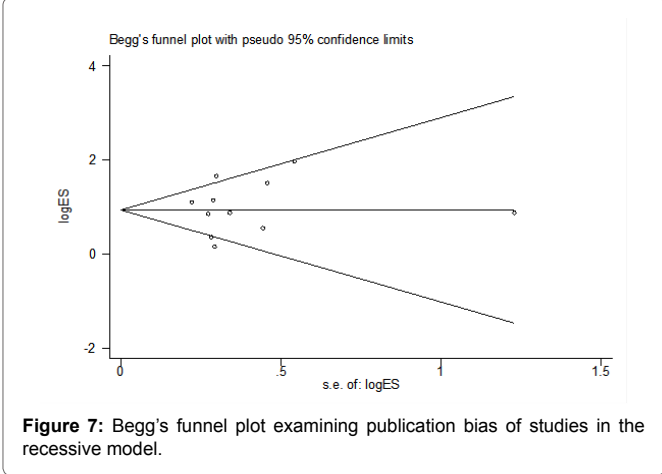**Figure 6:** Sensitivity analysis for the association between the Q141K variant and gout risk.

Figure 7: Begg's funnel plot examining publication bias of studies in the recessive model.

and certain limitations to this meta-analysis suggest that additional investigations with large samples well-designed methods and more homogeneous population studies should be performed.

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