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Original Article

A systematic review and meta-analysis of 4 candidate polymorphisms with the risk of gout

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Abstract: The purpose of this research was to assess the contribution of 4 genetic polymorphisms to the risk of gout. A systematic search was performed for qualified case-control studies on 4 variants with gout among PubMed, EMBASE, CNKI and China Wanfang literature databases. Using the REVMAN software, odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to evaluate the contribution of the 4 genetic variants to gout. We harvested a total of 19 studies among 6,797 cases and 15,904 controls for the current meta-analyses. Our results showed that *ABCG2* rs2231142 (OR = 2.13, 95% CI = 1.81-2.50, P < 0.00001), *SLC2A9* rs3733591 (OR = 0.78, 95% CI = 0.67-0.91, P = 0.002), *SLC2A9* rs16890979 (OR = 0.33, 95% CI = 0.18-0.58, P = 0.0002), and *SLC2A9* rs6855911 (OR = 0.66, 95% CI = 0.56-0.77, P < 0.00001) were significantly associated with the risk of gout. Our results showed four genetic variants (including *ABCG2* rs2231142, *SLC2A9* rs3733591, rs16890979 and rs6855911) were significantly associated with gout.

Keywords: Gout, *ABCG2*, *SLC2A9*, meta-analysis, polymorphism

Introduction

Gout is a common disease based on hyperuricemia, which is caused by urate crystals deposited in synovial fluid and adjacent connective tissues [1]. The typical clinical manifestations of gout are comprised of a high level of serum urate, crystal inflammatory arthritis, unbearable pain tophi, uric acid urolithiasis and uric acid nephrolithiasis [2]. Gout is known to be caused by unhealthy life-styles and dietary habits, such as excessive alcohol drinking and a surfeit of seafood consumption [3].

The incidence of gout and hyperuricemia was increasing recently in the world. Domestic survey in 1980s showed that the prevalence rate of hyperuricemia was 1.3% to 1.4% [4], and it rose to 12.5% for hyperuricemia and 1.93% for gout in 2006 [5]. Family members of gout patients have an increased risk of asymptomatic hyperuricaemia, and gout is often seen in the middle-aged men to elderly men and postmenopausal women [6].

Genome-wide association studies have identified numerous genetic loci associated with gout, and those genetic loci may help provide a cost-effective and personalized gout treatment in clinic [7]. Meanwhile, case-control studies have also identified gene polymorphisms associated with gout [8, 9]; however, other literatures have found opposite results [10, 11]. The discrepancies in the association results may be due to various ethnic populations or the limited detection power in association tests the moderate sample size [12, 13]. Meta-analysis is able to combine the data from various studies and overcome the limitation in the case-control study with moderate sample size. Here, the goal of our meta-analyses is to establish the association of four genetic variants with gout.

Materials and methods

Literature search

Our literature search was conducted among electronic databases including PubMed, EM-

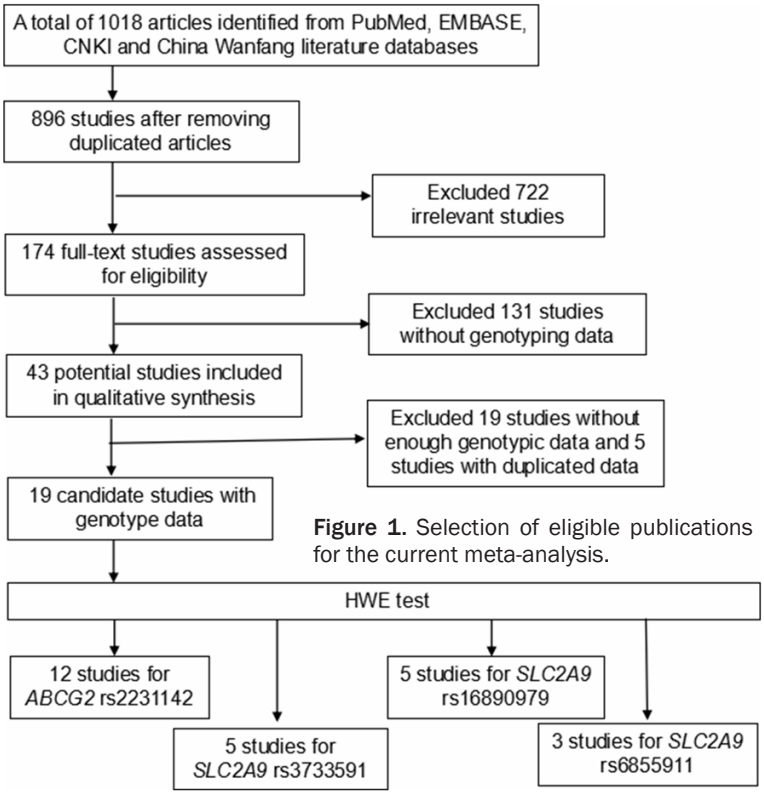


Figure 1. Selection of eligible publications for the current meta-analysis.

BASE, CNKI and China Wanfang literature databases. The search terms in the PubMed and EMBASE were "gout", "podagra", "arthrolithiasis", "uarthritis", "crystal arthritis", "crystal arthropathy", or "tophus" combined with "polymorphism", "allete", "genotype", "variant", or "SNP". And the equivalent Chinese terms were also used to search for related publications in CNKI and China Wanfang literature databases.

Data extraction and quality assessment

Publications were excluded if they didn't have genotyping or allelic data or odds ratio (OR) to infer the combined statistics in the meta-analysis. We focused on four genetic variants with at least three independent genotypic datasets. The details (the name of first author, publication year, country, and genotype) for the data extraction were described previously [14-17]. In addition, the risk-of-bias in the included studies was also assessed with the Review Manager software (version 5.2, Cochrane Collaboration, Oxford, United Kingdom) by using the logistic regression with odds ratios (ORs) and 95% confidence intervals (95% CIs). Hardy-Weinberg equilibrium (HWE) was analyzed by the chi-square test.

Statistical analysis

All the statistical analyses were performed using the Review Manager software (version 5.2, Cochrane Collaboration, Oxford, United Kingdom). Heterogeneity of the meta-analyses was measured by using Cochran's Q statistic and the inconsistency index (I^2). $I^2 \geq 50\%$ indicated a significant heterogeneity among the studies in the meta-analyses. Random-effect model was used in the meta-analysis with large heterogeneity; otherwise the fixed-effect model was used instead. A two-sided $P < 0.05$ was considered as significant. Funnel plot was used to judge whether publication bias existed in the meta-analysis.

Results

Characteristics of the involved studies

Our initial search for the eligible studies retrieved 1018 articles from PubMed, EMBASE, CNKI and China Wanfang literature databases updated through December, 2015. Among them, we discarded 122 duplicate studies, 722 studies with irrelevant titles and abstracts, 131 studies lacking of genotyping data. Among the remaining articles, we further discarded 19 studies with less than three independent genotypic datasets for the same genetic variants, and 5 studies with duplicate data. Finally, 19 studies (including 14 English and 5 Chinese articles) involving with 6,797 cases and 15,904 controls were included in the current meta-analyses (**Figure 1**).

A total of four variants on two genes were eligible for the present meta-analyses. These variants comprised *ABCG2* rs2231142 and *SLC2A9* rs3733591, rs16890979, and rs6855911. A Hardy-Weinberg equilibrium (HWE) test showed that the genotype distribution in healthy controls didn't meet HWE ($P = 0.003$ and 0.025, **Table 1**) for *ABCG2* rs2231142 [18] and *SLC2A9* rs6855911 [19] in two studies,

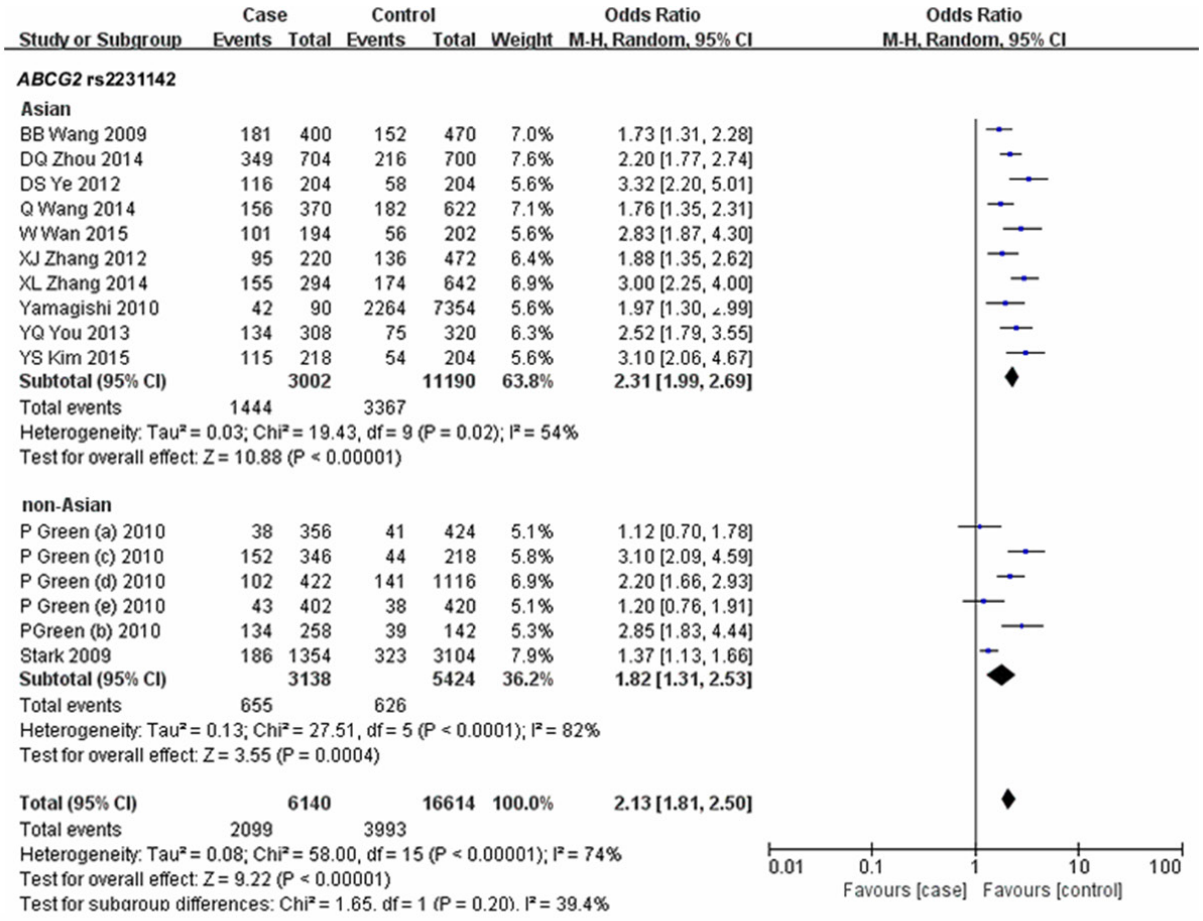
Table 1. The detailed information of the enrolled studies in the meta-analysis*

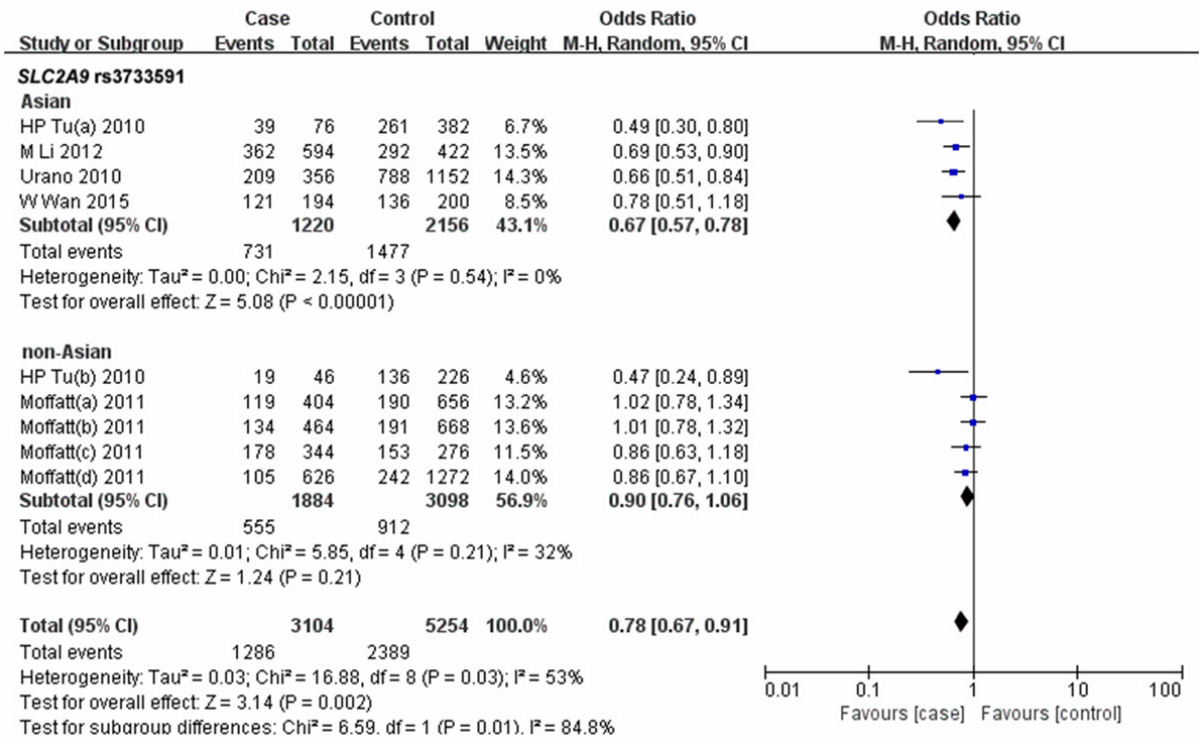
SNP	Year	Author	Ethnic Group	Case/ Control	Genotype (Case/Control)			p (HWE)	Allele (Case/Control)	
ABCG2 rs2231142					CC	CA	AA		C	A
	2009	Matsuo	Japanese	159/865	41/462	87/316	31/87	0.003	169/1240	149/490
	2009	Stark	German	677/1552	500/1241	168/299	9/12	0.191	1168/2781	186/323
	2010	BB Wang	Chinese	200/235	64/103	91/112	45/20	0.172	219/318	181/152
	2010	P Green (a)	Maori	178/212	142/172	34/39	2/1	0.440	318/383	38/41
	2010	P Green (b)	Pacific Islander	173/109	58/69	78/36	37/4	0.793	194/174	152/44
	2010	P Green (c)	Caucasian	211/558	122/425	76/125	13/8	0.728	320/975	102/141
	2010	P Green (d)	Eastern P	201/210	160/173	39/36	2/1	0.547	359/382	43/38
	2010	P Green (e)	Western P	129/71	29/36	66/31	34/4	0.419	124/103	134/39
	2010	Yamagishi	Japanese	45/3677	15/1767	18/1556	12/354	0.670	48/5090	42/2264
	2012	DS Ye	Chinese	102/102	23/53	42/40	37/9	0.713	88/146	116/58
	2012	XJ Zhang	Chinese	110/236	35/120	55/96	20/20	0.897	125/336	95/136
	2013	YQ You	Chinese	154/160	48/98	78/49	28/13	0.064	174/245	134/75
	2014	DQ Zhou	Chinese	352/350	87/167	181/150	84/33	0.935	355/484	349/216
	2014	Q Wang	Chinese	185/311	64/157	86/126	35/28	0.707	214/440	156/182
	2014	XL Zhang	Chinese	147/321	30/167	79/134	38/20	0.312	139/468	155/174
	2015	W Wan	Chinese	97/101	22/54	49/38	26/9	0.539	93/146	101/56
	2015	YS Kim	Korean	109/102	26/53	51/44	32/5	0.275	103/150	115/54
SLC2A9 rs3733591					CC	CT	TT		C	T
	2010	Urano	Japanese	178/576	27/56	93/252	58/268	0.771	147/364	209/788
	2010	HP Tu (a)	Chinese	38/191	NA	NA	NA	NA	37/121	39/261
	2010	HP Tu (b)	Solomom Islander	23/113	NA	NA	NA	NA	27/90	19/136
	2011	Moffatt (a)	Maori	202/328	101/164	83/138	18/26	0.684	285/466	119/190
	2011	Moffatt (b)	E Polynesian	232/334	119/169	92/139	21/26	0.726	330/477	134/191
	2011	Moffatt (c)	W Polynesian	172/138	39/33	88/57	45/48	0.054	166/123	178/153
	2011	Moffatt (d)	Caucasian	313/636	217/417	87/196	9/23	0.996	521/1030	105/242
	2012	M Li	Chinese	297/211	47/21	138/88	112/102	0.753	232/130	362/292
	2015	W Wan	Chinese	97/100	12/9	49/46	36/45	0.569	73/64	121/136
SLC2A9 rs16890979					CC	CT	TT		C	T
	2009	Moffatt (a)	Maori	55/117	53/83	2/30	0/4	0.534	108/196	2/38
	2009	Moffatt (b)	Pacific Islander	68/40	68/35	0/5	0/0	0.673	136/75	0/5
	2009	Moffatt (c)	Caucasian	131/551	103/338	24/183	4/30	0.427	230/859	32/243
	2010	Urano	Japanese	180/591	178/580	2/11	0/0	0.819	358/1171	2/11
	2012	YQ You	Chinese	154/160	102/43	42/69	10/48	0.084	246/155	62/165
	2012	M Li	Chinese	297/211	293/204	4/7	0/0	0.806	590/415	4/7
	2015	YS Kim	Korean	109/102	0/0	0/2	109/100	0.920	0/2	218/202
SLC2A9 rs6855911					AA	AG	GG		A	G
	2009	Stark	German	677/1546	429/829	233/603	15/114	0.763	1091/2261	263/831
	2010	Urano	Japanese	179/581	177/570	2/11	0/0	0.818	356/1151	2/11
	2011	M Guan	Chinese	166/206	160/197	6/9	0/0	0.749	326/403	6/9
	2012	DS Ye	Chinese	102/102	101/65	1/37	0/0	0.025	203/167	1/37

*: NA stands for not available.

and thus the two studies were not included in the follow-up meta-analyses.

As shown in **Figure 2**, there was significant heterogeneity for *ABCG2* rs2231142 (I^2 = 72%), *SLC2A9* rs3733591 (I^2 = 53%) and rs16890979 (I^2 = 62%). No heterogeneity was observed for *SLC2A9* rs6855911 (I^2 = 0%, **Figure 2**). Thus, a random-effect model was applied for the meta-analyses of *ABCG2* rs2231142, *SLC2A9* rs3733591 and rs16890979, and a fixed-effect model was applied for the meta-


Case
Control
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
ABCG2 rs2231142
Asian
BB Wang 2009 181 400 152 470 7.0% 1.73 [1.31, 2.28]
DQ Zhou 2014 349 704 216 700 7.6% 2.20 [1.77, 2.74]
DS Ye 2012 116 204 58 204 5.6% 3.32 [2.20, 5.01]
Q Wang 2014 156 370 182 622 7.1% 1.76 [1.35, 2.31]
W Wan 2015 101 194 56 202 5.6% 2.83 [1.87, 4.30]
XJ Zhang 2012 95 220 136 472 6.4% 1.88 [1.35, 2.62]
XL Zhang 2014 155 294 174 642 6.9% 3.00 [2.25, 4.00]
Yamagishi 2010 42 90 2264 7354 5.6% 1.97 [1.30, 2.99]
YQ You 2013 134 308 75 320 6.3% 2.52 [1.79, 3.55]
YS Kim 2015 115 218 54 204 5.6% 3.10 [2.06, 4.67]
Subtotal (95% CI) 3002 11190 63.8% 2.31 [1.99, 2.69]
Total events 1444 3367
Heterogeneity: Tau² = 0.03; Chi² = 19.43, df = 9 (P = 0.02); I² = 54%
Test for overall effect: Z = 10.88 (P < 0.00001)
non-Asian
P Green (a) 2010 38 356 41 424 5.1% 1.12 [0.70, 1.78]
P Green (c) 2010 152 346 44 218 5.8% 3.10 [2.09, 4.59]
P Green (d) 2010 102 422 141 1116 6.9% 2.20 [1.66, 2.93]
P Green (e) 2010 43 402 38 420 5.1% 1.20 [0.76, 1.91]
PGreen (b) 2010 134 258 39 142 5.3% 2.85 [1.83, 4.44]
Stark 2009 186 1354 323 3104 7.9% 1.37 [1.13, 1.66]
Subtotal (95% CI) 3138 5424 36.2% 1.82 [1.31, 2.53]
Total events 655 626
Heterogeneity: Tau² = 0.13; Chi² = 27.51, df = 5 (P < 0.0001); I² = 82%
Test for overall effect: Z = 3.55 (P = 0.0004)
Total (95% CI) 6140 16614 100.0% 2.13 [1.81, 2.50]
Total events 2099 3993
Heterogeneity: Tau² = 0.08; Chi² = 58.00, df = 15 (P < 0.00001); I² = 74%
Test for overall effect: Z = 9.22 (P < 0.00001)
Test for subgroup differences: Chi² = 1.65, df = 1 (P = 0.20), I² = 39.4%
0.01 0.1 1 10 100
Favours [case] Favours [control]


Case
Control
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
SLC2A9 rs3733591
Asian
HP Tu(a) 2010 39 76 261 382 6.7% 0.49 [0.30, 0.80]
M Li 2012 362 594 292 422 13.5% 0.69 [0.53, 0.90]
Urano 2010 209 356 788 1152 14.3% 0.66 [0.51, 0.84]
W Wan 2015 121 194 136 200 8.5% 0.78 [0.51, 1.18]
Subtotal (95% CI) 1220 2156 43.1% 0.67 [0.57, 0.78]
Total events 731 1477
Heterogeneity: Tau² = 0.00; Chi² = 2.15, df = 3 (P = 0.54); I² = 0%
Test for overall effect: Z = 5.08 (P < 0.00001)
non-Asian
HP Tu(b) 2010 19 46 136 226 4.6% 0.47 [0.24, 0.89]
Moffatt(a) 2011 119 404 190 656 13.2% 1.02 [0.78, 1.34]
Moffatt(b) 2011 134 464 191 668 13.6% 1.01 [0.78, 1.32]
Moffatt(c) 2011 178 344 153 276 11.5% 0.86 [0.63, 1.18]
Moffatt(d) 2011 105 626 242 1272 14.0% 0.86 [0.67, 1.10]
Subtotal (95% CI) 1884 3098 56.9% 0.90 [0.76, 1.06]
Total events 555 912
Heterogeneity: Tau² = 0.01; Chi² = 5.85, df = 4 (P = 0.21); I² = 32%
Test for overall effect: Z = 1.24 (P = 0.21)
Total (95% CI) 3104 5254 100.0% 0.78 [0.67, 0.91]
Total events 1286 2389
Heterogeneity: Tau² = 0.03; Chi² = 16.88, df = 8 (P = 0.03); I² = 53%
Test for overall effect: Z = 3.14 (P = 0.002)
Test for subgroup differences: Chi² = 6.59, df = 1 (P = 0.01), I² = 84.8%
0.01 0.1 1 10 100
Favours [case] Favours [control]

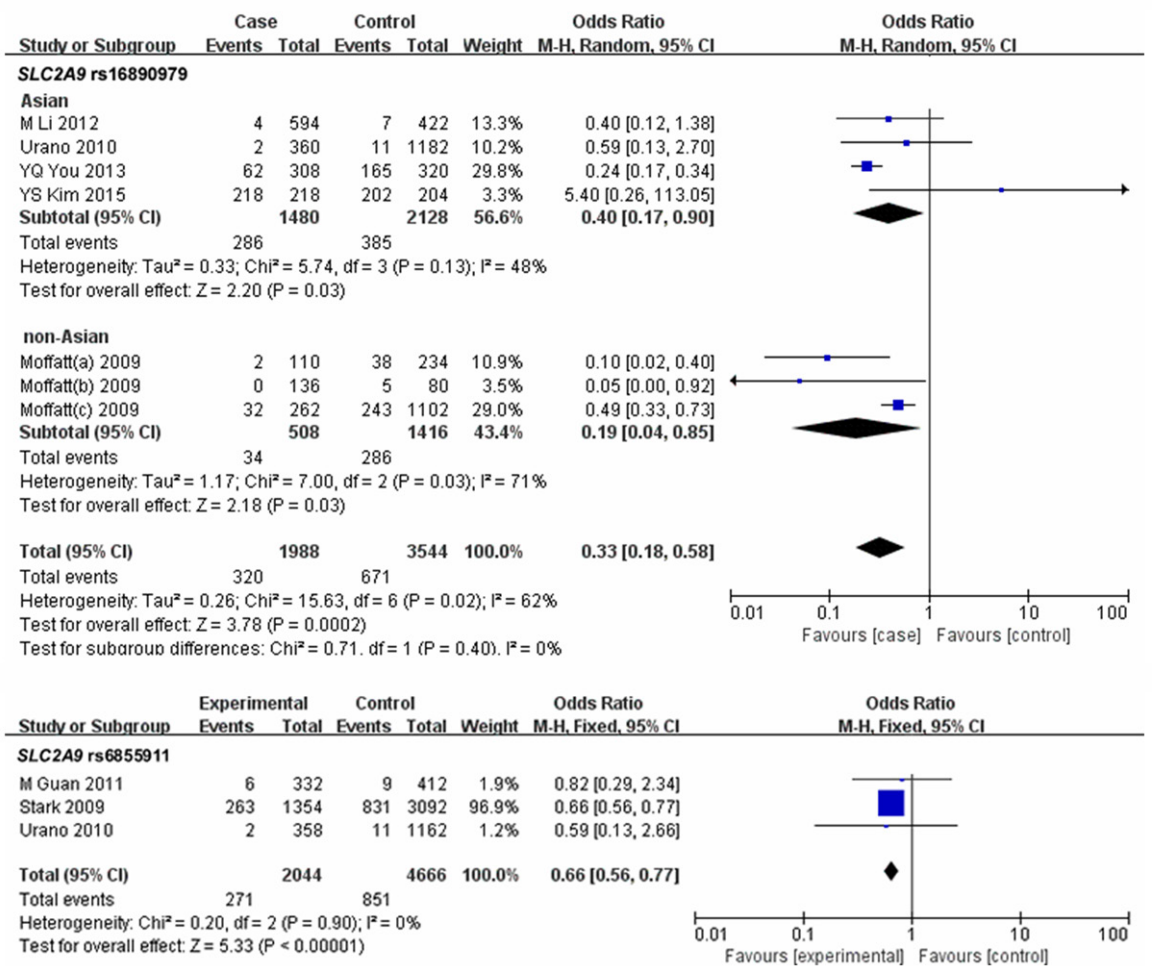


Figure 2. Forest plots for the meta-analyses of four polymorphisms.

analysis of *SLC2A9* rs6855911. In addition, funnel plots were demonstrated that there was no publication bias for all the meta-analyses (**Figure 3**).

Results of meta-analysis

Meta-analysis of *ABCG2* rs2231142 was involved with 12 studies [19-30] among 3,070 gout cases and 8,307 controls. Meta-analysis of *SLC2A9* rs3733591 was involved with 5 studies [30-34] among 1552 gout cases and 2627 controls. Meta-analysis of *SLC2A9* rs16890979 was involved with 5 studies among 994 gout cases and 1,772 controls [24, 28, 33-35]. Meta-analysis of *SLC2A9* rs6855911 was involved with 3 studies among 1,022 gout cases and 2,333 controls [26, 34, and 36]. As shown in **Figure 2**, *ABCG2* rs2231142 was associated with the risk of gout (overall OR = 2.13, 95% CI = 1.81-2.50, P < 0.00001), and three *SLC2A9* variants were associated with the protection of gout (rs3733591: the overall OR = 0.78, 95% CI = 0.67-0.91, P = 0.002; *SLC2A9* rs16890979: the overall OR = 0.33, 95% CI = 0.18-0.58, P = 0.0002; *SLC2A9* rs6855911: the overall OR = 0.66, 95% CI = 0.56-0.77, P < 0.00001).

Further subgroup meta-analyses by ethnic populations showed that *SLC2A9* rs3733591 was significantly associated with gout in Asian populations (the overall OR = 0.67, 95% CI = 0.57-0.78, P < 0.00001) but not in non-Asian populations. However, the rest three variants were shown to be significantly associated with gout in both Asian and non-Asian populations. In addition, the power was 1.000 for the meta-analyses of all the four variants.

Discussion

In the present study, we carried out a comprehensive systematic overview of genetic associ-

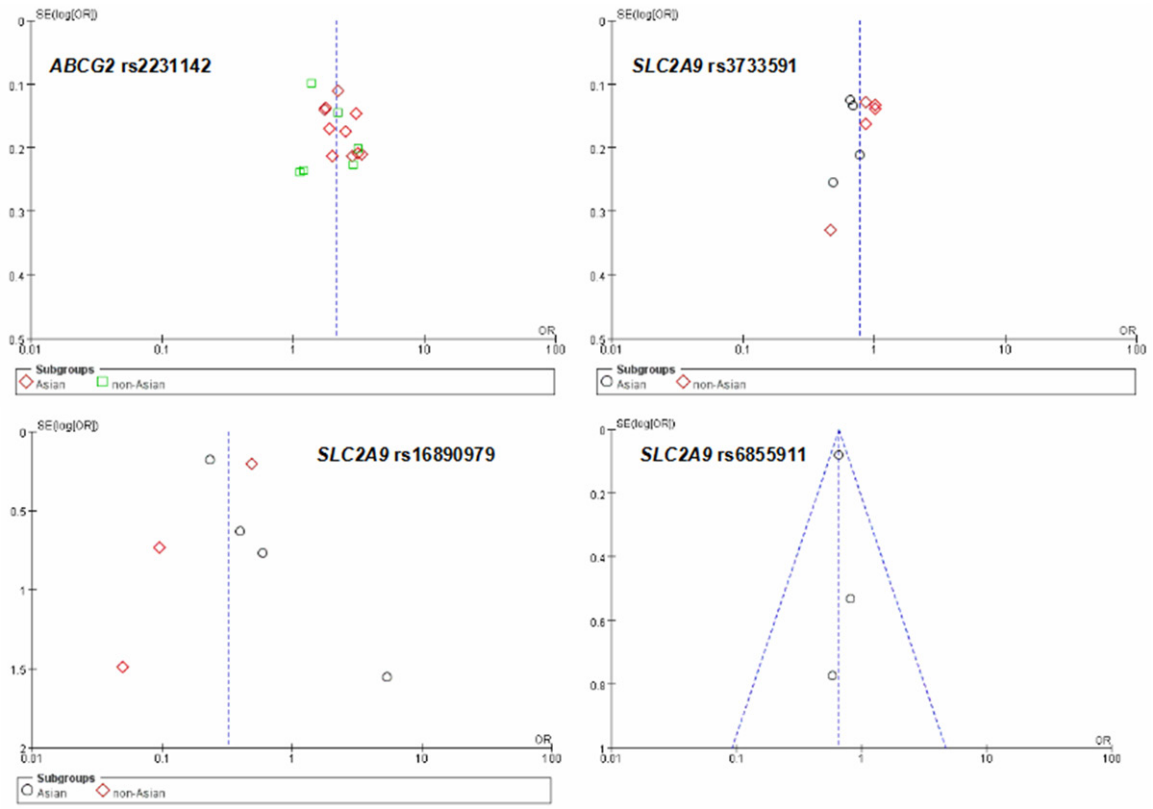


Figure 3. Funnel plots for the meta-analyses of four polymorphisms.

ation studies with gout. Our meta-analyses established significant association of four variants with gout. Specifically, our results indicated that *ABCG2* rs2231142-A was a risk allele of gout, and *SLC2A9* rs37333591-T, rs16890979-T, and rs6855911-G were protective alleles of gout. Our observation was also supported by a recent GWAS of gout in different populations [37]. Since the GWAS provided an adjusted OR, their data was not included in the current meta-analysis.

ABCG2 encodes a multi-specific apical membrane transporter expressed in several tissues [38]. *ABCG2* is able to transport nucleotide analogs that are structurally similar to urate [39]. SLC2A9 encodes a putative fructose transporter [40] highly expressed in the proximal renal tubular cells [41]. *SLC2A9* is an important modulator responsible for the urate reabsorption in the apical membrane of the renal proximal tubules [42]. Our meta-analyses were involved with three *SLC2A9* variants (rs3733591, rs16890919 and rs6855911). The linkage disequilibrium (LD) among these three variants showed a significant LD between rs16890979 and rs6855911 (r^2 = 0.784 in HapMap CEU and r^2 = 0.494 in HapMap CHB). However, much weaker LD values were observed between rs3733591 and rs16890979 (r^2 = 0.098 in HapMap CEU; r^2 = 0.058 in HapMap CHB), and between rs3733591 and rs6855911 (r^2 = 0.086 in HapMap CEU; r^2 = 0.028 in HapMap CHB). This might explain that the association of *SLC2A9* rs3733591 with gout was found only in Asian populations, however, the association of other two *SLC2A9* variants with gout was found in Asian and non-Asian populations.

Prior to the current meta-analyses, there were four meta-analyses of the *ABCG2* rs2231142 and gout [43-46]. Compared with the previous meta-analyses [43-46], ours included 8, 7, 6 and 3 more articles, respectively. We didn't include the data from unpublished data in the meta-analysis by Dong et al [43], and we also discarded the data of the Abbas's study [37] in the meta-analysis by Lv et al [44], since it provided an adjusted OR value.

There were several limitations in our study. Selection or publication biases might exist although our analyses didn't identify them among the studies in the current meta-analyses, since only publications in English and Chinese languages were included in the current meta-analyses. Meanwhile, there was a lower chance of publication for the investigations with negative findings. In addition, gout is a complicated disorder influenced by numerous factors, including gender, age and dietary differences. However, due to a lack of relative information in the original research articles, a subgroup meta-analysis by these factors could not be performed to test their interactions with genetic factors.

In conclusion, our meta-analyses established that *ABCG2* rs2231142, *SLC2A9* rs3733591, rs16890979 and rs6855911 were significantly associated with the risk of gout.

Acknowledgements

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Disclosure of conflict of interest

None.

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