A Meta-Analysis about ABCG2 Q141K polymorphism Association with Gout Risk and identification of genetic model

**Abstract**

***Background***: ABCG2 has been considered as one of the most important genes in gout pathogenesis and susceptibility. However, Published data have showed different effect size of the odds ratio for the genotype of rs2231142 and conflicting results on the relationship with sex in gout susceptibility. A meta-analysis is needed to provide a systematic review of the published findings.

***Methods***: Desirable articles published before Feb, 2013 were extracted and register into databases. The quality of each study was scored based on the predefined criteria. Potential sources of heterogeneity were sought out via stratification analysis and meta-regression, The published biases were estimated by performing funnel plots qualitatively.

***Results***: Ultimately, 11 case–control researches were eligible for the meta-analysis of ABCG2 Q141K. Co-dominant model is proved most probably appropriate genetic model of the susceptibility. And the results suggest the rs2231142 polymorphism was strongly associated with gout susceptibility (OR=4.30, P = 0.000 in OR1; OR=2.36, P = 0.000 in OR3), and the TT genotype is more risk than GT genotype (OR=1.70, P = 0.000 in TT Vs GT). Our findings suggest no evidence for the interaction of rs2231142 association with gout in sex and age but significant in ethnicity. In the meta-analysis about rs2231142 we find the published year is a very important source of heterogeneity. The result of line regression (R2= 0.9869) suggested a causal relationship between serum uric acid and gout in three SNPs.

***Conclusions***: These findings suggest a predictive role for rs2231142 polymorphisms associated with gout susceptibility and this association isn’t modified by sex but modified by ethnicity. The T allele may be a predictive for uric acid and gout. Three SNPs influents gout through uric acid. This result

**Introduction**

Gout which was ever known as the ''Disease of Kings'' [[1](#_ENREF_1" \o "Matsuo, 2009 #2)] has been turned to a common disease which affects over 700,000 adults in the United Kingdom and nearly 3 million individuals in the United States [5]. while g with a non-neglectable trend Except for the kepidemiological s such as age, genetic predisposition was also thought to be an important factor[[4](#_ENREF_4" \o "Bleyer, 2006 #5)]. Molecular and cellular evidences has shown that reduced excretion of urate by the kidney is one of the main cause for elevated urate levels[[7](#_ENREF_7" \o "Anzai, 2007 #8)] and lead to gout [[8](#_ENREF_8" \o "Woodward, 2009 #9)].

Recently several independent evidences from GWAS, linkage analysis [[11](#_ENREF_11" \o "Cheng, 2004 #12)] and candidate gene association studies commonly support ABCG2 (binding cassette (ABC), subfamily G, member 2 gene locates in a gout-susceptibility locus (MIM 138900) on chromosome 4q [[11](#_ENREF_11" \o "Cheng, 2004 #12)]) [[10](#_ENREF_10" \o "Matsuo, 2011 #11)]is highly involved in the susceptibility or pathogenesis of the gout.. ABCG2 is a high-capacity urate exporter and that nonfunctional mutations of ABCG2cause gout [[10](#_ENREF_10" \o "Matsuo, 2011 #11)]. Some findings imply that ABCG2 could be a major causative gene in Pacific regions [[1](#_ENREF_1" \o "Matsuo, 2009 #2)]. And demonstrated by a genome-wide.

The optimal method for considering different genetic models in association studies is not clear

ABCG2missense SNP rs2231142 which is leads to a glutamine-to-lysine amino acid substitution (Q141K) in exon5 [[12](#_ENREF_12" \o "Wang, 2010 #13)]. and some researchers[[1](#_ENREF_1" \o "Matsuo, 2009 #2),[5](#_ENREF_5" \o "Dehghan, 2008 #6),[8](#_ENREF_8" \o "Woodward, 2009 #9),[10](#_ENREF_10" \o "Matsuo, 2011 #11),[12](#_ENREF_12" \o "Wang, 2010 #13)] suggest that the SNP rs2231142 polymorphism was associated with gout, but different studies use different genetic models and have different results, so this research was attempted to explore the genetic model and acquire a more reasonable and useful result by meta-analysis with the model. Many searches reported the associated between SNPs and uric acid or gout, but few searches take care of the relationship between uric acid beta coefficients and gout odds ratios across the SNPs. As to consider the relationship, two SNPs (rs6449213 and rs16890979) in SLC2A9 which is both associated with uric acid and gout [[13](#_ENREF_13" \o "Yang, 2010 #43)] and rs2231142 were employed.

Current medical treatment could be focused on the discovered target genes influenced by SNPs.

**Materials and Methods**

**Search Strategy**

A systematic literature search was performed for articles regarding three SNP (rs2231142 in ABCG2, rs6449213 and rs16890979 in SLC2A9) associated with gout or uric acid. The EMBASE database and PubMed database were used simultaneously with the combination of terms “rs2231142”, “gout” or “uric acid”; “rs6449213”, “gout” or “uric acid”; “rs16890979”, “gout” or “uric acid”; “GWAS” “gout”; “ABCG2”, “gout” up to July 1, 2012. The search was performed without any restriction on language.

**Study selection**

Studies concerning the association of three SNPs associated with gout or uric acid were included if the following condition were met:⑴ any study about gout or uric acid; ⑵ any study describe the association of three SNPs with gout or uric acid; ⑶ the studies about gout reported the numbers of both controls and gout cases; ⑷ results were expressed as odds ratio(OR) or beta with 95% confidence intervals(CI); ⑸ the studies about gout were case-control or nested case-control ones.

**Methodological quality appraisal**

To identify high-quality studies, 2 authors (Dong and Guo) assess the quality of each study independently using a prefined scale (Table 1). Our quality scoring criteria were followed from other studies [[14-16](#_ENREF_14" \o "Guo, 2012 #47)] and included some features about gout. The criteria cover six factors: the type of gout, Hardy-Weinberg equilibrium (HWE), circumstance (including complication, hobbies and so on), case size, the source of control, genotyping. Disagreements were resolved through discussion. Scores ranged from the lowest zero to the highest ten. A study with the score lower than 6 was considered as “low-quality” ones, whereas a study not lower than 6 was considered as “high-quality” ones.

**Data Extraction**

Two investigators (Dong and Guo) screened titles, abstracts and full texts independently and blind to journal names, country, institutions, supporting organizations and funds. The differences between two investigators were resolved by discussion.

The following data from each study were extracted: first author’s name, published year, country of study, continent, ethnicity, HWE, number of case and control, the sex ratio in case and control population, mean age in case and control population, minor allele frequency (MAF) in case and control population, the source of control, quality score, genotyping method, gout type and other descriptions.

**Statistical Analysis**

Hardy-Weinberg equilibrium (HWE) in controls was calculated by chi-square goodness of fit test in our meta-analysis. If P<0.05, the tests were considered to be statistically significant.

Odds ratios (OR) and 95% confidence intervals (95% CI) were used to assess the strength of associations between rs2231142 with gout risk. The significance of pooled ORs was tested by Z test (P<0.05 was considered significant).OR1, OR2, and OR3 regarding rs2231142 were calculated for genotypes TT versus GG, GT versus GG, and TT versus GT, respectively. The relative relationship with OR1, OR2 and OR3 and P-value were determined as the most appropriate genetic model. If OR1=OR3≠1 and OR2 = 1(POR1 and POR3<0.05, POR2>0.05), then a recessive model is suggested. If OR1=OR2≠1 and OR3 =1(POR1 and POR2<0.05, POR3>0.05), then a dominant model is suggested. If OR2= 1/OR3≠1 and OR1=1(POR2 and POR3<0.05, POR1>0.05), then a complete overdominant model is suggested. If OR1>OR2>1 and OR1>OR3>1, or OR1<OR2<1 and OR1<OR3<1(POR1 and POR2 and POR3<0.05), then a codominant model is indicated, details see[[17](#_ENREF_17" \o "Thakkinstian, 2005 #14)] (Table 2).

The Q statistic was used to test for heterogeneity among the studies included in the meta-analysis [[18](#_ENREF_18" \o "Higgins, 2002 #51)]. A fixed-effects model, using Mantel–Haenszel (M-H) method [[19](#_ENREF_19" \o "Mantel, 1959 #53)], was used to calculate the pooled ORs when homogeneity existed on the basis of Q-test with p value no less than 0.1. By contrast, a random-effects model, using DerSimonian and Laird method (D+L) [[20](#_ENREF_20" \o "DerSimonian, 1986 #54)], was utilized if there was heterogeneity based on Q-test p value less than 0.1.

To explore sources of heterogeneity across studies, a meta-regression model was used too [[21](#_ENREF_21" \o "Thompson, 2002 #57)]. Some factors including sex, published year, HWE, continent, quality of study, numbers of individuals were tested by meta-regression in codominant model. Each progresses of meta-regression only for one factor. And those values of P\*(P-value for heterogeneity), I2, Tau2 and R2 were tested. If P\*<0.1 or I2 >25% was considered as the source of heterogeneity [[22](#_ENREF_22" \o "Higgins, 2003 #58),[23](#_ENREF_23" \o "Zheng, 2012 #59)].

Sensitivity analysis was implied, in which the meta-analysis estimates were computed after every one study being omitted in each turn [[17](#_ENREF_17" \o "Thakkinstian, 2005 #14)].

Finally, publication biases were assessed by performing funnel plots qualitatively, and estimated by Begg’s [[24](#_ENREF_24" \o "Begg, 1994 #56)] and Egger’s tests quantitatively [[25](#_ENREF_25" \o "Sterne, 2001 #52)].

Statistical analyses were mainly performed using STATA statistical software (Version 12.0) and R (Version2.15.1).Two-tailed test if P<0.05 were considered statistically significant, except where otherwise specified.

**Result**

**Literature search and study selection**

14 published articles [[1](#_ENREF_1" \o "Matsuo, 2009 #2),[5](#_ENREF_5" \o "Dehghan, 2008 #6),[8](#_ENREF_8" \o "Woodward, 2009 #9),[10](#_ENREF_10" \o "Matsuo, 2011 #11),[26-35](#_ENREF_26" \o "Tin, 2011 #15)] and one unpublished data included in our meta-analysis after meeting requirements. 17 case–control samples come from those articles support the data (the origin data is 11 and the processed data is 6 case–control samples) to the meta-analysis of the associations between rs2231142 with gout(Table 3) and 6 case–control samples about uric acid; respectively including 5 case–control samples support the processed data to the meta-analysis of the associations between rs6449213 and rs16890979 with uric acid; respectively including 7 case–control samples support the processed data to the meta-analysis of the associations between rs6449213 and rs16890979 with gout;

2 studies [[8](#_ENREF_8" \o "Woodward, 2009 #9),[33](#_ENREF_33" \o "Yamagishi, 2010 #24)] are deviated from HWE. But considering that the number of participants in the study was large and given that sensitivity analyses would be conducted, we remained those two studies in our meta-analysis. The corresponding characteristics were seen in Table 1. The flow chart of study selection was illuminated in Figure 1.

11 origin data through quality appraisal scored on the basis of predefined criteria. 7 origin data with the score no less than 6 which were consider “high-quality” ones. The others were called “low-quality” ones (Table 3).

**Genetic model identified**

OR1 (P value), OR2 (P value), and OR3 (P value) of rs2231142 for overall were 4.30 (0.000), 1.70(0.000), and 2.36 (0.000). All three P-value were less than 0.05, in addition that OR1>OR2>1 and OR1>OR3>1. So the other genetic models were excluded and the codominant model was suggested. To make the result more powerful, we identified genetic model in subgroup. Codominant model is also the most probably appropriate genetic model ( Table 4).

**Meta-regression analysis**

The result show P\* value of published year were 0.08(OR1) and 0.007(OR3), the value of I2 after meta-regression progress reduced to 21.51% (OR1) and 0.00% (OR3); P\* value of the number of individuals were 0.063(OR1) and 0.254(OR3) , the value of I2 were 18.33% (OR1) and 35.00% (OR3); P\* value of the others such as sex(0.67 in OR1, 0.386 in OR3), age(0.231 in OR1, 0.235 in OR3) were not significance (Table 5).

**Cumulative Meta-analysis**

Cumulative meta-analysis of SNP rs2231142 associations were conducted the assortment of published year (Figure 2). As shown in Figure 2, OR increased along of published year nearer.

**Subgroup analysis**

Our meta-analysis divided ethnicity and sex into different subgroup respectively. Ethnicities including caucasian, mongoloid and polynesian; sex contains male and female. The subgroup of ethnicity had different OR value, in OR1 (TT Vs GG) model, Caucasian, mongoloid and Polynesian respectively show OR value 2.80(P = 0.001), 4.56(P = 0.000) and 8.20(P = 0.000); in OR3 (TT Vs GT) model, Caucasian, mongoloid and Polynesian respectively show OR value 1.66 (P = 0.033), 2.54 (P = 0.001) and 3.66 (P = 0.000). And the P\*-value of heterogeneity became larger, in OR1 (TT Vs GG) model, Caucasian, mongoloid and Polynesian respectively show P\* value 0.173, 0.301 and 0.452 comparing the pool P\* value 0.072; in OR3 (TT Vs GT) model, Caucasian, mongoloid and Polynesian respectively show P\* value 0.500, 0.013 and 0.910 comparing the pool P\* value 0.094. Those results suggest ethnicity divided is important to acquire the real OR value and the population of Polynesian have the highest gout risk and the risk of gout in Caucasian is lowest (Figure 3).

The subgroup of sex in OR1 (TT Vs GG) model, the OR and P-value of male and female are much similar (4.02, P = 0.000; 4.20, P = 0.000). In OR3 (TT Vs GT) model, the OR of male and female are different (2.06, P = 0.003; 4.17, P = 0.033). But the OR 95%CI of male were be included in female’s both in OR1 and OR3 model (Figure 4). And for the value of P\*, sex not the source of heterogeneity especially in OR1 model.

**Sensitivity Analysis**

Meta-analyses were conducted repeatedly when every one study had been deleted. The results indicated that the estimates the meta-analysis results change before and after the deletion of each study. As shown in (S.Figure 4). All results indicated high stability of the results when every study was removed.

**Publication Bias Analysi**s

Publication bias was preliminarily examined by funnel plots qualitatively and estimated by Begg’s and Egger’s tests quantitatively. Its funnel plot (Figure 7) showed that dots nearly symmetrically distributed, predominantly within pseudo 95% confidence limits. P values were 0.876(OR1), 0.840(OR3) in Begg’s test and 0.755 (OR1), 0.450 (OR3) in Egger’s test, separately, also suggesting no publication bias.

**SNP influence uric acid and their relationship with gout**

All 6 meta-analysis are limited in the processed data and show the effect of per mutant allele copy increment to uric acid and gout. All of them have done in additive genetic model (mutant allele Vs wide allele).

17 studies were included in the meta-analysis about the association between rs2231142 and gout (Figure 5). The result indicating that OR is 1.83 (P = 0.000). The meta-analysis of 6 studies about rs2231142 and uric acid show the combine beta value is 0.23 (P = 0.000) (S.Figure 1). The combinational beta about rs6449213 and rs16890979 with uric acid both are -0.29 (P = 0.000) (S.Figure 2), and their combinational OR about gout were similar too (0.708, P = 0.000; 0.600, P = 0.000) (S.Figure 3).The relationship of three SNPs between uric acid and gout have been showed in figure 6. Across SNPs, per mutant allele copy increment influence the odds ratio for gout was highly correlated with the effect size for uric acid.

**Discussion**

In the past, only a few of studies chose to pool using a genetic model and fewer took the biologic rationales into consideration. In 2005, a simple methods were found to solve the problem [[17](#_ENREF_17" \o "Thakkinstian, 2005 #14)]. And we identified SNP rs2231142 genetic model through it, codominant model is most probably appropriate genetic model( Table 4). Comparing with other results in other genetic models (S.Table 1), the obvious difference could be found. Making choice of the genetic model is necessary for pooling population-based on molecular association studies.

In our meta-analysis, a statistically significant association between rs2231142 and gout (codominant model) could be found. And the effect of per mutant allele copy increment is significant (OR=1.83 and P = 0.000 in additive model). Even though the TT (OR=4.30, P = 0.000) and GT (OR=1.70, P=0.00) both are significant increase the risk of gout. But the effect of TT and GT are very different (TT Vs GT, OR=2.36; P = 0.000) and TT is stronger than GT to induce the gout risk. In different ethnicities the OR is difference and ethnicity is the source of heterogeneity. So in the treatment or research disease like gout the different plan should be adopted to adjust the difference of different gene type and ethnicities.

What’s more, a factor for gout is very important and it could answer some problems we don’t solve by gene research, it is environment. Some studies have shown the association between environment and gout risk [[36-42](#_ENREF_36" \o "Choi, 2004 #30)]. So in our quality scoring criteria the habits and customs included. So this is the first quality scale was made for gout. Of course, in the study of the association between allele frequency and the prevalence [[43-46](#_ENREF_43" \o "Klemp, 1997 #36)], the finding show an amazing result (S.Figure 5). Why the MAF don’t show a linear association with the gout prevalence, we think the answer may be environment.

In our study, sex isn’t the sources of heterogeneity in both meta-regression and subgroup analysis, and in subgroup research the pool OR value of male and female have no significant differences. Those suggest the sex have no effect in the association between rs2231142 and gout risk. But some studies have shown the association between them and gout or uric acid [[5](#_ENREF_5" \o "Dehghan, 2008 #6),[32](#_ENREF_32" \o "Phipps-Green, 2010 #23),[47](#_ENREF_47" \o "Kolz, 2009 #42)]. For example, Dehghan[[5](#_ENREF_5" \o "Dehghan, 2008 #6)] proved it that The *ABCG2* Q141K variant have stronger effect in men than women in both whites and blacks but Choi[[48](#_ENREF_48" \o "Choi, 2010 #41)]have question to the situation. His point of view that the OR for gout among women from this study was not significant could be due to the lower prevalence of gout among women than men as well as the use of a less specific gout definition in this study [[48](#_ENREF_48" \o "Choi, 2010 #41)]. And we think this may be a cause for the result. So rs2231142 can be a signal for gout diagnosis in both male and female. And the result reminded us gout genetic risk factors in female as important as male. As for age, we only know it is associated with uric acid [[47](#_ENREF_47" \o "Kolz, 2009 #42)] and in our study suggest it have no relationship with gout by meta-regression.

High level of uric acid could increase the risk of gout. Recently the study made by Yang [[13](#_ENREF_13" \o "Yang, 2010 #43)] suggested a causal relationship between serum urate and gout with eight SNPs. And in our study, three new important SNPs were chosen to find the relation between uric acid and gout. The result showed a linear relationship between uric acid and gout and suggested SNPs cause gout through the change of uric acid level. Those findings call attention to the level of uric acid in gout prediction and treatment.

Certainly, some unavoidable limitations in our meta-analysis could be not ignored. Firstly, the genetic model we choose may be not the real genetic model. The genetic model of gene is very difficult to indentify, because many gene associate with some phenotypes but not one phenotype and the gene expression isn’t clear. So we try to find the most probably appropriate genetic model. Secondly, some information about studies we selection is less provided. Some studies not support the original data, so we can do few researches in detail. What’s more, Gout caused by many factors including genetic and environment, so one SNP’s study can’t explain all.

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