The Association between ABCG2 Q141K Polymorphism and Gout Risk in 18553 individuals: A Systematic Review and Meta-Analysis

**Abstract**

***Introduction***: Original studies employ different genetic models in association analysis induce different results especially conflicting results about the role of sex modify rs2231142 association with gout risk. Whether divergence of the association existing among ethnicity or not. A meta-analysis is needed to provide a systematic review of the published findings.

***Methods***: Desirable articles published before July 1, 2012 were extracted and register into databases. The quality of each study was scored based on the predefined criteria. Genetic model identified through stratification analysis then a meta-analysis including all publically available data was preformed to further test the association between rs2231142 and gout risk in subgroups. Potential sources of heterogeneity were sought out via stratification analysis and meta-regression analysis.

***Results***: Ultimately, 11 case–control researches in 7 articles were eligible for the meta-analysis of ABCG2 Q141K SNP. Codominant model is the most probably appropriate genetic model to interpret the susceptibility cause. And those results reveal the rs2231142 mutant increase gout risk seriously (OR=4.30, P = 0.000 in TT versus GG; OR=2.36, P = 0.000 in TT versus GT; OR=1.70, P = 0.000 in GT versus GG), and the TT genotype is much stronger than GT genotype (OR=2.36, P = 0.000 in TT versus GT). Our findings indicate no evidence for both sex and age modify the association between rs2231142 and gout risk. But the association show special among ethnicity. Meta-regression analysis of rs2231142 suggests the published year is a very important source of heterogeneity especially in TT versus GT model.

***Conclusions***: These findings highlight a predictive role for rs2231142 polymorphisms associated with gout risk. This association is modified by ethnicity not sex and its possible potential denotation for prevention, prediction and treatment of gout.

**Introduction**

Gout is often known as the ''Disease of Kings'' [[1](#_ENREF_1)]. Gout is one of the most common forms of arthritis [[2](#_ENREF_2), [3](#_ENREF_3)] and a common disease with a genetic predisposition [[4](#_ENREF_4)]. Gout currently affects over 700,000 adults in the United Kingdom and nearly 3 million individuals in the United States [[5](#_ENREF_5)], The prevalence of gout is about 1 to 2% in males, in Japan and other countries [[1](#_ENREF_1)].And the prevalence and incidence of gout are increasing in some epidemiological studies [[6](#_ENREF_6)]. Reduced excretion of urate by the kidney is the main cause for elevated urate levels [[7](#_ENREF_7)] and lead to gout [[8](#_ENREF_8)]. Other known risk factors for gout including hyperuricemia, obesity, hypertension, diuretic use, and alcohol consumption [[9](#_ENREF_9)].

Recent GWAS of SUA (serum uric acid) and gout both identified several transporter genes, such as ABCG2 [[10](#_ENREF_10)]–binding cassette (ABC), subfamily G, member 2 gene locates in a gout-susceptibility locus (MIM 138900) on chromosome 4q [[11](#_ENREF_11)]. ABCG2missense SNP rs2231142 which is leads to a glutamine-to-lysine amino acid substitution (Q141K) in exon5 [[12](#_ENREF_12)]. Previous study reported that ABCG2 variant (Q141K) have significantly lower ABCG2 protein in red cells than wide-type ABCG2 gene and one allele mutant reduce about 50% ABCG2 protein expression[[13](#_ENREF_13)]. In addition that Q141K variant also leads to reduce ABCG2 ATPase activity in some reports [[14](#_ENREF_14), [15](#_ENREF_15)]. Recently study identifies the importance role of Q141 residue in nucleotide-binding domain stability [[16](#_ENREF_16)].

Some associated researches [[1](#_ENREF_1), [5](#_ENREF_5), [8](#_ENREF_8), [10](#_ENREF_10), [12](#_ENREF_12)] suggest that the SNP rs2231142 polymorphism associated with gout. But different studies use different genetic models and bring about different results, for example, recessive model employed in Phipps-Green’s study [[17](#_ENREF_17)] but additive genetic model was assumed in Zhang’s study [[18](#_ENREF_18)]. So this research was attempted to explore the most appropriate genetic model and acquire a more reasonable and useful result by meta-analysis with it. Epidemiologic study explain that men have more gout risk than women [[19](#_ENREF_19)], but genetic analysis got conflicting results about the sex affect the association between rs2231142 and gout risk [[5](#_ENREF_5), [17](#_ENREF_17), [18](#_ENREF_18)]. So a meta-analysis is needed to solve this confliction. What’s more, the prevalence of gout is different in different ethnicities, and the diversity of the association between rs2231142 and gout risk is important to predictive and treatment.

**Materials and Methods**

**Search Strategy**

A systematic literature search was performed for articles regarding the SNP rs2231142 in ABCG2 associated with gout risk. The EMBASE database and PubMed database were used simultaneously with the combination of terms “rs2231142”, “gout” or “hyperuricemia” or “uric acid” or “urate”; “ABCG2”, “gout” or “hyperuricemia” or “uric acid” or “urate”; “GWAS”, “gout” or “uric acid” or “urate” up to July 1, 2012. The search was performed without any restriction on language. Because of the number of searched articles is too large, we selected 146 articles by judging abstract to next analysis.

**Study selection**

Studies concerning the association of SNP rs2231142 associated with gout were included if the following condition were met: ⑴ any studies about gout; ⑵ any studies describe the association between SNPs and gout; ⑶ any studies about gout reported the number of both controls and gout cases; ⑷ results were expressed as the number of each genotype; 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 predefined scale (Table 1). Our quality scoring criteria followed from other studies [[20-22](#_ENREF_20)] and including 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, methods for 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 the others were considered as “high-quality”.

**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 in study, 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 association between rs2231142 and 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 used to determine 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 an 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[[23](#_ENREF_23)] (Table 2).

The Q statistic was used to test for heterogeneity among the studies included in the meta-analysis [[24](#_ENREF_24)]. A fixed-effects model, using Mantel–Haenszel (M-H) method [[25](#_ENREF_25)], 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) [[26](#_ENREF_26)], 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 [[27](#_ENREF_27)]. Some factors including sex, published year, HWE, continent, quality of study, number of individuals and ethnicity were tested by meta-regression analysis in codominant model. Each progresses of meta-regression just for one factor. And those values of P\* (P-value for heterogeneity), I2, Tau2 and R2 were tested. If P\*<0.1 and I2 >25% was considered as the source of heterogeneity [[28](#_ENREF_28), [29](#_ENREF_29)].

Sensitivity analysis was implied, in which the meta-analysis estimates were computed after every one study being omitted in each turn [[23](#_ENREF_23)].

Finally, publication biases were assessed by performing funnel plots qualitatively, and estimated by Begg’s [[30](#_ENREF_30)] and Egger’s tests quantitatively [[31](#_ENREF_31)].

Statistical analyses were mainly performed using STATA statistical software (Version 12.0) and R (Version2.15.2). Two-tailed test if P<0.05 were considered as statistically significant, except where otherwise specified.

**Result**

**Literature search and study selection**

6 published articles [[1](#_ENREF_1), [8](#_ENREF_8), [17](#_ENREF_17), [32-34](#_ENREF_32)] and one unpublished data included in our meta-analysis after meeting requirements. 11 case–control studies come from those articles support the data to explore the association between rs2231142 and gout (Table 3, S.Table 1) in meta-analysis. The flow chart of study selection was illuminated in Figure 1.

2 studies [[8](#_ENREF_8), [33](#_ENREF_33)] 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 3.

11 origin data in studies 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 (S.Table 1).

**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 (Table 2). 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 (TT versus GG; GT versus GG; TT versus GT) also be the most probably appropriate genetic model (Table 4).

**Meta-regression analysis**

The result show P\* (P-value for heterogeneity) value of published year were 0.08 (TT versus GG) and 0.007 (TT versus GT), the value of I2 after meta-regression progress reduced to 21.51% (TT versus GG) and 0.00% (TT versus GT) (Table 5). Those suggest published year may be a source of heterogeneity. The diversity of ethnicity can explain 77% of all source of heterogeneity in TT versus GG model and 1.67% of all source of heterogeneity in TT versus GT model. So ethnicity brings heterogeneity to our data. P\* value of the number of individuals in TT versus GG model was 0.063 and product 65.91% heterogeneity; P\* value of the others such as sex (0.67 in TT versus GG, 0.386 in TT versus GT), age (0.231 in TT versus GG, 0.235 in TT versus GT), HWE (0.245 in TT versus GG, 0.656 in TT versus GT) were not significance. In GT versus GG model, we didn’t find factors create heterogeneity. The P\*-value 0.094 is similar to 0.1 may be a major reason.

**Cumulative Meta-analysis**

Cumulative meta-analysis of SNP rs2231142 association was conducted the assortment of published year (Figure 2). The result show us that OR increasing in pace with published year nearing in both model. The reason that OR increasing significantly in merely four years (2009-2012) may be the percent of T allele growing (Figure 3).

**Subgroup analysis**

Our meta-analysis divided ethnicity and sex into different subgroup respectively (Figure 4, Figure 5). Ethnicities including caucasian, mongoloid and polynesian; sex contains male and female. The subgroup of ethnicity had different OR value, in TT versus 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) (Figure 4A); in TT versus 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) (Figure 4B). And all the P\*-value of subgroup became larger and greater than 0.1 in TT versus GG model, Caucasian, mongoloid and Polynesian respectively show P\*-value 0.173, 0.301 and 0.452 comparing the pool P\* value 0.072 (Figure 4A); in TT versus GT model, Caucasian, mongoloid and Polynesian respectively show P\* value 0.500, 0.013 and 0.910 comparing the pool P\* value 0.094 and two P\* greater than 0.1 (Figure 4B). Those results also suggest ethnicity may be a source of heterogeneity and subgroup of ethnicity is an important role to acquire the real OR value. Besides, the ethnicity of Polynesian show the highest gout risk but the risk of gout in Caucasian is lowest in our study.

The subgroup of sex in TT versus GG model, both OR and P-value between male and female are much similar (4.02, P = 0.000; 4.20, P = 0.000) (Figure 5A). In TT versus GT model, the OR of male and female are different (2.06, P = 0.003; 4.17, P = 0.033) (Figure 5B). But the OR 95%CI of male were included in female’s both in TT versus GG and TT versus GT model. And in TT versus GG model the pool value of P\* is 0.470 greater than 0.1, divided sex makes the P\*-value become less (0.392 in male, 0.338 in female). So we believe that sex is not a factor to modify the association between rs2231142 and gout risk.

**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 1). All three model (TT versus GG, TT versus GG and GT versus GG) 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 showed that dots nearly symmetrically distributed, predominantly within pseudo 95% confidence limits. P values were 0.876 (TT versus GG), 0.755 (TT versus GT), 1.000 (GT versus GG) in Begg’s test and 0.840 (TT versus GG), 0.450 (TT versus GT), 0.503 (GT versus GG) in Egger’s test, separately, also suggesting no publication bias.

**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 this problem [[23](#_ENREF_23)]. Codominant model is SNP rs2231142 most probably appropriate genetic model through it in subgroup analysis (Table 4). Comparing with other results in other genetic models (S.Table 2), the obvious difference could be found. For example, in dominant model the association between rs2231142 and gout is not significance in female but significance in male may mislead researchers. 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 risk could be found in codominant model (P = 0.000). And the effect of per mutant allele copy increment is significant (OR=2.36, P = 0.000 in TT versus GT; OR=1.70, P = 0.000 in GT versus GG) (Figure 4A, C). Even though the TT (OR=4.30, P = 0.000) and GT (OR=1.70, P=0.000) both are significant increase the risk of gout. But the effect of TT is stronger than GT to induce gout (TT versus GT, OR=2.36; P = 0.000) (Figure 4B).

Meta-regression result suggests published year is an important factor brings about heterogeneity (Table 5). Published year explains almost 100% source of heterogeneity in TT versus GT model and 59.01% heterogeneity in TT versus GG. Cumulative meta-analysis show us that OR increasing in pace with published year nearing (Figure 2). The reason that OR increasing significantly in merely four years (2009-2012) may be the percent of T allele growing and that possible owe to developing technology of sequencing and Enhanced awareness of medical in public (Figure 3).

Both in meta-regression analysis and subgroup analysis, we detect ethnicity is one major source of heterogeneity particularly in TT versus GG model (Table 5, Figure 4A). In this model 77% heterogeneity come from ethnicity diversity. However in three ethnicities, rs2231142 associated with gout risk significantly (Caucasian, P=0.001; mongoloid, P=0.000; Polynesian, P=0.000). Based on those different OR in different ethnicities makes sense to suggest the gout risk divergence among ethnicity. Forasmuch for different ethnicities, special prevention, prediction and treatment of gout should be utilized. And in the research complex disease like gout the different plan should be adopted to adjust the difference of gene and ethnicity.

In our study, sex isn’t a source of heterogeneity in both meta-regression and subgroup analysis, and the pool OR value between male and female have no significant difference (Table 5, Figure 5). Those reveal the sex have no effect in the association between rs2231142 and gout risk. As for some studies have shown the difference between male and female [[5](#_ENREF_5), [17](#_ENREF_17), [18](#_ENREF_18)] possibly mislead by case number or others genetic models. For example, Dehghan[[5](#_ENREF_5)] proved it that The ABCG2Q141K variant have stronger effect in men than women in both whites and blacks but Choi[[35](#_ENREF_35)]have question to the situation. His point of view that less female gout than male definition in this study causes OR for gout among women was not significant [[35](#_ENREF_35)]. So rs2231142 can be a signal for gout diagnosis in both male and female. And this result reminded us gout genetic risk factors in female as important as male.

Epidemiologic study suggest the prevalence of gout increase with age [[19](#_ENREF_19)]. But in our study we didn’t find any evidences support age affect gout in rs2231142 by meta-regression analysis (P = 0.231 in TT versus GG; P = 0.944 in TT versus GT; P = 0.235 in GT versus GG) (Table 5). We believe this situation may be caused by the year changes enhance environment factors influence on gout risk.

Certainly, some unavoidable limitations in our meta-analysis could not be 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 not one phenotype and the gene expression isn’t clear. So we attempt to use the most probably appropriate genetic model in our meta-analysis. 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 like genetic and environment, one SNP’s study can’t explain all. As shown in Figure 6, gout prevalence can’t correspond with the percent of T allele, reminding the limit one gene research again.

**Conclusions**

These findings suggest a predictive role for rs2231142 polymorphisms associated with gout susceptibility and this association isn’t modified by sex and age but affected by ethnicity diversity. This study supports possible potential denotation for prevention, prediction and treatment of gout.

**Reference**

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