Original Article

An Exploration of ABCG2 and SLC2A9 Gene Interactions with Gout

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Background: Currently, there is no systematic analysis of single nucleotide polymorphisms (SNPs) in the urate transporter genes (ABCG2 and SLC2A9), and the influence of their combination and gene-gene (G×G) interactions on gout is still unknown in the Thai population.

Objective: To investigate the interaction between ABCG2 and SLC2A9 with gout.

Materials and Methods: A matched case-control study with 116 Thai adults (58 gout patients and 58 control subjects) was done. Genotyping using a TaqMan SNP Genotyping Assays was performed. G×G interactions for gout risk were analyzed using an interaction analysis in multiple conditional logistic regression.

Results: The results show that the rs2231142 (G/T+T/T) variants in ABCG2 was associated with gout. On the contrary, the rs2280205 (G/A+A/A) and rs6820230 (C/T–T/T) variant in SLC2A9 were not associated with gout. The result indicated that the participants carrying ABCG2 variant with SLC2A9 wild-type (i.e., original base pairs) had a significant association with gout. The present study results also revealed that epistatic interaction pairs (rs2231142:rs6820230 and rs2231142:rs2280205) were strongly associated with gout.

Conclusion: The authors concluded that the ABCG2 and SLC2A9 interactions were a significant association with gout. The stronger combined effect of SNPs in the ABCG2 and SLC2A9 genes via G×G interaction may help to predict gout risk and its prognosis. However, further studies with larger sample sizes should be performed to confirm these results.

Keywords: Gene-gene interactions, Gout, ABCG2 gene, SLC2A9 gene

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Serum uric acid (SUA) is the major end-product of purine metabolism in humans, and hyperuricemia (HUA) can lead to a variety of disorders including, hypertension, metabolic syndrome, diabetes mellitus, cardiovascular disease, and a painful type of arthritis called gout[1-5]. Most of the epidemiologic and genetic research on HUA has been conducted in populations of European and Asian ancestries[6-8]. Importantly, the prevalence of HUA in the Thai population is estimated between 10.6% to 24.4%, being significantly more common in males than females[9,10]. Previous epidemiological studies had found both environmental exposure, such as use of diuretics or alcohol consumption together with genetic factors including male, obesity, hypertension, insulin resistance, type 2 diabetes, dyslipidemia, and metabolic syndrome, play the important roles in the etiology of HUA and gout[11-13]. There are several genomic loci associated with HUA and gout[14-17]. However, strong genetic variants in the SLC2A9 and ABCG2 were associated with gout in Asians[14,18-22]. In a subsequent functional study, glucose transporter 9 (GLUT-9), encoded by SLC2A9 gene, is the molecule needed to reabsorb uric acid in kidneys, but that protein encoding function may be lost from mutation of the gene[23]. GLUT-9 plays a critical role in reabsorption of filtered urate in

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the proximal tubules and imbalances can cause renal hypouricemia[23-26]. Expression of SLC2A9 might interfere with uric acid metabolism, which associated with HUA and gout[27]. A previous study also suggests that mono-sodium urate crystal-induced arthritis was developed by SLC2A9 expressed in human articular chondrocytes[28]. In addition, the ABCG2 encodes for a urate transporter that mediates urate excretion in the kidney, but reduced function from mutation leads to reduced ability to excrete uric acid. ABCG2 variants are also expressed in the liver and the apical membrane of epithelial cells in the small intestine and might be involved in the extrarenal excretion of uric acid[23]. However, the gene polymorphism influence of both SLC2A9 and ABCG2 on the development of gout needs to be investigated within different Asian populations, especially in Thai population. Currently, there is no systematic analysis of single nucleotide polymorphisms (SNPs) in these two genes, as well as the influence of their combination and gene-gene (G×G) interactions on gout risk. Therefore, authors sought to investigate the potential effect of ABCG2-SLC2A9 interactions with gout by performing a comprehensive association analysis in a matched case-control study in the Thai population.

Materials and Methods

Study design and participants

This matched case-control study used data from the genetic variation of urate transporter genes in HUA and gout among the Thai population database, from which the present study aimed to show a preliminary association of the genetic variations of urate transporter genes in HUA and gout among the Thai population. The participants were selected from people aged 25 and over years old who attended at the HRH Princess Maha Chakri Sirindhorn Medical Center. Patients who were diagnosed with gout according to the Rome criteria were included in the present study. Inclusion criteria for control subjects were normal with SUA less than 7 mg/dL in males and less than 6 mg/dL in females, no evidence of gout, and no signs and symptoms with gout. Patients and control subjects with cardiovascular disease due to acute heart disease, kidney disease or kidney dysfunction, cancer, or other stress, or used anti-depression drugs were excluded from the study. Patients and control subjects were also excluded if they were pregnant or lactating, volunteered for withdrawal, or were not available for the study. There were 269 cohort members who had data about the genetic variation of urate transporter genes in HUA and gout among the Thai population project. The sample size was calculated using Stata, version 14.0 (StataCorp LP, College Station, TX, USA). A previous study reported that 46.7% of the patients had the genotype with gout and odds ratio was 3.32[21]. Thus, the calculated sample size was 58 patients per group to achieve 80.18% power at a 5% significant level. One matched gout case (58 cases) per control group (58 controls) was randomly selected and matched by gender and age (±10 years) with the control group. The ethical committee of the Khon Kaen University gave ethical approval for the present study (HE612369). All participants provided written informed consent.

Clinical and biochemical data

Clinical and biochemical data were collected from all subjects. Data included the patient age and body mass index (BMI). The obesity status of the adults was classified based on BMI cut-off points for Asian populations[29]. Systolic blood pressure (SBP) and diastolic blood pressure (DBP), total cholesterol (TC), triglyceride (TG), and high- and low-density lipoprotein cholesterol (HDL-C and LDL-C, respectively) were collected using data extraction form.

Selection of genotyping

The two common variants of the SLC2A9, namely rs2280205 (C>T) and rs6820230 (G>A), and a common rs2231142 (C>A) variants in ABCG2 gene were genotyped in all participants. DNA was extracted from peripheral blood leucocytes using DNA extraction kit (QIAamp DNA Mini Kit®, Qiagen). DNA samples were stored at –20°C until use. Twenty-five µl PCR volume mixture consisted of 5 µl of DNA, 1X TaqMan SNP genotyping assays kit (Applied Biosystems, USA) and 1X CAPITAL™ qPCR Probe Mix included ROX passive reference (BiotechRabbit, Germany). Each reaction was performed in StepOnePlus® Real-time PCR Systems (Applied Biosystems, USA), which thermal profile was 3 minutes at 95°C, 45 cycles of 15 seconds at 95°C, and 30 seconds at 60°C.

Statistical analysis

Statistical analyses were performed using Stata, version 14.0 (StataCorp LP, College Station, TX, USA). Genotype and allele distributions for polymorphism were determined by the Hardy-Weinberg equilibrium (HWE)[30]. The associations between SNP pairs with gout were measured by conditional logistic regression. A p-value of less than

Table 1. Baseline characteristics among gout cases and control subjects

Parameters	Gout (n=58) Mean±SD	Control (n=58) Mean±SD	p-value
Sex (female/male), n	10/48	10/48	-
Age (years)	60.58±13.23	56.84±14.58	0.151
Body mass index (kg/m^2)	25.77±4.97	24.63±3.53	0.106
Systolic blood pressure (mmHg)	142.57±19.00	130.34±13.29	<0.001
Diastolic blood pressure (mmHg)	81.88±12.21	80.60±10.51	0.548
Total cholesterol (mg/dL)	191.59±54.19	205.34±41.69	0.030
Triglycerides (mg/dL)	157.89±103.42	140.74±76.46	0.391
HDL-C (mg/dL)	53.34±23.32	55.40±10.95	0.086
LDL-C (mg/dL)	103.75±46.58	124.50±37.49	<0.001
Fasting plasma glucose (mg/dL)	107.64±27.03	108.24±44.62	0.070
Serum uric acid (mg/dL)	6.15±2.31	6.18±1.27	0.473

HDL-C=high density lipoprotein cholesterol; LDL-C=low density lipoprotein cholesterol; SD=standard deviation

5% were considered statistically significant.

Results

One hundred sixteen subjects divided into study and control group, which each group included 48 males and 10 females, were enrolled in the present study. There was no significant difference in age, BMI, DBP, TG, HDL-C, fasting plasma glucose, and SUA. However, the SBP in gout cases was higher than in healthy controls. In addition, the LDL-C and TC were lower than in healthy controls, possibly because most of the gout cases were likely to have received a cholesterol-lowering treatment such as simvastatin (Table 1).

All SNPs in gout patients and control subjects were not found to have a significant difference in HWE (Table 2). After adjusted for all confounders, the rs2231142 (G/T+T/T) variants in ABCG2 were determined to have significantly associated with gout, adjusted OR was approximately 5-fold. Furthermore, the rs2280205 (G/A+A/A) and rs6820230 (C/T+T/T) variant in SLC2A9 were not associated with gout (Table 3). Next, the present study results showed a significant association of the two SNP pairs rs2231142 variant plus rs2280205 (G/G) and rs2231142 variants plus rs2280205 variant with increased gout risk (Table 4). Moreover, the combinations of rs2231142 variant plus rs6820230 (C/C) were only significantly related to gout, but the combinations of rs2231142 variants plus rs6820230 variant did not associate. Meanwhile, there were no interactions between the polymorphisms of rs2280205 plus rs6820230 in SLC2A9 on gout risk. When compared with reference participants who had ABCG2 wild-type [i.e., rs2231142 (G/G)] and SLC2A9 wild-type [i.e., rs6820230 (C/C) and rs2280205 (G/G)], the authors found that the rs2231142 variants plus SLC2A9 wild-type were significantly associated with gout. The rs2231142 variants plus SLC2A9 (rs6820230 and rs2280205) variants were strongly associated with gout (Table 4).

Discussion

In the present study matched the cases and controls in a Thai population. The findings indicate that dysfunctional rs2231142 genotype is a major cause of gout, conferring an adjusted odds ratio of 4.34. The rs2231142 variants are associated with gout because these SNPs is a high capacity urate transporter, about 53% less urate transport activity by encoded of ABCG2 protein, which physiologically excretes urate for the regulation of SUA from the tubules, thus leading to a lowered renal clearance of urate and promoting HUA[31]. The rs2231142 variant plays a critical role in the development of gout[31,32]. Previous studies suggest that the rs2231142 variant influence gout susceptibility in Caucasian people[32,33], Western Polynesians[34], Asians[35], the Chinese Han population[36], Japanese[22], and the population of Taiwan[18]. Therefore, the present results, combined with those from several previous studies, suggest that the rs2231142 variants led to higher the risk of gout in Thai population as it does in other populations. Although the present study results indicated that both of the GLUT-9 encoded by SLC2A9 were not associated with gout, several

Table 2. Genotypes and alleles distribution among gout cases and control subjects

Gene	SNPs	Genotypes and alleles	Frequencies; n (%)		p-value for HWE
			Gout (n=58)	Control (n=58)	
SLC2A9	rs2280205	G/G	35 (60.34)	39 (67.24)	0.280
		G/A	20 (34.48)	15 (25.86)	
		A/A	3 (5.17)	4 (6.90)	
		G/A+A/A	23 (39.66)	19 (32.76)	
		Allele, G (%)	90 (78.00)	93 (80.00)	
		Allele, A (%)	26 (22.00)	23 (20.00)	
SLC2A9	rs6820230	C/C	48 (82.76)	52 (89.66)	1.000
		C/T	10 (17.24)	6 (10.34)	
		T/T	0 (0.00)	0 (0.00)	
		C/T+T/T	10 (17.24)	6 (10.34)	
		Allele, C (%)	106 (91.00)	110 (95.00)	
		Allele, T (%)	10 (9.00)	6 (5.00)	
ABCG2	rs2231142	G/G	15 (25.86)	41 (70.69)	0.670
		G/T	32 (55.17)	16 (27.59)	
		T/T	11 (18.97)	1 (1.72)	
		G/T+T/T	43 (74.14)	17 (29.31)	
		Allele, G (%)	62 (53.00)	98 (84.00)	
		Allele, T (%)	54 (47.00)	18 (16.00)	

HWE=Hardy Weinberg equilibrium test; SNPs=single nucleotide polymorphisms; G/G and C/C=normal homozygotes or wild-type; G/A, C/T, and G/T=mutant heterozygotes; A/A and T/T=mutant homozygotes

Table 3. Odds ratio for the genetic risk factors association between 3 SNPs and gout risk in dominant model

Gene	SNPs	Frequencies; n (%)		OR	Adj OR (95% CI)[a]	p-value
		Gout (n=58)	Control (n=58)			
SLC2A9	rs2280205					
	• G/G	35 (60.34)	39 (67.24)	1.00		
	• G/A+A/A	23 (39.66)	19 (32.76)	1.36	1.77 (0.40 to 7.84)	0.440
SLC2A9	rs6820230					
	• C/C	48 (82.76)	52 (89.66)	1.00		
	• C/T+T/T	10 (17.24)	6 (10.34)	1.80	3.00 (0.50 to 17.91)	0.290
ABCG2	rs2231142					
	• G/G	15 (25.86)	41 (70.69)	1.00		
	• G/T+T/T	43 (74.14)	17 (29.31)	4.71	4.34 (1.41 to 13.33)	<0.001*

Adj OR=adjusted odds ratio; CI=confidence interval; OR=odds ratio; SNPs=single nucleotide polymorphisms

[a] Adjusted odds ratio was used conditional logistic regression adjusted for baseline body mass index, triglyceride level, HDL cholesterol level, blood pressure, and fasting plasma glucose; * p<0.05 is considered statistically significant

previous studies identified that the SLC2A9 may causally be associated with SUA level in the Sardinia and Chianti cohorts[37] and the Framingham Heart Study[32,38]. Not unexpectedly, the SLC2A9 variants are associated with gout in several ethnicities, namely Caucasian, Solomon Island, New Zealand Maori and Pacific Island, Chinese, with odds ratios from 1.3 to 5.0[21,32,33,38-40]. Moreover, the functional study demonstrated that the SLC2A9 is also the molecule to reabsorb uric acid in kidneys, but that loss of function from mutation in this gene causes renal hypouricemia and plays an essential role of GLUT-9 in reabsorption

Table 4. The best gene-gene interaction models, as identified by multiple conditional logistic regression

Best combination	OR[a]	Adj OR (95% CI)[b]	p-value
SNP-SNP term			
rs2231142-rs2280205			<0.001*
• G/G-G/A+A/A	0.29	0.36 (0.03 to 4.25)	
• G/T+T/T-G/G	3.05	5.52 (1.31 to 23.28)	
• G/T+T/T-G/A+A/A	5.19	6.35 (1.22 to 33.19)	
rs2231142-rs6820230			0.078
• G/G-C/T+T/T	14.39	14.52 (0.88 to 23.96)	
• G/T+T/T-C/C	11.94	19.53 (3.83 to 99.54)	
• G/T+T/T-C/T+T/T	5.56	9.74 (0.91 to 20.11)	
rs2280205-rs6820230			0.285
• G/G-C/C+T/T	2.49	2.24 (0.49 to 10.14)	
• G/A+A/A-C/C	1.65	1.86 (0.70 to 4.92)	
• G/A+A/A-C/T+T/T	1.28	1.88 (0.09 to 39.19)	
Gene-gene term			
ABCG2-SLC2A9[c]			<0.001*
• No-Yes	2.30	2.26 (0.36 to 14.08)	
• Yes-No	6.05	9.95 (1.83 to 54.23)	
• Yes-Yes	8.39	12.36 (2.39 to 63.90)	

OR=odds ratio; Adj OR=adjusted odds ratio; CI=confidence interval; SNPs=single nucleotide polymorphism

[a] Odds ratio performed by using simple conditional logistic regression; [b] Adjusted odds ratio performed by using multiple conditional logistic regression adjusted for baseline body mass index, triglyceride level, HDL cholesterol level, blood pressure, and fasting plasma glucose; [c] ABCG2 "No" was rs2231142 G/G wild-type, ABCG2 "Yes" was rs2231142 G/T+T/T variants, SLC2A9 "No" was rs6820230 C/C and rs2280205 G/G wild-type, SLC2A9 "Yes" was rs6820230 C/T+T/T and rs2280205 G/A+A/A variant; * p<0.05 is considered statistically significant

of filtered urate proximal tubules[23-26].

Even though the authors' single locus effects results found that the rs2231142 plays a role in a genetic risk factor for gout occurrence, it does not for the other rs2280205 and rs6820230 in SLC2A9. Gout is a complex disorder caused by the complement of inherited genetic risk variants. Several previous studies identified that the two genetic variants in SLC2A9 and ABCG2 were strongly associated with gout risk in Asian region[14,15,18-20,22,41]. However, the influence of their combination and SNP-SNP interactions on gout risk is not known. Therefore, the current study showed a significant association of the rs2231142 variant plus rs2280205 (G/G), and rs2231142 variants plus rs2280205 variant, which increased gout risk. Moreover, the adjusted odds ratios for these combinations reached 5.52 and 5.19, respectively. The combination of rs2231142 variant plus rs6820230 (C/C) was significantly related to an increased risk of gout, but there were no associations between the combinations of rs2231142 variant plus rs6820230 variant with gout risk. Meanwhile, there were no interactions between the polymorphisms of rs2280205 plus rs6820230 in SLC2A9 on gout risk. The present study results also found that polymorphism in the SLC2A9 revealed an associated effect dependent on rs2231142 variant. For example, polymorphisms of rs2280205 that regulates SLC2A9 function showed an additive significant association with gout in those with rs2231142 genotypes. The present study suggests that the SLC2A9 interacts with rs2231142 genotypes in the development of gout.

On the other hand, the authors examined the interaction between a number of biologically plausible polymorphisms in different genes that are involved in a wide range of gout-related processes, not just SNPs in a single gene or in genes acting on a specific pathway. The present study results demonstrated that the participants carrying the ABCG2 variant with SLC2A9 wild-type had an increased susceptibility to gout, and this was higher genetic risk still in ABCG2 variant with SLC2A9 variant. Although the observed interactions have not been previously reported, some studies showed renal HUA was caused by dysfunction in the SLC2A9 via its decreased urate reabsorption on the renal proximal tubules[23-26]. Here, the current results demonstrate that those with mutations in both ABCG2 and SLC2A9 genes cause an additive interaction effect for gout occurrence. The present results also confirm the notion that G×G interactions could facilitate the understanding of the additional missing heritable components of gout risk, possibly through interplay in several pathways contributing to gout etiology. To further confirm this result, gene transcripts of these two genes were examined.

The present study is the first to show the possible associations between the main joint effect of the polymorphisms in SLC2A9 and ABCG2 on gout in the Thai population. However, the current study has some limitations, which should be considered. Firstly, the present findings are based on a small number of case subjects, and the replication in a larger study is unclear and so should be interpreted with caution. Future large independent studies are warranted to further validate the present study results. Secondly, the authors only studied two SNPs of SLC2A9 and one of ABCG2. Therefore, G×G interaction with some other genes should be investigated in future studies. Third, gene-environment interactions might also play a significant role in gout risk, which represents

a limitation of the present study. Therefore, more environmental factors such as alcohol consumption, smoking, and dietary consumption should be included in the gene-environment analysis. Finally, the gout case-control sample sets were drawn from the population of the genetic variation of urate transporter genes in HUA and gout among Thai population project. Only ten participants were female, which may limit the generalizability. Additionally, we also further emphasize the need to replicate and extend these findings elsewhere, not only in the Thai population. However, population homogeneity is the study strength by reducing genetic variability.

Conclusion

In conclusion, the present study found that, combined with their activities as urate transporters and their strong associations with SUA concentrations, GLUT9 and ABCG2 appeared to be important modulators of uric acid levels and likely the risk of gout. The authors believe that the current findings reflect important, sound biology to clinical medicine rather than simply statistical findings. In the context of the current study, the stronger combined effect of SNPs in the SLC2A9 and ABCG2 genes via G×G interaction may help to predict gout risk and its prognosis. The authors' data have potential implications in genetic counseling, gout screening, and gout prognosis in Thai population.

What is already known on this topic?

The mutants in both ABCG2 and SLC2A9 gene cause an additive interaction effect for gout occurrence. Therefore, the G×G interactions could facilitate the understanding of the additional missing heritable components of gout risk, possibly through interplay in several pathways contributing to gout etiology.

What this study adds?

There are several genomic loci and environmental factors that have associated with HUA and gout, which those factors still play a crucial development role in gout. Therefore, the G×G interaction with some other gene and gene-environment interactions should be investigated in future studies.

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Conflicts of interest

The authors declare no conflict of interest.

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