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ASSOCIATION STUDY OF *SLC22A12* RS475688 POLYMORPHISM WITH GOUT IN A VIETNAMESE POPULATION

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ABSTRACT

Gout is a prevalent inflammatory disease resulting from the precipitation of monosodium urate (MSU) crystals. Approximately 90% of cases are caused by impaired renal excretion of uric acid. It is also suggested that genetic factors significantly affect the uric acid-associated traits, with the estimated heritability ranging from 40 - 70%. Although the association between *SLC22A12* variants and gout risk has been reported in multiple cohorts, the obtained results vary across different populations. This study investigated the relationship between the *SLC22A12* rs475688 variant and gout risk in a Vietnamese population. A total of 470 subjects, comprising 157 gout patients and 313 healthy controls, were recruited for the current study. Genotypes of the *SLC22A12* rs475688 were identified using the polymerase chain reaction - restriction fragment length polymorphism (PCR-RFLP) method. The results showed that the frequencies of the minor allele T in cases, controls, and whole study populations were 0.376, 0.324, and 0.341, respectively. Statistical analysis revealed that the genotype distribution of rs475688 followed Hardy-Weinberg equilibrium ($p > 0.05$). Further analysis indicated that no significant association was observed between rs475688 and gout in four models, including additive (CT vs. CC: OR = 1.498, 95% CI: 0.994 - 2.267, p = 0.053; TT vs. CC: OR = 1.383, 95% CI: 0.695 - 2.683, p = 0.342), dominant (CT + TT vs. CC: OR = 1.476, 95% CI: 0.996 - 2.202, p = 0.052), recessive (TT vs. CC + CT: OR = 1.109, 95% CI: 0.580 - 2.055, p = 0.755), and allele (T vs. C: OR = 1.254, 95% CI: 0.944 - 1.664, p = 0.116). This study adds genetic population-specific evidence to the association between single-nucleotide polymorphisms (SNPs) on the *SLC22A12* gene and gout in the Vietnamese population.

Keywords: Gout, PCR-RFLP, rs475688, *SLC22A12*, Vietnamese population.

INTRODUCTION

Gout, a widely encountered type of inflammatory arthritis, is characterized by severe and recurrent attacks of joint pain and swelling (Choi *et al.*, 2005; Dalbeth *et al.*, 2021). Globally, gout has emerged as a public health burden, with its prevalence being 55.8 million in 2020. By 2050, the affected population is forecasted to increase significantly to 95.8 million (Cross *et al.*, 2024). Epidemiological data from the

Community Oriented Program for Control of Rheumatic Diseases (COPCORD) demonstrate that the prevalence increased from 0.14% to around 1.0% by 2014, representing approximately 940,000 individuals in Vietnam (Hung *et al.*, 2022; Minh Hoa *et al.*, 2003). A primary risk factor for gout is hyperuricemia, an excessive accumulation of serum urate in the bloodstream, resulting from the evolutionary loss of the uricase enzyme in humans (Johnson *et al.*, 2005; Roman, 2023). When the levels of uric acid surpass 7 mg/dL in men and 6 mg/dL in women, MSU crystals form and deposit (Akashi *et al.*, 2022; Yang *et al.*, 2019). The condition is mainly triggered by impaired renal excretion, which accounts for approximately 90% of cases (Choi *et al.*, 2005). Besides, genetic factors significantly affect the uric acid-associated traits, with the estimated heritability ranging from 40 - 70% (Nath *et al.*, 2007; Wilk *et al.*, 2000; Yang *et al.*, 2005). In some genome-wide association studies (GWAS), meta-analyses, and independent association studies performed on Caucasian and Asian populations, several transporter-coding genes have been linked to uric dysregulation and gout risk (Dehghan *et al.*, 2008; Duong *et al.*, 2019; Kolz *et al.*, 2009; Köttgen *et al.*, 2013; C. Li *et al.*, 2015; Matsuo *et al.*, 2016; Nakayama *et al.*, 2017; Tin *et al.*, 2011).

SLC22A12, located on chromosome 11q13, consists of 10 exons (Enomoto *et al.*, 2002; Yee *et al.*, 2022). The gene encodes urate transporter 1 (URAT1) - a member of the organic anion transporter (OAT), which regulates urate levels through reabsorption in the kidneys (Enomoto *et al.*, 2005; Enomoto *et al.*, 2002; Mori *et al.*, 1997). Human URAT1 (hURAT1) consists of 555 amino acids and contains 12 transmembrane domains, organized into two pseudo-symmetric halves: the N-terminal and C-terminal domains (Wang *et al.*, 2019). Functionally, hURAT1 exhibits higher affinity for urate, with a Michaelis constant (Km) of approximately 371 ± 28 μM, compared to rURAT1 from rat, which has a Km of 1773 μM (Enomoto *et al.*, 2002; Sato *et al.*, 2011). Interestingly, URAT1 is also influenced by sex hormones. Testosterone has been shown to enhance URAT1 level, whereas estradiol suppresses it, resulting in 2.3-fold higher URAT1 expression in male mice compared with that in the females (Hosoyamada *et al.*, 2004; Hosoyamada *et al.*, 2010; Takiue *et al.*, 2011). Moreover, the interaction with PDZK1 and several proteins through its C-terminal PDZ-binding may regulate the function of URAT1 (Anzai *et al.*, 2004; M. Li *et al.*, 2015).

Multiple studies have identified polymorphism in the *SLC22A12* gene as a major risk factor of gout among distinct populations, including Vietnamese, Han Chinese, Korean, European, and Polynesian (Cho *et al.*, 2015; Duong *et al.*, 2019; Flynn *et al.*, 2013; Li *et al.*, 2014; Zhou *et al.*, 2015). Among *SLC22A12* variants, the rs475688 has been investigated for its association with gout susceptibility across various cohorts (Kuo *et al.*, 2017; Tu *et al.*, 2010; Tu *et al.*, 2016; Tu *et al.*, 2018; Wu *et al.*, 2021; Zhen *et al.*, 2022; Zou *et al.*, 2018). Given the increasing prevalence of gout and the potential role of this variant, it has been widely studied, however, its association remains unknown in the Vietnamese population. Therefore, this case-control study aims to assess the association between rs475688 and gout in a Vietnamese cohort.

MATERIALS AND METHODS

Study subjects

A cohort comprising 157 gout patients and 313 healthy controls was enrolled at Nguyen Trai Hospital, Ho Chi Minh City, Vietnam. All 470 participants provided written consent forms. Gout diagnosis was established according to the American College of Rheumatology guideline, while control participants were confirmed to have good health and no personal or family record of gout or diabetes. Ethical approval for this study was granted by the Institutional Review Board of the Institute of Genome Research, Vietnam Academy of Science and Technology (No. 1-2017/NCHG-HDDD).

Methods

SNP genotyping

Peripheral blood samples from 470 donors were collected to extract genomic DNA using GeneJet Whole Blood Genomic DNA Purification Kit (Thermo Fisher). To evaluate both the quality and quantity of the extracted DNA, samples were first electrophoresed on a 0.8% agarose gel, and then quantified with a NanoDrop One spectrometer (Thermo Fisher). Next, the targeted DNA region containing the *SLC22A12* rs475688 was amplified by PCR using specific primers: 5'-GGTAAAGGTCAGTGATAGAGATT-3' (forward) and 5'-AGAGACCACATATCTGCTCA-3' (reverse). The reaction volume was 7 µL, consisting of 3.535 µL nuclease-free water, 0.7 µL DreamTaq buffer (10X), 0.42 µL dNTPs (2.5 mM), 0.14 µL each of forward and reverse primers (10 pmol), 0.05 µL DreamTaq DNA Polymerase (5 U/µL), and 1.7 µL DNA template (10 ng/µL). After amplification, PCR products were run on a 1% agarose gel for quality control. Successful amplicons were digested with *Hin*fI at 37°C for 5 hours and were run on a 3.5% agarose gel. The genotypes of *SLC22A12* rs475688 were assigned based on the numbers and sizes of the obtained DNA bands (Table 1).

Table 1. Genotypes of *SLC22A12* rs475688 based on PCR-RFLP.

Genotype	Number of DNA bands	DNA lengths (bp)
TT	1	223
CT	3	223, 20, 203
CC	2	203, 20

Statistical analysis

Statistical analyses were carried out using computational software such as Microsoft Excel (Microsoft Corp., Washington DC, USA) and R version 4.0 (R Core Team, 2022). The differences in demographic and clinical characteristics between the two groups were assessed using the Mann-Whitney U test, except for hyperuricemia, which was assessed using the Chi-squared test. The genotype distribution of *SLC22A12* rs475688 was examined with a Chi-squared test to assess Hardy-Weinberg equilibrium (HWE). The association between the SNP and gout was evaluated in four inheritance

models: additive, dominant, recessive, and allelic. Finally, the odds ratios (ORs) with 95% confidence intervals (CIs) were computed to assess the association. All statistical analyses were conducted using two-sided tests, and p-values below 0.05 were statistically significant.

RESULTS

The demographic and clinical characteristics of 157 gout patients and 313 healthy controls are described in Table 2. Serum uric acid (SUA) and hyperuricemia were significantly higher in the patient group than in the control group ($p < 0.001$), while age showed no significant differences between the two groups ($p > 0.05$).

Table 2. Demographic and clinical characteristics of gout patients and controls.

Characteristic	Control (n = 313)	Case (n = 157)	p-value
Age	53 (13)	54 (20)	0.513 (1)
SUA (mg/dL)	6.88 (2.0)	9.26 (2.1)	**<0.001** (1)
Hyperuricemia*	146 (46.7%)	145 (92.4%)	**<0.001** (2)

*Data presented as either median (interquartile range) or * counts (percentage); n: number of individuals in groups; (1) p-value calculated using Mann-Whitney U test; (2) p-value calculated using Chi-squared test; p < 0.05 (in bold) indicates statistical significance; SUA: serum uric acid.*

Genotyping *SLC22A12* rs475688

In a total of 470 samples, consisting of 157 patients with gout and 313 healthy controls, the region containing the *SLC22A12* rs475688 underwent PCR amplification with specific primers. The PCR products were digested with *Hin*fI (Thermo Fisher) for genotype determination. An electrophoretic analysis of 8 representative samples of a 3.7% agarose gel is shown in Figure 1. Samples 2, 3, 6, and 8 exhibited the homozygous CC genotype, characterized by two bands at 203 bp and 20 bp. Samples 5, 7, and 9 displayed the heterozygous CT genotype, showing three bands at 223 bp, 203 bp, and 20 bp. Because the 20 bp band is small, it was not visible on a 3.7% agarose gel. Sample 4 showed a single undigested band of 223 bp, corresponding to the homozygous TT genotype.

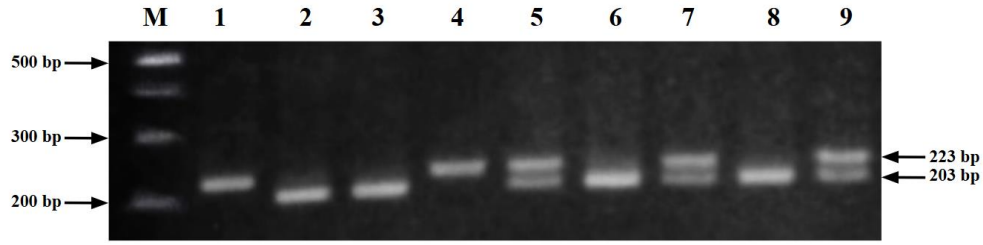

Figure 1. *Hin*fI-digested PCR products on a 3.7% agarose gel. M: Marker 100 bp, 1: Undigested PCR product; 2, 3, 6, 8: Samples with the CC genotype (2 bands with 203 bp, and 20 bp); 4: Sample with the TT genotype (223bp); 5, 7, 9: Samples with the CT genotype (3 bands with 223 bp, 203 bp, and 20 bp).

Table 3. Alleles and genotypes of *SLC22A12* rs475688 obtained from 470 samples.

	Genotype			Allele frequency		HWE p-value
	CC	CT	TT	C	T	
Case (n = 157)	56	84	17	0.624	0.376	0.091
Control (n = 313)	141	141	31	0.676	0.324	0.699
Total	197	225	48	0.65	0.341	0.183

HWE: Hardy-Weinberg equilibrium; n: number.

Table 4. Association between *SLC22A12* rs475688 and gout.

Test model	Control (n = 313)	Case (n = 157)	OR	95% CI	p-value
Additive					0.146
CC	141 (45.05%)	56 (35.67%)	1.000		
CT	141 (45.05%)	84 (53.5%)	1.498	0.994 - 2.267	0.053
TT	31 (9.90%)	17 (10.83%)	1.383	0.695 - 2.683	0.342
Dominant					
CC	141 (45.05%)	56 (35.67%)	1.000		
CT + TT	172 (54.95%)	101 (64.33%)	1.476	0.996 - 2.202	0.052
Recessive					
CC + CT	282 (90.10%)	140 (89.17%)	1.000		
TT	31 (9.90%)	17 (10.83%)	1.109	0.580 - 2.055	0.755
Allele					
C	423 (67.57%)	196 (62.42%)			
T	203 (32.43%)	118 (37.58%)	1.254	0.944 - 1.664	0.116

n: number; OR: odds ratio; 95% CI: 95% confidence intervals; p-value was measured using the Chi-squared test.

Association analysis of *SLC22A12* rs475688 with the risk of gout disease

The genotype distribution of *SLC22A12* rs475688 in both the case and control groups followed Hardy-Weinberg equilibrium ($p > 0.05$) (Table 3). Additionally, a Chi-squared test was used to assess the relationship between this variant and gout under four different models: additive, dominant, recessive, and allelic (Table 4). The p-values across all genetic models exceeded 0.05, suggesting no significant association between *SLC22A12* rs475688 and gout susceptibility in the Vietnamese population.

DISCUSSION

SLC22A12 codes for URAT1, which participates in the urate reabsorption in renal

tubules. Multiple types of variants in this gene were reported in association with gout, including noncoding and synonymous variants (Cho *et al.*, 2015; Dehghan *et al.*, 2008; Nakayama *et al.*, 2017; Pavelcova *et al.*, 2020; Zhou *et al.*, 2015), variants in important regions such as the C-terminal and N-terminal domains, as well as at exon-intron boundaries of URAT1 (Graessler *et al.*, 2006; Li *et al.*, 2010). Additionally, it has been reported that several intronic SNPs within the *SLC22A12* gene were also linked to serum uric acid levels and the risk of gout across distinct study populations, possibly by affecting mRNA processing or through linkage disequilibrium with causative variants (Li *et al.*, 2010; Shima *et al.*, 2006).

Polymorphism rs475688 (C>T) is an intronic variant within the *SLC22A12* gene. A previous study revealed that this variant functions as an expression quantitative trait locus (eQTL) that upregulates *SLC22A12* mRNA expression, thereby potentially increasing hURAT1 activity (Fujii *et al.*, 2025). Previous case-control studies have consistently reported a strong association between the C allele of rs475688 and increased gout risk in populations such as the Taiwanese, Han Chinese, and Solomon Islanders (Kuo *et al.*, 2017; Tu *et al.*, 2010; Tu *et al.*, 2016; Tu *et al.*, 2018; Zou *et al.*, 2018). Particularly, the association between rs475688 and serum uric acid levels was also observed ($\beta = 0.24$, $p = 0.03$) in Han Chinese populations (Tu *et al.*, 2010). In addition to the independent relationship of rs475688 with risk of gout (recessive model, $p = 0.0001$) in Han individuals, participants carrying this polymorphism and other high-risk variants together exhibited an elevated risk (OR = 33.91; positive predictive value (PPV) = 80%) (Tu *et al.*, 2018). In contrast, Flynn *et al*. (2013) analyzed 1,003 gout cases, divided into four groups consisting of European Caucasian, Eastern Polynesian, Western Polynesian, and mixed Polynesian, and found that the T allele correlated with a higher risk of gout in European Caucasian with a weak effect (OR = 1.26, $p = 0.043$) (Flynn *et al.*, 2013). A meta-analysis, comprising of seven case-control studies involving a total of 1216 gout patients and 1844 controls, provided strong evidence for the involvement of the rs475688 polymorphism in gout susceptibility across three genetic inheritance models (C vs. T: OR = 1.464, 95% CI: 1.078 - 1.989, $p = 0.015$; CC + CT vs. TT: OR = 2.028, 95 %CI: 1.488 - 2.763, $p < 0.001$; CC vs. CT + TT: OR = 2.226, 95% CI: 1.746 - 2.838, $p < 0.001$) (Zou *et al.*, 2018). In contrast, another meta-analysis of 20 studies showed that rs475688 exerted a protective effect against hyperuricemia under both dominant (OR = 0.53, $p = 0.002$) and recessive (OR = 0.46, $p = 0.003$) models (Zhen *et al.*, 2022). Although some studies supported a strong association between rs475688 and disease risk, others reported no significant correlation ($p > 0.05$). For instance, no significant correlation between these SNPs and disease risk was observed in the Shanghai cohort treated with losartan (Wu *et al.*, 2021), the Polynesian groups (Flynn *et al.*, 2013), and the aboriginal group in Taiwan (Tu *et al.*, 2018). In this study, there was also no association between this polymorphism and gout in the Vietnamese population ($p > 0.05$). This discordance in associations across different populations might be explained by differences in genetic backgrounds, lifestyle factors, dietary patterns, and environmental exposures.

CONCLUSION

SLC22A12 rs475688 was examined using the PCR-RFLP method with the frequencies

of CC/CT/TT being 0.419, 0.479, and 0.102, respectively. Statistical analysis indicated that *SLC22A12* rs475688 was not associated with gout in this cohort. Further studies on various single-nucleotide polymorphisms of the *SLC22A12* gene and other related urate transporter genes, are needed to enhance our understanding of associations between different genetic variants and gout in the Vietnamese population.

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