Joint Effects of Alcohol Consumption and *ABCG2* Q141K on Chronic Tophaceous Gout Risk

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ABSTRACT. ***Objective.*** To investigate the joint effects of alcohol consumption and *ABCG2* gene variants on tophaceous gout occurrence.

Methods. The V12M (rs2231137), Q126X (rs72552713), and Q141K (rs2231142) of the *ABCG2* gene were genotyped among controls, nontophaceous, and tophaceous gout cases in Taiwanese Han (n = 446, 77, 177) and Taiwan Aborigines (n = 1105, 203, 330).

Results. The missense variations V12M (C) and Q141K (T) significantly associated with tophaceous gout (p trend = 4.08×10^{-2}, 9.00×10^{-12} in Han; 1.81×10^{-3}, 9.34×10^{-10} in Aborigines). The nonsense variation Q126X (T) exerted a significant effect only in Han ($p = 1.10 \times 10^{-2}$), but not in Aborigines. In the prediction of tophaceous gout, the Q141K (T) OR were 1.51 in Han, 1.50 in Aborigines, and 1.55 ($p = 7.84 \times 10^{-5}$) in pooled analysis when compared to nontophaceous gout. We found the joint effects of alcohol consumption and Q141K (T/T) highly associated with tophaceous gout (adjusted OR ≥ 5.11; $p \leq 7.78 \times 10^{-4}$); specifically the ever drinkers carrying the Q141K (T/T; adjusted OR 25.05, $p = 9.21 \times 10^{-4}$ in Han; adjusted OR 14.87, $p = 1.08 \times 10^{-8}$ in Aborigines).

Conclusion. Our findings showed alcohol consumption and *ABCG2* Q141K, independently and jointly, associated with the risk of chronic tophaceous gout. (J Rheumatol First Release Feb 15 2014; doi:10.3899/jrheum.130870)

Key Indexing Terms:
TOPHACEOUS GOUT ALCOHOL CONSUMPTION *ABCG2* Q141K

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Gouty arthritis is characterized by the deposition of monosodium urate, which may subsequently form visible tophi surrounding the fibrous tissue in connective tissues, leading to destructive arthropathy when deposited in articular structures[1,2]. Large subcutaneous tophi can cause deformities and disabilities and often require lengthy treatments to "melt" the tophus or to remove the chalky mass of tophaceous deposits[1,2,3].

Several epidemiologic studies have demonstrated that environmental factors (e.g., alcohol intake) and genetic predisposition [e.g., ATP-binding cassette, subfamily G, member 2 (*ABCG2*) gene] together contribute to the elevated urate levels in gout[4,5,6]. Alcohol intake is strongly associated with hyperuricemia and may partially explain the incidence and prevalence of gout[4,7]. The *ABCG2* is a well-studied hyperuricemic gene that resides in the 4q22–q23; and proximal to the 4q21–25 region of gout-susceptibility gene *GOUT1 (MIM ID %138900)* that we previously associated in Taiwanese Han and Taiwan aborigines using genome-wide linkage study[8,9].

Functionally, *ABCG2* encodes for the urate transporter of the proximal tubule nephrons in the regulation of urate homeostasis[5,10,11]. A variant of *ABCG2*, for example, a loss-of-function variant at amino acid position 141 in the nucleotide-binding domain of the *ABCG2* gene imparts a 50% reduction in urate transport velocity *in vitro* and is correlated with reduced renal function in the J-SHIPP Suita study[5,10,11]. Although *ABCG2* gene variants are clearly

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associated with uric acid and gout, less is known about its influence on progression to tophaceous gout. We hypothesized that the joint effects of alcohol consumption and *ABCG2* gene variants may contribute to an increased tophaceous gout occurrence.

MATERIALS AND METHODS

Study participants. Two case-control studies were conducted on the ethnic groups of Taiwan (Han and Aborigines). A total of 700 Han participated, comprising 446 controls and 254 patients with gout (77 tophaceous gout), and a total of 1638 Aborigines participated, comprising 1105 controls and 533 patients with gout (203 tophaceous gout). All patients satisfied the American College of Rheumatology gout survey criteria[12]. Tophaceous gout was diagnosed with confirmed crystals or with 1 or more tophi clearly visible and palpable from patients' arms, legs, ears, or articular cartilage, accompanied by hyperuricemia at time of collection. The nontophaceous gout cases were recruited from the same hospitals as described[13,14]. We determined that all controls were gout-free using clinical history and routine physical examinations and further ascertained that none had received hypouricemics for medical conditions.

Our questionnaire included sociodemographic characteristics such as age, sex, and ethnicity; medical history, including diabetes mellitus, hypertension (HTN), and gout status; the age of gout onset and duration (about 70% of gout cases provided information); and a complete history of alcohol consumption. Alcohol drinkers were categorized into those who currently consumed alcoholic beverages (irrespective of quantity) greater or equal to twice per week, and "ever drinker" was defined as those who consumed alcoholic beverages at least twice per week for more than 1 year habitually but had quit at least 1 year prior to our interview[15]. We do not have details on the type of alcohol used. Also, it is noteworthy that compared to Han gouty cases, the aboriginal medical history was limited regarding those receiving treatment (currently or in the past). The institutional review boards and ethics committees of the participating hospitals approved this study design. All participants gave their written informed consent.

Genotype determination. Total genomic DNA was obtained from peripheral blood leukocytes using a genomic DNA extraction kit (QIAGEN-Gentra Puregene Blood Kit, Gentra Systems). The *ABCG2* gene polymorphisms V12M (rs2231137), Q126X (rs72552713), and Q141K (rs2231142)[5,10,16] were genotyped using TaqMan single-nucleotide polymorphism (SNP) Genotyping Assays with ViiA 7 Real-Time PCR System (Applied Biosystems).

Statistical analysis. The differences of demographic and clinical information between gouty cases versus controls and tophaceous versus nontophaceous gout in the 2 ethnicities were analyzed by chi-square test for categorical variables (e.g., sex, comorbidity of diabetes mellitus or HTN, etc.) and t test for continuous variables [e.g., age, blood pressure, body mass index (BMI), etc.]. Fisher's exact test was performed on small sample sizes and for sparse tables. The distribution of plasma triglyceride (TGC) levels was normalized by taking a log transformation of the original values because of the skewed distributions of the original values. Hardy-Weinberg equilibrium (HWE) was verified for all SNP by use of PLINK software[17]. Additive genetic effects were modeled by defining a continuous variable with levels 0, 1, 2 (e.g., G/G, G/T, and T/T for rs2231142) and also compared the T/G and T/T genotypes separately with the reference genotype G/G. Crude OR with 95% CI and p-values were determined for each case-control study separately, assuming an additive genetic model using a multinomial logistic regression. Multiple logistic regression adjusted for sex, BMI, log (TGC), creatinine, diabetes mellitus, and alcohol use, and in the pooled analysis, ethnicity, was used for inferring the risk of the rs2231142 on tophaceous gout. Pooled analysis was performed using the Cochran-Mantel-Haenszel test method in PLINK software, and a Breslow-Day test was used to assess the homogeneity of the OR from different populations. General linear regression adjusting for age, sex, BMI, total cholesterol, log (TGC), creatinine, alcohol use, and HTN, and in the pooled analysis, ethnicity, was used for inferring the influence of the rs2231142 on age of onset and duration of disease assuming an additive genetic model. A general linear regression model including an ethnicity × rs2231142 interaction term was applied. The potential independent effects of *ABCG2* Q141K and alcohol use were evaluated using the multinomial logistic regression after adjustment for gout risk factors of age, sex, BMI, total cholesterol, log (TGC), creatinine, and HTN. For the joint analyses, we used 3 categories of *ABCG2* Q141K genotypes (G/G, G/T, T/T) and 3 categories of alcohol use (nondrinker, ever drinker, current drinker). To calculate these measures in additive interaction between 2 risk factors, a new composite variable of 9 categories was computed and adjusted for gout risk factors by a multinomial logistic regression model. The multinomial logistic regression analysis then estimated the adjusted OR using this new indicator variable. This investigation at a single locus Q141K (rs2231142) for tophaceous gout when compared to nontophaceous gout demonstrated an 87.9% statistical power to detect an OR of 1.50 at $\alpha = 0.05$. Power was calculated using Quanto v1.2.4. data handling, and associations were performed using the software packages SAS, version 9.3 (SAS Institute Inc.).

RESULTS

Baseline demographics for Taiwan ethnic groups are presented in Appendix 1. There were 254 Han gout cases [77 (30%) tophaceous gout cases] and 446 controls [mean ages: 50.8 yrs (cases) and 54.6 yrs (controls), $p = 0.001$]. There were 533 aboriginal gout cases [203 (38%) tophaceous gout cases] and 1105 controls [ages, 51.1 (cases) and 52.1 (controls), $p = 0.201$]. Gout cases had higher mean TGC, creatinine, and uric acid levels as well as greater rates of comorbidity with hyperuricemia and HTN ($p < 0.05$). Han gout cases had higher BMI and total cholesterol levels ($p < 0.001$). We found that *ABCG2* rs2231142 Q141K T/T significantly associated with tophaceous gout (Table 1). None of the SNP had deviated from HWE for the 2 control groups. There were significant associations of tophaceous gout susceptibility for the 2 variants in the 2 ethnicities (V12M C p trend = 4.08×10^{-2}, Q141K T p trend = 9.00×10^{-12} in Han; V12M C p trend = 1.81×10^{-3}, Q141K T p trend = 9.34×10^{-10} in Aborigines). In terms of the nonsense SNP Q126X, the T allele associated with tophaceous gout in Han, but its effect could not be tested in Aborigines (frequency 0%). The frequencies of controls and patients, without/with tophi, for the rs72552713 Q126X T allele were 0.11% (1/892) in controls, 0.28% (1/354) for non-tophi, and 1.95% (3/154) for tophi ($p = 2.44 \times 10^{-3}$; Fisher's exact $p = 1.08 \times 10^{-2}$); allelic OR when compared to the C allele: the T allele was related to tophi (OR 17.70, 95% CI 1.83–171.19, $p = 1.31 \times 10^{-2}$) and non-tophi (OR 2.52, 95% CI 0.16–40.45, $p = 0.513$).

To better illustrate the association of the *ABCG2* Q141K variant in tophaceous gout versus nontophaceous gout, we provided a summary in Table 2. The Q141K T OR for tophaceous gout were 1.51 (frequency 0.64 vs 0.52) in Han and 1.50 (frequency 0.61 vs 0.50) in Aborigines, when compared to nontophaceous gout after adjusting for covariates. The effect estimate from the pooled analysis was consistent with further evidence of homogeneity for the OR

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Table 1. ABCG2 V12M, Q141K, and Q126X variants and tophaceous gout risk.

		Controls				Nontophaceous Gout Cases				Tophaceous Gout Cases				Nontophaceous Gout Cases vs Controls		Tophaceous Gout Cases vs Controls	
	1/2	11	12	22	1	11	12	22	1	11	12	22	1	OR (95% CI)	p	OR (95% CI)	p
Taiwanese Han																	
rs2231137 V12M	C/T	199	184	63	0.65	87	75	15	0.70	44	26	7	0.74	1.25 (0.96–1.61)	9.71×10^{-2}	1.48 (1.02–2.15)	4.08×10^{-2}
rs2231142 Q141K	T/G	49	180	217	0.31	55	74	48	0.52	34	30	13	0.64	2.20 (1.72–2.82)	3.34×10^{-10}	3.40 (2.39–4.84)	9.00×10^{-12}
rs72552713 Q126X*	T/C	0	1	445	0.001	0	1	176	0.003	0	3	74	0.02	2.53 (0.16–40.63)	5.13×10^{-1}/ 4.88×10^{-1}	18.03 (1.85–175.67)	1.28×10^{-2}/ 1.10×10^{-2}
Taiwan Aborigines																	
rs2231137 V12M	C/T	518	471	116	0.68	179	126	25	0.73	120	69	14	0.76	1.28 (1.05–1.55)	1.32×10^{-2}	1.47 (1.16–1.88)	1.81×10^{-3}
rs2231142 Q141K	T/G	223	518	364	0.44	95	142	93	0.50	80	88	35	0.61	1.29 (1.09–1.52)	3.57×10^{-3}	1.94 (1.57–2.39)	9.34×10^{-10}
rs72552713 Q126X	T/C	0	0	1105	0.00	0	0	330	0.0	0	0	203	0.00	—	—	—	—

P is p-trend/exact p; 1, risk allele; 2, nonrisk allele; 11 indicates the at-risk homozygote, 12 indicates the heterozygote, and 22 indicates the wild-type homozygote. "—" indicates not calculated. None of the SNP deviated from HWE in the 2 control groups. Crude OR with 95% CI and p values were determined for each case-control study separately under an additive model (genotypic trend effect with a 1-degree-of-freedom test) of inheritance using a multinomial logistic regression analysis without covariates adjustment. Exact p value: Fisher's exact test. *Frequencies of controls and patients, without and with tophi, with the rs72552713 Q126X (T) allele were 0.11% (1/892) in controls, 0.28% (1/354) for non-tophi and 1.95% (3/154) for tophi ($p = 2.44 \times 10^{-3}$; Fisher's exact $p = 1.08 \times 10^{-2}$). SNP: single-nucleotide polymorphism; HWE: Hardy-Weinberg equilibrium.

Table 2. ABCG2 Q141K (T) associate with tophaceous gout.

	Tophaceous Gout Cases vs Nontophaceous Gout Cases Adjusted OR (95% CI)	p
Taiwanese Han		
rs2231142 Q141K		
G/G	1.00	
G/T	1.31 (0.59–2.88)	5.09×10^{-1}
T/T	2.04 (0.92–4.54)	8.01×10^{-2}
G-allele	1.00	
T-allele	1.51 (1.00–2.28)	5.02×10^{-2}
Taiwan Aborigines		
rs2231142 Q141K		
G/G	1.00	
G/T	1.65 (1.01–2.68)	4.36×10^{-2}
T/T	2.12 (1.28–3.52)	3.60×10^{-2}
G-allele	1.00	
T-allele	1.50 (1.16–1.94)	2.31×10^{-3}
Pooled analysis		
rs2231142 Q141K		
G/G	1.00	
G/T	1.61 (1.07–2.42)	2.18×10^{-2}
T/T	2.21 (1.45–3.37)	2.20×10^{-4}
G-allele	1.00	
T-allele	1.55 (1.25–1.92)	7.84×10^{-5}

Adjusted OR and their p values were adjusted for sex, body mass index, log (triglycerides), creatinine, diabetes mellitus, and alcohol use, and for the pooled analysis, ethnicity, using a multiple logistic regression model. Pooled analysis was performed by the Cochran-Mantel-Haenszel test method using the PLINK v1.07. Single-nucleotide polymorphism rs2231142 Q141K revealed evidence of homogeneity in the association with tophaceous gout ($p_{\text{Breslow-Day test}} = 0.85$).

between the 2 populations (OR 1.55, 95% CI 1.25–1.92, $p = 7.84 \times 10^{-5}$; $p_{\text{Breslow-Day test}} = 0.85$) after controlling for ethnicity and other gout risk factors. We can demonstrate that the number of risk alleles of Q141K showed additive effects on the risk of tophaceous gout, by comparing tophaceous gout cases carrying the reference Q141K G/G with Q141K G/T to show an OR 1.61 (95% CI 1.07–2.42, $p = 2.18 \times 10^{-2}$) and with Q141K T/T to show an OR 2.21 (95% CI 1.45–3.37, $p = 2.20 \times 10^{-4}$) after adjustment of covariates. Thus, the Q141K T/T was robust and informative on the risk of tophaceous gout.

Aborigines who had tophaceous gout and carried Q141K T were better correlated with an earlier age of visit to the clinician (G/G = 45.22 yrs, G/T = 40.37 yrs, and T/T = 35.89 yrs; p trend = 0.0014) and a longer duration of the disease (G/G = 9.72 yrs, G/T = 10.64 yrs, and T/T = 14.58 yrs; p trend = 0.0019). However, this finding was not observed in the Han or in the nontophaceous gout cases in either ethnicity. Estimates per risk allele copy in the tophaceous gout cases, corrected for covariates, showed an earlier age of onset and longer duration of disease at rs2231142 T of –1.26 and –2.61 years and 1.24 and 2.61 years in both ethnicities, and –2.24 years (p trend = 0.0010) and 2.27 years (p trend = 0.0010) in the pooled group (Appendix 2). We also observed an ethnicity-specific interaction of Q141K with earlier age of visit to the clinician among the gout cases (p for interaction = 0.0286; Appendix 3).

In terms of alcohol consumption, Table 3 shows that

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Table 3. *ABCG2* Q141K (T/T) and alcohol use predict risk of tophaceous gout.

	Taiwanese Han				Taiwan Aborigines			
	Tophaceous Gout Cases vs Controls Adjusted OR (95% CI)	p	Nontophaceous Gout Cases vs Controls Adjusted OR (95% CI)	p	Tophaceous Gout Cases vs Controls Adjusted OR (95% CI)	p	Nontophaceous Gout Cases vs Controls Adjusted OR (95% CI)	p
Model 1:								
rs2231142 Q141K								
G/G	1.00		1.00		1.00		1.00	
G/T	2.70 (1.29–5.64)	8.42×10^{-3}	1.84 (1.17–2.90)	8.24×10^{-3}	1.85 (1.19–2.88)	6.12×10^{-3}	1.16 (0.85–1.60)	0.3584
T/T	9.50 (4.33–20.83)	1.93×10^{-8}	3.94 (2.28–6.83)	9.90×10^{-7}	3.79 (2.37–6.04)	2.45×10^{-8}	1.82 (1.27–2.61)	1.20×10^{-3}
Alcohol use								
Nondrinker	1.00		1.00		1.00		1.00	
Drinker	2.08 (1.14–3.80)	1.70×10^{-2}	0.86 (0.53–1.38)	0.5204	2.29 (1.56–3.34)	2.10×10^{-5}	2.66 (1.96–3.60)	2.83×10^{-10}
Model 2:								
rs2231142 Q141K								
G/G	1.00		1.00		1.00		1.00	
G/T	2.89 (1.36–6.14)	5.80×10^{-3}	1.84 (1.17–2.90)	8.31×10^{-3}	1.95 (1.25–3.05)	3.49×10^{-3}	1.17 (0.85–1.60)	0.3442
T/T	9.85 (4.42–21.94)	2.18×10^{-8}	3.95 (2.28–6.85)	1.01×10^{-6}	3.60 (2.24–5.80)	1.34×10^{-7}	1.83 (1.27–2.63)	1.07×10^{-3}
Alcohol use								
Nondrinker	1.00		1.00		1.00		1.00	
Ever drinker	7.03 (2.80–17.64)	3.24×10^{-5}	1.06 (0.41–2.75)	0.8974	5.69 (3.45–9.38)	9.22×10^{-12}	3.22 (2.01–5.17)	1.28×10^{-6}
Current drinker	1.18 (0.57–2.43)	0.6640	0.82 (0.49–1.37)	0.4420	1.62 (1.08–2.43)	2.02×10^{-2}	2.59 (1.90–3.54)	2.33×10^{-9}

Adjusted OR and their p values were adjusted for age, sex, body mass index, total cholesterol, log (triglycerides), creatinine, hypertension, and alcohol use categories using a multinomial logistic regression model.

Q141K T/T and ever drinker were 2 important predictors (OR 9.85, $p = 2.18 \times 10^{-8}$ and OR 7.03, $p = 3.24 \times 10^{-5}$ in Han; OR 3.60, $p = 1.34 \times 10^{-7}$ and OR 5.69, $p = 9.22 \times 10^{-12}$ in Aborigines). Being an ever drinker significantly influenced tophaceous gout risk, suggesting that alcohol use in patients with gout and tophi occurrence were linked. The Aborigines had a higher tendency toward gout as well as higher alcohol intake (75% vs 28% in Han). Further, for the current drinker, multiple logistic-regression analysis also verified alcohol use adjusted OR 1.62 ($p = 2.10 \times 10^{-5}$) to be more a significant predictor of tophaceous gout risk in Aborigines than in Han (OR 1.18, p = 0.6640).

Table 4 shows the joint effects of rs2231142 Q141K T/T and alcohol consumption. To explore the extent to which rs2231142 Q141K T/T was an important risk factor for tophaceous gout occurrence, we performed a multiple logistic-regression analysis on tophaceous gout cases according to alcohol intake categories, compared to nondrinkers carrying wild-type genotype Q141K G/G as reference. We found that Q141K T/T increased from OR 6.21 without alcohol use to OR 12.69 with alcohol use in Han and from OR 2.63 without alcohol use to OR 5.11 with alcohol use in Aborigines. We found especially that the ever drinkers with carriers of rs2231142 Q141K T/T were the most deterministic of tophaceous gout out of both ethnicities (OR 25.05, $p = 9.21 \times 10^{-4}$ in Han; OR 14.87, $p = 1.08 \times 10^{-8}$ in Aborigines).

DISCUSSION

We studied 2338 persons from 2 different Taiwan ethnic groups and found that an important variant, Q141K T, in the *ABCG2* gene, significantly associated with the odds of nontophaceous gout risk ($p = 3.34 \times 10^{-10}$ and 3.57×10^{-3} in Han and Aborigines), the odds of tophaceous gout occurrence ($p = 9.00 \times 10^{-12}$ and 9.34×10^{-10} in Han and Aborigines), and in comparing tophaceous gout versus nontophaceous gout (OR 1.55; $p = 7.84 \times 10^{-5}$). Further, we found that Q141K associated with tophaceous gout across the alcohol consumption categories, with a stronger association in ever drinkers (OR 25.05 and OR 14.87 in Han and Aborigines) than in current drinkers (OR 12.69 and OR 5.11 in Han and Aborigines).

The variants V12M and Q141K, associated with tophaceous gout in Han and Aborigines owing to missense polymorphisms, were correlated ($D' = 0.94$ in Han; $D' = 0.99$ in Aborigines). The other variant, Q126X T, is also associated with tophaceous gout (OR 18.03, $p = 1.28 \times 10^{-2}$) but only in Han (T 2% vs 0.1%). The *ABCG2* mediates high-capacity urate transport even under high-urate conditions from its ATP dependence and kinetic analysis. Of patients with gout, 10.1% (vs 0.9% of controls) possessed the genotype combinations Q126X and Q141K (OR 25.8) and reduced > 75% of the *ABCG2* function, indicating that nonfunctional variants of *ABCG2* can essentially block gut and renal urate excretion, to elevate gout

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Table 4. Different alcohol use status and rs2231142 Q141K in association with tophaceous gout.

		Controls	Nontophaceous Gout Cases	Tophaceous Gout Cases	Nontophaceous Gout Cases vs Controls		Tophaceous Gout Cases vs Controls	
					Adjusted OR (95% CI)	p	Adjusted OR (95% CI)	p
Taiwanese Han, n (%)								
rs2231142 Q141K	Alcohol Use							
G/G	Nonuse	165 (37.0)	38 (21.5)	12 (15.6)	1.00		1.00	
G/T	Nonuse	137 (30.7)	59 (33.3)	12 (15.6)	1.81 (1.08–3.04)	2.52×10^{-2}	1.01 (0.39–2.60)	9.90×10^{-1}
T/T	Nonuse	39 (8.7)	41 (23.2)	21 (27.3)	3.49 (1.84–6.62)	1.32×10^{-4}	6.21 (2.47–15.64)	1.05×10^{-4}
G/G	Ever used	11 (2.5)	3 (1.7)	1 (1.3)	0.76 (0.16–3.64)	7.28×10^{-1}	1.35 (0.14–13.32)	7.97×10^{-1}
G/T	Ever used	6 (1.4)	2 (1.1)	9 (11.7)	2.05 (0.34–12.38)	4.36×10^{-1}	23.65 (5.87–95.30)	8.68×10^{-6}
T/T	Ever used	2 (0.5)	4 (2.3)	5 (6.5)	5.19 (0.78–34.52)	8.83×10^{-2}	25.05 (3.73–168.37)	9.21×10^{-4}
G/G	Current use	41 (9.2)	7 (4.0)	0 (0.0)	0.61 (0.24–1.58)	3.08×10^{-1}	—	9.71×10^{-1}
G/T	Current use	37 (8.3)	13 (7.3)	9 (11.7)	1.36 (0.62–2.99)	4.46×10^{-1}	2.69 (0.93–7.79)	6.74×10^{-2}
T/T	Current use	8 (1.8)	10 (5.7)	8 (10.4)	5.61 (1.84–17.11)	2.46×10^{-3}	12.69 (2.88–55.86)	7.78×10^{-4}
Taiwan Aborigines, n (%)								
rs2231142 Q141K	Alcohol Use							
G/G	Nonuse	189 (17.1)	16 (4.9)	11 (5.4)	1.00		1.00	
G/T	Nonuse	266 (24.1)	36 (10.9)	22 (10.8)	1.59 (0.84–3.03)	1.55×10^{-1}	1.53 (0.69–3.41)	2.95×10^{-1}
T/T	Nonuse	121 (11.0)	29 (8.8)	18 (8.9)	2.76 (1.40–5.44)	3.36×10^{-3}	2.63 (1.13–6.12)	2.46×10^{-2}
G/G	Ever used	25 (2.3)	16 (4.9)	9 (4.4)	5.58 (2.38–13.08)	7.48×10^{-5}	4.13 (1.41–12.08)	9.49×10^{-3}
G/T	Ever used	28 (2.5)	15 (4.6)	24 (11.8)	4.44 (1.88–10.50)	6.99×10^{-4}	10.89 (4.45–26.65)	1.70×10^{-7}
T/T	Ever used	19 (1.7)	15 (4.6)	30 (14.8)	5.97 (2.44–14.65)	9.44×10^{-5}	14.87 (5.90–37.52)	1.08×10^{-8}
G/G	Current use	150 (13.6)	61 (18.5)	15 (7.4)	3.45 (1.86–6.41)	8.68×10^{-5}	1.29 (0.54–3.06)	5.63×10^{-1}
G/T	Current use	224 (20.3)	91 (27.6)	42 (20.7)	3.72 (2.05–6.73)	1.47×10^{-5}	2.34 (1.11–4.94)	2.50×10^{-2}
T/T	Current use	83 (7.5)	51 (15.5)	32 (15.8)	6.35 (3.31–12.15)	2.47×10^{-8}	5.11 (2.30–11.36)	6.25×10^{-5}

Adjusted OR and their p values were adjusted for age, sex, body mass index, total cholesterol, log (triglycerides), creatinine, and hypertension using a multinomial logistic regression model.

risk[5]. Our study verified this effect in the Han but not in Aborigines.

The genetics and mechanism of how gout progresses into tophaceous gout are poorly understood. We posited that the worst clinical outcome category, tophaceous gout versus nontophaceous gout cases, could validate our hypothesis that the Q141K sufficiently predisposes patients with existing gout to develop tophi. Our findings showed that Q141K T contributed to about a 50% increase (OR ≥ 1.50) in tophaceous gout compared to nontophaceous gout, across ethnic groups. This effect was persistently higher for tophaceous gout versus controls than for nontophaceous gout versus controls. The tophaceous and nontophaceous gout carriers of Q141K T from hospital-based and population-based settings shared similar allele frequencies; thus our analysis of Q141K T should have no misclassification bias as a true susceptibility locus for gouty arthritis.

The frequency of Q141K T is highly variable in the human population. The T allele ranges 1–3% in Africans, 11% in whites, 9% in Eastern Polynesians, 29% in Western Polynesians, 30% in Asians, and 44% in Taiwan Aborigines[16,18,19]. Gout prevalence in US individuals of Asian ancestry (T allele 30%) is about 3 times higher than in US individuals of European ancestry (T allele 11%)[20]. The prevalence of gout in individuals of European ancestry is 1.4%[21]; in Taiwanese Han it is 2.1–4.4%[22]. For Taiwanese Aborigines, hyperuricemia can be as prevalent as 41% to 82% and gout as much as 12%[22,23]. In our study, the risk allele Q141K T has a frequency of 44% in Aborigines and 31% in Han. Other supporting evidence is that the aboriginal patients with tophaceous gout who were carriers of Q141K T/T presented at an earlier age to the clinician. This remained consistent with a Q141K T allele estimated OR of 1.94 and a 3.4-fold increased risk of tophaceous gout compared to noncarriers.

It is estimated that 5–10% of adult Americans have hyperuricemia, of whom 20% develop gout[7]. Thus hyperuricemia alone is often not sufficient for the expression of gout. Environmental factors (high dietary purine intake and alcohol) and genetic predisposition contribute to higher serum uric acid and gout risk[4,6,24]. Our study showed that alcohol intake and Q141K T/T, independently and jointly, associated with the risk of tophaceous gout. The joint risk among tophaceous gout carriers of Q141K T/T who are ever drinkers (OR ≥ 14.87) was significantly higher than for current drinkers (OR ≥ 5.11). The alcohol self-reporting is roughly accurate and is in accordance with previous reports that alcohol-associated disorders affect 42.2–54.7% of Taiwanese aboriginals[25] and 22.1% of Taiwanese Han[15]. Thus alcohol consumption by ethnicity has been similarly represented in our study.

There are limitations to our study that warrant attention.

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First, the record of current and past treatment of patients with gout or those with lower serum urate among aborigines was limited because of the relatively poor primary healthcare for the Aborigines. It is reported that aboriginal patients with tophaceous gout were not being treated for their disease on a regular basis[26]. In our study, the proportion of tophi in aboriginals with gout was 38% (203/533, Appendix 1) and higher compared to other reports (9.2%–17.2%)[26]. This may affect the gout onset and duration because the rate of formation of tophaceous deposits in primary tophaceous gout is correlated with the degree and duration of hyperuricemia. However, it should also be noted that progression to chronic tophaceous gout has numerous causes such as poor compliance with, ineffectiveness of, or inability to tolerate prescribed regimens, and serum urate levels have not been shown to directly correlate with tophi occurrence.

Second, we do not have details about the alcohol types consumed (e.g., beer or wine); they may contain varying amounts of purines being metabolized into uric acid. However, acute alcohol intake causes lactate production, and because lactate is an antiuricosuric agent, it will reduce renal urate excretion and exacerbate hyperuricemia[7]. Taking uricosuric medications (probenecid, sulfinpyrazone, and benzbromarone) in conjunction with alcohol consumption may alter the effectiveness of urate-lowering therapies. Last, a strong sex specificity of Q141K in men has been described[10,16]; however, we found no evidence for an interaction considering sex in our studied groups ($p > 0.05$), which might be due to the small number of women with gout, resulting in low power to detect the effect size of the variants. We found that *ABCG2* Q141K T have similar allele frequencies between men and women (test of homogeneity, $p_{\text{Breslow-Day test}} > 0.3$) by ethnicity and associated with gout among women in the 2 ethnic groups ($p < 0.05$; Appendix 4).

Our results corroborate with previous finding that *ABCG2* increases gout risk. Additionally, we showed the Q141K *ABCG2* variant increases severe or tophaceous gout. Further, alcohol consumption has an additive increase in the OR of alcohol drinkers who harbor the variant Q141K T/T. Our findings were consistently observed in 2 distinct ethnic groups from Taiwan, and highlight potentially exciting new clinical intervention and gout treatment opportunities.

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APPENDIX 1. Characteristics of the study participants.

	Taiwanese Han					Taiwan Aborigines				
	Tophaceous gout cases	Non-tophaceous gout cases	Controls	P_1	P_2	Tophaceous gout cases	Non-tophaceous gout cases	Controls	P_1	P_2
n	77	177	446			203	330	1105		
Age (SD), years	51.7 (14.2)	50.4 (15.0)	54.6 (14.9)	0.001	0.506	50.9 (13.2)	51.2 (14.9)	52.1 (16.9)	0.201	0.833
Men, n (%)	77 (100.0)	166 (93.8)	433(97.1)	0.322	0.038	170 (83.7)	237 (71.8)	449 (40.6)	<0.001	0.002
Age of onset (SD), years	42.2 (13.1)	44.1(14.8)		-	0.412	39.4 (13.9)	42.1 (15.8)		-	0.076
Duration of gout (SD), years	10.0 (7.7)	7.3 (6.2)		-	0.012	12.1 (8.5)	7.9 (6.8)		-	<0.001
Systolic pressure (SD), mmHg	132.9 (17.2)	134.7 (17.3)	132.0 (19.4)	0.170	0.479	140.7 (21.3)	137.8 (21.6)	131.2 (20.5)	<0.001	0.144
Diastolic pressure (SD), mmHg	81.6 (12.5)	85.2 (11.0)	83.6 (11.7)	0.613	0.040	90.0 (14.0)	88.1 (13.9)	83.5 (12.7)	<0.001	0.150
Body mass index (SD), kg/m^2	26.0 (4.2)	26.5 (3.5)	24.6 (3.4)	<0.001	0.340	25.4 (3.8)	27.1 (4.3)	26.3 (4.3)	0.486	<0.001
Hypertension, n (%)	17 (22.1)	51 (28.8)	83 (18.6)	0.012	0.265	92 (45.3)	141 (42.7)	345 (31.2)	<0.001	0.558
Type 2 diabetes mellitus, n (%)	2 (2.6)	2 (1.1)	13 (2.9)	0.268	0.388	23 (11.3)	19 (5.8)	83 (7.5)	0.792	0.020
Total cholesterol (SD), mg/dL	214.0 (42.1)	203.5 (43.2)	191.0 (38.6)	<0.001	0.074	184.9 (45.8)	188.3 (49.5)	184.7 (48.0)	0.374	0.431
Triglycerides (SD), mg/dL	244.0 (122.0)	192.5 (111.6)	155.6 (174.6)	<0.001	0.001	265.8 (263.4)	269.9 (277.0)	202.3 (256.5)	<0.001	0.867
Creatinine (SD), mg/dL	1.4 (0.4)	1.4 (0.4)	1.2 (0.2)	<0.001	0.320	1.2 (0.6)	1.1 (0.6)	1.0 (0.3)	<0.001	0.049
Uric acid (SD), mg/dL	8.9 (2.0)	7.8 (2.3)	6.2 (1.5)	<0.001	<0.001	9.3 (2.4)	9.2 (2.4)	7.1 (2.0)	<0.001	0.504
*Hyperuricaemia, n (%)	61 (79.2)	109 (61.6)	122 (27.4)	<0.001	0.006	169 (83.3)	283 (85.8)	672 (60.8)	<0.001	0.434
Alcohol use, n (%)	32 (41.6)	39 (22.0)	105 (23.5)	0.196	0.001	152 (74.9)	249 (75.5)	529 (47.9)	<0.001	0.881
Non-drinker	45 (58.4)	138 (78.0)	341 (76.5)			51 (25.1)	81 (24.6)	576 (52.1)		
Ever drinker	15 (19.5)	9 (5.0)	19 (4.3)			63 (31.0)	46 (13.9)	72 (6.5)		
Current drinker	17 (22.1)	30 (17.0)	86 (19.3)	0.023	<0.001	89 (43.8)	203 (61.5)	457 (41.4)	<0.001	<0.001

Plasma triglyceride levels were log-transformed to normality prior being used in statistical models.

P_1: data of continuous and categorical variables were analyzed by *t* test and chi-square test to make comparisons between gouty cases and controls.

P_2: tophaceous versus non-tophaceous gout cases.

*Hyperuricaemia was defined by urate levels exceeding 7.0 mg/dL and 6.0 mg/dL in men and women, respectively.

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APPENDIX 2. *ABCG2* rs2231142 [T/T] association with the age of visit to clinician and duration among tophaceous gout cases

	Tophaceous gout cases						Non-tophaceous gout cases					
	rs2231142 Q141K						rs2231142 Q141K					
	GG	GT	TT	*P*-trend*	β(SE) †	*P*-trend†	GG	GT	TT	*P*-trend*	β(SE) †	*P*-trend†
Taiwanese Han												
n	11	21	26				30	50	38			
Age of onset (SD), years	42.00(12.42)	42.95(13.49)	41.65(13.48)	0.8766	-1.26 (1.36)	0.3567	45.90(15.78)	43.66(15.72)	43.18(13.08)	0.4698	0.45 (0.92)	0.6248
Duration of disease (SD), years	6.66(4.92)	11.45(9.08)	10.23(7.30)	0.3389	1.24 (1.34)	0.3609	7.14(5.83)	7.40(6.31)	7.17(6.44)	0.9974	-0.08 (0.74)	0.9152
Taiwan aborigines												
n	29	78	71				58	86	62			
Age of onset (SD), years	45.22(12.11)	40.37(13.85)	35.89(13.78)	0.0014	-2.61 (0.81)	0.0015	46.15(14.39)	40.92(15.99)	39.91(16.21)	0.0316	-0.94 (0.61)	0.1271
Duration of disease (SD), years	9.72(7.25)	10.64(7.53)	14.58(9.30)	0.0019	2.61 (0.81)	0.0015	7.20(6.61)	7.76(6.41)	8.75(7.37)	0.2068	0.94 (0.61)	0.1271
Combined group												
n	40	99	97				88	136	100			
Age of onset (SD), years	44.33(12.12)	40.92(13.74)	37.44(13.87)	0.0049	-2.24 (0.67)	0.0010	46.06(14.79)	41.93(15.89)	41.16(15.11)	0.0325	-0.43 (0.52)	0.4046
Duration of disease (SD), years	8.88(6.77)	10.82(7.84)	13.41(8.98)	0.0017	2.27 (0.68)	0.0010	7.18(6.32)	7.63(6.35)	8.15(7.04)	0.3091	0.64 (0.47)	0.1758

SD: standard deviation; SE: standard error. *P-trend was obtained by conducting general linear model without covariates adjustment. †β (regression coefficient) and their P-trend were represent the changes in age of onset and duration of disease for per copy increment in the risk allele after adjustment of age, sex, body mass index, total cholesterol, log (triglycerides), creatinine and hypertension, and, for the pooled analysis, ethnicity, using a general linear model. Estimates per risk allele copy in the tophaceous gout cases, corrected for covariates, showed an earlier age of onset and longer duration of disease at rs2231142 [T] of -1.26 and -2.61 years and 1.24 and 2.61 years in both ethnicities, and -2.24 years (P-trend=0.0010) and 2.27 years (P-trend=0.0010) in pooled group.

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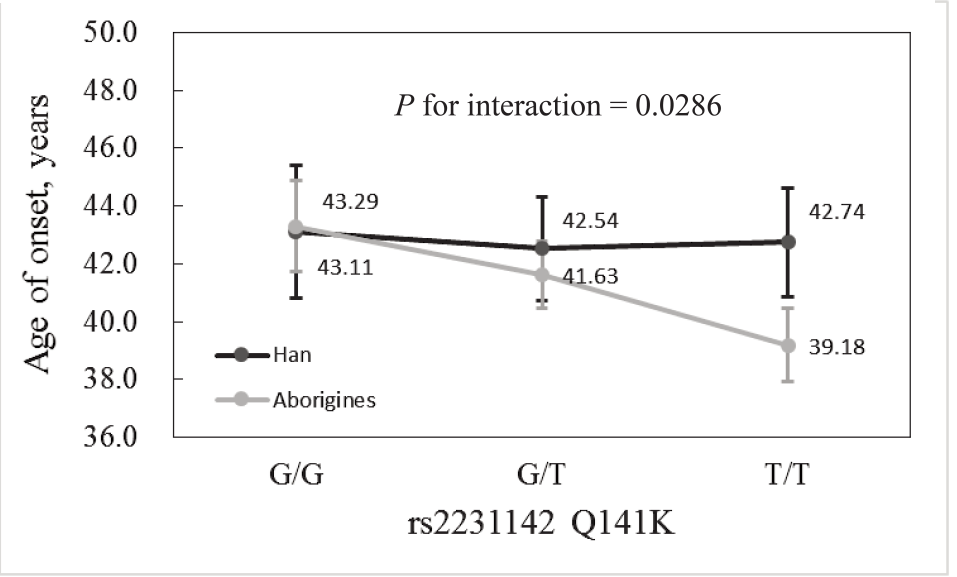
APPENDIX 3. Interaction of ethnicity and rs2231142 Q141K with age of onset among gout cases. A general linear model including ethnicity × rs2231142 Q141K interaction term was applied. P for interaction was adjusted for age, sex, body mass index, total cholesterol, log (triglycerides), creatinine, alcohol use, and hypertension. Error bars indicate 95% CI.



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APPENDIX 4. *ABCG2* rs2231142 Q141K[T] association with risk of gout

		Gout cases				Controls				Allelic OR (95% CI)*	Allelic *P*-value
	1/2	11	12	22	1	11	12	22	1		
Taiwanese Han											
Men											
rs2231137 V12M	C/T	124	98	21	0.71	193	178	62	0.65	1.32 (1.04-1.68)	2.25×10^{-3}
rs2231142 Q141K	T/G	82	104	57	0.55	47	175	211	0.31	2.73 (2.17-3.43)	3.84×10^{-18}
Women											
rs2231137 V12M	C/T	7	3	1	0.77	6	6	1	0.69	1.51 (0.41-5.54)	0.5322
rs2231142 Q141K	T/G	7	0	4	0.64	2	5	6	0.35	3.31 (1.01-10.83)	0.0449
All†											
rs2231137 V12M	C/T	131	101	22	0.71	199	184	63	0.65	1.33 (1.05-1.69)	1.71×10^{-3}
rs2231142 Q141K	T/G	89	104	61	0.56	49	180	217	0.31	2.76 (2.20-3.45)	3.87×10^{-19}
Taiwan aborigines											
Men											
rs2231137 V12M	C/T	232	145	30	0.74	204	194	51	0.67	1.46 (1.18-1.80)	4.12×10^{-4}
rs2231142 Q141K	T/G	138	171	98	0.55	85	210	154	0.42	1.66 (1.37-2.01)	1.90×10^{-7}
Women											
rs2231137 V12M	C/T	67	50	9	0.73	314	277	65	0.69	1.22 (0.90-1.65)	0.2018
rs2231142 Q141K	T/G	37	59	30	0.53	138	308	210	0.45	1.39 (1.06-1.83)	0.0159
All†											
rs2231137 V12M	C/T	299	195	39	0.74	518	471	116	0.68	1.36 (1.15-1.60)	2.77×10^{-4}
rs2231142 Q141K	T/G	175	230	128	0.54	223	518	364	0.44	1.54 (1.33-1.79)	6.79×10^{-9}

1, risk allele; 2, non-risk allele; 11 indicate the at-risk homozygote, 12 indicate the heterozygote, and 22 indicate wild-type homozygote; OR: odds ratio; CI: confidence interval. Controls' genotypes were used to confirm Hardy-Weinberg equilibrium ($p>0.05$). *Allelic ORs calculated by logistic regression models. †*ABCG2* rs2231137 V12M and rs2231142 Q141K were revealed homogeneity between males and females by ethnicity in the association with gout ($P_{Breslow\text{-}Day\ test}>0.30$).

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