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Original Article

Association analysis between genetic variants in interleukin genes among different populations with hyperuricemia in Xinjiang Autonomous Region

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Abstract: To investigate whether functional variants of five interleukin genes (IL-1β, IL-10, IL-8, IL-18 and IL-18RAP) are associated with susceptibility to hyperuricemia among different nationalities (including Uygur, Kazak and Han populations) in the Xinjiang Autonomous Region of China. A total of 884 hyperuricemia patients and 1316 matched controls were recruited from the First Affiliated Hospital of Xinjiang Medical University in Urumqi. After genotyping of rs4073 in IL-8, rs16944 in IL-1, rs187238 in IL-18, rs1800871 in IL-10 and rs13015714 in IL-18RAP by TaqMan allele discrimination assays, an association analysis was performed using the χ^2 test as well as a genotype-phenotype analysis. For the Uygur population, IL-8 rs4073, IL-18 rs187238 and IL-18RAP rs130154 polymorphisms were all associated with hyperuricemia (P<0.001 by genotype and P=0.008, OR 0.802 by allele for IL-8; P=0.01 by genotype and P=0.006, OR 1.332 by allele for IL-18 rs187238; P=0.007 by genotype and P=0.005, OR 1.27 by allele for IL-18RAP rs130154). For the Kazak population, only IL-18 rs187238 showed statistical significance with hyperuricemia (P=0.002 by genotype and P=0.007, OR 1.823 by allele). However, no differences were found between the five SNPs and hyperuricemia among the Han population. This study demonstrated genetic polymorphisms of different interleukin genes related to hyperuricemia vary in different nationalities in the Xinjiang Autonomous Region because of different geographical environments. IL-8, IL-1RL1 and IL-18 might be involved in the development of hyperuricemia in the Uygur population, whereas only IL-18 might be involved in the Kazak population.

Keywords: Hyperuricemia, susceptibility, interleukins, nationalities

Introduction

Uric acid is a breakdown product of purines, and its excretion allows the removal of nitrogenous wastes from the body. Recently, Rock et al. suggested that uric acid may play an essential role in immunity as a danger signal that acts as endogenous adjuvant when tissues are injured during immune presentation [1]. The excessive accumulation of blood uric acid-hyperuricemia causes significant damage to the body, including gouty attacks, tophi, and nephrolithiasis [2, 3]. In the present study, hyperuricemia was defined according to sex-specific SUA (serum uric acid) levels: SUA≥420 mmol/L (7.0 mg/dL) for men and SUA≥360 mmol/L (6.0 mg/dL) for women [4, 5]. In 2011, William et al. [6] suggested that hyperuricemia might be partially responsible for a proinflammatory endocrine imbalance in adipose tissue, as it has a close relationship with inflammatory responses. Monosodium urate (MSU) crystals have been shown to be deposited in or around the joints and tissues to stimulate inflammatory signals by activating macrophages through the NALP3 (NACHT, LRR and pyrin domain-containing protein) inflammasome [7]. This subsequently leads to the processing of procaspase-1 to caspase-1 and the production and secretion of active IL-1β and IL-18, eventually leading inflammatory responses and arthritic disease [8]. The hallmark of the response to MSU is

acute inflammation with an infiltration of neutrophils. In recurrent attacks gouty arthritis the plasma concentrations of IL-18, IL-6, and IL-8 were elevated caused by constantly rising serum uric acid levels [9]. Studies focused on the interleukins produced by neutrophils suggest they play extremely important roles during the inflammatory process.

IL-1β, an important inflammatory cytokine, is considered a master cytokine in both types of arthritis, and its relationship with innate inflammation has been identified [10]. IL-8 is a chemokine related to the initiation and amplification of acute and chronic inflammatory processes [11], while IL-10 is a cytokine with anti-inflammatory and stimulatory properties that can indirectly inhibit cytokine production [12], which might be related to gout or hyperuricemia. IL-18 is considered to be relevant to autoimmune diseases [13-15], while the IL-18 receptor accessory protein gene (IL-18RAP) codes for the beta-chain of IL-18R (IL-18 receptor), which forms the signaling chain of the IL-18 receptor complex and is crucial for IL-18 signaling [16]. This indicates IL-18RAP is also a functionally relevant candidate gene for hyperuricemia. These interleukins released by neutrophils are related to inflammatory processes; however, no study has reported on the relationship between interleukins and hyperuricemia.

China is the world's largest developing country and is characterized by distinct regional, multiethnic and economic diversity. There has been common consensus that Uygur, Kazak and Han populations in the Xinjiang Autonomous Region have different racial genes based on genetics and different living habits. However, to date, no national cross-sectional studies have been performed to determine the genetic variants of hyperuricemia in different nationalities in China. Furthermore, no studies have focused on the relationship between the interleukin gene polymorphisms and hyperuricemia. Therefore, we aimed to identify differences between Han, Uygur and Kazak ethnicities based on the polymorphisms of rs4073 in IL-8, rs16944 in IL-1, rs187238 in IL-18, rs1800871 in IL-10 and rs13015714 in IL-18RAP.

Materials and methods

Study subjects

A total of 884 hyperuricemia patients and 1316 matched controls of three nationalities including Uygur, Kazak and Han populations were recruited from the First Affiliated Hospital of Xinjiang Medical University in Urumqi, and cases and controls for Kazaks were recruited from Toli County in the Tacheng area of the Xinjiang Autonomous Region. There were 228 male patients (mean age 42.50±12.45 years) with hyperuricemia and 443 ethnically matched controls (mean age 42.85±11.79 years) of Han ethnicity; 576 male patients (mean age 42.92±12.87 years) with hyperuricemia and 600 ethnically matched controls (mean age 44.00±11.10 years) of Uygur ethnicity and 80 male patients (mean age 45.31±13.23 years) with hyperuricemia and 273 ethnically matched controls (mean age 43.55±11.88 years) of Kazak ethnicity. Subjects that underwent random testing three times and who had serum uric acid levels ≥420.0 μmol/l (7.0 mg/dl) without other diseases that could increase blood uric acid were diagnosed with primary hyperuricemia. Samples from controls without a personal or familial history of hyperuricemia or other serious illness were collected. Biochemical parameters including blood glucose, uric acid, total cholesterol (TC), triglycerides (TG), urea nitrogen, creatinine in the plasma and patients' characteristics including demographic data and clinical parameters (disease-related complications) were measured or recorded. All subjects provided written informed consent, and the study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University.

Genotyping

Genomic DNA was extracted from peripheral blood leukocytes (5 ml) using standard methods. The target region was amplified using the TaqMan allele discrimination assay with a VIC/FAM labeled probe. The segments of the five polymorphisms were replicated using the following primers: forward primer 5'TTATCTAGAAATAAAAAAGCATACA3' and reverse primer 5'TTGATAATTCACCAAATTGTGGAGC3' for rs4073 of IL-8; forward primer 5'TACCTTGGGTGCTGTTCTCTGCCTC3' and reverse primer 5'GGAGCTCTCTGTCAATTGCAGGAGC3' for rs16944 of IL-1; forward primer 5'TGTAATATCACTATTTTCATGAAAT3' and reverse primer 5'TTTTCTTCCGTAAAAGTTGGGGCTC3' for rs187238 of IL-18; forward primer 5'AGTGAGCAAACTGAGGCACAGAGAT3' and reverse primer 5'TTACATCACCTGTACAAGGGTACAC3' for rs1800871 of IL-10; and forward primer 5'CGGCTATGGGTTTCCCTTTTCC-

Table 1. Demographic and clinical characteristics of the study population of the three nations

Parameter	Kazak			Uygur			Han		
	Hyperuricemia (n=80)	Normal (n=273)	P	Hyperuricemia (n=576)	Normal (n=600)	P	Hyperuricemi (n=228)	Normal (n=443)	P
Age (years)	45.31±13.23	43.55±11.88	0.258	42.92±12.87	44.00±11.10	0.124	42.50±12.45	42.85±11.79	0.717
BMI (kg/m^2)	26.45±4.66	24.67±3.66	0.002	27.43±4.79	26.46±4.10	<0.001	25.41±2.37	24.62±2.84	<0.001
Systolic pressure (mmHg)	126.13±18.50	118.92±16.93	0.001	126.12±19.32	124.59±18.17	0.162	125.94±16.05	125.64±18.76	0.830
Diastolic pressure (mmHg)	82.53±13.15	82.05±45.56	0.926	80.56±13.19	81.26±13.74	0.372	82.66±10.55	81.73±12.56	0.342
Blood glucose (mmol/L)	4.91±1.11	5.12±1.57	0.270	5.06±1.38	4.95±1.31	0.159	5.26±1.20	5.11±0.846	0.066
Uric acid (μmol/L)	479.89±59.36	284.48±71.84	<0.001	498.12±87.39	290.80±69.835	<0.001	467.40±47.77	329.73±53.83	<0.001
Triglycerides (mmol/L)	1.98±1.19	1.56±1.16	0.006	2.34±1.85	2.21±2.01	0.249	2.58±1.79	1.89±2.04	<0.001
Total cholesterol (mmol/L)	4.85±1.33	5.04±5.19	0.752	4.26±1.54	4.22±1.50	0.635	5.05±1.02	4.96±1.06	0.302
Urea nitrogen (mmol/L)	5.65±1.65	4.90±1.82	0.001	6.25±4.06	5.02±1.99	<0.001	5.17±1.26	5.20±1.220	0.722
Creatinine (μmol/L)	73.80±25.40	74.80±38.93	0.827	88.66±44.75	75.43±33.03	<0.001	82.10±15.93	77.32±14.23	<0.001

Table 2. The distribution of genotypic and allelic frequency of IL-8 rs4073, IL-1 rs16944, IL-18 rs187238, IL-10 rs1800871 and IL-18 RAP rs130154 between cases and controls

Polymorphism	Kazak			Uygur			Han		
	(1) Hyperuricemia patients	(2) Control	P OR (95% CI)	(1) Hyperuricemia patients	(2) Control	P OR (95% CI)	(1) Hyperuricemia patients	(2) Control	P OR (95% CI)
IL-8 rs4073	n=80	n=224		n=576	n=599		n=228	n=384	
Genotypes									
AA	10	49	0.202	151	153	<0.001	61	88	0.421
AT	40	99		223	306		96	181	
TT	30	76		202	140		71	115	
Alleles									
A	100	251	0.531	628	586	0.008	238	411	0.654
T	60	197	0.892 (0.624-1.276)	526	612	0.802 (0.682-0.943)	218	357	1.055 (0.836-1.330)
IL-1 rs16944	n=80	n=208		n=576	n=599		n=222	n=373	
Genotypes									
GG	25	66	0.858	150	193	0.059	61	106	0.811
AG	42	103		294	274		104	180	
AA	13	39		132	132		57	87	
Alleles									
G	92	235	0.827	594	660	0.086	226	392	0.583

A	68	181	0.96 (0.664-1.387)	558	538	0.868 (0.738-1.021)	218	354	1.068 (0.844-1.351)
IL-18 rs187238	n=80	n=273		n=575	n=595		n=222	n=443	
Genotypes									
CC	45	205	0.002	361	406	0.01	168	337	0.666
CG	34	61		175	170		47	97	
GG	1	7		39	19		7	9	
Alleles									
C	124	471	0.007	897	982	0.006	383	771	0.700
G	36	75	1.823 (1.170-2.842)	253	208	1.332 (1.085-1.634)	61	115	1.068 (0.765-1.491)
IL-10 rs1800871	n=80	n=223		n=577	n=599		n=222	n=383	
Genotypes									
AA	23	56	0.812	144	156	0.723	94	160	0.793
AG	38	110		263	279		101	169	
GG	19	57		170	164		27	54	
Alleles									
A	84	222	0.554	551	591	0.442	289	489	0.661
G	76	224	0.897 (0.625-1.287)	603	607	1.066 (0.906-1.253)	155	277	0.947 (0.741-1.209)
IL-18 RAP rs130154	n=75	n=209		n=576	n=580		n=221	n=366	
Genotypes									
GG	15	27	0.313	102	120	0.007	50	93	0.094
GT	31	99		258	293		105	193	
TT	29	83		216	167		66	80	
Alleles									
G	61	153	0.378	462	533	0.005	205	379	0.073
T	89	265	0.842 (0.575-1.234)	290	627	1.27 (1.077-1.497)	237	353	1.241 (0.980-1.573)

Table 3. Association between the polymorphisms of IL-8 rs4073 (A/T) characteristics among hyperuricemia patients

dbSNP ID (allele 1/allele 2)*	(1) 1/1*	(2) 1/2*	(3) 2/2*	(1) vs. (2) vs. (3)	(1) vs. (2)	(1) vs. (3)	(2) vs. (3)	(1) vs. (2+3)	(1+2) vs. (3)
	(n)	(n)	(n)	*P* value	*P* value	*P* value	*P* value	*P* value	*P* value
				OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
IL-8 rs4073(A/T) of Uygur	151	223	202						
Demographic characteristics (Mean ± SD)									
Age (yr)	29.53±10.11	41.16±8.45	54.88±6.06	0.000	0.117	0.107	0.564	0.000	0.000
BMI (kg/m^2)	26.47±5.12	27.64±4.59	27.93±4.66	0.012	0.527	0.004	0.020	0.451	0.060
WHR	0.93±0.09	0.96±0.09	0.97±0.09	0.000	0.172	0.000	0.004	0.907	0.777
Serum biochemistry (Mean ± SD)									
Systolic pressure (mmHg)	125.09±19.90	125.65±20.26	127.42±17.77	0.479	0.346	0.263	0.784	0.166	0.869
Diastolic pressure (mmHg)	80.10±14.49	80.48±13.20	80.99±12.17	0.814	0.687	0.529	0.786	0.597	0.094
Blood Glucose (mmol/L)	4.90±1.13	5.00±1.28	5.25±1.63	0.049	0.066	0.021	0.506	0.003	0.577
Uric acid (μmol/L)	495.18±87.10	488.83±72.87	510.59±100.32	0.033	0.035	0.329	0. 844	0.033	0.080
Triglycerides (mmol/L)	1.97±1.72	2.63±2.11	2.29±1.57	0.003	0.056	0.109	0.001	0.109	0.001
Total cholesterol (mmol/L)	4.17±1.46	4.44±1.43	4.13±1.69	0.081	0.126	0.995	0.211	0.010	0.105
Urea nitrogen (mmol/L)	5.78±2.79	5.83±2.99	7.06±5.51	0.002	0.016	0.014	0.997	0.000	0.026
Creatinine (μmol/L)	81.76±32.41	82.67±26.23	100.42±62.99	0.000	0.001	0.001	0.989	0.000	0.035
Clinical characteristics									
Age at diagnosis (yr)									
<25	26/151	0/224	0/202	0.000	0.000	0.000		0.000	0.000
					2.792 (2.426-3.213)	2.616 (2.279-3.002)		4.408 (3.778-5.143)	1.579 (1.482-1.682)
25-44	115/151	183/224	0/202	0.000	0.193	0.000	0.000	0.000	0.000
					0.716 (0.432-1.186)	6.611 (4.893-8.932)	5.927 (4.484-7.835)	4.242 (2.785-6.460)	3.623 (2.996-4.382)
45-64	4/151	29/224	184/202	0.000	0.001	0.000	0.000	0.000	0.000
					0.183 (0.063-0.532)	0.003 (0.001-0.008)	0.015 (0.008-0.027)	0.027 (0.010-0.075)	0.009 (0.005-0.017)
65-84	6/151	11/224	18/202	0.103	0.669	0.068	0.102	0.210	0.036
					0.801 (0.290-2.215)	0.423 (0.164-1.093)	0.528 (0.243-1.147)	0.566 (0.230-1.392)	0.485 (0.244-0.964)
Past history									
Hypertension	30/151	49/224	51/202	0.467	0.640	0.234	0.412	0.362	0.252
					0.885 (0.532-1.475)	0.734 (0.441-1.223)	0.829 (0.529-1.298)	0.808 (0.511-1.278)	0.790 (0.528-1.182)
Diabetes	4/151	12/224	11/202	0.388	0.203	0.197	0.968	0.169	0.522
					0.481 (0.152-1.520)	0.472 (0.147-1.514)	0.983 (0.424-2.279)	0.477 (0.162-1.402)	0.774 (0.352-1.701)
Obesity&	38/151	59/224	61/202	0.724	0.799	0.447	0.569	0.574	0.446
					0.940 (0.586-1.509)	0.832 (0.519-1.336)	0.885 (0.581-1.348)	0.886 (0.580-1.352)	0.864 (0.593-1.259)

*: The major allele was referred to as allele 1 and the minor allele as allele 2; Obesity&: Obesity is defined by the World Health Organization (WHO) as a BMI > 30 kg/m^2.

TTT3' and reverse primer 5'GTTAAATAACAG-TTCTGCCACAAAA3' for rs13015714 of IL-18-RAP. Probe and primers were both synthesized by Life Technologies Company. Polymerase chain reactions (PCR) were carried out in a final volume of 25 μl containing 2×PCR Master Mix of 12.5 μl, 20×SNP Genotyping Assay of 1.25 μl, and DNA sample and DNase-free water of 11.25 μl. The reaction was carried out as follows: 95°C for 3 min, followed by 95°C for 15 s and 60°C 1 min for 40 cycles. After expansion, we analyzed the genotypes combining a scatter diagram and the amplification curve.

Statistical analysis

SPSS 19.0 software was used for statistical analysis. The Student's t-test was used to assess a significant difference in demographic and clinical characteristics between cases and controls. Hardy-Weinberg equilibrium of the allele distribution was tested. The odds ratio (OR) and 95% confidence interval (CI) were used as a measure of the strength of relationships in the genotype distribution and allele frequencies between the cases and controls. Pearson's χ^2 test was used to compare the genotypic and allelic frequencies between controls and patients (if expected values were below 5, Fisher's exact test was used). An analysis of variance (ANOVA) was used to calculate the association between genotypes and demographic and clinical characteristics among patients of hyperuricemia, including age, Body Mass Index (BMI), blood pressure, Waist-to-Hip Ratio (WHR), hypertension, diabetes, obesity and serum biochemistry. *P* values less than 0.05 were considered statistically significant.

Results

Demographic and clinical characteristics of the study population

The clinical characteristics of three ethnic groups enrolled in the study are summarized in **Table 1**. Kazak subjects with hyperuricemia had significant higher BMI values, systolic pressure levels, uric acid levels, TG levels and urea nitrogen levels compared with controls. Uygur subjects with hyperuricemia had higher BMI values, uric acid levels, urea nitrogen and creatinine levels compared with controls and Han subjects with hyperuricemia had significantly higher BMI values, blood glucose levels, uric acid levels, TG levels and creatinine levels than controls (P<0.05). In addition, the population involved in the study was age-matched. There was no statistically significant difference of mean age between cases and controls among the three ethnic groups.

Hardy-Weinberg equilibrium

Analysis of the five gene polymorphisms demonstrated the genotype distributions all followed the Hardy-Weinberg equilibrium among the control population (P=0.123 in IL-8 rs4073, P=0.915 in IL-1 rs16944, P=0.345 in IL-18 rs187238, P=0.841 in IL-10 rs1800871 and P=0.765 in IL-18RAP rs130154).

Analysis of genotypic and allelic frequency

Associations between genotypic and allelic frequency of the five SNPs between cases and controls are shown in **Table 2**. There was a difference in the distribution of the SNPs between the Kazak, Uygur and Han people. For IL-8 rs4073, the distribution of allelic frequency was statistically significance (P<0.001 by genotype and P=0.008, OR 0.802, 95% CI [0.682-0.943] by allele) in the Uygur population, while no differences were observed in Kazak and Han people. For IL-1 rs16944 and IL-10 rs1800871, no statistical significance was observed in any of the three ethnic groups. For IL-18 rs187238, a C/G polymorphism, the G allele appeared to be the risk allele for predisposition to hyperuricemia for both Kazaks (P=0.002 by genotype and P=0.007, OR 1.823, 95% CI [1.170-2.842] by allele) and Uygurs (P=0.01 by genotype and P=0.006, OR 1.332, 95% CI [1.085-1.634] by allele), whereas there was no statistical significance among Han people. Similarly, for IL-18RAP rs130154, the distributions of allelic frequency showed statistical significance (P=0.007 by genotype and P=0.005, OR 1.27, 95% CI [1.077-1.497] by allele) in the Uygur population; however no differences were observed in Kazak and Han people by genotype or allele (**Table 2**).

Genotype-phenotype analysis

Because the polymorphisms of IL-8 rs4073 in Uygur people were significantly associated with hyperuricemia, ANOVA was used for the genotype-phenotype analysis of hyperuricemia patients (**Table 3**). A significantly different geno-

typic distribution was observed for age, BMI, WHR, serum blood glucose, uric acid, triglycerides, urea nitrogen levels and serum creatinine levels (P<0.05) (**Table 3**). In addition, patients with an AT genotype showed higher BMI and WHR than those with the AA genotype (27.64±4.59 vs. 26.47±5.12, P=0.004 for BMI; 0.96±0.09 vs. 0.93±0.09, P<0.001 for WHR). Moreover, for serum biochemistry analysis, genotypic frequencies demonstrated statistical differences in serum blood glucose (TT genotypes higher than AA genotypes, P=0.021), uric acid levels (AA genotypes higher than AT genotypes, P=0.035), triglycerides levels (AT genotypes higher than TT genotypes, P=0.001), urea nitrogen levels (AT genotypes higher than AA genotypes, P=0.016; TT genotypes higher than AT genotypes, P=0.014) and serum creatinine levels (AT genotypes higher than AA genotypes, P=0.001; TT genotypes higher than AT genotypes, P=0.001). For clinical characteristics data, patients with the AA genotype were younger than those with AT and TT genotypes. However, we did not observe significant differences in disease history among the three genotypes in the Uygur population.

Discussion

In this study, we enrolled 884 patients with hyperuricemia and 1316 matched controls to investigate whether the functional polymorphisms of five interleukin SNPs (rs4073 in IL-8, rs16944 in IL-1, rs187238 in IL-18, rs1800871 in IL-10 and rs13015714 in IL-18 RAP) were associated with hyperuricemia among the three nationalities of the Xinjiang Autonomous Region. We observed a significant difference in frequency between IL-8 rs4073 and IL-1RL1 rs130154 and hyperuricemia in the Uygur population, but no significant association between these two SNPs and hyperuricemia in the Kazak or Han population. This is in accord with a previous study on IL-8 and gout in the Han population [11]. Regarding IL-18 rs187238, we demonstrated that the frequency of the G allele was higher in hyperuricemia patients than in controls in both the Kazak and Uygur populations. However, we did not observe a significant association between IL-18 rs187238 and hyperuricemia in the Han population, which was also in accord with a previous study of the Han population in China [17]. There were no statistically significant differences among any ethnic groups for IL-1 rs16944 and IL-10 rs1800871 polymorphisms between the cases and controls. To our knowledge, this is the first report on the relationship between genetic variants of interleukin genes and different populations with hyperuricemia in the Xinjiang Autonomous Region in China.

Uric acid is a breakdown product of purines (ATP, GTP, and nucleic acids) and it is the final oxidation product. High levels of blood uric acid often reflect dietary choices, including a high intake of purine-rich foods and fructose-containing foods [18]. Hyperuricemia is a condition that occurs when blood uric acid levels are above 7.0 mg/dL, which increases the risk for gouty attacks, tophi, or both. Currently, it is important that we consider this condition, as the incidence of gout appears to be increasing. William et al. suggested that hyperuricemia might have a close relationship with inflammatory responses as uric acid increased the expression and secretion of MCP-1. Furthermore, lowering uric acid reduced macrophage infiltration [2]. Moreover, the mechanism of how uric acid causes gout includes activation of macrophages by uric acid crystals through the NALP3 inflammasome, which enhances the production and secretion of IL-1β to drive inflammation. IL-1β is a key mediator of inflammation and accordingly, IL-1β antagonists are effective therapeutics for gouty arthritis [19]. Moreover, Chapman [20] demonstrated that when isolated mononuclear cells were incubated with MSU crystals, IL-1 was released by monocytes. Similarly, IL-8 is an important chemokine related to the initiation and amplification of acute and chronic inflammatory processes [21]. Terkeltaub suggested that microcrystal-induced secretion of IL-8 by mononuclear phagocytes might mediate a number of forms of crystal-induced inflammation [22]. IL-18 and IL-10 also have important roles in mediating inflammation. Taku et al. [9] demonstrated that plasma concentrations of IL-18 were elevated in the presence of gouty arthritis. Moore [12], indicated IL-10 has anti-inflammatory and stimulatory activities, levels of which can be influenced by functional single-nucleotide polymorphisms in the IL-10 promoter [23]. IL-18RAP is also related to many immune and inflammatory diseases [24, 25] and polymorphisms of rs13015714, a G/T variation on human chromosome 2, contribute to the etiology of celiac disease, a chronic inflammation of the small intestine in genetically predisposed individuals [26].

China is a multi-ethnic country and the prevalence of hyperuricemia may vary because of the different geographical environment, dietary habits, lifestyle, and ethnic factors. The Xinjiang Autonomous Region is a region of various nationalities, including Uighur, Kazak and Han ethnic groups with unique genetic backgrounds [27, 28]. Previous studies investigated the association of the five interleukin gene polymorphisms with gout and hyperuricemia in other areas. Therefore, we focused on subjects from three ethnic groups in the Xinjiang Autonomous Region to determine whether there were differences between case and control populations.

This study demonstrated different genetic variants were present among the three ethnic groups. For the Uygur population, IL-8 rs4073, IL-1RL1 rs130154 and IL-18 rs187238 polymorphisms were all associated with hyperuricemia ($P<0.05$), while for the Kazak population only IL-18 rs187238 showed statistical significance with hyperuricemia ($P<0.05$). However, we did not observe an association between the five SNPs and hyperuricemia among the Han population. Therefore, this indicates the different nationalities in the Xinjiang Autonomous Region have different genetic variants that enhance susceptibility to inherited hyperuricemia. Because hyperuricemia is an important metabolic disease related to lifestyle and dietary habits and higher uric acid levels were independently associated with higher BMI [29], our results indicated that hyperuricemia patients were more likely to have higher BMI than normal subjects, independent of ethnic differences.

Several limitations of the current study should be considered, such as the small sample size and the single limited area of the population. Additional research is needed for further evaluation of the potential relationships between interleukin gene variants and hyperuricemia in a larger size sample. Overall, these results provide evidence that polymorphisms of different genes might vary by distinct regions.

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Disclosure conflict of interest

None.

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