Associations Between the NLRP3 and IL-1β Gene Polymorphisms and Gout Susceptibility

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Abstract

Objective Gout is a common form of inflammatory arthritis which characteristics by joint and surrounding soft tissues pain with sudden onset,fever,redness and swelling,caused by the monosodium urate crystals deposited.Studies have demonstrated that genetic factors occupies a certain role in the pathogenesis of gout.Therefore,in our study we aimed to explore the associations between the NLRP3 and IL-1β gene polymorphisms and gout susceptibility,in order to provide experimental basis for the diagnosis and treatment of gout furtherly.

Methods We selected 715 Han individuals as our research object which included 267 male gout patients and 448 male healthy controls.Recorded demographic informations and collected blood samples.Then measured biochemical indicators and extracted the genomic DNA.The genotypes of NLRP3 gene rs7525979,rs3806268 and rs10754558 loci and IL-1β gene rs16944,rs1143623 and rs1143634 loci were detected through polymerase chain reaction(PCR) amplification technique.All data were analysised used Statistical Package for Social Sciences version 23.0(SPSS 23.0) software.

Results The distribution of genotype and allele frequency were significant differences in gout patients and controls for rs3806268 of NLRP3 gene and rs1143634 of IL-1β gene(P<0.05).NLRP3 gene rs3806268 loci AA genotype compared with GG genotype in additive model(OR = 0.58,95%CI:0.41–0.84) and AA genotype compared with GG + GA genotype in recessive model(OR = 0.61, 95%CI:0.44–0.85) and IL-1β gene rs1143634 loci AA + GA genotype compared with GG genotype in dominant model(OR = 0.45, 95%CI:0.24–0.84) could reduced the risk of gout.TC and LDL-C concentrations were significantly differences when gout patients were divided into AA + GA and GG genotype groups (P<0.05).

Conclusion There are some associations between rs3806268 of NLRP3 gene and rs1143634 of IL-1β gene and gout susceptibility.Rs3806268 and rs1143634 loci variants may be the protect factors of gout.

1. Introduction

Gout is a kind of inflammatory arthritis caused by the monosodium urate(MSU) crystals deposited in joints and the surrounding soft tissues,which derives from long-standing hyperuricemia[1].The course of gout include four stages:asymptomatic hyperuricemia,acute gouty arthritis,intercritical gout and chronic gouty arthritis[2].Patients can suffer significantly attack mainly about the joint pain with sudden onset,fever,redness and swelling when acute gout episodes[3].This process can affect the patient's quality of life seriously,even functional disability,therefore,gout aroused people's attention increasingly.Nevertheless,with the continuous improvement of people's dietary patterns and lifestyle,the prevalence of gout are on the increase remarkable[4].A large number of epidemiological data showed that the prevalence of gout in the world is about 0.1–10% on average[5–6].In western developed countries,there are 3–6% of men and 1–2% of women have gout[7].There is evidenced that[8] the prevalence of gout is more than 1% in Japanese men who older than 30 years,and in China,there might be 2 per 100 inhabitants suffer from gout[9].

At present,the pathogenesis of gout is still in exploration.Previous studies have confirmed that environmental,diet and genetic factors play roles in the development and incidence of gout.For example,vegetarian diet can reduce the risk of gout in Taiwan by Chiu THT *et al*[10].And from a genetic standpoint,substantial genome-wide association studies(GWAS), meta-analyses and case-control studies have found that ABCG2,PKD2,SLC2A9,KCNQ1,SLC22A12,SLC17A1,NLRP3 and so on gene polymorphism are influence the susceptibility of gout[11–12].Researchers also agreed that genetic factors are the main factors affecting the onset of gout.

MSU,as endogenous danger signaling molecules,can activate the NOD-like receptors signaling pathways,to promote the inflammatory response,eventually causd acute gout.It can activation NLPR3 inflammatory corpuscle effectively,make the inactive IL-1β and IL-18 precursor into mature IL-1β and IL-18 and released into the extracellular,cause inflammation finally[13].Therefore,in this study we will select patients with gout and health individuals as our object,aiming at NLRP3 and IL-1β gene,through the method of molecular biology to detect SNP loci genotype,aim to discuss the associations between NLRP3 and IL-1β gene variants and gout susceptibility,in order to explore more genetic factors about the occurrence of gout,and provide experimental basis for the diagnosis and treatment of gout furtherly.

2.materials And Methods

2.1 Individuals

This study was approved by the medical ethics committee of the First Affiliated Hospital of Xinjiang Medical University and conducted by Helsinki Declaration.We recruited 715 individuals participate in the study totally,and all of them are males of Han.Among them,267 were patients with gout and 448 were healthy controls.All subjects were from a hospital in urumqi,xinjiang,during 2012–2019.All of the individuals were informed consent and signed the commitment.Inclusion criteria include the following points:(1)Gout diagnosis followed the criteria published by the American College of Rheumatology in 2015[14];(2)Controls choosed age-matched Healthy check-up crowd randomly; (3)Age between 20 to 70 years old;(4)There is no blood relationship between the participants.Rule out individuals who have cancer,blood disease,liver or renal dysfunction,autoimmune diseases or treatment with an anti-hyperuricemia agent recently.

2.2 Data Collection

Collected the informations about participants's demographic,diseases histories,medical histories and so on by the questionnaire.Measured height,weight,waist circumference,hip circumference and blood pressure,then record detailedly.Collected peripheral venous blood samples after an overnight fasting.Sufficient anticoagulation then packing into two pieces.

2.3 Index Detection

Taked out a peripheral venous blood samples,separated the serum used low speed centrifuge(3500r/h,3 min),then measured serum uric acid (SUA),triglycerides(TG),total cholesterol(TC),blood urea nitrogen(BUN),fasting plasma glucose(FPG),serum creatinine(SCR),high-density lipoprotein cholesterol(HDL-C) and low-density lipoprotein cholesterol(LDL-C) by an autoanalyzer(Modular 7060,Hitachi,Ltd,Japan) used the chemiluminescence methods.

2.4 Snp Selection And Genotyping

Selected six single nucleotide polymorphisms(SNPs) in NLRP3(rs7525979,rs3806268 and rs10754558) and IL-1β(rs16944,rs1143623 and rs1143634) gene for further genotyping used the International Haplotype Mapping(HapMap)(http://www.hapmap.org).According to the manufacturer's instructions,we extracted genomic DNA from peripheral venous blood samples used the genomic DNA extraction kits.Used the primers which had been

designed by Primer 3 software for polymerase chain reaction(PCR) amplification.Then samples were genotyped with TaqMan assays(Prism 3100;Applied Biosystems,USA).

Table 1
The PCR primers sequence of NLRP3 and IL-1β gene SNP loci

Gene/SNP	Primer-Forward	Primer-Reverse
NLRP3/rs7525979	CACTTCCAGTTTTTGCCGGG	GGGAATGGCTGGTGCTCAAT
NLRP3/rs3806268	GCTGTTTGACCCCGATGATGAG	CCCCAGGCTCCTCTGTGTCA
NLRP3/rs10754558	CTTTACGCCAGGGTGAGGAAGAC	AGCGGGAATGATGATATGAGCAA
IL-1β/rs16944	TAAATGGGTACAATGAAGGGCCA	CAATTTTCTCCTCAGAGGCTCCT
IL-1β/rs1143623	ACGTTGGATGATGTGCCAGGTATCGTGCTC	ACGTTGGATGACCTATTTCCCTCGTGTCTC
IL-1β/rs1143634	CTACTGGTGTTGTCATCAGAC	AGCTTTTTTGCTGTGAGTCCC

2.5 Statistical Analyses

Used Statistical Package for Social Sciences version 23.0(SPSS 23.0) software to analysis the data.We used *t*-test to compared the differences between groups in clinical characteristics after tested normality,the results were presented by means ± standard.Used Chi-squared test(x^2) to assessmented the Hardy-Weinberg equilibrium for the control group.Used x^2 test to analyzed the differences between groups in genotypes and alleles or Fisher's exact test if the expected values were 5.Used Logistic regression analysis model to tested the differences between groups in genetic model(additive,dominant,recessive),the strength of the relationships were assessed by Odds ratios(*OR*) and 95% confidence intervals(95%*CI*).All statistical tests were two-sides and the *P* value was 0.05 was considered statistically significant.

3.results

3.1 Comparison the clinical indicators in gout patients and controls

Through statistical analysis found that age is in balanced and comparable in two groups(*P* 0.05).BMI,DBP,SUA,GLU,BUN,CREA,TG,HDL-C and LDL-C had statistically significant differences between gout patients and controls(*P* 0.05),and excepted HDL-C,the concentration were higher in gout patients than in controls.Only SBP and TC had no significant differences between two groups(*P* 0.05).(Table 2).

Table 2
The comparison of clinical indicators in gout patients and controls

index	gout patients	controls	*t*	*P*
Age	46.52 ± 10.71	45.63 ± 11.26	-1.04	0.30
BMI	26.79 ± 3.53	25.02 ± 2.77	-7.45	**<0.01**
SBP	125.93 ± 13.64	124.57 ± 13.17	-1.31	0.19
DBP	81.25 ± 10.26	76.49 ± 9.27	-6.39	**<0.01**
SUA	448.12 ± 49.60	338.01 ± 50.07	-28.54	**<0.01**
GLU	5.70 ± 1.57	5.31 ± 0.98	-4.10	**<0.01**
BUN	5.34 ± 1.83	5.09 ± 1.25	-2.11	**0.04**
CREA	91.77 ± 25.83	85.73 ± 11.62	-4.28	**<0.01**
TG	1.94 ± 1.19	1.70 ± 1.09	-2.70	**<0.01**
TC	4.58 ± 1.05	4.67 ± 0.88	1.22	0.22
HDL-C	1.08 ± 0.29	1.33 ± 0.23	12.46	**<0.01**
LDL-C	2.75 ± 0.76	2.62 ± 0.71	-2.26	**0.02**

Remarks:BMI(body mass index),SBP(Systolic Blood Pressure),DBP(diastolic blood pressure),SUA(Serum uric acid),GLU(glucose),BUN(blood urea nitrogen),CREA(Creatinine),TG(triglyceride),TC(total cholesterol),HDL-C(high-density lipoprotein),LDL-C(low density lipoprotein).

3.2 Genotype and allele frequency distribution in gout patients and controls

First of all,assessmented the HWE for NLRP3 gene rs7525979,rs3806268 and rs10754558 loci and IL-1β gene rs16944,rs1143623 and rs1143634 loci in control group respectively,the results showed that all six loci meet the requirements(P>0.05).(Table 3).Then further analysis found that the distribution of genotype and allele frequency in gout patients and controls,only rs3806268 of NLRP3 gene and rs1143634 of IL-1β gene had significant differences(P<0.05).(Table 4).

Table 3
The analysis of Hardy-Weinberg equilibrium(HWE)

Gene	SNP	genotype	actual frequency	theoretical frequency	x^2	*P*
		CC	289	292		
NLRP3	rs7525979	CT	146	139	1.14	0.56
		TT	13	17		
		AA	106	113		
NLRP3	rs3806268	GA	238	224	1.75	0.42
		GG	104	111		
		CC	119	124		
NLRP3	rs10754558	GC	234	223	1.02	0.60
		GG	95	101		
		AA	107	103		
IL-1β	rs16944	GA	216	224	0.52	0.77
		GG	125	121		
		CC	169	168		
IL-1β	rs1143623	GC	211	213	0.03	0.99
		GG	68	67		
		AA	1	0.23		
IL-1β	rs1143634	GA	18	19.55	2.83	0.24
		GG	429	428.22		

Table 4
The distribution of NLRP3 and IL-1β gene SNP loci genotype and allele frequency in gout patients and controls

Gene/SNP	genotype and allele	gout patients	controls	x^2	*P*
NLRP3	CC	177(66.3)	289(64.5)		
rs7525979	CT	81(30.3)	146(32.6)	0.47	0.79
	TT	9(3.4)	13(2.9)		
	C	435(81.8)	724(80.8)	0.09	0.76
	T	99(18.5)	172(19.2)		
NLRP3	GG	59(22.1)	104(23.2)		
rs3806268	GA	118(44.2)	238(53.1)	8.93	**0.01**
	AA	90(33.7)	106(23.7)		
	G	236(44.2)	446(49.8)	4.18	**0.04**
	A	298(55.8)	450(50.2)		
NLRP3	GG	48(18.0)	95(21.2)		
rs10754558	GC	135(50.6)	234(52.2)	2.38	0.31
	CC	84(31.5)	119(26.6)		
	G	231(43.3)	424(47.3)	2.23	0.14
	C	303(56.7)	472(52.7)		
IL-1β	AA	61(22.8)	107(23.9)		
rs16944	GA	116(43.4)	216(48.2)	2.77	0.25
	GG	90(33.7)	125(27.9)		
	A	238(44.6)	430(48.0)	1.57	0.21
	G	296(55.4)	466(52.0)		
IL-1β	CC	104(39.0)	169(37.7)		
rs1143623	GC	120(44.9)	211(47.1)	0.33	0.85
	GG	43(16.1)	68(15.2)		
	C	328(61.4)	549(61.3)	0.003	0.96
	G	206(38.6)	347(38.7)		
IL-1β	GG	243(91.0)	429(95.8)		
rs1143634	GA	23(8.6)	18(4.0)	6.81	**0.02***
	AA	1(0.4)	1(0.2)		

Remarks:*meanused Fisher's exact test.

Gene/SNP	genotype and allele	gout patients	controls	x^2	*P*
	G	509(95.3)	876(97.8)	6.59	**0.01**
	A	25(4.7)	20(2.2)		
Remarks:*meanused Fisher's exact test.					

3.3 Correlation Analysis In Different Genetic Models

Selected additive,dominant and recessive genetic models to analysised the association between NLRP3 and IL-1β gene polymorphisms and gout.The results revealed that NLRP3 gene rs3806268 loci AA genotype could reduced the risk of gout compared with GG genotype in additive model(*OR* = 0.58,95%*CI*:0.41–0.84),and in recessive model AA genotype compared with GG + GA genotype could also reduced the risk of gout(*OR* = 0.61, 95%*CI*:0.44–0.85).AA + GA genotype compared with GG genotype in rs1143634 of IL-1β gene could reduced the risk of gout in dominant model(*OR* = 0.45, 95%*CI*:0.24–0.84).Beyond that,we not found any significant differences in gout patients and controls in different genetic models(95%*CI* include 1).(Table 5).

Table 5
The association between NLRP3 and IL-1β gene polymorphisms and gout in different genetic models

Gene/SNP	genetic models	genotype	gout patients	controls	*OR*	95%*CI*
NLRP3	additive	CC	177(66.3)	289(64.5)	1	
rs7525979		CT	81(30.3)	146(32.6)	0.89	0.37–2.11
		TT	9(3.4)	13(2.9)	0.80	0.33–1.96
	dominant	CC	177(66.3)	289(64.5)	1	
		CT + TT	90(33.7)	159(35.5)	1.08	0.79–1.49
	recessive	CC + CT	258(96.6)	435(97.1)	1	
		TT	9(3.4)	13(2.9)	0.86	0.36–2.03
NLRP3	additive	GG	59(22.1)	104(23.2)	1	
rs3806268		GA	118(44.2)	238(53.1)	0.67	0.44–1.02
		AA	90(33.7)	106(23.7)	**0.58**	**0.41–0.84**
	dominant	GG	59(22.1)	104(23.2)	1	
		AA + GA	208(77.9)	344(76.8)	0.94	0.65–1.35
	recessive	GG + GA	177(66.3)	342(76.3)	1	
		AA	90(33.7)	106(23.7)	**0.61**	**0.44–0.85**
NLRP3	additive	GG	48(18.0)	95(21.2)	1	
rs10754558		GC	135(50.6)	234(52.2)	0.72	0.46–1.12
		CC	84(31.5)	119(26.6)	0.82	0.58–1.16
	dominant	GG	48(18.0)	95(21.2)	1	
		CC + GC	219(82.0)	352(78.8)	0.81	0.55–1.20
	recessive	GG + GC	183(68.5)	329(73.4)	1	
		CC	84(31.5)	119(26.6)	0.79	0.57–1.10
IL-1β	additive	AA	61(22.8)	107(23.9)	1	
rs16944		GA	116(43.4)	216(48.2)	0.79	0.52–1.20
		GG	90(33.7)	125(27.9)	0.75	0.52–1.06
	dominant	AA	61(22.8)	107(23.9)	1	
		GA + GG	206(77.2)	341(76.1)	0.94	0.66–1.35
	recessive	AA + GA	177(66.3)	323(72.1)	1	
		GG	90(33.7)	125(27.9)	0.76	0.55–1.06
IL-1β	additive	CC	104(39.0)	169(37.7)	1	

Gene/SNP	genetic models	genotype	gout patients	controls	*OR*	95%*CI*
rs1143623		GC	120(44.9)	211(47.1)	0.97	0.62–1.53
		GG	43(16.1)	68(15.2)	0.90	0.58–1.40
	dominant	CC	104(39.0)	169(37.7)	1	
		GC + GG	163(61.0)	279(62.3)	1.05	0.77–1.44
	recessive	CC + GC	224(83.9)	380(84.8)	1	
		GG	43(16.1)	68(15.2)	0.93	0.62–1.41
IL-1β	additive	GG	243(91.0)	429(95.8)	1	
rs1143634		GA	23(8.6)	18(4.0)	0.57	0.04–9.10
		AA	1(0.4)	1(0.2)	1.28	0.08–21.86
	dominant	GG	243(91.0)	429(95.8)	1	
		AA + GA	24(9.0)	19(4.2)	**0.45**	**0.24–0.84**
	recessive	GG + GA	266(99.6)	447(99.8)	1	
		AA	1(0.4)	1(0.2)	0.60	0.04–9.55

3.4 The association between genotypes and Clinical indicators in gout patients

Lastly we analysised the association between genotypes and Clinical indicators in gout patients.The results obtained that TC and LDL-C concentrations were significantly differences when gout patients were divided into AA + GA and GG genotype groups (P 0.05).(Table 6).

Table 6
The association between rs1143634 genotype and Clinical indicators in gout patients

index	genotype		*t*	*P*
	AA + GA	GG		
BMI	26.38 ± 3.84	26.83 ± 3.50	0.35	0.56
SBP	121.21 ± 10.95	126.39 ± 13.87	3.15	0.08
DBP	80.46 ± 8.70	81.33 ± 10.42	0.16	0.69
SUA	452.99 ± 71.34	447.64 ± 47.09	0.25	0.62
GLU	5.74 ± 2.09	5.69 ± 1.52	0.02	0.90
BUN	5.00 ± 1.39	5.37 ± 1.87	0.90	0.34
CREA	82.31 ± 24.37	92.71 ± 25.83	3.58	0.06
TG	1.71 ± 0.98	1.96 ± 1.21	0.96	0.33
TC	4.04 ± 1.02	4.63 ± 1.04	7.07	**0.01**
HDL-C	1.05 ± 0.20	1.08 ± 0.30	0.30	0.59
LDL-C	2.40 ± 0.89	2.78 ± 0.74	5.76	**0.02**

Remarks:BMI(body mass index),SBP(Systolic Blood Pressure),DBP(diastolic blood pressure),SUA(Serum uric acid),GLU(glucose),BUN(blood urea nitrogen),CREA(Creatinine),TG(triglyceride),TC(total cholesterol),HDL-C(high-density lipoprotein),LDL-C(low density lipoprotein).

4.discussion

Gout is a self-limited inflammatory joint disease which pathogenesis is complex and it attack is the outcome of combined action of multiple factors.Such as excessive intake sea food or alcohol is considered the predominant risk factor of gout,and the result from Horvathova V *et al* revealed that[15] as the increase of the age,the risk of gout is also increasely and the gout patients compare to healthy individuals have higher BMIs.Studies have shown that[16–18] there are close correlations between gout and kidney disease,obesity,hypertension,diabetes mellitus,cardiovascular and cerebrovascular diseases and so on.Our analysis showing that BMI,DBP,SUA,GLU,BUN,CREA,TG,HDL-C and LDL-C are the risk factors of gout which in line with most of the research conclusion[19–20].However,in particular,gout is a polygenic hereditary disease and genetic factors are still play crucial role in gout.

NLRP3 belongs to NOD-like receptor protein family which as pattern-recognition receptors,in order to identify danger signals of endogenous and exogenous,participate the processing and secretion of inflammatory cytokines,to induced the inflammation or apoptosis in cell eventually.MSU crystals can effectively activation the NLRP3 inflammasome as irritant.To begin with,it can act on NLRP3 protein in macrophages,activation Leucine repeat (LRR) at the C-terminus of NLRP3 protein;then recruiting apoptotic-related spot-like protein(ASC) by pyrin domain (PYD) area of NLRP3 protein;at that time,ASC through interaction of caspase recruitment domains prompt pro-caspase-1 into the activation of caspase-1.The activation of caspase-1 can pyrolysis pro-IL-1β,make it convert to mature bioactive IL-1β and release to extracellular which cause inflammation[21–23].There are many pathogenesis of gout,but some scholars believe that MSU crystals stimulus NLRP3 protein lead to the release of IL-1β have a crucial role in gout.And

increasing evidence indicates that[24–26] NLPR3 participate the onset of gout,diabetes,rheumatoid arthritis,systemic lupus erythematosus,Sjogren's syndrome,atherosclerosis,autoinflammatory syndromes and so on.

IL-1β is a kind of pro-inflammatory cytokines,to a certain extent,production and release of IL-1β can resistance infection,but at the same time,there are correlations with gout,rheumatoid arthritis,chronic kidney disease,atherosclerosis and so on[27–28].Studies have demonstrated that[29] IL-1β can promote the recruitment of neutrophil in the part of inflammation so that cause gout.In addition,IL-1β can make the person produces strong pain by activation injured receptor which exist in peripheral sensory nerve system sensitively and directly.The processing and secretion of IL-1β not only can through NOD-like receptor signaling pathways,but also can by Toll-like receptor signaling pathways.When MSU crystals are identified by Toll-like receptor,TLRs are able to interact with MyD88,make the MyD88 activation,leading to the activation of nuclear factor kappa B (NF-κB) and enter the nucleus to produce IL-1β,cause inflammation eventually through the cascade amplification effect[30–31].

The associations between NLRP3 and IL-1β gene polymorphisms and diseases susceptibility have been studied.The results from a meta-analysis of Lee YH et al have revealed that rs10754558 of NLRP3 gene variant was no association with autoimmune and inflammatory diaeases[32].There was correlation between rs3806268 of NLRP3 gene polymorphism and nontuberculous mycobacteria lung disease in female by Wu MF et al[33].And studies have observed that rs16944 loci variant of IL-1β gene has no association with breast cancer but rs1143634 carriers T allele may reduced the risk of rheumatoid arthritis[34–35].Our results found that the distribution of genotype and allele frequency in rs3806268 of NLRP3 gene and rs1143634 of IL-1β gene had significant differences in gout patients and controls(P<0.05),and further explore discovered that NLRP3 gene rs3806268 loci AA genotype and rs1143634 of IL-1β gene AA + GA genotype was protective factors for gout(95%CI<1).Our results were consistent with Deng J et al and Wang LF et al,but did not agree with the result of Zhang QB et al[36–38].

Limitations

This research is still exist some limitations,summarized as followed:(1)Sample size is not big enough and the object of this study are collected from the same hospital;(2)This research is a case control study,but more prospective studies are necessary in the future;(3)This study did not consider geographical factors,thus the results can not promotion widely;(4)If this study gain the detection of the cytokine and mRNA level,the results may be more persuasive.

5.conclusions

In our study,we detected six loci include rs7525979,rs3806268,rs10754558,rs16944,rs1143623 and rs1143634 to analysised the association between the NLRP3 and IL-1β gene polymorphisms and gout susceptibility.Our results found that there are some associations between rs3806268 of NLRP3 gene and rs1143634 of IL-1β gene and gout susceptibility and rs3806268 and rs1143634 loci variants may be the protect factors of gout.

Ethics approval and consent to participate:

This study was approved by the medical ethics committee of the First Affiliated Hospital of Xinjiang Medical University and conducted by Helsinki Declaration. All of the individuals were informed consent and signed the commitment.

Consent for publication:

All authors agreed to publish.

Declarations

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Consent for publication: All authors agreed to publish.

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