Genetic association between the *PTPN22, IRF5* and *TYK2* gene variants and susceptibility to juvenile idiopathic arthritis

YUFENG QIAN, BINGQIAN CHEN, ZHENGFEI WANG and YUQIN PENG

Department of Orthopedics, Changshu Hospital Affiliated to Soochow University, First People's Hospital of Changshu City, Changshu, Jiangsu 215500, P.R. China

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Abstract. Juvenile idiopathic arthritis (JIA) refers to a group of chronic childhood arthropathies of unknown etiology. In the present study, the genetic association between the variants in *PTPN22, IRF5 and TYK2* genes and susceptibility to JIA was investigated. The distributions of 16 variants in *PTPN22*, *IRF5* and *TYK2* genes were analyzed by direct sequencing in 378 patients with JIA and 378 healthy controls. Odds ratios and 95% confidence intervals were used to evaluate the association between the gene variants and JIA. The gene-gene interactions were investigated using multifactor dimensionality reduction. All allelic and dominant models of *PTPN22* rs1214414, rs1214418, rs1746853, rs3765598 and rs3811021 were significantly associated with JIA risk (P<0.05). *IRF5* rs10954213 in both allelic and dominant models, as well as the allelic model of rs2004640, was significantly related to JIA risk (P<0.05). In addition, the allelic, recessive and dominant models of *TYK2* rs280500, rs280519, rs2304256 and rs12720270 were significantly related to JIA risk (P<0.05). In addition, three haplotypes (H_{CAGTCC}, H_{CAGTTC} and H_{CGTTCT}) in *PTPN22* gene, three haplotypes (H_{DTAA}, H_{ITAC} and H_{DTGC}) in *IRF5* gene and two haplotypes (H_{AGGAT} and H_{GAGGT}) in *TYK2* gene were associated with the risk of JIA (P<0.05). Furthermore, a three-way interaction between *IRF5* rs10954213, rs2004640 and *PTPN22* rs1214414 was shown to be associated with JIA risk. In conclusion, *PTPN22* rs1214418, rs1746853, rs3765598, *IRF5* rs2004640, *TYK2* rs280500, rs2304256 and a three-way interaction between *IRF5* rs10954213, rs2004640 and *PTPN22* rs1214414 may be risk factors for JIA.

Correspondence to: Mr Yufeng Qian, Department of Orthopedics, Changshu Hospital Affiliated to Soochow University, First People's Hospital of Changshu City, 1 Shuyuan Street, Changshu, Jiangsu 215500, P.R. China
E-mail: yarbj@163.com

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Introduction

Juvenile idiopathic arthritis (JIA) refers to chronic inflammation of the joints in children under 16 years of age that persists for more than six weeks (1,2). It is the most common rheumatoid disease in childhood, characterized by manifestations and recurrent arthritis, with a prevalence of 1/10,000 (3). The pathogenesis of JIA is not well understood and may be related to many factors, such as infection, immunity and heredity (4). An increasing number of publications have confirmed that JIA has a complex genetic background. One of the most studied is human leukocyte antigen (HLA) (5). In addition, certain *HLA* loci have been shown to be associated with JIA (6). The genetic associations between non-*HLA* genes including protein tyrosine phosphatase non-receptor type 22 (*PTPN22*) (7), Toll-like receptor 4 (*TLR4*) (8), *TNF-α* (9) and JIA susceptibility have been extensively studied and confirmed.

PTPN22, located in 1p13.2, encodes lymphospecific protein tyrosine phosphatase (LYP), which is a member of the family that inhibits T-cell activation and serves an important role in immune homeostasis (10). A variant of the *PTPN22* gene (rs2476601) is reported to be related to multiple autoimmune diseases, including lupus erythematosus (SLE), rheumatoid arthritis (RA) and ankylosing spondylitis (AS) in Caucasian and Asian populations (10-12). Multiple studies have suggested that *PTPN22* rs2476601 is associated with JIA in Caucasian (13,14) and Chinese Han populations (15). However, studies have suggested that *PTPN22* rs2476601 is not polymorphic in the Chinese Han population (10,11). Furthermore, the studies referred to the rare relationship between other variants in the *PTPN22* gene and JIA risk. Thus, it is necessary to investigate new JIA-related loci in the *PTPN22* gene.

Chronic arthritis, a common feature of RA, AS, SLE and JIA, is suggested to be associated with dysregulation of the immune response (16). IFN and IFN regulatory factors serve an important role in the immune response, as well as in the occurrence and progression of autoimmune diseases (17). IFN regulatory factor 5 (IRF5), a member of the interferon regulatory factor family, is a class of transcription factors that mainly regulate the expression of IFN and IFN responsive genes (18). The *IRF5* gene can induce IFN production and participate in the expression of inflammatory factors, which suggests that the *IRF5* gene may serve a role in the pathogenesis of

autoimmune diseases (19). In addition, tyrosine kinase 2 (TYK2), a member of the receptor tyrosine kinase Janus kinase (JAK) family, has been shown to serve an important role in the type I IFN signaling pathway (20). Furthermore, *IRF5* and *TYK2* genes variants are suggested to be related to the susceptibility of autoimmune diseases including SLE, RA and multiple sclerosis (MS) (21-23). However, few studies on the genetic association between the *IRF5* and *TYK2* gene variants and JIA susceptibility have been reported.

To further evaluate the role of the variants in *PTPN22, IRF5 and TYK2* genes in the pathogenesis of JIA, a case-control study on the genetic associations between the variants in *PTPN22, IRF5* and *TYK2* genes and JIA risk was performed in a Han Chinese population by using direct sequencing.

Materials and methods

Subjects. The protocol of the present study was performed following the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments and approved by the Local Ethics Committee of the Changshu Hospital affiliated with Soochow University (protocol number: EC-19-024). Written informed consent was obtained from the participants' parents before the study.

A total of 378 healthy individuals from Changshu Hospital Affiliated to Soochow University (between 06/01/2019 and 12/31/2020) were randomly selected as the normal control group (67 male and 311 female participants), with an average age of 7.38±1.42 years, excluding heart, liver, kidney and vascular inflammatory diseases. A total of 378 patients with JIA (68 male and 311 female patients) were selected as the case group. All the patients were ranked as systemic JIA. The mean age was 7.29±2.58 years and the mean age of onset was 6.3±1.3 years. The clinical characteristics of JIA patients and healthy controls are summarized in Table I. The diagnosis of JIA was confirmed by typical clinical symptoms and laboratory tests according to the International League of Associations for Rheumatology (24), but not European Alliance of Associations for Rheumatology (EULAR) as the validity of the EULAR criteria is low since it often exclude patients from subgroup classification and the possibility of having more than one diagnosis is not negligible (25). All patients received non-steroidal anti-inflammatory drugs and methotrexate therapy at the initial stage of the disease. All subjects were unrelated individuals of Han ethnic group in Jiangsu Province.

Sample collection and DNA extraction. A total of 2 ml fasting venous blood was collected from the right arm of all subjects'. The blood cells were used for DNA extraction and the blood plasma was stored at -80˚C. Genomic DNA was extracted from 200 μl anticoagulant blood cells using a QIAamp DNA Mini kit (Qiagen GmbH).

PCR and genotyping. Variants in the *PTPN22, IRF5 and TYK2* genes in the present study were selected according to Tang *et al* (10,11,21). The primer sequence was synthesized by Dalian Bao Biological Engineering Co., Ltd. Genomic DNA was extracted from peripheral leukocytes using the standard phenol-chloroform method. The total volume of PCR amplification was 25 μl, including 12.5 μl 2X GoTap Green Master Mix (Promega Corporation; 400 μmol/l dNTP, 3 mmol/l $MgCl_2$), 1.5 μl 10 μmol/l upstream and downstream primers and 200 ng DNA, respectively. The cycle parameters were pre-denatured at 94˚C for 5 min, then denatured at 94˚C for 30 sec, annealed at 57˚C for 30 sec and extended at 72˚C for 30 cycles and finally, extended at 72˚C for 5 min. The PCR was performed using the Bio-Rad CFX384 PCR thermocycler (Bio-Rad Laboratories, Inc.). The PCR amplification product was stained with 8% ethidium bromide on 1% Nusieve 3:1Agrose gel. Electrophoresis was performed at 100 V for 15 min. Markers under UV light and D2000 plus DNA ladder (Beijing Solarbio Science & Technology Co., Ltd.) were compared to estimate DNA molecular weight. The product was purified by adding 60 μl of 75% ethanol. Sequencing reactions were performed with ABI PRISM BigDye Terminator V3.1 Sequencing kit (cat. no. 4336913; Applied Biosystems; Thermo Fisher Scientific, Inc.), with one-way sequencing primer identical to PCR forward primer. The reaction system was supplemented with 5 μl reaction system, including 2 μl PCR amplification product, 1 μl 1 μM one-way primer, 0.5 μl ABI PRISM BigDye and 1 μl 5X reaction mix buffer, supplemented with ddH_2O to 5 μl. The reaction conditions of sequencing PCR were denaturation at 96˚C for 45 sec, followed by 30 cycles of 96˚C for 10 sec, 55˚C for 5 sec and 60˚C for 2.5 min. Sequencing reaction products were purified using multiScreen 96-well filtration plates. Sequencing electrophoresis was performed according to ABI 3730XL DNA Sequencer instructions (Applied Biosystems; Thermo Fisher Scientific, Inc.). The sequencing primers of the variants are listed in the Table SI. GeneScan 3.7 Software (Applied Biosystems; Thermo Fisher Scientific, Inc.) was used for data analysis.

Statistical analysis. The subjects were compared with Hardy-Weinberg equilibrium (HWE), genotype and allele

Table I. Clinical characteristics of JIA patients and healthy controls.

Clinical features	JIA (mean ± SD)	Control (mean ± SD)	P-value
Sex (Female/Male)	311/67	311/67	1.00
Age (years)	7.29±2.58	7.38±1.42	>0.05
Onset age (years)	6.3±1.3	-	-
DAS28	3.2±1.2	-	-
RF+, %	12.15	-	-
CCP+, %	18.54	-	-
ANA+, %	18.31	-	-
ESR (mm/h)	36.8±12.3	4.2±2.1	<0.01
CRP (mg/l)	18.4±7.5	3.6±1.3	<0.01
IgA mg/ml	11.1±2.7	2.7±1.4	<0.01
IgG mg/ml	26.6±3.1	9.4±1.7	<0.01
IgM mg/ml	6.1±1.9	1.9±0.7	<0.01

JIA, juvenile idiopathic arthritis; SD, Standard Deviation; RF, rheumatoid factor; DAS28, Disease activity score 28, a score for evaluation of RA activity by assessing the state of 28 joints; CCP, cyclic citrullinated peptide; ANA, antinuclear antibodies.

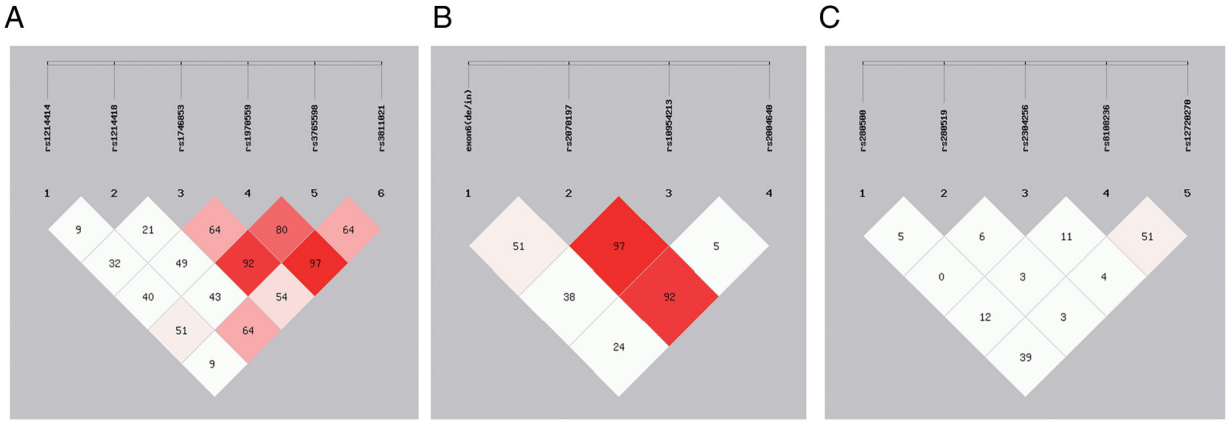

Figure 1. Linkage disequilibrium analysis of the variants in (A) *PTPN22*, (B) *IRF5* and (C) *TYK2* genes in cases of juvenile idiopathic arthritis and controls.

frequency by four-table χ^2 test and RC contingency table χ^2 test. The relative risk was estimated by odds ratio (OR) and 95% confidence interval (95% CI). Haplotypes were constructed with the lowest frequency threshold (LFT) >0.01. Multiple comparison correction was performed to adjust P-values (q value) using the Benja Mini-Hochberg method based on the False Discovery Rate (FDR) standard. The SHEsis software was used to analyze the data (http://analysis.bio-x.cn/myAnalysis.php) (26). The multifactor dimensionality reduction (MDR) 3.0.2 software was used to analyze the gene-gene interactions (https://sourceforge.net/projects/mdr/) (27). Calculation power was obtained at the 0.05 level of significance, assuming an OR of 1.5 (small effect size) by using the G*Power software (www.gpower.hhu.de) (28). P<0.05 was considered to indicate a statistically significant difference.

Results

The HWE test was performed for the frequencies of variants in the healthy control group. The results showed that distributions of these variants in this group were in HWE (P>0.05), indicating that the selected subjects were representative of the population. The results of linkage disequilibrium showed that the *PTPN22* rs1746853 and rs3765598, as well as rs1970559 and rs3811021, were in strong linkage (D'>85; Fig. 1A). In addition, similar results were found for *IRF5* rs2070197 and rs10954213, as well as rs2070197 and rs2004640 (D'>85; Fig. 1B). However, the variants in the *TYK2* gene were found to be in strong linkage with each other (D'<85; Fig. 1C). In addition, a calculation power of 71.3% at the 5% significance level (two-tailed) was obtained (Table II).

For *PTPN22*, the rs2476601 was found to be not polymorphic and was deleted from the subsequent analysis. All the allelic and dominant models of the five variants (rs1214414, rs1214418, rs1746853, rs3765598 and rs3811021) except for rs1970559 were significantly associated with JIA risk, even after correction with the FDR method (P<0.05; Table II). In addition, the recessive models of rs1746853 and rs3765598 were found to be associated with JIA risk (P<0.05). However, these significant associations disappeared after correction with the FDR method (P>0.05; Table II).

For *IRF5*, significant associations were observed between the allelic and dominant models of rs10954213 and the allelic model of rs2004640 and JIA risk, even after correction with the FDR method (P<0.05). By contrast, no association was detected between the recessive models of the rs10954213 and rs2004640 and JIA susceptibility (P>0.05). In addition, the exon6(de/in) and rs2070197 were not significantly associated with the risk of JIA (P>0.05; Table II).

For *TYK2*, all the allelic, recessive and dominant models of the four variants (rs280500, rs280519 and rs2304256, except for rs8108236) were significantly associated with JIA risk, even after correction with the FDR method (P<0.05; Table II). At the same time, the allelic and dominant models but not the recessive model of rs12720270 were detected to be significantly associated with the risk of JIA (P<0.05; Table II).

The haplotype results revealed that the frequencies of *PTPN22* haplotypes including H_{CAGTCC}, H_{CAGTTC} and H_{CGTTCT} in the JIA patient group were significantly different from those in the healthy group (P<0.05). The H_{CATTCT} was the most common haplotype both in cases and controls with the frequencies of 0.661 and 0.622, respectively (Table III). For *IRF5*, a total of nine haplotypes (LFT>0.01) were observed. The frequencies of *IRF5* haplotypes (H_{DTAA} and H_{ITAC}) were significantly higher in the case group (P<0.05). Furthermore, the frequency of H_{DTGC} was found to be significantly lower in the case group (P<0.05; Table III). For *TYK2*, a total of 11 haplotypes (LFT>0.01) were detected. The H_{AGGAT} frequency was significantly higher in the case group (P<0.05). In comparison, the frequencies of H_{GAGGT} and H_{GGGAT} were found to be significantly lower in the case group (P<0.05; Table III).

The MDR results revealed that *IRF5* rs10954213 had the highest testing balanced accuracy among the tested variants, with 61.84% testing balanced accuracy (TBA). *IRF5* rs10954213, rs2004640 and *PTPN22* rs1214414 suggested a three-way interaction between *PTPN22* and *IRF5* genes and JIA with 78.95% TBA and cross-validation consistency (CVC) (10/10) (P<0.0001) (Fig. 2).

Discussion

In the present study, 378 unrelated patients with JIA and 378 healthy controls were genotyped for the 16 variants in *PTPN22, IRF5 and TYK2* genes. The results indicated that five variants in the *PTPN22* gene, two variants in the *IRF5*

Table II. Distributions of *PTPN22*, *IRF5* and *TYK2* genes polymorphisms in cases and controls.

Gene	Polymorphisms (A<B) (MAF, Asian)	Case (AA/AB/BB)	Control (AA/AB/BB)	Allele model [P, OR (95%CI)][a]	q (P_{adj}[b])	Dominant model [P, OR (95%CI)]	q (P_{adj}[b])	Recessive model [P, OR (95%CI)]	q (P_{adj}[b])	HWE in control group (P)	Power
PTPN22	rs2476601 (T<C) (0.0006)	0/0/378	0/0/378	-	-	-	-	-	-	1.000	71.3
	rs1214414 (T<C) (0.2006)	0/31/347	3/86/289	$1.01x10^{-8}$, 0.31 (0.20-0.47)	$3.54x10^{-8}$	$4.08x10^{-8}$, 0.29 (0.19, 0.45)	$9.25x10^{-8}$	0.2, 0.14 (0.01, 2.75)	0.47	0.211	
	rs1214418 (G<A) (0.1508)	5/80/293	3/35/340	$2.91x10^{-7}$, 2.36 (1.61, 3.46)	$6.79x10^{-7}$	$5.93x10^{-7}$, 2.60 (1.72, 3.92)	$2.07x10^{-6}$	0.48, 1.68 (0.40, 7.06)	0.67	0.058	
	rs1746853 (G<T) (0.2703)	27/133/218	14/90/274	$5.20x10^{-6}$, 1.78 (1.37, 2.30)	$9.10x10^{-6}$	$4.42x10^{-5}$, 1.93 (1.43, 2.62)	$3.09x10^{-4}$	0.04, 2.00 (1.03, 3.88)	0.14	0.061	
	rs1970559 (C<T) (0.0665)	0/36/342	0/31/347	0.53, 1.17 (0.72, 1.91)	0.62	0.52, 1.18 (0.71, 1.95)	0.61	-	-	0.410	
	rs3765598 (T<C) (0.2006)	15/109/254	3/44/331	$5.07x10^{-12}$, 3.18 (2.26, 4.47)	$3.55x10^{-11}$	$1.29x10^{-10}$, 3.44 (2.37, 4.99)	$7.74x10^{-10}$	0.01, 5.17 (1.48, 17.99)	0.07	0.262	
	rs3811021 (C<T) (0.2271)	14/89/275	20/132/226	0.0003, 0.62 (0.48-0.81)	0.0042	0.0002, 0.56 (0.41, 0.76)	0.007	0.29, 0.69 (0.34, 1.38)	0.51	0.899	
IRF5	exon6 (de/in) (in<de) (0.4685)	103/169/106	87/183/108	0.35, 1.10 (0.90, 1.35)	0.47	0.87, 1.03 (0.75, 1.41)	0.87	0.18, 1.25 (0.90, 1.74)	0.24	0.576	
	rs2070197 (C<T) (0.0007)	0/3/375	0/2/376	0.66, 1.50 (0.25, 9.01)	0.66	0.66, 1.50 (0.25, 9.05)	0.88	-	-	0.958	
	rs10954213 (G<A) (0.4814)	34/116/228	49/197/132	$9.12x10^{-10}$, 0.50 (0.40, 0.63)	$3.65x10^{-9}$	$2.26x10^{-11}$, 0.35 (0.26, 0.47)	$9.04x10^{-11}$	0.08, 0.66 (0.42, 1.05)	0.16	0.064	
	rs2004640 (A<C) (0.3245)	20/156/202	10/136/232	0.02, 1.35 (1.06, 1.71)	0.04	0.03, 1.38 (1.04, 1.85)	0.06	0.07, 2.06 (0.95, 4.45)	0.28	0.056	
TYK2	rs280500 (A<G) (0.0178)	34/196/148	12/124/242	$2.31x10^{-11}$, 2.20 (1.74-2.78)	1.16e-010	$2.14x10^{-11}$ 2.77 (2.06, 3.71)	$1.07x10^{-10}$	0.001, 3.01 (1.54, 5.92)	0.005	0.416	
	rs280519 (A<G) (0.4938)	93/184/101	124/185/69	0.001, 0.72 (0.58, 0.88)	0.002	0.006, 0.61 (0.43, 0.87)	0.01	0.01, 0.67 (0.49, 0.92)	0.025	0.999	
	rs2304256 (A<G) (0.4075)	24/159/195	10/89/279	$6.15x10^{-10}$, 2.24 (1.73, 2.90)	1.54e-09	$1.82x10^{-9}$, 2.64 (1.95, 3.59)	$4.55x10^{-9}$	0.02, 2.49 (1.18, 5.29)	0.033	0.371	
	rs8108236 (A<G) (0.0055)	30/128/220	29/128/221	0.91, 1.01 (0.80, 1.28)	0.91	0.94, 1.01 (0.76, 1.35)	0.94	0.89, 1.04 (0.61, 1.77)	0.89	0.089	
	rs12720270 (G<T) (0.3897)	2/42/334	1/68/309	0.02, 0.63 (0.43-0.93)	0.025	0.01, 0.59 (0.39, 0.89)	0.013	0.7, 2.01 (0.18, 22.21)	0.87	0.170	

[a]OR and 95% CI are calculated for the minor allele of each polymorphisms. [b]Multiple comparison correction was performed to adjust P-values (q value) using Benja Mini-Hochberg method based on False Discovery Rate standard. MAF, minor allele frequency (Asian); OR, odds ratio; 95% CI, 95% confidence intervals; -, not calculated; HWE, Hardy-Weinberg equilibrium.

Table III. Haplotypes structure and frequencies of *PTPN22*, *IRF5* and *TYK2* genes.

Gene	Haplotypes[a]	Case (freq)	Control (freq)	P, OR [95%CI][b]	q (P_{adj}[c])
PTPN22	C A G T C C	0.014	0.036	0.006, 0.384 [~0.189-0.781]	0.008
	C A G T T C	0.115	0.043	$5.02x10^{-7}$, 2.809 [~1.852-4.261]	2.00e-006
	C A T T C T	0.661	0.622	0.307, 1.123 [~0.898-1.404]	0.307
	C G T T C T	0.068	0.019	$3.62x10^{-6}$, 3.779 [~2.075-6.884]	7.24e-006
IRF5	D T A A	0.144	0.096	0.004, 1.578 [1.151~2.163]	0.010
	D T A C	0.300	0.290	0.644, 1.054 [~0.844-1.314]	0.736
	D T G A	0.029	0.028	0.918, 1.032 [~0.564-1.887]	0.918
	D T G C	0.029	0.113	$2.22x10^{-10}$, 0.235 [~0.145-0.379]	1.77e-09
	I T A A	0.052	0.030	0.027, 1.799 [~1.063-3.047]	0.432
	I T A C	0.256	0.191	0.002, 1.460 [~1.144-1.864]	0.008
	I T G A	0.034	0.064	0.007, 0.513 [~0.314-0.839]	0.140
	I T G C	0.152	0.185	0.083, 0.787 [~0.601~1.032]	0.111
TYK2	A A G A T	0.034	0.025	0.297, 1.374 [~0.755-2.501]	0.363
	A A G G T	0.080	0.064	0.210, 1.285 [~0.867-1.904]	0.330
	A G G A T	0.080	0.021	$1.29x10^{-7}$, 4.102 [~2.338-7.197]	7.095e-007
	A G G G T	0.054	0.062	0.524, 0.869 [~0.563-1.341]	0.576
	G A A A T	0.033	0.022	0.189, 1.516 [~0.810-2.837]	0.416
	G A A G T	0.067	0.052	0.192, 1.330 [~0.865-2.045]	0.352
	G A G A T	0.051	0.074	0.065, 0.673 [~0.440-1.028]	0.178
	G A G G T	0.150	0.275	$4.48x10^{-9}$, 0.468 [~0.362-0.605]	4.93e-008
	G G A G T	0.045	0.041	0.689, 1.107 [~0.673-1.819]	0.689
	G G G A T	0.033	0.062	0.008, 0.519 [~0.316-0.852]	0.029
	G G G G T	0.214	0.193	0.277, 1.149 [~0.894-1.478]	0.381

[a]The program, SHEsis, was used to estimate common (frequency >0.01) haplotypes constructed by six variants in *PTPN22* (re1217414-rs121 7418-rs1746853-rs1972559-rs3765598-rs3811021), four variants [exon6(de/in), rs2070197, rs10954213, rs2004640] in *IRF5* and five variants (rs280500, rs280519, rs2304256, rs8108236, rs12720270) in *TYK2*. R620W (rs2476601) was not polymorphic enough and was excluded from the haplotype analysis. [b]Each haplotype was compared with the other haplotypes combined. [c]Multiple comparison correction was performed to adjust P-values (q value) using Benja Mini-Hochberg method based on False Discovery Rate standard. OR, odds ratio; 95% CI, 95% confidence intervals.

gene and four variants in the *TYK2* gene were associated with JIA susceptibility in the Chinese Han population. MDR analysis suggested a three-way interaction (*IRF5* rs10954213, rs2004640 and *PTPN22* rs1214414) between *PTPN22* and *IRF5* genes and JIA.

The *PTPN22* R620w variant (rs2476601) is found to be associated with susceptibility to autoimmune diseases (29,30). *PTPN22* R620W causes an alteration of arginine to tryptophan at codon 620 in the SH3 region, which downregulates the T-cell receptor (TCR) signaling system, decreased the affinity between C-Src tyrosine kinase and LYP, abolished the inhibition of tyrosine kinases LCK and Fyn and then activated the TCR signaling pathway (31,32). The genetic association between the *PTPN22* R620W and autoimmune diseases such as RA, SLE, Wegener's granulomatosis, Type-1 diabetes, MS and JIA has been widely reported (33-36). The *PTPN22* rs2476601 has been shown to increase JIA risk in American, Greek and Norwegian populations (14,34-38). However, negative results have been reported in Czech, Hungarian and Finnish populations (7,39,40). Furthermore, meta-analysis suggests that the *PTPN22* rs2476601 is a JIA susceptibility factor in Caucasian populations (41-43). However, no studies have been conducted on the genetic association between the *PTPN22* rs2476601 and JIA risk in the Chinese population. In the present study, rs2476601 was found to be not polymorphic in the Chinese Han population and no genetic association was detected between rs2476601 and JIA susceptibility. The discordance among the studies might be due to the different genetic backgrounds among multiple ethnic groups.

In the present study, *PTPN22* rs1214414, rs1214418, rs1746853, rs3765598 and rs3811021 were found to be significantly associated with JIA risk in the Chinese Han population, which was similar to previous results reported by Tang *et al* (10,11) on the relationship of *PTPN22* variants and RA, SLE and AS risk. Notably, most of the selected variants were in the introns of the *PTPN22* gene and may not affect the function of LYP. There are an increasing number of new pathogenic variants located in introns and studies have suggested that many disease-related intronic variants are responsible for aberrant splice processes (44,45). These observations indicate that the intronic variants in the *PTPN22* gene might affect the splice processes of LYP, leading to aberrant expression of the *PTPN22* and thereby influencing the susceptibility to JIA.

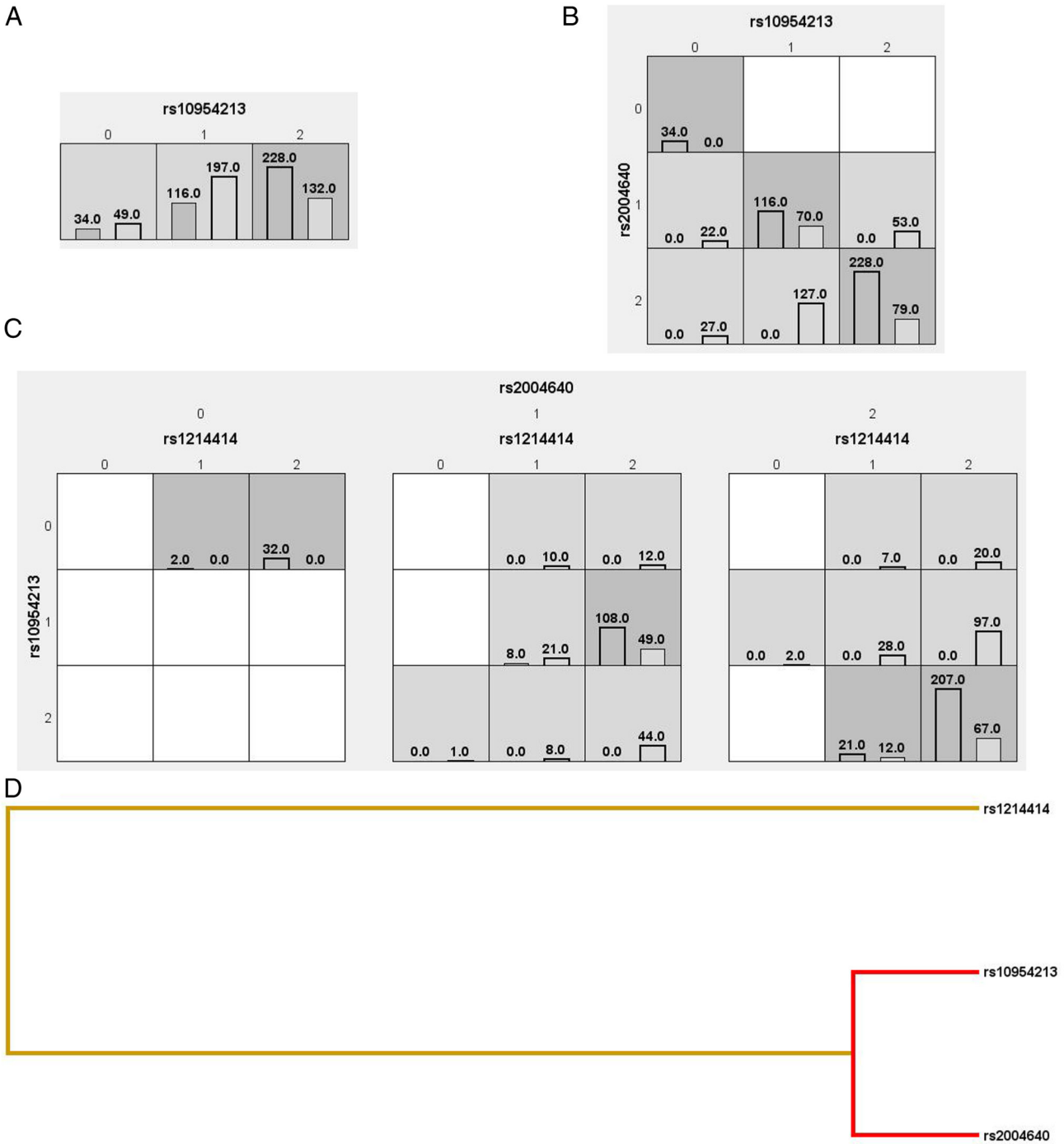

Figure 2. The optional models as determined by multifactor dimensionality reduction for the variants in *PTPN22*, *IRF5* and *TYK2* genes. (A) *IRF5* rs10954213. (B) *IRF5* rs10954213 and rs2004640. (C) *IRF5* rs10954213, rs2004640 and *PTPN22* rs1214414. The numbers in the square represent number of cases of juvenile idiopathic arthritis (left) and controls (right). For each square, dark-shading indicates high risk of disease, whereas light shading represents low risk of disease. (D) The entropy of the best model.

IRF5 and Toll-like receptors (TLRs) form a pathway to induce the expression of inflammatory factors (46). The lipopolysaccharide and nucleic acid of the pathogen can be recognized by specific TLRs, causing IRF5 to be activated, thus activating the downstream target gene and serving the function of immune defense. At the same time, processing and presenting foreign antigens, inducing T-cell differentiation and activating acquired immunity (47). The *IRF5* gene contains nine exons and is located on the human genome 7q32 (48). Studies have shown that loci in *IRF5*, including exon 6(de/in), rs2004640, rs10954213, rs2280714 and rs2070197 are important susceptibility factors for autoimmune diseases (21-23). The *IRF5* rs2004640T allele creates a 5'-donor splicing site in intron 1, resulting in the expression of untranslated exon 1B (49). The *IRF5* rs10954213 changes the polyadenylate sites of IRF5, which is related to the mechanism of the increased IRF5 level in patients with autoimmune diseases (50). The genetic associations between these two variants and autoimmune diseases, including SLE, RA, Sjogren syndrome and JIA, have been widely reported (21,51,52). However, no association

between the *IRF5* rs2004640 and JIA risk was detected in Russian populations (53). In the present study, *IRF5* rs2004640 and rs10954213 were first found to be significantly related to the susceptibility to JIA in a Chinese Han population. The inconsistency might be due to the relatively small sample size and genetic backgrounds between the Russian and Chinese Han populations. A larger number of subjects from multiple ethnicity is necessary to confirm these results.

Several studies have demonstrated the important role of TYK2 in the type I interferon signaling pathway. Activated TYK2 can selectively activate STAT3 and STAT5 in the downstream substrates, initiating the JAK-STAT signaling pathway and finally triggering the expression of the type I IFN gene (54). TYK2 is also involved in the signaling of colony-stimulating factors, angiotensin II, Platelet-activating factor and some cytokines, such as IL-6 and IL-10 (55). Therefore, changes in TYK2 function may also lead to the restriction of other cytokine signaling pathways, such as IL-10, which has been previously reported to be associated with SLE (56). In addition, animal experiments suggest that *TYK2* gene-deficient mice are not susceptible to experimental arthritis (57). These studies have confirmed the importance of TYK2 in autoimmune diseases. *TYK2* gene located in human 19p13.2. Previous linkage analyses have shown that this region is susceptible to autoimmune diseases. Several *TYK2* variants were associated with the susceptibility to autoimmune diseases, such as SLE and RA, and have been investigated and confirmed (21,58,59). Significant associations have been detected between *TYK2* rs280519, rs12720270, rs2304256 and SLE in the United Kingdom (60). Similar results are reported in a Chinese Han population conducted by Tang *et al* (21). However, previous studies found no association between the *TYK2* rs12720270, rs2304256 and SLE risk in Japanese and Hong Kong populations (58,61). Notably, only *TYK2* rs34536443 has been investigated and no genetic association with JIA risk was found in a northern Greece population (62). In the present study, variants reported by Tang *et al* (21) were selected. All the selected variants except for rs8108236 were associated with JIA susceptibility in the Chinese Han population. The genetic associations between the *TYK2* variants and JIA were detected for the first time. The results indicated that *TYK2* rs280500, rs280519, rs2304256 and rs12720270 might be the susceptibility factors for JIA in a Jiangsu Chinese Han population.

The association between haplotypes and JIA was also analyzed in the present study to evaluate the combined influence of multiple variants in the *PTPN22*, *IRF5* and *TYK2* genes. Three haplotypes (H_{CAGTCC}, H_{CAGTTC} and H_{CGTTCT}) in the *PTPN22* gene, two haplotypes (H_{DTAA} and H_{ITAC}) in the *IRF5* gene and one haplotype (H_{AGGAT}) in the *TYK2* gene were detected to be risk factors for JIA. In addition, the haplotype (H_{DTGC}) in the *IRF5* gene and two haplotypes (H_{GAGGT} and H_{GGGAT}) in the *TYK2* gene were found to be protective factors for JIA. This is the first study, to the best of the authors' knowledge, on the association between JIA and haplotypes in *PTPN22, IRF5 and TYK2* genes. Nevertheless, further investigation with a large sample size and haplotype analysis with more variants are required to confirm the current study results.

In addition to focusing on the effect of a single gene on JIA, the variants of the *PTPN22, IRF5 and TYK2* genes were analyzed by the MDR method in the present study. The present study found a three-way interaction between *IRF5* rs10954213, rs2004640 and *PTPN22* rs1214414 and JIA risk, suggesting that gene-gene interactions between *PTPN22* and *IRF5* genes may increase JIA susceptibility in the Han Chinese population.

Limitations should be motioned. First, the present study enrolled limited number of studies for analyzing the association between the variants in *PTPN22, IRF5* and *TYK2* genes and susceptibility of JIA, which may have resulted in insufficient authority for identifying relationship of *PTPN22, IRF5* and *TYK2* genes and JIA risk. Second, although significant associations were found between haplotypes and JIA, the protein data of the expression of three genes is unavailable. It is impossible to distinguish the haplotype for each individual, especially subjects with haplotypes.

In summary, the present study suggested that *PTPN22* rs1214418, rs1746853, rs3765598, *IRF5* rs2004640, *TYK2* rs280500 and rs2304256 might be risk factors for JIA. In addition, *PTPN22* rs1214414, rs3811021, *IRF5* rs10954213, *TYK2* rs280519 and rs12720270 might be protective factors for JIA. A three-way interaction between *IRF5* rs10954213, rs2004640 and *PTPN22* rs1214414 might be a risk factor for JIA in Han Chinese population. However, future studies in other cohorts of patients with JIA need to be performed to validate it.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

YQ and BC participated in study design and data collection, carried out the initial analysis and drafted the article. ZW aided in data acquisition, data analysis and statistical analysis. YP carried out literature search, data acquisition and manuscript editing. ZW and YP confirm the authenticity of all the raw data. BC and ZW performed manuscript review. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The protocol of this study was performed following the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments and approved by the Local Ethics Committee of the Changshu Hospital affiliated to Soochow University (protocol number: EC-19-024). Written informed consent was obtained from the participants' parents before the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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