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Original article

The role of the immune response mediator genes polymorphism in the predisposition to juvenile idiopathic arthritis

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Abstract: *Objective* — The aim of the work was to study the contribution of the immune response mediator genes polymorphism (*TNFA* rs1800629, *LTA* rs909253, *IL1B* rs16944, *IL2-IL21* rs6822844, *IL2RA* rs2104286, *IL6* rs1800795, *IL10* rs1800872, *MIF* rs755622, *CTLA4* rs3087243, *NFKB1* rs28362491, *PTPN22* rs2476601, *PADI4* rs2240336) to the formation of the predisposition to juvenile idiopathic arthritis (JIA) and its clinical variants.
Material and Methods — The JIA group included 330 patients and the control group – 342 volunteers without autoimmune diseases from the Republic of Bashkortostan, Russia. Genotyping was conducted by the real-time polymerase chain reaction.
Results — Taking into account the differences by sex, it was established, that the alleles/genotypes of the *TNFA* rs1800629, *LTA* rs909253, *IL2-IL21* rs6822844, *PTPN22* rs2476601 polymorphic loci and the *TNFA* rs1800629*G – *LTA* rs909253*G haplotype are associated with the development of JIA as a whole ($p<0.05$); alleles/genotypes of the *LTA* rs909253, *IL1B* rs16944, *IL2-IL21* rs6822844, *IL2RA* rs2104286, *IL6* rs1800795, *IL10* rs1800872, *MIF* rs755622, *CTLA4* rs3087243, *NFKB1* rs28362491, *PTPN22* rs2476601 polymorphic loci and the *TNFA* rs1800629*G – *LTA* rs909253*G haplotype – with some of JIA clinical variants ($p<0.05$).
Conclusion — In this work, the relationship of the alleles, genotypes and haplotypes of a number of the immune response mediator genes polymorphic loci with the risk of the development of JIA and its clinical variants was established. Specific associations were observed for girls and boys, which indicates the existence of sexual dimorphism in the JIA pathogenesis.

Keywords: juvenile idiopathic arthritis, predisposition, polymorphic loci, association, sexual dimorphism.

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Introduction

Juvenile idiopathic arthritis (JIA) is one of the most common chronic rheumatic diseases in children [1]. An important role in the JIA development is given to the immune response disorders, arising in genetically predisposed individuals [2-4].

Among the key mediators of the immune response, the cell surface molecules (including proteins of the major histocompatibility complex), pro- and anti-inflammatory cytokines, transcription factors, enzymes and other regulatory molecules can be particularly highlighted. Polymorphism, which is characteristic for many of the corresponding genes, causes pronounced interindividual variability, including the variability in the predisposition to JIA [2-4].

In recent years, a relatively large number of studies, including genome-wide association studies (GWAS), have been performed to detect the specific JIA risk markers. Nevertheless, the question is still open [3, 4]. Only for a small number of candidate genes polymorphic variants the association was confirmed in independent studies, and their total contribution to the explanation of the hereditary predisposition to JIA is rather small [3, 4]. In addition, the results of replicative studies are often contradictory, which may be due to a variety of factors, such as the use of different approaches for describing JIA phenotypes and for patients grouping, incorrect selection criteria and insufficient sample size, genotyping errors, and true population differences [4].

The aim of the work was to study the contribution of the immune response mediator genes polymorphism (*TNFA* rs1800629, *LTA* rs909253, *IL1B* rs16944, *IL2-IL21* rs6822844, *IL2RA* rs2104286, *IL6* rs1800795, *IL10* rs1800872, *MIF* rs755622, *CTLA4* rs3087243, *NFKB1* rs28362491, *PTPN22* rs2476601, *PADI4* rs2240336) to the formation of the predisposition to JIA and its clinical variants.

Material and Methods

Study design and subjects

A case-control study was conducted. The study was approved by the expert council on biomedical ethics of Bashkir State Medical University (Ufa, Russia). The JIA group included 330 patients who

underwent examination and treatment in the cardio-rheumatological department of the Republican Children's Clinical Hospital in 2011-2017. The JIA diagnosis was established according to the International League of Associations for Rheumatology (ILAR) criteria [5]. The presented JIA clinical variants and their ratio in our sample are shown in *Table* 1. As a control group, 342 volunteers without autoimmune diseases were selected. All participants of the study (for the JIA group – parents of all patients) signed the voluntary informed consent. The age of the examined patients was 9.05 (4.99, 13.30) years, and of the controls – 18.00 (18.00, 19.00) years (data presented as median with low and upper quartiles). The ratio of males and females in the JIA and control groups was 34.24%/65.76% and 30.99%/69.01%, respectively. All the individuals included in the study were residents of the Republic of Bashkortostan (Russia) and belonged to the following ethnic groups: Tatars (25.54%), Russians (21.72%), Bashkirs (13.13%), mixed and others (39.62%).

Genotyping

DNA isolation from the lymphocytes of the whole blood samples was performed using a standard phenol-chloroform method [6]. Genotyping of all the individuals for the 12 polymorphic loci (*TNFA* rs1800629, *LTA* rs909253, *IL1B* rs16944, *IL2-IL21* rs6822844, *IL2RA* rs2104286, *IL6* rs1800795, *IL10* rs1800872, *MIF* rs755622, *CTLA4* rs3087243, *NFKB1* rs28362491, *PTPN22* rs2476601, *PADI4* rs2240336) was conducted by the real-time polymerase chain reaction (StepOnePlus™ Real-Time PCR System, Applied Biosystems, USA). Sequence-specific primers and allele-specific probes were designed and synthesized by the "DNK-syntez" company (Russia). The distribution of the polymorphic loci variants in patients with JIA and in the control group is shown in the *Supplementary Tables* 1-5 (*Appendix 1*).

Statistical analysis

Statistical processing of the results was carried out using Microsoft Excel, SNPStats, R v.3.4.2, PowerMarker v.3.25, STATISTICA v.10 (StatSoft, Inc.) [7-9].

To compare the genotype and allele frequency distribution in the JIA patients group and in the control group the two-tailed Fisher's Exact test was used. The differences were considered statistically significant at $p<0.05$. A similar analysis was also performed separately for boys and girls and for specific clinical variants of the disease. The multiple testing correction of the p-values was carried out by applying a permutation test with a 10^4 permutes (p_{cor}) [7, 10].

Table 1. Clinical characteristics of the JIA group

JIA clinical variants	*Total* n_i ($p_{i(w)}$, %)	*Boys / Girls* n_i ($p_{i(var)}$, %)
Systemic arthritis	29 (8.79)	14/15 (48.28/51.72)
Rheumatoid factor positive polyarthritis	6 (1.82)	1/5 (16.67/83.33)
Rheumatoid factor negative polyarthritis	86 (26.06)	17/69 (19.77/80.23)
Persistent oligoarthritis	98 (29.70)	33/65 (33.67/66.33)
Extended oligoarthritis	46 (13.94)	5/41 (10.87/89.13)
Enthesitis related arthritis	35 (10.61)	29/6 (82.86/17.14)
Psoriatic arthritis	8 (2.42)	3/5 (37.50/62.50)
Undifferentiated arthritis	22 (6.67)	11/11 (50.00/50.00)
The whole group	330 (100)	113/217 (34.24/65.76)

Hereinafter: n_i, number of patients in the groups; p_i, frequency; $p_{i(w)}$, frequency in the whole JIA group; $p_{i(var)}$, frequency in the corresponding JIA clinical variant group.

In addition, the odds ratio (OR) with the Baptista-Pike exact conditional 95% confidence interval (95% CI) were calculated [11].

Given that the *TNFA* and *LTA* genes are located in the same cluster on chromosome 6, the linkage disequilibrium test for the *TNFA* rs1800629 and *LTA* rs909253 polymorphic loci was performed in the SNPStats package, which showed almost complete linkage disequilibrium at 99.94% (D=0.0807, D'=0.9994, r=0.5438, p=0.000). Therefore, the haplotypes of these loci have also been studied as the potential risk markers for the development of JIA and its clinical variants.

Testing for the deviations from the Hardy-Weinberg equilibrium was carried out in the SNPStats package. There were no significant deviations from the Hardy-Weinberg equilibrium for the *TNFA* rs1800629, *LTA* rs909253, *IL1B* rs16944, *IL2RA* rs2104286, *IL6* rs1800795, *IL10* rs1800872, *MIF* rs755622, *CTLA4* rs3087243, *NFKB1* rs28362491, *PTPN22* rs2476601, *PADI4* rs2240336 polymorphic loci in both groups (JIA and control) ($p>0.05$). A slight deviation from the Hardy-Weinberg equilibrium was established for the *IL2-IL21* rs6822844 polymorphic locus in the control group ($p=0.019$), but considering that the controls were selected according to the specified criteria (age, sex, the absence of autoimmune diseases), this locus was kept for the subsequent analysis.

Results

The established relationship of the alleles, genotypes and haplotypes of a number of the immune response mediator genes polymorphic loci with the risk of the development of JIA and its clinical variants is shown in the *Table* 2.

Taking into account the differences by sex, the risk predictors of the development of JIA as a whole were identified among the alleles/genotypes of the loci *TNFA* rs1800629 (for girls), *LTA* rs909253 (for boys), *IL2-IL21* rs6822844 (for girls), *PTPN22* rs2476601 (for girls), as well as among the haplotypes of the *TNFA* rs1800629 – *LTA* rs909253 loci (for boys). In addition, the predictors of the formation of some JIA clinical variants were established:

- Rheumatoid factor positive polyarthritis (alleles/genotypes of the loci *LTA* rs909253 (only for the general group of boys and girls), *MIF* rs755622 (only for the general group of boys and girls));

- Rheumatoid factor negative polyarthritis (alleles/genotypes of the loci *LTA* rs909253 (for boys), *IL2RA* rs2104286 (for boys), *IL10* rs1800872 (for boys) and the haplotype *TNFA* rs1800629*G – *LTA* rs909253*G (for boys));

- Persistent oligoarthritis (alleles/genotypes of the loci *LTA* rs909253 (only for the general group of boys and girls), *IL1B* rs16944 (for boys), *IL2-IL21* rs6822844 (for boys), *IL6* rs1800795 (both for girls and for boys), *IL10* rs1800872 (only for the general group of boys and girls), *NFKB1* rs28362491 (only for the general group of boys and girls), *PTPN22* rs2476601 (for girls) and the haplotype *TNFA* rs1800629*G – *LTA* rs909253*G (for girls));

- Extended oligoarthritis (alleles/genotypes of the loci *IL2-IL21* rs6822844 (for girls), *CTLA4* rs3087243 (for girls), *PTPN22* rs2476601 (for girls));

- Enthesitis related arthritis (alleles/genotypes of the loci *LTA* rs909253 (for boys), *IL6* rs1800795 (only for the general group of boys and girls), *NFKB1* rs28362491 (for boys), *PTPN22* rs2476601 (for boys) and the haplotype *TNFA* rs1800629*G – *LTA* rs909253*G (for boys));

Table 2. The relationship between the immune response mediator genes polymorphic loci variants and the risk of the development of JIA and its clinical variants

JIA and its clinical variants	The sex	The risk predictors
JIA as a whole	the general group of boys and girls	*TNFA* rs1800629*AA (p=0.021, p_{cor}=0.020, OR=0.112, 95% CI 0.010-0.681), *PTPN22* rs2476601*GA (p=0.029, p_{cor}=0.029, OR=1.551, 95% CI 1.041-2.304), *PTPN22* rs2476601*GG (p=0.035, p_{cor}=0.034, OR=0.662, 95% CI 0.450-0.960), haplotype *TNFA* rs1800629*G - *LTA* rs909253*G (p=0.016, OR=1.41, 95% CI 1.07-1.85)
	girls	*TNFA* rs1800629*AA (p=0.031, p_{cor}=0.032, OR=0.000, 95% CI 0.000-0.757), *IL2-IL21* rs6822844*TT (p=0.039, p_{cor}=0.037, OR=0.132, 95% CI 0.012-0.861), *PTPN22* rs2476601*GG (p=0.039, p_{cor}=0.041, OR=0.608, 95% CI 0.391-0.952), *PTPN22* rs2476601*A (p=0.029, p_{cor}=0.031, OR=1.583, 95% CI 1.048-2.392)
	boys	*LTA* rs909253*AA (p=0.043, p_{cor}=0.043, OR=0.569, 95% CI 0.334-0.991), haplotype *TNFA* rs1800629*G - *LTA* rs909253*G (p=0.018, OR=1.79, 95% CI 1.11-2.89)
Rheumatoid factor positive polyarthritis	the general group of boys and girls	*LTA* rs909253*AG (p=0.007, p_{cor}=0.007, OR=NA (NA - not available), 95% CI 1.841-NA), *LTA* rs909253*AA (p=0.030, p_{cor}=0.031, OR=0.00, 95% CI 0.00-0.745), *MIF* rs755622*C (p=0.031, p_{cor}=0.028, OR=3.591, 95% CI 1.119-11.472), *MIF* rs755622*GG (p=0.042, p_{cor}=0.040, OR=0.132, 95% CI 0.011-0.975)
Rheumatoid factor negative polyarthritis	boys	*LTA* rs909253*AA (p=0.034, p_{cor}=0.035, OR=0.265, 95% CI 0.090-0.887), *IL2RA* rs2104286*G (p=0.023, p_{cor}=0.023, OR=0.130, 95% CI 0.012-0.724), *IL2RA* rs2104286*AG (p=0.039, p_{cor}=0.037, OR=0.132, 95% CI 0.012-0.87), *IL2RA* rs2104286*AA (p=0.021, p_{cor}=0.020, OR=8.58, 95% CI 1.313-92.61), *IL10* rs1800872*CC (p=0.040, p_{cor}=0.037, OR=0.296, 95% CI 0.101-0.993), *IL10* rs1800872*A (p=0.047, p_{cor}=0.046, OR=2.151, 95% CI 1.029-4.375), haplotype *TNFA* rs1800629*G - *LTA* rs909253*G (p=0.041, OR=2.36, 95% CI 1.04-5.36)
Persistent oligoarthritis	the general group of boys and girls	*LTA* rs909253*GG (p=0.033, p_{cor}=0.029, OR=2.108, 95% CI 1.094-4.152), *IL6* rs1800795*C (p=0.002, p_{cor}=0.003, OR=1.667, 95% CI 1.201-2.303), *IL6* rs1800795*CC (p=0.010, p_{cor}=0.008, OR=2.318, 95% CI 1.284-4.115), *IL6* rs1800795*GG (p=0.019, p_{cor}=0.019, OR=0.550, 95% CI 0.338-0.903), *IL10* rs1800872*A (p=0.042, p_{cor}=0.039, OR=0.683, 95% CI 0.471-0.981), *NFKB1* rs28362491*D (p=0.049, p_{cor}=0.049, OR=0.713, 95% CI 0.512-0.989), *PTPN22* rs2476601*GA (p=0.024, p_{cor}=0.022, OR=1.903, 95% CI 1.120-3.293), *PTPN22* rs2476601*A (p=0.035, p_{cor}=0.035, OR=1.677, 95% CI 1.048-2.665), *PTPN22* rs2476601*GG (p=0.029, p_{cor}=0.029, OR=0.539, 95% CI 0.321-0.923), haplotype *TNFA* rs1800629*G - *LTA* rs909253*G (p=0.015, OR=1.62, 95% CI 1.10-2.39)
	girls	*IL6* rs1800795*GG (p=0.046, p_{cor}=0.048, OR=0.543, 95% CI 0.295-0.988), *PTPN22* rs2476601*GA (p=0.012, p_{cor}=0.012, OR=2.304, 95% CI 1.250-4.204), *PTPN22* rs2476601*A (p=0.007, p_{cor}=0.008, OR=2.192, 95% CI 1.287-3.786), *PTPN22* rs2476601*GG (p=0.006, p_{cor}=0.006, OR=0.413, 95% CI 0.222-0.77), haplotype *TNFA* rs1800629*G - *LTA* rs909253*G (p=0.02, OR=1.77, 95% CI 1.10-2.87)
	boys	*IL1B* rs16944*CC (p=0.044, p_{cor}=0.045, OR=2.439, 95% CI 1.085-5.475), *IL1B* rs16944*T (p=0.013, p_{cor}=0.012, OR=0.448, 95% CI 0.241-0.837), *IL2-IL21* rs6822844*GG (p=0.041, p_{cor}=0.040, OR=4.295, 95% CI 1.133-19.229), *IL2-IL21* rs6822844*T (p=0.034, p_{cor}=0.033, OR=0.234, 95% CI 0.053-0.898), *IL6* rs1800795*CC (p=0.003, p_{cor}=0.003, OR=3.943, 95% CI 1.682-8.998), *IL6* rs1800795*G (p=0.010, p_{cor}=0.008, OR=0.466, 95% CI 0.270-0.820)
Extended oligoarthritis	the general group of boys and girls	*IL2-IL21* rs6822844*GG (p=0.048, p_{cor}=0.045, OR=2.849, 95% CI 1.032-7.623), *IL2-IL21* rs6822844*T (p=0.022, p_{cor}=0.021, OR=0.329, 95% CI 0.126-0.889), *PTPN22* rs2476601*GA (p=0.035, p_{cor}=0.037, OR=2.189, 95% CI 1.085-4.482)
	girls	*IL2-IL21* rs6822844*T (p=0.021, p_{cor}=0.020, OR=0.271, 95% CI 0.087-0.841), *CTLA4* rs3087243*GG (p=0.026, p_{cor}=0.026, OR=2.171, 95% CI 1.081-4.370), *CTLA4* rs3087243*A (p=0.044, p_{cor}=0.042, OR=0.563, 95% CI 0.321-0.971), *PTPN22* rs2476601*GA (p=0.028, p_{cor}=0.029, OR=2.407, 95% CI 1.176-5.081)
Enthesitis related arthritis	the general group of boys and girls	*LTA* rs909253*AG (p=0.002, p_{cor}=0.003, OR=3.316, 95% CI 1.564-6.769), *LTA* rs909253*G (p=0.041, p_{cor}=0.042, OR=1.700, 95% CI 1.041-2.758), *LTA* rs909253*AA (p=0.004, p_{cor}=0.003, OR=0.307, 95% CI 0.143-0.691), *IL6* rs1800795*CC (p=0.048, p_{cor}=0.0499, OR=2.519, 95% CI 1.115-5.867), *PTPN22* rs2476601*GA (p=0.029, p_{cor}=0.028, OR=2.547, 95% CI 1.122-5.608), *PTPN22* rs2476601*A (p=0.022, p_{cor}=0.024, OR=2.202, 95% CI 1.128-4.170), *PTPN22* rs2476601*GG (p=0.021, p_{cor}=0.019, OR=0.393, 95% CI 0.183-0.833), haplotype *TNFA* rs1800629*G - *LTA* rs909253*G (p=0.0014, OR=2.57, 95% CI 1.44-4.56)
	boys	*LTA* rs909253*AG (p=0.001, p_{cor}=0.001, OR=4.331, 95% CI 1.819-10.374), *LTA* rs909253*G (p=0.025, p_{cor}=0.026, OR=2.011, 95% CI 1.124-3.689), *LTA* rs909253*AA (p=0.002, p_{cor}=0.002, OR=0.224, 95% CI 0.087-0.578), *NFKB1* rs28362491*DD (p=0.037, p_{cor}=0.037, OR=2.755, 95% CI 1.036-6.563), *PTPN22* rs2476601*GA (p=0.013, p_{cor}=0.014, OR=3.459, 95% CI 1.303-8.797), *PTPN22* rs2476601*GG (p=0.037, p_{cor}=0.038, OR=0.363, 95% CI 0.152-0.966), haplotype *TNFA* rs1800629*G - *LTA* rs909253*G (p=0.0028, OR=3.11, 95% CI 1.50-6.44)
Psoriatic arthritis	the general group of boys and girls	haplotype *TNFA* rs1800629*G - *LTA* rs909253*G (p=0.039, OR=3.09, 95% CI 1.07-8.95)

Table 3. Genetic predictors of the development of JIA and its clinical variants

		TNFA rs1800629	*LTA* rs909253	*Haplotypes* rs1800629-rs909253	*IL1B* rs16944	*IL2-IL21* rs6822844	*IL2RA* rs2104286	*IL6* rs1800795	*IL10* rs1800872	*MIF* rs755622	*CTLA4* rs3087243	*NFKB1* rs28362491	*PTPN22* rs2476601	*PADI4* rs2240336
JIA	f+m	*AA*	-	**G-G**	-	-	-	-	-	-	-	-	**GA**, *GG*	-
	f	*AA*	-	-	-	*TT*	-	-	-	-	-	-	**A**, *G, GG*	-
	m	-	*AA*	**G-G**	-	-	-	-	-	-	-	-	-	-
Clinical variants of JIA														
Systemic arthritis	f+m, f, m	-	-	-	-	-	-	-	-	-	-	-	-	-
Rheumatoid factor positive polyarthritis	f+m	-	**AG**, *AA*	-	-	-	-	-	-	**C**, *G, GG*	-	-	-	-
Rheumatoid factor negative polyarthritis	f+m	-	-	-	-	-	-	-	-	-	-	-	-	-
	f	-	-	-	-	-	-	-	-	-	-	-	-	-
	m	-	*AA*	**G-G**	-	-	**AA, A**, *AG, G*	-	**A**, *C, CC*	-	-	-	-	-
Persistent oligoarthritis	f+m	-	**GG**	**G-G**	-	-	-	**CC, C**, *GG, G*	**C**, *A*	-	-	**I**, *D*	**GA, A**, *GG, G*	-
	f	-	-	**G-G**	-	-	-	*GG*	-	-	-	-	**GA, A**, *GG, G*	-
	m	-	-	-	**CC, C**, *T*	**GG, G**, *T*	-	**CC, C**, *G*	-	-	-	-	-	-
Extended oligoarthritis	f+m	-	-	-	-	**GG, G**, *T*	-	-	-	-	-	-	**GA**	-
	f	-	-	-	-	**G**, *T*	-	-	-	-	**GG, G**, *A*	-	**GA**	-
	m	-	-	-	-	-	-	-	-	-	-	-	-	-
Enthesitis related arthritis	f+m	-	**AG, G**, *AA, A*	**G-G**	-	-	-	**CC**	-	-	-	-	**GA, A**, *GG, G*	-
	f	-	-	-	-	-	-	-	-	-	-	-	-	-
	m	-	**AG, G**, *AA, A*	**G-G**	-	-	-	-	-	-	-	**DD**	**GA**, *GG*	-
Psoriatic arthritis	f+m	-	-	**G-G**	-	-	-	-	-	-	-	-	-	-

Hereinafter in the tables: f+m, female and male; f, female; m, male; alleles, genotypes and haplotypes for which OR>1 (p<0.05) **are highlighted in bold underlined font on a gray background**; alleles, genotypes and haplotypes for which OR<1 (p<0.05) are *italicized.*

- Psoriatic arthritis (the haplotype *TNFA* rs1800629*G – *LTA* rs909253*G (only for the general group of boys and girls)).

It should be noted that the Rheumatoid factor positive polyarthritis and Psoriatic arthritis patients samples were small, which is why the sex stratification was not carried out.Associations with the development of the Systemic arthritis for the studied polymorphic variants of the immune response mediator genes were not detected, including in the sex-stratified analysis (p>0.05).

Discussion

As a result of this work, the relationship of the alleles, genotypes and haplotypes of a number of the immune response mediator genes polymorphic loci with the risk of the development of JIA and its clinical variants – Rheumatoid factor positive polyarthritis, Rheumatoid factor negative polyarthritis (only in boys), Persistent oligoarthritis, Extended oligoarthritis, Enthesitis related arthritis, Psoriatic arthritis – was established. Specific associations were observed for girls and boys, which indicates the existence of sexual dimorphism in the JIA pathogenesis. For girls, the risk markers of JIA in general, as well as of Persistent oligoarthritis and Extended oligoarthritis were established, and for boys – of JIA in general and of Rheumatoid factor negative polyarthritis, Persistent oligoarthritis, Enthesitis related arthritis (*Table* 3).

Some of the examined polymorphic variants of the immune response mediator genes have previously been studied for a relationship with the JIA development in separate ethnic groups, but the results are contradictory. Nevertheless, the data of a number of papers are generally consistent with the results of the present study. The protective effect on the development of JIA and/or its clinical variants was shown for the *TNFA* rs1800629*A allele in the work of Schmeling H. et al. (2006), Kaalla M.J. et al. (2013), Reinards T.H. et al. (2015); for the *IL2-IL21* rs6822844*T allele – in the works of Albers H.M. et al. (2009), Hinks A. et al. (2010); for the *IL2RA* rs2104286*G allele – in the works of Hinks A. et al. (2009), Thompson S.D. et al. (2010) [12-18]. According to Crawley E. et al. (1999), the presence of ATA-containing genotypes of the *IL10* gene rs1800896, rs1800871 and rs1800872 polymorphic loci haplotypes was significantly more characteristic for patients with Extended oligoarthritis, than for those with Persistent oligoarthritis [19]. A number of authors have shown that the *PTPN22* rs2476601*A allele marks an increased risk of the development of JIA in general and of some of its variants [2, 13, 18, 20-22]. According to the latest data, the association of the *PTPN22* rs2476601*A allele with the JIA development is characteristic only for girls [23].

At the same time, according to a number of studies, the *TNFA* rs1800629*A allele marks an increased risk of the development of JIA in general (in the Mexican population) or its polyarticular (in the Serbian population) and oligoarticular (in the British population) variants [24-26]. Several studies have reported the absence of a relationship between the *TNFA* rs1800629 polymorphic locus variants and the risk of the JIA development in the Portuguese, Spanish, Turkish, Czech, German, French and Italian populations [27-32]. A replicative study of Ellis et al. (2013) did not reveal the relationship of the *IL2-IL21* rs6822844 polymorphic locus alleles with the JIA development in the Australian population [33]. Prahalad et al. (2009) and Reinards et al. (2015) reported the absence of a relationship of the *IL2RA* rs2104286 polymorphic locus alleles with the development of JIA or its variants in children of European descent, and Ellis et al. (2013) – with the development of JIA in the Australian population [14, 33, 34]. Oen et al. (2005) also reported the absence of associations of the *IL10* rs1800896, rs1800871 and rs1800872 polymorphic loci genotypes and the genotypes of their haplotypes with the development of JIA and its variants in children of European descent [35]. In the Chinese and Hungarian populations, no relationship was found between the *PTPN22* rs2476601 polymorphic locus variants and the development of JIA, however, the sample size in these studies was relatively small [36, 37].

When analyzing the *MIF* rs755622 polymorphic locus, Donn et al. (2002) found that the *MIF* rs755622*C allele marks an increased risk of the JIA development in children from the UK [38]. Several studies (on samples of European origin (from the USA and Germany), as well as in the Turkish population) have reported on the absence of a relationship of the *MIF* rs755622 polymorphic locus alleles and genotypes with the development of JIA and / or its variants [13, 27, 39]. At the same time, Reinards et al. (2015) found that the *MIF* rs755622*C allele marks a protective effect on the JIA development in children of European descent [14].

The *CTLA4* rs3087243 polymorphic locus has been studied in JIA by several authors groups. Suppiah et al. (2006), Prahalad et al. (2008) and Ellis et al. (2013) did not reveal any independent associations of the *CTLA4* rs3087243 polymorphic locus variants (in isolated analysis, excluding haplotypes) with the JIA development in individuals from Northern Ireland, the USA (predominantly of Northern European ancestry) and Australia, respectively [33, 40, 41]. However, Hinks et al. (2010) on a sample of European origin from the UK, as well as in a meta-analysis with the inclusion of the Prahalad et al. (2008) data showed a borderline significance level (p=0.05) for the rarer occurrence of the *CTLA4* rs3087243*A allele in JIA patients than in controls [16].

The observed inconsistency of the results is probably related to the samples characteristics (including sample size, ethnic factors), the pronounced clinical heterogeneity of JIA and the presence of sexual dimorphism in the disease pathogenesis, which indicates the need to consider these aspects when studying the molecular genetic basis of JIA.

Conclusion

In this work, the relationship of the alleles, genotypes and haplotypes of a number of the immune response mediator genes polymorphic loci with the risk of the development of JIA and its clinical variants was established. Specific associations were observed for girls and boys, which indicates the existence of sexual dimorphism in the JIA pathogenesis.

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Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the standards of the Local ethical committee of Bashkir State Medical University (Ufa, Russia) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Appendix 1. Supplementary Tables

Supplementary Table 1. Analysis of the distribution of the polymorphic loci alleles and genotypes in patients with JIA and in the control group

Polymorphic locus			*Subjects*	*The whole group (f+m)*		*Female (f)*		*Male (m)*		n_i
Gene	rs	Alleles		Alleles and genotypes frequencies, %		Alleles and genotypes frequencies, %		Alleles and genotypes frequencies, %		The total number of genotyped subjects, n_i
		(1)/(2)		(2)	(11)/(12)/(22)	(2)	(11)/(12)/(22)	(2)	(11)/(12)/(22)	f+m : f : m
TNFA	1800629	G/A	patients	10.2	80.0/19.7/0.3	10.4	79.3/20.7/0.0	9.7	81.4/17.7/0.9	330 : 217 : 113
			controls	13.2	76.3/21.1/2.6	14.4	73.7/23.7/2.5	10.4	82.1/15.1/2.8	342 : 236 : 106
LTA	909253	A/G	patients	32.4	45.8/43.6/10.6	30.4	48.8/41.5/9.7	36.3	39.8/47.8/12.4	330 : 217 : 113
			controls	29.4	49.1/43.0/7.9	30.3	47.0/45.3/7.6	27.4	53.8/37.7/8.5	342 : 236 : 106
IL1B	16944	C/T	patients	36.2	41.2/45.2/13.6	37.3	37.8/49.8/12.4	34.1	47.8/36.3/15.9	330 : 217 : 113
			controls	37.9	38.9/46.5/14.6	37.1	39.0/47.9/13.1	39.6	38.7/43.4/17.9	342 : 236 : 106
IL2-21	6822844	G/T	patients	9.4	82.1/17.0/0.9	10.1	80.2/19.4/0.5	8.0	85.8/12.4/1.8	330 : 217 : 113
			controls	12.1	78.7/18.4/2.9	12.3	78.8/17.8/3.4	11.8	78.3/19.8/1.9	342 : 236 : 106
IL2RA	2104286	A/G	patients	17.0	69.1/27.9/3.0	18.4	66.8/29.5/3.7	14.2	73.5/24.8/1.8	330 : 217 : 113
			controls	17.4	68.4/28.4/3.2	16.7	69.9/26.7/3.4	18.9	65.1/32.1/2.8	342 : 236 : 106
IL6	1800795	G/C	patients	38.5	37.6/47.9/14.5	38.0	35.0/53.9/11.1	39.4	42.5/36.3/21.2	330 : 217 : 113
			controls	34.2	42.1/47.4/10.5	32.8	43.2/47.9/8.9	37.3	39.6/46.2/14.2	342 : 236 : 106
IL10	1800872	C/A	patients	29.8	50.3/39.7/10.0	27.6	52.5/39.6/7.8	34.1	46.0/39.8/14.2	330 : 217 : 113
			controls	31.6	47.7/41.5/10.8	32.6	46.2/42.4/11.4	29.2	50.9/39.6/9.4	342 : 236 : 106
MIF	755622	G/C	patients	19.1	65.5/30.9/3.6	18.7	65.4/31.8/2.8	19.9	65.5/29.2/5.3	330 : 217 : 113
			controls	21.8	60.2/36.0/3.8	22.2	59.7/36.0/4.2	20.8	61.3/35.8/2.8	342 : 236 : 106
CTLA4	3087243	G/A	patients	32.0	47.9/40.3/11.8	32.3	47.0/41.5/11.5	31.4	49.6/38.1/12.4	330 : 217 : 113
			controls	34.6	42.7/45.3/12.0	36.4	39.4/48.3/12.3	30.7	50.0/38.7/11.3	342 : 236 : 106
NFKB1	28362491	I/D	patients	43.0	32.7/48.5/18.8	43.3	31.3/50.7/18.0	42.5	35.4/44.2/20.4	330 : 217 : 113
			controls	44.9	31.0/48.2/20.8	47.2	28.4/48.7/22.9	39.6	36.8/47.2/16.0	342 : 236 : 106
PTPN22	2476601	G/A	patients	12.7	76.4/21.8/1.8	14.1	74.2/23.5/2.3	10.2	80.5/18.6/0.9	330 : 217 : 113
			controls	9.4	83.0/15.2/1.8	9.4	82.6/16.2/1.3	9.4	84.0/13.2/2.8	341 : 235 : 106
PADI4	2240336	G/A	patients	42.9	32.1/50.0/17.9	42.9	32.7/48.8/18.4	42.9	31.0/52.2/16.8	330 : 217 : 113
			controls	43.1	32.3/49.3/18.5	43.2	32.6/48.3/19.1	42.9	31.4/51.4/17.1	341 : 236 : 105

Hereinafter: (1), the major allele; (2), the minor allele; (11) and (22), genotypes homozygous for the major and minor alleles, respectively; (12), heterozygous genotype; f+m, female and male; f, female; m, male.

Supplementary Table 2. Analysis of the distribution of the polymorphic loci alleles and genotypes in patients with Rheumatoid factor negative polyarthritis and in the control group

Polymorphic locus			*Subjects*	*The whole group (f+m)*		*Female (f)*		*Male (m)*		n_i
Gene	rs	Alleles		Alleles and genotypes frequencies, %		Alleles and genotypes frequencies, %		Alleles and genotypes frequencies, %		The total number of genotyped subjects, n_i
		(1)/(2)		(2)	(11)/(12)/(22)	(2)	(11)/(12)/(22)	(2)	(11)/(12)/(22)	f+m : f : m
TNFA	1800629	G/A	patients	11.0	77.9/22.1/0.0	10.9	78.3/21.7/0.0	11.8	76.5/23.5/0.0	86 : 69 : 17
			controls	13.2	76.3/21.1/2.6	14.4	73.7/23.7/2.5	10.4	82.1/15.1/2.8	342 : 236 : 106
LTA	909253	A/G	patients	27.3	53.5/38.4/8.1	23.2	60.9/31.9/7.2	44.1	23.5/64.7/11.8	86 : 69 : 17
			controls	29.4	49.1/43.0/7.9	30.3	47.0/45.3/7.6	27.4	53.8/37.7/8.5	342 : 236 : 106
IL1B	16944	C/T	patients	37.8	37.2/50.0/12.8	38.4	36.2/50.7/13.0	35.3	41.2/47.1/11.8	86 : 69 : 17
			controls	37.9	38.9/46.5/14.6	37.1	39.0/47.9/13.1	39.6	38.7/43.4/17.9	342 : 236 : 106
IL2-21	6822844	G/T	patients	11.0	79.1/19.8/1.2	12.3	76.8/21.7/1.4	5.9	88.2/11.8/0.0	86 : 69 : 17
			controls	12.1	78.7/18.4/2.9	12.3	78.8/17.8/3.4	11.8	78.3/19.8/1.9	342 : 236 : 106
IL2RA	2104286	A/G	patients	16.3	70.9/25.6/3.5	19.6	65.2/30.4/4.3	2.9	94.1/5.9/0.0	86 : 69 : 17
			controls	17.4	68.4/28.4/3.2	16.7	69.9/26.7/3.4	18.9	65.1/32.1/2.8	342 : 236 : 106
IL6	1800795	G/C	patients	34.3	40.7/50.0/9.3	37.0	36.2/53.6/10.1	23.5	58.8/35.3/5.9	86 : 69 : 17
			controls	34.2	42.1/47.4/10.5	32.8	43.2/47.9/8.9	37.3	39.6/46.2/14.2	342 : 236 : 106
IL10	1800872	C/A	patients	33.7	43.0/46.5/10.5	30.4	47.8/43.5/8.7	47.1	23.5/58.8/17.6	86 : 69 : 17
			controls	31.6	47.7/41.5/10.8	32.6	46.2/42.4/11.4	29.2	50.9/39.6/9.4	342 : 236 : 106
MIF	755622	G/C	patients	18.6	67.4/27.9/4.7	18.1	68.1/27.5/4.3	20.6	64.7/29.4/5.9	86 : 69 : 17
			controls	21.8	60.2/36.0/3.8	22.2	59.7/36.0/4.2	20.8	61.3/35.8/2.8	342 : 236 : 106
CTLA4	3087243	G/A	patients	34.3	44.2/43.0/12.8	35.5	40.6/47.8/11.6	29.4	58.8/23.5/17.6	86 : 69 : 17
			controls	34.6	42.7/45.3/12.0	36.4	39.4/48.3/12.3	30.7	50.0/38.7/11.3	342 : 236 : 106
NFKB1	28362491	I/D	patients	47.1	23.3/59.3/17.4	47.1	23.2/59.4/17.4	47.1	23.5/58.8/17.6	86 : 69 : 17
			controls	44.9	31.0/48.2/20.8	47.2	28.4/48.7/22.9	39.6	36.8/47.2/16.0	342 : 236 : 106
PTPN22	2476601	G/A	patients	9.9	81.4/17.4/1.2	10.9	79.7/18.8/1.4	5.9	88.2/11.8/0.0	86 : 69 : 17
			controls	9.4	83.0/15.2/1.8	9.4	82.6/16.2/1.3	9.4	84.0/13.2/2.8	341 : 235 : 106
PADI4	2240336	G/A	patients	44.2	29.1/53.5/17.4	44.9	27.5/55.1/17.4	41.2	35.3/47.1/17.6	86 : 69 : 17
			controls	43.1	32.3/49.3/18.5	43.2	32.6/48.3/19.1	42.9	31.4/51.4/17.1	341 : 236 : 105

Supplementary Table 3. Analysis of the distribution of the polymorphic loci alleles and genotypes in patients with Persistent oligoarthritis and in the control group

Polymorphic locus			*Subjects*	*The whole group (f+m)*		*Female (f)*		*Male (m)*		n_i
Gene	rs	Alleles		Alleles and genotypes frequencies, %		Alleles and genotypes frequencies, %		Alleles and genotypes frequencies, %		The total number of genotyped subjects, n_i
		(1)/(2)		(2)	(11)/(12)/(22)	(2)	(11)/(12)/(22)	(2)	(11)/(12)/(22)	f+m : f : m
TNFA	1800629	G/A	patients	11.2	78.6/20.4/1.0	10.0	80.0/20.0/0.0	13.6	75.8/21.2/3.0	98 : 65 : 33
			controls	13.2	76.3/21.1/2.6	14.4	73.7/23.7/2.5	10.4	82.1/15.1/2.8	342 : 236 : 106
LTA	909253	A/G	patients	35.7	43.9/40.8/15.3	36.2	40.0/47.7/12.3	34.8	51.5/27.3/21.2	98 : 65 : 33
			controls	29.4	49.1/43.0/7.9	30.3	47.0/45.3/7.6	27.4	53.8/37.7/8.5	342 : 236 : 106
IL1B	16944	C/T	patients	32.7	43.9/46.9/9.2	37.7	35.4/53.8/10.8	22.7	60.6/33.3/6.1	98 : 65 : 33
			controls	37.9	38.9/46.5/14.6	37.1	39.0/47.9/13.1	39.6	38.7/43.4/17.9	342 : 236 : 106
IL2-21	6822844	G/T	patients	8.2	83.7/16.3/0.0	10.8	78.5/21.5/0.0	3.0	93.9/6.1/0.0	98 : 65 : 33
			controls	12.1	78.7/18.4/2.9	12.3	78.8/17.8/3.4	11.8	78.3/19.8/1.9	342 : 236 : 106
IL2RA	2104286	A/G	patients	16.8	69.4/27.6/3.1	16.9	69.2/27.7/3.1	16.7	69.7/27.3/3.0	98 : 65 : 33
			controls	17.4	68.4/28.4/3.2	16.7	69.9/26.7/3.4	18.9	65.1/32.1/2.8	342 : 236 : 106
IL6	1800795	G/C	patients	46.4	28.6/50.0/21.4	41.5	29.2/58.5/12.3	56.1	27.3/33.3/39.4	98 : 65 : 33
			controls	34.2	42.1/47.4/10.5	32.8	43.2/47.9/8.9	37.3	39.6/46.2/14.2	342 : 236 : 106
IL10	1800872	C/A	patients	24.0	58.2/35.7/6.1	23.8	56.9/38.5/4.6	24.2	60.6/30.3/9.1	98 : 65 : 33
			controls	31.6	47.7/41.5/10.8	32.6	46.2/42.4/11.4	29.2	50.9/39.6/9.4	342 : 236 : 106
MIF	755622	G/C	patients	18.9	65.3/31.6/3.1	20.0	63.1/33.8/3.1	16.7	69.7/27.3/3.0	98 : 65 : 33
			controls	21.8	60.2/36.0/3.8	22.2	59.7/36.0/4.2	20.8	61.3/35.8/2.8	342 : 236 : 106
CTLA4	3087243	G/A	patients	33.2	46.9/39.8/13.3	34.6	46.2/38.5/15.4	30.3	48.5/42.4/9.1	98 : 65 : 33
			controls	34.6	42.7/45.3/12.0	36.4	39.4/48.3/12.3	30.7	50.0/38.7/11.3	342 : 236 : 106
NFKB1	28362491	I/D	patients	36.7	39.8/46.9/13.3	40.0	35.4/49.2/15.4	30.3	48.5/42.4/9.1	98 : 65 : 33
			controls	44.9	31.0/48.2/20.8	47.2	28.4/48.7/22.9	39.6	36.8/47.2/16.0	342 : 236 : 106
PTPN22	2476601	G/A	patients	14.8	72.4/25.5/2.0	18.5	66.2/30.8/3.1	7.6	84.8/15.2/0.0	98 : 65 : 33
			controls	9.4	83.0/15.2/1.8	9.4	82.6/16.2/1.3	9.4	84.0/13.2/2.8	341 : 235 : 106
PADI4	2240336	G/A	patients	38.3	38.8/45.9/15.3	35.4	43.1/43.1/13.8	43.9	30.3/51.5/18.2	98 : 65 : 33
			controls	43.1	32.3/49.3/18.5	43.2	32.6/48.3/19.1	42.9	31.4/51.4/17.1	341 : 236 : 105

Supplementary Table 4. Analysis of the distribution of the polymorphic loci alleles and genotypes in patients with Extended oligoarthritis and in the control group

Polymorphic locus			*Subjects*	*The whole group (f+m)*		*Female (f)*		*Male (m)*		n_i
Gene	rs	Alleles		Alleles and genotypes frequencies, %		Alleles and genotypes frequencies, %		Alleles and genotypes frequencies, %		The total number of genotyped subjects, n_i
		(1)/(2)		(2)	(11)/(12)/(22)	(2)	(11)/(12)/(22)	(2)	(11)/(12)/(22)	f+m : f : m
TNFA	1800629	G/A	patients	7.6	84.8/15.2/0.0	8.5	82.9/17.1/0.0	0.0	100.0/0.0/0.0	46 : 41 : 5
			controls	13.2	76.3/21.1/2.6	14.4	73.7/23.7/2.5	10.4	82.1/15.1/2.8	342 : 236 : 106
LTA	909253	A/G	patients	31.5	50.0/37.0/13.0	32.9	48.8/36.6/14.6	20.0	60.0/40.0/0.0	46 : 41 : 5
			controls	29.4	49.1/43.0/7.9	30.3	47.0/45.3/7.6	27.4	53.8/37.7/8.5	342 : 236 : 106
IL1B	16944	C/T	patients	39.1	37.0/47.8/15.2	35.4	41.5/46.3/12.2	70.0	0.0/60.0/40.0	46 : 41 : 5
			controls	37.9	38.9/46.5/14.6	37.1	39.0/47.9/13.1	39.6	38.7/43.4/17.9	342 : 236 : 106
IL2-21	6822844	G/T	patients	4.3	91.3/8.7/0.0	3.7	92.7/7.3/0.0	10.0	80.0/20.0/0.0	46 : 41 : 5
			controls	12.1	78.7/18.4/2.9	12.3	78.8/17.8/3.4	11.8	78.3/19.8/1.9	342 : 236 : 106
IL2RA	2104286	A/G	patients	16.3	69.6/28.3/2.2	17.1	68.3/29.3/2.4	10.0	80.0/20.0/0.0	46 : 41 : 5
			controls	17.4	68.4/28.4/3.2	16.7	69.9/26.7/3.4	18.9	65.1/32.1/2.8	342 : 236 : 106
IL6	1800795	G/C	patients	38.0	34.8/54.3/10.9	40.2	31.7/56.1/12.2	20.0	60.0/40.0/0.0	46 : 41 : 5
			controls	34.2	42.1/47.4/10.5	32.8	43.2/47.9/8.9	37.3	39.6/46.2/14.2	342 : 236 : 106
IL10	1800872	C/A	patients	26.1	56.5/34.8/8.7	26.8	53.7/39.0/7.3	20.0	80.0/0.0/20.0	46 : 41 : 5
			controls	31.6	47.7/41.5/10.8	32.6	46.2/42.4/11.4	29.2	50.9/39.6/9.4	342 : 236 : 106
MIF	755622	G/C	patients	17.4	67.4/30.4/2.2	15.9	70.7/26.8/2.4	30.0	40.0/60.0/0.0	46 : 41 : 5
			controls	21.8	60.2/36.0/3.8	22.2	59.7/36.0/4.2	20.8	61.3/35.8/2.8	342 : 236 : 106
CTLA4	3087243	G/A	patients	25.0	56.5/37.0/6.5	24.4	58.5/34.1/7.3	30.0	40.0/60.0/0.0	46 : 41 : 5
			controls	34.6	42.7/45.3/12.0	36.4	39.4/48.3/12.3	30.7	50.0/38.7/11.3	342 : 236 : 106
NFKB1	28362491	I/D	patients	44.6	30.4/50.0/19.6	45.1	31.7/46.3/22.0	40.0	20.0/80.0/0.0	46 : 41 : 5
			controls	44.9	31.0/48.2/20.8	47.2	28.4/48.7/22.9	39.6	36.8/47.2/16.0	342 : 236 : 106
PTPN22	2476601	G/A	patients	14.1	71.7/28.3/0.0	15.9	68.3/31.7/0.0	0.0	100.0/0.0/0.0	46 : 41 : 5
			controls	9.4	83.0/15.2/1.8	9.4	82.6/16.2/1.3	9.4	84.0/13.2/2.8	341 : 235 : 106
PADI4	2240336	G/A	patients	51.1	23.9/50.0/26.1	51.2	24.4/48.8/26.8	50.0	20.0/60.0/20.0	46 : 41 : 5
			controls	43.1	32.3/49.3/18.5	43.2	32.6/48.3/19.1	42.9	31.4/51.4/17.1	341 : 236 : 105

Supplementary Table 5. Analysis of the distribution of the polymorphic loci alleles and genotypes in patients with Enthesitis related arthritis and in the control group

Polymorphic locus			*Subjects*	*The whole group (f+m)*		*Female (f)*		*Male (m)*		n_i
Gene	rs	Alleles		Alleles and genotypes frequencies, %		Alleles and genotypes frequencies, %		Alleles and genotypes frequencies, %		The total number of genotyped subjects, n_i
		(1)/(2)		(2)	(11)/(12)/(22)	(2)	(11)/(12)/(22)	(2)	(11)/(12)/(22)	f+m : f : m
TNFA	1800629	G/A	patients	7.1	85.7/14.3/0.0	16.7	66.7/33.3/0.0	5.2	89.7/10.3/0.0	35 : 6 : 29
			controls	13.2	76.3/21.1/2.6	14.4	73.7/23.7/2.5	10.4	82.1/15.1/2.8	342 : 236 : 106
LTA	909253	A/G	patients	41.4	22.9/71.4/5.7	33.3	33.3/66.7/0.0	43.1	20.7/72.4/6.9	35 : 6 : 29
			controls	29.4	49.1/43.0/7.9	30.3	47.0/45.3/7.6	27.4	53.8/37.7/8.5	342 : 236 : 106
IL1B	16944	C/T	patients	40.0	42.9/34.3/22.9	33.3	50.0/33.3/16.7	41.4	41.4/34.5/24.1	35 : 6 : 29
			controls	37.9	38.9/46.5/14.6	37.1	39.0/47.9/13.1	39.6	38.7/43.4/17.9	342 : 236 : 106
IL2-21	6822844	G/T	patients	5.7	88.6/11.4/0.0	8.3	83.3/16.7/0.0	5.2	89.7/10.3/0.0	35 : 6 : 29
			controls	12.1	78.7/18.4/2.9	12.3	78.8/17.8/3.4	11.8	78.3/19.8/1.9	342 : 236 : 106
IL2RA	2104286	A/G	patients	17.1	68.6/28.6/2.9	25.0	50.0/50.0/0.0	15.5	72.4/24.1/3.4	35 : 6 : 29
			controls	17.4	68.4/28.4/3.2	16.7	69.9/26.7/3.4	18.9	65.1/32.1/2.8	342 : 236 : 106
IL6	1800795	G/C	patients	38.6	45.7/31.4/22.9	33.3	50.0/33.3/16.7	39.7	44.8/31.0/24.1	35 : 6 : 29
			controls	34.2	42.1/47.4/10.5	32.8	43.2/47.9/8.9	37.3	39.6/46.2/14.2	342 : 236 : 106
IL10	1800872	C/A	patients	37.1	42.9/40.0/17.1	33.3	50.0/33.3/16.7	37.9	41.4/41.4/17.2	35 : 6 : 29
			controls	31.6	47.7/41.5/10.8	32.6	46.2/42.4/11.4	29.2	50.9/39.6/9.4	342 : 236 : 106
MIF	755622	G/C	patients	14.3	74.3/22.9/2.9	8.3	83.3/16.7/0.0	15.5	72.4/24.1/3.4	35 : 6 : 29
			controls	21.8	60.2/36.0/3.8	22.2	59.7/36.0/4.2	20.8	61.3/35.8/2.8	342 : 236 : 106
CTLA4	3087243	G/A	patients	32.9	45.7/42.9/11.4	16.7	66.7/33.3/0.0	36.2	41.4/44.8/13.8	35 : 6 : 29
			controls	34.6	42.7/45.3/12.0	36.4	39.4/48.3/12.3	30.7	50.0/38.7/11.3	342 : 236 : 106
NFKB1	28362491	I/D	patients	52.9	28.6/37.1/34.3	50.0	33.3/33.3/33.3	53.4	27.6/37.9/34.5	35 : 6 : 29
			controls	44.9	31.0/48.2/20.8	47.2	28.4/48.7/22.9	39.6	36.8/47.2/16.0	342 : 236 : 106
PTPN22	2476601	G/A	patients	18.6	65.7/31.4/2.9	25.0	66.7/16.7/16.7	17.2	65.5/34.5/0.0	35 : 6 : 29
			controls	9.4	83.0/15.2/1.8	9.4	82.6/16.2/1.3	9.4	84.0/13.2/2.8	341 : 235 : 106
PADI4	2240336	G/A	patients	51.4	22.9/51.4/25.7	58.3	16.7/50.0/33.3	50.0	24.1/51.7/24.1	35 : 6 : 29
			controls	43.1	32.3/49.3/18.5	43.2	32.6/48.3/19.1	42.9	31.4/51.4/17.1	341 : 236 : 105