Interaction of immune response mediator genes in a predisposition to juvenile idiopathic arthritis

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Abstract/Background/objective — The goal of our study was to investigate the role of interaction between the polymorphic loci of immune response mediator genes (TNFA rs1800629, LTA rs909253, IL1B rs16944, IL2-IL21 rs6822844, IL2RA rs2104286, IL6 rs1800795, IL10 rs1800872, MIF rs755622, CTLA4 rs3087243, NFkB1 rs28362491, PTPN22 rs2476601, and PADI4 rs2240336) in the formation of a genetic predisposition to juvenile idiopathic arthritis (JIA). Material and Methods — The study involved 330 JIA patients and 342 volunteers from the Republic of Bashkortostan. Genotyping was conducted via the real-time polymerase chain reaction. The gene–gene interactions were studied using the multifactor dimensionality reduction algorithm. Results — In general analysis, the best model of gene–gene interaction in JIA was a combination of IL1B rs16944 – IL10 rs1800872 – NFkB1 rs28362491 – PADI4 rs2240336 polymorphic loci. However, after gender-based stratification the best results were obtained when examining the combinations of IL6 rs1800795 – PADI4 rs2240336 loci in girls and of IL10 rs1800872 – IL6 rs1800795 – IL2RA rs2104286 loci in boys. Within all of these models, the genotype combinations associated with both augmented and reduced JIA risks were identified (taking into account gender-specific differences). Conclusion — The results of our study implied that an important role in the formation of a predisposition to JIA is played by gene–gene interactions of IL1B rs16944, IL2RA rs2104286, IL6 rs1800795, IL10 rs1800872, NFkB1 rs28362491, and PADI4 rs2240336 polymorphic loci (taking into account gender-specific differences).

Keywords: juvenile idiopathic arthritis, immune system, genetics, polymorphic loci, gene–gene interactions, multifactor dimensionality reduction algorithm.

Introduction

Juvenile idiopathic arthritis (JIA) is the most common form of childhood arthritis, but the genetic basis of the disease is still not fully understood and requires further research [1,2]. To date, a large number of genetic determinants has been analyzed, including polymorphic loci of the immune response mediator genes (such as genes of interleukins (ILs) and their receptors (ILRs), tumor necrosis factor-alpha (TNF-α), lymphotxin alpha (LT-α), macrophage migration inhibitory factor (MIF), nuclear factor kappa B (NF-κB), cytotoxic T-lymphocyte associated protein 4 (CTLA-4), protein tyrosine phosphatase non-receptor type 22 (PTPN22), peptideyl arginine deiminase 4 (PADI4)). However, the results are often contradictory [3–5].

We have previously studied the association of separate variants of the polymorphic loci of immune response mediator genes (TNFA rs1800629, LTA rs909253, IL1B rs16944, IL2-IL21 rs6822844, IL2RA rs2104286, IL6 rs1800795, IL10 rs1800872, MIF rs755622, CTLA4 rs3087243, NFkB1 rs28362491, PTPN22 rs2476601, and PADI4 rs2240336), as well as of the haplotypes of TNFA rs1800629 and LTA rs909253 polymorphic loci, with the development of JIA and its clinical variants [5]. When analyzing the results, for a number of loci, we found no statistically significant associations with the development of JIA (in general). Taking into account the data on the presence of corresponding relationships presented in some publications, we suggested that the observed inconsistency was probably related to specific features of the samples, clinical heterogeneity, and sexual dimorphism of JIA [5]. However, a growing body of research suggested that the lack of association in some cases could be caused by an isolated examination of the polymorphic loci variants [6–9]. Therefore, in our study, we attempted to examine the role of the interaction between the polymorphic loci of the corresponding genes in the formation of JIA (in general), which may contribute to a deeper understanding of the disease pathogenesis, and possibly further optimization of its therapeutic strategies. The relevance of the issue was confirmed by the data on the features of immune system functioning [6–10]. Various intracellular and extracellular stimuli trigger a signaling cascade, in which many pathways and mediators are simultaneously involved [11, 12]. These mediators

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could significantly modify – weaken or enhance – the effects of each other. For instance, the interrelation has been reported between the levels of cytokines and other factors that were presumably involved in the JIA pathogenesis [3, 5, 12-19].

Material and Methods

Study design, subjects, and genotyping

The objective of our study was to investigate the role of interaction between the polymorphic loci of immune response mediator genes (TNFA rs1800629, LTA rs909253, IL1B rs16944, IL2-IL21 rs6828244, IL2RA rs2104286, IL6 rs1800795, IL10 rs1800872, MIF rs755622, CTLA4 rs3087243, NFKB1 rs28362491, PTPN22 rs2476601, PADI4 rs2240336) in the formation of a genetic predisposition to JIA.

This study was carried out as an extension of our earlier research, using the results of genotyping obtained in that previous study; the sample characteristics (330 JIA patients and 342 volunteers from the Republic of Bashkortostan, Russia) and the parameters of molecular genetic analysis were described in detail in the preceding publication [5].

Statistical analysis

The role of gene-gene interactions in forming a genetic predisposition to JIA was examined via the multifactor dimensionality reduction algorithm, using the MDR v.3.0.2 software [20]. Two-locus, three-locus and four-locus models were analyzed (proper gene-gene interactions), along with single-locus models. The model quality was established by the value of the adjusted balanced testing accuracy (with a minimum threshold of 0.55) and the cross-validation consistency (CVC) (with a minimum threshold of 9/10). The statistical significance of the models was assessed using a permutation test with 1,000 permutes ($p_{cor}$). Identification of the best models was performed in an automatic mode via “exhaustive search” method; for the models with CVC less than 9/10, the results were validated by the “forced search” method. The case-control status information gain from the knowledge about the genotypes of one or two loci (pairwise analysis) was estimated by the level of the entropy reduction. Based on the obtained data, a cluster analysis was conducted with a loci interaction dendrogram constructing. To visualize the results of all pairwise comparisons, an interaction graph was built.

The frequencies of the genotype combinations within the best models were compared in patients versus control subjects using Fisher’s exact two-sided test with a cut-off threshold $p$-value of 0.05. In the absence of statistically significant differences, the corresponding combinations were categorized as unclassified. For statistically significant combinations, the odds ratio (OR) with the Baptista-Pike exact conditional 95% confidence interval (95% CI) were additionally calculated using Microsoft Excel and R v.3.4.2 (R Core Team, 2017) [21].

Results

The role of complex interaction between all studied loci of immune response mediator genes in the formation of a genetic predisposition to JIA is visualized on an interaction graph (Figures 1A, 1D).

When examining separate polymorphic loci, the largest information gain was noted for the TNFA rs1800629 (0.81%) and PTPN22 rs2476601 (0.51%). Nonetheless, the best interaction model was represented by four-locus combination, IL1B rs16944 – IL10 rs1800872 – NFKB1 rs28362491 – PADI4 rs2240336 (“forced search” method: adjusted balanced testing accuracy of 0.57, CVC of 10/10, $p_{cor}=0.001$) (Figures 1B, 1C, 1D).

It should be noted that investigation of the separate loci of IL1B rs16944 – IL10 rs1800872 – NFKB1 rs28362491 – PADI4 rs2240336 model was uninformative (a reduction in the entropy level by no more than 0.06%), while their pairwise analysis exhibited a significant information gain (up to 0.59%). A synergistic relationship was observed between the IL10 rs1800872, NFKB1 rs28362491, and PADI4 rs2240336 loci, while IL1B rs16944 locus was characterized by an independent effect. Within the considered model, the genotype combinations associated with both augmented JIA risk (CC-CC-DD-DG, $p=0.010$, $p_{cor}=0.010$, OR=9.505, 95% CI: 1.569-104.682) and declined JIA risk (CC-CA-DD-GG, $p=0.021$, $p_{cor}=0.019$, OR=0.112, 95% CI: 0.010-0.677 and CT-CA-ID-GG-CC, $p_{cor}=0.0044$, OR=0.299, 95% CI: 0.121-0.674) were identified.

In girls, the best results were obtained for the combination of IL6 rs1800795 – PADI4 rs2240336 polymorphic loci. That interaction was synergistic (“forced search” method: adjusted balanced testing accuracy of 0.57, CVC of 10/10, $p_{cor}=0.009$) (Figure 2A). Within this model, an association was established of GC-GA genotype combination with an increased JIA risk in girls ($p=0.018$, $p_{cor}=0.018$, OR=1.696, 95% CI: 1.113-2.626), and GG-GA genotype combination with a reduced JIA risk in girls ($p=0.028$, $p_{cor}=0.027$, OR=0.565, 95% CI: 0.341-0.921).

In boys, the three-locus model, IL10 rs1800872 – IL6 rs1800795 – IL2RA rs2104286, was the best (“forced search” method: adjusted balanced testing accuracy of 0.61, CVC of 10/10, $p_{cor}=0.009$) (Figure 2B). The interaction of IL6 rs1800795 locus with the rest turned out to be synergistic and was most pronounced in the pair, IL6 rs1800795 – IL10 rs1800872. At the same time, examination of IL10 rs1800872 – IL2RA rs2104286 loci combination yielded a decrease in the information gain. In the subsequent comparative analysis, we established that in boys with JIA, the CA-GG-AA genotype combination of the considered model was found much more frequently ($p=0.0031$, $p_{cor}=0.0030$, OR=4.784, 95% CI: 1.550-13.370); whereas the CC-GG-AG genotype combination was detected much less frequently ($p=0.0045$, $p_{cor}=0.0052$, OR=0.140, 95% CI: 0.031-0.578) than in control male subjects.

Discussion

In this study, the role of interaction between the polymorphic loci of immune response mediator genes in the formation of a genetic predisposition to JIA was investigated. The best model of gene-gene interaction in JIA (in general) was a combination of IL1B rs16944 – IL10 rs1800872 – NFKB1 rs28362491 – PADI4 rs2240336 polymorphic loci. However, after gender-based stratification, in girls, the best results were obtained when studying the combination of IL6 rs1800795 – PADI4 rs2240336 loci, while in boys, for IL10 rs1800872 – IL6 rs1800795 – IL2RA rs2104286 loci. Within all of these models, the genotype combinations associated with both enlarged and reduced JIA risks were identified (taking into account gender-specific differences). However, in our previous isolated analysis, we demonstrated that the frequency distribution of the separate IL1B rs16944, IL10 rs1800872, NFKB1 rs28362491, PADI4 rs2240336 loci variants did not differ

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significantly between JIA patients (in general) and control subjects [5]. Also, previously, we did not detect associations with JIA (in general) for the separate variants of IL10 rs1800872, IL6 rs1800795, and IL2RA rs2104286, and of IL6 rs1800795 and PADI4 rs2240336 loci for girls. Only a trend towards a rarer occurrence of IL6 rs1800795*GG genotype in girls with JIA (in general) was observed [5]. In the current study, we found that this tendency reached the statistical significance level when we considered the combination of IL6 rs1800795*GG genotype with PADI4 rs2240336*GA genotype. Consequently, bearing in mind the results of this research, we could assume that the gene-gene interactions may have an important modifying role in manifesting the potential effects of corresponding polymorphic variants and the JIA risk.

The analysis of published sources confirmed the presence of a functional relationship between the genes of the models identified in this study. First of all, we analyzed the data on the IL18 rs16944 – IL10 rs1800872 – NFkB1 rs28362491 – PADI4 rs2240336 model. This model includes two cytokines (proinflammatory IL-1β and anti-inflammatory IL-10), transcription factor (NF-kB1), and deaminase (PADA) [14,22]. NF-kB1 (p50) belongs to the family of transcription factors NF-kB, and in homodimeric form (p50/p50), it has an anti-inflammatory effect, enhancing the IL10 gene transcription and inhibiting the TNFA gene transcription [23,24]. In turn, IL-10 has been shown to selectively induce nuclear translocation and DNA-binding of NF-kB1 p50/p50 homodimer [14]. IL-10 also suppresses the production of IL-1β, and IL-1β can downregulate the IL-10 secretion [14,25]. Abbas et al. (2014) suggested that the p50 homodimers could repress PADI4 gene transcription, which could be beneficial for preventing chronic inflammation [26]. Protein arginine deiminases (PADs) are the enzymes that control protein citrullination and, presumably, play an important role in inflammation and autoimmunity [22]. PADI4 is assumed to be required for optimal inflammasome assembly and IL-1β release [22]. IL-10 reduction was found in the lung vs. its augmented content in the kidney of PADI4-deficient mice (PADI4−/−), compared with wild-type mice in the study of the dual insult model [27].

Next, we examined the IL6 rs1800795 – PADI4 rs2240336 loci combination. IL-6 is a pleiotropic cytokine that regulates many functions of the immune system [13,18]. The recent study on the animal model for rheumatoid arthritis showed the presence of IL-6 dependent PADI4 production in synovial neutrophils in the preclinical phase of the disease [18]. When studying the dual insult model, IL-6 was significantly reduced in PADI4−/− mice lung tissue compared with wild-type mice [27].

Finally, the IL10 rs1800872 – IL6 rs1800795 – IL2RA rs2104286 model was analyzed. IL-2Rα (CD25) is one of three components of the IL-2 receptor. CD25 has been shown to be dysregulated in autoimmune diseases, cancer, and inflammation [28]. According to Dehó et al. (2014), CD25-negative mast cells (compared with CD25-positive cells) secreted higher amounts of IL-6 in response to IgE and Ag stimulation and higher levels of IL-10 when stimulated with PMA and ionomycin [28]. At the same time, Caudy et al. (2007) showed that CD25 expression was required for IL-10 production by CD4 lymphocytes [29]. In turn, IL-10 suppressed IL-6 production; however, IL-6 could stimulate IL-10 secretion [14,25].

Figure 1. Interactions between polymorphic loci of immune response mediator genes in susceptibility to JIA (in general): (A) general interaction graph; (B) interaction graph for the best model; (C) dendrogram of the best model; (D) line colors interpretation.

Here and below on the graphs (and dendrogram), only the names of genes of the studied polymorphic loci are given (TNFA, tumor necrosis factor-alpha gene, rs1800629; LTA, lymphotoxin alpha gene, rs909253; IL1B, interleukin 1 beta gene, rs16944; IL2-IL21, intergenic region of interleukin 2 and interleukin 21 genes, rs6822844; IL2RA, interleukin 2 receptor subunit alpha gene, rs2104286; IL6, interleukin 6 gene, rs1800795; IL10, interleukin 10 gene, rs1800872; MIF, macrophage migration inhibitory factor gene, rs755622; CTLA4, cytotoxic T-lymphocyte associated protein 4 gene, rs3087243; NFkB1, nuclear factor kappa B subunit 1 gene, rs28362491; PTPN22, protein tyrosine phosphatase non-receptor type 22 gene, rs2476601; PADI4, peptidyl arginine deiminase 4 gene, rs2240336). The color of lines indicates the type of interactions between loci. The length of lines on the dendrogram is inversely proportional to the interaction strength between the loci. The percentage values on the loci correspond to the values of information gain.
Conclusion

In conclusion, we would like to point out that the results of our study implied that an important role in the formation of a predisposition to JIA is played by gene-gene interactions of IL1B rs16944, IL2RA rs2104286, IL6 rs1800795, IL10 rs1800872, NFKB1 rs28362491, and PAI4 rs2240336 polymorphic loci (taking into account gender-specific differences).

Study limitations

The limitations of our research are as follows: relatively small number of the studied polymorphic loci, along with the lack of analysis for JIA subtypes due to insufficient number of patients. Further research is needed to clarify the functional significance of identified models, as well as to confirm the revealed associations on samples of a different ethnicity.

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Conflict of interest

The authors declare that they have no conflicts of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the standards of the local ethics committee at Bashkir State Medical University (Ufa, Russia) and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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