DETECTION OF THE SNP-SNP INTERACTIONS IN THE JUVENILE ARTHRITIS SUSCEPTIBILITY USING MDR ANALYSIS

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Background: Juvenile idiopathic arthritis (JIA) is the most common chronic arthropathy of childhood which is considered to be a complex disease. The genes encoding HLA complex account for only 14% of the JIA risk. Hence, it is suggested that substantial role in genetic predisposition to JIA belongs to the non-HLA genes variation.

Objectives: The aim of the study was to estimate interactions between SNPs of the genes implicated in immune and inflammatory responses: STAT4 (rs7574865), CTLA4 (rs5742909), MIF (rs755622), TRAF1/C5 (rs3671847), RUNX3 (rs11249215) and their effect on the JIA susceptibility.

Methods: 119 patients diagnosed with JIA (mean age 8.4± 5.06), and 197 hospital controls with no signs of autoimmune or inflammatory diseases (mean age 14.19± 2.56) were included into the study. DNA extraction from peripheral blood samples was performed with phenol-chloroform method. SNPs were genotyped using the PCR-RFLP assay. Multifactor dimensionality reduction (MDR) analysis was performed using MDR 3.0.2 software package with the following configuration: attribute count range – from 1 to 5; cross-validation count – 10; track top models – 1000; search method configuration – exhaustive; ambiguous cell analysis – Fisher’s exact test; ambiguous cell assignment – unclassified. The best model was selected on the basis of maximum crossvalidation consistency and testing balance accuracy values.

Results: Model-free nonparametric statistical approach of MDR analysis revealed the best model for JIA susceptibility prediction with cross-validation consistency of 9.10 and testing balanced accuracy of 0.5786. The model includes SNPs of STAT4, TRAF1/C5 and RUNX3 genes and is characterized by 0.8727 sensitivity; 0.7083 specificity, OR = 4.9921; 95%CI [2.10-10.20], p < 0.0001. Gene-gene interaction analysis discovered three genotype combinations for higher JIA risk. The most statistically significant was: GA (RUNX3 rs11249215), GT (STAT4 rs7574865) and GG (TRAF1/C5 rs3671847), OR = 2.92, combined entropy – 4.83%. Separate data analysis for males and females didn’t show any statistically significant model of SNP interactions associated with JIA. However, MIF rs755622 with entropy of 2.92% was more informative in females, while STAT4 rs7574865 with entropy value of 1.12% - in males.

Conclusion: MDR analysis of the JIA case-control data set identified a statistically significant high-order interaction of three polymorphisms: STAT4 (rs7574865), TRAF1/C5 (rs3671847), RUNX3 (rs11249215). This combination may contribute to JIA genetic susceptibility in the Belarusian population.

Disclosure of Interests: None declared.