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Disclosure of Interests: None declared

AB0004 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 implicated in immune and inflammatory responses: HLA gene variations.

Objectives: The aim of the study was to estimate interactions between SNPs of the genes implicated in immune and inflammatory responses: HLA gene variations.

Methods: 119 patients diagnosed with JIA (mean age 8.48 ± 5.06), and 197 hospital controls with no signs of autoimmunity 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 0.5768. The model includes SNPs of STAT4, TAF1/C5 and RUNX3 genes and is characterized by 0.8727 sensitivity; 0.7083 specificity, OR = 4.9921; 95%CI [2.4-10.20], 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 (TAF1/C5 rs3761847), OR = 2.92, combined entropy - 4.83%. Separate data analysis for males and females did not show any statistically significant model of SNP interactions associated with JIA. However, MIF rs756622 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), TAF1/C5 (rs3761847) and RUNX3 (rs11249215). This combination may contribute to JIA genetic susceptibility in the Belarusian population.

Disclosure of Interests: None declared

AB0005 FAVORABLE RESPONSE TO RITUXIMAB IN A PATIENT WITH HYPOCHOLEMPENEMETRIC URTICARIAL VASCULITIS ASSOCIATED WITH A HOMOZYGOUS FRAMESHIFT AGBL3 VARIANT

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Background: Last year we described a homozygous AGBL3 variant in a patient with autoinflammatory features and hyPOCHOLEMPENEMETRIC urticarial vasculitis. Whole exome sequencing revealed a deleterious homozygous c.769C>T mutation in AGBL3 (ATP/GTP binding protein-like 3) gene, which results in early termination of the protein (p.Gln257Ter) and deletion of the functional carboxylpeptide domain. This protein belongs to metallocarboxypeptidases that mediate both deglutamylation and deasparylation of target proteins, and AGBL3 is suggested to catalyze the deglutamylation of polyglutamate side chains, especially in proteins such as tubulins. This variant was not found before in all reported databases including 1000 Genomes Project data.

Objectives: To define the clinical phenotype and treatment responses of a patient with newly defined monogenic hyPOCHOLEMPENEMETRIC urticarial vasculitis associated with a homozygous AGBL3 variant.

Methods: We collected all clinical, serologic, and pathological data regarding the clinical findings of the index case as well as recorded all treatment responses throughout the follow-up period during the last 8 years.

Results: The index case was 23-year-old male patient of Assyrian origin, who had consanguineous parents. He was evaluated in our clinic because of recurrent attacks of fever, urticarial rash on the extremities and trunk, conjunctival injections and arthralgia, without a trigger or more frequently following an infection. His 2 to 3 days lasting attacks started when he was 13 and recurrent more frequently during warm weather conditions or following hot baths. He had highly elevated CRP and ESR during attacks, but his acute phase response did not return to normal values in between the flares. Low C3 and C4 values were also observed during asymptomatic periods. His ANA test became positive during the course of his disease with an increase in titers during the last years. The biopsy of skin lesions revealed findings compatible with urticarial vasculitis. He responded only partially to corticosteroids, canakinumab and anakinra treatments. His treatment was switched to rituximab last year, and a favorable response was observed following the first two infusions. He developed less frequent and milder attacks only after infections, and acute phase response was reduced to near normal values in between attacks.

Conclusion: The AGBL3 metallocarboxypeptidase gene was recently identified as a novel autoinflammatory gene associated with hyPOCHOLEMPENEMETRIC urticarial vasculitis phenotype, and it was different from the previously defined variants including DNASE1L3 mutations. The clinical features of the index case included both autoinflammatory and autoimmune findings including autoantibodies; and his inflammatory attacks did respond to rituximab treatment but not IL-1 blockade. Long-term follow-up and search for other patients associated with AGBL3 variants among idiopathic hyPOCHOLEMPENEMETRIC urticarial vasculitis are required for better clarification of the AGBL3-associated clinical phenotype.

Disclosure of Interests: None declared

AB0006 ASSOCIATION OF HLA-DPB1*16:01 ALLELE WITH PR3-ANCA POSITIVE GRANULOMATOSIS WITH POLYANGIITIS IN TURKISH PATIENTS

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Background: ANCA associated vasculitides (AAV) comprise an important subset of small vessel vasculitides with a multifactorial pathogenesis, which is considered to be associated with the interaction of genetic and environmental factors. Certain HLA Class 2 alleles have been reported among the genetic risk factors for AAV from different geographic regions such as Europe and Asia (1,2).

Objectives: In this study, we aimed to analyse the distribution of HLA Class 2 genotypes among a series of Turkish AAV patients in comparison with the healthy Turkish subjects and the previously reported data of AAV cohorts from other countries.

Methods: Ninety-eight patients (aged between 18-75 years) diagnosed with AAV according to 2012 Chapel Hill Consensus Criteria were enrolled into the study. Records of age-and birthplace-matched 196 healthy kidney donors were used as the control group. Patients were classified according to the clinical subgroups (GPA, e-GPA, MPA) and ANCA serotypes (MPO-AAV, PR3-AAV). HLA Class II genotyping were carried out using NGS-Onyx Human HLA Kit at the EFI accredited HLA Typing Lab of Department of Medical Biology. Allele distributions were compared by Chi-square test, and P value lower than 0.05 was accepted as significant.

Results: AAV patients were classified as PR3-AAV (54%) and MPO-AAV (31.6%) according to autoantibodies and GPA (71.4%), MPA(20.4%), e-PPA (8.2%) according to clinical subgroups. HLA-DPB1*16:01 allele was significantly lower in the GPA group (%8.5 vs. %22.4; p<0.05, OR=0.29 %95 CI 0.15-0.57), and HLA-DPB1*02:01 (%7 vs. %22.4; p<0.05, OR=0.28 %95 CI 0.13-0.6) alleles were significantly lower in the PR3-AAV group. HLA-DPB1*16:01 allele was significantly higher in the PR3-AAV group (%8.5 vs. %0.26 p<0.01, OR=36.2 %95 CI 4.5-289.7). In clinical subgroups, HLA-DPB1*04:01 (%7.9 vs. %35.9; p<0.01, OR=0.15 %95 CI 0.08-0.29) and HLA-DPB1*02:01 (%7.9 vs. %22.4; p<0.01, OR=0.29 %95 CI 0.15-0.57) alleles were significantly lower in the GPA-AAV group. HLA-DPB1*16:01 allele

Disclosure of Interests: None declared

was significantly higher in the GPA-AAV group (%7.14 vs. %0.26, p<0.01, OR=30, 95% CI 1.28–71.41). No significant difference was detected between the MPO-AAV and control groups.

**Conclusion:** HLA analysis of this small series of Turkish AAV patients revealed a negative correlation between PR3-ANCA positivity and HLA-DRB1*04:01 and HLA-DPB1*02:01 alleles in opposition to the results reported from different European AAV cohorts (1.3). On the other hand, a significant increase in both GPA and PR3-AAV subgroups for a previously unpublished HLA-DRB1*16:01 allele may suggest that HLA association may show ethnic or regional differences, and further analyses in larger series of AAV patients may reveal the molecular basis of this observation.

**REFERENCES**


**Disclosure of Interests:** None declared


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**AB0007**

**IL12B POLYMORPHISMS ARE ASSOCIATED WITH ELEVATED SERUM LEVELS OF IL-12p40, IL-23 AND GENETIC PREDISPOSITION TO RHEUMATOID ARTHRITIS**

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**Background:** Rheumatoid arthritis (RA) is the most common type of autoimmune arthritis in which genetic predisposition in close interaction with environmental triggers seems to be the major factor in the disease pathogenesis. Genetic analyses suggest a polygenic inheritance, as the largest genetic contribution to RA susceptibility remains the HLA-DRB1 gene, residing within the HLA gene complex. Since immune dysregulation plays a key role in immune-mediated inflammatory disorders, genetic variations within cytokine loci may contribute to variability in the immune response determining susceptibility or resistance to a certain autoimmune disease.

**Objective:** We aimed to investigate whether IL12B polymorphisms are involved in causation of RA and in variations of circulating IL-23 and IL-12p40 levels in our Bulgarian population.

**Methods:** A total of 125 RA patients aged from 18 to 79 years in comparison to 239 age- and sex-matched healthy controls (HC) were genotyped for rs17860508 and rs3212227. Both IL12B polymorphisms were investigated by polymerase chain reaction (PCR) - based methods. Serum IL-12p40 and IL-23 concentrations measurement was done using ELISA test in 67 RA patients and 55 age-matched HC.

**Results:** An association between the rs17860508 polymorphism and RA development was established under the allelic model (allele 2 vs allele 1; OR = 1.68, 95%CI = 1.17–2.42; p = 0.0044), the co-dominant model (2.2 vs 1.1, OR = 2.83, 95%CI = 1.37–5.86; 1.2 vs 1.1 OR = 1.76, 95%CI = 0.91–3.41; p = 0.017), the dominant model (1.2 vs 2.2 vs 1.1 OR = 2.12, 95%CI = 1.15–3.90, p = 0.014), and the recessive model (2.2 vs 1.1 vs 1.2 OR = 2.00, 95%CI = 1.10–3.62, p = 0.022). These results suggest that the homozgyous 2.2 genotype can be predisposing, while 1.1 genotype might be protective factor to RA susceptibility. No association between the rs3212227 and RA risk was revealed under the same genetic models.

**Conclusions:** In the subgroup patients with early onset we performed genetic tests. Rare variants of PI3 genes were detected in 7/22 (32%) patients. Mutations affecting the genes previously associated with CNO were found only in two patients: one of them carried heterozygous variant IL1RN c.170G>T (p.C57F) and another had IL1RN c.512T>C (p.V171A). No mutation of LPIN2 was revealed. Other detected variations included one pathogenic MEFV p.M694V mutation in heterozygous state and a number of VUS in CD40LG, NLRP12, CR2, NLRP3, IL12B, PLCG2, SH3BP2, CARD14, IFIH8, CAPS10 and NFKB1A genes.

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**Disclosure of Interests:** None declared


**AB0008**

**CLINICAL AND GENETIC FEATURES OF NON-BACTERIAL OSTEOMYELITIS IN RUSSIAN FEDERATION**

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**Background:** Chronic non-bacterial osteomyelitis (CNO) is a Data about incidence, prevalence and clinical and genetic features of chronic non-bacterial osteomyelitis (CNO) in Russia is scarce.

**Objectives:** The aim of our study was to evaluate clinical and genetic peculiarities of CNO in Russia.

**Methods:** The diagnosis of CNO was made with criteria, proposed by Jansson[1, 2], after the exclusion of other causes of bone disease. Our cohort consists of three main subtypes: i) early-onset (<5 years) CNO (n=22); ii) CNO, associated (n=20) and iii) not associated (n=59) with rheumatic diseases (RD). Targeted next generation sequencing (NGS) analysis of 302 genes related to primary immune deficiency syndromes and autoinflammatory syndromes was performed.

**Results:** We selected a subgroup of the CNO patients having the following features: 1) early disease onset (<5 years); 2) all children were initially diagnosed as having tuberculosis (TB) due to bone morphology findings (granulomatosis, e.g. tuberculosis-like inflammation), but had negative TB culture test; 3) initial treatment with combination of 3-4 anti-MBT drugs during 1-2 years was ineffective, and the patient continued to develop new inflammatory bone foci; 4) patients had very severe clinical (fever and symptomatic arthritis) and radiological signs of disease; 5) all patients were from areas with traditionally high prevalence of consanguinity (table).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>EO-CNO (n=22)</th>
<th>CNO w/o RD (n=59)</th>
<th>CNO with RD (n=20)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset age, years</td>
<td>3.0 (2.1-4.8)</td>
<td>7.3 (2.8-11.7)</td>
<td>10.3 (6.2-12.2)</td>
<td>0.0009</td>
</tr>
<tr>
<td>Fever at onset, n (%)</td>
<td>14 (64)</td>
<td>23 (39)</td>
<td>5 (25)</td>
<td>0.03</td>
</tr>
<tr>
<td>Foci number, n (%)</td>
<td>5.0 (1.5-6.0)</td>
<td>3.0 (1.0-4.0)</td>
<td>2.0 (1.0-6.0)</td>
<td>0.048</td>
</tr>
<tr>
<td>Symptomatic arthritis, n (%)</td>
<td>20 (91)</td>
<td>33 (56)</td>
<td>17 (85)</td>
<td>0.003</td>
</tr>
<tr>
<td>North Caucasian origin, n (%)</td>
<td>22 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Granulomatous inflammation, n (%)</td>
<td>22 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Tuberculosis-like, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Prevalence of CNO</td>
<td>1 (0.04)</td>
<td>1,450.000 (1.375,000)</td>
<td>1.337,000 (&lt;0.0001)</td>
<td>0.000</td>
</tr>
</tbody>
</table>

**Disclosure of Interests:** Mikhail Kosk: Pfizer, UCB, Novartis; Maria Makhova: Pfizer, UCB, Novartis; Anna Sokolonenko: None declared; Georgi Vasilev: None declared; Lyuba Miteva: None declared; Rumen Stolinov: Speakers bureau: Abbvie, Pfizer, UCB, Novartis; Spaska Stanilova: None declared


**AB0009**

**INFECTION, IMMUNITY AND INFLAMMATION**

**AB0010**

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