Genetics, genetic basis of disease and antigen presentation

**AB0001**  
ASSOCIATION OF MDR1 GENE G2677T POLYMORPHISM WITH METHOTREXATE RESISTANCE IN PATIENTS WITH UZBEK RHEUMATOID ARTHRITIS

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**Background:** Methotrexate (MTX) is the most widely prescribed disease-modifying antirheumatic drug (DMARD) for treatment of rheumatoid arthritis (RA)[1]. According to different authors, in 25–40% [3] of cases “complete clinical remission” or “low disease activity” is not achieved, by reason of refractoriness to methotrexate and this may be related to the activity of the MDR1 (ABC B1) gene which is involved in its metabolism. According to many studies on the C3435T isoform MDR1 polymorphism CC genotype is associated with methotrexate refractoriness [2]. But a certain interest is also influenced by the other isoform of the MDR1 gene (G2677T) for the presence of resistance to methotrexate.

**Objectives:** The aim of this research was to study the effect of MDR1 gene polymorphisms G2677T (rs2032582) on resistance to treatment with methotrexate in Uzbek patients with RA.

**Methods:** The study involved 76 patients with RA of Uzbek nationality and 24 healthy people. The average age of patients was 48.9±15.9 years. RA was diagnosed according to the criteria of the American College of Rheumatology (ACR). 75.6% of patients had high and 24.4% moderate RA activity (DAS 28). All patients took methotrexate in monotherapy, at a dose of 7.5-15 mg for 5-6 months. All patients were genotyped by the MDR1 gene G2677T polymorphisms by using the polymerase chain reaction (PSR-Real time).

**Results:** Genotyping of the G2677T isoform of MDR1 gene revealed the following results: in patients with CC genotype was found in 22 patients (28.9%), GT genotype was found in 31 patients (40.7%) and TT genotype was found in 23 patients (30.2%). In patients treated with methotrexate, the following disease activity was observed in patients with CC genotype, the disease activity was DAS28 <2.6, with CT genotype DAS28 3.2–4.5. Patients with the TT genotype had an activity of DAS28>5.1. Despite the increase in the dose of methotrexate, the remission was not achieved.

**Conclusion:** TT genotype G2677T isoform of MDR1 gene is associated with resistance to methotrexate. Patients who carry mutant genotype are recommended to replace methotrexate with other DMARD preparations. Patients are recommended to conduct genotyping to the MDR1 gene for personal selection of drugs.

**REFERENCES**


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**AB0003**  
GENETICS IN PAIN IN WOMEN WITH FIBROMYALGIA: THE PROMISING ROLE OF REDUCING SEDENTARY BEHAVIOUR

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**Background:** Fibromyalgia is characterised by chronic pain and a heterogeneous presentation of other symptoms (e.g., fatigue and depression) [1]. It is widely accepted that pain is promoted by both genetic susceptibility and environmental factors such as people’s behaviours [2]. In addition to genotype individual associations and gene-gene interactions, when considering complex phenotypes such as pain, gene-environmental interactions are likely present and can help to better understand the disease (i.e. by unravelling underlying mechanisms [3]).

**Objectives:** To test the individual association of 64 polymorphisms (34 candidate-genes) and the gene-gene, gene-physical activity, and gene-sedentary behaviour interactions with pain and pain-related cognitions in fibromyalgia.

**Methods:** In 274 women with fibromyalgia, saliva samples were collected for extracting DNA. We measured physical activity and sedentary behaviour by accelerometers for a week, pain with algometry and questionnaires, and pain cognitions with questionnaires. Age, body fat, and analgesics and antidepressants consumption were included as covariates. Significance was set at P-values lower than Bonferroni’s correction or P- and false discovery rate values lower than 0.05.

**Results:** The rs6311 and rs813 polymorphisms were individually related to algometer scores. The interaction of rs4818 and rs1799971 polymorphisms was related to pain catastrophizing. Five gene-behaviour interactions were significant: the interactions of sedentary behaviour with rs1383914, rs6860, rs4860, rs165599, and rs12994338 polymorphisms were associated with the bodily pain subscale of the SF-36.

**Conclusion:** The HTR2A gene (individually), COMT and OPRM1 gene-gene interaction, and the interactions of sedentary behaviour with ADR1A, CDH1 and CCMT1A, COMT, and SCN9A genes were associated with pain-related outcomes in fibromyalgia females. Besides indicating the relevance of genetic background for pain and pain-catastrophizing, the observed genotype-behaviour interactions suggest that the effects of sedentary behaviour on pain may depend on the genotype of women with fibromyalgia. Future clinical experimental research should examine whether reducing sedentary behaviour is particularly beneficial for reducing pain in women with specific genotypes.

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DETECTION OF THE SNP-SNP INTERACTIONS IN THE ASSOCIATION OF HLA-DPB1*16:01 ALLELE WITH PR3-FAVORABLE RESPONSE TO RITUXIMAB IN A PATIENT WITH JUVENILE IDIOPATHIC ARTHRITIS

Objectives: The aim of the study was to estimate interactions between SNPs of HLA gene variations which are 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 gene variations.

Methods: The study was to estimate interactions between SNPs of the genes implicated in immune and inflammatory responses: STAT4 (rs7574865), CTLA4 (rs5724990), MIF (rs755622), TRAF1/C5 (rs3761847), RUNX3 (rs11249215) and their effect on the JIA susceptibility.

Results: 119 patients diagnosed with JIA (mean age 8.48 ± 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 of each patient 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 – 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.

Conclusion: 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, 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 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 rs755622 with entropy of 2.92% was more informative in females, while STAT4 rs7574865 with entropy value of 1.12% – in males.

Disclosure of Interests: None declared.


FAVORABLE RESPONSE TO RITUXIMAB IN A PATIENT WITH HYPOCHROMOCOMPLEMENTEMIC URICARTIAL 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 hypocomplementemic uricartial 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 carboxy-peptidase domain. This protein belongs to metalcarboxypeptidases that mediate both deglutamylation and desapartylation 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.

Objective: To define the clinical phenotype and treatment responses of a patient with newly defined monogenic hypocomplementemic uricartial 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 recurred 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 titer 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 metalcarboxypeptidase gene was recently identified as a novel autoinflammatory gene associated with hypocomplementemic uricartial 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 hypocomplementemic uricartial vasculitis are required for better clarification of the AGBL3-associated clinical phenotype.

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