Genetics, genomic 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% 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 (ABCB1) 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 with CT and GT genotypes 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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**AB0002**

**INCREASED SENSITIVITY TO DNA DAMAGE AGENTS IN HUMAN PERIPHERAL BLOOD MONONUCLEAR CELLS FROM PATIENTS WITH RHEUMATOID ARTHRITIS**

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**Background:** Rheumatoid arthritis (RA) is a chronic autoimmune disorder with not fully elucidated pathogenesis. Rheumatoid arthritis patients have increased risk of developing lymphomas. One of the possible mechanisms of this predisposition is increased genomic instability and impaired DNA repair. It is unclear how this genomic instability contributes to diseases pathogenesis.

**Objectives:** The aim of this study was to analyze the sensitivity and repair efficiency of mononuclear cells isolated from RA patients to DNA damaging agents. Patients were recruited to conduct genotyping to the MDR1 gene for personal selection of drugs.

**Methods:** The study group consisted of 22 patients with RA (age years - 60.77±13.00 women-17, men- 5) hospitalized in the Department of Rheumatology between 2017 and 2018 and 10 healthy controls without autoimmune and oncological diseases in clinical history (age 44.09±16.56; women-5, men-6). The peripheral blood mononuclear cells (PBMC) from all subjects were isolated. Using comet assay the degree of intracellular DNA damage as a result of exposure to standard damage factors: tert-butyl hydroperoxide (TBH), bleomycin, methyl methanesulfonate (MMS) and UV radiation was assessed.

**Results:** RA patients show a statistically significant higher level of endogenous damage in PBMC than controls (mean RA: 8.46% vs. 4.68% in control; p<0.001). The extent of the DNA damage induced by TBH, MMS as well as UV was significantly higher in PBMC derived from RA patients than in healthy counterparts (p<0.0001). The DNA of RA patients treated with TBH was repaired less effectively than in control (p<0.0001). Significantly higher percentage of DNA damage in RA DNA (p<0.0001) under the influence of bleomycin and clearly marked repair processes were observed. Among the healthy controls lower percentage of DNA was damaged, and although the repair process was slower but the final percent of DNA damage was lower in than in RA cases (p<0.0001).

**Conclusion:** DNA of people with rheumatoid arthritis is significantly more susceptible to damage in baseline and induced. The kinetics of DNA repair from RA patients after the introduction (TBH and bleomycin) was statistically less effective as compared to healthy control. Understanding the ethology of this phenomenon in RA may provide insight into disease pathogenesis and explain the increased susceptibility of patients to malignancies.

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