AB0014

GENETIC MARKERS OF METHOTREXATE HEPATOTOXICITY IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: Methotrexate (MT) is a first-line drug in the treatment of rheumatoid arthritis (RA). The effectiveness and tolerability of the use of MT largely determines the prognosis of the course of the disease, the speed of achieving remission. The development of hepatotoxicity (HT) is the most common adverse reaction, it is noted in 5-12.5% of cases and often requires the abolition of MT. In this regard, predicting the development of HT seems to be an important area of research.

Objectives: to study genetic predictors of HT development in patients with RA using MT.

Methods: 44 patients with a reliable diagnosis of RA were included in study. All of the patients used MT at a dose of 15.0 (12.5-17.5) mg/week in combination with folic acid 3-5 mg / day outside of MT. The average age was 46.7 ± 12.3 years; females- 81.8% (n = 36); male 18.2% (n = 8). The duration of RA is 5.3 ± 2.2 months. All patients were divided into two groups: the first study group (n = 17) included patients with RA who developed a HT reaction to MT, which required the abolition of MT; in the second- (n = 27) - comparison group - patients with good efficacy and tolerability of MT.

Genotypes for polymorphic alleles were analyzed in all patients: C677T (rs1801133) and A1298C (rs1801131) of the methylenetetrahydrofolate reductase gene (MTHFR); 347C>G single-nucleotide polymorphism of the gene of aminoimidazole-carboxamidobioside transformylase / inosine monophosphate cyclohydrolase (ATIC); c.80G>A locus of the SLC19A1 gene encoding the folate transporter membrane carrier protein. Groups were compared according to possible inheritance models: dominant, recessive, codominant. Statistical data processing was carried out using the STATISTICA 10.0 software package using descriptive and nonparametric statistics methods.

Results: The frequency of occurrence of various mutations in genes that affect the metabolism of MT among patients with RA in the study and comparison groups are presented in table 1

Table 1. The frequency of occurrence of various mutations in genes that affect the metabolism of MT

Genetic option	Study group ΓT+, n=17	Comparison group ΓT <<->, n=27
MTHFR-A1298C		
CC	5	6
CA	2	8
AA	10	13
MTHFR -C677T		
CC	7	9
CT	8	17
TT	2	1
347C>G ATIC		
CC	9	6
CG	6	19
GG	2	2
SLC19A1c80A>G		
AA	11	22
AG	6	4
GG	0	0

ΓT- hepatotoxicity

When analyzing inheritance models, it was found that differences in hepatotoxicity for comparing genotypes (MTHFR-A1298C, MTHFR-C677T, SLC19A1c80A>G) were not statistically significant. A statistically significant increase in the risk of hepatotoxicity was found for dominant (2.18 (1.06-4.47), $x^2 = 4.38$, $p = 0.03$) and codominant (0.42 (0.19-0.92), $x^2 = 5.23$, $p = 0.02$) models for the 347C>G ATIC gene.

Conclusion: Thus, an increase in the risk of hepatotoxicity for the dominant and codominant models for the 347C>G ATIC gene allows recommending genotyping of the alleles of this gene before MT administration in order to reduce the risk of hepatotoxic reactions.

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AB0015

IDENTIFICATION OF KEY GENES TO SUPPORT SYSTEMIC LUPUS ERYTHEMATOSUS, RHEUMATOID ARTHRITIS AND ANKYLOSING SPONDYLITIS DIAGNOSIS BY TRANSCRIPTOMIC APPROACH

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Background: Early diagnosis of inflammatory rheumatic diseases (IRD), as Systemic Lupus Erythematosus (SLE), Rheumatoid Arthritis (RA) and axial Spondyloarthritis (axSpA) represents in our days a major clinical challenge. Increasing evidence has determined that early diagnosis, prompt treatment initiation and early achievement of remission are the best predictors of long-term clinical, functional and radiographic outcomes. Therefore, identification of sensitive biomarkers to support an early diagnosis to enable early therapy is of utmost importance [1,2].

Objectives: This study aims to identify novel genes that may improve the current clinical diagnosis approach for early SLE, RA and axSpA.

Methods: A cross-sectional study was conducted on 44 participants, 12 with axSpA (according to ASAS criteria), 11 with RA (according to ACR/EULAR criteria for RA), 10 with SLE (according to ACR classification criteria for SLE) and 11 Healthy Controls (HC), gender and age matched. Patients with co-occurrence of other IRD or having received biological therapies were excluded. Peripheral blood samples were collected into PAXgene tubes and stored in -80°C. mRNA profiling by RNA-seq was performed. Unpaired t-tests with multivariate permutation correction were applied to identify differentially expressed genes (DEGs) between patients and HC for each disease and within diseases. Enrichment analysis, Gene ontology (GO) and Kyoto Enrichment of Genes and Genomes (KEGG) analysis were also performed. DEGs that allow to distinguish each disease from HC and between diseases. The top DEGs (axSpA n=2, RA n=2, SLE n=3) identified were confirmed by quantitative RT-PCR.

Results: For axSpA, genes involved in negative regulation of cytokines by JAK/STAT pathway and in osteoblast differentiation through STAT3 pathway, were confirmed. In SLE, genes involved in trap for immune complexes in peripheral blood and involved in nucleosome regulation, were also confirmed. Regarding RA, no genes were confirmed.

Conclusion: Our work provides new insights into IRD pathogenesis, and discloses new biomarkers, which may be useful as either predictive biomarkers for diagnosis or therapeutic targets to improve IRD approach. Further validation are needed in different cohorts.

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AB0016

ASSOCIATION OF PTPN22 GENETIC VARIANTS WITH DISEASE SUSCEPTIBILITY AND CLINICAL VARIABLES IN PRIMARY SJÖGREN SYNDROME

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Background: Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease characterized by dysfunction of exocrine glands secondary to lymphocytic infiltration. Lymphoid tyrosine phosphatase (LYP) regulates T and B lymphocyte activation. PTPN22 gene encodes LYP; multiple polymorphic variants have been described as genetic risk factor of autoimmune diseases.

Objectives: The aim was to analyze the PTPN22 rs2488457G>C, rs33996649G>A, and rs2476601C>T genetic variants relationship with the development risk of pSS in the western Mexico population.

Methods: One hundred and eighty healthy subjects (HS) and 150 pSS patients, classified according to EULAR 2016 criteria, were included. The genetic variants and mRNA expression were determined through PCR-RFLP and qPCR assays.