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Influence of Mdr1 Gene Polymorphism on the Course of Rheumatoid Arthritis

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Abstract: The aim of study: examine the MDR1 gene C3435 T polymorphism and it's clinical relevance in rheumatoid arthritis patients. materials and methods. The study was carried out on 76 patients with RA and 24 healthy people. results and discussion. From the results of our study, it follows that the possessor of the CC of the genotype C3435T isoform of the MDR1 gene showed high drug resistance and on the contrary, the possessor of the TT genotype showed a high drug response and a longer remission. The MDR1 gene C3435T polymorphism may have a certain effect on the course and efficiency of treatment rheumatoid arthritis.

Keywords: MDR1, C3435T, rheumatoid arthritis, genotype, polymorphism**.**

1. Introduction

Rheumatoid arthritis (RA) is the most common inflammatory rheumatic disease, the characteristic feature of which is a progressive course with the formation of deformities and severe functional disorders of the musculoskeletal system, damage to internal organs, which leads to disability and reduced life expectancy of patients [5,6,8] . Over the past decade, there have been major changes in approaches to the management of RA patients, which have significantly improved treatment outcomes and made it possible to set the main goal - achieving clinical remission (recommendations EULAR , 2015) . The planned progress is associated not only with the use of basic disease-modifying antirheumatic drugs, but also with specially developed innovative genetically engineered biological drugs [1,2,14]. However, despite the entire arsenal of modern drugs in the treatment of this disease, in 25-30% of cases "complete clinical remission" or "low disease activity" is not achieved due to refractoriness to treatment [5, 10]. This is due to the fact that RA is currently considered as a complex disease. whose development is influenced by both genetic factors and environmental factors [2, 3, 7, 8] . According to some estimates [4 , 11, 19], from 50 to 90% of adverse pharmacological responses are determined by the genetic characteristics of individuals [1,6,12,18]. The study of individual genetic differences underlying the variability of the body's response to a particular drug is of paramount importance for optimizing pharmacotherapy. It follows from this that it is necessary to search for new approaches in the treatment of RA, i.e. expansion of research in pharmacogenetics , in particular the study of the relationship of genotype with a clinically significant effect of a drug and with a perverted reaction to the drug, as well as the study of the relationship of genotype with drug metabolism. Therefore, in recent years, most attention has been paid to the peculiarities of methotrexate metabolism in the liver under the predominant influence of transport proteins, in particular, proteins of the P - glycoprotein (P - gp) group , which is encoded by the MDR 1 gene (multi drug resistancegene 1) [4, 7, 15, 17]. The product of the MDR 1 gene, P - gp , acts as a transmembrane pump and affects the action of many drugs [5, 9, 14, 16], in particular, methotrexate. According to [1, 10, 13], the activity of this protein primarily depends on the polymorphism of the gene encoding its structure.
Therefore, genetic studies aimed at studying the features in the protein transport system (MDR 1) involved in the metabolism of basic drugs can solve problems regarding the prognosis of the clinical course of RA, as well as the selection of effective doses of basic therapy to achieve the main goal of "clinical remission" of the disease.

2. Materials and Methods

The study was conducted in the 3-City Clinical Hospital No. 3 in the Department of Rheumatology in Tashkent. The study was conducted in 76 patients (73 women, 3 men, 24-65 years old) with RA. The control group consisted of 24 practically healthy volunteers, without burdened rheumatological anamnesis (Table No. 1).

Table 1 Characteristics of patients with RA

Indicators	**Characteristics , n=76**
Women / men	73/3

Average age (in years)	48.5±5.5
Duration of illness (in years)	5.5 ± 3.1
Disease activity according to Das28	>5.1
ESR	35.2 ± 4.1

RA was diagnosed according to the American College of Rheumatology (ACR) criteria and disease activity was calculated using the Das 28 calculator.
To carry out gene genotyping C 3435T was taken into enous blood in a volume of 3 ml from patients during their hospitalization in the department of rheumatology and stored in EDTA tubes. Genomic DNA was extracted from blood samples using RIBO prep reagents (AmpliSens , Russia). For genotyping, a set of reagents was used to determine the C3435T polymorphism of the MDR1 gene (SINTOL, Russia). Polymorphism of the C3435T gene was determined using polymerase chain reaction (PCR), which was carried out in a 7500 Fast amplifier Real Time PSR Systems (Applied Biosystems USA).
Statistic processing of the data obtained during the study was carried out using the computer program EXCEL and STATISTICA 6.0. Comparative analysis was carried out using the standard X^2 Pearson test and Fisher's two-tailed test, where $p<0.05$ was considered statistically significant.

3. Results

In our study, 76 patients with RA and 24 healthy volunteers without a history of rheumatology were studied. All patients underwent genotyping of the C3435T polymorphism of the MDR 1 gene. According to the results of genotyping, all patients were divided into three groups: the first group was patients with a healthy CC genotype, the second group was patients with a heterozygous CT genotype, and the third group was carriers of a mutant TT genotype.

As can be seen from the table, the first group with a healthy CC genotype of the C3435T gene occurred in 31.5% of patients, while in the control group it occurred in 20.8% of cases.
In the second group, whose representatives were heterozygous patients, the CT genotype was found in 39.5% of patients, and in the control group it was significantly higher and amounted to 62.5% of cases. The frequency of occurrence of the mutant TT genotype (third group) was 29.0% and in the control group 16.6%. (Table #2)
As can be seen from Table 3, the percentages of C and T alleles were almost the same in healthy and sick people. The T3435C allele of the isoform was found in 51.3% of patients and in 52.0% of healthy individuals. The T allele was found in 48.7% of RA patients and in 48% of healthy controls.

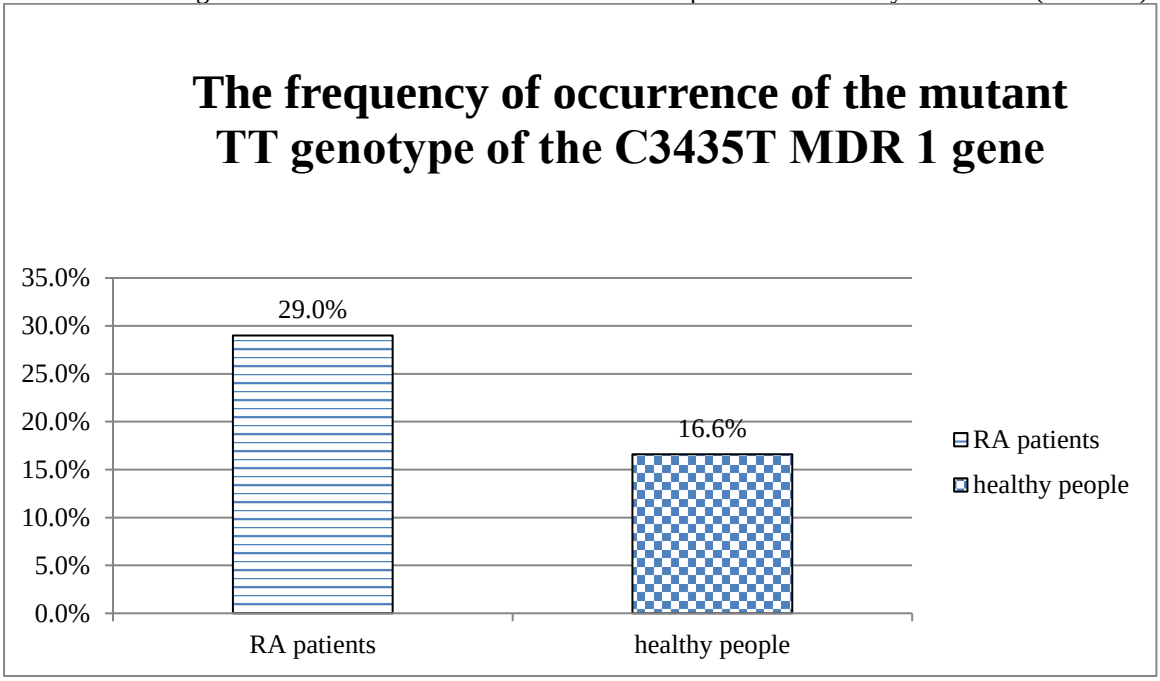
Table 2 Distribution of genotypes of polymorphism C3435T MDR 1 gene

MDR 1 gene	Group #1 3435CC	%	Group #2 3435CT	%	Group 3435TT	%
RA patients n=76	24	31.5 _	thirty	39.5	22	29.0
Control group n =24	5	20.8	15	62.5	4	16.6

Table 3 Distribution of alleles of polymorphism C3435T MDR 1 gene

allele	N	%
C	78	51.3
T	74	48.7
Control group		
C	25	52.0
T	23	48.0

Since the mutant genotype C3435T of the gene is also found in healthy people, in a comparative analysis, we revealed a significant difference in indicators between RA patients and healthy volunteers. (Picture 1)



Picture 1. The frequency of occurrence of the mutant TT genotype of the C3435T MDR- 1 gene polymorphism
All patients who participated in our study were prescribed basic therapy and patients were observed for a long time. Based on the carriage of three genotypes of the C3435T isoform of the MDR 1 gene , we identified three phenotypic groups depending on the clinical response to RA treatment.

The first group (P = 31.5%), carriers of a healthy CC genotype, were clinically characterized by a short remission in less than three months and a poor clinical response to treatment with methotrexate .
The second group (P = 39.5%), carriers of the heterozygous CT genotype , was phenotypically characterized by a longer clinical remission in comparison with the first group in a period of 3 to 6 months against the background of basic therapy including methotrexate . The third group (P = 29.5 %), carriers of the mutant TT genotype, was phenotypically characterized by a long-term remission for more than 6 months, as well as a good clinical response against the background of basic therapy, including methotrexate .

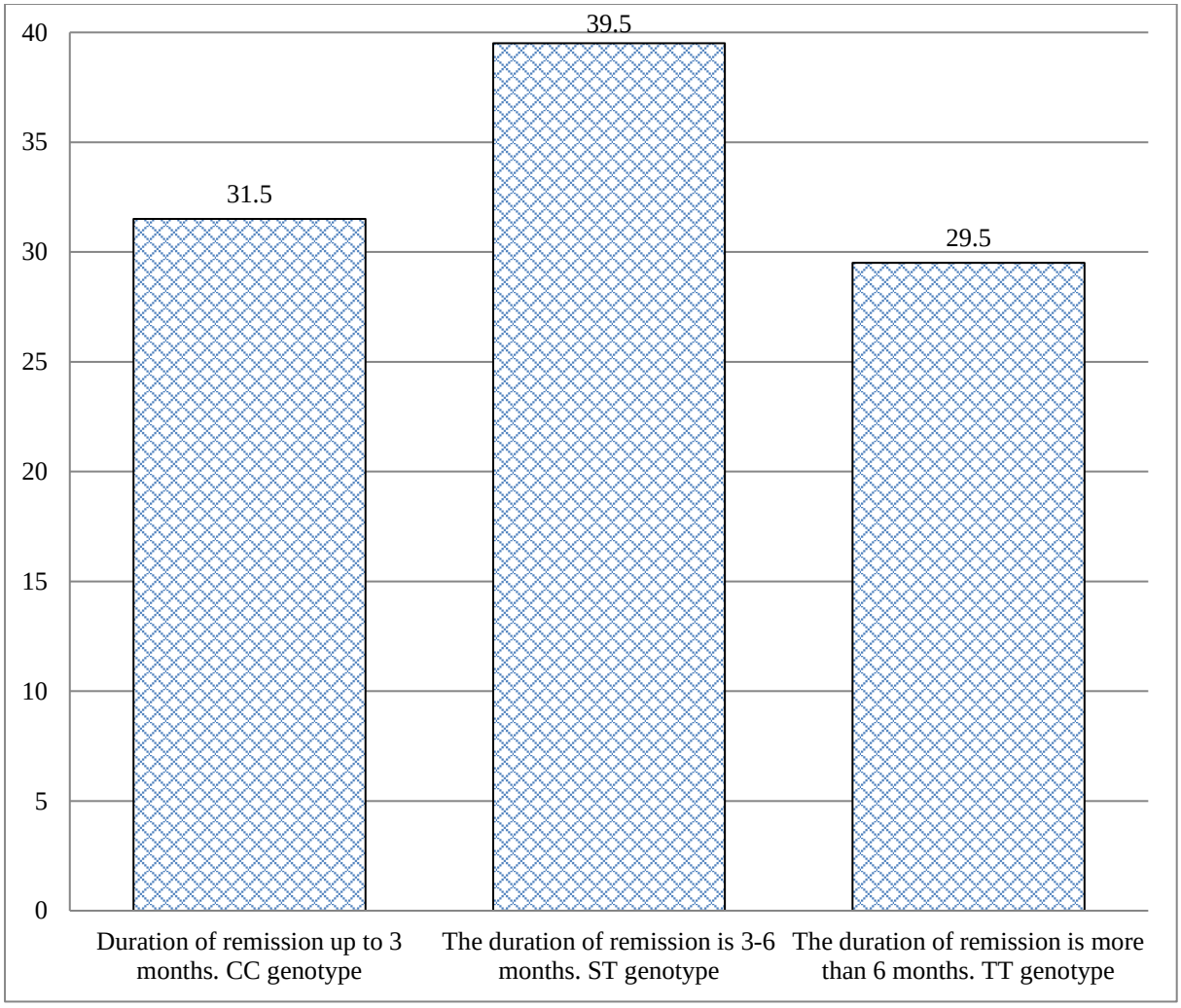


Figure 2. Duration of remission in patients with different genotypes of C3435T MDR 1 gene polymorphism
The presence of a mutant TT genotype indicates a good drug response to treatment and a longer remission of more than 6 months. The presence of a healthy CC genotype, on the contrary, indicates the presence of a poor drug response and a short remission for a period of not more than three months. The carriage of the CT genotype is characterized by an average duration of remission for a period of 3-6 months (Figure 2)

4. Discussion

As mentioned above, drug resistance is one of the important factors affecting the effectiveness of RA therapy. The individualization of pharmacotherapy, which is dealt with by pharmacogenetics , consists of identifying polymorphic markers associated with a change in the body's response to drugs, developing methods for genotyping patients and introducing this approach into practical medicine. Some researchers suggest [10] that there is an association of MDR 1 gene polymorphisms with the efficacy and safety of many drugs. A number of researchers (Takatori et. al.; Sharma et al .) conducted cohort studies of C3435T with the MDR1 gene isoform (ABCB1) in patients with RA and concluded that the TT genotype is associated with poor response to treatment, and the CC genotype is associated with a good response to treatment. Opposite other researchers (Chen et. al.; Drozdzik et. al.; Pawlik et. al.) conducted similar studies and concluded that the CC genotype is associated with resistance to RA treatment. Despite a large number of studies devoted to the study of MDR1 gene polymorphism, the results remain contradictory, which aroused our interest.
According to our data, there were no significant differences in the distribution of alleles of the C3435T polymorphism of the MDR1 gene in RA patients and healthy controls. But when comparing genotypic variants, we revealed differences: healthy CC and mutant TT genotypes were more common in patients, and the heterozygous CT genotype was more common in healthy people.

According to the results of genotyping, we revealed phenotypic differences in the manifestation of the disease and phenotypically identified three groups of patients. The first group (representatives of a healthy CC genotype) phenotypically had a poor drug response to basic therapy and, accordingly, clinically had a short remission (Das 28 <2.6) less than 3 months. The second group (representatives of the heterozygous CT genotype) phenotypically had a moderate drug response against the background of basic RA therapy with a remission duration (Das 28 <2.6) of 3-6 months.

5. Conclusions

Gene polymorphism genotype studies MDR 1 in patients with RA made it possible to identify their relationship with the clinical course of the disease, the activity of the pathological process and the effectiveness of the basic therapy. In patients with RA with the CC genotype, the disease can proceed with a higher degree of activity, as well as a short duration of remission, compared with patients with CT and TT genotypes.
Genotyping of RA patients can be used to determine the effectiveness of drug therapy and personalized selection of treatment methods for patients.

6. Literature

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