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PTPN22 GENETIC VARIANTS AS PREDICTORS OF DISEASE SEVERITY AND JOINT DESTRUCTION IN RHEUMATOID ARTHRITIS: EVIDENCE FROM THE UZBEK POPULATION

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Abstract

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by progressive inflammation and joint destruction. The aim of the study was to determine the relationship between the *PTPN22* (rs2476601) gene polymorphism and the clinical and immunological manifestations and disease activity in RA patients of the Uzbek population. 120 patients with RA and 60 healthy individuals in the control group were examined. Disease activity was assessed using the DAS28-ESR, CDAI, and SDAI indices, levels of CRP, ACPA, and AMCV were measured, and radiological changes were evaluated using the Sharp scale. Carriers of the minor T-allele demonstrated significantly higher disease activity, autoantibody concentrations, and joint destruction severity compared to those with the CC genotype. An association between the T-allele and high-positive autoantibody status was established (OR = 2.56; $p < 0.05$). The obtained data suggest a possible role of the *PTPN22* polymorphism as a genetic predictor of aggressive RA course in patients of the Uzbek population.

Introduction.

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease characterized by complex immunopathogenetic mechanisms and the presence of a wide spectrum of autoantibodies. Antibodies to citrullinated proteins (ACP) have the greatest clinical significance, among which antibodies to cyclic citrullinated peptide (anti-CCP) and antibodies to modified citrullinated vimentin (anti-MCV) play a special role [1,15]. Anti-MCV is considered a more dynamic marker reflecting the current inflammatory activity and radiological progression of the disease, while anti-CCP is characterized by high specificity and diagnostic stability. Genetic predisposition is an important component of the pathogenesis of RA. The rs2476601 (C1858T) polymorphism of the PTPN22 gene is of particular interest, as it is associated with a disruption in the regulation of the autoimmune response and a

predisposition to the development of various autoimmune diseases. According to the meta-analysis performed by specialists of the V.A. Nasonova Research Institute, the minor T-allele of this gene is associated with an increased risk of RA development in people of European descent [3]. Similar patterns have been identified for other autoimmune diseases, including systemic lupus erythematosus, Graves' disease, type 1 diabetes mellitus, and juvenile idiopathic arthritis [2]. Nevertheless, data on the relationship between PTPN22 polymorphism, autoantibody levels, and RA activity in the Uzbek population are extremely limited. This study aimed to determine the prevalence of the T-allele and assess its potential relationship with disease activity, the severity of destructive changes, and the level of autoantibodies (anti-CCP, anti-MCV) in patients with rheumatoid arthritis.

Materials and Methods

The study was conducted at the rheumatology department of the 3rd City Clinical Hospital in Tashkent. It included 120 patients with rheumatoid arthritis who constituted the main group and 60 healthy volunteers matched by gender and age as the control group. The age of the participants ranged from 18 to 72 years, with a mean of 48.9±13.4 years. The average disease duration at the time of inclusion was 7.5±6.1 months (ranging from 1.5 to 24 months). Of these, 73 patients (59.8%) were first observed within the first six months of disease onset. The concentration of ACCP was determined by enzyme-linked immunosorbent assay using the Axis-Shield Diagnostic Ltd. kit (Great Britain) according to the manufacturer's instructions [4]. The upper limit of normal (ULN) was 5 U/mL. Patients with ACCP levels >5 U/mL were classified as ACCP-positive, while those with ≤5 U/mL were ACCP-negative. Genomic DNA was isolated by salt extraction using sodium chloride [5]. The distribution of polymorphic variants of the PTPN22 gene (+1858 C>T, rs2476601) was studied by real-time polymerase chain reaction (RT-PCR) using sequence-specific primers and fluorescent probes (NPF "DNA-Technology," Russia). Amplification recording and result interpretation were performed on the domestic detecting amplifier DT-96 ("DNA-Technology" LLC, Russia). To verify the reliability of the results, DNA sequencing was performed using the Sanger method on the ABI PRISM® 310 Genetic Analyzer (Applied Biosystems, USA) platform. Statistical analysis was carried out using SPSS v17.0 and Epi Info v7 software packages [6]. To assess differences in the distribution of genotypes and alleles, the $\chi 2$ test was used, and for risk analysis, odds ratios (OR) with 95% confidence intervals (CI) were calculated. The Mann-Whitney test was used to compare independent samples. The critical level of statistical significance

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was set at $p<0.05$. The Mann-Whitney criterion was used to compare independent samples.

Results.

The study included 120 patients with rheumatoid arthritis (RA) and 60 healthy volunteers, matched for gender and age. The gender distribution in both groups was identical: the proportion of women was 80.0% ($p=0.99$), which excludes the influence of gender on the observed differences. The median age of patients with RA was 52 [44-60] years, which did not statistically differ from the control group (51 [43-59] years; $p=0.58$). The median disease duration in the patient cohort was 48 [12-96] months, reflecting variability in the course and stage of the pathological process (Table 1).

Table-1

Clinical and immunological characteristics of patients

Parameter	RA (n=120)	Control (n=60)	p
Women, n (%)	96 (80.0%)	48 (80.0%)	0.99
Age, years, Me [IQR]	52 [44-60]	51 [43-59]	0.58
RA duration, months, Me [IQR]	48 [12-96]	-	-
DAS28-ESR, score	5.8 [5.1-6.5]	-	-
CDAI, score	23 [18-31]	-	-
SDAI, score	27 [20-36]	-	-
CRP, mg/L	21.4 [8.6-45.2]	1.2 [0.4-2.1]	<0.001
ESR, mm/h	42 [28-64]	10 [6-14]	<0.001
ACPA, U/mL	168 [72-380]	-	-
MCV, U/mL	310 [120-880]	-	-
ACPA-positive, n (%)	102 (85.0%)	0	<0.001

Disease activity indices were characterized by predominantly moderate to high values: the median scores for DAS28-ESR, CDAI, and SDAI were 5.8 [5.1-6.5], 23 [18-31], and 27 [20-36], respectively, indicating a persistent inflammatory process and suboptimal control of disease activity in most patients.

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Inflammatory laboratory markers demonstrated significantly higher values compared to the control group. The concentration of C-reactive protein in RA patients reached 21.4 [8.6-45.2] mg/l versus 1.2 [0.4-2.1] mg/l in individuals without inflammatory pathology ($p<0.001$), and the erythrocyte sedimentation rate was 42 [28-64] mm/h compared to 10 [6-14] mm/h in the control group ($p<0.001$). These data confirm the presence of a pronounced systemic inflammatory response.

Serological profiling revealed a high frequency of autoimmune markers. The average concentrations of antibodies to cyclic citrullinated peptide (anti-CCP) and antibodies to modified citrullinated vimentin (anti-MCV) in RA patients were 168 [72-380] and 310 [120-880] U/ml, respectively. Anti-CCP positivity was established in 85% of patients in the main group, while no positive results were registered among the control subjects ($p<0.001$).

Collectively, the obtained data indicate that the examined sample of patients with rheumatoid arthritis is represented predominantly by middle-aged women, has a long-standing course of the disease, accompanied by moderate to high disease activity, pronounced inflammatory syndrome, and high seropositivity for key autoantibodies [7].

Analysis of the distribution of genotypes and alleles of the rs2476601 (C1858T) polymorphism of the PTPN22 gene in 120 patients with RA and 60 healthy individuals showed a tendency towards an increased frequency of the T-allele among patients.

Table 2.

Distribution of PTPN22 rs2476601 genotypes and T-allele frequency

Genotypes / alleles	Control (n=60)	RA (n=120)	OR (95% CI)	p
CC	47 (78.3%)	82 (68.3%)		
CT	12 (20.0%)	34 (28.3%)		
TT	1 (1.7%)	4 (3.3%)		
Allele C (2n)	106 out of 120 (86.7%)	198 out of 240 (82.5%)	1.61 (0.84-3.07)	0.167
Allele T (2n)	14 out of 120 (13.3%)	42 out of 240 (17.5%)	1.61 (0.84-3.07)	0.167

In the control group, the CC genotype was predominant (78.3%), while among RA patients, its proportion decreased to 68.3%, with the frequency of the CT genotype increasing to 28.3% (compared to 20.0% in the control group). The homozygous TT variant occurred in 3.3% of patients and 1.7% of control subjects. In the allelic model, the proportion of the T-allele in patients was 17.5%, compared

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to 13.3% in the control group. Calculation of the odds ratio showed a moderate increase in the probability of RA development with the presence of the T-allele (OR=1.61; 95% CI 0.84-3.07; p=0.167). Analysis using the dominant model (CT+TT vs. CC) also indicated a tendency towards increased risk in T-allele carriers (OR=1.68; 95% CI 0.81-3.46; p=0.219). Despite the absence of statistically significant differences, the obtained results are consistent with literature data confirming the involvement of the rs2476601 variant of the PTPN22 gene in the development of autoimmune inflammation. The observed trend suggests the participation of the T-allele in the mechanisms of predisposition to rheumatoid arthritis, which justifies the need for further expansion of the sample size and inclusion of additional clinical and immunological indicators.

A comparative analysis of clinical, immunological, and instrumental indicators in patients with rheumatoid arthritis (RA) was conducted, depending on the polymorphic variant of the studied gene. The group of wild-type genotype carriers (CC) included 80 patients, while the subgroup of minor allele carriers (CT+TT) included 40 people (Table 3).

Table 3.

Association of T-allele carriage with disease activity and autoantibodies

Indicator	CC (n=80)	CT+TT (n=40)	Δ or OR	p
DAS28-ESR, points	5.5 [4.9-6.2]	6.1 [5.6-6.7]	+0.6	0.002
CDAI, points	21 [16-28]	27 [22-34]	+6	0.003
SDAI, points	25 [18-33]	32 [24-40]	+7	0.004
Total Sharp score	72 [51-95]	98 [74-126]	+26	0.001
ACPA, Units/ml, Me [IQR]	142 [60-320]	220 [110-420]	+78	0.01
MCV, Units/ml, Me [IQR]	260 [100-720]	420 [180-980]	+160	0.008
Highly positive ACPA (>3×ULN), n (%)	51 (63.8%)	33 (82.5%)	OR 2.56 (1.13-5.82)	0.02
Highly positive MCV (>60 U/ml), n (%)	52 (65.0%)	33 (82.5%)	OR 2.47 (1.07-5.72)	0.03

Based on the assessment of disease activity, it was established that patients with the T-allele were characterized by a more pronounced inflammatory process. The mean values of DAS28-ESR, CDAI, and SDAI indices in the CT+TT subgroup were significantly higher than in carriers of the CC genotype: 6.1 [5.6-6.7] versus 5.5 [4.9-6.2] points (p=0.002), 27 [22-34] versus 21 [16-28] points (p=0.003), and 32 [24-40] versus 25 [18-33] points (p=0.004), respectively. These differences indicate higher clinical disease activity in carriers of the minor variant.

The indicators of structural joint damage, assessed by the Sharp total score, also demonstrated a statistically significant increase in patients with the CT+TT

genotype: the median was 98 [74-126] points versus 72 [51-95] points in the CC group (p=0.001), indicating a more pronounced destruction of joint structures in minor allele carriers.

Analysis of autoimmune markers revealed a tendency towards higher antibody production in patients with CT+TT variants. The concentration of anti-citrullinated protein antibodies (ACPA) in them was 220 [110-420] U/ml, which was 78 U/ml higher than the level of CC-genotype carriers (142 [60-320] U/ml, p=0.01). A similar pattern was observed in relation to antibodies to modified citrullinated vimentin (anti-MCV): 420 [180-980] U/ml versus 260 [100-720] U/ml (p=0.008).

The proportion of highly positive patients (>3×ULN) for ACPA among CT+TT carriers was 82.5% versus 63.8% in the CC-genotype group. Calculation of the odds ratio showed a significant association of the minor allele with a pronounced autoantibody response (OR 2.56; 95% CI 1.13-5.82; p=0.02). Similar results were obtained for highly positive anti-MCV (>60 U/ml): the frequency was 82.5% versus 65.0%, with OR 2.47 (95% CI 1.07-5.72; p=0.03).

Thus, the presence of a minor T-allele was associated with more pronounced clinical activity, higher levels of inflammatory and autoimmune markers, as well as an intensification of radiologically confirmed destructive joint damage. This allows us to consider the indicated genetic variant as a potential factor in the unfavorable course of RA.

Conclusions.

A study conducted among patients with rheumatoid arthritis in the Uzbek population demonstrated that the disease is characteristic primarily of middle-aged women with a prolonged course, moderately high clinical activity, and a pronounced inflammatory response [8,12]. For most patients, elevated levels of C-reactive protein and erythrocyte sedimentation rate, as well as high seropositivity for antibodies to cyclic citrullinated peptide (anti-CCP) and modified citrullinated vimentin (anti-MCV), are typical, reflecting the systemic nature of the inflammatory process and autoimmune joint damage [9,11].

Analysis of genetic characteristics showed that carriage of the minor T-allele of the studied gene is associated with a more unfavorable clinical and immunological phenotype of the disease [13]. In such patients, significantly higher values of the DAS28-ESR, CDAI, and SDAI indices were identified, indicating increased disease activity. In addition, carriers of CT+TT genotypes exhibited more pronounced structural changes in the joints according to the Sharp total score, as well as significantly higher concentrations of ACCP and AMCV compared to patients with the CC genotype.

It has been established that the presence of a minor T-allele increases the likelihood of a highly positive autoantibody response by more than twofold, confirming the involvement of this genetic variant in the mechanisms of chronic inflammation and autoimmune activation in rheumatoid arthritis [14]. Thus, the obtained data suggest a possible role of the studied polymorphism as a **genetic predictor of a more active and destructive course of rheumatoid arthritis in patients of the Uzbek population,** which has potential significance for prognostic stratification and the selection of individualized therapy.

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