ORIGINAL INVESTIGATIONS

Association of *ERAP1* and *IL23R* gene polymorphisms with ankylosing spondylitis

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Currently, the causes of extra-axial and extra-skeletal manifestations of ankylosing spondylitis (AS) and the possible impact of genetic aspects on its course and clinical features remain unresolved.

Objective: *to investigate the association of the polymorphic markers rs10050860 and rs17482078 in the ERAP1 gene and rs11209026 in the IL23R gene with the development and clinical manifestations of AS.*

Patients and methods. *An allele-specific polymerase chain reaction assay was carried out to assess the alleles and corresponding genotypes of ERAP1 and IL23R gene polymorphisms in 70 patients (49 men and 21 women; mean age, 38 [31; 49] years) with AS and in 20 healthy donors. The activity indices, ESR, CRP, and extra-axial and extra-skeletal manifestations of AS were assessed in patients at the time of the investigation and in their history.*

Results and discussion. *The results of genotyping showed a significant association of the studied markers with AS. The carriage of the C/T genotype of the polymorphic markers rs10050860 and rs17482078 in the ERAP1 gene was associated with the history of peripheral arthritis (p=0.029) and the presence of incomplete right bundle branch block (IRBBB) (p=0.003 and p=0.006); the carriage of the G/A genotype of the marker rs11209026 in the IL23R gene was significantly associated with psoriasis (p=0.017) and IRBBB (p=0.03) in patients with AS.*

Conclusion. *The polymorphic markers of the ERAP1 and IL23R genes are associated with the risk of developing AS in this sample of patients. There is a significant correlation between the studied polymorphisms and some clinical manifestations of AS, which can be considered as a predictor of a more severe disease course.*

Keywords: *ankylosing spondylitis; ERAP1; IL23R; clinical features; extra-skeletal manifestations.*
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Introduction. Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease from the group of spondyloarthritis (SpA), which is characterized by obligatory involvement of the sacroiliac joints and/or the spine which results in ankylosis. AS belongs to severe diseases with a variety of clinical symptoms [1]. Extra-axial manifestations of AS include skeletal lesions other than the spine: arthritis, enthesitis, dactylitis [2]. It is especially important to diagnose such extra-axial manifestations as damage to the mandibular and hip joints, which are predictors of a more severe course of AS [3–5]. Extra-skeletal manifestations of AS include damage to other organs and systems, which is typical of the whole SpA group. According to Russian SpA experts, extra-skeletal manifestations of AS include damage to the eyes (uveitis), skin (psoriasis), colon (Crohn's disease and ulcerative colitis) and heart (disorders of the conducting system) [2, 6]. Despite the fact that the association of the risk of developing AS with the presence of the HLA-B27 antigen, the ERAP1 and IL23R genes has been described in detail and demonstrated in many modern studies [7–12], the question of the reasons for the development of extra-axial and extra-skeletal manifestations of AS and possible influence of genetic aspects on the course and clinical features of AS remains poorly understood.

The aim of this research was to study the association of single nucleotide polymorphisms (SNPs) rs10050860 and rs17482078 of the *ERAP1* gene and SNP rs11209026 of the *IL23R* gene with the development and features of the clinical manifestations of AS.

Patients and methods. The study included 8 patients with AS diagnosed in accordance with the Russian version of the modified New York criteria [13] and 62 patients with AS, whose diagnosis met the modified New York criteria 1984 [14]. All participants signed an informed consent form. The studied cohort of patients included 49 (70%) men and 21 (30%) women (mean age 38 [31; 49] years) with the median duration of the disease 16 [11; 26] years. HLA-B27 antigen was detected in the majority of patients (92.9%). General characteristics of patients are presented in Table 1.

All patients were comprehensively examined according to the clinical guidelines of the Russian Association of Rheumatologists. The following indices were determined in all patients: BASDAI (Bath Ankylosing Spondylitis Disease Activity Index), ASDAS-CRP (Ankylosing Spondylitis Disease Activity Score by the level of C-reactive protein) [13, 15], BASFI (Bath Ankylosing Spondylitis Functional Index) [15, 16], MASES (Maastricht Ankylosing Spondylitis Enthesitis Score) [17]. The presence of extra-axial and extra-skeletal manifestations of AS at the time of the study and in the history was determined in all of the studied patients.

Several single nucleotide polymorphisms associated with AS according to the data of numerous studies [7–12] were selected for genotyping: rs10050860 *(ERAP1)*, rs17482078

(ERAP1), and rs11209026 *(IL23R)*. The material for the molecular genetic study was genomic DNA samples obtained by the method of nucleic acid reprecipitation using the Proba-NK reagent (DNA-Technology, Russia) from the biomaterial (swabs from the oral mucosa) of 70 patients with AS and 20 healthy persons of the control group, matched by sex and age. The study of SNPs of these genes was carried out by the method of allele-specific hybridization in the format of polymerase chain reaction with fluorescence detection in real time (TaqMan) using the primer sets (Research and Production Company «Syntol», Russia) on the detecting amplifier DTlite («DNA-Technology», Russia). The data were checked for the correspondence of the observed distribution of genotypes to the theoretically expected at Hardy-Weinberg equilibrium [18].

Statistical data processing was performed using the «Statistica 10» software. Median (Me) and interquartile range [25; 75 ‰] were calculated to describe quantitative variables. The statistical significance of differences in the frequencies of alleles and genotypes of the studied patients and the healthy controls was analyzed using the Pearson χ^2 test, odds ratio (OR) and relative risk (RR) values with a 95% confidence interval (CI). Differences were considered significant at $p < 0.05$.

Results. The results showed that the distribution of the tested *ERAP1* and *IL23R* SNPs genotypes and the alleles did not deviate from the Hardy–Weinberg equilibrium [18] both in patients with AS and in the healthy controls [18].

According to the statistical analysis, the major allelic variants [C] of the rs10050860 and rs17482078 *ERAP1* polymorphisms were significantly more frequent in patients with AS than in the healthy controls (OR 3.00; 95% CI 1.22–7.41; p=0.014 and OR 3.10; 95% CI 1.33–7.22; p=0.007, respectively). The frequencies of the genotypes of these polymorphic markers also significantly differed in patients with AS and the healthy controls (Table 2) and contributed to the association with AS. Thus, the patients with AS carried the homozygous C/C genotype of the rs10050860 and rs17482078 *ERAP1* polymorphisms 1.3 times more often than the controls (OR 2.67; 95% CI 0.92–7.77; p=0.067 and OR 2.76; 95% CI 0.97–7.83; p=0.052, respectively), and the level of differences was close to statistical significance. Carriage of heterozygous C/T genotypes of the rs10050860 and rs17482078 *ERAP1* polymorphisms in 2 groups was comparable (OR 0.58; 95% CI 0.19–1.79; p=0.34 and OR 0.64; 95% CI 0.21–1.94; p=0.43, respectively). Patients with AS were significantly less likely to carry the homozygous T/T genotype of the rs17482078 *ERAP1* polymorphism than the group of healthy controls (OR 0.08; 95% CI 0.01–0.84; p=0.01). The homozygous T/T genotype containing the minor [T] allele of the rs10050860 *ERAP1* polymorphism was found only in the controls.

Table 1 *Characteristics of 70 AS patients included in the study*

Parameter/Criterion	Value/Median
Male/ female gender, n (%)	49/21 (70/30)
HLA-B27 positivity, n (%)	65 (92.9)
Median age, years, [25;75‰]	38 [31; 49]
Median age at disease onset, years, [25;75‰]	21 [18; 26]
Median disease duration, years, [25;75‰]	16 [11; 26]
Axial form, n (%)	46 (65.7)
BASDAI score, [25;75‰]	4.95 [3.5; 6.9]
ASDAS-CRP score, [25;75‰]	3.25 [2.6; 4.2]
CRP, mg/L, [25;75‰]	9.02 [3.67; 19.97]
ESR, mm/hour, [25;75‰]	19.5 [10; 30]
BASFI score, [25;75‰]	5 [2; 7.1]
MASES score, [25;75‰]	3 [2; 5]

The frequency of the major allelic variant [G] of the rs11209026 *IL23R* polymorphism in patients with AS was almost 3 times as frequent as in the healthy controls (OR 9.86; 95% CI 1.84–52.96; p=0.002), which indicates that this allele of the rs11209026 *IL23R* polymorphism in the studied patients is a strong risk factor for predisposition to AS (Table 2). The G/G genotype of the rs11209026 *IL23R* polymorphism in patients with AS was found almost 3 times more often than in the healthy controls (OR 11.33; 95% CI 2.00–64.09; p=0.002). Patients with AS were significantly less likely to carry the heterozygous G/A genotype of this polymorphism than the controls (OR 0.09; 95% CI 0.02–0.50; p=0.002). A homozygous A/A genotype containing the minor [A] allele of the rs11209026 *IL23R* polymorphism was found neither in the main group, nor in the control group.

Further study of the relationship between the features of clinical manifestations of AS and genetic aspects revealed that the heterozygous C/T genotype of the rs10050860 *ERAP1* polymorphism was 1.5 times more frequent in patients with the history of peripheral arthritis than in patients without this extra-axial manifestation of AS (RR 1.60; 95% CI 1.16–2.21; p=0.029). In addition, we established a significant association between the C/T genotype of this polymorphism and arthritis of the temporomandibular joint (p=0.044), but the RR did not reach statistical significance. The heterozygous C/T genotype of the rs10050860 *ERAP1* polymorphism was 8 times more frequent in patients with incomplete right bundle branch block (RBBB) compared with patients without this disorder of the cardiac conduction system (RR 8.0; 95% CI 1.63–39.36; p=0.003; Table 3).

Since the homozygous T/T genotype of the rs17482078 ERAP1 polymorphism in the study sample was found only in 1 (1.43%) patient, we excluded it from the further study of associations between extra-axial, extra-skeletal manifestations of AS and this SNP. According to the results presented in Table 4, the heterozygous C/T genotype of the rs17482078 *ERAP1* polymorphism was significantly more often detected in patients with incomplete RBBB (RR 7.20; 95% CI 1.46–35.59; p=0.006).

The heterozygous G/A genotype of the rs11209026 *IL23R* polymorphism was significantly associated with incomplete RBBB (RR 6.80; 95% CI 1.34–34.45; p=0.03) and was 8.5 times more frequent in patients with skin psoriasis compared with patients without this extra-skeletal manifestation of AS (RR 8.50; 95% CI 1.58–45.64; p=0.017; Table 5).

Discussion. Today, a large number of studies have been conducted, which have confirmed the association of the rs10050860,

Table 2 *Frequencies of alleles and genotypes of ERAP1 and IL23R genes polymorphisms in AS patients and controls*

Gene, SNP	Allele, genotype	Number (frequency) of alleles and genotypes		χ^2	p-value	OR (95% CI)
		AS patients, n=70	Healthy controls, n=20			
ERAP1 rs10050860	C	126 (0.9)	30 (0.75)	6.06	0.014*	3.00 (1.2–7.41)
	T	14 (0.1)	10 (0.25)			0.33 (0.14–0.82)
	C/C	56 (0.80)	12 (0.60)	8.52	0.015*	2.67 (0.92–7.77)
	C/T	14 (0.20)	6 (0.30)			0.58 (0.19–1.79)
	T/T	–	2 (0.10)			0.00
ERAP1 rs17482078	C	123 (0.88)	28 (0.7)	7.34	0.007*	3.10 (1.33–7.22)
	T	17 (0.12)	12 (0.3)			0.32 (0.14–0.75)
	C/C	54 (0.77)	11 (0.55)	7.99	0.019*	2.76 (0.97–7.83)
	C/T	15 (0.22)	6 (0.30)			0.64 (0.21–1.94)
	T/T	1 (0.010)	3 (0.15)			0.08 (0.01–0.84)
IL23R rs11209026	G	138 (0.99)	35 (0.88)	10.20	0.002*	9.86 (1.84–52.96)
	A	2 (0.01)	5 (0.12)			0.10 (0.02–0.55)
	G/G	68 (0.97)	15 (0.75)	10.63	0.002*	11.33 (2.00–64.09)
	G/A	2 (0.03)	5 (0.25)			0.09 (0.02–0.50)
	A/A	–	–			–

* – significant value; OR – odds ratio; 95% CI – 95% confidence interval

rs17482078 *ERAP1* polymorphisms and the rs11209026 *IL23R* polymorphism with an increased risk of AS. Our study confirmed a strong association of these polymorphisms with the risk of AS in the Russian population, which is consistent with the results of most other research works [7, 10, 12]. At the same time, there is almost no information about the influence of genetic aspects, including *ERAP1* and *IL23R* polymorphisms, on the clinical manifestations of AS.

Endoplasmic reticulum aminopeptidase 1, encoded by the *ERAP1* gene, is a multifunctional enzyme that is involved in the regulation of immune and inflammatory responses [19]. One of the functions of *ERAP1* is the N-terminal proteolysis of antigenic peptides to the optimal length (8-9 amino acid residues) for their further presentation by the HLA-B27 [20]. One of the functions of *ERAP1* is trimming N-terminal residues to generate antigenic peptides that have an optimal length for loading onto major histocompatibility complex (MHC) class I molecules, in particular HLA-B27 [20]. However, the markers rs10050860 and rs17482078, which are single nucleotide nonsynonymous substitutions in the coding region of the *ERAP1* gene, affect the specificity and activity of the aminopeptidase and can lead to the formation of peptides of different lengths that bind differently to HLA-B27. Such HLA-B27-aberrantly linked peptides exhibit highly immunogenic properties and overstimulate cytotoxic T cells, thereby triggering a proinflammatory cascade, increasing susceptibility to AS and affecting the severity of the disease [12, 19, 21]. Our results are consistent with these data and indicate that the heterozygous C/T genotypes of the rs10050860 and rs17482078 *ERAP1* polymorphisms are reliably associated with an extra-axial manifestation of AS, like peripheral arthritis, and extra-skeletal manifestation in the form of a disorder of the cardiac conduction system. This indicates the need for additional study of the contribution of genetic factors to the severity of this disease.

Table 3 *Distribution of genotypes of the rs10050860 ERAP1 polymorphisms depending on the clinical manifestations of AS*

Clinical manifestations of AS	AS patients with C/C genotype, n=56	AS patients with C/T genotype, n=14	χ^2	p-value	RR (95% CI)
Extra-axial manifestations of AS, n (%):					
Peripheral arthritis	19 (33.93)	5 (35.71)	0.02	0.90	1.05 (0.48–2.32)
History of peripheral arthritis	30 (53.57)	12 (85.71)	4.82	0.029*	1.60 (1.16–2.21)
Enthesitis	33 (58.93)	8 (57.14)	0.02	0.90	0.97 (0.59–1.61)
Coxitis	3 (5.36)	1 (7.14)	0.07	0.80	1.33 (0.15–11.87)
History of coxitis	8 (14.29)	1 (7.14)	0.51	0.48	0.50 (0.07–3.68)
Dactylitis	7 (12.5)	–	1.94	0.16	0.00
History of dactylitis	17 (30.36)	2 (14.29)	1.46	0.23	0.47 (0,.2–1.80)
Extra-skeletal manifestations of AS, n (%):					
Incomplete RBBB	2 (3.57)	4 (28.57)	8.93	0.003*	8.0 (1.63– 39.36)
Sinus tachycardia	4 (7.14)	3 (21.43)	2.54	0.11	3.0 (0.76– 11.90)
Uveitis	3 (5.36)	1 (7.14)	0.07	0.80	1.33 (0.15– 11.87)
Psoriasis	5 (8.93)	–	1.35	0.25	0.00
Crohn's disease	1 (1.79)	–	0.25	0.62	0.00

* – significant value; RR – relative risk; 95% CI – 95% confidence interval

Table 4 *Distribution of genotypes of the rs17482078 ERAP1 polymorphism depending on the clinical manifestations of AS*

Clinical manifestations of AS	AS patients with C/C genotype, n=54	AS patients with C/T genotype, n=15	χ^2	p-value	RR (95% CI)
Extra-axial manifestations of AS, n (%):					
Peripheral arthritis	18 (33.33)	6 (40)	0.23	0.63	1.20 (0.58– 2.48)
History of peripheral arthritis	29 (53.70)	12 (80)	3.37	0.07	1.49 (1.05– 2.12)
Enthesitis	32 (59.26)	9 (60)	0.01	0.96	1.01 (0.63– 1.62)
Coxitis	3 (5.56)	1 (6.67)	0.03	0.87	1.20 (0.13– 10.72)
History of coxitis	8 (14.81)	1 (6.67)	0.69	0.41	0.45 (0.06– 3.32)
Dactylitis	7 (12.96)	–	2.16	0.14	0.00
History of dactylitis	16 (29.63)	3 (20)	0.55	0.46	0.68 (0.23– 2.01)
Extra-skeletal manifestations of AS, n (%):					
Incomplete RBBB	2 (3.70)	4 (26.67)	7.80	0.006*	7.20 (1.46– 35.59)
Sinus tachycardia	4 (7.41)	2 (13.33)	0.52	0.47	1.80 (0.36– 8.90)
Uveitis	3 (5.56)	–	0.87	0.35	0.00
Psoriasis	5 (9.26)	–	1.50	0.22	0.00
Crohn's disease	1 (1.85)	–	0.28	0.60	0.00

* – significant value; RR – relative risk; 95% CI – 95% confidence interval

The study investigated the effect of the *IL23R* gene polymorphism on the clinical manifestations of AS. The *IL23R* gene, being a key genetic marker encoding the receptor for interleukin-23 (IL-23), is responsible for the activation of the IL-23/IL-17 immune axis, which plays an important role in the pathogenesis of AS. We have found that the heterozygous G/A genotype of the rs11209026 *IL23R* polymorphism is reliably associated with an extra-skeletal manifestation of the disease, like impairment of the cardiac conduction system and psoriasis in patients with AS. It is generally known that IL-23 is a heterodimeric cytokine that is produced by antigen-presenting cells, including dendritic cells, macrophages, and keratinocytes [22]. IL-23 signals are transmitted through the IL-23 receptor, encoded by the *IL23R* gene, leading to the differentiation of CD4 + T-helper cells in a pro-inflammatory context into a special subpopulation of Th17-cells synthesizing mainly IL-17A and tumor necrosis factor α (TNFα), which support inflammation and pathological bone proliferation at the border of the cartilage and bone tissue [23]. This is accompanied by the development of psoriasis in our patients, carriers of the heterozygous genotype G/A of the rs11209026 marker of the *IL23R* gene. Excessive stimulation of the IL23 receptor in AS also leads to slow and abnormal folding of the HLA-B27 heavy chain, which is involved in the pathogenesis of AS according to some authors [24–25]. However, there are not enough works devoted to the study of the influence of the IL23R gene on the clinical features of AS.

Taking into consideration that AS is a multifactorial disease, in further studies of the influence of *ERAP1* and *IL23R* polymorphisms on clinical manifestations of AS, it is necessary to determine the functions of these allelic variants of genes, as well as possible influence of additional environmental factors.

Conclusion. Thus, based on the representative clinical material of the Russian population of AS patients, it was confirmed that the major [C] alleles of the rs10050860 and rs17482078 *ERAP1* polymorphisms and the minor allele [A] of the rs11209026 *IL23R* polymorphism are strong risk factors for predisposition to AS.

Table 5 *Distribution of genotypes of the rs11209026 IL23R polymorphism depending on the clinical manifestations of AS*

Clinical manifestations of AS	AS patients with G/G genotype, n=68	AS patients with G/A genotype, n=2	χ^2	p-value	RR (95% CI)
Extra-axial manifestations of AS, n (%):					
Peripheral arthritis	24 (35.29)	–	1.07	0.30	0.00
History of peripheral arthritis	40 (58.82)	2 (100)	1.37	0.24	1.70 (1.39–2.07)
Enthesitis	40 (58.82)	1 (50)	0.06	0.80	0.85 (0.21–3.45)
Coxitis	4 (5.88)	–	0.13	0.72	0.00
History of coxitis	9 (13.24)	–	0.30	0.58	0.00
Dactylitis	7 (10.29)	–	0.23	0.63	0.00
History of dactylitis	18 (26.47)	1 (50)	0.54	0.46	1.89 (0.45–7.98)
Extra-skeletal manifestations of AS, n (%):					
Incomplete RBBB	5 (7.35)	1 (50)	4.51	0.03*	6.80 (1.34–34.45)
Sinus tachycardia	7 (10.29)	–	0.23	0.63	0.00
Uveitis	4 (5.88)	–	0.13	0.72	0,00
Psoriasis	4 (5.88)	1 (50)	5.70	0.017*	8.50 (1.58–45.64)
Crohn's disease	1 (1.47)	–	0.03	0.86	0.00

* – significant value; RR – relative risk; 95% CI – 95% confidence interval

A higher frequency of heterozygous C/T genotypes of the rs10050860 and rs17482078 *ERAP1* polymorphisms was revealed in patients with the history of peripheral arthritis and disorders of the cardiac conduction system. The heterozygous G/A genotype of the rs11209026 *IL23R* polymorphism was statistically significantly associated with incomplete RBBB and psoriasis in AS patients. Further studies are required to clarify the genetic features of ankylosing spondylitis and to determine the prognostic value of the identified differences.

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