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THE POLYMORPHISM OF MATRILIN-3 (RS77245812) AND INTERLEUKIN-10 (RS1800872) GENES IN OSTEOARTHRITIS PATIENTS WITH ARTERIAL HYPERTENSION, OBESITY AND TYPE 2 DIABETES MELLITUS

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Abstract

Introduction. Osteoarthritis (OA) is a multifactorial disorder in which ageing, genetic, hormonal and mechanical factors are major contributors to its onset and progression.
Objectives. To evaluate the genotypes frequencies of Matrilin-3 (*MATN3*, rs77245812) and Interleukin-10 (*IL-10*, rs1800872) genes polymorphism in OA patients combined with arterial hypertension (AH), abdominal obesity (AO) and type 2 diabetes mellitus (DM2).
Methods. The polymorphic variants of genes *MATN3* (C908T) and *IL-10* (C-592A) were analyzed by PCR in 74 OA patients with AO, AH, DM2 and 25 healthy individuals.
Results. Distribution of *MATN3* gene polymorphic variants in observed groups was as follows: CC-genotype – in 94.59% OA patients, and in 96.0% of control ($p>0.05$); CC-genotype – in 5.41% and 4% respectively. The *C*-allele prevails over *T*-allele by 94.95% ($p<0.001$) with preservation of the population equilibrium: among the OA patients – 97.30% vs 2.70% ($p<0.001$), among the healthy – 98.0% vs

Résumé

Le polymorphisme des genes matrilin-3 (RS77245812) et interleukine-10 (RS1800872) chez les patients arthritiques avec de l'hypertension artérielle, obesité et diabète sucré de type 2

Introduction. L'arthrose (OA) est un trouble multifactoriel dont les facteurs vieillissants, génétiques, hormonaux et mécaniques sont tous des facteurs majeurs de son apparition et de sa progression.
Objectifs. L'objectif de notre étude est de faire une analyse de la fréquence du polymorphisme des gènes matrilin-3 (*MATN3*; rs77245812) et de l'interleukine-10 (*IL-10;* rs1800872) chez les patients souffrant d'OA combinés avec l'hypertension artérielle (AH), l'obésité abdominale (AO) et le diabète sucré de type 2 (DM2).
Méthodes. Les variantes polymorphes des gènes *MATN3* (C908T) et *IL-10* (C-592A) ont été analysées par la réaction en chaîne par polymérase chez 74 patients atteints d'OA avec AO, AH, DM2 et 25 personnes en bonne santé.

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2.0% (p<0.001) accordingly. Distribution of *IL-10* gene polymorphic variants in observed groups was as follows: CC-genotype – in 52.7% OA patients vs 68.0% in control (p>0.05); CA-genotype – in 37.84% vs 32.0% (p>0.05) respectively; CC-genotype was found in 9.46% OA patients and none of control. C-allele of *IL-10* gene dominated over the A-allele: among patients – 2.52 times (p<0.001), among control group – 5.25 times (p<0.001). The wild C-allele of *IL-10* gene dominated 2.96 times (p<0.001) generally in the observed population.

Conclusions. Polymorphic variants of genes *MATN3* and *IL-10* are not additional risk factors of the OA occurrence in the observed population of Northern Bukovina.

Key words: matrilin-3 gene (rs77245812), interleukin-10 gene (rs1800872), osteoarthritis, risk.

Abbreviations: AH – arterial hypertension, AO – abdominal obesity, DM – diabetes mellitus, FDDJ – functional disorders degree of the joints, OA – osteoarthritis.

Résultats. La distribution des variantes polymorphes du gène *MATN3* dans les groupes observés était la suivante: le génotype CC a été trouvé chez 94.59% patients OA et chez 96.0% dans le groupe de contrôle (p>0.05); le génotype CT – chez 5.41% et 4% respectivement. L'allèle C sauvage prévaut sur l'allèle *T* de 94.95% (p<0.001) avec la préservation de la loi d'équilibre de la population: parmi les patients atteints d'OA – 97.30% contre 2.70% (p<0.001), parmi les personnes saines – 98.0% vs 2.0% (p<0.001) en conséquence. La distribution des variantes polymorphes du gène *IL-10* dans les groupes observés était la suivante: le génotype CC a été trouvé chez 52.7% patients OA et chez 68.0% dans le groupe témoin (p>0.05); le génotype CA – chez 37.84% et 32.0% (p>0.05) respectivement; le génotype CC a été trouvé chez 9.46% patients OA et aucun dans le groupe témoin, respectivement. L'allèle C du gène IL-10 dominée par l'allèle A: parmi les patients – 2,52 fois (p<0.001), parmi le groupe témoin – 5,25 fois (p<0.001). L'allèle C sauvage du gène *IL-10* a dominé 2,96 fois (p<0.001) parmi la population examinée en général.

Conclusions. Les variantes polymorphes des gènes *MATN3* et *IL-10* ne sont pas des facteurs de risque supplémentaires pour l'apparition de l'OA chez la population examinée dans la Bucovine du Nord.

Mots-clés: gène matrilin-3 (rs77245812) et gène interleukine-10 (rs1800872), arthrose, risque.

Abréviations: OA – arthrose, DM – diabète sucré, AO – obésité abdominale, AH – hypertension artérielle

Introduction

Osteoarthritis (OA) is one of the most frequent diseases in the sphere of bones, muscles and joints. It afflicts all joint components: cartilage, subchondral bone, synovial membrane, ligaments, capsule and muscles of the joint. OA severity correlates with age and it reaches its highest indices (13.9%) at the age of 45 and older. Men prevail among young patients, although among elderly patients it changes drastically and women become more susceptible to the disease[1]. In the United States of America, OA occurs only in 2% of population younger than 45 years, in 30% – at the age of 45-64, and in 63-85% – in people older than 65 years[2,3].

Morphogenesis and functioning of the cartilage structures are genetically predetermined[4,5].

Genes which have potentially an indirect impact upon the functional state and morphology of connective tissue and cartilage can be conditionally divided into two groups – structural and genes that affect meolism: structural genes, that code mainly connective tissue matrix proteins (chiefly structural proteins of the same name) – *COL2A2* і *COL9A1*; COMP (Cartilage Oligomeric Matrix Protein) – genes that code oligomeric extracellular cartilage matrix protein, the main function of which is connecting polymeric collagen fibers situated in the intercellular space of the connective tissue[6,7]; *MATN*3 – matrilin-3; AGC (aggrecan gene) – genes that code aggrecan and are associated with OA; *FRZB* (secreted frizzled-related protein 3 gene) – gene that codes the mature protein's ability to counteract transmitting Wnt signals in the chondrocytes while affecting the metabolism inside; *GDF5* – expression regulator genes of the osteo- and chondrogenesis initiator genes; *SMAD3* – genes regulating *TGF*-β activity; *ASPN* (asporin gene) – the ones adjusting cartilage metabolism through binding with *TGF*-β; *DVWA* – genes that code intercellular matrix protein of interaction with tubulin which also have

binding functions; *DIO2* – genes that are associated with regulation of thyroid hormones; *VDR* (vitamin D receptor gene) – the ones connected to vitamin D metabolism; genes that code pro- or anti-inflammatory cytokines synthesis and activity[8-12].

Numerous researches are dedicated to the role ascertainment of the above-mentioned genetic causes in the multifactorial disorders occurrence, including the OA. But some pathogeny links of OA remains under-developed. There is a lack of data concerning effect of combined pathology (diabetes mellitus (DM), abdominal obesity (AO), arterial hypertension (AH) and metabolic syndrome) on the OA background, depending on genes polymorphism, cartilage metabolism and individual immunological or metabolic factors[8-15].

Therefore, studying of OA genetic-molecular aspects with comorbid AH, AO and DM background can help to improve the early diagnosis of OA severity and disease progression, metabolic and immunological disorders, etc.

The objective of our study was to evaluate the alleles and the genotypes frequencies of matrilin-3 (rs77245812) and interleukin-10 (rs1800872) genes polymorphism in OA patients combined with AH, AO and type 2 DM.

Material and methods

There were 74 OA patients with AO, AH and type 2 DM who took part in the study and provided their written consent for the participation. The control group included 25 healthy individuals; representatives by age and gender. Patients' average age was 58.03 ± 14.91 years, and the disease duration was within the limits of 5-32 years (12.17 ± 8.83 years). The gender distribution was as follows: 78.38 % (58) females and 21.62 % (16) males.

OA diagnosis was based upon complaints, medical history (anamnesis), the results of clinical, laboratory and instrumental examination according to diagnostic criteria of Ministry of Healthcare of Ukraine (2016) "Clinical Protocol of Providing Medical Care for OA Patients" and American College of Rheumatology (ACR, 1991)[16,17].

All patients were examined comprehensively: general clinical, laboratory and instrumental examination upon recommendation. Anthropometric data were assessed by height, weight, waist and hips circumference measurement (WC, HC), body mass index (BMI) calculation. The obesity and abdominal obesity were determined according to international criteria: WC >94 cm for men and WC>80 cm for women, BMI ≥ 30 kg/m^2 [18].

The diagnosis of AH was verified in compliance with Ministry of Healthcare Order of Ukraine #384 dated 24.05.2012 and National Ukrainian (2012) and European (ESC, ESH, 2013) recommendations[19,20]. DM diagnosis was verified in accordance to Ministry of Healthcare Order of Ukraine #1118 dated 21.12.2012 and based on „Unified Clinical Protocol of Specialized Medical Help: Type 2 DM" (2012).

Genomic DNA was extracted from peripheral blood leukocytes, using the "innuPREP Blood DNA Mini Kit" (Analytik Jena, Germany), with primers specific to the genes' alleles. Modified protocols with oligonucleotide primers using PCR method and further restriction fragment length polymorphism analysis was used to establish polymorphic variants *C908T* of *MATN3* gene (rs77245812) and *C-592A* of *IL-10* gene (rs1800872)[21,22]. The examined gene areas were amplified by specific primers („Metabion", Germany). Peculiar fragments of genes MATN3 (C908T) and IL-10 (C-592A) were amplified using commercial set Dream Taq Green PCR Master Mix („Thermo Scientific", USA) in amplifier „FlexCycler BU" (Analytik Jena, Germany).

Products of DNA fragment amplification (amplicons) of genes *MATN3* and *IL-10* were subjected to hydrolytic cleavage by endonuclease restriction enzymes *AflIII* ("New England BioLabs", Great Britain) and *RsaI* ("Thermo Scientific", USA) accordingly.

Reaction of restricting gene area of *MATN3 (C908T)* was conducted in a micro thermostat at 37°C for 1 hour according to protocol recommendations. *IL-10 (C-592A)* gene restriction was conducted at the same temperature level of 37°C but for 12 hours. In both cases, the restriction reactions were stopped by raising the temperature to 80°C for 20 minutes. Then the states of restricted fragments of genes *MATN3 (C908T)* and *IL-10 (C-592A)* were analyzed in a 3% agarose gel ("Cleaver Scientific", Great Britain) adding ethidium bromide. Molecular mass marker GeneRuler 50 bp DNA Ladder ("Thermo Scientific", USA) was added in the gel for size assessment of obtained restricted fragments and afterwards visualization in transilluminator. The received image of electrophoregrams was processed by using computer program Vitran and then it was archived.

Statistical analysis was performed using Statistica 7.0 (SPSS, StatSoft Inc, USA) software and Microsoft Excel 2007. Nominal data were represented in quantitative and percentage value. *Hardy-Weinberg* equilibrium was calculated by a chi-square test using Online Encyclopedia for Genetic Epidemiology Studies (http://www.oege.org/ software/hwe-mr-calc.shtml). The probability of differences in distribution

of genotypes and alleles frequencies between the groups was determined by χ^2-criterion. The odds ratio (OR) and confidential interval (CI) 95% were calculated for estimating the relative OA risk. P values <0.05 were considered statistically significant.

Results and discussion

Analysis of multiplicative codominant model of OA inheritance stated that the genotypes and alleles relative frequency of *MATN3* (*C908T*) and *IL-10* (*C-592A*) genes polymorphisms in patients and in control group did not differ reliably (Table 1). However, CC-genotype and C-allele of *MATN3* (rs77245812) gene were found in both groups more frequently, 17.5-49 times (p<0.001). In *IL-10* (*C-592A*) gene polymorphism C-allele also dominated over the minor A-allele: among patients – 2.52 times (χ^2=55.35, p<0.001), among control group – 5.25 times (χ^2=46.24, p<0.001). Out of 198 selected alleles in the examined population, the wild C-allele of gene *IL-10* (rs1800872) was dominant 2.96 times (p<0.001).

The *C908T* genotypes distribution in *MATN3* gene polymorphism in the examined group corresponds to *Hardy-Weinberg* population equalibrium law (p>0.05), without significant difference between expected and observed heterozygosities. The *C-592A* genotypes distribution in *IL-10* gene polymorphism in the examined group corresponds to *Hardy-Weinberg* (p>0.05) with the insignificant heterozygosity excess in the control group (F=-0.19, p>0.05), which in general did not disturb the population equilibrium.

Electrophoregram of products of amplification (amplicons) of genes *MATN3* after hydrolytic cleavage by means of endonuclease restriction *AflIII* ("New England BioLabs", Great Britain) is shown in Figure 1. In the presence of restriction site 5'-A↓CRYGT-3' fragments with molecular mass 513 nucleotide pairs (np) and 373 np – genotype CC of gene *MATN3* were obtained. The restriction site was getting lost when the nucleotide changes of C for *T* in the position 908 happened, that is why the fragment size remained without changes, accordingly, – 886 np for *TT* variant (the given genotype was not present in any of the examined gene). DNA restricted fragments with length 886, 513 and 373 pn correspond to heterozygous polymorphous variant *CT* (Figure 1).

Figure 2 depicts the electrophoregram of distributing the restricted analysis products of amplification area of gene *IL-10 (C-592A)*. Amplicons were subjected to the hydrolytic cleavage by means of endonuclease *RsaI* ("ThermoScientific", USA) in the presence of restriction site 5'-GT↓AC-3', which appears as a result of the nucleotide change of C for A in position 592. Consequently, in the presence of AA genotype, the restricted fragments in size 236 and 176 base pair (bp) were obtained. In the absence of the restriction site, the restricted fragments remained unchanged – 419

Table 1. The genotypes and alleles frequency of *MATN3 (C908T)* and *IL-10 (C-592A)* genes polymorphism in the observed population of Northern Bukovina

Examined genes, n (%)		*Study group, n=74 (%)*	*Control group, n=25 (%)*	*OR [95% CI]*	*χ^2 p*
MATN3 (*C908T*), n (%)	CC	70 (94.59)	24 (96.0)	1.37 [0.15-12.88]	χ^2<1.0 p>0.05
	CT	4 (5.41)	1 (4.0)		
χ^2 P		χ^2 =117.73 p<0.001	χ^2 =42.32 p<0.001	–	–
MATN3 (*C908T*), n (%)	C-allele	144 (97.30)	49 (98.0)	1.36 [0.15-12.47]	χ^2<1.0 p>0.05
	T-allele	4 (2.70)	1 (2.0)		
χ^2 P		χ^2 =264.86 p<0.001	χ^2 =92.16 p<0.001	–	–
IL-10 (*C-592A*), n (%)	CC	39 (52.70)	17 (68.0)	0.52 [0.20-1.36]	χ^2=1.36 p>0.05
	CA	28 (37.84)	8 (32.0)	1.29 [0.49-3.39]	χ^2<1.0 p>0.05
	AA	7 (9.46)	0	–	–
χ^2 P		χ^2 =32.15 p<0.001	χ^2 =6.48 p=0.011	–	–
IL-10 (*C-592A*), n (%)	C-allele	106 (78.38)	42 (84.0)	0.48 [0.21-1.11]	χ^2=3.03 p>0.05
	A-allele	42 (21.62)	8 (16.0)		
χ^2 P		χ^2 =55.35 p<0.001	χ^2 =46.24 p<0.001	–	–

Note. OR –odds ratio; n – absolute quantity.

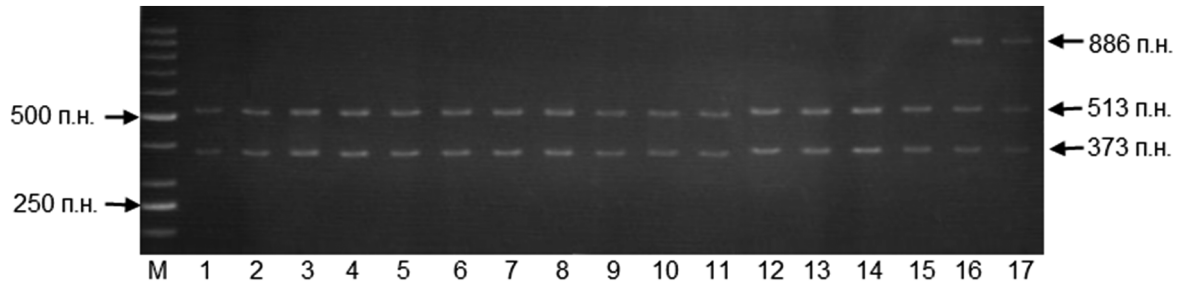

Figure 1. Electrophoregram of restricted fragments distribution of gene *MATN3 (C908T).* Samples 1-15 correspond to *CC*-genotype; samples 16-17 – *CT* genotype; M – molecular mass marker.

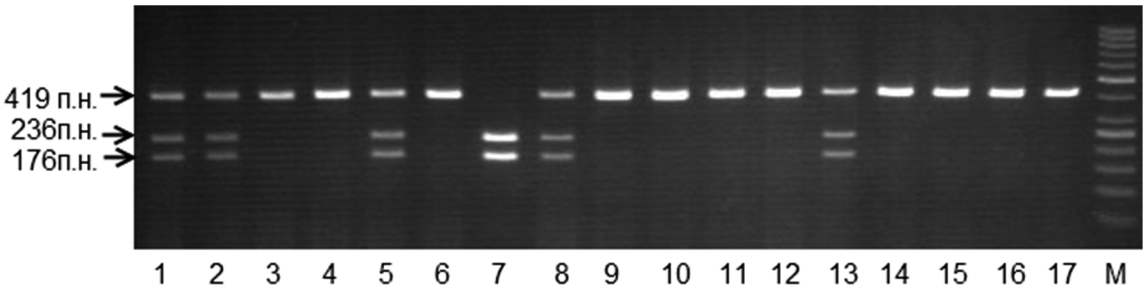

Figure 2. Electrophoregram of restricted fragments distribution of gene *IL-10 (C-592A).* Samples 3, 4, 6, 9-12, 14-17 – *CC* genotype*;* samples 1, 2, 5, 8, 13 – *CA* genotype*;* sample 7 – *AA* genotype; M – molecular mass marker.

bp, which related to CC genotype. Heterozygotes (AC genotype) had all three types of restricted fragments: 419 bp, 236 bp and 176 bp.

The OA occurrence risk among the citizens of the Northern Bukovina depending on the polymorphic variants of the gene *MATN3* (rs77245812) is shown in the Table 2. The analyzed gene alleles are not additional risk factors for OA occurrence in general, and specifically the disease severity, affecting specific joints or the functional disorders degree of the joints

Table 2. *MATN3* (rs77245812) gene polymorphic variants as risk factors of the Osteoarthrosis occurrence in the observed population

MATN3 gene genotypes		*RelR*	*OR*	*95%CI RR*	*95%CI OR*	P
OA in general	CC	0.98	0.73	0.89-1.08	0.08-6.85	>0.05
	CT	1.35	1.37	0.16-11.53	0.15-12.88	>0.05
OA I stage	CC	1.07	3.56	0.95-1.19	0.35-35.95	>0.05
	CT	0.30	0.28	0.03-2.74	0.03-2.83	>0.05
OA II and III stages	CC	0.94	0.28	0.84-1.05	0.03-2.83	>0.05
	CT	3.34	3.56	0.36-30.68	0.35-35.95	>0.05
FDDJ I stage	CC	1.04	2.04	0.92-1.19	0.27-15.44	>0.05
	CT	0.51	0.49	0.08-3.41	0.06-3.70	>0.05
FDDJ II and III stages	CC	0.96	0.49	0.84-1.09	0.06-3.70	>0.05
	CT	1.96	2.04	0.29-13.10	0.27-15.44	>0.05
Gonarthrosis	CC	1.0	0.90	0.91-1.09	0.09-9.10	>0.05
	CT	1.10	1.11	0.12-10.12	0.11-11.17	>0.05
Coxarthrosis	CC	0.97	0.51	0.83-1.12	0.05-5.32	>0.05
	CT	1.88	1.95	0.21-16.82	0.19-20.20	>0.05
Small joints	CC	1.05	-	1.10-1.11	-	>0.05
	CT	CT genotype carriers are absent in the patients with OA of small joints				

Note. OA – osteoarthritis; FDDJ –functional disorders degree of the joints; *RelR* – relative risk; *OR* – Odds Ratio; *95%CI RR, OR* – 95% confidence interval (*RR*), (*OR*).

(FDDJ). Although, in the presence of *CT*-genotype, the probability of OA I stage was rising, and the presence of *CT*-genotype increased the risk of OA II and III stage by 3.34 times [OR=3.56; 95%CI OR: 0.35-35.95; p>0.05]. The probability of OA II and III FDDJ raised almost twice [OR=2.04; 95%CI OR: 0.27-15.44; p>0.05], with higher risk of affecting hip joint [OR=1.95; 95%CI OR: 0.19-20.20; p>0.05].

Epidemiological analysis of the OA occurrence risk, depending on the polymorphic variants of the gene *IL-10* (*rs*1800872), is shown in Table 3. CC-genotype is associated with the lesser X-ray OA stage (Ist stage) [OR=1.71; 95%CI OR=0.68-4.29; p>0.05]. Instead, the minor A-allele and AA genotype raise the risk of the more severe X-ray OA stages (II and III stages) [OR=1.50-1.55; 95%CI OR=0.32-7.46; p>0.05], the higher level of functional joint disability (II and III stages of FDDJ) [OR=2.92; 95%CI OR=0.60-14.23; p>0.05] and the gonarthrosis occurrence [OR=2.32; 95%CI OR=0.27-20.42; p>0.05].

Many studies have determined the connection between MATN3 gene polymorphism and OA of small hands joints and gonarthrosis[5,23,24]. Some of them established the tight connection between *MATN3* gene polymorphism (rs77245812) and OA of hand joints, but not the knee joints[15,25]. In Egypt population, it was found a high risk of OA (OR=2.250; 95% CI=1.011- 5.008) in relationship with *MATN3* gene polymorphism[24]. Quite interesting is the susceptibility to AO inheritance in Iceland: 2% of country's population with OA had a missense mutation of the gene that codes *MATN3*, that increases the OA risk by 2.1 times in these families[15].

Population and racial analysis verified that the minor *T*-allele frequency of gene *MATN3* in observed patients did not reliably differ from the prevailing majority of Caucasian race populations (p>0.05). However, it is more than the populations of the Equatorial race, where T-allele was not evident (P_T=0), and in some Asian populations (East Asian countries) (P_T=0.001; p<0.001). On the contrary, the frequency of C-allele in our studies is somewhat less than in some populations of Asian and Equatorial races (P_C=0.97-0.98 versus P_C=0.999-1.0; p<0.05)[26].

Table 3. *IL-10* (*rs*1800872) gene polymorphic variants as risk factors of the Osteoarthrosis occurrence in the observed population

IL-10 gene genotypes		*RelR*	*OR*	*95%CI RR*	*95%CI OR*	p
OA in general	CC	0.77	0.52	0.55-1.09	0.20-1.36	>0.05
	CA	1.18	1.29	0.62-2.25	0.49-3.39	>0.05
	AA	–	–	–	–	–
OA I stage	CC	1.29	1.71	0.83-2.02	0.68-4.29	>0.05
	CA	0.78	0.67	0.43-1.40	0.26-1.71	>0.05
	AA	0.67	0.64	0.16-0.80	0.13-3.11	>0.05
OA II and III stages	CC	0.78	0.59	0.50-1.21	0.23-1.47	>0.05
	CA	1.29	1.50	0.72-2.31	0.58-3.86	>0.05
	AA	1.49	1.55	0.36-6.18	0.32-7.46	>0.05
FDDJ I stage	CC	1.02	1.04	0.64-1.62	0.40-2.74	>0.05
	CA	1.28	1.47	0.66-2.48	0.53-4.04	>0.05
	AA	0.38	0.34	0.09-1.58	0.07-1.67	>0.05
FDDJ II and III stages	CC	0.98	0.96	0.62-1.55	0.37-2.51	>0.05
	CA	0.78	0.68	0.40-1.52	0.25-1.88	>0.05
	AA	2.61	2.92	0.63-10.78	0.60-14.23	>0.05
Gonarthrosis	CC	1.02	1.04	0.66-1.58	0.41-2.60	>0.05
	CA	0.87	0.79	0.51-1.48	0.31-1.99	>0.05
	AA	2.21	2.32	0.28-17.42	0.27-20.42	>0.05
Coxarthrosis	CC	1.10	1.24	0.67-1.82	0.39-3.89	>0.05
	CA	1.09	1.16	0.56-2.12	0.37-3.67	>0.05
	AA	–	–	–	–	–
Small joints	CC	0.85	0.72	0.43-1.67	0.20-2.55	>0.05
	CA	1.16	1.30	0.58-2.35	0.37-4.62	>0.05
	AA	1.24	1.27	0.16-9.38	0.14-11.63	>0.05

Note. OA – osteoarthritis; FDDJ – functional disorders degree of the joints; *RelR* – relative risk; *OR* – Odds Ratio; *95%CI RR, OR* – 95% confidence interval (*RR*), (*OR*).

The genotype and the allele frequency of polymorphic gene site *IL-10* (*C-592A*) (*rs*1800872) in the examined group did not differ from the ones for the Caucasian populations (P_C=0.78-0.84, P_A=0.16-0.22 against P_C=0.76-1.0 and P_A=0.16-0.24 accordingly, p>0.05). However, the minor A-allele frequency in our studies happened to be significantly higher and the C-allele frequency – lower than in the Asian populations (P_A=0.46-0.75, P_C=0.23-0.54; p<0.05) and Equatorial races (P_A=0.44-0.50, P_C=0.50-0.66; p<0.05) respectively[26].

Riyazi N et al reported that the IL-10 single nucleotide promoter polymorphism (SNP) (-2849, –276 3, –1330, –1082, –819, and –592) is associated with differential corresponding cytokines reduction, but does not play a major role in the susceptibility of distal interphalangeal OA in the Dutch population[27]. Similarly, in other research, Satu Hämäläinen et al. did not find significant association between IL10 SNP –1082 and hand OA[28].

Thus, our results suggest that the polymorphic variants of studied genes *MATN3* (rs77245812) and *IL-10* (*rs*1800872) may play an important role in the etiology and the pathogenesis of OA, but did not increase the suggestive risk of the disease in observed population of Northern Bukovina.

Limitations of the Study. The present study was limited by the small number of enrolled subjects.

Conclusions

1. *IL-10* (rs1800872) gene mutation in the homozygous state among the adult OA patients of Northern Bukovina appears with a frequency of 9.46%, whereas among the healthy population is almost absent. Among the examined genes, the wild C-allele of *IL-10* gene dominates over the *A*-allele: by 56.76% in OA patients, by 68% – in the control group.

2. Homozygous state of *MATN3* (rs77245812) gene mutation in the observed population did not occur at all. The wild C-allele prevails over the *T*-allele by 94.95%: among the OA patients – 97.30% vs 2.70%, in control group – 98.0% vs 2.0% accordingly (p<0.001).

3. Polymorphic variants of *MATN3* (rs77245812) and *IL-10* (*rs*1800872) genes are not additional risk factors for the OA occurrence in the observed population of Northern Bukovina.

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