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Original scientific paper

ASSOCIATION OF RHEUMATOID ARTHRITIS ACCORDING TO THE DEGREE OF GENETIC HOMOZYGOSITY AND GENDER: PILOT STUDY

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Rheumatoid arthritis (RA) is a chronic synovial inflammatory autoimmune disease with multifactorial origin. With epigenetic and genetic mechanisms playing a role in the development of RA, **t**he aim of our study was to evaluate the anthropogenetic variability in tested individuals that were diagnosed with rheumatoid arthritis, and the possible influence of gender in expression of illness. 100 patients with rheumatoid arthritis (RA) and 100 healthy control individuals were evaluated. For the estimation of the degree of recessive homozygosity, the homozygously recessive characteristics (HRC) test was performed testing 20 HRCs. There was a significant difference in the individual variations of 20 HRCs between the individuals of the control group and patients with RA (ΣX^2=135.191; p<0.001). The mean values of the tested HRCs significantly differed between individuals of the control group and RA group ($MV \pm SD_{Control\ group}$-5.97±2.02, $MV \pm SD_{RA\ group}$-7.34±2.00, p=<0.001). There was a decrease in variability in the RA group versus the control group ($V_{RA\ group}$=27.19%; $V_{Control\ group}$=33.79%).There was significant difference in the frequencies of HRCs between those with and without RA in males (p<0.023) and in females (p<0.001). Our findings pointed to the higher degree of recessive homozygosity along with decreased variability in RA patients compared to a

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healthy control group. Therefore, it may be assumed that different genes in different proportions have certain influence in the processes responsible for RA susceptibility and its different degrees of expression.

Key words: gender, genetic homozygosity, rheumatoid arthritis, variability

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic synovial inflammatory autoimmune disease with multifactorial origin (FIRESTEIN, 2018; ARAKI, MIMURA, 2016). Recently, it was stressed that epigenetic mechanisms might play the potential role in the development of RA (ARAKI, MIMURA, 2016). Such condition affects around 1% of the human population, seen more commonly in females (ARAKI, MIMURA, 2016). Although class II major histocompatibility complex (MHC) genes, mainly HLA-DR were suggested to have the most dominant influence, there is still ongoing search for genetic variance (FIRESTEIN, 2018). So far, more than 100 genetic loci were noticed to be associated with RA (YARWOOD *et al.*, 2016). Several studies including meta-analyses, demonstrated association between certain gene polymorphisms and susceptibility to RA (BERCZI *et al.*, 2017; LI *et al.*, 2017; LU *et al.*, 2018). However, it should be underlined that RA has subclinical stages before the clinical onset of the symptoms, thus it was proposed that genetic factors, along with stochastic risk factors might interact in the transition between different stages of the disease (YARWOOD *et al.*, 2016). Worth mentioning are the different groups of RA, which include seropositive and seronegative (YARWOOD *et al.*, 2016). Lack of the more precise role of genetic factors in the development of RA, could be referred to the fact that different phenotypes of such condition could correlate to different genotypes (WEYAND *et al.*, 1998). The studies dealing with the investigations of prediction risk for RA pointed out high specificity (80-90%) but lower sensitivity (around 40%) in detection of those with a high risk (YARWOOD *et al.*, 2016).

The genes that are know so far to be involved in susceptibility to RA are 6q30 (OMIM number 180300), 7q15.3, and 22q11.23 (OMIM number 604302) (OMIM). However, in a genome-wide meta-analysis of ETZEL *et al.* (2006) strong evidence for RA was pointed on chromosomes 8 and 16, and in the HLA region on the chromosome 6.

Assuming that RA could have genetically controlled susceptibility, we hypothesized that an increase of genetic homozygosity level along with changed variability in the group of patients with RA, could be a population-genetic parameter for predicting such condition.

The aim of our study was to evaluate the anthropogenetic variability in tested individuals that were diagnosed with rheumatoid arthritis and the possible influence of gender in expression of illness.

MATERIAL AND METHODS

Study group

We evaluated 100 patients that were diagnosed with rheumatoid arthritis at the Institute for Rheumatology, and an additional 100 healthy individuals in this cross-sectional study through 2017-2018. All participants (patients and controls) were of similar age, socioeconomic status and belonged to the same ethnic group (Serbian population). Both, healthy individuals from the control group and patients from RA group were chosen randomly by computer (method of simple random sampling). Prior to enrollment in the study, eligible participants were informed and consent was obtained. The study followed the principles of good clinical practice and Declaration of Helsinki.

Rheumatoid arthritis was diagnosed by Board certified physicians in the Rheumatology Institute through clinical examination, biochemical analyses and imaging methods. Healthy control individuals were assessed as well in order to exclude the presence of RA. We have additionally evaluated both groups separately for gender (males and females).

Study methods

In order to estimate the degree of recessive homozygosity and variability in the healthy control group and patients with RA, the homozygously recessive characteristics (HRC) test was applied (MARINKOVIC *et al.,* 1990; MARINKOVIC, CVJETICANIN, 1991; MARINKOVIC, CVJETICANIN, 2013). The HRC test was used for assessing the proportion of clearly expressed homozygously recessive characteristics, which are considered as qualitative traits in every individual, indicating the degree of genetic homozygosity in humans (CVJETICANIN, MARINKOVIC, 2005; CVJETICANIN, MARINKOVIC, 2005; MARINKOVIC *et al.,* 2008; NIKOLIC *et al.,* 2009; PETRICEVIC, CVJETICANIN, 2011; MARINKOVIC, CVJETICANIN, 2013; BRANKOVIC, CVJETICANIN, 2016). Considering that the HRCs tested are the markers of genes located on different chromosomes (CVJETICANIN, MARINKOVIC, 2009), insight into the prevalence of homozygous or heterozygous loci on different chromosomes could be determined. The HRCs tested are the markers of genes that are located on different chromosomes (CVJETICANIN, MARINKOVIC, 2009). It is performed by direct observation of tested phenotype traits, and is a reliable method for the estimation of the individual and group homozygosity of populations (MARINKOVIC *et al.,* 1990; MARINKOVIC, CVJETICANIN, 1991; MARINKOVIC, CVJETICANIN, 2013; CVJETICANIN, MARINKOVIC, 2005; CVJETICANIN, MARINKOVIC, 2005; MARINKOVIC *et al.,* 2008; PETRICEVIC, CVJETICANIN, 2011; BRANKOVIC, CVJETICANIN, 2016; NIKOLIC *et al.,* 2009; CVJETICANIN, MARINKOVIC, 2009). In order to maintain the same objectivity and equal criteria for determination of tested HRCs, one individual performed the testing.

Tested determinants

We tested the presence of 20 HRCs in both groups of individuals, where only the characteristics with extreme appearances were noted as the present trait. In the region of the human head, we tested 13 HRCs: attached ear lobe (OMIM number 128900), continuous frontal hair line (OMIM number 194000), blue eyes (gene location 15q12, 15q13, OMIM number 227220; 5p13 OMIM number 227240; 14q32.1, OMIM number 210750; 9q23 OMIM number 612271), straight hair (1q21.3, OMIM number 139450), soft hair and blond hair (gene location 15q12, 15q13, OMIM number 227220; 14q32.1, OMIM number 210750; 12q21.3 OMIM number 611664; 11q13.3, OMIM number 612267), double hair whorl, opposite hair whorl orientation (OMIM number 139400), an inability to roll, fold and curve the tongue (OMIM number 189300), ear without Darwinian notch, ability to produce a guttural "r" and color blindness (gene location Xq28, OMIM number 303800). In the region of human arms, we tested 8 HRCs: proximal thumb hyperextensibility, index finger longer than the ring finger in males and index finger shorter than the ring finger in females (OMIM number 136100), left-handedness (gene location 2p12-q22, OMIM number 139900), right thumb over left thumb (hand clasping) (OMIM number 139800), top joint of the thumb >45 degrees, three tendons in the wrist and thumb backward movability (OMIM).

Statistical analysis

HRC frequencies in individuals of the control group and patients of the RA group were presented as whole numbers and percentages, while continuous variables as mean values (MV) and standard deviation (SD). The chi-squared test (X^2) was used to compare frequencies of HRCs between individuals from the control group and RA group. The variation coefficient (V) was used to compare variability between studied groups. The Mann – Whitney U test was used to compare the HRC mean values between the control group and RA group in the total sample, as well as the males and females in the control group and RA group. For the estimation of correlation between tested variables we used the effect size (Cohen's d) parameter. An odds ratio (OR) was used to evaluate the strength of association of the significant predictors separately for every tested HRC, and for the number of HRCs between tested groups. Statistical significance was set on $p<0.05$.

RESULTS

In Table 1, the distribution of HRC frequencies for the control group and patients with rheumatoid arthritis was presented. There were 7 HRCs that significantly differed, of which 5 (straight hair, soft hair, inability to roll tongue, right thumb over left thumb and index finger shorter than the ring finger Females) occurred significantly more frequently in patients with rheumatoid arthritis, while 2 (blond hair and index finger longer than the ring finger Males) occurred significantly more frequently in the control group. There was a significant difference in the individual variations of 20 HRCs between individuals of the control group and patients with rheumatoid arthritis ($\Sigma X^2=135.191$; degrees of freedom (df)=20, $p<0.001$) (Table 1).

Table 1. Frequencies of homozygously recessive characteristics among individuals of control group and patients with rheumatoid arthritis.

HRC	Control group N = 100, n (%)	RA group N = 100, n (%)	X^2	OR (95% CI)
Blond Hair	19 (19)	10 (10)	4.263*	2.11 (0.93-4.81)
Straight Hair	44 (44)	63 (63)	8.205**	0.46 (0.26-0.81)*
Double Hair Whorl	14 (14)	18 (18)	1.143	0.74 (0.35-1.59)
Opposite Hair Whorl	19 (19)	9 (9)	5.263*	2.37 (1.02-5.54)
Soft Hair	40 (40)	52 (52)	3.600	0.62 (0.35-1.08)
Continuous Frontal Hairline	29 (29)	40 (40)	4.172*	0.61 (0.34-1.10)
Attached Ear Lobe	31 (31)	34 (34)	0.290	0.87 (0.48-1.58)
Ear without Darwinian Notch	36 (36)	30 (30)	1.000	1.31 (0.73-2.37)
Blue Eyes	32 (32)	39 (39)	1.531	0.74 (0.41-1.32)
Colour Blindness	3 (3)	2 (2)	0.333	1.52 (0.25-9.27)
Speaking Deficiency	5 (5)	2 (2)	1.800	2.58 (0.49-13.62)
Inability to Curve Tongue	45 (45)	57 (57)	3.200	0.62 (0.35-1.08)
Inability to Roll Tongue	48 (48)	88 (88)	33.333***	0.13 (0.06-0.26)***
Right Thumb over the Left Thumb	35 (35)	54 (54)	10.314**	0.46 (0.26-0.81)*
Top Joint of the Thumb >45 degrees	28 (28)	37 (37)	2.892	0.66 (0.36-1.20)
Proximal Thumb Hyperextensibility	23 (23)	21 (21)	0.174	1.12 (0.58-2.20)
Thumb Backward movability	25 (25)	17 (17)	2.560	1.63 (0.82-3.25)
3 tendons in the wrist	73 (73)	89 (89)	3.507	0.33 (0.16-0.72)**
Left-handedness	9 (9)	4 (4)	2.778	2.37 (0.71-7.98)
Index finger longer than the ring finger - Males	9 (9)	3 (3)	4.000*	3.20 (0.84-12.18)
Index finger shorter than the ring finger - Females	30 (30)	65 (65)	40.833***	0.23 (0.13-0.42)***
				$\Sigma X^2 = 135.191$***

*p<0.05; **p<0.01; ***p<0.001

The mean values of the tested HRCs significantly differed between individuals of the control group and RA group ($MV\pm SD_{Control\ group}$ - 5.97±2.02, $MV\pm SD_{RA\ group}$ - 7.34±2.00, z=4.515, p=<0.001), with the effect size between groups being 68.16% (Figure 1). The most frequent average number of HRCs in the control group was 5 (23%), while for those with rheumatoid arthritis it was 8 (22%) (Figure 1).

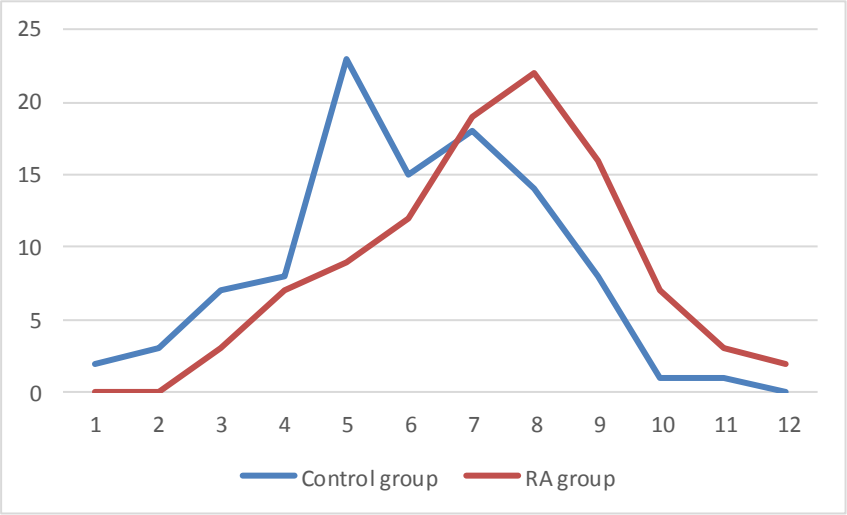

Figure 1. Frequencies of homozygous recessive characteristics (HRC) in controls and RA patients. MV- mean value; SD- standard deviation; z- Mann Whitney U test; V-variability. Control group: N=100, MVS±D=5.97±2.02. RA group: N=100, MV±SD=7.34±2.00 (z=4.515, p<0.001; Cohen's d=68.16%). $V_{Control\ group}$=33.79%, $V_{RA\ group}$=27.19%.

For the control group, the mean values of the tested HRCs did not differ significantly between males and females ($MV\pm SD_{Males}$ - 5.95±2.00, $MV\pm SD_{Females}$ - 5.98±2.05, z=0.094, p=0.928), with the effect size between groups being 1.48% (Figure 2). The most frequent average number of HRCs in males of control group was 5 (30.23%), while for females of the control group 5,6 and 8 HRCs had equivalent frequencies (17.54%) (Figure 2).

For the RA group, the mean values of the tested HRCs did not differ significantly between males and females ($MV\pm SD_{Males}$ - 7.32±2.08, $MV\pm SD_{Females}$ - 7.35±1.99, z=-0.132, p=0.897), with the effect size between groups being 1.47% (Figure 3). The most frequent average number of HRCs in males of RA group was 7 and 9 (21.05%), while for females of RA group it was 8 (24.69%) (Figure 3).

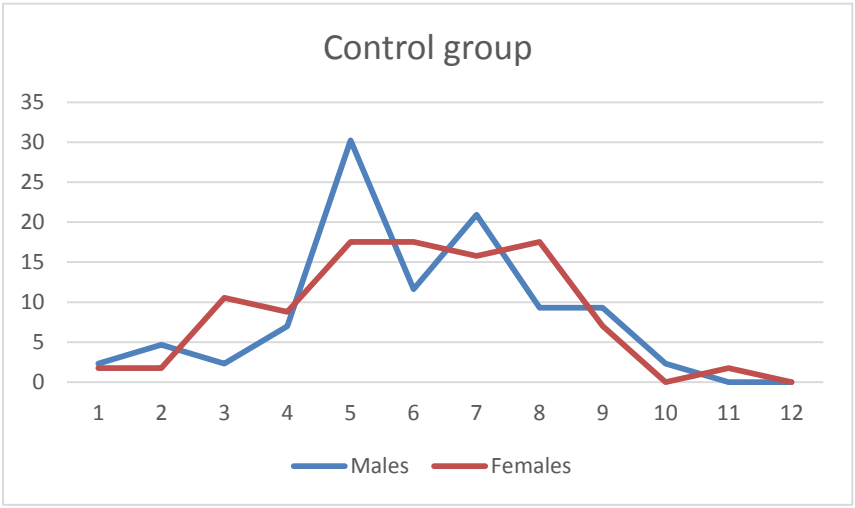

Figure 2. Frequencies of homozygous recessive characteristics (HRC) in Control group regarding gender. MV- mean value; SD- standard deviation; z- Mann Whitney U test; V-variability. Males: N=43, MVS±D=5.95±2.00. Females: N=57, MV±SD = 5.98±2.05 (z=0.094, p=0.928; Cohen's d=1.48%). V_{Males}=33.58%, $V_{Females}$=34.24%.

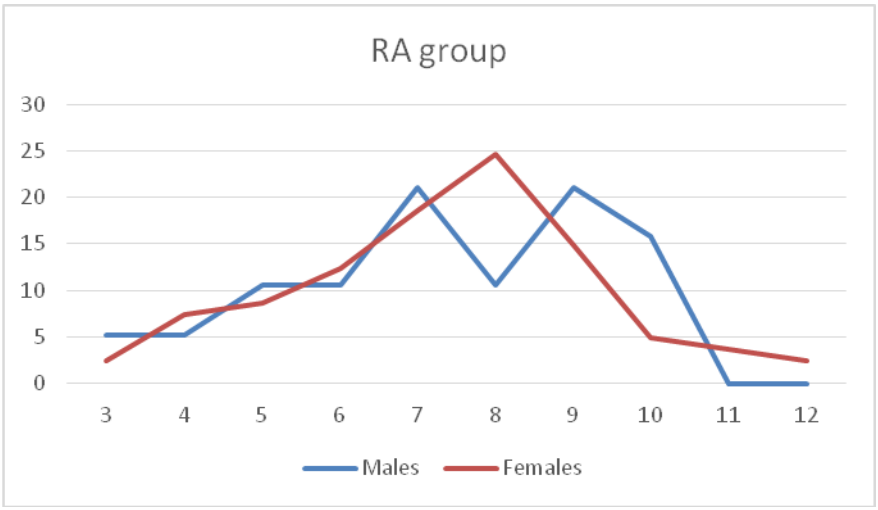

Figure 3. Frequencies of homozygous recessive characteristics (HRC) in RA group regarding gender. MV- mean value; SD- standard deviation; z- Mann Whitney U test; V-variability. Males: N=19, MVS±D=7.32±2.08. Females: N=81, MV±SD=7.35±1.99 (z=-0.132, p=0.897; Cohen's d=1.47%). V_{Males}=28.47%, $V_{Females}$=27.06%.

We found a significant difference in the frequencies of HRCs between those with and without rheumatoid arthritis in males ($p<0.023$) and in females ($p<0.001$) (Table 2). The effect size between the groups for males was 67.14%, while for females it was 67.81% (Table 2).

Table 2. Statistical evaluation of frequencies of homozygous recessive characteristics between groups with regards to the presence of rheumatoid arthritis.

Gender	Control group/ RA group		
	Z*	p	Cohen's d (%)
Males	-2.283	0.023	67.14
Females	3.580	<0.001	67.81

*Mann Whitney *U* test

In Table 3, we presented an association between the frequencies of HRCs between controls and rheumatoid arthritis group regarding gender. For males, 10 HRCs was the highest predictor (OR=0.13) for rheumatoid arthritis. For females, 9 HRCs (OR = 0.43) and 11 HRCs (OR = 0.46) were the highest predictors for the development of rheumatoid arthritis (Table 3).

Table 3. Association between frequencies of homozygous recessive characteristics between controls and rheumatoid arthritis group regarding gender.

No. of HRCs	OR (95% CI)	
	Males (Control group/ RA group)	Females (Control group/ RA group)
1	-	-
2	-	-
3	0.43 (0.03-7.24)	4.65 (0.90-23.92)
4	1.35 (0.13-13.88)	1.20 (0.35-4.15)
5	3.68 (0.74-18.30)	2.25 (0.80-6.32)
6	1.12 (0.20-6.35)	1.51 (0.58-3.91)
7	0.99 (0.26-3.74)	0.83 (0.33-2.04)
8	0.87 (0.15-5.22)	0.65 (0.28-1.52)
9	0.38 (0.09-1.74)	0.43 (0.13-1.42)
10	0.13 (0.01-1.31)	-
11	-	0.46 (0.05-4.58)
12	-	-

DISCUSSION

So far, there is no clear consensus regarding the exact role of genetic and/or environmental factors in susceptibility and development of RA. Previous studies and meta-analyses have demonstrated the influence of numerous loci on different chromosomes on RA development (ETZEL *et al.*, 2006; OKADA *et al.*, 2012; STAHL *et al.*, 2010). Further, it was shown that in different ethnic groups different genes might have influence on RA susceptibility (YARWOOD *et al.*, 2016).

The tested HRCs that are used in this study as markers of the degree of homozygosity, indicate the amount of genetic loads that are present in the evaluated group of patients with RA. The degree of recessive homozygosity for RA patients is significantly higher than in the control group of healthy individuals.

Our results pointed to the presence of a different distribution for certain tested individual HRCs between studied patients with RA and healthy control individuals. Among the tested HRCs, 5 of them were significant predictors, with the highest strength of association for RA susceptibility being the inability to roll the tongue. Such findings imply to a certain degree that possible intrinsic changes could exist between two groups (control group and RA group) on the population genetic level, pointing that there might be the possibility that preferential phenotypes could have certain influence in the development of RA. Furthermore, in tested patients with RA, the genes that are controlling the expression of HRCs, could have an influence of different degrees to the susceptibility for RA development and expression (CVJETICANIN, MARINKOVIC, 2009).

In the study of PETRICEVIC *et al* (2011), it was suggested that genes which are responsible for the expression of certain phenotype traits along with environmental risk factors could potentially have an influence for the development of certain diseases and conditions interacting in the different degrees by multifactorial mechanisms or through mutations on genes which are responsible for the control of homozygous recessive traits expression (PETRICEVIC, CVJETICANIN, 2011).

In the group of RA patients, about every third of the 20 studied traits was expressed as homozygously recessive, which is significantly higher compared to the healthy control group, where every fourth trait was homozygously recessive. Further, in the RA group of patients, the variability for tested genes decreased when compared to the healthy control group. Such findings strongly stress towards the presence of significant population-genetic differences between tested samples of individuals. A higher degree of genetic homozygosity and lower variability in the RA group might bring these individuals into a specific state of genetic-physiological homeostasis enabling easier development and expression of such pathological condition. It should be mentioned as well that an increase in genetic homozygosity may enlarge the degree of genetic load in an individual that will potentially cause a decrease in body immunity (SAVIC *et al.*, 2010), altering predisposition levels for RA expression.

Our findings pointed to the non-significant increase of the degree of recessive homozygosity in RA females versus RA males, along with decreased variability in RA females. We may presume that decreased variability for tested genes in females somehow have an influence of easier expression of RA which is in correlation with the fact that female individuals are 3 times more affected with RA. These results might also point to the assumption that preferential phenotypes could exist and that there could be the possible role of gender for the predisposition for RA, even though there was a non-significant difference in the degree of recessive homozygosity. Such absence in the wider discrepancy regarding recessive homozygosity degrees between genders of RA patients, could be in the potential influence of both gender and environmental factors. Despite the fact that more frequent presentation in females of such condition is still not fully understood, with a female to male ratio of 3:1, it is proposed that hormonal and genetic (X-linked) factors are likely to have an influence of certain degree (VAN VOLLENHOVEN, 2009). This hypothesis might be supported further by the findings of our study, where we noticed a significantly higher increase in the degree of recessive

homozygosity between females of the RA and control group, as compared to males of the RA and control groups.

The presence of the increased degree of recessive homozygosity as well as relatively decreased variability for tested genes in studied individuals with RA, could be the result of the pleiotropic effects of genes that are responsible for the expression of certain morpho-physiological traits (CVJETICANIN, MARINKOVIC, 2005; CVJETICANIN, MARINKOVIC, 2005; CVJETICANIN, MARINKOVIC, 2009).

This study has several limitations. The first limitation refers to the population representation, where individuals only from one (Serbian) population were studied. Possible presence of specific variations (environmental and/or genetic) in different populations should be taken into future studies. Additionally, the number of patients might be considered as a limiting factor, thus, larger sample studies are advised.

In conclusion, our findings pointed to the higher degree of recessive homozygosity along with decreased variability in RA patients when compared to a healthy control group. Thus, it could be assumed that different genes in different proportions have certain influence in the processes responsible for RA susceptibility and its different degree of expression.

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POVEZANOST REUMATOIDNOG ARTRITISA I STEPEN GENETIČKE HOMOZIGOTNOSTI U ODNOSU NA POL: PILOT STUDIJA

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Izvod

Reumatoidni artritis (RA) je hronična autoimuna bolest koja nastaje zbog upale sinovijuma sa etijologijom multifaktorskog porekla. Imajući u vidu epigenetičke i genetičke mehanizme koji imaju ulogu u razvoju RA, cilj našeg istraživanja je da se proceni antropogenetička varijabilnost u ispitivanih osoba kojima je dijagnostikovan reumatoidni artritis, kao i mogući uticaj pola na izražavanje bolesti. Ispitivano je 100 pacijenata sa RA i 100 zdravih kontrolnih osoba. Za procenu stepena genetičke homozigotnosti, korišćen je test homozigotno recesivnih osobina (HRO) na 20 HRO. Pokazano je da postoji značajna razlika u individualnim varijacijama 20 HRO između pojedinaca kontrolne grupe i pacijenata sa RA (ΣX^2=135,191; p<0,001). Srednje vrednosti testiranih HRO značajno su se razlikovale između osoba iz kontrolne grupe i RA grupe ($MV \pm SD_{Kontrolna\ grupa}$-5,97±2,02, $MV \pm SD_{RA\ grupa}$-7,34±2,00, p=<0,001). Smanjenja varijabilnosti je pokazana u RA grupi u odnosu na kontrolnu grupu ($V_{RA\ grupa}$=27,19%; $V_{Kontrolna\ group}$=33,79%). Postojala je značajna razlika u učestalosti HRO između osoba sa i bez RA kod muškaraca (p <0,023) i kod žena (p <0,001). Naši nalazi ukazuju na viši stepen genetičke homozigotnosti, zajedno sa smanjenom varijabilnosti u RA bolesnika u odnosu na kontrolnu grupu. Rezultati naše studije ukazuju na to da se može pretpostaviti da različiti geni u različitom stepenu imaju određeni uticaj na procese koji su odgovorni za razvoj RA u odnosu na pol.

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