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Original scientific paper

MORPHOGENETIC VARIABILITY AND GENETIC LOADS AMONG PATIENTS WITH DIFFERENT EXPRESSION OF DEVELOPMENTAL HIP DYSPLASIA

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Assuming that developmental hip dysplasia (DDH) is a genetically controlled disease, we made a hypothesis that an increased homozygosity level and genetic loads, among the patients with DDH, could be some kind of predisposition for the degree of illness expression. Using HRC-test (test for determination of homozygously recessive characteristics in humans) we analyzed presence, distribution, and individual combination of 20 selected genetically controlled morphophysiological traits among DDH patients (N=200) and controls (N=200). Among groups of DDH patients the increase in the degree of genetic homozygosity correlates with the degree of illness expression (dysplasia/subluxations-39%; luxations-45%). There is significant difference in mean HRC value between tested groups of patients with dysplasia/luxations ($p<0.05$) and subluxations/luxations ($p<0.05$). Our results showed increase of morphogenetic homozygosity in the group of patients with bilateral hip dislocation (BL) (45%), compared to group with unilateral expression (UL) (41%) and control (23.5%). There is significant difference in mean HRC value between tested groups of patients with UL and BL ($p<0.05$). Also, surgically treated patients showed significant increase of genetic homozygosity (43%) compared to those conservatively treated (37%) and controls. We found significant difference in mean HRC value between tested groups of patients that were treated conservatively and surgically

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($p<0.05$). Our results showed increase of genetic homozygosity in the groups of DDH female patients (44%), compared to male patients (39%), while in controls there was no difference between gender. Female DDH patients show a significant increase in average homozygosity of tested genetic markers ($p<0.05$) than male DDH patients. The enlargement of genetic loads correlates with severity of the disease (in studied groups of DDH patients) which may indicate some kind of predisposition for the degree of illness expression.

*Key words***:** developmental hip dysplasia, genetic loads, homozygously recessive characteristics, morphogenetic variability

INTRODUCTION

Developmental hip dysplasia (DDH) is congenital malformation caused by abnormal development of hip joints and associated structures resulting in hip joint instability and abnormal seating of the femoral head in the acetabulum. This prenatal malformation may be expressed in different forms of severity, as a dysplasia, subluxation and luxation as the most severe form of the disease. Also DDH may appear in one or both hip joints as unilateral or bilateral dysplasia, as more severe form. Female individuals are about five times more affected than males (CVJETICANIN and MARINKOVIC, 2005a; HIGUCHI, 1984; WEINSTEIN, 1987).

DDH is polygenically determined (CARTER and WILKINSON, 1964) and because various environmental factors have influence to the expression of this malformation, numerous scientists suggest multifactorial type of inheritance (CVJETICANIN and MARINKOVIC, 2005a; EIDELMAN *et al.*, 2002; HIGUCHI, 1984; LI *et al.*, 2013; WYNNE-DAVIES, 1970). Familial segregation studies point out, as well, that DDH is a multifactorial inherited malformation (LI *et al.*, 2013; STEVENSON *et al.*, 2009) and that genetic factors play the primary role in the expression of the malformation. There is misunderstanding whether dysplasia or laxation of ligaments is being inherited, but most researchers assume that both of these phenomena should be observed together (WYNNE-DAVIES, 1970). Some scientists support the opinion that DDH (acetabular dysplasia) is a single gene disorder[6] and while some researchers point to the autosomal dominant inheritance (FELDMAN *et al.*, 2013; HORTON *et al.*, 1979; MABUCHI *et al.*, 2006), others indicate that abnormality is probably inherited as autosomal recessive (SOLLAZZO *et al.*, 2000).

The genes which are so far known to be involved in determining susceptibility to DDH are 13q 22, 3p 21, 4q 35 (OMIM 142700) (OMIM).

On the assumption that DDH could have genetically controlled predispositions, we hypothesized that a generally increase genetic homozygosity level, as well as changed variability in the groups of patients with different expression of malformation, could be a population-genetic parameter for predicting such abnormality.

Only a small number of loci with allelic genes controlling an exact biochemical process are known, determining genetic homozygosity in humans is highly delicate. Provided the type of inheritance and variability Is known, it can be seen that a series of morphophysiological traits are controlled by one or several genes. Considering the above, by using the homozygous recessive characteristics (HRC) test several authors of Belgrade population-genetic school have studied the distribution and frequency of a series of highly expressed recessive morphophysiological traits in order to estimate individual and group differences (i.e. comparison between ill and healthy individuals, pupils from special and regular schools, carriers of different blood types etc.) (BLAGOJEVIC *et al.*, 1989; CVJETICANIN and MARINKOVIC, 2005a; CVJETICANIN and MARINKOVIC,

2009; MARINKOVIC *et al.*, 1990; MARINKOVIC *et al.*, 1994; MARINKOVIC *et al.*, 2007; MARINKOVIC *et al.*, 2008; MARKOVIC-DENIC *et al.*, 1992; NIKOLIC *et al.*, 2010; PETRICEVIC and CVJETICANIN, 2011).

Taking all this into account, our assumption was that groups of DDH patients with severe expression of malformation may have a higher degree of recessive homozygosity and a changed variability for tested allelic genes, when compared with the values present in general population and with groups of DDH patients with mild expression of abnormality. Also, we may presume that average homozygosity level is different between genders.

MATERIAL AND METHODS

The HRC-test has been developed to determine the proportion of such clearly expressed recessive characteristics in every individual, as markers of chromosomal homozygosities (MARINKOVIC *et al.*, 1990; MARINKOVIC *et al*,. 1994; MARINKOVIC and CVJETICANIN, 2013). HRC-test is a highly suitable method for estimating individual homozygosity, as it takes only a few of minutes to analyze the presence of 20 characteristics of the person observed. In this study HRC-test was methodology applied to estimate the recessive homozygosity level in a series groups of DDH patients showing different expression of malformation. Comparative analyses were made by the same person, with equal criteria for determining extremely pronounced homozygously recessive characters in tested groups of observed individuals. The presence of the studied genetically controlled recessive characteristics was used as a parameter for homozygosity of corresponding genes and chromosomes.

The tested homozygously recessive characters are obviously controlled by genes located on different human chromosomes; thus they could be considered genetic markers on these chromosomes, as well as on numerous surrounding genes controlling different fitness elements. The amount of recessive homozygosity established by our HRC-test is practically an estimation of genetic loads present in any specific sample of humans.

Tested homozygously-recessive traits in the region of human head are: unattached 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, hair whorl orientation-opposite from clock-wise (OMIM number 139400), as well as an inability to roll, fold and curve the tongue (OMIM number 189300), a guttural "r and Daltonism (gene location Xq28, OMIM number 303800) (ISCHICHARA, 1973; OMIM). Such homozygously-recessive traits are also clearly expressed in human arms and legs, such as distal or proximal hyperextensibility of the thumb, index finger shorter than the ring finger (OMIM number 136100), left-handedness (gene location 2p12-q22, OMIM number 139900), hand clasping pattern (OMIM number 139800) (OMIM).

Variations in presence of homozygously recessive traits were estimated by applying standard statistical procedures, and by comparing the means, variances, and the distribution shapes between different groups of DDH patients and control group.

Based on the DDH expression, tested subjects (N=200) were divided into the following categories: patients with hip dysplasia (D) - mild expression of DDH (N=44); patients with hip subluxation (S) - moderate expression of DDH (N=40) and patients with hip luxation (L) - severe

expression of DDH (N=116). According to the site of expression, patients were divided into: group with unilateral expression of DDH (UL) (N=132) and those with bilateral expression of DDH (BL) (N=68). Regarding treatment options, patients were grouped into those that were conservatively treated (CT) (N=29) and group that was surgically treated (ST) (N=171). Regarding gender subjects were grouped as: female DDH affected individuals (F_{DDH}) (N=152) and male DDH affected individuals (M_{DDH}) (N=48).

Control sample (C) was consisted of 200 randomly chosen school children from Belgrade. They were grouped regarding gender into: females control (FC) (N=74) and males control (MC) (N=126).

All groups of tested individuals (DDH patients and control) belong to the same age (between 3 and 16), locality and ethnic group (Serbian population).

Prior inclusion in the study, parents or legal guardians were informed about study protocol and informed consent was obtained. The study followed the principles of good clinical practice, was approved by Institutional Review Board of School of Medicine and was carried according to the Declaration of Helsinki.

Statistical analysis

For frequency and distribution presentation of recessive genetic homozygosity whole numbers and mean values (MV) with standard error of mean (SEM) was used. Comparison of mean values of HRC between DDH group and control group was done by Student's t-test. Comparisons of HRC mean values between groups of different expression of DDH, side of hip affection and gender we used students t-test. Variation coefficient (V) was used to compare variability between tested groups of individuals.

RESULTS

On examining the HRC frequency distribution in the group of DDH patients and the control group (Table 1), it is obvious that the mean value of HRC in the complete sample of affected individuals is significantly higher, while variability decrease comparing to the control group (DDH:8.5±0.2, C:4.7±0.2; V_{DDH}=32.6%, VC=54.2%). With regard to the distribution of HRC frequencies in the control group members and DDH affected individuals, it can be seen that HRC values in the group of DDH patients show tendency towards higher values, suggesting that significant population-genetic differences exist between the two tested samples (Figure 1).

Table 1. Distribution of mean HRC values based on the study of 20 qualitative morpho-physiological traits in the groups of DDH affected individuals and in control group

	Control	DDH affected	D group	S group	L group
_ N	200	200	44	40	116
$\bar{x}_{HRC/20}$ (MV±SEM)	4.7±0.2	8.5±0.2†	7.9±0.4$^{\dagger\dagger;\P;\P\P}$	7.7±0. 2$^{\dagger\dagger\dagger;\S\S}$	9.0±0.3§
HRC (%)	23.5%	42.5%	39.5%	38.5%	45.0%
V (%)	54.2%	32.6%	32.4%	19.3%	34.4%

HRC-homozygous recessive characteristics; DDH-developmental hip dysplasia; MV-mean value; SEM-Standard error of Mean; V-Variation coefficient; D-dysplasia; S-subluxation; L-luxation; Students t-test: †C/DDH=14.05**; ††C/D=7.32**; †††C/S=6.93**; §C/L=13.26**; ¶D/S=0.47; ¶¶D/L=2.22*; §§S/L=2.70*; *p<0.05, **p<0.0001

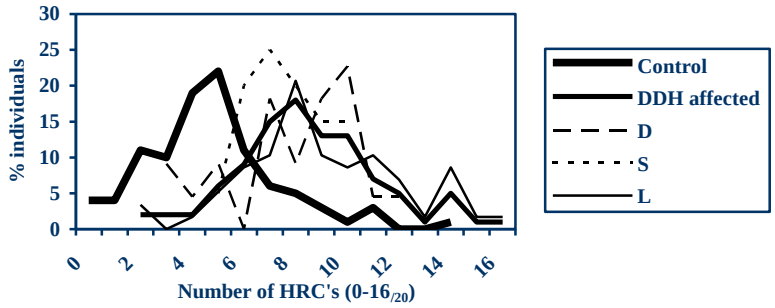

Figure 1. Distribution of homozygously-recessive characteristics (HRC-test) based on the study of 20 qualitative morpho-physiological traits in the groups of DDH affected individuals (dysplasia (D); subluxation (S); luxation (L)) and in control group

Distribution of average HRC values among DDH affected individuals with different expression of malformation (patients with hip dysplasia- mild expression of DDH, subluxation- moderate expression of DDH and luxation- severe expression of DDH) is presented in Table 1. Mean values of HRC in the all groups of DDH patients are significantly higher than in control group. Moreover, with the increase of severity of DDH expression, degree of genetic homoyzgosity also increase (C:4.7±0.2; D:7.9±0.4, S:7.7±0.2; L:9.0±0.3). The significant difference in mean HRC value is evident between tested groups of patients with D/L and S/L ($t_{D/L}$ =2.22, $t_{S/L}$=2.70; $p<0.05$), suggesting correlation in increase of genetic homozygosity with possible increase of genetic loads. In all tested groups with different severity of DDH expression, genetic variability for tested genes decrease compared with control (V_C=54.2%; V_D=32.4%; V_S=19.3%; V_L=34.4%).

As for the distribution of HRC frequency among the DDH patients with different expression of abnormality and control, it can be seen that HRCs systematically move towards higher values with an increase of DDH severity, suggesting that different genetic dispositions at the polygenic level exist among the tested samples (Figure 1).

Table 2. Distribution of mean HRC values in the groups of DDH patients regarding affection side and treatment option, and in the control sample of individuals

	Control	Hip affection		Treatment	
		UL group	BL group	CT group	ST group
_ N	200	132	68	29	171
$\bar{x}_{HRC/20}$ (MV±SEM)	4.7±0.2	8.2±0.3†,¶	9.0±0.3††	7.3±0.4§,‡	8.6±0.2§§
HRC (%)	23.5%	41.0%	45.0%	36.5%	43.0%
V (%)	54.2%	35.6%	26.4%	30.8%	32.1%

HRC-homozygous recessive characteristics; DDH-developmental hip dysplasia; MV-mean value; SEM-Standard error of Mean; V-Variation coefficient; UL-unilateral; BL-bilateral; CT-conservatively treated; ST-surgically treated; Students t-test: †C/UL=11.41**; ††C/BL=12.11**; ¶UL/BL=1.99*; §C/CT=5.21**; §§C/ST=14.18**; ‡CT/ST=2.39*; *p<0.05, **p<0.0001

Distribution of mean HRC values in the groups of DDH patients regarding the presence of unilateral (UL) or bilateral (BL) hip affections is present in Table 2. Mean HRC values significantly increase in both groups of DDH patients (UL, BL) compared with control (C:4.7±0.2; UL:8.2±0.3, BL:9.0±0.3). The significant difference in mean HRC value is evident between tested groups of patients as well ($t_{UL/BL}$=1.99; $p<0.05$), suggesting correlation in increase of genetic homozygosity with possible increase of genetic loads. With increase of genetic homozygosity and severity of DDH expression, genetic variability for tested genes decrease (V_C=54.2%; V_{UL}=35.6%; V_{BL}=26.4%).

Observing the distribution of the HRC frequencies among DDH patients with unilateral and bilateral malformation and in the control group it is obvious that HRCs in the both groups of affected individuals are moved towards higher values (Figure 2).

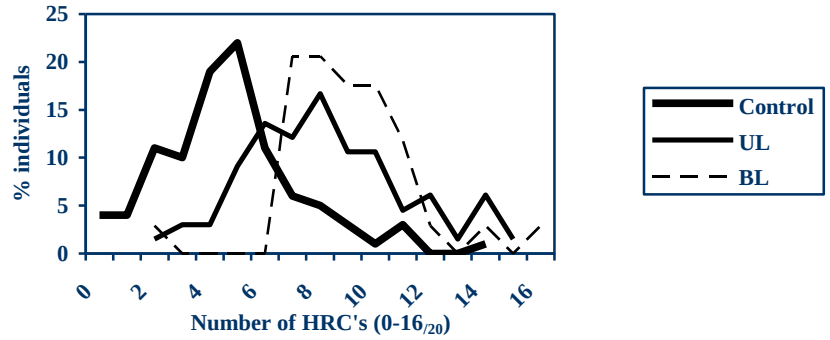

Figure 2. Distribution of mean HRC values in the groups of patients with unilateral (UL) and bilateral (BL) DDH and in the control sample of individuals

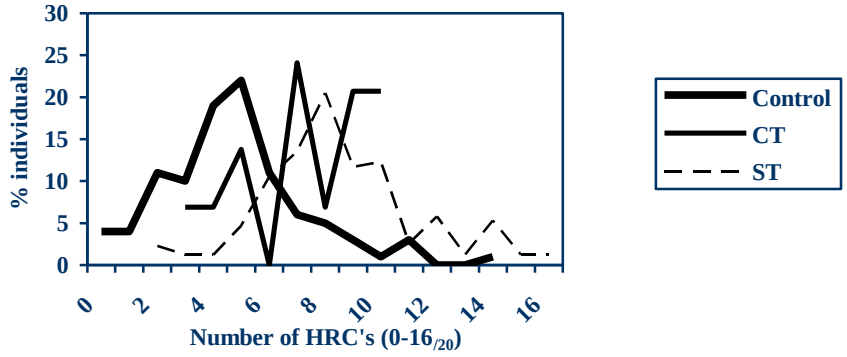

Figure 3. Distribution of mean HRC values in the groups of conservatively (CT) and surgically (ST) treated DDH patients and in the control sample of individuals

Distribution of mean HRC values in the groups of DDH patients who were treated conservatively (CT-individuals with mild expression of malformation) and those surgically treated (ST-individuals with severe expression of malformation) is present in Table 2. Mean HRC values significantly increase in both groups of DDH patients (CT, ST) compared with control (C:4.7±0.2; CT:7.3±0.4; ST:8.6±0.4). The significant difference in mean HRC value is evident between tested groups of patients too ($t_{CT/ST}$=2.39; $p<0.05$), suggesting correlation in increase of genetic homozygosity with increase of expression of malformation. With increase of genetic homozygosity and severity of DDH expression, genetic variability for tested genes decrease (V_C=54.2%; V_{CT}=30.8%; V_{ST}=32.1%).

With regard to the distribution of HRC frequencies in the control group members and DDH affected individuals who were treated conservatively and surgically, it can be seen that HRC values in the both group of DDH patients show tendency towards higher values. Also, correlation between severity of expression of abnormality and higher degree of genetic homozygosity is evident (Figure 3), what may suggest an increase of genetic loads in the groups with severe expression of malformation.

Results of our study have shown that girls are three times more affected than boys (152(76%)/48(24%)). It showed be noticed that average value of genetic homozygosity between genders in control group of individuals shows no difference, while in the group of DDH affected patients difference is significant (Table 3). Female DDH patients (F_{DDH}**)**, who are three times more affected than boys (M_{DDH}**)**, show an increase average homozygosity of such genetic markers (F_{DDH}: 8.7±0.2, M_{DDH}: 7.8±0.3; t=2.0; $p<0.05$), suggesting higher level of genetic loads too.

Table 3. Distribution of mean HRC values among gender in the groups of DDH patients and control

	Control		DDH group	
	Females	Males	Females	Males
_ N	74	126	152	48
$\bar{x}_{HRC/20}$ (MV±SEM)	4.9±0.3	4.7±0.3†	8.7±0.2	7.8±0.3§
HRC (%)	24.5%	23.5%	43.5%	39%
V (%)	43.4%	60.0%	33.6%	25.1%

HRC-homozygous recessive characteristics; DDH-developmental hip dysplasia; MV-mean value; SEM-Standard error of Mean; V-Variation coefficient; Students t-test: †FC/MC=0.06; $^{\S}F_{DDH}/M_{DDH}$=2.0*; *p<0.05

DISCUSSION

The homozygosity markers degree, used in this study to indicate amount of genetic loads present in all groups of DDH patients, is evidently higher than in control group of individuals. The twenty studied morpho-physiological characteristics are clearly the markers, whose genes, located at different chromosomes, manifest a general degree of homo- or heterozygosity in the cells of observed individuals.

In the complete sample of DDH patients, one out of two (1/2) of the 20 studied characters (i.e. 8.5±0.2) was expressed as homozygously recessive, what is significantly higher than in control group of individuals, where one out of four (1/4) tested traits was homozygously recessive (C:4.7±0.2; $t_{C/DDH}$=14.05, $p<0.0001$). Also, in the group of DDH patients variability for tested genes decrease comparing to the control group (V_{DDH}=32.6%, VC=54.2%). These results

strongly point to a significant population-genetic difference that exists between the two tested samples. A higher degree of genetic homozygosity and lower variability in the group of DDH patients may bring such organisms into a specific state of genetic-physiological homeostasis which enables easier appearance and expression of malformation. Increased genetic homozygosity may enlarge the genetic load degree, thus potentially causing decreased body immunity, which is a good predisposition for DDH expression.

Results of our study show also that in all groups of DDH patients with different expresion of abnormality degree (dysplasia, subluxation, luxation; unilateral versus bilateral DDH patients; and conservatively versus surgically treated individuals) genetic homozygosity is higher and variability for tested genes is lower than in control group of individuals. Moreover, the type of individual variation in the studied groups was significantly differed showing that their genetic dispositions were remarkably different.

Furthermore, results of this study show correlation between severity of expressed abnormality and higher degree of genetic homozygosity which points to systematic and visible changes in the genetic predispositions of the studied groups of DDH patients. Patients with hip luxation (severe degree of expressed malformation) have significantly higher amount of genetic homozygosity compared to the groups of patients with hip dysplasia and subluxation (mild and moderate level of expressed malformation; Table 1- $t_{D/L}$=2.22, $t_{S/L}$=2.70; $p<0.05$).

In the group of patients with both affected hips genetic homozygosity degree is significantly higher compared to the group of DDH individuals with one affected hip (Table 2- $t_{UL/BL}$=1.99; $p<0.05$). Finally, group of DDH patients who needed surgical treatment (severe degree of expressed malformation) show an additionally increased average homozygosity of such genetic markers compared with the group of patients conservatively treated with sucess (Table 2-$t_{CT/ST}$=2.39; $p<0.05$). Those results strongly implicate to the enlargement of genetic loads with increase of genetic homozygosity, suggesting a complex polygenic differences among observed systems, what may decrease body resistance and enables easier expression of different DDH forms.

Numerous clinical studies of DDH have shown that females are a few times more affected than males (CVJETICANIN and MARINKOVIC, 2005a; HIGUCHI, 1984; WEINSTEIN, 1987). In our study we established that proportion among affected females and males is 3:1 (152:48). According to the data presented in this study, the frequency distribution of the tested HRC was not different between genders in control group of individuals. But, it is interesting that female DDH patients who are three times more affected than males, show an increase of average homozygosity of such genetic markers compared with affected males (F_{DDH}:8.7±0.2, M_{DDH}:7.8±0.3, $t_{FDDH/MDDH}$=2.0; $p<0.05$), suggesting higher expressivity level of genetic loads too, what may be exeptional predisposition for DDH expresion. The facts we established in this study, may lead to a presumption that increase of genetic homozygosity and higher level of genetic loads as well as the genetic-physiological state of the female organism (i.e. functioning of some hormones and flexibility of pelvic bones and joints) are more suitable for expression of DDH (CVJETICANIN and MARINKOVIC, 2005a).

The genes which control the qualitative characteristics studied here are markers not only of different chromosomes but also of surrounding groups of polygenes which may have direct impact on the predisposition for DDH expression (CVJETICANIN and MARINKOVIC, 2005a; CVJETICANIN and MARINKOVIC, 2005b; MARINKOVIC and CVJETICANIN, 2013). The genes that determine expression of tested traits may influence to a certain degree the addaptive value of the

organism, and thus provide certain advantages or disadvantage in specific enviromental conditions (CVJETICANIN and MARINKOVIC, 2005a; CVJETICANIN and MARINKOVIC, 2005b; CVJETICANIN and MARINKOVIC, 2009; MARINKOVIC and CVJETICANIN, 2007; MARINKOVIC *et al.*, 2008; MARINKOVIC *et al.*, 2013; NIKOLIC *et al.*, 2010).

The significantly higher degree of genetic homozygosity and lower variability for tested genes in all groups of DDH patients, established in this study, may result in pleiotropic efects of specific genes responsible for expressing of DDH predisposition. In this case, these genes will determine not only the DDH expression, but a group of other properties as well.

The changes described here show that genetically controlled morhophysiological characters can be used to manifest, at population-genetic level, the intrinsic changes in samples of individuals differing from other such samples in their preferences or capabilities and probably also in their physiological and health capacities.

Given the facts above, it may be concluded that all groups of DDH patients with different expression of abnormality, as well as in gender, show the higher degree of recessive homozigosity and the lower variability for tested allelic genes, in comparison to the control group of individuals. Correlation between severity of DDH expression, on different levels, and increase of genetic homozygosity degree is evident.

Taking all this into account, even normal variations in physical abilities may be seen to correlate with their immune-genetic properties, as well as their variations in such morphophysiological traits.

Despite obtained results from our study, we should stress out study limitation that is referred to a different proportion between males and females in group of patients compared to control group.

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REFERENCES

BLAGOJEVIC, J., D. MARINKOVIC, Z. RADOVANOVIC (1989): Population-genetic study of Balkan endemic nephropathy in surrounding of Loznica. Genetika, *21:* 83-94.

CARTER, C.O., J.A. WILKINSON (1964): Genetic and environmental factors in the etiology of congenital dislocation of the hip. Clin. Orthop., *33:* 119-128.

CVJETICANIN, S., D. MARINKOVIC (2005a): Genetic variability in the group of patients with congenital hip dislocation. Russ. J. Genet., *41*: 936-940.

CVJETICANIN, S., D. MARINKOVIC (2005b): Genetic variability and frequencies of ABO blood types among different samples of patients from Serbia. Korean. J. Genetics, *27*: 35-40.

CVJETICANIN, S., D. MARINKOVIC (2009): Morphogenetic variability during selection of elite water polo players. J. Sports Sci., *27*: 941-947.

EIDELMAN, M., A. CHEZAR, V. BIALIK (2002): Developmental dysplasia of the hip incidence in Ethiopian Jews revisited: 7-year prospective study. J. Pediatr. Orthop. B., *11*: 290-292.

FELDMAN, G.J., J. PARVIZI, M. LEVENSTEIN, K. SCOTT, J.A. ERICKSON, P. FORTINA, M. DEVOTO, C.L. PETERS (2013): Developmental dysplasia of the hip: linkage mapping and whole exome sequencing identify a shared variant in CX3CR1 in all affected members of a large multigeneration family. J. Bone Miner. Res., *28*: 2540-2549.

HIGUCHI, F. (1984): Genetic study on the congenital dislocation of the hip. Bull. Tokyo Med. Dent. Univ., *31*: 195-207.

HORTON, W.A., R.N. SCHIMKE, J. KENNEDY, A. DE SMET (1979): Autosomal Dominant Inheritance of Congenital hip Dislocation. Am. J. Hum. Genet., *31*: 74A.

ISCHICHARA, S. (1973): Test for colour blindness. Kanehara Shuppa Co., Tokyo, Japan.

LI, L., K. SUN, L. ZHANG, Q. ZHAO, X. CHENG, Y. DANG (2013): Heritability and sibling recurrent risk of developmental dysplasia of the hip in Chinese population. Eur. J. Clin. Invest., *43*: 589-594.

MABUCHI, A., S. NAKAMURA, Y. TAKATORI, S. IKEGAWA (2006): Familial osteoarthritis of the hip joint associated with acetabular dysplasia maps to chromosome 13q. Am. J. Hum. Genet., *79*: 163-168.

MARINKOVIC, D., S. CVJETICANIN (2007): Population-genetic study of Balkan endemic nephropathy in Serbia. Russ. J. Genet., *43*: 942-946.

MARINKOVIC, D., S. CVJETICANIN (2013): Anthropogenetic homozygosity and adaptive variability. HRC-test in studies of human populations. (Monographs DCLXXII, Book 8) Serbian Academy of Sciences and Arts, Belgrade, Serbia.

MARINKOVIC, D., S. CVJETICANIN, M. STANOJEVIC (2008): Population genetic analyses of susceptibility to developing alcohol dependence. Addict. Res. Theory, *16*: 331-337.

MARINKOVIC, D., M. ILIC , B. SPREMO (1990): Studies of Human Population - Genetic Variation. Comparasion of Homozygously Recessive Traits in Attendants of Special and Regular Schools in Serbia. Arch. Biol. Sci., *42*: 11–12.

MARINKOVIC, D., D. JOVANOVIC, S. CVJETICANIN, M. SAVIC, S. BRANKOVIC (1994): Genetic Homozygosity and Normal vs. Pathological Human Variation. Genetika, *36*: 147–156.

MARKOVIC-DENIC, LJ., D. MARINKOVIC, S. JANKOVIC, Z. RADOVANOVIC (1992): Population Genetics Analyses of Chronic Lymphocytic Leukemia. Arch. Biol. Sci., *44*: 3–4.

NIKOLIC, D., S. CVJETICANIN, I. PETRONIC, B. JEKIC, R. BRDAR, T. DAMNJANOVIC, V. BUNJEVACKI, N. MAKSIMOVIC (2010): Degree of genetic homozygosity and distribution of ABO blood types among patients with spina bifida occulta and spina bifida aperta. Arch. Med. Sci., *6*: 854-859.

ONLINE MENDELIAN INHERITANCE IN MAN (OMIM): Retrieved from http://www.ncbi.nlm.nih.gov

PETRICEVIC, B., S. CVJETICANIN (2011): Morphogenetic variability and handedness in Montenegro and Serbia. Russ. J. Genet., *47*: 358-363.

SOLLAZZO, V., G. BERTOLANI, E. CALZOLARI, G. ATTI, C. SCAPOLI (2000): A two-locus model for non-syndromic congenital dysplasia of the hip (CDH). Ann. Hum. Genet., *64(Pt 1)*: 51-59.

STEVENSON, D.A., G. MINEAU, R.A. KERBER, D.H. VISKOCHIL, C. SCHAEFER, J.W. ROACH (2009): Familial predisposition to developmental dysplasia of the hip. J. Pediatr. Orthop., *29*: 463-466.

WEINSTEIN, S. (1987): Natural history of congenital hip dislocations (CDH) and hip dysplasia. Clin. Orthop. Rel. Res., *225*: 62-76.

WYNNE-DAVIES, R. (1970): A family study of neonatal and late-diagnosis congenital dislocation of the hip. J. Med. Genet., *7*: 315-333.

MORFOGENETIČKA VARIJABILNOST I GENETIČKA OPTEREĆENJA KOD PACIJENATA SA RAZLIČITIM STEPENOM EKSPRESIJE RAZVOJNOG POREMEĆAJA KUKA

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Izvod

Polazeći od činjenice da je razvojni poremećaj kuka (RPK) genetički kontrolisana malformacija, postavili smo hipotezu da uvećani stepen homozigotnosti i genetičkih opterećenja, kod pacijenata sa RPK, može biti na izvestan način predispozicija za različiti stepen težine ispoljenosti ove bolesti. Korišćenjem HRC-testa (test za utvrđivanje homozigotno recesivnih karakteristika kod ljudi) analizirali smo prisustvo, distribuciju i individualnu varijabilnost 20 selektovanih genetički kontrolisanih morfofizioloških karakteristika kod pacijenata sa RPK (N=200) i u kontrolnom uzorku (N=200). Među ispitivanim grupama pacijenata sa RPK, uvećanje stepena genetičke homozigotnosti korelira sa stepenom ekspresije bolesti (displazija/subluksacija-39%; luksacija-45%). Naši rezultati su pokazali uvećanu morfogenetičku homozigotnost u grupi pacijenata sa bilateralnom dislokacijom kuka (45%), u odnosu na grupu sa unilateralnom ekspresijom (41%) i kontrolom (23.5%). Takođe, kod hirurški tretiranih pacijenata je ustanovljeno značajno uvećanje genetičke homozigotnosti (43%) u odnosu na one koji su konzervativno lečeni (37%). Pokazano je da osobe ženskog pola sa RPK imaju uvećanu genetičku homozigotnost (44%), u odnosu na osobe muškog pola (39%), dok u kontrolnom uzorku nije bilo razlika među polovima. Pokazano je postojanje statistički značajne razlike u srednjim vrednostima testiranih homozigotno recesivnih osobina između grupa displazija/luksacije ($p<0,05$) i sublukasije/luksacije ($p<0,05$), kao i između grupa sa bilateralnom i unilateralnom ekspresijom ($p<0,05$) i između pacijenata sa RPK ženskog i muškog pola ($p<0,05$). Povećanje stepena genetičkog opterećenja korelira sa težinom bolesti (u ispitivanoj grupi pacijenata sa RPK) što može da upućuje na potencijalnu predispoziciju za ispoljavanje različitog stepena težine RPK.

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