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## ANALYSIS OF SOME PHENOTHYPIC TRAITS IN A SAMPLE OF MULTIPLE SCLEROSIS PATIENTS

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### ABSTRACT

In the frame of complex researches of multiple sclerosis (MS) in Western Croatia, high risk zone for MS, the authors compared the genetic structure of MS patients (N=105) with that of healthy persons (N=334). A complex of 50 phenotypic traits was observed under the assumption that each trait is controlled by a corresponding gene. A statistically significant difference was found in 31 phenotypic traits between the group of MS patients and that of healthy controls, which indicates that the genetic structure in two groups could differ in 62% of allelogenes. Although an increased recessive homozygosity was noticed in the entire population, it was nevertheless by 23% higher in the sample of MS patients than in controls. Genes determining the phenotypic traits with evident differences between MS patients and controls could be the markers for polygenes participating in the process of creating either susceptibility or resistance to MS. Genetic loads arising as the consequence of increased recessive homozygosity in MS patients may disrupt the genetic-physiological homeostasis of the body and be the cause of reduced resistance towards environmental triggers of MS.

**Key words:** multiple sclerosis, genetics, phenotypic traits

### INTRODUCTION

Apart from classic epidemiologists, who in order to clarify the role of genetic factors in the etiology of the disease studied its possible relation with variables of time

and environment, modern genetic epidemiology regards its connection also with the individual genetic constitution and genetic structure of the population [1].

From that point of view some authors have made a research of the inbreeding level in parents, i.e. of the influence the resulting increased homozygosity has on their offspring affected by various diseases [2, 3, 4, 5, 6]. Also, one group of researchers has developed an original method of examining the distribution for various phenotypic characteristics in persons affected by various diseases, wherein qualitative morpho-physiological features characterized by simple genetic determination and by a dominant-recessive type of expression have been examined [7].

In this study, in the framework of complex MS research performed in Western Croatia, as a MS high risk zone [8], the authors studied the frequency of basic variants of 50 phenotypic characteristics in a sample of MS patients and tried to ascertain whether the patients manifested an increased recessive homozygosity of the analyzed features, as compared to healthy persons from the same area. Therefore, what makes this study different from MS studies performed so far is the attempt to compare the genetic structure of ill and healthy persons, wherein the analyzed phenotypic characteristics represent a random parameter of their genetic congruity or diversity. The obtained results could suggest the type of genetic-physiological homeostasis (constitution) of subjects, with an estimate of who among them could be more inclined to contracting MS.

### SUBJECTS AND METHODS

During 1999, 105 unrelated MS patients (69 women and 36 men) from Western Croatia were examined. All patients were affected by a form of clinically definite and laboratory supported definite MS according to Poser's diagnostic criteria [9]. The random control group consisted of 334

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persons from the same area, who did not have any neurodegenerative diseases in their personal and family anamneses.

In both groups HRC testing (test for determination of homozygously recessive characters in humans) [10] of 50 phenotypic traits was done. Since the monogenetic control of inheriting selected phenotypic characteristics is frequently questioned due to the relatively frequent occurrence of phenotypic variability within one genotype, we made a conditional hypothesis that each examined trait is characterized by a simple monogenetic (or oligogenetic) determination and defined alternative phenotypes for each characteristic. Before the testing a questionnaire was made up with a list of recessive manifestations of the selected characteristics and their presence or absence was marked with signs + and - The analysis was performed by one person with equal criteria in the determination of alternative phenotypes.

The discrimination of alternative phenotypes of observed

characteristics was determined on the basis of original hypotheses of the mechanisms of their genetic control, as well as the works that confirmed them [11, 12, 13]. The determination of defective color vision was done by pseudo-isochromatic test-tables [14], wherein protanopy and protanomaly were included in protodefects, and deuteranopy and deuteranomaly in deuterodefects. The discrimination of alternative phenotypes regarding the bitter taste of PTC was done with 0.00812% water solution of PTC, after it was shown that this was the adequate concentration for the distinction of alternative phenotypes in European population. Individuals belonging to alternative types of other phenotypic characteristics were determined by direct observation of MS patients and controls. The statistical significance of differences in the frequency of recessive phenotypes between the diseased and the control group was defined by Chi-square test ( $\chi^2$ ) and Fisher exact test. The degree of genetic differentiation, i. e. of departure from

**Table 1.** Incidence of the recessive phenotypes of phenotypic characteristics of the hair, auricles and eyes in MS patients (N=105) and in the control group (N=334)

PHENOTYPIC TRAITS	MS PATIENTS	CONTROLS	p-values
	a%	a%	
1. Flat scalp	61.9	51.1	0.0707+
2. Straight hair	71.4	68.2	0.6236+
3. Light hair	13.3	16.5	0.5380+
4. <b>Soft hair</b>	76.2	61.1	<b>0.0067+</b>
5. Reverse top of the hair	19.0	23.3	0.4296+
6. <b>Double top of the hair</b>	18.1	7.5	<b>0.0030+</b>
7. <b>Attached ear lobe</b>	53.3	24.8	<b>0.0000</b>
8. Ear without Darwinian knot	53.3	45.5	0.1975+
9. <b>Hair on the edge of the auricle</b>	20.9	3.9	<b>0.0000+</b>
10. <b>Abnormal ear shape</b>	22.9	5.4	<b>0.0000+</b>
11. Light eyes	40.0	32.0	0.1660+
12. Cross-eyed	1.9	1.1	0.6326*
13. <b>Daltonism</b>	2.8	0.3	<b>0.0441*</b>
14. <b>Protodefects</b>	11.4	1.8	<b>0.0001*</b>
15. <b>Deuterodefects</b>	26.7	4.5	<b>0.0000+</b>
16. Myopia	21.9	26.6	0.3987+
17. Hyperopia	13.3	12.2	0.9071+

Phenotypical characteristics showing statistically significant differences are typed in boldface.

a%-frequency of the recessive phenotype

+ Yates corrected  $\chi^2$

\*Fisher exact test



etic proportions based on the Hardy-Weinberg hypothesis was defined using the fixation index (F) by determination of the Wahlund's variance [15]. It was also analyzed whether in the group of MS patients and in the control group existed an increased recessive homozygosity related to the 50 examined phenotypic characteristics, i.e. whether there were any genetic loads. The statistical significance of observed and expected differences in recessive homozygosity was estimated by  $\chi^2$  test.

## RESULTS

Comparing the frequencies of recessive phenotypes in MS patients and controls it was observed that 29 out of the examined 50 traits display a significant degree of mutual difference ( $p < 0.05$ ), wherein MS patients have a greater frequency of the recessive phenotype in 21 characteristics (Tables 1-3). The values of the fixation index indicate that 31 features show statistically significant differences in incidence between the group of MS patients and the control

**Table 2.** Incidence of the recessive phenotypes of phenotypic characteristics of the face, trunk and fist in MS patients (N=105) and in the control group (N=334)

PHENOTYPIC TRAITS	MS PATIENTS	CONTROLS	p-values
	a%	a%	
<b>8. Hare lip</b>	<b>31.4</b>	<b>2.7</b>	<b>0.0000</b>
<b>9. Chin without pits</b>	<b>55.2</b>	<b>71.2</b>	<b>0.0033</b>
10. Albinism	0.0	0.6	1.0000*
<b>11. Accentuated spottedness</b>	<b>1.9</b>	<b>13.5</b>	<b>0.0016+</b>
<b>12. Hairless face</b>	<b>21.9</b>	<b>54.5</b>	<b>0.0000</b>
<b>13. Small chin</b>	<b>47.6</b>	<b>17.4</b>	<b>0.0000</b>
14. Narrow face	38.1	28.1	0.0703+
<b>15. Ingrate teeth</b>	<b>17.1</b>	<b>27.8</b>	<b>0.0383+</b>
16. Lingua scrotalis	32.4	25.1	0.1830+
<b>17. Thin lips</b>	<b>65.7</b>	<b>26.0</b>	<b>0.0000+</b>
18. Small nose	24.8	34.4	0.0834+
<b>19. Facial asymmetry</b>	<b>69.5</b>	<b>20.9</b>	<b>0.0000</b>
<b>20. Disconnected eyebrows</b>	<b>31.4</b>	<b>67.1</b>	<b>0.0000+</b>
<b>21. Small forehead</b>	<b>36.2</b>	<b>20.9</b>	<b>0.0024+</b>
<b>22. Chicken breast</b>	<b>21.9</b>	<b>6.9</b>	<b>0.0000+</b>
<b>23. Long neck</b>	<b>13.3</b>	<b>36.8</b>	<b>0.0000+</b>
<b>24. Midphalangeal hairlessness</b>	<b>60.0</b>	<b>42.2</b>	<b>0.0021+</b>
<b>25. Digital index</b>	<b>55.2</b>	<b>41.9</b>	<b>0.0226+</b>
<b>26. Straight small finger of the fist</b>	<b>76.2</b>	<b>46.4</b>	<b>0.0000+</b>
<b>27. Long thin fingers</b>	<b>55.2</b>	<b>43.4</b>	<b>0.0447+</b>
<b>28. Three ligaments in the root of the fist</b>	<b>33.3</b>	<b>50.3</b>	<b>0.0034+</b>
<b>29. Hitchhiker's thumb</b>	<b>32.4</b>	<b>35.3</b>	<b>0.6626+</b>

Phenotypical characteristics showing statistically significant differences are typed in boldface.

a%-frequency of the recessive phenotype

+ Yates corrected  $\chi^2$

\*Fisher exact test



**Table 3.** Incidence of the recessive phenotypes of phenotypic characteristics of different functions in MS patients (N=105) and in the control group (N=334)

PHENOTYPIC TRAITS	MS PATIENTS	CONTROLS	p-values
	a%	a%	
<b>40. Inability to tongue rolling (vertical)</b>	<b>52.4</b>	<b>26.9</b>	<b>0.0000+</b>
<b>41. Inability to tongue rolling (transversal)</b>	<b>26.7</b>	<b>8.1</b>	<b>0.0000+</b>
<b>42. Insensitivity to PTC</b>	<b>71.4</b>	<b>41.9</b>	<b>0.0000+</b>
43. Stuttering	3.8	2.4	0.4923*
44. Guttural R	0.9	8.1	<b>0.0225+</b>
45. Lefthandedness	7.6	9.3	0.7693+
46. Thumb proximal hyperextensibility	18.1	26.3	0.1124+
47. Hand clasping (R type)	49.5	41.6	0.1893+
48. Arm folding (R type)	49.5	41.9	0.2084+
49. Leg folding (R type)	75.2	68.9	0.2603+
50. Congenital dislocation of the hip	2.9	5.9	0.3150+

Phenotypical characteristics showing statistically significant differences are typed in boldface.

a%-frequency of the recessive phenotype

+ Yates corrected  $\chi^2$

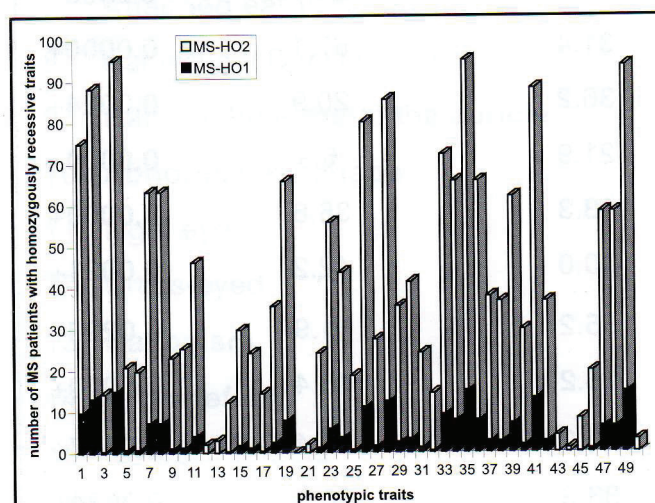
\*Fisher exact test

group, which in this case are being observed as local populations (Table 4).

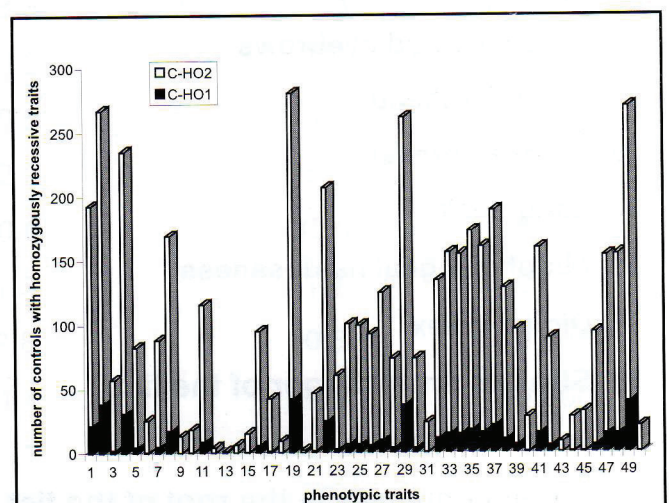
The total number of recessive phenotypic characteristics was considerably higher in MS patients than in controls (Table 5). As far as the appearance of the hair, au-

ricles, eyes, face, fist and functions is concerned, there was a significant difference between ill and healthy persons ( $p < 0.001$ ).

Specific calculations have also been effected for 30 out of the 50 phenotypic characteristics, the manifestation of



**Fig. 1.** Relation of the expected (H01) and obtained (H02) recessive homozygosity of 50 phenotypic characteristics in the MS patients (numbers on the abscissa correspond to ordinal numbers of phenotypic characteristics stated in Tables 1-3.)



**Fig. 2.** Relation of the expected (H01) and obtained (H02) recessive homozygosity of 50 phenotypic characteristics in the control group (numbers on the abscissa correspond to ordinal numbers of phenotypic characteristics stated in Tables 1-3.)



**Table 4.** Genetic heterogeneity of the group of MS patients and of the control group

PHENOTHYPIC TRAITS	MS PATIENTS	CONTROLS	F	
	q	q		
Soft hair	0.87	0.78	0.0190	16.68****
Double top of the hair	0.42	0.27	0.0063	5.56*
Attached ear lobe	0.73	0.50	0.0436	38.32****
Ear without Darwinian knot	0.73	0.67	0.0074	6.51*
Hair on the edge of the auricle	0.46	0.20	0.0190	16.67****
Abnormal ear shape	0.46	0.23	0.0165	14.49****
Protodefects	0.34	0.13	0.0081	7.12**
Deuterodefects	0.52	0.21	0.0324	28.42****
Hare lip	0.56	0.16	0.0595	52.21****
Chin without pits	0.74	0.84	0.0190	16.72****
Accentuated spottedness	0.14	0.37	0.0107	9.39***
Hairless face	0.47	0.74	0.0583	51.16****
Small chin	0.69	0.42	0.0479	42.10****
Ingrate teeth	0.41	0.53	0.0065	5.68*
Thin lips	0.81	0.51	0.0921	80.90****
Small nose	0.50	0.59	0.0048	4.23*
Facial asymmetry	0.83	0.46	0.1352	118.73****
Disconnected eyebrows	0.56	0.82	0.0778	68.27****
Small forehead	0.60	0.46	0.0112	9.87***
Chicken breast	0.47	0.26	0.0136	11.97****
Long neck	0.36	0.60	0.0289	25.37****
Midphalangeal hairlessness	0.77	0.65	0.0179	15.68****
Digital index	0.74	0.65	0.0092	8.08***
Straight small finger of the fist	0.87	0.68	0.0636	55.85****
Long thin fingers	0.74	0.66	0.0075	6.62**
Three ligaments in the root of the fist	0.58	0.71	0.0154	13.56****
Inability to tongue rolling (vertical)	0.72	0.52	0.0337	29.56****
Inability to tongue rolling (transversal)	0.52	0.28	0.0211	18.53****
Insensitivity to PTC	0.84	0.65	0.0541	47.51****
Guttural R	0.10	0.28	0.0048	4.19*
Leg folding (R type)	0.87	0.83	0.0045	3.96*

q-relative frequency of the recessive allele

F-fixation index

\* p&lt;&lt;0.05

\*\*p&lt;&lt; 0.01

\*\*\*p&lt;&lt; 0.005

\*\*\*\*p&lt;&lt; 0.001

 $\chi^2$ - Chi-Square test



**Table 5.** Total number of recessive phenotypic characteristics in MS patients (N=105) and controls (N=334)

REGIONS	RECESSIVE TRAITS MS PATIENTS		RECESSIVE TRAITS CONTROLS		$\chi^2$ *	p-values
	+	-	+	-		
<b>HAIR</b>	273	357	761	1243	5.55	<b>0.018</b>
<b>EARS</b>	158	262	266	1070	53.75	<b>0.000</b>
<b>EYES</b>	124	611	263	2075	15.55	<b>0.000</b>
<b>FACE</b>	534	1146	1517	3827	6.98	<b>0.008</b>
<b>FIST</b>	328	302	867	1137	14.62	<b>0.000</b>
<b>FUNCTIONS</b>	376	779	944	2730	20.48	<b>0.000</b>
<b>Total</b>	1791	3461	4618	12082	80.06	<b>0.000</b>

Phenotypical characteristics showing statistically significant differences are typed in boldface.

+ presence of recessive traits

- absence of recessive traits

\*\* Yates corrected  $\chi^2$

which was fully alternative, so that it may be assumed with greater confidence that it is a question of genetically conditioned qualitative traits. In this case as well the total number of recessive characteristics was considerably higher in MS patients than in the controls ( $p < 0.001$ ).

The average homozygosity in MS patients amounts to  $17.05 \pm 3.76$  and in the control group to  $13.83 \pm 3.58$ . Fig. 1 shows the relation between observed and expected recessive homozygosity in MS patients while Fig. 2 describes their relation in the control group. The differences between observed and expected values of recessive homozygosity for all observed traits are statistically highly significant in both groups ( $p < 0.001$ ). This points at a significant increase of recessive homozygosity compared to the expected homozygosity in the entire population, emphasizes however that the observed number of homozygotes is greater for almost all features in the group of MS patients.

**DISCUSSION**

Most authors in contemporary studies relate the role genetic factors are likely to play in the ethiology of the disease to polygenic determination of susceptibility for MS [16, 17]. However, although the results of recent studies have shown that several regions of the human genome are associated with MS susceptibility [18, 19, 20, 21, 22, 23], there have been no reliable data so far confirming that any genetic marker, acting either individually or in combination with other markers, would determine either predisposition or resistance to MS.

In this connection in the present study we tried to determine a possible association of MS with certain phenotypic characteristics as probable genetic markers for polygenes which may have a direct influence on susceptibility and/or resistance to environmental factors provoking MS. The comparison of frequencies between recessive variants of observed phenotypic characteristics found in MS

patients and the control group indicated that the sample of patients departs significantly from the phenotypic status of healthy persons.

The examination of the degree of genetic distance between MS patients and controls indicated that the population-genetic structure in the two groups differs in 31 out of the 50 observed traits. Considering the fact that the traits were selected at random and assuming they have a simple genetic determination, we may conclude that the genetic structure in the two groups could differ in 62% of allelogenes.

The significant difference in the examined phenotypic characteristics between MS patients and healthy persons indicates that those genes determining the features with manifested differences could be the markers of polygenes included in the regulatory processes generating susceptibility or resistance to MS. The mentioned difference in the phenotypic status between MS patients and controls could also derive from the possibility that the patients represent a sample of population with different genetic structure or that genetic loads, arising as a consequence of increased general homozygosity, are the cause of decreased resistance of the organism to environmental factors triggering the disease.

The achieved results show a significant increase of recessive homozygosity in the entire population which denies the possibility that patients originate from some other population, whose members had a decreased resistance to MS. However, the possibility that genetic loads cause a decreased resistance to the disease is not excluded, since although the difference between observed and expected values of recessive homozygotes is not significant in the group of patients only, but also in that of healthy controls, the group of MS patients manifests nevertheless a considerably higher recessive homozygosity. It seems that each



departure from optimal homozygosity, being it an increased or decreased value, may lead to the disruption of the genetic-physiologic homeostasis of the organism.

Moreover, the results of other studies on the distribution of phenotypic characteristics in persons suffering from various diseases indicate the existence of differences in the genetic structure between patients and healthy persons [7]. The average increase of recessive homozygosity amounted to 43% in neuropsychiatric patients and patients affected by diabetes, 27% in children suffering from allergy disturbances, 24% in patients with urogenital diseases, 15% in women with carcinoma of the uterus, 14% in patients with endemic nephropathy and in 13% of patients affected by chronic lymphocyte leukemia. The recessive homozygosity in patients suffering from allergic bronchial asthma was increased only by 2% if compared to that in healthy persons, while somewhat lower values were found in women with breast cancer but it was a question of an exceptionally small number of examined characteristics. In each of the mentioned studies the characteristic groups of traits were differently frequent among diseased and healthy individuals, which suggests a correlation with different combinations of polygenes which may be included in regulatory processes of resistance to different diseases [7].

In this study the average increase of recessive homozygosity amounted to 23% in MS patients if compared to healthy controls from the same area. Therefore the existence of genetic loads found in MS patients could indicate that it is a question of genetic background suitable for the breaking out of the disease. In the framework of such genetic-physiological constitution it appears that some persons are more susceptible to exposures to dangerous environmental factors and that contract more frequently MS or some other disease of similar ethiology.

The obtained results are in conformity with the association of the MS with certain genetic markers which has been ascertained so far [18, 19, 20, 21, 22, 23]. Each allele or haplotype found to be associated with MS, both in case of HLA antigens or genetic markers studied in this work, may be one of the polygenes the contribution of which increases the genetic load conditioning MS susceptibility. The fact that all patients do not necessarily have all the genetic markers found to be associated with the disease may explain that for susceptibility to the disease it is necessary a sufficient number of certain genes in the system leading to a genetic encumbrance of the organism. In small populations these polygenes are probably wide-spread which results in a more frequent family aggregation of the disease and in the formation of MS focuses.

Considering the fact that MS is still a disease of unknown ethiology with no possibility of a successful therapeutic treatment, and that it affects younger adults in the age of full life and professional activity, each study of this complex disease, as well as of the factors likely to influence its variable expression, may have an indisputable medical, ethic, economic and social significance.

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