BANTAO Journal 3 (2): p 156; 2005

Population-Genetic Properties of Balkan Endemic Nephropathy

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Introduction

Using specific population-genetic markers it should be possible to predict a predisposition of some individuals, or even of their groups, to suffer of some diseases. Such markers exist at biochemical, as well as at morpho-physiological levels, and among the later ones we selected about thirty characters proven to be inherited as *homozygously recessive*, which can be differently present among individuals of a population (HRC-test, Marinkovic 1989, Blagojevic et al. 1989, Marinkovic et al. 1990, 1991, 1994, etc.).

In some of individuals only two of such HRCs are present, in others even 18 out of 30 observed, and it came out that among the patients from the hospitals with *urogenital*, *pulmonal, hormonal, cardiovascular, neuropsy- chiatric* and some other diseases (as among *alcoholics*!), the presence of such homozygously recessive characters turns out to be significantly higher than among healthy people as a control (Tables 1&2; Ph.D. theses of Cukuranovic 1992,Janakova 1993,Pesut 1994,Cvjeticanin 2000; synthesized in Cvjeticanin and Marinkovic 2005a,b). The studied homo-recessive characters are obviously controlled by genes located at different chromo-somes, and could be considered not only as markers of these chromosomes but also of numerous surrounding genes that are involved in a control of development of different components of fitness, such as in the resistance to specific factors that provoke a disease.

Table 1. HRC-test in healthy individuals and patients with Diabetes mellitus from Belgrade. Average number of homo-recessive characters, out of 30 inspected, in control sample (Nc = 102 ind.) 4.4 + 0.2 ; in sample of patients (Nd = 95 ind.) 6.3 + 0.3 ; t= 5.28; p<0.001 .

Number of homozygously-recessive characters												
1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*
10	*12*	*13*	*18*	*17*	*8*	*6*	*7*	*3*	*2*	*2*	*2*	*0%C*
4	*6*	*7*	*8*	*14*	*13*	*12*	*11*	*9*	*7*	*4*	*3*	*2%D*

Table 2. HRC-test in healthy individuals and patients with urogenital diseases from Novi Sad. Average number of homo-recessive characters, out of 30 inspected, in control sample (Nc = 72 ind.) 5.86 + 0.19 , in sample of patients (Nu=85) 7.31 + 0.22 ; t = 5.0; p< 0.001 .

Number of homozygously-recessive characters												
1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*
0	*1*	*6*	*9*	*25*	*22*	*17*	*15*	*5*	*0*	*0*	*0*	*0%C*
0	*0*	*0*	*3*	*18*	*22*	*12*	*21*	*10*	*5*	*3*	*4*	*2%U*

Material and methods

The presence of selected 20-30 morphophysiological characters, previously verified to be homozygously recessive, was determined individually in a sample of BEN-affected persons, as well as in another group of healthy individuals from the same region considered as a control. Such an analysis has been proceeded in BEN-affected regions near Loznica and Aleksinac, as among the patients on dyalisis from Nis hospitals, origina-ting mostly from south Serbian villages. In village Chepure near Paracin a detailed analysis of family-relationships (horizontal and vertical) has been proceeded, including ca. twenty large families where BEN was present in one or more individuals, with more than 600 first to sixth degree relatives of BEN probants.

The application of HRC-tests is broadly described, e.g., in Marinkovic et al. 1990, 1991, 1994, as well as in PhD theses of R. Cukuranovic (1992), Z. Janakova (1993), D. Pesut (1994), S. Cvjeticanin (2000), or in the recent papers of Cvjeticanin and Marinkovic (2005a,b).

The use of population- and quantitative-genetic parameters when estimating the contribution of genetic and environmental factors in the appearance of BEN is appropriately described, e.g., by Tucic&Marinkovic (1979), Banjevic&Tucic (1979), , Blagojevic et al. (1989), Marinkovic et al. (1994), and others.

Results and discussion

In this report we submit our analyses of HRC tests on the patients with Balkan endemic nephropathy, and from BEN-

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affected regions, to distinguish if populations from such regions should be considered to be different from the neighbouring regions where BEN is absent. Initial studies sugest a positive answer in both directions, to be compared with earlier publications (e.g., Bulic 1967, Marinkovic et al. 1970, Milosevic et al. 1970, Hrisoho 1970, Dimitrov 1970, Bruckner et al. 1971,Polenakovic and Hrisoho 1979, Radovanovic 1979,2000, Toncheva et al.1985,1988, etc.).
In our analyses proceeded so far in BEN regions near Loznica, Chepure village near Paracin, Aleksinac, and among the patients on dialysis in Nis hospitals, HRC-test showed increased values of homo-recessive characters compared to control samples, estimating genetic loads that exist in studied samples of individuals in such populations (Tables 3&4). Corresponding genes located at different chromosomes could be considered as markers of numerous surrounding genes that influence the resistance to environmental factors which may provoke BEN disease.

Table 3. HRC-test in healthy individuals and patients with Balkan endemic nephropathy from Aleksinac. Average number of homo-recessive characters, out of 30 inspected, 7.6 + 1.4 in control sample (Nc = 60 ind.); 8.7 +1.7 in sample of BEN patients (Nb = 60 ind.).

Number of homozygously-recessive characters									
4	***5***	***6***	***7***	***8***	***9***	***10***	***11***	***12***	***13***
2	***5***	***8***	***35***	***20***	***19***	***8***	***3***	***0***	***0%C***
0	***2***	***5***	***17***	***27***	***15***	***24***	***7***	***2***	***2%BEN***

Table 4. The presence of ten homozygously-recessive characters in ben-patients and healthy individuals in two localities in Serbia

	****DOBRIC / LOZNICA***			*****NIS / ALEKSINAC***		
	BEN (64)	***CONTROL (50)***	***q***	***BEN (60)***	***CONTROL (60)***	***q***
Blue eyes				*38%*	*28%*	*.62/.53*
Blond hair				***10***	***6***	***.32/.24***
Straight hair	***89%***	***76%***	***.94/.87***	***98***	***78***	***.99/.88***
Soft hair	***61***	***60***	***.78/.77***	***86***	***32***	***.93/.56***
Double hair whorl	***12.5***	***6***	***.35/.24***			
Chin whole	***15.6***	***6***	***.40/.24***	***8***	***18***	***.04/.15***
Attach.earlobe	***36***	***39***	***.60/.65***	***12***	***18***	***.35/.42***
Cut leaps	***4.7***	***2***	***.22/.14***			
Tongue roll inability	***58***	***70***	***.76/.84***	***40***	***36***	***63/.60.***
Lefthanded	***17.2***	***2***	***.41/.14***	***14***	***4***	***.37/.20***
Abs. of hair in finger articles	***24***	***28***	***.48/.53***	***66***	***52***	***.81/.72***
Thumb hiper-extensibilty	***22***	***12***	***.47/.35***	***8***	***12***	***.28/.35***
Sign. HRCs	***6/10***	***2/10***	***1.4+.2***	***6/10***	***3/10***	***1.2+.1***

The disbalance between ecological surroundings and genetic (i.e. familial) origins of a population is probable cause that many individuals of such a population suffer of Balkan nephropathy in numerous specific regions distributed mostly along Danube river tributaries.

Detailed population-genetic analyses in village Chepure near Paracin, initiated by Marinkovic and Milosevic since 1970s, discovered one of foci where BEN is present in about 200 out of cca. 1400 inhabitans (Tables 5&6).

Table 5. The incidence of diseased progenies in Chepure village near Paracin depending on the presence of BEN in one or in both parents

	Both parents	**One parent**	**Father**	**Mother**
Analysed families	15	34	18	16
Observed progenies	56	125	69	56
% diseased	57.0	27.0	36.2	18.0%

Table 6. BEN in relatives of diseased probant individuals in Chepure village near Paracin.

Probants	Inspected relatives	Percent of diseased in		
		I-II	III-IV	V-VI degree rel.
20	646	56.8%	39.7%	20.1%

Analysing some twenty large families where BEN is present, with 650 I-VI degree relatives of probants, inheritance of both or one affected parent was estimated. We could easily calculate that relatively small number of genes should be involved in BEN resistance, or in development of this disease. Heritability amounts even 70%, although higher inheritance from fathers to sons than from mothers to daughters clearly suggests also the influence of environmental factors (same versus different home among the progenies). The prevalence of autosomal recessive individual loci in a multigenic (i.e.oligogenic) determinaion of BEN development, and/or in the

resistance to BEN-affected factors, seem to be evident. It has been proven by location of some of these genes by Bulgarian geneticists at long arm of third chromosomes (Toncheva et.al 1988), pleiotropic effects of its deletions being possibly of crucial importance.

The application of non-invasive HRC-tests in appearantly healthy individuals should be used as a preventive method, to discover individuals which have extremely many, or a small number of homozygous traits, which may result in some weaknesses in the resistance to different diseases. Such individuals should be more carefully followed, to prevent the appearance of possible diseases in their bodies. The choice of characters that determine the degree of homozygosity should be further specified and properly selected, including more biochemical traits. The cooperation among medical specialists, as well as with scientists (such as geneticists and molecular biologies) is not only suggested but it is by all means necessary.

Summary

Several authors of Belgrade population-genetic school have studied distribution and frequency of a series of extremely expressed homozygously recessive traits to estimate individual and group differences in their presence. Measured by a developed HRC-test, their scope was found to be quite different among observed individuals, and frequently also between samples of ill and healthy individuals, pupils from special and regular schools, carriers of different blood types, members of different populations. The studied homozygous characters are controlled by genes located at different human chromosomes, and could be considered as their markers, as well as of numerous surrounding genes that control different components of fitness. The amount of recessive homozygosity among BEN patients from Loznica, Aleksinac, Nis-hospitals, was found to be higher than in samples of control-healthy individuals, suggesting an increase of genetic loads in samples of individuals affected by this disease. Detailed population-genetic analyses in village Chepure near Paracin suggested also clear inheritance, with high heritability, most probably of the resistance to environmental factors that are provoking BEN disease. Such a trait is estimated to be gene-tically determined as multifactorial, with the possibility of a pleiotropic contribution of individual autosomally-recessive loci.

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