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 from some diseases. Such markers exist at biochemical, as well as at morphophysiological 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, neuropsychiatric 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 chromosones, 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>
<thead>
<tr>
<th>Number of homozygously-recessive characters</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 2 3 4 5 6 7 8 9 10 11 12 13</td>
</tr>
<tr>
<td>10 12 13 18 17 18 6 7 3 2 2 2 0% C</td>
</tr>
<tr>
<td>4 6 7 8 14 13 12 11 9 7 4 3 2% D</td>
</tr>
</tbody>
</table>

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 .

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<td>1 2 3 4 5 6 7 8 9 10 11 12 13</td>
</tr>
<tr>
<td>0 1 6 9 25 22 17 15 5 0 0 0 0% C</td>
</tr>
<tr>
<td>0 0 0 3 18 22 12 21 10 5 3 4 2% U</td>
</tr>
</tbody>
</table>

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 .

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 dialysis 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.


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

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<tr>
<td>4 5 6 7 8 9 10 11 12 13</td>
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<tr>
<td>2 5 8 35 20 19 8 3 0 0% C</td>
</tr>
<tr>
<td>0 2 5 17 27 15 24 7 2 2% BEN</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>*DOBRIC / LOZNICA</th>
<th>**NIS / ALEKSINAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>BEN (64)</td>
<td>CONTROL (50)</td>
</tr>
<tr>
<td>Blue eyes</td>
<td>38%</td>
</tr>
<tr>
<td>Blond hair</td>
<td>10</td>
</tr>
<tr>
<td>Straight hair</td>
<td>89%</td>
</tr>
<tr>
<td>Soft hair</td>
<td>61</td>
</tr>
<tr>
<td>Double hair whorl</td>
<td>12.5</td>
</tr>
<tr>
<td>Chin whole</td>
<td>15.6</td>
</tr>
<tr>
<td>Attach.earlobe</td>
<td>36</td>
</tr>
<tr>
<td>Cut leaps</td>
<td>4.7</td>
</tr>
<tr>
<td>Tongue roll inability</td>
<td>58</td>
</tr>
<tr>
<td>Lefthanded</td>
<td>17.2</td>
</tr>
<tr>
<td>Abs. of hair in finger articles</td>
<td>24</td>
</tr>
<tr>
<td>Thumb hiper-extensibility</td>
<td>22</td>
</tr>
<tr>
<td>Sign. HRCs</td>
<td>6/10</td>
</tr>
<tr>
<td>6/10</td>
<td>3/10</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Analysed families</th>
<th>15</th>
<th>34</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both parents</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>Observed progenies</td>
<td>56</td>
<td>125</td>
</tr>
<tr>
<td>% diseased</td>
<td>57.0</td>
<td>27.0</td>
</tr>
</tbody>
</table>

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).
Correspondence to: _______________________________
samples of control-healthy individuals, suggesting an
Aleksinac, Nis-hospitals, was found to be higher than in
homozygosity among BEN patients from Loznica,
different components of fitness. The amount of recessive
well as of numerous surrounding genes that control
chromosomes, and could be considered as their markers, as
carriers of different blood types, members of different
individuals, pupils from special and regular schools,
frequently also between samples of ill and healthy
to be quite different among observed individuals, and
Measured by a developed HRC-test, their scope was found
individual and group differences in their presence.
expressed homozygously recessive traits to estimate
studied distribution and frequency of a series of extremely
Several authors of Belgrade population-genetic school have
not only suggested but it is by all means necessary.
cooperation among medical specialists, as well as with
selected, including more biochemical traits. The
homozygosity should be further specified and properly
prevent the appearance of possible diseases in their bodies.
Such individuals should be more carefully followed, to
The choice of characters that determine the degree of
homozgyosity 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 homozgyously 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 homozgyous 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
homozgyosity 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.

References
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8. Cukuranovic R. PhD thesis at Nis University. 1992
15. Marinkovic D, Genetika 1989;21(3)179-188
17. Marinkovic et al. Genetika 1994;26(3)147-156

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

<table>
<thead>
<tr>
<th>Probants</th>
<th>Inspected relatives</th>
<th>Percent of diseased in</th>
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<tr>
<td></td>
<td>I-II IV-VI degree rel.</td>
<td></td>
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<td>20</td>
<td>646</td>
<td>56.8% 39.7% 20.1%</td>
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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
fluence of environmental factors (same versus different
home among the progenies). The prevalence of autosomal
recessive individual loci in a multigenic (i.e. oligogenic)
determination 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 apparently
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.
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