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Segregation Analysis of Systolic and Diastolic Blood Pressure in Middle Dalmatia Island Population

This paper is dedicated to the memory of our late colleague, teacher and friend Professor Emil K. Ginsburg.

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A B S T R A C T

A complex segregation analysis of systolic and diastolic blood pressure has been performed on pedigree data from rural populations inhabiting Middle Dalmatian islands of Brač, Hvar and Korčula and the Pelješac peninsula. The purpose of the performed analysis was to possibly elucidate a signal of a large-effect gene responsible for high prevalence of hypertension present in this population (the age-adjusted prevalence of developed hypertension being 31.82% in males and 28.23% in females). The analysis was performed on a sample of 389 two- and three-generation families consisting of 2 to 19 observed individuals (1126 examinees in total, 526 males and 600 females, aged 17 to 83). Since the examinees were randomly selected from census data encompassing 22.6% of the total population – the family relations having been established afterwards – the selected sample can be considered representative for the examined populations. By applying the usual transmission probability tests, the major gene model has been accepted for systolic as well as for diastolic blood pressure. The most parsimonious models showed that: a) inheritance of blood pressure in the Middle Dalmatia population can be attributed to the effect of a major gene responsible for 34% (systolic) and 36% (diastolic) blood pressure variation; b) alleles of that major gene act in co-dominant fashion; c) allele frequency for high blood pressure (A_2) is 18% (systolic) and 15% (diastolic blood pressure); and d) the residual (non-major gene) familial correlation is negligible and can be constrained to zero. Since the results are also indicating heterogeneity within the sample in the genetic determination of the systolic blood pressure, the obtained results thus justify further search for the most promising subpopulation for incoming genetic epidemiological investigations of hypertension.

Key words: *blood pressure, complex segregation analysis, family data, island population, Croatia*

Introduction

Blood pressure is a complex trait that when elevated represents one of the most important risk factors for many common causes of morbidity and mortality including stroke, myocardial infarction, congestive heart failure and end-stage renal disease[1,2]. The genetic component in the variation of systolic as well as diastolic blood pressure has been documented by numerous family and twin studies[3–12]. In several studies, it has been reported that the mode of inheritance of blood pressure in different populations can be described in terms of a major gene model[13–19]. Various susceptibility genes for essential hypertension have been proposed in recent years but their importance was not ubiquitarily found in all populations. Since gene frequencies as well as environmental conditions (and consecutively gene-gene and gene-environment interactions) are not uniformly shared in all human populations, the complex segregation analyses of prevalent phenotypes in different populations

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could show directions for choosing the most appropriate population for the complex trait in question.

Isolated, particularly island populations are becoming increasingly interesting for genetic studies because of expectedly reduced number of potential genes having a pronounced role in determination of complex traits[20]. The populations inhabiting Middle Dalmatian islands are relatively isolated and inbreed populations sharing very homogenous environments (climate, economy, nutrition, life style, etc.) that all makes them very promising targets for genetic investigations.

The population of the Middle Dalmatian islands of Brač, Hvar, Korčula and the Pelješac peninsula has been extensively investigated in the course of the last decades[10–12,21–28] and the studies of the variability of the blood pressure has revealed so far that:

- The population of this area is characterized by high prevalence of hypertension (being 31.82% in males and 28.23% in females for developed hypertension)[25,26].
- The four islands/peninsula in both sexes do not differ in age-adjusted mean values of systolic and diastolic blood pressure or in prevalence of hypertension, either in the impact of age or BMI covariates on blood pressure variation[25,26].
- The opposite trend is found when the variability within each island is considered. Namely, the variability among sub-regions and among villages is substantial indicating the presence of founder effect and genetic drift[25,26].
- As an indirect measure of village isolation the effect of endogamy (the percentage of mothers and fathers inhabiting the same village as their offspring) showed to have significant effect on blood pressure variation. (In villages with endogamy of over 80% the prevalence of developed hypertension is over 40%)[25,26].
- A strong linear relationship was found between the inbreeding coefficient of a particular village (F) and mean values of both systolic and diastolic blood pressure. It was estimated that the increase in F of 0.01 corresponded to an increase of 3 mm Hg in systolic and 2 mm Hg in diastolic blood pressure. Similarly, the mean prevalence of hypertension increases with coefficient of inbreeding in a particular village and the impact of recent inbreeding (3–5 generations) accounts for as much as 36% of all hypertension in this population[27].

The above characteristics of blood pressure variation in Middle Dalmatia imply that within such a small area with relatively uniform environmental conditions the source of BP variation is primarily of genetic origin. The significant proportion of genetic variance in blood pressure variation has been already proven in this population and analyses of family data (obtained by various methods) suggested a higher heritability estimates for diastolic blood pressure (32–44%) compared to the systolic (15–24%)[11–12].

The aim of the present study is to explore whether the family aggregation of the blood pressure values found in rural island/peninsular populations of Middle Dalmatia, Croatia, can at least partially be attributed to the effect of one large-effect gene. Namely, complex phenotypes depend on the action of numerous different genes, and the gene (or group of co-segregating genes) with the largest effect in particular population would be responsible for the acceptance of the major gene model. A positive result would thus justify further search for potentially promising subpopulation for the exploration of genes responsible for high prevalence of hypertension in this population.

Material and Methods

The Middle Dalmatia island populations have been extensively studied over the last 30 years by the research team of the Institute for Anthropological Research in Zagreb, Croatia. The field researches taking place from 1978–1987 encompassed 3,834 individuals from 37 rural populations of neighboring islands of Brač, Hvar, Korčula and the Pelješac peninsula. The data have been gathered from randomly selected individuals through voting registers. Since the sample accounts for 22.6% of the total adult rural population, it adequately represents the general population[26]. Only rural settlements were included into the study in order to reduce environmental covariance to minimum by incorporating individuals having very similar life stile (occupation, nutrition, economic level, education). In addition, villages are more isolated and not subjected to recent admixtures since the immigration (although low) is taking place primarily in towns.

The number of subjects included in the present study (1126 examinees, 526 males and 600 females, aged 17 to 83) was determined by the coincidence that two (or more) participants of the original random sample are

TABLE 1
MEAN VALUES (X) AND STANDARD DEVIATIONS (SD) OF AGE, SYSTOLIC AND DIASTOLIC BLOOD PRESSURE IN THE PEDIGREE SAMPLE FROM MIDDLE DALMATIA (1126 EXAMINEES, 526 MALES AND 600 FEMALES)

	Males	Females	Total sample
	X (SD)	X (SD)	X (SD)
Age (years)	45.5 (14.5)	48.0 (14.7)	46.8 (14.7)
Systolic B.P. (mm Hg)	140.6 (17.2)	142.3 (22.6)	141.5 (20.3)
Diastolic B.P. (mm Hg)	88.2 (11.3)	87.5 (11.7)	87.8 (11.5)

TABLE 2
CORRELATIONS BETWEEN SYSTOLIC AND DIASTOLIC BLOOD PRESSURE AND FAMILY CORRELATIONS FOR THE BLOOD PRESSURE VALUES. THE NUMBER OF CORRELATED PAIRS ARE INDICATED IN PARENTHESES. FOR SIBLINGS, THE FIRST NUMBER INDICATES THE NUMBER OF FAMILIES AND THE SECOND ONE THE NUMBER OF SIBLING PAIRS

	Diastolic B.P.	Family correlations		
		Spouses	Parent-offspring	Siblings
Systolic B.P. (mm Hg)	0.626*** (1118)	0.095 NS (90)	0.208*** (436)	0.249*** (254, 297)
Diastolic B.P. (mm Hg)	–	0.076 NS (93)	0.265*** (445)	0.243*** (258, 302)

NS – corresponds to $p > 0.05$;
* to $p < 0.05$; ** to $p < 0.01$; *** to $p < 0.001$

the members of the same family. The sample consisted of 389 two and three-generation pedigrees. Their size is distributed as follows: 229 pedigrees having two observed individuals, 85 having 3 individuals, 63 having from 4 to 6 individuals and 12 families having from 7 to 19 individuals each. The blood pressure was measured by an auscultation method using mercury sphygmomanometer, on the left upper arm, in the sitting position, after 15 minutes' rest.

The mean values of age, systolic and diastolic blood pressure in males, females and in the total sample are shown in Table 1. Inter-correlations of age and sex adjusted and standardized systolic and diastolic blood pressures as well as family correlations for those traits are presented in Table 2.

To standardize the effects of sex, age and to bypass possible population heterogeneity in the effects of micro-regional environmental conditions on blood pressure phenotypes, the systolic and diastolic blood pressure measures were adjusted for sex and age and standardized within each island/peninsula separately. The standardized data from each island/peninsula were pooled together forming the population pedigree data subjected to segregation analysis.

Segregation analysis

Segregation analysis of pedigree data has been performed by the implementation of the program package MAN developed by Ginsburg (1997)[29]. The major gene model of quantitative trait inheritance is described by the following parameters:

p is the population frequency of the first of two major gene (MG) alleles (A_1);

μ_g is the average trait value in individuals having genotype g ; g = 1, 2 and 3, corresponding to genotypes A_1A_1, A_1A_2 and A_2A_2, respectively. Average phenotypic value: $A_1A_1 \leq A_2A_2$;

σ_g^2 is the trait variance in individuals having the same MG genotype . It estimates the variation caused by the effects of all possible environmental factors and potential minor genes;

ρ, β, ε are the partial correlations between residuals in spouses, parents and offspring and in sibs, respectively; they reflect all non-MG effects causing co-segregation in relatives; partial correlation between residuals in any pair of relatives notbelonging to the same nuclear pedigree was assumed equal to zero;

All the above given parameters correspond to those used in the program package S.A.G.E.[30] and PAP[31], taking into account that the partial residual correlations are used here instead of the pairwise ones.

The major gene (MG) hypothesis was tested by means of two transmission probability tests[32], namely, $\chi_A^2 = 2[LH(\hat{\tau}) - LH(\tau_0)]$ and $\chi_E^2 = 2[LH(\hat{\tau}) - LH(\bar{\tau})]$, where $LH(\tau)$ is the maximum log-likelihood value obtained with transmission probability $\tau = (\tau_1\ \tau_2\ \tau_3)$, where $\tau_g = Pr(A_1|g)$ is the probability that an individual with genotype g transmits allele A_1 to his/her offspring. For Mendelian model τ_0 = (1.0, 0.5, 0.0); $\hat{\tau}$ represents a triplet of the maximum likelihood estimates of transmission probabilities; and $\bar{\tau}$ is the same for transmission probabilities constrained to be equal. The MG model of the trait inheritance is accepted if 1) χ_E^2 exceeds the critical value corresponding to df = 2 and the a priori established type I error α = 0.01 (the hypothetical independence of offspring's MG genotype from the genotypes of his/her parents is rejected), and 2) concurrently, χ_A^2 does not exceed the critical value corresponding to df = 3 and type I error α = 0.05 (the hypothesis of Mendelian transmission probabilities is accepted).

Additional characteristics of the tested model evaluating its fit to the analyzed pedigree data were: $H^2 = (\sigma_\mu^2 / \sigma_X^2)$ is the trait heritability defined as the proportion of phenotypic variance attributable to the hypothetical MG effect; D^2 (= $H^2 + d^2$) is the proportion of the trait variance attributable to both the MG effect and the non-major-gene (multifactorial) effects described by correlations ρ, β and ε; correlation $R(x,\tilde{x})$ evaluates the prediction ability of the chosen model, where x denotes the measured trait value in an individual and $\tilde{x}$ is the trait value as predicted by the chosen MG model on the basis of trait values of the individual relatives[29,33].

Results

Segregation analysis of systolic blood pressure

The segregation analysis of systolic blood pressure performed on total pedigree sample (362 pedigrees, 1043 observed individuals) resulted in rejecting the MG mode of inheritance for this trait. Namely, the rejection of the equal τ's model (χ^2_E = 14.36, df = 2, p < 0.01) was accompanied by the rejection of the Mendelian model as well. The obtained maximal likelihood values were: –1409.67 for the general model and –1417.60 for the Mendelian model, gives the likelihood ratio test value, χ^2_A = 15.86, which substantially exceeds the critical value for 3 degrees of freedom that is 7.81.

Assuming that the sample heterogeneity was responsible for this result, we applied the method of data reduction proposed by Livshits et al. (1999)[14] where the pedigrees showing inconsistency with MG model were excluded from the sample. The pedigree consistency with the model was measured by specific (per one observed individual) log-likelihood. After the exclusion of only 5 pedigrees consisting totally of 12 observed individuals (1.38% families or 1.15% individuals that entered the analysis), the segregation analysis of the systolic blood pressure was repeated and then the MG model was not rejected.

The results of segregation analysis of the retained 357 pedigrees (1031 individuals) are given in Table 3. The first three columns present estimates of parameters and maximal log-likelihood value for the general model (column 1), for its version with Mendelian transmission probabilities (column 2) and the version with equal τ's (column 3). As seen from the comparison of the models presented in columns 2 and 3 with the first one, the transmission probability tests permit to accept the MG model of inheritance of systolic blood pressure: χ^2_A = 3,16 (p > 0.05) and χ^2_E = 13,68 (p < 0.01). The last three columns present the results for the most parsimonious MG model (column 5), and its versions with arbitrary and equal τ's (columns 4 and 6, respectively). As seen from Table 3, the mode of inheritance of systolic blood pressure can be satisfactorily described by the MG model with codominant MG effect on the blood pressure level, with equal residual variances, and zero correlation between residuals in spouses, between parents and offspring and in sibs. The MG effect, H^2, as well as the whole model effects, D^2, were responsible for 34% of systolic blood pressure variance (sex and age adjusted data). The correlation between the adjusted values of systolic blood pressure and the values as predicted by its most parsimonious MG model, $R(x,\bar{x})$, was 0.276, n = 770, for offspring; 0.265, n = 345, for parents; and 0.269, n = 1115, for the total sample. The last number exceeds the number of individuals in the sample (n = 1031) because in complex three-generation pedigrees, some individuals are offspring in one nuclear pedigree and, at the same time, they are parents in another nuclear pedigree.

TABLE 3
SEGREGATION ANALYSIS OF SYSTOLIC BLOOD PRESSURE (STANDARDIZED VALUES) IN PEDIGREE SAMPLE FROM MIDDLE DALMATIA, CROATIA

Parameter		General Models			Most Parsimonious Models		
		General 1	Mendelian 2	Equal τ's 3	Arbitrary 4	Mendelian 5	Equal τ's 6
1	p	0.624	0.653	0.435	0.787	0.821±0.074	0.899
2	μ_1	–0.496	–0.578	–1.200	–0.387	–0.389±0.124	–0.201
3	μ_2	0.118	0.126	–0.099	0.713#	0.674#	1.157#
4	μ_3	1.586	1.518	0.829	1.813	1.738±0.344	2.516
5	σ^2_1	0.687	0.651	0.337	0.623	0.637±0.062	0.737
6	σ^2_2	0.517	0.476	0.343	0.623!	0.637!	0.737!
7	σ^2_3	0.454	0.484	0.753	0.623!	0.637!	0.737!
8	ρ	0.148	0.116	0.296	[0.000]	[0.000]	[0.000]
9	β	0.046	0.011	0.280	[0.000]	[0.000]	[0.000]
10	ε	0.047	0.043	0.122	[0.000]	[0.000]	[0.000]
11	τ_1	1.000+	[1.000]	0.433	1.000+	[1.000]	0.940
12	τ_2	0.642	[0.500]	0.433!	0.655	[0.500]	0.940!
13	τ_3	0.000+	[0.000]	0.433!	0.000+	[0.000]	0.940!
LogLH		–1392.00	–1393.58	–1398.84	–1396.84	–1398.30	–1414.57
χ^2		–	3.16 NS (1)	13.68 ** (1)	9.68 NS (1)	2.92 NS (4)	35.46 ** (4)

NS = p > 0.05; ** = p < 0.01; (N) = number indicating the comparative column; [ ] = parameter is fixed to shown value; ! = parameter is constrained to be equal to the parameter above in the Table; # = model is codominant; + = parameter estimate achieved its limit. For parameter definitions see Material and Methods section.

TABLE 4
SEGREGATION ANALYSIS OF DIASTOLIC BLOOD PRESSURE (STANDARDIZED VALUES) IN PEDIGREE SAMPLE FROM MIDDLE DALMATIA, CROATIA

Parameter		General Models			Most Parsimonious Models		
		General 1	Mendelian 2	Equal τ's 3	Arbitrary 4	Mendelian 5	Equal τ's 6
1	p	0.566	0.592	0.080	0.808	0.853±0.039	0.856
2	μ_1	–0.387	–0.389	0.112	–0.388	–0.352±0.070	–0.287
3	μ_2	–0.142	–0.157	–0.369	0.791#	0.849#	0.934#
4	μ_3	1.325	1.304	0.132	1.970	2.050±0.280	2.154
5	σ_1^2	0.867	0.887	1.096	0.609	0.634±0.049	0.688
6	σ_2^2	0.514	0.500	0.358	0.609!	0.634!	0.688!
7	σ_3^2	0.571	0.575	1.161	0.609!	0.634!	0.688!
8	ρ	0.122	0.121	0.018	[0.000]	[0.000]	[0.000]
9	β	0.187	0.192	0.230	[0.000]	[0.000]	[0.000]
10	ε	0.060	0.063	0.116	[0.000]	[0.000]	[0.000]
11	τ_1	1.000+	[1.000]	0.856	1.000+	[1.000]	0.890
12	τ_2	0.586	[0.500]	0.856!	0.611	[0.500]	0.890!
13	τ_3	0.000+	[0.000]	0.856!	0.000+	[0.000]	0.890!
LogLH		–1429.32	–1429.89	–1434.12	–1434.18	–1434.90	–1456.93
χ^2		–	1.14 NS (1)	9.60 ** (1)	9.72 NS (1)	1.44 NS (4)	45.50 ** (4)

NS = p > 0.05; ** = p < 0.01; (N) = number indicating the comparative column; [ ] = parameter is fixed to shown value; ! = parameter is constrained to be equal to the parameter above in the Table; # = model is codominant; + = parameter estimate achieved its limit.

Segregation analysis of diastolic blood pressure

Segregation analysis of diastolic blood pressure was performed on 365 pedigrees (1049 observed individuals) and the results are shown in Table 4, whose structure is the same as the one in Table 3. No additional pedigree exclusion was needed for the acceptance of the MG model of diastolic blood pressure inheritance. As seen from the transmission probability tests, χ_A^2 and χ_E^2, the MG mode of the diastolic blood pressure inheritance can be accepted when the general form of the MG model is tested, as well as for its most parsimonious form. The most parsimonious model was found very similar to the one obtained for systolic blood pressure. It showed codominant MG effects, equal residual variances, and zero correlation between residuals in spouses as well as in parents and offspring. $H^2 = D^2$ was found to amount to 36%. The prediction ability of this model evaluated by $R(x,\tilde{x})$ was 0.305, n = 783, for offspring; 0.333, n = 355, for parents; and 0.314, n = 1138 for the total analyzed sample.

Discussion

Composite nature of blood pressure regulation implies a number of different genes responsible for blood pressure variation and susceptibility for hypertension (in addition to all other environmental, temporal and random factors). A number of studies suggested the existence of major gene effect in blood pressure phenotype. The complex segregation analysis is considered a robust but reliable tool for a preliminary selection of traits controlled by a large-effect gene[34]. Acceptance of major gene model indicates a possibility that one gene (or several co-segregating genes) may be responsible for substantial portion of genetic variation in a particular population.

The presented results of segregation analysis clearly showed that the inheritance of systolic and diastolic blood pressure in Middle Dalmatian islander population could be described in terms of a major gene model. By applying the usual transmission probability tests, the hypothesis has been accepted that a significant part of the variation of each blood pressure is controlled by a putative large-effect gene. In the process of the most parsimonious model construction, all possible parameter constraints have been tested and if they are not shown in the most parsimonious model, it means that they were statistically rejected. In particular, the environmental model, describing the trait inheritance without any major gene effect was rejected for both systolic and diastolic blood pressure.

In the present analysis, the hypothesis has been accepted that approximately one third of the variation of sex- and age-adjusted values of systolic (32%) and diastolic (36%) blood pressure is explained by major gene model. The obtained most parsimonious models for both blood pressures are very simple and are described by only four estimated parameters. They showed exactly

the same structure in both blood pressures and have the following characteristics: a) the major gene alleles act in codominant fashion; b) frequency of «hypertensive« allele (A_2) allele is 0.18 for systolic, and 0.15 for diastolic blood pressure; and c) the residual (non-major gene) familial correlation – indicating all other genetic (polygenic) and environmental family effects – is negligible and can be constrained to zero.

Within the context of current genetic-epidemiological studies, one of the most efficient designs is thought to be genetic investigation of isolated populations (preferably recently founded)[20]. The most important reason is low genetic heterogeneity – i.e. expectedly reduced number of genes responsible for determining particular complex phenotype. In island, particularly rural populations with village sizes rarely exceeding 1,000 inhabitants (as in presently investigated population), the significant genetic drift is to be expected, implying that genetic difference among neighboring populations could be expected as well.

Population stratification of island/peninsular populations of Middle Dalmatia in blood pressure variability has already been reported by Smolej and Rudan[25–27]. According to the same authors the age-adjusted prevalence of developed hypertension (systolic BP ≥ 160 and/or diastolic BP ≥ 95 mm Hg), is exceptionally high in this population, being 31.82% in males and 28.23% in females[26]. It has been also shown that the substantial proportion of heterogeneity in blood pressure variation found at the subpopulation level (regions and villages) could be attributed to genetic factors (endogamy and inbreeding)[25–27].

Bearing in mind that segregation analysis was performed here on a pooled sample composed of inhabitants of four (although neighboring) island/peninsula, and that the results showed pedigree sample heterogeneity (explicitly displayed for systolic BP), the presented results should be taken as preliminary. That is primarily true for additional characteristics of the obtained model since in the context of presumed isolation, the allele frequencies and importance of particular «major gene« could differ among subpopulations. Nevertheless, we have found that the segregation analysis performed on larger (pooled) sample provided a major gene signal even in the case of subpopulation heterogeneity, which justifies further search for particular subpopulation in which the involvement of more complex genetic-epidemiological tools would be effective.

Conclusion

The results of the complex segregation analysis of blood pressure in Middle Dalmatian island/peninsular population have showed that the major gene model cannot be rejected. High prevalence of hypertension detected in examined non-selected population, with a trend for the prevalence of hypertension to be increasingly higher as the village is more endogamous and inbred, along with heterogeneity detected by segregation analysis found in the investigated population points to the need of further genetic investigation of blood pressure in this population. The forthcoming investigations applying segregation analysis of blood pressure for each island could help finding the population with the most pronounced one--gene signal and thus with the highest prospects for further molecular genetic investigation of hypertension.

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ANALIZA SEGREGACIJE SISTOLIČKOG I DIJASTOLIČKOG KRVNOG TLAKA U OTOČKOM STANOVNIŠTVU SREDNJE DALMACIJE

S A Ž E T A K

Analiza kompleksne segregacije sistoličkog i dijastoličkog krvnog tlaka provedena je na obiteljskim podacima seoskog stanovništva srednjodalmatinskih otoka Brača, Hvara i Korčule te poluotoka Pelješca. Svrha provedene analize bila je prepoznati potencijalnu prisutnost jednog gena velikog učinka (tzv. major gena) odgovornog za visoku prevalenciju hipertenzije u ovoj populaciji (standardizirana po dobi prevalencija razvijene hipertenzije iznosi 31.82% kod muškaraca i 28.23% kod žena). Analiza je napravljena na uzorku 389 obitelji (dvije i tri generacijske) koje su imale od 2 do 19 izmjerenih članova (ukupno 1126 ispitanika, 526 muškaraca i 660 žene, dobi od 17 do 83 godine). Kako je obiteljski uzorak dio populacijskog uzorka odabranog metodom slučajnog odabira ispitanika iz biračkih popisa koji je uključivao 22.6% populacije, ovaj uzorak može se smatrati reprezentativnim za ispitivanu populaciju. Primjenom uobičajenih testova vjerojatnosti nasljeđivanja, major genski model prihvaćen je kako za sistolički, tako i za dijastolički krvni tlak. Najparsimoničniji model pokazao je da: a) nasljedna komponenta oba krvna tlaka u ovoj populaciji može se pripisati učinku major gena koji je odgovoran za 34% (sistolički) i 36% (dijastolički) varijabilnosti krvnog tlaka; b) aleli tog major gena djeluju kodominantno (tj. aditivno); c) učestalost alela za visok krvni tlak (A_2) je 18% (sistolički) i 15% (dijastolički); d) rezidualna obiteljska koreliranost (ne major-genska) je zanemariva. Kako rezultati također indiciraju heterogenost uzorka u genetičkoj determiniranosti sistoličkog krvnog tlaka, dobiveni rezultati opravdavaju daljnju potragu za potencijalno najpogodnijom subpopulacijom za nadolazeća genetičko-epidemiološka istraživanja hipertenzije.