

Overview of Human Population-Genetic Studies in Bosnia and Herzegovina during the Last Three Centuries: History and Prospective

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ABSTRACT

Modern Bosnia and Herzegovina is a multi-ethnic and multi-religion country, with a very stormy history. Certain archaeological findings indicate continuous population of its territory since the Paleolithic. In time, vast number of different factors jointly influenced fascinating diversity of local human populations. A great number of small, more or less isolated, indigenous populations, make this area quite attractive for population-genetic surveys of different levels and approaches. Austro-Hungarian military physicians conducted the very first known bio-anthropological analyses of Bosnia-Herzegovina population at the end of the 19th century. Thus, the first step towards resolving the genetic structures of local B&H human populations was made. The studies that followed (conducted throughout most of the 20th century) were primarily based on the observation of various phenotypic traits. This stage was followed by the examination of various cytogenetic and fundamental DNA based molecular markers. The efforts undertaken over the last three centuries revealed »human genetic treasure« in Bosnia and Herzegovina. However, even now, after all the studies that were conducted, many interesting features remain to be discovered and described within the existing local human populations.

Key words: population genetic studies, phenotypic traits, molecular markers

Introduction

The sources discussing the history of the region state that the area of modern Bosnia and Herzegovina has been inhabited at least since Neolithic¹. However, the latest archeological findings indicate continuous population since Paleolithic². In the early Bronze Age, this region was populated by different Indo-European tribes known as the Illyrians, which established probably the first known civilization in this part of Europe³. After one hundred-year long war Illyrian provinces were conquered and, thence on, controlled by the Romans for more than half a millennium⁴. During that time, Latin-speaking settlers from all over the Empire settled among the Illyrians. Furthermore, Roman soldiers were encouraged to retire in the region¹. Following the fall of the Roman Empire this area remained a borderline between the two ensuing cultures –Eastern and Western empires. Such geographical position destined it to become plunder ground

for various tribes as well as great ethnic crossroads in the coming ages.

Therefore, the contacts between the local population and the first immigrants (the Avars and the Slavs) that massively infiltrated the region in the immediate future were frequent. Two mayor events, along with a number of minor historical episodes, laid the foundations for what is contemporary structure of B&H human population. The first of those is large migration of the peoples during the 6th and 7th centuries, which brought about the final collapse of Roman Empire and moved different Gothic and Slavic clans into the area. The second mayor event is the expansion of the Ottoman Empire into this part of the Balkans in the fifteenth century, which caused numerous migrations during the following half of the millennium⁵.

TABLE 1
BRIEF HISTORICAL OVERVIEW OF HUMAN POPULATION-GENETIC STUDIES IN BOSNIA AND HERZEGOVINA

Period	Phenotypic and genotypic traits	Sample	Level of data analysis
1887–1905	Height, weight, eye color, hair color, lifestyle	B&H soldiers in Austrian Army and B&H citizens from six, mostly »urban areas«	Arithmetical mean, proportional data
1934–1935	ABO, Rh i MN	Citizens from mostly urban areas	Frequencies of phenotypic and genotypic traits
1953–1966	Blood type		Genetic equilibrium test.
1967–1976	Set of biochemical, physiological, static and dynamic morphological traits	Citizens from mostly urban areas	Complex genetic distance
1977–2002		Citizens from mostly rural area	
2002 →	Autosomal STRs, mtDNA (HV1, HV2)	Citizens from the isolated rural areas	Complex genetic distance
2004. →	NRY-chromosome STR and bi-allelic (SNP indel)	Representative sample of the B&H human population	Haplogroups and haplotypes frequencies
2005 →	Population based studies – genetic markers possibly linked to schizophrenia and different types of cancer – cytogenetic markers possibly linked to »depleted uranium« syndrome	Targeted groups and sample of the B&H human population	Frequencies, arithmetical mean, statistical tests of significance Synthetic statistics

The historical events left their stamp on the structure of recent B&H inhabitants and created fascinating diversity of local human population. Great number of small, more or less isolated, indigenous populations, indicate this area as a very attractive one for population-genetic surveys of different levels and approaches. This paper is a short historical overview (Table 1), initiated in our earlier publications^{5,6}, of the »Bosnian genetic treasures« studies that were performed over the last three centuries.

Observation of Phenotypic Traits in B&H Human Population

The very first known bio-anthropological survey of Bosnia-Herzegovina population that was conducted by Austria-Hungarian military physicians may be considered an initial phase in determining the genetic structure of B&H human population⁷. In 1887, Austria-Hungarian military physician Himmel published the first frequencies of heritable qualitative traits using data on average height, weight, eye color, hair color, and other anthropological (body) measures in group of 180 Herzegovinian soldiers recruited by the Austrian Army⁸. In this study, he applied the same approach as in the studies conducted in the other regions of Austria-Hungarian Empire. Almost one decade later, another Austrian physician performed, judging by the general approach and the big sample size (3803), significant study⁹. Weissbach subdivided his sample according to the geographical origin of the subjects in 6 sections located in 6 different counties developed around big cities (Figure 1) and investigated, for the first time, possible differences among »Bosnian Catholics, Muslims (Mohammedans) and Orthodox (Greek-Orthodox church)«

The same author compared these results with other regional Slavic populations a few years later, searching



Fig. 1. First population study with samples collected directly in B&H – Weissbach 1895⁹.



Fig. 2. First comparison of B&H and other regional data – Weissbach 1895¹⁰.

for similarities as well as differences among them (Figure 2,¹⁰). Weissbach developed interesting »questionnaire approach« to the study and some of his questions may be considered quite unusual today, such as: What is an average marriage age of women?; What kind of family hierarchy exists between a wife and a husband?; What an average duration of nursing?; What is the preferred position in nursing? etc.

During the period prior to the World War II various studies on distributions of ABO, Rh and MN blood types in the area of Former Yugoslavia including Bosnia and Herzegovina were performed^{11,12}. However, these studies did not treat subjects according to their origin. On the other hand, some authors, possibly responding to the concurrent political situation in Europe, performed studies with the main goal of determining the races and racial biodiversity in Yugoslavia, including Bosnia and Herzegovina (Figure 3,¹³).

Research into blood types distributions, but now clearly aimed at the examination of population diversity of B&H inhabitants, continued after the WWII^{14–16}. The first reliable and medically relevant data about ABO, Rh and MN blood groups distributions in Bosnia and Herzegovina were published by Kaunic et Grin¹⁷, Boskovic¹⁸, Bucic¹⁹ and especially by Berberovic^{20–24}.

Besides the analysis of blood groups, investigation of local human population structure and gene frequencies included various other observations such as a set of biochemical and physiological^{25–34} and static and dynamic morphological traits^{35–42}.

The next phase included more sophisticated study approach such as the analysis of genealogy and genetic distance based on an array of biochemical, physiological and morphological traits. Between 1980 and 1991 significant number of resulting papers was published^{43–51}. These surveys included over 7100 subjects, which represented approximately 0.16% of the total B&H human population from that time. Overall, 15 characters were observed: ABO blood groups, ABH antigen secretion, PTC tasting, red color vision, green color vision, ear lobe type, fissured tongue, chin dimple, midphalangeal hairiness, nail form, position of distal phalange of the little finger, digital index, tongue rolling, distal and proximal extensibility of the thumb.

Estimation and detection of specificity in the examined local human populations (regarding its ethnic and geographic background, propagation isolation, migratory status, patrilocality, reduced effective population size etc.) were highlighted central topics in all these studies. As a result of all this work, another population-genetic approach was introduced and used in the most studies from that time (index of genetic specificity^{43–45}). Currently, biochemical, physiological and morphological markers are still used, even after the introduction of various molecular markers in human population-genetics studies in Bosnia and Herzegovina. In order to estimate the influence of war caused massive migration on genetic structure of local populations the same markers and methods of 20 years ago were employed once again⁵².

As the results obtained through the analysis of phenotypic markers serve as a good model for additional test-



Fig. 3. First studies of races and racial biodiversity in Yugoslavia (including Bosnia and Herzegovina – Škerlj 1938¹³).

ing of new possible theoretical hypothesis and approaches, more studies can be expected in this, the most fruitful field of B&H population genetics until today.

Observation of Molecular Markers in Recent B&H Human Population Studies

Initiated by very interesting studies from the closest neighborhood⁵³, the very first steps were taken towards the analysis of a variety of fundamental, molecular markers. Nuclear and mitochondrial DNA markers were applied in diversity analyses of isolated Bosnia-Herzegovina mountain populations at the beginning of this century (Figure 4, ^{54–57}). Allele frequencies, nuclear genetic diversity (based on the observation of 15 STR loci) among sampled groups and genetic distance between them, together with some other analysis parameters were examined. In addition, the data were complemented by the results of other analysis of mtDNA HV1 and HV2 regions to obtain integral »molecular picture« of actual existing relations on the field. The existence of classic »islands in the land« in this Bosnian mountainous region, as main goal of these studies, was ascertained.

Following the analysis of STR marker variation, autosomal⁵⁸, and Y-chromosome markers⁵⁹ were studied in order to incorporate molecular genetic diversity of B&H into regional and European frame⁵, but also to provide necessary reference for statistical calculations used in forensic genetics. In order to ensure the most relevant calculation, the data are still periodically updated⁶⁰.

Finally, the most recent results were obtained by observing Y-chromosome biallelic markers in B&H population. Certain preliminary data population was concurrent with earlier regional studies^{61–62}. This study was constructed on the ground of regional data and designed to include 256 male individuals (Figure 5)^{63,64}. The results of it showed that the three populations (three main Bosnian and Herzegovinian ethnic groups) were genetically extremely close to each other, and closely related to



Fig. 5. Y-chromosome (biallelic markers) study of representative B&H human population sample (256 male individuals from more than 50 towns) – Marjanović 2005⁶³.

other populations in the Balkans. Of course, further elaboration of this issue required additional studies with multidisciplinary approach, application of additional molecular markers, expansion of the sample and structural investigation of each ethnic group⁵, as well as the analysis of ancient genetic material from the archeological skeletal samples.

Regardless of relatively short duration of molecular genetic survey in recent B&H human population, significant results were already obtained. Thus, a lot should be expected from other, similar studies very soon.

Population Based Human Genetic Association Studies

During the earlier elaborated period of intense infrastructure and human resources development in the area of population genetic studies, the knowledge about com-

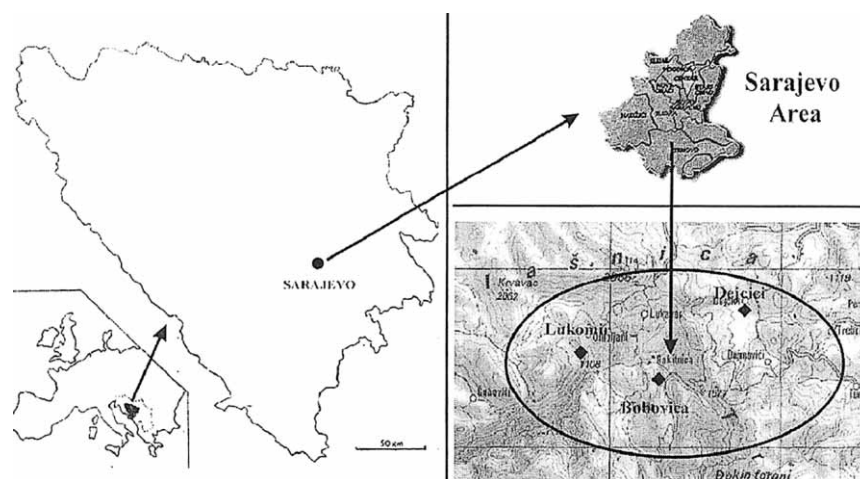


Fig. 4. First studies of isolated B&H mountain populations by usage of molecular markers – Marjanović 2004⁵⁴.



Fig. 6. Preparation of tumor specimens for DNA/RNA extraction.

plex genetic traits and methodology of their dissection was simultaneously accumulated. The main approach in population based genetic association studies is generally based on relative differences in allele, genotype or haplotype frequencies distribution between two population subgroups – case (experimental) and control group. Positive association of certain value with the analyzed trait or condition (normal or abnormal character) may be an indication of positive gene identification, but in most cases this finding needs to be replicated in order ascertain true association. Application of the latest molecular genetic techniques in Bosnia and Herzegovina positively influenced development of scientific research in this field.

Population based human genetic association studies in Bosnia and Herzegovina may generally be divided into two main streams with overlapping methodology and infrastructure. Provisionally, both are classified as fundamental establishment of research capacities for common diseases with clear genetic background: major mental disorders (schizophrenia and bipolar disorders) and common cancers (breast and colon cancer).

Strategy of genetic association analysis in identification of possible molecular-genetics markers was applied in the study of genetic predisposition to major psychotic disorder – schizophrenia – in patients from Bosnia and Herzegovina. Case-control design was applied in association analysis of ten putative candidate regions (at chromosomes 1, 5, 8, 12, 13 and mtDNA) observed at allele, genotype a haplotype level. The most significant findings are related to putative position at 5q region⁶⁵ that, according to the previous studies, might be a possible locus of schizophrenia gene. Further research in this field is oriented at correlating the 5q region with larger number of linked genetic markers in order to replicate positive findings.

Unfortunately, the incidence of various cancer types in Bosnia and Herzegovina has dramatically increased over the last few years. Recent molecular-genetics studies in the field of genetic basis of common cancers are focused on possible population genetics specificity of B&H

population. In that respect tumor databanks were compiled containing corresponding DNA, RNA and cDNA sections as well as the section harboring general data about patients. Procedures for successful tumor transport and conservation, protocols for genetic analysis and storage (Figure 6,⁶⁶) as well as complex genetic analysis using sequence specific genotyping of oncogenic factors (BRCA1, TP53 etc.) were established^{67,68}. Further research activities in that sense will be focused on genotype-phenotype correlation analysis between the established genetic signatures and specific pre-treatment and post-therapeutical endpoints.

Population Based Cytogenetic Association Studies

During the last war conflict, thousands of B&H citizens were unfortunately exposed to various genotoxic agents. Broader cytogenetic investigation of Bosnian populations was initiated after UNEP confirmation of depleted uranium presence in the environment⁶⁹. Such sad occasion inaugurated and oriented scientific research in a somewhat unexpected direction.

This, a bit controversial, research, included analysis of peripheral blood samples from three local populations: 1.) individuals who lived in the area of Sarajevo during and after the war, where they were directly exposed to potential subsequent genotoxic agents, 2.) employees of the Tank Repair facility in Hadzici (small city near Sarajevo that was heavily shelled with depleted uranium charged ammunition in 1995), who were directly exposed to depleted uranium in their professional and personal environment, and 3.) inhabitants of West Herzegovina (Posušje) who were not exposed to war activities at all.

Individuals with increased frequency of micronuclei were found in all the three analysed populations, in particular in the Hadžići population. Arithmetic mean of frequencies of binucleated cells with micronuclei and micronuclei in binucleated cells in population from Hadžići, deviate significantly in comparison with the results from the other two populations^{70,71}.

Pearson's correlation coefficient illustrated significant correlation between the results of micronucleus test and still unpublished results of chromosome aberrations analysis, confirming fidelity of the applied cytogenetic tests and recommending them for similar future investigations.

Continuous monitoring and control of the environment and health of the exposed individuals are essential. Further possible comprehensive research of genotoxic effects of depleted uranium in other local populations should help in establishing adequate mechanisms and measures for the protection of recent and future generations.

Conclusion

Describing something that lasts for three centuries as »a beginning« is quite unusual. However, that is the

truth in the case of human population-genetic studies in Bosnia and Herzegovina. There are still many interesting features hidden within the existent diversity of local

human populations in this small, but intriguing, country that are still waiting to be discovered and described.

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PREGLED HUMANIH POPULACIJSKO-GENETIČKIH ISTRAŽIVANJA U BOSNI I HERCEGOVINI TIJEKOM POSLJEDNJA TRI STOLJEĆA

S A Ž E T A K

Moderna Bosna i Hercegovina predstavlja multireligijsku i multietničku državu sa izuzetno burnom poviješću. Određeni arheološki nalazi sugeriraju da je njen teritorij kontinuirano naseljen još od doba Paleolitika. Tijekom tog vremena, zajedničkim djelovanjem različitih faktora oblikovana je biološka raznolikost recentne bosansko-hercegovačke humane populacije. Prisutnost relativno velikog broja manje ili više izoliranih lokalnih populacija promoviralo je lokalno stanovništvo kao izuzetno zanimljiv predmet populacijsko-genetičkih istraživanja najširega spektra. Kao prva zvanično zavedena antropološka studija javlja se ispitivanje koje su sproveli austrijski liječnici još krajem 19. stoljeća. Na osnovu dobivenih rezultata ovo istraživanje se uistinu može uzeti kao inicijalni moment »razotkrivanja« genetičke strukture bosansko-hercegovačkoga stanovništva. Nakon toga je sproveden čitav niz zanimljivih istraživanja koja su se u svojim ranijim fazama zasnivala prvenstveno na opservaciji fenotipskih karakteristika. U novije vrijeme realiziran je veliki broj studija koji je ispitivao »bosansko genetičko blago« primjenom velikoga broja molekularnih biljega. No, čak i danas, nakon svih tih populacijsko genetičkih »screeninga« Bosna i Hercegovina i dalje krije veliki broj »genetičkih unikata« koji čekaju da budu otkriveni i opisani.