Frequency of *CCR5*Δ32 allele in healthy Bosniak population

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Abstract

Recent evidence has demonstrated the role of *CCR5*Δ32 in a variety of human diseases: from infectious and inflammatory diseases to cancer. Several studies have confirmed that genetic variants in chemokine receptor *CCR5* gene are correlated with susceptibility and resistance to HIV infection. A 32-nucleotide deletion within the *CCR5* reading frame is associated with decreased susceptibility to HIV acquisition and a slower progression to AIDS. Mean frequency of *CCR5*Δ32 allele in Europe is approximately 10%. The highest allele frequency is observed among Nordic populations (about 12%) and the lowest in the regions of Southeast Mediterranean (about 5%). Although the frequency of *CCR5*Δ32 was determined in numerous European populations, there is a lack of studies on this variant in the Bosnia and Herzegovina population. Therefore, the aim of our study was to assess the frequency of *CCR5*Δ32 allele in the cohort of Bosniaks and compare the results with European reports. *CCR5*Δ32 was detected by sequence-specific PCR in a sample of 100 healthy Bosniaks (DNA collected 2011-2013). Mean age of the cohort being 58.8 (±10.7) years, with 82% of women. We identified 17 heterozygotes and one mutant homozygote in study group, with mean Δ32 allele frequency of 9.5%. *CCR5*Δ32 allele frequency among Bosniaks is comparable to that found in Caucasian populations and follows the pattern of the north-southern gradient observed for Europe. Further studies on larger cohorts with adequate female-to-male ratio are necessary.

KEY WORDS: cytokine receptor; del32 variant; genetic epidemiology; HIV susceptibility

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INTRODUCTION

Chemokines are cytokines crucial for leukocyte migration into inflammatory sites, where they stimulate cellular differentiation or activation. Additionally, their role in the pathogenesis of several immune-mediated diseases has been recognized [1-3]. Chemokines are divided based on the tertiary structure and cysteine placement near the N-terminus with two major subfamilies. One major chemokine subfamily is called "CXC" because the two amino acids nearest the N-termini of these proteins are separated by a single amino acid. On the other hand, second major subfamily is called "CC" because these two cysteines are adjacent [4,5].

One of the most commonly studied chemokine receptors is CCR5- a G protein coupled receptor inhibiting cAMP production, stimulating of Ca2+ ion release, and being the activator of MAP and Jun-N-terminal kinases [6].

In vitro studies identified potent CC-chemokine activators of CCR5 i.e. CCL3 (chemokine ligand 3, also known as macrophage inflammatory protein-1a), CCL4 (macrophage inflammatory protein-1b) and CCL5 (also known as RANTES - regulated on activation normal T cell expressed and secreted) [7].

Chemokine receptor *CCR5* was cloned in 1996 and is encoded by *CMKBR* gene located on 3p21.31 [8,9]. *CCR5* gene is polymorphic and these DNA alterations might affect gene expression and thereby protein function [10]. A 32 base pair deletion (*CCR5*Δ32, *CCR5*del32) within the *CCR5* gene leads to a frame shift and loss of receptor function as well as inability to bind the specific ligands [11]. The CCR5 receptor is a major entry site for macrophage-tropic (CCR5 tropic) HIV-1 strains into host cells. *CCR5*Δ32/Δ32 homozygotes, lacking functional CCR5, are completely protected against infections with these HIV strains. Clinically it was shown that *CCR5*Δ32 allele is not only associated with decreased

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susceptibility to HIV infection, but is also linked to the delay in the progression towards AIDS [12]. Additionally, recent studies have confirmed the protective role of *CCR5*Δ32 allele with the course of certain diseases including hepatitis C, multiple sclerosis, acute myocardial infarction, atherosclerosis and rheumatoid arthritis [1-3, 13, 14]. Furthermore, the recently reported fact, that this allele is a risk factor for clinical manifestations of the West Nile virus infection, is tremendously interesting [15].

The frequency of *CCR5*Δ32 allele has been extensively studied in Europe and worldwide. Several hypotheses regarding *CCR5*Δ32 origin and persistence in the human population have been proposed. Lucotte ***et al.*** suggest that the *CCR5*Δ32 spread with the Vikings [16]. In this case, this would result in lower mutated allele prevalence in the areas where their expansion was limited: Balkans and South of Europe. An alternative hypothesis administered bubonic plague and viral diseases e.g. smallpox or viral hemorrhagic diseases, Ebola or Marburg viruses as the cause of *CCR5*Δ32 spread [17, 18].

This genetic mutation is most commonly found in populations of European ancestry being rare among other populations. Among Caucasians, it is the most prevalent in Sweden and Great Britain (12.7 and 12.3%, respectively) [4, 6, 19-21]. This allele has not been found, or is almost absent among South American native Indians (0%), Chinese cohorts (0%) and Egyptians (0.6%) [22-24].

To the best of our knowledge there are no data of this variant in the Bosniak population, which would complement the gaps in epidemiology European frequency of Δ32 allele *CCR5*.

We also wanted to fill the gaps for polymorphism CCR5 (decreased susceptibility to HIV infection among subjects with Δ32 allele) because Bosnia and Herzegovina is a country progressively opening to tourism. Therefore, the aim of our study was to assess genetic epidemiological data in the cohort of Bosniaks.

MATERIALS AND METHODS

Subjects

The study group consisted of 100 healthy Bosniaks, inhabitants from Bosnia and Herzegovina aged from 24-82 (mean: 58.8±10.7) years. There were 18 males and 82 females in the study group. Samples were collected at the Laboratory for Molecular Medicine, Center for Genetics, Faculty of Medicine, University of Sarajevo and Department of Gastroenterology and Hepatology, University Clinical Center Tuzla (in 2011-2013). Sample collection was focused on the buccal swabs and venous blood containing EDTA (anticoagulant).

The present study was performed in accordance with the ethical standards and the Declaration of Helsinki. Written informed consent was obtained from all participants.

DNA extracting and genotyping of CCR5Δ32

Genomic DNA from buccal swabs was extracted by PrepFilerTM Forensic DNA Extraction Kit (Life Technologies USA). QIAamp DNA Blood Mini Kit (QIAGEN, Hilden, Germany) was used to extract genomic DNA from whole blood samples. The extraction was performed following to the manufacturer's protocols. Samples of DNA were stored at 4°C for further analyses.

For the analysis of CCR5Δ32 mutation, sequence specific polymerase chain reaction (PCR) was run using the following primer pair: forward 5'-GCGTCTCTCCCAGGAATCATC-3' and reverse 5'-GGTGAAGATAAGCCTCACAGCC-3' (TIB MOL BIOL, Poznań, Poland). The protocol of amplification was previously described [25]. All resulting reaction products were electrophoresed on a 3% agarose gel (Agarose DNA Grade Electran) stained with DNA-star dye (Lonza, Inc, Rockland, USA), and visualized under UV light. The wild type and mutant Δ32 allele were detected as 242 and 210 base pair fragments, respectively (Figure 1). We verified the correctness of results by performing re-genotyping of randomly selected samples. All results were reliable.

RESULTS

This is an epidemiologic study of the Bosniak population with the aim of determining the frequencies of *CCR5*Δ32 allele known to be associated with susceptibility and resistance to

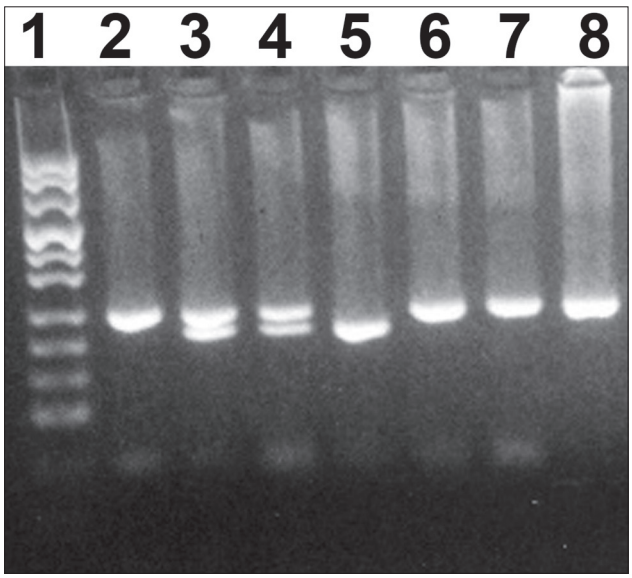

FIGURE 1. Genotyping of theΔ32 polymorphism in the CCR5 gene. Line 1- pUC Mix Marker 8, ready to use (Fermentas, Latvia). Lines- 1, 6, 7, 8 - wt/wt genotype. Line 3, 4- wt/Δ32 genotype. Line 5- Δ32/Δ32 genotype

HIV infection. *CCR5*Δ32 allele frequency was determined in 100 healthy Bosniaks with identification of 17% CCR5 wt/Δ32 heterozygotes and 1% Δ32/Δ32 homozygotes. The results were conforming to the expected Hardy-Weinberg equilibrium (χ^2 = 0.013; p = 0.909), and overall CCR5 Δ32 allele frequency in the group was 9.5%.

DISCUSSION

Study of the inter-population differences in the distribution of the key genetic variation, including *CCR5*Δ32 mutation, commonly associated with diseases susceptibility and diseases progression provides vital insight into human molecular epidemiology. This study is filling the gaps in the knowledge on the human genetic variation for European countries. We also wanted to fill the gaps for polymorphism *CCR5*, despite the fact that the HIV infection is still uncommon among Bosniaks, since Bosnia and Herzegovina is a country progressively opening to tourism. Distribution of the *CCR5*Δ32 variant in the studied group is in accordance to the frequencies observed for the Caucasian populations. Its mean frequency among subjects of European descent is around 10%, with a North to South decreasing gradient. The only exception to this gradient was a population of Ashkenazi Jews, where observed *CCR5*Δ32 allele frequency was approximately 20%, probably due to a founder effect or genetic drift [26, 27]. In the normal Caucasian population, the genotype frequencies are approximately 1% for Δ32/Δ32 and between 10 and 15% for wt/Δ32 heterozygotes [28, 29].

The highest allele frequencies are observed among North European populations - for example in Denmark being 12.9% (n=105), Sweden 12.7% (n=1057) and Great Britain 12.3% (n=367), but also a high prevalence of the mutant allele was observed in Slovakia 14.4% (n =335) [4,6,19-21,29, 30]. The *CCR5*32 allele frequency among European populations decreases in the Southern Europe being 4.6% in Serbia (n=352), 5.0% in Southeast Mediterranean, Croatia and Italy (n=1443, 1255 respectively) [13,21,31-38] and 7% in Spain (n=1242) [14,39-43]. Similar studies conducted from Germany and Poland showed that *CCR5*Δ32 allele frequency is approximately 10.0% [44-51].

Results of this study should be compared to the neighboring population of Croats where the frequency of the *CCR5*Δ32 allele was found to be 5% (n=1443) and Serbs (n=352) 4.6% [31, 32, 34,36]. Allele frequency observed in our report was notably higher for the Bosniaks. The frequency of the *CCR5*Δ32 allele among cohort from Bosnia and Herzegovina was also higher than that reported for Italy (5%) [13, 21, 31, 33, 35, 37, 38].

On the other hand, in our study it was found that the *CCR5*Δ32 allele frequency among Bosniaks was comparable to that found in other North-European Slavic Caucasians: Poles (10.0%, n=1049), Czechs (10.8%, n=933), Russians (9.1%, n=171) and Slovenes (8.3%, n=495) [18, 44, 45, 47, 48, 50, 52- 54]. This value approximately agrees with the north-south gradient of distribution observed for Europe: Sweden (12.7%), Great Britain (10.9%), Germany (10.3%), Poland (10.0%) and Bosnia and Herzegovina (9.5%) and supports the hypothesis of a European origin of this allele and its introduction to the continent through migration [4, 6, 19-21, 44-50] (Figure 2).

CONCLUSION

*CCR5*Δ32 allele frequency among Bosniaks was found to be 9.5% and is comparable to that found in Caucasian

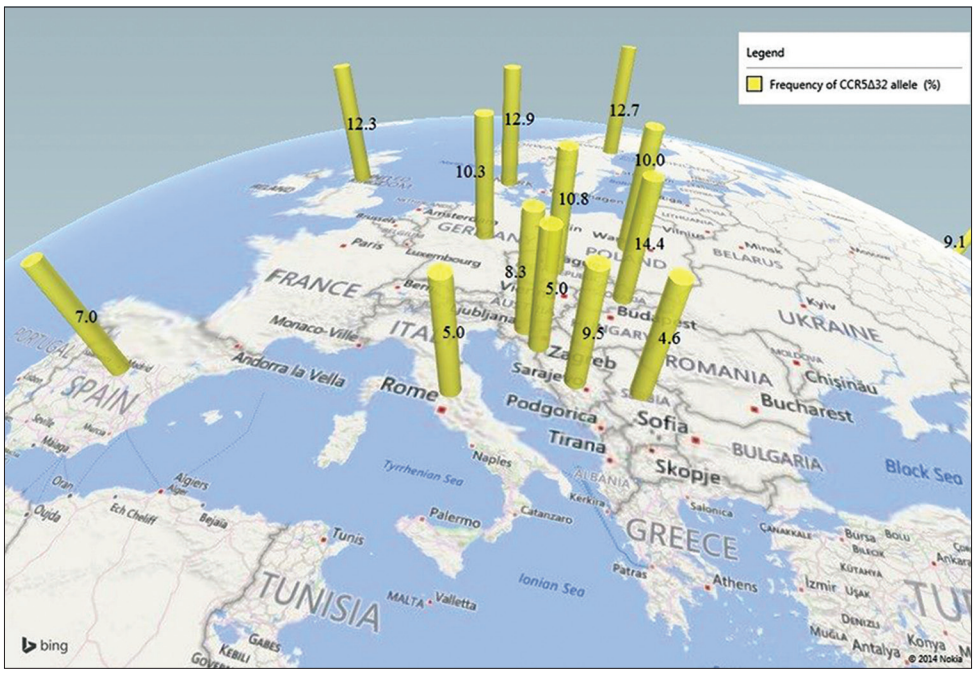

FIGURE 2. Frequency of the CCR5Δ32 allele in defined populations

populations following the pattern of the north-southern gradient observed for Europe. Further studies on larger cohorts with adequate female-to-male ratio are necessary to confirm a frequency of allele *CCR5*Δ32 in the cohort of Bosniaks. In our opinion it would be interesting to examine and to fill the gaps in the genetic epidemiology data for frequency of allele Δ32 *CCR5* for Bosnian Croats and Bosnian Serbs.

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DECLARATION OF INTEREST

The authors state no conflict of interests.

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