Pathol. Oncol. Res. (2012) 18:177–182
DOI 10.1007/s12253-011-9425-4

RESEARCH

The Consequence of a Founder Effect: CCR5-Δ32, CCR2-64I and SDF1-3'A Polymorphism in Vlach Gypsy Population in Hungary

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Received: 5 April 2011 / Accepted: 31 May 2011 / Published online: 11 June 2011

Abstract Frequencies of genetic polymorphisms of the three most frequent HIV-1 resistance-conferring alleles playing an important role in HIV-1 pathogenesis were analysed in Vlach Gypsy populations living in Hungary, as the largest minority. Mutations in the encoding genes, such as CCR5-Δ32, CCR2-64I and SDF1-3'A are shown to result in protective effects against HIV-1 infection and disease progression. 560 samples collected from Vlach Gypsy individuals living in 6 North-East Hungarian settlements were genotyped by PCR-RFLP method. Overall allele frequencies of CCR5-Δ32, CCR2-64I and SDF1-3'A were found as 0.122, 0.186 and 0.115 respectively. All the observed genotype frequencies were in accordance with Hardy-Weinberg equilibrium . In regions, however, Vlach Gypsies live in majority and in ethnically homogenous communities, a higher CCR5-Δ32 mutations were found, with allele frequencies of 0.148 and 0.140 respectively, which are remarkably higher than those in general Hungarian people, and ten times higher than in regions of North-Western India from where present day Hungarian Gypsies originated in the Middle Ages. In the background of this higher CCR5-Δ32 allele frequency in the population analysed in our study a genetic founder effect could be assumed. Allele frequency of CCR2-64I was found to be among the highest in Europe. SDF1-3'A allele frequency in Vlach Gypsies was significantly lower than in ethnic Hungarians. 63% of the total 560 individuals tested carried at least one of the mutations studied. These results could partially explain the low incidence of HIV/AIDS among Vlach Gypsies in Hungary.

Keywords CCR5 · CCR2 · SDF1 · HIV-1 · Gypsy · Hungary

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Introduction

Gypsies as the largest minority represent approximately 6% of the Hungarian population. Gypsies living in the present in Hungary originated from India in the Middle Ages and some of the Gypsy subpopulations preserved their ethnic identity due to their socio-cultural conditions. Because of this, many genetic examinations were performed among Gypsies in Hungary, investigating the genetic background of severe diseases such as different *neuromuscular disorders* (e.g. congenital myasthenia syndrome, limb-girdle muscular dystrophy), *ophthalmologic diseases* (e.g. primer congenital glaucoma, retinitis pigmentosa), *cancer*s (e.g. familiar breast and testicular cancer), *metabolic disorders* (e.g. galaktokinase deficiency) or *complex polygenic neurological disorders* (e.g. tauopathies, Alzheimer's disease, schizophrenia) [1, 2]. In connection with this complex population genetics research, it was particularly interesting to study the three most frequent HIV-1 resistance-conferring alleles. Here we report the analysis of the genetic polymorphism of CCR5-Δ32, CCR2-64I and SDF1-3'A mutations in 560 members of the Vlach Gypsy population with no known history of HIV-1 infection or AIDS symptoms living in 6 villages of North-East Hungary.

Entry of HIV-1 into host cells requires expression of the cellular receptor CD4 and fusion coreceptors. Several chemokine receptors and closely related 7-transmembrane molecules function as coreceptors for HIV entry. Among these, the chemokine receptors CCR5 and CXCR4, which are the principal receptors for macrophage-tropic and T cell-tropic viruses, respectively, are the most commonly used [3]. Some M-tropic HIV-1 strains can use other coreceptors, such as CCR2 or CCR3, to enter into macrophages [4].

The chemokine receptor CCR5 represents the major coreceptor for the macrophage tropic HIV-1 strains. When this coreceptor is not available on the cell surface, HIV-1 is not able to infect the cell. The Δ32 mutation involves the deletion of 32 nucleotides (gtcagtatcaattctggaagaatttccagaca) of the CCR5 gene (encoded on chromosome 3p21.3-p24). The translation machinery encounters a stop codon too soon, resulting in a truncated version of the peptide being manufactured. This mutated version of the protein may remain in the cytoplasm, unable to migrate to the cell surface [5]. It was also demonstrated that CCR5-Δ32 protein interacts with CCR5 and CXCR4 and down modulates their cell surface expression [6]. Individuals homozygous for this mutation are resistant to infection by the HIV-1 virus while those heterozygous for this allele who are HIV-positive have a delayed onset to AIDS of 2–3 years [5, 7]. The CCR5-Δ32 allele is still the most important host factor known to be associated to HIV resistance. CCR5-Δ32 is primarily found in populations of European descent [8]. In Europe its frequency shows a decreasing gradient from North (0.15 allele frequency) to South (0.04) [9, 10]. In non-European populations only sporadic occurrences are observed, probably due to Caucasian admixture in these populations [7, 8].

CCR2 is considered a minor coreceptor for HIV-1 infection. A G-to-A nucleotide substitution at position 190 (counting from the ATG start codon) results in the switch from Valine to Isoleucine at position 64 in the first transmembrane domain of CCR2 [11]. CCR2-64I has been associated with slower disease progression to AIDS [12]. CCR2-64I results in normal levels of expression of the CCR2 receptor and it exerts no influence on the incidence of HIV infection. However, unlike normal CCR2 peptides, the CCR2-64I protein product can preferentially dimerize with the CXCR4 polypeptide, sequestering it in the endoplasmic reticulum [4, 10]. CCR2 and CCR5 genes are separated by only 19 kb on chromosome 3, but CCR2-64I and CCR5-Δ32 are independently associated with delayed disease progression [13]. The frequency of CCR2-64I allele varies from 0.1 to 0.25 among different ethnic populations [4].

SDF1 (CXCL12) is the principal ligand for CXCR4, a coreceptor with CD4 for T-cell tropic HIV-1. The SDF1-3'A is a G-to-A transition at position 801 (counting from the ATG start codon) in the highly conserved 3' untranslated region of the β transcript gene coding the SDF1, causing overproduction of SDF1. This restricts the emergence of X4 HIV-1 strains because SDF1 binds to and blocks the CXCR4 receptors [4, 12, 14]. SDF1-3'A genotype could have a possible late-stage effect on the clinical outcome of HIV-1 patients. The frequency of SDF1-3'A allele varies significantly between different ethnic populations. In Europeans 0.149–0.217, in South Asians 0.06–0.43 allele frequencies were reported [4].

A functional interaction of CCR5/CCR2 and SDF1-3'A might explain enhanced protection against HIV/AIDS. It is suggested that CCR5/CCR2 variants slow disease progression by limiting the number of CCR5 coreceptors that mediate R5 HIV-1 infection and the SDF1-3'A variant restricts the emergence of X4 HIV-1 strains [4, 12].

The present AIDS situation in Hungary is favourable, comparing it to that in the neighbouring Central European countries. The exact definitive number of HIV infected persons belonging to Gypsy population is not known, but the prevalence of HIV among Gypsies is lower than the Hungarian average.

Materials and Methods

Whole blood samples were collected from 560 individuals belonging to Vlach Gypsy population living in 6 North-East Hungarian settlements, namely in Tiszadada, Tiszadob, Tiszalök (North-Tisza region), Tiszavasvári, Tokaj and in villages of a north-east Hungarian county, Borsod (Borsod region).

DNA was isolated from the EDTA anticoagulated blood by Gentra Capture Column Kit (Qiagen).

For determination of CCR5-Δ32 PCR was used with primers 5′-CTTCATTACACCTGC AGCTCT-3′ and 5′-CACAGCCCTGTGCCTCTTCTT-3′ [15]. The 25 μL reaction mixture was set up with 12.5 μL REDTaq ReadyMix (Sigma) containing in final concentration 0.75 unit Taq DNA polymerase, 10 mM Tris–HCl, 50 mM KCl, 1.5 mM MgCl2, 0.2 mM dNTP, 25 pmol of each primer and 2 μL (100–250 ng) genomic DNA. The reaction mixture was subjected to an initial denaturation of 94°C for 5 min followed by 35 cycles of 94°C for 30 s, 55°C for 30 s and 72°C for 45 s. Final extension was done at 72°C for 7 min. The amplified products were analyzed on a 2% agarose gel and bands were visualized on UV-transilluminator. The wild type gene resulted in an 184 bp fragment, while the Δ32 mutant variant resulted in a 152 bp fragment. Heterozygotes produced both of the bands.

CCR2-64I gene polymorphism was studied by PCR–RFLP following the previously described protocols [16]. A 380 bp product of CCR2 gene was amplified using the

following primers: 5′-GGATTGAACAAGGACG CATTTCCCC-3′ and 5′-TTGCACATTGCATTCCCA AAGACCC-3′. The 25 μL reaction mixture was set up with the same conditions as in case of CCR5Δ32 analysis. The reaction mixture was subjected to an initial denaturation at 94°C for 5 min followed by 40 cycles at 94°C for 30 s, 63°C for 30 s and 72°C for 1 min. A final extension step at 72°C for 7 min was also done. 10 μL PCR products were used for the RFLP analysis performed in a 20 μL reaction volume using 4 U *Bse*GI enzyme (Fermentas). After an overnight incubation at 55°C the digested products were analyzed on a 2% agarose gel. The wild type gene was determined by a single 380 bp fragment, while *Bse*GI restriction enzyme produced two bands at 215 bp and 165 bp only when an ATC triplet coding for isoleucine was present. For heterozygotes, three bands at 380 bp, 215 bp, and 165 bp were present.

Detection of SDF1-3'A mutation was confirmed also by PCR-RFLP using primers 5′-CAG TCAACCTGGG CAAAGCC-3′ and 5′-AGCTTTGGTCCTGAGAGTCC-3′ and *Msp*I restriction endonuclease (Fermentas) [17, 18]. The PCR reaction mixture was set up with the same conditions as in case of CCR5Δ32 analysis. PCR run with the following program: 94°C for 5 min, 35 cycles at 94°C for 30 s, 58°C for 30 s, 72°C for 1 min and finally 72°C for 7 min. PCR was followed by a digestion of 10 μL PCR amplicon with 5 U *Msp*I in a 20 μL reaction volume at 37°C for 3 h. Digested products were analyzed on a 2% agarose gel after electrophoresis. For the wild type gene the 302 bp product yielded two bands at 100 bp and 202 bp. For heterozygous mutants, the bands were at 302, 202, and 100 bp and for homozygous mutants there was only a single band at 302 bp.

Statistical methods: allele frequencies were calculated by allele counting. Hardy-Weinberg equilibrium was tested by using a chi-square goodness-of-fit test. Comparison of allele frequencies between Gypsy and other populations was determined using chi-square test. The level of statistical significance was set at 0.05.

Results

The 560 samples collected from Vlach Gypsy individuals were distributed into four groups according to the location of collection. Samples from Tiszadada, Tiszadob and Tiszalök were considered as one group (North-Tisza region) because of the near geographical location, and where Gypsies are living as ethnically homogenous community, as in the Borsod region too. Samples from Tiszavasvári and Tokaj were grouped separately as their exact ethnical distribution was not known. (Table 1). Major differences were found between settlements: allele frequency of CCR5-

Table 1 CCR5-Δ32, CCR2-64I and SDF1-3'A allele frequencies in Vlach Gypsy populations living in different settlements in Hungary

Settlement	Sample	CCR5-delta32				CCR2-64I				SDF1-3A			
	n	wt/wt	wt/mt	mt/mt	Allele frequency	wt/wt	wt/mt	mt/mt	Allele frequency	wt/wt	wt/mt	mt/mt	Allele frequency
Borsod region	270	196	68 (25%)	6	0.148	182	84	4	0.17	214	51	5	0.113
North-Tisza region (Tiszadada, Tiszadob, Tiszalök)	128	93	34 (26%)	1	0.14	93	33	2	0.144	101	27	0	0.105
Tokaj	60	51	8 (13%)	1	0.083	40	17	3	0.191	41	18	1	0.166
Tiszavasvári	102	91	11 (11%)	0	0.054	54	40	8	0.274	81	21	0	0.103
Summary	560	431 (77.0%)	121 (21.6%)	8 (1.4%)	0.122	369 (65.9%)	174 (31.1%)	17 (3.0%)	0.186	437 (78.0%)	117 (20.9%)	6 (1.1%)	0.115

n number of subjects, *wt/wt* wild type, *wt/mt* heterozygous mutant, *mt/mt* homozygous mutant

Δ32 mutation varied between 0.140 or over (Borsod region, North-Tisza region) and 0.054 (Tiszavasvári). In the Borsod region and the North-Tisza region wt/mt heterozygous mutants were found in 25% and 26.6% respectively. This was 13.3% in Tokaj samples, and 11% is Tiszavasvári samples, where the exact ethnical distribution of the Gypsy population is not known. Homozygous mt/mt mutations were also found, in 2.2% of individuals in the Borsod region, and interestingly in 1.6% among Gipsy individuals from Tokaj. In the samples of North-Tisza region it was 0.8%. No homozygous mutation was detected in samples of Tiszavasvári.

When we compared allele frequencies in regions Gipsies live in majority in ethnically homogenous communities such as the Borsod region and the North-Tisza region, the CCR5 allele frequencies were as high as 0.148 and 0.140 respectively. These data are remarkably higher than the 0.11 allele frequency of CCR5 in the general Hungarian population as we and others reported earlier [15, 19]. As a summary, out of the 560 subjects studied, 121 individuals (21.6%) were heterozygous and 8 subjects (1.4%) were found homozygous for CCR5-Δ32 mutation giving on overall allele frequency of 0.122.

In case of CCR2-64I mutation the lowest occurance was 0.144 and the highest 0.274. Genotyping of the CCR2-64I polymorphism revealed 17 homozygous (3%) and 174 heterozygous (31.1%) subjects among the 560 PCR-RFLP analyzed samples giving an overall allele frequency of 0.186. The significantly low CCR5-Δ32 and high CCR2-64I allele frequency observed in Tiszavasvári support our conception to distinguish this group from the other three.

The allele frequency of SDF1-3'A varied between 0.103 and 0.166. 6 homozygous (1.1%) and 117 heterozygous (20.9%) were detected positive for the presence of SDF1-3'A allele giving a polymorphism frequency of 0.115. The observed overall genotype frequencies were in accordance with the Hardy–Weinberg equilibrium, as P(CCR5-Δ32) = 0.88, P(CCR2-64I) = 0.514 and P(SDF1-3'A) = 0.553.

Discussion

In general Hungarian population CCR5-Δ32 allele frequency was found around 0.11, as we and others reported earlier [15, 19]. In our recent study in 398 Vlach Gypsy individuals in two regions of North-East Hungary the allele frequency of CCR5-Δ32 was found 0.148 and 0.140 respectively, which is higher than those in general Hungarian people. Although the occurrence of overall frequency of this protective allele was 0.122 in individuals studied, remarkably higher CCR5-Δ32 mutations were found in regions where Gypsies are living in majority, and in ethnically homogenous communities.

The frequency of CCR5-Δ32 mutation in the studied Vlach Gypsy population of Hungary is similar to data observed in white population of some Northern-European countries. This mutation was found to be rare in North India (<0.015) from where European Gypsies are originated [20–25]. Gypsy population migrated in the 15th century to Europe and they remained genetically different from Hungarians as some data shows. When smaller groups break apart from a large population and migrate away, like Gypsies from India, some mutations occur just in these smaller groups, but not in the surrounding populations, according to the definition of a genetical *founder effect*. Many mutations can cause or influence the same disease, but in a given ethnic group just one mutation occurs frequently because of founder effect. The strict genetic isolation and the high inbreeding coefficient due to consanguineous marriages in Gypsy groups increase the frequency of such mutations. It could be assumed, that in the background of the obtained high CCR5-Δ32 allele frequency in the population analysed in our study there is a founder effect, although it may not as obvious as in cases of the C283Q mutation in limb-girdle muscular dystrophy or the 1267delG mutation in congenital myasthenia syndrome found in Hungarian Gypsy populations [26, 27]. Recent gene flow from Caucasians and the role of positive selection effect in connection with other diseases could also be assumed [28]. Based on the Hardy-Weinberg equilibrium, this selection effect however might lose its impact in recent time, due to the modern health care. However, the observed allele frequencies of CCR5-Δ32 and CCR2-64I in Tiszavasvári samples are in contrast with the other three groups, suggest that these mutations are under genetic modification in this settlement among Gypsies.

Allele frequency of CCR2-64I observed in our study group is 0.186 which is significantly higher than in general Hungarian population (0.114) [29]. The CCR2-64I mutation occurs at more constant frequency across different racial groups than CCR5-Δ32 [17]. In North India 0.09–0.14, in South Indian populations 0.03–0.17 allele frequencies were reported [22, 23, 30]. In Europe the allele frequency ranges from 0.065 to 0.17 [17]. The CCR2-64I allele frequency among Vlach Gypsies living in Hungary (0.186) is even higher than the so far highest frequency (0.17) in Europe, reported in Cyprus [17].

The allelic frequency of SDF1-3'A observed in our study (0.115) was significantly lower than that reported in Hungarian population (0.2126) or even in North Indians (0.146–0.204) [15, 22, 23]. 63% of the total 560 individuals tested carried at least one of the mutations studied. 14.3% of the samples carried two of the examined mutations and 0.5% of the individuals had all the three mutations.

Two other major Gypsy populations live in Hungary, the *Romungro* and the *Beas* populations. The Romungros, also

called Hungarian Gypsies, are assimilated to Hungarians to such an extent that they cannot be considered as a genetically discreted Gypsy population. Similarly to Vlachs, Beas Gypsies however retained their ethnic identity and live rather separately in ethnically homogenous blocks in South-West Hungary. Study of this population is in progress and could complete our knowledge about the occurrence of HIV-1 resistance-conferring alleles in Gypsies living in Hungary in the near future.

Summarizing, we noted that CCR5-Δ32 allele frequency in Vlach Gypsy population living in homogenous ethnic communities in Hungary is higher than that observed in the general Hungarian population and it is also in accordance with the European allele frequencies, and ten times higher than that observed in the land of origin of European Gypsies, in India. CCR2-64I allele frequency was found to be among the highest in Europe, whereas occurrence of SDF1-3'A allele was found relatively lower comparing to data of general Hungarian and even Indian population. Currently there is no definitive explanation for this. 63% of the individuals studied carried at least one of the mutations. However, interpretation of mutation frequencies should be handled cautiously, when comparison of populations is taken by limited number of genetic markers, as the changing climate, environmental pressure, other socie-economic factors, could also influence results.

Our recent results can partially provide an explanation for the low incidence of HIV/AIDS among Vlach Gypsies in Hungary, though exact data about the ratio of Gypsies among HIV infected patients diagnosed so far in Hungary is not known. Due to ethical statement, it is not allowed to register the ethnical state of HIV infected patients in Hungary. None of the 560 Gypsy individuals investigated however, had symptomatic AIDS. Investigation of serostatus in connection with STI pathogens was not the aim of this study.

It is supposed that the number of HIV infections in Hungary will increase due to HIV pandemia and it will influence also Gypsy populations. Therefore the genetic polymorphisms observed could be useful to better characterize the genetic epidemiology of HIV-1 infection, to detect persons at high risk of a faster disease progression and maybe also to influence the future individualization of HAART therapy.

Acknowledgements We thank Prof. Bela Melegh and the Department of Medical Genetics and Child Development, University of Pécs for the DNA samples originated from Borsod. We also thank the expert work of Béla Kemény at the initial phase of the project, and Mónika Kapás for technical support. This research was supported by the Doctoral School of Semmelweis University and partly by OTKA 048917 Research Grant. The research was permitted by the Ethics Committee of Hungarian Council of Medical Sciences (TUKEB: 78/2000).

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