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Prevalence of HIV/AIDS Protective Alleles (CCR5-△32, CCR2-64I, and SDF1-3'A) in Turkish Population

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Research Article

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ABSTRACT

Aims: Genetic variants of the genes encoding Human Immunodeficiency Virus-1 (HIV-1) chemokine receptors and their ligands may be involved in the susceptibility to HIV-1 infection and AIDS progression. The variants most frequently investigated are CCR5-Δ32, CCR2-64I, and SDF1-3'A. In this study, we investigated the frequency of the above polymorphisms within the Turkish population, evaluating their protective genetic contribution against HIV infection.

Methods: A total of 205 participants were recruited among blood donors from Sinop, Turkey. Genotyping was initially performed by polymerase chain reaction (PCR) analysis for the three variants examined and this allowed to analyze 32-bp deletion in CCR5 gene. CCR2 and SDF1 amplicons were further subjected to restriction fragment length polymorphism (RFLP) analysis for genotype determination.

Results: The CCR5-Δ32 allele frequency in our population was 3.17% and no homozygous subjects were detected. Genotyping of the CCR2-64I polymorphism revealed 9 homozygous (4.39%) and 55 heterozygous (26.83%) subjects giving an allele frequency of 17.80%. Screening for the SDF1-3'A polymorphism yielded 12 homozygous (5.85%) and 87 heterozygous (42.44%) subjects with a high allele frequency of 27.07%. The frequency of the CCR5-Δ32 allele in our population seems lower when compared to other Caucasian groups, however, CCR2-64I and SDF1-3'A alleles are common.

Conclusion: The interaction between HIV and the chemokine system advanced our understanding of the pathogenesis of HIV/AIDS and the investigation of resistance-conferring variants in different populations may be useful for prophylactic measures.

INTRODUCTION

Acquired Immune Deficiency Syndrome (AIDS) was first recognized as a new disease in 1981 and a retrovirus, now termed Human Immunodeficiency Virus Type I (HIV-1) was subsequently identified as the causative agent [1]. Simian immunodeficiency virus (SIV) from chimpanzees and gorillas have crossed the species barrier on at least four occasions, leading to HIV-1 group M, N, O, and P in humans, yet among these groups, only HIV-1 group M has spread worldwide [2]. HIV-1 was first identified in 1983 and HIV-2 in 1985. Both viruses infect CD4+ cells of the lymphocyte and mononuclear phagocyte lineages, and have similar genetic structures with nearly identical open reading frames [3]. HIV-1 spreads by sexual, percutaneous, and perinatal routes [1].

Polymorphisms in the genes for HIV coreceptors CCR5, CCR2, and natural ligand of CXCR4, SDF1 play an important role in HIV pathogenesis and transmission. The most important CCR5 coreceptor polymorphism is an inactivating 32 bp deletion in CCR5 gene (CCR5-Δ32) which results in truncation of the CCR5 protein that fails to express on the cell surface. While homozygote

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individuals appear to resist infection and display high resistance to HIV-1 infection, heterozygotes for this mutation appear partially protected against HIV infection and have a delayed and slower disease progression for the onset of AIDS [4-6].

CCR2 is another putative HIV-1 chemokine coreceptor with a less clear role. CCR2 polymorphism results in substitution of an isoleucine for a valine (V→I) at position 64, is located in a transmembrane domain of CCR2. CCR2-64I variant has no protective effect against HIV infection but is associated with a significant delay in the onset of AIDS even in the heterozygous condition both CCR5Δ32 and CCR2-64I are independent and potent additive effects to delay progression to AIDS [6,7].

Stroma cell-derived factor 1 (SDF1) is the natural chemokine ligand of CXCR4, the major coreceptor for T-tropic HIV strains. SDF1-3'A polymorphism is a single nucleotide change of G to A at codon 801 located in the 3' untranslated region of an alternatively spliced mRNA transcript. HIV-infected individuals homozygous for SDF1-3'A variant showed a remarkable protection level against AIDS [6-8].

The global, ethnic and regional distribution of these HIV/AIDS protective variants varies significantly, thus giving each population a different natural genetic resistance profile for HIV infection/AIDS progression. In the present study, we aimed to investigate the frequency of CCR5-Δ32, CCR2-64I and SDF1-3'A polymorphisms in Turkish population and compare the ratios with other populations in the world.

MATERIALS AND METHODS

Study Population

Two hundred five blood samples were recruited from blood donors in Sinop province of Turkey. All the donors were unrelated Turkish residents. The study has been approved by Ondokuz Mayis University research ethics committee and informed consent was obtained from all the participants. Genomic DNA was extracted from 10 ml EDTA treated venous blood samples using the salting-out method [9].

Genotyping

Genotyping for the CCR5-Δ32, CCR2-64I and SDF1-3'A mutations was initially performed by PCR with some modifications using pairs of primers before mentioned in the literature [10]. Since CCR5-Δ32 is a 32-bp deletion (gtcagtatcaattctggaagaatttccagaca) mutation, it was determined with PCR, and the detection of two other mutations (CCR2-64I and SDF1-3'A) was confirmed by PCR-RFLP.

For determination of CCR5-Δ32, 25 µl PCR reaction mixture contained 1x Taq DNA polymerase buffer, 1.5 unit Taq DNA polymerase (Thermo-Fisher Scientific), 2 mM $MgCl_2$, 0.2 mM dNTP, 1 µM of each primer and 1 µl (100-300 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, 63°C for 30 s and 72°C for 45 s and a final extension step at 72°C for 7 min completed the reaction. The amplicons were analyzed on a 2.5% EtBr agarose gel and bands were visualized on UV gel documentation system. The wild type gene (wt/wt) results in 184 bp fragment, while the Δ32 mutant (Δ32/Δ32) results in 152 bp fragment. Heterozygotes (wt/Δ32) produce both of the fragments **(Figure 1)**.

CCR2-64I polymorphism was determined by PCR-RFLP. A 380 bp CCR2 gene product was amplified in 25 µl PCR reaction mixture with the same conditions as in case of CCR5-Δ32. 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, 62°C for 30 s and 72°C for 45 s and a final extension step at 72°C for 7 min completed the reaction. 10 µl PCR products were used for the RFLP analysis performed in a 25 µl reaction volume using 6U BseGI restriction enzyme (Thermo-Fisher Scientific). After an overnight incubation at 55°C, the digested products were analyzed on a 2.5% EtBr agarose gel and bands were visualized on UV gel documentation system. The wild type gene (GG) was determined by a single 380 bp fragment, while restriction with BseGI determined the mutant profile (AA) with the production of two bands at 215 bp and 165 bp. The heterozygotes (GA) produced three bands at 380 bp, 215 bp, and 165 bp **(Figure 2)**.

SDF1-3'A polymorphism was also determined by PCR-RFLP. A 302 bp SDF1 gene product was amplified in 25 µl PCR reaction mixtures with the same conditions as in the case of CCR5-Δ32 and PCR run followed the same program of CCR2-64I. PCR was followed by the digestion of 10 µl PCR products with 6 U MspI (Thermo-Fisher Scientific) in a 25 µl reaction volume at 37°C overnight and the digested products were visualized. The wild type gene (GG) yielded two bands at 100 bp and 202 bp, while the homozygous mutant (AA) was determined with a single band at 302 bp. The heterozygous mutants (GA) produced three bands at 302 bp, 202 bp, and 100 bp **(Figure 3)**.

Statistical Analysis

SPSS 22 statistical package program was used for the analysis. Allele frequencies in the study were calculated by allele counting and the comparison of allele frequencies between Turkish and other populations was determined using z-test statistics. When the allele frequency difference increases between two populations, p value becomes closer to zero; p value increases when the allele frequency difference lowers. Hardy-Weinberg equilibrium was calculated with the R 3.1.3 program. The test results were evaluated at the statistical significance level of α=0.05.

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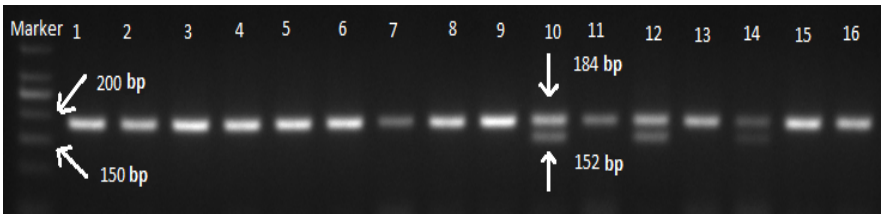

Figure 1. Representative DNA fragments for CCR5-Δ32 allele. Lanes: 1-9) wild-type, 10) heterozygous, 11) wild-type, 12) heterozygous 13) wild-type, 14) heterozygous, 15-16) wild-type, Marker is Gene Ruler 50 bp DNA Ladder.

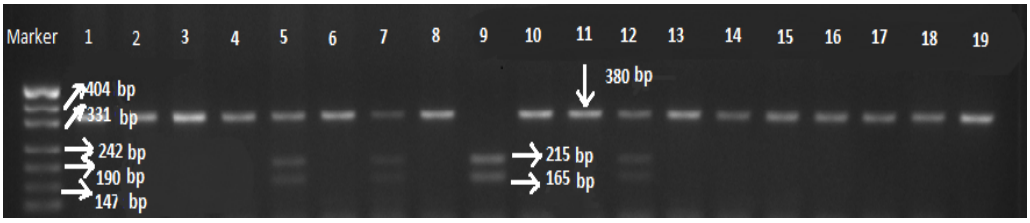

Figure 2. Representative DNA fragments for CCR2-64I allele. Lanes: 1-4) wild-type, 5) heterozygous, 6) wild-type, 7) heterozygous, 8) wild-type 9) homozygous, 10-11) wild-type, 12) heterozygous, 13-19) wild-type, Marker is pUC19 DNA/MspI.

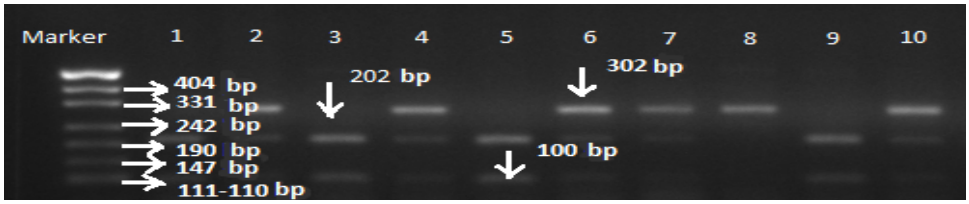

Figure 3. Representative DNA fragments for SDF1-3'A allele. Lanes: 1) wild-type, 2) heterozygous, 3) wild-type, 4) heterozygous, 5) wild-type 6-7) heterozygous, 8) homozygous, 9) wild-type, 10) heterozygous, Marker is pUC19 DNA/MspI.

RESULTS

The genotype and allele distributions for CCR5-Δ32, CCR2-64I, and SDF1-3'A loci in Turkish population are shown in **Table 1**. Genotyping of the CCR5-Δ32 polymorphism revealed 13 heterozygous subjects (6.34%) among 205 PCR analyzed samples giving an allele frequency of 3.17%. No homozygous subjects were detected for CCR5-Δ32 deletion. Genotyping of the CCR2-64I polymorphism revealed 9 homozygous (4.39%) and 55 heterozygous (26.83%) subjects giving an allele frequency of 17.80%. Genotyping of the SDF1-3'A polymorphism displayed 12 homozygous (5.85%) and 87 heterozygous (42.44%) subjects with a high allele frequency of 27.07% **(Table 1)**.

Table 1. Genotypes and allelic frequencies of HIV/AIDS protective mutations within Turkish population.

	wt/wt[a]		wt/mt[b]		mt/mt[c]		Mutated allele frequencies (%)
	n	%	n	%	n	%	
CCR5	192	93.66	13	6.34	-	-	3.17
CCR2	141	68.78	55	26.83	9	4.39	17.8
SDF1	106	51.71	87	42.44	12	5.85	27.07

The frequencies of CCR5-Δ32, CCR2-64I and SDF1-3'A alleles were surveyed in a group of 205 blood donors from both genders with the age ≥ 18 from Sinop, Turkey. It was determined that; 64.6% of the individuals (n=132) tested carried at least one of the polymorphisms studied either in homozygous or heterozygous state, 19% of the individuals (n=39) carried two of the polymorphisms either in homozygous or heterozygous state, and only one individual (0.5%) carried all three polymorphisms investigated in heterozygous state. The 33.2% of the individuals (n=68) carried none of the polymorphisms tested. The observed overall genotype frequencies were in accordance with the Hardy-Weinberg equilibrium, as P(CCR5-Δ32) = 0.639, P(CCR2-64I) = 0.232 and P(SDF1-3'A) = 0.284. **Table 2** shows the allele frequencies of CCR5-Δ32, CCR2-64I, and SDF1-3'A in different populations of the world from previous studies.

Table 2. Frequencies of HIV/AIDS protective alleles in different populations.

Population	n	CCR5-Δ32	CCR2-64I	SDF1-3'A	References
		(%)	(%)	(%)	
Hungary *Vlach Gypsies*	560	12.2	18.6	11.5	[10]
Cretan	200	3.25	11.75	29.75	[11]
Ecuador	225	0.5	16.6	48	[12]
Jordan	540	0.6	17.5	34.2	[13]

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Cameroon	147	0	17.6	100	[14]
North India	500	1.5	9.1	20.4	[7]
Egypt-Syria	200	0.6	-	-	[15]
Central Asian Natives	107	0.5	-	-	[16]
France	1836	9.2	-	-	[17]
North France	-	11.2	-	-	-
South France	-	6.3	-	-	-
South India/Andra Pradesh	525	-	-	-	[18]
Castes and Tribes	277	~0	≤10	17-24	-
Muslims	248	~0	Apr-17	22-35	-
Tunusia	145	1.03	19.31	-	[19]
Israel	-	-	-	-	[20]
Aşkenazi	-	13.8 (n=363)	9.2 (n=142)	-	-
Sefarad	-	4.9 (n=257)	13.4 (n=67)	--	-
Russia/Moscow	171	9.06	10.61	22.18	[21]
Belgium	310	11.9	7.4		[22]
Mexico	472	3.28	-	-	[23]
Poland	1063	-	11.3	14.6	[24]
Japan	393	-	-	34.47	[25]
Colombia	100	4	-	-	[26]
Finland	98	15.8	-	-	[4]
Lithuania	283	11.5	-	-	[4]
Sweden	201	14.2	-	-	[4]
Norway	100	10.5	-	-	[4]
Denmark	100	11	-	-	[4]
Spain	-	-	-	-	[4]
Murcia	100	9.5	-	-	-
Basks	89	6.2	-	-	-
Portugal	101	6.4	-	-	[4]
Italy/Milano	98	8.7	-	-	[4]
Sardinia	100	4	-	-	[4]
Greece	240	5.2	14.6	-	[27]
Greeks in Cyprus	1002	2.9	-	-	[28]
Croatia	303	7.1	-		[29]
Luxemburg	158	10.76	7.39	0.8	[30]
China	-	-	-	-	[31]
Han	1406	0.02	20.44	27.76	-
Uygur	316	3.48	19.15	20.41	-
Mongol	134	1.12	24.63	20.02	-
Tibetan	330	0	28.79	19.1	-
Hui	386	0.13	21.76	24.87	-
Zhuang	378	0	23.41	25.93	-
Dai	101	0	20.79	20.3	-
Jinbo	114	0	16.23	17.7	-
Netherlands/Amsterdam	108	10.2	9.7	-	[32]
Serbia	352	4.55	-	-	[33]
Iran	395	1.4	12.2	-	[34]
Brazil	100	3.5	-	-	[35]
Bahrain	304	2.8	8.9	26.5	[36]
Turkey	205	3.17	17.8	27.07	Present study

DISCUSSION

We present a population survey of the allele frequencies for three HIV/AIDS modifying genes in Turkish population. The frequencies of CCR5-Δ32, CCR2-64I and SDF1-3'A were surveyed in a group of 205 blood donors from Sinop, Turkey and the allele frequencies were found as 3.17, 17.80, and 27.07, respectively. Distribution of CCR5-Δ32, CCR2-64I and SDF1-3'A allele frequencies varies in different ethnic populations, and thus each population has its own specific signature in terms of the investigated alleles.

Very close proportion of the CCR5-Δ32 allele was observed in Crete and Greeks in Cyprus that is geographically closest to Turkey. However, similar frequencies were determined in either ethnically or geographically distant populations (Mexico, Brazil, Uygurian in China, Bahrain). CCR5-Δ32 allele was found with high frequency in Caucasians, the frequencies range from 4 to

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16% across Europe and display a North-South gradient, but the mutation is nearly absent in African, Asian and Native American populations. The marked geographical distribution is compatible with the hypothesis of a single and recent origin of the mutation in Northern Europe [22,37]. The age of CCR5-Δ32-bearing haplotype and possibly the CCR5-Δ32 variant was computed as ~ 700 years old, ranging from 275-1,875 years [38]. Sporadic occurrences of this mutation in other non-European populations (South Carolina Blacks, Brazilian Blacks, Tibetans, Cambodians etc.) are probably due to Caucasian admixture in these populations [39]. The sharp discrimination example of North-South gradient is reported earlier in the population analysis of France [17] **(Table 2)**. [37] reported the allele frequency of CCR5-Δ32 in Uygurian population as 4.40% and this ratio was similar with a previous report with a ratio of 3.48 [31]. Our allele frequency value for CCR5-Δ32 (3.17) is also close to this value. What is surprising is that though allele frequency was nearly absent for the other investigated populations in China (with the exception of a low allele frequency of Mongolian population, f=1.12%), it was as high as 3.48% in Uygurian population **(Table 2)**. The relative high frequency in Uygurian and Mongolian populations may be explained with the close relationships they exhibited for the years with Russia and Caucasians since they are located on the North and West parts of China, and/or also a common origin with the Turkish population, thus reflecting a possible gene flow. Our CCR5-Δ32 allele frequency seems much higher than Asian populations, but lower than the European populations with some exceptions. Differently from the political map, the ethnical map of Europe is quite complex because of the reason of the intensive blending of different populations due to historical events and processes such as migrations, assimilations, and international marriages [33]. Thus, the origin and spread of the allele in the European population necessitate further studies with larger populations in various groups.

CCR2-64I mutation by contrast appears to be common in all populations studied. This may be related with the fact that since this mutation is ancient, it could have occurred before the split of the three major races [31]. The frequency of the CCR2-64I allele in populations ranges from 3% to 43%, and this allele is virtually absent in several Southeast Asian populations [39]. The frequency of CCR2-64I allele is common with the following allele frequencies: 10% in whites, 15% in African-Americans, and 25% in Asians [15]. Compared with the **(Table 2)**, similar CCR2-64I frequencies were observed in Cameroon, Jordan, Hungary Vlach Gypsies, Ecuador, Tunisia, and Uygurian in China.

Similar SDF1-3'A frequencies were observed in China Han population, Bahrain, and Crete **(Table 2)**. The prevalence of SDF1-3'A polymorphism is quite wide-ranging, quite high in Oceania, Asians, and Australia and relatively low in African populations [15,36,37]. It is exceptionally high in Oceania, especially in the New Guinean Highlanders reaching as high as 72% and relatively low in the populations of African descent. Individuals homozygous for the SDF1-3'A allele had been reported to show a better disease prognosis and slower progression to AIDS [40]. On the other hand, some studies stated that the homozygous situation of the allele was associated with an accelerated disease progression. The effect of SDF1-3'A allele associated with acceleration and progression from HIV infection to AIDS is clearly implied in the Tunisian population; frequency of the homozygous genotype for the SDF1-3' allele observed in the HIV-infected population was 37.1% while it was only 5.4% in the healthy population. However, the same effect was not observed in terms of heterozygous genotype between the HIV-infected population (40%) and healthy donors (42.6%). It seems that SDF1-3'A homozygosity is associated with a faster CD4 T cell decrease and a rapid progression to AIDS [41]. Therefore, in contrast to the strict protective effect of the CCR5-Δ32 allele, an uncertainty about the effect of SDF1-3'A allele on disease prognosis exists, and the investigation of this allele in diverse populations which consist of both the HIV-infected individuals and the healthy donors may help to better clarify the biological basis of the effect.

CONCLUSION

Genetic epidemiology studies of protective markers in HIV-1 infection would be useful in many ways such as detecting individuals at high risk for disease progression, the need for the use of different or more aggressive therapeutic strategies, and monitoring those people in a shorter period of time. Because of these reasons, the evaluation of variant frequencies offering genetic resistance to HIV/AIDS in different populations may be helpful in predicting the dynamics of HIV/AIDS epidemics as well as gaining insight about the variants. More extensive studies on larger data sets in different populations may merit conclusive results.

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CONFLICT OF INTEREST

None of the authors has any conflict of interest to declare.

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