

## Letters to the Editor

### Contrasting Frequencies of *CCR5Δ32* and *CCR2-64I* Alleles in the Tunisian Population

*To the Editor:* The human CC-chemokine receptor 5 (*CCR5*) is the major coreceptor on CD4<sup>+</sup> cells for most of the transmitting strains of HIV-1 (1,2). The complete absence of the *CCR5* protein expression on the surface of CD4<sup>+</sup> T cells in approximately 2% of the white population, due to homozygosity for a 32-nucleotide long deletion in the *CCR5* coding region (*CCR5Δ32* allele), has been shown to be a protective mechanism against HIV-1 transmission in a number of HIV-1-exposed but uninfected individuals (3-6). Furthermore, *CCR5Δ32* heterozygotes were shown to progress more slowly in several AIDS study cohorts (5,6). Furthermore, a conservative substitution of a valine for an isoleucine at position 64 in the coding region of the *CCR2* (*CCR264I*), was also shown to be protective against disease progression (7). Interestingly, *CCR264I* was found to be in strong linkage disequilibrium with *CCR5-59653T*, a mutation in the *CCR5* regulatory region (8). More recently, it has been reported that infected individuals homozygous for a multisite haplotype of the *CCR5* regulatory region containing the promoter allele *CCR5PI* progress to AIDS more rapidly than those with other *CCR5* promoter genotypes (9).

We have studied the frequencies of the *CCR5-Δ32*, *CCR2-64I*; and *CCR5-59653T* alleles in 145 healthy HIV-1 uninfected Tunisian individuals by the spectral genotyping assay (10). We found that the *CCR5-Δ32* allele is significantly less frequent (Fisher exact test *p* value <.0001) compared with previous studies on white populations (8). The genotype distribution is in equilibrium as predicted by the Hardy-Weinberg equation (*p* = .8998) showing that no strong selection process is currently affecting the population (Table 1). In contrast to the *CCR5-Δ32* allele, the *CCR2-64I* allele is significantly more frequent in the Tunisian population (Fisher exact test *p* value = .0108). Furthermore, the *CCR-59653T* mutant allele is in complete linkage disequilibrium with *CCR2-64I* as previously reported (8).

**TABLE 1.** Percentages of *CCR5* and *CCR2* genotypes

Genotype	Number	Frequency (%)	HWE <sup>a</sup>	
			χ <sup>2</sup>	( <i>p</i> -value)
<b>CCR5</b>				
Total	145	1.03	0.0158	.8998
CCR5- <sup>+/+</sup>	143			
CCR5- <sup>+/Δ32</sup>	3			
CCR5-Δ32/Δ32	0			
<b>CCR2</b>				
Total	145	19.31	1.9101	.1670
CCR2- <sup>+/+</sup>	97			
CCR2- <sup>+/64I</sup>	40			
CCR2-64I/64I	8			

<sup>a</sup>Hardy-Weinberg equilibrium; the value of χ<sup>2</sup>, with the associated *p* value for significant departures.

Our results of the *CCR5Δ32* and *CCR264I/CCR5-59653T* allele frequency obtained in the Tunisian population are consistent with results from previously published studies indicating that *CCR5Δ32* allele frequencies decrease in their frequency from Northern European to sub-Saharan populations (3-6,11) with intermediate values found in Mediterranean populations (12-14). In contrast, the *CCR264I* mutation, which is in complete linkage disequilibrium with the *CCR5-59653T*, shows an inverse gradient, with higher values in the south and lower values in the north (15). The reason for the differences in *CCR5Δ32* and *CCR264I* alleles frequencies observed in the Tunisian population compared with other white populations from Central or Northern Europe is unknown (15). One possible explanation, however, is that the modern Tunisian population is a mosaic resulting from the melding, through 3,000 years of history, of several populations such as Berber, Phoenician, Roman, Vandalic, Arabian, Black African, Spanish, Turkish, French, and other populations.

**Acknowledgment:** This work was funded by the National Institutes of Health under RO1A143868.

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### REFERENCES

1. Dragic T, Litwin V, Allaway PA, et al. HIV-1 entry into CD4<sup>+</sup> cells is mediated by the Chemokine receptor CC-CKR-5. *Nature* 1996; 381:667-73.
2. Deng H, Liu R, Ellmeier W, et al. Identification of a major coreceptor for primary isolates of HIV-1. *Nature* 1996;381:661-6.
3. Liu R, Paxton WA, Choe S, et al. Homozygous defect in HIV-1 coreceptor accounts for resistance of some multiply-exposed individuals to HIV-1 infection: *Cell* 1996;86:367-77.
4. Samson M, Libert F, Doranz BJ, et al. Resistance to HIV-1 infection in Caucasian individuals bearing mutant alleles of the CCR-5 Chemokine receptor gene. *Nature* 1996;382:722-5.
5. Dean M, Carrington M, Winkler C, et al. Genetic restriction of HIV-1 infection and progression to AIDS by a deletion allele of the CCR5 structural gene. *Science* 1996;273:1856-62.
6. Huang Y, Paxton WA, Wolinsky SM, et al. The role of mutant CCR5 allele in HIV-1 transmission and disease progression. *Nat Med* 1996;2:1240-3.
7. Smith MW, Carrington M, Winkler C, et al. CCR2 chemokine receptor and AIDS progression. *Nat Med* 1996;3:1052-3.
8. Kostrikis LG, Huang Y, Moore JP, et al. A chemokine receptor CCR2 allele delays HIV-1 disease progression and is associated with a CCR5 promoter mutation. *Nat Med* 1998;4:350-3.
9. Martin MP, Dean M, Smith MW, et al. Genetic acceleration of

- AIDS progression by a promoter variant of CCR5. *Science* 1998; 282:1907-11.
10. Kostrikis LG, Tyagi S, Mhlanga MM, et al. Spectral genotyping of human alleles. *Science* 1998;279:1228-9.
  11. Elharti E, Elaouad R, Simons M-J, et al. Frequency of the CCR5 $\Delta$ 32 allele in the Moroccan population. *AIDS Res Hum Retroviruses* 2000;16:87-9.
  12. Christodoulou C, Poullikas M, Neumann AU, et al. Low frequency of CCR5 $\Delta$ 32 allele among Greeks in Cyprus. *AIDS Res Hum Retroviruses* 1997;13:1373-4.
  13. Zamarchi R, Indraccolo S, Minuzzo S, et al. Frequency of a mutated CCR5 allele (delta 32) among Italian healthy donors and individuals at risk of parenteral HIV infection. *AIDS Res Hum Retroviruses* 1999;15:337-44.
  14. Alvarez V, Lopez-Larrea C, Coto E. Mutational analysis of the CCR5 and CXCR4 genes (HIV-1 co-receptors) in resistance to HIV-1 infection and AIDS development among intravenous drug users. *Hum Genet* 1998;102:483-6.
  15. Martinson JJ, Hong L, Karanicolos R, et al. Global distribution of the CCR2-64I/CCR5-59356T HIV-1 disease-protective haplotype. *AIDS* 2000;14:483-9.