Impact of Natural Chemokine Receptor Polymorphisms on Perinatal Transmission of Human Immunodeficiency Virus Type 1

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The rate of progression of human immunodeficiency virus type 1 (HIV-1) disease exhibits an extraordinary variation among individuals. The most commonly transmitted strains of HIV-1 fuse with their target cells after interacting with CD4 and the CC-chemokine receptor 5 (CCR5). CCR5 is the major co-receptor for the most commonly transmitted strains of HIV-1 (Alkhatib, '96; Choe, '96; Deng, '96; Doranz, '96; Dragic, '96). Over the past few years, several mutations in CCR5 have been identified as natural genetic polymorphisms that are able to influence the probability of acquiring HIV-1 infection or to affect the rate of disease progression, in infected adults or infants (Buseyne, '88; Dean, '96; Huang, '96; Liu, '96; Samson, '96; Michael, '97; Zimmerman, '97; Shearer, '98). A deletion of 32-nucleotides in the CCR5 gene (denoted CCR5-Δ32) results in a truncated protein that is not expressed on the cell surface; individuals homozygous for this deletion have an absolute resistance to infection by CCR5-using HIV-1 variants (Dean, '96; Liu, '96; Samson, '96), whereas heterozygotes for CCR5-Δ32 do not resist HIV-1 infection, but progress more frequently to acquired immunodeficiency syndrome (AIDS). Another mutation in a closely linked chemokine receptor gene, CCR2, also affects HIV-1 disease progression. This mutation, denoted CCR2-64I, is a G-to-A substitution that results in a replacement of valine with isoleucine at position 64 of the CCR2 protein (Smith, '97). The ho-

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We studied the impact of five CCR5 and CCR2 polymorphisms -CCR5-59353-T/C, CCR5-59356-C/T, CCR5-59402-A/G, CCR5-Δ32, and CCR2-64I- in the setting of maternal-infant HIV-1 transmission from the following four pediatric cohorts in United States: Women and Infants Transmission Study Cohort (WITS), ARIEL Project Cohort, New York City-Western New England Cohort and Newark Perinatal Cohort (Kostrikis, '99). Figure 1A demonstrates the genomic organization of the CCR2 and CCR5 genes on chromosome 3, as well as the location of the above polymorphic sites. The overall racial distribution for the combined cohorts was 47.9% African-Americans, 13.5% Caucasians, 34.1% Hispanics, and 4.5% other racial groups (Fig. 1B). The clinical significance of each genotype was assessed by measuring whether it influenced the rate of perinatal HIV-1 transmission among 667 AZT-untreated mother-infant pairs (554 uninfected and 113 HIV-1 infected). We have evaluated each mutation by comparing the genotype and mutant allele frequencies between HIV-1-infected and -uninfected groups and by comparing the fraction of HIV-1-infected children among the different genotypes. We found the CCR5-Δ32 deletion to be significantly more prevalent among Caucasians than among African-Americans and Hispanic individuals, consistent with previous report. Untreated CCR5-Δ32 heterozygotes had lower HIV-1 transmission rates than were found in CCR5 wild-type homozygous infants, but this difference was not statistically significant. The distribution of the CCR2-64I genotypes was similar among the three racial groups, consistent with previous reports. In the untreated group, there was no effect of CCR2-64I on HIV-1 transmission. The frequency of the CCR5-59353C allele was high in the combined population, but was significantly lower among African-Americans than in Hispanic individuals and Caucasians. In the AZT-untreated group, the CCR5-59353C allele had no observable effect on transmission. The frequency of the CCR5-59402G mutant allele was significantly lower among African-Americans than in the Caucasian and Hispanic groups. In the untreated group, there was a trend for a reduced HIV-1 transmission rate to infants who are CCR5-59402G mutant homozygotes, compared with CCR5-59402A wild-type homozygous infants.

Most significantly, we found that the mutant CCR5-59356T allele was relatively common in African-Americans (20.6% allele frequency among 552 infants), and rare in Caucasians and Hispanics (3.4% and 5.6% of 174 and 458 infants, respectively; P < 0.001). In fact,
A. Genomic organization of the CCR2 and CCR5 genes

B. Racial distributions of the CCR2 and CCR5 polymorphisms

C. Significance of CCR5 and CCR2 polymorphisms on perinatal HIV-1 transmission

Figure 1.
CCR5-59356T mutant homozygotes were most found among African-Americans: 35 of the 38 infants mutant homozygous for CCR5-59356T, 35 were African-Americans. By comparing the fractions of untreated, HIV-1-infected infants in the three CCR5-59356 genotypes, we found a significantly higher rate of transmission among CCR5-59356-T mutant homozygotes (47.6% of 21 CCR5-59356-T mutant homozygote infants), compared with both CCR5-59356-A wild-type homozygotes (13.4% of 187; P < 0.001) and CCR5-59356 heterozygotes (14.1% of 71; P = 0.001). In other words, about one-half of the untreated infants in the four combined cohorts who are homozygotes for the CCR5-59356-T mutation are infected with HIV-1, an unexpectedly large fraction. Infants who are CCR5-59356-T mutant homozygotes are associated with an increased relative risk of HIV-1 infection of 5.9 (95% confidence interval, 2.3 to 15.3) (P < 0.001). The enhancing effect of the CCR5-59356-T mutation on HIV-1 transmission was not observed in the AZT-treated group.

The central finding from our study was that the CCR5-59356T/T mutant genotype, which was predominantly found in African-Americans, was associated with a significantly higher rate of perinatal HIV-1 infection. Although the frequency of the CCR5-59356T/T mutant genotype among African-Americans was not sufficient to cause a significant overall increase in the rate of perinatal HIV-1 infection among African-Americans, it remains possible that higher frequencies of the CCR5-59356T/T mutant genotype in African populations may contribute to the relatively high rate of perinatal HIV infection in Africa. We are currently expanding our studies in two pediatric cohorts from Africa: the pediatric Cohort in Butare, Rwanda, and the South African Pediatric Cohort in Soweto, South Africa. We are also investigating the biological basis for this adverse epidemiological effect of the CCR5-59356T allele.

Using gel-shift assays and protein extracts CD4+ and CD8+ T lymphocytes, monocytes, and dendritic cells, we showed that the CCR5-59356T mutation creates a binding site for an unknown cellular protein. The CCR5-59356T-binding protein was present in T cells and monocytes from all the donors tested, including African-American individuals who are CCR5-59356T/T mutant homozygotes. This preliminary finding may suggest that any donor-dependent influence of the CCR5-59356T-binding protein on HIV-1 transmission is more likely to be mediated by the presence or absence of its binding site within the CCR5 regulatory region, rather than whether or not the factor itself is expressed.

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LITERATURE CITED


