

CC Chemokine Receptor 5 Genotype and Susceptibility to Transmission of Human Immunodeficiency Virus Type 1 in Women

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The human gene for CC chemokine receptor 5, a coreceptor for human immunodeficiency virus type 1 (HIV-1), affects susceptibility to infection. Most studies of predominantly male cohorts found that individuals carrying a homozygous deleted form of the gene, $\Delta 32$, were protected against transmission, but protection did not extend to $\Delta 32$ heterozygotes. The role played by this mutation in HIV-1 transmission to women was studied in 2605 participants in the Women's Interagency HIV Study. The $\Delta 32$ gene frequency was 0.026 for HIV-1-seropositive women and 0.040 for HIV-1-seronegative women, and statistical analyses showed that $\Delta 32$ heterozygotes were significantly less likely to be infected (odds ratio, 0.63 [95% confidence interval, 0.44–0.90]). The CCR5 $\Delta 32$ heterozygous genotype may confer partial protection against HIV-1 infection in women. Because $\Delta 32$ is rare in Africans and Asians, it seems plausible that differential genetic susceptibility, in addition to social and behavioral factors, may contribute to the rapid heterosexual spread of HIV-1 in Africa and Asia.

Human immunodeficiency virus type 1 (HIV-1) currently infects ~40 million people worldwide [1]. More than 95% of all new cases occur in developing countries, with heterosexual transmission being the predominant route of infection [1]. Rates of HIV-1 infection continue to increase, particularly among nonwhites and women [1]. In sub-Saharan Africa, a region that accounts for 70% of infected individuals globally, women with HIV-1 now outnumber men with HIV-1 [1].

Host differences may contribute to the rapid spread

of HIV-1 in some areas of the world; specific genetic traits have been found to influence susceptibility to HIV-1 transmission and disease progression. In addition to CD4, the primary HIV-1 receptor, a functional secondary receptor is required to initiate infection. Human β -che-

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mokine receptors serve this function, with CCR5 serving as co-receptor for macrophage-tropic strains of HIV-1 [2]. A 32-bp deletion ($\Delta 32$) in the *CCR5* gene renders this receptor non-functional, and cells that are homozygous for this mutation are highly resistant to infection by macrophage-tropic strains of HIV-1 [3].

The mutation is most common in white populations, where the frequency of the $\Delta 32$ allele ranges from 4% to 16%; ~20% of whites are heterozygous, and 1% are homozygous for $\Delta 32$ [4]. However, this allele is less common among US blacks and Latinas and was absent in Africans and Asian populations studied in anthropological surveys and investigations of non-HIV-related conditions [4].

Investigation of large cohorts of individuals exposed sexually or parenterally to HIV-1 found that the homozygous $\Delta 32$ mutation confers a high level of resistance to infection [5–8]. These studies, primarily composed of white men, also found that $\Delta 32$ heterozygotes exhibit delayed HIV-1 disease progression but were not protected against transmission [6–8]. However, a more recent study of high-risk HIV-1–seronegative men did demonstrate partial protection against HIV-1 infection in those with the $\Delta 32$ heterozygous genotype [9]. Because $\Delta 32$ heterozygotes of either sex express a reduced number of CCR5 receptors, compared with individuals with the wild-type genotype, the partial protection and delayed disease progression in heterozygotes may be related to the decreased number of CCR5 receptors and the resulting decreased virus load.

Transmission studies involving women showed variable results; 2 studies suggested that the heterozygous state confers partial protection against HIV-1 infection [5, 10], whereas 3 other studies did not [9, 11, 12]. However, all the previous analyses had a suboptimal statistical power for assessing this question, with no more than 630 women in each study. Recently, investigators constructed a mathematical model of the dynamics of HIV-1 transmission in populations with or without the $\Delta 32$ mutation. This model predicted that the $\Delta 32$ allele would slow the heterosexual spread of the epidemic in populations where the mutation was common [13]. This prediction, coupled with the results from previous cohort studies, points out the importance of studying the role of the $\Delta 32$ deletion in HIV-1 transmission in a larger cohort of women.

Studies have documented sex-specific differences in HIV-1 transmission, infection, and disease progression [10, 14–18]. Because the routes and mechanisms of HIV-1 infection may differ in significant ways between men and women, we investigated the relationship of CCR5 genotype to the likelihood of HIV-1 infection among women enrolled in the Women's Interagency HIV Study (WIHS), a large study of HIV-1 infection in women conducted in 5 US cities.

SUBJECTS AND METHODS

Study population. We studied a total of 2605 women, 2047 HIV-1–seropositive and 558 seronegative, who were enrolled in WIHS. WIHS is the largest US cohort ever assembled to study the natural history of HIV-1 infection in women. Participants reflect the racial and ethnic background of the groups in the US, in which the HIV-1 epidemic is spreading most rapidly, as well as the risk behaviors [1, 19]. WIHS participants were recruited and evaluated in Chicago, San Francisco Bay Area, Los Angeles, Washington, DC, and 2 sites in New York (Bronx-Manhattan and Brooklyn). We grouped the WIHS participants into the following racial and ethnic categories: black, Latina, white, or other. The HIV-1 risks at study entry were injection drug use (IDU), heterosexual exposure, transfusion, or risk not identified. The risk categories are hierarchical and mutually exclusive with respect to the order listed above (e.g., individuals in the IDU category also may have had heterosexual or transfusion risks) [20, 21]. Approximately one-third of the participants ($n = 843$; 32.4%) had a history of IDU, making this one of the largest cohorts of IDU among women studied.

The WIHS methods and baseline characteristics of the cohort have been described elsewhere [15, 19]. The HIV-1–seropositive and –seronegative participants were very similar with respect to high-risk behaviors and a wide array of other variables, including drug use, history of chronic illness, income, demographics, reproductive history, perceived health status, and history of sexual abuse [19].

Ten WIHS participants were excluded from the analysis because of limited numbers bearing their specific unusual characteristics; this group comprised 9 seroconverters, all of whom were homozygous wild type and 1 uninfected CCR5 $\Delta 32$ homozygote. The CCR5 $\Delta 32$ homozygote was an uninfected white heterosexual.

Clinical sample and data collection. WIHS participants were interviewed by use of a structured questionnaire and given a physical examination every 6 months. Blood samples were collected, and T cell subsets were determined, as described elsewhere [15]. Quantitation of HIV-1 RNA in plasma was performed by use of the isothermal nucleic acid sequence–based amplification (NASBA) method (bioMérieux). Notification of patient death was obtained by the WIHS from relatives, medical providers, or friends or through local and national death registries. Diagnoses of clinical AIDS-defining illnesses were self-reported and were in accordance with class C clinical conditions in the 1993 Centers for Disease Control and Prevention (CDC) case definition of AIDS [22]. These diagnoses of AIDS do not include immunologic criteria of low CD4⁺ cell counts. Self-reporting of AIDS-defining conditions in the WIHS has been found to be accurate [23].

CCR5 genotyping. The CCR5 genotype was determined by

use of polymerase chain reaction (PCR) and restriction analysis, as described elsewhere [5, 24]. Independent duplicate analyses were performed for every sample. To confirm that the results were specific for *CCR5* genotypes, the *CCR5* gene was cloned and sequenced from several individuals known to be homozygous for the wild-type or mutant allele [24]. We verified the presence of the 32-bp deletion by comparing the *CCR5* sequences obtained from wild-type homozygotes with those from $\Delta 32$ homozygotes.

Statistical analysis. *CCR5* genotypes were categorized into 2 groups: wild type (+/+) or heterozygotes (+/ Δ). Analyses were performed by comparing these 2 groups overall and then by stratifying the groups according to racial and ethnic group and risk status. The association of *CCR5* $\Delta 32$ and HIV-1 infection was measured by an odds ratio (OR) and 95% confidence interval (CI). The OR provided a measure of the likelihood of HIV-1 infection among *CCR5* $\Delta 32$ heterozygotes, compared with that among individuals homozygous for the wild-type allele.

We also assessed the frequency of the *CCR5* $\Delta 32$ heterozygous genotype by comparing HIV-1-uninfected and -infected women stratified by CD4⁺ cell count at entry. This was done to examine the consistency of our observations and to assess whether bias due to rapid disease progression and early death (and, therefore, exclusion from our cohort) might result in spurious association. Four CD4⁺ cell count strata were used: 0–199, 200–349, 350–499, and ≥ 500 cells/ μ L.

Key multivariate analyses included the number of sexual partners (for all women) and drug injection frequency (for IDU only) as covariates, to ensure that genotype observations were independent of risk factor distributions. In addition, site was included in key multivariate analyses to determine whether genetic differences within racial/ethnic groups that might differ from varying geographic regions affect the association of *CCR5* genotype with HIV-1 infection [25].

RESULTS

The *CCR5* genotypes and *CCR5* $\Delta 32$ allelic frequencies for 2605 WIHS participants are shown in table 1. The 2047 HIV-1-seropositive and 558 HIV-1-seronegative women were stratified into groups according to their racial and ethnic background, as well as their transmission risk. Approximately 80% of the women were black or Latina. The $\Delta 32$ frequency for the entire cohort of 2605 women was 0.029 and, when subjects were stratified according to racial and ethnic group, was 0.018 among blacks, 0.024 among Latinas, 0.068 among whites, and 0.041 among others. The frequency of the $\Delta 32$ allele was significantly greater among the whites than among any of the other racial/ethnic groups ($P < .001$).

Transmission. HIV-1-infected women were less likely to

have the *CCR5* $\Delta 32$ allele than were HIV-1-uninfected women (OR, 0.63; 95% CI, 0.44–0.90). The frequency of the $\Delta 32$ heterozygous genotype among HIV-1-infected versus HIV-1-uninfected women in the cohort is shown in table 2. To compare models adjusted for ethnicity and transmission risk, the study population was restricted to the 2579 persons with the *CCR5* genotype for whom we had complete data on these parameters. Within this group, the crude OR (0.66; CI, 0.46–0.95) and adjusted OR (0.61; CI, 0.41–0.89) did not differ significantly. Stratifying by racial and ethnic group showed that this effect was seen in all 4 groups, with ORs ranging from 0.43 to 0.78, but was statistically significant only among whites (table 2). Similarly, when subjects were stratified by exposure status, the protective effect of *CCR5* $\Delta 32$ was observed in all risk groups (range of ORs, 0.44–0.75) but was statistically significant only in the IDU group (table 2). Neither the number of sexual partners nor the geographic site of volunteer residence confounded or interacted with race/ethnicity or transmission risk in our multivariate models (data not shown).

The comparative frequency of the $\Delta 32$ heterozygous genotype by baseline CD4⁺ cell count is shown in table 3. The protective effect was seen in all 4 strata, with OR point estimates ranging from 0.45 to 0.89. The protective association was statistically significant among women with baseline CD4⁺ cell counts <200 and 200–349 cells/ μ L, was of borderline significance in the group with CD4⁺ cell counts >500 cells/ μ L ($P = .082$), and was not significant in the subgroup with a CD4⁺ cell counts of 350–499 (table 3). No significant trend was noted across the CD4⁺ cell count strata among the HIV-1-infected women ($P = .307$). Race/ethnicity was noted to be an effect modifier for the association of $\Delta 32$ allelic frequency and HIV-1 risk when CD4⁺ cell count was used as a surrogate for the rapidity of disease progression (table 3). The associations all had an OR <1, regardless of CD4⁺ cell count stratum or race/ethnicity group. The association of the $\Delta 32$ heterozygous genotype and lower HIV-1 risk was stronger in non-Latina whites and women with CD4⁺ cell counts lower than those in other groups.

DISCUSSION

Early analyses of *CCR5* in relation to HIV-1 transmission and disease progression focused primarily on cohorts of white men, in whom the prevalence of the $\Delta 32$ allele is $\sim 10\%$ [4–8]. However, worldwide HIV-1 transmission now occurs approximately equally in both sexes [1] and is most prevalent in nonwhite populations, which have a much lower frequency of the $\Delta 32$ allele, than in white populations [4]. We analyzed the association of *CCR5* genotype with HIV-1 infection in WIHS, a large, predominantly nonwhite cohort of HIV-1-infected and -uninfected women. We found that, among 2605 women in WIHS,

Table 1. Distribution of *CCR5* genotypes among human immunodeficiency virus type 1 (HIV-1)-uninfected subjects and HIV-1-infected subjects, in the Women's Interagency Human Immunodeficiency Virus Study (WIHS).

Characteristic	CCR5 genotype					
	Wild type		Heterozygote		$\Delta 32$ allele frequency	
	HIV-1 uninfected	HIV-1 infected	HIV-1 uninfected	HIV-1 infected	HIV-1 uninfected	HIV-1 infected
WIHS subjects	513	1940	45	107	0.040	0.026
Race/ethnicity						
Black	283	1096	13	39	0.022	0.017
Latina	148	461	9	22	0.029	0.023
White	66	331	20	43	0.116	0.057
Other	16	52	3	3	0.079	0.027
Transmission risk ^a						
Injection drug use	137	656	16	34	0.052	0.025
Heterosexual	132	797	12	50	0.042	0.030
Transfusion	14	75	1	4	0.033	0.025
Not identified	226	393	15	19	0.031	0.023
WIHS site						
Bronx-Manhattan	108	395	6	23	0.026	0.028
Brooklyn	81	300	5	11	0.029	0.018
Chicago	55	256	3	15	0.026	0.028
Washington, DC	86	278	15	14	0.074	0.024
Los Angeles	102	395	9	25	0.041	0.030
San Francisco	81	316	7	19	0.040	0.028

NOTE. Data are no. (%) of participants, unless otherwise indicated.

^a There were 24 women with missing data on transmission risk status.

the presence of the $\Delta 32$ heterozygous genotype was associated with lower rates of HIV-1 infection, strongly suggesting partial protection against HIV-1 transmission. Two previous cohort studies that included women also reported evidence for partial protection for $\Delta 32$ heterozygotes [5, 10]. Three other investigations, however, did not find a protective effect in women, perhaps because of the lower statistical power in these smaller studies [9, 11, 12].

We found that the association between the $\Delta 32$ heterozygous genotype and partial protection from HIV-1 transmission was statistically significant among whites. Because of the low frequency of the $\Delta 32$ allele in nonwhite populations, however, it is difficult to assess the protective effect of the heterozygous state in other racial and ethnic groups, even with our large sample size. In the WIHS cohort, the $\Delta 32$ allelic frequency was 0.018 among 1431 blacks and 0.024 among 640 Latinas, whereas the frequency was much higher among whites, 0.068, which is consistent with the findings of other studies [4]. Heterozygotes in all transmission risk groups had lower rates of HIV-1 infection, although IDU was the only category in which the putative protective effect reached statistical significance. Because individuals in the IDU category also may have heterosexual or transfusion risks [20, 21], we were unable to fully distinguish

the effect of the $\Delta 32$ heterozygous genotype on sexual as opposed to parenteral transmission.

Ideally, to study the effect of *CCR5* genotype or any other immunogenetic trait on HIV-1 transmission to women, we would need to identify thousands of high-risk, uninfected women and prospectively follow them up for many years. This sort of study has been carried out to some extent in overwhelmingly male, largely white cohorts [5–12, 26, 27]. To investigate transmission, the ideal cohort would be ethnically and genetically diverse. In addition, the study subjects would continue to show a substantial rate of seroconversion, despite investigators' best efforts to reduce risk [28]. This "incident cohort" would be both costly and logistically complex. Because of the lack of feasibility of the ideal transmission study, we have engaged a large multi-center natural history study, WIHS.

The present study suggests the importance of immunogenetic factors in HIV-1 transmission, although it examines a "prevalent cohort" and uses a case-control design. However, inference is limited, because the occurrence of infection was not actually observed; unseen distortions in data may exist, such as the loss of prospective subjects with rapidly progressive disease who died before being recruited into WIHS [29]. It is noteworthy that systematic underrepresentation of subjects with rapid disease

Table 2. Frequency of the CCR5 Δ 32 heterozygous genotype among human immunodeficiency virus type 1 (HIV-1)-infected women versus HIV-1-uninfected women.

Category	No. of participants	Participants heterozygous for Δ 32, %	Crude OR	Adjusted OR (95% CI)
WIHS subjects	2605	5.8	0.63	
Race/ethnicity				
Black	1431	3.6	0.77	0.77 (0.4–1.5)
Latina	640	4.8	0.78	0.72 (0.3–1.6)
White	460	13.7	0.43	0.38 (0.2–0.7)
Other	74	8.1	0.31	0.30 (0.1–1.7)
Transmission risk ^a				
IDU	843	5.9	0.44	0.42 (0.2–0.8)
Heterosexual	991	6.3	0.69	0.65 (0.3–1.3)
Transfusion	94	5.3	0.75	0.78 (0.1–7.7)
Risk not identified	653	5.2	0.73	0.67 (0.3–1.3)
WIHS site				
Bronx-Manhattan	532	5.4	1.05	NA
Brooklyn	397	4.0	0.58	NA
Chicago	329	5.5	1.05	NA
Washington, DC	393	7.4	0.28	NA
Los Angeles	531	6.4	0.70	NA
San Francisco	423	6.1	0.53	NA

NOTE. Estimates were adjusted for no. of lifetime sexual partners at study entry and Women's Interagency Human Immunodeficiency Virus Study (WIHS site). CI, confidence interval; IDU, injection drug use; NA, not applicable; OR, odds ratio.

^a There were 24 women with missing data on transmission risk status.

progression in our study would have diminished its statistical power but would not have introduced bias. At all baseline CD4⁺ cell count strata, a protective association of CCR5 Δ 32 heterozygous genotype and HIV-1 infection was suggested, although the strength and statistical significance of the association were lower among persons with higher CD4⁺ cell counts than among those with lower counts. We cannot exclude an interaction of race/ethnicity or immunogenetic profile with rapid progression or with earlier HIV-1 infection, because we do not know the date of seroconversion for these subjects. However, the consistent trend for protection across all CD4⁺ cell count strata suggests that any such interaction would merely modulate the strength of the association, rather than confound it.

Multivariate analyses identified race and ethnicity as effect modifiers on the basis of the negative association of the Δ 32 heterozygous state with HIV-1 infection risk (i.e., OR <1), non-Latina white women with lower CD4⁺ cell counts had stronger, significant associations, whereas all other women had weaker, nonsignificant but nonetheless protective associations (i.e., all subgroups had an OR <1). Therefore, we cannot make definitive statements that may apply to all subgroups.

The consistency of our OR point estimates is remarkable; ORs are <1 in every race and ethnic group, every transmission risk group, every CD4⁺ cell count subgroup, and in all CD4⁺

cell count by race/ethnicity subgroups. Despite statistical power concerns revealed by subgroup analyses that were not based on previous hypotheses, the present study suggests strongly that partial protection from HIV-1 infection is conferred by the CCR5 Δ 32 heterozygous genotype. That the Δ 32 allele might also slow disease progression would not be surprising, but we cannot address this issue with the “prevalent cohort” study design. An “incident cohort” might confirm our cross-sectional analysis, but a sufficiently powered prospective transmission study is not likely to be conducted because of its complexity and cost [26, 27, 29–31].

Previous studies have observed a slower rate of disease progression among HIV-1-infected Δ 32 heterozygotes who were not treated with highly active antiretroviral therapy (HAART) [5–7]. The effect of CCR5 genotype on virus load and CD4⁺ cell count, which influence the rate of disease progression, has been seen in early but not in advanced HIV-1 infection [6, 32, 33]. Two factors inhibit our ability to look at this question: most women in WIHS receive HAART, and WIHS is a cohort of women with relatively advanced disease [5, 19].

In this analysis of the influence of CCR5 genotype on HIV-1 infection in women, we found that Δ 32 heterozygotes were less likely to be HIV-1 infected, which suggests partial resistance to transmission. It is possible that sex contributed to the dif-

Table 3. Frequency of the CCR5 Δ 32 heterozygous genotype among human immunodeficiency virus type 1 (HIV-1)-uninfected and HIV-1-infected women, stratified by CD4⁺ cell count at entry.

HIV-1 status	No. of subjects	Participants heterozygous for Δ 32, no. (%)	OR	Exact 95% CI	Exact <i>P</i> ^a
Uninfected	542	45 (8.3)	1	NA	NA
Infected, CD4 ⁺ cell count, cells/ μ L					
<200	593	29 (4.9)	0.57	0.34–0.94	.027
200–349	458	18 (3.9)	0.45	0.24–0.81	.007
350–499	403	30 (7.4)	0.89	0.53–1.47	.718
\geq 500	518	28 (5.4)	0.63	0.37–1.05	.082

NOTE. CI, confidence interval; NA, not applicable; OR, odds ratio.

^a Test for trend. *P* = .012 (χ^2 test); *P* = .307 (χ^2 test) among HIV-1-infected categories only.

ferent results in our cohort, compared with those previously reported for predominantly male study populations. Routes and mechanisms of HIV-1 infection may differ in men and women. Recent studies, including a study that compared WIHS to the Multicenter AIDS Cohort Study, a large cohort of men, have documented such sex-specific differences in the biology of HIV-1 [14–18].

A possible explanation for the sex-specific difference may lie in the variable expression of CCR5 receptors in different tissues, such as those in the vagina and rectum. Differential expression of CCR5 has been reported in the female genital tract versus that in the blood and other tissues [34, 35]. In addition, the level of CCR5 expression was found to be increased in the female genital tract by sexually transmitted diseases and progesterone [36]. Because men and women are exposed sexually to HIV-1 through different tissues, quantitative differences in CCR5 expression in those tissues may provide a basis for partial protection against HIV-1 transmission in Δ 32 heterozygotes. Interestingly, in our study, the *CCR5* genotype had a greater effect on transmission among those with a history of IDU than among heterosexuals or transfusion recipients, which suggests that, as reported in other studies, those with a history of IDU had a high degree of sexual exposure, perhaps due to trading sex for drugs [20, 21].

Heterosexual transmission of HIV-1 has been spreading rapidly in Africa and Asia. It is unclear why the epidemic is spreading faster in certain communities and parts of the world than others, but the explanation is probably multifactorial. Frequency of other sexually transmitted infections, behavioral risk factors, and background prevalence rates are likely to dominate any predictive model that describes the variability in the incidence of HIV-1 infection around the world. However, differences in genetic susceptibility to HIV-1 among populations may be quite relevant to the pace of the epidemic. For example, persons with a low prevalence of “genetic resistance” pro-

files, such as blacks in the United States, have not experienced epidemic spread of the magnitude seen in Africa. Thus, the absence of a protective immunogenetic profile among persons in a given population does not necessarily result in very high transmission if there are comparatively lower frequencies of high-risk behavioral activity or cofactors for transmission, such as reproductive tract infections. Nevertheless, the current proportion of cumulative AIDS cases among black women in the United States (58.0%) exceeds the proportion of blacks in the US population (12.3%); this increase in cases also is seen among Latinas (19.6% of AIDS cases and 12.5% of the US population) [37, 38].

One mathematical model predicted that the Δ 32 allele would limit the heterosexual HIV-1 epidemic in populations where this allele is common [13]. The data presented here support this prediction, which suggests that the low frequency of the Δ 32 allele in nonwhite women may render these populations somewhat more susceptible to transmission of HIV-1 than populations with higher frequencies of the protective deletion in *CCR5*.

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