Combined Genotypes of CCR5, CCR2, SDF1, and HLA Genes Can Predict the Long-Term Nonprogressor Status in Human Immunodeficiency Virus-1–Infected Individuals

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Human immunodeficiency virus (HIV)-1–infected long-term nonprogressors (LT-NP) represent less than 5% of HIV-1–infected patients. In this work, we tried to understand whether combined genotypes of CCR5-Δ32, CCR2-64I, SDF1-3′A and HLA alleles can predict the LT-NP status. Among the chemokine receptor genotypes, only the frequency of the CCR5-Δ32 allele was significantly higher in LT-NP compared with the group of standard progressors. The predominant HLA alleles in LT-NP were HLA-A3, HLA-B14, HLA-B17, HLA-B27, HLA-DR6, and HLA-DR7. A combination of both HLA and chemokine receptor genotypes integrated in a multivariate logistic regression model showed that if a subject is heterozygous for CCR5-Δ32 and homozygous for SDF1 wild type, his odds of being LT-NP are increased by 16-fold, by 47-fold when a HLA-B27 allele is present with HLA-DR6 absent, and by 47-fold also if at least three of the following alleles are present: HLA-A3, HLA-B14, HLA-B17, HLA-DR7. This model allowed a correct classification of 70% of LT-NPs and 81% of progressors, suggesting that the host's genetic background plays an important role in the evolution of HIV-1. The chemokine receptor and chemokine genes along with the HLA genotype can serve as predictors of HIV-1 outcome for classification of HIV-1–infected subjects as LT-NPs or progressors.

IN HUMAN immunodeficiency virus (HIV)-1 disease, a small fraction (<5%) of infected individuals remains asymptomatic and clinically healthy for long periods.[1] These individuals usually have a lower viral load and higher and relatively stable peripheral blood $CD4^+$ cell counts compared with the normal/rapid progressors.[2] It is still unclear whether these subjects represent a distinct group, sharing a common biological phenomenon for such a resistance to progression or if they are only casual and extremely rare exceptions to the general rule. Some investigators proposed that the HIV-1 disease-free progression might be genetically controlled.[3] The first candidates were the major histocompatibility complex genes (MHC-HLA in humans). Combination of HLA class I (HLA-A1, HLA-A2, HLA-B14, HLA-B17, HLA-B27) and class II antigens (HLA-DR5 and HLA-DR6) have been correlated with low rates of disease progression.[4-7] In contrast, the presence of HLA-B35, HLA-DR1, HLA-DR3, HLA-DQ1 antigens was significantly associated with a bad prognosis and a rapid progression to acquired immunodeficiency syndrome (AIDS).[8-11]

More recently, several groups showed that the polymorphic genes of the chemokine receptor family and particularly the CCR5 and CCR2 genes, which were identified as coreceptors for HIV-1 entry into the cell,[12-16] also influence disease-free survival of HIV-1–infected patients. A truncated form of CCR5 (a Δ32-bp, observed in white individuals only[17]) and a mutated form of the CCR2 (64I) were more frequently found in individuals whose progression to AIDS was postponed compared with rapid progressors.[18-21] Two recent reports showed that, in whites, the CCR2 and CCR5 mutant alleles are in strong linkage disequilibrium.[19,22]

Despite important studies, it is still controversial whether the CCR5Δ32 allele protects from progression to AIDS. In seroconverters, for which long-term data were available, the CCR5Δ32 heterozygotes were shown to develop the AIDS-defining illness significantly later than patients without the Δ32bp.[18] On the other hand, other investigators reported only a slightly different disease course with a lower proportion of AIDS-free individuals during the first 4 to 6 years after seroconversion and a higher proportion of AIDS-free individuals after 10 years.[23] Our group found that the protective effect of the Δ32 deletion was detectable during the first 7 years of infection.[24]

Other genetic factors, namely an SDF1 chemokine gene variant SDF1-3′A, which is the ligand for the CXCR4 chemokine receptor, conferred a recessive protective effect in long-term nonprogressors (LT-NP).[25]

In this report, we studied chemokine receptors (CCR2, CCR5), chemokine (SDF1), and HLA class I and II genotypes in LT-NP and attempted to find out whether any particular pattern of host genetics could be implicated in the LT-NP phenotype. Data presented in this report show for the first time that the combined host genetic background strongly influences the evolution of HIV-1 disease. The CCR5/CCR2/SDF1 and HLA loci appeared to influence independently disease progression. Mutated variants of CCR5, CCR2, and SDF1 genes along with the HLA genotype can serve as predictors of HIV-1 infection outcome and allowed the correct classification of 70% of HIV-1–infected subjects as LT-NP and 81% as progressors.

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MATERIALS AND METHODS

Studied cohorts. Subjects from two different French cohorts were included in our study: a cohort of LT-NP (French ALT) and a cohort of standard progressors (IMMUNOCO). From the two cohorts, only subjects of white origin were taken into account for statistical analysis: 70 from French ALT and 83 from IMMUNOCO. A total of 153 subjects were analyzed. The main characteristics of individuals are presented in Table 1. The evolution of the immune and virologic status of both cohorts has been described elswhere (ALT: Hadida et al; Candotti et al, XI International Conference on AIDS 1996, V Conference on Retroviruses and Opportunistic Infections 1998 and manuscript in preparation; IMMUNOCO: Autran et al, XI International Conference on AIDS 1996 and manuscript in preparation).

Genotyping assay. The presence of the CCR5Δ32 allele was determined using a polymerase chain reaction (PCR)-based assay as already described.[17] The CCR2-64I allele was detected by PCR-restriction fragment length polymorphism (RFLP) assay. The 380-bp fragment from the NH_2-terminal domain of the gene was amplified using 5′-GGATTGAACAAGGACGCATTTCCCC-3′ and 5′-TTGCACATTGCATTCCCAAAGACCC-3′ as forward and reverse primers, respectively. PCR was run for 40 cycles at 63°C annealing temperature. Digestion with *Fok* I restriction endonuclease yielded 215-bp and 165-bp fragments only when an ATC triplet coding for isoleucine (64I) was present. The SDF1-3′A allele was detected by PCR-RFLP as described by Winkler et al.[25] HLA class I (HLA-A, HLA-B) typing was performed by standard serological methods and class II (HLA-DRB1) by generic molecular typing.

Statistical analysis. We performed a case-control analysis with cases defined as subjects included in the ALT cohort and controls as subjects included in the IMMUNOCO cohort. Cases and controls were compared for baseline characteristics using the χ^2 test for categorical variables (sex, transmission) and the nonparametric Mann-Whitney test for continuous variables (age at first positive test, time since first positive test, CD4 counts and CD8 counts). These data are presented in Table 1. For the comparison of genotypes between case and control subjects, we considered only those HLA alleles present in at least 10% of all subjects (cases + controls). Alleles were compared between the two groups and only those alleles with a comparison χ^2 P value less than .20 were retained for further analysis. This is nearly equivalent to the limits chosen by Kaslow et al[5] in their recent report. Similar analysis was performed to assess the role of CCR2, CCR5, and SDF1 genotype and that of different potential confounding factors. Age and transmission group (homo/bisexual men, heterosexuals, intravenous [IV] drug users, others) were considered as potential confounding factors because they are associated in the literature with disease progression. Age was considered as a continuous variable. We also studied linkage disequilibrium between CCR5 and CCR2, as well as HLA genes. A multivariate stepwise logistic regression was used to assess the roles of HLA genotypes, CCR2, CCR5, and SDF1 genotypes and potential confounding factors. All 2×2 interactions were tested and when interaction was detected, combined variables were used in further analysis. Only genotypes and confounding factors selected as significant in the multivariate analysis were further considered. As described by Kaslow et al,[5] we also constructed a summary HLA score by counting the number of HLA genotypes that were found associated with long-term nonprogression. To assess the goodness of fit of the final model, the distribution of the standardized residuals was compared with a normal distribution. The robustness of our model was explored by performing an estimation of the logistic model parameters 50 times on a random sample of 80% of the subjects. The frequency of significantly positive variables included in the model was evaluated and the odds-ratio values were compared.

RESULTS AND DISCUSSION

In this study, we performed a comparative analysis of subjects included in two French cohorts of LT-NP (ALT) and of progressors (IMMUNOCO), taking into account the contribution to the slow progression of the HIV-1 infection, of confounding factors, and genetic components such as the CCR5, CCR2, and SDF1 genes and the HLA class I and II alleles. The confounding factors (sex, age, and transmission group) were similar between the two cohorts (Table 1).

We screened for three frequent modifications in chemokine receptors: CCR5-Δ32, CCR2-64I, and a chemokine gene SDF1-3′A. When taking into account the genetic background of HIV-1–infected subjects, we observed a higher frequency of the CCR5-Δ32 allele in LT-NP with 37% of heterozygotes compared with the 14% found in progressors (Table 2), confirming earlier published studies.[20,26] This finding is not very surprising because the CCR5-Δ32 allele was already suggested as protective against rapid progression in HIV-1 disease.[18,20,23,24,26] We did not find any homozygous individual for this mutated allele in any of the two groups. The two other mutated alleles, CCR2-64I and SDF1-3′A, occurred at similar frequencies in both LT-NP and progressors and few homozygous individuals were found for either mutation. To avoid samples too small for a meaningful statistical analysis, two groups were created with one group of individuals bearing at least one mutation, and in the other, group wild-type individuals (Table 2). After regrouping, we observed 23% of CCR2 wild/mut genotypes among LT-NP and 16% among progressors ($P = .258$). Similarly, 36% of LT-NP had at least one mutant SDF1 allele versus 44% in progressors ($P = .335$). A detailed description of the different genotypes comprising CCR2, CCR5, and SDF1 genes is presented in Table 3. We did not find a clear linkage disequilibrium between the CCR2 and CCR5 genes (2×2 analysis, $P = .074$). This finding is not necessarily in contradiction with the report by Smith et al,[19] because the design of both studies was slightly different (ours a case/control study *v* a cohort study by these investigators) or could also be explained by a lack of power in our study. As with Smith et al, we did not find any CCR2 mut/mut individual bearing also the Δ32 modification of the CCR5 gene. It is worth noting that only two LT-NP subjects were found SDF1 mut/mut compared with four progressors at variance to the results reported by Winkler et al[25] (Table 2). This difference may be due to the following reasons: (1) our study was based on the precisely characterized group of LT-NPs compared with the control group of normal progressors, while Winkler analyzed the slow/nonprogressors category issued from the cohort of seroprevalent subjects without giving any clear definition of this group; (2) Winkler et al stated that although SDF1-3′A/3′A protection was more apparent in later stages of HIV-1 infection, the principal effect may involve a strong protection against rapid progression to AIDS. Because we did not study the rapid progressors, it is not surprising that in our particular group of LT-NP subjects, we did not find the same results as Winkler et al.

However, it seems more likely that several other mechanisms predispose an individual to a rapid or a slow evolution of the HIV-1 disease. Many investigators propose, following studies on independent samples, that HLA genes may also play a part in

Table 1. Characteristics of the Two Cohorts of LT-NP (ALT) and Standard Progressors (IMMUNOCO) at Inclusion

	ALT (LT-NPs) n = 70	IMMUNOCO (progressors) n = 83	*P* Value*
Cohort started	1996	1991-1992	
Inclusion criteria	18 yr of age or more and Time since first HIV+ test equal to or above 8 yr and No AIDS symptoms (stage A) and No antiviral treatment and CD4 counts >600/μL during last 5 yr	18 yr of age or more and Any time and Any stage and With or without antiviral treatment and CD4 counts >150/μL at entry	
Sex (% men)	53 (76%)	67 (81%)	.453
Time since first HIV+ test (yr)†	9.7 (7.8-12.4)	4.3 (0.2-9.1)	<.001
Age at first HIV+ test (yr)†	27.8 (12.2-56.1)	29.7 (18.6-49.2)	.096
Transmission group			
Homosexual/bisexual men	37 (53%)	56 (67%)	.181
Heterosexuals	6 (9%)	8 (10%)	
IV drug users	16 (23%)	13 (16%)	
Others	11 (15%)	6 (7%)	
No. of CD4 cells/μL†	672 (278-1,286)	361 (115-1,331)	<.001
No. of CD8 cells/μL†	955 (391-2,265)	949 (242-2,534)	.502

**P* values were computed using Mann-Whitney and the χ^2 tests.

†All CD4 and CD8 cell measures were performed in our laboratory; data is presented as median values with, in parentheses, the minimum-maximum values. All participants of both cohorts gave consent for the studies.

delaying the AIDS symptoms, as they are strongly implicated in the control of the cellular response to pathogens.

In both cohorts, we measured the frequency of HLA alleles (class I and II). We report in Table 2 only those markers found in more than 10% and less than 90% of the individuals, for which the *P* value was lower than .20. The predominant HLA alleles found were HLA-A3, HLA-B14, HLA-B17, HLA-B27, HLA-DR6, and HLA-DR7 in LT-NP subjects and HLA-B12 in progressors (Table 2).

Table 2. The Frequency of CCR5, CCR2, SDF1, and HLA Genotypes in LT-NP and Progressors

Gene or Genotype	ALT (LT-NPs) n = 70 (%)	IMMUNOCO (progressors) n = 83 (%)	*P* Value
CCR5			
Wild/mut*	26 (37)	9 (11)	.001
CCR2			
Wild/mut	14 (20)	13 (16)	.221
Mut/mut	2 (3)	0	
SDF1			
Wild/mut	23 (33)	32 (39)	.581
Mut/mut	2 (3)	4 (5)	
HLA-A3	22 (31)	13 (16)	.021
HLA-B12	13 (19)	27 (33)	.050
HLA-B14	14 (20)	9 (11)	.114
HLA-B17	19 (27)	11 (13)	.031
HLA-B27	14 (20)	3 (4)	.001
HLA-DR6	21 (30)	16 (19)	.123
HLA-DR7	28 (40)	24 (29)	.149

*To simplify the presentation of results, we substituted the mutation symbols −Δ32, 64I and 3′A, by mut. Thus, the heterozygous genotype was noted as wild/mut and the homozygous genotypes were noted as wild/wild and mut/mut for each of the three screened genes.

We then looked for possible genetic links between these markers. Statistically significant associations were found in all subjects of both cohorts for the following allelic couples: HLA-B5/HLA-DR6, HLA-B12/HLA-DR7, HLA-B17/HLA-B12, and HLA-B17/HLA-DR7. Next, we proceeded with a multivariate analysis and, as a result, retained only six single alleles as being significantly more frequent in the LT-NP group: HLA-A3, HLA-B14, HLA-B17, HLA-B27, HLA-DR6, and HLA-DR7, for which the *P* value was lower than .05. The HLA-B12 allele was not retained after this analysis. These alleles have been already proposed by others as associated with an increased probability for AIDS-free infection.[4-6]

All data were collated to build a genetic model, predictive for long-term nonprogression of HIV-1 disease. We then looked for

Table 3. The Distribution of Composite SDF1/CCR5/CCR2 Genotypes in LT-NP and Progressors

	CCR2		
	Wild/wild	Wild/mut	Mut/mut
SDF1 wild/wild and CCR5 wild/wild	18/39*	8/6	0/0
SDF1 wild/wild and CCR5 wild/mut	17/2	2/0	0/0
SDF1 wild/mut and CCR5 wild/wild	12/19	3/6	2/0
SDF1 wild/mut and CCR5 wild/mut	5/7	1/0	0/0
SDF1 mut/mut and CCR5 wild/wild	1/3	0/1	0/0
SDF1 mut/mut and CCR5 wild/mut	1/0	0/0	0/0

*Results are presented as a ratio of the number of ALT (LT-NP) subjects over IMMUNOCO (progressor) patients.

interactions between the different genes and their impact when LT-NP and progressors were compared. Interactions were evident between the CCR2/CCR5/SDF1 genes and between HLA-B27 and HLA-DR6, respectively. We constructed combined variables (Table 4). The first one comprised the CCR2, CCR5, and SDF-1 genes. The combination CCR2 wild/mut, CCR5 wild/wild, and SDF1 wild/wild was associated with an odds-ratio of being LT-NP of 4.6 ($P = .036$). The most frequently observed combination in nonprogressors was the CCR2 wild/wild or wild/mut, CCR5 wild/mut, and SDF1 wild/wild ($P = .0002$). The odds-ratio of being LT-NP was estimated as 25.8 for a subject bearing this composite genotype compared with a subject with only wild-type genotype (Table 4). In other words, in HIV-1–infected subjects with this gene combination, the odds of meeting the criteria of LT-NP increase by 26-fold. Apparently, the CCR5 mutated allele dominates over the two other genes during restriction to AIDS. Although we did not find any protective effect by SDF1 mut/mut allele itself as Winkler et al,[25] the role of this gene in AIDS avoidance seems to be important, as its wild-type allele is strongly associated with the Δ32 deletion of CCR5 in our combined genotype. As was reported for CCR2 and CCR5 genes,[19] SDF1 might also be in linkage disequilibrium with an as yet unidentified marker, which could influence the LT-NP status.

The second combined variable investigated was the combination of HLA-B27 present and HLA-DR6 allele absent, which was found much more frequently in the LT-NP than in progressors, with an odds-ratio estimated as 81 as compared with a subject without HLA-B27 or HLA-DR6. The third combined variable was built out of the four following alleles: HLA-A3, HLA-B14, HLA-B17, and HLA-DR7 because no interaction was found between them. We simply assessed how many of these alleles were present in a given subject and attributed an HLA score of: 0 when no allele was present, 1 when one or two alleles were present, and 2 when three or four alleles were present. As shown in Table 4, LT-NPs were more likely to present either one or two markers (70% *v* 54%) or three or four markers (10% *v* 1%) compared with progressors. We found that this HLA score was an independent predictor of long-term nonprogression. For an individual with one or two of the above HLA markers, the odds-ratio of being LT-NP was estimated as 4.4 as compared with an individual with none of these four alleles. For an individual with at least three HLA markers, the odds-ratio of being LT-NP was estimated as 49.5.

When assessing goodness of fit of our model, no departure from normality was observed when checking the distribution of the standardized residual. Similarly, the three variables included in the final model were found significant in 50 of 50 parameter estimations performed on 50 independent random samples including 80% of the subjects, showing the robustness of the analysis. Of course, our model deserves to be confirmed on another independent set of subjects. When all analyzed genetic factors were integrated in the logistic model, 70% of LT-NP and 81% of progressors were correctly classified, suggesting that the host's genetic background plays an important role in the evolution of HIV disease.

We showed for the first time that LT-NP share a particular genotype for both HLA and chemokine receptor loci, which independently influence the outcome of their disease. The most important point seems to be that the chemokine and chemokine receptor genes act in a particular combination with the most significant effect observed with the CCR5-Δ32 and SDF1 wild-type alleles. We are still far from a definitive understanding of the LT-NP phenomenon. However, in our opinion, a complex screening of the genetic background of HIV-1–infected subjects would increase the predictive ratio of disease evolution. The lesson we will learn from these subjects could modify the follow-up and the differential administration of treatment to those with progressive disease and serve, besides viral load and CD4 cells counts, as a decision-making tool for management of HIV-1–infected patients.

Table 4. Predictive Value of CCR2, CCR5, and SDF1 Alleles and HLA Genotypes for the LT-NP Status

			ALT (LT-NPs) N = 70	IMMUNOCO (progressors) N = 83	Multivariate Odds-ratio*	Overall *P* Value
CCR2	CCR5	SDF1				.003
Wild†	Wild	Wild	18	38	1	
Wild	Wild	Mut	13	21	1.2 [0.4-3.3]	
Mut	Wild	Wild	8	6	**4.6** [1.1-19.5]	
Mut	Wild	Mut	5	6	2.7 [0.6-11.8]	
Wild or mut	Mut	Wild	19	3	**25.8** [4.7-141.1]	
Wild or mut	Mut	Mut	7	9	3.4 [0.9-13.7]	
B27	DR6					.001
Absent	Absent		38	66	1	
Absent	Present		18	14	3.9 [1.5-10]	
Present	Absent		11	1	**51.0** [4.9-526.8]	
Present	Present		3	2	5.1 [0.5-55.3]	
HLA score‡						.001
0 marker			14	37	1	
1 or 2 markers			49	45	**4.7** [1.7-12.6]	
3 or 4 markers			7	1	**49.5** [4.5-541.7]	

*The values in brackets represent the 95% confidence interval; odds-ratio are statistically significant if the CI95% values are above 1.0.
†Wild stands for wild/wild genotypes and mut stands for wild/mut (CCR5, CCR2, SDF1) or mut/mut (CCR2 and SDF1) genotypes.
‡HLA score was constructed with the following markers: HLA-A3, HLA-B14, HLA-B17, and HLA-DR7.

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APPENDIX

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REFERENCES

1. Buchbinder SP, Katz MH, Hessol NA, O'Malley PM, Holmberg S: Long-term HIV-1 infection without immunologic progression. AIDS 8:1123, 1994

2. Sheppard HW, Lang W, Ascher MS, Vittinghoff E, Winklestein W: The characterization of long-term non-progressors: Long-term HIV-1 infection with stable CD4+ T-cell level. AIDS 7:1159, 1993

3. Detels R, Mann D, Carrington M, Hennessey K, Wu Z, Hirji KF, Wiley D, Visscher BR, Giorgi JV: Resistance to HIV infection may be genetically mediated. AIDS 10:102, 1996

4. Itescu S, Rose S, Dwyer E, Winchester R: Certain HLA-DR5 and DR6 major histocompatibility complex class II alleles are associated with a CD8 lymphocytic host response to human immunodeficiency virus type 1 characterized by low lymphocyte viral strain heterogeneity and slow disease progression. Proc Natl Acad Sci USA 91:11472, 1994

5. Kaslow RA, Carrington M, Apple R, Park L, Munoz A, Saah AJ, Goedert JJ, Winkler C, O'Brien SJ, Rinaldo C, Detels R, Blattner W, Phair J, Erlich H, Mann DI: Influence of combinations of human major histocompatibility complex genes on the course of HIV-1 infection. Nat Med 2:405, 1996

6. Nelson GW, Kaslow R, Mann DL: Frequency of HLA allele-specific peptide motifs in HIV-1 proteins correlates with the allele's association with relative rates of disease progression after HIV-1 infection. Proc Natl Acad Sci USA 94:9802, 1997

7. Theodorou I, Autran B, Goubar A, Costagliola D, Bouley JM, Sanson F, Gomard E, Rivière Y, Katlama C, Agut H, Clauvel JP, Sicard D, Rouzioux C, Raffoux C, Charron D, Debré P: HLA phenotypes in long-term asymptomatic, HIV-infected adult individuals in France. Proceedings of the Twelfth International Histocompatibility Workshop and Conference, vol II, 1997, p 698

8. Kaslow RA, Duquesnoy R, Van Randen M, Kingsley L, Marrari M, Friedman H, Su S, Saah AJ, Detels R, Phair J: A1, Cw7, B8, DR3 HLA antigen combinations associated with rapid decline of T helper lymphocytes in HIV-1 infection. A report from the Multicenter AIDS Cohort Study. Lancet 335:927, 1990

9. Sahmoud T, Laurian Y, Gazengel C, Sultan Y, Gautreau C, Costagliola D: Progression to AIDS in French haemophiliacs: Association with HLA B35. AIDS 7:497, 1992

10. Just JJ, Abrams EG, Louie LG, Urbano R, Wara DS, Nicholas SW, Stein Z, King MC: Influence of host genotype on progression to acquired immunodeficiency syndrome among children infected with human immunodeficiency virus type 1. J Pediatr 127:544, 1995

11. Feng Y, Broder CC, Kennedy PE, Berger EA: HIV-1 entry cofactor: Functional cDNA cloning of a seven-transmembrane, G protein-coupled receptor. Science 272:872, 1996

12. Kroner BL, Goedert JJ, Blattner WA, Wilson SE, Carrington MN, Martin DL, the Multicenter Hemophilia Cohort and Hemophilia Growth and Development Studies: Concordance of human leukocyte antigen haplotype-sharing, CD4 decline and AIDS in hemophilic siblings. AIDS 9:275, 1995

13. Alkhatib G, Combadiere C, Broder CC, Feng Y, Kennedy PE, Murphy PM, Berger EA: CC CKR5: A RANTES, MIP-1α, MIP-1β receptor as a fusion cofactor for macrophage-tropic HIV-1. Science 272:1955, 1996

14. Deng H, Liu R, Ellmeier W, Choe S, Unutmaz D, Burkhart M, DiMarzio P, Marmon S, Sutton RE, Hill CM, Davis CB, Peiper SC, Schall TJ, Littman DR, Landau NR: Identification of a major co-receptor for primary isolates of HIV-1. Nature 381:661, 1996

15. Dragic T, Litwin V, Allaway GP, Martin SR, Huang Y, Nagashima KA, Cayanan C, Maddon PJ, Koup RA, Moore JP, Paxton WA: HIV-1 entry into CD4+ cells is mediated by the chemokine receptor CC-CKR-5. Nature 381:667, 1996

16. Doranz BJ, Rucker J, Yi Y, Smyth RJ, Samson M, Peiper SC, Parmentier M, Collman RG, Doms RW: A dual-tropic primary HIV-1 isolate that uses fusin and the β-chemokine receptors CKR-5, CKR-3 and CKR-2b as fusion cofactors. Cell 85:1149, 1996

17. Samson M, Libert F, Doranz BJ, Rucker J, Liesnard C, Farber CM, Saragosti S, Lapoumeroulie C, Cognaux J, Forceille C, Muyldermans G, Verhofstede C, Burtonboy G, Georges M, Imai T, Rana S, Yi Y, Smyth RJ, Collman RG, Doms RW, Vassart G, Parmentier M: Resistance to HIV-1 infection in Caucasian individuals bearing mutant alleles of the CCR-5 chemokine receptor gene. Nature 382:722, 1996

18. Dean M, Carrington M, Winkler C, Huttey GA, Smith MS, Allikmets R, Goedert JJ, Buchbinder SP, Vittinghoff E, Gomperts E, Donfield S, Vlahov D, Kaslow R, Saah A, Rinaldo C, Detels R, Hemophilia Growth and Development Study, Multicenter AIDS Cohort Study, Multicenter Hemophilia Cohort Study, San Francisco City Cohort, ALIVE Study, O'Brien SJ: Genetic restriction of HIV-1 infection and progression to AIDS by a deletion allele of the CKR5 structural gene. Science 273:1856, 1996

19. Smith MW, Dean M, Carrington M, Winkler C, Huttley GA, Lomb DA, Goedert JJ, O'Brien TR, Jacobson LP, Kaslow R, Buchbinder S, Vittinghoff E, Vlahov D, Hoots K, Hilgartner MW, Hemophilia Growth and Development Study (HGDS), Multicenter AIDS Cohort Study (MACS), Multicenter Hemophilia Cohort Study (MHCS), San Francisco City Cohort (SFCC), ALIVE Study, O'Brien SJ: Contrasting genetic influence of CCR2 and CCR5 variants on HIV-1 infection and disease progression. Science 277:959, 1997

20. Zimmerman PA, Buckler-White A, Alkhatib G, Spalding T, Kubofcik J, Combardiere C, Weissman D, Cohen O, Rubbert A, Lam G, Vaccarezza M, Kennedy PE, Kumaraswami V, Giorgi JV, Detels R, Hunter J, Chopek M, Berger EA, Fauci AS, Nutman TB, Murphy PM: Inherited resistance to HIV-1 conferred by an inactivating mutation in CC chemokine receptor 5: Studies in populations with contrasting clinical phenotypes, defined racial background and quantified risk. Mol Med 3:23, 1997

21. Rizzardi GP, Morawetz RA, Vicenzi E, Ghezzi S, Poli G, Lazzarin A, Pantaleo G, the Swiss HIV Cohort: CCR2 polymorphism and HIV disease. Nat Med 4:252, 1998

22. Kostrikis LG, Huang Y, Moore JP, Wolinsky SM, Zhang L, Guo Y, Deutsch L, Phair J, Neumann AU, Ho DD: A chemokine receptor CCR2 allele delays HIV-1 disease progression and is associated with a CCR5 promoter mutation. Nat Med 4:350, 1998

23. Huang Y, Paxton WA, Wolinsky SM, Neumann AU, Zhang L, He

T, Kang S, Ceradini D, Jin Z, Yazdanbakhsh K, Kunstman K, Erickson D, Dragon E, Landau NR, Phair J, Ho DD, Koup RA: The role of a mutant CCR5 allele in HIV-1 transmission and disease progression. Nat Med 2:1240, 1996

24. Meyer L, Magierowska M, Hubert JB, Rouzioux C, Deveau C, Sanson F, Debre P, Delfraissy JF, Theodorou I, and the Seroco Study Group: Early protective effect of CCR-5 Δ32 heterozygosity on HIV-1 disease progression: Relationship with viral load. AIDS 12:1519, 1997

25. Winkler C, Modi W, Smith MW, Nelson GW, Wu X, Carrington M, Dean M, Honjo T, Tashiro K, Yabe D, Buchbinder S, Vittinghoff E, Goedert JJ, O'Brien TR, Jacobson LP, Detels R, Donfield S, Willoughby A, Gomperts E, Vlahov D, Phair J, ALIVE Study, Hemophilia Growth and Development Study (HGDS), Multicenter AIDS Cohort Study (MACS), Multicenter Hemophilia Cohort Study (MHCS), San Francisco City Cohort (SFCC), O'Brien SJ: Genetic restriction of AIDS pathogenesis by an SDF-1 chemokine gene variant. Science 279:389, 1998

26. Michael NL, Chang G, Louie LG, Mascola JR, Dondero D, Birx DL, Sheppard HW: The role of viral phenotype and CCR-5 gene defects in HIV-1 transmission and disease progression. Nat Med 3:338, 1997