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Distinctive effects of CCR5, CCR2, and SDF1 genetic polymorphisms in AIDS progression.

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The Genetics of Resistance to Infection by HIV-1 (GRIV) cohort represents 200 nonprogressor/slow-progressor (Slowprog) and 90 fast-progressor (Fastprog) HIV-1-infected patients. Using this unique assembly, we performed genetic studies on three recently discovered polymorphisms of CCR5, CCR2, and SDF1, which have been shown to slow the rate of disease progression. The increased prevalence of mutant alleles among Slowprogs from the GRIV cohort was significant for CCR5 ($p < .0001$) but not for CCR2 ($p = .09$) or SDF1 ($p = . 12$), emphasizing the predominant role of CCR5 as the major HIV-1 coreceptor. However, the prevalence of the CCR2 mutant allele (64I) was significantly increased among Slowprogs homozygous for wild-type CCR5 compared with Fastprogs ($p = .04$). The prevalence of double mutants SDF1-3'A/3'A genotypes was also increased among Slowprogs homozygous for wild-type CCR5 compared with Fastprogs ($p = .05$). The effects of the CCR2 and SDF1 mutations are overshadowed by the protective effects of the CCR5 deletion. Predictive biologic markers such as CD4 cell counts or viral load in the Slowprog population did not show significant differences between Slowprog groups with wild-type or mutant alleles for the three genes. Thus, our data suggest that the effects of these genes are exerted earlier in infection and no longer evident in the Slowprog of the GRIV cohort whose average duration of HIV infection is 12 years. We conclude that these genes, whose products serve as viral coreceptors or their ligands, may play a role early in infection and delay the onset of disease. However, among Slowprogs, whose duration of infection is >8 years, they are no longer influential for maintenance of their longterm nonprogression status. Other genetic determinants may be responsible for late protective effects.

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