

HIV/AIDS Pathogenesis: Genetic variation in chemokine gene cluster influences HIV-1 transmission and progression

Staff Medical Writers

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-- Genetic variation in the CCL18-CCL3-CCL4 chemokine gene cluster influences HIV-1 transmission and disease progression.

According to recent research from the United States, "CCL3 (MIP-1 alpha), CCL4 (MIP-1 beta), and CCL18 (DC-CK1/PARC/AMAC-1) are potent chemoattractants produced by macrophages, natural killer cells, fibroblasts, mast cells, CD4+ T cells, and CD8+ T cells.

"CCL3 and CCL4 are natural ligands for the primary human immunodeficiency virus type 1 (HIV-1) coreceptor CCR5 and are also known to activate and enhance the cytotoxicity of natural killer cells."

"Genomic DNAs from 13,000 participants enrolled in five United States based natural-history cohorts with acquired immunodeficiency syndrome (AIDS) were genotyped for 21 single-nucleotide polymorphisms (SNPs) in a 47-kb interval on chromosome 17q12 containing the genes CCL3, CCL4, and CCL18.

"All 21 SNPs were polymorphic in African Americans (AAs), whereas 7 of the 21 had minor-allele frequencies <0.01 in European Americans (EAs)," reported W.S. Modi and colleagues at the U.S. National Institutes of Health.

The authors continued, "Substantial linkage disequilibrium was observed in a 37-kb interval containing 17 SNPs where many pairwise D' values exceeded 0.70 in both racial groups, but particularly in EAs.

"Four and three haplotype blocks were observed in AAs and EAs, respectively. Blocks were strongly correlated with each other, and common haplotype diversity within blocks was limited."

"Two significant associations are reported that replicate an earlier study. First, among AA members of the AIDS Link to the Intravenous Experience cohort of injection drug users, frequencies of three correlated SNPs covering 2,231 bp in CCL3 were significantly elevated among highly exposed, persistently HIV-1-uninfected individuals compared with HIV-1-infected seroconvertors (p=0.02-0.03).

"Second, seven highly correlated SNPs spanning 36 kb and containing all three genes were significantly associated with more-rapid disease progression among EAs enrolled in the Multicenter AIDS Cohort Study cohort (p=0.01-0.02)," wrote investigators.

Modi concluded, "These results reiterate the importance of chemokine gene variation in HIV-1/AIDS pathogenesis and emphasize that localized linkage disequilibrium makes the identification of causal mutations difficult."

Modi and colleagues published their study in *American Journal of Human Genetics* (Genetic variation in the CCL18-CCL3-CCL4 chemokine gene cluster influences HIV type 1 transmission and AIDS disease progression. Am J Hum Genet. 2006 Jul;79(1):120-8).

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Reference

Modi WS, Lautenberger J, An P, *et al.*, "Genetic variation in the CCL18-CCL3-CCL4 chemokine gene cluster influences HIV Type 1 transmission and AIDS disease progression", Am J Hum Genet. 2006 Jul;79(1):120-8.

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