

Polymorphisms In Irf-1 Associated With Resistance To Hiv-1 Infection In Highly Exposed Uninfected Kenyan Sex Workers

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Abstract:

OBJECTIVE: To determine the correlation between polymorphisms in the IL-4 gene cluster and resistance to HIV-1 infection. **DESIGN:** : A cross-sectional genetic analysis of polymorphisms within the IL-4 gene cluster was conducted in a well-described female sex worker cohort from Nairobi, Kenya, known to exhibit differential susceptibility to HIV-1 infection. **METHODS:** Microsatellite genotyping was used to screen six microsatellite markers in the IL-4 gene cluster for associations with HIV-1 resistance. Further analysis of the interferon regulatory factor 1 (IRF-1) gene was conducted by genomic sequencing. Associations between IRF-1 gene polymorphisms and the HIV-1 resistance phenotype were determined using the chi-square test and Kaplan-Meier survival analysis. The functional consequence of IRF-1 polymorphism was conducted by quantitative Western blot. **RESULTS:** Three polymorphisms in IRF-1, located at 619, the microsatellite region and 6516 of the gene, showed associations with resistance to HIV-1 infection. The 619A, 179 at IRF-1 microsatellite and 6516G alleles were associated with the HIV-1-resistant phenotype and a reduced likelihood of seroconversion. Peripheral blood mononuclear cells from patients with protective IRF-1 genotypes exhibited significantly lower basal IRF-1 expression and reduced responsiveness to exogenous IFN-gamma stimulation. **CONCLUSION:** Polymorphisms in the IRF-1 gene are associated with resistance to infection by HIV-1 and a lowered level of IRF-1 protein expression. This study adds IRF-1, a transcriptional immunoregulatory gene, to the list of genetic correlates of altered susceptibility to HIV-1. This is the first report suggesting that a viral transcriptional regulator might contribute to resistance to HIV-1. Further functional analysis on the role of IRF-1 polymorphisms and HIV-1 resistance is underway