A Genetic Polymorphism of FREM1 Is Associated with Resistance against HIV Infection in the Pumwani Sex Worker Cohort

Abstract:

A subgroup of women enrolled in the Pumwani sex worker cohort remain seronegative and PCR negative for human immunodeficiency virus type 1 despite repeated exposure through high-risk sex work. Studies have shown that polymorphisms of genes involved in antigen presentation and viral restriction factors are associated with resistance to HIV infection. To discover other possible genetic factors underlying this HIV-resistant phenotype, we conducted an exploratory nonbiased, low-resolution, genome-wide single-nucleotide polymorphism (SNP) analysis comparing 60 HIV-resistant women to 48 HIV-infected controls. The SNP minor allele rs1552896, in an intron of FREM1, was significantly associated with the resistant phenotype (P = 1.68 × 10⁻⁵; adjusted P = 2.37 × 10⁻⁴; odds ratio [OR], 9.51; 95% confidence interval [CI], 2.82 to 32.05). We expanded the sample size by genotyping rs1552896 in the Pumwani cohort and comparing 114 HIV-resistant women to 609 HIV-infected controls and confirmed the association (P = 1.7 × 10⁻⁴; OR, 2.67; 95% CI, 1.47 to 4.84). To validate the association in a second cohort, we genotyped 783 women enrolled in a mother-child health study and observed the minor allele of rs1552896 enriched in HIV-uninfected women (n = 488) compared to HIV-infected enrollees (n = 295) (P = 0.036; OR, 1.69; 95% CI, 0.98 to 2.93). Quantitative reverse transcription-PCR showed that FREM1 mRNA was highly expressed in tissues relevant for HIV-1 infection, and immunohistochemical analysis revealed that FREM1 protein is expressed in the ectocervical mucosa of HIV-resistant women. The significant association of rs1552896 with an HIV-resistant phenotype, together with the expression profile of FREM1 in tissues relevant to HIV infection, suggests that FREM1 is a potentially novel candidate gene for resistance to HIV infection.