HuGE Fact Sheet

CCR5 receptor gene and HIV infection

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CCR5 Gene

The gene for CCR5 is located on chromosome 3 in the p21.3-p24 region. CCR5 is a chemokine receptor present in different cells, especially in macrophages, monocytes, and T cells, where it acts as a co-receptor for HIV-1 in these cells. Chemokines and their receptors are believed to be involved in the inflammatory response, mediating leukocyte movement and activation.

Prevalence of Gene Variants

At least 23 alleles have been described for the coding region of this gene, and most of them are very rare. The most common and most studied is the ? 32 allele, a 32 base pair (bp) deletion that confers almost absolute protection from infection with macrophage tropic (M-tropic) viruses in homozygous individuals and provides an average 2 to 3 year delay in the progression to AIDS in those heterozygous for the deletion. The allele's prevalence varies by ethnicity, being as high as 10%-15% in Caucasians, ~2% in African Americans, and virtually absent in native Africans and East Asians (3,6). Several single nucleotide polymorphisms (SNPs) were described in the promoter region of CCR5, accounting for six different important haplotypes. Many studies showed that the 64I allele of another chemokine receptor coding gene, CCR2, is in very strong linkage disequilibrium with one allele of the promoter region of CCR5 (1), invariably in combination with CCR5+ (now named haplotype F*2). These findings led to the modern classification of 9 haplotypes for CCR5 (A, B, C, D, E, F*1, F*2, G*1, and G*2; the latter corresponding to the CCR5 ? 32 allele) that actually encompass its open reading frame, the promoter region, and the CCR2 gene (3,8). Gonzales et al. have recently published world-wide distributions of these haplotypes, showing great variation in their frequencies (3).

Disease Burden

Ninety percent of the infections caused by HIV 1 involve the so-called M-tropic (or R5-tropic) strains. In addition to the CD4 receptor present in macrophages, monocytes, and T cells, these strains also need the presence of a CCR5 receptor on the cell surface to infect. The 32 bp deletion causes the resultant protein to be truncated and inactive, and individuals homozygous for the ? 32 allele present undetectable concentrations of the receptor, while heterozygous individuals have 20%-30% of the wild type concentrations (5,6). The result is that homozygous individuals exposed to M-tropic strains are protected from infection, while infected heterozygous individuals present a slower progression to both AIDS and death. In a cohort of 2,996 people, Marmor et al. showed only one seroconversion among 39 CCR5-? 32/ ? 32 participants, but this was a T-tropic strain that uses the CXCR4 receptor instead of the CCR5 receptor. In the same study, the risk ratio (RR) for seroconversion was 0.30 (95% Confidence Interval: 0.08-0.96) in the CCR5 ? 32/+ group compared with the CCR5+/+ group when controlled for unprotected receptive anal sex (4). In another study that combined five different cohorts totaling 3,003 patients, Smith et al. showed that seropositive heterozygous individuals had a prolonged survival time to AIDS (Relative Hazard (RH) = 0.68, p = 0.002) and to death (RH = 0.67, p = 0.02) (7).

In a recent study by Tang et al., some features of the nine CCR5 haplotypes were studied, and the haplotype G*2, especially the genotype A/G*2, was more frequent in individuals highly exposed to HIV and persistently seronegative (OR = 0.54, 95% CI: 0.32-0.89) (8). Viral load during the first 42 months of infection was lower in G*2 carriers, especially among those with genotypes A/G*2 and F*2/G*2). Progression to AIDS was also delayed for G*2 carriers.

Interactions

Several factors interact in HIV 1 transmission since the infection depends on variables related to susceptibility, transmissibility, and host response to infection. Several other genes may play a role in the

susceptibility of the cells to HIV infection. The role of gene expression of CCR5 chemokine ligands in HIV infection has been the subject of intense research, since the suppression of these ligands, secondary to $CD8^+$ cell depletion in HIV-positive patients, has been demonstrated to lead, at least in part, to accelerated viral replication. Although there is strong evidence of potent inhibition of HIV replication in vitro, studying RANTES, MIP-1? and MIP-1? expressions in HIV positive cohorts has shown conflicting results (2).

Laboratory Tests
Several different methods have been used for CCR5 genotyping, but the most common methods are DNA-PCR, followed by restriction fragment length polymorphism (RFLP) or sequencing.

Population testing
To date, no recommendation on population testing has been issued. Since the major factor in HIV infection is exposure to the virus, protective measures against the exposure continue to be recommended as public health policy.

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Web sites
UNAIDS **-** http://www.unaids.org/
JAMA HIV/AIDS Resource Center - http://www.ama-assn.org/special/hiv/hivhome.htm
Johns Hopkins AIDS Service - http://www.hopkins-aids.edu/
Centers for Disease Control and Prevention, Office of Genomics and Disease Prevention
http://www.cdc.gov/genomics/info/books/21stcent2c.htm#Chapter10