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Host Genetic Factors and HIV-1 Progression in Perinatally Infected Children

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In the pre-antiretroviral therapy (ART) era, HIV infection in perinatally infected children was described to follow three distinct courses. An *in utero* infection coincident with immunological cell expansion in the fetus can lead to rapid spread of virus and culminates in a rapid disease course, with onset of AIDS and symptoms during the first few months of life and a median survival time of 6-9 months, if untreated. The majority of perinatally infected newborns (60-80%) in developed countries present with a much slower progression of disease, with a median survival time of 6 years representing the 2nd pattern of disease. The 3rd pattern of disease occurs in a small percentage (<5%) of perinatally infected children referred to as long-term non-progressors (LTNPs), who have minimal or no progression of disease with relatively normal CD4 counts and very low viral loads for longer than 8 years [1,2].

This variation in susceptibility to HIV-1 infection and its rate of progression is partly explained by host genetic factors. Supporting a role for genetic factors in the host, several studies have shown that susceptibility to HIV-1 *in vitro* largely varies among cells from genetically distinct individuals. Conversely, primary cells from homozygotic twins display much less variation in their susceptibility to infection. In order to complete a replicative cycle, HIV-1 must use the cellular machinery at multiple steps and rely on host cellular proteins. Only a fraction of these host proteins have been identified, but their role in the HIV-1 susceptibility and progression is currently a subject of intense investigation [3]. The study by Palchaudhuri, *et al.* [4] in the current issue is the first such study on perinatally infected Indian children linking specific genetic markers with HIV progression. Approaches used to study these host genetic factors *in vivo* have predominantly used LTNPs. Studies on perinatally infected children in a French cohort have demonstrated this population to be 2% of the infected population [5].

Prevalence studies have not been done in India [6].

The host genetic factors involved in HIV infection and progression can be grouped into those that modulate viral entry, those that modulate post entry viral replication, and those that modulate the innate immune response against HIV-1 infection [7]. Among factors modulating viral entry, HIV-1 co-receptor CCR5 and CXCR4 polymorphisms are being investigated. High level of wild type CCR5 expression on CD4-positive primary T cells is associated with high viral loads and accelerated disease progression. Studies have characterized the CCR5Δ32 allele, which has been unequivocally associated with protection to HIV-1 infection in homozygotic individuals. CCR5Δ32 expresses a truncated co-receptor that is not transported to the cell surface and thus is incompetent for viral entry [7]. Individuals homozygous for the Δ32 allele seem to have a normal life expectancy. Though the CCR5Δ32 allele occurs at a frequency of 4-15% in the Caucasian population, it is rarely found in Asians and Africans [8]. Recently, CCR5 promoter polymorphisms like CCR5 5902G have been described to affect HIV progression [9,10]. This allele has been described to have a high prevalence among LTNPs in the present study.

The beta-chemokines MIP-1α(CCL3), MIP-1β(CCL4), and RANTES (CCL5) are the natural ligands of CCR5, which after binding to it, induce its internalization. Thus, high levels of these chemokines are postulated to provide the host immunity against viral replication [11]. SDF-1 (also known as CXCL12) is the only known ligand of CXCR4, which also induces internalization of the receptor [12]. A polymorphism in the noncoding region of SDF-1 has been reported (SDF1-3'A). In the homozygous form, the presence of an A at position 801 has been associated with slower progression to AIDS, as compared to heterozygous or wild-type

homozygous. A number of reports have failed to confirm this association in other cohorts [13]. Thus, it is not clear whether the SDF1-3'A variant plays a role in disease progression. In the present study by Palchaudhuri, *et al.*, only a prevalence of the allele has been described in the LTNP population, which has not been compared with controls.

Factors that modulate the innate immune response include the MHC genes, which are the targets of active research. Associations have been reported between faster HIV-1 disease progression and HLA types: A23, A24, A26, B21, B38. Conversely, some studies have shown associations between delayed AIDS progression and DR4, DR7, B17, B27, B51, and B57. The exact role of HLA haplotypes in AIDS progression remains elusive. One possible mechanism is the variable ability of different HLA molecules in presenting the HIV-1 antigen and inducing a strong immune response [14]. In the study by Palchaudhuri, *et al.* [4], HLA-B*57 polymorphic allele was found in one Slow progressor (SP) and in one LTNP, while HLA-B*27 was found in one LTNP. Mannose binding lectin (MBL) deficiency has also been associated with increased HIV-1 vertical transmission [15].

Intracellular antiviral host factors such as APOBEC3G (Apolipoprotein B mRNA Editing Catalytic Polypeptide 3G) formerly known as CEM15, is an endogenous inhibitor of intracellular HIV-1 replication. An APOBEC3G variant containing a non-synonymous substitution of Arg for His at amino acid position 186 is present in African-Americans and is strongly associated with more rapid decline of CD4⁺ T cells and accelerated progression to AIDS [16].

It is thus anticipated that in the near future, the map of genes involved in HIV-1 pathogenesis will be greatly enhanced. Identification of these genes and the variants associated with slow progression and resistance to infection will allow physicians to predict better the outcome of disease and to design antiretroviral regimens tailored to patient-specific genotypes. As it has occurred with the CCR5Δ32 allele, the discovery of new variants might invigorate the development of approaches to combat HIV-1 infection.

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