1. Introduction
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Human immunodeficiency virus type 1 (HIV-1) is a causative agent of acquired immunodeficiency syndrome (AIDS) in humans. HIV-1 has continued to spread across the globe, despite attempts by the medical and scientific communities to curb the epidemic. Since the first AIDS case was diagnosed in 1981, nearly 21 million people have died worldwide and nearly 33.2 million people are living with HIV-1 infection globally. In 2007 alone, 2.1 million people have died and 6800 new HIV infections occur daily. In India, adult HIV prevalence is approximately 0.36%, which corresponds to an estimated 2.5 million people living with HIV in the country (NACO, 2007)

AIDS is a complex and long-term chronic disease, triggered by initial infection with HIV-1, which gradually leads to depletion of the CD4-T-lymphocyte cell population a prelude to immune system collapse. However, a small fraction of HIV-1 infected individuals remain both clinically and immunologically healthy for 10 years or more after seroconversion (Buchbinder et al., 1994; Cao et al., 1995; Pantaleo et al., 1995). Conversely, the disease of another significant fraction is characterized by an extremely rapid progression to AIDS within 1 year. There are also individuals not infected with HIV-1 who have had repetitive sexual exposure to HIV-1 in extremely high-risk situations (Goh et al., 1999; Akridge et al., 1999; Schmechel et al., 2001; Hladik et al., 2003; Liu et al., 2004).

Understanding the mechanism that account for slower disease progression and the protection against HIV-1 infection is important for the development of more potent therapeutic regimens and a vaccine.

The primary risk factors for HIV-1 infection are unprotected sexual intercourse, sharing of syringes and being an infant born to an infected mother. Although a myriad of social and economic factors strongly influence the HIV-1 pandemic, a possible role of host genetics probably account for a portion of the observed epidemiological heterogeneity in infection susceptibility and in progression rate. Significant studies in the past have demonstrated that genetic polymorphisms in human genes can influence the risk for HIV-1 infection and disease progression (Paxton et al., 1996a; Dean et al., 1996; Ping et al., 2002; O'Brien et al., 2004; Gonzalez et al., 2005).
Extensive meta-analyses of several large AIDS cohorts have revealed numerous genes which are implicated in the outcome of HIV-1 infection, leading to the characteristic variability of disease progression seen following HIV-1 infection. The genes that have been identified were called as AIDS restriction genes (ARGs) and are involved in several stages of HIV-1 replication, including viral entry, immune regulation following infection and adaptive immunity to HIV-1 (O’Brien et al., 2004). Variations in the genes encoding chemokine receptors have been found to be important for both susceptibility to HIV-1 infection and the rate of disease progression following HIV-1 infection. CCR5 delta 32 is a polymorphism in the gene encoding the CCR5 chemokine receptor in which a 32-base pair region has been deleted. Individuals who have two copies of this mutation (i.e. CCR5-Δ32 homozygous or CCR5-Δ32/Δ32) have non-functional receptors. This non-functionality renders CCR5-Δ32/Δ32 individuals immune to R5 strains of HIV-1 (Liu et al., 1996; Dean et al., 1996; Samson et al., 1996). Individuals who possess one copy of CCR5-Δ32 and one copy of CCR5-wildtype (CCR5-Δ32 heterozygous or CCR5-Δ32/wt) may have altered chemokine receptor activity (Stewart et al., 1997; Schinkel et al., 1999). The impact of the CCR5-Δ32/wt genotype on susceptibility to HIV-1 infection has been somewhat controversial (Morawetz et al., 1997). Single nucleotide polymorphisms (SNPs) in the CCR5 promoter region also affect levels of CCR5 expression and rates of HIV-1 disease progression (Martin et al., 1998; Clegg et al., 2000). An association with the disease progression was also reported for an A/G polymorphism (59029 base pair), located in the first CCR5 intron (McDermott et al., 1998).

Recent attention has focussed on polymorphisms in the gene coding for the chemokine MIP-1αP (CCL3L1) and RANTES (CCL5). MIP-1αP, also known as CCL3L1, is the most potent CCR5 agonist and the strongest inhibitor of infection by R5 HIV-1 strains (Irving et al., 1990). Recent studies examined the effect of CCL3L1 copy number, which varies due to segmental duplication, on susceptibility to HIV-1 and concluded that CCL3L1 dose plays a central role in HIV/AIDS pathogenesis. Possession of a CCL3L1 copy number lower than the population average is associated with markedly enhanced HIV/AIDS susceptibility (Gonzalez et al., 2005). RANTES is also an endogenous ligand for
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CCR5 coreceptor for M-tropic HIV-1 strains. Several SNPs in the RANTES gene have been reported to influence the natural course of HIV-1 infection by up- or down-regulating RANTES gene activity. The most frequent of those polymorphic sites comprise RANTES -403 G/A and RANTES -28 C/G in the promoter region and RANTES In1.1 T/C in the first intron region (Liu et al., 1999a; An et al., 2002). Both promoter polymorphism increase RANTES transcription and may delay HIV-1 disease progression (Liu et al., 1999a; Nickel et al., 2000). Conversely, the RANTES In1.1 C allele seems to decrease RANTES transcriptional activity and is probably associated with an increased risk for HIV-1 infection and progression to AIDS (An et al., 2002).

Other genetic variants influencing HIV/AIDS susceptibility were reported in HIV-1 intermediary receptors: DC-SIGN and DC-SIGNR. Dendritic cell-specific intercellular adhesion molecule-3 (ICAM-3) grabbing nonintegrin (DC-SIGN) is a receptor on dendritic cells (DCs) that binds to ICAM-3 expressed on T cells to facilitate the initial interaction between DCs and T cells. DC-SIGN has been considered important in HIV research because it acts as an intermediate receptor for binding to HIV-1 at mucosal sites and then enhancing trans-infection of CD4 T cells in regional lymph nodes (Geijtenbeek et al., 2000b). A homologue of DC-SIGN called DC-SIGNR (DC-SIGN related) shares 77% amino acid identity and exhibits similar capacity of binding to HIV-1 (Pohlmn et al., 2001b; Bashirova et al., 2001). DC-SIGN is expressed at high levels on DCs and some type of macrophages (Soilleux et al, 2002b, Granelli-Piperno et al., 2005), whereas DC-SIGNR is expressed on endothelial cells in liver and lymph nodes (Pohlmn et al., 2001a; Bashirova et al., 2001; Soilleux et al., 2002a). Because DC-SIGN and DC-SIGNR have an apparent role in DC-T cell interaction and HIV-1 infection, the polymorphisms associated with these genes may have an impact on the transmission of HIV-1 as shown in several studies (Lichterfeld et al., 2003; Liu et al., 2004; Liu et al., 2006; Gramberg et al., 2006).

Host cells are endowed with another mechanism to halt HIV-1 infection before integration occurs. The human apolipoprotein B mRNA-editing enzyme-catalytic polypeptide-like-3G (APOBEC3G), formerly known as CEM15, is an endogenous inhibitor of HIV-1 replication (Harris et al. 2003; Mangeat 2003; Zhang 2003). In the absence of the viral protein Vif, APOBEC3G is incorporated into HIV-1 particles in the producer cell, and during reverse transcription deaminates cytosine
bases to uracil in the negative-sense single-stranded DNA, resulting in G to A hypermutations in the complementary, positive sense DNA strand. This hypermutation leaves the viral cDNA vulnerable to degradation by nucleases. Those cDNAs that manage to integrate into the host chromosomes carry multiple mutations that likely result in aberrant viral products (Lecossier et al., 2003; Mariani et al., 2003; Yu et al., 2004a). A variant of APOBEC3G common in African-Americans has been identified, which contains a non-synonymous substitution. This allele carries Arg instead of His at position 186 (186R) and is strongly associated with faster decline of CD4 T cells and accelerated progression to AIDS (An et al., 2004). However, no associations with 186R variant in the APOBEC3G gene have been identified among French individuals (Do et al., 2005).

The study of host genes involved in differential susceptibility and disease course is crucial for understanding of the immunopathogenesis of HIV-1 infections and for the development of immunotherapeutic and prophylactic strategies. Thus, in the present study, we have taken molecular epidemiology approach to evaluate the impact of CCR5, CCL3L1, RANTES, DC-SIGN, DC-SIGNR and APOBEC3G host genetic variants participating in the viral life cycle for their role in modulating HIV-1 infection among North Indian individuals.