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Original Article

Mutation in AIDS restriction gene affecting HIV infection and disease progression in a high risk group from Northeastern India

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ABSTRACT

Background: HIV estimates for 2009 released by National AIDS Control Organization (NACO) reveals that 2.4 million people in India were living with HIV, 39% being female, 4.4% children and 82.4% adult males between the age group of 15 and 49 years. Persons with host genetic polymorphism CCR5Δ32 mutation are known to be partially or fully resistant to HIV infection. Persons with mutation affecting both the alleles (homozygous) are resistant to HIV infection whereas single allele (heterozygous) polymorphism leads to slower progression to AIDS. CCR5Δ32 mutation is commoner in Caucasians but less prevalent amongst Africans and Asians thereby rendering them susceptible to HIV infection.

Method: 571 HIV serologically naive subjects from a young and homogenous male population hailing from the seven northeastern states; West Bengal and Gorkha people were selected. All the subjects belonged to a special high risk group, sexually active and typically working in difficult and uncongenial terrain involved in frequent moves including overseas missions. Their family lives are severely disrupted. 181 HIV seropositive cases of which 92 cases that were admitted in a large tertiary care hospital were also included. The distribution of CCR5Δ32 polymorphism amongst both HIV seronegative (HSN) and HIV seropositive study cohorts (HSP) using molecular methods was studied.

Results and conclusion: There was failure to detect any CCR5Δ32 amongst this study group suggesting that this population from the northeastern India, West Bengal and Gorkha people are not protected by this specific host polymorphism in respect of acquisition of HIV infection as well as progression to AIDS.

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Introduction

HIV estimates for 2009 released by National AIDS Control Organization (NACO) reveal that 2.4 million people in India were living with HIV, 39% being female, 4.4% children and 82.4% adult male between the age group of 15 and 49 years. Despite a decrease in prevalence rates from 0.36% in 2006 to 0.31% in 2009 and the progress made by India in advancing towards prescribed national targets, much remains to be done

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for halting and reversing HIV infections considering that in absolute terms; a large proportion of India's populous is infected or affected with HIV.[1]

The hallmark of HIV infection is the progressive loss of CD4 + T cells that results in a dysfunctional immune system failing to combat the onslaught of opportunistic pathogens. Interestingly, there is significant heterogeneity among individuals in infection susceptibility, the time period necessary to deplete the CD4 T-lymphocytes and progress to AIDS-defining diseases.[2–4] Various virologic and host genetic factors appear to account for a part of the discordance in infection susceptibility and in progression rates to AIDS and death.[5–7]

Host genes collectively known as AIDS restriction genes (ARGs) have been shown to modify individual response to HIV-1 exposure, infection and pathogenesis markedly.[6–8] CCR5, a chemokine receptor has been studied extensively. A 32 base pair deletion in the gene encoding the CCR5 receptor, resulting in CCR5Δ32 mutation has been shown to significantly affect the entry of the HIV and also the progression of the disease to AIDS.[8–11] Individuals who do not exhibit this particular gene polymorphism are prone to the disease.[12] In contrast, individuals who are homozygous for this defect appear to be resistant to HIV infection,[6,8] and it has therefore been assumed that individuals who are heterozygous for this deletion are partially resistant Various other genes are known to affect HIV infection and progression to the disease.

The seven sister states of Northeastern India (NE states) are Assam, Manipur, Nagaland, Arunachal Pradesh, Mizoram, Tripura and Meghalaya. This region is primarily inhabited by Tibeto-Burman speakers who are culturally and genetically distinct from the Indo-European and Dravidian speakers present in the other geographical regions of India.[13,14] Considering the distinct genetic makeup of this population and the high risk group involved, we decided to undertake a study on the presence of host genetic polymorphisms of the CCR5 gene within this specific high risk population. The study period was of 41 months (Aug 2007–Jan 2010). The present prevalence of HIV infection and other demographic parameters of the NE states are incorporated in Table 1.

Material and methods

Two distinct set of populations were selected:

(a) Persons with unknown status for HIV infection.
(b) Persons known seropositive for HIV infection.

A total of 571 males were recruited for the study whose HIV infection status was not known. All these persons belonged to a single homogenous professional background with common peculiarities identified as risk factors individually and collectively that were as follows: In the age group between 18 and 40 years, sexually active with phases of sexual deprivation due to long separation from family. Frequent movements and an inherent risk taking ethos are inbuilt into the profession. Being financially independent they are centers for attraction by sex workers and their middlemen.

All the subjects belonged to either of the following geographical locations:

(a) The 07 sister states in northeastern India namely Assam, Manipur, Nagaland, Arunachal Pradesh, Mizoram, Tripura and Meghalaya
(b) The state of West Bengal, Eastern India.
(c) The Gorkha population belonging to West Bengal, Nepal (but working in India) and other parts of the country.

Subsequently 03 cases were reduced from the figure of 571 as these were detected seropositive during testing and shifted to the group, 'Persons known seropositive for HIV infection'. Therefore, a total of 568 cases were analyzed in the seronegative group.

We also included 181 known HIV seropositive patients (HSP) in this study of which 92 cases belonged to the specified high risk group admitted in a tertiary care hospital for medical management; 61 cases were male intravenous drug users (IDUs) from the state of Manipur and 28 cases were female sex workers (FSW's) from parts of West Bengal. The blood samples of these 89 cases from Manipur (IDU) and West Bengal (FSW) were processed strictly on ''Unlinked and Anonymous'' basis.

Samples were obtained after detailed pre-test counseling and an informed written consent. Permission to carry out the study was obtained from the institutional ethical committee. All samples were serologically tested for Anti-HIV antibodies 1&2; HBsAg; Anti-HCV antibodies by Enzyme linked immune sorbent assay (ELISA). Test for syphilis was carried out using *Treponema pallidum* hemagglutination (TPHA). Post-test counseling was done after the laboratory reports were available. The entire study population was medically followed up six monthly for 41 months to ascertain incidence of HIV infection in HSN and progression to AIDS in HSP group.

Molecular characterization of mutant CCR5Δ32 alleles was performed, using previously published PCR primers[15] for CCR5Δ32 namely Forward: 5′-CTCGGATCCACCAGATCT-CAAAAA GAAGGTCT-3′ and Reverse: 5′-CTCGTCGACAT-GATGTGTAAGATAAGCCT-CAC-3′ in a PTC 200 system (USA) under standard conditions and then separated by 2% agarose-gel electrophoresis. A 100 base pair ladder was incorporated. Based on the characteristics of CCR5Δ32 alleles, the expected banding patterns were as under: Homozygotes for the normal allele (wild type): 217 bp; Heterozygote for the mutant allele: 217 bp and 185 bp and Homozygote for the mutant allele: 185 bp. Appropriate positive and negative controls were incorporated. Amplified PCR products were randomly selected and sequenced to ascertain the correctness of CCR5Δ32 electrophoresis band patterns.

Results

Of the 568 HIV negative samples and the 181 HIV positive samples, all were wild types or homozygotes for the normal allele. No CCR5Δ32 mutations were detected (Fig. 2). All sequenced PCR products showed homology with the CCR5 gene.

The total statewise distribution of known HIV seronegative (HSN) subjects is depicted in Fig. 1. Out of a total of 568 HSN persons, a state-wise ethnic identity of 24 persons could not be ascertained with certainty although it was given to understand through official records that all these 24 persons did belong to

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