STUDIES ON THE POSSIBLE ASSOCIATION OF POLYMORPHISMS IN IMMUNOREGULATORY GENES WITH HIV INFECTION AMONG HIV / AIDS SEROPOSITIVE NORTH INDIANS

SUMMARY

Human immunodeficiency virus (HIV) is an enveloped retrovirus belonging to the Lentivirus genus of the family Retroviridae. HIV Infection causes Acquired Immunodeficiency Syndrome (AIDS), a condition that progressively weakens the immune system to the point where an affected person is vulnerable to a wide range life-threatening opportunistic infections and cancers that result in death if not treated. HIV/AIDS has rapidly spread worldwide and has become the major health problem and the cause of about 0.5% of the global burden of disease, ranking fourth after ischemic heart disease, strokes and acute respiratory infections in terms of mortalities.

Since the emergence of AIDS in 1981, the concerted efforts of epidemiologists, immunologists, and molecular biologists have resulted in spectacular advances in understanding this disorder. Despite all this progress, however, the prognosis of patients with AIDS remains dismal. Although the mortality rate due to AIDS-related deaths has declined as a result of the use of potent combinations of antiretroviral drugs, the treated patients still carry viral DNA in their lymphoid tissues. Moreover, antiretroviral drugs are expensive and routine access to antiretroviral medication is not available in all countries. There is in fact currently no publicly available vaccine or cure for HIV or AIDS. It has been postulated that only a vaccine can halt the pandemic because it would possibly cost less, thus being affordable for developing countries, and would not require daily treatments.

Susceptibility to HIV infection and the rate at which the infection progresses to AIDS varies considerably between individuals, some progressing rapidly after primary infection, while others remain asymptomatic with no evidence of immune dysfunction for over 15 years. The reasons for these variations are multifactorial and may involve genetic, virological or immunological factors that function in different ways. Host genetic variability plays a major role in determining individual susceptibility or resistance to potentially pathogenic infections. With regard to HIV/AIDS the role of host genetic variations has been intensively examined in different populations and in all major risk groups. These have revealed that genetic polymorphisms in genes for chemokine receptors or in those of their natural ligands are likely to influence susceptibility or resistance to HIV infection as well as the subsequent rate of disease progression. Genes for human leukocyte antigens (HLA) that regulate host immune response to infection have also been correlated with the clinical course of HIV infection. So far, in addition to polymorphic variants in genes encoding for HIV coreceptors and their ligands and those of HLA alleles, allelic variants of some cytokine genes have also been implicated to influence the rate of disease progression in HIV seropositive patients either positively or negatively.

In the current study, the possible associations of SNPs in LMP2 (Arg/Cys), LMP7 (Gln/Lys), TAP1 (C/T intron 7), TAP2 (A/G exon 11), IL-18-137G/C, IL-18-607C/A, IL-27p28(964A/G) and TGFβ1(T509C) genes with the risk of HIV/AIDS were examined in 500 HIV seropositive and an equal number of age and sex matched seronegative controls from North Indian
Genomic DNA samples of the study subjects were screened using polymerase chain reaction- restriction fragment length polymorphism (PCR-RFLP) assay for the LMP2, LMP7, TAP1, TAP2, IL-27p28 and TGFβ1 genes while that of IL-18-137G/C and IL-18-607C/A gene was carried out with polymerase chain reaction-sequence specific primer (PCR-SSP) assay.

Analysis of the obtained data demonstrated that the genotypes A/G [OR (95% CI): 1.39(1.06-1.83)] and G/G [OR (95% CI): 3.38(1.56-7.46)] of TAP2 (A/G exon 11), Gln/Lys [OR 1.94, 95% CI= 1.39-2.70] and Lys/Lys [OR= 2.60, 95 % CI= 1.46-4.64] of LMP7 codon 145(Gln/Lys) and G/G [OR=(95%CI):2.15(1.18-3.94)] of IL-18-137(G/C) respectively were associated with statistically significant elevated risk of HIV-1/AIDS. On the other hand, the A/A [OR=0.57, 95 % CI= 0.33-0.98] genotype of IL-18-607(C/A) gene showed statistically significant reduced risk for susceptibility of HIV/AIDS. Meanwhile, no statistically significant risk of the disease was associated with any of the polymorphic forms of TAP1(C/T intron7), LMP2 codon 60(Arg/Cys), IL-27p28 (-964A/G) and TGFβ1 (T509C).

In the present study, some of the genes are found to be significantly correlated with resistance or susceptibility to HIV/AIDS disease. As AIDS is a multifactor infectious disease, which is regulated by a range of different factors, it is necessary to understand how an individual’s genetic profile becomes important in regulating the outcome of the disease. On the one hand, an increased understanding of the role played by host genetic factors in determining the response to HIV infection will undoubtedly contribute to our understanding of the nature of the disease process, and will ultimately assist the development of therapeutic strategies – such as development of vaccines – that can augment the genetically determined host immune response to HIV infection. This study provided evidence that host genetic variability do play great role in promoting or reducing risk of HIV susceptibility and disease progression. However, the results of the present findings need to be further evaluated in large cohort study both within same and different ethnic backgrounds.

Key words: Confidence Interval (CI), Interleukin-18 (IL-18), Large multicatalytic Proteasome (LMP), Major Histocompatibility Complex(MHC), Odds Ratio (OR), Single Nucleotide Polymorphisms (SNPs) Transforming growth factor beta one (TGFβ1), Transporter associated with antigen presentation (TAP).

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