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Exploring the Effects of IL-1βcytokine gene polymorphism on HIV-1/AIDS infection

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Abstract
*The pro-inflammatory cytokine interleukin1β (IL-1β) gene is a member of the IL-1 gene family clustered on Chromosome 2.Several studies have reported that interleukin-1 ß enhanced HIV-1 replication, suggesting that this cytokine may be contributing to the pathogenesis and progression of HIV infection. Therefore, we aimedin this study to investigate the association between polymorphisms in the IL-1β(-511) and HIV-1/AIDS infection in North Indian population.**Methods**: Polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) were used to analyze IL-1βC/T at (-511) polymorphism in 300 positively diagnosed cases with HIV-1/AIDS and an equal number of negatively diagnosed controls of the matched age.**Results**: No significant differences on the allelic and genotypicfrequencies were found among cases and control groups.**Conclusions**: The present study on the Indian population showed no significant association between IL-1βC/T (-511) polymorphism and the risk of HIV-1/AIDS infection.*

Keywords: *IL-1 β, Pro-inflammatory, Cytokine, polymorphism,RFLP, HIV-1/AIDS.*

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I. Introduction

The clinical syndrome of AIDS due to infection with the human immunodeficiency virus (HIV) which causes a progressive immunodeficiency is characterized by the loss of CD4 T lymphocytes coupled with an immunosuppression related to activation of immune system. It has been known that individuals with a higher HIV load tend to progress to AIDS and death at a more rapid rate than those with lower viral loads, and that different prognostic information can be derived from the CD4 cell count and the viral load. The conventional wisdom is that the CD4 cell count represents the current state of the immune deficiency, whereas the viral load reflects the rate at which the immune system will further deteriorate[1,2]

The biological correlates of an effective immune response that could contain or prevent HIV infection remain elusive despite substantial scientific accomplishments in understanding the interactions among the virus, the individual and the community. Since the reporting of the first cases of AIDS in 1981, there has been substantial scientific progress in the development of both effective antiretroviral therapy and the understanding of virus–host cellular interactions[3].Two phenomena have indicated that natural resistance to HIV-1 infection;1) there are individuals who have been exposed to HIV, in some cases repeatedly and over long periods of time, who have remained HIV uninfected. Such exposed-uninfected have been reported among commercial sexworkers[4,5]. individuals having unprotected sex with seropositive partners[6,7]. Infants born to HIV-infected mothers[8,9]. Health workers with accidental occupationalexposure[11], intravenous drug users using contaminated needles[12]and hemophiliacs exposed to HIV-infected blood[13].There are individuals who have become infected with HIV, but whose disease has not progressed or has progressed very slowly as compared to the average experience.Criteria defining these long-term non-progressors have varied among reports, but usually include survival with HIV infection more than 7 years with consistently low levels of HIV-1RNA and little or no loss of the primary target of HIV, CD4+ T-cells. Long-termnon-progressors have been identified among various groups, including homosexual men, women, injectable drug users and children. Some common genetic mutations have been found in both exposed uninfected populations and in long-term non-progressor populations, suggesting a unifying theory for both conditions, namely that host traits that prevent or hinderHIV-1 entry into cells will reduce the likelihood of infection and, should infection occur, slow or entirely eliminate the development of serious disease[13,14].

It is well known that the primary HIV-1 infection represents a period of intense viral replication followed by stabilization of viral load at a set point level that is maintained for months to years[15,16]. A number of investigators have studied cytokine levels in HIV-1 infection. Interleukin (IL)-6 is elevated at all phases of chronic infection,IL-10, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ are also elevated in chronic infection, while IL-2 and IL-4 are not[17,18,19]. Individuals identified during symptomatic primary HIV-1 infection

show elevations of IL-1β., TNF-α, IFN-γ,IFN-α, and IL-10 Normal or decreased levels *of* IL-2, IL-4, IL-6, IL-10, IL-12, tumor growth factor (TGF)-β, and TNF-α have been reported in primary HIV-1 infection[29,21,22,23].

IL-1β is a pro-inflammatory cytokine released by macrophages in systemic inflammatory responses. It plays important role against viral infection in addition to regulation of other inflammatory reaction and immune response throughpromoting expressions of the cytokines such as IL-6 andIL-12[24].Several studies demonstrated that HIV infection is associated with an acquired defect in the intracellular processes regulating IL-1 secretion[25]. Other authors while working on experimental animals and humans reported that both in interleukin-1 ß enhanced HIV-1 replication *in vitro*, suggesting that cytokines may contribute to the pathogenesis and progression of HIV infection[26,27,28,29].The production of IL-1β is dependent on severalfactors, there is an increasing evidence that the geneticfactors play an important role. The IL-1β located on chromosome 2q14, within a 360 kbregion. This gene has two diallelic polymorphismsat positions (-511) and(-31) in the promoter region andat position (+3954) in the fifth exon. In*vitro* and in *vivo* studies indicatedthat IL-1β -511 T allele enhanced IL-1β production and the circulating levels of this cytokine in humans[30,31].To clarify the impact of polymorphisms in IL-1β -511 C/T, we examined the relationship between the different genotypes of IL-1β-511C/T and HIV-1/AIDS in Indian population.

II. Materials and Methods

- **Subjects**

All the patients included in this study visited the Internal Medicine Immunodeficiency Clinic of the Post Graduate Institute of Medical Education and Research (PGIMER) Chandigarh- India. Information regarding age, sex, mode of transmission, medical history and occupation was gathered from subjects on a structural proformadesigned for the population. Peripheral blood samples (5ml) of 300 positively diagnosed patients and an equal number of controls; negatively diagnosed were collected from the same geographic area after they confirmed to be seronegative for HIV-1/AIDS by ELISA test. According of WHO staging guideline of HIV-1/AIDS and Physician's observations, the subjects were classified into four stages, the mean of CD4 count was used for comparative propose. DNA was isolated from peripheral blood by using the standard phenol-chloroform procedure and stored at -20^{o}C. DNA samples were amplified to detect the polymorphisms in IL-1β-511 C/Tto explore its influence on HIV-1/AIDS infection among north Indian population.

- **Genotyping**

IL-1β -511genotypes were determined by PCR restriction fragment length polymorphism (PCR-RFLP)assay. for promoter region amplification was carried out by using the primer pair5-TGGCATTGATCTGGTTCATC-3 and 5- GTTTAGGAATCTTCCCACTT-3[32]. Reaction was performed using50 ng genomic DNA, 20 pmol of each primer, 1U Taqpolymeras), 0.1 mM dNTP,15mM $MgCl_2$, 60 mMTris-HCl und 15 mM ammoniumsulfate.PCR conditions were as follows: 95 °C for 1 min,55 °C for 1 min, 74 °C for 1 min, then 38 cycles of 95 °Cfor 2 min, 55 °C for 1 min, 74 °C for 1 min and finally 74 °Cfor 4 min. The products were digested with 6 U of *AvaI*at37 ^{0}C for 3h. Fragments were analyzed by electrophoresis and stained with ethidium bromide. This gave products that either remained intact (*IL-1 β -511T* allele; allele 2) or were cut into two fragments of 190 and 114 bp (*IL β 1-511C* allele; allele 1).

III. Results

- **Subject characteristics**

The study included 300 HIV/AIDS cases and an equal number of negative controls from north India. The distribution of mean age, gender, standard deviation, P values has been summarized in Tables 1 and 2. In terms of mean age and gender distribution, there was no statistically significant difference among cases and controls.

- ***Analysis of the IL1β-511 C/T polymorphism***

No significant difference in the genotype distribution between healthy controls and HIV-1/AIDS patients with respect to IL-1β -511 C/T (P>0.05) genotypes was observed. As well as no statistically significant variation in frequency of alleles was found. The distribution of IL-1β -511 C/T genotypes and frequency of alleles between controls and cases has been given in Tables 1. and 2 respectively. The proportions of individuals homozygous for C/C, heterozygous and variant homozygous for the T/T were 19, 58 and 23%, respectively in the cases; the values were statistically not significantly different from those in the controls (24 %, 55.0 and 21.0 respectively, p>0.05). The frequency of C (allele 1) and T (allele 2) alleles was 48 and 52% in cases against 51.5 and 48.5 % in controls (p>0.05).

Table no1: Distribution of IL-1β C/T (511) genotypes among cases and controls

IL-1β Genotypes	**Cases(n=300)**	**Control(n=300)**	**OR(95% CI)**	**p-value**
CC	57 (19.0)	72 (24.0)	Reference	
CT	174 (58.0)	165 (55.0)	1.33 (0.87-2.04)	0.20
TT	69 (23.0)	63 (21.0)	1.38 (0.83-2.32)	0.23

Table no 2: Distribution of *IL-1β C/T (511)* alleles among cases and controls

IL-1β Alleles	**Cases**	**Control**	**OR(95% CI)**	**p-value**
C	288 (48.0)	309 (51.5)	1.15 (0.91-1.45)	0.24
T	312 (52.0)	291 (48.5)		

IV. Discussion

Cytokines are involved in the early pathogenesis of HIV infection and disease progression as a component of immunologic dysregulation and immunodeficiency and as determinants controlling virus replication. Several steps, before and after retroviral integration into host DNA in T cells and macrophages, are affected by cytokines[33].Previous studies showed that IL-1 (either alpha or beta) directly induced HIV replication as well as expression and potently synergized with other cytokines[33,33].Other studies have been reported that the T allele (allele 2) of IL-1β 511) *(*-enhanced IL-1β production and the circulating levels of the cytokine in humans. This aimed in the present study to explore the effect of IL-1β (-511) polymorphism on HIV-1/AIDS infection[34].

In this case -control study polymorphism of the pro-inflammatory IL-1 β -511 cytokine genewere investigated. No significant association between IL-1β polymorphisms and HIV-1/AIDS infection was found. There was also no correlation between the composite genotype (formed by at least one copy of the allele 2 of both polymorphisms) and the disease in the study population[35,36]..

Several studies have demonstrated that a number of single nucleotide polymorphisms (SNPs) in the IL-1 β cluster quantitatively affect mRNA synthesis and their frequencyis associated with the incidence and severity of severalinfectious and inflammatory diseases, such as rheumatoidarthritis[36], and chronic periodontitis[38,39]. On other hand some studies reported noassociation between thedistribution of IL-1 β -511 polymorphisms and chronic periodontitis as well as cachexia respectively[39]. The presented study failed to detect statistical variation between specific alleles of IL-1 β - (-511) polymorphisms and HIV-1/AIDSinfection in north Indian population. Even though the IL-1 gene do affect the production of the cytokine, it is speculated that the total influence might be weak and these alleles may not represent a risk factor for HIV-1/AIDS in Indianpatients, although the IL-1 βmay induce the expression and replication of HIV[40].

Further functional studies with large sample size are necessary to give a clearer picture about the role of IL-1 β polymorphism for HIV-1/AIDS infection.

V. Conclusion

The present study on the Indian population showed no significant association between IL-1β C/T (-511) polymorphism and the risk of HIV-1/AIDS infection.

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