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ASSOCIATION OF CLASS I AND CLASS II HUMAN LEUKOCYTE ANTIGEN GENES WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION.

Pathology

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ABSTRACT

Background: Discernable genetic variation among people and populations has an important role in human immunodeficiency virus (HIV) infections and acquired immune deficiency syndrome (AIDS). Various human leukocyte antigens (HLA) class I and class II genes are positively or negatively associated with disease contractibility and progression.

Methods: 50 HIV seropositive patients from Armed Forces including families and 50 HIV seronegative healthy, volunteer, randomly selected male blood donors from Armed Forces were studied over a period of two years and their HLA class I and class II genetic profiling was done by polymerase chain reaction-sequence specific probe (PCR-SSP) method.

Results: There was increased frequency of HLA-A24 and a decreased frequency of HLA-A2 in HIV positive subjects as compared to healthy controls.

Conclusion: Observations on major histocompatibility complex (MHC) genomics among study population suggest high vulnerability to HIV infection in HLA-A24 and a resistance to infection in HLA-A2 subjects.

KEYWORDS

Human leukocyte antigen, Human immunodeficiency virus.

INTRODUCTION

The natural course of HIV-1 infection varies considerably from one individual to another, with some individuals progressing to AIDS rapidly after primary infection known as *Rapid progressors* (succumb to AIDS in 1–5 years), while others remain clinically asymptomatic and maintain their normal CD4 counts with no evidence of immune dysfunction, termed as *long term survivors* (5% of total HIV seropositive subjects). Further, infected individuals have heterogeneity in the strength of their innate, humoral and cell-mediated immune responses as well as differences in how they respond to antiretroviral treatment. Also, there is a group of individuals, *highly exposed persistently seronegative HEPS,* who do not get infection even after repeated exposures including discordant couples who have unprotected intercourse, commercial sex workers (CSW), hemophiliacs receiving HIV-contaminated blood products, healthcare workers receiving needle stick injuries, and infants of HIV-infected mothers who have been exposed in utero, intra partum and during breastfeeding. [1].

This inter-individual variability is governed by multiple host genetic factors including chemokine receptors, their ligands, MHC molecules, cytokines, and their receptors, factors that are directly involved in HIV-1 cell entry, immune recognition and antigen presentation, [1]. Apart from these factors other cofactors such as, age, gender, lifestyle, and immune suppression by causes other than HIV itself have also been suggested as cofactors in HIV disease progression, but evidence is lacking or inconclusive [2,3,4]. Understanding these correlates of different HIV outcomes will undoubtedly help to develop an effective universal polyepitope vaccine ultimately.

The present study was undertaken with an aim of finding any strong positive or negative associations of HLA- A, B or DR alleles in HIV positive subjects from the study population of Armed Forces and their families.

MATERIALAND METHODS

The study was conducted in the Department of Pathology and Immunodeficiency centre of INHS Asvini, Mumbai. 50 HIV seropositive patients from Armed Forces including families and 50 HIV seronegative healthy, volunteer, randomly selected blood donors from Armed Forces were included in this study. The study group consisted of both symptomatic (n=15) and asymptomatic individuals (n=35).The symptomatic group comprised of opportunistic infections including TB and other STD's. The ethnic background of the controls was same as that of the patients and the age group also matched predominantly. The age group of patients varied from 9 to 59 years with a median of 31 years and age group of controls varied from 19 to 46 years with a median of 26 years. There were 6 female patients in the study group whereas all the controls happened to be males. Heterosexual route of transmission was the predominant route of transmission in all but one case of mother to child transmission.

Peripheral blood sample were collected into EDTA vacutainer tubes with complete aseptic and universal precautions. The samples collected were processed on the same day for the DNA isolation by the commercially available *Extra Gene* kit. Isolated DNA was stored at -20ºC for subsequent HLA typing by PCR-SSP (polymerase chain reaction-sequence specific probe) method using commercially available kit from BAG, Germany.

RESULTS

HLA-A locus

A total of 19 HLA-A alleles were studied and their comparison in HIV infected subjects and healthy controls is presented in table 1 below and depicted in Fig 1.

Since several HLA alleles were tested and compared between the healthy and HIV positive, therefore the P values were corrected (Pc) by use of conferring inequality method, by multiplying the P value with the number of alleles compared at each locus.

As shown in **Table 1** and **Figure 1**, HLA-A*24 occurred with a significantly higher phenotype frequency (30%) in the patients as compared to healthy controls (13%, p=0.002). The difference remained significant (pc=0.028) when correction factor for the p value was applied. On the contrary, HLA-A*02 occurred with a significantly reduced frequency in the HIV positive subjects (6%) as compared to healthy controls (21%, p=0.001, pc=0.014). No other deviations in HLA-A were statistically significant.

HLA-B locus

The low / intermediate HLA typing techniques of PCR-SSP permitted an analysis of 22 alleles and the data is presented in Table 2. None of the HLA-B alleles occurred with a significantly different frequency in HIV positive subjects as compared to healthy controls.

HLA-DR locus

DNA based techniques of PCR-SSP was employed to identify 17 specific HLA-DRB1 alleles. There was no statistically significant difference in the DRB1* alleles among healthy controls and HIV positive subjects.

DISCUSSION

HIV-1 is rapidly diversifying in African, Asian and Caucasoid populations, which in parallel displays extensive polymorphism of genes encoding human MHC. Immune responses mediated by HLA

class I molecules are imprinting mutations in HIV-1, which in turn affects HIV-1 diversity. Intra- and inter-ethnic studies have shown reproducible association of HLA class I alleles and haplotypes with HIV-1 infection and development of AIDS. [5, 6,7, 8, 9 and 11].

HIV infection and HLA-A, HLA-B and HLA-DR association
The class I analysis revealed a positive association with HLA-A*24 and a negative association with HLA-A*02. In a large study during 2006 in North Indian population Mehra etal found a positive association with HLA-A24(38%) indicating a rapid onset and a negative association with HLA-A2(20%) indicating a possible resistance to HIV infection.[14].However, the authors also found a positive association with HLA-B35 and DRB1*03 and a negative association with HLA-B27. No significant associations were seen in our study, possibly due to the small sample size.

In another study carried out on south Indian patients, HLA-DR2 was positively associated and HLA-A11 was negatively associated with HIV infection. [15].

HLA-B*27 and HLA-B*57 have been consistently associated with a favorable prognosis, irrespective of differences in ethnicity, virus clade, and risk group. [16].

At the other extreme, several allele groups (HLA-B*35 and B*53) have been rather convincingly associated with unfavorable prognosis or higher viral RNA levels in infected persons. [17].

A study from Japan showed that HLA-B*5101 is associated with reduced viremia in Japanese HIV infected people.[18].

Higher frequency of HLA-DRB1*03 in infected infants and DRB1*15 allele in uninfected infants born from HIV positive mothers has also been reported. [19].

In sharp contrast to HLA class I, fewer class II alleles/haplotypes have been implicated in HIV-1 disease [10, 11, 12, and 13]. In a group of African sex-workers from Nairobi, the Pumwani sex worker cohort, a strong protective effect against HIV seroconversion was reported in individuals carrying HLA- DRB1*01, (in particular DRB1*0102) suggesting that DRB1- restricted CD4+ cells may play a role in protecting against HIV challenge. These studies have indicated that HLA class II alleles may also play an important role in influencing HIV-1 disease progression.

In our study, the class II analysis revealed no statistically significant association of HLA-DRB1 in HIV positive subjects. This was possibly due to the small sample size of HIV positive subjects (n=50).

Population studies based on genetic associations are important not only for elucidating the mechanisms of disease pathogenesis but also for developing screening tests for identifying people at risk and determining their responses to drugs and vaccine trials.

Further research in this field of genetic association analysis of several large AIDS cohorts for polymorphic variants in genes loci that predispose or protect against HIV infection is recommended to be undertaken to further understand their genetic variation in modulating HIV infection and disease progression.

Conflicts of interest
None identified

TABLE 1. Percent phenotype frequencies of HLA-A alleles in HIV+ subjects and controls

HLA	Controls(N=50)	Total HIV	X2	P	pc
A*01	9	4	1.415	0.234	-
A*02	21	6	9.944	0.002	0.028(S)
A*03	10	12	0.058	0.809	-
A*11	17	17	0	1	-
A*23	2	2	0	1	-
A*24	13	30	10.445	0.001	0.014(S)
A*25	1	1	0	1	-
A*26	3	2	0	1	-
A*29	0	0	-	-	-
A*30	1	2	0	1	-
A*31	2	5	0.614	0.433	-
A*32	4	0	2.344	0.126	-
A*33	9	12	0.241	0.623	-
A*34	0	0	-	-	-
A*36	0	0	-	-	-
A*38	0	0	-	-	-
A*68	7	5	0.095	0.758	-
A*74	1	2	0	1	-
A*80	0	0	-	-	-

S=Significant

TABLE 2. Percent phenotype frequencies of HLA-B alleles in HIV+ subjects and controls

HLA	Controls(N=50)	Total HIV	X2	P
B*07	9	7	0.074	0.758
B*08	6	1	2.458	0.117
B*13	4	6	0.111	0.739
B*15	7	11	0.61	0.435(NS)
B*18	3	0	1.375	0.241
B*27	2	3	0	1
B*35	12	13	0	1
B*37	1	2	0	1
B*38	1	3	0	1
B*39	0	0	-	-
B*40	10	17	1.826	0.177(NS)
B*44	7	11	0.61	0.435(NS)
B*45	0	0	-	-
B*48	1	0	0	1
B*49	1	1	0	1
B*50	0	0	-	-
B*51	4	5	0	1
B*52	6	4	0.111	0.739
B*53	0	3	1.375	0.241
B*55	2	1	0	1
B*57	5	4	0	1
B*58	4	3	0	1

NS=Not significant

TABLE 3. Percent phenotype frequencies of HLA-DR alleles in HIV+ subjects and controls

HLA	Controls(N=50)	Total HIV	X2	p
DR*01	2	6	1.233	0.269(NS)
DR*03	6	6	0	1
DR*04	8	11	0.26	0.61
DR*07	13	15	0.05	0.824
DR*08	0	2	0.51	0.475
DR*09	0	0	-	-
DR*10	5	2	0.614	0.433
DR*11	7	8	0	1
DR*12	3	2	0	1
DR*13	10	5	1.255	0.263(NS)
DR*14	6	3	0.488	0.485
DR*15	20	16	0.391	0.532
DR*16	0	0	-	-

NS=Not significant

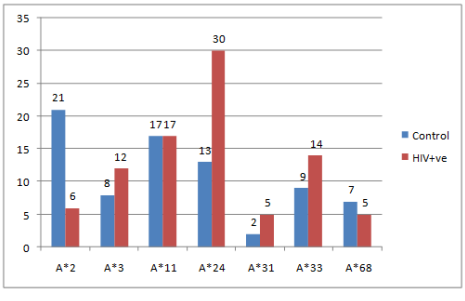

FIGURE1. Frequency distribution of selected HLA-A alleles among HIV positive subjects and controls.

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