

Role of HLA-A, HLA-B, HLA-DRB1 and HLA-DQB1 Alleles in HIV-1 Patients with Pulmonary Tuberculosis Co-infection from India

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ABSTRACT We studied the role of HLA HLA-A, B, DRB1 and DQB1 in HIV-1 patient's co infected with pulmonary tuberculosis (PTB). A total of 102 HIV-1+ patients co-infected with pulmonary tuberculosis and 200 healthy controls were included in HLA analysis. HLA-A*, HLA B* HLA-DRB1* and DQB1* typing was done molecularly by PCR-SSOP (Polymerase Chain reaction-Sequence Specific Oligonucleotide Probing) method using kit (Dynal Kit – Invitrogen). The frequencies of the HLA-A*, HLA-B* HLA-DRB,1* and HLA-DQB1* alleles were determined using standard software. The HLA alleles identified among HIV+ve/PTB+ve co-infected patients was compared with healthy controls. Our results showed a significantly increased frequency of HLA-B*08:01:01 (p=0.011, OR 3.335, 95% CI 1.35-8.18) HLA-DQB1*03:01:03 (p<0.0001, OR 107.5, 95% CI 6.195-1865.3) in HIV+ve/PTB+ve co-infected patients when compared with healthy controls. Similarly HLA-DQB*06:01:02 (p=0.003, OR 4.808, 95% CI 1.72-13.39), HLA DQB1*03:01:01 (p=0.045, OR 0.219, 95% CI 0.051-0.940), HLA-DQB1*06:01:01:01 (p=0.012, OR 0.334, 95% CI 0.145-0.770), allele frequency was observed in HIV+ve/PTB+ve co-infected patients when compared with healthy controls. We can conclude that different HLA alleles may render susceptibility or protection to in different ethnic population.

INTRODUCTION

Acquired immunodeficiency syndrome (AIDS) caused by HIV infection is endemic all over the globe and it is on the rise especially in resource limited countries. Over 33 million people are living with HIV, 2.5 million are newly infected and 2.1 million people have died of AIDS (NACO, report 2008). Individuals with impaired cell mediated immunity due to AIDS have a greatly increased risk of co-infection with *Mycobacterium tuberculosis* (Vijaya-lakshmi et al. 2006). The co-infection of HIV-1 and *Mycobacterium tuberculosis* causes two infectious diseases endangering human health significantly. The pathogenesis of HIV-1 and PTB co-infection is unavailable. The factors influencing the greater inter individual variability to susceptibility to PTB co-infection and progression of AIDS is yet to be identified. This

may be due to considerable varied immune responses of HIV-1 and MTB exposed individuals may result from the different genetic background. MHC class-I restricted CD8⁺ T cells are important for the generation of protective immune response in *Mycobacterium tuberculosis* infection. CD8⁺ CTL (Cytotoxic T lymphocytes) - derived IFN- γ may be especially important both for cells lacking MHC class-II molecules.

MATERIALS AND METHODS

Both HLA Class I and class II genes have been shown to be associated with susceptibility or resistance to HIV infection (Carrington and O'Brien 2003). Among the HLA Class-II alleles, HLA-DQB1 and HLA-DBP1 alleles have shown to be associated with HIV infection (Achord et al. 1996; Odum et al. 1990). However, we have much less information about the HLA linked genetic control of susceptibility to HIV-1 and MTB co-infection. We have attempted to study the role of HLA-A, B, DRB1 and DQB1 in HIV-1 patients with pulmonary tuberculosis (PTB). A total of 102 HIV-1+ patients co-infected with pulmonary tuberculosis confirmed clinically for their HIV Positivity (by serology and western blot) and pulmonary tuberculosis infection (x-ray and sputum

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positivity) along with 200 healthy controls were included in HLA analysis. HLA typing was done molecularly by PCR-SSOP (Polymerase Chain reaction-Sequence Specific Oligonucleotide Probing) method using kit (Dynal Kit – Invitrogen). The frequencies of the HLA-A, B, HLA-DRB1 and DQB1 alleles were determined by using standard software.

RESULTS

The HLA class I and class II alleles identified among HIV+ve/PTB+ve co-infected patients as compared with healthy controls are given in Table 1. Significantly increased frequency of HLA-B*08:01:01 was observed in HIV+ve/PTB+ve co-infected patients when compared with healthy controls ($p=0.011$, OR 3.335, 95% CI 1.35-8.18). Likewise HLA-DQB1*03:01:03 was significantly increased in HIV+ve/PTB+ve co-infected patients as against healthy controls ($p<0.0001$, OR 107.5, 95% CI 6.195-1865.3). Similarly HLA-DQB1*06:01:02 allele frequency was observed in HIV+ve/PTB+ve co-infected patients as against healthy controls ($p=0.003$, OR 4.808, 95% CI 1.72-13.39). A significantly increased frequency of HLA-A*02:11 ($p=0.015$, OR 1.762, 95% CI 1.13-2.73), HLA-B*57:01:01 ($p=0.017$, OR 1.973, 95% CI 1.15-3.37), HLA-B*56:01:01 ($p=0.029$, OR 2.606, 95% CI 1.16-5.85), HLA-DRB1*04:03:01 ($p=0.006$, OR 7.727, 95% CI 1.79-33.3), HLA-DRB1*09:01:02 ($p=0.012$, OR 9.143, 95% CI 1.63-51.174), HLA-DRB1*14:01:03 ($p=0.024$, OR 13.526, 95% CI 1.381-132.49), HLA-DQB1*05:02:01 ($p<0.0001$, OR 28.556, 95% CI 8.36-242.16), and a significantly decreased frequency was observed in HLA-B*51:01:01 ($p=0.009$, OR 0.434, 95% CI 0.236-0.799), HLA-DQB1*03:01:01 ($p=0.045$, OR 0.219, 95% CI 0.051-0.940), HLA-DQB1*06:01:01:01 ($p=0.012$, OR 0.334, 95% CI 0.145-0.770), alleles in HIV+ve/PTB+ve co-infected patients when compared with healthy controls.

DISCUSSION

We have studied, HLA-A, B, DRB and DQB loci to find out the role of these HLA alleles in HIV+ve/PTB+ve co-infection. Significantly increased frequency of HLA-B*08:01:01 and HLA-DQB1*03:01:03 in HIV+ve/PTB+ve co-infected patients against controls may suggest

Table 1: Significant HLA alleles identified among the TB co-infected HIV patients from India

<i>HIV+ PTB+ (n=102) vs controls (n=200)</i>	<i>HIV+ PTB+ (n=102) vs controls (n=200)</i>
<i>Increased frequency</i>	<i>Decreased frequency</i>
HLA-B*08:01:01	HLA-B*51:01:01
HLA-B*55:01:01	HLA-DQB1*03:01:01
HLA-B*57:01:01	HLA-DQB1*06:01:01
HLA-A*02:11	
HLA-DRB1*04:03:01	
HLA-DRB1*09:01:02	
HLA-DRB1*14:01:03	
HLA-DQB1*03:01:03	
HLA-DQB1*06:01:02	
HLA-DQB1*05:02:01	

that, these alleles play an associative role in HIV infection and PTB development. Our study reveals that, HLA-B*08:01:01 and HLA-DQB1*03:01:03 are associative to enhance HIV infection. The decreased frequency of HLA-DQB1*03:01:01 has been reported in PTB patients from China (Wang J et al. 2001). In our study, HLA-DQB1*03:01:01 is decreased in HIV+ve/PTB+ve co-infected patients compared to controls suggesting that it may play a protective role in HIV+ve/PTB+ve co-infection. Whereas HLA-DQB1*03:01:03 is associative in HIV. Among South Indians an increased frequency of HLA-DQB1*06:01:01:01 has been reported in HIV-ve PTB+ve and HIV+ve PTB+ve patients, suggesting that HLA-DQB1*06:01:01:01 is associated with susceptibility to PTB as well as development of PTB in HIV patients (Selvaraj et al. 2008; Shankarkumar et al. 2009). Further earlier association of HLA-DQB1*06:01:01:01 with susceptibility to PTB has also been reported in south India (Ravikumar et al. 1999). In contrast to the above studies on South Indian population, it is reported that HLA-DQB1*06:01:01:01 plays a protective role against HIV disease progression in Europeans (Vyakarnam et al. 2004). In our study a significantly increased frequency of HLA-DQB1*06:01:02 in HIV+ve/PTB+ve co-infected patients when compared to controls and HIV+ve PTB-ve patients may suggest its strong association with both HIV infection and PTB co-infection. On the contrary HLA-DRB1*06:01:01:01 frequency was significantly decreased in HIV+ve/PTB+ve co-infected patients compared to controls, thereby may protect from HIV infection and PTB development. HLA-DQB1*05:02:01 allele is reportedly related to high risk of developing TB in population from Asia and

Latin America (Dubaniewicz et al. 2005). In the present study, frequency of HLA-DQB1*05:02:01 is increased in HIV+ve/PTB+ve co-infected patients compared to healthy subjects to show that HLA-DQB1*05:02:01 may be associated with HIV+ve/PTB+ve co-infection. There was no considerable change in frequency of HLA-A*26:01:01 in HIV+ve/PTB+ve co-infected patients when compared with controls and decreased frequency was observed when compared with HIV+ve PTB-ve patients. This suggests that, HLA-A*26:01:01 may not be associated with HIV infection and may play a protective role in PTB development. HLA-A*31 and HLA-B*41 antigens and the HLA-DRB1*10 and HLA-DQB1*05 were over represented in Brazilian patients with AIDS and tuberculosis, suggesting association to tuberculosis with AIDS (Fernando de Castro et al. 2008). As reported earlier HLA-DRB1*13 is associated with susceptibility to HIV-1 infection whereas HLA-DQB1*02:03 and DRB1*01 are resistant to HIV-1 infection which may vary in different ethnic groups (Patricia et al. 2002). HLA-DRB1*15 is susceptible in PTB development and DRB1*11 may be protective allele in Chinese population⁶. In the present study, HLA-DRB alleles HLA-DRB1*04:03:01, DRB1*09:01:02, DRB1*14:01:03 and HLA-DQB1*05:02:01 allele are significantly increased in HIV+ve/PTB+ve co-infected patients compared to healthy controls. Thus, these alleles may be associated to susceptibility of HIV+ve/PTB+ve co-infection among Indians.

CONCLUSION

Based on our observations, it can be concluded that different HLA alleles may be involved in susceptibility or protection to an infection in different ethnic population. HLA alleles may influence immune pathogenesis towards either HIV and/or PTB infection. Further study on the HIV progression and resistant TB

would enlighten the mechanism of action of the HLA in HIV and PTB infection.

REFERENCES

- Achord AP, Lewis RE, Brackin MN et al. 1996. HIV-1 disease association with HLA-DQ antigen in Africans Americans and Caucasians. *Pathobiology*, 64: 204-208.
- Carrington M, O'Brien SJ 2003. The influence of HLA genotype on AIDS. *Annu Rev Med*, 54: 535-551.
- Dubaniewicz A, Moszowska G, Szczerkowska Z 2005. Frequency of DRB1-DQB1 two locus haplotypes in tuberculosis: Preliminary report. *Tuberculosis*, 85: 259-267.
- Fernando de Castro JF, Maria de Lourdes VR, Neifi Hassam SD et al. 2008. HLA profile in patients with AIDS and Tuberculosis. *Brazilian Journal of Infectious Diseases*, 12(4): 278-280.
- National AIDS Control Organization (NACO) Report 2008. *Ministry of Health and Family Welfare, Government of India News letter October 2008*.
- Odum N, Georgsen J, Fugger L et al. 1990. HLA-DP antigens in HIV infected individuals. *Dis Markers*, 8: 113-116.
- Patricia M, Karina M, Adrian S et al. 2002. Association of HLA-DQ and HLA-DR alleles with susceptibility or resistance to HIV-1 infection among population of Chaco province, Argentina. *Medicina*, 62: 245-248.
- Ravikumar M, Dheenadhayalan V, Rajaram K et al. 1999. Associations of HLA-DRB1, DQB1 and DPB1 alleles with pulmonary tuberculosis in South India. *Tuber Lung Dis*, 79: 309-317.
- Shankarkumar U, Pawar A, Prabu G, Ghosh K 2009. Role of HLA class I (HLA-A, B) and HLA class II (HLA-DRB, DQB) in HIV-1 patients with and without pulmonary tuberculosis. *J Acquir Immune Defic Syndr*, 51(5): 640-641.
- Selvaraj P, Ragavan S, Swaminathan S et al. 2008. HLA-DQB-1 and HLA-DPB-1 allele profile in HIV patients infected with or without pulmonary tuberculosis of South India. *Infection, Genetics and Evolution*, 8: 664-671.
- Wang J, Song C, Wang S 2001. Association of HLA-DRB1 genes with pulmonary tuberculosis. *Chinese Journal of Tuberculosis and Respiratory Disease*, 24: 302-305.
- Vijayalakshmi V, Shilpa SR, Anuradha B et al. 2006. Role of HLA-B51 and HLA-B52 in susceptibility to pulmonary tuberculosis. *Infection, Genetics and Evolution*, 6: 436-439.
- Vyakarnam A, Sidebottom D, Murud S et al. 2004. Possession of human leucocytes antigen DQ6 alleles and the rate of CD4 T- cell decline in human immunodeficiency virus-1 infection. *Immunology*, 112: 136-142.