

## Association of HLA Class-I Antigens with Delusional Disorder

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**KEY WORDS** Delusion; etiology; HLA antigens; paranoid symptoms.

**ABSTRACT** Delusional Disorder is characterized by monosymptomatic paranoid symptoms. In the field of psychiatry it is the only disease where delusion is recorded as a discrete symptom. Delusional disorder is probably heterogeneous group of illness and occurs in a variety of psychiatric and medical conditions. Although delusions remain one of the basic problems in psychopathology, attempts to understand its pathogenesis have been dominated by unsubstantiated speculation. Etiology and psychopathology of delusional disorder is not known. The main purpose of the present study was to investigate the incidence of HLA Class-I antigens in the patients with delusional disorder. Two psychiatrists conducted the screening process following the criteria of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) to 60 unrelated patients who visited Department of Psychiatry, North Bengal Medical College and Hospital, Siliguri. In the delusional disorder patients significant increases were found for HLA – A3 antigen. This preliminary study of allelic association of polymorphic HLA allele with delusional disorder may lead to develop future strategies to understand the genetic basis of this disorder.

### INTRODUCTION

Delusional disorder, the contemporary conceptualization of paranoia, is an uncommon condition characterized by the presence of one or more nonbizarre delusions and the relative absence of associated psychopathology. In contemporary classifications of mental disorders, delusions are considered as cornerstone symptoms for the diagnosis of psychotic disorders. Recent studies reveal that delusional disorders is not rare as previously thought as these are under diagnosed in most of the cases,

resulting in poor anticipation of their implications (Ulzen and Carpentier 1997). It is well known that delusions occur in a variety of psychiatric and medical conditions and is probably heterogeneous group of illness (Manschreck 1999).

The etiology of delusional disorder is imperfectly understood. Recent epidemiological and clinical studies suggest that certain risk factors like advanced age, sensory impairment, personality features, family history etc. may be relevant to etiology (Kendler 1982). Genetic or family studies lead to convincing data like increased prevalence of delusional disorder and related personality traits (e.g. suspiciousness, jealousy and secretiveness) in the relatives of delusional disorder probands (Kaplan and Saddock 1994) and also indicate possible specific family transmission of delusional disorder. Several attempts have been made to identify genetic markers associated with delusional disorder. A recent study of genetic variation in the DNA sequence coding for Dopamine type 4 (DRD4) Exon 3 strongly suggests the involvement of the relevant gene in conferring susceptibility to delusional disorder (Serretti et al. 2001). However, these studies are not uniformly consistent and needs to be replicated on a large sample size to confirm the tentative results of dopaminergic mechanisms responsible for paranoid symptoms (Morimoto et al. 2002)

In the absence of single pathogenic mutation, the genetics of Human Leukocyte Antigen (HLA) system has been considered for association studies in the delusional disorder. The HLA complex on chromosome 6 contains over 200 genes, more than 40 of which encode leukocyte antigens (Forbes and Trowsdale 1999). A large group of diseases including psychiatric illnesses like depressive disorders (Weitkamp et al. 1981), Schizophrenia (McGuffin and Sturt 1986; Sasaki

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et al. 1999) involve genes in the HLA region that are linked to (or associated with) specific class I and Class II alleles or combinations of alleles (haplotypes).

In the present investigation we studied the distribution of HLA class-I antigens on the patients with delusional disorder. From this analysis we conclude that genes of a locus on chromosome 6 may have a strong association with delusional disorder.

### MATERIALS AND METHODS

**Subjects:** The subjects were recruited from Indian- born Bengali patients referred to the Department of Psychiatry, North Bengal Medical College and Hospital and they met DSM-IV criteria (American Psychiatric Association, 1994) for delusional disorder. A total number of 60 unrelated patients (32 women and 28 men) were studied for a period of four years between 1998-2002. Patients suffering from paranoid schizophrenia, paranoid personality disorder, dementia presenting with paranoid features, patients with substance abuse disorder, patients presenting with delusion with any other comorbidity, both physical and psychiatric, were excluded from the present study. In our study it was observed that maximum patients were clustered between 25 to 55 age group. Patients were mostly from middle class urban society belonging to a nuclear family. Equal numbers of healthy donors belonging to the same population were considered as control.

**Serological Typing of HLA Class-I Antigens:** Approximately 5ml. of blood sample was obtained from each individual. Each person gave written consent to take part in this analysis. Serological typing of HLA class-I antigens was done by

using 72 well Terasaki trays (NUNC, Denmark) and with the help of standard two-stage microlymphocytotoxicity assay (Terasaki and McClelland 1964).

A total number of 37 antigen specificities (13 HLA-A and 24 HLA-B) including split specificity and control (positive and negative) sera were used with repetition of certain specificities.

**Statistical Analysis:** The phenotype frequencies were calculated by direct count. The frequency of each antigen in the patient group as a whole was compared with the control population using chi-square test, and which was followed by Fisher's exact test. Since testing for a large number of antigens can reveal at least one positive association where none really exists, the *p* values from each Fisher's exact test had to be less than the Bonferroni *p* (0.05 divided by the number of antigens tested [*n*= 37] minus two degrees of freedom (one for each of the two loci examined), which equals to 0.0014) to be called statistically significant.

### RESULTS

Table 1 shows the frequency of only few HLA antigens with higher statistical values in the delusional disorder group as a whole compared to controls and the relative risk values. We found increased frequencies of HLA-A3 (66.66% vs. 15%, *p*<0.01) in the patient group. The increase in HLA-A3 in the delusional patients was statistically significant with the Bonferroni correction. Apart from this, we also observed increased frequencies of HLA-B37 (13.33% vs. 5%, *p*<0.05), HLA-B53 (6.66% vs. 0.00%, *p*<0.05) and decreased frequencies of HLA-A24 (10% vs. 23.33%, *p*< 0.05). However, none of the association between HLA-B37, HLA-B53 or

**Table 1: Prevalence of HLA-A and HLA-B antigens in patients and controls**

| Antigens | % Phenotype Patient<br>N= 60 | Frequency Control<br>N= 60 | Chi Square ( $\chi^2$ ) | Relative Risk (RR) | <i>p</i>    |
|----------|------------------------------|----------------------------|-------------------------|--------------------|-------------|
| A3       | 66.66                        | 15                         | 33.147**                | 11.333             | Significant |
| A24      | 10                           | 23.33                      | 3.84                    | 0.365              | NS          |
| A26      | 6.66                         | 15                         | 2.157                   | 0.405              | NS          |
| B8       | 6.66                         | 15                         | 2.157                   | 0.405              | NS          |
| B21      | 10                           | 3.33                       | 2.143                   | 3.222              | NS          |
| B37      | 13.33                        | 5                          | 3.927*                  | 4.462              | NS          |
| B44      | 15                           | 6.66                       | 2.157                   | 2.471              | NS          |
| B53      | 6.66                         | 0.00                       | 4.138*                  | 0                  | NS          |

\**p*<0.05, \*\**p*<0.01

NS= Not Significant; *p* must be < 0.0014 to be declared significant.

HLA-A24 and delusional disorder patients remained statistically significant with Bonferroni correction.

Relative risk values of several antigens were found to be more than one but in case of A3 it is very high.

### DISCUSSION

In this work, we observed strongest association between delusional disorder and HLA-A3 antigens. When the strength of association was measured by cross product ratio or relative risk of developing a disease, the antigen A3 showed a very high value i.e. RR 11.333, thus reflecting a very positive association. However, the exact nature of the mechanism underlying the empirically observed association between HLA-A3 antigen and the delusional disorder is not fully understood. It is also to be noted that this result could not be an artifact arising from inadvertent ethnic mismatching of cases and controls, as there is no ethnic group known for which the HLA –A3 frequency is higher than about 16%. The pattern of HLA-A3 distribution in Indian subcontinent and rest of the countries are as follows: in South African San Population it is 15.5, in Mongolian population 4.8, in Italian population 12.9, in Australian Aborigines 6.6 and in Indian Tribe it is 6.0 (Imanishi et al. 1992).

At this moment, it is very difficult to conclude that HLA-A3 antigen is the sole determinant of delusional disorder. However, this significant association might contribute to the disease risk or else that there might be a separate susceptibility gene in strong linkage disequilibrium with the A3 gene. Further extensive study is presently going on in our laboratory considering the pattern of HLA haplotype inheritance in the affected families, which would definitely help to determine the validity and

specificity of A3 antigen as genetic marker of delusional disorder.

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