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The association of the HLA in patients with schizophrenia, schizoaffective disorder, and in their biological relatives

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Abstract

To determine the association of the HLA in 50 patients with schizophrenia, schizoaffective disorder, 48 healthy controls, 41 biological relatives without psychiatric disease, and 48 biological relatives with mood disorder, the HLA genotype at the class I and class II were determined. The subjects were interviewed by structured diagnostic criteria categorized according to DSM-IV, axis I, (SCID-IV). Significant positive association was found with HLA-B*15 in patients, family with humor disorder and without mental disorder ($p=0.003$) and negative association of the HLA-B*35 in relatives without psychiatric disease ($p=0.03$). The HLA-B*15 frequency was significantly increased in a subgroup of patients with age at onset in the early 20s, lower educational achievement, occupational disability, chronically ill, more paranoid type. These findings suggest the existence of some involvement of an immunogenetic mechanism in a subgroup of schizophrenic, schizoaffective patients, and biological relatives.

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1. Introduction

Various diseases with a noticeable autoimmune component and frequent occurrence in family show a statistically significant correlation with specific

human leukocyte antigens (HLA). This correlation was also found in studies of HLA in psychiatric disorders (Gattaz and Beckmann, 1982).

The possible existence of a susceptibility locus for schizophrenia on the short arm of chromosome 6 in an area close to the HLA region at the 6p21.3 band has been the subject of several investigations (Levinson et al., 1996; Lindholm et al., 1999; Schwab et al., 2002).

Wright et al. (2001) published a review of the HLA association with schizophrenia. They listed positive

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association with A9 or the A24 sub specificity, A28, A10, DRB1*01, and DRw6. Negative association with DQB1*0602 and DRB1*04 with schizophrenia have also been reported. In a study of transmission disequilibrium analysis of HLA class II DRB1, DQA1, DQB1 and DPB1 polymorphisms in schizophrenia using family trios, a nontransmission of the DRB1*03 allele and a preferential transmission for the DRB1*13 allele were detected (Li et al., 2001).

The expression of HLA-B35 was significantly reduced in the schizophrenic populations compared to control population. The reduction of incidence of HLA-B35 in schizophrenic population could thus be related to susceptibility to some specific infections or an autoimmune component (Blackwood et al., 1996).

The present study evaluated the association of HLA class II (DRB1) and class I (A, B) in schizophrenic and schizoaffective patients, biological relatives and healthy controls.

2. Methods

The subjects were 50 schizophrenic and schizoaffective adults outpatients of the Psychiatric Ambulatory at Londrina State University (UEL), Paraná, Brazil. The patients were in remission, in chronic treatment with typical antipsychotic (Haloperidol) and atypical antipsychotic agents (olanzapine, clozapine, risperidone, ziprasidone), 48 first-degree relatives with mood disorders, and 41 first-degree relatives without mental disorders and 50 healthy volunteers as control.

After approbation of this research by the Ethics Research Committee of UEL, patients, controls and first-degree relatives had given written informed consent, and samples of peripheral blood was drawn.

Subjects younger than 18 years old and older than 55 years were excluded from all groups. All subjects were of the White race. They were required to be in good health conditions, defined as the absence of chronic diseases, which affect the immune system.

The schizophrenic and schizoaffective outpatients were interviewed by structured diagnostic criteria categorized according to the fourth edition of the American Psychiatric Association's Diagnostic and

Statistical Manual of Mental Disorders or DSM-IV, Axis I, (SCID-IV) criteria (American Psychiatric Association, 1994), translated to the Portuguese language by Del Bem et al. (2001). The schizophrenic patients diagnosed were classified as undifferentiated type ($n=1$), paranoid type ($n=20$) disorganized type ($n=10$), residual type ($n=7$), and schizoaffective disorder ($n=12$).

The 50 volunteers were recruited from the community, free of any serious medical illnesses, and had never taken psychotropic drugs or presented current or past psychiatric disorder as determined by their reported history during the clinical interview and by structured diagnostic criteria categorized according to DSM-IV, Axis I. Two controls were excluded from the study after blood test detected hepatitis virus C infection, a chronic illness known to affect the immune system.

First-degree relative volunteers were recruited with ages ranging from 18 to 55 years. All members were 90 first-degree relatives, and were interviewed by the structured interview (DSM-IV, Axis I, SCID-IV). One first-degree relative was excluded from the study after blood test detected HIV infection. The 89 relatives included were 2 fathers, 2 mothers, 50 sisters, 30 brothers, 1 son, and 4 daughters. The 48 first-degree relatives had been diagnosed as Major Depressive Disorder ($n=45$) and Bipolar I Disorder ($n=3$).

The HLA typing was performed using polymerase-chain-reaction based on genotyping method. The DNA was extracted using the Puregene DNA Isolation Kit (Gentra Systems, Minneapolis, MN, USA). Final concentration of DNA was 100 ng/ μ l with the A269/A280 ratio between 1.65 and 1.80. Individuals were genotyped for class I and class II alleles by Micro SSP™ 384 System DNA Typing Trays (One Lambda, Canoga Park, CA, USA).

The Statistical Analyses Groups were compared in demographic and clinical variables by using Chi-square test (χ^2) or Exact Fisher's test and Kruskal–Wallis test (H). The HLA associations with groups were analyzed using Chi-square test (χ^2) or Fisher's exact test. Odds ratio (OR) and 95% confidence intervals (CI 95%) were calculated for comparison between reference groups. Differences between the groups were considered to be statistically significant when $p < 0.05$.

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