Review article

Influence of human histocompatibility antigens on susceptibility to and clinical expression of psychiatric diseases

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INTRODUCTION

Genetic, immunologic and environmental factors are involved in the pathogenesis of psychiatric diseases. Human leukocyte antigens (HLA) stand out for their polymorphism and ability to provide susceptibility or resistance to several immunomediated disorders. According to pathology and sometimes to the ethnic groups under investigation, there are variations in the association between HLA and disease. It is believed that histocompatibility molecules may have an influence on age of onset, treatment response and clinical course of some diseases. Development of new methods to typify HLA alleles and recent nomenclature updates have been contributing to a better understanding of this system. Unfortunately, such knowledge has not been adequately disclosed in the clinical literature.[1]

This review aims at presenting more information about the association of the major histocompatibility complex with some psychiatric diseases to professionals in the mental health area. To do so, the article has been structured in the following manner: HLA structure and function, detection methods, nomenclature, association with general psychiatric diseases, and more detailed association with schizophrenia, autism and bipolar disorder.

Bibliographic sources were surveyed using MEDLINE and LILACS databases. Articles published in the past 10 years were selected. Keywords used in several combinations were: 1) HLA; 2) *mental disorders*; 3) *psychiatric diseases*; 4) *schizophrenia*; 5) *bipolar disorder*; and 6) *autism*.

HLA structure and function

Located in the short arm of chromosome 6, HLA is composed of more than 200 genes, of which about 20% codify histocompatibility molecules expressed on the cell surface.[2] These genes, which take part in the immunologic response, are didactically divided into three classes: I, II and III, being different between themselves as to structure and function.[3] Class I region has three main *loci*: HLA-A, HLA-B and HLA-C, whereas class II HLA contains the HLA-DR, HLA-DQ and HLA-DP *loci*. Class I and II HLA genes codify classical histocompatibility molecules. Class III

HLA genes codify complement factors, tumor necrosis factor and 21-hydroxylase enzyme, among others.

HLA molecules play a major role in the immune response, so that T lymphocytes recognize the antigens presented by cells from several tissues only if they are connected to HLA molecules. Due to this important participation in the immunologic response, the association of HLA antigens/alleles with several diseases is studied.[3] Some HLA antigens/alleles seem to be associated with susceptibility to certain diseases, whereas others probably provide protection.[2] Some of the hypotheses suggested to explain such associations are:[3] 1) HLA molecules may work as receptors to some infectious agents; 2) HLA molecules may participate in the pathogenesis of diseases by selecting which antigenic peptide will be presented to the T lymphocyte; 3) HLA molecules may cause diseases by the molecular mimicry between HLA antigens and certain microorganisms; 4) the aberrant expression of class II HLA molecules may trigger self-immune mechanisms, presenting to T lymphocytes antigens resulting from the degradation of the tissue itself, leading to self-immune diseases; and 5) variation of HLA molecules affinity with certain peptides may induce a strong T cell response, causing tissue lesion or repression of immune response, which may lead to chronic persistence of the antigen.

Detection methods of HLA antigens and alleles

Cell or molecular methods may be used to detect HLA polymorphism. Traditional cell cytotoxicity, also called serological method, is based on a reaction dependent on the complement system, which occurs between the HLA antigen and an antibody present in the serum. Class I HLA antigens are typified through total lymphocytes or peripheral blood T lymphocytes, whereas B lymphocytes are used for class II. Due to the inexistence of specific serum, HLA-DP is not typified by serology. Although the serological method continues to be used, the tendency is to be replaced by molecular methods.[1,3]

In methods based on molecular biology, typing of alleles is performed based on the genomic DNA, extracted from nucleated cells, peripheral blood or from another tissue, and amplified by the polymerase chain reaction (PCR). The most used molecular techniques are the sequence specific primers (SSP) and the sequence specific oligonucleotide probes (SSOP).[1,3]

HLA system nomenclature

The HLA system nomenclature is routinely updated by an international committee that promotes periodic meetings to confer new names to recently discovered genes or to change the official nomenclature. This nomenclature differs according to the detection method used.[1,3]

The HLA antigens, defined by serology, are designated by the denomination of the gene *locus* (e.g., HLA-A, HLA-DR), followed by the numerical identification of the antigen (e.g., HLA-A1, HLA-DR1). The nomenclature of the C *locus* incorporates the letter "w" (e.g., HLA-Cw1, HLA-Cw2) to differentiate it from the complement system.

The nomenclature of HLA alleles defined by molecular biology varies according to their class. For class I, the denomination HLA-A, HLA-B and HLA-C is used to designate antigens defined by serology. An asterisk is added to define the method as being molecular biology (e.g., HLA-A*), and two to eight digits are then added (e.g., HLA-A*0201). The first two digits refer to the antigen serological typing; the third and fourth are related to the denominations of specific alleles; the fifth and sixth describe allele variations; and the seventh and eighth represent variations at introns (5' or 3' gene regions).[1,3,4] For class II HLA, the procedure is not exactly the same. After the designation of the HLA and its gene *locus*, the letter "A" or "B" is added to represent the polymorphic α and β chains of the HLA-DR and HLA-DQ, and only the letter "B" to represent the polymorphic β chain of the HLA-DP (e.g., HLA-DQA, HLA-DRB, HLA-DPB). Since some regions have several genes for the α and β chains, each *locus* receives a corresponding number (e.g., HLA-DRB1). Next, as defined for class I HLA, four to eight digits are added after an asterisk (e.g., HLA-DRB1*0101).[1,4]

Association of HLA with psychiatric diseases

Evidence found in studies using twins (identical or not) and adopted children indicate that a genetic component may partly explain why some people present higher risk of developing psychiatric diseases than others. It can be seen that the risk fraction attributable to genetic components is more important to certain disorders, being approximately 70% for bipolar disorder, for example. However, such risk is usually lower than 50% for most psychiatric disorders.[5] One cannot forget that genetic factors are not sufficient neither necessary for the development of some diseases. It has been confirmed that other factors, such as environmental, are equally responsible for the development process of the disease.[6]

Advances in molecular genetics have allowed the DNA analysis to be routinely performed in the investigation of genetic risk factors associated with psychiatric diseases.[7] Linkage studies have low statistical power to find genes for complex diseases, such as psychiatric diseases, in which several environmental and genetic factors play a role. These disadvantages have led to studies of allelic association, which have proven to have more statistical power to detect moderate to low effect genes.[6] The most promising candidate genes are those whose protein codified by them are directly associated with the pathogenesis of the disease or those whose great polymorphism has a major functional effect on the organism. Among the latter ones are the HLA alleles, which play a major role in the immune response of the human body. It has been suggested that certain psychiatric diseases are associated with abnormalities of the immune system; hence considering the participation of the HLA in the pathogenesis of these diseases.

Improvement in serotyping techniques and development of HLA genotyping have demonstrated a level of allelic polymorphism that had never been imagined before.[7] In addition, most recent researches about the association between psychiatric disorders and HLA have benefited from the application of more manageable diagnostic criteria, such as the Diagnostic and Statistical Manual (DSM) and the International Classification of Diseases (ICD); therefore, these studies are

more reliable and more easily comparable between themselves.[7] These aspects have facilitated the investigation of the possible associations between psychiatric disorders and the HLA system.

There are several main benefits of finding these new genetic risk factors. Among them, the following stand out: better understanding of the complex pathogenesis of these diseases and the possibility of estimating the risk each person has to develop or not those diseases.[6]

Scientific investigations to date have managed to show the influence of the HLA on some mental diseases, such as schizophrenia, bipolar disorder and autism. The main associations between the HLA and these diseases are summarized in table 1.

Table 1 - Association between HLA and schizophrenia, bipolar disorder and autism

Psychiatric disease	**HLA alleles/antigens associated with susceptibility**	**HLA alleles/antigens associated with protection**
Schizophrenia	HLA-A9, HLA-A24, HLA-A19, HLA-A28, HLA-A10, HLA-A11, HLA-A29 HLA-DRB1 (HLA-DRB1*0101) HLA-DQB1*0602 in Caucasians	HLA-A2 HLA-DRB1*04 HLA-DQB1*0602 in non-Caucasians
Bipolar disorder	HLA-A10, HLA-A29 HLA-B7, HLA-B16 and HLA-B21	
Autism	HLA-DR4 HLA-DRB1*0401, HLA-DRB1*0404, HLA-DRB1*0701, HLA-DRB1*0101	HLA-DR13 and HLA-DR14

Schizophrenia

Schizophrenia has a complex genetic inheritance and its pathogenesis is not clear.[7,8] Its association with HLA is due to reports of family inheritance and a possiblly autoimmune etiology in some cases. The presence of antibodies against hippocampus antigens, cingulate gyrus and septal region has been reported.[9] First-degree relatives of schizophrenic patients present higher risk of developing autoimmune diseases, such as, for example, a higher incidence of thyroiditis in mothers of schizophrenics.[8] Some studies suggest the existence of a gene *locus* located in the short arm of chromosome 6, which provides susceptibility for this psychiatric disorder; it is possible that this *locus* is located inside the HLA complex.[10]

The first publications about the association of schizophrenia with HLA focused on class I HLA, whereas the most recent ones have focused on class II HLA. Although Wright et al. have found higher frequency of antigens HLA-A9, HLA-A24, HLA-A19 and HLA-A28,[7] Gibson et al. have not confirmed these findings.[11] The antigens HLA-A10, HLA-A11 and HLA-A29 were most frequently found, and the HLA-A2 was less frequently detected in schizophrenic patients, compared with controls.[12] With regard to alleles, the HLA-DRB1 is the most frequently reported in association with schizophrenia.[7] These findings have also been described in Japan, where a higher frequency of the antigen HLA-DR1 and of the allele HLA-DRB1*0101 has been shown.[13,14]

Transmission of some HLA alleles from healthy parents to schizophrenic children seems to occur with some peculiarities. It has been suggested that the alleles HLA-DRB1*03 are rarely transmitted to children, whereas the alleles HLA-DRB1*13 are more frequently transmitted.[15] The alleles HLA-DRB1*04 do not seem to be preferentially transmitted to children; this could represent a factor that, whenever present, may reduce the risk of development of the disease.[16]

The association between HLA and the severe form of schizophrenia, which has its onset in childhood and may cause several cognitive and behavioral sequelae, has not been confirmed.[17] Besides onset age, HLA has not been associated with gender of schizophrenic patients either.[18] Association of HLA with the season in which the patient with the disorder was born seems to be

controversial. In Japan, the HLA-DR1 was more frequent in patients who were born in the winter. The hypothesis that this association is due to higher frequency of infectious insults at that time of year has been raised.[18] In another Japanese research, however, such association has not been found.[19]

Some studies have tried to demonstrate the association between HLA and schizophrenia based on known negative associations of this psychiatric disorder with other diseases, which are more consistently associated with HLA. Since type 1 diabetes mellitus (DM1) and rheumatoid arthritis (RA) seem to occur less frequently in schizophrenics, it has been considered that HLA alleles positively associated with these autoimmune diseases are less frequent in these patients. The allele HLA-DQB1*0602, which is positively associated with DM1, has been negatively associated with schizophrenia in female African-Americans[20] and in Chinese of both genders.[21] Inversely, in German, this allele has been more frequently reported in schizophrenic patients, mainly in non-paranoid schizophrenics; the same allele has also been associated with other diseases, such as multiple sclerosis and narcolepsy.[22] Negative association of the allele HLA-DQB1*0602 has not been seen in Caucasians from England[23] or Sweden,[24] suggesting that this association is only present in non-Caucasian populations. On the other hand, the allele HLA-DRB1*04, which corresponds to the antigen HLA-DR4, positively associated with RA, has been negatively associated with schizophrenia in Caucasians.[13,23] Nevertheless, this negative association has not been confirmed by a Scottish study.[25]

Some aspects regarding the pharmacological treatment of schizophrenia have been associated with HLA. HLA alleles and haplotypes could be associated with agranulocytosis related to the use of clozapine.[26] It is likely that the HLA system has an influence on this idiosyncratic response to the drug.[27] Studies in Jewish Caucasians have shown association between agranulocytosis caused by antipsychotics and the alleles HLA-DRB1*0402, HLA-DRB4*0101, HLA-DQA1*0301, HLA-DQB1*0201 and HLA -DQB1*0302, whereas in non-Jewish Caucasians the higher association was with the alleles HLA-DRB1*1601, HLA-DRB5*02, HLA-DQA1*0102,

HLA-DQB1*0201 and HLA-DQB1*0502.[28,29] Response to treatment with clozapine has also been associated with HLA. The antigen HLA-A1 has been associated with a more effective response to the use of clozapine in refractory patients to the conventional treatment with other antipsychotics,[30] which is also a possible predictive factor of low risk to develop agranulocytosis.[31] The antigens HLA-A2 and HLA-B35 have been considered independent predictors of good response to clozapine in Italians.[32]

Bipolar disorder

Over the years, some scientific articles have demonstrated the association between bipolar disorder and some genetic alterations. In this context, the HLA system has played a major role, despite the lack of consistency in some of the results reported to date.[33] The antigen HLA-B16 has been generally associated with mood disorders, including maniac and purely depressive disorders.[9] The antigens HLA-A10, HLA-A29, HLA-B7, HLA-B16 and HLA-B21 have been more frequently found in patients with bipolar disorder, compared with healthy controls.[34] Studies in a Korean population have not shown association between HLA alleles, typified by the molecular method, and bipolar disorder.[33] Another study, using a sample of Turkish Caucasians, has not identified association of HLA antigens and type I bipolar disorder either.[34] Both publications suggest that the HLA is not a susceptibility factor for the development of the disorder in these populations, or that the sample size was not enough to show association, which probably has low intensity. These results do not invalidate new investigations in this area, since the HLA varies considerably between different ethnic groups/races; it is possible that, in some populations, such association does exist.

Lithium is a mood-stabilizing agent often used for the treatment of bipolar disorder. Some researches have suggested that, as other chemotherapy agents, this drug may change the expression of HLA molecules.[35] The two main HLA classes seem to be affected differently by the drug; changes in class II HLA are more significant from the functional perspective. Reduction and loss of expression of class I histocompatibility molecules on the cell surface have been reported, whereas

changes in class II HLA have occurred at the genomic DNA level. A participation of these DNA changes in teratogenicity associated with the use of lithium during pregnancy has been suggested.[35] It is still unknown how lithium is able to cause these changes, which may be present 2 weeks after taking the drug in usual therapeutic doses.[35]

Autism

Although the pathogenesis of autism is unclear, participation of genetic, environmental and immunological factors is accepted.[36] Among the aspects related to immune response, abnormalities in T cell function and number and natural killers[37] and presence of self-antibodies against brain endothelial cells have been reported.[38] In addition, some studies have shown higher frequency of self-immune disorders, such as DM1, RA, systemic lupus erythematosus and hypothyroidism in mothers and first-degree relatives of autistic patients.[39] Despite the participation of the immune system on the central nervous system not being completely understood, it is possible that defects in immune response since childhood promote changes in brain development.[40]

Among all psychiatric diseases, autism seems to be the one that has the most predisposing genetic factor, although a gene strongly associated with its susceptibility has not been discovered yet.[38] Researches in the immunogenetic area have found evidence about the association of the disease with genes present in chromosome 6,[41] among them the HLA genes.[38] Increase in expression of HLA-DR molecules on the lymphocyte surface in the serum of autistic patients has been reported, thus indicating activation of these cells.[42] An extended haplotype, which comprehends, among others, alleles in regions HLA-B, HLA-DR4 and HLA-C4B null (this region is part of the HLA complex, but it does not belong to classical regions and it does not codify any protein), has been associated with the disease.[36,43] Another extended haplotype, with alleles in regions HLA-B44, HLA-SC30 (part of the HLA complex, but not in classical regions I and II) and HLA-DR4, has also been associated with autism, with the important participation of the following alleles: HLA-DRB1*0401, HLA-DRB1*0404, HLA-DRB1*0701 and HLA-DRB1*0101.[37] The

alleles HLA-DR4 have been associated with susceptibility to diseases in the autism spectrum, whereas the alleles HLA-DR13 and HLA-DR14 have been found as protective factors for the disorder.[38] The alleles HLA-DR4 are more frequently inherited from parents by autistic patients, whereas the alleles HLA-DR13 are less frequently inherited.[38] A study performed with 90 families, with at least one autistic member, has not shown association of the disease with the HLA system.[40] However, a higher frequency of the alleles HLA-A2 and HLA-DR11 has been noted, alone or composing the same haplotype, in autistic patients, compared with healthy controls.[36]

CONCLUSION

Although it is not the only component participating in the pathological process, studies show that the HLA complex influences risk, clinical status and therapeutic response of some psychiatric disorders. Major associations were: schizophrenia and HLA-DRB1*0101, autism and HLA-DR4, and bipolar disorder with class I HLA antigens (e.g., HLA-A10, HLA-B27). However, the type and strength of the association vary according to ethnic group, disease and clinical presentation. It is also important to remember that the fact of having an HLA gene or allele associated with an illness does not necessarily mean that this disease will manifest itself.

Extensive HLA polymorphism, the few published studies with different ethnic groups and disagreeing results point to the need of more researches about the participation of HLA in the pathogenesis of psychiatric diseases. This knowledge will be useful to estimate the risk a person has to develop a certain mental disease, and thus allow more adequate prophylactic and therapeutic interventions.

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ABSTRACT

Understanding the molecular basis of diseases is increasingly more important for their diagnosis, prevention, and treatment. Located in the short arm of chromosome 6, the human histocompatibility system – human leukocyte antigens (HLA) – participates in the pathogenesis of some psychiatric disorders. Development of new molecular methods to typify HLA alleles and recent nomenclature updates have been contributing to a better understanding of this system. Unfortunately, this information has not been adequately disclosed in the medical literature. This article aims to review HLA structure, antigen function, detection methods, and current nomenclature, as well as to describe its association with schizophrenia, bipolar disorder, and autism. Articles published between 1995 and 2005 (to reflect the most recent knowledge of the subject) were searched in the MEDLINE and LILACS databases. It is concluded that HLA antigens

*influence risk, clinical status, and therapeutic response of some mental disorders, even if they do not act alone on these pathologic processes. Although HLA has been associated with schizophrenia (HLA-DRB1*0101), autism (HLA-DR4), and bipolar disorder (HLA class I), these associations vary across different ethnicities and clinical manifestations. The best definition of genetic markers associated with mental disorders is important to understand possible pathogenic mechanisms, predict individual risk of developing these diseases, and contribute to future prophylactic or therapeutic interventions.*

Keywords: *HLA antigens, psychiatric diseases, major histocompatibility complex.*

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