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Association of HLA-DR/DQ polymorphisms with schizophrenia in Tunisian patients

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BACKGROUND AND OBJECTIVES: The hypothesis that human leukocyte antigens (HLAs) confer susceptibility to schizophrenic disorders has been tested by studying linkage and association in family samples. Our goal was to evaluate the role of HLA in the risk of developing schizophrenia in a Tunisian population.

DESIGN AND SETTINGS: Blood samples for this case-control study were collected from patients of the Department of Psychiatry at the Military Hospital of Tunisia between July 2012 and May 2013.

METHODS: A total of 140 patients with schizophrenia were recruited for genetic analysis. Controls included 100 persons matched for age, sex, and risk factors. Participants were tested for HLA class II alleles. HLA-DRB1 and HLA-DQB1 alleles were genotyped using polymerase chain reaction sequence-specific primers.

RESULTS: This study indicates that the alleles most responsible for disease susceptibility are DRB1*03 ($P<10^{-3}$) and DQB1*02 ($P<10^{-3}$) (P denotes probability values). The most protective alleles are DRB1*13 ($P=.013$) and DQB1*05 ($P<10^{-3}$). Further results revealed that DRB1*0301/DQB1*0201($P<10^{-3}$), DRB1*0401/DQB1*0301 ($P<10{-3}$) and DRB1*1101/DQB1*0301 ($P<10^{-3}$) are haplotypes most conducive to disease susceptibility.

CONCLUSION: The present findings support an association between schizophrenia and the HLA-DR-DQ locus among a Tunisian population. To our knowledge, this is the first study performed to analyze the association of HLA DRB1/DQB1 alleles on schizophrenia susceptibility in Tunisia.

Schizophrenia is a severe disabling neuropsychiatric disorder characterized by a collection of symptoms that may include paranoia, auditory hallucinations, thought poverty, anhedonia, social withdrawal, and cognitive impairment. Schizophrenia affects approximately 1% of the population and is a leading cause of psychiatric admissions.[1] The functional pathology of schizophrenia is yet to be fully elucidated but multiple genetic, immune, and environmental risk factors are known to influence an individual's susceptibility to develop schizophrenia.[2-4] Immunological, genetic, and expression studies indicate that immune system dysfunction might play a pivotal role in the etiopathogenesis of schizophrenia.[5]

Molecular genetics have been a turning point in schizophrenia research.[6] A number of studies have implicated a variety of genetic risk factors and, in particular, HLA loci have recently become particularly impor-

tant in schizophrenia research.[3,7-12] Genome-wide research has found significant associations of schizophrenia with markers spanning the major histocompatibility complex (MHC), also known as the human leukocyte antigen (HLA) system on chromosome 6p21.3.[7] Most of these studies have examined HLA Class I antigens that may be of less material importance if the immunological abnormalities in schizophrenia are due to an autoimmune process. Studies involving Class II antigens, which are more relevant with respect to autoimmune diseases, have detected significant associations.[13] Therefore, the most frequently reported association between HLA and schizophrenia has involved HLA-DRB1 alleles.[14,15] For example, an increased frequency of HLA-DRB1*0101 has been consistently found in HLA-schizophrenia association studies in Japanese and Turkish populations, whereas DRB1*03 was found to be a risk factor for schizophrenia in a Saudi Arabian

population.[16,17] Chowdari et al also suggested a probable association between DQB1*0402 and schizophrenia.[18] Moreover, a negative association between HLA-DRB1*04 and schizophrenia is reported in English and Kuwaiti populations.[5,19] A strong association of HLA DQB1*0602 with a protective effect have also been established among Chinese and African American populations.[20,21]

The association between HLA class II and schizophrenia in the Tunisian population was investigated in this study by noting the difference of frequency of HLA-DR and HLA-DQ antigens in patients with schizophrenia as compared to healthy controls.

SUBJECTS AND METHODS

Subjects

A total of 140 (124 males, 16 females) unrelated patients with schizophrenia, aged 39.2 (12.4) years (mean [SD]) were recruited for genetic analysis. Two board-certified psychiatrists directly interviewed the patients. Diagnoses were assigned using standard diagnostic criteria (DSM-IV) and were based on the individual interview and medical records. The final diagnoses of schizophrenia were made on agreement between the 2 psychiatrists.

Potential participants were excluded from this study if they suffered from any organic brain disorders, mental retardation, and severe head trauma, or exhibited psychotic symptoms due to medical conditions or treatments.

The 100 controls (89 males, 11 females) aged 40.6 (11.0) years (mean [SD]) were recruited among patients admitted to the Emergency Department. Subjects with cancer, systemic disease, neurological disease, and immune disease were excluded from the study. Controls also were screened for the absence of psychotic illness and past or current substance abuse. Patients were matched to controls according to sex and age. The number of controls was chosen to coincide with similar numbers chosen for Tunisian HLA studies. The frequencies fc for examined HLA type II alleles in the study were found to be commensurate with a published report.[22] Patients (140, 280 alleles) and controls (100) were chosen to detect an absolute difference of at least 10% with 80% power and α=.05 (the type I error rate) when the frequency of affected controls was 12% or less.[23] The final study population consisted of 140 cases and 100 controls.

All participants in the study (or their legal proxies) gave informed consent for giving a blood sample for genetic analysis. The study protocol was approved by the ethics committee of the Military Hospital of Tunisia and has, therefore, been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

HLA-typing by DNA amplification

Genomic DNA was extracted from peripheral blood samples of patients and healthy individuals using the QIAamp DNA Blood Mini Kit (QIAGEN GmbH, Hilden, Germany). Low-resolution HLA typing was performed by polymerase chain reaction sequence-specific primer (PCR-SSP) techniques according to Micro SSP DNA Typing Trays DRB/DQB (One Lambda Inc. Canoga Park, California, USA). Amplified DNA fragments were detected by agarose gel electrophoresis (2.5% agarose gel), stained with ethidium bromide, and UV transillumination. One Lambda DNA/LMT software version 3.98 was used to detect specific DRB1 and DQB1 alleles.

Statistical analysis

Allele frequencies were estimated by using the direct counting method. Haplotype frequencies were estimated using the expectation–maximization algorithm, and deviations from Hardy–Weinberg equilibrium were both performed using the Arlequin v.3.1 software. All analyses related to the case–control study were performed using the SPSS, version 16.0 (IBM, Armonk, NY USA). Differences between cases and controls were evaluated by using the chi-square (χ^2) test for qualitative variables. The odds ratios (OR) and 95% confidence intervals (CI) were also calculated. The threshold for statistical significance was set at a P value (P) of .05. The Bonferroni correction was used to mitigate the possibility of committing type 1 errors due to multiple comparisons.

RESULTS

The study included 140 patients and 100 controls (Table 1). The mean age of patients was not significantly different from controls (patients, 39.2 [12.4] years; controls, 40.6 [11.0] years; mean [SD]).

The HLA-DRB1 allele frequencies for the 2 groups are shown in Table 2 section (a). Overall, the allelic distributions of several alleles were significantly different between the patient and controls. In particular, the frequency of HLA DRB1*03 significantly elevated among patients than among controls (χ^2=30.83, P<10^{-3}, OR=3.88, 95% CI= [2.31-6.71]). DRB1*03 allele seems to be associated with a significant increase in risk for schizophrenia, while HLA DRBI*13 was significantly less common among patients (χ^2=9.61, P=.013,

OR=0.37, 95% CI=[0.18-0.73]) conferring protection against schizophrenia.

Table 2 (section b) shows the frequencies of the HLA-DQB1 allele for patients and controls. HLA-DQB1*02 was the most frequent allele observed in patients and it was found at a significantly higher frequency for patients over controls (x^2=21.16, P<10^{-3}, OR=2.52, 95% CI=[1.66-3.84]), which indicates a strong predisposing effect. Conversely, the frequency of HLA-DQB1*05 significantly increased for controls over patients (x^2=26.96, P<10^{-3}, OR=0.22, 95% CI=[0.11-0.41]) and indicates a conferring of protection against schizophrenia.

Table 3 shows the frequencies of HLA-DR/DQ generic allele haplotypes for patients and controls. Only haplotypes exhibiting significant linkage disequilibrium (LD) parameters between alleles were considered for the study. The calculation of the LD parameter of 2 locus haplotypes, in both cases and controls, revealed that the most significant values of the LD parameters were for the pairs DRB1*03/DQB1*02, DRB1*04/DQB1*03 and DRB1*11/DQB1*03.

Table 4 shows the frequencies of HLA-DR/DQ-specific allele haplotypes. A positive association with DRB1*0301/DQB1*0201 (x^2=41.25, P<10^{-3}, OR=5.44, 95% CI=[3.06-10.09]), DRB1*0401/DQB1*0301 (x^2=19.55, P<10^{-3}; OR=4.96, 95% CI=[2.25-12.42]), and DRB1*1101/DQB1*0301 (x^2=18.8, P<10^{-3}, OR=3.91, 95% CI=[1.99-8.25]) was noted.

DISCUSSION

Schizophrenia is a complex disorder that has garnered extensive study in the field of molecular genetics. Currently, it is presumed that various susceptibility genes are involved in the etiology. Considerable attention has been given to the immune system, with special focus on the HLA system alleles; however, results are still inconclusive. Our findings support the role of several HLA-DR-DQ alleles and haplotypes in both schizophrenia susceptibility and protection.

This study investigated the DRB1 locus as a possible candidate for schizophrenia. Specifically, the DRB1*03 was implicated as a genetic vulnerability in the development of schizophrenia. This is in accordance with previous investigations of a Saudi Arabian population where the frequency of DRB1*03 was found to be significantly higher in patients with schizophrenia than in controls.[17] However, with regard to specific HLA alleles, several Japanese studies have reported an elevated frequency of HLA-DR1 (DRB1*0101) alleles in schizophrenia.[24] Ozcan et al also reported a higher rate of DR1 in Turkish patients

Table 1. Characteristics of schizophrenic patients and controls.

Characteristics	Schizophrenic patients (n=140)	Controls (n=100)
Sex		
Male	124.0 (88.6)	89 (89)
Female	16.0 (11.4)	11 (11)
Age (SD) y	39.2 (12.4)	40.6 (11.0)
Male	38.8 (11.5)	39.2 (10.6)
Female	41.8 (19.2)	47.9 (10.8)
Age at onset (SD) y	26.7 (8.5)	-
Male	25.9 (6.8)	-
Female	32.9 (16.0)	-

Table 2. Allele frequencies in schizophrenic patients and controls.

HLA	Schizo-phrenic patients (2N=280) n (%)	Controls (2N= 200) n (%)	OR (95% CI)	P
[a]**HLA-DRB1**				
DRB1* 04	48.0 (17.1)	27.0 (13.5)	1.3 (0.8-2.3)	.27
DRB1*11	56.0 (20.0)	28.0 (14.0)	1.5 (0.9-2.6)	.56 *
DRB1*03 (s)	94.0 (33.6)	23.0 (11.5)	**3.9 (2.3-6.7)**	**<10^{-3} ***
DRB1*15	18.0 (6.4)	13.0 (6.5)	1.0 (0.4-2.2)	.97
DRB1*01	16.0 (5.7)	17.0 (8.5)	0.6 (0.3-1.4)	.23
DRB1*13 (p)	16.0 (5.7)	28.0 (14.0)	**0.4 (0.2-0.7)**	**.013***
DRB1*07	32.0 (11.4)	36.0 (18.0)	0.6 (0.3-1.0)	.28*
[b]**HLA-DQB1**				
DQB1*02 (s)	126.0 (45.0)	49.0 (24.5)	**2.5 (1.7-3.8)**	**<10^{-3}***
DQB1*03	104.0 (37.1)	69.0 (34.5)	1.1 (0.8-1.7)	.55
DQB1*06	34.0 (12.1)	25.0 (12.5)	1.0 (0.5-1.8)	.90
DQB1*05 (p)	16.0 (5.7)	43.0 (21.5)	**0.2 (0.1-0.4)**	**<10^{-3} ***

CI: Confidence interval; OR: odds ratio; P: probability value.
 *denotes Bonferroni-corrected P value; significant P value is in bold, P<.05. (s), confers susceptibility; (p), confers protection; OR detected with at least 80% power is in bold.

with schizophrenia. The current research was unable to replicate these findings.[25]

However, a significant negative association between DRB1*13 and schizophrenia was noted in our sample. This is in sharp contrast with studies in a Kuwaiti population that found a high incidence of the HLA-DRB1*13 allele in patients with schizophrenia

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Table 3. The frequencies of HLA DR/DQ haplotypes in schizophrenic patients and controls.

HLA-DRB1/DQB1	Schizo-phrenic patients (2N=280) n (%)	Controls (2N=200) n (%)	OR (95% CI)	P
DRB1*03/DQB1*02 (s)	94.0 (33.6)	17.0 (8.5)	5.4 (3.1-10.1)	<10⁻³*
DRB1*04/DQB1*03 (s)	48.0 (17.1)	16.0 (8.0)	2.4 (1.3-4.6)	.021*
DRB1*11/DQB1*03 (s)	56.0 (20.0)	16.0 (8.0)	2.9 (1.6-5.5)	.0014*
DRB1*15/DQB1*06	18.0 (6.4)	13.0 (6.5)	1.0 (0.4-2.2)	.97
DRB1*13/DQB1*06	16.0 (5.7)	12.0 (6.1)	0.9 (0.4-2.2)	.89
DRB1*01/DQB1*05	16.0 (5.7)	17.0 (8.5)	0.6 (0. 3-1.4)	.23
DRB1*07/DQB1*02	32.0 (11.4)	29.0 (14.5)	0.8 (0.4-1.4)	.31

CI: Confidence interval; OR: odds ratio; P value: probability value.
*denotes Bonferroni-corrected P value; significant P value is in bold, P<.05. (s), confers susceptibility; OR detected with at least 80% power is in bold.

Table 4. The frequencies of HLA DR/DQ allele haplotypes in schizophrenic patients and controls.

HLA-DRB1/DQB1	Schizo-phrenic patients (2N=280) n (%)	Controls (2N=200) n (%)	OR (95% CI)	P
DRB1*0301/DQB1*0201 (s)	94.0 (33.6)	17.0 (8.5)	5.4 (3.1-10.1)	<10⁻³*
DRB1*0401/DQB1*0301 (s)	48.0 (17.1)	8.0 (4.0)	5.0 (2.2-12.4)	<10⁻³*
DRB1*1101/DQB1*0301 (s)	56.0 (20.0)	12.0 (6.0)	3.9 (2.0-8.2)	<10⁻³*

CI: Confidence interval; OR: odds ratio; P: probability value.
*denotes Bonferroni-corrected P value; significant P value is in bold, P<.05. (s), confers susceptibility; OR detected with at least 80% power is in bold.

compared to controls of similar ethnic background.[19] Wright et al have reported a negative association, that is, a protective effect of DRB1*04 with schizophrenia.[5] However, a Kuwaiti study found an increased frequency of DRB1*04 in patients with schizophrenia.[19]

This study has also investigated the DQB1 locus as a possible candidate for schizophrenia associations. DQB1*02 appeared to be a risk factor for this disorder. Furthermore, DQB1*05 appeared to be negatively associated with schizophrenia in our sample. However, Nimgaonkar et al reported a positive association with DQB1*0303 and a negative association with DQB1*0602 in a Singapore Chinese population.[20] The latter negative association has also been seen in Caucasian and African American populations.[21,26] However, investigations of Caucasians residing in Sweden, the USA, and Britain found no significant difference between patients with schizophrenia

and controls with regard to the frequency of HLA-DQB1 alleles.[5,26,27]

In the present study, the frequencies of haplotypes were studied and revealed statistically significant differences in the distribution of DRB1*0301/DQB1*0201, DRB1*0401/DQB1*0301, and DRB1*1101/DQB1*0301 between patients with schizophrenia and controls.

A study of family trees from a Han Chinese population found a significant haplotype effect, with an excess of the DRB1*13/DQA1*01 haplotype and a deficit of DRB1*03/DQA1*05.[28] The DRB1*03/DQB1*02 haplotype has also been associated with other autoimmune disease in Tunisians; such as, myasthenia gravis and diabetes.[29,30]

The proposition that HLA confers risk to schizophrenia has been long debated but accumulating evidence from multiple immunological, genetic, and imaging studies argue in favor of a significant role of HLA in schizophrenia.[31] The earliest evidence supporting HLA as a schizophrenia susceptibility locus dates back to the early 70s of the last century.[32] A recent meta-analyses based on genome-wide association studies indicate highly significant associations with schizophrenia in the HLA region.[33] In explaining the mechanism of HLA and disease association, Roitt suggests that the disease occurs when a foreign antigen, capable of eliciting an immune response, is morphologically similar to an endogenous antigen (e.g., HLA-DR).[34]

B-lymphocytes, containing fragments of endogenous antigens, bind to HLA molecules and then activate T-cell receptors, thereby provoking cytokine secretion. An autoimmune process is thus initiated leading to destruction of certain structures.

There may be a degenerative process occurring related to immunological aberration. Under pathological or inflammatory conditions, microglial cells undergo activation as characterized by an increased monocytic HLA-DR antigens and microglial HLA-DR expression[15,35] This stronger expression of MHCII might have led to the exacerbation of structural damage and psychotic symptoms; the HLA-DR gene might be genetically involved in an immune response in schizophrenia.[36]

Although the mechanism of the association in schizophrenia is unknown, schizophrenia has been associated with a large range of autoimmune diseases. It has been suggested that an infectious process (viral, retroviral, etc.) taking place at an early stage of neurodevelopment could initiate an autoimmune response and thereby cause direct damage to various anatomical structures or to neurodevelopmental processes.[37,38]

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Alternatively, the lack of consistency in HLA association findings argues that a gene not involved in immune function, but located in the 6p21.3 region, could explain the diverse HLA associations seen in schizophrenia.

To our knowledge, this is the first study performed to analyze the association of HLA DRB1/DQB1 alleles with schizophrenia susceptibility in Tunisia and, as such, this study is preliminary. The validity of the results awaits confirmation with larger scale studies.

In conclusion, the present study provides evidence suggestive of an association between schizophrenia and the HLA-DRB1 and HLA-DQB1 gene loci in the Tunisian population.

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