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Potential Involvement of Human Leukocyte Antigen-DR/DQ Polymorphisms with Schizophrenia Among Patients with Schizophrenia in Yemen

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ABSTRACT

Objectives: To evaluate the hypothesis that human leukocyte antigens (HLAs) confer susceptibility to schizophrenic disorders, by assessing their contribution to the risk of schizophrenia in a Yemeni population. ***Methods***: The researchers approached patients who had been diagnosed with schizophrenia at Al-Amal Hospital for Psychiatric Diseases, Sana'a. Controls were drawn randomly from the general population. The HLA class II alleles of the participants were examined. The genotypes of the HLA-DQB1 and HLA-DRB1 alleles were determined by polymerase chain reaction using sequence-specific primers. ***Results:*** The subjects comprised 110 patients with schizophrenia, matched by an equal number of controls. The prevalence of HLA-DRB1*04 was significantly higher among patients than among controls (7.3% vs. 0.0%; $p = 0.003$), as was HLA-DRB1*07 (62.7% vs. 17.3%, odds ratio (OR) = 8.1, 95% CI: 4.3–15.1; $p < 0.001$). HLA-DRBI*14 was significantly less prevalent among patients (0.9% vs. 11.8%, OR = 0.06, 95% CI: 0.01–0.50, $\chi^2 = 10.9$; $p < 0.001$). HLA-DQB1*07 was the most common allele discovered in schizophrenia patients and was found to have a much higher incidence in patients than the control group (22.7% vs. 4.5%, OR = 6.2, 95%CI: 2.3–16.8, $\chi^2 = 15.4$; $p < 0.001$). ***Conclusions:*** The HLA-DQB1 and HLA-DRB1 gene loci are linked to schizophrenia in the Yemeni population, according to the current study's evidence.

Schizophrenia is a mental disorder that manifests as persistent or recurrent psychotic episodes. The most important symptoms include disorganized thinking, hallucinations, and delusions. Apathy, reduced emotional expressiveness, and social withdrawal are further signs. Generally, symptoms develop progressively, starting from youth, and in numerous cases never resolving. Schizophrenia is diagnosed based on a record of observed behavior, comprising the reported experiences of the patient and others who have interacted with the patient.[1] Symptoms and functional impairment for diagnosis of schizophrenia must have been present for one month (ICD-11) or for six months (DSM-5).[1] Clinical picture of some cases of schizophrenia could be associated with other mental disorders, particularly depressive disorders, anxiety disorders, obsessive-compulsive disorder, and substance use disorders.[1,2] Globally, the prevalence of schizophrenia is estimated between 0.3% and 0.7%.[2,3]

The understanding of schizophrenia changed dramatically with the advent of molecular genetics. Studies on genetics, immunology, and expression of schizophrenia suggest that immune system dysfunction may be important in the pathophysiology of the disease.[1,4,5] Numerous studies have suggested the involvement of several genetic factors, specifically, the loci of human leukocyte antigen (HLA).[4,6–8] Significant relationships between schizophrenia and markers crossing the major histocompatibility complex, as well as the HLA on chromosome 6p21, have been found in genome-wide studies.[6] Most of these have looked at HLA class I antigens, which may not be as significant if schizophrenia's immunological abnormalities are caused by an autoimmune process. Significant correlations between class II antigens and autoimmune disorders have been observed.[4,9,10] As a result, HLA-DRB1 alleles have been frequently associated with schizophrenia.[4] For instance, a stably increased

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HLA-DRB1*0101 frequency was discovered in HLA and schizophrenia association studies in Turkish and Japanese populations, while DRB1*03 was discovered to be a schizophrenia risk factor in individuals from Saudi Arabia.[11,12] Chowdari et al,[13] drew a possible connection between DQB1*0402 and schizophrenia in a Chinese population. Sayeh et al,[4] linked schizophrenia and DRB1*03 and DQB1*02 in a Tunisian study. Furthermore, a negative connection between schizophrenia and HLA-DRB1*04 has been described in English and Kuwaiti populations.[5,14] A significant connection of HLA-DQB1*0602 with a protective effect has also been instituted with Chinese and African-American populations.[15,16]

There is a dearth of studies in the Arabian Peninsula that investigated HLA and schizophrenia as well as studying HLA-related other disorders.[17–19]

Regarding Yemen, it has been through political unrest and war since the beginning of 2011. Yemen's people and Sana'a residents in particular, have experienced unprecedented emotional and physical stresses with potential to impair their mental health. During the turmoil, few studies could be conducted into mental health issues such as schizophrenia, as well as its other potential causes such as immune disorders, and how HLAs are related to those disorders. HLA class I and II variants, for instance, are linked to patients with chronic renal failure and hypertensive patients with end-stage renal failure, respectively.[20–23]

Thus, Yemen's 'lost decade' severely constrained mental health research, especially timely verification in the local population of modern insights into the genetic and immunological triggers of schizophrenia, especially the roles of HLA-DR and HLA-DQ alleles. The current study has sought to narrow the research gap by investigating the relationship between HLA class II and schizophrenia in the Yemeni population by comparing the frequencies of HLA-DR and HLA-DQ antigens in schizophrenia patients and healthy controls.

METHODS

The researchers approached patients who had been diagnosed with schizophrenia at Al-Amal Hospital for Psychiatric Diseases. Using the card-shuffle method, patients were chosen at random from this list. Patients were considered for inclusion in the study if a check of their records indicated that they had been diagnosed with schizophrenia by following DSM IV criteria, including the presence of certain characteristic symptoms for longer than six months and evidence of impairment in social or occupational functioning. In addition, the patients had to be at least 18 years old and should have visited the clinics between January and December 2021. Controls came from the general public and were chosen at random from a list of census results in the governorate of Sana'a. They were selected by simple random sampling to create statistical conclusions regarding the population. The random selection was done by computer, after which each of the selected adult residents was contacted or reached. Data was collected from them by telephone or by direct access.

The sample size was calculated at a 99% confidence level and a power of 80% under the assumption that the control exposure to DRB1*03 was 11.5% and the case (patient) exposure to DRB1*03 was 33.6%.[4] The sample size of the matched case-control study was estimated at 84 cases with 84 controls, but we increased the sample size to 110 cases and 110 controls to compensate for potential dropouts and other issues.

Exclusion criteria were mental retardation, biological brain diseases, severe head trauma, and the presence of psychotic symptoms as a result of underlying illnesses or therapeutic interventions. Additionally, the controls were examined for the lack of psychotic disorders and past or present substance usage. According to sex and age, patients were matched to controls.

From the patients' and controls' peripheral blood samples, genomic DNA was extracted using the PREP-GS GENETICS and PREP-RAPID GENETICS Kits (DNA-Technology, Russian biotech). The automatic analysis for HLA-DQB1 REAL-TIME PCR Genotyping Kit was on DNA-Technology made by DTlite1, DTprime2, and DT-96 REAL-TIME Thermal Cyclers. The software version 7.5.5.23 (current at the time of the study) was downloaded from http://www.dna-technology.ru/eng/support/. Amplified DNA fragments were found using agarose gel electrophoresis (2.5% agarose gel), ethidium bromide staining, and UV transillumination.

The direct counting approach was used to estimate allele frequencies. Considering the presence of haplotypes, comparisons were made between

schizophrenia cases and healthy controls (outcome variable). The Chi-square test for qualitative variables was used to assess the differences between cases and controls. Additionally, the odds ratios (OR) and 95% CI were calculated. A *p*-value of 0.050 was chosen as the cut-off for statistical significance. Epi-Info version 7 (CDC, Atlanta, USA) was used to calculate all analyses.

The Medical Ethics and Research Committee at Sana'a University Faculty of Medicine and Health Sciences provided ethical permission (No:1699 dated January 1, 2021) for the study.

RESULTS

The study comprised110 people with schizophrenia, 105 (95.5%) of whom were male. The mean age was 33.7±9.6 (range= 20–75) years. The control mean age was 28.6±7.5 (range = 18–48) years [Table 1].

Table 1: Age and sex distribution of schizophrenic patients and controls tested for HLA-DRB and HLA-DQB genes in Sana'a, Yemen.

Characteristics	Cases (n =110) n(%)	Control (n=110) n (%)
Sex		
Female	5 (4.5)	29 (26.4)
Male	105 (95.5)	81 (73.6)
Age, years		
20–29	44 (40.0)	78 (70.9)
30–39	48 (43.6)	18 (16.4)
40–49	6 (5.5)	14 (12.7)
≥ 50	12 (10.9)	0 (0.0)
Mean age, years	33.7	28.6
SD, years	9.6	7.5
Median, years	33	27
Mode, years	35	28
Min, years	20	18
Max, years	75	48

The HLA-DRB1 allele frequencies of the cases and control groups are presented in Table 2. The highest HLA-DRB1 values in cases where HLA-DRB1*07 (62.7% in cases vs. 17.3% in controls), followed by HLA-DRB1*04 (7.3% vs. 0.0%), and HLA-DRB1*03 (5.5% vs. 1.8%). The highest HLA-DQB1 values were in cases with HLA-DQB1*07 (22.7% vs. 4.5%), followed by HLA-DQB1*11 (6.4% vs. 0.0%), HLA-DQB1*14 (6.4% vs. 2.7%), and HLA-DQB1*03 (4.5% vs. 1.8%). In addition, overall, there was a substantial difference between patients with schizophrenia and healthy controls in the allelic distributions of numerous alleles. For instance, the prevalence of HLA-DRB1*04 was much higher in patients, occurring in 7.3% of patients vs. 0.0% in the control group ($p = 0.003$). Also, the HLA-DRB1*07 frequency was significantly higher in patients than in controls with the rate among patients being 62.7% vs. 17.3% among the control group, with a significant association with an associated increased risk of schizophrenia of 8.1, while HLA-DRBI*3 was less common among patients (5.5%) and controls (1.8%) with an OR associated with an increased risk of schizophrenia equal to 3.1, but the differences were not significant ($p = 0.140$). HLA-DRBI*14 was significantly less common among patients (0.9% vs. 11.8%). The HLA-DQB1 allele frequencies for patients and controls are displayed in Table 2. The most prevalent allele detected in patients was HLA-DQB1*07, which was substantially more common in patients than in the control group (22.7% vs. 4.5%), with an OR associated with developing schizophrenia equal to 6.2, indicating a strong predisposing effect. Additionally, HLA-DQB1*04 was considerably more common in cases than in controls (3.6% vs. 0.0%). Also, HLA-DQB1*11 was much more common in cases compared to controls (6.4% vs. 0.0%).

DISCUSSION

Numerous studies in the field of molecular genetics have been conducted on the complex illness of schizophrenia and several susceptibility genes have been identified. The role of the immune system has also been in focus, and the alleles of the HLA system have received particular attention. Yet, most findings are still ambiguous. The current study's findings suggest that several HLA-DR-DQ alleles and haplotypes contribute to schizophrenia susceptibility and protection in the Yemeni population.

This investigation looked at the DRB1 gene as potentially schizophrenia linked. Particularly, DRB1*07 was of concern as a genetic defect in schizophrenia development with an associated OR of 8.1 ($p < 0.001$). This differs from previous investigations of Tunisian populations where DRB1*07 repeats were found to be equal in patients with schizophrenia and healthy controls.[4] However, in terms of specific HLA alleles, research conducted in Tunisia,[4] Saudi Arabia,[12] and Japan[24] found that schizophrenia patients had

Table 2: Allele association of HLA-DRB and HLA-DQB genes with schizophrenia in patients compared with healthy controls in Sana'a Yemen.

HLA gene	Patients (n =110) n (%)	Controls (n= 110) n (%)	OR (95% CI)	χ^2	*p*-value
HLA-DRB1					
HLA-DRB1*03	6 (5.5)	2 (1.8)	3.1 (0.6–15.7)	2.1	0.140
HLA-DRB1*04 (S)	8 (7.3)	0 (0.0)	undefined	8.3	0.003*
HLA-DRB1*07 (S)	69 (62.7)	19 (17.3)	8.1 (4.3–15.1)	47.3	< 0.001*
HLA-DRB1*08	0 (0.0)	2 (1.8)	undefined	2.0	0.150
HLA-DRB1*11	2 (1.8)	0 (0.0)	undefined	2.0	0.150
HLA-DRB1*14 (P)	1 (0.9)	13 (11.8)	0.06 (0.01–0.5)	10.9	< 0.001*
HLA-DRB1*15	0 (0.0)	2 (1.8)	undefined	2.0	0.150
HLA-DQB1					
HLA-DQB1*0	0 (0.0)	2 (1.8)	undefined	2.0	0.150
HLA-DQB1*02	2 (1.8)	0 (0.0)	undefined	2.0	0.150
HLA-DQB1*03	5 (4.5)	2 (1.8)	2.5 (0.5–13.3)	1.2	0.250
HLA-DQB1*04 (S)	4 (3.6)	0 (0.0)	undefined	4.1	0.040*
HLA-DQB1*07 (S)	25 (22.7)	5 (4.5)	6.2 (2.3–16.8)	15.4	< 0.001*
HLA-DQB1*08	2 (1.8)	0 (0.0)	undefined	2.0	0.150
HLA-DQB1*09	2 (1.8)	0 (0.0)	undefined	2.0	0.150
HLA-DQB1*11 (S)	7 (6.4)	0 (0.0)	undefined	7.3	0.007*
HLA-DQB1*14	7 (6.4)	3 (2.7)	2.4 (0.6–9.6)	1.6	0.190

HLA: human leukocyte antigens; OR: odds ratio detected with at least 80% power; S: susceptibility; P: protection.
**Bonferroni-corrected p-value; p-value is statistically significant.*

greater frequencies of the HLA-DR1 (DRB1*031) and HLA-DR1 (DRB1*0101) alleles, respectively. Additionally, Ozcan et al,[25] observed increased DR1 in Turkish schizophrenia patients. DRB1*04 was identified as a genetic impairment in the development of schizophrenia in the current study as its incidence in cases was 7.3% and 0.0% in the control group, which differs from a study by Sayeh et al,[4] in the Tunisian population where DRB1*04 was not significantly different in cases compared to controls (17.1% vs. 13.5%).

Regarding HLA-DRB1*03 in the current study, the rate of HLA-DRB1*03 in cases was 5.5% vs. 1.8% in controls, comparing to a study from Tunisia[4] where HLA-DRB1*03 was elevated in schizophrenia (33.6% vs. 11.5%). In the current study sample, there was a substantial (protective) negative correlation between DRB1*14 and schizophrenia (0.9% in cases vs. 11.8% in controls). In contrast, research in Tunisian and Kuwaiti populations found that patients with schizophrenia had a low or absent occurrence of the HLA-DRB1*14 allele when compared to controls from the same ethnic background.[4,14] Wright et al,[5] discovered a detrimental correlation between schizophrenia and the preventive effect of DRB1*04. However, the current investigation and a Kuwaiti study discovered that people with schizophrenia have more DRB1*04 repeats.[14]

The DQB1 locus was also looked into in this study as a possible candidate for links with schizophrenia. It appears that DQB1*07 is a risk factor for schizophrenia as the rate in our cases was 22.7% vs. 4.5% in controls. This differs from the finding in Tunisia where DQB1*02 was an associated risk factor for schizophrenia.[4] Moreover, DQB1*11 appeared to be a risk factor for schizophrenia in Yemen as the rate in cases was 6.4% vs. 0.0% in the control group.

However, among our participants, there was no evidence that HLA-DQB1 was unfavorably related to schizophrenia. While a study among the Chinese community in Singapore found a positive connection with DQB1*0303 and a negative association with DQB1*0602.[15] Additionally, Caucasian and African-American populations showed the second unfavorable connection.[16,26] Studies on Caucasians living in the USA, Britain, and Sweden found no discernible difference between schizophrenia patients and controls in the frequency of HLA-DQB1 alleles.[5,26,27]

It was in the early 1970s that preliminary data emerged supporting HLAs as a source of

susceptibility to schizophrenia.[28] In 1991, Roitt suggested that schizophrenia may develop when a foreign antigen that is morphologically similar to an endogenous antigen (such as HLA-DR) is capable of inducing an immune response.[29] Since then, evidence has been mounting. Currently, the involvement of HLA in schizophrenia is supported by a number of genetic, immunological, and imaging studies. The HLA region has been shown to have significant connections with schizophrenia in meta-analyses based on genome-wide association studies.[12,14,16]

Self-antigen-containment B cells attach to HLA molecules, activate T-cell receptors, and release cytokines as a result. The autoimmune course that follows leads to the destruction of some structures in the nervous system. There may be a degenerative development happening associated with immune aberration. Micro-glial cells become activated under inflammatory or pathogenic situations, and they also express more HLA-DR on their own and on monocyte.[30] The structural damage and psychotic symptoms are likely made worse by the increased expression of MHCII; thus, the immunological response to schizophrenia may be genetically influenced by the HLA-DR gene.

A number of autoimmune illnesses have been linked with schizophrenia. It has also been hypothesized that a viral infectious process early in the formation of the nervous system can start an autoimmune reaction, which in turn can directly damage different anatomical structures or neuro-developmental processes.[30,31] The lack of consistency in HLA binding results, on the other hand, dispute the idea that a gene not connected to immune function, but present in the 6p21.3 region, could explain the various HLA bindings observed in schizophrenia.[4]

Regarding the limitations of the study, eliciting satisfactory responses from some respondents and the research population's lack of representativeness of the entire country were two challenges. The ethnicities of Yemen's southern and coastal regions are less concentrated in the Sana'a region. Additionally, there were wartime and COVID-19-related constraints, communication problems, power outages, and a lack of government cooperation.

However, to our knowledge, this is the first study to examine the connection between HLA-DRB1/DQB1 alleles and schizophrenia susceptibility in Yemen. The pan-Yemeni applicability of the findings of this pioneering study needs to be confirmed by future studies with participants from all major regions of the country.

CONCLUSION

The HLA-DQB1 and HLA-DRB1 gene loci are associated with schizophrenia in the Yemeni population. HLA-DRBI*14 may have a protective role against schizophrenia in this population.

Disclosure

The authors declared no conflicts of interest. No funding was received for this study.

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