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Research Article

Association of hla-drb and hla-dqb genes with severe negative symptoms in patients with schizophrenia in sana'a city, yemen

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Abstract

Background and objective: Human leukocyte antigens (HLAs) were evaluated for their potential to increase a patient's risk of developing schizophrenia and to be associated with patients who exhibit significant negative symptoms. Our objective was to assess, in a sample of Yemeni schizophrenia patients, the contribution of HLA to the probability of developing schizophrenia, particularly the occurrence of severe negative symptoms.

Methods: The researcher approached a patient diagnosed with schizophrenia who was an inpatient at Al-Amal Hospital for Psychiatric Diseases. The card-shuffling method was then used to randomly choose patients from this list. Patients were included for the study if, upon assessment of their medical records, it was determined that they met the DSM IV criteria for schizophrenia, were at least eighteen years old, and had visited the clinics between January and December of 2021. Controls came from the general public and were chosen at random from the Sana'a governorate census list using basic random selection. HLA class II alleles were examined in the participants. Primers unique to certain sequences of the polymerase chain reaction were used to genotype the HLA-DRB1 and HLA-DQB1 alleles.

Results: In general, there was a significant difference in the allelic distributions of several alleles between individuals diagnosed with schizophrenia and healthy controls. Specifically, there was a substantial increase in HLA DRB1*04 frequency (7.3% versus 0%, $p = 0.003$) and HLA DRB1*07 frequency (62.7% versus 17.3%, OR= 8.1, 95% CI = 4.3 - 15.1, $p < 0.001$) among patients compared to controls. The most prevalent allele in patients was HLADQB1*07, which was discovered at a frequency that was noticeably higher for patients compared to those in the control group (22.7% vs. 4.5%, OR=6.2, 95% CI = 2.3–16.8, $X2 = 15.4$, $p < 0.0001$), suggesting a significant predisposing influence. With a significantly higher frequency than patients with slight/moderate negative symptoms (95% vs 44.3%, OR=23.9, 95% CI = 5.3 –106, $X2 = 28$, $p < 0.0001$), HLADRB1*07 was the most common allele seen in patients with severe negative symptoms. This suggests a strong predisposing effect for developing severe symptoms. Additionally, patients with severe symptoms had a substantially higher HLA DQB1*07 than the group with slight to moderate negative symptoms (45% vs. 10%, OR= 7.3, 95% CI = 2.7 – 19.9, $p < 0.001$).

Conclusion: In summary, the current study provides evidence suggesting an association between the occurrence of severe negative symptoms with the HLA-DRB1 and HLA-DQB1 gene loci and schizophrenia in general in the Yemeni population.

Keywords: hla-dr/dq polymorphisms; schizophrenia; severe negative symptoms; yemen

Introduction

Psychotic episodes that are prolonged or repeated are a common sign of schizophrenia. Delusions, disorganized thinking, and hallucinations—which typically involve hearing voices—are the most significant symptoms. Apathy, reduced emotional expressiveness, and social disengagement are further signs. Typically, symptoms begin in childhood and worsen steadily over time, sometimes never going away. Based on the patient's own experiences and the accounts of individuals who can be connected to them, observed behavior serves as the basis for the diagnosis

of schizophrenia [1]. In order to diagnose schizophrenia, a patient's symptoms and functional impairment must have existed for either six months (DSM-5) or one month (ICD-11) [1]. In instance, depressive disorders, anxiety disorders, obsessive-compulsive disorder, and substance use disorders are frequently identified in patients with schizophrenia [1,2]. Between 0.3% and 0.7% of people worldwide have received a diagnosis of schizophrenia at some point in their lives [2, 3]. Although the exact pathophysiology of schizophrenia is still unknown, a number of immunological, genetic, and environmental risk factors have been shown to influence a person's propensity to develop the disorder. Studies on expression, immunology, and genetics suggest that immune system dysfunction may be a key factor in the aetiology of schizophrenia [1, 4, 5]. A major development in the study of schizophrenia was the discovery of molecular genetics. Numerous studies have shown a variety of genetic risk factors, and HLA loci in particular have drawn special attention in the field of schizophrenia research [4, 6–8]. Comprehensive genome-wide studies have identified significant correlations between schizophrenia and markers that cross the major histocompatibility complex (MHC), also known as human leukocyte antigen (HLA) on chromosome 6p21 [6]. Most of these research have examined HLA class I antigens, which might not be as significant if an autoimmune disease is the cause of the immunological abnormalities in schizophrenia. Significant correlations have been reported in studies relating class II antigens, which are mostly linked to autoimmune disorders [4,9,10]. Thus, HLADRB1 alleles have been linked to schizophrenia more frequently than any other HLA [4]. For example, HLA and schizophrenia association studies in Turkish and Japanese populations revealed a stable increase in the frequency of HLA-DRB1*0101, while DRB1*03 was identified to be a risk factor for schizophrenia in Saudi Arabian populations [11,12]. DQB1*0402 may also be linked to schizophrenia, according to Chowdari et al.'s suggestion [13]. Furthermore, Sayeh et al. hypothesized a potential link between schizophrenia in the Tunisian population and DRB1*03 and DQB1*02 [4]. Moreover, it has been documented that HLADRB1*04 and schizophrenia are negatively correlated in Kuwaiti and English populations [5,14]. African American and Chinese communities have also demonstrated a strong correlation between HLA DQB1*0602 and a protective effect [15, 16]. Deficits in other cognitive functions or in typical emotional reactions are considered negative symptoms. The five identified domains of negative symptoms are: blunted affect (asociality, or the absence of desire to make relationships); alogia (lack of speech); anhedonia (displaying flat expressions with little emotion) ; and avolition (lacking motivation); and apathy [17,18]. It is believed that motivational deficiencies arising from compromised reward processing cause anhedonia and volition [19,20]. Motivation is mostly driven by reward, which is primarily mediated by dopamine [20]. It has been suggested that negative symptoms are multidimensional and they have been categorised into two subdomains of apathy or lack of motivation, and diminished expression [17, 21]. Apathy includes avolition, anhedonia, and social withdrawal; diminished expression includes blunt affect, and alogia [22] . Sometimes diminished expression is treated as both verbal and non-verbal [23]. Additionally, a correlation has been shown between HLA and schizophrenia, particularly when severe negative symptoms occur. These convergent lines of evidence imply that immunological systems play a significant role in the pathophysiology of schizophrenia. Single nucleotide variations in the major histocompatibility complex region, other immune-related genes, and enhancers expressed in immune cell types have a high genome-wide link with negative symptoms of schizophrenia [24,25]. Yemen has been plagued by political unrest and warfare since the beginning of 2011. Insecure living conditions and physical and psychological stress are common among Yemeni people, and Sana'a residents in particular, can have a negative impact on mental health. It is evident that the number of studies on immunological disorders, particularly the relationship between human leukocyte antigens and these diseases, is quite low in Yemen. For instance, human leukocyte antigen class I and II variants are linked to patients with chronic renal failure, and HLA-DR and HLA-DQ alleles are linked to patients with hypertensive end-stage renal failure [26–29]. However, there are no studies on the relationship between HLA-DR and HLA-DQ alleles and schizophrenia in Yemen. The objective of this study was to assess, in a sample of Yemeni schizophrenia patients, the contribution of HLA to the probability of developing schizophrenia, particularly the occurrence of severe negative symptoms.

Materials And Methods

Study sample

The researcher approached a patient diagnosed with schizophrenia who was an inpatient at Al-Amal Hospital for Psychiatric Diseases. The card-shuffling method was then used to randomly choose patients from this list. Patients were included for the study if, upon assessment of their medical records, it was determined that they met the DSM IV criteria for schizophrenia, were at least eighteen years old, and had visited the clinics between January and December of 2021. Controls came from the general public and were chosen at random from the Sana'a governorate census list using basic random selection. To draw statistical inferences about the population, a simple random sampling method was used to choose the comparator (control). Additionally, randomization contributes to high internal validity because it is the most effective strategy to reduce the impact of potentially confusing variables. Because the Sana'a Governorate had a comprehensive list of every person living there, the necessary foundations were set up in this fashion. Following a computer-generated random selection process, every one of the 110 residents was called or reached. They were contacted over the phone or granted access to provide data.

Sample size: If the case exposure to DRB1*03 is 33.6% and the control exposure to DRB1*03 is 11.5%, the sample size was computed at a 99% confidence level and an 80% power [4]. The matched case-control study had a sample size of 84 cases and 84 controls; however, in order to get more insightful results, we extended the sample to 110 cases and 110 controls.

Exclusion criteria: Any organic brain problems, mental retardation, severe head trauma, or psychotic symptoms resulting from medical illnesses or treatments disqualified potential participants from this study. The controls were also examined for the presence of substance misuse in the past or present, as well as psychiatric disease. Patients and controls were matched based on age and gender.

HLA-typing by DNA amplification

Genomic DNA was extracted from peripheral blood samples of patients and healthy individuals 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 DTlite1 , DTprime2 , and DT-96 REAL-TIME Thermal Cyclers; software version is not lower than 7.5.5.23; the current version of the software was download from Amplified DNA fragments were detected by agarose gel electrophoresis (2.5% agarose gel), stained with ethidium bromide, and UV transillumination.

Data analysis: Direct counting was the approach used to estimate allele frequencies. Comparisons of the haplotype prevalent in schizophrenia cases and healthy controls (outcome variable). The chi-square ($\chi 2$) test was used to assess differences between cases and controls for qualitative variables. Additionally, the 95% confidence intervals (CI) and odds ratios (OR) were computed. At a P value (P) of.05., the threshold for statistical significance was established. Epi-Info version 7 was used to calculate all analyses (CDC, USA).

Ethical Consideration: The Medical Ethics and Research Committee of the Faculty of Medicine and Health Sciences of Sana'a University granted ethical approval No:1699, dated January 1, 2021. The review committee's ethical rules were followed during the trial.

Results

The HLA-DRB1 allele frequencies of the cases and control groups are presented in section A of Table 1.

1. Results

HLA	Schizophrenic patients (N=110) n (%)	Controls (N= 110) n (%)	OR (95% CI)	X^2	p
HLA-DRB1					
HLA-DRB1-03	6 (5.5)	2 (1.8)	3.1 (0.6-15.7)	2.1	0.14
HLA-DRB1-04 (S)	8 (7.3)	0 (0)	undefined-undefined	8.3	0.003
HLA-DRB1-07 (s)	69 (62.7)	19 (17.3)	8.1 (4.3-15.1)	47.3	<0.0001
HLA-DRB1-08	0 (0)	2 (1.8)	0 (undefined-undefined)	2	0.15
HLA-DRB1-11	2 (1.8)	0 (0)	undefined-undefined	2	0.15
HLA-DRB1-14 (P)	1 (0.9)	13 (11.8)	0.06(0.008-0.5)	10.9	0.0009
HLA-DRB1-15	0 (0)	2 (1.8)	0 (undefined-undefined)	2	0.15
HLA-DQB1					
HLA-DQB1-0	0 (0)	2 (1.8)	0 (undefined-undefined)	2	0.15
HLA-DQB1-02	2 (1.8)	0 (0)	undefined-undefined	2	0.15
HLA-DQB1-03	5 (4.5)	2 (1.8)	2.5(0.5-13.3)	1.2	0.25
HLA-DQB1-04	4 (3.6)	0 (0)	undefined-undefined	4.1	0.04
HLA-DQB1-07	25 (22.7)	5 (4.5)	6.2(2.3-16.8)	15.4	<0.0001
HLA-DQB1-08	2 (1.8)	0 (0)	undefined-undefined	2	0.15
HLA-DQB1-09	2 (1.8)	0 (0)	undefined-undefined	2	0.15
HLA-DQB1-11	7 (6.4)	0 (0)	undefined-undefined	7.3	0.007
HLA-DQB1-14	7 (6.4)	3 (2.7)	2.4(0.6-9.6)	1.6	0.19

Table 1: Allele association with schizophrenic patients comparing with healthy controls (tested for HLA-DRB and HLA-DQB genes) in Sana'a City, Yemen

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

Overall, the allelic distributions of several alleles were significantly different between patients with schizophrenia compared to healthy controls. In particular, the frequency of HLA DRB1*04 was significantly increased among patients than among controls with the rate being 7.3% versus 0% for the control group (p = 0.003). Also, the frequency of HLA DRB1*07 was significantly increased among patients compared to the control group with the rate among patients being 62.7% versus 17.3% among the control group, with a significant association with an associated increased risk of schizophrenia of 8.1, 95% CI = 4.3 - 15.1 , p < 0.001, while HLA DRBI*3 was less common among patients (5.5%) and controls (1.8%) with an odds ratio associated with an increased risk of schizophrenia equal to 3.1, but the differences were not statistically significant (p = 0.14). While HLA DRBI*14 was significantly less common among patients (0.9% vs. 11.8% among the control group) with OR = 0.06, CI = 0.008–0.5, χ^2 = 10.9, p = 0.0009; grant protection against schizophrenia. Table 2 (section b) shows the HLA-DQB1 allele frequencies for patients and controls. HLADQB1*07 was the most common allele observed in patients and was found at significantly higher frequency for patients above the control group (22.7% vs 4.5%), with an OR associated with developing schizophrenia equal to 6.2, 95% CI = 2.3–16.8, χ^2= 15.4. , p < 0.0001, indicating a strong predisposing effect. Also, the frequency of HLA-DQB1*04 significantly increased for cases over controls (3.6% vs 0%), χ^2 = 4.1 and p = 0.04. Also, the frequency of HLA-DQB1*11 increased significantly for cases over controls (6.4% vs 0%), with χ^2 = 7.3 and p = 0.007. Negative symptoms are deficiencies in normal emotional responses, or in other thought processes. The five known areas of negative symptoms are: poor affectivity - showing flat expressions or little emotion; alogia - poverty of speech. anhedonia - inability to feel pleasure; Sociability - lack of desire to form relationships, lack of solitude - lack of motivation and apathy. HLADRB1*07 was the most common allele seen in patients with severe negative symptoms. This suggests a strong predisposing effect for developing severe symptoms. Additionally, patients with severe symptoms had a substantially higher HLA DQB1*07 than the group with slight to moderate negative symptoms (45% vs. 10%, OR= 7.3, 95% CI = 2.7 – 19.9, p < 0.001) (Table 2).

HLA	High Negative symptoms (N=40) n (%)	Slight and moderate Negative symptoms (N= 70) n (%)	OR (95% CI)	X^2	p
HLA-DRB1					
HLA-DRB1-03	4 (10)	2 (2.9)	3.8 (0.6-21.6)	2.5	0.11
HLA-DRB1-04	6 (15)	2 (2.9)	6.0 (1.1-31.3)	5.6	0.04
HLA-DRB1-07	38 (95)	31 (44.3)	23.9 (5.3 -106)	28	<0.0001
HLA-DRB1-11	2 (5)	0 (0)	undefined	3.6	0.059
HLA-DRB1-14	0 (0)	1 (1.4)	0 (undefined)	0.57	0.44

HLA-DQB1					
HLA-DQB1-02	2 (5)	0 (0)	undefined	3.6	0.059
HLA-DQB1-03	3 (7.5)	2 (2.9)	2.7 (0.4-17)	1.2	0.26
HLA-DQB1-04	3 (7.5)	1 (1.4)	5.6 9 (0.5 – 55.7)	2.7	0.1
HLA-DQB1-07	18 (45)	7 (10)	7.3 (2.7 -19.9)	17.7	<0.0001
HLA-DQB1-08	2 (5)	0 (0)	undefined	3.6	0.059
HLA-DQB1-09	2 (5)	0 (0)	undefined	3.6	0.059
HLA-DQB1-11	4 (10)	3 (4.3)	2.4 (0.5 -11.7)	1.39	0.23
HLA-DQB1-14	3 (7.5)	4 (5.7)	1.3 (0.28 – 6.3)	0.13	0.7

Table 2: Allele association with severe negative symptoms compared to mild/moderate negative symptoms in patients with schizophrenia (tested for HLA-DRB and HLA-DQB genes) in Sana'a city, Yemen

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

Discussion

Schizophrenia is a multifaceted illness that has been offered d extensive study in the subject of molecular genetics. At present, various susceptibility genes are hypothesized to be involved in the etiology. Great interest it was given to the immune system, with a particular focus on alleles of the HLA system; nevertheless, the results still inconclusive. The current study findings provide a role for a number of HLA-DR-DQ alleles and haplotypes in both susceptibility and protection for schizophrenia. This study investigated the DRB1 locus as a potential candidate for schizophrenia. Specifically, DRB1*07 was concerned as a genetic impairment in the development of schizophrenia having an associated OR of 8.1 ($p < 0.0001$). This differs from previous investigations of Tunisian populations where DRB1*07 repeats were found to be equal in patients with schizophrenia and in healthy controls [4]. However, with respect to specific HLA alleles, a Tunisian study [4] and Saudi study [12] reported a higher frequency of HLA-DR1 (DRB1*3 alleles in schizophrenia, and a number of Japanese studies also reported a higher frequency of HLA-DR1 (DRB1 *0101) Alleles in schizophrenia patients [30]. Ozcan *et al.* also reported elevated DR1 in Turkish patients with schizophrenia [31]. 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% ($p = 0.003$), and 0% in the control group, which differs from a study by Sayeh *et al.* [4] in the Tunisian population where DRB1*04 was not significant difference in cases compared to controls (17.1% in cases vs 13.5% in controls). Regarding HLA-DRB1-*03 in the current study, the rate of HLA-DRB1-*03 in cases was 5.5% versus 1.8% in controls ($p = 0.14$), which differs sharply from that reported in Tunisia [4] where HLA-DRB1-*03 is elevated in schizophrenia (33.6% in cases vs. 11.5% in controls). There was a significant (protective) negative association between DRB1*14 and schizophrenia observed in the current study sample (7.3% in cases vs 0% in controls, $p = 0.0009$). This is in contrast to studies in Kuwaiti populations and Tunisian populations that recovered a low or absent incidence of the HLA-DRB1*14 allele in patients with schizophrenia compared to controls of similar ethnic locale [4,14].

Wright *et al.* [14] reported a negative association, the protective effect of DRB1*04 with schizophrenia [5]. However, in the current study and a Kuwaiti study found an increase in DRB1*04 repeats in schizophrenic patients. The current study has also investigated the DQB1 locus as a potential candidate for schizophrenia associations. DQB1*07 appears to be a risk factor for schizophrenia disorder as the rate in cases was 22.7% versus 4.5% in controls with an associated OR of 6.2, $p < 0.001$. This differs from that reported in Tunisia where DQB1*02 was an associated risk factor for schizophrenia disorder [4]. Moreover, DQB1*011 appeared to be a risk factor for schizophrenia in Yemen as the rate in cases was 6.4% versus 0% in the control group, and $p < 0.001$. But, HLA-DQB1 was not shown to be negatively associated with schizophrenia in the current study sample. However, Nimgaonkar *et al.* reported a positive association with DQB1*0303 and a negative association with DQB1*0602 in the Singapore Chinese population [15]. The second negative association was also seen in African American and Caucasian populations [16, 32]. However, investigations in Caucasians residing in the USA, Britain and Sweden, did not find a significant difference between schizophrenia patients and controls regarding the frequency of HLADQB1 alleles [5, 32, 33]. The hypothesis that human leukocyte antigens causes the risk of schizophrenia has been long debated, but evidence has accumulated. Numerous genetic, immunological, and imaging studies argue for an important role for HLA in schizophrenia. The oldest evidence supporting HLA as a susceptibility locus in schizophrenia is from early seventies of the last century [34]. Meta-analyses based on genome-wide association studies have indicated extremely important associations with schizophrenia in the HLA region. As for the explanation of the HLA mechanism and schizophrenia disease, Roitt [35] evokes, is that schizophrenia occurs when a foreign antigen is able to trigger an immune response, morphologically analogous to an endogenous antigen (eg, HLA-DR) [35]. B lymphocytes, which contain fragments of self-antigens, bind to HLA molecules and then activate T-cell receptors, which leads to cytokine secretion. Thus, an autoimmune process begins, which leads to the destruction of some structures in the nervous system. There may be a degenerative development happening associated with immune aberration. Under inflammatory or pathological conditions, micro-glial cells undergo activation and are also characterized by increased monocyte HLA-DR antigens and micro-glial HLA-DR expression [36]. This stronger expression of MHCII probably exacerbated the structural damage and psychotic symptoms; The HLA-DR gene may be genetically engaged in the immune response to schizophrenia. Even though the mechanism of association in schizophrenia is mysterious. Also schizophrenia has been associated with a variety of autoimmune diseases. In addition, it has been suggested that a viral infectious process that occurs early in the development of the nervous system can initiate an autoimmune response and thus cause direct damage to various anatomical structures or to neuro-developmental processes [37,38]. On the other hand, the lack of stability in HLA binding results disputes that a gene not implicated in immune function, but located in the 6p21.3 region, could explain the diverse HLA bindings seen in schizophrenia [4].

The most prevalent allele found in those exhibiting severe negative symptoms was HLADRB1*07. This implies a significant risk factor for the development of severe symptoms. Furthermore, HLA DQB1*07 was significantly greater in patients with severe symptoms (45% vs. 10%, OR= 7.3, 95% CI = 2.7 – 19.9, $p < 0.001$) than in the group with minimal to moderate unfavorable symptoms (Table 2). Both Urhan-Kucuk et al. [39] and Ilani et al. [40] discovered a link between severe negative symptoms and elevated DRD3 gene expression in lymphocytes. But no research has been conducted to determine whether having HLA DQB1 or HLADRB1 strongly predisposes one to experiencing severe symptoms. Fernandez-Egea et al. discovered considerably increased DRD3 gene expression in CD4+ T cells in schizophrenia, and higher DRD3 expression was linked to proportionally lower

counts of memory and activated Treg cells. This finding helps to explain this outcome. The correlation between CD4+ DRD3 expression levels and CD4+ sub-class cell counts may be explained, in part, by the possibility that aberrant dopamine receptor expression on naïve T cells inhibits their differentiation due to immune synaptic contact with antigen-presenting cells, resulting in comparatively fewer committed Treg cells. Before it is possible to make a firm determination regarding the usefulness of immune cell counts or transcripts as biomarkers of the severity of psychotic symptoms, anti-psychotic medication treatment, or treatment resistance, there is still a great deal of unanswered research regarding the interactions between peripheral and central dopamine signaling in health and disease [41].

Limitation of the study

This is the first study to examine the relationship between HLA DRB1/DQB1 alleles and schizophrenia susceptibility in Yemen; therefore, the study is preliminary, and the validity of the findings is awaiting confirmation by large-scale studies with wider and larger sample sizes. Despite our best efforts, we were unable to locate any prior research on this topic in Yemen. But pointing up these flaws in the current study shouldn't make readers and reviewers less of a believer in its scientific usefulness.

Conclusion

In summary, the current study provides evidence suggesting an association between the occurrence of severe negative symptoms with the HLA-DRB1 and HLA-DQB1 gene loci and schizophrenia in general in the Yemeni population.

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Conflict Of Interest

No conflict of interest associated with this work.

Author's Contributions

This article is part of a research conducted by Dr. Sami Mohammed Abdo Hassan for his Ph.D., who carried out clinical and laboratory works with the assistance and supervision of Professor Hassan Al-Shamahy. Both contributed to the evaluation of clinical and laboratory findings, data analysis, and writing of the manuscript.

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