Potential Involvement of HLA-DR/DQ Polymorphisms with Schizophrenia Among Yemeni Schizophrenia Patients

Hassan Abdulwahab Al-Shamahy[1,2*] and Sami Mohammed Abdo Hassan[1]

[1]Medical Microbiology and Clinical Immunology Department, Faculty of Medicine and Health Sciences, Sana'a University, Republic of Yemen

[2]Medical Microbiology department, Faculty of Medicine, Genius University for Sciences & Technology, Dhamar city, Republic of Yemen.

Received: 28 June 2023

Accepted: 26 July 2023

DOI 10.5001/omj.2024.46

*** Corresponding author:** shmahe@yemen.net.ye; al-shamahy@gust.edu.ye; h.shmahe15@su.edu.ye

Abstract

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 objective was to assess the contribution of HLA to the schizophrenia risk in the Yemeni community.

Methods: The researchers approached patients who had been diagnosed with schizophrenia at Al-Amal Hospital for Psychiatric Diseases. Controls were drawn at random from the list of census takers in the Sana'a governorate and were drawn 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 occurrence of HLA DRB1*04 was increased significantly with patients than with controls (7.3% versus 0%, $p = 0.003$), also HLA DRB1*07 was significantly increased with patients (62.7% versus 17.3%, OR= 8.1, 95% CI = 4.3 - 15.1 , $p < 0.001$), at the same time as HLA DRBI*14 was less common significantly with patients (0.9% vs. 11.8% with the control group) with OR = 0.06, CI = 0.008–0.5, $X^2 = 10.9$, $p = 0.0009$; grant protection against schizophrenia. HLADQB1*07 was the generally common allele discovered in patients and was found at extensively higher incidence for patients above the control group (22.7% vs. 4.5%, OR=6.2, 95% CI = 2.3–16.8, $X^2 = 15.4$., $p < 0.0001$), indicating a strong predisposing effect.

Conclusion: The HLA-DQB1 and HLA-DRB1 gene loci have been linked to schizophrenia in the Yemeni population, according to the current study's evidence.

Keywords: HLA-DR/DQ polymorphisms, schizophrenia, Yemen

Introduction

Schizophrenia is a mental disorder that manifests as persistent or recurrent psychotic episodes. The most important symptoms include disorganized thinking, hallucinations (usually hearing voices), and delusions. Apathy, reduced emotional expressiveness, and social withdrawal are further signs. Generally symptoms develop progressively, starting for the period of youth, and in numerous cases never resolving. Schizophrenia diagnosis is depends on the observed behaviors, which is a record that consists of the reported experiences of the person, and the others reports who can be identified with the person (1). Symptoms and functional impairment for diagnosis of schizophrenia must have been presented for one month (ICD-11) or for six months (DSM-5) (1). Clinical picture of some patients with schizophrenia could be associated with other mental disorders, particularly depressive disorders, anxiety disorders, obsessive-compulsive disorder, and substance use disorders (1, 2). Globally, prevalence of schizophrenia is approximately 0.3% to 0.7%) (2, 3). Although the etiology of schizophrenia has not yet been fully understood, there are numerous immunological, genetic, and environmental risk factors that can influence someone's propensity to develop schizophrenia. Studies on the genetics,

immunology, and expression of schizophrenia suggest that immune system dysfunction may be an important factor in the pathophysiologies of the disease (1, 4, 5). The study of schizophrenia changed dramatically with the advent of molecular genetics. Numerous researches have suggested diversity of genetic possibility factors, and in specific, the loci of HLA has drawn special attention in studies on schizophrenia (4, 6–8). Significant relationships between schizophrenia and markers crossing the MHC, as well recognized as the HLA on chromosome 6p21, have been found in genome-wide studies (6). The majority of these researches have looked at HLA class I antigens, which may not be as significant if schizophrenia's immunological abnormalities is caused by an autoimmune process. Significant correlations between class II antigens and autoimmune disorders have been observed in studies (4, 9, 10). As a result, HLADRB1 alleles have been associated with schizophrenia most frequently (4). For instance, a stably increased of 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.* also assumed a possible connection involving DQB1*0402 and schizophrenia (13). Also, Sayeh *et al.* assumed a possible connection between schizophrenia and DRB1*03 and DQB1*02 in the Tunisian population (4). Furthermore, a negative connection between schizophrenia and HLADRB1*04 has been described in Kuwaiti and English populations (5, 14). A significant connection of HLA DQB1*0602 with a protective effect has also been instituted with African American and Chinese populations (15, 16). It is clear that there are few studies in the Arabian Peninsula that investigated HLA and schizophrenia as well as studying HLA-related other disorders (17-19).

Yemen has been through political unrest and war since the beginning of 2011. Yemen's people and Sana'a residents in particular, experience an unstable pace of life and may experience emotional and physical stress that may impair their mental health. It is evident that there aren't many studies in Yemen that have looked at immune disorders, particularly how human leukocyte antigens are related to those disorders. Human leukocyte antigen 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), but studies on HLA-DR and HLA-DQ alleles linked to schizophrenia in Yemen are lacking. This study investigated 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. Then, 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 in accordance with DSM IV criteria, including the presence of certain characteristic symptoms for longer than 6 months and evidence of impairment in social or occupational functioning. In the ICD-10, symptoms must persist for only 1 month and functional consequences are not specified. In addition, patients had visited the clinics between January 2021 and December 2021; they were 18 years old. Controls came from the general public and were chosen at random from a list of census results in the governorate of Sana'a. The comparator (control) was selected by simple random sampling in order to create statistical conclusions regarding the population. The greatest strategy to reduce the impact of potentially confounding variables is by randomization, which also helps to assure good internal validity. In this way, the basic requirements were prepared for this, as a complete list of each member of the population was obtained in Sana'a Governorate. The random selection was done by computer, after which each of the 110 adults selected residents was contacted or reached. Data was collected from them by telephone or access to them.

Sample size was calculated at a 99% confidence level and a power of 80% if the control exposure to DRB1*03 is 11.5% and the case exposure to DRB1*03 is 33.6% (4). The sample size of the matched case-control study is 84 cases: 84 controls, but we increased the sample to 110 cases: 110 controls to obtain more valuable results.

Exclusion criteria were mental retardation, biological brain diseases, and severe head trauma, and the presence of psychotic symptoms as a result of underlying illnesses or therapeutic interventions served as grounds for exclusion from the study. 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.

The study comprised 110 people with schizophrenia in total. Most of the patients (95.5%, 105) were male, while only 4.9% were female, 5. The mean age of the patients was 33.7 ± 9.6 years; the minimum age was 20

years, and the maximum. 75 years old. Most of the patients were in the age groups 20-29 years (40%) and 30-39 years (43.6%). As for the control group, it was 73.6% for males and 26.4% for females. The mean control age was 28.6 ± 7.5 years, the minimum and maximum ages were 18 and 48 respectively (Table 1).

Table 1: Age and Gender Distribution of schizophrenic patients and control tested for HLA-DRB and HLA-DQB genes in Sana'a City, Yemen

Characters	**Cases n=110 Number (%)**	**Control n=110 Number (%)**
Gender		
Female	5 (4.9)	29 (26.4)
Male	105 (95.5)	81 (73.6)
Age groups		
20 – 29 years	44 (40)	78 (70.9)
30-39 years	48 (43.6)	18 (16.4)
40 – 49 years	6 (5.5)	14 (12.7)
≥ 50 years	12 (10.9)	0 (0.0)
Total	**110**	**110 (100)**
Mean age	33.7 years	28.6 years
SD	9.6 years	7.5 years
Median	33 years	27 years
Mode	35 years	28ears
Min	20 years	18 years
Max	75 years	48 years

From patients' and healthy individuals' 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 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 downloading 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 Haplotype, comparisons between schizophrenia cases and healthy controls (outcome variable). The chi-square (2) test for qualitative variables was used to assess differences between cases and controls. Additionally, the odds ratios (OR) and 95% confidence intervals (CI) were calculated. A P value (P) of.05. was chosen as the cutoff for statistical significance. Epi-Info version 7 (CDC, USA) was used to calculate all analyses.

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

Results

The HLA-DRB1 allele frequencies of the cases and control groups are presented in section A of 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% I cases vs. 0.0% in controls), and HLA-DRB1 -03 (5.5% in cases vs. 1.8%). The highest HLA-DQB1 values were in cases with HLA-DQB1-07 (22.7% in cases vs. 4.5% in controls), followed by HLA-DQB1-11 (6.7% in cases vs. 0% in controls), HLA-DQB1-14 (6.7% in cases vs. 2.7% in controls) and HLA-DQB1-03 (4.5% in cases vs. 1.8% in controls). In addition, the overall, there was a substantial difference between patients with schizophrenia and healthy controls in the allelic distributions of numerous alleles. In instance, the prevalence of HLA DRB1*04 was considerably higher in patients compared to controls, occurring in 7.3% of patients versus 0% in the control group ($p = 0.003$). Also, the HLA DRB1*07 frequency was significantly increased with patients contrast 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. The HLA-DQB1 allele frequencies for patients and controls are displayed in Table 2 (section b). The most prevalent allele detected in patients was HLADQB1*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, 95% CI = 2.3–16.8, χ^2= 15.4., p < 0.0001, indicating a strong predisposing effect. Additionally, HLA-DQB1*04 was considerably more common in cases than in controls (3.6% vs. 0%), χ^2 = 4.1 and p = 0.04. Also, HLA-DQB1*11 was much more common in cases compared to controls (6.4% vs. 0%), with χ^2 = 7.3 and p = 0.007.

Table 2: Allele association with schizophrenic patients comparing with healthy controls (tested for HLA-DRB and HLA-DQB genes) in Sana'a City, Yemen.

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 (S)	4 (3.6)	0 (0)	undefined-undefined	4.1	0.04
HLA-DQB1-07 (S)	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 (S)	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

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

Numerous studies in the field of molecular genetics have been conducted on the complex illness of schizophrenia. Several susceptibility genes are currently thought to play a role in the pathogenesis. The immune system has drawn a lot of attention, with the HLA system's alleles receiving particular attention; yet, the findings are still ambiguous. The current study's findings suggest that a number of HLA-DR-DQ alleles and haplotypes contribute to schizophrenia susceptibility and protection.

This investigation looked at the DRB1 gene as a potential schizophrenia possibility. Particularly, DRB1*07 was of concern as a genetic defect in schizophrenia development with 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, in terms of specific HLA alleles, research conducted in Tunisia (4), Saudi Arabia (12), and Japan (24) found that schizophrenia patients had 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% ($p = 0.003$), 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). In the current study sample, there was a substantial (protective) negative correlation between DRB1*14 and schizophrenia (7.3% in cases vs. 0% in controls, $p = 0.0009$). In contrast, research in Kuwaiti and Tunisian 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. (14) discovered a detrimental correlation between schizophrenia (5) 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.

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 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 $p < 0.001$. However, in the sample used for this investigation, there was no evidence that HLA-DQB1 was unfavorably related to schizophrenia. The Singapore Chinese community, however, was found to have a positive connection with DQB1*0303 and a negative association with DQB1*0602 by Nimgaonkar *et al.* (15). Both Caucasian and African American populations (16, 26) showed the second unfavorable connection. There was no discernible difference between schizophrenia patients and controls in the frequency of HLADQB1 alleles, according to studies done on Caucasians living in the USA, Britain, and Sweden (5, 26, 27).

There has been much discussion about the theory that human leukocyte antigens increase the risk of schizophrenia, but the evidence is mounting. A significant involvement for HLA in schizophrenia is supported by a number of genetic, immunological, and imaging studies. Early in the 1970s of the 20th century is when the earliest data supporting HLA as a site of susceptibility in schizophrenia emerged (28). The HLA region has shown to have very significant connections with schizophrenia in meta-analyses based on genome-wide association studies. According to Roitt (29) explanation of the HLA mechanism and schizophrenia disease, schizophrenia develops when a foreign antigen, which is morphologically similar to an endogenous antigen (such as HLA-DR), is capable of inducing an immune response.

Self-antigen-containment B cells attach to HLA molecules, activate T-cell receptors, and release cytokines as a result. Thus, an autoimmune course begins, which 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 (31). The structural damage and psychotic symptoms were likely made worse by the increased expression of MHCII; the immunological response to schizophrenia may be genetically influenced by the HLA-DR gene. Despite the fact that the associational process in schizophrenia is unknown. Additionally, a number of autoimmune illnesses have been linked with schizophrenia. In addition, it has been hypothesized that a viral infectious process that happens 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 (31, 32). 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).

This study has limitation. This is the first study to look at the connection between HLA DRB1/DQB1 alleles and schizophrenia susceptibility in Yemen; as a result, it is preliminary, and the validity of the findings must be confirmed by in-depth investigations using a wider and larger population. Despite searching and checking, we were unable to find a prior study on this topic in Yemen. However, pointing out these flaws in the current study should not make readers and reviewers less likely to accept it as a legitimate scientific study.

Conclusion

The HLA-DQB1 and HLA-DRB1 gene loci are connected with schizophrenia in the Yemeni population, according to the findings of the current study. HLA DRBI*14 was less common significantly with patients than the control group grant protection against schizophrenia.

Acknowledgments

We sincerely appreciate the great help from the Yemeni Sana'a University Faculty of Medicine and Health Sciences.

Conflict of interest

Regarding this project, there is no conflict of interest.

Author's contributions

This essay is a result of study of Dr. Sami Mohammed Abdo Hassan completed for his Ph.D. He worked in the lab and on patients under the guidance of Professor Hassan Abdulwahab Al-Shamahy. Both participated in the analysis of the data, drafting of the report, and evaluation of the clinical and laboratory findings.

References

1. Abdo Hassan Sami Mohammed, Al-Shamahy Hassan A. Clinical Symptoms and Risk Factors Associated with Schizophrenic Patients in Yemen. Biomedical Research and Clinical Trials. 2022; 1(1); DOI:10.31579/2835-7949/004

2. US National Institute of Mental Health (2022)."Schizophrenia". Health topics. US National Institute of Mental Health. April 2022. Retrieved 22 November 2022.

3. WHO. "Schizophrenia Fact sheet". World Health Organization. 10 January 2022. Retrieved 23 November 2022.

4. Sayeh A, Cheikh CB, Mrad M, Lakhal N, Gritli N, Galelli S, Oumaya A, Fekih-Mrissa N. Association of HLA-DR/DQ polymorphisms with schizophrenia in Tunisian patients. Ann Saudi Med. 2014; 34(6):503-7. doi: 10.5144/0256-4947.2014.503. PMID: 25971824; PMCID: PMC6074579.

5. Wright P, Donaldson PT, Underhill JA, Choudhuri K, Doherty DG, Murray RMl. Genetic association of the HL A-DRB1 gene locus on chromosome 6p21.3 with schizophrenia. Am J Psychiatry 1996;153:1530-3.

6. Lee SH, Decandia TR, Riphe S, Yang J. Estimating the proportion of variation in susceptibility to schizophrenia captured by common SNPs. Nat Genet 2012;44:247-50.

7. de Jong S, Van Eijk KR, Zeegers DW, Strengman E, Janson E, Veldink JH, et al. Expression QTL analysis of top loci from GWASmeta-analysis highlights additional schizophrenia candidate genes. Europ J of Hum Genet 2012; 20:1004-8.

8. Lehner T. The genes in the Major Histocompatibility Complex as risk factors for schizophrenia: De Omnibus Dubitandum. Biol Psychiatry 2012; 72:615-6.

9. Amirzargar A, Mytilineos J, Farjadian S, Doroudchi M, Scherer S, Opelz G, Ghaderi A. Human leukocyte antigen class II allele frequencies and haplotype association in Iranian normal population. Hum Immunol. 2001; 62(11):1234-8. doi: 10.1016/s0198-8859(01)00320-2. PMID: 11704285.

10. Prasard S, Semwal P, Deshpande S, Bhatia T, Nimgaonkar VL, Thelma BK. Molecular genetics of schizophrenia: past, present and future. J Biosci 2002;27:35-52

11. Ozcan ME. Human leukocyte antigen DR1 in Japanese and Turkish patients with schizophrenia. Prog. Neuropsychopharmacol. Biol Psychiatry 2006;30:423-8.

12. Kadasah S, Arfin M, Tariq M. HL A-DRB1 association with schizophrenia in Saudi Arabian patients. Int. J. Psychiatry Clin. Pract 2011; 15:112-7.

13. Chowdari KV, Xu K, Zhang F, Ma C, Li T, Xie BY, *et al.* Immune related genetic polymorphisms and schizophrenia among the Chinese. Hum Immunol 2001;62:714-24.

14. Haider MZ, Zahid MA, Dalal HN, Razik MA. Human leukocyte antigen (HL A) DRB1 alleles in Kuwaiti Arabs with schizophrenia. Am J Med Genet 2000;96:870-2.

15. Nimgaonkar VL, Rudert WA, Zhang X, Tsoi WF, Trucco M, Saha N. Further evidence for an association between schizophrenia and the HL A DQB1 gene locus. Schizophr Res 1995;18:43-9.

16. Nimgaonkar VL, Rudert WA, Zhang X, Trucco M, Ganguli R. Negative association of schizophrenia with HL A DQB1*0602: evidence from a second African-American cohort. Schizophr Res 1997;23:81-6.

17.Al-Mamari F, Al-Shirawi A, Banodkar D, Al-Hashmi S, Al-Yahyaae F, Varghese M, Raeburn J. HLA Antigens in Omani Psoriasis Vulgaris Patients. Oman Med J. 2009 Jan;24(1):27-9. doi: 10.5001/omj.2009.7. PMID: 22303505; PMCID: PMC3269622.

18. Al-Balushi M, Al-Badi S, Al-Yaarubi S, Al-Riyami H, Al-Shidhani A, Al-Hinai S, Alshirawi A, Hasson S, Said E, Al-Jabri A, Al Ansari A. The Association of Human Leukocyte Antigens Complex with Type 1 Diabetes in the Omani Population. Sultan Qaboos Univ Med J. 2023 Feb;23(1):68-75. doi: 10.18295/squmj.2.2022.016. Epub 2023 Feb 23. PMID: 36865417; PMCID: PMC9974035.

19. AL-Eitan LN, Alghamdi MA, Al Momani RO, Aljamal HA, Elsy B, Mohammed HM, Abdalla AM. Genetic Association between Interleukin Genes and Alopecia Areata in Jordanian Patients. OMAN MEDICAL JOURNAL 2022; 37 (5): E421

20. Nassar MY, Al-Shamahy HA, Masood HA. The Association between Human Leukocyte Antigens and hypertensive End-Stage Renal Failure among Yemeni Patients. .Sultan Qaboos Univ Med J. 2015; 15(2):e241-9. Epub 2015 May 28.PMID: 26052458

21. Nassar MY, Al-Shamahy HA, Al-Samawi AS, Abu Asba NW, El-Nono IH, Masood HA. Human Leukocyte Antigen Class I and II Variants in Yemeni Patients with Chronic Renal Failure. Iran J Immunol. 2017;14(3):240-249. PMID: 28919587.

22. Al-dossary OAI, Al-Kholani AIM, AL-Haddad KA, Al-Najhi MMA, Al-Shamahy HA, Al-adhami IAA, Aldhorae K. Interleukin-1β levels in the human gingival sulcus: Rates and factors affecting its levels in healthy subjects. Universal J Pharm Res 2022; 7(5):42-48. https://doi.org/10.22270/ujpr.v7i5.838

23. Al-Mansor MI, Al-Moyed KAA, Al-Shehari MM, Al-Shamahy HA, Al-gunaid EA, Al-Haddad AM. Association of epstein-barr virus with systemic lupus erythematosus by limited materials: Patient characteristics and clinical manifestations in Yemen. Universal J Pharm Res 2022; 7(5):49-56. https://doi.org/10.22270/ujpr.v7i5.839

24. Akaho R, Matsushita I, Narita K, Okazaki Y, Okabe Y, Matsushita M et al. Support for an association between HL A-DR1 and schizophrenia in the Japanese population. Am J Med Genet 2000; 96:725-7.

25. Ozcan ME, Taskin R, Banoglu R, Babacan M, Tuncer E. HL A antigens in schizophrenia and mood disorders. Biol Psychiatry 1996;39:891-5.

26. Nimgaonkar VL, Ganguli R, Rudert WA, Vavassori C, Rabin BS, Trucco M. A negative association of chizophrenia with an allele of the HL A DQB1 gene among African-Americans. Schizophr Res 1992;8:199-209.

27. Jönsson EG, Zhang F, Nimgaonkar VL, Rudert WA, Sedvall GC. Lack of association between schizophrenia and HL A DQB1 alleles in a Swedish sample. Schizophr Res 1998;29:293-6.

28. Cazzullo CL , Smeraldi E, Penati G. The leucocyte antigenic system HL A as a possible genetic marker of schizophrenia. Br J Psychiatry 1974;125:25-7.

29. Roitt IM. Essential immunology. 8th edn. Blackwell Scientific Publications, Oxford, 1991.

30. Steiner J, Bielau H, Brisch R, Danos P, Ullrich O, Marwin C, et al. Immunological aspects in the neurobiology of suicide: Elevated microglial density in schizophrenia and depression is associated with suicide. Journal of psychiatric research 2008;42:151-7.

31. Kirch DG. Infection and autoimmunity as etiologic factors in schizophrenia: a review and reappraisal. Schizophr Bull 1993;19:355-70.

32. Narita K, Sasaki T, Akaho R, Okazaki Y, Kusumi I, Kato T, *et al*. Human leukocyte antigen and season of birth in Japanese patients with schizophrenia. Am. J. Psychiatry 2000;157:1173-5.