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ORIGINAL ARTICLE

Prevalence of HLA-DQ among Patients with *H. Pylori* and cytotoxic-associated gene (Cag A)

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ABSTRACT

Background: *Helicobacter pylori is an important intestinal bacterium associated with gastritis, peptic ulcer disease, and gastric cancer. Antibodies produced against its cytotoxin-binding gene A (CagA) are protective. The host immunological response to H. pylori antigens may be significantly influenced by human leukocyte antigens.* ***Objective:*** *This study was designed to investigate the relation between HLA-DQ genotypes and H. pylori* ***Methodology:*** *One hundred fifty patients have H. pylori and one hundred healthy. H. pylori infection was determined by urea breath test (UBT). Serum concentrations of anti-Cag A IgG were analyzed by ELISA method and HLA-DQ genotypes were analyzed by SSP-PCR.* ***Results:*** *The study showed that patients aged 25-34 years were the most susceptible age group to H. pylori infection. Furthermore, the current study showed a higher incidence of H. pylori infection among females (63.33%), while 36.66% of males were infected with H. pylori. The current study also showed that approximately 72% (48%) of the total number of H. pylori patients were CagA positive (t = 45.00, p = 0.0001). Furthermore, the current study showed that when comparing H. pylori -positive patients with healthy controls, we detected a significantly higher frequency of the HLA-DQA1*05:01 allele (p = 0.0001). The prevalence of the HLA-DQB1*05:02 allele was also found to be not statistically significant in H. pylori patients compared to healthy individuals (P = 0.895).* ***Conclusion:*** *The study showed no significant correlation between the HLA-DQB1*0502 genotype and H. pylori infection; however, HLA-DQA1*0501 may make patients more susceptible to superficial gastritis.*

INTRODUCTION

H. pylori affects around half of the world's population and colonizes the stomach mucosa[1]. Its prevalence is influenced by socioeconomic variables, urbanization, access to clean water, and sanitation[2]. The infection usually contracted in early childhood by oral-oral or fecal-oral pathways, the illness normally lasts a lifetime and is seldom cleared on its own[3]. The most common gastritis in the world is caused by the bacterium *H. pylori*, which is classified as a class I carcinogen[4], it's responsible for up to 90% of stomach cancer[5]. CagA is one of the main virulence factors of *H. pylori* and is associated with severe inflammation and malignant alterations in the stomach lining[6]. Oncoproteins: CagA-positive strains are linked to stomach adenocarcinoma, precancerous lesions, and peptic ulcers[7].

HLA gene variants range among ethnic groups, affecting susceptibility to certain diseases. HLA class II genes, in particular, have been regularly examined for their connection with *H. pylori* infections[8]. The link between *H. pylori* and HLA involves both genetic predisposition and immunological response: some HLA alleles enhance the risk of *H. pylori*-related illnesses such as peptic ulcers and stomach cancer, while others may provide protection. The degree of the inflammatory response is also influenced by these HLA polymorphisms, and this in turn influences the likelihood of stomach cancer development. Some HLA alleles may raise the risk of gastric cancer even in the absence of the cagA gene[9]. MHC class I or II molecules are usually involved in the immune response to bacterial infections, depending on whether the infection is intracellular or extracellular[10]. Studies have demonstrated that *H. pylori's* attachment to gastric epithelial cells that express particular HLA molecules can cause apoptosis to varied degrees[11]. Additionally, host HLA polymorphisms contribute to an increased risk of gastric cancer, particularly when virulent strains of *H. pylori*, like those that include the CagA protein, enhance inflammation. Certain HLA alleles may provide host peptides that the CagA protein mimics, causing immunological reactions that may result in persistent gastritis or even extragastric disorders[12].

Additionally, HLA gene polymorphisms have been linked to the emergence of gastrointestinal disorders, along with other variables like age, gender, and the presence or absence of an *H. pylori* infection, which makes them prospective biomarkers for the early

diagnosis of gastric cancer[13]. Clinical results can be impacted by the genetic variance in HLA genes, which can alter the intensity of immune responses[14]. HLA molecules are crucial for presenting foreign antigens to CD4+ T helper cells, which aid in the removal of infections[15].The aim of this study to investigate the relation between HLA-DQ genotypes and *H. pylori*.

METHODOLOGY

Sample collection:

A study of case-control design included 250 cases (150 patients and 100 healthy controls). The samples were collected during a period extending from September 2024 to January 2025 from the Center of Gastrointestinal Disease in Nasiriyah city, southern Iraq**.** Five ml of blood were collected from patients with gastric disease. Blood samples were divided into two parts: 2 ml of whole blood were placed in a tube (EDTA) for use in complete blood count (CBC) and genomic DNA extraction, while the remaining 3 ml of blood were placed in a gel tube and allowed to clot for about 15-30 minutes at room temperature. Serum was separated by centrifugation at 3000 rpm for 5 minutes for immunological studies (CagA IgG); the samples were stored at -20°C.

Cag A ELISA test:

Serum samples were collected and frozen at -20°C until ELISA analysis. Serum concentrations of anti-CagA IgG (human IgG raised against the CagA protein of *H. pylori*) were analyzed by the ELISA method. ELISA steps were followed according to the manufacturer's protocol written in the kit insert (Human Anti-Cytotoxin-Associated Protein Antibody IgG (Cag A-IgG) Kit No: CE715124B25 Sunlog, China).

DNA extraction:

Recovered DNA from every sample using the Promega DNA extraction kit (Genomic DNA Kit). in accordance with the manufacturer's suggested procedure. The purified DNA was kept at -20°C until it was examined further.

PCR amplification:

A conventional PCR assay was used for HLADQA1 and HLADQB1 genotypes. The PCR conditions used for HLA gene amplification were as follows: an initial denaturation at 95°C for 1 minute, followed by 35 cycles of 30 seconds at 95 °C, annealing at 55°C for 30 seconds, extension at 72°C for 30 seconds, and a final extension at 72°C for 5 minutes. Bands of the expected size from the PCR assay were excised from 2.5-gram agarose gels, and DNA was purified through filter tips.

Statistical Analysis:

The samples underwent statistical analysis according to the Statistical Package for the Social Sciences (SPSS). Chi square (x2),T test and p-value indicated a significant level between the samples.

Ethical consideration:

The current investigation was carried out in compliance with the Declaration of Helsinki's ethical guidelines. Before taking a sample, the patient's verbal and analytical consent was obtained. A local Ethics Committee examined and approved the study protocol, subject information, and permission during the period extended from September 2024 to January (2025) in accordance with document number199/2024.

RESULTS

The ages of patients with *H. pylori* infection ranged from 15 to 70 years. The results shown in the table (1) indicate that there was no significant difference in relation to age to *H.pylori* infection between controls and patients (*p*-value= 0.706) and show the highest rate (41.33%) of *H. pylori* infection among the patients age range between 25 and 34 years old, while the lowest rate (1.33%) of infection was found among patients with age > 65 years old.

Table 1: Frequency age of patient with *H. pylori* and controls

Age groups (years)	Patients No. %	Controls No. %
15-24	33 (22%)	23(23%)
25-34	62 (41.33%)	33(33%)
35-44	30 (20%)	21(21%)
45-54	14 (9.33%)	15(15%)
55-64	9 (6%)	7(7%)
> 65	2 (1.33%)	1(1%)
Total	150	100

X^2 = 2.96 df=5 *p*-value= 0.706
(significant difference P≤ 0.05**)**

Studying the distribution of gastritis patients and controls according to sex. The results showed no significant difference in relation to sex to *H. pylori* infection between controls and patients (x^2 = 0.006, *p*-value = 0.9361), and the study showed a high rate (63.33%) of *H. pylori* infection was among females while (36.66%) of males have *H .pylori*.

Table 2: Frequency sex of patient with *H. pylori* and controls

Sex	Patients No. (%)	Controls No. (%)
Male	55 (36.66%)	38(38%)
Female	95 (63.33%)	62(62%)
Total	150	100

X^2 = 0.006 df =1 *p*-value=0.9361
(significant difference P≤ 0.05**)**

The current study showed the proportion of CagA antibodies in which a significant difference was found: 48% (72 out of 150) of patients were positive for CagA compared to 0% in the control group (P = 0.0001). The result is shown in table 3.

Table 3: Distribution of anti Cag A among patients with H. pylori

Cag A	Patients (%)	Controls (%)	Level of anti-cag A(IgG) mean± SD
Anti Cag A IgG (+)	72 (48%)	0 (0%)	1.117±0.18
Anti Cag A IgG (-)	78 (52%)	100 (100%)	0.161±0.01
Total	150	100	----

t = 45.00 *p*-value = 0.0001 (significant difference P≤ 0.05**)**

The present study showed significant increasing in the frequency of HLA-DQA1*0501 allele among patients with *H.pylori* 88(58.56%) compared to control group (39%), but showed non-significant increase in the frequency of HLA-DQB1*0502 allele among patients with *H.pylori* 29 (19.33%) compared to control group (28%) as listed in table 4.

Table 4: Frequency of HLA-DQ alleles among patients with *H. pylori* and control

HLA-DQ	NO. Patients	NO. Controls	*p*-value	X2
HLA-DQA1*05:01	88 (58.56%)	39 (39%)	0.0001	18.91
HLA-DQB1*05:02	29 (19.33%)	28 (28%)	0.895	0.018

p-value significant difference less than 0.05

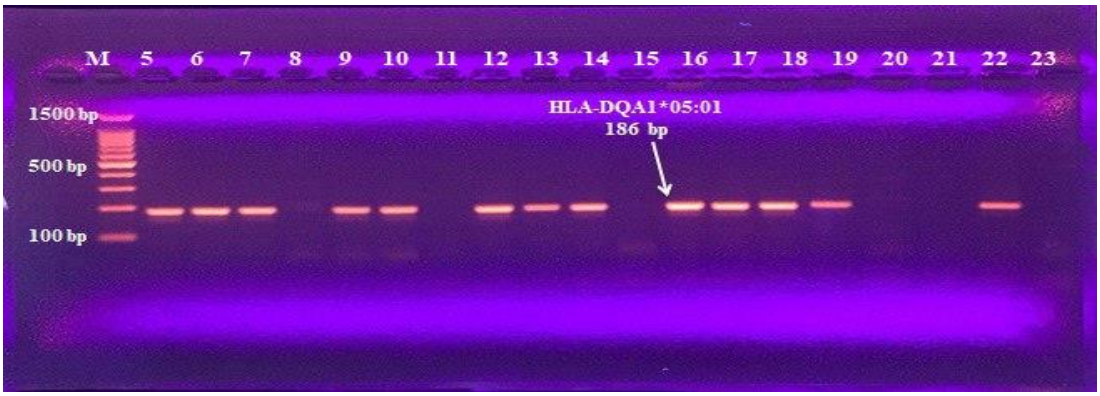

Fig. 1: Gel electrophoresis amplified DNA(HLA-DQA1*05:01)

DISCUSSION

H. pylori affects around half of the world's population and colonizes the stomach[1].Cag A, is a major virulence component of *Helicobacter pylori*[16], is also a highly antigenic protein and is associated with a prominent inflammatory response due to the induction of interleukin-8 (IL-8) production[17]. The pathophysiology of *H. pylori* gastritis involves a complex interaction between bacterial virulence factors and host immune responses. This interaction disrupts the gastric mucosal barrier and leads to chronic inflammation[18].The human leukocyte antigen (HLA) system is a group of genes which are essential for presenting antigens (bacterial proteins) to T cells, initiating an immune response[19]. The effectiveness of this presentation influences how well the immune system controls the infection. We hypothesized that certain HLA alleles are associated with increased susceptibility or protection from *H. pylori* infection.

The present study include 150 patients indicated having *H.pylori*, and 100 were healthy. the aged (25-34) patients appeared to be more likely to have *H. pylori* infection (41.33%), while the aged group of > 65 years old showed the lowest percentage of *H. pylori* infection (1.33%).

The current study agrees with a study of Al-Ezzy[20] who found people aged 24-41 years old are the most likely to be infected with H. *pylori,* and the lowest is in the age >68 years old. A recent study conducted in Baghdad City by Albadri[21]**,** revealed the mean age 21-41 years old was more likely to H. pylori infection. This may be due to more exposure to this infection[22].

The present study a high significant of prevalence *H. pylori* among females and males. The study agrees with a study achieved by Majeed[23] in Erbil city that showed high positivity rate of females (59.72%) and low positivity of males (43.75%). The hormonal variation between the two genders may explain these results or may be related to social reasons that females are more concerned with food preparation than males and spend more time in the kitchen[24].

Based on whether anti-Cag A IgG antibodies were present or not, the distribution of the cag A gene among *H. pylori* patients; 72 individuals (48%) tested positive for Cag A. According to this research, the greater antibody levels in the positive group indicate that the presence of the Cag A gene in *H. pylori* is linked to a robust immune response. The findings might suggest that Cag A-positive *H. pylori* strains are more virulent, as they are known to elicit a stronger immune response. The present study agrees with a study in Baghdad City, Iraq (2013), that shows an increase in Cag A among patients (39.22%)[25]. Also the results agree with the study by Abu-Taleb[26], which found the prevalence of the Cag A gene (57.4%) among patients with *H. pylori*, and disagree with the study of Al-Sabary[27], who found a higher prevalence, with 70% of patients testing positive for Cag A. This disparity could be the result of different approaches to identifying Cag A in *H. pylori* infections, geographic variables, or variances in the populations under study.

The present study also showed a significant increase in the frequency of the HLA-DQBA1*05:01 gene in 88 patients, representing (58.56%) of all patients, in comparison with (39%) for the control group (P = 0.0001). In contrast, the HLA-DB1*05:02 gene did not show a significant difference, as it was found in 29 patients (19.33%) and (28%) For all control groups (P = 0.895)

The current study investigated the association between patients with *H. pylori* and the HLA-DQA1 allele. Individuals carrying HLA-DQA1*05:01 genotypes were noted to be at a significantly greater risk for developing gastritis with *H. pylori*. Our study is in agreement with the results of Al-Ammar et al[28], that showed an increased frequency of the HLA-DQA1*05:01 allele in the patients with positive *H. pylori* tests (68.85%) when compared to patients with negative *H. pylori* tests (46.15%). Another study by Herrera-Goepfert et al[29] in Mexico found significant increases in frequencies of the HLA-DQA1*05:01 allele in the patients with positive *H. pylori* (p-value = 0.0005), the HLA-DQA1*05:01 allele was found at higher frequencies in individuals with *H. pylori* CagA-positive serology compared to *H. pylori* CagA-negative individuals and healthy controls.

Scientists believe that in the Mexican Mestizo population, the HLA-DQ locus might play a special role in causing diffuse-type stomach cancer and chronic gastritis related to *Helicobacter pylori.* Their findings are consistent with the literature, which shows that environmental factors and the gastric milieu trigger the genetic constitution through the HLA-DQ locus, affecting disease mechanisms and clinical and pathologic outcomes[29].

The current study disagrees with the study of Zhao[30], in the Indonesian population, that found that HLA-DQA1*0501 might protect in the presence of *H. pylori*, as it was associated with a specific immune response that limits the long-term effects of the infection. HLA-DQ5 has been also reported in association with atrophy and intestinal metaplasia of the gastric mucosa[31]. Other associations between HLA-DQA locus and gastric diseases have been described by Azuma et al[32] who found a protective effect of the HLA-DQA1*0102 allele against *H. pylori* infection and intestinal-type adenocarcinoma, as well as a high susceptibility for *H pylori* gastritis and duodenal ulcer in patients carrying the HLA-DQA1*0301 allele[33]. These discrepancy findings highlight the complex role of host genetics in the pathogenesis of *H. pylori*-related gastric conditions.

For HLA-DQB1 genotyping the results showed there is no correlation between HLA-DQB1*05:02 and *H. pylori*. This agreement is with the study of Al-Ammar et al[28] in Basra City, Iraq, that found non-significant HLA-DQB*1 between patients with *H. pylori* and healthy patients. The present study agrees with the study of Zhao[30] to study the relationship between host HLA-DQ variation and the prevalence of *H. pylori* in an Indonesian population, that show Individuals carrying the DQB1*0401 gene were found to be more susceptible to *H. pylori* infection than those carrying the DQB1*0502 gene. HLA-D antigenic peptides significantly influence immune responses to pathogens, such as bacteria and toxins[34].

The HLA-D region accounts for more than 50% of inheritance in hosts[35].It also seems to be responsible for the variation in how different people react to different exogenous antigens, indicating that hosts' reactions to the same organism can vary and that people with different HLA types have different immune responses. Differences in HLA-DQ genes and how likely someone is to get infected or resist *Helicobacter pylori* might be affected by specific pieces of proteins on T cells[29]. In China, there have been reports of possible correlations between *Helicobacter pylori* infection and HLA-DQ genotypes[36].Other host factors, such as oncogenes or suppressor genes[37],and genetic polymorphisms linked to bacterial infection and inflammatory cytokines, which are known to be linked to *Helicobacter pylori* infection and related lesions/diseases, such as gastritis, gastric/duodenal ulcers, and gastric cancer[38] ,seem to be significant in addition to the HLA-DQ genes .Host, bacterial, and environmental/vector variables combine to generate bacterial infections, which is why H. pylori strains and genotypes are significant.

CONCLUSION

Gastritis may be influenced by genetic factors. The study found no significant correlation between the HLA-DQB1*0502 genotype and H. pylori infection; however, HLA-DQA1*0501 may make patients more susceptible to superficial gastritis.

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Author contribution

Alaa and Talib conceptualized the project, conducted the experimental procedures, drafted the initial articles, and conducted the statistical analysis. Alaa and Talib managed the data collection. All authors collaborated on writing, reviewing, and editing the material. The authors have reviewed and approved the final manuscript.

Conflicts of interests

no conflicts of interest occur

Competing interests: The author(s) declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article. This manuscript has not been previously published and is not under consideration in another journal.

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