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Association of Celiac Disease and *H. pylori* Infection with ATG5 Polymorphism and Interleukin-33

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Abstract

Background: Celiac disease (CD) is an inflammatory small intestine autoimmune disease. The study aims to investigate the association and the detection of ATG5 polymorphism between celiac disease (CD) and *H. pylori* infection, and the association with Interleukin-33 (IL-33).

Methods: The study groups included patients from Iraq, ages 4 to 35. Two primary patient groups were created: sixteen had positive *H. pylori* and celiac disease, and thirty had positive CD and negative *H. pylori* disease. The levels of tissue transglutaminase IgA (TTG IgA), *H. pylori* IgG, and IL-33 were measured using the ELISA method. The primers were amplified using PCR.

Results: With celiac disease, the patient group's TTG IgA levels increased dramatically. The test also showed significant variations (P=0.054) in the *H. pylori* IgG levels between the patient and control groups. The *H. pylori* seropositivity test showed a statistically significant difference (p ⩽0.033) between seropositive and seronegative individuals, while the patient group's IL-33 levels did not significantly differ (P ⩽0.299) from the control group.

Conclusions: Our results showed that CD is more common in women and occurs in the age range of 24-35 years. It also showed that the mutant variant of ATG5 is associated with CD, and the significance of *H. pylori* IgG serum levels in the patient group may indicate that the bacteria involved in CD. Furthermore, *H. pylori* infection is more strongly linked to serum IL-33 levels than CD.

Introduction

CD is a chronic autoimmune disorder triggered by gluten in genetically predisposed individuals, specifically those with HLA DQ2 and/or DQ8 alleles [1-3]. CD is the most common inflammatory autoimmune disease affecting the intestines. Recent epidemiological research [3,4,5] shows that prevalence rates in emerging economies, especially in Africa, the Middle East, and India, are comparable to those in Europe. The current diagnosis guidelines for CD include demonstrating enteropathy in small intestine biopsies, determining the specific antibodies that are circulating, and doing historical investigations [1, 6]. *Helicobacter pylori* (*H. pylori*), a common stomach infection bacterium, is thought to infect over half of the world's population [7]. Infants are more likely to get *H. pylori* infection, which typically lasts until treatment. Although it can cause iron deficiency anemia, peptic ulcer disease, and chronic immunological thrombocytopenic purpura, the majority of infected children and adolescents do not exhibit any symptoms [8]. 95% specificity and sensitivity can be achieved by histologically identifying *H. pylori* in stomach tissues; however, suitable sampling and interpretation are required. A biological process known as autophagy governs the majority of cells. Numerous illnesses, including liver disease, heart disease, inflammatory and neurological disorders, and cancer, are associated with its process. Several cytokines have a significant impact on autophagy as a result of inflammatory and immunological reactions [9]. Autophagy, regulated by ATG genes like ATG5, is crucial for cellular homeostasis and is implicated in various diseases, including CD [10,11]. ATG5 polymorphisms have been linked to multiple autoimmune disorders [12,13].

IL-33 is a cytokine that promotes Th2 responses and is released by damaged cells, playing a significant role in immune regulation and potentially in CD pathogenesis [14,15].

The study aimed to investigate the association between CD and *H. pylori* infection. In addition, find out the difference in the levels of antibodies against *H. pylori* in patients and investigating the association of *H. pylori* IgG with CD diagnostic markers (TTG IgA). Furthermore, to study the genetic polymorphism of ATG5 in celiac patients in the presence or absence of *H. pylori* infection. Finally, to investigate the association of IL-33 with CD diagnostic markers (TTG IgA) and *H. pylori infection* (*H. pylori* IgG).

Methods

Sample size and study groups

From January 28, 2021, to September 1, 2021, 70 participants—46 females and 24 males—were divided into study groups. The participants' ages ranged from 4 to 36 years old. The patients provided some information by answering a questionnaire that the researchers had created, which included the following information: personal information, presence of autoimmune diseases, inflammatory diseases, antibiotics intake within the last two weeks, gastric treatment, family history, histological test, and the using of nonsteroidal anti-inflammatory drugs (NSAIDs): aspirin, naproxen, indomethacin, etc. A total of 46 CD patients who had been diagnosed by specialists at Iraqi hospitals were included in the study, along with 24 visitors to the hospital who appeared healthy on the outside (control group).

Inclusion criteria, exclusion criteria, and limitations

This cross-sectional study included patients with celiac disease of any age or gender, with or without *H. pylori* infection. Patients with inflammatory or autoimmune illnesses, those who had used antibiotics during the previous two weeks and those who used NSAIDs, proton pump inhibitors, or other medications that targeted the stomach were not included in the study.

The period of coronavirus restrictions presented significant limitations for our research. We faced a low number of celiac cases referred to the hospitals, as well as curfews and travel restrictions that made it difficult to recruit participants. Additionally, taking blood samples from apparently healthy individuals during the coronavirus pandemic was also challenging, and contributed to a lower overall sample size. Notwithstanding these drawbacks, we think that our research offers insightful information about the risk factors and prevalence of CD in our community. We have taken steps to address the lower sample size, including conducting sensitivity analyses to ensure that our results are robust and providing detailed information on the recruitment challenges faced during the study.

Specimen's collection

Five to ten milliliters of blood were drawn from each patient. For the Polymerase Chain Reaction (PCR) test, each sample was split into two tubes: an EDTA tube and a blank tube. The blank tube was allowed to coagulate before the serum was separated using a 10-minute centrifugation. In addition, the serum was divided among three Eppendorf tubes and kept cold (- 20 °C) until the ELISA analyses were completed. On the same day, the leftover blood is used for the *H. pylori* rapid test.

Ethical consideration

Patients or their families provided ethical authorization, which was received from the Medical City Department and the Research Committee of the

Baghdad Health (Al-Rusafa Department). The purpose of collecting the sample was explained to the patients.

ELISA analysis

The analysis and determinations of TTG IgA (DE7720, Demeditec Diagnostics GmbH, Germany), *H. pylori* IgG (0322 REF HPG, INSCAGG, CE, Dia. Pro Diagnostic Bio probe, SrI, Italy), and IL-33 (SEB980Ra, Cloud Clone Corporation, Belgium) were done by kit protocols of ELISA technique.

Gene detection and sequencing

After amplification, the data was analyzed using the generous program to ascertain the sequencing variance between samples of a particular gene (ATG-5). DNA extraction, PCR amplification, sequencing, and assembly are all steps in the process. The ABIO pure Extraction technique was followed when extracting DNA.

Lyophilized primers rs510432-F and rs510432-R (detailed below) (Macrogen Company, Korea) were dissolved in nuclease-free distilled water to obtain 100 pmol/µl of stock solution. The primer working solution was prepared by adding 10 µl of the stock solution to 90 ml of nuclease-free distilled water to have a solution of 10 pmol/µl. PCR amplification (Thermal Cycler, Bio-Rad, USA) and thermal cycling were performed as illustrated by instructions and protocol.

Primer name	Sequence
rs510432-F	5′-TGTAAAACGACGGCCAGTTTAGTCCAACTCCAAGAAGA-3′
rs510432-R	5′-CAGGAAACAGCTATGACCAAACCTCTCCAAGTTCATAG-3′

The automated DNA sequencer (ABI3730XL, Macrogen Corporation, Korea) was used to perform Sanger sequencing on the PCR products after they were transmitted to Macrogen Corporation Company. Geneious software was used to examine the results that were acquired.

Data analysis

The statistical program SPSS (Version 28) was used for statistical analysis. Based on its nature and type, the raw data was categorized. Various statistical tests, both parametric and non-parametric, were employed based on how well the requirements were met.

Results

Study group samples for infected CD

There were 70 samples in total; 46 patients (65.7%) and 24 control subjects (34.3%) made up the patient group. The study's focus was on the age ranges of 5 to 35 years old, with a total of 23 (32.9) men and 47 (67.1%) females in this age range (Table 1).

Age groups

The study's cases were divided into three age groups (G): G1 (ages 5 to 14), G2 (15 to 24), and G3 (ages 25 to 35). According to Table 1, the most common infection among patients was G3, with G3 = 19 (8.74%) being greater than G1 = 16 (7.36%) and G2 = 11 (5.06%).

Celiac disease

The ELISA test was used to perform diagnostic tests for CD. The study's findings show that the patients' mean ± SD serum TTG IgA concentration was 23.67389± 6.658566 U/ml, compared to 1.86750± 1.191908 U/ml in the control group (Table 2). When compared to the control group's serum levels, the TTG-IgA levels in the patient's serum were statistically considerably higher (P<0.001) in the current study.

H. pylori seropositivity

The results of the study group's *H. pylori* seropositivity (positive and negative) patients were 28 (60.9%), and 18 (39.1%), respectively, compared to the control group's 11 (45.8%) and 13 (54.2%). No significant differences were found in either the Pearson Chi-Square or Fisher's Exact Tests (Table 1).

Interleukin-33

The serum IL-33 concentrations in the patients (1.00727±2.445775 pg/ml) and the control group (0.73347±.904229 pg/ml) are shown in Table 2 as the mean ± SD.

ATG5 polymorphism analysis

Twenty-one samples—nine from the patient's group and two from the control group—were used in the genetic polymorphism study. Seven have wild-type AA and fourteen have mutant-type AG according to the data of rs510432. Significant findings (p=0.035) are shown in Figures 1 and 2 and Table 1. Patients of the wild and mutant types (26.3% and 73.7%, respectively), as well as the control wild and mutant types (100.0% and 0.0%, respectively), comprise the study group.

Correlation between study variables

The research group and gender, age, and SNP showed a statistically significant low negative connection (p-value = -0.328, 0.006; -0.305, 0.028; -0.459, 0.036) (Table 3).

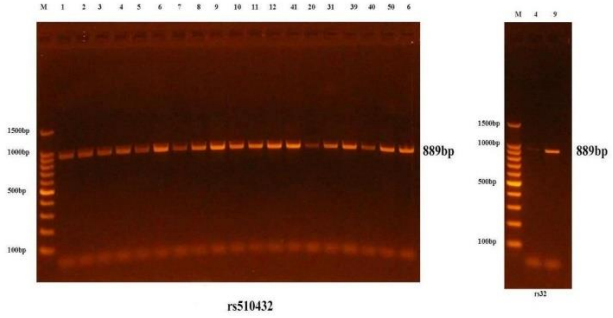

Figure 1: Results of amplified rs510432 region of DNA samples, and the separation using 1.5% agarose gel electrophoresis with ethidium bromide stain. M: Ladder marker with 100 bps.

Variable	Study groups									FE
	Patients			Control			Total			
	Count	PSG(%)	PG(%)	Count	PSG(%)	PG(%)	Count	PSG(%)	PG(%)	
Gender										
Male	10	21.7	43.5	13	54.2	56.5	23	32.9	100	0.008
Female	36	78.3	76.6	11	45.5	23.4	47	67.1	100	
Total	46	100	65.7	24	100	34.3	70	100	100	
PChi-S p-value	0.006									
Variable	Patients			Control			Total			FE
	Count	PSG(%)	PHpS(%)	Count	PSG(%)	PHpS(%)	Count	PSG(%)	PHpS(%)	
H. pylori										
Positive	28	60.9	71.8	11	45.8	28.2	39	55.7	100	0.312
Negative	18	39.1	58.1	13	54.2	41.9	31	44.3	100	
Total	46	100	65.7	24	100	34.3	70	100	100	
PChi-S p-value	0.229									
Variable	Patients			Control			Total			
	Count	PSG(%)	PSNP(%)	Count	PSG(%)	PSNP(%)	Count	PSG(%)	PSNP(%)	
SNP										
Wild	5	26.3	71.4	2	100	28.6	7	33.3	100	
Mutant	14	73.7	100	0	0	0	14	66.7	100	
Total	19	100	90.5	2	100	9.5	21	100	100	
PChi-S p-value	0.035									

Pearson Chi-Square (PChi-S); Percent within Study Group (PSG); Percent within Gender (PG). Pearson Chi-Square (PChi-S); Percent within Study Group (PSG); Percent within *H. pylori* Seropositivity (PHpS). Percent within Study Group (PSG); Percent within SNP (PSNP). Fisher's exact tests (FE).

Table 1: Chi-square and Fisher's exact tests for study groups.

T-test	Study Groups	N	Mean	Std.Dev.	Std.Er.M.	P-value
TTG IgA	Patients	46	23.67389	6.658566	1.569439	<0.001
	Control	24	1.86750	1.191908	0.243297	
IL-33	Patients	46	1.00727	2.445775	0.402083	0.299
	Control	24	0.73347	0.904229	0.207444	

Standard Deviation (Std.Dev.); Standard Error of Mean (Std.Er.M); Number (N).

Table 2: The independent T-test for variations in IL-33 levels and Anti-TTG antibodies between research groups.

Variable	Correlation	Gender	Age	TTG IgA	Hp.IgG	IL-33	Hp.Ser	SNP
Study Groups	Pearson Correlation	-0.328**	-0.305*	-0.825**	-0.034	0.127	0.144	0.459*
	PCS.2	0.006	0.028	0.000	0.779	0.299	0.235	0.036
Gender	Pearson Correlation		0.141	0.087	0.039	0.106	0.073	0.316
	PCS.2		0.320	0.477	0.749	0.385	0.550	0.163
Age	Pearson Correlation			0.028	0.079	-0.099	-0.085	0.135
	PCS.2			0.846	0.578	0.489	0.550	0.592
TTG IgA	Pearson Correlation				0.063	-0.039	0.051	-0.301
	PCS.2				0.609	0.753	0.679	0.185
Hp. IgG	Pearson Correlation					-0.068	-0.859**	0.287
	PCS.2					0.579	0.000	0.208
IL-33	Pearson Correlation						0.128	-0.280
	PCS.2						0.296	0.232
Hp. Ser	Pearson Correlation							-0.357
	PCS.2							0.112

* Correlation is significant at the 0.05 level (2-tailed); ** Correlation is significant at the 0.01 level (2-tailed). *H. pylori* Seropositivity (Hp. Ser); *H. pylori* IgG (Hp. IgG); Pearson Correlation Sig. (2-tailed) (PCS.2).

Table 3: Correlation among study markers.

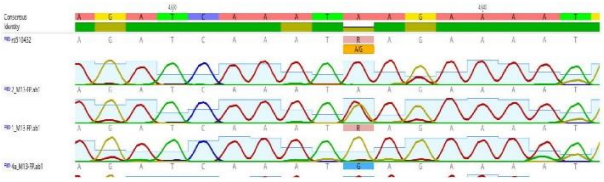

Figure 2: rs510432 SNP analysis by Sanger sequencing. A single "A" peak denoting a homozygous "A" allele. An allele homozygous for G is indicated by a single "G" peak. The A/G heterozygous allele is indicated by the presence of the "A" and "G" peaks.

Discussion

Gluten is a trigger for the disease CD, which is influenced by environmental factors as well as a human genetic predisposition. Less than 2.0% of people in the general population have CD [16]. Within study groups, the proportion of females affected by CD was found to be higher than that of males; in the patients' group, this was 78.3% of the total, whereas, in the control group, this was 45.8% of the total, with males making up 54.2%. These findings are consistent with [17], where the authors noted that the frequency of CD was twice as high in females (68.75%) as it was in males (31.25%) and that the immunoregulation mechanisms linked to varying hormone levels across genders explained this discrepancy. Our results were not in line with the findings of the Seattle Children's Hospital study by Dickerson et al., [18], which reported that 55% of patients were male and 45% were female. The size of the study sample and differences in ethnic groups may be the source of this gender discrepancy in the patients.

Additionally, the age group analysis results agreed with Khatoon et al., [19] study, which found that about 75% of CD patients were at an age less than 40 years old, and the highest percentage of prevalence (11.81%) was the age group between 20 and 30 years old. This finding may be due to the presence of 88.3% of patients who have iron deficiency anemia [17]. However, our findings contradict the findings of the Khan et al., [19] study, which indicates that all positive indicators were detected in patients younger than 15 years old, possibly as a result of their predominantly wheat-based diet.

The results of TTG IgA concentrations are in agreement with Abdullah and Al-Bhawani [20], who observed that there was a higher proportion of TTG IgA patients (38%) as compared to the control group (0.0%). However, the findings of Ertekin et al., [5], who studied 1263 Turkish children on a wheat-based diet, disagree, with the finding that only 11 of the children had positive TTG IgA with seropositivity of 0.87%. There may be differences between our study and earlier research because of the patient sample size, the study population, the groups that were chosen, and the symptoms of the patients.

Antibodies against *H. pylori* in human serum are indicators of infection. Reports from several nations have confirmed the diagnosis of positive *H. pylori* IgG findings with high sensitivity and specificity. Nonetheless, the outcomes vary among nations, particularly between wealthy and poor nations. These discrepancies could result from various ideal cut-off values for IgG levels as opposed to the cut-off established by the supplier of the *H. pylori* antibody serologic test kit. For different populations or subgroups, the manufacturer's optimal cut-off value might not always be appropriate. The manufacturer's recommended IgG cut-off point was 0–5 IU/mL, as per the instructions provided. Significant differences ($p=0.054$) in *H. pylori* IgG were found between the patient and control groups based on statistical analysis and a non-parametric test (Table 1). According to Bayrak et al., [21], there is low evidence of a link ($P<0.01$) between *H. pylori* infection and CD patients. Our results conflict with those of Simondi et al., [22], who found that compared to controls (41%), there was a 36% correlation between CD patients and *H. pylori* and a 19% correlation between CD patients and patients with duodenal intraepithelial lymphocytosis. Our findings indicate that there is no discernible difference between CD patients and controls and those with *H. pylori* infection. However, Obaidat et al., [23] found that there is a significant seroprevalence (88.6%) in the Jordanian population.

When compared to the control group, the serum levels of IL33 in the patients did not differ significantly ($P\leqslant0.299$). This finding is consistent with the findings of Abaas et al., [24], but it is at odds with the findings of López-Casado et al., [25], who found that the serum levels of IL-33 in celiac patients were significantly higher than in the control group ($p=0.05$). A statistically significant difference ($p \leqslant0.033$) was found between seropositive and seronegative participants when IL-33 serum levels were analyzed in connection with *H. pylori* seropositivity (Asymptotic Sig., two-sided test). Our findings were consistent with a prior study that found that patients with peptic ulcers had a considerably higher amount of IL-33 in their serum compared to the uninfected group ($P = 0.001$) [26].

The study of ATG5 polymorphisms revealed that 7 had wild-type AA and 14 had mutant-type AG. Results from a prior study indicated that genotypes (AA+GA) bearing rs510432 allele A were independently linked to cirrhosis compared to chronic hepatitis viral infection without HCC [27]. The ATG5 rs510432 A allele frequency was found to be significantly higher in severe sepsis shock than in mild sepsis in another study [28]. This suggests that the rs510432 G allele, rather than the A allele, within the promoter of the ATG5 gene

influences the progression of sepsis from mild to severe sepsis shock.

Lastly, a modest negative connection was found between the study group and SNP, gender, and age in the correlation analysis of the research variables. A variant in the gene that distinguishes patients from healthy individuals may be the cause of the association between the SNP and the study groups. Furthermore, there was a statistically significant negative connection (Pearson connection, p-value = -0.825, 0.000) between the TTG antibody levels and the research groups. The patients are interacting with the control group in a downward direction.

Our research showed that CD is more common in women and has the highest frequency in the 24- to 35-year-old age range. Our study highlights the significant association of ATG5 polymorphism with CD and suggests that *H. pylori* infection may play a role in CD pathogenesis. Further research into larger sample sizes is warranted to confirm these findings.

Author Contributions

The data collection and experiments were done by Sura Mumtaz. Ahmad Abood and Ansam Atrooz did all the statistical analysis and formulated the ideas, research goals, and aims. Omar Atrooz supervised the research and prepared, revised, and edited the article.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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