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https://doi.org/10.31925/farmacia.2026.3.17 **ORIGINAL ARTICLE**

THE RELATIONSHIP BETWEEN PEPSINOGEN GENE C POLYMORPHISM AND *HELICOBACTER PYLORI* INFECTION IN THE JORDANIAN POPULATION

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Abstract

Helicobacter pylori infection is a major risk factor for gastric diseases, including chronic gastritis and gastric cancer. This case-control study investigated the association between pepsinogen C gene (*PGC*) polymorphisms and *H. pylori* infection susceptibility in 382 Jordanian subjects (239 infected, 143 controls). *PGC* polymorphisms were genotyped using PCR, detecting six alleles: A1 (510 bp), A2 (480 bp), A3/4 (450/460 bp), A5 (400 bp), and A6 (310 bp). Allele A6 was significantly more frequent in infected subjects (46.5%) compared to controls (28.6%) (OR = 1.82, 95% CI: 1.31 - 2.53, p = 0.0004). Under a dominant model, A6 carriers had a significantly higher infection risk (OR = 3.21, 95% CI: 2.01 - 5.12, p < 0.001). Multivariable analysis confirmed that A1/A6 (OR = 2.12, p = 0.015) and A6 (OR = 4.66, p < 0.001) genotypes were associated with increased infection odds. Age ≤ 60 years showed a trend toward increased risk that did not reach statistical significance (OR = 1.94, p = 0.052). These findings suggest that *PGC* polymorphisms, particularly allele A6, may influence *H. pylori* susceptibility in Jordanians, with potential implications for gastric cancer risk stratification.

Rezumat

Infecția cu *Helicobacter pylori* reprezintă un factor de risc pentru afecțiunile gastrice, precum gastrita cronică și cancerul gastric. Acest studiu de tip caz–control a investigat asocierea dintre polimorfismele genei pepsinogenului C (PGC) și susceptibilitatea la infecția cu *H. pylori* la 382 de subiecți iordanieni (239 infectați și 143 din grupul de control). Polimorfismele PGC au fost genotipate prin reacția de polimerizare în lanț (PCR), fiind identificate șase alele: A1 (510 pb), A2 (480 pb), A3/4 (450/460 pb), A5 (400 pb) și A6 (310 pb). Alela A6 a fost semnificativ mai frecventă la subiecții infectați (46,5%) comparativ cu lotul martor (28,6%) (OR = 1,82; IC 95%: 1,31 - 2,53; p = 0,0004). În cadrul unui model dominant, purtătorii alelei A6 au prezentat un risc semnificativ mai mare de infecție (OR = 3,21; IC 95%: 2,01 - 5,12; p < 0,001). Analiza multivariată a confirmat că genotipurile A1/A6 (OR = 2,12; p = 0,015) și A6 (OR = 4,66; p < 0,001) au fost asociate cu o probabilitate crescută de infecție. Vârsta ≤ 60 de ani a evidențiat o tendință de creștere a riscului, care nu a atins semnificație statistică (OR = 1,94; p = 0,052). Aceste rezultate sugerează că polimorfismele genei PGC, în special alela A6, pot influența susceptibilitatea la infecția cu *H. pylori* în populația iordaniană, având posibile implicații în stratificarea riscului de cancer gastric.

Keywords: *Helicobacter pylori*, pepsinogen, *pepsinogen gene C*, gastric cancer

Introduction

Helicobacter pylori (H. pylori) is a Gram-negative, microaerophilic bacterium that infects the epithelial lining of the stomach and invades the mucosa (1). Several gastrointestinal conditions are closely linked to *H. pylori* infection, including peptic ulcers, chronic gastritis, and gastric cancers such as adenocarcinoma and mucosa-associated lymphoid tissue lymphoma (2). Although the rate of *H. pylori* infection has decreased in many countries due to improved living standards, the bacterium remains prevalent, particularly in the Far East. According to regional prevalence estimates from 2015, approximately 4.4 billion individuals globally were affected by *H. pylori*. The highest prevalence rates were observed in Africa (79.1%), Latin America and the Caribbean (63.4%), and Asia (54.7%). Conversely, *H. pylori* prevalence is lowest in Northern America (37.1%) and Oceania (24.4%) (3, 4).

Pepsinogen (PG) is a precursor of pepsin, which is activated in an acidic environment. In humans, there are two groups of pepsinogens: *pepsinogen A (PGA)* and *pepsinogen C (PGC). PGA* is predominantly found in the gastric fundus, while *PGC* is distributed throughout the stomach and proximal duodenum. *Pepsinogen C* protein is secreted by the glands in the antrum,

chief cells in the corpus, and the duodenal bulb (5, 6). *PGC* gene is located on chromosome 6 between regions 6p11 - 6p21.3 (Figure 1) and is expressed in the stomach epithelium as a protein called progastricsin, the precursor of *pepsin C* or gastricsin (7).

In the *PGC* gene, specifically between exons 7 and 8, there are approximately 100 bp insertion/deletion polymorphisms that produce several alleles: 510 bp (A1), 480 bp (A2), 460 bp (A3), 450 bp (A4), 400 bp (A5), and 310 bp (A6) (Figure 1). Previous studies have reported a relationship between polymorphisms in this gene and susceptibility to gastric cancers. In addition, the *PGA/PGC* ratio is a useful marker for *H. pylori*-related corpus-predominant or multifocal atrophy (8, 9).

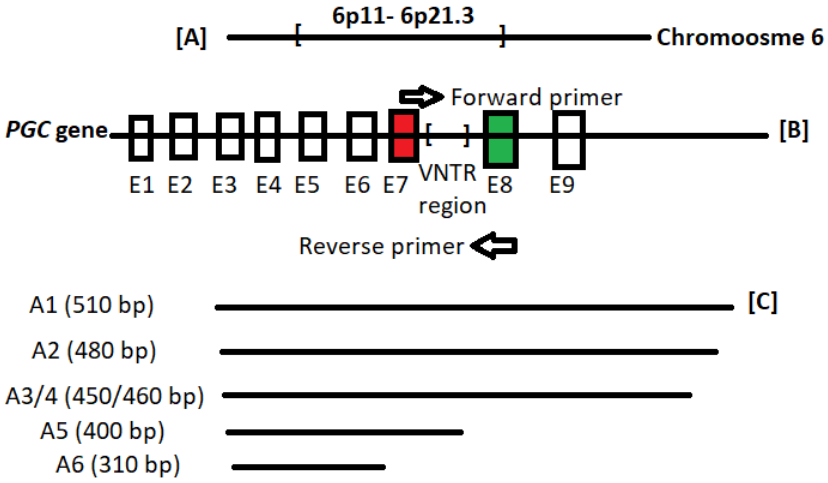

Figure 1.

Schematic representation of the PGC gene polymorphism. (A) Chromosomal location of PGC on 6p11 - 6p21.3. (B) Structure of the PGC gene showing exons (vertical boxes) and the VNTR region between exons 7 and 8. Arrows indicate primer positions for PCR amplification. (C) Allelic variants (A1-A6) resulting from insertion/deletion polymorphisms, with fragment sizes indicated in base pairs (bp)

However, the association between *PGC* gene polymorphism and *H. Pylori* infection has not been investigated among Jordanians. Therefore, the goal of this study was to examine the association between the genetic polymorphism of *PGC* and *H. Pylori* infection in Jordan.

Materials and Methods

This case-control study involved patients with *H. Pylori* infection (n = 239) and controls (n = 143). Subjects with chronic diseases (diabetes, hypertension, heart disease, asthma, chronic pulmonary embolism, hypothyroidism, and stroke) were excluded. Participants were recruited from the outpatient clinics of King Abdullah University Hospital. To determine *H. pylori* infection status, all participants underwent upper gastrointestinal endoscopy. During the procedure, gastric mucosal biopsy samples were obtained and immediately sent for histopathological examination. Concurrently, peripheral blood samples were drawn and centrifuged to obtain serum. The serum samples were then transported to the laboratory and analyzed using a commercial enzyme-linked immunosorbent assay (ELISA) kit to detect *H. pylori*-specific IgG antibodies [R-Biopharm AG, Darmstadt, Germany]. Infection status was definitively determined using a combination of methods to ensure accuracy. Patients were classified as *H. pylori*-positive if they had a positive result from the biopsy specimen (histopathology) and a positive result from serological testing (ELISA IgG).

The assay was performed according to the manufacturer's instructions. The optical density (OD) values were measured at 450 nm, and results were interpreted using the recommended cutoff index (COI) of ≥ 1.1 for positive infection. The kit has been validated with reported sensitivity and specificity of 96% and 93%, respectively, in prior clinical studies.

Ethical approval

The study was approved by the institutional review board (IRB) of The Hashemite University. Informed consent was obtained from all participants after a full explanation of the study objectives, risks/benefits, and procedures. Blood samples were collected in EDTA vacutainer tubes and stored until DNA extraction.

Sociodemographic, clinical, and exposure assessment

Core demographic data included age (collected as a continuous variable and categorized as ≤ 60 *vs*. > 60 years) and biological sex at birth (male/female).

Health and behavioral factors such as smoking status (current/former/never), alcohol consumption (yes/no), and history of chronic diseases (diabetes, hypertension, etc.) were collected *via* self-reported questionnaires. Participants with chronic diseases were excluded from the study.

DNA extraction

DNA was extracted from blood samples using a Zymo Research Kit according to the manufacturer's instructions. Extracted DNA was checked for purity and concentration using spectrophotometric techniques as described previously (10).

PCR amplification

PGC polymorphisms were detected by polymerase chain reaction as outlined in previous research in a Caucasian population (7). The PCR was performed using 1 µM forward primer 5'-AGCCCTAAGCCTC TTTTTGG-3', 1 µM reverse primer 5'-GGCCAGAT CTGCGTGTTTTA-3', 10 µL GoTaq® Green Master Mix from Promega (Madison, WI, USA), and 0.1 µg DNA. The reaction volume was adjusted to 20 µL with deionized H_2O. The Bio-Rad thermal cycler was programmed as follows: 95°C for 5 min for initial denaturation, followed by 35 cycles of denaturation (94°C for 1 min), annealing (55°C for 1 min), and extension (72°C for 1 min). A final extension at 72°C for 7 min was performed.

Genotyping

Amplified DNA fragments were visualized using 3% agarose gel electrophoresis. Genotypes were assigned based on the sizes of amplified PCR fragments: allele 1 (A1: 510 bp), allele 2 (A2: 480 bp), allele 3/4 (A3/4: 450/460 bp), allele 5 (A5: 400 bp), and allele 6 (A6: 310bp) (Figure 2).

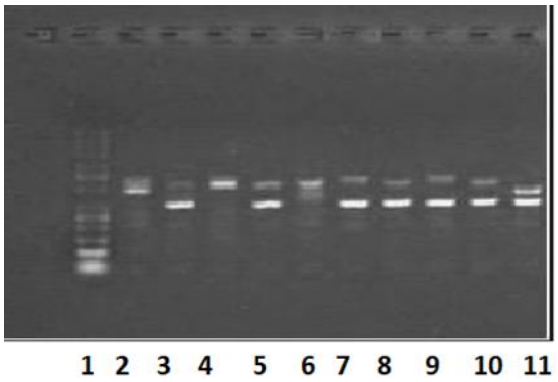

Figure 2.

Analysis of *PGC* polymorphism in an *H. pylori*-positive sample by PCR. Lane 1: 50 bp DNA ladder. Lane 2: A2/5. Lanes (3, 5, 7 - 10): A1/A6. Lanes (4, 6): A6. Lane 11: A3/4. Allele 1 (510 bp), Allele 2 (480 bp), Allele 3/4 (450/460 bp), Allele 5 (400 bp), and Allele 6 (310 bp)

Genotyping quality control

Following PCR amplification and agarose gel visualization, all genotypes were confirmed by two independent investigators blinded to the case/control status. Any discrepancies were resolved by repeat PCR and genotyping.

Statistical analysis

Data was analyzed using IBM SPSS (Statistical Package for the Social Sciences) version 24.0. Descriptive analysis was used to report percentages, frequencies, means, and standard deviations of categorical variables. Variables with $p < 0.25$ in univariate logistic regression were included in a multiple logistic regression model. Adjusted odds ratios and 95% confidence intervals (CIs) were reported. Statistical significance was defined as p-value < 0.05.

Genetic association analysis

Genetic association was evaluated using multiple approaches. First, allele frequencies were compared between cases and controls using chi-square tests, and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for each allele relative to the (A3/4) allele (reference). Second, three genetic models were tested using logistic regression: dominant (presence *vs*. absence of each allele), recessive (homozygosity *vs*. other genotypes), and additive (*per*-allele effect). To assess whether the control population was in Hardy-Weinberg Equilibrium (HWE), we performed chi-square goodness-of-fit tests for each allele system separately. Expected genotype frequencies under HWE were calculated from observed allele frequencies.

Results and Discussion

Hardy-Weinberg equilibrium analysis in controls

Significant deviations from HWE were observed for the allele systems. For the A1/A6 locus (n = 69), the observed genotype distribution (A1/A1 = 0, A1/A6 = 44, A6/A6 = 25) differed significantly from HWE expectations (A1/A1 = 7, A1/A6 = 30, A6/BA6 = 32; $\chi^2 = 15.12$, df = 1, p = 0.0001). For the A2/A5 locus (n = 34), all individuals were heterozygous (A2/A5 = 34), resulting in a marked deviation from the expected distribution of 8.5 A2/A2, 17 A2/A5, and 8.5 A5/A5 ($\chi^2 = 34.0$, df = 1, $p = 5.5 \times 10^{-9}$). Similarly, the A3/A4 locus (n = 40) showed complete heterozygosity (A3/A4 = 40) *vs*. the expected 10 A3/A3, 20 A3/A4, and 10 A4/A4 ($\chi^2 = 40.0$, df = 1, $p = 2.5 \times 10^{-10}$). The consistent absence of homozygous genotypes across these loci warrants careful interpretation. Given the modest size of our control group (n = 143), the observed HWE deviations are most likely attributable to technical factors (*e.g.*, potential under-calling of homozygotes during genotyping) or sampling bias. Although theoretical possibilities such as heterozygote advantage cannot be entirely excluded, these explanations remain speculative. These findings underscore the importance of validating these results in larger, well-powered studies with independent genotyping methods.

Gastric cancer is one of the most common cancers in Jordan. In general, cancer development involves various environmental and genetic factors; a major factor influencing gastric cancer is *H. pylori*. The Jordanian population has shown a high positive rate for *H. pylori*. Studies on *H. pylori* in Jordan are limited,

partly due to the lack of a national screening system (11, 12). Table I shows the frequency distribution of the samples' Sociodemographic characteristics.

Table I

Frequency distribution of the samples' sociodemographic characteristics

Variables	Frequency (%)
Gender	
Male	175 (45.8)
Female	207 (54.2)
Age	
≤ 60	339 (88.7)
> 60	43 (11.3)
Genotype	
A1/A6	122 (31.9)
A6	132 (34.6)
A2/A5	59 (15.4)
A3/A4	69 (18.1)
Disease status	
H. pylori (-)	143 (37.4)
H. pylori (+)	239 (62.6)

The study included 382 participants, with a majority being females under 60 years of age. The A1/A6 and A6 genotypes represented nearly two-thirds of the samples (66.5%). Clinical diagnosis indicated that approximately 62% of the sample had *H. pylori* infection.

The analytical approach in this study addressed several methodological considerations often lacking in genetic association studies. Allele-based testing revealed that the association between *PGC* polymorphism and *H. pylori* infection is driven primarily by allele A6, which showed a 1.8-fold increased risk *per* allele. This finding was consistent across dominant, recessive, and additive genetic models, strengthening the validity of the association (13).

Pepsinogen is a growth factor and an inactive digestive enzyme secreted by gastric chief cells; it converts to pepsin, an active enzyme, under specific conditions such as the acidic environment of the gastric lumen. Various studies have shown the insertions or deletions in this enzyme can affect the stomach and contribute to the development of gastric cancer, making it a potential marker of gastric cancer (14).

To date, this is the first study in Jordan to examine the role of *PGC* polymorphism in relation to *H. pylori*. The current study showed that genotyping A1/A6 and A6 genotypes were significantly associated with *H. pylori* infection (Table II). This finding differs from results in Caucasian populations (15). In Chinese populations, allele A6 showed no significant frequency difference between the case and control groups. These studies suggest that ethnicity plays a major role in this association. Genetics may be important when considering ethnic identity and health, as different ethnic groups may have varying allele frequencies at certain loci linked to health conditions or disease processes (16).

Table II

Univariate logistic regression analysis between sociodemographic factors and disease state

Variables	B	S.E.	Wald	df	Sig.	Exp(B)	95% CI
Sex	-0.249	0.213	1.365	1	0.243	0.779	(0.514, 1.183)
Age (≤ 60 *vs.* > 60)	0.741	0.326	5.166	1	0.023	2.097	(1.107, 3.968)
Genotype A1/A6	0.741	0.306	5.851	1	0.016	2.097	(1.152, 3.822)
Genotype A6	1.562	0.324	23.199	1	0.00	4.767	(2.527, 8.996)
Genotype A2/A5	-0.035	0.357	0.01	1	0.922	0.966	(0.480, 1.944)
Genotype A3/A4 (Ref.)	-	-	-	-	-	-	-

Univariate logistic regression showed that age and genotypes A1/A6 and A6 were significantly associated with *H. Pylori* infection. Participants aged ≤ 60 years had a significantly higher risk of *H. Pylori* infection compared to those > 60 years. Participants with A1/A6 and A6 genotypes had a higher risk of acquiring *H. Pylori* infection than those with A3/A4 genotypes (OR = 2.097 and 4.767, respectively, $p < 0.05$). [B (regression coefficients), S.E. (Standard error), Wald (ODD ratio)].

The mechanism by which *PGC* polymorphism contributes to gastric cancer development is not fully understood. However, a study done by Lv Z *et al*. showed that the SNP interactions of *PGC* with its neighboring lncRNA increase the risk of gastric cancer in conjugation with environmental factors such as smoking, alcohol consumption, and *H. pylori* infection (16).

The expression of *PGC* mRNA changes in individuals with gastric cancer and *H. pylori* infection, leading to increased pepsinogen levels and potentially facilitating bacterial entry into host cells (17).

The multivariable logistic regression also examined the relationship between age and *H. pylori* infection. Participants aged 60 or younger showed a trend toward increased odds of infection (OR = 1.939) compared to those older than 60 years, though this association did not achieve statistical significance ($p = 0.052$). This borderline finding aligns partially with a previous study from South Korea, which reported that serum pepsinogen levels were elevated in young individuals (age < 60) with *H. pylori* infection, suggesting potential utility in predicting gastric cancer risk (18, 19). However, unlike the Korean study, which demonstrated clear statistical significance, our results only suggest a possible trend that warrants further investigation. Therefore, while our data suggests a

potential age- related pattern in *H. pylori* infection risk, this finding should be considered preliminary and interpreted with appropriate caution. Future studies with larger sample sizes, particularly among older adults, and more comprehensive adjustment for confounders are needed to clarify the true relationship between age and *H. pylori* infection susceptibility in the Jordanian population. In contrast, the association between *PGC* genotypes (A1/A6 and A6) and *H. pylori* infection was robust and statistically significant, even after multivariable adjustment (20, 21). Participants with A1/A6 (OR = 2.12, $p < 0.05$) and A6 (OR = 4.655, $p < 0.05$) genotypes had a significantly higher risk of acquiring *H. pylori* infection than those with A3/A4 genotype (Table III). This aligns with a previous study in South Korea (20, 21). These findings are consistent with the hypothesis that genetic variation in the *pepsinogen C* gene may influence susceptibility to *H. pylori* colonization or persistence (22, 23).

Table III

Multivariable logistic regression analysis

Variables	B	S.E.	Wald	df	Sig.	Exp(B)	95% CI
Sex	-0.289	0.225	1.648	1	0.199	0.749	(0.482, 1.163)
Age (≤ 60 *vs.* > 60)	0.662	0.341	3.767	1	0.052	1.939	(0.994, 3.782)
Genotype A1/A6	0.751	0.309	5.903	1	0.015	2.12	(1.157, 3.882)
Genotype A6	1.538	0.327	22.123	1	0.000	4.655	(2.452, 8.837)
Genotype A2/A5	-0.054	0.36	0.022	1	0.881	0.948	(0.468, 1.919)
Genotype A3/A4 (Ref.)	-	-	-	-	-	-	-

The multivariable logistic regression analysis revealed that genotypes A1/A6 (OR = 2.12, 95% CI: 1.157 - 3.882, $p = 0.015$) and A6 (OR = 4.655, 95% CI: 2.452 - 8.837, $p < 0.001$) were significantly associated with higher odds of *H. pylori* infection compared to the A3/A4 genotype, after adjusting for age and sex.

Regarding age, participants aged 60 years or younger demonstrated a trend towards increased risk of *H. pylori* infection compared to those older than 60 years (OR = 1.939, 95% CI: 0.994 - 3.782). However, this association did not reach statistical significance ($p = 0.052$), indicating that the observed age-related effect should be interpreted with caution. Sex was not significantly associated with infection status in the multivariable model ($p = 0.199$).

The significant HWE deviations observed in our control population warrant careful consideration. The complete absence of homozygotes at the A2/A5 and A3/A4 loci, and the heterozygote excess at the A1/A6 locus, are most plausibly explained by technical or sampling factors (Table IV and Table V). Potential technical artifacts, such as preferential amplification of certain alleles or difficulties in visualizing homozygous bands on agarose gels, could produce this pattern. Additionally, the relatively small control sample may not adequately represent the broader population, leading to chance deviations from HWE expectations. Future studies with larger samples and independent genotyping methods (*e.g.*, Sanger sequencing) are needed to validate these findings (24, 25).

Table IV

Allele frequencies and association with *H. pylori* infection

Allele	Cases, n (%)	Controls, n (%)	OR (95% CI)	P-value
A1 (510 bp)	122 (25.5)	62 (21.7)	1.24 (0.87 - 1.76)	0.23
A2 (480 bp)	42 (8.8)	28 (9.8)	0.89 (0.54 - 1.47)	0.65
A3/4 (450/460 bp)	58 (12.1)	80 (28.0)	Reference	-
A5 (400 bp)	34 (7.1)	34 (11.9)	0.59 (0.34 - 1.03)	0.06
A6 (310 bp)	222 (46.5)	82 (28.6)	1.82 (1.31 - 2.53)	0.0004
Total Alleles	478 (100%)	286 (100%)		

Allele-based analysis revealed significant differences in allele frequencies between cases and controls (Table IV). Allele A6 was significantly more frequent in *H. pylori*-positive subjects (46.5%) compared to controls (28.6%) (OR = 1.82, 95% CI: 1.31 - 2.53, $p = 0.0004$). Allele A5 showed a trend toward a protective effect but did not reach statistical significance ($p = 0.06$).

Genetic model testing (Table V) confirmed that the presence of allele A6 is associated with increased risk of *H. pylori* infection under dominant (OR = 3.21, 95% CI: 2.01 - 5.12, $p < 0.001$), recessive (OR = 2.89, 95% CI: 1.68 - 4.97, $p < 0.001$). These results indicate that both heterozygosity and homozygosity for allele A6 confer increased susceptibility to *H. pylori* infection.

Table V

Genetic model analysis for allele A6 and *H. pylori* infection

Genetic model	Cases, n (%)	Controls, n (%)	OR (95% CI)	P-value
Dominant model (A6 carriers)				
A6 carriers (A1/A6 + A6/A6)	201 (84.1)	53 (37.1)	3.21 (2.01 - 5.12)	< 0.001
Non- carriers	38 (15.9)	90 (62.9)	Reference	-
Recessive model (A6/A6)				
A6/A6	112 (46.9)	20 (14.0)	2.89 (1.68 - 4.97)	< 0.001
Other genotypes	127 (53.1)	123 (86.0)	Reference	

Limitations

Our study has several limitations that should be considered when interpreting the results.

First, the generalizability of our findings may be limited. Our sample was drawn from a single hospital in Jordan. The relationship between *PGC* polymorphisms and infection may vary across different sub-populations within Jordan due to distinct environmental exposures or genetic ancestry.

Second, while we focused on *PGC*, gastric physiology involves complex interactions between multiple host genetic factors (*IL-1β, TLR4*), the infecting *H. pylori* strain (CagA/VacA status), and the environment. Our study of a single polymorphism provides an important but incomplete picture of this multifactorial relationship.

Conclusions

In conclusion, this study provides evidence for an association between *PGC* gene polymorphism and *H. pylori* infection in the Jordanian population. Specifically, alleles 1 and 6 were significantly associated with increased odds of infection, suggesting that genetic variation in the *pepsinogen C* gene may influence susceptibility to *H. pylori*. Regarding age, we observed a non-significant trend toward increased infection risk among individuals aged 60 years or younger, a finding that requires confirmation in larger, adequately powered studies. These findings contribute to understanding host genetic factors in *H. pylori* susceptibility and may inform risk stratification for gastric cancer. However, replication in larger, independent cohorts and functional studies are needed to confirm these observations and elucidate underlying mechanisms.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Ethics approval and consent to participate

This project was supported by Ethical Approval of Research from IRB of The Hashemite University, Project number (19/2/2024/ 2025).

AI use disclosure

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

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