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ORIGINAL RESEARCH

The Influence of *IL-1B* Gene Polymorphisms on *H. pylori* Infection and Triple Treatment Response Among Jordanian Population

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Muhamad Ali K Shakhatreh[1]
Omar F Khabour[1]
Karem H Alzoubi[2]
Mohammed N BaniHani[3]
Ahmed Abu-Siniyeh[4]
Nabil A Bashir[5]
Salsabeel H Sabi[2]
Mahmoud Mahafdah[3]

[1]Department of Medical Laboratory Sciences, Jordan University of Science and Technology, Irbid, Jordan; [2]Department of Clinical Pharmacy, Jordan University of Science and Technology, Irbid, Jordan; [3]Department of General Surgery and Urology, Jordan University of Science and Technology, Irbid, Jordan; [4]Department of Clinical Laboratory Sciences, College of Applied Medical Sciences, Taif University, Taif, Kingdom of Saudi Arabia; [5]Department of Physiology and Biochemistry, Jordan University of Science and Technology, Irbid, Jordan

Background: *Helicobacter pylori* (*H. pylori*) is considered the main cause of gastritis, peptic ulcer and gastric carcinoma in the human populations. *H. pylori* infection influences the secretion level of several proinflammatory cytokines including IL-1β, which encoded by the *IL-1B* gene.

Objective: The current study aimed to investigate whether *IL-1B* gene polymorphisms are associated with *H. pylori* infection among the Jordanian population and responses to triple therapy.

Subjects and Methods: The gastroscopic examination was performed on 412 subjects for *H. pylori* infection diagnosis, 257 subjects were found to be infected by *H. Pylori* (positive cases), whereas 155 subjects were uninfected (negative controls). The *IL-1B* gene T-31C and C3954T polymorphisms were genotyped by PCR-RFLP.

Results: It was found that the T-31C polymorphism has a significant association with *H. pylori* infection ($P<0.05$), and the TT genotype frequency was significantly higher in infected subjects (50.2%) compared to controls (38.7%). On the other hand, no significant association was detected between C3954T SNPs and *H. pylori* infection among the Jordanian population. In addition, none of the examined polymorphisms were found to influence the responses to triple therapy.

Conclusion: The *IL-1B* gene T-31C SNP might be associated with an enhanced risk of *H. pylori* infection among the Jordanian population.

Keywords: *IL1B* gene, IL-1β, single nucleotide polymorphism, *Helicobacter pylori*, interleukins

Introduction

One of the main risk factors in human gastrointestinal diseases is *Helicobacter pylori* (*H. pylori*), which is gram-negative microaerophiles human pathogen bacteria. Different gastrointestinal diseases such as chronic gastritis, peptic ulcer, and gastric carcinoma have been linked to *H. pylori* infection.[1,2] A strong association was found between *H. pylori* and the host immune system during progress of gastrointestinal diseases,[3] where *H. pylori* induces the production of many proinflammatory cytokines, such as interleukin 1 beta (IL- 1β), interleukin 10 (IL-10) and tumor necrosis factor-alpha.[4]

It has been found that certain polymorphisms have an impact on the secretion levels of these cytokines, such as IL-1β, which is encoded by *IL-1B* gene on the long arm of chromosome 2 at band q13.[5] IL-1β is produced by activated

Correspondence: Muhamad Ali K Shakhatreh
Email mkshakhatreh@just.edu.jo

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macrophages as a proprotein that is proteolytically processed to its active form by caspase 1.[6] IL-1β plays an important role as a mediator of inflammatory response and has been shown to be involved in cell proliferation, differentiation, and apoptosis.[7] It was also shown to be a vital pro-inflammatory cytokine in the pathogenesis of *H. pylori* associated gastrointestinal diseases.[8] Two key single nucleotide polymorphisms (SNPs) were detected in the *IL-1B* gene (*IL-1B* T-31C and *IL-1B* C3954T), where they were shown to reduce the *IL-1B* gene expression levels.[9] Consequently, reduced IL-1β levels decrease gastric acid secretion,[10] which provides a proper environment for *H. pylori* to provoke an infection in the human stomach. The correlation between *IL-1B* promoter polymorphisms and *H. pylori* infection has been studied previously in populations such as Turkish, Brazillian, and Italian.[11–13] For example, in meta-analysis studies, a strong synergistic interaction between *IL-1β* polymorphisms and *H. pylori* infection in the development of gastric cancer was detected.[14–18] In addition, an association between *IL-1β* polymorphisms and *H. pylori* infection was reported in Asian, European, and Latin American populations.[19–24] Polymorphisms in IL-1B have also been shown to influence the responses to *H. pylori* triple therapy in different populations including American,[25–27] Japanese,[28–30] and Korean.[31] However, no association between IL-1B and response to triple therapy was detected among the Chinese population.[32] Thus, the association between IL-1B and *H. pylori* infection/response to triple treatment could be population-specific and affected by the genetic background of the individual. Therefore, in the current study, the impact of *IL-1β* on *H. pylori* infection and its eradication by triple therapy were examined in the Jordanian population.

Subjects and Methods

Subjects

The study participants were adult patients who underwent a gastroscopic examination at King Abdullah University Hospital (KAUH) for suspected *H. pylori* infection. Inclusion criteria were patients diagnosed with non-ulcer dyspepsia in the gastroscopy examination with normal finding/mild gastritis. Exclusion criteria were individuals who had gastric surgery or were under medications of anticoagulants, antibiotics, and proton pump inhibitors.[33,34] This study procedure was conducted in accordance with the Declaration of Helsinki. The IRB of Jordan University of Science and Technology approved the study (approval ID number: 16/6/14/3141). Written informed consent was obtained from all participants according to the IRB regulations. Of the invited subjects, 412 agreed to participate from which 257 subjects were found to be *H. pylori* positive (cases). The rest 155 patients were found to be *H. pylori* negative and were considered as control group.[35] Demographics of the participants and medical information were obtained using a structured form and medical files.

Diagnosis of *H. pylori* Infection

To diagnose *H. pylori* infection, biopsy samples from the gastric antrum were obtained from all participants by an expert physician. Biopsy samples were directly sent to the pathological examination to diagnose *H. pylori* infection.

In brief, samples were stained using Harris' hematoxylin-eosin and Giemsa staining as previously described.[36] Stained sections were evaluated for the presence of *H. pylori* infection by two experts under the oil immersion objective (1,000×). Positive diagnosis of *H. pylori* was reported for cases that showed typical *H. pylori* morphology (comma/S-shaped bacilli of 2 to 4 μm long and 0.5 to 1 μm thick) attached to the surface of the cells or free in the mucous layer, and forming small colonies for the least. Otherwise, the diagnosis was considered negative.[37] To validate the result, a positive control tissue and a negative control tissue were included with every run.

Therapeutic Regimens

Patients who participated in the study were revisited after taking their standard *H. pylori* eradication therapy as per hospital procedures. The used triple eradication therapy consisted of clarithromycin 500 mg twice daily, amoxicillin 1g twice daily, and PPIs twice daily, for 14 days. Responsiveness to therapy was defined as improvement in clinical symptoms and reduction in IgG serum levels 3 months after treatment, which are considered as alternative less invasive methods for detection of responsiveness of treatment compared to endoscopy.[38]

Isolation of Genomic DNA

DNA was isolated from whole blood (collected in EDTA tubes) using a Promega kit (Madison, USA) according to the manufacturer's instructions.[39,40] The quality and quantity of isolated DNA were evaluated using a Bio-Rad

SmartSpect_3000 instrument (Hertfordshire, UK). Samples were stored at - 20° C until used for the genotyping of IL-1B SNPs.

Genotyping of IL-1B Polymorphisms

The *IL-1B* T-31C and C3954T polymorphisms were genotyped by polymerase chain reaction-restriction fragment length polymorphisms (PCR-RFLP) as previously described.[41–43] The PCR reaction was done using Eppendorf thermocycler (Hamburg, Germany). Amplification was performed in 0.2 µL PCR tubes containing 50 ng of DNA, 1 µ of each primer and ready to use PCR master mix obtained from Promega (Madison, USA). Table 1 shows primer used, PCR conditions and restriction conditions. Digestion of the PCR products of the *IL-1B* T-31C and C3954T polymorphisms was mediated by the *AluI* and *Taq I* restriction enzymes (New England Biolabs, Beverly, CA, USA) respectively. The restriction reaction contained 10 µg of the PCR, 10 units of the restriction enzyme and appropriate amounts of deionized H_2O and the smart cut buffer (supplied with the kit). The reaction mixture was incubated in the water bath at 37°C for 16 hours. The reaction was then heat inactivated by incubation at 80°C for 20 minutes. Electrophoresis conditions were 1% TBE buffer, 2% agarose, 80 volts for 45 minutes.

Statistical Analysis

Analysis of the association between IL-1B polymorphisms and *H. pylori* infection/response to triple treatment was achieved using SNPstat statistical software. G. Power version 3.0.10 was used for power analysis (Franz Faul, Universität Kiel, Kiel, Germany). Distribution of examined SNPs according to Hardy–Weinberg equilibrium was also examined using SNPstat. A *P* value of less than 0.05 was used to infer statistical significance.

Table 2 Demographics of Participants

Parameter	Control Group	Cases Group
Mean age ± SD	42.6 ± 14.7	40.8 ± 15.2
Gender (%) Male Female	 41.3% 48.7%	 49% 51%
Mean BMI ± SD	28.0 ± 4.51	28.49 ± 5.22
Hypertension (%) Diabetes mellitus Thyroid dysfunction Kidney/liver diseases	16.1% 9.0% 5.1% 1.9%	22.2% 13.6% 3.5% 3.1%

Abbreviations: SD, standard deviation; BMI, body mass index.

Results

Table 2 shows the demographics of the study subjects. The mean age of the control group was 43 years and for the cases was 41 years. Male participants represented 51.3% of the control group and 49% of the cases group. No differences in medical history and other demographics were detected between the two groups (Table 2).

The association between SNPs of the *IL1B* gene (C3954T and T-31C) and *H. pylori* infection is shown in Table 3. A significant association between T-31C and *H. pylori* infection was detected ($P<0.05$). The frequency of the TT genotype was significantly higher in cases (50.2%) compared to controls (38.7%). Thus, homozygotes TT state was associated with higher *H. pylori* infection risk compared to other genotypes. In addition, the T allele was enriched in cases (66%) compared to controls (60%). With respect to C3954T SNP, no significant association was detected with *H. pylori* infection ($P>0.05$, Table 3).

Haplotype analysis of C3954T and T-31C SNPs is shown in Table 4. Among all examined haplotypes, the

Table 1 PCR and Restriction Conditions of IL-1B Gene Polymorphisms

Polymorphism	Primers: 5′-3′	PCR Conditions	Restriction Conditions	Fragment Sizes
T-31C	F: AGA AGC TTC CAC CAA TAC TC R: ACC ACC TAG TTG TAA GGA	35 cycles: 94°C for 30s, 61°C for 45s, 72°C for 45s	*Alu I*, 37°C, 16 h	C allele: 239 T allele: 152, 87
C+3954T	F: GTT GTC ATC AGA CTT TGA CC R: TTC AGT TCA TAT GGA CCA GA	35 cycles: 94°C for 45s, 55°C for 45s, 72°C for 45s	*TaqI*, 37°C, 16 h	T allele: 249 C allele:135, 114

Table 3 Association Between *IL1B* SNPs and *H. pylori* Infection

IL-1β SNP	Cases	Controls	Odds Ratio (95% CI)	P value
C3954T	**N (%)**	**N (%)**		
CC	117 (46)	55 (35)	1.00	
CT	123 (48)	90 (58)	1.56 (1.02–2.37)	0.12
TT	17 (7)	10 (6)	1.25 (0.54–2.91)	
Allele C	357 (69)	200 (65)		
Allele T	157 (31)	110 (35)		0.14
T31C	**N (%)**	**N (%)**		
CC	46 (17.9)	30 (19.4)	1.00	
TC	82 (31.9)	65 (41.9)	1.70 (1.09–2.66)	0.043
TT	129 (50.2)	60 (38.7)	1.40 (0.81–2.44)	
Allele C	174 (34)	125 (40)		
Allele T	340 (66)	185 (60)		0.061

Abbreviation: CI, confidence interval.

TC haplotype was present in 2.58% of cases compared to 8.62% of controls ($P<0.005$). Thus, TC haplotype seems to lower the risk of *H. pylori* infection. No significant association between the rest of the haplotype and *H. pylori* infection was observed ($P>0.05$) (Table 4).

Among the 257 patients, 41 patients showed resistance to triple therapy (resistance rate of 16%). The *IL-1B* C3954T and T-31C SNPs were tested for their association with triple therapy response (Table 5). The results showed no association between examined SNPs and response to triple therapy ($P>0.05$). In addition, none of the haplotypes were associated with response to triple therapy (data not shown). Thus, *IL-1B* SNPs might not be associated with response to triple therapy treatment of *H. pylori* infection among Jordanians.

Discussion

The aim of the study is to assess whether there is an association between *IL-1B* gene polymorphisms and *H. pylori* infection in the Jordanian population. Current data revealed a significant association between *IL-1B* - T-31C genetic polymorphism and *H. pylori* infection. The TT genotype was higher in *H. pylori* positive subjects compared to the control ones.

Table 4 Analysis of *IL-1B* Haplotypes of the Examined Polymorphisms

	Cases Frequency	Controls Frequency	Odds Ratio (95% CI)	P-value
CT	38.2	32.82	1.00	——
CC	31.27	31.7	1.12 [0.78–1.60]	0.55
TT	27.97	26.86	1.19 [0.77–1.83]	0.44
TC	2.58	8.62	4.04 [1.77–9.20]	0.001

Abbreviation: CI, confidence interval.

Table 5 *IL-1B* SNPs Association with Triple Therapy Response

IL-1β SNP	Resistance to Triple Therapy	Responsive to Triple Therapy	Odds Ratio (95% CI)	P-value
CC	19 (46)	98 (46)	1.00	
CT	19 (46)	104 (48)	1.06 (0.53–2.12)	0.97
TT	3 (7)	14 (6)	0.90 (0.24–3.46)	
T31C	**N (%)**	**N (%)**		
CC	6 (15)	40 (19)	1.00	
TC	10 (24)	72 (33)	2.00 (0.88–4.52)	0.19
TT	25 (61)	104 (48)	1.67 (0.64–4.35)	

The study findings are consistent with previous studies that reported a role for *IL-1B*-C31T SNP in the development of *H. pylori*-related diseases, particularly gastroduodenal diseases.[12,44] Similarly, *IL-1B* T-31C has a significant association with *H. pylori* infection among Uzbeks population.[45] In a case–control study among the Chinese population that was conducted on 392 patients, an association between *IL-1B* T-31C and gastric cancer was reported, which further augmented by *H. pylori*.[46] In the Brazilian population, a strong association was found between *IL-1B* −31TT and *H. pylori* infection.[47] Thus, *IL-1B* T-31C seems to be associated with *H. pylori* infection in several populations worldwide. The current study also reported lack of association between C3954T SNP and *H. pylori* infection in the Jordanian population. Similar findings were reported among Brazilian population.[12,47] The mechanism by which *IL-1B* T-31C polymorphism might modulate *H. pylori* infection needs to be investigated. This might involve changes in IL-1B protein level in the gastric epithelium and the subsequent modulation of gastric acid secretion.[12,48-50]

The clinical significance of *IL-1B* T-31C polymorphism in the modulation of infection risk has been examined in several studies. For example, the TT genotype at IL-1B-31 has been showed to increase the risk of chronic HBV infection.[51]

Our haplotype analysis of T-31C and C3954T SNPs showed that the frequency of TC haplotype was lower in cases than in controls, which indicate that TC haplotype might reduce the risk of *H. pylori* infection among Jordanian population. More studies are required to confirm the present findings.

Among all patients, only a small number (16%) showed resistance to *H. pylori* triple therapy, and current results did not show any association between response to

triple therapy, and *IL-1B* SNPs/haplotypes. The role of *IL-1B* polymorphisms in *H. pylori* eradication has been studied in different populations and came up with controversial findings. For example, in Japanese population, *IL-1B* polymorphisms were found to influence triple therapy of *H. pylori* infection.[28] However, no effect for *IL-1B* polymorphisms was detected on the eradication of *H. pylori* in the Chinese population.[32] Thus, *H. pylori* eradication might be influenced by different factors, such as lifestyle behavior, bacterial resistance to antibiotics, treatment adherence, and bacterial virulence factors. This might explain the reason for the inconsistency observed in the different studies.[10,52]

In conclusion, current results indicated that the *IL-1B* T-31C polymorphism was significantly correlated to *H. pylori* infection among Jordanian, while no association was detected between *H. pylori* infection and *IL-1B* C3954T polymorphism. Examining other cytokine polymorphisms such as IL-8 SNPs that previously has been reported to associate with H. pylori infection[53,54] is strongly recommended in future studies.

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Disclosure

The authors report no conflicts of interest in this work.

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