Journal of Advances in Medical and Biomedical Research | ISSN:2676-6264

IL-1B Gene Polymorphisms and Their Association with Chronic Gastritis and Gastric Cancer in *Helicobacter pylori* Positive Patients in Northwestern Iran

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Article Info

10.22034/JAMBR.34.1.7257.1

Received: 2025/08/15;
Accepted: 2026/02/20;
Published Online: 28 Feb 2026;

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ABSTRACT

Background & Objective: Interactions between *Helicobacter pylori (H. pylori)* and the human host particularly gastric inflammation and cytokine-mediated signaling have been extensively investigated due to their critical role in the pathogenesis of gastric disorders. This study aimed to evaluate the association between IL1B gene polymorphisms and the risk of chronic gastritis and gastric cancer in *H. pylori*–infected individuals from Northwestern Iran, a region with a considerable burden of gastric disease.

Materials & Methods: A total of 210 participants were enrolled and stratified into three groups: healthy controls, patients with chronic gastritis, and patients with gastric cancer (70 individuals per group). Peripheral blood samples collected in EDTA tubes were used for serological detection of *H. pylori* using an ELISA assay (Pishtaz Teb diagnostic kit) and for genomic DNA extraction. Genotyping of IL1B polymorphisms at positions −31, −511, and +3954 was performed using polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) analysis.

Results: Of the 210 participants, only seven individuals in the gastritis group were positive for *H. pylori*. The CT genotype of IL1B −31 was more frequently observed in *H. pylori*–negative patients with gastritis. At the IL1B −511 locus, the CC genotype was significantly more prevalent among *H. pylori* negative healthy controls, suggesting a protective effect against gastritis ($p = 0.023$). Additionally, the combined CT+TT genotypes at this locus were significantly associated with gastritis in *H. pylori* positive individuals ($p = 0.010$). No significant associations were detected between the IL1B +3954 polymorphism and disease status or *H. pylori* infection.

Conclusion: These findings demonstrate a significant association between IL1B gene polymorphisms and susceptibility to chronic gastritis and gastric cancer, particularly in the context of *H. pylori* infection. Further large-scale studies across diverse populations are warranted to elucidate the contribution of host genetic factors to gastric disease risk.

Keywords: IL-1β, Polymorphism, Gastritis, Gastric Cancer, *H. pylori*

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How to Cite This Article:

Sadighi A, Mehdizadeh A, Somi M H, Gerami S M, Rahbarnia L, Esmaeillou M, et al. IL-1B Gene Polymorphisms and Their Association with Chronic Gastritis and Gastric Cancer in *Helicobacter pylori* Positive Patients in Northwestern Iran. J Adv Med Biomed Res. 2026;34(1):41-50.

1. Introduction

Gastrointestinal cancers account for more than one-third of all common cancers and drive high mortality rates (1). Gastric cancer remains a prevalent gastrointestinal malignancy with substantial annual fatalities (2). *H. pylori*

infection of the gastric mucosa is a global phenomenon and is associated with various gastrointestinal diseases, including gastritis, gastric cancer, and peptic ulcers (3). Since 1994, the World Health Organization (WHO) has classified *H. pylori* as a class I carcinogen because of its strong association with stomach cancer (4). Inflammatory diseases of the gastric mucosa arise through multifactorial processes involving imbalances between aggressive and defensive factors (5). Chronic gastritis progression shows a strong association with *H. pylori* infection, which researchers have conclusively linked to cancer development (6). *H. pylori* infection drives expansion of gastric mucosal inflammation, creating conditions that favor gastritis, gastrointestinal ulcers, and gastric adenocarcinoma (7). Host genetic characteristics may also influence *H. pylori* pathogenesis (8). Understanding the mechanisms that govern gastric inflammation is therefore essential for clarifying gastric cancer pathogenesis (9). For example, *H. pylori* triggers an inflammatory reaction that induces the release of several cytokines, including interleukin-1β (IL-1β) (10).

Interleukin-1β (IL-1β) functions as a key inflammatory cytokine and mediates host responses to infectious agents (11). *H. pylori* infection induces IL-1β production, suppresses gastric acid secretion, and promotes inflammation, which permits colonization of the proximal stomach by *H. pylori* and related bacteria (12). The *IL1B* gene on chromosome 2q13–q21 includes three commonly studied single-nucleotide polymorphisms (SNPs), *IL1B* −511 C/T, *IL1B* −31 C/T, and *IL1B* +3954 C/T that influence IL-1β expression (13). These variants associate with higher or lower IL-1β production. Studies have identified changes at −511 (dbSNP: rs16944), −31 (dbSNP: rs1143627), and +3954 (dbSNP: rs1143634), with −511 and −31 located in the promoter TATA box region and +3954 in the coding region (14). Moreover, two of these SNPs show linkage disequilibrium (15). IL-1β not only predicts a pro-inflammatory phenotype but also appears to sustain and worsen *H. pylori* infection (16). Individuals with a gastric pro-inflammatory genotype overproduce IL-1β after *H. pylori* exposure, leading to increased gastrin, intensified gastric inflammation, atrophy, hypochlorhydria, and potential tumour progression (17). El-Omar et al. reported that the *IL1B* −511T and −31C genotypes associate with increased susceptibility to gastric cancer (18). Given the roles of host genetics and *H. pylori* infection in gastric cancer development, this study examined the relationship between *IL1B* polymorphisms and gastritis and gastric cancer in *H. pylori*-infected patients from Northwestern Iran to support earlier identification of individuals at higher risk of severe gastric disease.

2. Materials and Methods

2.1 Patients

The study population comprised 113 males and 97 females who underwent diagnostic endoscopy at Imam Reza Hospital, Tabriz, Iran. Data collection included age, sex, family history of gastric cancer or gastritis, nutritional habits, smoking, and drug use for all patients. Participants provided written informed consent, and the Ethics Committee of Tabriz University of Medical Sciences approved sample collection (Code: IR.TBZMED.REC.1396, 235).

2.2 Sample Collection

Two hundred and ten samples (age range, 23–80 years) were collected from January 2019 to January 2022 from control, gastritis, and cancer groups, with 70 individuals in each group. Patients provided 5 ml of EDTA-anticoagulated blood for enzyme-linked immunosorbent assay (ELISA) to detect *H. pylori* and some EDTA treated blood for genotyping by polymerase chain reaction (PCR). The EDTA treated samples were stored at −80 °C until the use.

2.3 DNA Extraction

A modified salting-out method was used to extract genomic DNA from whole blood. Quality and quantity assessment were performed using a Thermo Scientific NanoDrop spectrophotometer. The OD260/OD280 purity ratio ranged from 1.8 to 2.0, with a concentration of around 30 ng/uL. The *IL1B* gene sequence came from the NCBI SNP database. Primer pairs for PCR were designed using Primer3Plus, and BLAST searches and DNA melt analysis were performed to verify specificity and secondary structure.

2.4 PCR-RFLP

Polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) was used to investigate *IL-1B* promoter polymorphisms at positions −31, −511, and +3954. The primers used for PCR appear in Table 1. Amplified products were separated on a 1.5% agarose gel, then digested with the specific restriction enzymes TaqI, AvaI, and AluI. The resulting fragments were visualized on a 2.5% agarose gel, with genotype-specific patterns for each polymorphism.

2.5 Statistical Analysis

Analyses used SPSS 16.0. The Chi-square test assessed genotype and allele distributions across groups. Evaluation of allelic distribution considered deviations from the Hardy-Weinberg equilibrium. Multivariate logistic regression was used to estimate the relative risk with 95% confidence intervals. Additional tests included the t-test, ANOVA, and logistic regression to determine genotype frequencies, odds ratios, and confidence intervals. Statistical significance was set at $p < 0.05$.

Table 1. Primers used for PCR.

Polymorphism	Primer Sequences
Rs1143627 (−31)	F: 5′- AGAAGCTTCCACCAATACTC-3′
	R: 5′- AGCACCTAGTTGTAAGGAAG-3′
Rs16944 (−511)	F: 5′- GCCTGAACCCTGCATACCGT-3′
	R: 5′- GCCAATAGCCCTCCCTGTCT-3′
RS1143634 (+3953)	F: 5′- AATTTTGCCACCTCGCCTCA-3′
	R: 5′- CGGAGCGTGCAGTTCAGTGT-3′

3. Result

The analysis assessed the frequency of specific polymorphisms (*IL1B* −31, *IL1B* −511, and *IL1B* +3953) and their associations with disease susceptibility. The results showed notable differences in both allelic and genotypic frequencies across the study groups, indicating the potential of these polymorphisms as genetic markers for assessing gastric disorder risk.

Table 2 presents the demographic characteristics of the study groups. The mean ages for gastritis, gastric cancer, and healthy controls were 39.39 ± 12.14, 48.03 ± 10.78, and 38.74 ± 10.75 years, respectively. The mean age was significantly higher in the gastric cancer group than in the gastritis and control groups ($P < 0.001$). Sex distribution differed significantly across the three groups ($P < 0.05$). The proportions of non-smokers and current or former smokers did not differ substantially among the groups ($P > 0.01$). The severity of atrophy differed significantly among the groups ($P = 0.003$). *H. pylori* infection also differed significantly across groups, with the highest prevalence in the gastritis group and absence in the control group ($P < 0.01$).

Table 3 presents allelic and genotypic frequencies of the *IL1B* −31, *IL1B* −511, and *IL1B* +3953 polymorphisms across cancer, gastritis, and healthy groups, stratified by *H. pylori* status. For *IL1B* −31, the CT genotype occurs more frequently in patients with gastritis who do not have *H. pylori* than in healthy controls. Cancer patients with *H. pylori* (HP+) exhibit a higher frequency of the TT genotype compared to healthy controls, with a P-value of 0.004, indicating a strong association between this genotype and cancer in the presence of *H. pylori*. For *IL1B* −511, healthy *H. pylori*-negative individuals (HP−) show a notable enrichment of the CC genotype, $P = 0.023$, suggesting a protective effect against gastritis. The combined CT+TT genotypes also differ significantly ($P = 0.010$), indicating an association with healthy status compared to gastritis in *H. pylori*-negative individuals. For *IL1B* +3953, higher P values indicate no clear association between genotype and disease state or *H. pylori* status.

Table 4 presents associations between three interleukin-1β gene polymorphisms (*IL1B* −31, *IL1B* −511, and *IL1B* +3954) and the presence of gastritis and gastric cancer compared with healthy individuals. For *IL1B* −31, none of the genotypes differed significantly between groups; in the healthy versus cancer comparison, the CT genotype showed an elevated odds ratio (OR 1.725) that did not reach statistical significance ($P = 0.163$). For *IL1B* −511, in the healthy versus gastritis comparison, the CC genotype showed a trend toward a protective effect with an OR less than 1 that approached significance ($P = 0.061$). In the comparison between healthy and cancer individuals, the CC genotype showed a statistically significant protective effect (OR 0.411, $P = 0.024$), whereas the CT genotype showed a significant association with increased cancer risk (OR 2.881, $P = 0.010$). For *IL1B* +3954, the data did not show statistically significant associations between genotypes and either gastritis or cancer.

Table 2. Socio-demographic features in patients and controls.

Characteristic		Controls (N=70)	Gastritis (N=70)	Gastric Cancer (N=70)	P-value
Age	(mean ± sd; years)	38.74±10.75	39.39±12.14	48.03±10.78	<0.001
Gender n (%)	Male	39(34.5)	27(23.9)	47(41.6)	0.003
	Female	31(32)	43(44.3)	23(23.7)	
Region n (%)	Urban	42(34.7)	39(32.2)	40(33.1)	0.003
	Rural	28(31.4)	31(34.8)	30(33.8)	
Family history of gastritis and/or ulcer n (%)	No	61(38.6)	47(29.7)	50(31.6)	0.016
	Yes	9(17.3)	23(44.2)	20(38.4)	
Smoking habit n (%)	No	9(26.4)	13(38.2)	12(35.4)	>0.01
	Current smoker or former smoker	61	57	58	
Family History n (%)	No	61(38.6)	47(29.7)	50(31.6)	>0.01
	Yes	9(17.3)	23(44.2)	20(38.4)	
Helicobacter Pylori n (%)	No	70(34.4)	63(31.03)	70(34.4)	<0.01
	Yes	0(0)	7(100)	0(0)	
Atrophy n (%)	None	70(34.3)	68(33.3)	66(32.4)	0.003
	Low	0(0)	2(40)	3(60)	
	Moderate	0(0)	0(0)	1(100)	
	Severe	0(0)	0(0)	0(0)	

Table 3. The allelic and genotypic frequencies for IL1B-31, IL1B-511 and IL1B +3953 polymorphisms in patients with gastritis and gastric cancer and controls.

Polymorphisms	with and without *H. Pylori*	Genotype	Cancer n (%)	Gastritis n (%)	Healthy n (%)	P Value
IL1B-31	HP-	CC	9(13)	1(1)	14(20)	0.156
		CT	18(26)	7(10)	11(16)	0.044
		TT	10(14)	4(6)	14(20)	0.070
		CT+TT	28(40)	11(16)	25(36)	0.054
	HP+	TT	19(27)	12(17)	7(10)	0.004
		CT	14(20)	17(24)	10(14)	0.228
		CC	11(16)	24(34)	8(11)	0.087
		CT+CC	25(36)	41(58)	18(25)	0.034
IL1B-511	HP-	CC	12(17)	4(5)	22(31)	0.023
		CT	16(23)	4(5)	8(11)	0.023
		TT	9(13)	4(5)	9(13)	0.103
		CT+TT	25(36)	8(10)	17(24)	0.010
	HP+	TT	15(21)	24(34)	16(23)	0.363
		CT	15(21)	16(23)	8(11)	0.058
		CC	3(4)	18(26)	7(10)	0.050
		CT+CC	18(25)	34(49)	15(21)	0.089

Polymorphisms	with and without *H. Pylori*	Genotype	Cancer n (%)	Gastritis n (%)	Healthy n (%)	P Value
IL1B +3953	HP-	CC	10(14)	2(3)	11(16)	0.184
		CT	17(24)	6(8)	15(21)	0.052
		TT	11(15)	5(7)	12(17)	0.069
		CT+TT	28(40)	11(16)	27(38)	0.059
	HP+	TT	9(13)	16(24)	15(21)	0.084
		CT	13(16)	18(24)	8(11)	0.317
		CC	12(15)	23(34)	11(15)	0.076
		CT+CC	25(31)	42(58)	29(41)	0.058

Table 4. Genotype distributions of interleukin-1B-31 and interleukin-1B-511 gene polymorphisms among healthy, gastritis and gastric cancer.

Polymorphisms	Group type	Genotype	P value	OR (95%CI)
IL1B-31	Healthy & Gastritis	TT	0.130	0.573(0.278-1.179)
		CT	0.478	1.302(0.628-2.699)
		CC	0.409	1.353(0.659-2.776)
	Healthy & Cancer	TT	0.231	0.620(0.284-1.355)
		CT	0.163	1.725(0.801- 3.715)
		CC	0.821	0.913(0.414- 2.011)
	Gastritis & Cancer	TT	0.816	1.105(0.479-2.548)
		CT	0.573	1.246(0.580-2.677)
		CC	0.423	0.723(0.327-1.597)
IL1B-511	Healthy & Gastritis	CC	0.061	0.515(0.258- 1.030)
		CT	0.348	1.451(0.666-3.162)
		TT	0.239	1.585(0.737- 3.409)
	Healthy & Cancer	CC	0.024	0.411(0.190- 0.888)
		CT	0.010	2.881(1.283-6.467)
		TT	0.816	0.895(0.353-2.271)
	Gastritis & Cancer	CC	0.606	0.819(0.383-1.752)
		CT	0.081	2.012(0.916-4.419)
		TT	0.168	0.537(0.222- 1.300)
IL1B +3953	Healthy & Gastritis	CC	0.082	1.024(0.347- 1.104)
		CT	0.257	1.322(0.781-1.576)
		TT	0.326	1.463(0.648- 2.318)
	Healthy & Cancer	CC	0.055	1.344(0.285- 1.875)
		CT	0.051	1.572(0.374-2.256)
		TT	0.725	1.984(0.662-2.056)
	Gastritis & Cancer	CC	0.732	1.617(0.572-1.975)
		CT	0.076	1.103(0.724-2.012)
		TT	0.257	1.056(0.534- 1.452)

4. Discussion

This study examined *IL1B* gene polymorphisms in patients from Northwestern Iran with gastritis or gastric cancer and concurrent *H. pylori* infection. Gastrointestinal cancers, including gastric cancer, are associated with substantial morbidity and mortality, and *H. pylori* infection represents a major contributing factor (19). Interactions between *H. pylori* and the human host, particularly gastric inflammation and cytokine signaling, have been studied extensively because of their implications for the development of gastric diseases (20). The *IL1B* gene encodes interleukin-1β (IL-1β), a pro-inflammatory cytokine that plays a crucial role in host immune responses, particularly in infection-induced inflammation and tissue injury (17). In recent years, numerous studies have examined interleukins in this context. Research on *IL1B* polymorphisms suggests an increased risk of stomach cancer (17). Specifically, three single-nucleotide polymorphisms (SNPs), −31 T/C, −511 C/T, and +3954 C/T, located in the promoter region (−31, −511) and coding region (+3954) on chromosome 2q, are reported to increase IL-1β expression (1).

Since 2000, studies have examined distinct *IL1B* haplotypes in Scottish and Polish populations in relation to gastric cancer (21). Carriers of the homozygous *IL1B* −31 genotype exhibit a higher risk of hypochlorhydria in the context of *H. pylori* infection, suggesting an early interaction between genetic background and environment in the development of stomach cancer. Machado et al. (22) investigated the etiological role of *IL1B* −511 and its association with an increased risk of intestinal-type gastric carcinoma in the Portuguese population, reporting that this variant relates to a higher risk of gastric cancer and its putative precursors, atrophic gastritis and hypochlorhydria. Studies in Japanese and Chinese populations reported similar findings (23). Polymorphisms in pro-inflammatory cytokine genes, including IL-1β and TNF-α (TNF), have been associated with an increased risk of gastric carcinoma across various gastric subsites, regardless of patient ethnicity (24). Multiple studies in Asian and Caucasian populations have found *IL1B* −511 to be significantly associated with gastric carcinoma risk (25).

Several investigations have reported that *IL1B* −511 increases the likelihood of stomach cancer in Caucasians. A particularly elevated risk also appeared in Hispanics with *H. pylori* infection, but not in Asians (26). Kimang'a et al (27) investigated the association of these SNPs with *H. pylori* infection and various gastric mucosal diseases in Africa, excluding gastric cancer. The study reported that the *IL1B* −511 allele showed significant associations with gastritis, gastric ulcer, and gastroesophageal reflux.

The study revealed notable differences in the allelic and genotypic distributions of IL-1β polymorphisms among patients with gastritis, gastric cancer, and healthy individuals, both in the presence and absence of *H. pylori* infection. Certain *IL1B* variants are associated with an increased risk of gastric carcinoma, including the CT genotype of IL1B at −511. These results align with findings from Chinese (28) and Indian (29) cohorts, but differ from Swedish data (30). The pattern also agrees with studies from Portugal (31) and Mexico (32), which suggest that specific genotypes may confer susceptibility to severe gastric disease, particularly in the setting of *H. pylori* infection. Iranian data show similar trends. Ismaili et al (33) reported a significantly higher frequency of the +3954 A2A2 genotype, equivalent to TT, in gastric cancer cases, approximately 45 percent versus 7.6 percent in controls. Seylanian Tousi et al (34) observed a protective effect of the −511 CT genotype in north-eastern Iran, OR about 0.30, p = 0.01. Taken together, these findings support a role for *IL1B* polymorphisms, especially at −511 and +3954, as modifiers of gastric cancer risk in Iranian populations.

The demographic characteristics of the study groups, including age, sex, smoking status, and the presence of *H. pylori* infection, were analyzed and showed significant differences among the cohorts. These results offer valuable insights into the intricate interplay of genetic, environmental, and demographic factors that contribute to susceptibility to gastric disorders.

5. Conclusion

The study provides evidence of a link between *IL1B* gene polymorphisms and susceptibility to chronic gastritis and gastric carcinoma in *H. pylori*-positive patients in Northwestern Iran. The observed differences in allelic and genotypic frequencies, particularly in relation to *H. pylori* status, suggest a potential role for *IL1B* variants as genetic markers for estimating the risk of severe gastric disease. These findings support the importance of accounting for genetic variability in *H. pylori*-related gastric pathogenesis and offer insight into mechanisms that shape disease susceptibility. The identification of specific IL1B polymorphisms associated with an increased risk of gastric carcinoma and gastritis carries clinical relevance, with the potential to aid in the early detection of high-risk individuals and guide targeted interventions and personalized management. Further research in larger and more diverse populations should validate and extend these findings, advancing precision medicine approaches for the prevention and management of *H. pylori*-associated gastric disorders.

6. Declarations

6.1 Acknowledgments

This study received financial support from the Liver and Gastrointestinal Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.

6.2 Ethical Considerations

The Ethics Committee of Tabriz University of Medical Sciences approved this research project (Code: IR.TBZMED.REC.1396, 235).

6.3 Authors' Contributions

Data curation: Ali Sadighi. Formal analysis: Amir Mehdizadeh. Funding acquisition: Ali Bahadori. Investigation: Sousan Mirnajd Gerami. Methodology: Ali Sadighi, Leila Rahbarnia. Project administration: Ali Bahadori. Resources: Mahsa Esmaeillou. Software: Ali Sadighi, Mahsa Esmaeillou. Supervision: Ali Bahadori. Validation: Mohammad Hossein Somi, Leila Rahbarnia. Suna Kızılyıldırım. Visualization: Mohammad Hossein Somi, Suna Kızılyıldırım. Writing–original draft: Ali Sadighi. Writing–review & editing: Ali Sadighi, Amir Mehdizadeh, Leila Rahbarnia. All authors reviewed, edited, and approved the final version of the manuscript.

6.4 Conflict of Interest

The authors declare that they have no conflicts of interest.

6.5 Fund or Financial Support

The Liver and Gastrointestinal Diseases Research Center at Tabriz University of Medical Sciences provided financial support for this project.

6.6 Using Artificial Intelligence Tools (AI Tools)

The authors confirm that no artificial intelligence (AI) or automated text-generation tools were used in preparing this manuscript. All stages of the research- including data collection, analysis, and writing- were completed solely by the authors. This ensures that the content reflects their original work and complies with ethical publication standards.

6.7 Consent to Participate

All participants provided their written informed consent prior to their inclusion in the study. The research team conducted this work in accordance with the ethical guidelines set forth by the Ethics Committee of Tabriz University of Medical Sciences. The investigators clearly explained the study's purpose, procedures, potential benefits, and foreseeable risks to participants in easily understandable language. Participation was strictly voluntary, and participants retained the right to decline or withdraw at any time without any impact on their clinical care. The investigators maintained rigorous confidentiality, restricted data access to authorized personnel only, and anonymized all records to safeguard participant identities.

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