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Original Article

TLR2 Arg677Trp but not TLR2 -196 to -174 ins/del and Arg753Gln polymorphism alter the risk of peptic ulcer in north of Iran

Maryam Habibzadeh [a], Mehdi Tourani [b], Javad Shokri-Shirvani [c], Amrollah Mostafazadeh [d], Soraya Khafri [e], Hamid Reza Nouri [a,*]

[a] *Cellular and Molecular Biology Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran*
[b] *Student Research Committee, Babol University of Medical Sciences, Babol, Iran*
[c] *Department of Internal Medicine, Babol University of Medical Sciences, Babol, Iran*
[d] *Department of Immunology, School of Medicine, Babol University of Medical Sciences, Babol, Iran*
[e] *Biostatistics & Epidemiology Department, Babol University of Medical Science, Babol, Iran*

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Abstract

Background: Most polymorphisms that occur in TLR-2 are associated with gastrointestinal disorders such as peptic ulcer disease (PUD). Hence, in current study, association between TLR2-196 to -174 ins/del, Arg753Gln and Arg677Trp polymorphisms and risk of PUD development in north of Iran was evaluated.

Methods: This case-control study included 50 patients with PUD as cases and 50 people without peptic ulcer as control group. Blood and endoscopic biopsies were collected. *Helicobacter pylori* infection was screened by rapid urease test, specific IgG measurement and specific PCR for glmM gene. Then, TLR2-196 to -174 ins/del polymorphism was assessed by using allele-specific PCR. The Arg753Gln and Arg677Trp polymorphism in TLR2 gene were analyzed by the PCR-restriction fragment length polymorphism (RFLP).

Results: There was no significant difference in the allele and genotype frequencies of polymorphisms in the TLR2-196 to -174 ins/ins and Arg753Gln genes between controls and patients, respectively. However, an association with increased risk for PUD was observed for polymorphism TLR-2 Arg677Trp (odds ratio [OR] = 7.9; 95% confidence interval [CI] = 0.94−67.5). Further analysis showed that *H. pylori* infection was associated with a significant difference in genotype and allele frequencies of TLR2-196 to -174 ins/ins and Arg753Gln polymorphism, respectively. Furthermore, there was no association between variant haplotypes and PUD development in *H. pylori* infected subjects. However, no association was detected between gender and genotypic frequencies of all polymorphisms in TLR2.

Conclusion: Our findings showed that TLR2 Arg677Trp polymorphism and *H. pylori* infection may play crucial roles in peptic ulcer development respectively in north of Iran.

Keywords: Genetic polymorphism; Peptic ulcer; TLR2

1. Introduction

Peptic ulcer disease or PUD is one of the most common disease and some of its complications are main causes of morbidity and mortality in the world.[1] Although, around 4% of the world's population suffered from PUD,[2] but its prevalence differs between countries; the Asian countries has much higher incidence rates than the European countries.[3]

Peptic ulcer was defined as a circumscribed mucosal break of at least 0.5 cm in diameter and a perceptible depth.[4−6] It is characterized by an imbalance between the factors that damage the mucosa and those for its protection, resulting in a lesion of the lining of the upper digestive tract.[7]

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

* Corresponding author. Dr. Hamid Reza Nouri, Cellular and Molecular Biology Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran.

E-mail address: nourihr851@gmail.com (H.R. Nouri).

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The *Helicobacter pylori* (*H. pylori*) is a major etiological factor for PUD that leads to inflammation of the gastric mucosa in 80% of peptic ulcer cases.[8] However, 50% of the world's population are infected with *H. pylori*, but a small percentage of those develop PUD and other gastric diseases.[9] It seems that other factors such as host genetic factors may play an important role in development of peptic ulcer.

Host genetic factors such as polymorphisms of Toll-like receptors (TLRs) and immune response genes can affect in magnitude the host immune response against infection and lead to the variation in the level of cytokine response that may influence the susceptibility to inflammatory disease.[10–12] TLRs are pattern recognition receptors that play some critical roles in immune response against harmful pathogens.[13] The immune response against *H. pylori* initiates expression of TLRs in the surface of infected gastric epithelial cells. These receptors can induce cellular signaling pathways including activation of nuclear factor (NF)-κ B and inflammatory cytokine production.[14]

Among the TLRs, most studies have shown that the TLR2 acts an initial barrier against *H. pylori* and is a much better receptor to recognize bacterial LPS.[15] Expression of TLR2 leads to activation of transcription factors, mainly NF-kB that induce the production of pro-inflammatory cytokines such as IL-1β, IL-2, IL-6, IL-8, IL-12.[9] TLR2 activation also leads to expression of TLR4 and proliferation of gastric epithelial cells to metaplasia, to dysplasia, and adenocarcinoma.[16,17]

Single nucleotide polymorphisms (SNPs) occurring in TLR2 gene have been associated with an increased susceptibility to various infectious and inflammatory diseases such as asthma, tuberculosis, lepromatous leprosy and septic shock in different populations.[18,19] These polymorphisms can influence the pathogenesis of inflammatory diseases. It can be a cause of variation in expression of pro-inflammatory cytokines genes and increase of inflammatory response.[20] Therefore, increases of inflammatory response can lead to atrophy and eventually ulcers in the stomach and also may increase the risk of stomach cancer.[21]

Recently, TLR2-196 to -174 ins/del polymorphism was found to be associated with susceptibility to intestinal metaplasia[14] and gastric cancer.[8] Studies demonstrated the TLR2-196 to -174 ins/del polymorphism may influence TLR2 promoter activity. It has been reported that the TLR2-196 to -174 del/del genotype showed decreased transactivation of responsive promoters. It is considered that this polymorphism is associated with gastro-duodenal disease.[22] Likewise, it has been reported that TLR2 gene (Arg677Trp and Arg753Gln) polymorphisms have been associated with an increased susceptibility to various diseases such as tuberculosis, lepromatous leprosy and septic shock.[18,23,24]

Therefore, polymorphisms in TLR2 gene may play a key role in susceptibility to PUD. Hence, in the current study, we investigated the role of the genetic variants of TLR2-196 to -174 ins/del, Arg753Gln and Arg677Trp in susceptibility to peptic ulcer in north of Iran.

2. Methods

2.1. Patients and samples

In this case-control study, patients with dyspepsia who underwent endoscopy at Ayatollah Rohani Hospital (Babol University of Medical Sciences, Babol, Iran) between January 2016 and September 2016 were enrolled. The demographic data, information about symptoms of abdominal pain, and data regarding history of chronic stomach disorders were obtained via a standardized questionnaire. Patients receiving antimicrobial therapy, proton-pump inhibitors, H_2-receptor blockers, and non-steroidal anti-inflammatory drugs were excluded. All biopsy samples were taken from the gastric antrum. Three biopsy samples were taken from each patient during endoscopy. One of the biopsy samples was applied for the rapid urease test and the second one processed for histopathological examination. The third biopsy sample was preserved in transport medium for *H. pylori* detection via PCR. Based on the endoscopic observation by an expert gastroenterologist and histopathological assessments, subjects were divided into two groups including peptic ulcer (PUD) as case and non-peptic ulcer (NPUD) including normal or gastritis as control group. The Research Ethics Committee of Babol University of Medical Science approved this work (MUBABOL.REC.1394.106), and written informed consents were obtained from all participating individuals.

2.2. Detection of H. pylori infection

The presence of *H. pylori* infection was determined on the basis of histopathological examination including Giemsa staining, rapid urease test (RUT), and anti-*H. pylori* IgG antibody. Briefly, anti-*H. pylori* IgG antibody was measured in serum samples of the participants with a direct enzyme-linked immunosorbent assay (ELISA) kit (Pishtaz Teb, Tehran, Iran). According to the manufacture instructions, a finding of 10.0 IU/ml or higher was regarded as seropositive. In addition, to prove the presence of *H. pylori* in the biopsy samples, the *Helicobacter* species-specific PCR was performed using specific primers for the ureC (glmM) gene as previously described.[25] Patients were considered infected with *H. pylori* if the results were positive by at least two methods.

2.3. Genotyping for TLR2-196 to -174 ins/del polymorphism

Peripheral venous blood was collected from all participants in EDTA containing tubes, and genomic DNA was extracted using the salting-out procedure.[26] DNA was stored at −20 °C until use for genotyping. Allele-specific polymerase chain reaction (ASPCR) method was applied to investigate -196 to -174 ins/del polymorphism. The nucleotide sequences of the sense and antisense primer was described in Table 1. In brief, the PCRs were performed separately in 20 μl reaction volume containing 50 ng of genomic DNA, 12.5 pmol of each primer,

Table 1
Primer sequences fragment sizes for TLR2 polymorphism.

Fragment (bp)	Primers 5′−3′ sequence	Genes
Ins/ins: 286; ins/del: 286, 264	F: CACGGAGGCAGCGAGAAA	TLR2-196 to -174 ins/del
del/del: 264	R: CTGGGCCGTGCAAAGAAG	
GG: 104 and 25 pb	F: CATTCCCCAGCGCTTCTGCAAGCTCC	Arg753Gln
GA: 125, 104 and 25 bp; AA: 129 bp	R: GGAACCTAGGACTTTATCGCAGCTC	
CC: 124 and 75 pb	F: GCC TAC TGG GTG GAG AAG CTT	Arg677Trp
CT: 199, 124 and 75 pb; TT: 199 bp	R: CCA GTT CAT ACT TGC ACC ACT C	

1.2 μl $MgCl_2$ (25 mM), 0.8 μl dNTP (10 mM), 2 μl 10 × reaction buffer, and 1.5 units of Taq polymerase (GeNet Bio, Korea). The PCR cycling parameters were as follows: initial denaturation at 94 °C for 10 min, then 35 continuous cycles of denaturation at 94 °C for 30 s, annealing temperature at 66 °C for 40 s, extension at 72 °C for 45 s and final extension step was prolonged to 10 min at 72 °C. The PCR products were analyzed by electrophoresis in 3% agarose gel, stained with ethidium bromide, and then visualized on a UV transilluminator, and photographed using the Gel Image System. A single band at 286 bp was considered as wild type, and a single 264 bp band was considered as homozygous type, while heterozygous type showed two bands of 286 bp and 264 bp.

2.4. Genotyping for TLR2 Arg753Gln and Arg677Trp polymorphism

The Arg753Gln and Arg677Trp polymorphism in the TLR2 were identified by PCR-restriction fragment length polymorphism (PCR-RFLP). The primers for detection of these two single nucleotide polymorphism (SNPs) were listed in Table 1. The PCR condition for these reactions was as same as the first one described earlier for TLR2-196 to -174 ins/del polymorphism but the other thermocycling parameters were quite different. The PCR thermocycling parameters for TLR2 Arg753Gln polymorphism were as follows: initial denaturation at 94 °C for 5 min, then amplification was carried out by 35 cycles of denaturation at 94 °C for 30 s, annealing temperature at 60 °C for 30 s, extension at 72 °C for 30 s and final extension cycle for 10 min at 72 °C. The PCR thermocycling parameters for TLR2 Arg677Trp polymorphism were similar to Arg753Gln polymorphism, but only annealing and extension time was changed to 40 s. Then, TLR2 Arg753Gln and Arg677Trp polymorphism PCR products were digested with 0.3 μL (10 U/μL) of the Aci I and 1.0 μL (10 U/μL) of the Msp I specific enzymes, respectively in a 10 μL total volume including 1.0 μL 10 × buffer (Jena Bioscience, Jena, Germany) at 37 °C overnight. The digested products were electrophoresed on a 3% agarose gel and visualized on a UV transilluminator. The TLR2 Arg753Gln (G > A) product was digested into the fragments of 104 bp, 25 bp length in the presence of wild-type allele (G) whereas, the enzyme had no effect on the mutant allele (A) and only 129 bp fragment was observed. In addition, TLR2 Arg677Trp (C > T) showed 124 bp and 75 bp fragment in the presence of wild-type allele (C) and 199 bp fragment in the presence of mutant allele (T).

2.5. Statistical analysis

Hardy−Weinberg equilibrium of the TLR2 gene allele in the NPUD and PUD groups was tested by χ^2 statistics. Differences of TLR2 genotype frequencies between NPUD and PUD were determined by the chi-square and Fisher's exact test. The results are shown as odds ratios (OR) and 95% confidence intervals (CI). Since, frequency of polymorphic homozygous for the minor allele vs. homozygous for the major allele was low for all polymorphism, the ORs were calculated using a dominant model. Data were analyzed using GraphPad Prism v 6.07 (GraphPad Software Inc., La Jolla, CA, USA). $P < 0.05$ was considered statistically significant.

3. Results

3.1. Characteristics of the subjects and infection with H. pylori

The characteristics of the subjects are summarized in Table 2. The mean age ± SD was 47.7 ± 13.5 years for the NPUD as control and 50.7 ± 16.1 years for PUD as case group. The percentages of males were 52% in the NPUD and 54% in the PUD. There was no significant difference in term of gender. Statistical analysis showed that the study population is adjusted to age and sex. According to the results of UreC-PCR, measuring specific IgG antibody as well as rapid urease, participants who were positive in two tests were considered as *H. pylori* positive. *H. pylori* infection was present in (55%) of subjects in this study (20/50 in NPUD and 35/50 in PUD). About 70% (35) of the PUD group patients were

Table 2
The demographic and clinical data in patients with non PUD and PUD.

Demographics and clinical complications	NPUD (n = 50)	PUD (n = 50)	*P*
Age (years) Mean ± SD	47.7 ± 12.5	50.7 ± 16.1	0.401
Range	22−75	22−78	
Gender (Female/Male) N (%)	24/26 (48/52)	23/27 (46/54)	0.841
Smoking	5	7	0.538
Drinking	1	3	0.307
Vomiting	6	8	0.564
Epigastric pain	16	32	0.001*
Nausea	3	6	0.294
H. pylori infection (%)			
Positive, N (%)	20 (40%)	35 (70%)	0.002*
Negative, N (%)	30 (60%)	15 (30%)	

*P-value < 0.05 was significant.

infected with *H. pylori*, while about 40% (20) of the NPUD individuals were infected with this bacterium. More analysis showed that infection with *H. pylori* in PUD individuals were higher than NPUD and there was a statistically significant association between *H. pylori* infection and PUD (OR = 0.28, 95% CI: 0.12−0.65; $P = 0.002$).

3.2. Association of TLR2 Arg677Trp with peptic ulcer development

One hundred subjects including NPUD and PUD were genotyped for the TLR2-196 to -174 ins/del, Arg677Trp and Arg753Gln polymorphisms. Hardy−Weinberg equilibrium was used for genotype and allele frequency distribution of the polymorphisms in both PUD and NPUD groups. The genotype distribution of TLR2-196 to -174 ins/del, Arg677Trp and Arg753Gln polymorphisms in NPUD followed the Hardy−Weinberg equilibrium (HWE = 0.86, 1.0 and 0.95, respectively). Also, the frequency of TLR2-196 to -174 ins/del, Arg677Trp and Arg753Gln polymorphism in the PUD group did not deviate significantly from those expected under the Hardy−Weinberg equilibrium (HWE = 0.85, 1.0 and 0.90, respectively).

There was no significant difference in the allele frequency of the TLR2-196 to -174 ins/del polymorphism in the PUD patients as compared to the NPUD as control group (OR 0.88, 95% CI 0.46−1.7; $P = 0.72$). There was also no statistically significant difference in genotype frequencies of PUD patients who carried the ins/ins genotype and those who carried ins/del + del/del genotype as compared to the NPUD group, respectively (OR 1.2, 95% CI 0.51−2.7; $P = 0.66$). The distribution of TLR2 genotypes is shown in Table 3. Similarly, no difference in genotype distributions (GG vs. GA + AA) of the TLR2 Arg753Gln polymorphisms between PUD patients and NPUD was found. As shown in Table 3, the allele frequencies of G and A were also similar in PUD and NPUD groups (Table 3). On analyzing TLR2 Arg677Trp genotype frequencies, it was observed that individuals carrying CC genotype had increased risk of PUD (OR 7.9, 95% CI 0.94−67.5; $P = 0.03$). Further, allele frequencies showed no significant association with PUD patients as compared to NPUD (OR 1.3, 95% CI 0.75−2.3; $P = 0.32$).

3.3. TLR2-196 to -174 ins/del polymorphism is associated with H. pylori status

The distribution of TLR2 allele and genotypes frequencies in *H. pylori* positive and negative individuals is shown in Table 4. In a logistic model including all subjects, the univariate analysis showed that *H. pylori*-positivity was associated with TLR2-196 to -174 ins/del polymorphism. In comparison with the ins/del + del/del genotype, ins/ins genotype was associated with an increased risk of *H. pylori* infection (OR 2.3, 95% CI 1.0−5.5; $P = 0.04$). There was also statistically significant difference in allele frequencies of the TLR2 Arg753Gln polymorphism in *H. pylori*-positive subjects compared with *H. pylori*-negative ones (OR 0.1, 95% CI 0.01−1.1; $P = 0.03$). There was no significant difference in the genotype and allele frequency of the TLR2 Arg677Trp polymorphism in *H. pylori* infected subjects as compared to the subjects without *H. pylori*.

In addition, we evaluated the associations between TLR2-196 to -174 ins/del, Arg677Trp and Arg753Gln polymorphisms, and risk of peptic ulcer development in presence of *H. pylori* infection. As shown in Table 5, among 55 *H. pylori* positives, no association was found between TLR2-196 to -174 ins/del, Arg677Trp and Arg753Gln polymorphisms in PUD and NPUD patients that were infected with *H. pylori*.

The distribution of TLR2 Arg677Trp and Arg753Gln haplotypes between PUD and NPUD was analyzed and there was no significant difference between TLR2 haplotypes. In details, the frequency of GC haplotype was 46.9% and 52% in PUD and NPUD, respectively. In addition, the frequency of GT, AC and AT haplotypes in PUD patients was 48.9%, 2.1% and 2.1%, respectively. The frequency of the same haplotypes in NPUD group was 46%, 1% and 1%, respectively.

In addition, there was no association between sex and TLR2-196 to -174 ins/del, Arg677Trp and Arg753Gln polymorphisms (data are not shown).

Table 3
Genotype and allele frequencies of TLR2 polymorphisms in PUD and NPUD groups.

TLR2 polymorphism	Genotype/allele	Study population		OR† (95% CI)	*P*
		PUD, No. (%)	NPUD, No. (%)		
Ins/del	i/i	35 (70)	33 (66)	1.2 (0.51−2.7)	0.66
	i/d + dd	15 (30)	17 (34)		
	ins	79 (0.79)	81 (0.81)	0.88 (0.46−1.7)	0.72
	del	21 (0.21)	19 (0.19)		
Arg753Gln	GG	49 (98)	45 (90)	5.4 (0.61−48.4)	0.09
	GA + AA	1 (2)	5 (10)		
	G	98 (0.98)	93 (0.93)	3.6 (0.74−18.2)	0.08
	A	2 (0.02)	7 (0.07)		
Arg677Trp	CC	7 (14)	1 (2)	7.9 (0.94−67.5)	0.03*
	CT + TT	43 (86)	49 (98)		
	C	57 (0.56)	49 (0.49)	1.3 (0.75−2.3)	0.32
	T	43 (0.44)	51 (0.51)		

i: Insertion, d: deletion, † OR: Odds ratio, PUD: peptic ulcer, NPUD: non peptic ulcer. * *P*-value < 0.05 was significant.

Table 4
Genotype and allele frequencies of TLR2 polymorphisms in *H. pylori* positive and negative individuals.

TLR2 polymorphism	Genotype/allele	*H. pylori* infection		†OR (95% CI)	*P*
		Positive, No. (%)	Negative, No. (%)		
Ins/del	i/i	42 (76.5)	26 (57.8)	2.3 (1.0−5.5)	0.04*
	i/d + dd	13 (23.6)	19 (42.2)		
	ins	93 (0.85)	67 (0.74)	1.8 (0.93−3.7)	0.07
	del	17 (0.15)	23 (0.26)		
Arg753Gln	GG	50 (90.9)	44 (97.8)	0.2 (0.02−2.0)	0.15
	GA + AA	5 (9.1)	1 (2.2)		
	G	102 (0.93)	89 (0.99)	0.1 (0.01−1.1)	0.03*
	A	8 (0.07)	1 (0.01)		
Arg677Trp	CC	4 (7.3)	3 (6.7)	1.0 (0.23−5.1)	0.90
	CT + TT	51 (92.7)	42 (93.2)		
	C	58 (0.53)	47 (0.52)	1.0 (0.58−1.70)	0.94
	T	52 (0.47)	43 (0.48)		

i: Insertion, d: deletion, † OR: Odds ratio, PUD: peptic ulcer, NPUD: non peptic ulcer. * *P*-value < 0.05 was significant.

Table 5
Genotype and allele frequencies of TLR2 polymorphisms in *H. pylori*-infected patients with PUD and NPUD.

TLR2 polymorphism	Genotype/allele	*H. pylori* positive subjects		†OR (95% CI)	*P*
		PUD, No. (%)	NPUD, No. (%)		
Ins/del	i/i	26 (74.3)	16 (80)	0.72 (0.19−2.7)	0.63
	i/d + dd	9 (25.7)	4 (20)		
	ins	59 (0.84)	34 (0.85)	0.94 (0.32−2.8)	0.92
	del	11 (0.14)	6 (0.15)		
Arg753Gln	GG	33 (94.3)	20 (100)	0.32 (0.01−7.1)	0.27
	GA + AA	2 (5.7)	0.0 (0.0)		
	G	68 (0.97)	40 (1.0)	0.33 (0.01−7.2)	0.28
	A	2 (0.03)	0 (0.0)		
Arg677Trp	CC	1 (2.9)	3 (15)	0.16 (0.02−1.7)	0.09
	CT + TT	34 (97.1)	17 (85)		
	C	36 (0.51)	23 (0.57)	0.78 (0.36−1.7)	0.53
	T	34 (0.49)	17 (0.43)		

i: Insertion, d: deletion, † OR: Odds ratio, PUD: peptic ulcer, NPUD: non peptic ulcer.

4. Discussion

In the current study, we investigated the association of the TLR2-196 to -174 ins/del, Arg753Gln and Arg677Trp polymorphisms in the development of peptic ulcer disease in the north population of Iran.

Several studies have shown that the TLR2 polymorphisms are associated with susceptibility to inflammatory diseases and allelic and genotypic frequencies of TLR2 polymorphisms are diverse between different populations.[27] This is the first study to report the TLR2-196 to -174 ins/del, Arg753Gln and Arg677Trp polymorphisms in patients with peptic ulcer from North of Iran. In the present study, we found that TLR2 Arg677Trp polymorphism was associated with an increased risk (OR 7.9, 95% CI 0.94−67.5; $P = 0.03$) of peptic ulcer in this population. Presence of 1 in 95% CI with $P = 0.03$, was due to imbalance and very few finding (one sample for CC genotype in Table 3) of these genotypes in data. No significantly association were observed between TLR2-196 to -174 ins/del and Arg753Gln with susceptibility to peptic ulcer. In recent years, some studies have reported divergent results. For example, Tahara et al. reported no association between TLR2-196 to -174 ins/del polymorphism and gastric ulcer development.[14] However, in 2012, de Oliveira et al. reported that the TLR2 ins/del and del/del genotypes were significantly higher in the gastric cancer group compared to the healthy individuals.[8] Nevertheless, other studies have shown the association of TLR2-196 to -174 ins/del polymorphism at risk of severe intestinal metaplasia in older patients.[8] Studies reported that genotypes of the TLR2 Arg677Trp and Arg753Gln polymorphism were not observed in the Guangxi Zhuang population of China.[27] The present data demonstrated that the frequency of the TLR2 Arg677Trp CC genotype was significantly higher in the PUD than in NPUD. It is suggested that the risk of peptic ulcer development is higher in subjects carrying the C allele compared to the T allele.

Concerning *H. pylori* infection, we demonstrated that there was more prevalent of *H. pylori* infection in the patients with peptic ulcer compared to NPUD group (70% vs. 40%). This finding is in accordance with high prevalence (65−100%) of *H. pylori* infection in Iranian patients with peptic ulcer and is in contrast to studies in European patients (33.9−57.7%).[3,28] We have investigated the effect of TLR2 polymorphisms on subjects with and without *H. pylori* infection. Our results demonstrated an association between TLR2-196 to -174 ins/del and Arg753Gln polymorphisms with *H. pylori* infection.

An increased risk of *H. pylori* infection was observed in subjects with ins/ins genotype of TLR2-196 to -174 ins/del polymorphisms. It is possible that polymorphisms within the TLR2 genes lead to alteration of TLR2 activity, and then favor the development of *H. pylori* infection.[22]

It should be noted that for more analysis, *H. pylori*-negative individuals were excluded because we wanted to focus the influence of TLR2 polymorphisms on the risk of PUD development in *H. pylori* infected patients. Data analysis in PUD and NPUD individuals that were infected by *H. pylori* infection showed no significant association, while some TLR2 polymorphism were associated with *H. pylori* infection status.

The strength of this study was the significant association between TLR2 Arg677Trp polymorphism with PUD developments in north of Iran compared with other studies on gastroduodenal diseases. However, this study had some limitations. We acknowledge that the key limitation of our study is the small sample size, which may also have a significant effect on observed statistical significance. In this study, minimal CC genotype frequency fluctuations of TLR2 Arg677Trp polymorphism would obliterate the positive association result. A large cohort study is recommended to replicate and validate the associations of SNPs with the PUD development in infected *H. pylori* individuals.

In conclusion, this study showed TLR2 Arg677Trp polymorphism was associated with increased susceptibility to peptic ulcer. Although no association was observed for TLR2-196 to -174 and Arg753Gln polymorphisms and peptic ulcer development, but these polymorphisms have a significant effect on *H. pylori* infection. However, further studies are needed to investigate these polymorphisms effects on peptic ulcer development in other populations to achieve a more reliable interpretation.

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