Associations between cytokine gene polymorphisms and susceptibility to Helicobacter pylori infection and Helicobacter pylori related gastric cancer, peptic ulcer disease: A meta-analysis

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Abstract

Objectives
The aim of this study is to clarify the associations between IL-1B31C/T, IL-1B-511C/T, IL-8-251T/A gene polymorphisms and the risk of Helicobacter pylori (H. pylori) infection together with H. pylori-related gastric cancer (GC), peptic ulcer disease (PUD).

Methods
All eligible literature published up to July 2016 were identified by searching Pubmed, Embase, Web of Science and CNKI. Pooled odds ratio (OR) and 95% confidence interval (95% CI) were calculated using a fixed or random effects model.

Results
29 case-control studies were eligible, and each of them may focus on more than one gene polymorphism. Ultimately, there were 21 studies (3159 cases and 2816 controls) for IL-1B-31C/T, 16 studies (2486 cases and 1989 controls) for IL-1B-511C/T polymorphisms, 9 studies (1963 cases and 1205 controls) for IL-8-251T/A polymorphisms. Overall, an increased risk of H. pylori infection was found for IL-1B-31C/T polymorphisms [OR = 1.134, 95%CI = 1.008–1.275 for recessive model; OR = 1.145, 95%CI = 1.007–1.301 for TT vs CC model]. While, for IL-1B-511C/T and IL8-251T/A polymorphisms, no evidence indicated that they were associated with the risk of H. pylori infection in all genetic models.

Furthermore, we found an increased risk of H. pylori-related GC with IL-1B-511C/T polymorphisms [OR = 1.784, 95%CI = 1.289–2.469 for recessive model; OR = 1.772, 95%CI = 1.210–2.594 for TT vs CC model] and IL8-251T/A polymorphisms [OR = 1.810, 95%CI = 1.229–2.667 for recessive model; OR = 1.717, 95%CI = 1.143–2.580 for TT vs AA model], an increased risk of H. pylori-related PUD with IL8-251T/A polymorphisms [OR = 1.364, 95%CI = 1.010–1.843 for recessive model; OR = 1.427, 95%CI = 1.039–1.959 for AA vs TT model].
Conclusions

IL-1B-31C/T gene polymorphisms might increase *H. pylori* infection risk. IL-1B-511-C/T and IL-8-251T/A gene polymorphisms might act as a risk factor to *H. pylori*-related diseases including GC or PUD

Introduction

*Helicobacter pylori* (*H. pylori*) is well known as a special bacterium that usually establishes in the human stomach, which is a special etiological factor of various gastro-duodenal diseases, including chronic gastritis, peptic ulcer disease (PUD) including gastric ulcer and duodenal ulcer, some forms of gastric cancer (GC), even colonic cancer and pancreatic cancer [1,2,3,4]. However, in most cases the *H. pylori* infection is asymptomatic [5]. Pathogenic factors of *H. pylori* infection and the development of *H. pylori*-related gastric diseases were influenced by the degree of virulence of the *H. pylori* strain, the host genetic susceptibility and environmental factors [6,7]. Increasing researches indicated that genetic factors that regulate cytokine production can effect an individual's susceptibility to *H. pylori* infection, which plays a major role in the pathogenic process of *H. pylori*-related diseases such as PUD, GC [8,9]. The expression of pro-inflammatory cytokine creates a condition of hypoacidity that favors the survival and colonization of *H. pylori* [10,11].

IL-1β (encoded by IL-1B gene) is involved in many cellular activities including inflammatory response and secretion of gastric acid [12,13]. It has been shown IL-1B-31C/T and IL-1B-511C/T polymorphisms are closely related to GC, they are found to more frequently occur in Chinese GC patients [14,15]. *H. pylori* infection may have an interactive relationship with IL-1β gene. *H. pylori* infection induces IL-1β expression, increasing the mucosal IL-1β levels, while the IL-1β levels decreases after *H. pylori* eradication [16,17]. In addition, the -31C allele of IL-1B seems to be as a potent depressor of gastric acid secretion, IL-1β is a 100-fold more potent inhibitor than PPIs, and 6000-fold more potent than H2 receptor antagonists on a molar basis, which allows the expansion and reproduction of *H. pylori* colonization [18].

It has been reported that IL-8 gene has a polymorphism of an A/T base pair in the promoting region (−251), which is strongly associated with increasing the synthesis of interleukin by gastric epithelial cells [19,20,21]. IL-8 is a pro-inflammatory chemokine and plays an important role in the pathogenesis of *H. pylori*-induced diseases [22]. A powerful and strong evidence has shown that, during *H. pylori* infection, particularly the cag-PAI-positive strain of *H. pylori*, high expression of IL-8 from gastric epithelial cells plays an important role in the initiation, modulation and maintenance of inflammatory responses, which can amplify the inflammatory responses via recruiting neutrophils and monocytes, leading to a development degree of gastritis [23]. It is also reported that IL8-251TT genotype seems to act as a protective factor against *H. pylori* infection while IL8-251TA genotype may increase the risk of *H. pylori* infection [24]. Ivy Bastos Ramis reported that *H. pylori* infection patients with the A/A genotype at the IL-8-251 position have an increased risk of PUD [25].

Although many previous studies have concentrated the association of *H. pylori* infection or *H. pylori*-related diseases with the IL-1B-31C/T, IL-1B-511C/T, IL-8-251T/A polymorphism, they drew complicated and inconsistent results. Zhao Y et al [26] reported that no statistical significance was found about the correlation between IL-1B-31C/T and *H. pylori* infection, but one recent meta-analysis suggested that IL-1B-31C/T polymorphism might confer susceptibility to *H. pylori*-related GC [27]. Caleman Neto A et al [24] revealed that it was IL-8-251T/A
polymorphism associated with H. pylori infection instead of IL-1B-511 C/T polymorphisms, but Park MJ [28] suggested that H. pylori infection might increase the association between IL-1B-511C/T and stomach carcinoma. Additionally, an interesting observation has shown that the IL1B-511TT genotype was associated with the risk of PUD and H. pylori [29]. The results remain inconclusive and a comprehensive analysis is necessary. Therefore, we conducted this meta-analysis to clarify the associations between IL-1B31C/T, IL-1B-511C/T, IL-8-251T/A gene polymorphisms and the risk of H. pylori infection together with H. pylori-related GC and PUD.

Materials and methods

Search strategy
In this work, we conducted a meta-analysis about the association between IL-1, IL-8 gene polymorphisms and H. pylori infection. This study was approved by Wuhan University Renmin Hospital. A systematic literature search was conducted for articles about IL-1B31C/T, IL-1B-511C/T, IL-8-251T/A gene polymorphism associated with H. pylori infection or H. pylori-related disease in a manner with combination of free terms and subject terms. Relevant researches were searched using the terms [interleukin or cytokine or IL] AND [gene] AND [variants or polymorphism or single nuclear polymorphism or mutation] AND [Helicobacter pylori infection or Helicobacter pylori-related diseases or H. pylori or H. pylori-related diseases] via the Pubmed, Embase, Chinese National Knowledge Infrastructure (CNKI), Web of Science Databases without the language restriction. The search was restricted to humans. Additional studies were acquired by screening references in the retrieved articles and preceding reviews on the topic.

Study selection
The studies included must meet the following criteria: 1) case-control studies, 2) described the association of IL-1B31C/T, IL-1B-511C/T, IL-8-251T/A gene polymorphism with H. pylori infection, 3) studies had detailed the numbers of both controls and cases so that we could obtain available genotype frequencies. Accordingly, the exclusion criteria: 1) case-only studies, case reports, and review articles, 2) duplicate data, 3) only for benign disease compared with controls, 4) studies that investigated target gene variants as marks for response to therapy.

Data extraction and quality assessment
Two investigators selected the article and extracted the data independently, reaching a consensus on all of the terms. If they generated different results, it’s necessary to check the data again and have a discussion until an agreement. If they could not reach an agreement, an expert (Dong WG) would join in the discussion to reach an agreement. The data extracted from any article included the first author’s name, the publication year, country, ethnicity, study design, genotype method, the number of case and control. The ethnicities were classified as Asian or Caucasian population. The quality of selected studies was independently evaluated on basis of Newcastle-Ottawa scale (NOS) [30]. Studies with six or more stars were considered as high quality.

Statistical analysis
The meta-analysis was performed using the Cochrane Collaboration Revman 5.2 and STATA package version 11.0 (Stata corporation, College Station, Texas). The risk of H. pylori infection associated with IL-1B31C/T, IL-1B-511C/T, IL-8-251T/A gene polymorphism was estimated for each eligible study by odd ratios (OR) corresponding to a 95% confidence interval (95% CI). A χ²-based Q statistical test and I² index were performed to assess the between-study
heterogeneity [31,32]. If $P < 0.10$ or $I^2 > 50\%$, the ORs were pooled using a random effect model. Hardy-Weinberg equilibrium (HWE) in control people was judged by $\chi^2$ test. We evaluated the associations of IL-1B31C/T, IL-1B-511C/T, IL-8-251T/A gene polymorphisms with \textit{H. pylori} infection under dominant, recessive, co-dominant, and heterozygote models. Then, stratification analyses were further performed on ethnicity, study design, GC and PUD. Analysis of sensitivity was performed to evaluate the stability of the results. Finally, Publication bias was diagnosed with Begg’s funnel plot and Egger’s linear regression [33,34]. $P < 0.05$ was considered as statistically significant.

Results

Study characteristics

346 potentially relevant studies were retrieved by our search strategy. According to the inclusion and exclusion criteria, 29 studies with full text were ultimately eligible for this meta-analysis and 317 studies were excluded. The flow chart of study selection is summarized in Fig 1. Each of eligible studies may focus on more than one gene polymorphism, and even more than one group in the research. Ultimately, there were twenty-one studies with 3159 cases and 2816 controls concerning IL-1B-31C/T gene polymorphisms, sixteen studies with 2486 cases and 1989 controls concerning IL-1B-511C/T gene polymorphisms, nine studies with 1963 cases and 1205 controls concerning IL-8-251T/A gene polymorphisms. The major characteristics of the included studies are summarized in Table 1. Ethnicity include Asian and Caucasian, two type of study design mean hospital-based population (HB) and Publication-based (PB). PCR-RFLP, PCR-CTPP or Taqman were performed in including studies. Among the enrolled studies, three studies focus on the risk of \textit{H. pylori} infection GC patients for IL-1B-31C/T, six studies focus on the risk of GC in \textit{H. pylori} infection individuals for IL-1B-511C/T, three focus on the risk of GC in \textit{H. pylori} infection individuals for IL-8-251T/A, five focus on the risk of PUD in \textit{H. pylori} infection individuals for IL-8-251T/A. Blood samples were used to determine genetic polymorphisms in all of the included studies. The distribution of genotype in the controls was consistent with HWE for the selected studies except only one study ($P_{\text{HWE}}$ was shown in the Table 1). The qualities of all enrolled studies were categorized as high quality according to the NOS score shown in the Table 1.

Quantitative data synthesis

For IL-1B-31C/T, twenty-one case-control studies with 3159 cases and 2816 controls concerning IL-1B-31C/T gene polymorphisms were identified [15,24,26,35–47]. Overall, there is a significant difference in IL-1B-31C/T genotype distribution between \textit{H. pylori} infection and control [OR = 1.13, 95\%CI = 1.01–1.28 for recessive model, $p = 0.04$; OR = 1.15, 95\%CI = 1.01–1.30 for TT vs CC model, $p = 0.04$] (Fig 2). Furthermore, a significant association was also found in subgroup analysis under recessive model based on Asian population [OR = 1.18, 95\%CI = 1.02–1.37, $p = 0.03$] and GC group [OR = 1.54, 95\%CI = 1.11–2.13, $p = 0.01$], but not in the Caucasian population [OR = 1.06, 95\%CI = 0.87–1.29, $p = 0.56$] (Table 2). Meantime, the association between IL-1B-31C/T gene polymorphisms and \textit{H. pylori} infection seems not to be related to the subgroup analysis based on study design including PB and HB under all genetic compared model (shown in the Table 2).

For IL-1B-511C/T, sixteen studies with 2486 cases and 1989 controls concerning IL-1B-511C/T gene polymorphisms were identified [15,24,37–39,41,44,45,48–54]. Overall, there is no significant difference in IL-1B-511C/T genotype distribution between \textit{H. pylori} infection and control, neither in various subgroup analysis including ethnicity and study design [OR = 1.02, 95\%CI = 0.93–1.12 for dominant model, $p = 0.71$; OR = 1.03, 95\%CI = 0.90–1.19 for recessive
model, p = 0.66) (Table 2). While, six studies with 647 H. pylori-related GC cases and 660 H. pylori infection controls concerning IL-1B-511-C/T gene polymorphisms were further identified [15,41,49,51,54]. We found an increased risk of H. pylori-related GC with IL-1B-511C/T polymorphisms [OR = 1.78, 95%CI = 1.29–2.47 for recessive model, p < 0.001; OR = 1.77, 95% CI = 1.21–2.59 for TT vs CC model, p = 0.003] (Fig 3, Table 3).

For IL-8-251T/A, nine studies with 1963 cases and 1205 controls concerning IL-8-251T/A gene polymorphisms were identified [24,25,35,55–60]. Overall, there is no significant difference in IL-8-251C/T genotype distribution between H. pylori infection case and control [OR = 1.01, 95%CI = 0.88–1.17 for dominant model, p = 0.86; OR = 1.12, 95%CI = 0.91–1.39 for recessive model, p = 0.28], neither in various ethnicity-based subgroup analysis including Asian population [OR = 0.95, 95%CI = 0.78–1.16 for dominant model, p = 0.64; OR = 1.10, 95%CI = 0.69–1.76 for recessive model, p = 0.69] and Caucasian population [OR = 1.07, 95% CI = 0.88–1.31 for dominant model, p = 0.48; OR = 1.11, 95%CI = 0.84–1.46 for recessive model, p = 0.46] (shown in the Table 2). While, three studies [25,58,59] focus on the risk of H. pylori-related GC and five studies [25,56,57,58] focus on the risk of H. pylori-related PUD for IL-8-251T/A gene polymorphisms. The results are rather interesting and exciting. We found an increased risk of H. pylori-related GC with IL-8-251T/A polymorphisms [OR = 1.81, 95% CI = 1.23–2.67 for recessive model, p = 0.003; OR = 1.72, 95%CI = 1.14–2.58 for TT vs AA model, p = 0.01] (Fig 4, Table 3), an increased risk of H. pylori-related PUD with IL-8-251T/A polymorphisms [OR = 1.36, 95%CI = 1.01–1.84 for recessive model, p = 0.04; OR = 1.43, 95% CI = 1.04–1.96 for AA vs TT model, p = 0.03] (Fig 5, Table 3).

Heterogeneity and sensitivity analysis

The heterogeneity of each included studies pertaining to each polymorphism is clearly presented in the Table 2 and Table 3. No significant heterogeneity was observed between enrolled...
### Table 1. Characteristics of studies included in the meta-analysis.

| Study (author) | Year | Country | Ethnicity | Design | Genotype Method | Method | Number | Case/Control | $P_{HWE}$ | NOS score |
|----------------|------|---------|-----------|--------|-----------------|--------|--------|-------------|----------|-----------|
| **IL-1B-31C/T** |      |         |           |        |                 |        |        |             |          |           |
| Abdiev S       | 2010 | Uzbek   | Caucasian | PB     | PCR-CTPP        |        | 124/42 |             | 0.534    | 6         |
| Caleman Neto A | 2014 | Brazil  | Caucasian | PB     | PCR-RFLP        |        | 30/30  |             | 0.876    | 6         |
| Hamajima N     | 2002 | Japan   | Asian     | HB     | PCR-CTPP/RFLP   |        | 324/207|             | 0.070    | 7         |
| Hamajima N(1)  | 2001 | Japan   | Asian     | HB     | PCR-CTPP/RFLP   |        | 82/36  |             | 0.863    | 6         |
| Hamajima N(2)  | 2001 | Japan   | Asian     | HB     | PCR-CTPP/RFLP   |        | 69/54  |             | 0.669    | 6         |
| He BS (1)      | 2011 | China   | Asian     | HB     | PCR-RFLP        |        | 251/141|             | 0.505    | 6         |
| He BS (2)      | 2011 | China   | Asian     | HB     | PCR-RFLP        |        | 240/268|             | 0.299    | 6         |
| Hu S           | 2005 | China   | Asian     | PB     | PCR-RFLP        |        | 96/159 |             | 0.650    | 7         |
| Kang WK        | 2004 | Korea   | Asian     | HB     | PCR-RFLP        |        | 33/68  |             | 0.977    | 6         |
| Katsuda        | 2003 | Japan   | Asian     | PB     | PCR-CTPP        |        | 242/195|             | 0.431    | 7         |
| Kumar S(1)     | 2009 | India   | Caucasian | HB     | PCR-RFLP        |        | 111/25 |             | 0.922    | 7         |
| Kumar S(2)     | 2009 | India   | Caucasian | HB     | PCR-RFLP        |        | 56/54  |             | 0.058    | 7         |
| Li J           | 2010 | China   | Asian     | HB     | PCR-RFLP        |        | 53/75  |             | 0.554    | 6         |
| Queiroz DM     | 2009 | Brazil  | Caucasian | HB     | PCR-CTPP        |        | 370/171|             | 0.222    | 7         |
| Saito Y        | 2007 | Japan   | Asian     | PB     | TaqMan          |        | 237/173|             | 0.666    | 7         |
| Tseng FC       | 2006 | Jamaica | Asian     | HB     | TaqMan          |        | 36/147 |             | 0.928    | 8         |
| Uno M (1)      | 2002 | Brizil  | Caucasian | PB     | PCR-CTPP        |        | 196/198|             | 0.163    | 7         |
| Uno M (2)      | 2002 | Brizil  | Caucasian | PB     | PCR-CTPP        |        | 261/292|             | 0.061    | 7         |
| Yang J(1)      | 2004 | China   | Asian     | PB     | PCR-RFLP        |        | 151/126|             | 0.722    | 8         |
| Yang J(2)      | 2004 | China   | Asian     | PB     | PCR-RFLP        |        | 164/94 |             | 0.414    | 8         |
| Zhao Y         | 2013 | Indonesia | Asian  | PB     | PCR-CTPP        |        | 33/261 |             | 0.889    | 7         |
| **IL-1B-511C/T** |      |         |           |        |                 |        |        |             |          |           |
| Arango MT      | 2010 | Colombia | Caucasian | HB     | PCR-CTPP/RFLP   |        | 66/45  |             | 0.295    | 7         |
| Caleman Neto A | 2014 | Brazil  | Caucasian | PB     | PCR-RFLP        |        | 30/30  |             | 0.543    | 6         |
| Hamajima N     | 2001 | Japan   | Asian     | HB     | PCR-CTPP/RFLP   |        | 149/90 |             | 0.414    | 6         |
| He BS          | 2011 | China   | Asian     | HB     | PCR-RFLP        |        | 491/409|             | 0.52     | 6         |
| Hu S           | 2005 | China   | Asian     | PB     | PCR-RFLP        |        | 96/159 |             | 0.858    | 6         |
| Jiang          | 2007 | China   | Asian     | HB     | PCR-RFLP        |        | 118/50 |             | 0.586    | 7         |
| Kang WK        | 2004 | Korea   | Asian     | HB     | PCR-RFLP        |        | 33/68  |             | 0.977    | 6         |
| Kimang’a AN    | 2012 | Kenya   | Caucasian | HB     | PCR-RFLP        |        | 151/119|             | 0.096    | 7         |
| Kumar S        | 2009 | India   | Caucasian | HB     | PCR-RFLP        |        | 167/79 |             | 0.195    | 6         |
| Li C           | 2007 | China   | Asian     | HB     | PCR-RFLP        |        | 374/289|             | 0.973    | 7         |
| Li Q           | 2010 | China   | Asian     | HB     | PCR-RFLP        |        | 182/44 |             | 0.25     | 7         |
| Saito Y        | 2007 | Japan   | Asian     | PB     | TaqMan          |        | 237/173|             | 0.518    | 7         |
| Tseng FC       | 2006 | Jamaica | Asian     | HB     | TaqMan          |        | 34/149 |             | 0.283    | 7         |
| Yakar T        | 2015 | Turkey  | Caucasian | HB     | PCR-RFLP        |        | 66/45  |             | 0.295    | 7         |
| Zeng ZR (1)    | 2003 | China   | Asian     | HB     | PCR-RFLP        |        | 135/142|             | 0.46     | 8         |
| Zeng ZR (2)    | 2003 | China   | Asian     | HB     | PCR-RFLP        |        | 157/98 |             | 0.069    | 8         |
| **IL-8-251T/A** |      |         |           |        |                 |        |        |             |          |           |
| Abdiev S       | 2010 | Uzbek   | Caucasian | PB     | PCR-CTPP        |        | 124/42 |             | 0.031    | 6         |
| Caleman Neto A | 2014 | Brazil  | Caucasian | PB     | PCR-RFLP        |        | 30/30  |             | 0.218    | 6         |
| Chakravorty M  | 2008 | India   | Caucasian | PCR    |                |        | 153/157|             | 0.998    | 6         |
| Farshad S      | 2010 | Iran    | Asian     | HB     | PCR-RFLP        |        | 90/371 |             | 0.587    | 7         |
| Kang JM        | 2009 | Korea   | Asian     | PB     | PCR              |        | 884/160|             | 0.478    | 7         |
| Kumar S        | 2015 | India   | Caucasian | PB     | PCR-ARMS        |        | 394/82 |             | 0.898    | 8         |

(Continued)
studies in all comparisons under each model (P > 0.05, or I² < 50%). Then, sensitivity analysis was performed to evaluate the stability of the results by removing one study one by one. The estimated pooled odd ratio did not change after removing any single study. The above analysis indicated that the results were stable and statistically robust.

Publication bias

Begg’s funnel plot and Egger’s test were conducted to clarify potential publication bias. The shape of funnel plots showed a nearly symmetrical distribution, indicating no evidence of publication bias in all genetic models (Fig 6). Egger’s test also reveal no statistical significance for evaluation of publication bias under recessive model for H. pylori infection risk [IL-1B-31C/T: P = 0.275, IL-1B-511C/T: P = 0.06, IL-8-251A/T: P = 0.184], for H. pylori-related GC [IL-1B-511C/T: P = 0.781, IL-8-251A/T: P = 0.88], for H. pylori-related PUD [IL-8-251A/T: P = 0.71].

Discussion

GC is one of the major causes of cancer-related death worldwide [61], and PUD is also a common disease worldwide with a lifetime prevalence in the adult population around 5% to 10% over the past decade [62]. It has been widely accepted that H. pylori infection is the most important etiological factor for the development of GC, and meanwhile plays a key roles in the pathogenesis of PUD. H. pylori infection is present in approximately 50% of the world population [63]. However, not every H. pylori infection individuals developed GC, PUD or other related diseases. In recent years, gene single nuclear polymorphisms (SNPs) have been identified as a very powerful tool for predicting some complex diseases. Prevalent inflammation related gene IL-1B and IL-8 polymorphisms may potentially alter the expression of them, which depress the secretion of gastric acid, amplify the inflammatory responses, thus being is favorable to H. pylori infection or H. pylori-related diseases. Increasing researchers have been focusing attention on the possible association between human inflammation related gene polymorphisms and H. pylori infection or H. pylori-related diseases. However, the associations have not been proved well. Therefore, we designed this meta-analysis to clarify the correlations between IL-1B-31C/T, IL-1B-511C/T, IL-8-251T/A gene polymorphisms and the risk of H. pylori infection together with H. pylori-related GC and PUD.

Our results revealed that there is a significant difference in IL-1B-31C/T genotype distribution between H. pylori infection and control, and IL-1B-511C/T gene polymorphism might have no relation with the risk of H. pylori infection. For IL-1B-31C/T, the individuals’ susceptibility to H. pylori infection were increased in Asian population, but not in Caucasian population in the subgroup analysis, the frequency of IL-1B-31TT was higher among H. pylori infection.
Fig 2. Meta-analysis of the association between IL-1B-31C/T polymorphisms and susceptibility to *H. pylori* infection. (a). Recessive model. (b) TT vs CC model.

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infection than controls. Additionally, six studies with 647 \textit{H. pylori}-related GC cases and 660 \textit{H. pylori} inflection controls concerning IL-1B-511C/T gene polymorphisms, we found an increased risk of \textit{H. pylori}-related GC with IL-1B-511C/T polymorphisms. And we found that different studies had inconsistent results about IL-1B-31C/T, IL-1B-511C/T gene polymorphisms with the risk of \textit{H. pylori} infection or \textit{H. pylori}-related diseases. For instance, El-Omar EM et al\cite{64} said that the polymorphisms of IL-1B-511T and IL-1B-31C alleles are significantly associated with \textit{H. pylori} related diseases and the clinical presentations in a Caucasian research, they also concluded that IL-1B-31T allele is the wild type and the IL-1B-31C allele is a mutant, but Chang et al\cite{65} said that mucosal IL-1\(\beta\) levels in \textit{H. pylori}-infected GC patients were higher in patients homozygous for IL-1B-31T compared with IL-1B-31C/T and IL-1B-31C/C. To our knowledge, ethnic origin is a potent and key determinant of the frequency of genetic markers in a population which might well explain this mutation difference about IL-1B-31C/T gene in Asian and Caucasian population, which in turn means individuals with IL-

**Table 2. Summary of ORs of the IL-1B-31C/T, IL-1B-511C/T, IL-8-251A/T gene polymorphisms and \textit{H. pylori} infection.**

| Gene          | N  | Dominant model |  | Recessive model |  | Homozygous model |  | Heterozygous model |  |
|---------------|----|----------------|---|----------------|---|----------------|---|-------------------|---|
|               |    | OR(95%CI) P\(^a\) |  | OR(95%CI) P\(^b\) |  | OR(95%CI) P\(^c\) |  | OR(95%CI) P\(^d\) |  |
| IL-1B-31C/T   |    |                |   |                |   |                |   |                |   |
| Total         | 21 | 1.06 (0.97,1.15) | 0.20 | 0.29 | 13% | 1.13 (1.01,1.28) | 0.04 | 0.15 | 25% | 1.15 (1.01,1.30) | 0.04 | 0.19 | 32% | 1.06 (0.96,1.18) | 0.24 | 0.99 | 0% |
| Asian         | 14 | 1.06 (0.96,1.17) | 0.28 | 0.14 | 30% | 1.18 (1.02,1.37) | 0.03 | 0.22 | 21% | 1.17 (0.99,1.37) | 0.06 | 0.92 | 0% | 1.06 (0.94,1.20) | 0.36 | 0.35 | 9% |
| Caucasian     | 7  | 1.05 (0.91,1.21) | 0.49 | 0.62 | 0% | 1.06 (0.87,1.29) | 0.56 | 0.18 | 32% | 1.11 (0.89,1.37) | 0.37 | 0.22 | 28% | 1.07 (0.89,1.27) | 0.47 | 0.75 | 0% |
| PB            | 11 | 1.04 (0.94,1.16) | 0.422 | 0.86 | 0% | 1.15 (0.99,1.34) | 0.06 | 0.24 | 21% | 1.13 (0.96,1.32) | 0.14 | 0.45 | 0% | 1.04 (0.91,1.19) | 0.55 | 0.88 | 0% |
| HB            | 10 | 1.07 (0.94,1.16) | 0.30 | 0.05 | 47% | 1.10 (0.91,1.34) | 0.33 | 0.14 | 34% | 1.17 (0.95,1.45) | 0.14 | 0.71 | 0% | 1.10 (0.93,1.29) | 0.26 | 0.26 | 20% |
| GC \(^c\)     | 3  | 1.14 (0.91,1.43) | 0.24 | 0.88 | 0% | 1.54 (1.11,2.14) | 0.01 | 0.43 | 0% | 1.51 (1.05,2.17) | 0.03 | 0.66 | 0% | 1.14 (0.87,1.49) | 0.34 | 0.83 | 0% |
| IL-1B-511C/T  |    |                |   |                |   |                |   |                |   |
| Total         | 16 | 1.02 (0.93,1.12) | 0.71 | 0.33 | 11% | 1.03 (0.90,1.19) | 0.66 | 0.54 | 0% | 1.04 (0.89,1.21) | 0.64 | 0.54 | 0% | 1.02 (0.91,1.14) | 0.70 | 0.22 | 21% |
| Asian         | 11 | 1.03 (0.92,1.14) | 0.65 | 0.41 | 3% | 0.99 (0.85,1.16) | 0.92 | 0.32 | 13% | 1.03 (0.86,1.22) | 0.77 | 0.35 | 9% | 1.04(0.92,1.17) | 0.55 | 0.45 | 0% |
| Caucasian     | 5  | 0.99 (0.80,1.23) | 0.92 | 0.19 | 35% | 1.19 (0.88,1.61) | 0.26 | 0.99 | 0% | 1.08 (0.76,1.50) | 0.65 | 0.67 | 0% | 0.95 (0.73,1.24) | 0.71 | 0.11 | 46% |
| IL-8-251A     |    |                |   |                |   |                |   |                |   |
| Total         | 9  | 1.01 (0.88,1.17) | 0.86 | 0.15 | 34% | 1.12 (0.91,1.39) | 0.28 | 0.15 | 34% | 1.10 (0.88,1.37) | 0.43 | 0.11 | 39% | 0.99 (0.83,1.17) | 0.87 | 0.17 | 31% |
| Asian         | 4  | 0.95 (0.78,1.16) | 0.64 | 0.28 | 21% | 1.10 (0.89,1.76) | 0.69 | 0.07 | 58% | 1.00 (0.83,1.50) | 0.99 | 0.04 | 64% | 0.91 (0.72,1.44) | 0.40 | 0.64 | 0% |
| Caucasian     | 5  | 1.07 (0.88,1.31) | 0.48 | 0.32 | 15% | 1.11 (0.84,1.46) | 0.46 | 0.29 | 19% | 1.13 (0.85,1.52) | 0.40 | 0.41 | 0% | 1.09 (0.85,1.40) | 0.50 | 0.22 | 31% |

N. number of studies.
OR, odds ratio; 95%CI, 95% confidence interval.
\(^a\) Text for overall effect.
\(^b\) Text for heterogeneity, a random effects model was used when the P for heterogeneity test < 0.10 or I\(^2\) > 50%, otherwise, a fixed effects model was used.
\(^c\) In this subgroup, the \textit{H. pylori} infection individuals were from gastric cancer patients.

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1B-31TT genotype might have a high risk of *H. pylori* infection in Asian population. Another recent and new research investigated that *H. pylori* infection reinforces the relation between IL-1β-511 T allele with susceptibility to gastric cancer [OR = 2.04, 95%CI = 1.15–3.62 for recessive model], which means *H. pylori* infection as a risk factor might have synergistic effect with IL-1B-511T allele the development of GC [28]. However, it exists a high Heterogeneity [P < 0.0001, I² = 84%]. In this meta-analysis, IL-1B-511TT genotype or T allele carriers might
act as a potential candidate of biomarker for *H. pylori*-related GC risk \[OR = 1.78, 95\% CI = 1.29–2.47 for recessive model, \(p < 0.001\); OR = 1.77, 95\% CI = 1.21–2.59 for TT vs CC model, \(p = 0.003\)\], and there was no significant heterogeneity was observed between enrolled studies in all comparisons under each model \[\(P > 0.10, I^2 < 50\%\]\. Despite the decline in OR compared with the previous study, it is noteworthy that a significant risk between IL-1B-511C/T polymorphisms and *H. pylori*-related GC risk could be seen. But this result should be interpreted with caution because of limited studies and absence further research.
The meta-analysis of IL-8-251T/A included nine studies with 1963 cases and 1205 controls. No significant difference was found in IL-8-251T/A genotype distribution between *H. pylori* infection case and control, then we further conducted ethnic-based subgroup analysis, but there was no change in the association between IL-8-251T/A polymorphism and *H. pylori* infection. Interestingly, for IL-8-251T/A gene polymorphisms, three studies showed a significant increase risk of *H. pylori*-related GC, and five studies showed a significant increase risk of *H. pylori*-related PUD. Although there was only limited studies in this meta-analysis, some

### Table 1: Meta-analysis of IL-8-251T/A Polymorphism and Susceptibility to *H. pylori*-Related GC

| Study ID          | OR (95% CI)     | Weight |
|-------------------|-----------------|--------|
| Chakravorty M2008 | 1.12 (0.63, 1.98) | 27.80  |
| Farshad S2010     | 1.09 (0.40, 2.98) | 8.97   |
| Fashad S 2010(1)  | 1.95 (1.16, 3.26) | 33.97  |
| Kang JM2009       | 1.06 (0.56, 2.00) | 22.49  |
| Ramis IB2015      | 1.62 (0.51, 5.13) | 6.77   |
| Overall           | 1.36 (1.01, 1.84) | 100.00 |

### Table 2: Meta-analysis of IL-8-251T/A Polymorphism and Susceptibility to *H. pylori*-Related PUD

| Study ID          | OR (95% CI)     | Weight |
|-------------------|-----------------|--------|
| Chakravorty M2008 | 1.15 (0.63, 2.09) | 27.71  |
| Farshad S2010     | 1.05 (0.36, 3.09) | 8.70   |
| Fashad S 2010(1)  | 2.04 (1.19, 3.51) | 34.49  |
| Kang JM2009       | 1.21 (0.63, 2.35) | 23.05  |
| Ramis IB2015      | 1.44 (0.40, 5.24) | 6.05   |
| Overall           | 1.43 (1.04, 1.96) | 100.00 |

**Fig 5.** Meta-analysis of the association between IL-8-251T/A polymorphisms and susceptibility to *H. pylori*-related PUD. (a) Recessive model. (b) TT vs AA model.

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Fig 6. Begg’s funnel plot for publication bias under dominant model. (a) IL-1B-31C/T. (b) IL-1B-511C/T. (c) IL-8-251T/A.

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new and recent researches came to support our results. For instance, Hofner et al [66] reported a higher frequency of the IL-8-251T/A genotype among H. pylori-related duodenal ulcer patients than controls. Another interesting Japanese research also indicated that the IL-8-251AA and AT genotypes might increase the individuals’ susceptibility to H. pylori-related diseases, but not increase the risk of H. pylori infection [9]. In terms of the mechanism, the allele A of IL-8-251T/A gene promoter region might increase the expression level of IL-8 gene, and the allele A carriers have a higher gastric mucosal neutrophil infiltration score, thus increasing the susceptibility to H. pylori-related diseases[67]. Considering the above evidences, the association between IL-8-251T/A polymorphism and H. pylori-related diseases should be raised more attention, it’s necessary to conclude more case-control research to further clarify.

This research shed lights on the relationship of gene polymorphism and the increased susceptibility to H. pylori infection or H. pylori-related diseases systematically. The exhaustive inclusion criteria and studies combined with a series of subgroup analysis enhanced the power and persuasion of our conclusion. Additionally, all including literatures were consistent with HWE (P>0.05) and accepted as high quality (at least 6 score according to the NOS score). However, we were also aware of some limitations of our study. Firstly, it is also possible that language bias might exist, as our meta-analysis only included articles published in Chinese, English and only one Korean. Secondly, the tendency not to publish negative results may also have produced bias. Thirdly, the number of studies, especially for the relationship of IL-8-251T/A polymorphism and H. pylori-related GC, was not sufficiently large, more studies involving much larger sampling sizes and well-designed character should be conducted.

Conclusions

This meta-analysis indicated that IL-1B-31TT genotype might increase the individuals’ susceptibility to H. pylori infection, and this relationship was enhanced in Asian population. Additionally, IL-1B-511-C/T and IL-8-251T/A gene polymorphisms might act as a risk factor to H. pylori-related diseases including GC or PUD. Large and well-designed studies with different ethnicities are warranted to clarify our conclusions.

Supporting information

S1 Checklist. Meta-analysis on genetic association studies checklist.
(DOCX)

S2 Checklist. PRISMA checklist.
(DOC)

Author Contributions

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References
1. Liu YE, Gong YH, Sun LP, Xu Q, Yuan Y (2012) The relationship between H. pylori virulence genotypes and gastric diseases. Pol J Microbiol 61: 147–150. PMID: 23163215
2. Venerito M, Selgrad M, Malfertheiner P (2013) Helicobacter pylori: gastric cancer and extragastric malignancies—clinical aspects. Helicobacter 18 Suppl 1: 39–43.
3. Sonnenberg A, Genta RM (2013) Helicobacter pylori is a risk factor for colonic neoplasms. Am J Gastroenterol 108: 208–215. https://doi.org/10.1038/ajg.2012.407 PMID: 23208272
4. Risch HA, Lu L, Kidd MS, Wang J, Zhang W, et al. (2014) Helicobacter pylori seroposities and risk of pancreatic carcinoma. Cancer Epidemiol Biomarkers Prev 23: 172–178. https://doi.org/10.1158/1055-9965.EPI-13-0447 PMID: 24234587
5. Atherton JC (1998) H. pylori virulence factors. Br Med Bull 54: 105–120. PMID: 9604436
6. Go MF (1997) What are the host factors that place an individual at risk for Helicobacter pylori-associated disease? Gastroenterology 113: S15–S20. PMID: 9394754
7. Wang J, Zhang Q, Liu Y, Han J, Ma X, et al. (2015) Association between HLA-gene polymorphism and Helicobacter pylori infection in Asian and European population: A meta-analysis. Microb Pathog 82: 15–26. https://doi.org/10.1016/j.micpath.2015.03.011 PMID: 25773770
8. Kulimbetova GN, Imambekova MK, Logvinenko AA, Sukashev AT, Filipenko ML, et al. (2014) Association of cytokine gene polymorphisms with gastritis in a Kazakh population. Asian Pac J Cancer Prev 15: 7763–7768. PMID: 25292060
9. Ohyamauchi A, Imatani A, Yonechi M, Asano N, Miura A, et al. (2005) The polymorphism interleukin 8–251 A/T influences the susceptibility of Helicobacter pylori related gastric diseases in the Japanese population. Gut 54: 330–335. https://doi.org/10.1136/gut.2003.033050 PMID: 15710978
10. Kuipers EJ, Uyterlinde AM, Pena AS, Roosendaal R, Pals G, et al. (1995) Long-term sequelae of Helicobacter pylori gastritis. Lancet 345: 1525–1528. PMID: 7791437
11. Shin A, Kim J, Park S (2011) Gastric cancer epidemiology in Korea. J Gastric Cancer 11: 135–140. https://doi.org/10.5230/jgc.2011.11.3.135 PMID: 22076217
12. Jayaraman P, Sada-Ovalle I, Nishimura T, Anderson AC, Kuchroo VK, et al. (2013) IL-1beta promotes antimicrobial immunity in macrophages by regulating TNFR signaling and caspase-3 activation. J Immunol 190: 4196–4204. https://doi.org/10.4049/jimmunol.1202688 PMID: 23487424
13. Waghray M, Zavros Y, Saqui-Salces M, El-Zaatari M, Alam elumangapuram BM, et al. (2010) Interleukin-1beta promotes gastric atrophy through suppression of Sonic Hedgehog. Gastroenterology 138: 562–572, 571–572. https://doi.org/10.1053/j.gastro.2009.10.043 PMID: 19883649
14. El-Omar EM, Rabkin CS, Gammon MD, Vaughan TL, Risch HA, et al. (2003) Increased risk of noncardia gastric cancer associated with proinflammatory cytokine gene polymorphisms. Gastroenterology 124: 1193–1201. PMID: 12730860
15. He BS, Pan YQ, Xu YF, Zhu C, Qu LL, et al. (2011) Polymorphisms in interleukin-1B (IL-1B) and interleukin 1 receptor antagonist (IL-1RN) genes associate with gastric cancer risk in the Chinese population. Dig Dis Sci 56: 2017–2023. https://doi.org/10.1007/s10620-010-1557-y PMID: 21243433
16. Furuta T, Shirai N, Takashima M, Xiao F, Hanai H, et al. (2001) Effect of genotypic differences in CYP2C19 on cure rates for Helicobacter pylori infection by triple therapy with a proton pump inhibitor, amoxicillin, and clarithromycin. Clin Pharmacol Ther 69: 158–168. https://doi.org/10.1067/mcp.2001.113959 PMID: 11240980
17. Wang M, Furuta T, Takashima M, Futami H, Shirai N, et al. (1999) Relation between interleukin-1beta messenger RNA in gastric fundic mucosa and gastric juice pH in patients infected with Helicobacter pylori. J Gastroenterol 34 Suppl 1: 10–17.
18. Sugimoto M, Furuta T, Shirai N, Nakamura A, Xiao F, et al. (2007) Different effects of polymorphisms of tumor necrosis factor-alpha and interleukin-1 beta on development of peptic ulcer and gastric cancer. J Gastroenterol Hepatol 22: 51–59. https://doi.org/10.1111/j.1440-1746.2006.04442.x PMID: 17201881

19. Taguchi A, Ohmiya N, Shirai K, Mabuchi N, Itoh A, et al. (2005) Interleukin-8 promoter polymorphism increases the risk of atrophic gastritis and gastric cancer in Japan. Cancer Epidemiol Biomarkers Prev 14: 2487–2493. https://doi.org/10.1158/1055-9965.EPI-05-0326 PMID: 16284368

20. Vinagre RM, Corvelo TC, Arnaud VC, Leite AC, Barile KA, et al. (2011) Determination of strains of Helicobacter pylori and of polymorphism in the interleukin-8 gene in patients with stomach cancer. Arq Gastroenterol 48: 46–51. PMID: 21537542

21. Hull J, Thomson A, Kwiakowski D (2000) Association of respiratory syncytial virus bronchiolitis with the interleukin 8 gene region in UK families. Thorax 55: 1023–1027. https://doi.org/10.1136/thorax.55.12.1023 PMID: 11083887

22. Miftahussurur M, Yamaoka Y (2015) Helicobacter pylori virulence genes and host genetic polymorphisms as risk factors for peptic ulcer disease. Expert Rev Gastroenterol Hepatol 9: 1535–1547. https://doi.org/10.1586/17474124.2015.1095089 PMID: 26470920

23. Sugimoto M, Furuta T, Yamaoka Y (2009) Influence of inflammatory cytokine polymorphisms on eradication rates of Helicobacter pylori. J Gastroenterol Hepatol 24: 1725–1732. https://doi.org/10.1111/j.1440-1746.2009.06047.x PMID: 20136959

24. Caleman NA, Rasmussen LT, de Labio RW, de Queiroz VF, Smith MA, et al. (2014) Gene polymorphism of interleukin 1 and 8 in chronic gastritis patients infected with Helicobacter pylori. J Venom Anim Toxins Incl Trop Dis 20: 17. https://doi.org/10.1186/1678-9199-20-17 PMID: 24803922

25. Ramis IB, Vianna JS, Goncalves CV, von Groll A, Dellagostin OA, et al. (2015) Polymorphisms of the IL-6, IL-8 and IL-10 genes and the risk of gastric pathology in patients infected with Helicobacter pylori. J Microbiol Immunol Infect.

26. Zhao Y, Wang JW, Tanaka T, Hosono A, Ando R, et al. (2013) Association between TNF-alpha and IL-1beta genotypes vs Helicobacter pylori infection in Indonesia. World J Gastroenterol 19: 8758–8763. https://doi.org/10.3748/wjg.v19.i46.8758 PMID: 24379587

27. Ying HY, Yu BW, Yang Z, Yang SS, Bo LH, et al. (2016) Interleukin-1B 31 C>T polymorphism combined with Helicobacter pylori-modified gastric cancer susceptibility: evidence from 37 studies. J Cell Mol Med 20: 526–536. https://doi.org/10.1111/jcmm.12737 PMID: 26805397

28. Park MJ, Hyun MH, Yang JP, Yoon JM, Park S (2015) Effects of the interleukin-1beta-511 C/T gene polymorphism on the risk of gastric cancer in the context of the relationship between race and H. pylori infection: a meta-analysis of 20,000 subjects. Mol Biol Rep 42: 119–134. https://doi.org/10.1007/s10933-014-3748-7 PMID: 25258120

29. Chakravorty M, Ghosh A, Choudhury A, Santra A, Hembrum J, et al. (2006) Interaction between IL1B gene promoter polymorphisms in determining susceptibility to Helicobacter pylori associated duodenal ulcer. Hum Mutat 27: 411–419. https://doi.org/10.1002/humu.20299 PMID: 16550552

30. Stang A (2010) Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 25: 603–605. https://doi.org/10.1007/s10654-010-9491-z PMID: 20652370

31. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327: 557–560. https://doi.org/10.1136/bmj.327.7414.557 PMID: 12958120

32. Higgins JP, Thompson SG (2002) Quantifying heterogeneity in a meta-analysis. Stat Med 21: 1539–1558. https://doi.org/10.1002/sim.1186 PMID: 12111919

33. Begg CB, Mazumdar M (1994) Operating characteristics of a rank correlation test for publication bias. Biometrics 50: 1088–1101. PMID: 7786990

34. Egger M, Davey SG, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ 315: 629–634. PMID: 9310563

35. Abdiev S, Ahn KS, Khadjibaev A, Malikov Y, Bahramov S, et al. (2010) Helicobacter pylori infection and cytokine gene polymorphisms in Uzbekis. Nagoya J Med Sci 72: 167–172. PMID: 20942272

36. Hamajima N, Ito H, Matsu K, Tajima K, Tominaga S (2002) Helicobacter Pylori Seropositivity, the Interleukin 1B Polymorphism, and Smoking among First-visit Outpatients. Asian Pac J Cancer Prev 3: 23–28. PMID: 12718604

37. Hamajima N, Matsu K, Saito T, Tajima K, Okuma K, et al. (2001) Interleukin 1 polymorphisms, lifestyle factors, and Helicobacter pylori infection. Jpn J Cancer Res 92: 383–389. PMID: 11346459

38. Hu S, Song QB, Yao PF, Hu QL, Hu PJ, et al. (2005) No relationship between IL-1B gene polymorphism and gastric acid secretion in younger healthy volunteers. World J Gastroenterol 11: 6549–6553. https://doi.org/10.3748/wjg.v11.i41.6549 PMID: 16425433
39. Kang WK, Park WS, Chin HM, Park CH (2004) [The role of interleukin-1beta gene polymorphism in the gastric carcinogenesis]. Korean J Gastroenterol 44: 25–33. PMID: 15266130
40. Katsuda N, Hamajima N, Tamakoshi A, Wakai K, Matsuo K, et al. (2003) Helicobacter pylori seropositivity and the myeloperoxidase G-463A polymorphism in combination with interleukin-1B C-31T in Japanese health checkup examinees. Jpn J Clin Oncol 33: 192–197. PMID: 12810834
41. Kumar S, Kumar A, Dixit VK (2009) Evidences showing association of interleukin-1B polymorphisms with increased risk of gastric cancer in an Indian population. Biochem Biophys Res Commun 387: 456–460. https://doi.org/10.1016/j.bbrc.2009.07.033 PMID: 19607807
42. Li J, Wang F, Zhou Q, Ou Z, Jia H, et al. (2011) IL-1 polymorphisms in children with peptic symptoms in South China. Helicobacter 16: 246–251. https://doi.org/10.1111/j.1525-5378.2011.00837.x PMID: 21585612
43. Queiroz DM, Saraiva IE, Rocha GA, Rocha AM, Gomes LI, et al. (2009) IL2-330G polymorphism allele is increased in risk of Helicobacter pylori infection in adulthood. Microbes Infect 11: 980–987. https://doi.org/10.1016/j.micinf.2009.07.008 PMID: 19638314
44. Saijo Y, Yoshioka E, Fukui T, Kawaharada M, Sata F, et al. (2007) H pylori seropositivity and cytokine gene polymorphisms. World J Gastroenterol 13: 4445–4451. https://doi.org/10.3748/wjg.v13.i33.4445 PMID: 17724799
45. Tseng FC, Brown EE, Maiase EM, Yeager M, Welch R, et al. (2006) Polymorphisms in cytokine genes and risk of Helicobacter pylori infection among Jamaican children. Helicobacter 11: 425–430. https://doi.org/10.1111/j.1525-5378.2006.00433.x PMID: 16961803
46. Uno M, Hamajima N, Ito LS, Oba SM, Marie SK, et al. (2002) Helicobacter pylori seropositivity and IL-1B C-31T polymorphism among Japanese Brazilians. Int J Mol Med 10: 321–326. PMID: 12165808
47. Yang J, Hu Z, Xu Y, Shen J, Niu J, et al. (2004) Interleukin-1B gene promoter variants are associated with an increased risk of gastric cancer in a Chinese population. Cancer Lett 215: 191–198. https://doi.org/10.1016/j.canlet.2004.07.012 PMID: 15488638
48. Arango MT, Jaramillo C, Montealegre MC, Bohorquez MH, Delgado MP (2010) [Genetic characterization of the interleukin 1 b polymorphisms -511, -31 y +3954 in a Colombian population with dyspepsia]. Biomedica 30: 199–206. PMID: 20890567
49. Jiang S (2007) The Research on the Relationship Between IL-1β-511 Gene Polymorphisms and Helicobacter pylori infection and Stomach Carcinoma. Journal of HuBei College of TCM: 31–32.
50. Kimang’A AN (2012) IL-1B-511 Allele T and IL-1RN-L/L Play a Pathologic Role in Helicobacter Pylori infection, IL-1 and IL-8 (-251 A/T) gene polymorphisms in H. pylori mediated gastric disorders. Iran J Immunol 7: 96–103.
51. Li C, Xia HH, Xie W, Hu Z, Ye M, et al. (2007) Association between interleukin-1 gene polymorphisms and Helicobacter pylori infection in gastric carcinogenesis in a Chinese population. J Gastroenterol Hepatol 22: 234–239. https://doi.org/10.1111/j.1440-1746.2006.04379.x PMID: 17295877
52. Li Q (2010) Influence of the IL-1B and IL-1RN Genes Polymorphisms on peptic ulcer disease: Anhui Medical University. 63 p.
53. Yakar T, Serin E, Cosar AM, Arslan TD, Atac FB (2015) The relationship of recurrent apthous stomatitis and Helicobacter pylori, cytokine gene polymorphism and cobalamin. Turk J Gastroenterol 26: 304–308. https://doi.org/10.5152/tjg.2015.0161 PMID: 26039006
54. Zeng ZR, Hu PJ, Hu S, Pang RP, Chen MH, et al. (2003) Association of interleukin 1B gene polymorphism and gastric cancers in high and low prevalence regions in China. Gut 52: 1684–1689. PMID: 14633943
55. Zhao Y, Wang JW, Tanaka T, Hosono A, Ando R, et al. (2013) Association between TNF-alpha and IL-1beta genotypes vs Helicobacter pylori infection in Indonesia. World J Gastroenterol 19: 8758–8763. https://doi.org/10.3748/wjg.v19.i46.8758 PMID: 24379597
56. Chakravorty M, Datta DD, Choudhury A, Santra A, Roychoudhury S (2008) Association of specific haplotype of TNFalpha with Helicobacter pylori-mediated duodenal ulcer in eastern Indian population. J Genet 87: 299–304. PMID: 19147919
57. Farshad S, Rasouli M, Jamshidzadeh A, Hosseinkhani A, Japoni A, et al. (2010) IL-1rs (+3953 C/T) and IL-8 (-251 A/T) gene polymorphisms in H. pylori mediated gastric disorders. Iran J Immunol 7: 96–108. https://doi.org/10.1016/j.ijimid.2010.07.011 PMID: 20574123
58. Kang JM, Kim N, Lee DH, Park JH, Lee MK, et al. (2009) The effects of genetic polymorphisms of IL-6, IL-8, and IL-10 on Helicobacter pylori-induced gastroduodenal diseases in Korea. J Clin Gastroenterol 43: 420–428. https://doi.org/10.1097/MCG.0b013e318178d1d3 PMID: 19077731
59. Kumar S, Kumari N, Mittal RD, Mohindra S, Ghoshal UC (2015) Association between pro-(IL-8) and anti-inflammatory (IL-10) cytokine variants and their serum levels and H. pylori-related gastric
carcinogenesis in northern India. Meta Gene 6: 9–16. https://doi.org/10.1016/j.mgene.2015.07.008 PMID: 26380815

60. Qadri Q, Rasool R, Afroze D, Naqash S, Guizar GM, et al. (2014) Study of TLR4 and IL-8 gene polymorphisms in H.pylori-induced inflammation in gastric cancer in an ethnic Kashmiri population. Immunol Invest 43: 324–336. https://doi.org/10.3109/08820139.2013.854378 PMID: 24295404

61. Siegel RL, Miller KD, Jemal A (2015) Cancer statistics, 2015. CA Cancer J Clin 65: 5–29. https://doi.org/10.3322/caac.21254 PMID: 25559415

62. Miftahussurur M, Yamaoka Y (2015) Helicobacter pylori virulence genes and host genetic polymorphisms as risk factors for peptic ulcer disease. Expert Rev Gastroenterol Hepatol 9: 1535–1547. https://doi.org/10.1586/17474124.2015.1095089 PMID: 26470920

63. Mitchell HM (1999) The epidemiology of Helicobacter pylori. Curr Top Microbiol Immunol 241: 11–30. PMID: 10087654

64. El-Omar EM, Carrington M, Chow WH, McColl KE, Bream JH, et al. (2000) Interleukin-1 polymorphisms associated with increased risk of gastric cancer. Nature 404: 398–402. https://doi.org/10.1038/35006081 PMID: 10746728

65. Chang YW, Jang JY, Kim NH, Lee JW, Lee HJ, et al. (2005) Interleukin-1B (IL-1B) polymorphisms and gastric mucosal levels of IL-1beta cytokine in Korean patients with gastric cancer. Int J Cancer 114: 465–471. https://doi.org/10.1002/ijc.20724 PMID: 15551344

66. Hofner P, Gyulai Z, Kiss ZF, Tiszai A, Tiszlavicz L, et al. (2007) Genetic polymorphisms of NOD1 and IL-8, but not polymorphisms of TLR4 genes, are associated with Helicobacter pylori-induced duodenal ulcer and gastritis. Helicobacter 12: 124–131. https://doi.org/10.1111/j.1523-5378.2007.00481.x PMID: 17309748

67. Taguchi A, Ohnuya N, Shirai K, Mabuchi N, Itoh A, et al. (2005) Interleukin-8 promoter polymorphism increases the risk of atrophic gastritis and gastric cancer in Japan. Cancer Epidemiol Biomarkers Prev 14: 2487–2493. https://doi.org/10.1158/1055-9965.EPI-05-0326 PMID: 16284368