Association of the IL-1RN variable number of tandem repeat polymorphism and Helicobacter pylori infection: A meta-analysis

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Abstract

The aim of this study was to clarify the association of IL-1RN variable number of tandem repeat (VNTR) polymorphism and H. pylori infection. We performed a meta-analysis of studies retrieved by systematic searches of Pubmed, Embase and the Cochrane Library. Data were analyzed with STATA 13.1 using pooled odds ratios (ORs) with 95% confidence intervals (CIs). A total of 18 studies were included in our meta-analysis, and IL-1RN VNTR was found to be significantly associated with H. pylori infection in the comparisons of 22+2L vs LL (OR = 1.17, 95% CI = 1.02–1.33) and 2 allele vs L allele (OR = 1.18, 95% CI = 1.00–1.40). Stratified analyses on study designs and ethnicities were also conducted. IL-1RN VNTR was positively correlated with H. pylori infection in Asian subgroup and Hospital-Based subgroup (i.e., study samples obtained from hospital inpatients). In conclusion, our study demonstrated that IL-1RN VNTR polymorphism might increase the risk of H. pylori infection, especially in Asians.

Introduction

Helicobacter pylori is a pathogen that was discovered by Warren and Marshall in 1983 [1], and is thought to be involved in gastritis, peptic ulcers, gastric cancer, and mucosa-associated lymphoid tissue (MALT) lymphoma [2–4]. More than half of the world’s population is infected with H. pylori. Multiple factors influence the outcomes of H. pylori infection. Host genetic factors, interacting with H. pylori virulence (VacA, CagA etc.), and environmental factors (high salt intake and nitrate consumption, etc.), are involved in the pathogenesis of gastric cancer [5–7]. H. pylori infection elicits adaptive and innate immune responses in the gastric mucosa that produce significant inflammation [6]. H. pylori can stimulates host secretion of cytokines including interleukin (IL)-1, -2, -4, -8, -10, -1 receptor antagonist (rα), tumor necrosis factor (TNF)-α and others that may contribute to persistent infection [6, 8–10]. Host genetic polymorphisms of several cytokine genes (e.g., IL-1B-511*T, IL-1-RN*2, IL-10-1082/-819/-592, TNF-A-308*A, and IL-8-251*A), innate immune response gene (TLR4+896*G), HLA...
(DQA1*03:01, DQA1*04:01, and DQB1*05:01:01) are involved in all stages of the neoplastic process in gastric carcinoma [6, 11–16]. Previous reports of the relationship of host genetic polymorphisms and \textit{H. pylori} susceptibility are inconsistent. To begin to address these inconsistencies, we previously conducted two meta-analysis of the relationship between host IL1B -31C > T and TNFA gene polymorphisms and \textit{H. pylori} infection [9, 10]. This meta-analysis focuses on the association of host IL-1RN variable number of tandem repeat (VNTR) polymorphism and \textit{H. pylori} infection.

The IL-1 genes cluster is located on the long arm of human chromosome 2, comprising IL-1A, IL-1B and IL-1RN [17]. IL-1RN encodes IL-1r\alpha, which is the endogenous receptor antagonist of IL-1\alpha and IL-1\beta. A penta-allelic 86-bp VNTR polymorphism is located in intron 2 of the IL-1RN gene. Alleles 1–5 contain 4 repeats, 2 repeats, 5 repeats, 3 repeats, and 6 repeats, respectively. The repeats can be divided into a long allele (IL-1RN*1L, including alleles 1, 3, 4 and 5) and a short allele (IL-1RN*2, including allele 2) [18]. LL and 2L are homozygous genotypes, while 2L is heterozygous genotype. Some studies reported that IL-1RN VNTR polymorphism is associated with the secretion of IL-1r\alpha, which could influence \textit{H. pylori} infection by antagonizing IL-1\alpha and IL-1\beta [19, 20].

The association between IL-1RN VNTR polymorphism and \textit{H. pylori} related-diseases has been extensively investigated [21–23]. One meta-analysis reported that the short genotype of IL-1RN VNTR significantly increases the risk of gastric cancer [24]; another paper found that IL-1RN VNTR has no association with duodenal ulcer [25]. A number of studies performed on \textit{H. pylori} related-diseases have explored the association between IL-1RN VNTR polymorphism and \textit{H. pylori} infection simultaneously, but their results have been inconsistent. Therefore, we performed this meta-analysis to explore and analyze these inconsistent results. This is the first meta-analysis that focused on clarifying the relationship between IL-1RN VNTR polymorphism and \textit{H. pylori} infection.

**Materials and methods**

**Search strategy**

A systematic literature search of the Pubmed, Embase and Cochrane Library databases entries to August 2016 was conducted. The following search terms were used: (IL-1RN OR IL1RN OR interleukin-1RN) AND (polymorphism OR polymorphisms OR SNP) AND (\textit{Helicobacter pylori} OR \textit{H. pylori} OR HP). The search was limited to the English language publications with available full-text. The reference lists of retrieved papers were also examined to search for potentially relevant studies. We contacted authors requesting the full-text of their work if necessary. When more than one report of the same case series had been published, only the study with the largest sample size was included in the meta-analysis.

**Selection criteria**

The inclusion criteria of our meta-analysis were (1) investigation of the association of \textit{IL-1RN} VNTR polymorphism and \textit{H. pylori} infection was evaluated; (2) case-control designed on unrelated individuals; (3) use of objective and clearly described methods for detecting \textit{H. pylori} infection; and (4) reporting of genotype data sufficient to calculate odds ratios (ORs) with 95% confidence intervals (CIs).

**Data extraction and quality appraisal**

The authors; year of publication; country; ethnicity of participants; study design; number of cases and controls; methods of detecting \textit{H. pylori} infection and distribution of polymorphism
were extracted from each article. We evaluated study quality with the Newcastle-Ottawa scale (NOS) [26], which adopts three main criteria: selection of cases and controls; comparability of cases and controls; and exposure to risk factors. NOS scores were ranged from 0 to 9 stars. Articles with a final score 7 or more were considered to be of high quality, whereas those with a final score 5 or less were considered of low quality. Two authors (JZ and XS) independently extracted the data and performed the quality appraisal. Any disagreements between these two authors were resolved by discussion with the other authors.

**Statistical analysis**

All statistical analyses were carried out using STATA 13.1 (STATA Corp, College Station, TX, USA). The combined ORs and their corresponding 95% CIs were used to assess the strength of the association between *IL-1RN* VNTR polymorphism and *H. pylori* infection. The Q-test and $I^2$ index were used to determine heterogeneity across studies, with $P < 0.10$ or $I^2 > 50\%$ considered significant [27]. The ORs were pooled using a random effect model in the presence of significant heterogeneity; otherwise, a fixed effect model was used. Sensitivity analyses were conducted to identify the effect of each study on the combined results by omitting each one in turn. Subgroup analyses were conducted based on ethnicities (Asian or Non-Asian) and study designs (population-based (PB) or hospital-based (HB)). Publication bias was evaluated by Begg’s funnel plots and Egger’s plots, with a significance of 0.05. Hardy-Weinberg equilibrium (HWE) was calculated by the $\chi^2$-square test.

**Results**

**Study characteristics**

The study selection process is shown in Fig 1. A total of 139 articles were retrieved in the initial search. 59 articles were excluded after screening the titles and abstracts, and 64 articles were excluded after reading the full text. Two articles were added after scanning references lists. In total, 18 articles were included in our meta-analysis [18, 19, 28–43]. Table 1 lists the major characteristics of the included studies. Of the included studies, 11 were performed in Asians, 1 was in Europeans, 1 was in Africans and 5 were in mixed-ethnicity populations.

**Meta-analysis results**

*IL-1RN* VNTR polymorphism was significantly associated with *H. pylori* infection in the comparisons of 22+2L vs. LL and 2 allele vs. L allele (22+2L vs. LL, OR = 1.17, 95% CI = 1.02–1.33; 22 vs. 2L+LL, OR = 1.24, 95% CI = 0.82–1.86; 22 vs. LL, OR = 1.19, 95% CI = 0.77–1.83; 2 allele vs. L allele, OR = 1.18, 95% CI = 1.00–1.40; Fig 2).

Our subgroup analysis on ethnicity showed that in Asian populations, *IL-1RN* VNTR significantly increased the risk of *H. pylori* infection in the comparisons of 22 vs. 2L+LL and 22 vs. LL. When the analysis was stratified by study design, *IL-1RN* VNTR was significantly correlated with *H. pylori* infection in the comparisons of 22+2L vs. LL, 22 vs. 2L+LL and 2 allele vs. L allele for HB subgroup, but not for PB subgroup. The meta-analysis results are summarized in Table 2.

**Heterogeneity and sensitivity analysis**

Significant heterogeneity among studies existed in the comparison of 22 vs. 2L+LL, 22 vs. LL and 2 allele vs. L allele. A study by Queiroz et al. [39] was found to be the source of heterogeneity by omitting each study in turn. When sensitivity analyses were conducted, the pooled ORs were not significantly altered.
Publication bias

Funnel plots are commonly used to evaluate publication bias, with asymmetry indicating possible publication bias. Begg's funnel plot was performed in our meta-analysis, and the plot showed a nearly symmetrical distribution for the comparison of 22+2L vs. LL (Fig 3).
Publication bias was not indicated by either Begg’s or Egger’s tests (22+L vs. LL, Begg’s test $P = 0.76$, Egger’s test $P = 0.93$; 22 vs. 2L+LL, Begg’s test $P = 0.75$, Egger’s test $P = 0.30$; 22 vs. LL, Begg’s test $P = 1.00$, Egger’s test $P = 0.30$; and 2 allele vs. L allele, Begg’s test $P = 0.60$, Egger’s test $P = 0.94$).

**Discussion**

Previous studies demonstrated that polymorphisms of some host cytokine genes such as IL-1β, IL-8 *et al.* are correlated with *H. pylori* infection related-diseases [17, 44, 45]. IL-1α can influence IL-1β levels, and some studies have focused on the relationship between *IL-1RN* VNTR polymorphism and *H. pylori* infection related-diseases [46, 47]. Others have investigated the association between *IL-1RN* VNTR polymorphism and *H. pylori* infection. Because the conclusions of the available studies were not consistent [9, 48], we performed this meta-analysis to investigate the role of *IL-1RN* VNTR polymorphism on the risk for *H. pylori* infection.

We found that *IL-1RN* VNTR polymorphism has significant association with *H. pylori* infection, especially in Asians. This results differ from the findings of a genome wide association study in Europeans [49]. Based on including studies of our meta-analysis, we found that the frequency of *IL-1RN* ‘2’ in Asians is lower than that in other ethnicities. Different ethnicities with different genetic background and living habits might be the source of discrepancy. Genetic differences of *H. pylori* (cagA positive or negative) might also influence the association of host *IL-1RN* VNTR polymorphism and *H. pylori* infection. Nearly all *H. pylori* in East Asian, but not Western, are cagA positive strains [50]. Stratified analysis revealed that *IL-1RN* VNTR polymorphism increased the risk of *H. pylori* infection for HB subgroups. This indicates that *IL-1RN* VNTR polymorphism may be associated with outcomes of *H. pylori*.
infection and warrants further investigation. Studies included in meta-analyses frequently differ to an extent that leads to significant heterogeneity. In this analysis, the heterogeneity decreased after excluding the study of Queiroz et al, which included 125 Brazilian children and adolescents undergoing gastrointestinal endoscopy. Specific ethnicity and age composition

Fig 2. Forest plots of IL-1RN VNTR polymorphism and *H. pylori* infection for all genetic models.

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Table 2. Meta-analysis of the association between IL-1RN VNTR polymorphism and *H. pylori* infection.

| Study Group | Study(n) | 22+2L vs. LL OR (95% CI) | 2 vs. 2L+LL OR (95% CI) | 22 vs. LL OR (95% CI) | 2 allele vs. L allele OR (95% CI) |
|-------------|----------|--------------------------|--------------------------|------------------------|----------------------------------|
| Overall     | 18       | 1.17 (1.02–1.33)         | 1.24 (0.82–1.86)         | 1.19 (0.77–1.83)       | 1.18 (1.00–1.40)                 |
| Asian       | 11       | 1.14 (0.98–1.33)         | 1.54 (1.13–2.12)         | 1.48 (1.06–2.08)       | 1.18 (0.97–1.44)                 |
| PB          | 4        | 1.00 (0.81–1.23)         | 0.60 (0.29–1.22)         | 0.62 (0.30–1.29)       | 0.97 (0.79–1.18)                 |
| HB          | 14       | 1.28 (1.09–1.51)         | 1.60 (1.22–2.11)         | 1.40 (0.90–2.17)       | 1.28 (1.03–1.58)                 |

Significant results were shown in bold.

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**IL-1RN** gene encodes the cytokine IL-1ra, which is an endogenous receptor antagonist of IL-1β. Previous studies indicated that carriers of the *IL-1RN^2* allele had significantly higher expression of the IL-1β than carriers of other genotypes had [51, 52]. A high level of IL-1β in the gastric mucosa can inhibit the function of gastrin-stimulated enterochromaffin cells and parietal cells, which leads to low histamine concentration and decreased gastric acid secretion [53, 54]. In addition, IL-1β can also amplify immune responses by activating neutrophils, T cells and B cells [55]. The combined activity change from the decreased acid secretion and amplified immune responses may lead to tissue damage of the gastric mucosa, which can facilitate the colonization of *H. pylori* from the gastric antrum to the corpus [56]. This colonization can contribute to persistent *H. pylori* infection and increase the risk of developing atrophic gastritis and gastric cancer.

CagA is an important *H. pylori* virulence factor, and is associated with severe gastritis and gastric carcinoma [57, 58]. CagA-negative *H. pylori* is weakly pathogenic or nonpathogenic. Differences of the repeat sequences of the 3' region of cagA have led to recognition of East Asian-type and Western-type CagA [5]. East Asian-type cagA strains have greater pathogenicity and posing an increased risk of peptic ulcer or gastric cancer than Western-type cagA strains. CagA can be inserted into gastric epithelial cells by the cag PAI-encoded type IV
secretion system and perform virulence through phosphorylation-dependent and phosphorylation-independent manner. Src homology-2 domain-containing phosphatase 2 (SHP2) is an important intracellular target of CagA in phosphorylation-dependent pathway [5, 57, 59]. The difference of East Asian-type and Western-type CagA in pathogenicity may result from the higher binding affinity of East Asian-type CagA for SHP-2 by Glu-Pro-Ile-Tyr-Ala (EPIYA)-D segments than Western-type CagA, which binds to SHP-2 by EPIYA-C segments [50]. East Asian-type cagA strains primarily circulate in East Asia (e.g., China, Japan, and Korea). Although the H. pylori cagA genotype has a significantly wider geographical distribution, our analysis was not stratified by H. pylori cagA genotypes because only one of the 18 articles selected for analyses assayed host IL-1RN gene polymorphism and H. pylori cagA genotypes [42]. The investigators found that host IL-1 polymorphism and the H. pylori cagA genotype influenced gastric mucosal cytokine levels in patients in Thailand [42].

This is the first meta-analysis that investigated the association between IL-1RN VNTR polymorphism and H. pylori infection across multiple studies. However, there were some limitations to our study. Most of included studies were performed on Asian populations, so further research with other ethnic populations is needed. We only chose the English literatures retrieved from databases of PubMed, Embase and Cochrane library, which might lead to bias on collecting literatures.

**Conclusion**

Based on including studies of our meta-analysis, we concluded that IL-1RN VNTR*2 may increase the risk of H. pylori infection, especially in Asians. Our findings provide insights into the role of IL-1RN VNTR polymorphism in H. pylori infection and related diseases. Further studies with larger sample sizes and various ethnicities are required to validate these results.

**Supporting information**

S1 File. PRISMA flow diagram.
(DOC)

S2 File. PRISMA checklist.
(DOC)

S3 File. Meta-analysis on genetic association studies checklist.
(DOCX)

S4 File. Articles excluded from the meta-analysis.
(DOCX)

S5 File. Search strategy.
(DOCX)

**Author Contributions**

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