PERSISTENT **HELICOBACTER PYLORI** INFECTION AND GENETIC POLYMORPHISMS OF THE HOST

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**ABSTRACT**

*Helicobacter pylori* (HP) infection elevates the risk of gastric diseases including peptic ulcer and gastric cancer. The infection induces inflammatory cytokines, which could work both for and against lifetime infection in the human stomach. Genetic polymorphisms of the cytokines and other related ligands, receptors, and enzymes may influence persistent HP infection. This paper summarizes studies done on the associations between anti-HP antibody seropositivity and polymorphism genotypes. To date, the associations with the polymorphisms of fucosyl transferase 2 (FUT2 or secretor gene), FUT3 (Lewis gene), interleukin 1A (IL-1A), IL-1B, IL-1RN, IL-8, IL-10, myeloperoxidase (MPO), and tumor necrosis factor A (TNF-A) and TNF-B have been reported. Polymorphisms of other related genes, CD14, CXC chemokine receptor 2 (CXCR2), IL-1RI, nuclear factor KB2 (NF-KB2), and Toll-like receptor 4 (TLR4), have the potential to influence persistent infection. Unpublished results from our datasets are reported here for all these polymorphisms except TLR4. Gene-environment interactions between these genotypes and smoking are reviewed. An effect on OR due to the involvement of unexposed subjects is demonstrated to elucidate a disadvantage in the studies done in areas where the majority of the population is not exposed to HP.

Key Words: *Helicobacter pylori*, Polymorphisms, Interleukins, Odds ratio dilution

**INTRODUCTION**

*Helicobacter pylori* (HP) is a gram-negative bacterium which, upon infecting in the gastric mucosa, increases the risk of gastric diseases including peptic ulcers and stomach cancer. Person-to-person infection largely depends on sanitary conditions, especially in childhood. In addition, lifestyle factors such as salty food intake, fruit intake, and smoking are considered to influence the infection rate. Meanwhile, a twin study reported that the concordance of anti-HP antibody status was higher in monozygotic twin pairs than in dizygotic twin pairs, strongly underscoring the genetic role in persistent HP infection.

This paper reviews the reports on the associations between anti-HP antibody seropositivity and polymorphism genotypes. The associations between HLA genotypes and that seropositivity have also been reported, but they are not covered here. First, the mechanism of signal transduction from HP is described to provide biological background on the selected gene polymorphisms. After the polymorphism studies are introduced, the limitations of association studies are discussed.
BIOLOGICAL MECHANISMS

Gram-negative bacteria such as *HP* have a cell wall that contains lipopolysaccharide (LPS). The innate immune response, a preprogrammed nonspecific first line of defense responsible for eliminating pathogens at the site of entrance into the host, recognizes LPS with a pattern recognition receptor, CD14, on the cell surface. CD14 is a 55-kd glucosylphosphatidylinositol-anchored receptor lacking an intracellular domain, which binds LPS with high affinity. The LPS-CD14 complex then activates Toll-like receptor 4 (TLR4) with an intracellular domain for signal transduction. TLR4 is stabilized in the form of a homodimer by MD-2. The signal from LPS is transduced through MyD88, IRAK (IL-1 receptor-associated kinase), TRAF6 (TNF receptor-associated factor 6), NIK/MKK (KF-κB-inducing kinase/mitogen-activated protein kinase), and IKK (inhibitory κB kinase) to NF-κB.16) (Fig. 1)

NF-κB is a group of proteins (NF-κB/REL proteins) that bind a common sequence motif known as the κB site.17) They transcribe inflammation-related genes such as *IL-1A*, *IL-1B*, *IL-2*, *IL-6*, *IL-8*, *TNF-A*, *TNF-B*, and *GM-CSF*.18) Other pathways of LPS signaling may also exist for *IL-1B*,19) and for *TNF-A* through extracellular signal-regulated kinase (ERK).20) LPS-induced IL-1β and TNF-α induce other cytokines and enzymes for inflammation as well as IL-1β and TNF-α themselves through the NF-κB pathway.21) IL-1 receptor antagonist coded by *IL-1RN* disturbs IL-1β binding to IL-1 receptor I (IL-1RI), resulting in the inhibition of the IL-1β function.

![Fig. 1](image_url)  
**Fig. 1** Signal pathway from *Helicobacter pylori* to cytokine gene expression.
IL-1β and TNF-α inhibit gastric acid secretion. The inhibited acid secretion causes HP distribution to the corpus, resulting in gastric atrophy. Accordingly, the level of cytokines could influence persistent HP infection. IL-8 is a CXC chemokine that mediates the activation and migration of neutrophils into tissue from peripheral blood. As is the case with IL-1β and TNF-α, IL-8 induced in gastric epithelial cells and in neutrophils by HP serves to trigger the inflammation. It combines CXCR-1 (previously called IL-8RA) and CXCR-2 (IL-8RB) with similar affinity. IL-10, a cytokine produced by type 2 T-helper cells (Th2 cells), inhibits the production of IL-1β and IL-8. In mice, cytokine expressions by Helicobacter felis are modified by a concurrent infection of the enteric helminth, Heligmosomoides polygyrus, which drives the immune response through type 2 T-helper cells (Th2 cells). The co-infection increases the mRNA of interleukin 10 in comparison with Helicobacter felis infection alone, resulting in reduced Helicobacter-associated gastric atrophy and high Helicobacter colonization. These findings suggest that a high level of IL-10 and a lower level of IL-8 create favorable conditions for prolonging the HP infection in human gastric mucosa. MPO is a lysosomal enzyme in polymorphonuclear leukocytes and monocytes. Hypochlorous acid produced by MPO shows microbicidal activity against a wide range of organisms producing tissue inflammation. It was reported that HP water extract can activate neutrophils and enhance the secretion of MPO.

Another line of genetic traits involved in the susceptibility to HP concerns HP binding to gastric epithelium. HP with babA2 gene is attached to gastric mucosa with blood group antigen-binding adhesion (BabA). BabA binds both Lewis b and H type I blood group carbohydrate structure on the foveolar epithelium of human gastric mucosa. Type I precursor is converted to H type I antigen by fucosyltransferase 2 (FUT2, secretor enzyme), then to Lewis b antigen by fucosyltransferase 3 (FUT3, Lewis enzyme). FUT3 also converts type I precursor to Lewis a antigen. Although other binding mechanisms exist in HP, individuals lacking H type I and/or Lewis b may have a lower susceptibility to persistent HP infection.

POLYMORPHISMS

The molecules on the pathways originating from LPS seem to have a potential to enhance the susceptibility to HP infection and prolong the infection. The candidate molecules and their polymorphisms are discussed below in alphabetical order. Table 1 summarizes the findings of reported studies on the associations with these polymorphisms. “Unpublished data” in Table 1 are derived from our own unpublished studies on the same subjects as those in published reports.

**CD14**

CD14, located in chromosome 5q31.1, has a single nucleotide polymorphism (SNP) C-159T. Serum soluble CD14 was reported to be significantly higher in those with -159TT (n=42, median=4.5 μg/ml) than in those with -159CC (n=67, median=4.1 μg/ml). Our unpublished data indicated no association with this polymorphism (Table 1).

**CXCR2**

CXCR2 in 2q35 was reported to have three SNPs; C785T causing a silent codon change in leucine, and T1208C and G1440A in the 3’ untranslated region of exon 3. These SNPs are tightly linked, forming a haplotype with 785C, 1208T, and 1440G. Accordingly, any SNP may be used for a pilot association study on disease risk. Our pilot study showed no substantial difference in the seropositive rate among the three genotypes of C785T.
Table 1  Sex-age-adjusted odds ratios (OR) and 95% confidence interval (95%CI) of polymorphism genotypes for *Helicobacter pylori* seropositivity

<table>
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<tr>
<th>Authors and year</th>
<th>Enrolled subjects</th>
<th>Polymorphism</th>
<th>N</th>
<th>OR</th>
<th>95% CI</th>
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<td></td>
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<td>CC</td>
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<td>Sese</td>
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<td>outpatients</td>
<td>lele</td>
<td>98</td>
<td>1.95</td>
<td>1.08–3.50</td>
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<tr>
<td>Hamajima et al. 2002</td>
<td>679 first-visit</td>
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<td>353</td>
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<td>leLe</td>
<td>59</td>
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<tr>
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<td>LeLe</td>
<td>235</td>
<td>1</td>
<td></td>
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<td>465 health-checkup</td>
<td>examinees</td>
<td>Lele</td>
<td>155</td>
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<td>0.69–1.63</td>
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<td>lele</td>
<td>33</td>
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<td>100%</td>
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<td>42</td>
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<td>133</td>
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<td>66</td>
<td>2.46</td>
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<td>IL-1B C-31T</td>
<td>116</td>
<td>1</td>
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<td>0.97*</td>
<td>0.59–1.57</td>
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<td></td>
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<td>TT</td>
<td>163</td>
<td>1.73*</td>
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<td>116</td>
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<td></td>
<td>reference</td>
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<td>outpatients*5</td>
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<td>0.84–2.08</td>
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<tr>
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<td></td>
<td>TT</td>
<td>178</td>
<td>1.35</td>
<td>0.83–2.18</td>
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<tr>
<td>Uno et al. 2002</td>
<td>963 Japanese</td>
<td>IL-1B C-31T</td>
<td>226</td>
<td>1</td>
<td></td>
<td>reference</td>
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<td>Brazilians</td>
<td>CC</td>
<td>432</td>
<td>1.30</td>
<td>0.94–1.81</td>
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<td></td>
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<td>TT</td>
<td>289</td>
<td>1.45</td>
<td>1.02–2.06</td>
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</table>
**IL-1B C-511T**

- **Kato et al. 2001**
  - 499 patients with gastric diseases other than gastric cancer
  - **HP+**: 143, 53.1% ± 6%

- **Hamajima et al. 2001**
  - 241 non-cancer outpatients
  - **HP+**: 217, 62.2%

**IL-1RN VNTR 4/4**

- **Unpublished data**
  - 241 non-cancer outpatients
  - **HP+**: 93, 64.5%

**IL-1RI C-116T**

- **Hamajima et al. 2003**
  - 454 health-checkup examinees
    - **TT**: 114, 57.9%

- **Hamajima et al. 2003**
  - 241 non-cancer outpatients
    - **TT**: 32, 71.9%

**IL-8 T-251A**

- **Hamajima et al. 2003**
  - 454 health-checkup examinees
    - **TT**: 234, 1 reference

- **Hamajima et al. 2003**
  - 241 non-cancer outpatients
    - **TT**: 220, 1 reference

**IL-8 & IL-10 TT&TT**

- **Hamajima et al. 2003**
  - 454 health-checkup examinees
    - **TT&TT**: 115, 1 reference

- **Hamajima et al. 2003**
  - 241 non-cancer outpatients
    - **TT&TT**: 57, 1 reference

**MPO G-463A**

- **Katsuda et al. 2001**
  - 241 non-cancer outpatients
    - **GA/AA**: 49, 0.69

**NF-KB2 -10G**

- **Unpublished data**
  - 1,374 participants
    - **Ins/Ins**: 513, 1 reference

**TNF-A T-1031C**

- **Hamajima et al. 2003**
  - 1,374 participants
    - **TT**: 952, 1 reference

**TNF-A C-857T**

- **Hamajima et al. 2003**
  - 1,374 participants
    - **CC**: 931, 1 reference

- **Hamajima et al. 2003**
  - -1031 & -857
    - **CC&CC**: 34, 1 reference
FUT2 (secretor gene) and FUT3 (Lewis gene)

Six alleles have been identified for FUT2 located in 19q13.3. They are Se1 (357C, 385A, 571C, 628C), Se2 (357T, 385A, 571C, 628C), sej (357T, 385T, 571C, 628C), se3 (357C, 385A, 571T, 628C), se4 (357C, 385A, 571C, 628T), and se5 (combined with a pseudogene). Se1 and Se2 exhibit full enzyme activity, sej shows very low activity, and the others reveal no activity. Accordingly, Se1 and Se2 are denoted by Se, and the others by se. Among Japanese, se3 and se4 are very rare.36)

FUT3 has three SNPs; T59G, G508A, and T1067A. An Le allele is defined as one with 59T, 508G, and 1067T, an le1 allele one with 59G, 508A, and 1067T, an le2 allele one with 59G, 508G, and 1067A, and an le3 allele one with 59G, 508G, and 1067T. The le1 and le2, denoted by le, lack enzyme activity. Since le3 shows almost full enzyme activity, it is grouped into Le.36)

Our first report successfully demonstrated that those with sese genotype who cannot synthesize H type I nor Lewis b had the lowest seropositive rate.37) In addition, LeLe genotype, which may disturb the synthesis of H type I by FUT2 through sharing the same substrate (type I precursor), showed the lowest rate.37) The odds ratio for study subjects with sese and LeLe was about one tenth of those with SeSe/lele, SeSe/Lele, or Sese/lele.37) In order to confirm that association, two datasets were analyzed, but the association was not reproduced.38) Unknown effect modification may exist among the three datasets.

IL-1A

IL-1A making a cluster in chromosome 2q14 with IL-1B and IL-1RN has two SNPs of C-889T and G4845T, as well as a 46-bp VNTR (variable number of tandem repeats) polymorphism.39) It was reported that the combination IL-1A -889TT and IL-1B -511T (TT or TC) was related to high plasma levels of IL-1β.40) Since among Japanese -889T allele represented only
8.5%, a large study is required to evaluate the association with HP seropositivity in that population. The 46-bp VNTR polymorphism was not polymorphic among Japanese in our study. Polymorphism G4845T was reported to be concordant with C-889T.

**IL-1B**

Three polymorphisms of IL-1B, C-511T, C-31T, and C3954T, have been studied for dozens of diseases. An electrophoretic mobility-shift assay demonstrated that C-31T was a functional polymorphism, while C3954T is unlikely to be functional. Since -511T and -511C are tightly linked with -31C and -31T, respectively, either one is enough for genotyping IL-1B.

Our team conducted four studies, all of which showed a similar result, i.e., study subjects with -31TT ran a higher risk of HP seropositivity. No studies other than ours focused on the associations between HP infection and IL-1B polymorphisms. The HP seropositivity constructed from a study by Kato et al. showed no association with C-511T. Meanwhile, there was a study reporting that -511T/-31C allele increased the risk for atrophic gastritis, intestinal metaplasia, and severe inflammation among the infected.

**IL-1RN**

IL-1RN has an 86-bp VNTR polymorphism. Among 241 Japanese, the allele frequency was 4.1% for 2 repeat allele, 0.2% for 3 repeat allele, 94.6% for 4 repeat allele, and 1.0% for 5 repeat allele. No difference in HP seropositivity was observed between 4/4 and other genotypes (Table 1). Since 4 repeat allele is dominant, studies on this polymorphism among Japanese pose difficulties. The 2 repeat allele (IL-1RN*2 allele) was reportedly associated with atrophic gastritis, intestinal metaplasia, and severe inflammation among the infected.

**IL-1RI**

There are two receptors for IL-1β; IL-1RI and IL-1RII. The former transduces the signal, but the latter does not. IL-1RI in 2q12 has reportedly four SNPs; C-116T (RFLP-A), C-90T, T49C, and RFLP-B at an unknown site. There are no reports on the association between these polymorphisms and HP seropositivity. As shown in Table 1, our unpublished pilot study for C-116T indicated no association.

**IL-8 and IL-10**

IL-8 located in chromosome 4q12-21 was reported to have nine polymorphisms (four in 5' upstream regions, four at introns, and one in 3' downstream region), and more are listed in GenBank Accession No. AF385628 including some rare allele polymorphisms. Among those polymorphisms, A-251T from the transcription start site (-353 from the translation start site) in Accession No. M28130 is considered to influence IL-8 expression; A allele has a greater expression than T allele. Among Europeans, two haplotypes, one with -1722delT, -251A, 396G, 781T, 1633T, and 2767T termed delTAGTTT in the order of those polymorphisms, and the other with delTTTCCA, are dominant with frequencies of 0.41 and 0.52, respectively. The haplotypes are more diverse among Africans; delTAGCCA (frequency 0.36), delTATCCA (0.19), instTATCCA (0.18), and delTTTCCA (0.10), respectively, but the genotyping of T-251A and T396G is sufficient for classifying the haplotypes. Our preliminary genotyping for 227 outpatients identified a strong linkage between the two polymorphisms; 396TT was found in 90.0% of 110 individuals with -251TT, 396TG in 90.5% of 95 individuals with -251TA, and 396GG in 100% of 22 individuals with -251AA. IL-8 -251AA was found to be more frequent among patients with tuberculosis than among the controls (OR=3.41, 95%CI, 1.52-7.64 for Caucasians and OR=3.46,
95% CI, 1.48-8.08 for African Americans).\(^{54}\)

**IL-10** G-1082A and T-819C polymorphisms are considered to influence the expression of **IL-10** mapped on 1q31-32; -1082A and -819T are reportedly higher expression alleles.\(^{55,56}\) Among Japanese, the -1082G allele frequency was found to be 0.04,\(^{57}\) and there were no Japanese studies on the T-819C allele frequency except ours.\(^{53}\)

Our first study found that high seropositivity was associated with the combination of **IL-8** -251TT and **IL-10** -819TT.\(^{53}\) That association was significant among smokers, as will be described later (Table 2).\(^{53}\) However, the other datasets did not reproduce such an association. On the contrary, for reasons that remain unclear, one dataset of 679 first-visit outpatients showed an opposite association.

**MPO**

While **MPO** Arg569Trp, Val173Cys, or Met251Thr causes fatal diseases such as chronic granulomatous disease due to severe enzyme activity deficiency,\(^{58}\) **MPO** G-463A exhibits a different level of expression; the G allele has a 25-fold higher transcription level than the A allele.\(^{59}\) This gene polymorphism located in 17q23.1 was found to show a similar association by univariate analysis in two datasets, though not a significant one (Table 1).\(^{60,61}\)

**NF-KB2**

**NF-KB2** coding NF-κB2 (p100) has Ins/Del -10G (or 1867GG/G\(^{62}\)), as well as two SNPs with a rare minor allele.\(^{62}\) The function of Ins/Del -10G was not demonstrated, but our unpublished data suggested no association with **HP** seropositivity (Table 1).

**TLR4**

In **TLR4**, two co-segregating polymorphisms have been reported, Asp299Gly and Thr399Ile. The 299Gly/399Ile allele is less sensitive to LSP than 299Asp/399Thr allele, resulting in lower NF-κB activity.\(^{63}\) The LPS-hyposensitive allele was found to be 5.9% among 879 blood donors in England\(^{64}\) and not found at all among 275 Japanese.\(^{65}\)

**TNF-A** and **TNF-B**

**TNF-A** and **TNF-B** genes are located between HLA-B and HLA-DR on 6p21.3. In the promoter area of **TNF-A**, G-238A, G-244A, G-308A, C-857T, C-863A, and T-1031C were reported.\(^{66,67}\) Among Japanese, -244A was not found,\(^{67}\) -238A and -308A alleles were rare (2.0% and 1.7%, respectively),\(^{66}\) and C-863A was tightly linked with T-1031C.\(^{66}\) Recently, a significant association between infection with CagA-positive *H. pylori* and **TNF-A** -308A allele (a high-expression allele\(^{69}\)) was reported among Koreans.\(^{70}\) In Germany, the -308A allele was not found among 14 **HP**-positive female patients with duodenal ulcer, while 26.8% of 98 **HP**-positive female patients without duodenal ulcer had at least one -308A allele. In those subjects, no difference in G-308A genotype distribution was observed between the *H. pylori* positive and negative patients (Table 1).\(^{71}\) Our study of 1,374 participants from three datasets showed that those with **TNF-A** -857TT and -1031TT ran the highest risk of being **HP** seropositive, and those with **TNF-A** -857CC and -1031CC the lowest.\(^{72}\)

**TNF-B** A252G, whose G allele is strongly linked with **TNF-A** -857C allele in Japanese,\(^{72}\) was not associated with seropositivity, as shown in Table 1. Another SNP, **TNF-B** Thr26Asn, was found in our dataset to link completely with A252G.
H. PYLORI INFECTION AND POLYMORPHISMS

Table 2  Age-sex-adjusted odds ratios (OR) and 95% confidence interval (95%CI) of polymorphism genotypes for Helicobacter pylori seropositivity, taking account of smoking habit

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<th>Authors and year</th>
<th>Polymorphism</th>
<th>Enrolled subjects</th>
<th>N*1</th>
<th>OR</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Hamajima et al. 2001[45]</td>
<td>IL-1B C-31T</td>
<td>Non-cancer outpatients</td>
<td>55 current smokers</td>
<td>CC</td>
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<td></td>
<td>CT</td>
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<td></td>
<td></td>
<td>TT</td>
<td>12</td>
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<tr>
<td>Katsuda et al. 2001[46]</td>
<td>IL-1B C-31T</td>
<td>Health checkup examinees</td>
<td>80 ever smokers</td>
<td>CC</td>
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<td>CT</td>
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<td>22</td>
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<td>Hamajima et al. 2002[47]</td>
<td>IL-1B C-31T</td>
<td>First visit outpatients*2</td>
<td>127 current smokers</td>
<td>CC</td>
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<td></td>
<td>CT</td>
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<td>TT</td>
<td>41</td>
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<tr>
<td>Uno et al. 2002[48]</td>
<td>IL-1B C-31T</td>
<td>Japanese Brazilians</td>
<td>124 Current smokers</td>
<td>CC</td>
<td>NA</td>
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<td>CT</td>
<td>NA</td>
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<td></td>
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<td>TT</td>
<td>NA</td>
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<tr>
<td>Hamajima et al. 2003[49]</td>
<td>IL-8 &amp; IL-10</td>
<td>Health checkup examinees</td>
<td>65 current smokers</td>
<td>TT&amp;TT</td>
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<td>Others</td>
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<tr>
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<td>Non-cancer patient</td>
<td>55 current smokers</td>
<td>TT&amp;TT</td>
<td>14</td>
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<td>Others</td>
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<td>IL-8 &amp; IL-10</td>
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<td>158 current smokers</td>
<td>TT&amp;TT</td>
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<td>Hamajima et al. 2001[50]</td>
<td>MPO G-463A</td>
<td>Non-cancer outpatients</td>
<td>55 current smokers</td>
<td>GG</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GA/AA</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>186 non-current smokers</td>
<td>GG</td>
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<td></td>
<td></td>
<td></td>
<td>GA/AA</td>
<td>39</td>
</tr>
<tr>
<td>Katsuda et al. 2001[51]</td>
<td>MPO G-463A</td>
<td>Health checkup examinees</td>
<td>64 current smokers</td>
<td>GG</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GA/AA</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>363 never smokers</td>
<td>GG</td>
<td>297</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>GA/AA</td>
<td>66</td>
</tr>
</tbody>
</table>

*1 Subjects successfully genotyped. Difference between enrolled subjects and a total of the successfully genotyped subjects yields subjects not genotyped.

*2 Those aged 40–69 years.

NA: data not available.
GENE-ENVIRONMENTAL INTERACTION

Inconsistent results observed in polymorphism studies are not rare. Such discrepancies are explained partly by gene-environment or gene-gene interaction. We have examined the interaction between genotypes and several lifestyle factors, among which smoking was found to be a major candidate for modifying the effect of genotypes.

Table 2 shows the odds ratios among smokers or for smoking in combination with genotypes. Concerning $IL-1B$ C-31T,$^{45-48}$ the odds ratios tended to be higher among smokers with one exception.$^{47}$ The first dataset for the combination of $IL-8$ -251TT and $IL-10$ -819TT showed a marked association among current smokers.$^{53}$ Subsequent datasets produced insignificant ORs with the same direction as the first report. A marginal interaction was observed for $MPO$ (GG vs. GA/AA) and smoking (current vs. non-current); OR=4.57 and $p=0.08$.$^{60}$ No difference in OR was observed between current smokers and never smokers in another dataset.$^{61}$

LIMITATIONS OF ASSOCIATION STUDIES

For the purpose of measuring the associations between $HP$ infection and genotypes, the optimal study population is one in which all subjects were exposed to $HP$. The true strength of the association is diluted with each increase in the proportion of the unexposed. If 50% of study subjects were not exposed to $HP$, OR = 4 among the exposed consisting of half with a high-risk allele and the rest without that allele, becomes 2 (Table 3). Accordingly, any study on the association with $HP$ infection is difficult in areas where the majority has not been exposed to $HP$.$^{73}$

We learned that the frequency of minor alleles varies widely among different ethnic groups. When the frequency is too low to generate sufficient statistical power for detecting a significant OR, such a study would be meaningless for that ethnic group. In this case, comparisons across different ethnic groups are impossible.

Gene-gene or gene-environment interactions are quite attractive themes in the field of polymorphism studies. However, studies on such interactions require a larger sample size, e.g., in the thousands. Only major research groups accustomed to routinely enrolling many participants could successfully conduct such a study.

Table 3  An example of odds ratio dilution

<table>
<thead>
<tr>
<th>Exposure to <em>Helicobacter pylori</em></th>
<th>Yes</th>
<th>No</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk allele</td>
<td>40</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>allele</td>
<td>25</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>65</td>
<td>35</td>
<td>0</td>
</tr>
</tbody>
</table>

The subjects consist of 100 exposed and 100 unexposed, a total of 200 individuals. The OR of high risk allele is 4 among the exposed, but 2 among all subjects.

*1 Seropositive, *2 Seronegative
CONCLUSIONS

The great majority of reports on the association between HP seropositivity and polymorphisms have been produced by our teams. The datasets were derived from 241 non-cancer outpatients who participated in an HP-eradication program, 465 health checkup examinees in Nagoya (454 of which were without a history of cancer), 679 first-visit outpatients to the Aichi Cancer Center (547 outpatients aged 40 to 69 years), and 963 Japanese Brazilians in Sao Paulo. We enjoyed some advantages, i.e., 1) our research team at the Aichi Cancer Center was fully cooperative, 2) a hospital-based epidemiologic research program (HERPACC) was ongoing, 3) a newly developed PCR method, PCR-CTPP (polymerase chain reaction with confronting two-pair primers) was available, and 4) HP exposure is very common in Japan, especially among the elderly.

Our findings were rather consistent for IL-1B and TNF-A, both of which encode cytokines that inhibit gastric acid secretion. The finding that acid inhibition from medication established favorable conditions for HP to form colonies provides biological plausibility for the polymorphisms of both cytokines. Another pathway to influence persistent HP infection may exist in relation to immunological response, but this remains to be investigated.

To date, strong and specific associations with polymorphisms have not been identified for HP infection. In the case of HIV, it is well known that the β chemokine receptor gene (CCR5) Δ32 homozygous genotype completely blocks the infection through inhibiting the successful cell surface transportation of the CCR5 molecule, the essential molecule for HIV to enter CD4-positive T cells. On the contrary, since HP remains restricted to the mucus layer of the stomach, similarly strong mechanisms specific to HP may not exist.

There are several studies reporting the associations between genotypes and stomach cancer risk. Such studies are essential in measuring the net contribution of genotypes to stomach carcinogenesis, which consists of three steps in areas where HP infection is prevalent.: 1) persistent HP infection among the exposed, 2) gastric atrophy among the infected, and 3) stomach cancer among those with gastric atrophy. In view of stomach cancer prevention, analytical studies on each step are required. The present paper reviewed progress to date in the first step to stomach carcinogenesis through Helicobacter pylori.

REFERENCES

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