Review Article

Genetic factors involved in the development of *Helicobacter pylori*-related gastric cancer

Nobuyuki Hamajima,[1,3] Mariko Naito,[1] Takaaki Kondo[2] and Yasuyuki Goto[1]

[1]Department of Preventive Medicine/Biostatistics and Medical Decision Making, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550; [2]Department of Medical Technology, Nagoya University School of Health Science, 1-1-20 Daikou Minami, Higashi-ku, Nagoya 461-0047, Japan

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Developmental process to gastric cancer by *Helicobacter pylori* infection consists of three steps: (1) *H. pylori* infection; (2) gastric atrophy development; and (3) carcinogenesis. In each step, genetic traits may influence the process, interacting with lifestyle. In the step of *H. pylori* infection, two lines of genetic polymorphisms were assumed: one influencing gastric acid inhibition interacting with smoking, and the other concerning innate immune response attenuation. The former includes functional polymorphisms of *IL-1B* (C-31T or tightly linked T-511C), and *TNF-A* (T-1031C and C-857T), and the latter possibly includes *NQO1* C609T. In the step to gastric atrophy, polymorphisms pertaining to the signal transduction from cytotoxin-associated gene A (*PTPN11* A/G at intron 3) and to T-cell responses (*IL-2* T-330G and *IL-13* C-1111T) were hypothesized. There are a limited number of epidemiological genotype studies on the final step of literal carcinogenesis, potentially interacting with smoking, a low vegetable and fruit intake, and salty foods, the well-documented risk factors. In past case-control studies on the associations between genotype and gastric cancer risk, the cases consisted of *H. pylori*-related and unrelated gastric cancer patients and the controls consisted of individuals including the uninfected (*H. pylori* unexposed and exposed) and the infected with and without gastric atrophy. Accordingly, it was not clear whether the observed risk was for *H. pylori*-related or -unrelated gastric cancer, nor which step was involved in the observed associations even when nearly all cases were *H. pylori*-related. In order to elucidate the genetic traits of *H. pylori*-related gastric cancer, stepwise evaluation will be required. (*Cancer Sci* 2006; 97: 1129–1138)

Helicobacter pylori is a gram-negative bacterium that colonizes the human gastric mucosa.[1] It is well known that the bacterium increases the risk of gastric diseases, including peptic ulcers and stomach cancer.[2,3] In areas where gastric cancer is highly prevalent, such as Japan, Korea and China, the great majority of gastric cancers are *H. pylori*-related. In Japan, the cumulative gastric cancer incidence rate of 0–84-year-olds was estimated to be 21.2% for infected males and 8.0% for infected females, under the conditions that half of the population are infected and the infected people have a five-times higher risk of gastric cancer than uninfected people.[4] As *H. pylori*-unrelated gastric cancer may develop in a different set of genetic or environmental factors from *H. pylori*-related cases, epidemiological and biological studies to elucidate the process should be conducted separately.

In *H. pylori*-related gastric cancer, the process has three steps: (1) *H. pylori* infection; (2) gastric atrophy development; and (3) carcinogenesis. In each step, genetic traits may influence the process, interacting with lifestyle. Fig. 1 shows the genetic polymorphisms with possible biological mechanisms and interacting lifestyle factors for the three steps. This paper briefly reviews the epidemiological findings, the biological background, and polymorphism studies according to these steps. Additionally, previous polymorphism studies of gastric cancer that did not consider these processes are reviewed. Although the pathological process model includes intestinal metaplasia and dysplasia,[5] epidemiological studies using serum pepsinogens (PG) as markers of gastric atrophy cannot distinguish the two pathologically defined stages, so that they are not regarded as different steps in the present paper. In the present paper, human leukocyte antigen (HLA) types were not included in polymorphism genotypes.[6]

Epidemiology of *H. pylori* infection

Helicobacter pylori transmits from person to person, largely depending on sanitary conditions, especially in childhood.[7–10] Lifestyle factors such as salty food intake,[11] fruit intake[12] and smoking[12–16] were also reported to influence the persistence of *H. pylori* infection. Meanwhile, a twin study reported that the concordance of anti-*H. pylori* antibody status was higher in monozygotic twin pairs than in dizygotic twin pairs,[17] strongly underscoring the role of genetics in infection.

The bacterium is classified into two main species, in terms of the cytotoxin-associated gene A (CagA) protein, a toxin injected through a type IV infection system into gastric epithelium: CagA negative and CagA positive. The CagA-positive species are more virulent than the CagA-negative species, and have stronger associations with gastric atrophy and gastric cancer.[18–20]

Biology of *H. pylori* infection

Gram-negative bacteria, including *H. pylori*, have a cell wall containing lipopolysaccharide (LPS). The innate immune response, a preprogrammed non-specific 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 glycosylphospatidylinositol-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 myeloid differentiation factor 88 (MyD88), interleukin (IL)-1 receptor-associated kinase (IRAK), tumor necrosis factor (TNF) receptor-associated factor 6 (TRAF6) and inhibitory κB kinase (IKK) to nuclear factor (NF)-κB (Fig. 2).[21]

A recent study delineated that the main signal transduction to NF-κB is through the peptidoglycan-derived peptide α-D-glutamyl-meso-diaminopimelic acid (iE-DAP), which is injected through a type IV secretion system. iE-DAP is a ligand of nucleotide-binding oligomerization domain protein 1 (NOD1), which is encoded by the caspase-recruitment domain 4 gene (*CARD4*)

[3]To whom correspondence should be addressed. E-mail: nhamajim@med.nagoya-u.ac.jp

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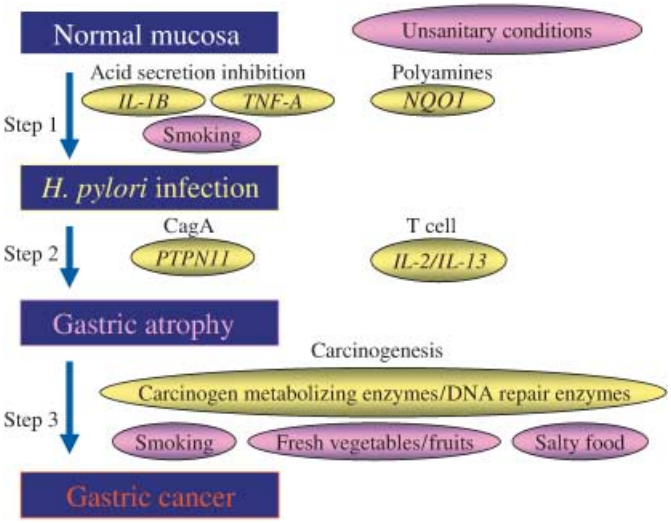

Fig. 1. Steps in *Helicobacter pylori*-related gastric cancer. IL, interleukin; NQO1, NAD(P)H : quinone oxidoreductase 1; TNF, tumor necrosis factor.

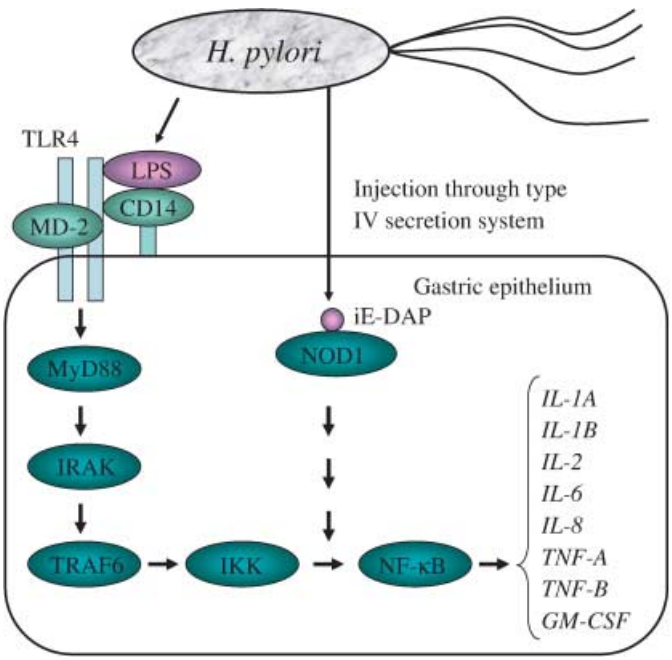

Fig. 2. Signal pathway from *Helicobacter pylori* to cytokine gene expression. iE-DAP, α-D-glutamyl-*meso*-diaminopimelic acid; IKK, inhibitory κB kinase; IL, interleukin; IRAK, interleukin-1 receptor-associated kinase; LPS, lipopolysaccharide; MyD88, myeloid differentiation factor 88; NF-κB, nuclear factor κB; NOD1, nucleotide-binding oligomerization domain protein; TLR, Toll-like receptor; TRAF6, TNF receptor-associated factor 6.

and expressed in epithelial cells.[22] It is hypothesized that the signal is transduced through several molecules to NF-κB.[23]

NF-κB is a group of proteins (NF-κB/REL proteins) that bind a common sequence motif known as the κB site.[24] They transcript inflammation-related genes such as *IL-1A*, *IL-1B*, *IL-2*, *IL-6*, *IL-8*, *TNF-A*, *TNF-B* and *GM-CSF*.[25] Other pathways of LPS signaling may also exist for *IL-1B*,[26] and for *TNF-A* through extracellular signal-regulated kinase (ERK).[27] 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.[28] The IL-1 receptor antagonist coded by *IL-1RN* disturbs IL-1β binding to IL-1 receptor I (IL-1RI), resulting in the inhibition of IL-1β function.

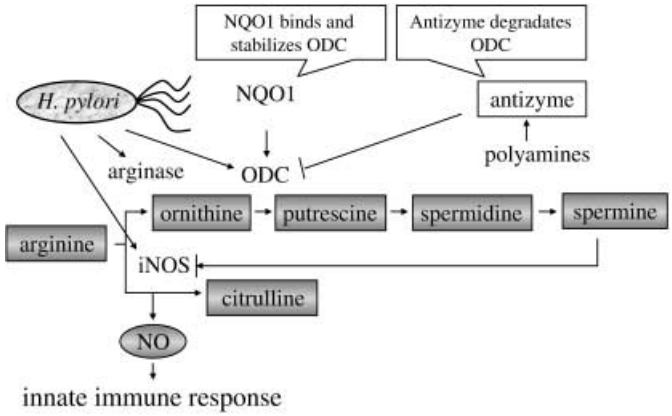

Fig. 3. Arginase–ornithine carboxylase (ODC) pathway to attenuate innate immune response by nitric oxide. iNOS, inducible nitric oxide synthase; NQO1, NAD(P)H : quinone oxidoreductase 1.

Interleukin-1β and TNF-α inhibit gastric acid secretion.[29] The inhibited acid secretion causes *H. pylori* distribution to the corpus, resulting in gastric atrophy.[30] Accordingly, the level of cytokines could influence the persistence of *H. pylori* infection.[31] 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,[1] and in neutrophils,[32] by *H. pylori* serves to trigger the inflammation. It binds 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.[33,34] In mice, cytokine expression by *Helicobacter felis* is modified by concurrent infection of the enteric helminth *Heligmosomoides polygyrus*, which drives the immune response through Th2 cells. Co-infection increases the mRNA of IL-10 in comparison with *Helicobacter felis* infection alone, resulting in reduced *Helicobacter*-associated gastric atrophy and high *Helicobacter* colonization.[35] These findings suggest that a high level of IL-10 and a lower level of IL-8 create favorable conditions for prolonging *H. pylori* infection in human gastric mucosa. Myeloperoxidase (MPO) is a lysosomal enzyme in polymorphonuclear leukocytes and monocytes. Hypochlorous acid produced by MPO shows microbicidal activity against a wide range of organisms,[36] producing tissue inflammation. It was reported that *H. pylori* water extract activates neutrophils[37] and enhances the secretion of MPO.[32]

Another line of innate immune response relating to persistent *H. pylori* infection is polyamine synthesis. *H. pylori* induces arginase II generating ornithine, as well as ornithine decarboxylase (ODC) generating polyamines (Fig. 3). Polyamines, especially spermine, restrain the immune response by inhibiting inducible nitric oxide synthase (iNOS) translation and nitric oxide (NO) production,[38] which are upregulated by *H. pylori*. The ODC level is regulated with antizyme, a polyamine-induced protein. NAD(P)H : quinone oxidoreductase 1 (NQO1) binds and stabilizes ODC. The regulation of ODC stability by NQO1 is prominent under oxidative stress.[39]

The mechanisms of *H. pylori* binding to gastric epithelium may be related to genetic traits of susceptibility to persistent *H. pylori* infection. *H. pylori* with the *babA2* gene is attached to gastric mucosa with blood group antigen-binding adhesion (BabA).[40,41] BabA binds both *Lewis b* and H type I blood group carbohydrate structures 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.

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Table 1. Polymorphisms reported in association with *Helicobacter pylori* infection and odds ratio (OR) or seropositive percentage (*HP*%)

Polymorphism	Subjects	OR or *HP*%
CD14 C-159T	1374 Japanese[42]	*TT*, *TC*:0.94, CC:1.16
CXCR2 C785T	241 Japanese[42]	*CC*(65%), *CT*(63%), *TT*(56%)
FUT2 Se/se	241 Japanese[43]	*SeSe*, *Sese*:0.79, *sese*:0.35*
	679 Japanese[44]	*SeSe*, *Sese*:1.51*, *sese*:1.50
	465 Japanese[44]	*SeSe*, *Sese*:1.57, *sese*:1.29
FUT3 Le/le	241 Japanese[43]	*LeLe*, *Lele*:1.95*, *lele*:2.80
	679 Japanese[44]	*LeLe*, *Lele*:0.98, *lele*:1.31
	465 Japanese[44]	*LeLe*, *Lele*:1.06, *lele*:1.40
IL-1 A C-889T	241 Japanese[45]	*CC*(62%), *CT/TT*(68%)
IL-1B C-31T	241 Japanese[45]	*CC*, *CT*:2.32*, *TT*:2.46*
	55 smokers	*CC*, *CT*:6.18*, *TT*:22.9*
	465 Japanese[46]	*CC*, *CT*:0.97, *TT*:1.73*
	80 ever smokers	*CC*, *CT*:1.68, *TT*:5.29*
	547 Japanese[47]	*CC*, *CT*:1.32, *TT*:1.35
	127 smokers	*CC*, *CT*:1.12, *TT*:1.01
	963 Japanese Brazilians[48]	*CC*, *CT*:1.30, *TT*:1.45*
	124 smokers	*CC*, *CT*:2.45, *TT*:3.49*
IL-1B C-511T	499 Japanese[49]	*CC*(53%), *CT*(54%), *TT*(52%)
	474 Koreans[50]	*CC*(88%), *CT*(86%), *TT*(86%)
IL-1RI C-116T	241 Japanese[42]	*CC*(65%), *CT*(58%), *TT*(72%)
IL-1RN VNTR	241 Japanese[45]	*4rpt/4rpt*(62%), *others*(67%)
	474 Koreans[50]	*non-2rpt*(87%), *2rpt*(80%)
IL-2 T-330G	454 Japanese[51]	*GG*, *TG*:1.10, *TT*:1.15
IL-4 C-33T	454 Japanese[51]	*CC*, *CT*:1.43, *TT*:1.25
IL-8 T-251A	454 Japanese[52]	*TT*, *TA*:0.86, *AA*:0.70
IL-10 T-819C	454 Japanese[52]	*TT*, *TC*:0.67, *CC*:0.82
IL-8 & *IL-10*	454 Japanese[52]	*TT* & *TT*, others:0.62*
	65 smokers	*TT & TT*, *others*:0.13*
	241 Japanese[42]	*TT & TT*, *others*:1.04
	55 smokers	*TT & TT*, *others*:0.45
	679 Japanese[42]	*TT & TT*, *others*:1.49*
	158 smokers	*TT & TT*, *others*:0.89
IL-13 C-1111T	454 Japanese[51]	*CC*, *CT*:0.73, *TT*:1.09
MPO G-463A	241 Japanese[53]	*GG*, *GA/AA*:0.69
	55 smokers	*GG*, *GA/AA*:0.21*
	454 Japanese[54]	GG, GA/AA:0.84
	64 smokers	GG, GA/AA:0.83
NF-KB2–10G I/D	1374 Japanese[42]	*II*, *ID*:1.03, *DD*:1.15
NQO1 C609T	241 Japanese[55]	*TT*, *TC*:1.13, *CC*:2.42*
	454 Japanese[55]	*TT*, *TC*:1.57, *CC*:1.70
PPAP Pro12Ala(C/G)	104 Chinese[56]	*CC*(62%), *CG/GG*(33%)
PTPN11 G/A at intron 3	454 Japanese[57]	*GG*(58%), *GA*(49%), *AA*(47%)
TCRBV6S1 A/B	383 Germans[58]	Significant association*
TNF-A T-1031C	1374 Japanese[59]	*TT*, *TC*:0.62, *CC*:0.43*
	963 Japanese Brazilians[60]	*CC*, *TC*:0.96, *TT*:1.18
TNF-A C-857T	1374 Japanese[59]	*CC*, *CT*:1.06, *TT*:1.69
	963 Japanese Brazilians[60]	*CC*, *CT*:1.17, *TT*:1.21
TNF-A –1031 & –857	1374 Japanese[59]	*CC & CC*, *TT & CC*:2.37*, *TC & CT*:2.84*, *TT & TT*:3.63*
	963 Japanese Brazilians[60]	*CC & CC*, *TT & CC*:1.08, *TC & CT*:1.03, *TT & TT*:1.27
		253 ever smokers *CC & CC*, *TT & CC*:2.01, *TC & CT*:1.76, *TT & TT*:2.30
TNF-A G-308A	393 Germans[61]	*GG*(52%), *GA*(56%), *AA*(56%)
	792 Italians[62]	*GG*(54%), *GA*(61%*), *AA*(–)
	474 Koreans[50]	*GG*(86%), *GA/AA*(89%)
TNF-B A252G	1374 Japanese[59]	*AA*, *AG*:1.05, *GG*:1.05

*Statistically significant ($P < 0.05$).

Genotype and *H. pylori* seropositivity

Molecules in related pathways seem to have the potential to enhance susceptibility to *H. pylori* infection at childhood, causing lifetime persistent infection. Table 1 shows the gene polymorphisms of such molecules reported for association with *H. pylori* infection.[42–62] In these polymorphisms, relatively consistent associations were found with *IL-1B* and *TNF-A*. The possible biological mechanism may be related to inhibition of gastric acid secretion. *NQO1* C609T also seems to have the potential to be a genetic trait for persistent *H. pylori* infection through stabilization of ODC.

IL-1β. IL-1β is encoded by *IL-1B* on chromosome 2q14, whose three polymorphisms (C-511T, C-31T and C3954T) have been studied in many diseases. Among Caucasians, the polymorphisms tend to be associated with gastric cancer risk, but not among Orientals.[49,63–67] In any ethnic group, 511T and −511C are tightly linked with −31C and −31T, respectively.[45,63] Although *–31T*, which makes a TATA box in the promoter region, seems to be a high-expression allele, there is controversy in its function. An electrophoretic mobility-shift assay demonstrated that transcription factors combine with *–31T*, not *–31C*,[63] and that the IL-1β level of antrum gastric mucosa was higher in *–511CC* (that is, *–31TT*) carriers than in *–511TT* carriers among *H. pylori*-infected Japanese.[68] A similar association was found among gastric cancer patients infected with *H. pylori* in Korea.[65] However, other studies have reported opposite findings among *H. pylori*-infected Japanese,[69] and among *H. pylori*-infected people in Thailand.[70] Among those with *IL-1A –889TT* in Finland, serum IL-1β levels were reported to be higher in *IL-1B –511T* allele carriers than in non-carriers.[71] A report on IL-1β mRNA showed no difference among *IL-1B* C-511T genotypes.[72] Concerning the function of C3954T, few biological studies have been reported, although its association with disease risk has been reported.

The effects of IL-1β can be modulated by the IL-1 receptor antagonist encoded by *IL-1RN*, IL-1 receptor I encoded by *IL-1R1*, and IL-1 receptor II encoded by *IL-1R2*,[73] so that polymorphisms of these molecules could affect persistent *H. pylori* infection. However, reports on the associations with *H. pylori* infection are limited.

TNF-α. *TNF-A* encoding TNF-α is located between HLA-B and HLA-DR on chromosome 6p21.3. In the promoter area, G-238A, G-244A, G-308A, C-857T, C-863A and T-1031C were reported.[74,75] The alleles *–238A*, *–244A* and *–308A* were rare (2.0%,[74] 0.0%[75] and 1.7%,[74] respectively, among Japanese people), and C-863A was tightly linked with T-1031C.[76] The function of these alleles is still controversial, but *–308A* is regarded as a high-expression allele.[77] As shown in Table 1, *H. pylori* infection tended to be more frequent among those with the −308A allele than among those without the allele. Our study of 1374 participants from three datasets showed that those with *TNF-A –857TT* and *–1031TT* had the highest risk of being *H. pylori* seropositive, and those with *TNF-A –857CC* and *–1031CC* the lowest,[59] although the association was not clear among Japanese Brazilians.[60]

NQO1. NQO1 is an obligate two-electron reductase whose gene is located in chromosome 16q22.[78] The gene has a functional polymorphism C609T (Pro187Ser); the *T* allele has null enzyme activity.[79] Our study found that the *CC* genotype favors persistent *H. pylori* infection.[55] As the molecules in connection with the innate immune response through the ODC–iNOS pathway were not fully examined in terms of their polymorphisms, further screening may detect the other polymorphisms associated with persistent *H. pylori* infection in this pathway.

Gene–environment interactions with smoking for *H. pylori* seropositivity

It is well known that the *H. pylori* eradication rate is lower among smokers.[80] One possible explanation is that it elevates gastric acid secretion. We have examined the interactions between genotypes and smoking for seropositivity. The published interactions concern *IL-1B*, *IL-8* and *IL-10*, *MPO* and *TNF-A* (Table 1). Concerning *IL-1B* C-31T,[45–48] the odds ratios (OR) of the *–31TT* genotype tended to be higher among smokers, with one exception.[47] The first dataset showed a marked elevation of *H. pylori* seropositivity for the combination of *IL-8 –251TT* and *IL-10 –819TT* among current smokers.[52] Subsequent datasets similarly produced an elevated OR, though insignificant.[42] A marginal interaction was observed for *MPO* (*GG* vs *GA*/*AA*) and smoking (current vs non-current) (OR = 4.57 and $P = 0.08$).[53] No difference in OR was observed between current smokers and never smokers in another dataset.[54] In a study on Japanese Brazilians, smokers with *TNF-A –857TT* and *–1031TT* tended to have an insignificantly higher OR (2.30) of infection than the whole subjects including both smokers and non-smokers (OR = 1.27).[60]

Epidemiology of gastric atrophy

There is no doubt that gastric atrophy is a result of inflammation induced by *H. pylori* infection.[81–87] In epidemiological studies, PG have been used as a marker of gastric atrophy[88] because of its less invasive method. To date, several risk factors including salty food intake,[89] low vegetable intake[81,87] and low vitamin C[82] have been reported for gastric atrophy among those with and without *H. pylori* infection. A recent study reported that rice, miso soup, cod roe and cuttlefish were high-risk foods among 1071 infected Japanese, indicating that traditional Japanese foods are a high-risk diet for gastric atrophy.[90] Another study showed that frequent rice intake significantly increased the risk of atrophic gastritis among 291 infected Japanese Brazilians.[91] A double-blind randomized controlled intervention study in Japan demonstrated that 5-year 500 mg of vitamin C supplementation slightly prevented the decrease in average PGI/II ratio relative to 50 mg of supplementation, with no difference in reduction of *H. pylori* seropositivity percentage between the two groups.[92]

Biology of gastric atrophy following *H. pylori* infection

CagA injected through a type IV secretion system from *H. pylori* into the gastric epithelial cells seems to play a pivotal role in gastric atrophy development (Fig. 4). The injected CagA is phosphorylated by Src family kinase, which binds SHP-2 (Src homology 2 domain-containing protein tyrosine phosphatase) at the phosphorylated site, then transduces its signal to other molecules.[93] Phosporylated CagA activates C-terminal Src kinase (Csk), which inhibits Src family kinase. This negative feedback regulates the signal from CagA.[94] Among the CagA, the East Asian type and Western type were recognized. The former is more virulent than the latter, and almost all *H. pylori* in Japan were reported to be East Asian CagA positive.[95]

IL-1β and TNF-α induced by *H. pylori* lead to chronic inflammation, resulting in gastric atrophy. Although the process to gastric atrophy has not been fully elucidated, immunological responses are involved through lifelong *H. pylori* infection. Extracellular bacterial infections typically induce a Th2 immune response, whereas *H. pylori* induces proinflammatory cytokines, indicating a Th1 immune response.[96–98] IL-2 is a multifunction cytokine with an autocrine activity to proliferate helper T cells. IL-4 causes Th0 cells to differentiate into Th2 cells, and is produced by Th2 cells. IL-13 is also a Th2 cytokine, which regulates inflammation, mucus production, tissue remodeling and fibrosis.[99]

Genotype and gastric atrophy measured with pepsinogens

Studies on the association between genotype and gastric atrophy among the infected are relatively limited (Table 2).[100–102] Significant associations were reported for *PNPN11*, and for *IL-2* and *IL-13* polymorphisms.

***PTPN11* G/A at intron 3 (IMS-JST057927, rs2301756).** IMS-JST057927 is a G-to-A single nucleotide polymorphism 223 bp upstream of exon 4 of *PTPN11* gene encoding SHP-2 on chromosome 12q24.1. The function of this polymorphism has not been reported. The first dataset showed that one (11.1%) out of nine infected individuals with the *AA* genotype had gastric atrophy, while 134 (56.1%) out of 239 infected individuals with the *G* allele had gastric atrophy.[57] If the polymorphism is functional or linked to a functional one, the association can be biologically explained by

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Table 2. Polymorphisms reported in association with gastric atrophy (GA) among *Helicobacter pylori* seropositives, as well as odds ratio (OR) and/or gastric atrophy percent (GA%)

Polymorphism	Subjects	OR and/or GA%
IL-1B C-31T	253 Japanese[46]	*CC*(54%), *CT*(52%), *TT*(56%)
	455 Japanese Brazilians[100]	*CC*, *CT*:0.61, *TT*:0.58
		CC(36%), *CT*(31%), *TT*(21%)
IL-2 T-330G	244 Japanese[101]	*GG*, *TG*:1.64, *TT*:2.78*
		GG(38%), *TG*(50%), *TT*(62%)
IL-4 C-33T	249 Japanese[101]	*CC*, *CT*:2.47, *TT*:1.80
		CC(38%), *CT*(60%), *TT*(53%)
IL-13 C-1111T	248 Japanese[101]	*CC*, *CT/TT*:0.41*
		CC(59%), *CT/TT*(45%)
PTPN11 G/A at intron 3	248 Japanese[57]	*GG*, *GA*:0.70, *AA*:0.09*
		GG(59%), *GA*(49%), *AA*(11%)
RANTES C-471T	344 Germans[102]	No association
TNF-A T-1031C	455 Japanese Brazilians[60]	*CC*(29%), *TC*(33%), *TT*(34%)
C-857T	456 Japanese Brazilians[60]	*CC*(32%), *CT*(36%), *TT*(39%)
–1031 & –857	455 Japanese Brazilians[60]	*CC* & *CC*(29%), *TT* & *CC*(33%),
		TC & *CT*(43%), *TT* & *TT*(39%)

*Statistically significant ($P < 0.05$).

the strength of signal transduction through the CagA–SHP2 complex. According to rs2301756 of the National Center for Biotechnology Information (NCBI) dbSNP, the frequency of the *G* allele (high-risk allele for gastric atrophy) is 0.802 among 1484 Japanese, 0.917 among 48 Chinese, 0.348 among 46 African American, and 0.064 among 46 Caucasians. This indicates that Japanese and Chinese become high-risk ethnic groups through CagA-positive *H. pylori* infection.

IL-2 T-330G and IL-13 C-1111T. T-330G of the *IL-2* gene on chromosome 4q26-27 was reported to be a functional polymorphism,[103] and IL-2 production is higher in the *GG* genotype than in the *TT* genotype.[104] The *TT* genotype was at a higher risk of gastric atrophy,[101] and was less frequent among Asians (38% out of 29 individuals) than among Caucasians (51% out of 199 individuals).[105]

The *IL-13* gene on chromosome 5q31 has several polymorphisms; at least three at the promoter region, two at intron 1 (Arg130Gln) and four at the 3′ untranslated region of exon 4.[106] The *–1111TT* genotype was reported to have increased binding of nuclear proteins, and to be associated with asthma.[106,107] Concerning gastric atrophy, *–1111TT* was a low risk genotype.[101] The biological mechanism has not yet been elucidated.

Genotype and advanced precancerous lesions

Some *H. pylori*-infected individuals go on to develop advanced precancerous lesions. A study in China showed no significant differences in genotype frequencies of *CYP2E1*, *GSTM1*, *GSTP1*, *GSTT1*, *ALDH2* and *ODC* between those with mild chronic atrophic gastritis (including 29.7% of *H. pylori*-negative patients) and those with deep intestinal metaplasia or dysplasia (including 20.2% of *H. pylori*-negative patients), but did show a significant interaction between *CYP2E1 Dra*I and smoking.[108] In Germany, harboring both *IL-1B –511T* and *IL-1RN 2rpt* alleles relative to lacking *IL-1B –511T* or/and *IL-1RN 2rpt* alleles was significantly associated with atrophic gastritis, intestinal metaplasia and severe inflammation.[109]

Epidemiology of gastric cancer

There are many epidemiological studies on risk factors for gastric cancer,[110,111] but studies on the gastric cancer factors among those with gastric atrophy are limited. The plausible risk factors among those with gastric atrophy are smoking, salty food and a lower intake of fresh fruit and vegetables, as well as family history of gastric cancer.[112,113]

Smoking elevates the risk of gastric cancer,[114–116] as well as of precancerous lesions, intestinal metaplasia and dysplasia.[117–119] Smoking was reported to promote the grade of atrophic gastritis in infected Japanese.[120] In addition to these epidemiological findings, biological studies on tobacco smoke carcinogenesis indicate that smoking plays a role also in the final step of carcinogenesis of *H. pylori*-related gastric cancer.[121]

Genotype and gastric cancer risk

To date, many genetic polymorphisms have been examined for associations with gastric cancer in case-control studies with mixed cases (*H. pylori*-related and *H. pylori*-unrelated) and controls at different stages (unexposed to *H. pylori*, exposed but uninfected, infected but without gastric atrophy, and with gastric atrophy), as shown in Fig. 5. As those case-control studies compared genotype frequencies between the mixed cases and heterogeneous controls, the estimated OR did not reflect any distinct step to gastric cancer. Controls unexposed to *H. pylori* have the same genotype frequency as the average among the exposed, which reduces the difference in the genotype frequency between the uninfected and infected. In order to measure the associations between genotypes and *H. pylori* infection, studies should be conducted at a region where exposure to the bacterium is highly prevalent. Usual case-control studies could provide estimates for the final step (i.e. literal carcinogenesis), when genotype frequency is different between gastric atrophy and gastric cancer, and the same among the uninfected, infected and those with gastric atrophy.

Table 3 lists the polymorphisms reported for gastric cancer risk, adopted from Gonzalez *et al.*[122] and recent studies.[123–138] The OR were listed if they were significant. Accordingly, it should be noted that there were many insignificant studies behind Table 3.

There are several studies to demonstrate the risks of both gastric atrophy and gastric cancer in comparison with the same controls without gastric atrophy. Individuals with the *IL-8 –251A* allele had OR = 1.50 with 95% confidence interval (95% CI) = 0.98–2.23 for gastric atrophy and OR = 1.50 with 95% CI = 1.00–2.25 for gastric cancer, indicating that the risk elevation was due to the risk for gastric atrophy, not for the step from gastric atrophy to gastric cancer.[139] The direct comparisons between controls with gastric atrophy and cases with gastric cancer have been reported; there were no associations with *p53* Arg72Pro,[140,141] nor with *PTPN11* G/A at intron 3.[57]

Table 3. Polymorphisms reported in association with gastric cancer risk: only significant associations are with odds ratio (OR) and 95% confidence interval (95%CI)

Polymorphism	Country	OR (95%CI)
ACE I/D	Germany[123]	*DD*, *DI*:0.55 (0.31–0.96), *II*:0.20 (0.08–0.54)
Cyclin D1 G870A	Germany[124]	Significant association ($P = 0.003$)
CYP1A1 Ile/Val	China[125]	*IleIle*, *ValVal*:4.84 (1.24–22.07)
CYP2C6 *1/*4	Japan[126]	**1*1/*1*4*, **4*4* : 3.14 (1.05–9.41)
CYP2C19 *1/*2/*3	Japan[127]	**1*1*, no*1:1.98 (1.07–3.65)
CYP2E1 Rsal	Japan†	
	Brazil†	
	China[128]	
E-cadherin C-160[a]	Taiwan[129]	*CC*, *AA*:0.20 (0.06–0.56)
EGF A61G	Japan[130]	
GSTM1 present/null	UK†	*Present*, *null*:2.9 (1.25–6.73)
	Japan†	*Present*, *null*:1.70 (1.05–2.8)
	Iran†	*Present*, *null*:2.3 (1.15–4.95)
	Poland†	
	China[125]	*Present*, *null*:2.81 (1.39–5.71)
	Taiwan[131]	*Present*, *null*:1.75 (1.04–2.96)
GSTM3 IVS6del3	Poland†	
GSTP1 I105V	Japan†	
	Poland†	
GSTT1 present/null	China†	*Present*, *null*:2.5 (1.01–6.2)
	Poland†	*Present*, *null*:3.1 (1.5–6.5) among current smokers
	Japan†	
IL-1B C-1473G	Korea[131]	
C-511T	Poland[63]	*CC*, *CT*:1.8 (1.3–2.4), *TT*:2.6 (1.7–3.9)
	Portugal†	*CC*, *CT/TT*:1.7 (1.1–2.7)
	Taiwan[116]	
C3954T	Poland[63]	
IL-1RN 86-bp VNTR	Poland[63]	*4rpt4rpt*, *2rp2rp*:3.7 (2.4–5.7)
	Taiwan[116]	
IL-1B C-511T + *IL-1RN* 86-bp VNTR	Portugal†	*CC* + *LL/L2rpt*, *CT/TT* +*2rpt2rp*:9.0 (3.5–23.0)
IL-2 G-384T, G114T	China[133]	
IL-4 C-590T	Taiwan[116,134]	
RP1/RP2	Taiwan[134]	
IL-4R Ile50Val	Taiwan[116]	
Gln576Arg	Taiwan[116]	
IL-10 G-1082A	Taiwan[116]	*AA*, *AG*:2.14 (1.07–4.30)
	China[133]	
T-819C	Taiwan[116]	*TT*, *TC*:1.83 (1.23–2.71), *CC*:1.95 (1.03–3.69)
	China[133]	
MK G-2669A	Taiwan[134]	
MTHFR C677T	China†	*CC*, *TT*:1.87 (1.00–3.48)
	Mexico[135]	*CC*, *TT*:1.62 (1.00–2.59)
C677T, A1298C	Korea[136]	
MUC1 VNTR	Portugal†	*Large*, *small*: 4.3 (1.8–10.5)
MUC6 VNTR	Portugal†	*Large*, *small*: $P < 0.05$
MYCL1(L-myc) *Eco*RI	Japan†	*LL*, *LS*:1.55 (1.03–2.34)
	Japan†	*LL*, *LS/SS*:3.09 (1.33–7.21)
NAT1	UK†	*Slow*, *rapid*:2.6 (1.3–5.3)
	Japan†	
NAT2	UK†	
	Japan†	
NQO1 C609T	Japan[137]	
OGG1 Ser327Cys	Japan†	
	Brazil†	
p16^{INK4A} C540G	Germany[124]	
C570G	Taiwan[134]	
p21 codon31	Taiwan[134]	
p53 codon72	Taiwan[134]	Significant association ($P = 0.02$)
PPAR Pro12Ala(C/G)	China[56]	*CC*, *CG/GG*:2.5 (1.1–5.8)
TFF2 VNTR	Portugal†	
TNF-A G-308A	Korea†	
	Taiwan[116]	
G-238A	Korea†	
	Taiwan[116]	
XRCC1 Arg194Trp	Brazil[138]	
Arg399Gln	Brazil[138]	
Arg194Trp + Arg399Gln	China†	*TrpTrp* + *ArgArg*, *ArgArg* + *ArgGln/GlnGln*:1.73 (1.12–2.69)
XRCC3 Thr241Met	Brazil[138]	

†Studies cited in the review by Gonzalez *et al*.[122]; *L*, alleles longer than *2rpt*.

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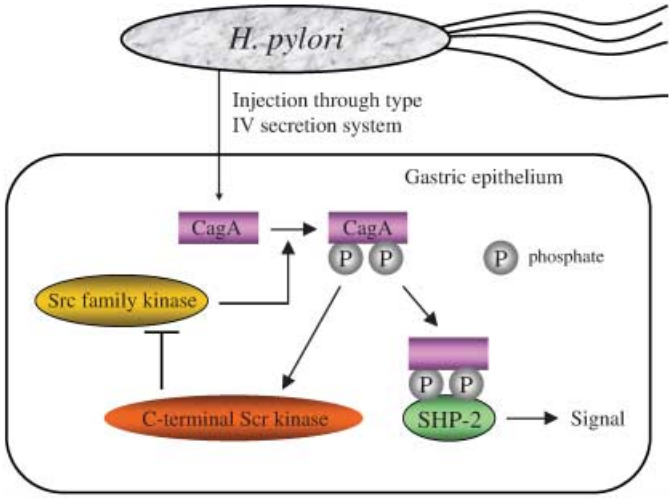

Fig. 4. Interaction of cytotoxin-associated gene A (CagA) with Src homology 2 domain-containing protein tyrosine phosphatase (SHP-2).

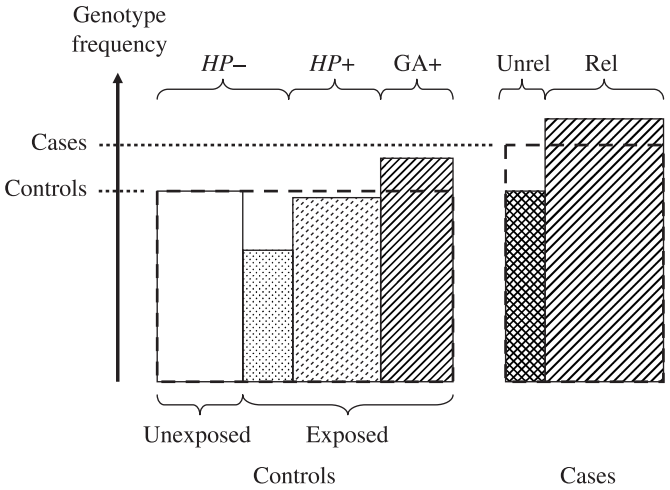

Fig. 5. Heterogeneity of subjects in case-control studies. Exposed, exposed to *Helicobacter pylori*; GA+, gastric atrophy positive; *HP–*, *H. pylori* negative; *HP+*, *H. pylori* positive; Rel, *H. pylori*-related gastric cancer; Unexposed, unexposed to *H. pylori*; Unrel, *H. pylori*-unrelated gastric cancer. In this case-control study, the average percentages of the targeted genotype for mixed cases and heterogeneous controls were measured.

Lifestyle factors may interact with genotype in the final step. Biologically, the interactions of smoking, fresh vegetable and fruit intake, and salty food intake with polymorphisms of carcinogen-metabolic enzyme and DNA repair enzymes are very plausible.

Conclusions

It is clear that *H. pylori*-related gastric cancer develops through several steps, including infection, gastric atrophy (histologically intestinal metaplasia, dysplasia) and cancer. Lifestyle factors such as smoking and diet could influence one or more steps. However, genotypes may be step specific because the biological process is distinct in the different steps. Accumulated findings on the associations between gastric cancer risk and polymorphism genotypes demonstrate that the strength of association varies among the studies. As most case-control studies examined the mixed effects on these steps, the inconsistent findings may be natural. In addition, the diversity of lifestyle factors interacting with the genotypes among the different study subjects may enlarge the inconsistency. In order to elucidate the genetic traits of *H. pylori*-related gastric cancer, studies on each step taking into account lifestyle factors should be conducted. Such studies will produce useful information for gastric cancer prevention.

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