

Genetic Factors Involved in the Genesis of Helicobacter Pylori-Induced Gastric Cancer

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1. Introduction

Gastric cancer is the second most frequent cause of cancer-related mortality in the world, and is the most common malignancy of the gastrointestinal tract in East Asian populations (Parkin et al., 1997; Parkin et al. 1999). *Helicobacter pylori* (*H. pylori*) is an established risk factor for developing gastric cancer and its precancerous lesions, which was evidenced by numerous epidemiological studies (Hamilton & Aaltonen, 2000; Tsuji et al., 2006). More than 50% of the world's population is estimated to be infected with this bacterium (Danesh, 1999). It is demonstrated that the risk of the subjects with *H. pylori* infection is from 2- to 6-fold (Eslick et al., 1999). In addition, some trials on *H. pylori* eradication revealed that cure of its infection reduces the gastric cancer development in high-risk populations (Fukase et al., 2008; Wong et al., 2004).

2. Genetic factors involved in the genesis of *Helicobacter pylori*-induced gastric cancer

Accumulated evidence has shown that there are three steps in gastric carcinogenesis: *H. pylori* infection, development of gastric precancerous lesions, and gastric carcinogenesis (Hamajima et al., 2006). For each of these three steps there are specific genetic traits that influence the process interacting with lifestyle factors (Figure 1).

2.1 Genetic traits for the persistence of *Helicobacter pylori* infection

H. pylori is transmitted from person to person through the oral-oral or fecal-oral route mainly during the childhood.

Such factors as will directly affect the *H. pylori* transmission like sewage systems are also essential determinants of the infection. Although there is limited supporting biological evidence, some lifestyle factors such as salty food intake, low fruits intake, or smoking might play a role in persistent *H. pylori* infection.

Genetic traits could influence persistent *H. pylori* infection interacting with lifestyle factors.

2.1.1 Genetic polymorphisms of the molecules associated with gastric acid secretion

Gastric acid is secreted from parietal cells, and regulated by histamine, gastrin, and acetyl choline. It is known that IL-1 β and TNF- α , proinflammatory cytokines, inhibit gastric acid

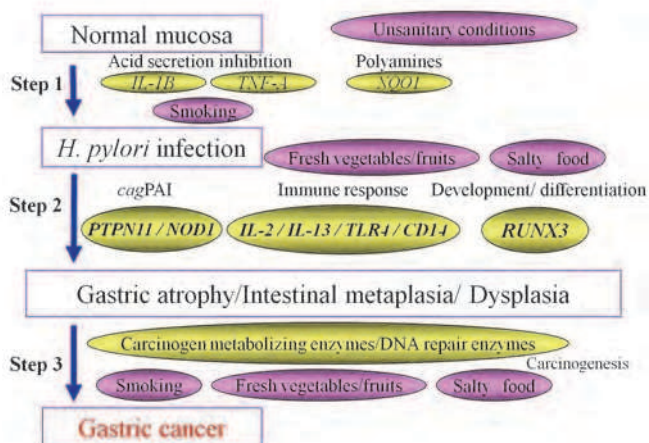


Fig. 1. Steps in *Helicobacter pylori*-induced gastric cancer.

secretion (Beales et al., 1998), and *H. pylori* infected patients showed a marked increase in IL-1 β mRNA in mucosa (Wang et al., 1999). A recent study demonstrated that IL-1 β decreased gastrin level (Chakravorty et al., 2009), elucidating the mechanism of the acid secretion reduction due to *H. pylori* infection. IL-1 β induces TNF- α , and vice versa. Although IL-1 β and TNF- α have several roles, polymorphisms connected to both molecules are classified as one group in this chapter (Table 1).

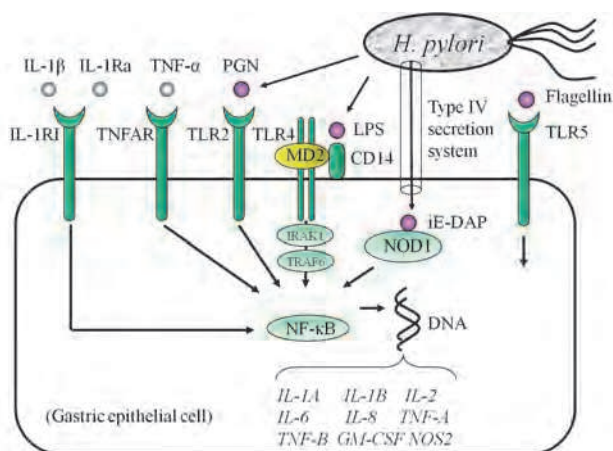


Fig. 2. Signal pathways from *Helicobacter pylori* infection to pro-inflammatory gene expression.

IL-1A

IL-1A making a cluster in chromosome 2q14 with IL-1B and IL-1RN has two single nucleotide polymorphisms (SNPs) of C-889T and G4845T, as well as a 46-bp variable

number of tandem repeats (VNTR) polymorphism (Bailly et al., 1993). It was reported that the combination *IL-1A* -889TT and *IL-1B* -511T (-511TT or -511TC) was related to high plasma levels of IL-1 β (Hullkonen et al., 2000). The association with *H. pylori* infection was examined only for a Japanese population (Hamajima et al., 2001), providing no association of *IL-1A* C-889T (Table 1). In the study, the association with 46-bp VNTR polymorphism was not examined, because the polymorphism was not found among Japanese (Hamajima et al., 2002a). Polymorphism G4845T was reported to be linked with C-889T (Armitage et al., 2000).

IL-1B

Three polymorphisms of *IL-1B* T-511C, C-31T, and C3954T located in chromosome 2q14, have been studied for many diseases. It is known that -511T and -511C are tightly linked with -31C and -31T, respectively (Hamajima et al., 2001a). An electrophoretic mobility-shift assay demonstrated that C-31T was a functional polymorphism (El-Omar et al., 2000), while C3954T is unlikely to be functional.

We conducted four studies for Japanese and Japanese Brazilians, all of which showed a similar result, that those with -31TT had a higher risk of *H. pylori* seropositivity (Hamajima et al., 2001a; Hamajima et al., 2002b; Uno et al., 2002). The risk elevation was marked for smokers except one study (Hamajima et al., 2002b). Since cigarette smoke includes about 4,000 chemicals, many genes may be upregulated or downregulated. A study on C-31T in Brazil showed a higher seropositive rate for those with -31TT genotype, though not significant (Queiroz et al., 2009). Concerning T-511C polymorphism, no associations were found among Japanese (Kato et al., 2001) and Koreans (Kim et al., 2006), while a Chinese study reported a significant association with -511T allele (-511TT + -511TC) (Liou, 2007), which was linked to -31C allele.

IL-1RI

There are two receptors for IL-1 β ; IL-1RI and IL-1RII. The former transduces the signal, but the latter does not. IL-1RI in 2q12 has reportedly four polymorphisms; C-116T (RFLP-A), C-90T, T49C, and RFLP-B at an unknown site (Bergholdt et al., 1995). There were no reports on the association between these polymorphisms and *H. pylori* seropositivity, except our study for C-116T indicating no association (Hamajima et al., 2003a).

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 (Hamajima et al., 2001a). No significant differences in *H. pylori* seropositivity among different genotypes of *IL-1RN* 86-bp VNTR were observed for Japanese, Koreans, and Chinese (Hamajima et al., 2001a; Kim et al., 2006; Liou et al., 2007). Since the minor alleles are rare for the three ethnic groups, statistical power of these studies was not enough.

TNF-A

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 (Kamizono et al., 2000; Yamaguchi et al., 2001). Among East Asians, -238A, -244A and -308A alleles were rare (2.0%, 0.0% and 1.7%, respectively in Japanese (Kamizono et al., 2000; Yamaguchi et al., 2001)), and C-863A was tightly linked with T-1031C (Higuchi et al., 1998). The functions of these alleles were controversial, but -308A was regarded as a high expression allele (D'Alfonso et al., 1994).

Subjects (Reference)	aOR or HP%			
<i>IL-1A</i> C-889T	CC		CT/TT	
241 Japanese (Hamajima, 2001a)	62% (n=201)		68% (n=39) / (n=1)	
<i>IL-1B</i> C-31T	CC		CT	TT
241 Japanese (Hamajima, 2001a)	1 (n=42)		2.32* (n=133)	2.46* (n=66)
55 smokers	1 (n=16)		6.18* (n=27)	22.9* (n=12)
465 Japanese (Uno, 2002)	1 (n=116)		0.97 (n=183)	1.73* (n=163)
80 ever smokers	1 (n=23)		1.68 (n=34)	5.29* (n=22)
547 Japanese (Hamajima, 2002a)	1 (n=116)		1.32 (n=237)	1.35 (n=178)
127 smokers	1 (n=23)		1.12 (n=60)	1.01 (n=41)
963 Jpn. Brazil. (Uno, 2002)	1 (n=226)		1.30 (n=432)	1.45* (n=289)
124 smokers	1 (n=ND)		2.45 (n=ND)	3.49* (n=ND)
541 Brazil. (Queiroz, 2009)	64% (n=112)		71% (n=265)	67% (n=164)
<i>IL-1B</i> T-511C	TT		TC	CC
499 Japanese (Kato, 2001)	52% (n=113)		54% (n=243)	53% (n=143)
474 Koreans (Kim, 2006)	86% (n=131)		86% (n=259)	88% (n=84)
663 Chinese (Liou, 2007)	67% (n=148)		64% (n=343)	55%* (n=172)
<i>IL-1RI</i> C-116T	CC		CT	TT
241 Japanese (Hamajima, 2003a)	65% (n=93)		58% (n=114)	72% (n=32)
<i>IL-1RN</i> VNTR	4rpt/4rpt		2rpt	Others
241 Japanese (Hamajima, 2001a)	62% (n=217)		-	67% (n=24)
474 Koreans (Kim, 2006)	-		80% (n=60)	87% (n=414)
663 Chinese (Liou, 2007)	-		66% (n=53)	61% (n=540)
540 Brazil. (Queiroz, 2009)	67% (n=378)		70% (n=162)	-
<i>TNF-A</i> T-1031C	TT		TC	CC
1,374 Japanese (Hamajima, 2003a)	1 (n=952)		0.92 (n=385)	0.43* (n=34)
963 Jpn. Brazil. (Atsuta, 2006)	1.18 (n=648)		0.96 (n=269)	1 (n=31)
<i>TNF-A</i> C-857T	CC	CT	TT	
1,374 Japanese (Hamajima, 2003a)	1 (n=931)		1.06 (n=373)	1.69 (n=42)
963 Jpn. Brazil. (Atsuta, 2006)	1 (n=613)		1.17 (n=301)	1.21 (n=36)
<i>TNF-A</i> -1031 & -857	CC&CC	TT&CC	TC&CT	TT&TT
1,374 Japanese (Hamajima, 2003a)	1(n=34)	2.37*(n=595)	2.84*(n=76)	3.63*(n=42)
963 Jpn. Brazil. (Atsuta, 2006)	1(n=30)	1.08 (n=377)	1.03 (n=67)	1.27 (n=35)
253 ever smokers	1(n=11)	2.01 (n=102)	1.76 (17)	2.30 (n=5)
<i>TNF-A</i> G-308A	GG		GA	AA
393 Germans (Kunstmann, 1999)	52% (n=277)		56% (n=89)	56% (n=18)
792 Italians (Zambon, 2005)	54% (n=ND)		61%* (n=ND)	- (n=ND)
474 Koreans (Kim, 2006)	86% (n=400)		89% for GA(n=59)/AA(n=2)	
539 Brazil. (Queiroz, 2009)	70% (n=403)		66% (n=123)	46% (n=13)
<i>TNF-B</i> A252G	AA	AG	GG	
1,374 Japanese (Hamajima, 2003a)	1 (n=501)		1.05 (n=656)	1.05 (n=204)

*: statistically significant ($p < 0.05$), Jpn. Brazil.: Japanese Brazilians, and ND: not described.

Table 1. Genetic polymorphisms of molecules potentially related with gastric acid secretion, reported on the associations with *Helicobacter pylori* infections: sex-age-adjusted odd ratio (aOR) or seropositive percentage (HP%)

Among the studies reported on the *TNF-A* polymorphisms (Queiroz et al., 2009; Kim et al., 2006; Hamajima et al., 2003b; Atsuta et al., 2006; Kunsmann et al., 1999; Zambon et al., 2005), significant associations were found for T-1031C and for the combination of T-1031C and A-857T among 1,374 Japanese (Hamajima et al., 2003), as well as for G-308A among 792 Italians (Zambon et al., 2005). If -1031T and -857T are the high expression alleles, the findings of the studies on *TNF-A* seemed rather consistent to indicate that high *TNF- α* expression favors persistent *H. pylori* infection.

TNF-B

TNF-B A252G, whose G allele is strongly linked with *TNF-A* -857C allele in Japanese (Hamajima et al., 2003b), was not associated with seropositivity, as shown in Table 1. Another polymorphism, *TNF-B* Thr26Asn, was found to link completely with A252G.

2.1.2 Genetic polymorphisms of molecules associated with innate immune responses

Innate immune responses have not completely been understood. The polymorphisms of the molecules possibly involved in the innate immune responses are selected in this section (Table 2).

CD14

CD14, located in chromosome 5q31.1, has a polymorphism C-159T. Serum soluble *CD14* was reported to be significantly higher in those with -159TT (n=42, median=4.5 μ g/ml) than in those with -159CC (n=67, median=4.1 μ g/ml) (Baldini et al., 1999). Although the polymorphism seemed functional, no association was found with *H. pylori* seropositivity (Hamajima et al., 2003a).

CXCR2

CXCR2 in 2q35 was reported to have three polymorphisms; C785T causing a silent codon change in leucine, and T1208C and G1440A in the 3' untranslated region of exon 3 (Renzoni et al., 2000). These polymorphisms are tightly linked, forming a haplotype with 785C, 1208T, and 1440G. Accordingly, any polymorphism of the three may be used for a pilot association study on disease risk. No significant difference was observed in the seropositive rate among the three genotypes of C785T in Japan (Hamajima et al., 2003a).

IL-2

T-330G of *IL-2* gene on chromosome 4q26-27 was reported to be a functional polymorphism; the production was higher in -330GG genotype than in TT genotype (Williams et al., 1988; Hoffmann et al., 2001). The -330TT was at a higher risk of gastric atrophy (Togawa et al., 2005) and less frequent among Asians (38% out of 29 individuals) than among Caucasians (51% out of 199 individuals) (Hoffmann et al., 2002). While the polymorphism was not associated with *H. pylori* seropositivity among Japanese (Togawa et al., 2005), -330TT genotype was significantly associated with the seropositivity relative to -330C allele (CC+CT) among Brazilians (Queiroz et al., 2009).

IL-4

IL-4 C-33T on chromosome 5q31.1 was reported to be functional; *IL-4* protein production was higher in -33TT genotype than in -33CC genotype (Nakashima et al., 2002). Our dataset showed no association with *H. pylori* seropositivity in Japanese (Togawa et al., 2005).

IL-8

IL-8 located in chromosome 4q12-q21 was reported to have nine polymorphisms (four in 5' upstream regions, four at introns, and one in 3' downstream region). 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), insTATCCA (0.18), and delTTTCCA (0.10), respectively (Hull et al., 2001), but the genotyping of T-251A and T396G is sufficient for classifying the haplotypes even among Africans. Among Japanese, there was 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 (Hamajima et al., 2003c), indicating that T-251A is a good marker for Japanese.

Although a study on IL-8 expression found that the A allele had a higher expression than the T allele (Hull et al., 2001). Plasma IL-8 levels was found to be higher in A allele carriers among those with *H. pylori* seronegative, but lower among the seropositives without gastric atrophy (Naito et al., 2010). Although no significant association was found with the seropositivity, the point estimate of the adjusted odds ratio was less than unity for the A allele carriers (Hamajima et al., 2003c).

IL-10

IL-10 G-1082A and T-819C polymorphisms were reported to influence the expression of IL-10 mapped on 1q31-32; -1082A and -819T are high expression alleles (Turner et al., 1997; Helminen et al., 2001). There is a large difference in -1082G allele frequency among different regions; 0.51 in Belfast, 0.52 in Glasgow, and 0.47 in Strasbourg (Donger et al., 2001), but 0.04 among Japanese (Ito et al., 2000). We found that there was no significant association between T-819C and *H. pylori* seropositivity.

As mentioned, a high level of IL-10 and a lower level of IL-8 create favorable conditions for prolonging the *H. pylori* infection in human gastric mucosa. Accordingly, the combination of IL-8 -251TT (the low expression genotype) and IL-10 -819TT (the high expression genotype) was expected to be favorable for persistent *H. pylori* infection. Among three studies, one study demonstrated that the other combinations were at a significantly lower risk of the persistent infection (Hamajima et al., 2003c), but another study was opposite (Hamajima et al., 2003a). When smokers were selected, the genotype combinations other than IL-8 -251TT and IL-10 -819TT were at a lower risk in the three studies, though not significant for two studies (Table 2).

IL-13

IL-13 is a Th2 cytokine, whose gene is located in 5q31. Closely linked polymorphisms, A-1512C, C-1111T, and Arg130Gln, have been examined for disease risk (Beghe et al., 2009). Although the association between gastric atrophy development and C-1111T was observed (Togawa et al., 2005), there was no association with the seropositivity.

MPO

Myeloperoxidase (MPO) is a lysosomal enzyme in polymorphonuclear leukocytes and monocytes. It produces hypochlorous acid to kill a wide range of organisms. While mutations, Arg569Trp, Val173Cys, or Met251Thr of MPO located in 17q23.1 cause fatal

diseases such as chronic granulomatous disease due to severe enzyme activity deficiency (Nauseef et al., 1994), *MPO* G-463A exhibits less influential, but the transcription level of *A* allele was reported to be one twenty-fifth of *G* allele (Piedrafita et al., 1996). Two studies showed the *A* allele carriers were at a lower risk of the seropositivity, though not significant (Hamajima et al, 2001b; Katsuda et al, 2003). Intuitively, low enzyme activity seemed to provide a favorable situation, but the results were opposite.

NF-KB2

NF-KB2 encoding NF- κ B2 (p100) has a Ins/Del polymorphism at -10G (or 1867GG/G), as well as two polymorphisms with a rare minor allele (Shinohara et al., 2001). Although the function of Ins/Del -10G has not been demonstrated, no association was found with *H. pylori* seropositivity (Hamajima et al., 2003a).

NOS2

Nitric oxide synthase (NOS) was three isozymes; neuronal constitutive NOS (nNOS) encoded by *NOS1*, inducible NOS (iNOS) encoded by *NOS2*, and endothelial constitutive NOS (eNOS) encoded by *NOS3*. There were several polymorphisms reported for *NOS2* in chromosome 17cen-q11.2, such as C-1173T, G-954C, (TAAA)_n, and (CCTTT)_n. A C150T (Ser608Leu) polymorphism at exon 16 was reported to have an association with type 1 diabetes (Johannsen et al., 2001), but the association with *H. pylori* was not observed among Japanese (Goto et al., 2006a). There were no studies with the other polymorphisms of *NOS2*.

NQO1

NQO1 is an obligate two-electron reductase, whose gene is located in chromosome 16q22 (Ross et al., 2000). The gene has a functional polymorphism C609T (Pro187Ser); the *T* allele has no enzyme activity (Siegel et al., 1999). The *CC* genotype was found that to favor persistent *H. pylori* infection among Japanese (Goto et al., 2005).

ODC

ODC in chromosome 2p25, encoding ornithine decarboxylase, has a functional polymorphism G317A in intron 1; the expression was higher in the *A* allele than in the *G* allele (Guo et al., 2000). Aspirin chemoprevention of colorectal adenoma recurrence was reported to be more effective among those with 317AA than those with the other genotypes. The 317AA genotype was 5-7% in Europe and the United States (Hubner et al., 2008), while it was 36% in Japan (Goto et al., 2007). The association with *H. pylori* seropositivity was not observed among Japanese (Goto et al., 2007).

TLR2

Arg677Trp, Arg753Gln, and Ins/Del at -196 to -174 were reported as polymorphisms of *TLR2* on chromosome 4q32 (Queiroz et al., 2009; Tahara et al., 2007). Although the minor allele was rare, the association with Arg753Gln was examined among Brazilians. They found no association with the polymorphism (Queiroz et al., 2009).

TLR4

In *TLR4* on chromosome 9q32-33, two polymorphisms, Asp299Gly and Thr399Ile, have been reported. The 299Gly/399Ile allele is less sensitive to LSP than 299Asp/399Thr allele, resulting in lower NF- κ B activity (Arbour et al., 2000). The LPS-hyposensitive allele was found to be 5.9% among 879 blood donors in England (Read et al., 2001), but not found

Subjects [Reference]	aOR or HP%					
<i>CD14</i> T-159C	<i>TT</i>		<i>TC</i>		<i>CC</i>	
1,374 Japanese (Hamajima, 2003a)	1	(n=413)	0.94	(n=678)	1.16	(n=413)
<i>CXCR2</i> C785T	<i>CC</i>		<i>CT</i>		<i>TT</i>	
241 Japanese (Hamajima, 2003a)	65%	(n=110)	63%	(n=100)	56%	(n=25)
<i>IL-2</i> T-330G	<i>GG</i>		<i>GT</i>		<i>TT</i>	
454 Japanese (Togawa, 2005)	1	(n=45)	1.10	(n=196)	1.15	(n=202)
541 Brazil. (Queiroz, 2009)	70%	(n=27)	63%	(n=221)	72%*	(n=293)
<i>IL-4</i> C-33T	<i>CC</i>		<i>CT</i>		<i>TT</i>	
454 Japanese (Togawa, 2005)	1	(n=42)	1.43	(n=183)	1.25	(n=227)
<i>IL-8</i> T-251A	<i>TT</i>		<i>TA</i>		<i>AA</i>	
454 Japanese (Hamajima, 2003c)	1	(n=234)	0.86	(n=177)	0.70	(n=37)
<i>IL-10</i> T-819C	<i>TT</i>		<i>TC</i>		<i>CC</i>	
454 Japanese (Hamajima, 2003c)	1	(n=220)	0.67	(n=177)	0.82	(n=37)
<i>IL-8</i> & <i>IL-10</i>	<i>TT&TT Others</i>					
454 Japanese (Hamajima, 2003c)	1	(n=115)	0.62*	(n=327)		
65 smokers	1	(n=ND)	0.13*	(n=ND)		
241 Japanese (Hamajima, 2003a)	1	(n=57)	1.04	(n=178)		
55 smokers	1	(n=ND)	0.45	(n=ND)		
679 Japanese (Hamajima, 2003a)	1	(n=164)	1.49*	(n=507)		
158 smokers	1	(n=ND)	0.89	(n=ND)		
<i>IL-13</i> C-1111T	<i>CC</i>		<i>CT</i>		<i>TT</i>	
454 Japanese (Togawa, 2005)	1	(n=310)	0.73	(n=127)	1.09	(n=11)
<i>MPO</i> G-463A	<i>GG</i>		<i>GA/AA</i>			
241 Japanese (Hamajima, 2001b)	1	(n=192)	0.69	(n=47)/(n=2)		
454 Japanese (Katsuda, 2003)	1	(n=354)	0.84	(n=77)/(n=6)		
<i>NF-KB2</i> -10G	<i>InsIns</i>		<i>InsDel</i>		<i>DelDel</i>	
1,374 Japanese (Hamajima, 2003a)	1	(n=513)	1.03	(n=648)	1.15	(n=199)
<i>NOS2</i> C150T (Ser608Leu)	<i>CC</i>		<i>CT</i>		<i>TT</i>	
454 Japanese (Goto, 2006a)	No association					
<i>NQO1</i> C609T (Pro187Ser)	<i>TT</i>		<i>TC</i>		<i>CC</i>	
241 Japanese (Goto, 2005a)	1	(n=48)	1.13	(n=107)	2.42*	(n=86)
454 Japanese (Goto, 2005a)	1	(n=83)	1.57	(n=210)	1.70	(n=153)
<i>ODC</i> A317G	<i>AA</i>		<i>AG</i>		<i>GG</i>	
465 Japanese (Goto, 2007)	1	(n=167)	1.09	(n=229)	1.02	(n=69)
<i>TLR2</i> Arg753Gln	<i>ArgArg</i>		<i>ArgGln</i>		<i>GlnGln</i>	
541 Brazil. (Queiroz, 2009)	68%	(n=531)	70%	(n=10)	-	(n=0)
<i>TLR4</i> Asp299Gly	<i>AspAsp</i>		<i>AspGly</i>		<i>GlyGly</i>	
541 Brazil. (Queiroz, 2009)	68%	(n=490)	71%	(n=51)	-	(n=0)
<i>TLR4</i> G3725C	<i>GG</i>		<i>GC</i>		<i>CC</i>	
1,592 Japanese (Hishida, 2009a)	1	(n=827)	0.95	(n=474)	0.72	(n=90)
<i>TLR5</i> Arg392Ter	<i>ArgArg</i>		<i>ArgTer</i>		<i>TerTer</i>	
541 Brazil. (Queiroz, 2009)	68%	(n=504)	71%	(n=34)	67%	(n=3)

* Statistically significant (p<0.05), Jpn. Brazil.: Japanese Brazilians, Brazil.: Brazilians

Table 2. Genetic polymorphisms of molecules potentially involved in innate responses, reported on the associations with *Helicobacter pylori* infection: sex-age-adjusted odds ratio (aOR) or seropositive percentage (HP%)

among 275 Japanese (Tahara et al., 2007). For Japanese, G3725C in 3'UTR was reported to have an association with periodontitis. We found that the polymorphism had an association with severe gastric atrophy, but did not with persistent *H. pylori* infection (Hishida et al., 2009a).

TLR5

A polymorphism *TLR5* Arg392Ter on chromosome 1q41-42 was examined for the association among Brazilians (Queiroz et al., 2009). There was no significant association in the study.

2.1.3 Genetic polymorphisms of molecules associated with adhesion to epithelial cells

BabA of *H. pylori* binds of H type I and Lewis b antigen carbohydrate structure on human epithelial cells. H type I is synthesized from Type I precursor with secretor enzyme encoded by *FUT2*, and further metabolized to Lewis b with Lewis enzyme encoded by *FUT3*. Both enzymes are fucosyltransferase.

FUT2 (secretor gene)

Although many polymorphisms were reported, main alleles of *FUT2* located in 19q13.3 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, while *sej* shows very low activity, and *se3*, *se4*, and *se5* reveal no activity. Accordingly, *Se1* and *Se2* are denoted by *Se*, and the others by *se*. Among Caucasians, *se3* and *se4* are common *se* alleles, whereas in East Asians *se5* and *sej* are main *se* alleles (Narimatsu et al., 1998). Since those with *sese* genotype cannot synthesize H type I nor Lewis b, they were expected to have the lower seropositive rate. Our first study fitted the expectation (Ikehara et al., 2001), but it was not confirmed in the second and third datasets (Hamajima et al., 2002b). Those with *sese* genotype was reported to be resistance for Norwalk virus infection (Lindsmith L et al., 2003).

Subjects [Reference]	aOR					
<i>FUT2</i>	<i>SeSe</i>		<i>Sese</i>		<i>sese</i>	
241 Japanese (Ikehara, 2001)	1	(n=61)	0.79	(n=127)	0.35*	(n=51)
679 Japanese (Hamajima, 2002c)	1	(n=170)	1.51*	(n=328)	1.50	(n=181)
464 Japanese (Hamajima, 2002c)	1	(n=139)	1.57	(n=218)	1.29	(n=107)
<i>FUT3</i>	<i>LeLe</i>		<i>Lele</i>		<i>lele</i>	
241 Japanese (Hamajima, 2002c)	1	(n=124)	1.95*	(n=98)	2.80	(n=17)
679 Japanese (Hamajima, 2002c)	1	(n=353)	0.98	(n=251)	1.31	(n=59)
424 Japanese (Hamajima, 2002c)	1	(n=235)	1.06	(n=155)	1.40	(n=33)

* Statistically significant (p<0.05)

Table 3. Genetic polymorphisms of other miscellaneous molecules, reported on the associations with *Helicobacter pylori* infection: sex-age-adjusted odds ratio (aOR) or seropositive percentage (HP%)

FUT3 (*Lewis gene*)

FUT3 has three polymorphisms; T59G, G508A, and T1067A. An *Le* allele is defined as one with 59T, 508G, and 1067T, an *le1* allele with 59G, 508A, and 1067T, an *le2* allele with 59G, 508G, and 1067A, and an *le3* allele 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* (Narimatsu et al., 1998). The *LeLe* genotype, which may disturb the synthesis of H type I by *FUT2* through sharing the same substrate (type I precursor), showed the lower seropositivity in the first dataset, while the finding was not reproduced by the second and third datasets (Hamajima et al., 2002b) (Table 3).

2.2 Genetic predisposition to *Helicobacter pylori*-induced gastric precancerous lesions

The presence of gastric lesions outside the tumor was recognized as gastric precancerous lesions in gastrectomy specimens or biopsies taken by flexible gastroscopes, which lead to the development of a model of gastric carcinogenesis generally accepted. Long-term follow-up of cohorts in high-risk populations has documented the dynamics of gastric precancerous process. Severe gastric atrophy, corpus-predominant gastritis, intestinal metaplasia and dysplasia are well-recognized predominant predispositions to gastric cancer (Correa P, 1988; Uemura et al., 2001).

There seems to be a considerable variation in the extent of these gastric damages due to *H. pylori* infection from one subject to another, suggesting that genetic factors are playing important roles in the long-term outcome of *H. pylori* infection.

Although biological mechanisms underlying the genesis of gastric precancerous conditions remain largely unknown, both direct effects by the virulence factors of *H. pylori*, such as cytotoxin-associated gene A (*CagA*), and indirect effects derived from pro-inflammatory immune response by the host seem to be involved (Takahashi et al., 2007) (Table 4).

2.2.1 *Cag* pathogenicity island-related genes and their polymorphisms

The main effects of *H. pylori* virulence factors on the development of gastric precancerous lesions may be represented by the *CagA*. *CagA* is a 120 to 145-kDa *H. pylori* protein encoded by the *cagA* gene, which is localized at one end of the *cag* pathogenicity island (*cagPAI*), a 40-kb DNA segment considered to be horizontally transfected to the *H. pylori* genome (Censini et al., 1996; Akopyants et al., 1998). *CagA* is delivered from *H. pylori* bacterium into host cell cytoplasm through the type IV secretion system and undergoes tyrosine phosphorylation. In the injected gastric epithelial cells, *CagA* induces cellular spreading and elongation called the 'hummingbird phenotype', which is thought to play important roles in *H. pylori*-induced gastric carcinogenesis. In this *CagA*-dependent morphologic transformation of gastric epithelial cells, a key molecule SHP-2 (src homology 2 domain-containing protein tyrosine phosphatase-2) is required. Binding of tyrosine phosphorylated *CagA* to the SH2 domains of SHP-2 causes a conformational change in SHP-2 itself which leads to the aberrant activation of SHP-2 phosphatase. SHP-2 plays a major role in intracellular signaling provoked by various growth factors, hormones or cytokines, and is widely expressed in both embryonic and adult tissues (Higashi et al., 2002). SHP-2 is required for full activation of the Ras-MAP kinase cascade in response to growth factor-receptor interaction and plays an important role in cell

morphogenesis as well as cell mortality (Higashi et al., 2002), which might partly explain the mechanism for the formation of hummingbird phenotype.

Meanwhile, CagA is shown to disrupt the tight junctions and causes loss of epithelial apical-basolateral polarity through the specific interaction of CagA with partitioning-defective-1 (PAR1)/ microtubule affinity-regulating kinase-2 (MARK2) (Sadaat et al., 2007) (Figure 3). PAR1b is localized to the basolateral membrane in normal polarized epithelial cells, while atypical protein kinase C (aPKC) complex is localized specifically to the apical membrane. When CagA is delivered and injected into normal polarized gastric epithelial cells, CagA inhibits the kinase activity of PAR1b by binding directly to its kinase domain, which subsequently leads to junctional and polarity defects followed by the disorganization of the epithelial monolayer (Sadaat et al., 2007). PAR1b exists as a homodimer in the cells, and two CagA protein bind to a PAR1b dimer, which is also essential for stable CagA-SHP2 interaction.

Recently, a cytosolic pattern recognition receptor, nucleotide-binding oligomerization domain protein 1 (NOD1), was found to respond to peptidoglycan delivered by *H. pylori* cagPAI (Viala et al., 2004). NOD1 is known to sense the essential gamma-D-glutamyl-meso-diaminopimelic acid (i.E.-DAP) dipeptide, which is uniquely contained in peptidoglycan of all gram negative and certain gram-positive bacteria (Neel et al., 2003).

As the precise relationship of gastric precancerous lesions like gastric atrophy (GA) and intestinal metaplasia (IM) with these cagPAI-associated molecules is largely left unknown, further investigations are required to clarify the roles of these cagPAI-related molecules in the genesis of gastric precancerous lesions.

PTPN11 (Protein tyrosine phosphatase, non-receptor type, 11)

The *PTPN11* G/A polymorphism at intron 3 (rs2301756), is a G-to-A single nucleotide substitution at 223 bp upstream of exon 4 in the *PTPN11* gene encoding SHP-2 at chromosome 12q24.1. The biological function of this polymorphism has not yet been reported. The first dataset showed that one (11.1%) out of 9 infected individuals with the AA genotype had gastric atrophy, while 134 (56.1%) among 239 infected with the G allele had atrophy (Goto et al., 2006a). Our recent report of 1,636 non-cancer Japanese subjects demonstrated that the risk of severe gastric atrophy was significantly reduced for those with at least one A allele of this *PTPN11* G/A polymorphism at intron 3 (OR = 0.62, 95% CI = 0.42-0.90), confirming the association of this *PTPN11* gene polymorphism with the risk of gastric precancerous lesions in *H. pylori*-infected subjects (Hishida et al., 2009a). If the polymorphism is functional or linked to a functional one, the association can be biologically explained by the difference in the strength of signal transduction through the CagA-SHP2 complex. According to the NCBI dbSNP, the frequencies of the G allele of rs2301756, high risk allele for gastric atrophy, is 0.802 among 1,484 Japanese and 0.917 among 48 Chinese, while the corresponding was 0.348 among 46 African American and 0.064 among 46 Caucasians, indicating that Japanese and Chinese become high risk ethnic groups through CagA-positive *H. pylori* infection, if the hypothesis that the G allele confers stronger signals via the CagA-SHP2 interaction is true.

NOD1

Recent report revealed that the carriage of the *NOD1* G796A (E266K) mutation increases the susceptibility for gastric atrophy strikingly: OR = 34.2 in *NOD1* 796AA and OR = 13.35 in *NOD1* 796GA compared to subjects with *NOD1* 796GG (Kara et al., 2010).

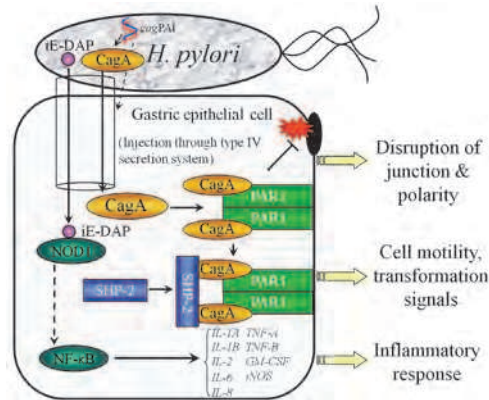


Fig. 3. Signal pathways induced by the *Helicobacter pylori* *cag* pathogenicity island related molecules.

2.2.2 Immune related genes and their polymorphisms

For the effects of pro-inflammatory immune response by the hosts, TLR4 is known to recognize lipopolysaccharide (LPS) of gram-negative bacteria and is proved to play important roles in *H. pylori* infection through the interaction of macrophage/monocyte TLR4 with *H. pylori* LPS. The initial recognition of LPS and subsequent signaling by TLR4 is supported by several accessory proteins: LPS first binds to lipopolysaccharide-binding protein (LBP) which works as an opsonin for CD14 which then acts as a catalyst for the binding of LPS to MD-2. The signal induced by LPS/MD-2/TLR4 complex is transmitted through myeloid differentiation factor 88 (MyD88), interleukin (IL)-1 receptor associated kinase (IRAK), tumor necrosis factor (TNF) receptor-associated factor 6 (TRAF6) and inhibitory κ B kinase (IKK) to nuclear factor (NF)- κ B, leading to the production of pro-inflammatory cytokines such as IL-1A, IL-1B, IL-6 or TNF-A. The human immune system is also balanced by the anti-inflammatory cytokines like IL-10, IL-4 or IL-13 which are controlled by regulatory T-cells. In these inflammatory processes, augmented expression of inducible nitric oxide synthase (iNOS) is shown to play important roles in the generation of oxygen radicals, while overexpressed cyclooxygenase-2 (COX-2) is demonstrated to contribute to the proliferation of the gastric epithelium through the up-regulation of cell-cycles as well as to the propagation of gastric inflammation *via* the prostaglandin pathways. The induction of iNOS is also supposed to be modulated by the activity of protein kinase C-eta (PRKCH) via the phosphorylation of nuclear factor-kappa B (NF- κ B) or activator protein-1 (AP-1) (Pham et al., 2003a; Pham et al., 2003b).

Oxidative DNA damage is also supposed to play important roles in the pathogenesis of *H. pylori*-induced gastric mucosal damage, where 8-OHdG is a potential sensitive marker of DNA oxidation (Farinati et al., 2008). The damaged bases in DNA are mainly repaired by the base excision repair (BER) system; the accumulation of 8-Hydroxy-2'-deoxyguanosine (8-OHdG) or 2-hydroxyadenine (2-OH-A) in DNA is prevented by the co-operation of mutT human homolog-1 (MTH1), 8-hydroxyguanine DNA glycosylase (OGG1) and mutY human homolog (MUTYH) (Nakabeppu et al., 2004). The number of studies that investigated the contribution of these molecules involved in inflammatory response, such as innate immune

response, oxygen radical production, oxidative DNA damage repair processes, together with cell-cycle regulation and/or cell proliferation in the genesis of *H. pylori*-induced gastric precancerous lesions is also limited, requiring further biological investigations in the near future.

TLR4

One study in Caucasians showed that the *TLR4* +896 A/G polymorphism (rs4986790) was associated with the risk of gastric atrophy, where the *TLR4* +896 G carriers had an 11-fold increased risk of gastric atrophy with hypochlorhydria (Hold et al., 2007). Subsequent Japanese study also clarified the possible association between another genetic variation in *TLR4* gene, the *TLR4* +3725G/C polymorphism (rs11536889), and the risk of severe gastric atrophy in Japanese (Hishida et al., 2009a), suggesting the significance of genetic variations in host innate immunity due to *TLR4* polymorphisms also in East Asian populations.

CD14

There is one single nucleotide polymorphism in the promoter region of the *CD14* gene, *CD14* C-159T polymorphism, which is critical for *CD14* expression (Zhang et al., 1994). Recent study by one Japanese group demonstrated that *CD14* promoter -159TT and T carrier were associated with lower risk of gastric atrophy in *H. pylori*-infected subjects who were 61 years or older (Tahara et al., 2007).

IL-2 and IL-13

IL-2 T-330G polymorphism was demonstrated to be a functional polymorphism (Williams et al., 1988), with higher *IL-2* production in GG genotype than in TT genotype (Hoffmann et al., 2001). Those with TT genotype were shown to be at a higher risk of gastric atrophy (Togawa et al., 2005), who were less frequent in Asians (38% out of 29 individuals) than in Caucasians (51% out of 199 individuals) (Hoffmann et al., 2002).

IL-13 gene in chromosome 5q31 has several polymorphisms; at least 3 polymorphisms at the promoter region, 2 polymorphisms at intron 1, Arg130Gln, and 4 polymorphisms at 3' UTR of exon 4 have been reported (Howard et al., 2001). The -1111TT genotype was shown to harbor increased binding ability of nuclear proteins, and was also reported to be associated with asthma (Howard et al., 2001; Van der Pouw Kraan et al., 1999). As for the risk of gastric atrophy, -1111TT was found to be a low risk genotype (Togawa et al., 2005). The biological mechanism involved was not yet clarified.

IL-4R

One study of Venezuelan subjects revealed that those with homozygotes with the low activity allele (GG) of the A398G polymorphism in the *IL-4R* gene (rs1805010) had a modestly increased risk of gastric atrophy (OR = 1.52, 95% CI = 1.05-2.21) (Kato et al., 2006), suggesting the role of genetic variability in the anti-inflammatory mediators in the genesis of *H. pylori*-induced gastric precancerous lesions.

iNOS C150T (rs2297518) and *PRKCH* rs3783799 G/A polymorphisms: *PRKCH* is shown to be involved in oxidative stress, by activating *iNOS* and nitric oxide production (Pham et al., 2003). The associations of the polymorphisms in these two genes (*iNOS* C150T [rs2297518] and *PRKCH* rs3783799 G/A polymorphisms) with the risk of gastric atrophy were investigated in Japanese population, which revealed that those with *PRKCH* rs3783799 AA genotype were at significantly higher risk of severe gastric atrophy (OR = 2.37, 95% CI = 1.11-5.05) (Goto et al., 2010), while there were no significant association between the *iNOS* C150T polymorphism and risk of gastric atrophy (Goto et al., 2006b).

2.2.3 Other miscellaneous genes and their polymorphisms

Recently, it was reported that the loss expression of sonic hedgehog (Shh), a regulatory gene essential for developmental patterning, and aberrant expressions of *caudal-type homeobox transcription factor 2 (CDX2)*, a master regulatory gene of intestinal development and differentiation, in *H. pylori*-induced atrophic gastritis are the early events correlated with the occurrence of intestinal metaplasia, which can be reversible by the eradication of *H. pylori*. In accordance with these findings, CDX2 expression has been demonstrated to be associated with intestinal phenotypes in gastric cancers (Shiotani et al., 2008).

Another important tumor suppressor gene in intestinal-type gastric cancer is *runt-related gene 3 (RUNX3)* encoding a subunit of polyomavirus enhancer binding protein 2 (Li et al., 2002), since expression of *RUNX3* is greatly reduced in intestinal metaplasias in human stomachs (Oshio et al., 2004) and *RUNX3*^{-/-} mouse gastric epithelial cells have a potential to differentiate into CDX-2 positive intestinal type cells (Oshio et al., 2004). Li and colleagues (Li et al., 2002; Levanon et al., 2003) reported that the gastric mucosa of *RUNX3* null mice showed hyperplasia, indicating that loss of *RUNX3* leads to gastric carcinogenesis in humans. Consistent with this, an analysis of *RUNX3* in human stomach cancer cell lines and primary human tumours revealed hemizygoty in 40% of the tumours examined, and silencing by promoter hypermethylation in 60% of the tumours, and this figure increased up to 90% in the advanced stage tumours. It is shown that the *RUNX3*^{-/-} mouse gastric mucosa exhibits hyperplasias due to the stimulated proliferation and suppressed apoptosis in the cells, suggesting that *RUNX3* is an attractive candidate as a tumor suppressor of gastric cancer. The CpG island of *RUNX3* P2 promoter is hypermethylated in human and mouse gastric cancer cell lines and in primary human tumors (Li et al., 2002; Waki et al., 2003), also suggesting the tumor suppressor function of *RUNX3* in the etiology of stomach cancer.

Heat-shock protein (HSP) 70 plays essential roles in cellular response to a variety of environmental stresses by acting as molecular chaperons in the folding of newly synthesized proteins in cells and assist in the folding of damaged proteins (Becker et al., 1994). HSP expression in the gastric mucosa is shown to be attenuated by *H. pylori* infection and aspirin intake, and one HSP inducer geranylgeranylacetone (GGA) reportedly protects gastric mucosa from iNOS induced by *H. pylori* infection (Yeo et al., 2004), suggesting that HSP has important roles in protecting gastric mucosa against *H. pylori* or aspirin induced injuries. Gastric carcinogenesis can also be regarded as a multistep process that initiates with the dysregulation of normal controls of apoptosis and cell proliferation, in which FAS receptor-ligand system is shown to be a key regulator of apoptosis (Hsu et al., 2008).

Pepsinogen C (PGC), alternatively called pepsinogen II or gastricsin, an inactive precursor of pepsin C, is an aspartic protease specifically produced by the gastric chief cells, cardiac cells, pylori cells and Brunner's glands from late infant stages to adulthood period. PGC is considered to be a differentiation marker of gastric epithelium, whose changes in expression may reflect the severity of gastric mucosal damage (Samloff et al., 1982).

RUNX3

Among *H. pylori* seropositive subjects, we found a significant association between *RUNX3* rs760805 T/A polymorphism and the risk of gastric atrophy with the age- and sex-adjusted OR of 1.51 (95% CI 1.11-2.05, P=0.008) in TA, 1.59 (95% CI 1.08-2.33, P=0.019) in AA, and 1.53 (95% CI 1.14-2.05, P=0.004) in TA+AA, compared with TT genotype (Hishida et al., 2009b). This finding was in accordance with the recent biological report that *RUNX3* expression correlated with chief cell differentiation in human gastric cancers (Ogasawara et al., 2009).

Polymorphism	Function	Rs number	Subjects ^(Reference)	OR and/or GA%
<i>IL-1B</i> C-31T	5'UTR	rs1143627	253 Japanese ^(Aitsuta, 2006)	CC (54%),CT (52%),TT (56%)
"			455 Jpn.Brazil. ^(Ueno, 2004)	CC,CT:0.61,TT:0.58 CC (36%), CT (31%), TT (21%)
"			1,328Venezuelan ^(Kato, 2007)	TT,CT:1.01,CC:0.91
<i>IL-2</i> T-330G	5'UTR	rs2069762	244 Japanese ^(Togawa, 2005)	GG,TG:1.64,TT:2.78*GG (38%),TG (50%),TT (62%)
<i>IL-4</i> C-33T	5'UTR	rs2070874	249 Japanese ^(Togawa, 2005)	CC,CT:2.47,TT:1.80 CC (38%),CT (60%),TT (53%)
<i>IL-4</i> T-590C	5'UTR	rs2243250	1,301 Venezuelan ^(Kato, 2006)	TT,CT:0.82,CC:0.81
<i>IL-4R</i> C-3223T	5'UTR	rs2057768	1,301 Venezuelan ^(Kato, 2006)	CC,CT:0.97,TT:1.01
<i>IL-4R</i> A398G	Non-synonymous (Ile50Val)	rs1805010	1,301 Venezuelan ^(Kato, 2006)	AA,AG:1.14,GG:1.52*
<i>IL-6</i> G-174C	5'UTR	rs1800795	1,315 Venezuelan ^(Kato, 2007)	GG,CG:0.98,CC:0.57
<i>IL-8</i> T-251A	5'UTR	rs4073	1,347 Venezuelan ^(Kato, 2007)	TT,AT:0.98,AA:1.07
<i>IL-10</i> G-1082A	5'UTR	rs1800896	1,301Venezuelan ^(Kato, 2006)	GG,AG:1.05,AA:1.14
<i>IL-13</i> C-1111T	5'UTR	rs1800925	248 Japanese ^(Togawa, 2005)	CC,CT+TT:0.41*CC (59%),CT+TT (45%)
<i>TNF-A</i> T-1031C	5'UTR	rs4647198	455 Jpn.Brazil. ^(Aitsuta, 2006)	CC (29%),TC (33%),TT (34%)
C-857T	5'UTR	rs1799724	456 Jpn.Brazil. ^(Aitsuta, 2006)	CC (32%),CT (36%),TT (39%)
-1031&-857			455 Jpn.Brazil. ^(Aitsuta, 2006)	CC&CC (29%),TT&CC (33%),TC&CT (43%),TT&TT (39%)
G-308A	5'UTR	rs1800629	1,327 Venezuelan ^(Kato, 2006)	GG,AG+AA:1.27
<i>MCPI</i> G-2518A	5'UTR	rs1024611	1,311 Venezuelan ^(Kato, 2007)	AA,AG:1.02,GG:1.18
<i>PTPN11</i> G/A at intron3	intron	rs2301756	248 Japanese ^(Goto, 2006a)	GG,GA+AA:0.70,AA:0.09*GG (59%),GA (49%),AA (11%)
"			979 Japanese ^(Hishida, 2009a)	GG,GA+AA:0.62*CG (22%),GA+AA (15%) [‡]
<i>NOD1</i> G796A	Non-synonymous (Glu266Lys)	rs2075820	150 Turks ^(Kar, 2010)	GG,GA:1.335*,AA:3.2*
<i>TLR4</i> A+896G	Non-synonymous (Asp299Gly)	rs4986790	103 Caucasians ^(Hoid, 2007)	AA,AG:1.10*AA (36%),AG (87%) [§]
"			717 Venezuelan ^(Kato, 2007)	GlyGly/ AspGly,AspAsp: 1.53
<i>TLR4</i> G+3725C	3'UTR	rs11536889	980 Japanese ^(Hishida, 2009b)	GG,GC+CC:1.33 GG(18%),GC+CC(22%) [‡]
<i>CD14</i> C-159T(C-260T)	5'UTR	rs2569190	717 Venezuelan ^(Kato, 2007)	CC,CT+TT:1.06
<i>PRKCH</i> rs3783799 G/A	intron	rs3783799	1,638 Japanese ^(Goto, 2010)	GG,GA:0.99,AA:2.37*
<i>iNOS</i> C150T	Non-synonymous (Ser608Leu)	rs2297518	250 Japanese ^(Goto, 2006a)	CC,CT+TT:0.75
<i>RUNX3</i> T/A at intron3	intron	rs760805	938 Japanese ^(Hishida, 2009)	TT,TA:1.51*,AA:1.59*TT (46%),TA (56%),AA (56%)
<i>HSP70-2</i> A/B (A1267G)	Synonymous (Gln351Gln)	rs1061581	137 Japanese ^(Tahara, 2009)	BB (45%),AA+AB (67%) [‡]
<i>FAS</i> G-1377A	5'UTR	rs2234767	109 Taiwanese ^(Hsu, 2008)	No association
<i>FAS</i> A-670G	5'UTR	rs1800682	109 Taiwanese ^(Hsu, 2008)	No association
<i>FASL</i> T-844C	5'UTR	rs763110	109 Taiwanese ^(Hsu, 2008)	TT,TC+CC:9.4*
<i>PGC</i> Ins/Del	Ins/Del	(unknown)	86 Chinese ^(Pham, 2003)	DD (90%),others(50%)*
<i>NQO1</i> C609T	Non-synonymous (Pro187Ser)	rs1800682	396 Japanese ^(Goto, 2005a)	TT,CT:1.25,CC:1.23
<i>GSTM1</i>	Ins/Del	(unknown)	396 Japanese ^(Goto, 2005a)	Null,Present:1.35
<i>GSTT1</i>	Ins/Del	rs71748309	396 Japanese ^(Goto, 2005a)	Null,Present:0.87
<i>ACE</i> Ins/Del	Ins/Del	rs1799752	271 Japanese ^(Goto, 2005c)	II,II,DD:1.12,DD:0.99
<i>RANTES</i> C-471T	5'UTR	rs2107538	344 Germans ^(Helming, 2005)	No association
<i>SDHC</i> J5T173800 C/G	3'UTR	rs3813632	249 Japanese ^(Goto, 2006c)	CC,GC:1.26,GG:0.51 CC (53%), GC (59%), GG (38%)
<i>IFNGR1</i> G-611A	5'UTR	rs1327474	805 Portugese ^(Caneado, 2008)	GG,GA:1.2,AA:1.2
<i>IFNGR1</i> C-56T	5'UTR	rs2234711	814 Portugese ^(Caneado, 2008)	CC,CT:1.4,TT:1.3

Table 4. Polymorphisms associated with gastric atrophy *Helicobacter pylori* seropositives.*Polymorphisms of other miscellaneous genes**HSP 70-2*

It is shown that the AA genotype of *HSP 70-2* A/B polymorphism (PsiI polymorphism, corresponding to A1267G polymorphism) had the highest level of mRNA expression compared with the other genotypes (AB or BB). Recently one Japanese group reported that the BB genotype of *HSP 70-2* gene is significantly associated with the reduced risk of severe gastric atrophy in *H. pylori* infected older subjects (Tahara et al., 2009), indicating the importance of this HSP polymorphism in the genesis of *H. pylori*-induced gastric precancerous lesions.

FASL

Lately one study group in Taiwan investigated the relations between precancerous gastric lesions and polymorphisms in the promoter regions of the death pathway genes FAS and FASL (FAS G-1377A, FAS A-670G and FASL T-844C) in 109 *H. pylori*-infected Taiwanese individuals, and found that FASL -844 C allele significantly increased the risk of atrophy in the gastric corpus, with an adjusted OR of 5.0 (95% CI = 1.5-6.8) (Hsu et al., 2008).

PGC

Recent study among Chinese demonstrated that subjects with *PGC Del/Del* genotype of the *PGC ins/del* polymorphism were at significantly higher risk of atrophic gastritis (OR=3.11; 95%CI 1.44-6.71), and *H. pylori*-seropositive subjects with *PGC Del/Del* genotype had significantly elevated risk of atrophic gastritis (OR=11.16; 95%CI 1.37-90.84) with the interaction of 6.48 (Sun et al., 2009), suggesting the positive link between *PGC* gene polymorphism and *H. pylori*-induced gastric atrophy.

2.3 Genetic factors for *Helicobacter pylori*-induced gastric carcinogenesis

To date, many genetic polymorphisms have been examined on the associations with gastric cancer in case-control studies with the 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. Since those case-control studies compared genotype frequencies between the mixed cases and heterogeneous controls, the estimated odds ratios 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, the studies are to be conducted at a region where the exposure to the bacterium was highly prevalent. Usual case-control studies could provide the estimates for the final step (ie, 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 5 lists the polymorphisms reported on gastric cancer risk, adopted from Gonzalez et al. (Gonzalez et al., 2002) and recent studies (Ebert et al., 2005; Geddert et al., 2005; Li et al., 2005; Tsukino et al., 2002; Sugimoto et al., 2005; Gao et al., 2002; Wu et al., 2002; Goto et al., 2005; Lai et al., 2005a; Lee et al., 2004; Savage et al., 2004; Lai et al., 2005b; Lacasana-Navarro et al., 2006; Kim et al., 2005; Hamajima et al., 2002a; Duarte et al., 2005). The ORs are listed in case of being significant. Accordingly, it should be noted that there were many insignificant studies behind Table 5.

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 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, indicating that the risk elevation was due to the risk for gastric atrophy, not for the step from gastric atrophy to gastric cancer. (Taguchi et al., 2005) The direct comparisons between controls with gastric atrophy and cases with gastric cancer were reported; no associations for *p53* Arg72Pro (Hiyama et al., 2002; Chung et al., 2006), and for *PTPN11* G/A at intron 3 (Goto et al., 2006a).

Lifestyle factors may interact with the genotypes in the final step. Biologically, the interactions of smoking, fresh vegetables/fruits and salty food with polymorphisms of carcinogen-metabolic enzyme and DNA repair enzymes are very plausible.

Polymorphism	Country(Reference)	OR (95%CI)
ACE1/D	Germany (Ibert, 2005)	DD, DI:0.55 (0.31-0.96), II:0.20 (0.08-0.54)
<i>cyclinD1</i> G870A	Germany(Giedert, 2005)	significant association (p=0.003)
CYP1A1 Ile/Val	China(Li, 2005)	IleIle, ValVal:4.84 (1.24-22.07)
CYP2C6 *1/*4	Japan(Tsukino, 2002)	*1*/1*4, *4*4:3.14 (1.05-9.41)
CYP2C19 *1/*2/*3	Japan(Sugimoto, 2005)	*1*1, no*1:1.98 (1.07-3.65)
CYP2E1 RsaI	Japan*	
	Brazil*	
	China(Cao, 2002)	
<i>E-cadherin</i> C-160A	Taiwan(Wu, 2002)	CC, AA:0.20 (0.06-0.56)
EGF A61G	Japan(Goto, 2005)	
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(Li, 2005)	present, null:2.81 (1.39-5.71)
	Taiwan(Lai, 2005)	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*	
<i>IL-1B</i> C-1473G	Korea (Lai, 2005)	
C-511T	Poland(El-Omar, 2000)	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(Wu, 2003)	
C3954T	Poland(El-Omar, 2000)	
<i>IL-1RN</i> 86-bp VNTR	Poland(El-Omar, 2000)	4rpt4rpt, 2rpt2rpt:3.7 (2.4-5.7)
	Taiwan(Wu, 2003)	
<i>IL-1B</i> C-511T+	Portugal*	CC+LL/L2rpt,
<i>IL-1RN</i> 86-bp VNTR		CT/TT+2rpt2rpt:9.0 (3.5-23.0)
<i>IL-2</i> G-384T, G114T	China(Savage, 2004)	
<i>IL-4</i> C-590T	Taiwan(Wu, 2003; Lai, 2005)	
RP1/RP2	Taiwan(Lai, 2005)	
<i>IL-4R</i> Ile50Val	Taiwan(Wu, 2003)	
Gln576Arg	Taiwan(Wu, 2003)	
<i>IL-10</i> G-1082A	Taiwan(Wu, 2003)	AA, AG:2.14 (1.07-4.30)
	China(Savage, 2004)	

T-819C	Taiwan ^(Wu, 2003)	TT, TC:1.83 (1.23-2.71), CC:1.95 (1.03-3.69)
	China ^(Savaps, 2004)	
MK G-2669A	Taiwan ^(Lai, 2005)	
MTHFR C677T	China*	CC, TT:1.87 (1.00-3.48)
	Mexico ^(Lacasaña-Navarro, 2006)	CC, TT:1.62 (1.00-2.59)
C677T, A1298C	Korea ^(Kim, 2005)	
MUC1 VNTR	Portugal*	Large, Small: 4.3 (1.8-10.5)
MUC6 VNTR	Portugal*	Large, Small: p<0.05
MYCL1 EcoRI	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 ^(Hamajima, 2002d)	
OGG1 Ser327Cys	Japan*	
	Brazil*	
p16 ^{INK4A} C540G	Germany ^(Geldert, 2005)	
C570G	Taiwan ^(Lai, 2005)	
p21 codon31	Taiwan ^(Lai, 2005)	
p53 codon72	Taiwan ^(Lai, 2005)	significant association (p=0.02)
PPARγ Pro12Ala(C/G)	China ^(Liao, 2006)	CC, CG/GG:2.5 (1.1-5.8)
TFF2 VNTR	Portugal*	
TNF-A G-308A	Korea*	
	Taiwan ^(Wu, 2003)	
G-238A	Korea*	
	Taiwan ^(Wu, 2003)	
XRCC1 Arg194Trp	Brazil ^(Duarte, 2005)	
Arg399Gln	Brazil ^(Duarte, 2005)	
Arg194Trp+	China*	TrpTrp+ArgArg, ArgArg+
Arg399Gln		ArgGln/GlnGln:1.73 (1.12-2.69)
XRCC3 Thr241Met	Brazil ^(Duarte, 2005)	

* Studies cited in the review by Gonzalez et al. (2002).

L: alleles longer than 2 μ t

Table 5. Polymorphisms reported on the associations with gastric risk> only significant are with odds ratio (OR) and 95% confidence interval (95%CI).

3. Conclusion

It is clear that *H. pylori*-related gastric cancer develops through several steps including the infection, gastric atrophy, (histologically intestinal metaplasia, dysplasia) and cancer. Lifestyle factors such as smoking and diet could influence one or more steps. On the other

hand, 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 demonstrated that the strength of associations varied among the studies. Since usual case-control studies examined the mixed effects on these steps, the inconsistent findings may be natural. In addition, the diversity of lifestyle 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, the studies on each step taking into account of the lifestyle factors will be requested. Such studies will produce useful information for gastric cancer prevention.

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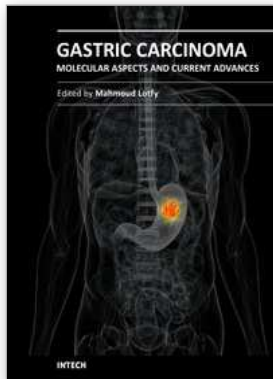
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Gastric cancer is one of the most common tumors worldwide. It has a heterogeneous milieu, where the genetic background, tumor immunology, oxidative stress, and microbial infections are key players in the multiple stages of tumorigenesis. These diverse factors are linked to the prognosis of the gastric cancer and the survival of gastric cancer patients. This book is appropriate for scientists and students in the field of oncology, gastroenterology, molecular biology, immunology, cell biology, biology, biochemistry, and pathology. This authoritative text carefully explains the fundamentals, providing a general overview of the principles followed by more detailed explanations of these recent topics efficiently. The topics presented herein contain the most recent knowledge in gastric cancer concerning the oncogenic signaling, genetic instability, the epigenetic aspect, molecular features and their clinical implications, miRNAs, integrin and E-cadherin, carbohydrate-associated-transferases, free radicals, immune cell responses, mucins, Helicobacter-pylori, neoadjuvant and adjuvant therapy, prophylactic strategy for peritoneal recurrence, and hepatic metastasis.

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