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META-ANALYSIS

Association of *Helicobacter pylori babA2* with peptic ulcer disease and gastric cancer

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Abstract

AIM: To investigate the association between *babA2* gene and peptic ulcer disease (PUD) and gastric cancer (GC) in *Helicobacter pylori*-infected populations.

METHODS: We evaluated the relationship between *babA2* and clinical outcomes (PUD and GC) using a meta-analysis. A literature search was performed using the PubMed and Web of Science databases for relevant case-control studies that met the defined inclusion criteria. The ORs and 95%CIs were calculated to estimate the association between *babA2* genotype and clinical outcomes. A fixed-effect or random-effect model was performed depending on the absence or presence of significant heterogeneity.

RESULTS: A total of 25 articles with 38 studies met the inclusion criteria and were finally included in this meta-analysis. The results showed that the *babA2* genotype was significantly associated with an increased risk of PUD (OR = 2.069, 95%CI: 1.530-2.794, $P < 0.001$) and especially in the subgroup of duodenal ulcer (OR = 1.588, 95%CI: 1.141-2.209, $P = 0.006$). Moreover, a significant association between *babA2* gene and PUD and duodenal ulcer (OR = 2.739, 95%CI: 1.860-4.032, $P < 0.001$; OR = 2.239, 95%CI: 1.468-3.415, $P < 0.001$, respectively) was observed in western countries but not in Asian countries.

CONCLUSION: We demonstrated that the presence of *babA2* may be associated with increased risks for PUD, especially duodenal ulcer, in western countries.

Key words: *Helicobacter pylori*; *babA2*; Peptic ulcer; Gastric cancer; Risk

Core tip: BabA encoded by *babA2* gene is an outer member protein of *Helicobacter pylori* (*H. pylori*), which plays a key role in facilitating bacterial colonization in the stomach. The association between *babA2* and *H. pylori*-related gastroduodenal diseases is still controversial. We summarized a total of 25 case-control articles with 38 studies in this meta-analysis and evaluated the relationship between *babA2* and clinical outcomes. The presence of *babA2* may contribute to increased risk of peptic ulcer disease (PUD), especially duodenal ulcer, in western countries. In Asians, *babA2* genotype only showed a marginal association with PUD risk, which requires further investigation.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is a Gram-negative spiral bacterium that may colonize the human gastric mucosa and establish a life-long infection[1]. Although *H. pylori* infects approximately half of the population worldwide, especially in developing countries, the majority of infected people remain asymptomatic. Only 15%-20% of those infected develop severe gastroduodenal diseases, such as peptic ulcer disease (PUD), gastric cancer (GC), and mucosa-associated lymphoid tissue lymphoma[2,3]. In addition to the host and environmental factors, another important reason for the diverse clinical outcomes is the differences in virulence factors among *H. pylori* strains[3]. For example, *H. pylori* strains harboring the vacuolating toxin A (*vacA*) and the cytotoxin-associated antigen (*cagA*) have been proposed as possible risk factors for PUD and GC[4].

Successful colonization in the stomach is the most important step for the pathogenicity of *H. pylori* infection. It is generally accepted that bacterial attachment to the gastric epithelium is the first critical stage of colonization by *H. pylori*[5]. The blood group antigen binding adhesin (BabA) is a well-described outer member protein of *H. pylori* that targets fucosylated Lewis^b blood group antigens presented on gastric epithelium[6,7]. Three *bab* allelic types have been identified, including *babA1*, *babA2* and *babB*; however, only the product of the *babA2* gene is necessary for endowing the bacteria with Lewis^b binding activity[6]. In 1999, Gerhard *et al*[8] first reported a positive association between a *babA2*-gene-positive strain and duodenal ulcer (DU) and GC. Subsequently, a series of studies of the association between *babA2* gene and PUD and GC have been done, but with inconsistent or conflicting conclusions[9-11].

We proposed a hypothesis that bacterial adherence factor BabA mediating close attachment to the epithelium may contribute to pathogenesis of PUD and/or GC. So far, it has not been possible to draw any causal conclusion about the relationship between the *babA2* gene and specific diseases, partly because of the small size of individual studies. Therefore, in the present study, we conducted a meta-analysis, combining available data from published case-control studies, to obtain a more precise estimate of the association between *babA2* gene and PUD and GC in *H. pylori*-infected populations.

MATERIALS AND METHODS

Literature search strategy

A literature search was performed using the PubMed and Web of Science databases for articles estimating the association between *babA2* gene and clinical outcomes in *H. pylori*-infected populations. All enrolled studies were published from January 1997 to October 2012 and retrieved using one of the keywords "*babA*" or "*babA2*" in combination with "*Helicobacter pylori*". The search was performed without restriction on language.

Inclusion criteria

The criteria used to select studies for this meta-analysis were as follows: (1) fully published case-control studies [case group included DU, gastric ulcer (GU), PUD or GC, and the control group included gastritis or nonulcer disease (NUD)]; (2) studies described the relationship between *babA2* gene status and clinical outcomes; (3) the presence of *babA2* was examined by polymerase chain reaction (PCR); and (4) the papers were written in English.

Exclusion criteria

The exclusion criteria were as follows: (1) the results came from review articles; (2) there was no integrated raw data; (3) *in vitro* studies or animal experiments; (4) studies with abstract only; and (5) studies with children.

Data extraction

Evaluation of all potentially relevant articles and extraction of raw data were independently performed by two investigators (Chen MY and He CY). Disagreements were resolved through discussion. We collected information on the following items from each study: first author's name, year of publication, countries and areas of the study population, *babA2* status and clinical outcomes (DU, GU, PUD and GC), and the total number of cases and controls.

Statistical analysis

All statistical analyses were performed using STATA version 11.0 (College Station, TX, United States). Two-sided *P* values were evaluated in this meta-analysis and $P < 0.05$ was considered statistically significant. The strength of the association between the *babA2* gene and clinical outcomes was estimated by OR and corresponding 95%CIs. The statistical heterogeneity among the included studies was assessed by χ^2-based Q and I^2 statistics. If the heterogeneity was considered not significant (with $P > 0.1$ for Q test) among studies, a fixed-effects model based on the Mantel-Haenszel method[12] was used to calculate the pooled OR. On the contrary, a random-effects model based on the DerSimonian and Laird method[13] was used to assess the pooled OR when the P value of the Q test was < 0.1. In addition, a sensitivity analysis was performed to estimate the effects of each included study on the overall risk of clinical outcomes. ORs and 95%CIs were recalculated when any single study was excluded in turn. Begg's test[14] and Egger's test[15] were performed to estimate the publication bias.

RESULTS

Characteristics of selected studies

According to the literature search strategy, a total of 220

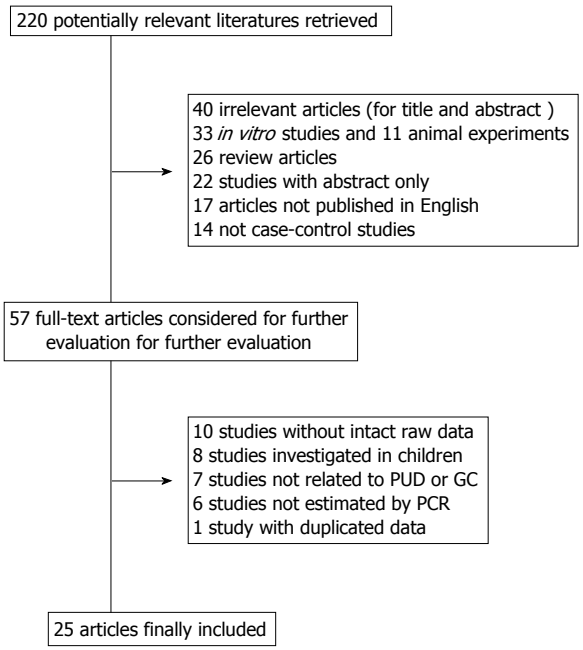

Figure 1 Flowchart of literature search and studies selection. PUD: Peptic ulcer disease; GC: Gastric cancer; PCR: Polymerase chain reaction.

possibly relevant studies were retrieved and 195 were excluded. The main reasons for exclusion were that the articles were reviews, *in vitro* studies, irrelevant to the theme of our research, or did not meet our inclusion criteria (Figure 1). Twenty-five case-control studies met the inclusion criteria[8-11,16-36]. Four of these studies[10,11,19,32] investigated the association between *babA2* gene and clinical outcomes in several different countries. Considering that these data partially evaluated the geographic variation of the influence of *babA2* gene status on the risk of *H. pylori*-related gastroduodenal diseases, data that came from different countries were treated as a separate study. Therefore, with respect to geographical location, 16 studies[11,17,19,22-26,29,33-36] were concerned with Asian populations, and 23[10,16,18,20,21,27,28,30-32] analyzed western populations. One of the latter group, which involved a study from Sweden[10], was excluded because of insufficient data. Finally, a total of 38 independent studies with 4556 patients were included in this meta-analysis (Table 1).

Association between babA2 gene and PUD

There were 36 studies[8-11,17-20,22-36] that investigated the distribution difference of *babA2* genotypes between patients with PUD and gastritis and/or NUD, which consisted of 1859 cases and 1909 controls. The overall prevalence of *babA2* gene was 73.96% (1375/1859) in PUD patients and 57.94% (1106/1909) in control subjects. Data from Oleastro *et al*[19] (Japan, South Korea, Brazil population), Sheu *et al*[26] and Lai *et al*[34] showed that the prevalence of *babA2* gene was 100% in both case and control groups, and the OR and standard error could not be estimated; thus, these studies were excluded. We found that the *babA2* gene significantly increased the risk of PUD in a random-effects model, with a pooled OR of 2.069 (95%CI: 1.532-2.794, $P < 0.001$), and moderate heterogeneity was observed ($I^2 = 62.8$, $P < 0.001$) (Figure 2).

To explore the source of heterogeneity, subgroup analysis was performed. PUD was classified into DU and GU. Among the total of 36 PUD-related studies, 19[8,9,11,17,22-24,26,27,29,31-35] could be used to evaluate risk for DU and eight[22,24,26,27,29,33-35] for GU. For DU analysis, the overall prevalence of *babA2* gene in DU and control subjects was 77.20% (813/1053) and 71.77% (811/1130), respectively. After removal of two studies with 100% prevalence of *babA2* genotype[26,27], the pooled OR based on the random-effects model was 1.588 (95%CI: 1.141-2.209, $P = 0.006$), and mild heterogeneity was observed ($I^2 = 45.8$, $P = 0.021$) (Figure 2). For GU analysis, the overall prevalence of *babA2* genotype seemed to be lower in GU (73.73%, 174/236) than in controls (80.89%, 402/497). Two studies with 100% prevalence of *babA2* genotype were also excluded because of statistical limitation[26,34]. No significant association was observed between *babA2* genotype and GU in a fixed-effects model (OR = 0.755, 95%CI: 0.496-1.150, $P = 0.191$), and there was no heterogeneity among the studies ($I^2 = 0.0\%$, $P = 0.845$) (Figure 2).

When geographical location was considered, data from different countries were subdivided into Asian and western groups. For PUD, the overall prevalence of *babA2* gene was 78.36% (822/1049) in Asian countries and 68.27% (553/810) in western countries. Furthermore, in western countries, the presence of *babA2* substantially increased PUD risk, with a pooled OR of 2.739 (95%CI: 1.860-4.032, $P < 0.001$), while in Asian countries, the *babA2* genotype was only borderline associated with PUD (OR = 1.370, 95%CI: 0.941-1.994, $P = 0.100$) (Figure 2). For DU, the *babA2* genotype significantly increased the risk of DU in western countries (OR = 2.239, 95%CI: 1.468-3.415, $P < 0.001$), but not in Asian countries (OR = 1.158, 95%CI: 0.802-1.672, $P = 0.433$) (Figure 2). The results suggested that differences in geographical distribution of *babA2* genotype may also confer heterogeneity to the studies. Only one study with a small sample size investigated the relationship of *babA2* gene and GU in a western country[27]; therefore, we did not perform subgroup analysis according to geographical area.

Sensitivity analysis was conducted to assess the influence of individual studies on the overall risk of PUD and DU by excluding any single study in turn and recalculating the pooled OR and 95%CI. A similar OR and 95%CI were generated, which indicated high stability of the results (Figure 3).

Association between babA2 and GC

A total of 16 studies[8,9,16,17,21-24,29,31-36] investigated the association between *babA2* gene and GC. The overall prevalence of *babA2* gene was 70.72% (384/534) in GC cases and 60.64% (607/1001) in gastritis or NUD controls. One study with both 100% prevalence of *babA2* in cases and controls was excluded from our meta-analysis[34]. In a random-effects model, the risk of GC increased 1.972-fold (95%CI: 1.103-3.525, $P = 0.022$) in the pres-

Table 1 Characteristics of studies included in the meta-analysis *n* (%)

Ref.	Population	Gastritis or NUD	PUD	GU	DU	GC
		babA2 +	*babA2* +	*babA2* +	*babA2* +	*babA2* +
Asian						
Saxena *et al*[36]	India	35 (26.32)	19 (52.78)			10 (28.57)
Talebi Bezmin Abadi *et al*[9]	Iran	17 (26.15)	10 (18.18)		10 (18.18)	38 (95.00)
Safaei *et al*[17]	Iran	30 (68.18)	20 (74.07)		20 (74.07)	8 (80.00)
Oleastro *et al*[19]	Japan	28 (100.00)	42 (100.00)			
Oleastro *et al*[19]	South Korea	37 (100.00)	28 (100.00)			
Chomvarin *et al*[24]	Thai	57 (91.94)	31 (91.18)	17 (85.00)	14 (100.00)	15 (93.75)
Erzin *et al*[23]	Turkey	7 (23.33)	14 (46.67)		14 (46.67)	29 (87.88)
Zhang *et al*[22]	China	89 (66.92)	89 (60.14)	28 (59.57)	61 (60.40)	54 (68.35)
Sheu *et al*[26]	Taiwan	85 (100.00)	60 (100.00)	30 (100.00)	30 (100.00)	
Zheng *et al*[25]	China	11 (37.93)	17 (39.53)			
Han *et al*[29]	China	28 (65.12)	50 (64.94)	15 (50.00)	35 (74.47)	12 (57.14)
Lai *et al*[34]	Taiwan	41 (100.00)	46 (100.00)	15 (100.00)	31 (100.00)	14 (100.00)
Maeda *et al*[33]	Japan	52 (96.30)	40 (95.24)	20 (100.00)	20 (90.91)	11 (100.00)
Yamaoka *et al*[32]	Korea	47 (88.68)	111 (96.52)		111 (96.52)	
Yamaoka *et al*[32]	Japan	112 (88.89)	172 (95.56)		112 (88.89)	
Mizushima *et al*[35]	Japan	34 (80.95)	73 (84.88)	38 (84.44)	35 (85.37)	36 (90.00)
Western						
Mattar *et al*[16]	Brazil	22 (64.71)				14 (41.18)
Oleastro *et al*[18]	Portugal	7 (11.67)	27 (47.37)			
Bartchewsky *et al*[21]	Brazil	102 (79.07)				40 (78.43)
Oleastro *et al*[19]	Portugal	16 (32.00)	25 (50.00)			
Oleastro *et al*[19]	France	3 (50.00)	22 (81.48)			
Oleastro *et al*[19]	Sweden	4 (40.00)	10 (83.33)			
Oleastro *et al*[19]	Germany	6 (60.00)	7 (77.78)			
Oleastro *et al*[19]	United States	12 (92.31)	10 (100.00)			
Oleastro *et al*[19]	Brazil	12 (100.00)	10 (100.00)			
Oleastro *et al*[20]	Portugal	18 (32.14)	25 (50.00)			
Gatti *et al*[27]	Brazil	16 (43.24)	20 (40.00)	11 (37.93)	9 (42.86)	
Gatti *et al*[28]	Brazil	37 (54.41)	3 (20.00)			
Olfat *et al*[10]	Finland	12 (46.15)	22 (70.97)			
Olfat *et al*[10]	Portugal	12 (19.67)	19 (63.33)			
Olfat *et al*[10]	Germany	19 (28.36)	22 (88.00)			
Oliveira *et al*[31]	Brazil	24 (31.58)	43 (53.75)		43 (53.75)	29 (55.77)
Zambon *et al*[30]	Italy	26 (27.96)	20 (48.78)			
Yamaoka *et al*[32]	Colombia	28 (70.00)	34 (85.00)		34 (85.00)	34 (82.93)
Yamaoka *et al*[32]	United States	28 (70.00)	35 (85.37)		35 (85.37)	19 (63.33)
Yamaoka *et al*[11]	United States	66 (71.74)	123 (84.83)		123 (84.83)	
Yamaoka *et al*[11]	Colombia	37 (71.15)	53 (82.81)		53 (82.81)	
Gerhard *et al*[8]	Munich	13 (37.14)	23 (100.00)		23 (100.00)	21 (77.78)

NUD: Nonulcer disease; PUD: Peptic ulcer disease; GU: Gastric ulcer; DU: Duodenal ulcer; GC: Gastric cancer.

ence of *babA2* compared with the controls; however, high heterogeneity among studies was observed (I^2 = 76.8%, $P < 0.001$). Meta-analyses were conducted repeatedly when each study was omitted. As showed in Figure 4, two studies[9,23] showed larger differences in the risk estimates compared with other studies in the sensitivity analysis. Sensitivity analysis excluding these studies generated an OR of 1.303 (95%CI: 0.881-1.927, $P = 0.185$) among homogeneous studies (I^2 = 45.0%, $P = 0.040$), which was different from the OR of 1.972 (95%CI: 1.103-3.525, $P = 0.022$) before the removal of those studies (Figure 4). In terms of geographical area, no statistically significant findings were found among the Asian or western subpopulations, with a pooled OR of 1.132 (95%CI: 0.763-1.680, $P = 0.539$) in the former and 1.303 (95%CI: 0.881-1.927, $P = 0.349$) in the latter (Figure 4).

Publication bias analysis

Publication bias was preliminarily estimated by Begg's and Egger's tests. No significant publication bias was observed in all the comparisons based on Begg's test (all $P > 0.1$), but P value was 0.08 in Egger's test, suggesting a slight publication bias.

DISCUSSION

The Gram-negative bacterium *H. pylori* is known to have a remarkably high level of genetic diversity, and is implicated in human diseases after decades of persistence in the stomach[37-39]. A crucial virulence factor BabA, encoded by the *babA2* gene, facilitates colonization by *H. pylori* in the stomach and may be involved in the pathogenesis of different *H. pylori*-related gastroduodenal diseases, such as PUD and gastric malignancy[8]. To date, there have been numerous relevant studies published but with divergent results on the relationship between the *babA2* gene and PUD and GC[9-11]; moreover, there is no comprehensive meta-analysis on the significance

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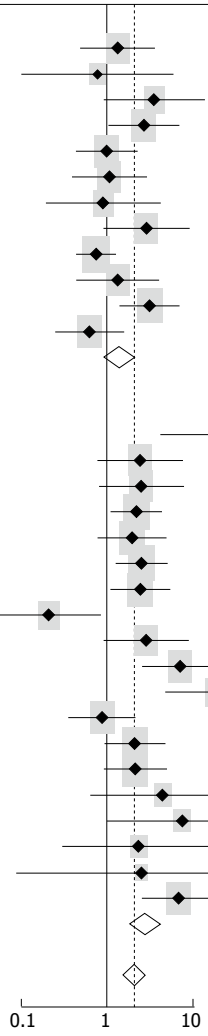
Ref.	Country	PUD *babA2*+/-	NUD/GS *babA2*+/-	OR (95%CI)	%Weight
Asian					
Mizushima *et al*[35]	Japan	73/13	34/8	1.32 (0.50, 3.49)	3.61
Maeda *et al*[33]	Japan	40/2	52/2	0.77 (0.10, 5.70)	1.62
Yamaoka *et al*[32]	South Korea	111/4	47/6	3.54 (0.96, 13.13)	2.75
Yamaoka *et al*[33]	Japan	172/8	112/4	2.69 (1.09, 6.61)	3.80
Han *et al*[29]	China	50/27	28/15	0.99 (0.45, 2.17)	4.15
Zheng *et al*[25]	China	17/26	11/18	1.07 (0.41, 2.82)	3.61
Chomvarin[24]	Thai	31/3	57/5	0.91 (0.20, 4.05)	2.37
Erzin *et al*[23]	Turkey	14/16	7/23	2.88 (0.95, 8.72)	3.23
Zhang *et al*[22]	China	89/59	89/44	0.75 (0.46, 1.22)	5.01
Safaei *et al*[17]	Iran	20/7	30/14	1.33 (0.46, 3.88)	3.34
Saxena *et al*[36]	India	19/17	35/98	3.13 (1.46, 6.69)	4.22
Talebi Bezmin Abadi *et al*[9]	Iran	10/45	17/48	0.63 (0.26, 1.51)	3.86
Subtotal (I^2 = 46.3%, P = 0.039)				1.37 (0.94, 1.99)	41.58
Western					
Gerhard *et al*[8]	Munich	23/0	13/22	78.33 (4.39, 1397.21)	0.92
Yamaoka *et al*[32]	Colombia	34/6	28/12	2.43 (0.81, 7.30)	3.26
Yamaoka *et al*[32]	United States	35/6	28/12	2.50 (0.83, 7.50)	3.26
Yamaoka *et al*[11]	United States	123/22	66/26	2.20 (1.16, 4.18)	4.57
Yamaoka *et al*[11]	Colombia	53/11	37/15	1.95 (0.81, 4.73)	3.85
Oliveira *et al*[31]	Brazil	43/37	24/52	2.52 (1.31, 4.84)	4.45
Zambon *et al*[30]	Italy	20/21	26/67	2.45 (1.15, 5.26)	4.21
Gatti *et al*[28]	Brazil	3/12	37/31	0.21 (0.05, 0.81)	2.66
Olfat *et al*[10]	Finland	22/9	12/14	2.85 (0.96, 8.51)	3.27
Olfat *et al*[10]	Portugal	19/11	12/49	7.05 (2.66, 18.69)	3.59
Olfat *et al*[10]	Germany	22/3	19/48	18.53 (4.96, 69.22)	2.74
Gatti *et al*[27]	Brazil	20/30	16/21	0.88 (0.37, 2.07)	3.92
Oleastro *et al*[20]	Portugal	25/25	18/38	2.11 (0.96, 4.64)	4.13
Oleastro *et al*[19]	Portugal	25/25	16/34	2.13 (0.94, 4.79)	4.06
Oleastro *et al*[19]	France	22/5	3/3	4.40 (0.68, 28.60)	1.78
Oleastro *et al*[19]	Sweden	10/2	4/6	7.50 (1.04, 54.12)	1.65
Oleastro *et al*[19]	Germany	7/2	6/4	2.33 (0.31, 17.54)	1.60
Oleastro *et al*[19]	United States	10/0	12/1	2.52 (0.09, 68.60)	0.72
Oleastro *et al*[18]	Portugal	27/30	7/53	6.81 (2.65, 17.52)	3.68
Subtotal (I^2 = 59.1%, P = 0.001)				2.74 (1.86, 4.03)	58.42
Overall (I^2 = 62.8%, P = 0.000)				2.07 (1.53, 2.79)	100.00
Note: Weights are from random effects analysis					



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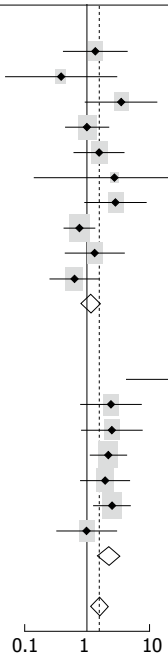
Ref.	Country	DU *babA2*+/-	NUD/GS *babA2*+/-	OR (95%CI)	%Weight
Asian					
Mizushima *et al*[35]	Japan	35/6	34/8	1.37 (0.43, 4.37)	5.18
Maeda *et al*[33]	Japan	20/2	52/2	0.38 (0.05, 2.92)	2.24
Yamaoka *et al*[32]	South Korea	111/4	47/6	3.54 (0.96, 13.13)	4.40
Yamaoka *et al*[32]	Japan	112/4	112/14	1.00 (0.46, 2.19)	7.92
Han *et al*[29]	China	35/12	28/15	1.56 (0.63, 3.87)	6.89
Chomvarin *et al*[24]	Thai	14/0	57/5	2.77 (0.14, 53.09)	1.15
Erzin *et al*[23]	Turkey	14/16	7/23	2.88 (0.95, 8.72)	5.48
Zhang *et al*[22]	China	61/40	89/44	0.75 (0.44, 1.29)	10.40
Safaei *et al*[17]	Iran	20/7	30/14	1.33 (0.46, 3.88)	5.73
Talebi Bezmin Abadi *et al*[9]	Iran	10/45	17/48	0.63 (0.26, 1.51)	7.10
Subtotal (I^2 = 23.1%, P = 0.231)				1.16 (0.80, 1.67)	56.49
Western					
Gerhard *et al*[8]	Munich	23/0	13/22	78.33 (4.39, 1397.21)	1.20
Yamaoka *et al*[32]	Colombia	34/6	28/12	2.43 (0.81, 7.30)	5.53
Yamaoka *et al*[32]	United States	35/6	28/12	2.50 (0.83, 7.50)	5.54
Yamaoka *et al*[11]	United States	123/22	66/26	2.20 (1.16, 4.18)	9.31
Yamaoka *et al*[11]	Colombia	53/11	37/15	1.95 (0.81, 4.73)	7.07
Oliveira *et al*[31]	Brazil	43/37	24/52	2.52 (1.31, 4.84)	9.19
Gatti *et al*[27]	Brazil	9/12	16/21	0.98 (0.33, 2.90)	5.65
Subtotal (I^2 = 28.1%, P = 0.214)				2.24 (1.47, 3.42)	43.51
Overall (I^2 = 45.8%, P = 0.021)				1.59 (1.14, 2.21)	100.00
Note: Weights are from random effects analysis					



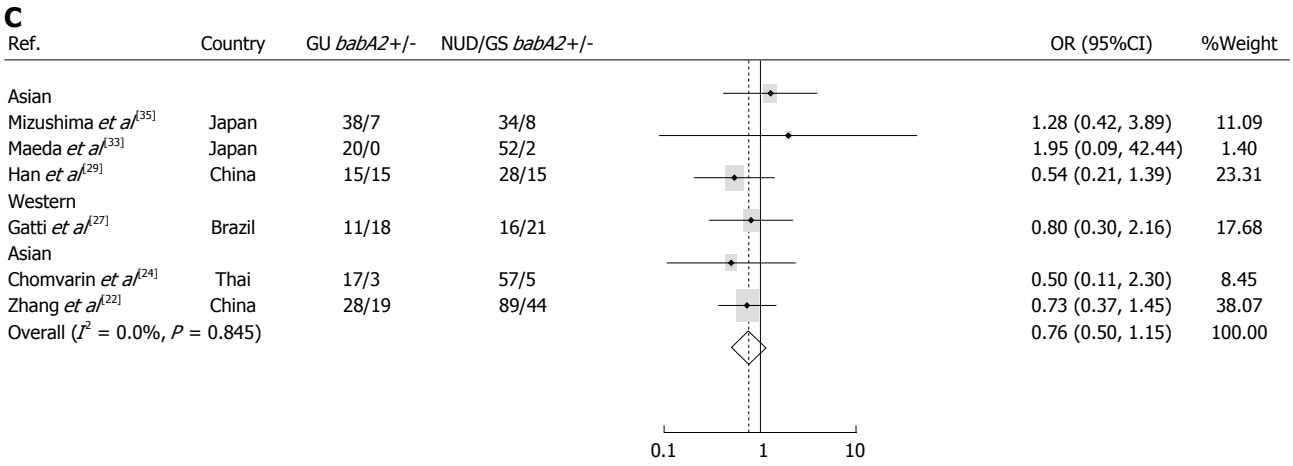


Figure 2 Results of the association between *babA2* gene and peptic ulcer disease, duodenal ulcer and gastric ulcer risk. A: Association between *babA2* and peptic ulcer disease (PUD); B: Association between *babA2* and duodenal ulcer (DU); C: Association between *babA2* and gastric ulcer (GU). ORs and 95%CIs were calculated by a random-effect (A, B) and fixed-effect (C) model. NUD: Nonulcer disease.

of *babA2*. Therefore, we performed the present meta-analysis of the available published literature to obtain a more precise conclusion. Our meta-analysis showed that *babA2* was significantly associated with increased risks of PUD, especially DU, with corresponding ORs of 2.069 and 1.588; moreover, statistically significant findings were more apparent in western populations with ORs of 2.739 for PUD and 2.239 for DU. The summary ORs for PUD and DU in Asians, however, were relatively small (1.370 and 1.158, respectively) and without statistical significance. No significant risk association was observed for GU and GC, but a decreased tendency was noted for GU with a pooled OR of 0.755.

Over the past 20 years, there has been marked progress in our understanding of the role of *H. pylori* infection in the etiology of gastroduodenal diseases. It is well known that *H. pylori* infection increases the risk of developing PUD, including both GU and DU subtypes[40]. Our meta-analysis confirmed a positive association of *H. pylori* with *babA2* genotype with PUD development. Among the major outer membrane proteins of *H. pylori*, BabA has significance not only in triggering bacterial colonization of the gastric epithelium, but also in regulating its functional interaction with host cells, which mainly acts through binding to Lewis^b and fucosylated ABO blood group antigens present in the stomach[41,42]. Gene inactivation experiments have demonstrated that only the product of *babA2* gene is essential for Lewis^b binding activity[7]. Rad *et al*[43] have reported a high density of *H. pylori* colonization in the stomach in the presence of *babA2* genotype, which increases interleukin-8 secretion and granulocytic infiltration, resulting in intense mucosal inflammation. In addition, Ishijima *et al*[41] have demonstrated that *babA2*-positive strains with Lewis^b binding activity are potentiators of the type IV secretion system (T4SS), implying a possible combined effect of *babA2* and other virulence factors related to T4SS. Although the detailed mechanism of the pathogenicity of *babA2* in PUD development has not been fully established, our meta-analysis suggests an important role of *babA2* genotype in distinguishing *H. pylori*-related PU and especially DU from NUD.

Intriguing findings in this study further suggested that individuals infected with *babA2*-positive pathogens have a unique pathogenicity in DU development; conversely, there was no significant association between *babA2* and GC. This difference may be partially due to the distinct etiologies of DU and GC development. Generally, *H. pylori*-related chronic severe gastritis could progress in two different directions[44]. One possibility is that *H. pylori*-related gastritis, predominating in the antrum as well as generating gastric acid, usually induces DU[45]. Patients with DU rarely develop atrophic gastritis of the corpus, and therefore GC risk may decrease in such cases[46]. Another possibility is that patients with extensive gastritis in the corpus and antrum, involving decreased acid output, tend to develop intestinal metaplasia, atrophic gastritis, and even GC[45]. It is speculated that *babA2* combined with other virulence factors may also lead to GC development. Studies conducted by Gerhard *et al*[8] and Erizin *et al*[47] have suggested that triple-positive *H. pylori* strains with *cagA, vacAs1* and *babA2* coexpression increase the risk of developing GC. Zambon *et al*[30] have also reported that infections with these triple-positive strains carry a higher risk of intestinal metaplasia, known as a gastric precancerous lesion. The different risk associations between GC and DU should be interpreted with caution, which should be further investigated in the future.

Our stratified analysis according to geographical areas demonstrated that *babA2* genotype is closely involved in the risk of PUD, especially DU in western populations, but not in Asian populations. This important information about geographical difference in the *babA2* gene suggests a potential biomarker distinguishing PUD, especially DU, from other NUDs in western populations, and reveals a phylogenetic difference between Asian and western *H. pylori* strains. Previous studies have also reported divergence in genes accounting for BabA and other virulence genes, such as *cagA* and *vacA*, between Asian and western strains[48-50]. The above-mentioned findings support the

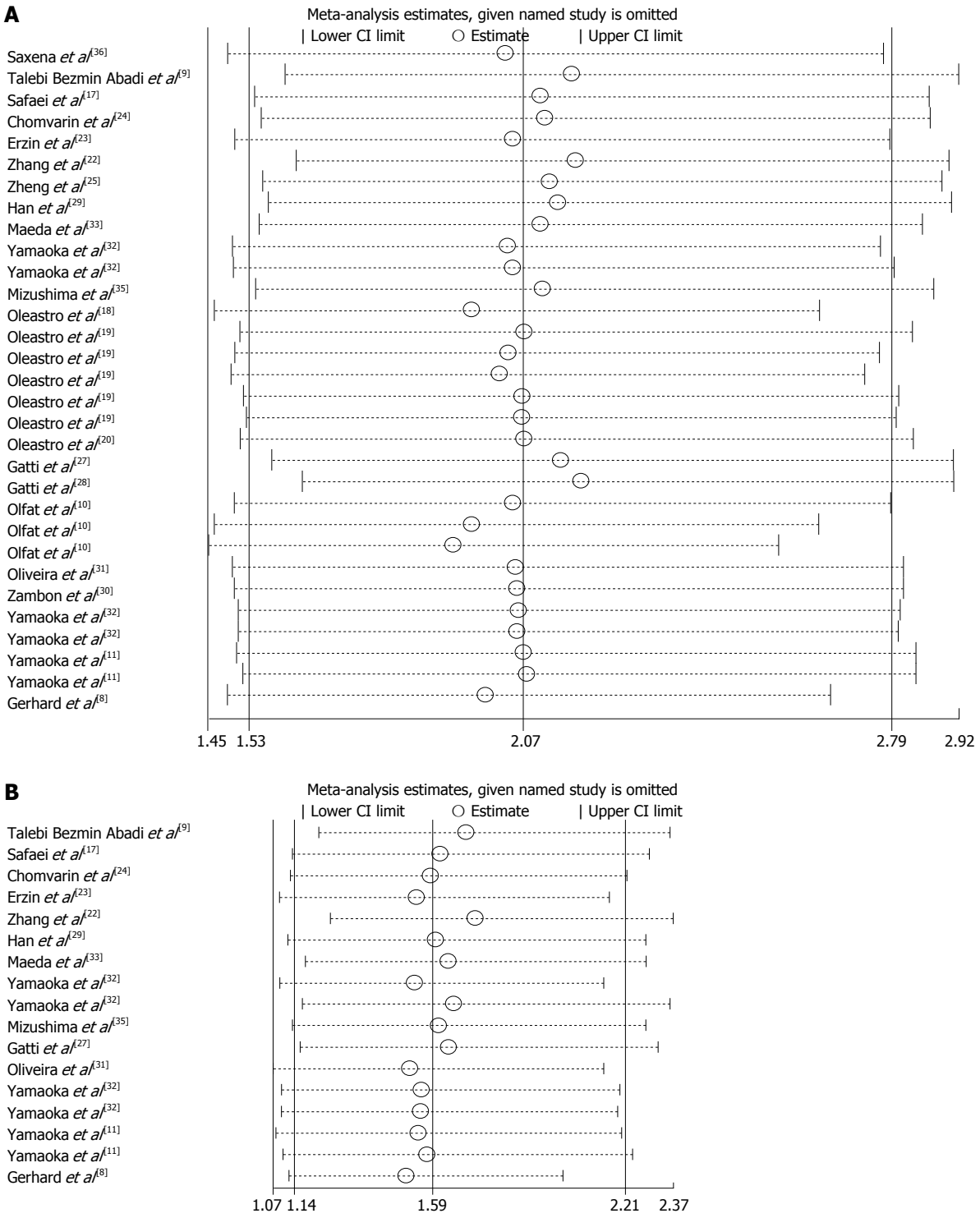
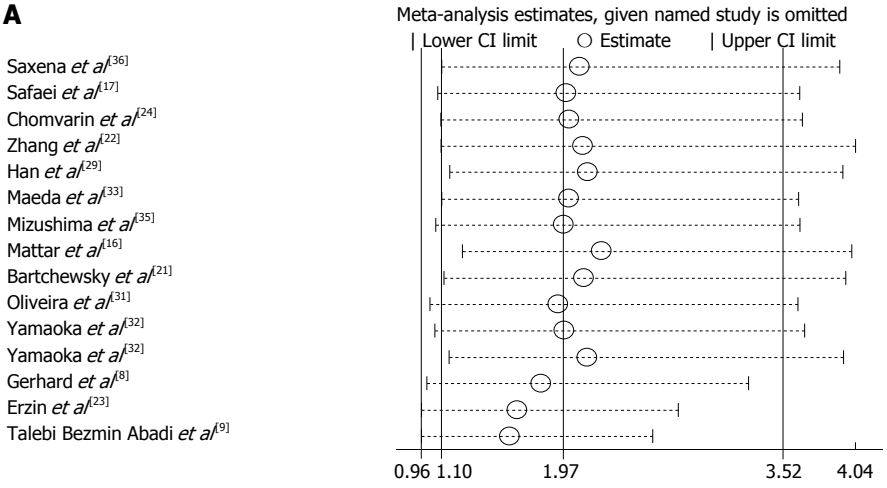


Figure 3 Influence of the summary OR coefficients on the association between *babA2* genotype and peptic ulcer disease and duodenal ulcer risk. A: *babA2* genotype and peptic ulcer disease (PUD) risk; B: *babA2* genotype and duodenal ulcer risk. Results were calculated by omitting each study (on the left) in turn. Bars, 95%CI. Meta-analysis random-effects estimates (exponential form) were used.

suggestion that genetic variability within the *H. pylori* genome, especially in probable host interaction genes, plays a critical role in its different adaptive ability and pathogenicity among different ethnicities[49].

There were several unavoidable limitations to our meta-analysis that should be considered. First, 17 studies[10,18-20,25,28,30,36] related to PUD lacked information about the distribution of DU and GU, which may have influenced the results of the stratified analysis. Second, a lack of original data on histopathological types of GC limited the subgroup analysis according to differences in these types. An unstable result was obtained according to the sensitivity analysis that assessed the relationship between *babA2* and GC, but there were insufficient data to explore

A



B

Ref.	Country	GC *babA2*+/-	NUD/GS *babA2*+/-	OR (95%CI)	%Weight
Asian					
Mizushima *et al*[35]	Japan	36/4	34/8	2.12 (0.58, 7.68)	6.19
Maeda *et al*[33]	Japan	11/0	52/5	1.10 (0.05, 24.38)	1.47
Han *et al*[29]	China	12/9	28/15	0.71 (0.25, 2.08)	7.84
Chomvarin *et al*[24]	Thai	15/1	57/5	1.32 (0.14, 12.13)	2.67
Zhang *et al*[22]	China	54/25	89/44	1.07 (0.59, 1.94)	13.11
Safaei *et al*[17]	Iran	8/2	30/14	1.87 (0.35, 9.96)	4.24
Saxena *et al*[36]	India	10/25	35/98	1.12 (0.49, 2.57)	10.21
Subtotal (I^2 = 0.0%, P = 0.918)				1.13 (0.76, 1.68)	45.73
Western					
Gerhard *et al*[8]	Munich	21/6	13/22	5.92 (1.90, 18.47)	7.27
Yamaoka *et al*[32]	Colombia	34/7	28/12	2.08 (0.72, 6.00)	7.93
Yamaoka *et al*[32]	United States	19/11	28/12	0.74 (0.27, 2.02)	8.41
Oliveira *et al*[31]	Brazil	29/23	24/52	2.73 (1.32, 5.67)	11.38
Bartchewsky *et al*[21]	Brazil	40/11	102/27	0.96 (0.44, 2.12)	10.65
Mattar *et al*[16]	Brazil	14/20	22/12	0.38 (0.14, 1.02)	8.63
Subtotal (I^2 =73.8%, P = 0.002)				1.43 (0.68, 3.00)	54.27
Overall (I^2 = 45.0%, P = 0.040)				1.30 (0.88, 1.93)	100.00

Note: Weights are from random effects analysis

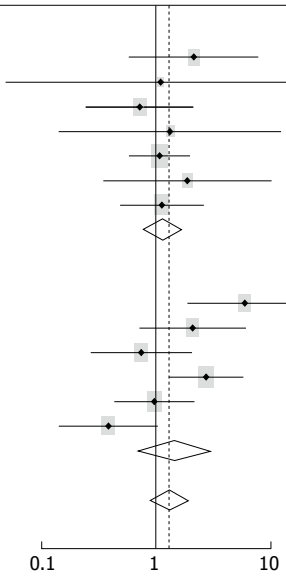


Figure 4 Influence of summary OR coefficients and results on the association between *babA2* genotype and gastric cancer risk. A: Influence analysis. Results were calculated by omitting each study (on the left) in turn. Bars, 95%CI. Meta-analysis random-effects estimates (exponential form) were used; B: Results. ORs and 95%CIs were calculated by a random-effect model.

the source of heterogeneity related to histopathological types. Third, most of the studies had a relatively small sample size.

In conclusion, our results suggest that the presence of *babA2* may contribute to increased risk of PUD, especially DU development, in western countries. In Asians, *babA2* genotype only showed a marginal association with PUD risk, which requires further investigation in the future.

COMMENTS

Background

Helicobacter pylori (*H. pylori*) is a common bacterium with a high prevalence rate and severe pathogenicity, which has been identified as a major cause of severe gastroduodenal diseases, such as peptic ulcer disease (PUD) and gastric cancer (GC). The genome of various *H. pylori* strains demonstrates significant genetic diversity. Genetic variation in specific virulence genes of *H. pylori* may participate in the pathogenic process of *H. pylori* infection in the stomach, thereby contributing to the variable risk of diverse clinical outcomes.

Research frontiers

BabA encoded by the *babA2* gene is a crucial virulence factor of *H. pylori*, which may be involved in the pathogenesis of PUD and GC. Although a few studies have focused on the association between *babA2* gene and the risks of *H. pylori*-related gastroduodenal diseases, those studies showed discrepant results. Moreover, there is no comprehensive meta-analysis integrating the currently available data on the relationship between *babA2* gene and PUD and GC.

Innovations and breakthroughs

This meta-analysis investigated the association between *babA2* gene and PUD and GC. They observed that the presence of *babA2* may contribute to increased risk of PUD, especially duodenal ulcer (DU) development, in western countries. However, in Asians, the presence of *babA2* only showed a marginal association with PUD risk, which requires further investigation. This meta-analysis achieved a relatively comprehensive conclusion on the relationship between *babA2* and clinical outcomes.

Applications

The study suggested that individuals infected with *H. pylori* harboring *babA2* gene were associated with increased risk of PUD, especially DU, in western countries. Eradication of *H. pylori*, in particular *H. pylori* harbouring *babA2*, may contribute to a lower incidence of PUD.

Terminology

babA2: Three *bab* allelic types have been identified, including *babA1*, *babA2* and *babB*, and only the product of the *babA2* gene is necessary for endowing *H. pylori* with Lewis^b antigen binding activity. *babA2* encodes the blood group antigen binding adhesion that binds to fucosylated Lewis^b blood group antigens on gastric epithelial cells.

Peer review

This was a well-performed meta-analysis of currently available studies on the association between *babA2* gene and PUD and GC, and concluded that the presence of *babA2* may be associated with increased risk of PUD, with an emphasis on DU and in western countries. This study was well designed and performed, and the results are well discussed.

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