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doi:10.3748/wjg.15.1465

World J Gastroenterol 2009 March 28; 15(12): 1465-1471
World Journal of Gastroenterology ISSN 1007-9327

Interleukin-1 and TNF-α polymorphisms and *Helicobacter pylori* in a Brazilian Amazon population

Hivana Patricia Melo Barbosa, Luisa Caricio Martins, Sidney Emanuel Batista dos Santos, Samia Demachki, Mônica Baraúna Assumpção, Charliana Damasceno Aragão, Tereza Cristina de Oliveira Corvelo

Hivana Patricia Melo Barbosa, Charliana Damasceno Aragão, Tereza Cristina de Oliveira Corvelo, Laboratory of Immunogenetics, Federal University of Pará, 66075-110, Belém, Brazil
Luisa Caricio Martins, Nucleus of Tropical Medicine, Federal University of Pará, 66055-240, Belém, Brazil
Sidney Emanuel Batista dos Santos, Laboratory of Human and Medical Genetics, Federal University of Pará, 66075-110, Belém, Brazil
Samia Demachki, Department of Pathology, João de Barros Barreto Universitary Hospital, Federal University of Pará, 66073-000, Belém, Brazil
Mônica Baraúna Assumpção, Department of Endoscopy, João de Barros Barreto Universitary Hospital, Federal University of Pará, 66073-000, Belém, Brazil
Author contributions: Melo Barbosa HP, Martins LC, dos Santos SE and Corvelo TC designed and performed the research; Melo Barbosa HP and Martins LC performed the majority of experiments; Aragão CD took part in the experiments and collected the control samples; Assumpção MB performed endoscopy and provided clinical advice; Demachki S performed the histological evaluation and provided clinical advice; Melo Barbosa HP and Martins LC wrote the paper.
Supported by Secretaria Executiva de Ciência, Tecnologia e Meio Ambiente-SECTAM and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior-CAPES
Correspondence to: Hivana Patricia Melo Barbosa, Laboratory of Immunogenetics, Federal University of Pará, 66075-110, Belém, Brazil. hivana@ufpa.br
Telephone: +55-91-32696857 Fax: +55-91-32017568
Received: October 19, 2008 Revised: February 9, 2009
Accepted: February 16, 2009
Published online: March 28, 2009

Abstract

AIM: To study the association between Interleukin-1 (IL-1) and tumor necrosis factor (TNF)-α polymorphisms, infection by *Helicobacter pylori* (*H pylori*) and the development of gastrointestinal diseases.

METHODS: Genomic DNA was extracted from the peripheral blood of 177 patients with various gastrointestinal diseases and from 100 healthy volunteers. The polymorphisms in IL-1β and TNF-α genes were analyzed using the polymerase chain reaction-restriction fragment length polymorphism method (PCR-RFLP) and those from IL-1RN with PCR. The presence of infection due to *H pylori* and the presence of the CagA toxin were detected by serology. The histopathological parameters in the gastric biopsies of the patients were according to the Sydney classification.

RESULTS: A comparison of the frequencies of the different polymorphisms studied among the patients and the control group demonstrated that the allele IL-1RN*2 was more frequent among patients with gastric ulcers and adenocarcinoma. Carriers of the allele IL-RN*2 and those with reactive serology for anti-CagA IgG had a greater risk of developing peptic ulcer and gastric adenocarcinoma, as well as a higher degree of inflammation and neutrophilic activity in the gastric mucosa.

CONCLUSION: Our results indicate a positive association between IL-1RN gene polymorphism and infection by positive *H pylori* CagA strains and the development of gastric ulcers and adenocarcinoma.

Key words: *Helicobacter pylori*; Interleukin 1β gene; Interleukin-1 receptor antagonist gene; TNF-α gene; Cag pathogenicity island

Peer reviewer: Siegfried Wagner, Professor, Medizinische Klinik II, Klinikum Deggendorf, Perlasberger Str. 41, Deggendorf 94469, Germany

Melo Barbosa HP, Martins LC, dos Santos SE, Demachki S, Assumpção MB, Aragão CD, Corvelo TC. Interleukin-1 and TNF-α polymorphisms and *Helicobacter pylori* in a Brazilian Amazon population. *World J Gastroenterol* 2009; 15(12): 1465-1471 Available from: URL: http://www.wjgnet.com/1007-9327/15/1465.asp DOI: http://dx.doi.org/10.3748/wjg.15.1465

INTRODUCTION

Helicobacter pylori (*H pylori*) infection is the major cause of chronic superficial gastritis in humans, and is a hypochloridria etiological factor in the pathogenesis of peptic ulcer disease (PUD) and some forms of stomach

cancer[1]. However, most people harboring *H pylori* are asymptomatic, and only a few patients infected with this bacterium develop peptic ulcer or stomach cancer[2]. The variability of clinical manifestations is associated with various factors, such as environmental, genetic susceptibility of the host and bacterial virulence[1,2].

One noteworthy factor for bacterial virulence is the CitoCagA toxin, codified by the *cagA* gene, a marker for the Cag-PAI pathogenicity island[3]. Infection by *H pylori* cagA-positive strains cause an intense inflammatory process, with dense neutrophilic infiltrate in the gastric mucosa[2,3]. However, bacterial virulence factors alone are not sufficient for determining clinical evolution of the infection. While virulent strains are frequent in both patients with peptic ulcers and those with gastric carcinoma[2,3], other factors in the host, mainly those that regulate immunological and inflammatory response may also contribute to a progression towards neoplasia[4].

Genetic polymorphisms, particularly those that occur in the region promoting genes that codify inflammatory cytokines, have been associated with an increase in synthesis of those interleukins and have emerged as a hypochloridria determining factor for cancer susceptibility[4,5].

Interleukin 1 beta (IL-1β) is a hypochloridria initiator and amplifier of the immune response, and is also a potent inhibitor of stomach acid secretion[5,6]. The antagonist of the IL-1 (IL-1RN) receptor is an anti-inflammatory cytokine that competes for the IL-1 receptors, modulating the effect of IL-1β[7]. Studies carried out in Caucasian and Asian populations have demonstrated that polymorphisms in genes IL-1β and IL-1RN are associated with an increased risk of hypochloridria and gastric carcinoma[7-9]. Another important cytokine is TNF-α, the biallelic polymorphism in position -308 of the region promoting the gene codifying that cytokine, which has been associated with the development of gastric carcinoma in studies carried out in Caucasians[10,11].

The objective of this study was to determine the frequency of polymorphisms in genes IL-1β, IL-1RN and TNF-α in patients from the state of Pará, in the northern region of Brazil, with various gastrointestinal diseases and in a control group, The relationship of these polymorphisms to infection by virulent strains of *H pylori* (CagA+) and to the histopathological characteristics of gastric tissue were also determined.

MATERIALS AND METHODS

Patient and control samples

Peripheral blood and gastric fragment samples were collected from 177 consecutive patients from the state of Pará-Brazil who had various gastrointestinal disturbances. Gastric fragment samples were obtained by the endoscopy service of the João de Barros Barreto Universitary Hospital. For the control samples, peripheral blood was collected from 100 patients who were without clinical or metabolic diseases and who were asymptomatic for gastrointestinal disturbances, and were thus not submitted to endoscopic examinations.

All patients and controls were enrolled in the study between September 2003 and September 2004 and were from the same socioeconomic level, and had similar cultural habits. All were natives of Pará state with the same ethnic background, approximately 50% Portuguese, 40% Amerindian and 10% African[12]. The study was approved by the Ethics Committee at João de Barros Barreto Universitary Hospital.

Detection of H pylori infection

In both patients and controls, the presence of the specific *H pylori* and CagA IgG antibodies in serum samples was determined. To detect *H pylori* antibodies the commercial HIK anti-*H pylori* EIA kit was used (Monobind, USA), and the Helicobacter P-120 EIA commercial kit (VIVA Diagnostica, Germany) was used to detect anti-CagA antibodies. Kits were used according to the manufacturers' technical descriptions.

IL-1β, IL-1RN and TNF-α genotyping

Genomic DNA was extracted from total blood using a leukocyte lysis solution (100 mmol/L Tris-HCl, 20 mmol/L EDTA, 200 mmol/L NaCl, 1% dodecyl-sodium sulfate, 0.2% β mercaptoethanol) and was purified using the phenol-chloroform method[13].

Polymorphisms of the IL-1β (-31, -511) and TNF-α (-308) genes were characterized using the polymerase chain reaction-restriction fragment length polymorphism method (PCR-RFLP). The volume for the PCR was 25 μL, containing 0.5 mmol/L of each primer, 1 X PCR buffer, 1.5 mmol/L of $MgCl_2$, 0.2 mmol/L of each nitrogenated base, 1.25 U of *Taq* DNA polymerase, 50 ng of DNA and sterile water.

To determine the polymorphism of the IL-1β gene in position -511, the PCR primers and conditions described by Wilkinson *et al*[14] were used. The PCR products were digested with *Ava*I overnight at 37℃ and separated by electrophoresis in 2% agarose gel stained with ethidium bromide. Those presenting two bands were called CC (114 and 190 bp), those with three bands, CT (114, 190 and 304 bp) and those with a single band, TT (304 bp).

Polymorphism of the IL-1β gene in the -31 position was investigated using the primers described by El-Omar *et al*[7]. The conditions of the PCR were as follows: initial denaturation at 95°C for 2 min followed by 35 cycles of denaturation at 95°C for 1 min, annealing and extension for 1 min, and final extension at 72℃ for 10 min. Annealing temperatures were set at 58℃ for primers. Negative and positive controls were used in all reactions. To discriminate alleles, the PCR products were digested with *Alu*I overnight at 37℃ and then separated by electrophoresis in 2% agarose gel stained with ethidium bromide. Those presenting a single band (235 bp) were called CC; those with three bands (98, 137 and 235 bp)

were called CT and TT was used for those with two bands (98 and 137 bp).

For genotyping polymorphism -308 in the TNF-α gene, the PCR primers and conditions as described by Wilson *et al*[15] were used. The PCR products were digested with *Nco*I overnight at 37℃ and separated by electrophoresis in 2% agarose gel stained with ethidium bromide.

The VNTR polymorphism at intron 2 of the IL-1RN gene was determined using the primers and conditions described by El-Omar *et al*[7]. The PCR products were separated by electrophoresis in 2% agarose gel stained with ethidium bromide. They were named allele 1 = 442 bp (4 repeats), allele 2 = 270 bp (2 repeats), allele 3 = 528 bp (5 repeats), allele 4 = 356 bp (3 repeats), allele 5 = 614 bp (6 repeats).

Histological evaluation

Biopsy specimens from the lesion and the adjacent area in each patient were obtained. The specimens were fixed in 10% buffered formalin solution, embedded in paraffin, cut into sequential 0.4-μm sections, and stained with hematoxylin and eosin (HE). The histopathological parameters were graded (0-3) using the criteria described in the updated Sydney classification system[16] for analysis of chronic inflammation, polymorphonuclear activity, and intestinal metaplasia.

Statistical analysis

Hardy-Weinberg equilibrium and heterogeneity among groups were tested using the Guo and Thompson[17] exact test. Maximum-likelihood haplotype frequencies were computed using an Expectation-Maximization (IN) algorithm[18,19]. Linkage disequilibrium was tested using a likelihood-ratio test[20]. All the aforementioned statistical procedures were carried out using Arlequin software[21].

To compare the variables of sex, age, CagA status, *H pylori* and genotype frequencies between patients and controls, the G test was utilized. The risks of carriers with different alleles developing gastric ulcers and adenogastric carcinoma, as well as having alterations in the gastric mucosa were calculated using the Odds ratio. The data were analyzed with BioEstat version 4.0 software[22]. Differences were considered statistically significant if *P* values were less than 0.05.

RESULTS

Clinical and demographic characteristics of patients and controls

One hundred and seventy-seven patients with various gastrointestinal pathologies were investigated; of these 80 (45%) had gastritis, 33 (19%) duodenal ulcer, 34 (19%) gastric ulcer and 30 (17%) had intestinal-type adenogastric carcinoma.

The epidemiological data of the two groups studied are described in Table 1. The patients had an average age of 45 years with ages ranging from 18 to 90 years. Subjects in the control group had an average age of 36 years, with ages ranging from 18 to 81 years. The patients with adenogastric carcinoma were older than those in the control group (Table 1).

Table 1 Epidemiological characteristics of the control group and patients *n* (%)

Demographic data	Control *n* = 100	Gastritis *n* = 80	DU *n* = 33	GU *n* = 34	AC *n* = 30
Age (yr)					
> 50	31	26 (32)	11 (33)	12 (35)	21 (70)
< 50	69	54 (68)	22 (67)	22 (65)	9 (30)
P value		NS	NS	NS	0.00
Sex					
Male	57	39 (49)	19 (58)	21 (62)	19 (63)
Female	43	41 (51)	14 (42)	13 (38)	11 (37)
P value		NS	NS	NS	NS
IgG-anti *H pylori*					
Positive	61	74 (92)	30 (91)	33 (97)	29 (97)
Negative	39	6 (8)	3 (9)	1 (3)	1 (3)
P value		0.00	0.00	0.00	0.00
anti-CagA IgG (HP+)					
Positive	38	53 (66)	29 (97)	31 (94)	28 (97)
Negative	23	21 (34)	1 (3)	2 (6)	1 (3)
P value		NS	0.00	0.00	0.00

DU: Duodenal ulcer; GU: Gastric ulcer; AC: Adenogastric carcinoma; G Test: Control *versus* disease; NS: Not significant.

The presence of IgG antibodies-*H pylori* and CagA specific was greater in patients with gastrointestinal diseases than in the control group (Table 1). A comparison of the presence of anti-CagA antibodies IgG in patients with various gastrointestinal diseases demonstrated that patients with gastric ulcer (G = 6.330, *P* = 0.011), duodenal ulcer (G = 8.076, *P* = 0.004) and adenogastric carcinoma (G = 7.702, *P* = 0.005) had greater seroprevalence of this antibody that patients with gastritis. However, when we compared the frequency observed in patients with gastric ulcer with that in patients with duodenal ulcer (G = 0.007, *P* = 0.932) and with stomach cancer (G = 0.013, *P* = 0.908) no differences were observed. A similar observation was made when we compared patients with duodenal ulcer and those with cancer (G = 0.506, *P* = 0.476).

IL-1β, IL-1RN and TNF-α polymorphisms

The polymorphisms studied were in the Hardy-Weinberg equilibrium for both the control group (IL-1β-31 *P* = 0.811; IL-1β-511 *P* = 0.902; IL-1RN *P* = 0.361; TNF-α-308 *P* = 0.363) and for patients with gastrointestinal diseases (IL-1β-31 *P* = 0.321; IL-1β-511 *P* = 0.791; IL-1RN *P* = 0.691; TNF-α-308 *P* = 0.552). An imbalance in linkage among alleles IL-1β-511T and IL-1β-31C ($P > 10^{-5}$) was observed in both groups studied.

A comparison of the genotype frequencies of polymorphisms in genes IL-1β analyzed in this study with those from other studies carried out in different countries, demonstrated that the frequency of the alleles for polymorphisms IL-1β-31, IL-1β-511 in our population did not differ statistically from that described for Caucasians[7] and Asiatic populations[23], and was

Table 2 Comparison of genotype frequencies for the polymorphisms of IL-1β genes studied with results of other studies in different ethnic and population groups *n* (%)

Genotypes	Pará (Brazil)	Minas Gerais (Brazil)	Caucasians	Asians
IL-1β-31				
TT	9	102 (35.8)[1]	7 (12)[2]	7 (4)[4]
TC	23	138 (48.4)	21 (36)	34 (20)
CC	68	45 (15.8)	30 (52)	128 (76)
P value	Reference	0.001	NS	NS
IL-1β-511				
CC	31	108 (37.9)[1]	29 (50)[2]	34 (20)[4]
CT	46	137 (48.1)	21 (36)	97 (57)
TT	23	40 (14)	8 (14)	38 (23)
P value	Reference	NS	NS	NS
IL-1RN				
11	58	175 (61.4)[1]	37 (64)[2]	163 (96)[4]
12	36	92 (32.3)	14 (24)	4 (3)
22	6	18 (6.3)	17 (10)	2 (1)
P value	Reference	NS	NS	0.001
TNF-α-308				
GG	86	223 (78.3)[1]	152 (72)[3]	274 (91.3)[5]
GA	13	54 (18.9)	52 (25)	24 (8)
AA	1	8 (2.8)	6 (3)	2 (0.7)
P value	Reference	NS	0.025	NS

G Test: Our study *versus* other papers. [1]Queiroz *et al*[25] 2004; [2]El-Omar *et al*[7] 2000; [3]El-Omar *et al*[24] 2003; [4]Zeng *et al*[23] 2003; [5]Yea *et al*[11] 2001. NS: Not significant.

Table 3 Distribution of genotypes for *IL-1β* (-511 and -31), *IL-1RN* and TNF-α in the control group and in patients with gastrointestinal pathologies *n* (%)

Genotypes	Control *n* = 100	Gastritis *n* = 80	DU *n* = 33	GU *n* = 34	AC *n* = 30
IL-1β-31					
T/T	9	3 (4)	1 (3)	2 (6)	1 (4)
C/T	23	21 (26)	9 (27)	7 (20)	4 (13)
C/C	68	56 (70)	23 (70)	25 (74)	25 (83)
P value		NS	NS	NS	NS
IL-1β-511					
C/C	31	26 (33)	9 (27)	10 (29)	6 (20)
C/T	46	34 (42)	13 (39)	14 (41)	11 (37)
T/T	23	20 (25)	11 (34)	10 (30)	13 (43)
P value		NS	NS	NS	NS
IL-1RN					
1/1	58	41 (51)	15 (46)	11 (32)	10 (33)
1/2	36	34 (43)	16 (49)	21 (62)	19 (63)
2/2	6	5 (6)	2 (6)	2 (6)	1 (4)
P value		NS	NS	0.00	0.00
TNF-α					
G/G	86	62 (77)	23 (70)	29 (85)	24 (80)
G/A	13	16 (20)	8 (24)	4 (12)	5 (16)
A/A	1	2 (3)	2 (6)	1 (3)	1 (4)
P value		NS	NS	NS	NS

DU: Duodenal ulcer; GU: Gastric ulcer; AC: Adenogastric carcinoma; G Test: Control *versus* disease; NS: Not significant.

in an intermediate position compared to that found in those populations. In contrast, the polymorphisms of the IL-1RN genes differed from those described in Asiatic populations[11] and gene TNF-α-308 differed from descriptions in Caucasian populations[24] (Table 2). When we compared our data with those obtained in Minas Gerais[25], we observed a difference in the frequency of the IL-1β-31 polymorphism, with the C allele being more frequent in our population than in the Minas Gerais population (Table 2).

In analyzing the distribution of the different genotypes among the patients and the control group we observed that the polymorphisms in genes IL-1β-31, IL-1β-511, TNF-α-308 did not differ. However, in relation to gene IL-1RN, we obtained a greater frequency of allele 2 carriers (IL-1RN*2) among patients with adenogastric carcinoma and gastric ulcer than in the control group (Table 3).

A combined risk analysis of the different polymorphisms studied demonstrated that there was no synergism between those polymorphisms and the development of gastric ulcers and adenocarcinoma. Individuals carrying only a polymorphism in gene IL-1RN*2 (OR = 3, $P = 0.86$) had a greater risk than individuals carrying polymorphisms in genes IL-31*C and IL-1RN*2 (OR = 1.2, $P = 0.51$) and the risk was similar to that for carriers of all the polymorphisms studied (OR = 3, $P = 0.71$).

In the association between the IL1-RN polymorphism and the presence of specific CagA antibodies, we found that carriers of allele IL-1RN*2 who were reactive for anti-CagA IgG had a greater risk of developing gastric ulcers and adenocarcinoma. This demonstrated an interaction between the presence of a virulent strain and allele IL-RN*2 in the development of these diseases (Table 4).

The relationship between IL-1RN genotypes and anti-CagA antibodies with histopathological data demonstrated that carriers of allele IL-1RN*2, who were seroreactive for CagA had high levels of inflammation and neutrophilic activity, with a heightened risk of developing intestinal metaplasia in the gastric mucosa (Table 5).

DISCUSSION

The state of Pará has a high prevalence and incidence of gastrointestinal diseases, principally adenogastric carcinoma. In addition, an increased prevalence of *H pylori* infection has been observed among patients with gastrointestinal diseases[26,27], with a predominance of virulent strains (*vacA*-s1b/m1/*cagA*-positive) that are associated with the development of both peptic ulcers and adenocarcinoma[28].

The patients with adenogastric carcinoma were older than those in the control group. These patients had been developing progressive gastric cancer lesions for a long time[29].

Some studies have demonstrated that polymorphisms in genes IL-1β, IL-1RN and TNF-α, together with *H pylori* infection are associated with an increased risk of developing stomach cancer[7,10,11]; therefore, to better understand the factors related to the high prevalence of stomach cancer in our region we analyzed the frequency of the genotypes of polymorphisms in genes IL-1β,

Table 4 Combined risk of polymorphism in the IL1-RN gene and IgG CagA antibody for development of gastric ulcers and adenogastric carcinoma

IL1-RN	CagA	Control	GU	OR[a] (95% IC)	*P*	AC	OR[b] (95% IC)	*P*
1/1	(-)	15 (24%)	2 (6%)	Ref.	-	1 (4%)	Ref.	-
2* carrier	(-)	8 (13%)	2 (6%)	1.875[c]	0.983	1 (4%)	1.875[c]	0.735
1/1	(+)	21 (35%)	9 (27%)	3.214 (0.605-17.063)	0.289	8 (30%)	5.714 (0.644-50.648)	0.185
2* carrier	(+)	17 (28%)	20 (61%)	8.823 (1.762-44.181)	0.008	19 (62%)	16.764 (1.997-140.707)	0.004
Total		61	33			29		

GU: Gastric ulcer; AC: Adenogastric carcinoma. [a]Control x GU; [b]Control x AC; [c]The confidence interval was not calculated, since, $n_1p_1q_1 < 5$ or $n_2p_2q_2 < 5$.

Table 5 Association of polymorphism for IL-RN gene and anti-CagA antibodies with histopathological findings from patients

IL1-RN	CagA	DI		OR (95% CI)	*P*	NA		OR (95% CI)	*P*	Metaplasia		OR (95% CI)	*P*
		1	2 and 3			1	2 and 3			+	-		
1/1	(-)	13	2	-	-	12	3	-	-	1	14	-	-
2* carrier	(-)	9	1	0.722[a]	0.706	8	2	1[a]	0.609	2	8	3.5[a]	0.706
1/1	(+)	24	34	9.2 00 (1.90-44.606)	0.004	26	32	4.923 (1.254-19.314)	0.032	17	41	5.804 (0.706-47.693)	0.139
2* carrier	(+)	20	63	20.475 (4.253-98.556)	0.001	23	60	10.434 (2.695-40.388)	0.003	35	58	8.448 (1.064-67.065)	0.038

DI: Degree of inflammation; NA: Neutrophilic activity. Histopathological parameters: 1: Light; 2: Moderate; 3: Intense. [a]The confidence interval was not calculated, since, $n_1p_1q_1 < 5$ or $n_2p_2q_2 < 5$.

IL-1RN and TNF-α and the presence of infection by CagA+ strains in patients with various gastrointestinal diseases and in a control group.

In this study, infection by virulent strains (CagA+) was greater in patients with peptic ulcers and adenocarcinoma than in patients with gastritis or in subjects in the control group. Similar results were found in a previous study carried out in Belém and other Brazilian states, where the presence of *H pylori* CagA+ strains was associated with the development of peptic ulcers and adenocarcinoma[28,29].

The frequency of polymorphisms in genes IL-1β-31 and IL-1β-511 in our study was similar to that described in Caucasian[7,24] and Asiatic populations[23,30], whereas the frequency of polymorphisms in genes IL-1RN and TNF-α-308 was significantly different from that reported in Asiatic[23] and Caucasian[7,24] populations, respectively. The genetic composition of the Brazilian population is made up of a genetic mix of various ethnic groups, including Portuguese, Africans and Amerindians[12]. The differences and similarities between the allelic frequencies of the polymorphisms studied in our population with those of other ethnic groups are products of the genetic mix that has occurred in Brazil.

In comparing the frequencies of the polymorphisms studied in our population with those from another Brazilian study carried out in Belo Horizonte, Minas Gerais, located in the central-western region of the country, we observed differences in relation to IL-1β-31 polymorphism. In Brazil, several states show differences in ethnic background, and the populations in the Amazon region are the ones which have an important indigenous genetic component[12], greater than that described for the Minas Gerais population[31], which may be reflected in the gene frequency of those polymorphisms.

An analysis of the genotypes of the polymorphisms in the patients and the control group demonstrated that IL-1RN*2 carriers were more frequent among patients with gastric ulcers and adenocarcinoma. The IL-1Ra protein (codified by the IL-1RN gene) acts competitively to inhibit action by IL-1β[7]. Carriers of IL-1RN*2 have higher levels of IL-1β in the gastric mucosa than those with IL-1RN1/1[32], and thus have a more severe and prolonged immune response, which may lead to hypochloridria due to destruction of the gastric glands and to action by IL-1β that inhibits synthesis of chloridic acid by the parietal cells[6,7]. El-Omar *et al*[7] have described an association between IL-1RN*2 and hypochloridria, and both gastric ulcer and stomach cancer reduce the synthesis of chloridic acid. Other studies have also described the association between the IL-1RN*2 polymorphisms and stomach cancer[23,24,33]. In Brazil, Rocha *et al*[34] obtained similar results in relation to the association of allele IL-RN*2 and an increased risk of developing stomach cancer, as well as the absence of an association between the IL-1β-31, TNF-α-308 polymorphisms and the risk of developing stomach cancer.

A combined analysis of the different polymorphisms demonstrated that there was no association between these polymorphisms and an increased risk of developing gastric ulcer or adenocarcinoma. In addition, we found an interaction between the presence of allele IL-RN*2 and infection by CagA+ strains. This finding is important for our region, which has a high incidence of stomach cancer, high prevalence of infection by CagA+

strains and a high frequency of the IL-1RN*2 allele. Reinforcing these data, our results have demonstrated that carriers of allele IL-RN*2 infected by CagA+ strains had a greater risk of developing an intense inflammatory process in the gastric mucosa, which confirms a synergistic action between the polymorphism of gene IL-1RN and another type of infecting strain. Other studies have also observed that both infection by virulent strains and gene IL-1RN polymorphism are important risk factors for gastric carcinogenesis[23,29,33]. In conclusion, our results suggest that bacterial virulence and genetic factors in the host act synergistically in the development of gastric ulcers and adenocarcinoma.

COMMENTS

Background

Helicobacter pylori (*H pylori*) infection is associated with a broad spectrum of gastrointestinal disorders. However, most people harboring *H pylori* are asymptomatic, and only a few patients infected with this bacterium develop peptic ulcer or stomach cancer. The variability of clinical manifestations is associated with various factors, such as environmental, genetic susceptibility of the host and bacterial virulence.

Research frontiers

This study indicated a possible association between IL-1RN gene polymorphism and infection by positive *H pylori* CagA strains and the development of gastric ulcers and adenocarcinoma.

Innovations and breakthroughs

This study determined the frequency of polymorphisms in genes IL-1β, IL-1RN and TNF-α in patients with various gastrointestinal diseases from the state of Pará, in the Brazilian Amazon, and in a control group. The relationship of these polymorphisms to infection by virulent strains of *H pylori* and to the histopathological characteristics of the gastric tissue were determined.

Applications

This study may represent a future strategy for distinguishing patients with a risk of developing gastrointestinal diseases, such as gastric cancer.

Terminology

The CitoCagA toxin is a factor for bacterial virulence. The antagonist of the IL-1 (IL-1RN) receptor is an anti-inflammatory cytokine.

Peer review

In this study, confirmatory new data on gene polymorphism in a Brazilian population and message is clearly shown.

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