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Role of the polymorphic *IL-1B*, *IL-1RN* and *TNF-A* genes in distal gastric cancer in Mexico

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Several cytokine gene polymorphisms have been associated with increased risk of distal gastric cancer (GC) and its precursor histological markers in Caucasian, Asian and Portuguese populations although little is known about their role in other ethnic groups. Our study investigates the role of the *IL-1B-31*, *IL-1RN* and *TNF-A-308* gene polymorphisms as risk factors for the development of GC in a Mexican population. We studied 278 patients who were enrolled at the Hospital Universitario Dr. José Eleuterio González, Universidad Autónoma de Nuevo León. The subjects were divided into 2 groups. Sixty-three patients with histologically confirmed distal GC (mean age = 58.8 years, range = 22–84, F:M = 0.56), and 215 patients with no evidence of distal or proximal GC (mean age = 56.1 years, range = 18–92, F:M = 1.17). The *IL-1B-31* and the *TNF-A-308* polymorphisms were determined by PCR-RFLP and pyrosequencing, respectively, in all cases and controls. The VNTR polymorphism in intron 2 of the *1L-1RN* gene was typed by PCR in 25 cases and 201 controls. The *H. pylori* status was determined by histology, rapid urease test, culture and serology for non-cancer controls and by histology for the GC cases. The carriage of the proinflammatory *IL-1B-31*C* allele was associated with increased risk of distal GC (odds ratio [OR] = 7.63, 95% confidence interval [CI] = 1.73-46.94, p = 0.003). When cases and controls were matched by age and gender, the OR value was higher (OR = 8.05, 95% CI = 1.8–50.22, p = 0.001). When only *H. pylori* GC cases and controls were compared, the OR value was 7.8 (95% CI = 1.05–161.8, p = 0.04). No association was found between any of the other polymorphisms studied and distal GC. In this Mexican population, the *IL-1B* proinflammatory genotype increases the risk of distal GC. These findings are similar to previous reports in Caucasian populations and underscore the importance of cytokine gene polymorphisms in the development of distal GC.
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Key words: Helicobacter; gastric cancer; interleukin-1; cytokine; premalignant conditions; *IL1-RN*; *TNF-A*; Mexico

The etiologic role of *Helicobacter pylori* in chronic gastritis, peptic-ulcer disease (PUD) and gastric cancer has been clearly recognized.[1] The bacterium remains the single most common organism that colonizes humans. Most *H. pylori* positive subjects develop no significant disease, and remain largely asymptomatic throughout their life. The reasons for the divergent clinical outcomes remain poorly understood, but it is thought that host, bacterial and environmental factors contribute to this process.[2]

The local inflammation in *H. pylori* infection is characterized by infiltration of neutrophils and specific lymphocytes into the gastric mucosa as well as by increased production of several cytokines.

It is now well recognized that the inter-individual variation in the expression of these cytokines and gastric inflammation is explained at least partly by polymorphisms in the genes that encode these proteins.[3,4] This fact has been employed in the study of the host response to *H. pylori* infection and its relationship with clinical outcomes, including the distal gastric cancer (GC).

The interleukin-1 (*IL-1*) gene cluster contains 3 related genes (*IL-1A*, *IL-1B* and *IL1-RN*), which encode the proinflammatory cytokines 1L-1α, IL-1β as well as their endogenous receptor antagonist IL-1ra respectively.[5] The IL-1β is upregulated in the presence of *H. pylori* and is important in initiating and amplifying the inflammatory response to this infection. 1L-1β is also a potent inhibitor of gastric acid secretion.[5] A biallelic polymorphism at position −31 in the promoter region of the *IL-1B* gene has been associated with the development of GC and its precursor histological markers in Scottish, Portuguese and Asian populations.[6–12]

A region within the second intron of the *IL-1 RN* gene contains a variable number of 86-bp tandem repeats and 5 different alleles have been identified. Alleles 1, 2, 3, 4 and 5, represent 4, 2, 5, 3 and 6 repeats of the 86 bp tandem repeat, respectively. The presence of allele 2 has been associated with increased risk of distal GC and its precursor histological markers in some populations.[5,8,10] Interestingly, the pro-inflammatory alleles of the *IL1B* and *IL1RN* genes that have been shown to increase the risk of severe corpus inflammation, gastric atrophy and distal gastric cancer have been shown to decrease the risk of gastroesophageal reflux disease.[13]

The pro-inflammatory cytokine tumor necrosis factor (TNF)-α also plays an important role in the inflammatory process. Several biallelic polymorphisms of the gene coding for this cytokine are known, including the *TNF-A*-308G/A, which is the first discovered, the *TNF-A*-376G/A and the -238G/A gene polymorphisms. A functional promoter polymorphism in the *TNF-A-308* play an important role in *H. pylori*-induced gastritis and has been found to influence the risk of GC.[6,11]

We investigated whether these cytokine gene polymorphisms are important host genetic factors in the susceptibility to distal GC in a Mexican population, a hitherto unstudied ethnic group.

Material and methods

Patient population

We studied 63 unrelated patients with histologically confirmed distal GC (mean age = 58.8 years, median age = 60, age range = 22–84, F:M = 0.56). Of the 63 cases of gastric cancer, 29 (46%) had the intestinal type and 34 (54%) the diffuse type. We also studied 215 ambulatory patients with no histological evidence of GC (mean age = 56.1 year, median age = 54, age range = 18–92, F:M = 1.17) who acceded to the Gastroenterology Service, Hospital Universitario "Dr. José Eleuterio González", Universidad Autónoma de Nuevo León for investigation of dyspeptic symptoms. The local ethical committee approved the study and written informed consent was obtained from all subjects.

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Histopathological examinations

For all the controls included in our study, 8 biopsy specimens were obtained for histological evaluation, 2 from lesser curvature, 2 from greater curvature, 2 from incisura angularis and 2 from the pre-pyloric region. For patients with distal GC, at least 8 biopsies were obtained from the tumor for histological evaluation. Biopsies from cases and controls were fixed, paraffin embedded and stained with hematoxylin-eosin. An experienced pathologist examined and reported the findings from all the histological slides.

Genotyping

The single nucleotide polymorphisms in *IL-1B* (−31 C/T) and *TNF-A* (−308 G/A), as well as the variable number of tandem repeats (VNTR) polymorphism of *IL-1RN* were assessed. The genomic human DNA used for genotyping was extracted from peripheral blood leucocytes in all controls and in 31 GC cases. In the remaining 32 GC cases, the DNA used for genotyping was extracted from several microdissections of paraffin embedded cancer tissue obtained from surgical resection specimens.

Extraction of genomic human DNA from peripheral blood

Genomic DNA was extracted by suspending 250 μL of whole blood in lysis buffer (100 mM Tris-HCl [pH 8.0], 5 mM EDTA, 0.2% sodium dodecyl sulfate [SDS], 200 mM NaCl). DNA was extracted twice with 1 volume of phenol-chloroform-isoamyl alcohol (25:24:1), precipitated with absolute ethanol, washed with 70% ethanol, air dried and resuspended in 200 μl of Tris-EDTA buffer.

Extraction of DNA from paraffin-embedded tissue sections

DNA was extracted following standard protocols. Sections from paraffin blocks were mixed with 100% xylene (1 ml/5 paraffin sections). The mixture was incubated at 60°C for 30 min and centrifuged 10,000*g* for 2 min. The pellet was washed twice with ethanol, air dried, suspended in extraction buffer (20 mM Tris-HCl [pH = 8], 0.5% [vol/vol] Tween 20) with proteinase K (0.5 mg/ml) (Promega, Madison, WI) and incubated at 55°C for 24 hr. DNA was extracted twice with phenol-chloroform-isoamyl alcohol (25:24:1), precipitated with 2 volumes of ethanol, washed with 70% ethanol, air dried, and resuspended in Tris-EDTA buffer. DNA extracts were stored at −20°C until required.

Genotyping of the −31 (C/T) polymorphism in the IL-1B *gene*

The polymorphism at position −31 of the *IL-1B* gene was determined by the PCR-restricted fragment length polymorphism (RFLP) method. Forward (5′-CCACCAATACTCTTTTTC-CCCTTTCC-3′) and reverse (5′-GATTGGCTGAAGAGAATC-CCAGAGC-3′) primers were used. Amplifications were carried out in a final volume of 50 μl containing 20 mM Tris-HCl (pH 8.3), 50 mM KCl, 2 mM $MgCl_2$, 18 mM NaCl, 0.2 mM of each dNTP, 200 nM of each primer, 1 U of Ampli*Taq* polymerase (Qiagen, Chatsworth, CA) and 100 ng of DNA. The thermocycling conditions were: 94°C for 5 min; then 40 cycles of 94°C, 55°C and 72°C for 1 min each, followed by 72°C for 5 min. The digestion of PCR products was carried out at 37°C with *Alu*I (New England Biolabs, Beverly, MA). The resulting DNA fragments were resolved by electrophoresis on a 2.5% agarose gel and stained with ethidium bromide. Gel images were captured using an Eagle eye II Still Video System (Stratagene, La Jolla, CA).

Genotyping of the −308 (G/A) polymorphism in the TNF-A *gene*

The polymorphism at position −308 of the *TNF-A* gene was determined by pyrosequencing. Initially, a PCR was carried out with the primers described by Grove *et al.*[14] with the forward primer biotinylated. The PCR conditions were: 94°C for 5 min and 40 cycles of 94°C, 59°C and 72°C for 1 min each, and a final extension at 72°C for 5 min. For pyrosequencing, biotinylated PCR templates were immobilized on streptavidin-coated paramagnetic Sepharose beads in binding buffer. Samples were incubated for 5 min in constant agitation at 1,400 rpm. After immobilization, the bead-template complexes were submerged in 70% alcohol and 0.5 M NaOH and were washed and the beads were then added to 45 μl of annealing buffer containing 15 pmol of the sequencing primer 5′-GGCTGAACCCCGTCC-3′. Annealing took place at 80°C for 2 min. Real-time pyrosequencing was carried out in an automated 96-well pyrosequencer using PSQ SNP 96 enzymes and substrates (Pyrosequencing AB, Uppsala, Sweden).

Genotyping of the polymorphism in the variable number of tandem repeats of the IL-1RN *gene*

The polymorphic region within intron 2 of the *IL-1RN* gene was amplified using the PCR conditions and primers as previously described (5). The size of the amplified product was determined by electrophoresis on a 2% agarose gel stained with ethidium bromide.

H. pylori *status of the studied population*

The *H. pylori* status of the control population was determined by histology, the Rapid Urease Test (RUT), serology and culture. For the RUT, an antral biopsy was analyzed by a validated non-commercial test.[15] For serology, ELISA was used to study the presence of IgG antibodies to whole cells in patient's serum samples.[16] Culture was carried out on 2 corpus and 2 antrum biopsies by standard methods.[17] Control patients were considered as infected with *H. pylori* when at least 2 of the diagnostic tests were positive. For GC patients, the diagnosis of infection was done only by histology.

Statistical analysis

Hardy-Weinberg equilibrium of alleles at individual loci was assessed by χ^2 statistics. Statistically significant differences were determined by Student's *t*-test, χ^2 or Fisher exact test (two-tailed as dictated by sample size; p-value < 0.05 was considered as statistically significant). Odds ratios (OR) with 95% confidence interval (CI) were computed using the Epi-Info 2000 software (Center for Disease Control and Prevention, Atlanta, Ga.). Two analyses were carried out, one in which all cases and controls were included in the analysis and the other in which the population-based controls were matched by 5-year age group and gender with the cancer cases.

Results

Genotype frequencies

Among controls, the genotype frequencies at the individual loci studied were in Hardy-Weinberg equilibrium, with non-significant χ^2 values. The genotype frequencies for the 3 polymorphisms included in our study are presented for both distal GC cases and controls (Table I).

TABLE I – GENOTYPE FREQUENCIES FOR *IL-1B-31, IL-1RN* AND *TNF-A-308* POLYMORPHISMS[1]

	IL-1B			*IL-1RN*					*TNF-A-308*		
	CC	CT	TT	1,1	1,2	2,2	2,4	1,3	AA	AG	GG
Cases	13 (20.6)	48 (76.2)	2 (3.2)	13 (52)	10 (40)	1 (4)	1 (4)	0	55 (87.3)	8 (12.7)	0
Controls	70 (32.6)	102 (47.4)	43 (20)	82 (40.8)	89 (44.3)	25 (12.4)	4 (2)	1 (0.5)	179 (83.26)	35 (16.3)	1 (0.5)

[1]Values are *n* (%).

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Effect of homozygous proinflammatory genotype on risk of GC

For the *IL-1B-31*, *IL-1RN* and *TNF-308*, the frequency of the homozygous genotypes of the proinflammatory alleles (*IL-1B-31*C*, *IL-1RN*2* and *TNF-308*G*) were compared between distal GC cases and controls, and no statistically significant differences were found (OR = 0.54, 95% CI = 0.26–1.1; OR = 0.29, 95% CI = 0.01–2.19 CI = 0.21–4.48 and OR = 0.0, 95% CI = 0.0–59.87 respectively).

Effect of carriage of a proinflammatory allele on risk of GC

Carriage of a proinflammatory allele, defined by having at least one copy of a proinflammatory allele of *IL-1B-31*C*, *IL-1RN*2* and *TNF-308*G*, is presented for both distal GC cases and controls (Table II).

Carriage of the pro-inflammatory *IL-1B-31*C* allele was associated with increased risk of distal GC (OR = 7.63, 95% CI = 1.73–46.94, $p = 0.003$). After each case was age and gender matched with 2 controls in a 1:2 ratio ($n = 156$), the OR value was even higher (OR = 8.05, 95% CI = 1.8–50.22, $p = 0.001$). In contrast, there were no significant differences in genotype frequencies of the *IL-IRN*, or *TNF-A* genes (OR = 0.65, 95% CI = 0.26–1.61 and OR = 0.72, 95% CI = 0.29–1.74, respectively) between cases and controls. Furthermore, no association was found when cases and controls were matched by age and gender and analyzed for these 2 cytokine polymorphisms.

Haplotype analysis comprising proinflammatory genotypes of *IL-1RN* and *IL-1B* showed no effect on risk of distal GC but the number of samples available for this analysis was small (GC cases, $n = 25$; controls, $n = 201$).

Effect of carriage of a proinflammatory allele on risk of GC in H. pylori *subjects*

Of the 215 controls included in our study, 116 (54%) were *H. pylori*-positive and 45 (38.8%) had the *IL-1B*-31 CC genotype, 47 (40.5%) CT genotype and 24 (20.7%) TT genotype. Of the GC patients studied, 31 (49.2%) were *H. pylori*-positive and 8 (25.8%) were CC, 22 (71%) were CT and 1 (3.2%) was TT. The OR for GC in infected subjects who carry at least one copy of *IL-1B-31*C* was 7.8 (95% CI = 1.05–161.8, $p = 0.04$).

Genotype frequencies for IL-1B-31 *polymorphism in non-GC cancer controls according to clinical presentation or histological findings*

The genotype frequencies for *IL-1B-31*C* polymorphism were studied in the non-GC controls. These controls were classified according to clinical presentation or histological finding as follow: non-ulcer dyspepsia patients (NUD) presenting with histological gastritis only ($n = 185$), patients with NUD and histological findings of intestinal metaplasia ($n = 22$) and patients with peptic ulcer disease (PUD, $n = 8$) (Table III). The genotype frequencies were compared among the different subgroups of the control population and no significant associations with any clinical or histological outcomes were found for any of the genotypes studied (Table III). When we removed the 22 patients with intestinal metaplasia and the 8 patients with ulcer disease from the non-cancer control group and we compared the frequency of the proinflammatory *IL-1B-31*C* allele, the OR for GC was essentially unaltered (OR = 6.4, 95%CI = 1.43–39.75, $p = 0.009$).

TABLE II – GENOTYPE FREQUENCIES FOR PROINFLAMMATORY CYTOKINES FOR BOTH DISTAL GASTRIC CANCER CASES AND CONTROLS[1]

Gene polymorphism	Cases	Controls
*IL-1B-31*C*	61 (98.8)	172 (80)
*IL-1RN*2*	12 (48)	118 (58.7)
TNF-A-308*G*	8 (12.7)	36 (16.7)

[1]Frequencies were determined by the addition of homozygotes and heterozygotes for the specific allele. Values are n (%).

TABLE III – GENOTYPE FREQUENCIES FOR *IL-1B-31* POLYMORPHISM IN NON-GASTRIC CANCER CONTROLS ACCORDING TO CLINICAL PRESENTATION OR HISTOLOGICAL FINDING[1]

Histological finding/clinical presentation	*IL-1B*		
	CC	CT	TT
Gastritis ($n = 185$)	63 (34.1)	90 (48.6)	32 (17.3)
Intestinal metaplasia ($n = 22$)	9 (40.9)	8 (36.4)	5 (22.7)
Peptic ulcer disease ($n = 8$)	3 (37.5)	5 (62.5)	0 (0)

[1]Values are n (%).

Discussion

IL-1 β is a potent proinflammatory cytokine that is also a powerful inhibitor of gastric acid secretion, making it a key player in the response to *H. pylori* infection. Its naturally occurring receptor antagonist, IL-1ra, is also a key mediator in the inflammatory response to infection. TNF-α amplifies the inflammatory response against infections and although not as potent as IL-1β, also inhibits gastric acid secretion.[5,18,19] Some specific polymorphisms of these cytokines are emerging as key determinants of disease outcome to *H. pylori* infection. We investigated the plausible association between distal GC and 3 key cytokine polymorphisms, *IL-1B-31*(C/T), *TNF-A-308* (G/A) and the VNTR polymorphism in the *IL-1RN* gene. The context of our study was a Mexican population, an ethnic group that has hitherto not been assessed with regard to these polymorphisms. We found that carriage of the *IL-1B-31*C* allele represents a significant risk factor (>7-fold) for distal GC. Our study is the first to show that *IL-1B* genetic markers are relevant to gastric cancer pathogenesis in a Hispanic population. The findings are similar to those reported for Caucasian and Asian populations from different countries and add further evidence that IL-1β is a key cytokine in the pathogenesis of *H. pylori*-related gastric cancer. The OR for gastric cancer in our study seem higher than those reported for Caucasians and Asians, but this may simply be a reflection of the smaller sample size of our study.

Most studies, including our current one, have shown that the proinflammatory *IL-1B-31*C* allele is a risk factor for gastric cancer and its precursors in almost all ethnic groups. The *IL-1B-31* locus is in near total linkage disequilibrium with the *IL-1B-511* locus and this has been confirmed in this Hispanic population (data not shown). Thus, our findings in relation to *IL-1B-31*C*, apply equally to the other known proinflammatory marker, *IL-1B-511*T*. Recent work has shown that this allele is associated with increased mucosal levels of IL-1β in *H. pylori* infected subjects.[9] The increased risk of distal gastric cancer reported in these studies is most likely related to the higher production of this important proinflammatory cytokine in *H. pylori* infected subjects.

Some studies from Asia have not confirmed the association between gastric cancer and *IL-1B* markers.[20,21] It is becoming evident, however, that even in these Asian populations, one has to consider the background incidence of the cancer in question. Thus, Zeng *et al.*[22] reported recently that *IL-1B-511T/T* genotype was a significant risk factor for gastric cancer in low incidence areas of China but that the effect of this genotype was less obvious in areas of high incidence. It is also evident that other polymorphisms within the *IL-1B* gene may be more relevant in a particular population than the more established ones such as −31 and −511 loci. Lee *et al.*[23] reported recently that a novel C/G promoter polymorphism at position −1473 of the *IL-1B* gene was associated with increased risk of gastric cancer in a Korean population, whereas the −31 and −511 loci had no effect. Even if there is no evidence of an increased association between these *IL-1B* markers and risk

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of gastric cancer, it has been shown that the same markers increase the risk of premalignant changes in *H. pylori* infected subjects.[24,25]

Another important consideration when studying the role of a particular host genetic marker is whether this genetic marker is being influenced by environmental exposures and whether it is acting in concert with other genetic factors. For example, it is known that the presence of other proinflammatory cytokine gene polymorphisms could enhance significantly the risk of developing GC. Subjects with 3 or 4 proinflammatory polymorphisms have been shown to have a 27-fold increased risk of distal gastric cancer in a Caucasian population based in the United States.[6] Figuereido *et al.*[8] also highlighted the important interaction between host genotype and bacterial virulence factors, adding another dimension to assessing risk of malignancy in the context of *H. pylori* infection.

We did not find any association between risk of GC and the *IL-1RN* genotype in our study. The most obvious explanation for this discrepancy is the fact that only 25 DNA samples from GC cases were suitable for genotyping. Our study was underpowered to address the role of IL-1RN in gastric cancer. The genotyping method used relies on obtaining a relatively large PCR product representing the presence of at least 2 86-bp repeats. The DNA for most of our GC cases came from paraffin embedded tissue sections, which is recognized as having a higher degree of degradation than DNA extracted from peripheral blood leucocytes. For an assay that relies on a PCR product >300 bp, this is a serious handicap but is one that is recognized by most laboratories. Thus, it is difficult to make any conclusions about the role of *IL-1RN* in our population and we shall await other adequately powered studies in Hispanics to answer this question.

TNF-α has been recognized as an important player in both inflammation and cancer development. Several polymorphisms have been associated with a higher production of this cytokine, including the G/A transitions at positions −238 and −308. In our study, only the polymorphism at position −308 was studied because this was shown to be relevant for GC risk in Caucasian populations.[6,11] We did not find any association between this marker and GC risk in our population. This may be due to the fact that this marker is not relevant to GC risk in Hispanics. Indeed, Asian populations have a very low prevalence of the proinflammatory TNF-A-308*A allele, suggesting that in some ethnic groups, this marker has been bypassed as an important polymorphism. Although the frequency of the A allele in our Hispanic population was comparable to Caucasians, there was clearly no association with GC risk. A bigger study may show a different result, but it is unlikely to do so in the absence of even a trend in our study. It remains likely that another marker within the *TNF-A* gene will emerge and will be a more relevant host genetic factor in Hispanics. An example of this is the role of the *TNF-A-1031*, *-863* and *-857* variants, which are observed in a relatively large proportion in Japanese populations and have a more marked influence on risk of several inflammatory conditions.[26]

In summary, our study has confirmed that the proinflammatory *IL-1B-31* genotypes contribute significantly to the risk of GC in a Hispanic population, mirroring the findings in Caucasians and Asians. This underscores the very important role that this cytokine plays in the pathogenesis of *H. pylori*-related gastric cancer. In 1990, GC was the second most frequent cancer in the world with 900,000 new cases diagnosed annually.[27] A steady decline in the incidence rate for this cancer has been observed, mainly in developed countries. However, GC still remains an important public health problem in developing countries.[27] The identification of a host genetic risk profile could help in targeting those populations most at risk. With such a strategy, it would be possible to institute rational screening programs that would be economically feasible. There is a great need for this approach in the developing world.

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