World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.3748/wjg.v20.i16.4503

World J Gastroenterol 2014 April 28; 20(16): 4503-4515
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (8): Gastric cancer

Role of gene polymorphisms in gastric cancer and its precursor lesions: Current knowledge and perspectives in Latin American countries

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Received: October 29, 2013 Revised: January 23, 2014
Accepted: March 12, 2014
Published online: April 28, 2014

Abstract

Latin America shows one of the highest incidence rates of gastric cancer in the world, with variations in mortality rates among nations or even within countries belonging to this region. Gastric cancer is the result of a multifactorial complex process, for which a multistep model of carcinogenesis is currently accepted. Additionally to the infection with *Helicobacter pylori*, that plays a major role, environmental factors as well as genetic susceptibility factors are significant players at different stages in the gastric cancer process. The differences in population origin, demographic structure, socio-economic development, and the impact of globalization lifestyles experienced in Latin America in the last decades, all together offer opportunities for studying in this context the influence of genetic polymorphisms in the susceptibility to gastric cancer. The aim of this article is to discuss current trends on gastric cancer in Latin American countries and to review the available published information about studies of association of gene polymorphisms involved in gastric cancer susceptibility from this region of the world. A total of 40 genes or genomic regions and 69 genetic variants, 58% representing markers involved in inflammatory response, have been used in a number of studies in which predominates a low number of individuals (cases and controls) included. Polymorphisms of *IL-1B* (-511 C/T, 14 studies; -31 T/C, 10 studies) and *IL-1RN* (variable number of tandem repeats, 17 studies) are the most represented ones in the reviewed studies. Other genetic variants recently evaluated in large meta-analyses and associated with gastric cancer risk were also analyzed in a few studies [*e.g.*, prostate stem cell antigen (*PSCA*), *CDH1*, *Survivin*]. Further and better analysis centered in gene polymorphisms linked to other covariates, epidemiological studies and the information provided by meta-analyses and genome-wide association studies should help to improve our understanding of gastric cancer etiology in order to develop appropriate health programs in Latin America.

Key words: Latin America; Gastric cancer; Precancerous lesions; Gene polymorphisms; Single nucleotide polymorphisms

Core tip: This article is a review about the current state of art of studies carried out in Latin America using gene polymorphisms to assess gastric cancer susceptibility. Latin America shows one of the highest incidence rates of gastric cancer in the world, with variations in mortality rates among nations or even within countries belonging to this region. Moreover, Latin America is a region with a particular genetic background, high rates of *Helicobacter pylori* infection and lifestyles condition. This review also gives special emphasis on the importance of the studies conducted in gastric precancerous diseases.

Chiurillo MA. Role of gene polymorphisms in gastric cancer and its precursor lesions: Current knowledge and perspectives in Latin American countries. *World J Gastroenterol* 2014; 20(16): 4503-4515 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i16/4503.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i16.4503

EPIDEMIOLOGY OF GASTRIC CANCER IN LATIN AMERICA

Gastric cancer is one of the most lethal types of cancer, accounting in 2008 for about 800000 deaths, but its incidence varies substantially worldwide[1]. There were approximately 870000 noncardia gastric cancer cases and 74.7% of them have been attributed to *Helicobacter pylori* (*H. pylori*) infection[1]. Although the rates of gastric cancer have been declining over the past 50 years in most Western countries, gastric cancer is still the fourth most common malignancy and the second leading cause of death due to cancer worldwide. The highest incidence (more than two-thirds) of gastric cancer is observed in East Asia, Eastern Europe, and the Andean region of South America, while North America, Northern Europe and North and East Africa show the lowest recorded rates[1].

Latin American countries display some of the highest mortality rates worldwide. For males the estimates age-standardized mortality rates (ASMR) are led by Honduras (25.9%), Ecuador (24.1%), Costa Rica (23.6%), Chile (23.1%) and Guatemala (22.3%), while for women the highest rates are found in Guatemala (22.0%), Honduras (19.0%), Ecuador (17.5%), Peru (17.1%) and Costa Rica (10.6%). In contrast, lower ASMR are observed for both sexes in Puerto Rico, Cuba, Dominican Republic, Mexico and Argentina[1,2].

Significant variations in the incidence of gastric cancer have been observed between different ethnic groups living in the same region; for example, African-Americans, Hispanics and Native Americans are affected more than Caucasians in the United States[3]. Moreover, in a comparison between Japanese migrants to the United States and Brazil, Japanese migrants to the United States show a significantly lower incidence rate than Japanese living in Japan, while Japanese migrants to Brazil show a similar rate to the latter group, suggesting that the geographical distribution of gastric cancer may not be solely attributable to ethnic differences[4].

Recently, Torres *et al*[5], with the apparent association between altitude and the incidence of gastric cancer in the countries of Western Latin America along the Pacific Rim, proposed that the altitude may be a surrogate for the clustering of host, bacterial, dietary, and environmental factors related to gastric cancer risk. The relation appears to be strongest in the mountainous regions of Central America and Andean South America, but it is absent in Chile, where risk is more strongly associated with the age of *H. pylori* acquisition and socio-economic determinants. Among possible explanations for this association could be that the host genetic background, as well as *H. pylori* genotypes, may cluster more readily in certain isolated mountainous communities[5].

CARCINOGENESIS: MULTISTEP MODEL

It has been proposed a multistep cascade model for the development of intestinal-type gastric adenocarcinoma, which consists of a progression from chronic superficial (non atrophic) gastritis, to chronic atrophic gastritis to intestinal metaplasia, and finally, gastric adenocarcinoma[6]. This model hypothesizes the sequence of precancerous lesions as a dynamic process from an initial superficial inflammation caused by *H. pylori* infection to a fully malignant neoplasm of the stomach. Thus, the chronic infection of the gastric mucosa by the *H. pylori* is a major attributable risk factor of gastric cancer[7].

More than 50% of the population worldwide is infected with *H. pylori* with a higher prevalence in developing countries and in groups with poor socio-economic conditions. The improvements in living conditions in developed countries has determined a declining in the prevalence of infection, while remaining high, about 80%, in the developing world. In Latin American countries it has been reported a prevalence of *H. pylori* infection ranging from 70% to 90%[8]. However, less than 2% of *H. pylori* carriers develop gastric cancer[9]. Moreover, the incidence of gastric cancer in areas of Africa and South Asia with high prevalence of *H. pylori* infections is much lower than in other countries[10].

Consistent with the multifactorial pathogenesis, the observed differences in the clinical outcomes and gastric cancer prevalence worldwide may be due to environmental factors (mainly diet, smoking and alcohol use) often playing a dominant role. Moreover, the influence of host factors, especially those governing the severity of the immune response, is also relevant.

GENE POLYMORPHISMS, GASTRIC CANCER AND ETHNICITY

The identification and discrimination of host genetic variants influencing susceptibility in populations with high incidence of gastric cancer has been a major challenge. These genetic variants may modulate the effects of exposure to environmental factors by regulating multiple biological pathways during gastric carcinogenesis.

Common susceptibility genetic variants have been identified as significantly associated with gastric cancer risk by candidate-gene studies, such as inflammatory [interleukin (IL)-1β, IL-8 and tumor necrosis factor-α (TNF-α)] and anti-inflammatory cytokines (IL-10), DNA repair genes and metabolic enzymes (such as the glutathione S-transferase family, cytochrome P450 superfamily, and metabolism of folate and arachidonic acid)[11-20].

Moreover, recent genome-wide and large scale gene association studies have focused on analyzing regions of

the genome in which have been detected candidate genes involved in cell proliferation, differentiation, and survival, such as *MUC1*[21], *PLCE1*[22], *PTGER4*, *PRKAA1*, *ZBTB20*[23,24], prostate stem cell antigen (*PSCA*)[25,26], genes participating in EGFR and FAS-mediated signaling pathway[27,28] and DNA repair pathways[29]. Chromosome 9p21.3 and 10q23 regions have been identified as genetic susceptibility loci for multiple disease phenotypes including gastric cancer[22,30].

The current understanding of host genetic polymorphisms and gastric cancer susceptibility is based largely on studies in Asians and Caucasians (from Europe and North America) populations. Moreover, ethnicity has been proposed as a factor modifying the risk of cancer[2].

The present-day population of Latin American countries is historically and anthropologically admixed, as the result of a mixing process between Native Americans, Europeans (mostly Spaniards, Portuguese and Italians) and Sub-Saharan Africans (mainly from Western Africa), whom came into contact for five centuries[31]. The populations of Latin America experienced different admixture processes with varying degrees of ancestral population proportions that came in different migration waves[32,33]. Therefore, in studies of genetic association to diseases, the addition of a population structure estimate could be very effective to identify and correct possible effects of the population substructure.

Genetic admixture studies have recently helped to identify variants associated with prostate and oral cancer in African-American and Hispanics populations, respectively[34,35]. A similar approach was applied recently by Pereira *et al*[36] using a panel of 103 ancestry informative markers (AIM) to test if individual Native American, European and African ancestries are risk factors for gastric cancer in an urban admixed sample in Peru. This work determined that Native American individual ancestry is associated with gastric cancer, but this was explained by the association of socioeconomic variables with both gastric cancer and Native American ancestry. Therefore, indicating that the high incidence of gastric cancer in the Peruvian population, with a very high Native American ancestry, does not seem to rely on a genetic basis. More recently, a study carried out in the Northern region of Brazil examined the effect of population substructure, by the analysis of a panel with 48 AIMs, on the association between five single nucleotide polymorphisms (SNP) of N-acetyltransferase 2 (*NAT2*) gene and the susceptibility to breast and gastric cancer[37]. They detected a higher African contribution in the study group with cancer, and a significant association of *NAT2* 282*T allele carriers with gastric cancer.

GASTRIC CANCER AND GENETIC VARIANTS IN LATIN AMERICAN COUNTRIES

The present overview included studies carried out on humans that were found in the databases of PubMed/MEDLINE, LILACS and SciELO, published up to 25 October 2013 and with no restriction regarding language. This review includes the analysis of 61 articles reporting studies of association between genetic variants and the risk of gastric cancer and/or known precancerous lesions. All studies correspond to case-control comparisons, including healthy, non-cancer (counting precancerous lesions), asymptomatic and population-based controls[12,37-96].

All reviewed studies were conducted with Latin American populations: Brazil (22), Chile (1), Colombia (6), Costa Rica (7), Honduras (1), Mexico (16), Peru (1) and Venezuela (7). Two-thirds of the articles considered the detection of *H. pylori* infection by urease test, culture, histology, serology or polymerase chain reaction (PCR). Some studies also included the typing of genetics variants of bacterial virulence factors by molecular methods. Regarding host genetic variants, studies evaluated 69 polymorphisms from 40 genes or genomic regions, including 2 microsatellites or variable number of tandem repeat (VNTR), 2 gene deletions, 3 insertion/deletions and 62 nucleotide substitutions (21 of them in protein coding regions, resulting in 3 synonymous and 18 nonsynonymous substitutions). Figure 1 shows a summary of gene polymorphisms included in the Latin American studies classified by functional categories: inflammatory response, mucosal protection, metabolic enzymes and transporters, oxidative damage, cellular adhesion, DNA repair, oncogene/tumor suppressor/stability genes, apoptosis.

Techniques used for detecting gene polymorphisms were dot blot hybridization, sequencing, conventional polymerase chain reaction (PCR), PCR-restriction fragment length polymorphism, PCR-single-strand conformation polymorphism, real-time PCR with fluorescent probes, PCR-sequence specific oligonucleotide probe, PCR-Sequence-Specific Primer, Amplification-refractory mutation system-PCR, and KASPar™ SNP genotyping system.

The largest number of studies investigating the association between gene polymorphisms and gastric cancer (and premalignant lesions) risk in different countries of the region includes the evaluation of interleukin-1 family variants: *IL-1B* (*IL-1B*-511 C/T, 14 studies -31 T/C, 10 studies, +3954, 8 studies) and *IL-1RN* (VNTR, 17 studies). Table 1 shows the main characteristics of these studies.

Genetic variants in inflammation-related genes, especially cytokines and their receptors are thought to influence the first stage of the precancerous cascade and are related to a more intense inflammatory response after gastritis associated to *H. pylori* infection[7]. The inflammatory-related genes that have been most frequently studied in relation to gastric cancer, sometimes with conflicting results, are the interleukin genes *IL-1B*, *IL-1RN*, *IL-8* and *IL-10*. SNPs within these and other functional cytokine regions that markedly influence expression and secretion profiles may modify the intensity of the inflammatory re-

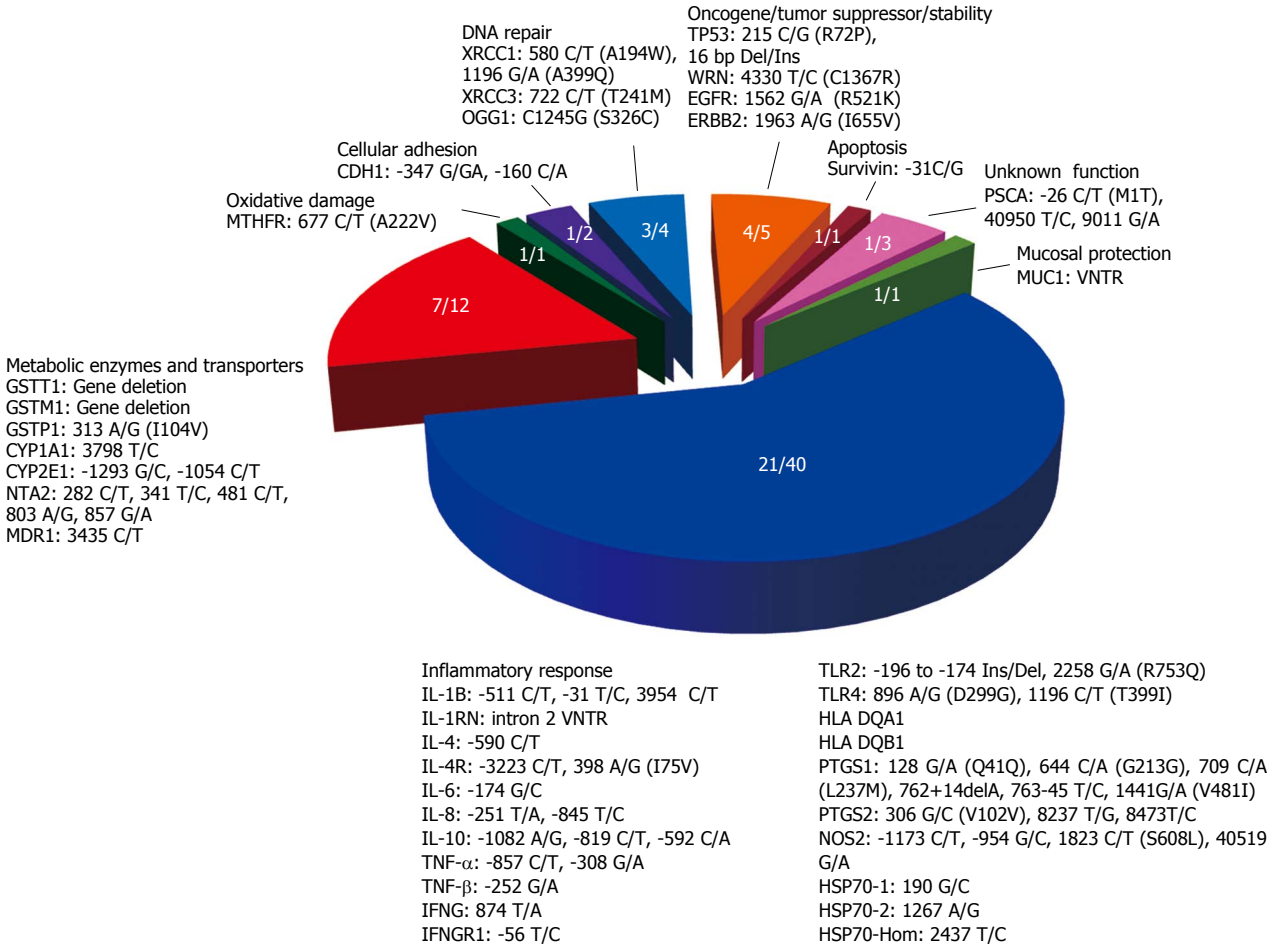

Figure 1 Graphic summary of gene polymorphisms included in the Latin American studies classified by functional categories. The fractions in each section of the cake indicated total number of genes/number of polymorphisms examined in each group[12,37-96].

sponse to infectious agents, thereby contributing to variations in gastric cancer risk[97].

Since the first study of El-Omar *et al*[98] in 2000, a significant number of studies have evaluated the association between genetic variations in the *IL-1* gene cluster (*IL-1B*-511 C/T, *IL-1B*-31 T/C, *IL-1B*+3954 C/T and *IL-1RN* intron 2 VNTR) and gastric cancer. This association (significantly with noncardia or with intestinal type of gastric cancer) has a fundamental principle: alleles *IL-1B*-31*C, -511*T, and *IL-1RN**2, lead to high-level expression of IL-1β, reduction of acid output, corpus-predominant colonization by *H. pylori*, pangastritis and atrophic gastritis, which are considered precursors as well as risk factors for gastric cancer[98]. Furthermore, *H. pylori* infection induces IL-1β production, and the consequent hypochlorydria favors further colonization by pH-sensitive *H. pylori*[99]. In addition, global meta-analyses have suggested race-specific associations of some cytokine variants in Caucasian and Asian populations[97,100-104].

A recent meta-analysis, showed that the profile of *IL-1B* risk alleles in Latin Americans mirrors that found in Asian populations with low or no associations with gastric cancer[105]. For example, in a high-incidence region of gastric cancer in Honduras, a sample of healthy (population-based) controls of Hispanic mestizo origin, had the *IL-1B*-511*T$^+$ and *IL-10*-1082*A$^+$ genotypes prevalence among the highest reported[45].

The meta-analysis of Xue *et al*[103] showed that *IL-1B*-511*T and *IL-1RN**2 alleles were significantly associated with an increased risk of developing gastric carcinoma among Caucasians, but not in Asians or Hispanics. On the other hand, in the case-controls comparisons carried out in 2013 by Bonequi *et al*[105], in which were analyzed studies from Brazil, Colombia, Costa Rica, Honduras, Mexico, Peru and Venezuela, it was identified the *IL-1RN**2 allele associated with a moderate increased risk for gastric cancer (overall OR = 1.51, 95%CI: 1.15-1.99), supporting its involvement in gastric carcinogenesis as has been previously reported in non-Asian populations[104].

Among pro-inflammatory cytokines, IL-8 acts as a potent chemoattractant and activator of neutrophils that may play a role in gastric cancer pathogenesis[14,106]. *IL-8* exhibits several functional polymorphisms, among them the *IL-8* -251 A/T SNP in the promoter region is associated with an increase in synthesis of that interleukin by gastric epithelial cells[14,106].

A study conducted in Mexico showed that the *IL-8* -251*A allele is a risk factor for the development of noncardia gastric cancer[60]. Similarly, Vinagre *et al*[95] observed

Table 1 Association studies of *interleukin -1* gene cluster and gastric cancer/precancerous lesions

Year	Study population	Number of populations	Target genes and variants	Main findings associated with increased susceptibility
2004	Brazil Gatti *et al*[70]	56 GC; 56 ChrG	*IL-1B*-511C/T; -31T/C *IL-1RN* intron 2 VNTR	There was no association
2005	Costa Rica Alpizar-Alpizar *et al*[40]	58 GC; 41 nonneoplastic lesions; 58 cancer free patients; 41 healthy controls	*IL-1B*-511C/T; -31T/C; +3954C/T *IL-10*-1082G/A; -819C/T; -592C/A *IL-1RN* intron 2 VNTR	Carriers of the *IL-1B*+3954*T alle had an increased risk for developing GC (OR = 3.7[2], 95%CI: 1.34-10.2). *IL-1RN* heterozygote genotype (*2/*L) was associated with GC (OR = 2.94[2], 95%CI: 1.09-7.93).
2005	Mexico Garza-González *et al*[12]	63 distal GC; 215 non-cancer lesions	IL-1B-31T/C *IL-1RN* intron 2 VNTR *TNF-α*-308G/A	Presence of *IL-1B*-31*C allele was associated with increased risk of distal GC (OR = 7.63[1], 95%CI: 1.73-46.94)
2005	Brazil Rocha *et al*[73]	168 GC *H. pylori* +; 541 asymptomatic controls	*IL-1B*-511C/T; -31T/C *IL-1RN* intron 2 VNTR *TNF-α*-308G/A	*IL-1RN**2 was associated with noncardia GC (OR = 1.93, 95%CI: 1.06-3.49)
2006	Mexico Sicinschi *et al*[58]	183 GC; 377 controls	*IL-1B*-31T/C; +3954 C/T *IL-10*-592C/A *IL-1RN* intron 2 VNTR	*IL-10*-592*C allele carrier was associated with intestinal-type of GC (OR = 2.08[1], 95%CI: 1.07-4.05). Subjects with *IL-1B*-31 CC genotype and *H. pylori* CagA positive serology had an increased risk of intestinal-type GC (OR = 3.19[2], 95%CI: 1.05-9.68)
2006	Honduras Morgan *et al*[45]	170 GC; 162 healthy controls	*IL-1B*-511C/T *IL-10*-1082G/A *IL-1RN* intron 2 VNTR *TNF-α*-308 G/A	*IL-1B*-511 TT + *IL-10*-1082 AA combination increased risk of GC (OR = 2.6, 95%CI: 1.0-6.8)
2007	Costa Rica Con *et al*[43]	58 AG; 31 corpus AG; 23 IM	*IL-1B*-511C/T; +3954C/T *IL-10*-1082G/A; -592C/A *IL-1RN* intron 2 VNTR	*IL-1B*+3954*T carrier and *IL-1RN* homozygous *2 allele were associated with IM (OR = 3.4[1], 95%CI: 1.2-10.00 and OR = 3.1[2], 95%CI: 1.1-9.00, respectively)
2008	Costa Rica Sierra *et al*[42]	25 ABG; 76 AAG; 253 NAG; 21 Normal mucosa; 21 healthy controls	*IL-1B*+3954C/T *IL-1RN* intron 2 VNTR	No association was found
2009	Peru Gehmert *et al*[46]	133 GC *vs* 133 NAG 86 NAG *vs* 43 ChrAG	*IL-1B*-511C/T *IL-1RN* intron 2 VNTR	*IL-1B*-511*C allele carrier and CT and CC genotypes were associated with AG (OR = 5.6[1], 95%CI: 2.02-15.51; OR = 4.8[2], 95%CI: 1.65-13.83; OR = 11.2[2], 95%CI: 2.27-55.37, respectively) and GC (OR = 2.36[1], 95%CI: 1.34-4.11; OR = 2.17[2], 95%CI: 1.23-3.84; OR = 4.15[2], 95%CI: 1.33-12.93, respectively)
2009	Brazil Melo Barbosa *et al*[74]	177 gastric benign pathologies; 100 asymptomatic controls	*IL-1B*-511C/T; -31T/C *IL-1RN* intron 2 VNTR *TNF-α*-308 G/A	Carriers of *IL-1RN**2 allele with *H. pylori* CagA-positive serology had a greater risk of developing GU (OR = 8.82, 95%CI: 1.762-44.181) and GC (OR = 16.76, 95%CI: 1.99-140.71)
2009	Costa Rica Con *et al*[44]	52 GC; 191 non-cancer *H. pylori* positive patients	*IL-1B*-511C/T; +3954C/T *IL-10*-1082G/A; -592C/A *IL-1RN* intron 2 VNTR	*IL-1B*+3954 TC (OR = 2.1[2], 95%CI: 1.0-4.3), *IL-1RN* *2/*L (OR = 3.5[2], 95%CI: 1.7-7.3), *IL-10*-592 AA (OR = 3.1[2], 95%CI: 1.2-8.2) and *IL-10*-592 CA (OR = 3.2[2], 95%CI: 1.5-6.8) genotypes, as well the *IL-1B*+3954 TC, *IL-1RN* *2/*L, *IL-10*-592 CA (OR = 4.7, 95%CI: 1.7-13.0) combination were associated with GC
2009	Venezuela Cañas *et al*[84]	84 GC; 84 ChrG	*IL-1B*-511T/C; +3954C/T *IL-10*-592C/A *IL-1RN* intron 2 VNTR	*IL-1B*+3954*C carrier and *IL-IRN* *2/*2 genotype were associated with GC (OR = 6.2[1], 95%CI: 1.3-28.8 and OR = 7.0[2], 95%CI: 2.3-21.5, respectively). The *IL-IRN* *2/*2 genotype was also associated with a well/moderately-differentiated adenocarcinoma (OR = 8.1[2], 95%CI: 2.5-26.8)
2010	Mexico Martínez-Carrillo *et al*[56]	100 ChrG; 28 GU 102 healthy controls	*IL-1B*-511C/T; -31T/C	The *IL-1B*-511 TC genotype and the -511*C allele were associated with ChrG (OR = 3.1[2], 95%CI: 1.4-6.8 and OR = 3.0[1], 95%CI: 1.4-6.3, respectively). The subjects carrying -31*T were found to be at a higher risk of having ChrG (OR = 2.8[1], 95%CI: 1.3-5.8). The *IL-1B*-511*C/-31*T haplotype was associated with ChrG (OR = 2.1, 95%CI: 1.2-3.8).
2010	Venezuela Chiurillo *et al*[85]	109 ChrG	*IL-1B*-511C/T; -31T/C; +3954C/T *IL-1RN* intron 2 VNTR	Carriage of *IL-1B*-511*T (OR = 5.4, 95%CI: 1.9–15.8) and -31*C (OR = 5.1, 95%CI: 1.8–14.7) alleles combined with iceA2+ *H. pylori* genotype increased the risk of ChrAG with severe histopathological changes.
2011	Colombia Martínez *et al*[88]	46 GC; 99 NAG	*IL-1B*-511C/T *IL-1RN* intron 2 VNTR	*IL-1B*-511 TT carriers had increased risk of GC (OR = 11.31[2], 95%CI: 1.20-106.54)
2011	Colombia Martínez *et al*[91]	58 GC; 89 DU (54 with precancerous lesions); 194 ChrG and normals	*IL-1B*-511C/T *IL-1RN* intron 2 VNTR *IL-10*-1082G/A; -819C/T; *TNF-α*-308G/A	Genotype *IL-1B*-511 TT was associated with GC (OR = 4.69[2], 95%CI: 1.22-18.09)

2011	Venezuela Chiurillo *et al*[86]	121 ChrG	*IL-1B*-511C/T; -31T/C; +3954C/T	There was association with severe histological changes only considering *H. pylori* genotypes
2012	Mexico López-Carrillo *et al*[57]	158 GC; 317 clinical controls	*IL-1B*-31T/C	*IL-1B*-31*C allele carriers who were both *H. pylori* CagA positive and with moderate to high Capsaicin consumption had increased risk of GC (OR = 3.41[1], 95%CI: 1.12-10.43)
2013	Brazil Mattar *et al*[94]	19 GC; 71 clinical controls; 196 inflammation of the upper gastrointestinal tract; 28 GU; 76 DU	*IL-1RN* intron 2 VNTR	The carriage of *IL-1RN* *2/*2 was an independent risk factor for GC (OR = 5.81, 95%CI: 1.06-31.98). The carriage of allele *2 had an independent protective effect on DU (OR = 0.45, 95%CI: 0.22-0.91)
2013	Brazil de Oliveira *et al*[79]	200 GC; 229 ChrG; 240 healthy individuals	*IL-1RN* intron 2 VNTR *TNF-α*-857C/T *TNF-α*-308G/A *TNF-β*-252G/A *IL-8*-251T/A *IL-8*-845T/C *IL-10*-592C/A TLR2–196 to –174 Ins/Del TLR4+896A/G (D299G); +1196C/T (T399I)	Association with GC was observed for *IL-1RN**2 (OR = 2.60[1], 95%CI: 1.65-4.10), *TNF-α* -857*T (OR = 1.70[1], 95%CI: 1.08-2.67), IL-8-845*C (OR = 3.46[1], 95 % CI: 1.69-7.07), *IL-10*-592*A (OR = 2.34[1], 95%CI: 1.47-3.70), TLR2 –196 to –174 *Del (OR = 2.20[1], 95%CI: 1.28-3.78) and TLR4+896*G (OR = 2.09[1], 95 % CI: 1.08-4.02) alleles. Association with ChrG was observed with *IL-1RN**2 (OR = 1.88[1], 95%CI: 1.25-2.83) and *IL-10*-592*A (OR = 3.00[1], 95%CI: 1.99-4.50) alleles

[1]Dominant; [2]Co-dominant. *H. pylori*: *Helicobacter pylori*; GC: Gastric cancer; ChrG: Chronic gastritis; ChrAG: Chronic atrophic gastritis; DU: Duodenal ulcer; NAG: Non-atrophic gastritis; GU: Gastric ulcer; AAG: Atrophic antral gastritis; ABG: Atrophic body gastritis; IM: Intestinal metaplasia.

that the AA (P = 0.026) and AT (P = 0.005) genotypes were most frequent in the group of patients with gastric adenocarcinoma from the state of Pará, Brazil. Furthermore, they also found the *IL-8* -251*A allele associated with the risk for developing gastric cancer. On the contrary, also in Brazil but in the state of São Paulo, Felipe *et al*[96] found the *IL-8* -251 AT genotype and *T carriers associated with an increased risk of gastric cancer. These authors also observed that individuals with AA genotype may have protective effect for gastric cancer, while patients harboring the TT genotype presented a lower median survival time. Whereas Garcia de Oliveira *et al*[79], in another region of the state of São Paulo, found only the *IL-8* -845 T/C SNP (P < 0.001) associated with risk for gastric cancer.

These results could suggest that the association between *IL-8* -251 A/T polymorphism and gastric cancer is likely influenced by environmental factors, and even ethnicity, considering that the geographical conditions and the proportion of the genetic ancestral contributions differ between the northern and southeast regions of Brazil[107,108]. Moreover, a recent meta-analysis suggest the potential influence of ethnicity in the association of *IL-8* -251 A/T polymorphism with gastric cancer, since it is generally stronger in Asian than in Caucasian population[109].

There are three functional promoter SNPs in the *IL-10* locus: -1082 A/G, -819 C/T and -592 C/A. In this locus only the -592 C/A SNP was found associated with gastric cancer in Latin American studies. Con *et al*[44] in Costa Rica and Garcia de Oliveira *et al* in Brazil[79] found that *IL-10*-592 AA and CA genotypes were individually associated with gastric cancer. Contrary, Sicinschi *et al*[58] in Mexico identified the *IL-10*-592 CC genotype associated with more than double of the risk of the intestinal-type gastric cancer. A recent meta-analysis based on 12 previous studies concluded that the *IL-10*-592 C/A polymorphism was not a risk factor for gastric cancer. However, when stratifying the data by race, the *IL-10*-592 AA genotype was found to be a protective factor against the development of this neoplasm in Asians but not among Caucasians and Latinos[110].

Toll-like receptors (TLR2 and TLR4), involved in *H. pylori* recognition in gastric mucosa, also have polymorphic variants that modulate their functional pattern[111]. Hence, some reports have studied SNPs in *TLRs* that are associated with impaired immune response and induction of a potent inflammatory response in the gastric mucosa, being then associated with susceptibility of gastric diseases. In Mexico two studies evaluated the association of *TLR4* +896A/G and +1196C/T SNPs with gastric cancer and precancerous diseases[60,93]. Although no association with gastric cancer was found in these studies, Trejo-de la *et al*[93], including also analysis of *TLR2* +2258 G/A SNP, showed that patients with *TLR4* polymorphisms expressed significantly lower levels of IL-1β, IL-6, IL-8 and GRO-α; and higher levels of TNF-α, IL-10, MCP-1 and MIP-1α. Moreover, Silva´s research group in two recent reports investigated *TLR2* -196 to -174 del, *TLR4* +896A/G and *TLR4* +1196C/T polymorphisms at risk of chronic gastritis and gastric cancer in a Brazilian population in the state of São Paulo[78,79]. In both studies *TLR2* -196 to -174*del and *TLR4* +896*G alleles showed an association with increased risk for gastric cancer.

The study of Garcia de Oliveira *et al*[79] mentioned above evaluated ten inflammatory-related gene polymorphisms in 669 samples (200 of gastric cancer, 229 of chronic gastritis, and 240 of healthy individuals), of which *IL-1RN* L/2 (P < 0.001), *TNF*-α-857 C/T (P = 0.022), *IL-8*-845 T/C (P < 0.001), *IL-10*-592 C/A (P < 0.001), *TLR2* ins/del (P < 0.001), and *TLR4*+896 A/G (P = 0.033) polymorphisms were observed associated with

the risk of gastric cancer using a dominant model. In addition, a combined analysis of these six polymorphisms revealed a profile with two to four combined genotypes, which confers a higher risk of gastric carcinogenesis.

Regarding polymorphisms in inflammation-related genes, three genes encoding heat shock proteins (HSP) were also evaluated in two studies. Partida-Rodríguez *et al*[61] studied *HSP70-1*+190 G/C, *HSP70-2*+1267 A/G and *HSP70-Hom*+2437 T/C SNPs in 447 Mexican patients, including 228 with non-atrophic gastritis, 98 with intestinal metaplasia, 63 with gastric cancer, 58 with duodenal ulcer, and 132 asymptomatic individuals. They also evaluated in this analysis the *TNF*-α-308 G/A and *TNF*-β-252 G/A polymorphisms. Compared with the asymptomatic group, they found significant association of *TNF*-β-252*A and *HSP70-1**C alleles with gastric cancer. More recently, Ferrer-Ferrer *et al*[41] in 2013 addressed the possible association between *HSP70-2*+1267 A/G and *HSP70-Hom*+2437 T/C polymorphisms and the risk of developing gastric cancer in a high-risk population in Costa Rica. These authors found that the GA genotype of *HSP70-2*+1267 was associated with increased risk of gastric cancer as compared to the GG genotype.

With regard to tumor-suppressor genes, seven studies conducted the analysis of the *TP53* Arg72Pro polymorphism related to the risk of gastric cancer. In Mexican patients, Pérez-Pérez *et al*[55] identified association of the Arg/Arg genotype with the increased risk of distal gastric cancer. Similarly, in Venezuela, individuals carrying the Arg allele had an elevated risk of developing gastric cancer, while the Arg/Arg genotype was associated with poor-differentiated gastric cancer[83]. However, the association of gastric cancer with *TP53* Arg72Pro polymorphism in Latin American countries was not consistent in the meta-analysis of Bonequi *et al*[105]. Differences in distribution of *TP53* Arg72Pro genotypes could be associated with the location, stage, and histological differentiation of gastric cancer. Moreover, a meta-analysis suggests that the *TP53* codon 72 polymorphism (Pro allele) may be associated with gastric cancer, particularly among Asians[112].

A Brazilian case-control study evaluated the effect of a functional SNP (-31C/G) of *Survivin*, which is involved in the regulation of apoptosis and cell cycle control[75]. Although this study included a small sample size, results suggest that the presence of the *C allele of *Survivin* gene promoter -31 C/G polymorphism in combination with D17S250 microsatellite instability (a marker of *TP53* gene) may be used as risk factor for gastric cancer in this population. Involvement in gastric carcinogenesis of Survivin can be taken from the observation that overexpression of this protein in gastric cells reduces cell death after infection with *H. pylori*[113].

The *CDH1* gene, encoding E-cadherin protein, is now established as a tumor suppressor in gastric cancer[114]. Polymorphisms at positions -347 G/GA and -160 C/A reduce the transcriptional activity of *CDH1*, although their association with susceptibility to gastric cancer is controversial[115,116]. Medina-Franco *et al*[62] analyzed a sample of 39 Mexican patients younger than 45 years old with diagnosis of diffuse gastric cancer and observed association with -160 CA and AA genotypes. Moreover, Borges *et al*[69] observed in Brazilian patients carrying *CDH1* -160*A and -347*GA alleles an increased probability of developing gastric cancer, especially of the diffuse-type.

SNPs in the *PSCA* gene was found associated with gastric cancer risk in a Genome-wide association study (GWAS), and subsequently validated in other Asian and Caucasian populations[26,117,118]. Although its function remains unknown, the expression of *PSCA* has been observed downregulated in the gastric tissue with intestinal metaplasia[119]. Rizatto *et al*[82] analyzed 3 SNPs in the *PSCA* gene (rs2294008 C/T, rs9297976 T/C and rs12155758 G/A) in gastric biopsies of 2045 subjects with gastric precancerous lesions and 180 cases of gastric cancer from a high-risk region of Western Venezuela. In this study the *T and *A alleles of rs2294008 and rs12155758, respectively, were found to be associated with gastric cancer.

GENE POLYMORPHISMS AND GASTRIC PRECANCEROUS LESIONS

The role of gene polymorphisms in precancerous lesions remains poorly understood, even for those that have been identified as associated with increased risk of gastric cancer. Identification of biomarkers of the precancerous process is needed for development of screening programs to prevent gastric cancer, as this may contribute to the understanding of gastric carcinogenesis.

Association between cytokine gene polymorphisms and gastric precancerous lesions were identified in a work carried out in Costa Rica by Con *et al*[43], in which the *IL-1B*+3954*T and *IL-1RN* *2/*2 genotypes were associated with intestinal metaplasia. Whereas in Peruvians, Gehmert *et al*[46] revealed an increased risk of atrophic gastritis associated with *IL-1B*-511*C allele. A Brazilian study in the state of São Paulo demonstrated the existence of an association of the anti-inflammatory cytokine variant alleles *IL-1RN**2 and *IL-10*-592*A with a higher risk of developing gastric cancer and chronic gastritis[79]. In a recent meta-analysis Peleteiro *et al*[120] showed an association of the *IL-1RN* *2/*2 genotype with the increased risk of gastric precancerous lesions, supporting a role for this polymorphism in the early stages of gastric carcinogenesis.

In the context of *H. pylori* infection, two studies of our group in Venezuela showed an association of chronic atrophic gastritis and severe histopathological changes with *IL-1B*-511*T, -31*C, +3954*C and *IL-1RN**2 polymorphisms only in presence of specific bacterial virulence genotypes[85,86]. Similarly, Melo-Barbosa *et al*[74] in Brazil, found that carriers of *IL-1RN**2 allele with *H. pylori* CagA-positive serology had a higher risk of developing gastric ulcer.

A research group have evaluated the prevalence of

gastric precancerous lesions in a large number of Venezuelans in relation with several genetic polymorphisms, most of them mediators of inflammation, and their interactions with other environmental factors. The first of them, by Kato *et al*[81], studied *IL-10*, *IL-4* and *IL-4R* SNPs in 2033 patients. Authors identified the *IL-10*-1082*A low activity allele associated with intestinal metaplasia and dysplasia, while homozygous of the low activity allele (GG) of the 398 A/G polymorphism in the *IL-4R* gene had a modest increase in the risk of atrophic gastritis.

This group of researchers also evaluated genetic polymorphisms in other mediators of inflammation: *IFNG*, *IFNGR1*, *NOS2A*, *PTGS1*, *PTGS2*[87]. A nonsynonymous substitution Ser608Leu of *NOS2A* gene (*A carriers) and the -56 C/T SNP located in the promoter of *IFNGR1* (CC genotype) were associated with higher risk of atrophic gastritis. Additionally, two SNPs of *PTGS2* were associated with risk of dysplasia (306 G/C -Val102Val- and 8473 T/C). More recently, in a further study of this group, the *T allele of the functional SNP rs2294008 in the *PSCA* gene was associated with atrophic gastritis and intestinal metaplasia[82].

SNPs of *HSP70-1* (+190*C allele) and *HSP70-2* (+1267 GA genotype) were associated with an increased risk of duodenal ulcer in patients of Mexico and Costa Rica, respectively[41,61]. Moreover, examination of *TLR4* +896A/G SNP in a Southeastern Brazilian population showed that the heterozygous AG genotype and allele *G frequencies were significantly higher in chronic gastritis and gastric cancer groups than in controls[78].

CONCLUSION

Latin America is a territorial and cultural entity with a particular genetic complexity, but also characterized by wide socio-economic divergences and rapid changes in life styles throughout the continent with a strong trend towards urbanization of its population. Therefore, the study of the etiology of multifactorial diseases, such as gastric cancer, in this region appears to be a major challenge, but also an opportunity.

Given in Latin America the common scenario of a population with high rates of infection with *H. pylori*, persistent poverty, particular dietary habits, coupled with secular trends in environmental exposures and lifestyle, genetic can offer a useful tool to compare populations and assess gene-environment interactions that underline gastric cancer development.

Most studies here analyzed were conducted with samples from populations with high prevalence of *H. pylori* infection. Therefore, it is not surprising that most research in this region of the world have been carried out with gene variants involved in inducing a more intense inflammatory response after gastritis associated to *H. pylori* infection. Moreover, as has been raised in Asians, due to the distribution of *IL-1B* high-risk alleles in some Latin American populations shows an elevated prevalence, could be suggested that they do not influence gastric cancer susceptibility in these populations, or in any case, its effect cannot be demonstrated.

Some research groups have been investigating the genetic contribution to gastric cancer in subjects of different ethnic backgrounds (mainly in Asians and Caucasians from United States and Europe), using previous GWASs information or conducting parallel GWASs with a large number of genes and new candidate loci for gastric cancer, as well as employing innovative techniques for genotyping and statistical analysis[22,27-30]. Therefore, to the analysis of human genetic risk factors in our populations, it would be appropriate to exploit and replicate GWASs findings, since a simple extrapolation of results from these studies to the use of biomarkers in Latin American populations is not completely adequate.

Genetic studies in admixed populations are particularly susceptible to confusion due to population stratification resulting from the difference in ancestry between cases and controls. However, such confounding can be handled by estimating individuals' genetic ancestry using AIMs and then adjusting the analysis for individual ancestry. If in this region the human genetic background influences the high incidence of gastric cancer then can be expected that genetic variants harbored in admixed population account for this high incidence. Therefore, it would be possible to apply the genome-wide strategy of admixture mapping to detect these variants.

Finally, it is necessary to advocate for multicenter studies involving several Latin American research groups and large number of samples for the analysis of genetic polymorphisms in relation to precancerous lesions and environmental variables (lifestyle, dietary habits, *H. pylori* infection), in order to contribute to the understanding of gastric carcinogenesis and for the development of screening programs to prevent gastric cancer.

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P- Reviewers: Chung YJ, Xuei X, Yuzhalin A **S- Editor**: Zhai HH
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ISSN 1007-9327