Effect of IL-1β and IL-1RN polymorphisms in carcinogenesis of the gastric mucosa in patients infected with Helicobacter pylori in Algeria

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Background: Infection with Helicobacter pylori is considered a potential risk of developing gastric cancer in association with contributing host genetic factor. IL-1β and IL-1RN polymorphisms appear to maintain and promote Helicobacter pylori infection and to stimulate neoplastic growth of the gastric mucosa.

Objective and methods: In order to elucidate the effect of these polymorphisms in combination with gastric cancer in a population from northwestern Algeria, a case-control study was carried out on 79 patients infected with H. pylori with chronic atrophic gastritis and/or gastric carcinoma, and 32 subjects were recruited as case-control. IL-1β-31 bi-allelic and IL-1β-511 bi-allelic polymorphisms and IL-1RN penta-allelic were genotyped.

Results: IL-1β-31C was associated with an increased risk of developing gastric carcinoma (OR = 4.614 [1.43 – 14.81], p = 0.01). However, IL-1RN2 heterozygous allele type was significantly associated with chronic atrophic gastritis (OR = 4.2 [1.23 – 13.61], p = 0.022). IL-1β-511T was associated with an increased risk of development of chronic atrophic gastritis (OR = 4.286 [1.54 – 11.89], p = 0.005).

Conclusion: IL-1β and IL-1RN polymorphisms associated with H. pylori infection contribute to the development of chronic atrophic gastritis and gastric carcinomas in an Algerian population. The alleles IL-1β-31C and IL-1RN were associated with an increased risk of developing gastric carcinoma, and IL-1β-511T with an increased risk of developing chronic atrophic gastritis with no significant association of developing gastric carcinoma.

Keywords: gastric mucosa; Helicobacter pylori; IL-1β; IL-1RN

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Helicobacter pylori (H. pylori) infection of the gastric mucosa is a worldwide pandemic increasingly related to various gastric diseases such as asymptomatic gastritis, peptic ulcers, and malignant tumors (1). Based on the strongest association between H. pylori and gastric cancer, the World Health Organization has considered this germ as a class I carcinogen since 1994 (2). The global prevalence of gastric cancer has increased from 1 to 3% among people infected with H. pylori. Furthermore, the clinical outcomes depend largely on the distribution and the severity of the infection (3). The justification for such divergent clinical outcomes is gradually revealed in the paradigm of interaction between two pathways, gastric acid secretion and gastritis induced by H. pylori (4). The ability and localization of high gastric acid secretion determine divergent diseases: a high acid secretion in response to a predominant antral gastritis tends to result in peptic ulcers, while low secretion with pangastritis tends to lead to cancer gastric (4).

The IL-1 cluster IL-1β gene encoding IL-1β and the IL-1RN gene coding for the anti-inflammatory antagonist (IL-1ra) of IL-1 receptor are located on chromosome 2q14 and have a number of functionally relevant polymorphisms that could be correlated with the high or low production of IL-1β (5–8). Substitution in the promoter region of the TATA box at the −511 position (CT; dbSNP: rs16944) and the −31 position (TC; dbSNP: rs1143627)
has been observed. The two single nucleotide polymorphisms (SNPs) are in linkage disequilibrium (9) by skewing this interaction, causing an unfavorable IL-1β to IL-1RN ratio (10). IL-1β is not only a determinant of a pro-inflammatory phenotype but also appears to be a major cofactor in maintaining and promoting H. pylori infection (11). Individuals with gastric pro-inflammatory genotype overexpressed IL-1β in response to H. pylori infection, which leads to gastrin overexpression, increased gastric inflammation, gastric atrophy, and hypochlorhydria, and possibly stimulates neoplastic growth (10, 12). El-Omar et al. were the first who reported that genotype IL-1β-511T+, IL-1β-31C+, and IL-1RN 2/2 are associated with an increased risk of developing gastric cancer (6). Their findings among Scottish and Polish ethnic groups in Portugal (13), USA (7), China (4), Japan (14), and Latin America (15).

Our study aims to evaluate the associations of these polymorphisms in the presence of H. pylori infection of the gastric mucosa in patients with gastric carcinoma (GC) and chronic atrophic gastritis (AG) in northwestern Algeria.

Methods

Patients

This study was conducted during 14 months (October 2014 to November 2015) on patients with AG (n = 39) and GC (n = 40) at two medical oncology and gastroenterology facilities in the northwestern region of Algeria. However, 32 other individuals were recruited as controls (HC).

All patients with chronic AG or GC were H. pylori positive. The control group was H. pylori negative with no family history of cancer. Infection with H. pylori was confirmed by histopathology of biopsies sampled during diagnostic endoscopy (at least four biopsies of the antrum and body gastric mucosa should be available for each case) and anti-HP IgG serum antibody tests. The corresponding tissue sections were stained for slide reading in the anatomopathology department of the University Hospital of Sidi-Bel-Abbes, Algeria.

The existence of H. pylori DNA in gastric biopsies and buccal swabs were analyzed by PCR amplification of the ureC gene using primers as described by Lage et al. (16) (forward: 5'-AAGCTTTAGGGGTATTAGGGTTT-3' and reverse: 5'-AAGCTTACTTCTAACACATACG C-3') at a hybridization temperature of 55°C. We employed a DNA volume of 25 µl according to PCR criteria, as described below. The amplified fragments were visualized by using the GelRed™ Nucleic Acid Gel Stain, 10,000 X (Biotium, Hayward, CA, USA), and 2.5% agarose gel. The obtained fragments were of 294 bp.

Information about personal data, sociodemographic characteristics, educational level, blood type, rhesus factor, eating habits, smoking, and alcohol consumption were evaluated using a predetermined questionnaire. Furthermore, all participants gave their consent after the study protocol had been explained to them.

Considering Decree No. 387 (article 25) dated 31 July 2006 about ethical trials in Algeria, we obtained the required access authorizations to the concerned health facilities in order to accomplish our study protocol. Furthermore, we obtained informed written consent from all participants and their treating physicians after the study protocol had been explained to them.

Analysis of IL-1β-31, IL-1β-511, and IL-1RN polymorphisms

IL-1β-31 and IL-1β-511 polymorphisms are single nucleotide changes in the promoter region, while the IL-1RN polymorphism is a repetition of 86 bp in the second intron. The DNA was extracted from 200 µl whole blood samples, 20 mg of fresh gastric biopsy, or buccal swab in H. pylori transport medium using an extraction kit (MagaZorbe® genomic DNA, Promega, Fitchburg, Wisconsin, USA) stored at −20°C. Genotyping of the two polymorphisms (IL-1β-31 and IL-1β-511) was performed using the restriction fragment length polymorphism method (PCR-RFLP) (Table 1) (6, 10). Briefly, 25–50 ng of DNA was used in a volume of 25 µl with 150 mM dNTP, 6.25 pmol of each primer, 1 U of DNA polymerase GoTaq® G2 Hot start polymerase (Promega, Fitchburg, Wisconsin, USA), 5% DMSO, 4 mM MgCl2, and 5 µl of 5x PCR buffer GoTaq. The amplified/digested fragments were visualized with the GelRed™ Nucleic Acid Gel Stain, 10,000 X (Biotium, Hayward, CA, USA) in 2.5% agarose gel.

Variable numbers of tandem repeats (VNTR) analysis in the second intron of the IL-1RN gene was carried out by PCR. The different alleles were identified by the size of the PCR fragments and encoded in a conventional manner (6, 13) as follows: allele 1 (four repetitions), allele 2 (two repetitions), allele 3 (five repetitions), allele 4 (three repetitions), and allele 5 (six repetitions). According to previous studies (6, 13), as described in Table 1, the IL-1RN alleles were dichotomized into two categories: long genotype (L: > three repetitions; alleles 1, 3, 4, 5) and short genotype (2: two repetitions; allele 2).

Statistical analysis

Data were processed and analyzed using SPSS 22.0 (Statistical Package for the Social Sciences, IBM Corporation; Chicago, IL, August 2013). Chi-square test was used to evaluate differences in the distribution of polymorphisms between different groups. All allelic distributions were examined for the corresponding differences of their Hardy-Weinberg equilibrium. The relative risk was evaluated by multivariate logistic regression based on categorical reference predictor models, adjusting for sex and age with a confidence interval (CI) of 95% and statistical significance set at p <0.05. Allelic combinations of models of the three variants closely related.
polymorphisms of IL-1β and IL-1RN were analyzed. The study of the haplotypes and linkage disequilibrium between loci (estimated by $r^2$ and $D^r$) was carried out via the web interface in the LinkDos (www.genepop.curtin.edu.au/linkC.html).

**Results**

The mean age of all participants was 45.0 ± 17.67 years, and ranged from 16 to 86 years. In healthy individuals, the mean age was 35.8 ± 12.72 years with a male-to-female ratio of 1:1 (Table 2). However, in patients with AG and/or GC, mean ages were 49.3 ± 19.35 (male-to-female ratio of 0.56:1) and 59.3 ± 14.00 years (male-to-female ratio of 2.27:1), respectively.

The frequencies of the tested genotypes were in Hardy-Weinberg disequilibrium according to the following results.

Linkage disequilibrium analysis between IL-1β-31 and IL-1β-511 for AG patients gave the following results: $r^2 = 0.6804$, $D^r = 0.46294$; moreover, analysis of linkage disequilibrium between IL-1β-31 and IL-1β-511 in GC patients: $r^2 = 0.69357$, $D^r = 0.48$.

Considering the whole studied population, IL-1RN was positively correlated ($r = 0.424$, $r^2 = 0.180$) with IL-1β-31 ($p = 0.023$) and with IL-1β-511 ($p = 0.006$). In patients with GC, we noticed weak positive correlations ($r = 0.377$, $r^2 = 0.142$) of IL-1RN with IL-1β-31 ($p = 0.550$) and IL-1β-511 ($p = 0.056$), respectively.

Non-significant correlations ($r = 0.454$, $r^2 = 0.206$) between IL-1RN, on the one hand, and IL-1β-31 ($p = 0.703$) and IL-1β -511 ($p = 0.072$), on the other hand, were observed in patients with AG. Nevertheless, the correlations were non-significant in healthy subjects ($p = 0.134$ for IL-1β-31 and $p = 0.058$ for IL-1β-511).

As depicted in Table 3, the frequency of L/L wild-type pattern of IL-1RN was 87.5% in controls compared to 62.5% in GC and 82.1% in AG patients. The IL-1RN2 allele rates, for either heterozygous or homozygous, were 37.5% in GC, 17.9% in AG, and 12.5% in controls.

Regarding the IL-1β-511, the proportions of C/C wild-type pattern were 56.3% in healthy subjects, 47.5% in GC, and 23.1% in AG patients. Individuals carrying the allele IL-1β-511T are represented by 76.9% of AG, 52.5% of GC, and 43.8% of healthy controls.

### Table 1. Primers and conditions for analysis of the IL-1β and IL-1RN polymorphisms

| Polymorphism | Primers | Screen; PCR method (restriction enzyme); and definition of the allele |
|--------------|---------|------------------------------------------------------------------------|
| IL-1β-31     | Forward: 5’-TCTTCTCCCTCTCTTACT3’ | 52°C, PCR-RFLP (AluI); C allele: 234 bp; T allele: 150 bp and 84 bp |
|              | Reverse: 5’-GAGAGACTCCCTTTAGACCATG-3’ | |
| IL-1β-511    | Forward: 5’-CTGCTAAGCTGTAGTTTCTTGC3’ | 59°C, PCR-RFLP (Ddel); C allele: 140 bp and 49 bp; |
|              | Reverse: 5’-GGAATCTCCACTTAAGATG-3’ | T allele: 109 bp, 49 bp and 31 bp |
| IL-1RN       | Forward: 5’-FCTCAAGAACACTCCTAT3’ | 60°C; PCR; 2-repeat allele: 240 bp, 3-repeat allele: |
|              | Reverse: 5’-TCCTGCTTGCAGGT3’ | 326 bp; 4-repeat allele: 412; 5-repeat allele: 498 bp |

Tm: melting temperature; IL-1β-31: cluster of gene encoding interleukin-1β in the promoter region of TATA box at the -31 position; IL-1β-511: cluster of gene encoding interleukin-1β in the promoter region of TATA box at the -511 position; IL-1RN: gene encoding the anti-inflammatory antagonist (interleukin-1ra).

### Table 2. Comparison between groups according to gender

|              | HC        | AG        | GC        | $\chi^2$ | p*        |
|--------------|-----------|-----------|-----------|----------|-----------|
| Female       | 16 (29.1%)| 25 (45.5%)| 14 (25.5%)|          |           |
| Male         | 16 (28.6%)| 14 (25.0%)| 26 (46.4%)| 6.694    | <0.05     |
| Total        | 32 (28.8%)| 39 (35.1%)| 40 (36.0%)|          |           |

AG: atrophic gastritis; GC: gastric carcinoma; HC: healthy controls; (*) comparison between the three groups using Chi-square test.
Our results show that 53.1% of healthy subjects, 35.9% of patients with AG, and 25.0% of patients with GC have the T/T wild-type pattern of IL-1β-31.

As illustrated in Table 4, we investigated major genotypes implicated as risk factors for having GC and AG compared to controls. When multivariate logistic regression analysis was performed, our results showed that the C/C homozygous 4.614 (95% CI, 1.437–14.817) and the C/T heterozygous 1.974 (95% CI, 0.562–6.939) genotypes of the IL-1β-31 each indicated a strong contribution to GC. Likewise, the same genotypes have non-significant risk of having AG (C/C: 2.429 [95% CI, 0.769–7.673] and C/T: 1.455 [95% CI, 0.402–5.260]). However, the association between the two homozygous and heterozygous genotypes C/T and T/T of IL-1β-511 was 4.286 (95% CI, 1.544–11.898) times more at risk of having AG compared to controls.

Concerning the heterozygous genotype L/2 of IL-1RN, our findings show that the odds ratio of having GC was 4.200 (95% CI, 1.230–14.337).

Table 4. Regression analysis of the distribution of the genotypes in the study

| Multivariate logistic regression analysis |   | OR (95% CI) |
|-----------------------------------------|---|-------------|
| GC * HC | IL-1β (-31) | T/T | 0.035 | Reference |
|         |              | C/C | 0.010 | 4.614 (1.437–14.817) |
|         |              | C/T | 0.289 | 1.974 (0.562–6.939) |
|         |              | C/T+C/C | 0.016 | 3.400 (1.254–9.216) |
| IL-1β (-511) | C/C | 0.968 | Reference |
|         | T/T | 0.800 | 0.880 (0.326–2.374) |
|         | C/T | 0.999 | 0.000 (–) |
|         | C/T+T/T | 0.461 | 1.421 (0.558–3.617) |
| IL-1RN | L/L | – | Reference |
|         | L/2 | 0.022 | 4.200 (1.230–14.337) |
|         | L/2+2/2 | 0.022 | 4.200 (1.230–14.337) |
| AG * HC | IL-1β (-31) | T/T | 0.303 | Reference |
|         |              | C/C | 0.131 | 2.429 (0.769–7.673) |
|         |              | C/T | 0.568 | 1.455 (0.402–5.260) |
|         |              | C/T+C/C | 0.148 | 0.494 (0.190–1.283) |
| IL-1β (-511) | C/C | 0.914 | Reference |
|         | T/T | 0.671 | 1.286 (0.404–4.094) |
|         | C/T | 0.998 | 0.000 (–) |
|         | C/T+T/T | 0.005 | 4.286 (1.544–11.898) |
| IL-1RN | L/L | 0.984 | Reference |
|         | L/2 | 0.999 | 0.000 (–) |
|         | 2/2 | 0.859 | 0.875 (0.200–3.828) |
| AG * GC | IL-1β (-31) | T/T | 0.497 | Reference |
|         |              | C/C | 0.238 | 0.526 (0.181–1.527) |
|         |              | C/T | 0.581 | 0.737 (0.249–2.178) |
|         |              | C/T+C/C | 0.294 | 0.595 (0.226–1.570) |
| IL-1β (-511) | C/C | 0.009 | Reference |
|         | T/T | 0.522 | 1.462 (0.457–4.674) |
|         | C/T | 0.026 | 0.264 (0.081–0.856) |
|         | C/T+T/T | 0.026 | 3.016 (1.144–7.952) |
| IL-1RN | L/L | 0.042 | Reference |
|         | L/2 | 0.999 | 0.000 (–) |
|         | 2/2 | 0.012 | 0.208 (0.061–0.706) |
|         | L/2+2/2 | 0.057 | 0.365 (0.129–1.030) |

AG: atrophic gastritis; GC: gastric carcinoma; HC: healthy controls; OR: odds ratio. GC * HC: regression analysis of combined gastric carcinoma and healthy controls, AG * HC: regression analysis of combined atrophic gastritis and healthy controls, AG * GC: regression analysis of combined atrophic gastritis and gastric carcinoma.

IL-1β-31: cluster in gene encoding interleukin-1β in the promoter region of TATA box at the –31 position; IL-1β-511: cluster in gene encoding interleukin-1β in the promoter region of TATA box at the –511 position; IL-1RN: gene encoding the anti-inflammatory antagonist (interleukin-1ra); L: long genotype (more than three repetitions; alleles 1, 3, 4, 5); 2: short genotype (two repetitions; allele 2); C or T: single nucleotide polymorphisms.
Further analysis of combined genotype between IL-1RN and IL-1β-31 (Table 5) and IL-1RN and IL-1β-511 (Table 6) was performed using χ² test. The association between IL-1β-31 and IL-1RN was significant in AG patients (p = 0.028) and in controls (p = 0.021). Furthermore, the relationship between IL-1RN and IL-1β-511 was significant for the same groups (AG: p = 0.014, and HC: p = 0.015).

Discussion
The paradigm of previous studies on GC with regard to different haplotypes of IL-1RN and IL-1β has been investigated since 2000 on Scottish and Polish populations (6, 7). The genotype carriers of homozygous IL-1β-31C and IL-1RN2 have a high risk of hypochlorhydria as a result of Helicobacter pylori infection with evidence for genetic–environmental interaction at an early stage of gastric cancer (6). Machado et al. (13) reported results on a Portuguese population by studying the etiological role of IL-1β-511T allele, IL-1RN2 allele, and their association with an increased risk of developing intestinal GC. Until now, polymorphisms in genes of the pro-inflammatory cytokines IL-1β and TNF-α constitute an increased risk of developing GC in different gastric anatomical sites when the patients’ ethnicity is not considered (17–19).

Several studies on the association between IL-1β and the IL-1RN genotype in Asian and Caucasian populations show that IL-1β-511T is significantly associated with the risk of GC (20). Other studies showed that IL-1β-511T and IL-1RN2 were associated with an increased risk of developing GC in Caucasians. Similarly, a significantly increased risk was noticed when analyses showed positive associated with H. pylori infection with a moderate increase among Hispanics, but not among Asians (15, 21–23).

To the best of our knowledge, only one study on the IL-1β and IL-1RN polymorphisms and their association with gastric cancer was performed in an Arab population, namely in Oman. One hundred eighteen GC cases and 245 controls were compared. The authors found that the IL-1RN2 polymorphism increases the risk of GC, but the IL-1β-31C allele was not associated with the risk of developing GC (24). In Africa, Kimang’a studied the association of these polymorphisms with H. pylori infection with different pathologies of the gastric mucosa without considering GC. He reported a significant effect of the IL-1β-511T allele on gastritis, gastrointestinal reflux and gastric ulcers (25).

In this study, we evaluated the association between IL-1β and IL-1RN VNTR polymorphisms and the risk of AG and CG in northwestern Algeria. According to GLOBOCAN 2012, GC is the fourth most common cancer (both genders) in Algeria, with about 686 cases per year (26). Our results show that the IL-1β-31C allele is associated with an increased risk of developing GC (OR = 4.614; p = 0.01). The IL-1RN2 heterozygous allele

Table 5. Distribution of genotypes among patient groups

| Sample type | IL-1RN | T/T n (%) | C/C n (%) | C/T n (%) | Total (%) | Chi-square test (p) |
|-------------|--------|-----------|-----------|-----------|-----------|-------------------|
| AG          | IL-1RN | 08 (25.0) | 10 (31.2) | 32 (100.0) | 0.028     |
|             | L/2    | 03 (75.0) | 01 (25.0) | 04 (100.0) |           |
|             | 2/2    | 00 (00.0) | 03 (100.0) | 03 (100.0) |           |
| Total       | 14 (35.9) | 11 (28.2) | 14 (35.9) | 39 (100.0) |           |
| GC          | IL-1RN | 09 (36.0) | 09 (36.0) | 25 (100.0) | 0.146     |
|             | L/2    | 02 (13.3) | 10 (66.7) | 15 (100.0) |           |
| Total       | 10 (25.0) | 11 (27.5) | 19 (47.5) | 40 (100.0) |           |
| HC          | IL-1RN | 00 (00.0) | 03 (75.0) | 04 (100.0) | 0.021     |
|             | L/2    | 00 (00.0) | 03 (75.0) | 04 (100.0) |           |
| Total       | 17 (53.1) | 08 (25.0) | 07 (21.9) | 32 (100.0) |           |
| Total       | IL-1RN | 23 (27.1) | 03 (100.0) | 03 (100.0) |           |

Regression analysis of combined (IL-1RN vs. IL-1β-31) Chi-square test. AG: atrophic gastritis; GC: gastric carcinoma; HC: healthy controls; IL-1β-31: cluster in gene encoding interleukin-1β in the promoter region of TATA box at the −31 position; IL-1β-511: cluster in gene encoding interleukin-1β in the promoter region of TATA box at the −511 position; IL-1RN: gene encoding for the anti-inflammatory antagonist (interleukin-1ra); L: long genotype (more than three repetitions; alleles 1, 3, 4, 5); 2: short genotype (two repetitions; allele 2); C or T: single nucleotide polymorphisms.

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type is significantly associated with AG (OR = 4.2; p = 0.022). These findings are in concordance with results on Caucasians but different from those of Asian and Arab populations in Oman (24, 27).

Considering the IL-1β-511T allele, no significant effect on GC was noticed in the studied patients. This result is in agreement with studies on Japanese and Korean populations (27, 28), but different from results from Caucasian populations (7, 13). Individuals carrying the IL-1β-511T allele have more risk of developing AG (OR = 4.286; p = 0.005) than GC. The same findings were observed in a German population (29). Contrariwise, in a recent study from Mexico, individuals carrying IL-1β-511C and IL-1β-31T alleles separately are more likely to develop AG and gastric ulcers (30).

One limitation of the present study is the small sample size. Moreover, this work investigated the association between H. pylori infection and polymorphisms in only two genes, IL-1β and IL-1RN, without invoking other carcinogenic factors; this could be considered as another limitation.

In conclusion, the presence of IL-1β and IL-1RN polymorphisms with H. pylori infection of the gastric mucosa contributes to the development of chronic AG and GCs in an Algerian population. Individuals carrying the IL-1β-31C and IL-1RN2 alleles are more likely to have an increased risk of developing GC. On the other hand, there is a positive correlation between chronic AG and IL-1β-511T. These results highlight the importance of ethnicity studies about the effect of IL-1β and IL-1RN polymorphisms associated with H. pylori infection on gastric carcinogenesis. Thus, large investigations needed to gain a proper understanding of gastric mucosa carcinogenesis in our region.

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### References

1. Wroblewski LE, Peek RM, Wilson KT. *Helicobacter pylori* and gastric cancer: factors that modulate disease risk. Clin Microbiol Rev. 2010; 23: 713–39.
2. IARC Monographs on the Carcinogenic Risks to Humans. Schistosomes, Liver Flukes and *Helicobacter Pylori*, IARC Monograph Vol. 61. Lyon, France: WHO Press;1994.
3. McLean MH, El-Omar EM. Genetics of gastric cancer. Nat Rev Gastroenterol Hepatol. 2014; 11: 664–74.
4. Zeng ZR, Hu PJ, Hu S, Pang RP, Chen MH, Ng M, et al. Association of interleukin 1β gene polymorphism and gastric cancers in high and low prevalence regions in China. Gut. 2003; 52: 1684–9.
5. Bidwell J, Keen L, Gallagher G, Kimberly R, Huizinga T, McDermott MF, et al. Cytokine gene polymorphism in human disease: on-balance line databases supplement 1. Genes Immun. 1999; 2: 61–70.
6. El-Omar EM, Carrington M, Chow WH, McColl KE, Bream JH, Young HA, et al. Interleukin-1 polymorphisms associated with increased risk of gastric cancer. Nature. 2000; 404: 398–402.
7. El-Omar EM, Carrington M, Chow WH, McColl KE, Bream JH, Young HA, et al. The role of the Interleukin-1 polymorphisms in the pathogenesis of gastric cancer. Nature. 2001; 412: 99.
8. Hwang JR, Kodama T, Kikuchi S, Sakai K, Peterson LE, Graham DY, et al. Effect of interleukin-1 polymorphisms on gastric mucosal interleukin 1β production in Helicobacter pylori infection. Gastroenterology. 2002; 123: 1793–803.
9. Xu J, Yin Z, Cao S, Gao W, Liu L, Yin Y, et al. Systematic review and meta-analysis on the association between IL-1B polymorphisms and cancer risk. PLoS One. 2013; 8: e63654.
10. Ruzzo A, Graziano F, Pizzagalli F, Santini D, Battistelli V, Panunzi S, et al. Interleukin 1β gene (IL-1B) and interleukin 1 receptor antagonist gene (IL-1RN) polymorphisms in Helicobacter pylori-negative gastric cancer of intestinal and diffuse histotype. Ann Oncol. 2005; 16: 887–92.
11. Take S, Mizuno M, Ishiki K, Nagahara Y, Yoshida T, Inaba T, et al. Interleukin-1beta genetic polymorphism influences the effect of cytochrome P 2C19 genotype on the cure rate of 1-week triple therapy for Helicobacter pylori infection. Am J Gastroenterol. 2003; 98: 2403–8.
12. Rozengurt E, Walsh JH, Gastrin, CCK, signaling, and cancer. Annu Rev Physiol. 2001; 63: 49–76.
13. Machado JC, Pharoah P, Sousa S, Carvalho R, Oliveira C, Figueiredo C, et al. Interleukin 1B and interleukin 1RN polymorphisms are associated with increased risk of gastric carcinoma. Gastroenterology. 2001; 123: 821–9.
14. Furuta T, El-Omar EM, Xiao F, Shirai N, Takashima M, Sugimura H. Interleukin 1β polymorphisms increase risk of hypochlorhydria and atrophic gastritis and reduce risk of duodenal ulcer recurrence in Japan. Gastroenterology. 2002; 123: 92–105.
15. Camargo MC, Mera R, Correa P, Richard MP Jr, Fontham ETH, Goodman KJ, et al. Interleukin-1β and interleukin-1 receptor antagonist gene polymorphisms and gastric cancer: a meta-analysis. Canc Epidemiol Biomarkers Prev. 2006; 15: 1674–87.
16. Lage AP, Godfroid E, Fauconnier A, Buretta A, Butzler JP, Bolten A, et al. Diagnosis of Helicobacter pylori infection by PCR: comparison with other invasive techniques and detection of cagA gene in gastric biopsy specimens. J Clin Microbiol. 1995; 33: 2752–6.
17. El-Omar EM, Rabkin CS, Gammon MD, Vaughan TL, Risch HA, Schoenberg JB, et al. Increased risk of noncardia gastric cancer associated with proinflammatory cytokine gene polymorphisms. Gastroenterology. 2003; 124: 1193–201.
18. Figura N, Marano L, Moretti E, Ponzetto A. Helicobacter pylori infection and gastric carcinoma: not all the strains and patients are alike. World J Gastrointest Oncol. 2016; 8: 40–54.
19. Machado JC, Figueiredo C, Canedo P, Pharoah P, Carvalho R, Nabais S, et al. A proinflammatory genetic profile increases the risk for chronic atrophic gastritis and gastric carcinoma. Gastroenterology. 2003; 125: 364–71.
20. Wang P, Xia HH, Zhang JY, Dai LP, Xu QX, Wang KJ. Association of interleukin-1 gene polymorphisms with gastric cancer: a meta-analysis. Int J Cancer. 2007; 120: 552–62.
21. Xue H, Lin B, Ni P, Xu H, Huang G. Interleukin-1B and interleukin-1RN polymorphisms and gastric carcinoma risk: a meta-analysis. J Gastroenterol Hepatol. 2010; 25: 1604–17.
22. Persson C, Canedo P, Machado JC, El-Omar EM, Forman D. Polymorphisms in inflammatory response genes and their association with gastric cancer: a HuGE systematic review and meta-analyses. Am J Epidemiol. 2011; 173: 259–70.
23. Bonequi P, Meneses-González F, Correa P, Rabkin CS, Camargo MC. Risk factors for gastric cancer in Latin America: a meta-analysis. Cancer Causes Control. 2013; 24: 217–31.
24. Al-Moundhri MS, Al-Nabhani M, Al-Bahrini B, Burney IA, Al-Madhani A, Ganguly SS, et al. Interleukin-1beta gene (IL-1B) and interleukin 1 receptor antagonist gene (IL-1RN) polymorphisms and gastric cancer risk in an Omani Arab population. Gastric Cancer. 2006; 9: 284–90.
25. Kimang’a AN. IL-1B-511 Allele T and IL-1RN-L/L play a pathological role in Helicobacter Pylori (H. Pylori) disease outcome in the African population. Ethiop J Health Sci. 2012; 22: 163–9.
26. Ferlay J, Soerjomataram I, Ervik M, Forman D, Brayet F, Dikshit R, et al. International Agency for Research on Cancer. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. Available from: globocan.iarc.fr [cited 6 January 2016].
27. Kato S, Onda M, Yamada S, Matsuda N, Tokunaga A, Matsukura N. Association of the interleukin-1 beta genetic polymorphism and gastric cancer risk in Japanese. J Gastroenterol. 2001; 36: 696–9.
28. Seong-Gene L, Byungskik S, Wonyong C, Inchul L, Jaewon C, Kyuyoung S. Lack of association between pro-inflammatory genotypes of the interleukin-1 (IL-1B -31 C/+ and IL-1RN *2/ *2) and gastric cancer/duodenal ulcer in Korean population. Cytokine. 2003; 21: 167–71.
29. Rad R, Prinz C, Neu B, Neuhofer M, Zeitner M, Voland P, et al. Synergistic effect of Helicobacter pylori virulence factors and interleukin-1 polymorphisms for the development of severe histological changes in the gastric mucosa. J Infect Dis. 2003; 188: 272–81.
30. Martínez-Carrillo DN, Garza-González E, Betancourt-Linares R, Mónico-Manzano T, Antúnez-Rivera C, Román-Román A, et al. Association of IL1B -511C/-31T haplotype and Helicobacter pylori vacA genotypes with gastric ulcer and chronic gastritis. BMC Gastroenterol. 2010; 10: 1–8.