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***Helicobacter pylori* and cytokine gene variants as predictors of premalignant gastric lesions**

Negovan A *et al*. Cytokine gene variants and gastric premalignancies

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**Abstract**

Gastric cancer remains the third leading cause of mortality from cancer worldwide and carries a poor prognosis, due largely to late diagnosis. The importance of the interaction between *Helicobacter pylori* (*H. pylori*) infection, the main risk factor, and host-related genetic factors has been studied intensively in recent years. The genetic predisposition for non-hereditary gastric cancer is difficult to assess, as neither the real prevalence of premalignant gastric lesions in various populations nor the environmental risk factors for cancer progression are clearly defined. For non-cardiac intestinal-type cancer, identifying the factors that modulate the progression from inflammation toward cancer is crucial in order to develop preventive strategies. The role of cytokines and their gene variants has been questioned in regard to non-self-limiting *H. pylori* gastritis and its evolution to gastric atrophy and intestinal metaplasia; the literature now includes various and non-conclusive results on this topic. The influence of the majority of cytokine single nucleotide polymorphisms has been investigated for gastric cancer but not for preneoplastic gastric lesions. Among the investigated gene variants onlyIL10T-819C, IL-8-251, IL-18RAP917997, IL-22 rs1179251, IL1-B-511, IL1-B-3954, IL4R-398 and IL1RN were identified as predictors for premalignant gastric lesions risk. One of the most important limiting factors is the inhomogeneity of the studies (*e.g*., the lack of data on concomitant *H. pylori* infection, methods used to assess preneoplastic lesions, and source population). Testing the modifying effect of *H. pylori* infection upon the relationship between cytokine gene variants and premalignant gastric lesions, or even testing the interaction between *H. pylori* and cytokine gene variants in multivariable models adjusted for potential covariates, could increase generalizability of results.

**Key words:** *Helicobacter pylori*; Gastritis; Premalignant; Glandular atrophy; Intestinal metaplasia; Single-nuclear polymorphism; Gene variants; Interleukins

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**Core tip:** The role of cytokines and their gene variants has been questioned in relation to *Helicobacter pylori* (*H. pylori*) gastritis and gastric cancer but only infrequently for preneoplastic lesions. To date, only the single nucleotide polymorphisms IL-10T-819C, IL-8-251, IL-18RAP917997, IL-22 rs1179251, IL1-B-511, IL1-B-3954, IL4R-398 and IL1RN appear to be predictors for premalignant gastric lesion susceptibility. In order to develop preventative strategies, further studies using multivariable models to test the modifying effect of *H. pylori* infection on the relationship between cytokine gene variants and premalignant lesions or to test the interaction between *H. pylori* and cytokine gene variants should be considered.

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**INTRODUCTION**

Gastric cancer (GC) remains the third leading cause of mortality from cancer worldwide[1], having the fifth highest incidence among cancers, despite the progress made in understanding its physiopathology, early detection, and treatment. Intestinal-type GC, the most frequent type of GC, is considered nowadays a consequence of the histopathologic cascade initialised by longstanding *Helicobacter pylori (H. pylori)* infection and gastritis, glandular atrophy (GA), intestinal metaplasia (IM), dysplasia, and cancer[2]. In the vast majority of cases, gastric atrophy, defined as “loss of appropriate glandular units”, is the result of a non‐self‐limiting inflammatory status[3]. The development of metaplasia (*i.e*. the transformation of gland structure to resemble intestinal glands) is considered an ‘adaptive’ process that occurs in response to various endogenous or exogenous aggressors (*e.g*., pH changes, hormones, chemicals, and microbiota), while the progression of metaplasia to dysplasia may be viewed as an ‘oncogenic’ phase[4,5]. The latest research results suggest that the risk for GC should be considered a consequence of the complex interplay between the aggressiveness of *H. pylori* strains, its genetic background, and host response, as well as the effect of various other environmental factors (*e.g.*, diet habits, smoking, *etc.*)[6].

The poor prognosis of GC and recent advances in the assessment of genetic predisposition emphasize the importance of early diagnosis and the possible role of biomarkers in the surveillance of at-risk individuals[7]. *H. pylori*-associated inflammation is considered the most important trigger of the cascade, and one of the suggested pathways of progression to GC is represented by the variability of the host inflammatory response against different strains of *H. pylori*[8]. Even though GC is a heterogeneous molecular disease, a growing body of evidence supports the influence of cytokine gene variants on the progression of *H. pylori* infection toward premalignant lesions[9].

The objective of the present review was to synthetize the current knowledge of the relationship between certain single nucleotide polymorphisms (SNPs) of cytokines and premalignant gastric lesion susceptibility by reviewing the relevant studies published between 2005-2018.

**Epidemiology of preneoplastic lesions and GC risk**

It is accepted today that both host and *H. pylori* genetics influence susceptibility to the development of chronic inflammation and to molecular and cellular events related to carcinogenesis, but they depend strongly on context[10]. In a recent meta-analysis, the pooled frequency of GC was 17.4% (95%CI: 16.4–18.5) in an *H. pylori*-infected population but varied markedly across countries; the highest rate of GC was observed in Asian *H. pylori*-infected individuals[11]. The differences between the prevalence of infection and the burden of GC in an African population, for example, are attributable to genetic modulation of the host response against infection, non-*H. pylori* gastric microbiota, possibly to a lack of cag A pathogenicity, or simply to inadequate samples or differences in life expectancy[6,12].

The prevalence of GA and IM worldwide is largely unknown[13]. In Western populations, a 7% prevalence of IM has been found in patients who underwent upper endoscopy in the United States[14]. In comparison, in a Romanian population of 300 consecutive patients investigated by endoscopy, the frequency of GA ± IM was 18.5%[15], comparable to a similar series of a Turkish endoscopic population (13.8%)[16]. Nevertheless, in a Japanese population for which endoscopy was performed for a health check-up, the frequency of GA was 29%, while GA + IM was 16.9%[17]. In certain subgroups of patients in whom endoscopy was performed for symptoms or anaemia, the frequency of premalignant gastric lesions increased to 32% among patients with previous gastric surgery for peptic ulcer[18], or 44% in consecutive patients treated with aspirin and proton pump inhibitors (PPIs) referred for digestive symptoms or anaemia[19].

Long-term follow-up observational studies in Western populations have demonstrated an increasing risk for GC based on progression on the Correa cascade; the standardised incidence ratios with gastritis at baseline are 1.8 (1.7 to 1.9), 2.8 (2.3 to 3.3) for GA and 3.4 (2.7 to 4.2) for IM[20]. A recent meta-analysis calculated an odds ratio (OR) of 3.58 (95%CI: 2.71–4.73, in 4,535 GC patients from among 402,636 participants) for the risk of GC in patients with IM, without data about the follow-up time[21]; yet, another failed to calculate a pooled OR due to the high heterogeneity of the studies[22]. Based on a Swedish population cohort study, even familial GA, IM, and dysplasia in first-degree relatives are associated with an increased risk for non-cardia GC[23], emphasizing the role of genetic predisposition. Despite the proven role of *H. pylori* eradication in decreasing the risk of cancer, certain histologic features, such as severe atrophy, IM in the gastric corpus, or treatment with PPI can still predispose to cancer development[24].

***H. pylori* gastritis – pathological assessment challenge**

In the first stage of *H. pylori* infection, active chronic inflammation with gastric gland preservation (non-atrophic gastritis) develops, which can lead to multifocal atrophic gastritis and IM[25,26].

Histologically, non-atrophic gastritis is characterized by the infiltration of lamina propria with chronic inflammatory cells (*e.g*., lymphocytes and plasma cells) and acute inflammatory cells (*e.g*., polymorphonuclear neutrophils). A marked acute inflammation can progress in the glandular epithelium, leading to the formation of microabscesses, whereas a marked chronic inflammation in the lamina propria can be accompanied by lymphoid aggregates with germinal centres[27,28]. In this stage, changes may be reduced by *H. pylori* eradication, however, longstanding chronic inflammation promotes the inhibition of gastric acid secretion *via*proinflammatory cytokines, ultimately influencing lesion progression[29].

Early *H. pylori* gastritis is typically antrum-predominant, with minimal involvement of the oxyntic mucosa. In some individuals, prolonged infection with *H. pylori* determines the extension of inflammation towards the gastric body. Hypochlorhydria, induced by the reduction of acid-producing mucosa, which can be exaggerated with use of PPI, and the progression of the disease from the antral mucosa promotes the proximal migration of the bacteria, facilitating the development of corpus gastritis[30]. In this stage, the determination of *H. pylori* infection and the assessment of extending lesions are highly dependent on the site, number and size of gastric biopsies[31,32].

The staining used to visualize the bacteria as well as the pathologist's experience to reduce false-positive or false-negative interpretations are also very important. Histochemical non-silver-based stains (*e.g*., Giemsa stain or Diff-Quik) are less expensive but have a blue background that makes it difficult to detect the bacteria. Silver-based stains (*e.g*., El-Zimaty dual stain or triple stain, Leung stain) are more sensitive, with the bacteria appearing larger, and provide a visible contrast with the background while having the additional benefits of intermediate cost and short technical time (9–10 min). Silver-based stains also make it easier to identify low numbers of bacteria, this being particularly useful in patients on PPI in whom bacteria are smaller[33,34]. Immunohistochemistry represents the gold standard to confirm the presence of *H. pylori*, reducing the false-positive rate and being more specific and more sensitive than the silver-based stains[35,36]. Both polyclonal and monoclonal antibodies are available, and an immunohistochemical staining can be performed using an autostainer with a shorter technical time and less technical errors. The coccoid shapes of the bacteria are also coloured and identified by this method, but there are still cases interpreted as false-negative, especially when the number of bacteria is very low.

**Gastric atrophy, IM – histology diagnosis challenge**

Although it is the most important parameter in the progression to carcinoma, GA is the most difficult stage to recognize during a routine microscopic examination[37-39]. GA, characterized by destruction of the atrophied glands and replacement with fibrous tissue (non-metaplastic atrophy) or a different type of epithelium (metaplastic atrophy), is considered the first step in the cascade of intestinal-type carcinoma[30,40]. A special category is represented by atrophic lesions localized exclusively in the corporeal region. These cases are considered autoimmune metaplastic atrophic gastritis associated with pernicious anaemia, having an increased risk of developing GC[41].

Several forms of metaplasia are described in the gastric mucosa, two of them with implications in the pathogenesis of GC: pseudopyloric metaplasia and IM, classified as complete or incomplete[28]. Pseudopyloric metaplasia, also called spasmolytic polypeptide-expressing metaplasia, is characterized by TFF1 and TFF2 spasmolytic polypeptide expression and it is considered another pathway for the development of gastric carcinoma[28,38,42].

Differential diagnosis between an oxyntic mucosa with pseudopyloric metaplasia of an antral mucosa or mucosa from the transitional area can be a diagnostic challenge, especially if the exact location of the biopsy is not known. This may be facilitated by certain particularities, some identifiable both on haematoxylin-eosin colouring and immunohistochemistry[43-45].

Histologically, the presence of sialomucin-secreting goblet cells, absorptive cells, and Paneth cells on the foveolar or glandular epithelium is defined as complete IM or small intestinal-type I metaplasia. Incomplete IM, also called enterocolic (or type IIA/II) and colonic (or type IIB/III), is defined by the presence of neutral/acid sialomucin-secreting goblet cells in type II as well as sulfomucin-secreting goblet cells in addition to columnar non-absorptive cells[25,26]. The presence of IM type III increases the risk of GC development six times compared to that for lesion-free individuals[46]. Differentiation is facilitated by histochemical stains, such as periodic acid Schiff, alciane blue, and high iron diamine.

To assess the presence of metaplasia, besides the usual histochemical methods, immunohistochemical determinations are also used. MUC1 and MUC5AC are expressed in the superficial epithelium, and MUC6 is specific for the deep part of the antral glands but is also expressed in the mucous neck cells of the oxyntic glands. MUC2 is an intestinal epithelium-specific mucin, expressed in both columnar and goblet cells of the metaplastic epithelium[47,48]. Thus, in IM there is a decrease in MUC1, MUC5AC and MUC6 immunoexpression, with *de novo* expression of MUC2[49,50]. Unique and multivariate immunohistochemical studies have identified MUC6 as an important marker for the malignant transformation of IM. This is positive in areas with high-grade dysplasia and intramucosal GC, and frequently associated with genetic alterations, especially microsatellite instability[51,52].

Runt-related transcription factor 3 (known as RUNX3) is a member of the RUNXs family and plays an important role in normal developmental processes as well as in the suppression of cell proliferation by tumour suppressor activity. On immunohistochemistry, RUNX3 expression is diminished or even absent in IM and GC due to the hypermethylation of CpG islands[51,52].

A marker used in the staging of IM and the diagnosis of GC is TFF1. This trefoil peptide is a key protein in the defence and regeneration of gastric mucosa after certain conditions[51]. It is co-expressed with MUC5AC in foveolar cells in the gastric mucosa and similarly expressed in GC, suggesting that decreased co-expression would play an important role in gastric carcinogenesis[53,54].

The caudal-related homeobox transcription factor (known as CDX2, and representing the suppressive gene involved in the development of colorectal cancer), has been studied in various types of GC and preneoplastic gastric lesions, being normally expressed by intestinal epithelial cells[55]. Under normal conditions, it is predominantly found in the small and large intestine and is missing in the gastric mucosa. Some studies have suggested that CDX2 immunoexpression decreases progressively with IM and dysplasia[55] and can be considered a prognostic factor in intestinal-type GC[50].

The chronic inflammatory changes in gastric mucosa related to *H. pylori* infection through the various and complex molecular events, including production of inflammatory mediators, create a “tumour microenvironment” that is thought to play an important role in lesion progression[56,57]. The studies questioning the potential effect of eradication therapies on regression of IM have generated discordant results, but it is accepted today that eradication does not prevent lesion progression in all patients, particularly in those with severe IM involving the corpus[58].

**Staging systems**

With the overwhelming frequency of *H. pylori* infection and related conditions in some populations[12], the importance of clinicopathological individual risk assessment for cancer is crucial. The gold standard for assessing the severity and distribution of any predisposing and premalignant gastric lesions is high-definition endoscopy with chromoendoscopy, which can guide biopsies for staging atrophic and metaplastic changes[46]. The guidelines recommend the use of the grading and staging systems of Operative Link for Gastritis Assessment (commonly referred to as OLGA) and Operative Link on Gastric Intestinal Metaplasia Assessment (commonly referred to as OLGIM), based on a standardized protocol of gastric biopsy sampling. Although recommended, the protocols are difficult and laborious to use and their contribution in improving the prognosis of patients with GC in real life should be assessed further[37,58].

Extension of GA into the corpus mucosa and increased intragastric pH seem to influence the efficacy of eradication therapy regimens; therefore, clinicians should be aware of these aspects when eradication therapy is offered to patients with severe scores, alongside timing of the histological follow-up[58]. The persistence of *H. pylori* infection and the severity of gastritis is influenced by the host inflammatory response, which itself is modulated by the host’s cytokine gene polymorphisms[9]. Current evidence support that the types and amounts of cytokines made in response to *H. pylori* infection have a significant impact on the risk of developing gastric cancer[59,60], but there are not published researches correlating la level of cytokine with OLGA/OLGIM score. The studies of cytokine SNPs in premalignant gastric lesion susceptibility have revealed different results in various populations, with no clear adjustment for the concomitant and/or persistent *H. pylori* infection, which could, alongside with race and other environmental factors, explain the different findings.

**Role of cytokines and their SNPs in *H. pylori*-related conditions**

Persistent infection with *H. pylori* is one of the triggers of chronic inflammation[61]. Inflammation is a key component of the tumour’s microenvironment, and it is considered to represent the seventh hallmark of cancer[62]. Extensive studies have unravelled the processes by which chronic inflammation predisposes to various types of cancer[63,64] and determined that the state is responsible for approximately 25% of cancer cases[65]. Chronic inflammation is associated with the generation and release of various mediators, including proinflammatory and oncogenic ones. During inflammation, the released mediators that may predispose to tumourigenesis are reactive nitrogen oxygen species, inflammatory cytokines [*i.e*. interleukins (ILs), tumour necrosis factor-alpha (TNF-α), interferon (IFN), *etc.*], growth factors, and chemokines[64].

An important role in inflammatory response regulation is attributed to the cytokines. Cytokines are classified into two groups: proinflammatory (IL-1β, IL-1α, IL-6, IL-8, IL-12, IL-17, IL-18, TNF-α, IFN-γ, *etc*)[66] and anti-inflammatory (Il-4, IL-10, IL-13, *etc*). Some of the cytokines have a dual role (*e.g*., IL-10, IL-22, and TGF-β1)[67]. Anti- and proinflammatory cytokines are involved in various cellular events, such as the induction of expression of other cytokines, proliferation and differentiation of cells, adhesion, angiogenesis, necrosis, and apoptosis, all these processes being influenced by the presence of *H. pylori*infection[8,68]. The inflammation induced by *H. pylori* infection leads to an increased gastric endothelial cell turnover and the deregulation of this inflammation, especially when it is associated with more virulent strains of *H. pylori*[8].

Genetic polymorphisms, such as SNPs, has been described in cytokine genes, and certain alleles of those genes are responsible for variations in cytokine expression and plasma levels, and may influence immune response, being therefore associated with susceptibility to cancer[69,70]. Furthermore, it was considered that cytokine SNPs may play important roles in *H. pylori*pathogenicity[71]. According to El-Omar *et al*[72] and Figueiredo *et al*[71], host genetic factors that influence cytokine SNPs may establish why certain subjects infected with *H. pylori* develop gastric malignancies while others do not. Therefore, cytokine SNPs are thought to be linked to individual susceptibility to *H. pylori* infection and to the development of GC. Indeed, SNPs of ILs and their receptors have been found to influence chronic inflammation and the risk of cancer lesions[73].

*H. pylori* also stimulates the production of various ILs (IL-1β, IL-2, IL-10, IL-12), IFN and TNF in the gastric immune response[8]. The IL factors IL-4 and IL-6, in particular, are involved in inflammation processes and are considered to be responsible for inflammatory cascade activation[74].

***TNF-α***

TNF-α levels may be influenced by SNPs. Most of the studied TNF- SNPs are located in the promoter region of the TNF-α gene, those being –308G>A (rs1800629), –238G>A (rs361525), and –376G>A (rs1800750). In a study performed on a Slovenian population, the presence of the variant genotype of TNFα –308G>A was not associated with the risk of developing intestinal adenocarcinoma and atrophic gastritis[75]. In a German study performed on 534 older adults with chronic atrophic gastritis and 534 adult controls with non-chronic atrophic gastritis, the variant genotype of TNFα –308G>A was not associated with an increased risk of chronic atrophic gastritis (OR = 1.02, 95%CI: 0.77–1.34)[76]. In a meta-analysis of seven studies performed by Peleteira *et al*[77], the TNFα -308 genotypes were not associated with premalignant gastric lesions (AA *vs* GG: OR = 0.93, 95%CI: 0.35-2.43; *I*2 = 0.0%). In a study using classification by country, Zhao *et al*[78] identified an association between the TNF-α gene 308G>A SNP and the risk to developing GC in a Chinese population (in the case of heterozygous AG genotype: OR = 1.57, 95%CI: 1.24–1.99, *P*heterogeneity= 0.133, *P =* 0.000, and in the case of variant AA + AG genotype: OR = 1.61, 95%CI = 1.27–2.03, *P*heterogeneity= 0.104, *P =* 0.000)[78].

***IL-1***

IL-1, a proinflammatory cytokine inhibiting the secretion of gastric acid, supports an increase in the colonization of *H. pylori* which leads to a more severe gastritis[79], being involved in the subsequent tumorigenesis and tumour progression[80,81]. IL-1 comprises three related genes, namely IL-1A, IL-1B, and IL-1RN, which encode the IL-1α, IL-1β, and IL-1 receptor antagonist (IL-1ra). IL-1ra (an anti-inflammatory cytokine) binds to the corresponding receptor for IL-1 and controls its action. IL‐1β is involved in initiating and amplifying the inflammation that manifests as a response to the *H. pylori* infection, decreasing the secretion of gastric acid[72]. Regarding IL-1ra, it binds to the IL-1β receptors; therefore, it may influence the effects of IL-1β[82].

The most studied SNPs for the IL‐1B gene in GC are −511C>T, −31T>C, and +3954C>T. In 2000, the association between IL-1B −511C>T and IL-1B −31T>C polymorphisms and the risk of developing GC was investigated by El-Omar *et al*[72], who reported that the *IL-1* gene polymorphisms are associated with a high risk of both hypochlorhydria produced by *H. pylori* and GC. For the IL1B -511 (TT *vs* CC) gene polymorphism, a meta-analysis of 13 studies did not find an association with premalignant gastric lesions (OR = 1.34, 95%CI: 0.87-2.07, *I*2 = 65.7%), even though the Peruvian study by Gehmert *et al*[83] found an increased risk for atrophic gastritis (OR = 5.60, 95%CI: > 2.02–15.51.6) associated with the IL-1B-511 C allele.

For the IL-1RNgene, an 86-bp variable number of tandem repeats was described at the 2nd intron, and it was presumed that it may increase the risk of GC. In the meta-analysis by Peleteira *et al*[77], the*IL1RN*\*22 genotype was associated with an increased risk of gastric precancerous lesions (22 *vs* LL: OR = 2.27, 95%CI: 1.40-3.70; *I*2 = 26.4%) when results from 12 studies were combined.

In two studies by Chiurillo *et al*[84,85], an association was found between GA and IL-1B -511\*T, -31\*C, +3954\*C and *IL-1RN*\*2 polymorphisms but only in the presence of *H. pylori*-cag strains. Caleman *et al*[86] suggested that the TT genotype of IL-1B –31T>C represents a protective factor against infection with *H. pylori* in the Brazilian population investigated. Regarding the IL-1B 3954C>T SNP, a positive association was found between the mentioned polymorphism and susceptibility for IM in a population from Costa Rica[87]. Similarly, no association between the IL-1B 3954C>T SNP and the risk of gastric lesions was found in Asians or Caucasians[88].

***IL-2***

IL-2 is an immunoregulatory cytokine produced by T cells, which induces the proliferation and differentiation of natural killer cells and stimulates the production of natural killer-derived cytokines, such as TNF-α and IFN-γ[89,90]. A recent study showed that IL-2 polymorphisms, such as the presence of variant GG genotype for IL-2 –330T>G (rs2069762), are associated with an increased risk of GC among Brazilian patients with *H. pylori* infection (OR = 6.43, 95%CI: 1.47–28.10, *P =*0.044)[89]. Similar findings were noticed for the IL-2 +114T>G (rs2069763) SNP[89]. Contrariwise, Shin *et al*[90] showed that there was no relation between IL-2 SNPs and gastric ulcers, duodenal ulcers, and GC in cases from South Korea. Haplotype analysis of IL-2 –330T>G and IL-2 114T>G revealed that presence of the IL-2 −330G/+114T haplotype was significantly associated (*P =* 0.012) with a high risk of developing GC[89].

A meta-analysis that included 3,060 patients and 3,435 controls indicated that the GG genotype of the IL-2 –330T>G SNP was significantly associated with cancer risk in Asians (OR = 2.03, 95%CI: 1.40–2.95)[91]. When Zhao *et al*[91] then stratified the analysis by cancer types, they found no association of IL-2 –330T>G SNP with GC. In contrast, Liu *et al*[92] reported no association between IL-2 –330T>G and IL-2 114T>G and GC risk.

***IL-4***

IL-4 is an important immunomodulatory cytokine that plays a major role in regulating the differentiation and activation of lymphocytes. In addition, IL-4 inhibits the secretion of proinflammatory cytokines to promote tumour cells, affecting IL-1, IL-6 and TNF-α in particular[93]. The IL-4 –590T (OR = 2.2, 95%CI: 1.1–4.4, *P =* 0.04) and IL-4 –33T (OR = 3.9, 95%CI: 1.7–8.9, *P =* 0.001) variant alleles were found to be more frequent among intestinal-type GC cases and to be associated with intestinal-type GC occurrence. A higher prevalence of IL-4 –590TT (OR = 6.7, 95%CI: 1.4–32.4, *P =* 0.01) and IL-4 –33TT (OR = 2.2, 95%CI: 1.7–2.8, *P =* 0.002) genotypes was found in intestinal-type GC patients[94]. Another study performed on 308 GC patients and 308 controls from South-Western China found the variant genotype of IL-4 590 C>T (rs2243250) to not be associated with overall GC risk (OR = 0.89, 95%CI: 0.61–1.28 for CT or CC *vs* TT)[95].

A small increase in susceptibility for GA was found in a Venezuelan study of 2033 subjects from a region with high prevalence of *H. pylori* infection conducted by Kato *et al*[96], specifically for the homozygous allele (GG) of the 398 A/G polymorphism in the IL-4R gene

***IL-6***

A previous study showed that IL-6 and IL-8 appear early during the inflammation process. IL-6 is a multifunctional cytokine that functions both as an endocrine regulator and as an inflammatory mediator. Moreover, IL-6 has a substantial role in host defence mechanisms, serving as a messenger between the innate and adaptive systems[97]. Some studies observed that presence of the IL6 -174G allele is associated with a higher production of Il-6[98] compared to that detected in individuals with the CC genotype. Another study revealed higher levels of IL-6 in the gastric mucosa in *H. pylori*-positive patients compared to *H. pylori*-negative cases[99].

Recently, it was reported that the IL6 –174C allele (OR = 2.7, 95%CI: 1.5–4.8, *P =* 0.0006) and IL-6 –174CC genotype (OR = 3.8, 95%CI: 1.7–8.7, *P =* 0.002) showed higher prevalence in diffuse-type GC, while the IL-6 –174CG genotype showed a higher prevalence (95%CI: 2.7–20.3, OR = 7.3) in a series of Portuguese intestinal-type GC cases[94]. The most recent published meta-analysis found that genetic polymorphisms of the IL-6 promoter are not associated with increased risk for GC, despite their role in susceptibility or prognosis of other cancers (*e.g*., breast, lung, *etc*)[100]. Other studies have reported that there is no association between the IL-6 SNPs and gastritis or *H. pylori* infection, but an association was observed between the IL-6 –174CG genotype and adenocarcinoma, regardless of the histological type of the tumour in a study from northern Brazil[101].

***IL-8***

IL-8 is considered to be one of the most important cytokines associated with both the immune response and the inflammatory process against *H. pylori*; indeed, increased IL-8 expression has been detected in patients with *H. pylori* infection and gastric disorders[8]. In a Japanese study, the IL-8 −251 A/A genotype, which is associated with higher expression of the IL-8 protein, found an increased susceptibility for neutrophil infiltration in gastric mucosa and for GA (OR = 2.35, 95%CI: 1.12-4.94) compared with the T/T genotype[102]. A high risk of developing severe chronic GA was found in Chinese cases with the IL-8 rs4073 AA homozygous genotype (OR = 2.62, 95%CI: 1.23–5.72) or for A allele carriers (OR = 1.81, 95%CI: 1.06–3.09). Similarly, an increased risk of IM was found in patients with heterozygous AT for the IL-8 rs4073 genotype (OR = 2.27, 95%CI: 1.25–4.14) or A allele carriers (OR = 2.07, 95%CI: 1.16–3.69)[103]. The same study reported an interaction between A allele carriers for IL-8 rs4073 and *H. pylori* infection and the risk to develop severe chronic atrophic gastritis (OR = 6.70, 95%CI: 1.29–9.78)[103].

In a Korean study-population, a significant positive association was found between the IL8 –251T>A polymorphism and risk of GC (OR = 1.70, 95%CI: 1.11–2.60, *P =* 0.0155) and severe GA (OR = 2.03, 95%CI: 1.05–3.90, *P =*0.035)[104]. The IL-8 –251T>A SNP was found to be associated with increased IL-8 production (*P =*0.0229)[104] and the IL-8 –251 T>A variant genotype (AA or TA) was found to be associated with an increased risk for non-cardia GC (adjusted OR = 2.58, 95%CI: 1.19–5.57)[95]. IL-8 –251T>A leads to an increased IL-8 production, which is more pronounced in intestinal-type GC as the result of the changes in gastric mucosa over several years[105]. By multivariate analysis, it was revealed that patients carrying the AA genotype of the IL-8 –251T>A SNP had a 2-fold increased risk for GC (OR = 2.02, 95%CI: 1.27–3.21) compared with those carrying the wild-type genotype[105]. Another study that included Caucasians from European countries showed that presence of the IL-8 –251A allele was associated with a significantly decreased risk of non-cardia GC (OR = 0.57, 95%CI: 0.37–0.87, *P =* 0.01) in *H. pylori* cases[100]. Wang *et al*[73] observed no significant correlation between IL-8 rs4073 and the risk of GC or chronic atrophic gastritis, IM and dysplasia in a high-risk Chinese population.

***IL-10***

IL-10 is an anti-inflammatory cytokine that plays an important role in the inflammatory response, inhibiting the synthesis of proinflammatory cytokines such as IL-1β, IL-6, IL-12, and TNF-α, and down-regulating inflammation[64,76]; it is also considered to be involved in the immune response to *H. pylori* infection[76]. IL-10 may influence both the susceptibility and development of cancer due to its immunosuppressive (tumour inhibition) and immunostimulating (tumour promotion) functions. Recently, the role of IL-10 –1082A>G, –819C>T, and –592A>C SNPs in susceptibility to GC were investigated in a Chinese population[106]. The authors reported that the CC genotype of the IL-10 –819C>T (rs1800871) SNP was associated with a decreased risk of atrophic gastritis and GC compared with the TT genotype. The CC genotype carriers demonstrated a significantly increased risk of atrophic gastritis compared with healthy subjects (OR = 1.79, 95%CI: 1.02–3.13, *P =* 0.043). The same study revealed no significant relationship between IL-10 –1082A>G and –592A>C polymorphisms and the risks of atrophic gastritis and GC. Furthermore, no interaction was found between IL-10 and *H. pylori*[106].

In contrast, significant associations were observed between IL-10 –1082A>G[105], IL-10 –592A>C[107] and GC risk only in cases with *H. pylori* infection. An elevated risk of GC has been identified in patients who carried the variant genotype of these SNPs and had *H. pylori* infection, indicating a synergistic effect for the combination of host genotype and the infection[105,107]. Ramis *et al*[108] demonstrated that, among Brazilian patients the IL-10 –819C/T genotype was not associated with either *H. pylori* infection or gastric carcinoma risk. In an Irish population study, carriage of the variant alleles IL-10-592, -819, and -1082were not associated with IM or gastritis[109]. In a large epidemiological study, a significant association was found between the CC genotype of the IL-10 –819C>T (rs1800871) SNP and the risk of chronic atrophic gastritis among older adults from Germany (OR = 1.67, 95%CI: 1.01–2.76)[76].

***IL-18***

IL-18, a proinflammatory cytokine, plays an important role in chronic inflammation and is linked with tumourigenesis. Myung *et al*[110] investigated the association of IL-18 SNPs rs187238 (–137G>C), rs360718 (113T>G), and rs360717 (127C>T) with the susceptibility to *H. pylori* infection in a Korean population and the findings suggested that they each play a role in *H. pylori*-associated diseases. Leung *et al*[111] showed that IL-18607C>A and IL-18 137G>C were not associated with an increased risk of gastric IM in individuals from the Shandong Province of China. The homozygous AA genotype of IL-18RA rs917997 (IL-18 receptor accessory protein) may contribute to individual susceptibility to GC (OR = 1.83, 95%CI: 1.14–2.92) or precancerous lesions such as chronic atrophic gastritis (OR = 1.55, 95%CI: 1.07–2.24) in individuals from the Linqu County of China[73].

IL-18 is also involved in cell-mediated immunity. Signalling of IL-18 requires an IL-1R-related protein (subunit of the receptor for IL18), encoded by IL-18RAP[73]. This protein enhances the IL-18-binding activity of the IL-18 receptor and plays a role in IL-18 signalling. Further, IL-18RAP has been shown to play an important role in the IL-18 signalling pathway *via* production of IFN-γ[112].

***IL-22***

IL-22 is a member of the IL-10 cytokine family[113], its expression being reported in the gastric tissues of *H. pylori-*infected patients and GC patients[114]. In a study by Wang *et al*[17], elevated risks of atrophic gastritis (OR = 2.64, 95%CI: 1.89–3.69), IM (OR = 5.58, 95%CI: 3.86–8.05), and dysplasia (OR = 1.64, 95%CI: 1.18–2.26) were observed in Chinese subjects who carried the IL-22 rs1179251 CC genotype.

***IL-32***

IL-32 is a cytokine involved in inflammation and cancer development, being induced mainly by pathogens and proinflammatory cytokines and more prominent in immune cells than in non-immune tissues[115]. In Chinese subjects, the risk for predisposing lesions for GC was elevated in those with the IL-32 rs2015620 A allele (AA + AT) or the IL-22 rs1179251 CC genotype and *H. pylori* infection, and significant interactions between these two SNPs and *H. pylori* infection were found[17].

***IFN-γ***

IFN-γ is one of the main products of Th1-specific proinflammatory cytokines and exerts several effects on host defence and immune regulation through its antiviral, antimicrobial and antitumour activities. IFN-γ can inhibit angiogenesis and exert direct antiproliferative and antimetabolic effects on a wide variety of tumour cells. In a study that included 1,339 subjects from the North of Portugal, it has been demonstrated that people under 40 years of age and who were TT homozygotes for IFN-γR1 –56C>T had a 4-fold increased risk for developing early-onset GC (OR = 4.1, 95%CI: 1.6–10.6)[116].

**Relevance of studies questioning cytokine gene variants and premalignant gastric lesions**

Extensive studies have aimed to correlate individual variations in inflammatory response with GC, but none with premalignant lesions. This is largely due to the inhomogeneity in study designs but is mostly due to the differences and the difficulties regarding the histological assessment of premalignant lesions and *H. pylori* infection[36]. To evaluate cytokine gene variants as univariate or multivariate predictors for premalignant gastric risk, we reviewed the mentioned scientific papers in an analytical scheme. We synthetized the sources of the data, the studied populations in whom clinical objectives were tested, the main outcomes, the potential confounding factors or other important covariates, the statistical control for bias, and the statistical methods used (Table 1).

In Table 2, we present the frequencies of the variant genotypes of the studied SNPs, along with the significance of the results obtained in Table 1. For every listed SNP of the cytokines, an association with GC was found in a specific population; whilst for premalignant gastric lesions, less association was detected. From among all the gene variants discussed above, only IL10T-819C, IL-8-251, IL-18RAP917997, IL-22 rs1179251, IL1-B-511, IL1-B-3954, IL4R-398 and IL1RN were predictors with age- and sex-adjustment for risk of premalignant gastric lesions. The different worldwide prevalence rates of infection and the risk of false-positive or false-negative results depends on the diagnostic method used (histological, serological, coproantigen or urea breath test)[12,36].

One of the most important limiting factors in the studies’ homogeneity is the lack of diagnosis of concomitant *H. pylori* infection. The most recent research, like that of Wang *et al*[73] and Liu *et al*[106], has tested the effect of certain cytokine gene variants on the risk of premalignant gastric lesions, controlling for the presence of *H. pylori* infection; a significant association was found but only for specific populations. Logistic models with interaction terms should be considered for testing the effect of cytokine variant genes on the risk of premalignant gastric lesions modified by *H. pylori* infection. The Synergy Factor could be used to measure binary interaction between cytokine genetic variants and *H. pylori* infection.

**Other**

Gastric cytokines are involved in the molecular events leading to proliferation, survival, angiogenesis, invasion, and metastasis of gastric tumour cells[117]. Except for cytokine gene variants, other molecular mechanisms have been questioned for potential relationship with the progression from inflammation toward GA and IM[118].

Current data support that infection with *H. pylori* carrying specific virulence factors is associated with increased risk of neoplastic lesions[9]. Even that *H. pylori* often is undetectable in gastric biopsies of patients with IM or GC, *H. pylori* and its genes were detected inside metaplastic, dysplastic, and neoplastic epithelial cells, and cagA and babA2 expression was co-localized[119]. The preneoplastic "acidic" MUC2 mucin was detected only in the presence of *H. pylori*, and MUC2 expression was higher in patients with IM, dysplasia, and cancer. The observations of Semino-Mora *et al*[119]. support the hypothesis that the persistent intracellular expression of *H. pylori* virulence genes, mainly cagA associated with aberrant expression of the MUC2 gene, play an important role in gastric carcinogenesis process[119].

An important study of Houghton *et al*[120] demonstrated that epithelial cancers emerge from the transformation of tissue stem cells and inflammation that favours the development of neoplasia has been linked to bone marrow–derived cells (BMDCs). Therefore, it was hypothesised that BMDCs, that are recruited toe the location of inflammation may represent a possible source of neoplasia. The same mouse model study[120] reveal that chronic infection of C57BL/6 mice with *H. pylori* may lead to the repopulation of the stomach with BMDCs. The findings of Houghton *et al*[120] indicate that epithelial malignancies can arise from BMDCs and therefore it have an important role in the multistep cancer progression. It was showed that several cytokines are critical for recruitment of BMDCs[120]. Considerable other data indicates that gastric cancer, and most of the cancers, may arise from aberrant stem cells that accumulate gene mutations[121].

A study of gene polymorphisms involved in oxidative stress (of *CAT*, *MnSOD* and *GPX1* genes) in relation to premalignant gastric lesions demonstrated contradictory results in different populations[122-124], despite the accepted role of oxidative stress as a consequence of *H. pylori* being a contributing factor in gastric carcinogenesis[118]. The gene variants of glutathione S-transferases (GSTs) involved in the metabolism of carcinogens, drugs, and reactive oxygen species were shown to be involved in GC predisposition, but with discordant results[125]. The GSTM1 and GSTT1 null genotypes seemed to increase the risk for premalignant lesions in a Caucasian population[126] but were not associated with GC in an Asian population in a study carried out by Chen *et al*[125]. The GSTP1Val allele seemed to reduce the risk of gastric premalignant lesions in Caucasians[126] but increased the risk for cancer in Asians[125]. The renin-angiotensin system component in the gastric mucosa seems to mediate inflammation and fibrosis[127], and the variant homozygous CC genotype of the AGT A-20C gene polymorphism was shown to increase the risk for peptic ulcer bleeding in Japanese aspirin consumers[128]. In a Romanian study, the frequency of premalignant gastric lesions decreased with increased AGT production according to genotype (AA 37.7% < AC 25.3% < CC 16.7%) but increased the risk of ulcer in carriers of the variant homozygous CC genotype[129].

Despite the lack of functional evaluation of all gene variants harbouring a risk for preneoplastic and neoplastic gastric lesions, the current research has increased our knowledge regarding GC, but while generating confusing results frequently. Our work summarized herein aimed to highlight the importance of research in populations with different prevalence rates of *H. pylori* infection and strains, with different genetic backgrounds and environmental exposures, linking inflammatory mechanisms with the neoplastic transformation of the gastric mucosa.

**Conclusion**

Even though the role of extension, localisation, or phenotype of premalignant lesions on GC risk is still a matter of debate, risk stratification and surveillance are nowadays unanimously accepted in order to decrease the burden of mortality[130,131]. At the same time, there are significant differences in the risk of progression to cancer in various populations. The endoscopic and histologic surveillance of premalignant gastric lesions should be continually evaluated, as recent research supports the importance of genetic events (*e.g.*, genetic instability, DNA damage, abnormal methylation, *etc*), rather than a direct transition from metaplasia to cancer[130]. The changes in acid secretion, pH, or gastric microbiota induced by gastric atrophy seem to be more important than the presence of histologic lesions[37].

Among all the gene variants studied for GC risk, only IL10T-819C, IL-8-251, IL-18RAP917997, IL-22 rs1179251, IL1-B-511, IL1-B-3954, IL4R-398 and IL1RN were predictors for premalignant gastric lesion occurrence. Further studies should question the role of cytokine polymorphisms in both premalignant lesions and GC risk, in order to clarify the mechanisms that link inflammatory response with gastric carcinogenesis. Larger studies in different populations assessing gene-gene and gene-environment interactions can also facilitate improvements in prevention and treatment strategies.

**REFERENCES**

1 **Ferlay J**, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Piñeros M, Znaor A, Bray F. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int J Cancer* 2019; **144**: 1941-1953 [PMID: 30350310 DOI: 10.1002/ijc.31937]

2 **Correa P**, Shiao YH. Phenotypic and genotypic events in gastric carcinogenesis. *Cancer Res* 1994; **54**: 1941s-1943s [PMID: 8137316]

3 **Rugge M**, Genta RM, Graham DY, Di Mario F, Vaz Coelho LG, Kim N, Malfertheiner P, Sugano K, Tsukanov V, Correa P. Chronicles of a cancer foretold: 35 years of gastric cancer risk assessment. *Gut* 2016; **65**: 721-725 [PMID: 26927528 DOI: 10.1136/gutjnl-2015-310846]

4 **Kinoshita H**, Hayakawa Y, Koike K. Metaplasia in the Stomach-Precursor of Gastric Cancer? *Int J Mol Sci* 2017; **18**: pii: E2063 [PMID: 28953255 DOI: 10.3390/ijms18102063]

5 **Giroux V**, Rustgi AK. Metaplasia: tissue injury adaptation and a precursor to the dysplasia-cancer sequence. *Nat Rev Cancer* 2017; **17**: 594-604 [PMID: 28860646 DOI: 10.1038/nrc.2017.68]

6 **Amieva M**, Peek RM Jr. Pathobiology of Helicobacter pylori-Induced Gastric Cancer. *Gastroenterology* 2016; **150**: 64-78 [PMID: 26385073 DOI: 10.1053/j.gastro.2015.09.004]

7 **Lott PC**, Carvajal-Carmona LG. Resolving gastric cancer aetiology: an update in genetic predisposition. *Lancet Gastroenterol Hepatol* 2018; **3**: 874-883 [PMID: 30507471 DOI: 10.1016/S2468-1253(18)30237-1]

8 **Gigek CO**, Calcagno DQ, Rasmussen LT, Santos LC, Leal MF, Wisnieski F, Burbano RR, Lourenço LG, Lopes-Filho GJ, Smith MAC. Genetic variants in gastric cancer: Risks and clinical implications. *Exp Mol Pathol* 2017; **103**: 101-111 [PMID: 28736214 DOI: 10.1016/j.yexmp.2017.07.004]

9 **de Brito BB**, da Silva FAF, de Melo FF. Role of polymorphisms in genes that encode cytokines and Helicobacter pylori virulence factors in gastric carcinogenesis. *World J Clin Oncol* 2018; **9**: 83-89 [PMID: 30254963 DOI: 10.5306/wjco.v9.i5.83]

10 **Kodaman N**, Pazos A, Schneider BG, Piazuelo MB, Mera R, Sobota RS, Sicinschi LA, Shaffer CL, Romero-Gallo J, de Sablet T, Harder RH, Bravo LE, Peek RM Jr, Wilson KT, Cover TL, Williams SM, Correa P. Human and Helicobacter pylori coevolution shapes the risk of gastric disease. *Proc Natl Acad Sci U S A* 2014; **111**: 1455-1460 [PMID: 24474772 DOI: 10.1073/pnas.1318093111]

11 **Pormohammad A**, Mohtavinejad N, Gholizadeh P, Dabiri H, Salimi Chirani A, Hashemi A, Nasiri MJ. Global estimate of gastric cancer in Helicobacter pylori-infected population: A systematic review and meta-analysis. *J Cell Physiol* 2019; **234**: 1208-1218 [PMID: 30132888 DOI: 10.1002/jcp.27114]

12 **Hooi JKY**, Lai WY, Ng WK, Suen MMY, Underwood FE, Tanyingoh D, Malfertheiner P, Graham DY, Wong VWS, Wu JCY, Chan FKL, Sung JJY, Kaplan GG, Ng SC. Global Prevalence of Helicobacter pylori Infection: Systematic Review and Meta-Analysis. *Gastroenterology* 2017; **153**: 420-429 [PMID: 28456631 DOI: 10.1053/j.gastro.2017.04.022]

13 **Jencks DS**, Adam JD, Borum ML, Koh JM, Stephen S, Doman DB. Overview of Current Concepts in Gastric Intestinal Metaplasia and Gastric Cancer. *Gastroenterol Hepatol (N Y)* 2018; **14**: 92-101 [PMID: 29606921]

14 **Sonnenberg A**, Lash RH, Genta RM. A national study of Helicobactor pylori infection in gastric biopsy specimens. *Gastroenterology* 2010; **139**: 1894-1901.e2; quiz e12 [PMID: 20727889 DOI: 10.1053/j.gastro.2010.08.018]

15 **Negovan A**, Iancu M, Moldovan V, Pantea M, Sarkany K, Bataga S, Cozlea L, Mocan S, Banescu C. Influence of MDR1 C3435T, CYP2C19\*2 and CYP2C19\*3 gene polymorphisms and clinical characteristics on the severity of gastric lesions: a case-control study. *J Gastrointestin Liver Dis* 2016; **25**: 258-260 [PMID: 27308662 DOI: 10.15403/jgld.2014.1121.252.mdr]

16 **Olmez S**, Aslan M, Erten R, Sayar S, Bayram I. The Prevalence of Gastric Intestinal Metaplasia and Distribution of Helicobacter pylori Infection, Atrophy, Dysplasia, and Cancer in Its Subtypes. *Gastroenterol Res Pract* 2015; **2015**: 434039 [PMID: 26635875 DOI: 10.1155/2015/434039]

17 **Song JH**, Kim YS, Heo NJ, Lim JH, Yang SY, Chung GE, Kim JS. High Salt Intake Is Associated with Atrophic Gastritis with Intestinal Metaplasia. *Cancer Epidemiol Biomarkers Prev* 2017; **26**: 1133-1138 [PMID: 28341758 DOI: 10.1158/1055-9965.EPI-16-1024]

18 **Pantea M**, Negovan A, Banescu C, Bataga S, Neagoe R, Mocan S, Iancu M. Factors Associated with Recurrent Ulcers in Patients with Gastric Surgery after More Than 15 Years: A Cross-Sectional Single-Center Study. *Gastroenterol Res Pract* 2018; **2018**: 8319481 [PMID: 30524477 DOI: 10.1155/2018/8319481]

19 **Negovan A**, Iancu M, Moldovan V, Sàrkàny K, Bataga S, Mocan S, Țilea I, Banescu C. The contribution of clinical and pathological predisposing factors to severe gastro-duodenal lesions in patients with long-term low-dose aspirin and proton pump inhibitor therapy. *Eur J Intern Med* 2017; **44**: 62-66 [PMID: 28576397 DOI: 10.1016/j.ejim.2017.05.017]

20 **Song H**, Ekheden IG, Zheng Z, Ericsson J, Nyrén O, Ye W. Incidence of gastric cancer among patients with gastric precancerous lesions: observational cohort study in a low risk Western population. *BMJ* 2015; **351**: h3867 [PMID: 26215280 DOI: 10.1136/bmj.h3867]

21 **Shao L**, Li P, Ye J, Chen J, Han Y, Cai J, Lu X. Risk of gastric cancer among patients with gastric intestinal metaplasia. *Int J Cancer* 2018 [PMID: 29707766 DOI: 10.1002/ijc.31571]

22 **Spence AD**, Cardwell CR, McMenamin ÚC, Hicks BM, Johnston BT, Murray LJ, Coleman HG. Adenocarcinoma risk in gastric atrophy and intestinal metaplasia: a systematic review. *BMC Gastroenterol* 2017; **17**: 157 [PMID: 29228909 DOI: 10.1186/s12876-017-0708-4]

23 **Song H**, Ekheden IG, Ploner A, Ericsson J, Nyren O, Ye W. Family history of gastric mucosal abnormality and the risk of gastric cancer: a population-based observational study. *Int J Epidemiol* 2018; **47**: 440-449 [PMID: 29161426 DOI: 10.1093/ije/dyx238]

24 **Shichijo S**, Hirata Y. Characteristics and predictors of gastric cancer after <i>Helicobacter pylori</i> eradication. *World J Gastroenterol* 2018; **24**: 2163-2172 [PMID: 29853734 DOI: 10.3748/wjg.v24.i20.2163]

25 **González CA**, Sanz-Anquela JM, Gisbert JP, Correa P. Utility of subtyping intestinal metaplasia as marker of gastric cancer risk. A review of the evidence. *Int J Cancer* 2013; **133**: 1023-1032 [PMID: 23280711 DOI: 10.1002/ijc.28003]

26 **Correa P**. A human model of gastric carcinogenesis. *Cancer Res* 1988; **48**: 3554-3560 [PMID: 3288329]

27 **González CA**, Pardo ML, Liso JM, Alonso P, Bonet C, Garcia RM, Sala N, Capella G, Sanz-Anquela JM. Gastric cancer occurrence in preneoplastic lesions: a long-term follow-up in a high-risk area in Spain. *Int J Cancer* 2010; **127**: 2654-2660 [PMID: 20178099 DOI: 10.1002/ijc.25273]

28 **Rugge M**, Capelle LG, Cappellesso R, Nitti D, Kuipers EJ. Precancerous lesions in the stomach: from biology to clinical patient management. *Best Pract Res Clin Gastroenterol* 2013; **27**: 205-223 [PMID: 23809241 DOI: 10.1016/j.bpg.2012.12.007]

29 **Graham DY**. Helicobacter pylori update: gastric cancer, reliable therapy, and possible benefits. *Gastroenterology* 2015; **148**: 719-31.e3 [PMID: 25655557 DOI: 10.1053/j.gastro.2015.01.040]

30 **Correa P**, Piazuelo MB. The gastric precancerous cascade. *J Dig Dis* 2012; **13**: 2-9 [PMID: 22188910 DOI: 10.1111/j.1751-2980.2011.00550.x]

31 **Rugge M**, Meggio A, Pennelli G, Piscioli F, Giacomelli L, De Pretis G, Graham DY. Gastritis staging in clinical practice: the OLGA staging system. *Gut* 2007; **56**: 631-636 [PMID: 17142647 DOI: 10.1136/gut.2006.106666]

32 **Dixon MF**, Genta RM, Yardley JH, Correa P. Classification and grading of gastritis. The updated Sydney System. International Workshop on the Histopathology of Gastritis, Houston 1994. *Am J Surg Pathol* 1996; **20**: 1161-1181 [PMID: 8827022]

33 **Lee JY**, Kim N. Diagnosis of Helicobacter pylori by invasive test: histology. *Ann Transl Med* 2015; **3**: 10 [PMID: 25705642 DOI: 10.3978/j.issn.2305-5839.2014.11.03]

34 **Shin CM**, Kim N, Lee HS, Lee HE, Lee SH, Park YS, Hwang JH, Kim JW, Jeong SH, Lee DH, Jung HC, Song IS. Validation of diagnostic tests for Helicobacter pylori with regard to grade of atrophic gastritis and/or intestinal metaplasia. *Helicobacter* 2009; **14**: 512-519 [PMID: 19889068 DOI: 10.1111/j.1523-5378.2009.00726.x]

35 **Testerman TL**, Morris J. Beyond the stomach: an updated view of Helicobacter pylori pathogenesis, diagnosis, and treatment. *World J Gastroenterol* 2014; **20**: 12781-12808 [PMID: 25278678 DOI: 10.3748/wjg.v20.i36.12781]

36 **Malfertheiner P**, Megraud F, O'Morain CA, Gisbert JP, Kuipers EJ, Axon AT, Bazzoli F, Gasbarrini A, Atherton J, Graham DY, Hunt R, Moayyedi P, Rokkas T, Rugge M, Selgrad M, Suerbaum S, Sugano K, El-Omar EM; European Helicobacter and Microbiota Study Group and Consensus panel. Management of Helicobacter pylori infection-the Maastricht V/Florence Consensus Report. *Gut* 2017; **66**: 6-30 [PMID: 27707777 DOI: 10.1136/gutjnl-2016-312288]

37 **Rugge M**, Sugano K, Scarpignato C, Sacchi D, Oblitas WJ, Naccarato AG. Gastric cancer prevention targeted on risk assessment: Gastritis OLGA staging. *Helicobacter* 2019; **24**: e12571 [PMID: 30773732 DOI: 10.1111/hel.12571]

38 **Isajevs S**, Liepniece-Karele I, Janciauskas D, Moisejevs G, Putnins V, Funka K, Kikuste I, Vanags A, Tolmanis I, Leja M. Gastritis staging: interobserver agreement by applying OLGA and OLGIM systems. *Virchows Arch* 2014; **464**: 403-407 [PMID: 24477629 DOI: 10.1007/s00428-014-1544-3]

39 **Eriksson NK**, Kärkkäinen PA, Färkkilä MA, Arkkila PE. Prevalence and distribution of gastric intestinal metaplasia and its subtypes. *Dig Liver Dis* 2008; **40**: 355-360 [PMID: 18291729 DOI: 10.1016/j.dld.2007.12.012]

40 **Correa P**, Haenszel W, Cuello C, Tannenbaum S, Archer M. A model for gastric cancer epidemiology. *Lancet* 1975; **2**: 58-60 [PMID: 49653]

41 **Coati I**, Fassan M, Farinati F, Graham DY, Genta RM, Rugge M. Autoimmune gastritis: Pathologist's viewpoint. *World J Gastroenterol* 2015; **21**: 12179-12189 [PMID: 26576102 DOI: 10.3748/wjg.v21.i42.12179]

42 **Xu Q**, Chen MY, He CY, Sun LP, Yuan Y. Promoter polymorphisms in trefoil factor 2 and trefoil factor 3 genes and susceptibility to gastric cancer and atrophic gastritis among Chinese population. *Gene* 2013; **529**: 104-112 [PMID: 23933418 DOI: 10.1016/j.gene.2013.07.070]

43 **Rugge M**, Pennelli G, Pilozzi E, Fassan M, Ingravallo G, Russo VM, Di Mario F; Gruppo Italiano Patologi Apparato Digerente (GIPAD); Società Italiana di Anatomia Patologica e Citopatologia Diagnostica/International Academy of Pathology, Italian division (SIAPEC/IAP). Gastritis: the histology report. *Dig Liver Dis* 2011; **43 Suppl 4**: S373-S384 [PMID: 21459343 DOI: 10.1016/S1590-8658(11)60593-8]

44 **Pittman ME**, Voltaggio L, Bhaijee F, Robertson SA, Montgomery EA. Autoimmune Metaplastic Atrophic Gastritis: Recognizing Precursor Lesions for Appropriate Patient Evaluation. *Am J Surg Pathol* 2015; **39**: 1611-1620 [PMID: 26291507 DOI: 10.1097/PAS.0000000000000481]

45 **Minalyan A**, Benhammou JN, Artashesyan A, Lewis MS, Pisegna JR. Autoimmune atrophic gastritis: current perspectives. *Clin Exp Gastroenterol* 2017; **10**: 19-27 [PMID: 28223833 DOI: 10.2147/CEG.S109123]

46 **Pimentel-Nunes P**, Libânio D, Marcos-Pinto R, Areia M, Leja M, Esposito G, Garrido M, Kikuste I, Megraud F, Matysiak-Budnik T, Annibale B, Dumonceau JM, Barros R, Fléjou JF, Carneiro F, van Hooft JE, Kuipers EJ, Dinis-Ribeiro M. Management of epithelial precancerous conditions and lesions in the stomach (MAPS II): European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter and Microbiota Study Group (EHMSG), European Society of Pathology (ESP), and Sociedade Portuguesa de Endoscopia Digestiva (SPED) guideline update 2019. *Endoscopy* 2019; **51**: 365-388 [PMID: 30841008 DOI: 10.1055/a-0859-1883]

47 **Babu SD**, Jayanthi V, Devaraj N, Reis CA, Devaraj H. Expression profile of mucins (MUC2, MUC5AC and MUC6) in Helicobacter pylori infected pre-neoplastic and neoplastic human gastric epithelium. *Mol Cancer* 2006; **5**: 10 [PMID: 16545139 DOI: 10.1186/1476-4598-5-10]

48 **Reis CA**, David L, Correa P, Carneiro F, de Bolós C, Garcia E, Mandel U, Clausen H, Sobrinho-Simões M. Intestinal metaplasia of human stomach displays distinct patterns of mucin (MUC1, MUC2, MUC5AC, and MUC6) expression. *Cancer Res* 1999; **59**: 1003-1007 [PMID: 10070955]

49 **Jung SH**, Chung WC, Lee KM, Paik CN, Jung JH, Lee MK, Lee YK, Chung IS. Risk factors in malignant transformation of gastric epithelial neoplasia categorized by the revised Vienna classification: endoscopic, pathological, and immunophenotypic features. *Gastric Cancer* 2010; **13**: 123-130 [PMID: 20602200 DOI: 10.1007/s10120-010-0550-7]

50 **Ikarashi S**, Nishikura K, Ajioka Y, Aoyagi Y. Re-evaluation of phenotypic expression in undifferentiated-type early gastric adenocarcinomas using mucin core protein and CDX2. *Gastric Cancer* 2013; **16**: 208-219 [PMID: 22829163 DOI: 10.1007/s10120-012-0172-3]

51 **Milne AN**, Sitarz R, Carvalho R, Carneiro F, Offerhaus GJ. Early onset gastric cancer: on the road to unraveling gastric carcinogenesis. *Curr Mol Med* 2007; **7**: 15-28 [PMID: 17311530]

52 **Ito K**, Liu Q, Salto-Tellez M, Yano T, Tada K, Ida H, Huang C, Shah N, Inoue M, Rajnakova A, Hiong KC, Peh BK, Han HC, Ito T, Teh M, Yeoh KG, Ito Y. RUNX3, a novel tumor suppressor, is frequently inactivated in gastric cancer by protein mislocalization. *Cancer Res* 2005; **65**: 7743-7750 [PMID: 16140942 DOI: 10.1158/0008-5472.CAN-05-0743]

53 **Song JY**, Kim BW, Lee AW, Lee KY, Chung IS, Lee BI, Choi H, Ji JS, Chae HS, Choi KY. Expression of MUC5AC and Trefoil Peptide 1 (TFF1) in the Subtypes of Intestinal Metaplasia. *Clin Endosc* 2012; **45**: 151-154 [PMID: 22866256 DOI: 10.5946/ce.2012.45.2.151]

54 **Schildberg C**, Abbas M, Merkel S, Agaimy A, Dimmler A, Schlabrakowski A, Croner R, Leupolt J, Hohenberger W, Allgayer H. COX-2, TFF1, and Src define better prognosis in young patients with gastric cancer. *J Surg Oncol* 2013; **108**: 409-413 [PMID: 24037722 DOI: 10.1002/jso.23416]

55 **Qin R**, Wang NN, Chu J, Wang X. Expression and significance of homeodomain protein Cdx2 in gastric carcinoma and precancerous lesions. *World J Gastroenterol* 2012; **18**: 3296-3302 [PMID: 22783055 DOI: 10.3748/wjg.v18.i25.3296]

56 **Zhang XY**, Zhang PY, Aboul-Soud MA. From inflammation to gastric cancer: Role of <i>Helicobacter pylori</i>. *Oncol Lett* 2017; **13**: 543-548 [PMID: 28356927 DOI: 10.3892/ol.2016.5506]

57 **Chung HW**, Lim JB. Role of the tumor microenvironment in the pathogenesis of gastric carcinoma. *World J Gastroenterol* 2014; **20**: 1667-1680 [PMID: 24587646 DOI: 10.3748/wjg.v20.i7.1667]

58 **Liu KS**, Wong IO, Leung WK. Helicobacter pylori associated gastric intestinal metaplasia: Treatment and surveillance. *World J Gastroenterol* 2016; **22**: 1311-1320 [PMID: 26811668 DOI: 10.3748/wjg.v22.i3.1311]

59 **Fujimoto A**, Ishikawa Y, Ishii T, Yamada A, Igarashi Y, Ohmoto Y, Kaise M. Differences between gastric signet-ring cell carcinoma and poorly differentiated adenocarcinoma: A comparison of histopathologic features determined by mucin core protein and trefoil factor family peptide immunohistochemistry. *Pathol Int* 2017; **67**: 398-403 [PMID: 28691258 DOI: 10.1111/pin.12559]

60 **Lahner E**, Carabotti M, Annibale B. Treatment of *Helicobacter pylori* infection in atrophic gastritis. *World J Gastroenterol* 2018; **24**: 2373-2380 [PMID: 29904244 DOI: 10.3748/wjg.v24.i22.2373]

61 **Del Prete A**, Allavena P, Santoro G, Fumarulo R, Corsi MM, Mantovani A. Molecular pathways in cancer-related inflammation. *Biochem Med (Zagreb)* 2011; **21**: 264-275 [PMID: 22420240]

62 **Colotta F**, Allavena P, Sica A, Garlanda C, Mantovani A. Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. *Carcinogenesis* 2009; **30**: 1073-1081 [PMID: 19468060 DOI: 10.1093/carcin/bgp127]

63 **Multhoff G**, Radons J. Radiation, inflammation, and immune responses in cancer. *Front Oncol* 2012; **2**: 58 [PMID: 22675673 DOI: 10.3389/fonc.2012.00058]

64 **Qu X**, Tang Y, Hua S. Immunological Approaches Towards Cancer and Inflammation: A Cross Talk. *Front Immunol* 2018; **9**: 563 [PMID: 29662489 DOI: 10.3389/fimmu.2018.00563]

65 **Hussain SP**, Harris CC. Inflammation and cancer: an ancient link with novel potentials. *Int J Cancer* 2007; **121**: 2373-2380 [PMID: 17893866 DOI: 10.1002/ijc.23173]

66 **Georgescu AM**, Bănescu C, Badea I, Moldovan V, Huțanu A, Voidăzan S, Dobreanu M, Azamfirei L. IL-6 gene polymorphisms and sepsis in ICU adult Romanian patients: a prospective study. *Rev Romana Med Lab* 2017; **25**: 75-89 [DOI: 10.1515/rrlm-2016-0044]

67 **Sanjabi S**, Zenewicz LA, Kamanaka M, Flavell RA. Anti-inflammatory and pro-inflammatory roles of TGF-beta, IL-10, and IL-22 in immunity and autoimmunity. *Curr Opin Pharmacol* 2009; **9**: 447-453 [PMID: 19481975 DOI: 10.1016/j.coph.2009.04.008]

68 **Hosono K**, Yamada E, Endo H, Takahashi H, Inamori M, Hippo Y, Nakagama H, Nakajima A. Increased tumor necrosis factor receptor 1 expression in human colorectal adenomas. *World J Gastroenterol* 2012; **18**: 5360-5368 [PMID: 23082052 DOI: 10.3748/wjg.v18.i38.536]

69 **Fei BY**, Lv HX, Cheng YW, Yang JM. Association between the IFN-γ and IL-1 genetic polymorphisms and colorectal cancer in the Chinese Han population. *J Genet* 2014; **93**: 235-239 [PMID: 24840847]

70 **Trifunović J**, Miller L, Debeljak Ž, Horvat V. Pathologic patterns of interleukin 10 expression--a review. *Biochem Med (Zagreb)* 2015; **25**: 36-48 [PMID: 25672465 DOI: 10.11613/BM.2015.004]

71 **Figueiredo CA**, Marques CR, Costa Rdos S, da Silva HB, Alcantara-Neves NM. Cytokines, cytokine gene polymorphisms and Helicobacter pylori infection: friend or foe? *World J Gastroenterol* 2014; **20**: 5235-5243 [PMID: 24833853 DOI: 10.3748/wjg.v20.i18.5235]

72 **El-Omar EM**, Carrington M, Chow WH, McColl KE, Bream JH, Young HA, Herrera J, Lissowska J, Yuan CC, Rothman N, Lanyon G, Martin M, Fraumeni JF Jr, Rabkin CS. Interleukin-1 polymorphisms associated with increased risk of gastric cancer. *Nature* 2000; **404**: 398-402 [PMID: 10746728 DOI: 10.1038/35006081]

73 **Wang YM**, Li ZX, Tang FB, Zhang Y, Zhou T, Zhang L, Ma JL, You WC, Pan KF. Association of genetic polymorphisms of interleukins with gastric cancer and precancerous gastric lesions in a high-risk Chinese population. *Tumour Biol* 2016; **37**: 2233-2242 [PMID: 26358252 DOI: 10.1007/s13277-015-4022-x]

74 **Bockerstett KA**, DiPaolo RJ. Regulation of Gastric Carcinogenesis by Inflammatory Cytokines. *Cell Mol Gastroenterol Hepatol* 2017; **4**: 47-53 [PMID: 28560288 DOI: 10.1016/j.jcmgh.2017.03.005]

75 **Stubljar D**, Jeverica S, Jukic T, Skvarc M, Pintar T, Tepes B, Kavalar R, Stabuc B, Peterlin B, Ihan A. The influence of cytokine gene polymorphisms on the risk of developing gastric cancer in patients with Helicobacter pylori infection. *Radiol Oncol* 2015; **49**: 256-264 [PMID: 26401131 DOI: 10.2478/raon-2014-0041]

76 **Gao L**, Weck MN, Michel A, Pawlita M, Brenner H. Association between chronic atrophic gastritis and serum antibodies to 15 Helicobacter pylori proteins measured by multiplex serology. *Cancer Res* 2009; **69**: 2973-2980 [PMID: 19318564 DOI: 10.1158/0008-5472.CAN-08-3477]

77 **Peleteiro B**, Lunet N, Carrilho C, Durães C, Machado JC, La Vecchia C, Barros H. Association between cytokine gene polymorphisms and gastric precancerous lesions: systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev* 2010; **19**: 762-776 [PMID: 20200422 DOI: 10.1158/1055-9965.EPI-09-0917]

78 **Zhao H**, Liu L, Liu B, Wang Y, Li F, Yu H. An updated association between TNF-α -238G/A polymorphism and gastric cancer susceptibility in East Asians. *Biosci Rep* 2018; **38**: pii: BSR20181231 [PMID: 30413607 DOI: 10.1042/BSR20181231]

79 **Santos JC**, Ladeira MS, Pedrazzoli J Jr, Ribeiro ML. Relationship of IL-1 and TNF-α polymorphisms with Helicobacter pylori in gastric diseases in a Brazilian population. *Braz J Med Biol Res* 2012; **45**: 811-817 [PMID: 22714811]

80 **Starzyńska T**, Ferenc K, Wex T, Kähne T, Lubiński J, Lawniczak M, Marlicz K, Malfertheiner P. The association between the interleukin-1 polymorphisms and gastric cancer risk depends on the family history of gastric carcinoma in the study population. *Am J Gastroenterol* 2006; **101**: 248-254 [PMID: 16454826 DOI: 10.1111/j.1572-0241.2006.00422.x]

81 **Bagheri V**, Memar B, Momtazi AA, Sahebkar A, Gholamin M, Abbaszadegan MR. Cytokine networks and their association with Helicobacter pylori infection in gastric carcinoma. *J Cell Physiol* 2018; **233**: 2791-2803 [PMID: 28121015 DOI: 10.1002/jcp.25822]

82 **Xue H**, Lin B, Ni P, Xu H, Huang G. Interleukin-1B and interleukin-1 RN polymorphisms and gastric carcinoma risk: a meta-analysis. *J Gastroenterol Hepatol* 2010; **25**: 1604-1617 [PMID: 20880168 DOI: 10.1111/j.1440-1746.2010.06428.x]

83 **Gehmert S**, Velapatiño B, Herrera P, Balqui J, Santivañez L, Cok J, Vargas G, Combe J, Passaro DJ, Wen S, Meyer F, Berg DE, Gilman RH. Interleukin-1 beta single-nucleotide polymorphism's C allele is associated with elevated risk of gastric cancer in Helicobacter pylori-infected Peruvians. *Am J Trop Med Hyg* 2009; **81**: 804-810 [PMID: 19861615 DOI: 10.4269/ajtmh.2009.08-0494]

84 **Chiurillo MA**, Moran Y, Cañas M, Valderrama E, Alvarez A, Armanie E. Combination of Helicobacter pylori-iceA2 and proinflammatory interleukin-1 polymorphisms is associated with the severity of histological changes in Venezuelan chronic gastritis patients. *FEMS Immunol Med Microbiol* 2010; **59**: 170-176 [PMID: 20482626 DOI: 10.1111/j.1574-695X.2010.00675.x]

85 **Chiurillo MA**, Moran YH, Cañas M, Valderrama EJ, Armanie E. Infection with specific Helicobacter pylori-cag pathogenicity island strains is associated with interleukin-1B gene polymorphisms in Venezuelan chronic gastritis patients. *Dig Dis Sci* 2011; **56**: 449-456 [PMID: 20585978 DOI: 10.1007/s10620-010-1316-0]

86 **Caleman Neto A**, Rasmussen LT, de Labio RW, de Queiroz VF, Smith Mde A, Viani GA, Payão SL. Gene polymorphism of interleukin 1 and 8 in chronic gastritis patients infected with Helicobacter pylori. *J Venom Anim Toxins Incl Trop Dis* 2014; **20**: 17 [PMID: 24803922 DOI: 10.1186/1678-9199-20-17]

87 **Con SA**, Con-Wong R, Con-Chin GR, Con-Chin VG, Takeuchi H, Valerín AL, Echandi G, Mena F, Brenes F, Yasuda N, Araki K, Sugiura T. Serum pepsinogen levels, Helicobacter pylori CagA Status, and cytokine gene polymorphisms associated with gastric premalignant lesions in Costa Rica. *Cancer Epidemiol Biomarkers Prev* 2007; **16**: 2631-2636 [PMID: 18086767 DOI: 10.1158/1055-9965.EPI-07-0215]

88 **Chen ML**, Liao N, Zhao H, Huang J, Xie ZF. Association between the IL1B (-511), IL1B (+3954), IL1RN (VNTR) polymorphisms and Graves' disease risk: a meta-analysis of 11 case-control studies. *PLoS One* 2014; **9**: e86077 [PMID: 24465880 DOI: 10.1371/journal.pone.0086077]

89 **Melchiades JL**, Zabaglia LM, Sallas ML, Orcini WA, Chen E, Smith MAC, Payão SLM, Rasmussen LT. Polymorphisms and haplotypes of the interleukin 2 gene are associated with an increased risk of gastric cancer. The possible involvement of Helicobacter pylori. *Cytokine* 2017; **96**: 203-207 [PMID: 28458166 DOI: 10.1016/j.cyto.2017.04.020]

90 **Shin WG**, Jang JS, Kim HS, Kim SJ, Kim KH, Jang MK, Lee JH, Kim HJ, Kim HY. Polymorphisms of interleukin-1 and interleukin-2 genes in patients with gastric cancer in Korea. *J Gastroenterol Hepatol* 2008; **23**: 1567-1573 [PMID: 18761558 DOI: 10.1111/j.1440-1746.2008.05479.x]

91 **Zhao H**, Wang R. IL-2 -330T/G polymorphism and cancer risk: a meta-analysis. *Onco Targets Ther* 2015; **8**: 1753-1760 [PMID: 26229483 DOI: 10.2147/OTT.S86136]

92 **Liu Y**, Xu Y, Wang Y, Yao Y, Yang J. Associations between interleukin gene polymorphisms and the risk of gastric cancer: A meta-analysis. *Clin Exp Pharmacol Physiol* 2018; **45**: 1236-1244 [PMID: 30071135 DOI: 10.1111/1440-1681.13021]

93 **Van Dyken SJ**, Locksley RM. Interleukin-4- and interleukin-13-mediated alternatively activated macrophages: roles in homeostasis and disease. *Annu Rev Immunol* 2013; **31**: 317-343 [PMID: 23298208 DOI: 10.1146/annurev-immunol-032712-095906]

94 **Sampaio AM**, Balseiro SC, Silva MR, Alarcão A, d'Aguiar MJ, Ferreira T, Carvalho L. Association Between IL-4 and IL-6 Expression Variants and Gastric Cancer Among Portuguese Population. *GE Port J Gastroenterol* 2015; **22**: 143-152 [PMID: 28868397 DOI: 10.1016/j.jpge.2015.04.001]

95 **Pan XF**, Wen Y, Loh M, Wen YY, Yang SJ, Zhao ZM, Tian Z, Huang H, Lan H, Chen F, Soong R, Yang CX. Interleukin-4 and -8 gene polymorphisms and risk of gastric cancer in a population in Southwestern China. *Asian Pac J Cancer Prev* 2014; **15**: 2951-2957 [PMID: 24815430]

96 **Kato I**, Canzian F, Franceschi S, Plummer M, van Doorn LJ, Lu Y, Gioia-Patricola L, Vivas J, Lopez G, Severson RK, Schwartz AG, Muñoz N. Genetic polymorphisms in anti-inflammatory cytokine signaling and the prevalence of gastric precancerous lesions in Venezuela. *Cancer Causes Control* 2006; **17**: 1183-1191 [PMID: 17006724 DOI: 10.1007/s10552-006-0060-4]

97 **Leja M**, Wex T, Malfertheiner P. Markers for gastric cancer premalignant lesions: where do we go? *Dig Dis* 2012; **30**: 268-276 [PMID: 22722551 DOI: 10.1159/000336990]

98 **Fishman D**, Faulds G, Jeffery R, Mohamed-Ali V, Yudkin JS, Humphries S, Woo P. The effect of novel polymorphisms in the interleukin-6 (IL-6) gene on IL-6 transcription and plasma IL-6 levels, and an association with systemic-onset juvenile chronic arthritis. *J Clin Invest* 1998; **102**: 1369-1376 [PMID: 9769329 DOI: 10.1172/JCI2629]

99 **Yamaoka Y**, Kita M, Kodama T, Sawai N, Imanishi J. Helicobacter pylori cagA gene and expression of cytokine messenger RNA in gastric mucosa. *Gastroenterology* 1996; **110**: 1744-1752 [PMID: 8964399]

100 **Crusius JB**, Canzian F, Capellá G, Peña AS, Pera G, Sala N, Agudo A, Rico F, Del Giudice G, Palli D, Plebani M, Boeing H, Bueno-de-Mesquita HB, Carneiro F, Pala V, Save VE, Vineis P, Tumino R, Panico S, Berglund G, Manjer J, Stenling R, Hallmans G, Martínez C, Dorronsoro M, Barricarte A, Navarro C, Quirós JR, Allen N, Key TJ, Binghan S, Caldas C, Linseisen J, Kaaks R, Overvad K, Tjønneland A, Büchner FC, Peeters PH, Numans ME, Clavel-Chapelon F, Trichopoulou A, Lund E, Jenab M, Rinaldi S, Ferrari P, Riboli E, González CA. Cytokine gene polymorphisms and the risk of adenocarcinoma of the stomach in the European prospective investigation into cancer and nutrition (EPIC-EURGAST). *Ann Oncol* 2008; **19**: 1894-1902 [PMID: 18628242 DOI: 10.1093/annonc/mdn400]

101 **Gatti LL**, Burbano RR, Zambaldi-Tunes M, de-Lábio RW, de Assumpção PP, de Arruda Cardoso-Smith M, Marques-Payão SL. Interleukin-6 polymorphisms, Helicobacter pylori infection in adult Brazilian patients with chronic gastritis and gastric adenocarcinoma. *Arch Med Res* 2007; **38**: 551-555 [PMID: 17560462 DOI: 10.1016/j.arcmed.2006.12.011]

102 **Taguchi A**, Ohmiya N, Shirai K, Mabuchi N, Itoh A, Hirooka Y, Niwa Y, Goto H. Interleukin-8 promoter polymorphism increases the risk of atrophic gastritis and gastric cancer in Japan. *Cancer Epidemiol Biomarkers Prev* 2005; **14**: 2487-2493 [PMID: 16284368 DOI: 10.1158/1055-9965.EPI-05-0326]

103 **Li ZW**, Wu Y, Sun Y, Liu LY, Tian MM, Feng GS, You WC, Li JY. Inflammatory cytokine gene polymorphisms increase the risk of atrophic gastritis and intestinal metaplasia. *World J Gastroenterol* 2010; **16**: 1788-1794 [PMID: 20380014]

104 **Chang YW**, Oh CH, Kim JW, Lee JW, Park MJ, Shim JJ, Lee CK, Jang JY, Dong SH, Kim HJ, Kim SS, Kim BH. Combination of Helicobacter pylori infection and the interleukin 8 -251 T &gt; A polymorphism, but not the mannose-binding lectin 2 codon 54 G &gt; A polymorphism, might be a risk factor of gastric cancer. *BMC Cancer* 2017; **17**: 388 [PMID: 28558668 DOI: 10.1186/s12885-017-3378-2]

105 **Lu W**, Pan K, Zhang L, Lin D, Miao X, You W. Genetic polymorphisms of interleukin (IL)-1B, IL-1RN, IL-8, IL-10 and tumor necrosis factor {alpha} and risk of gastric cancer in a Chinese population. *Carcinogenesis* 2005; **26**: 631-636 [PMID: 15579481 DOI: 10.1093/carcin/bgh349]

106 **Liu S**, Liu JW, Sun LP, Gong YH, Xu Q, Jing JJ, Yuan Y. Association of IL10 gene promoter polymorphisms with risks of gastric cancer and atrophic gastritis. *J Int Med Res* 2018; **46**: 5155-5166 [PMID: 30205739 DOI: 10.1177/0300060518792785]

107 **Con SA**, Takeuchi H, Con-Chin GR, Con-Chin VG, Yasuda N, Con-Wong R. Role of bacterial and genetic factors in gastric cancer in Costa Rica. *World J Gastroenterol* 2009; **15**: 211-218 [PMID: 19132772 DOI: 10.3748/wjg.15.211]

108 **Ramis IB**, Vianna JS, Gonçalves CV, von Groll A, Dellagostin OA, da Silva PEA. Polymorphisms of the IL-6, IL-8 and IL-10 genes and the risk of gastric pathology in patients infected with Helicobacter pylori. *J Microbiol Immunol Infect* 2017; **50**: 153-159 [PMID: 25888319 DOI: 10.1016/j.jmii.2015.03.002]

109 **Murphy G**, Thornton J, McManus R, Swan N, Ryan B, Hughes DJ, O'Morain CA, O'Sullivan M. Association of gastric disease with polymorphisms in the inflammatory-related genes IL-1B, IL-1RN, IL-10, TNF and TLR4. *Eur J Gastroenterol Hepatol* 2009; **21**: 630-635 [PMID: 19295440 DOI: 10.1097/MEG.0b013e3283140eea]

110 **Myung DS**, Lee WS, Park YL, Kim N, Oh HH, Kim MY, Oak CY, Chung CY, Park HC, Kim JS, Cho SB, Kweon SS, Joo YE. Association between interleukin-18 gene polymorphism and Helicobacter pylori infection in the Korean population. *Sci Rep* 2015; **5**: 11535 [PMID: 26096341 DOI: 10.1038/srep11535]

111 **Leung WK**, Chan MC, To KF, Man EP, Ng EK, Chu ES, Lau JY, Lin SR, Sung JJ. H. pylori genotypes and cytokine gene polymorphisms influence the development of gastric intestinal metaplasia in a Chinese population. *Am J Gastroenterol* 2006; **101**: 714-720 [PMID: 16635219 DOI: 10.1111/j.1572-0241.2006.00560.x]

112 **Cheung H**, Chen NJ, Cao Z, Ono N, Ohashi PS, Yeh WC. Accessory protein-like is essential for IL-18-mediated signaling. *J Immunol* 2005; **174**: 5351-5357 [PMID: 15843532]

113 **Zhuang Y**, Cheng P, Liu XF, Peng LS, Li BS, Wang TT, Chen N, Li WH, Shi Y, Chen W, Pang KC, Zeng M, Mao XH, Yang SM, Guo H, Guo G, Liu T, Zuo QF, Yang HJ, Yang LY, Mao FY, Lv YP, Zou QM. A pro-inflammatory role for Th22 cells in Helicobacter pylori-associated gastritis. *Gut* 2015; **64**: 1368-1378 [PMID: 25134787 DOI: 10.1136/gutjnl-2014-307020]

114 **Dixon BR**, Radin JN, Piazuelo MB, Contreras DC, Algood HM. IL-17a and IL-22 Induce Expression of Antimicrobials in Gastrointestinal Epithelial Cells and May Contribute to Epithelial Cell Defense against Helicobacter pylori. *PLoS One* 2016; **11**: e0148514 [PMID: 26867135 DOI: 10.1371/journal.pone.0148514]

115 **Hong JT**, Son DJ, Lee CK, Yoon DY, Lee DH, Park MH. Interleukin 32, inflammation and cancer. *Pharmacol Ther* 2017; **174**: 127-137 [PMID: 28223235 DOI: 10.1016/j.pharmthera.2017.02.025]

116 **Canedo P**, Corso G, Pereira F, Lunet N, Suriano G, Figueiredo C, Pedrazzani C, Moreira H, Barros H, Carneiro F, Seruca R, Roviello F, Machado JC. The interferon gamma receptor 1 (IFNGR1) -56C/T gene polymorphism is associated with increased risk of early gastric carcinoma. *Gut* 2008; **57**: 1504-1508 [PMID: 18593809 DOI: 10.1136/gut.2007.143578]

117 **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 [PMID: 26798436 DOI: 10.4251/wjgo.v8.i1.40]

118 **Díaz P**, Valenzuela Valderrama M, Bravo J, Quest AFG. *Helicobacter pylori* and Gastric Cancer: Adaptive Cellular Mechanisms Involved in Disease Progression. *Front Microbiol* 2018; **9**: 5 [PMID: 29403459 DOI: 10.3389/fmicb.2018.00005]

119 **Semino-Mora C**, Doi SQ, Marty A, Simko V, Carlstedt I, Dubois A. Intracellular and interstitial expression of Helicobacter pylori virulence genes in gastric precancerous intestinal metaplasia and adenocarcinoma. *J Infect Dis* 2003; **187**: 1165-1177 [PMID: 12695995 DOI: 10.1086/368133]

120 **Houghton J**, Stoicov C, Nomura S, Rogers AB, Carlson J, Li H, Cai X, Fox JG, Goldenring JR, Wang TC. Gastric cancer originating from bone marrow-derived cells. *Science* 2004; **306**: 1568-1571 [PMID: 15567866 DOI: 10.1126/science.1099513]

121 **Hayakawa Y**, Fox JG, Wang TC. The Origins of Gastric Cancer From Gastric Stem Cells: Lessons From Mouse Models. *Cell Mol Gastroenterol Hepatol* 2017; **3**: 331-338 [PMID: 28462375 DOI: 10.1016/j.jcmgh.2017.01.013]

122 **Steenport M**, Eom H, Uezu M, Schneller J, Gupta R, Mustafa Y, Villanueva R, Straus EW, Raffaniello RD. Association of polymorphisms in myeloperoxidase and catalase genes with precancerous changes in the gastric mucosa of patients at inner-city hospitals in New York. *Oncol Rep* 2007; **18**: 235-240 [PMID: 17549373]

123 **Yi JF**, Li YM, Liu T, He WT, Li X, Zhou WC, Kang SL, Zeng XT, Zhang JQ. Mn-SOD and CuZn-SOD polymorphisms and interactions with risk factors in gastric cancer. *World J Gastroenterol* 2010; **16**: 4738-4746 [PMID: 20872977]

124 **Negovan A**, Iancu M, Tripon F, Crauciuc A, Mocan S, Bănescu C. The CAT-262 C&gt;T, MnSOD Ala16Val, GPX1 Pro198Leu Polymorphisms Related to Oxidative Stress and the Presence of Gastric Lesions. *J Gastrointestin Liver Dis* 2018; **27**: 371-378 [PMID: 30574618 DOI: 10.15403/jgld.2014.1121.274.cat]

125 **Chen ZH**, Xian JF, Luo LP. Association between GSTM1, GSTT1, and GSTP1 polymorphisms and gastric cancer risk, and their interactions with environmental factors. *Genet Mol Res* 2017; **16**: [PMID: 28198496 DOI: 10.4238/gmr16018877]

126 **Negovan A**, Iancu M, Moldovan V, Mocan S, Banescu C. The Interaction between <i>GSTT1</i>, <i>GSTM1</i>, and <i>GSTP1</i> Ile105Val Gene Polymorphisms and Environmental Risk Factors in Premalignant Gastric Lesions Risk. *Biomed Res Int* 2017; **2017**: 7365080 [PMID: 28182092 DOI: 10.1155/2017/7365080]

127 **Garg M**, Angus PW, Burrell LM, Herath C, Gibson PR, Lubel JS. Review article: the pathophysiological roles of the renin-angiotensin system in the gastrointestinal tract. *Aliment Pharmacol Ther* 2012; **35**: 414-428 [PMID: 22221317 DOI: 10.1111/j.1365-2036.2011.04971.x]

128 **Shiotani A**, Nishi R, Yamanaka Y, Murao T, Matsumoto H, Tarumi K, Kamada T, Sakakibara T, Haruma K. Renin-angiotensin system associated with risk of upper GI mucosal injury induced by low dose aspirin: renin angiotensin system genes' polymorphism. *Dig Dis Sci* 2011; **56**: 465-471 [PMID: 20824505 DOI: 10.1007/s10620-010-1382-3]

129 **Negovan A**, Voidăzan S, Pantea M, Moldovan V, Bataga S, Cozlea L, Mocan S, Banescu C. AGT A-20C (rs5050) gene polymorphism and ulcer occurrence in patients treated with low-dose aspirin: a case-control study. *Rev Romana Med Lab 2015*; **23**: 179-87 [DOI: 10.1515/rrlm-2015-0017]

130 **Graham DY**, Zou WY. Guilt by association: intestinal metaplasia does not progress to gastric cancer. *Curr Opin Gastroenterol* 2018; **34**: 458-464 [PMID: 30138135 DOI: 10.1097/MOG.0000000000000472]

131 **Trieu JA**, Bilal M, Saraireh H, Wang AY. Update on the Diagnosis and Management of Gastric Intestinal Metaplasia in the USA. *Dig Dis Sci* 2019; **64**: 1079-1088 [PMID: 30771043 DOI: 10.1007/s10620-019-05526-5]

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Grade C (Good): C

Grade D (Fair): D

Grade E (Poor): 0

**Table 1 Statistical methods used in mentioned original research articles that analysed the relationship between cytokine gene variants and premalignant gastric lesions**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Target population (sample size)** | **Cytokine SNPs1** | **Outcomes** | **Confounding factors/other covariates** | **Control for confounding/covariate effect** | **Statistical methods** |
| [73] | Chinese adult patients (1330) | IL-8-4073, IL-18RAP917997, IL-1Brs1143627, IL-1B rs1143634, IL-1Brs16944, IL-4Rrs2057768, IL-10rs1800896, IL-22rs1179251, IL-32rs2015620 | ChAG risk  IM risk  DYS risk  GC risk | Age, sex, smoking status, *H. pylori* | Stratification, adjustment | *χ2* test, multivariable logistic model with interaction term, Synergy index |
| [75] | Slovenian adults (318) | TNF-α -308, IL-1RN,  IL-1B -511 | ChAG risk,  GC risk | Gender | Adjustment | *χ2* test, Multivariable logistic model |
| [76] | German older  adults (1068) | TNF-α -308, IL10T-819C, IL10A-1082G, IL1AC-889T, IL1B C-511T, IL1RN 9589T, IL8 T-251A | ChAG risk | Age, gender | Adjustment | Multivariable logistic model |
| [83] | Peruvian Amerindian adults (334) | IL-1B-511, IL-1RN | ChAG risk  GCrisk | Age, gender,  *H. pylori* | Adjustment | *χ2* test/Fisher’s exact test, multivariable logistic model |
| [84] | Venezuelan adults (109) | IL-1B-31, IL-1B-511, IL-1B+13954,  IL-1RN | ChAG risk  GI risk  LI risk | *H. pylori* | Adjustment | *χ2* test/Fisher’s exact test, univariable logistic model |
| [87] | Costa Rican  adults (223) | IL-1β-511, IL-1β-3954, IL-1RN intron 2, IL-10 -1082, IL-10 -592 | AG risk  CoAG risk  IM risk | Sex, age, *H. pylori* | Adjustment | *χ2* test/Fisher’s exact test, multivariable logistic model |
| [96] | Venezuelan adults (2033) | IL4 –590, IL4R -3223,  IL4R -398, IL10 –1082 | AG risk  IM risk  DYS risk | Age, sex, *H. pylori,* education, environmental factors | Adjustment | *χ2* test/Fisher’s exact test, multivariable logistic model |
| [101] | Brazilian adults (112) | IL-6 | ChG  GC | None | None | *χ2* test/Fisher’s exact test |
| [102] | Japanese adults (863) | IL-8 -251, IL-1B -511, IL-1RN | AG  GC | Age, sex, *H. pylori* | Adjustment | *χ2* test/Fisher’s exact test, multivariable logistic model |
| [103] | Chinese adults  (372) | IL-8-251 | Severe ChAG risk  IM risk | Age, gender | Stratification, adjustment | *χ2* test, multivariable logistic model, Synergy index |
| [106] | Chinese adult patients (556) | IL-10-1082, IL-10-819, IL-10-592 | AG risk  GC risk | Age, sex, *H. pylori* | Stratification, adjustment | *χ2* test, multivariable logistic model with interaction term |
|
|
| [108] | Brazilian adults (227) | IL-6-174, IL-8-251, IL-10-819 | Gastritis, peptic ulcer, GC | *H. pylori* infection | Stratification | *χ2* test/Fisher’s exact test |
| [111] | Chinese adults *H. pylori* (302) | IL-1B-511 | IM risk | Age | Adjustment | *χ2* test/Fisher’s exact test, univariable/multivariable logistic model |
|
|
|

Only the original research articles containing analysis of cytokines’ genotypes (not haplotypes) were included. 1Only the discussed cytokine SNPs of interest (and not all of SNPs mentioned in the above studies) are described. AG: Atrophic gastritis; CoAG: Corpus atrophic gastritis; ChAG: Chronic atrophic gastritis (the term used in original research); ChG: Chronic gastritis; DYS: Dysplasia; GC: Gastric cancer; GI: Granulocytic infiltration; IM: Intestinal metaplasia; LI: Lymphocytic infiltration; *H. pylori*: *Helicobacter pylori*.

**Table 2 Frequencies of studied cytokine SNP genotypes and significance of relationships with premalignant gastric lesions in the discussed scientific articles**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Ref.** | **SNP1** | **Variant genotypes** | **Frequency (%) of variant genotypes in premalignant gastric lesions *vs* control** | **Premalignant gastric lesions** |
| [73] | IL-8-4073 | TA | 145 (48.5)/144 (48.6) | ChAG susceptibility |
|  |  | AA | 53 (17.7)/50 (16.9) |  |
|  |  | TA | 148 (49.5)/144 (48.6) | IM susceptibility |
|  |  | AA | 50 (16.7)/50 (16.9) |  |
|  |  | TA | 140 (46.4)/144 (48.6) | DYS susceptibility |
|  |  | AA | 48 (15.9)/50 (16.9) |  |
|  | IL-18RAP917997 | AGa | 130 (43.9)/166 (56.3) | ChAG susceptibility |
|  |  | GG | 72 (24.3)/61 (20.7) |  |
|  |  | AG | 167 (56.4)/166 (56.3) | IM susceptibility |
|  |  | GG | 57 (19.3)/61 (20.7) |  |
|  |  | AG | 151 (50.0)/166 (56.3) | DYS susceptibility |
|  |  | GG | 66 (21.8)/61 (20.7) |  |
|  | IL-1Brs1143627 | TC | 152 (50.9)/144 (48.5) | ChAG susceptibility |
|  |  | CC | 59 (19.7)/66 (22.2) |  |
|  |  | TC | 148 (49.3)/144 (48.5) | IM susceptibility |
|  |  | CC | 68 (22.7)/66 (22.2) |  |
|  |  | TC | 158 (52.5)/144 (48.5) | DYS susceptibility |
|  |  | CC | 71 (23.6)/66 (22.2) |  |
|  | IL-1Brs1143634 | CT | 15 (5.0)/21 (7.1) | ChAG susceptibility |
|  |  | TT | 0 (0.0)/1 (0.3) |  |
|  |  | CT | 14 (4.7)/21 (7.1) | IM susceptibility |
|  |  | TT | 0 (0.0)/1 (0.3) |  |
|  |  | CT | 13 (4.3)/21 (7.1) | DYS susceptibility |
|  |  | TT | 0 (0.0)/1 (0.3) |  |
|  | IL-1Brs16944 | GA | 153 (51.2)/143 (48.2) | ChAG susceptibility |
|  |  | AA | 57 (19.0)/66 (22.2) |  |
|  |  | GA | 147 (49.0)/143 (48.2) | IM susceptibility |
|  |  | AA | 67 (22.3)/66 (22.2) |  |
|  |  | GA | 156 (51.6)/143 (48.2) | DYS susceptibility |
|  |  | AA | 70 (23.2)/66 (22.2) |  |
|  | IL-4Rrs2057768 | AG | 140 (46.8)/150 (50.7) | ChAG susceptibility |
|  |  | GG | 71 (23.8)/61 (20.6) |  |
|  |  | AG | 129 (43.1)/150 (50.7) | IM susceptibility |
|  |  | GG | 80 (26.8)/61 (20.6) |  |
|  |  | AG | 154 (51.2)/150 (50.7) | DYS susceptibility |
|  |  | GG | 59 (19.6)/61 (20.6) |  |
|  | IL-10rs1800896 | AG | 61 (20.4)/53 (17.9) | ChAG susceptibility |
|  |  | GG | 1 (0.3)/3 (1.0) |  |
|  |  | AG | 53 (17.6)/53 (17.9) | IM susceptibility |
|  |  | GG | 5 (1.7)/3 (1.0) |  |
|  |  | AG | 52 (17.3)/53 (17.9) | DYS susceptibility |
|  |  | GG | 2 (0.7)/3 (1.0) |  |
|  | IL-32rs2015620 | AT | 135 (45.8)/133 (45.7) | ChAG susceptibility |
|  |  | TT | 78 (26.4)/82 (28.2) |  |
|  |  | AT | 144 (48.8)/133 (45.7) | IM susceptibility |
|  |  | TT | 73 (24.8)/82 (28.2) |  |
|  |  | AT | 151 (50.0)/133 (45.7) | DYS susceptibility |
|  |  | TT | 76 (25.2)/82 (28.2) |  |
|  | IL-22rs1179251 | CGa | 82 (27.4)/143 (48.1) | ChAG susceptibility |
|  |  | GGa | 20 (6.7)/29 (9.8) |  |
|  |  | CGa | 47 (15.7)/143 (48.1) | IM susceptibility |
|  |  | GGa | 12 (4.0)/29 (9.8) |  |
|  |  | CG | 111 (36.7)/143 (48.1) | DYS susceptibility |
|  |  | GG | 28 (9.3)/29 (9.8) |  |
| [75] | TNF-α -308 | GA | 15 (29.4)/22 (20.4) | ChAG susceptibility |
|  |  | AA | 0 (0)/3 (2.8) |  |
|  | IL-1B -511 | CT | 18 (35.3)/53 (49.1) | ChAG susceptibility |
|  |  | TT | 3 (5.9)/13 (12.0) |  |
|  | IL-1RN | L/2 | 15 (29.4)/32 (29.6) | ChAG susceptibility |
|  |  | 2/2 | 2 (3.9)/13 (12.0) |  |
| [76] | TNF-α -308 | GA | 125 (23.4)/129 (24.2) | ChAG susceptibility |
|  |  | AA | 13 (2.4)/8 (1.5) |  |
|  | IL10T-819C | TC | 200 (37.5)/199 (37.3) | ChAG susceptibility |
|  |  | CCa | 44 (8.2)/28 (5.2) |  |
|  | IL10 A-1082G | AG | 246 (46.1)/262 (49.1) | ChAG susceptibility |
|  |  | GG | 109 (20.4)/116 (21.7) |  |
|  | IL1A C-889T | CT | 213 (39.9)/203 (38.0) | ChAG susceptibility |
|  |  | TT | 37 (6.9)/43 (8.1) |  |
|  | IL1B C-511T | CT | 205 (38.4)/230 (43.1) | ChAG susceptibility |
|  |  | TT | 59 (11.0)/52 (9.7) |  |
|  | IL1RN | AT | 212 (39.7)/219 (41.0) | ChAG susceptibility |
|  |  | TT | 39 (7.3)/35 (6.6) |  |
|  | IL8T-251A | TA | 273 (51.1)/254 (47.6) | ChAG susceptibility |
|  |  | AA | 100 (18.7)/114 (21.3) |  |
| [83] | IL-1B-511 | CTa | 21 (48.8)/28 (32.6) | ChAG risk |
|  |  | CCa | 7 (16.3)/3 (3.5) |  |
|  | IL-1RN | 2/L | 21 (50.0)/46 (53.5) | ChAG risk |
|  |  | 2/2 | 8 (19.0)/10 (11.6) |  |
| [84] | IL-1B 31C | CC+CT | 70 (84.3)/21 (80.8) | ChAG risk |
|  | IL-1B 31C | CC+CT | 18 (100)/73 (80.2) | moderate/severe GI risk |
|  | IL-1B 31C | CC+CT | 22 (91.7)/69 (81.2) | moderate/severe  LI risk |
|  | IL-1B 511T | TT+CT | 71 (85.5)/20 (76.9) | ChAG risk |
|  | IL-1B 511T | TT+CT | 18 (100)/73 (80.2) | Moderate/severe GI risk |
|  | IL-1B 511T | TT+CT | 22 (91.7)/69 (81.2) | Moderate/severe  LI risk |
|  | IL-1RN\*2 | \*1/\* 2+\*2/\* 2 | 40 (48.2)/10 (38.5) | ChAG risk |
|  | IL-1RN\*2 | \*1/\* 2+\*2/\* 2 | 7 (38.9)/43 (51.8) | Moderate/severe GI risk |
|  | IL-1RN\*2 | \*1/\* 2+\*2/\* 2 | 12 (50.0)/38 (44.7) | Moderate/severe  LI risk |
| [87] | IL-1β-511 | TT | 16 (27.6)/26 (15.8) | AG risk |
|  |  | TC | 30 (51.7)/88 (53.3) |  |
|  |  | TT | 8 (25.8)/34 (17.7) | CoAG risk |
|  |  | TC | 16 (51.6)/102 (53.1) |  |
|  |  | TT | 8 (34.8)/34 (15.2) | IM risk |
|  |  | TC | 12 (52.2)/106 (47.5) |  |
|  | IL-1β+3954 | TT | 1 (1.7)/2 (1.2) | AG risk |
|  |  | TC | 33 (56.9)/77 (46.7) |  |
|  |  | TT | 0 (0.0)/3 (1.6) | CoAG risk |
|  |  | TC | 19 (61.3)/91 (47.4) |  |
|  |  | TTa | 0 (0.0)/3 (1.3) | IM risk |
|  |  | TCa | 18 (78.2)/92 (41.2) |  |
|  | IL-1RN intron2 | 2/2 | 13 (22.4)/20 (12.1) | AG risk |
|  |  | 2/L | 18 (31.0)/49 (29.7) |  |
|  |  | 2/2 | 9 (29.0)/24 (12.5) | CoAG risk |
|  |  | 2/L | 8 (25.8)/59 (30.7) |  |
|  |  | 2/2a | 8 (34.8)/25 (11.2) | IM risk |
|  |  | 2/L | 5 (21.7)/62 (27.8) |  |
|  | IL-10 -1082 | AA | 35 (60.3)/81 (49.1) | AG risk |
|  |  | GA | 17 (29.3)/56 (33.9) |  |
|  |  | AA | 17 (54.8)/99 (51.6) | CoAG risk |
|  |  | GA | 10 (32.3)/63 (32.8) |  |
|  |  | AA | 12 (52.2)/104 (46/6) | IM risk |
|  |  | GA | 10 (43.5)/63 (28.3) |  |
|  | IL-10 -592 | AA | 8 (13.8)/12 (7.3) | AG risk |
|  |  | CA | 19 (32.8)/58 (35.1) |  |
|  |  | AA | 4 (12.9)/16 (8.3) | CoAG risk |
|  |  | CA | 10 (32.3)/67 (34.9) |  |
|  |  | AA | 4 (17.4)/16 (7.2) | IM risk |
|  |  | CA | 8 (34.8)/69 (30.9) |  |
| [96] | IL4–590 | CT | 111 (38.4)/414 (38.2) | AG risk |
|  |  | CC | 134 (46.3)/506 (46.7) |  |
|  | IL4–590 | CT | 197 (36.2)/414 (38.2) | IM risk |
|  |  | CC | 264 (48.6)/506 (46.7) |  |
|  | IL4–590 | CT | 48 (40.7)/414 (38.2) | DYS risk |
|  |  | CC | 51 (43.2)/506 (46.7) |  |
|  | IL4R–3223 | CT | 96 (33.2)/362 (33.4) | AG risk |
|  |  | CC | 22 (7.6)/74 (6.8) |  |
|  | IL4R–3223 | CT | 175 (32.2)/362 (33.4) | IM risk |
|  |  | CC | 36 (6.6)/74 (6.8) |  |
|  | IL4R–3223 | CT | 42 (35.6)/362 (33.4) | DYS risk |
|  |  | CC | 6 (5.1)/74 (6.8) |  |
|  | IL4R-398 | AG | 128 (44.3)/488 (45.1) | AG risk |
|  |  | GGa | 71 (24.6)/201 (18.6) |  |
|  |  | AG | 243 (44.8)/488 (45.1) | IM risk |
|  |  | GG | 106 (19.5)/201 (18.6) |  |
|  |  | AG | 49 (41.5)/488 (45.1) | DYS risk |
|  |  | GG | 26 (22.0)/201 (18.6) |  |
|  | IL10–1082 | AG | 102 (35.3)/406 (37.5) | AG risk |
|  |  | AA | 142 (49.1)/508 (46.9) |  |
|  |  | AG | 201 (37.0)/406 (37.5) | IM risk |
|  |  | AA | 274 (50.5)/508 (46.9) |  |
|  |  | AGa | 51 (43.2)/406 (37.5) | DYS risk |
|  |  | AAa | 60 (50.8)/508 (46.9) |  |
| [101] | IL-6 | GC | 26 (46%)/27 (48%) | ChG9 |
|  |  | CC | 5 (9%)/6 (11%) |  |
| [102] | IL-8 -251 | AAa | 26 (12.1%)/22 (8.7%) | AG risk |
|  |  | AT | 99 (46.0%)/105 (41.7%) |  |
|  | IL-1B -511 | TT | 46 (21.4%)/49 (19.6%) | AG risk |
|  |  | CT | 104 (48.4%)/133 (53.2%) |  |
|  | IL-1RN | 2/2 | 0 (40%)/2 (0.8%) | AG risk |
|  |  | 2/L | 17 (8.2%)/21 (8.8%) |  |
| [103] | IL-8-251 | TA | 70 (52.2)/64 (46.7) | Severe ChAG risk |
|  |  | AAa | 25 (18.7)/14 (10.2) |  |
|  |  | TAa | 65 (64.4)/64 (46.7) | IM susceptibility |
|  |  | AA | 11 (10.9)/14 (10.2) |  |
| [106] | IL-10-1082 | AG | 15 (12.9)/18 (7.8) | AG susceptibility |
| GG | 0 (0)/1 (0.4) |  |
| IL-10-819 | CT | 47 (40.5)/104 (44.8) | AG susceptibility |
| CC | 28 (24.1)/36 (15.5) |  |
| IL-10-592 | AC | 46 (39.7)/96 (41.4) | AG susceptibility |
| CC | 31 (26.7)/52 (22.4) |  |
| [108] | IL-6-174 | GC | 47 (35.9)/13 (34.2) | Gastritis |
| CC | 14 (10.7)/2 (5.3) |  |
| IL-8-251 | TA | 67 (51.1)/20 (52.6) | Gastritis |
| AA | 29 (22.1)/7 (18.4) |  |
| IL-10-819 | CT | 55 (41.9)/21 (55.3) | Gastritis |
| TT | 10 (7.6)/6 (15.8) |  |
|  | IL-6-174 | GC | 22 (44.9)/13 (34.2) | Peptic ulcer |
|  |  | CC | 3 (6.1)/2 (5.3) |  |
|  | IL-8-251 | TA | 27 (55.1)/20 (52.6) | Peptic ulcer |
|  |  | AA | 15 (30.6)/7 (18.4) |  |
|  | IL-10-819 | CT | 21 (42.9)/21 (55.3) |  |
|  |  | TT | 5 (10.2)/6 (15.8) |  |
|  |  | TT | 5 (10.2)/6 (15.8) |  |
| [111] | IL-1B-511 | CT | 67 (54.5)/88 (49.2) | IM susceptibility |
|  |  | TT | 34 (27.6)/40 (22.3) |  |

1Only the cytokine SNPs of interest (mentioned in the above studies) are described; relative frequencies (%) are described in relation to the size of each of the two groups (cases and control group); a*P* < 0.05. AG: Atrophic gastritis; CoAG: Corpus atrophic gastritis; ChAG: Chronic atrophic gastritis (the term used in original research); ChG: Chronic gastritis; DYS: Dysplasia; GC: Gastric cancer; GI: Granulocytic infiltration; IM: Intestinal metaplasia; LI: Lymphocytic infiltration.