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THE INFLUENCE OF GENETIC POLYMORPHISMS OF IL17A IN THE ACQUISITION OF *HELICOBACTER PYLORI* AND PUD (PEPTIC ULCER DISEASE) DEVELOPMENT

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Abstract

The *Helicobacter pylori* (*H. pylori*) is the major etiological risk factor for this malignancy, which progresses through a multi-step process, developing from gastritis, to gastric atrophy, intestinal metaplasia, dysplasia, and finally to carcinoma. Polymorphisms in IL-17 cytokines alter the activity of interleukins and may alter cytokine function, thus, dys regulating IL-17 expression, Single nucleotide polymorphisms (SNPs) in the interleukin-17 (IL-17) gene have been shown to be correlated with susceptibility to cancer. Our results indicated that rs2275913 and rs763780 polymorphisms significantly increase cancer risk, especially in gastric cancers. A total of (150) blood sample up to 5 ml of blood that used for serum separation and DNA extraction was collected as directions serum sample tested by used rapid test for *H. pylori* infection detection non-invasive techniques 40(26.6%) positive and remaining 110 (73.3%) negative cases as well as the positive samples were confirm by urea breath testing that given also 40(26.6%) positive and 110(73.3%) negative cases. The genotyping for *H. pylori* infection, and normal controls subjects for primer IL-17A1showed that A allele was significantly associated with increased susceptibility to *H. pylori* infection. Individuals with two A alleles (homozygous for the AA) were significantly over represented among the patients with *H. pylori* 24(60%), as compared with healthy control subjects, 3(8%) and had a 6-folds increased risk of developing *H. pylori* infection than other two genotypes (GA,GG) [odds ratio (0.11) 95% confidence interval (0.013-0.91), (0.65) 95% confidence interval (0.063-6.67)] respectively. The last finding suggest a productive role for (G) allele, in opposition to the role of the allele (A) which seems to be a predisposing factor to *H. pylori* infection when compare with the control individuals.

Key word: IL-17, polymorphism, *H. pylori* infection, gastric cancer

Introduction

Helicobacter pylori (*H. pylori*) infection is one of the most common infection in humans, affecting more than half of the population. The prevalence of the infection varies widely in rural developing areas (more than 80%) compared to urban developed ones (less than 40%), as a consequence of different socioeconomic and hygienic conditions. *H. pylori* infection is usually acquired during childhood; infected people usually remain asymptomatic, but about 30% of individuals may develop mild to severe upper gastrointestinal diseases such as gastritis, peptic ulcer, gastric cancer or MALT lymphoma (Manfredi *et al.*, 2018).

The clinical consequences of *H. pylori* infection are determined by multiple factors, including host genetic predisposition, gene regulation, environmental factors and heterogeneity of *H. pylori* virulence factors (Ana Flavia, 2014).

This usually chronic infection is thought to play an inevitable role in peptic ulcer diseases and gastric adenocarcinoma. *H. pylori*, as the most commonly prevalent and recognized bacterium, is carried by more than half of the world population (Hu *et al.,* 2017; Elhariri *et al*., 2017).

The transmission route is not clear yet; the person-to-person transmission, especially within the same family appears to be prevalent, but also environmental contamination is possible. The eradication without a specific therapeutic regimen is very unlikely and the reinfection rate after an effective eradication therapy is quite rare. The reinfection rate will increase if there are family members affected (Manfredi *et al.,* 2018).

During *Helicobacter pylori* (*H. pylori*) infection

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$CD4^+$ T cells in the gastric lamina propria are hyporesponsive and polarized by Th1/Th17 cell responses controlled by Treg cells (Razavi *et al.*, 2018).

Infections by Helicobacter can cause the stimulation of sophisticated immune response in mucosal immunity. Among the different lymphocytes, Th17 plays an important role in the defense against *H. pylori* and may cause gastritis and peptic ulcer due to the increased activation of Th17 and cytokine changes (Alborzi *et al.*, 2015).

The interleukin 17 (IL-17) family of cytokines contains 6 structurally related cytokines, IL-17A through IL-17F. IL-17A, the prototypical member of this family, just passed the 25th anniversary of its discovery. Although less is known about IL-17B-F, IL-17A (commonly known as IL-17) has received much attention for its pro-inflammatory role in autoimmune disease (Cau *et al.*, 2019).

The gene for human IL-17 is located in the human chromosome, 6p12 and have 1874 base pairs long (Wang *et al.*, 2016).

Single nucleotide polymorphisms (SNPs) serve as important mutations that can affect transcription and translation. Numerous studies have reported the associations of IL-17A and IL-17F polymorphisms and susceptibility to digestive system neoplasms, especially GC; however, the results were not consistent. Therefore, we further expanded the sample size to research the relation between the two polymorphisms and the risk of digestive system neoplasms in terms of cancer type, ethnicity and controls. The IL-17A rs2275913 and IL-17F rs763780 polymorphisms were associated with susceptibility to digestive system neoplasms. (Jie-Fang *et al.*, 2019).

Since then, several studies have reported the association of rs2275913G>A, rs3748067C>T in IL-17A and rs763780 T>C in IL-17F with gastric cancer susceptibility, but these results were inconsistent. Considering the importance of IL-17 and H. pylori infection in the development of gastric cancer, we conducted a meta-analysis of all eligible studies to estimate a more precise relationship of gastric cancer with IL-17A (rs2275913G>A, rs3748067C>T) and IL-17F (rs763780 T>C) polymorphisms and H. pylori infection (Ming *et al.*, 2015).

Single nucleotide polymorphism (SNP) is an important type of gene mutation, which affects gene regulation by altering transcription and translation by inducing abnormal expression of protein and causing abnormal cell proliferation. In 2009, Shibata *et al.*, reported the first study about the association of rs2275913 of IL-17A with gastric cancer risk in a Japanese population (Shibata *et al.*, 2009).

Materials and Methods

Diagnosis:

A total of (40) patients, who were suspected to have *H. pylori* infection after showing clinical manifestation for *H. pylori* infection were submitted for private laboratory diagnosis and were positive at least one of the diagnostic criteria. (150) blood samples enrolled in the present study from clinically confirmed cases by the physician which has *H .pylori* infection–like symptoms may be predicted to have *H. pylori* infection. To confirm the diagnosis of *H. pylori* infection in laboratory by serological tests and urea breath test that consider non-invasive methods was confirmed 40(26.6%) cases of *H. pylori* infections.

A total of (150) blood sample up to 5 ml of blood that used for serum separation and DNA extraction was collected as directions serum sample tested by used rapid test for *H. pylori* infection detection non-invasive techniques 40(26.6%) positive and remaining 110 (73.3%) negative cases as well as the positive samples were confirm by urea breath testing that given also 40(26.6%) positive and 110(73.3%) negative cases.

Results

The results of genotyping for *H. pylori* infection, and normal controls subjects for primer IL-17A1 are presented in table (1), showing the six phenotypes (GG,GA,AA) for IL-17A1.

The IL-17A1 A allele was significantly associated with increased susceptibility to *H. pylori* infection. Individuals with two A alleles (homozygous for the AA) were significantly over represented among the patients with *H. pylori* 24(60%), as compared with healthy control subjects, 3(8%) and had a 6-folds increased risk of developing *H. pylori* infection than

Table 1: genotypes and allele frequency of *H. pylori* patients and controls.

***gene* poly morphism rs2275913**	**Allele Frequen cyrs2275913**		**P val ue**	**Odd ratio (95% CI)**
	Healthy (n=20)	**Patient (n=40)**		
AA	5.0% (n=1)	60% (n=24)	0.036	6(1.22-29.48)
GA	5.0% (n=1)	32.5% (n=13)	0.04	0.11(0.013-0.91)
GG	90.0% (n=18)	7% (n=3)	0.85	0.65(0.063-6.67)
G	92% (n=37)	76% (n=61)	0.03	3.84(1.06-13.88)
A	8% (n=3)	24% (n=19)	0.05	0.26 (0.07-0.94)

other two genotypes (GA,GG) [odds ratio (0.11) 95% confidence interval (0.013-0.91), (0.65) 95% confidence interval (0.063-6.67)] respectively.

In contrast, the individuals with two G alleles (Homozygous for two allele G) were obviously more presented among control individuals, 90.0 % (n=18),when compared with *H. pylori* patients 3 (7%).

It observed that variation in the allelic frequencies were significant [Odds ratio= 3.84; 95% confidence interval (1.06-13.88), P-value =0.03] when the control group was compared with patients with *H. pylori* infection; the IL17A1 (A) Allele was more frequent among patients 76% (n=61) and (G) Allele was more frequent among control individuals 24 % (n=19), (Table 1).

Discussion

The last finding suggest a productive role for (G) allele, in opposition to the role of the allele (A) which seems to be a predisposing factor to *H. pylori* infection. Thus , a genetic defect in the production of IL17A1 in individuals homozygous for the AA allele was contribute to their increased risk of developing *H. pylori* infection. In addition, the results seem to reinforce the association of the A/A genotype with the susceptibility to the *H. pylori*, whereas the IL17A1.

G/G genotype might be related to production against *H. pylori* infection or even a partial production when the allele G is present in heterozygosis (GA).

Identification of genes involved in the genetic predisposition to or progression of cancer is important in clinical practice and in basic medical research. IL-17A and IL-17F are expressed by Th17 cells and are involved in coordinating local tissue inflammation (Lee *et al*., 2013; Park *et al.,* 2005).

In 2014, Yu (Yu *et al*., 2014) carried out a meta-analysis and revealed that the IL-17A G197A polymorphism was associated with a significantly increased gastric cancer risk. In their work, they identified only six case-control studies evaluating the association between the IL-17A G197A polymorphism and gastric cancer risk. In 2015, Li *et al.,* (Li *et al*., 2015) conducted a meta-analysis to assess the association between IL-17A G197A polymorphism and gastric cancer susceptibility with 11 case control studies and revealed that IL-17A G197A polymorphism was associated with gastric cancer risk.

Polymorphisms in IL-17 cytokines alter the activity of interleukins and may alter cytokine function, thus, dys regulating IL-17 expression (Ishigme *et al*., 2009).

The rs2275913 polymorphism is located at the 5' region of the IL-17A gene and, therefore, may regulate gene transcription (Arisawa *et al*., 2008). By contrast, the rs763780 polymorphism is located in the coding region and is a missense mutation, which may influence the protein structure and function (Qinghai *et al*., 2014; Kawaguchi *et al*., 2004).

We assessed SNP-SNP and SNP-environment interactions for these three positive associated SNPs. We found that there was a SNP-SNP interaction between rs2275913 and rs3819024, suggesting that these two SNPs had a joint effect in modulating the risk of GCa (Fei Zhou *et al*., 2016).

Conclution

We found that there was a significant association between IL-17A rs2275913G>A polymorphism and increased H. pylori infection risk, further well designed and large sample size studies are greatly needed to confirm our results.

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