EDITORIAL

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Genetic Susceptibility of Gastroduodenal Disease in Ethnic and Regional Diversity

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See "Investigation of -308G>A and -1031T>C Polymorphisms in the *TNFA* Promoter Region in Polish Peptic Ulcer Patients" by Aleksandra Sałagacka, et al, on page 632, Vol. 8. No. 6, 2014

Helicobacter pylori is a human pathogen that infects the stomach. More than half of the human population is infected with *H. pylori*, which is major cause of peptic ulcers, gastric cancers and mucosa-associated lymphoid tissue lymphoma. However, the majority of patients infected with *H. pylori* generally remain asymptomatic and never develop significant disease. *H. pylori* has high genetic diversity, and different genotypes of *H. pylori* are involved in different gastroduodenal disorders. The hosts' genetic factors also influence the development of peptic ulcers and gastric cancer, and plenty of evidence has demonstrated that genetics plays a role in susceptibility and contributes to the differences between those who develop *H. pylori* infection, peptic ulcers and gastric cancer.[1-3]

Numerous single nucleotide polymorphism (SNP) studies have been undertaken to identify candidate genes that most likely play a role in the development of peptic ulcers and gastric cancer.[4-8] Recently, a genome wide association study (GWAS) and next generation sequencing study identified several genetic loci that confer susceptibility for *H. pylori* infection and gastroduodenal disease.[9,10]

H. pylori prevalence is as high as 90% in some countries, but approximately 5% to 10% of a given population is never infected with *H. pylori*, even in the presence of high exposure rates.[9] A GWAS meta-analysis identified an association between Toll-like receptor 1 (TLR1) and *H. pylori* seroprevalence, suggesting that genetic variations in TLR1 may explain some of the observed variations in individual risk for developing *H. pylori* infection.[9]

The pathogenesis of different clinical outcomes is multifactorial and includes the virulence of *H. pylori*, environmental factors and host factors. Different types of *H. pylori* virulence factors (CagA, VacA1, babA2, and OipA) result in different prevalence rates of gastroduodenal disease in different geographic areas.

Genetic polymorphisms in the hosts' interleukin (IL)-10, tumor necrosis factor α (TNF-α), IL-IB and IL-1RN genes have served as important candidates.[3-8] IL-10 is an anti-inflammatory cytokine that downregulates cell-mediated immune responses and cytotoxic inflammatory responses. An IL-10 promoter polymorphism is associated with an increased risk of developing a peptic ulcer and gastric cancer. A hallmark of *H. pylori*-triggered mucosal inflammation is the continuous recruitment of neutrophils and mononuclear cells to the gastric lamina propria.

TNF-α plays a crucial role in the host's immunological defense against *H. pylori* infection. A TNF-α promoter SNP has been shown to be associated with an increased risk for the development of atrophic gastritis, peptic ulcers and gastric cancer. While the TNF-α 1031 and 863 promoter SNPs are significant risk factors for peptic ulcer in combination with *H. pylori* infection in Taiwan,[1] neither TNF-α 1031 nor 308 TNF-α is a risk factor for peptic ulcer after *H. pylori* infection in the Polish population.[10] In China, IL-B-511, IL-RN, and TNF-α 308 polymorphisms are not associated with the development of duodenal ulcers.[8] In Israel, the *H. pylori* iceA1 bacterial strain is associated with duodenal disease in children, and a TNF-α 238 G polymorphism has been found to be a risk factor for the development of peptic ulcers in children infected with *H. pylori*.[5] In Japan, polymorphisms in interferon-α, rather than IL-1β, are associated with an increased risk of developing gastric ulcers and

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cancer.[4] A GWAS that compared samples form duodenal ulcers and healthy controls in Japan identified two susceptible loci at the prostate stem cell antigen gene at the 8q24 and a locus at the ABO blood group gene at 9q34.[11]

In Korea, several studies have been undertaken to determine the role of polymorphisms in the IL-10 and TNF-α promoter genes in the development of peptic ulcers and gastric cancer. The IL-10-1082/592 and TNF-α 308 genetic polymorphisms were not found to be important risk factors for peptic ulcers and gastric cancer in Korea.[6] However, genetic polymorphisms in IL-1B and IL-1RN contribute to the development of gastric ulcers and gastric cancer after *H. pylori* infection.[7] *H. pylori* is a strong risk factor for gastric cancer. However, only a small portion of *H. pylori*-infected subjects eventually develop gastric cancer. Gastric carcinogenesis is affected by several factors, including the strain of *H. pylori*, environmental factors (smoking, high salt intake, and so forth) and host genetics. IL-10 polymorphisms (819C and 592C alleles have complete linkage disequilibrium with 819T) are associated with *H. pylori* infection and smoking, which increase the risk of developing noncardia gastric cancer, especially intestinal type, in Korea.[3]

In conclusion, host genetic polymorphisms, investigating currently known SNPs, the virulence of *H. pylori* and ethnic and regional differences should be considered when assessing the risk factors for the development of gastric ulcers and cancer.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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