SPECIFIC *HELICOBACTER PYLORI* VIRULENCE AND HOST GENETIC SUSCEPTIBILITY FACTORS: THE POTENTIAL ROLE IN GASTRODUODENAL DISEASES

ABSTRACT

Helicobacter pylori (H. pylori) is one of the most common human pathogens and affects over 50% of the world population. *H. pylori* is associated with gastritis, peptic ulcer, gastric cancer and gastric mucosa-associated lymphoid tissue lymphoma. The interaction of several factors like environmental, bacterial virulence and host genetic are believed to determine the severity and final outcome after *H. pylori* infection. The aim of this study was to determine the distribution of *H. pylori* virulence genes (*cagA, babA2, SabA*and *dupA*) and its correlation with clinical outcomes. This study also assessed the pattern of *H. pylori cagA* EPIYA motifs, EPIYA-A, -B, -C, or -D among different ethnic groups and its association with gastroduodenal disease. The current study also explored the presence of SNPs as genetic variants in the host genome which may be associated with susceptibility or protection to *H. pylori* infection. This was a cross-sectional and case-control study conducted between May 2012 to June 2014 among dyspeptic patients of different ethnicities (Malay, Indian and Chinese) at the Endoscopy Unit of Hospital Universiti Sains Malaysia and Hospital Kuala Lumpur. Genotyping of bacterial and host genome was performed using PCR and Affymetrix SNP 6.0 microarray. This study consists of 2 phases; in phase 1, a total of 105 patients who were confirmed positive to have *H. pylori* infection were recruited into the study. The mean age and SD were 54.48 ±12.94 years and age range of 26 to 86 years old. Fifty seven (54.3%) of the infected patients were males while forty eight (45.7%) were females. Based on the endoscopic findings, 78 patients had gastritis, nine gastric ulcer, five duodenal ulcer and 13 normal. The prevalence of *H. pylori cagA, babA2, sabA* and *dupA* genes in *H. pylori* dyspeptic patients were 69.5%, 41.0%, 43.8% and 22.9% respectively. *cagA* is more common in Indians (39.7%), *babA2* is common in Malays (39.5%) and *dupA* detection is more in Indian and Malay at the same rate (37.5%). The Chinese have the lowest prevalence of the four genes. Majority of Chinese patients were predominantly infected with *cagA* type A-B-D East

Asian strain (88.9%) while *cagA* type A-B-C Western strain (82.8%) was predominantly detected in the Indians while the Malays have mixed strain. There were statistically significant difference (***P*<0.001**) between ethnicity and *cagA* EPIYA motifs, although we could not find significant difference between *H. pylori* virulence genes and EPIYA types and clinical outcomes. In phase II, a total of 80 (42 *H. pylori* positive and 38 *H. pylori* negative) third generation patients with a mean age of 49.87 ± 12.335 years (age range 20-75 years) were recruited. The present study identified SNPs rs3770521 (***P*=1.33 x 10^{-5}**) of XRCC5 gene, rs7042986 of SMARCA2 (***P*=0.0001**) and rs10860808 (***P*=0.0002**) of DRAM1 gene as the susceptible SNPs to *H. pylori* infection among the Indian, Malay and Chinese gastritis patients respectively. This study also identified two protective SNPs rs1809578 (***P*=9.85x 10^{-6}**) of gene BANK1 and rs3776349 (***P*=0.0001**) of gene ARHGAP26 among *H. pylori* the Indian and Malay gastritis patients respectively. In conclusion, the lower prevalence of virulence genes and variations among the different ethnic groups suggest that the bacterial strains are geographically and ethnically dependent. No significant difference was observed between virulence genes and clinical outcome. This study also shows that EPIYA A-B-D and A-B-C are predominant in the Chinese and Indians respectively, while the Malays have mixed strain. Finally, the current GWAS study revealed five novel SNPs that may be associated with susceptibility and protection of *H. pylori* gastritis in the three ethnic groups.

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