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Virulence factors or ancestral origin of *Helicobacter pylori*: which is a better predictor of gastric cancer risk?

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We have read the recently published article by de Sablet *et al* with great interest. The article is well structured and has important findings about the ancestral origin of *Helicobacter pylori*, which can be used as a predictor of gastric cancer risk.[1] de Sablet *et al* performed multi-locus sequence typing (MLST) to determine phylogeographic variation, which was significantly associated with the different histopathological scores and the prevalence of gastric cancer in the specific regions that they studied. However, we think that the study by de Sablet *et al* has several limitations.

First, there was insufficient data about other virulence factors of *H pylori*. We examined the association between virulence factors, including *cag* pathogenicity island, *vacA*, *babA*, *iceA* and OipA, of *H pylori* strains isolated from Columbian subjects and clinical outcomes.[2] We found that although OipA and *cag* pathogenicity island are linked with each other, only OipA was an independent risk factor for duodenal ulcer. OipA tended to be associated with gastric cancer. Thus, in the study by de Sablet *et al*, OipA in *cagA*-positive strains may contribute to phylogeographic variation determined by MLST analysis. Furthermore, the difference in histopathological scores may be because of the different status of OipA. Thus, it is important to determine the correlation between other virulence factors and the phylogenetic tree by performing MLST.

Selection bias is another limitation of the study by de Sablet *et al* because they focused only on the 64 patients with *cagA*-positive/*vacA* s1m1 strains but not on the patients with *cagA*-negative strains. Subjects infected with hpEurope strains of *H pylori* showed higher histopathological scores than those infected with hpAfrica1 strains. However, all *cagA*-negative strains were considered to belong to hpEurope. Subjects infected with *cagA*-negative strains had very low histopathological scores. hpEurope strains without the presence of *cagA* can be less virulent. Thus, the presence of *cagA* rather than the phylogeographic origin is a better predictive factor of gastric cancer.

Our preliminary examination included determination of the phylogeographic origin of *H pylori* strains from Okinawa, Japan. Most strains from Okinawa were divided into three clusters belonging to hpEastAsia. The phylogeographic origin was significantly associated

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with clinical outcomes; however, it depended on the status of *cagA* (East-Asian type, Western type and *cagA* negative) and *vacA* (m1 or m2). Gastric cancer was more prevalent in the cluster containing most East Asian-type *cagA* strains. The results of MLST showed that the prevalence of gastric cancer in each group did not differ when only Western-type *cagA* strains or *cagA*-negative strains were used. This also suggests that *cagA* is a better predictive factor than the phylogeographic origin. Further studies are required to confirm the relationship between the ancestral origin of *H pylori* and clinical outcomes.

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