Clarifications Regarding the 3’ Repeat Region of the cagA Gene in Helicobacter pylori and Clinical Outcome

In a recent issue, Rota et al. (2) reported a study regarding the 3’ repeat region of the cagA gene of Helicobacter pylori in which they classified the cagA 3’ region into three types (A, B/D, and C) according to our previous report (5). They reported no association between 3’ repeat region subtypes and clinical outcome. However, multiple subtypes of the cagA repeat region were associated with gastric ulcer. Unfortunately, the PCR primers they used are located outside of the repeat regions, and strains isolated from East Asian and non-Asian countries are detected by PCR using these primers. As we previously described, the sequences of the second repeat regions in strains from East Asia are completely different from those in strains from non-Asian countries (3, 4). Non-Asian strains possess 102-bp second repeat regions, and East Asian strains possess 162-bp second repeat regions (3–5). Therefore, subtypes A through D cannot be applied to non-Asian strains. In East Asian strains, types A (around 648 bp) and B (around 756 bp) have one second repeat region and types C (around 810 bp) and D (around 756 bp) have two second repeat regions. The expected lengths of the PCR products in East Asian strains are equal to (423 + (57 × f) + (162 × s)), where f is the number of first repeat regions and s is the number of second repeat regions. In contrast, the expected lengths of PCR products in non-Asian strains are equal to (486 + (57 × f) + (102 × s) × b). We found that typically (>95%) there was only one first repeat region in non-Asian strains (3, 4) such that the expected lengths of the PCR products are (543 + 555) + (102 × s) × b. Thus, 650-, 750-, and 850-bp fragments indicate H. pylori with one, two, and three cagA non-Asian type second repeat regions, respectively, which is in complete agreement with data by Rota et al. confirming that the Brazilian strains have a non-Asian cagA structure. We reported that non-Asian H. pylori strains with three or more second repeat regions were associated with gastric atrophy and intestinal metaplasia (3). Recently, Kidd et al. reported that, compared to the prevalence in patients with gastritis alone, the prevalence of the shortest PCR fragment in the 3’ region of the cagA gene was high in peptic ulcer patients and the prevalence of the longest fragment was high in patients with gastric cancer (1). Rota et al. noted that the presence of multiple genotypes in the cagA repeat region was associated with gastric ulcer (which is typically associated with pangastritis and some atrophy) but not with duodenal ulcer (which typically has a non-atrophic gastritis) (2). Although neither Rota et al. nor Kidd et al. provided data about the presence of atrophy, both reports are consistent with the hypothesis that cagA second repeat regions are associated with the premalignant condition of gastric atrophy. Finally, the “Japanese methodology” was developed in Houston, Tex. (3).

REFERENCES


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Authors’ Reply

We are grateful to Dr. Yamaoka and Dr. Graham for their clarifying comments. The first point we want to make is that our primary goal was to verify if different cagA-positive H. pylori subtypes were related to distinct clinical outcomes in our population. At the time we designed our study, the only paper describing a classification method for different H. pylori subtypes was the one published by Yamaoka et al. in this journal (3). Based on this reference, we used primers flanking the repeat regions in our population of patients (the population studied was predominantly European derived) (1). We believed that these primers were appropriate to use in our study because we knew from the published cagA-positive sequences (GenBank accession numbers AF001357 and L117714) that they were not specific for Asian strains. Furthermore, this was later confirmed in another report from Yamaoka et al. (2) which showed that the flanking repeat region primers (named entire repeat region primers by them) can be used to detect H. pylori strains from Asian and non-Asian populations. We used the term “Japanese” to describe this methodology only because the original study was done to classify the cagA subtypes in a population of Japanese patients who underwent gastric endoscopy at the Hospital of the Kyoto Prefectural University of Medicine, Kyoto, Japan (3). However, with the information provided by Yamaoka and Graham that this technique comes from the United States, we agree that this is probably not the best term to describe the method. Second, it is important to remember that we did not intend to develop a diagnostic method capable of distinguishing between Asian and non-Asian H. pylori strains. Finally, we agree with the hypothesis raised by Yamaoka and Graham that the cagA second repeat region may be an important predictor of prognosis and that the presence of subtypes with a longer fragment length may be

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associated with premalignant conditions. It would be very important to continue this investigation using a larger sample of patients, preferably of different ethnic backgrounds, in order to prove this hypothesis.

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