Diversity of the cagA gene of Helicobacter pylori strains from patients with gastroduodenal diseases in the Philippines

Maria Celeste Colmenar Cortes

(Degree)
博士（医学）

(Date of Degree)
2010-12-08

(Resource Type)
doctoral thesis

(Report Number)
乙3137

(URL)
https://hdl.handle.net/20.500.14094/D2003137

氏　　名	Maria Celeste Colmenar Cortes
博士の専攻分野の名称	博士（医学）
学 位 記 番 号	博ろ第 3137 号
学位授与の 要 件	学位規則第 5 条第 2 項該当
学位授与の 日 付	平成 22 年 12 月 8 日

【 学位論文題目 】

Diversity of the cagA gene of Helicobacter pylori strains from patients with gastroduodenal diseases in the Philippines（フィリピンにおける胃・十二指腸疾患患者由来ヘリコバクターピロリの cagA 遺伝子多型）

審 査 委 員

主 査　教 授　戸田　達史
　　教 授　川端　眞人
　　教 授　堀田　博

学位論文の内容要旨

Diversity of the *cagA* gene of *Helicobacter pylori* strains from patients with gastroduodenal diseases in the Philippines

フィリピンにおける胃・十二指腸疾患患者由来ヘリコバクターピロリの*cagA*遺伝子多型

(指導教員：神戸大学大学院医学研究科医科学専攻東　健教授)

Maria Celeste C. Cortes

Helicobacter pylori is a Gram-negative bacterium that infects about 50% of the world's population. Infection with *H. pylori* can result in chronic active gastritis and is a risk factor for peptic ulcers, gastric cancer and gastric MALT lymphoma. A Working Group of the World Health Organization International Agency for Research on Cancer concluded that *H. pylori* is a group I carcinogen in humans. The prevalence of *H. pylori* infection is not the same in different parts of the world and recent studies reported that humans actually acquired *H. pylori* in the early days of their history, long before the migration of modern humans out of Africa, and the diverse distribution of *H. pylori* today is associated with waves of human migration in the past. The rate of *H. pylori* infection is high in Africa, East Asia and South Asia, however, the incidence of gastric cancer is high in East Asia but not in South Asia or Africa; this may be explained partly by the diversity of *H. pylori* strains in these regions. CagA protein is considered a major virulence factor associated with gastric cancer. There are two major types of CagA proteins, the Western and East Asian CagA. The East Asian CagA-positive *H. pylori* infection is more closely associated with gastric cancer. The prevalence of gastric cancer is quite low in Philippine although Philippine populations are considered to originate from an East Asia source. We investigated the characteristics of the *cagA* gene and CagA protein in Philippine *H. pylori* strains and compared them with previously characterized reference strains worldwide.

Patients with abdominal symptoms underwent non-emergent gastroduodenal endoscopy at the St. Luke's Medical Center, Philippines, were included in the study. All patients were unrelated and Filipino in origin. Four biopsy specimens were obtained from each patient: two from the gastric antrum and two from the gastric body. One specimen each from the antrum and body was fixed in buffered formalin and was used in histological analysis. One specimen each from the antrum and body was used for culture of *H. pylori*. Only specimens that were positive for *H. pylori* culture were included, and a total of 19 *H. pylori* strains from

19 patients were used in this study: 8 patients with gastritis, 3 patients with duodenal ulcer, 6 gastric ulcer, and 2 with gastric cancer. The full-length *cagA* gene was sequenced from 19 Philippine isolates, and phylogenetic relationships between the Philippine and 40 reference strains were analyzed.

All Philippine strains examined were *cagA* positive, and 73.7% (14/19) strains were Western CagA-positive. The phylogenetic tree of the complete amino acid sequences demonstrated the genetic relationship among the 19 Philippine strains, as well as 40 references. There were 2 major types: an East Asian and a Western type. In addition, there was a Japanese sub-type in Western CagA type (J-Western CagA sub-type) composed of Okinawa strains. All East Asian CagA-positive Philippine strains based on the EPIYA motif were included in the East Asian cluster. In contrast, all Western CagA-positive Philippine, Thailand, and Vietnam strains based on the EPIYA motif were included in the major Western cluster, not in J-Western CagA sub-type.

In conclusion, the present study found that *cagA* is present all *H. pylori* strains examined from the Philippines. Philippine populations are considered to originate from Austronesian expansions, however, the major type of CagA in the Philippines is Western type. These findings support that the modern Western influence has resulted in more Western type *H. pylori* strains in the Philippines, which may explain the low incidence of gastric cancer and *H. pylori* infected Filipinos can be considered at low risk of developing gastric cancer. In addition, J-Western strains are unique in Okinawa and different from other Western CagA-positive strains in Asian countries such as the Philippines, Thailand, and Vietnam.

神戸大学大学院医学系研究科（博士課程）

論文審査の結果の要旨			
受付番号	乙 第 2093 号	氏 名	Maria Celeste C. Cortes
論文題目 Title of Dissertation	Diversity of the *cagA* gene of *Helicobacter pylori* strains from patients with gastroduodenal diseases in the Philippines フィリピンにおける胃・十二指腸疾患患者由来ヘリコバクターピロリの *cagA* 遺伝子多型		
審査委員 Examiner	主 査 Chief Examiner 戸田 達史 副 査 Vice-examiner 山本 直人 副 査 Vice-examiner 堀田 博		

（要旨は１，０００字～２，０００字程度）

Helicobacter pylori is a Gram-negative bacterium that infects about 50% of the world's population. Infection with *H. pylori* can result in chronic active gastritis and is a risk factor for peptic ulcers, gastric cancer and gastric MALT lymphoma. A Working Group of the World Health Organization International Agency for Research on Cancer concluded that *H. pylori* is a group I carcinogen in humans. The prevalence of *H. pylori* infection is not the same in different parts of the world and recent studies reported that humans actually acquired *H. pylori* in the early days of their history, long before the migration of modern humans out of Africa, and the diverse distribution of *H. pylori* today is associated with waves of human migration in the past. The rate of *H. pylori* infection is high in Africa, East Asia and South Asia, however, the incidence of gastric cancer is high in East Asia but not in South Asia or Africa; this may be explained partly by the diversity of *H. pylori* strains in these regions. CagA protein is considered a major virulence factor associated with gastric cancer. There are two major types of CagA proteins, the Western and East Asian CagA. The East Asian CagA-positive *H. pylori* infection is more closely associated with gastric cancer. The prevalence of gastric cancer is quite low in Philippine, although Philippine populations are considered to originate from an East Asia source. We investigated the characteristics of the *cagA* gene and CagA protein in Philippine *H. pylori* strains and compared them with previously characterized reference strains worldwide.

Patients with abdominal symptoms underwent non-emergent gastroduodenal endoscopy at the St. Luke's Medical Center, Philippines, were included in the study. All patients were unrelated and Filipino in origin. Four biopsy specimens were obtained from each patient: two from the gastric antrum and two from the gastric body. One

specimen each from the antrum and body was fixed in buffered formalin and was used in histological analysis. One specimen each from the antrum and body was used for culture of *H. pylori*. Only specimens that were positive for *H. pylori* culture were included, and a total of 19 *H. pylori* strains from 19 patients were used in this study: 8 patients with gastritis, 3 patients with duodenal ulcer, 6 gastric ulcer, and 2 with gastric cancer. The full-length *cagA* gene was sequenced from 19 Philippine isolates, and phylogenetic relationships between the Philippine and 40 reference strains were analyzed.

All Philippine strains examined were *cagA* positive, and 73.7% (14/19) strains were Western CagA-positive. The phylogenetic tree of the complete amino acid sequences demonstrated the genetic relationship among the 19 Philippine strains, as well as 40 references. There were 2 major types: an East Asian and a Western type. In addition, there was a Japanese sub-type in Western CagA type (J-Western CagA sub-type) composed of Okinawa strains. All East Asian CagA-positive Philippine strains based on the EPIYA motif were included in the East Asian cluster. In contrast, all Western CagA-positive Philippine, Thailand, and Vietnam strains based on the EPIYA motif were included in the major Western cluster, not in J-Western CagA sub-type.

In conclusion, the present study found that *cagA* is present all *H. pylori* strains examined from the Philippines. Philippine populations are considered to originate from Austronesian expansions, however, the major type of CagA in the Philippines is Western type. These findings support that the modern Western influence has resulted in more Western type *H. pylori* strains in the Philippines, which may explain the low incidence of gastric cancer and *H. pylori*-infected Filipinos can be considered at low risk of developing gastric cancer. In addition, J-Western strains are unique in Okinawa and different from other Western CagA-positive strains in Asian countries such as the Philippines, Thailand, and Vietnam.

本研究は、フィリピンにおける胃・十二指腸疾患患者由来ヘリコバクターピロリの *cagA* 遺伝子多型を研究したものであるが、東アジアにおけるフィリピンの胃癌頻度の低さを遺伝子的に説明することにより、重要な知見を得たものとして価値ある集積であると認める。よって、本研究者は、博士（医学）の学位を得る資格があると認める。