様式第１９号

学位論文審査の結果の要旨

審査区分 (課)・論	第 668号	氏名	BUI HOANG PHUC
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論文題目

Helicobacter pylori type 4 secretion systems as gastroduodenal disease markers
（胃十二指腸疾患マーカーとしてのヘリコバクター・ピロリ４型分泌システム）

論文掲載雑誌名

Scientific Reports

論文要旨

Introduction

Although the type 4 secretion system of the integrating and conjugative elements (tfs ICE) is common in Helicobacter pylori, its clinical association with the cag pathogenicity island (cagPAI) have not yet been well-investigated.

Methods

Vietnamese patient H. pylori samples (46 duodenal ulcer (DU), 51 non-cardia gastric cancer (NCGC), 39 chronic gastritis (CG)) were fully sequenced using next-generation sequencing and assembled into contigs. tfs3, tfs4, and cagPAI genes were compared with the public database.

Results and Discussion

Most (94%) H. pylori strains possessed a complete cagPAI, which was the greatest risk factor for clinical outcomes, while the prevalences of tfs3 and tfs4 were 45% and 77%, respectively. Complete tfs3 and tfs4 were found in 18.3% and 17.6% of strains, respectively. The prevalence of H. pylori strains with complete tfs3 ICE in DU patients was significantly higher than that in NCGC patients (30.4% vs 11.7%, $P < 0.05$). In addition, the prevalence of strains with complete tfs3 ICE and cagPAI was significantly higher in DU patients than that in NCGC (28.4% vs 9.8%, $P = 0.038$) and CG patients (28.2% vs 7.7%, $P = 0.024$). cagPAI and complete tfs3 increased the risk of DU compared to NCGC (OR = 3.56, 95%CI: 1.1–14.1, $P = 0.038$) and CG (OR = 4.64, 95%CI: 1.1–27.6, $P = 0.024$). A complete cluster of tfs3 ICE was associated with gastroduodenal diseases in Vietnam. However, there was a low prevalence of the dupA/complete dupA cluster (15.4%) in the Vietnam strains. The prevalence of cagPAI in Vietnam strains was significantly higher than in US ($P = 0.01$) and Indonesia ($P < 0.0001$); the prevalence of the dupA cluster was also higher in the Vietnam strains than in the Indonesian strains ($P < 0.05$). In addition, the prevalence of ctkA, an accessory gene of tfs3, was significantly different between Vietnam and US strains (28% vs 2%, $P = 0.0002$).

Conclusion

The acquisition of tfs3/4 ICE was common in H. pylori strains in patients with gastroduodenal disease in Vietnam, and the complete cluster of tfs3 ICE was a reliable marker for the severity of disease in the H. pylori infected population.

本研究は，ベトナム人の胃十二指腸疾患マーカーとしてのヘリコバクター・ピロリ４型分泌システムをゲノム解析した。病原因子の解明に大変有用な研究である。

このため，審査員の合議により本論文は学位論文に値するものと判定した。

様式第２０号

最終試験の結果の要旨

~~学力の確認~~

審査区分 ㊟・論	第 668 号	氏名	BUI HOANG PHUC
審査委員会委員		主査氏名	村上和成
		副査氏名	浅山良樹
		副査氏名	千葉正一

学位申請者は本論文の公開発表を行い，各審査委員から研究の目的，方法，結果，考察について以下の質問を受けた。

1. This study was calculated by R, an open software with no product liability. Was there any comment about this point by the referees?
2. In the abstract section, it was stated that cagPAI and complete tfs3 increased the risk of duodenal ulceration compared to non-cardia-gastric-cancer and chronic gastritis in the logistic analysis. I could not find the results of the logistic analysis. However, I am talking about the results of the logistic analysis in the abstract section. What paramcter was the most relevant factor to the risk of the Vietnam gastro-duodenal diseases in the logistic analysis in this study?
3. In this study, I am very impressed by the idea that tfs3 would be an important player to suppress the progress of the Vietnam gastric cancer. How do you think about tfs3 in t he cancer progression?
4. In the sample collection of the methods section, you told that you got written informed consent from all patients. Did you get the informed consent by yourself in regards to this present study? Is this retrospective or prospective?
5. In this study you focused on duodenal ulcer, non-cardia gastric cancer, and chronic gastritis patients. Why did you exclude gastric cardia cancer, or gastric ulcer patients?
6. In the Abstract, line 8, you described that “complete tfs3 and tfs4 were found in 18. 3 % and 17.6% of strains, respectively.”. But I cannot find these results in the main t ext. Please tell me where they are.
7. In the last sentence of the abstract, you mentioned that the complete cluster of tfs3 ICE was a reliable marker for the severity of disease in the H. pylori infected population. But did you evaluate the severity of disease? What is the most severe disease in this paper? Did you mean that NCGC is most severe, and that DU in second seve re disease and CG is least severe disease?
8. The CagPAI has many pathogenic functions. What is the most important roles among them.
9. Fig. 4, The prevalence of CagPAI is highest among the countries. How about in Japan?

これらの質疑に対して，申請者は概ね適切に回答した。よって審査委員の合議の結果，申請者は学位取得有資格者と認定した。

（注）不要の文字は２本線で抹消すること

様式第８号 No. 1

学　位　論　文　要　旨

氏名 Bui Hoang Phuc

論　文　題　目

Helicobacter pylori type 4 secretion systems as gastroduodenal disease markers

(胃十二指腸疾患マーカーとしてのヘリコバクター・ピロリ４型分泌システム)

要　旨

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Most (94%) H. pylori strains possessed a complete *cag*PAI, which was the greatest risk factor for clinical outcomes, while the prevalences of *tfs3* and *tfs4* were 45% and 77%, respectively. Complete *tfs3* and *tfs4* were found in 18.3% and 17.6% of strains, respectively. The prevalence of *H. pylori* strains with complete *tfs3* ICE in DU patients was significantly higher than that in NCGC patients (30.4% vs 11.7%, $P < 0.05$). In addition, the prevalence of strains with complete *tfs3* ICE

and *cag*PAI was significantly higher in DU patients than that in NCGC (28.4% vs 9.8%, P = 0.038) and CG patients (28.2% vs 7.7%, P = 0.024). cagPAI and complete *tfs3* increased the risk of DU compared to NCGC (OR = 3.56, 95%CI: 1.1–14.1, P = 0.038) and CG (OR = 4.64, 95%CI: 1.1–27.6, P = 0.024). A complete cluster of *tfs3* ICE was associated with gastroduodenal diseases in Vietnam. However, there was a low prevalence of the *dupA*/complete *dupA* cluster (15.4%) in the Vietnam strains. The prevalence of *cag*PAI in Vietnam strains was significantly higher than in US (P = 0.01) and Indonesia (P < 0.0001); the prevalence of the *dupA* cluster was also higher in the Vietnam strains than in the Indonesian strains (P < 0.05). In addition, the prevalence of *ctkA*, an accessory gene of *tfs3*, was significantly different between Vietnam and US strains (28% vs 2%, P = 0.0002).

Conclusion

The acquisition of *tfs3/4* ICE was common in *H. pylori* strains in patients with gastroduodenal disease in Vietnam, and the complete cluster of *tfs3* ICE was a reliable marker for the severity of disease in the *H. pylori* infected population.