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Author(s)	Lai Lai San
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学位論文内容の要旨

Abstract of the dissertation
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博士の専攻分野の名称：博士（獣医学）　　　　　氏名：LAI LAI SAN

<div align="center">Name</div>

<div align="center">
学位論文題名

The title of the doctoral dissertation
</div>

<div align="center">
Insight into the Beijing genotype *Mycobacterium tuberculosis* clinical isolates in Myanmar

（ミャンマーにおける北京型結核菌臨床分離株に関する研究）
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Myanmar is one of the high burden countries of tuberculosis (TB), a major leading cause of death by infectious disease worldwide. Among the 30 high burden countries of TB all over the world, Myanmar ranked 10th position according to the world health organization (WHO) report in 2017. Moreover, Myanmar was included in 30 high burden countries of multidrug-resistant tuberculosis (MDR-TB) having 600,000 new with resistant TB and 490,000 MDR-TB cases worldwide. The predominant strain of East Asia, and China, called Beijing strain, was found the second largest proportion in total TB cases and the largest proportion in MDR-TB in Myanmar.

In Chapter I, a total of 265 multidrug-resistant *Mycobacterium tuberculosis* (MDR-MTB) isolates collected from pulmonary TB patients in Myanmar in 2010 and 2012 were characterized by spoligotyping, detection of the drug resistant associated mutations of *rpoB*, *rpoC*, *katG*, *gyrA* and *rrs* genes, and further discrimination of the Beijing genotype by MIRU-VNTR typing. The modern Beijing sublineage was mostly found out and had a strong association with the drug resistance as well as transmission.

Chapter II included the development of a new multiplex PCR method for differentiation of ancient and modern sublineage of the Beijing genotype and its evaluation using MTB complex isolates, non-tuberculous mycobacterium isolates and isolates of other bacterial species. This simple, robust, and one step method differentiated the modern and the ancient Beijing sublineages with 100% sensitivity and specificity. It helps to identify the potential virulent modern Beijing strains in a timely manner to provide rapid diagnosis for effective management in high burden settings.

In Chapter III, the sputum samples collected from pulmonary TB patients in Mawlamyine, Southern part of Myanmar, were used to determine the strains prevalence and transmission. Spoligotyping and multiplex PCR on Rv0679c gene were performed for determination of the Beijing lineage. Drug resistance associating mutations of *rpoB* and

katG genes were observed. The developed multiplex PCR in chapter II was used for the differentiation of the modern and the ancient Beijing genotype and 83% (33/40) of the Beijing strains showed modern subtype. The Beijing genotype were further discriminated by MIRU-VNTR typing and showed divergent. Combined analysis of the strains of chapter I revealed that there were some persistent strains among the community. The comparative analysis of the Beijing strains in a neighboring country, Thailand, indicated the possible cross border transmission.

In conclusion, this study indicated the importance of the Beijing genotype strains, especially possible virulent modern subtype in Myanmar. Although outbreak was rarely observed, it still had a potential to spread. The findings of cross-border transmission indicated to strengthen control strategy. The Beijing genotype strains were diverse and showed a higher tendency to develop drug resistance independently in each patient. It is important to strengthen the drug treatment strategy in Myanmar to control the subsequent development of MDR-TB. The newly developed multiplex PCR method will be able to contribute to the rapid determination of potentially virulent strains in high burden settings, such as in Myanmar, in order to manage TB in a timely manner.