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学位論文内容の要旨
Abstract of the dissertation

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学位論文題名
The title of the doctoral dissertation

Characterization of streptomycin and pyrazinamide resistance in clinical multidrug-resistant *Mycobacterium tuberculosis* isolates from Myanmar
ミャンマー由来臨床分離多剤耐性結核菌株のストレプトマイシン並びにピラジナミド耐性に関する研究

Abstract

Tuberculosis (TB) caused by Mycobacterium tuberculosis (MTB) remains one of the leading causes of morbidity and mortality worldwide, especially in developing countries. Control of TB has become more challenging with the emergence of drug resistance TB (DR-TB), multidrug-resistant TB (MDR-TB), and extensively drug-resistant TB (XDR-TB). Although MDR-TB is one of the emerging public health problems in Myanmar, limited studies had been reported to determine the prevalence of drug resistance-conferring mutations among those isolates. In addition, information regarding the frequency and pattern of mutations in drug-resistance associated genes among MDR-TB isolates is necessary for the developing of rapid DST for successful TB treatment.

Numerous studies report that mutations of *rpsL* (encoding the S12 protein), *rrs* (encoding 16S rRNA) and *gidB* (encoding rRNA methyltransferase) are responsible for STR resistance. In chapter I of this thesis, I explored the variation and frequency of mutations in *rpsL*, *rrs* and *gidB* in 141 STR-resistant MDR-TB isolates from Myanmar. Most isolates belonged to the Beijing genotype (105, 74.5%). Mutations in *rpsL* were identified in 69.5% (98/141) of the STR-resistant isolates, where the most prevalent (92.0%, 90/98) and significantly associated mutation with the Beijing genotype ($P < 0.001$) was Lys43Arg. Fifteen different types of mutations in *gidB* were found in 16.3% (23/141) of the

isolates, and most of them were novel. Sequence analysis of *rpsL*, *rrs* and *gidB* with a sensitivity of 83.7% satisfactorily predicted STR resistance in Myanmar isolates.

In chapter II, I had characterized the prevalence and pattern of mutations occurred in the drug target for pyrazinamide (PZA) in MDR-TB isolates in Myanmar. Forty-four percent of MDR-TB isolates had mutations likely to associate with phenotypic PZA resistance. In addition, the genetic backgrounds of these isolates were analyzed by spoligotyping and investigated whether any association of different genotypes with specific mutations in *pncA*. The most frequent mutations among MDR-TB isolates were found in three hot spot regions (codon 3-17, codon 61-85, codon 127-154) similar to those found worldwide. Majority of the isolates showed diverse *pncA* mutation with the same spoligotype, indicating that there is no large outbreak. However, 23 kinds of *pncA* mutation were found in multiple isolates. This fact may suggest that there is the possible transmission of those mutant strains in Myanmar because mutations in *pncA* occurred randomly and it might be rare same mutation to be carried by isolates without any correlation.

The findings from this study can provide the expanded knowledge on molecular drug resistance mechanism of anti-TB drugs of STR and PZA. Moreover, the frequency and patterns of drug resistance-associated mutations can support the development of rapid and easy applicable DST tools which could contribute to the development of control strategies for the increasing rate of DR-TB in Myanmar.