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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
Molecular characteristics of drug-resistant *Mycobacterium tuberculosis* in Thailand

（タイにおける薬剤耐性結核菌の遺伝学的特性）

Drug-resistant tuberculosis (TB) is a great challenge in TB control. The frequency and mutation characteristics can imply the efficiency of molecular tests for the rapid detection of TB drug resistance.

In Chapter 1, I examined the existence of mutations in *katG* and *inhA* promoter for isoniazid (INH) resistance, and *rpoB* for rifampicin (RIF) resistance. A total of 178 drug-resistant *Mycobacterium tuberculosis* (MTB) isolates were analyzed. Mutations in *katG* encoding and *inhA* regulatory regions were detected in 136/168 (81.0%) and 29/168 (17.3%), respectively, with the most prominent mutation of Ser315Thr substitution in *katG* in 126/168 (75.0%), and -15 C > T substitution in the regulatory region of the *inhA* (26/168; 15.5%). Two distinct *katG* mutations (Tyr337Cys, 1003InsG) were identified. Of 125 RIF-resistant isolates, 118 (94.4%) carried mutations affecting the 81-bp RIF resistance-determining region (RRDR) with the most commonly affected codons 450, 445, and 435 identified in 74 (59.2%), 26 (20.8%) and 12 (9.6%) isolates, respectively. The genetic mutations were highly associated with phenotypic INH and RIF resistance, and the majority shared similarities with those in previous studies in Thailand and other Asian countries. The data is useful for guiding the use and improvement of molecular tests for TB-drug resistance.

In Chapter 2, I characterised *M. tuberculosis* isolates during multidrug-resistant tuberculosis outbreaks in the Thamaka district, Kanchanaburi province in Thailand by genotyping. Seventy-two isolates were collected and genotyped by spoligotyping, 15-locus mycobacterial interspersed repetitive unit-variable-number tandem repeat (MIRU-VNTR) and single nucleotide polymorphism genotyping, and their drug resistance was analysed. The spoligotyping results showed that Beijing SIT1 was the predominant sub-lineage (n=38, 52.8%) while the remaining were non-Beijing sub-lineages (n=34). The MIRU-VNTR analysis showed thatthe most Beijing isolates (n=37) belonged to the modern type, forming 5 clusters and 13 individual patterns. In *katG*, only mutation Ser315Thr was identified. In *rpoB,* Ser531Leu was the predominant except His526Arg and Leu533Pro found in two isolates. A cluster of 14 Beijing strains contained these common mutations and shared the MIRU-VNTR genotype with isolates spreading previously in the Thamaka district. Two U SIT523 isolates contained mutations A1400G in *rrs* and Asp94Gly in *gyr*A genes, indicating a spread of extensively drug-resistant tuberculosis (XDR-TB). Most mutations were associated with drug resistance, and the specific MDR Beijing and XDR-TB in U SIT523 isolates are remaining. This genotyping was likely a key tool for tracking TB transmission in the Thamaka district, Thailand.