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学位論文内容の要旨

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Characterization of drug-resistant *Mycobacterium tuberculosis*
strains isolated in Nepal

(ネパールにおいて分離された薬剤耐性結核菌株の特徴)

Tuberculosis (TB) is a major public health problem in Nepal. The situation is further worsened with the emergence of multidrug-resistant tuberculosis (MDR-TB; TB caused by *Mycobacterium tuberculosis* strains resistant to more than two drugs including isoniazid (INH) and rifampicin (RIF)) and extensively drug-resistant tuberculosis (XDR-TB; TB caused by *M. tuberculosis* strains resistant to more than four drugs including INH, RIF, one of fluoroquinolones and any of the second-line anti-TB injectable drugs). However, information on drug-resistant associated mutations in MDR- and XDR-*M. tuberculosis* isolates from Nepal was lacking before our study.

As a part of my PhD work, I investigated the type and frequency of drug resistance-conferring mutations among MDR-*M. tuberculosis* isolates from Nepal. Mutations affecting the 81-bp RIF resistance-determining region (RRDR) of *rpoB* were identified in 106 of 109 (97.3%) RIF-resistant isolates. Codons 531, 526, and 516 were the most commonly affected, at percentages of 58.7, 15.6, and 15.6, respectively. Of 113 INH-resistant isolates, 99 (87.6%) had mutations in the *katG* gene, with Ser315Thr being the most prevalent (81.4%) substitution. Mutations in the *inhA* promoter region were detected in 14 (12.4%) INH-resistant isolates; 12 of which had mutation at position -15 in the *inhA* promoter. No mutation was detected in 2.8 % RIF-resistant and 6.2% of INH-resistant isolates.

Furthermore, 13 XDR-*M. tuberculosis* isolates were detected among 109 MDR isolates. Mutations predominant among XDR-TB were Ser531Leu in *rpoB* gene (92.3%), Ser315Thr in *katG* gene (92.3%), Asp94Gly in *gyrA* gene (53.9%) and A1400G in *rrs* gene

(61.5%). Spoligotyping and multilocus sequence typing of these isolates revealed 69% belonged to Beijing family, especially modern type. Infections of this family were more common among younger generation than those belonging to other spoligotype families. Further typing with 26-loci variable number of tandem repeats analysis suggested current spread of Beijing genotype XDR-*M. tuberculosis* among people in Nepal. The transmission of XDR-TB was speculated not only within a city but also between two cities, apart more than 650 Km.

In conclusion, our study provides valuable information on molecular mechanism of drug resistance in MDR- and XDR-*M. tuberculosis* isolates from Nepal. It can serve as a basis for developing or improving rapid molecular drug-susceptibility tests to monitor drug-resistant isolates. Additionally, genotypic data suggested the possible transmission of XDR-*M. tuberculosis* strains in Nepal that highlights an urgent need to identify patients suffering from this incurable disease and treat those patients in isolated wards to prevent further spread to the community, and to reinforce the TB policy with regard to control and detection strategies.