



Title	Genetic diversity of multidrug resistant Mycobacterium tuberculosis Central Asian Strain isolates in Nepal [an abstract of dissertation and a summary of dissertation review]
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学位論文内容の要旨
Abstract of the dissertation

博士の専攻分野の名称：博士（獣医学）

氏名：ヨゲンドラ サハ

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学位論文題名

Genetic diversity of multidrug resistant *Mycobacterium tuberculosis*
Central Asian Strain isolates in Nepal

(ネパールで分離された多剤耐性中央アジア型結核菌株の遺伝的多様性)

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* (MTB), which poses a major public health problem in Nepal. Multidrug-resistant TB (MDR-TB), resistant to rifampicin and isoniazid, is an emerging threat for successful TB control in Indian subcontinent region, including Nepal, India and Pakistan. Although, Central Asian strain (CAS) family has been reported as one of the dominant genotype of MTB in Nepal and neighboring countries, little information on the CAS family is available, especially related to MDR-TB.

As a part of my PhD work, I elucidated the genetic and epidemiological characteristics of total 145 MDR-MTB CAS isolates collected in Nepal from 2008 to 2013. In chapter I, I investigated those isolates by applying three molecular approaches, i.e. spoligotyping, 24-loci MIRU-VNTR analysis and drug resistance-associating gene (*rpoB*, *katG* and *inhA* promoter region) analysis. Spoligotyping analysis showed CAS1_Delhi SIT26 as a predominant subfamily (41.4%); however, by combining with MIRU-VNTR typing, 145 isolates were able to be discriminated into 116 different types including 18 clusters (clustering rate: 32.4%). Some of the clustered isolates shared rare point mutations in *rpoB* as well as sharing other genetic and geographical characteristics, which suggested acquisition of MDR-MTB via person-to-person contact.

In Chapter II, I constructed minimum-spanning trees (MSTs) with MIRU-VNTR data of 145 MDR CAS family isolates with additional information of spoligotype, isolated areas or years to see the correlation between clustering and those variants. Overall analysis of those MSTs strongly suggested that the Nepalese MDR CAS family isolates were genetically diverse. Since MDR CAS1_Delhi SIT26 (N=60) was also dominant in neighboring countries, I compared allelic diversity of its MIRU-VNTR with those of published data from India (N=16) and Pakistan (N=20), and drew MSTs as combined data to investigate possible epidemiological link. The allelic diversity was much higher in Pakistan isolates and they were genetically distant from Nepalese isolates. Whereas, an Indian isolate had an identical VNTR pattern with a Nepalese isolate cluster suggesting an evolutionary relationship between the two countries which share the open borders.

In conclusion, my study provides valuable information on the genetic diversity, epidemiological characteristics and evolutionary relationships of dominant MDR CAS family genotypes from Nepal and neighboring countries. Those molecular analyses demonstrated that the MDR CAS family is highly diverse in Nepal, which suggests that the bacteria progressively acquired drug resistance and ultimately became MDR in each patient by anti-TB treatment pressure. Nonetheless, the characteristics of some clusters showed evidence of actual MDR-MTB transmission. A large MDR-TB outbreak would be more likely to occur among the Nepalese population if transmission trends observed in the present study grew out of control. Thus, my results highlight the importance of laboratory diagnosis of TB, intensified finding of cases and timely and appropriate treatment of TB patients to cut the transmission chain. It is foreseen that the results from the present study will contribute to improve epidemiological surveillance, which in turn could lead to implementation of more effective control measures against the spread of MDR-MTB in Nepal and neighboring countries.