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Molecular Epidemiology of Drug-Resistant *Mycobacterium Tuberculosis* in Japan

Fuminori Mizukoshi¹, Nobuyuki Kobayashi^{2,3}, Fumiko Kirikae⁴, Ken Ohta^{2,5}, Kazunari Tsuyuguchi⁶, Noritaka Yamada⁷, Yoshikazu Inoue⁶, Masahide Horiba⁸, Noriko Kawata⁹, Akiko Ichinose^{10,11}, Tohru Miyoshi-Akiyama¹¹, Reiko Kiritani¹, Keiji Funatogawa¹, Teruo Kirikae⁴

¹ Tochigi Prefectural Institute of Public Health and Environmental Science, Utsunomiya, Tochigi, Japan.

² Department of Respiratory Medicine, National Hospital Organization (NHO) Tokyo National Hospital, Kiyose, Tokyo, Japan.

³ Department of Internal Medicine, Fureai Machida Hospital, Machida, Tokyo, Japan.

⁴ Department of Microbiology, Faculty of Medicine, Juntendo University, Bunkyo-ku, Tokyo, Japan.

⁵ Fukujuji Hospital, Japan Anti-Tuberculosis Association, Kiyose, Tokyo, Japan.

⁶ Clinical Research Center, National Hospital Organization Kinki-Chuo Chest Medical Center, Sakai, Osaka, Japan.

⁷ Department of Respiratory Medicine, NHO Higashinagoya National Hospital, Nagoya, Aichi, Japan.

⁸ Department of Respiratory Medicine, NHO Higashisaitama National Hospital, Hasuda, Saitama, Japan.

⁹ Department of Allergy and Respiratory Medicine, NHO Minami-Okayama Medical Center, Tsukubo, Okayama, Japan.

¹⁰ Department of Electrical Engineering and Bioscience, Faculty of Science and Engineering, Waseda University, Shinjuku-ku, Tokyo, Japan.

¹¹ Department of Infectious Diseases, Research Institute, National Center for Global Health and Medicine, Shinjuku-ku, Tokyo, Japan.

Abstract

Clinical isolates of drug-resistant (isoniazid and/or rifampicin-resistant) *Mycobacterium tuberculosis* were obtained from 254 patients diagnosed with drug-resistant tuberculosis in Japan from April 2015 to March 2017 in National Hospital Organization hospitals. The 254 patients were approximately 32% of all 795 patients who were diagnosed with culture-confirmed drug-resistant tuberculosis from 2015 to 2016 nationwide in Japan. The whole-genome sequences of all the isolates from the 254 patients and the lineages of these isolates were determined, and phylogenetic trees were constructed based on single nucleotide polymorphism concatemers. Of these patients, 202 (79.5%) were born in Japan and 52 (20.5%) were born elsewhere. Of the 254 drug-resistant isolates, 54 (21.3%) were multidrug resistant, being resistant to both isoniazid and rifampicin. The percentages of multidrug-resistant isolates were significantly higher in foreign-born (38.5% [20/52]) than Japanese-born patients (16.8% [34/202]). Of the 54 multidrug-resistant isolates, nine were extensively drug resistant, which were all obtained from Japanese-born patients. Five extensively drug-resistant isolates were obtained from patients with incipient tuberculosis. A significant number of multidrug-resistant *M. tuberculosis* strains were isolated from foreign-born patients from Asian countries that have a high tuberculosis burden. Foreign-derived isolates affect the nationwide genetic diversity of drug-resistant *M. tuberculosis* in Japan. Extensively drug-resistant *M. tuberculosis* isolates were transmitted among the Japanese population.

IMPORTANCE The incidence rate of tuberculosis (TB) in Japan was 11.5 per 100,000 of the population in 2019. Of TB patients in Japan, 61.1% were aged >70 years, and 10.7% were born outside Japan, mostly in Asian countries with a high burden of tuberculosis. Of the tuberculosis patients in the present study, 5.4% and 1.0% showed resistance to isoniazid and rifampicin, respectively, and 0.7% were multidrug resistant. The objective of this study was to clarify the molecular epidemiological properties of drug-resistant tuberculosis in Japan. Molecular epidemiology provides several clues to inform potential measures to control drug-resistant tuberculosis in Japan.

Keywords: Japan; drug-resistant *M. tuberculosis*; foreign born; whole-genome sequencing.

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