ANALYSIS OF BACTERIAL FACTORS ASSOCIATED WITH PATHOLOGICAL OR CLINICAL MANIFESTATIONS OF MYCOBACTERIUM AVIUM DISEASE BASED ON GENOME ANALYSIS

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Abstract  [Background] Infectious disease caused by Mycobacterium avium shows diverse pathological and clinical manifestations. This is possibly due to both host factors and bacterial factors, but many questions remain answered regarding these manifestations. [Methods] To assess the relationship between the different pathological and clinical manifestations of M. avium disease and bacterial factors, we performed comparative genome analysis using clinical isolates from patients with various symptoms. [Results] We determined the complete genome sequence of the previously unreported M. avium strain TH135 isolated from a patient with pulmonary M. avium disease, and further demonstrated the presence of a novel plasmid, pMAH135, encoding proteins involved in the pathogenicity and antimicrobial resistance of mycobacteria. Our analysis also showed that M. avium strains, which cause pulmonary and disseminated disease, have genetically distinct features, and isolates from patients with pulmonary disease were more resistant to seven antibiotics, including clarithromycin, than isolates from patients with disseminated disease. Comparative genome analysis of 79 M. avium strains comprising four subspecies revealed the presence of genetic elements specific to each lineage, which are thought to be acquired via horizontal gene transfer during the evolutionary process. Moreover, the analysis identified potential genetic determinants associated with not only the progression of pulmonary disease but also the host range characteristics of M. avium. Notably, this analysis indicated an association between the progression of pulmonary M. avium disease and several virulence genes including pMAH135. [Conclusion] These results suggest that bacterial factors play an important role in the diverse pathological and clinical manifestations of M. avium disease.

Key words: Mycobacterium avium disease, Pathological manifestation, Clinical manifestation, Bacterial factors, Genome analysis

INTRODUCTION

Nontuberculous mycobacteria (NTM) are ubiquitous in the environment, including natural water, soil, and household dust, and can cause significant disease in humans and animals. The incidence of NTM infection is increasing annually in many countries, including the United States and Japan. In Japan, the causative NTM strain for pulmonary disease with the highest incidence is Mycobacterium avium (approximately 60%), followed by M. intracellulare, M. kansasii, and M. abscessus, and the incidence per 100,000 population has increased remarkably from 5.7 in 2007 to 14.7 in 2014.

Among NTM species, M. avium is the most clinically significant species in humans and animals and comprises four subspecies that have specific pathogenic and host range characteristics as follows: M. avium subsp. avium (MAA) and M. avium subsp. silvaticum (MAS) are avian pathogens; M. avium subsp. paratuberculosis (MAP) causes John's disease in ruminants; and M. avium subsp. hominis suis (MAH) infects mainly pigs and humans. MAH is the causative pathogen of two main types of disease in humans: disseminated disease in immunocompromised hosts such as individuals infected with human immunodeficiency virus (HIV), and pulmonary disease in individuals without systemic immunosuppression. However, the genetic differences among the four subspecies are still unknown.

Pulmonary disease caused by NTM, which is both intractable and infectious, has variable clinical manifestations. Although some patients remain stable without treatment,