การทบทวนอย่างเป็นระบบเกี่ยวกับระบาดวิทยาระดับโมเลกุลของวัณโรคที่กลับมาระบาดในประเทศไทย

Systematic Review on Molecular Epidemiology of Re-emerging Tuberculosis in Thailand

พาณิภัค วิชญเธียร
โรงเรียนนิวตัน

Phaniphak Witchayathian
The Newton Sixth Form School

Corresponding author: phaniphak.w@gmail.com

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บทคัดย่อ

วัณโรค (Tuberculosis) ยังคงเป็นสาเหตุการเสียชีวิตอันดับต้น ๆ ทั่วโลก โดยในปี 2022 มีรายงานผู้ป่วยวัณโรคประมาณ 10 ล้านรายและเสียชีวิต 1.5 ล้านราย โดยในจำนวนนี้มีประมาณ 500,000 รายที่เป็นผู้ป่วยวัณโรคดื้อยาหลายขนาน (MDR-TB) ซึ่งส่งผลกระทบอย่างมากต่อการควบคุมวัณโรคและการแทรกแซงการแพร่เชื้อ ประเทศไทยติดอันดับ 1 ใน 30 ประเทศที่มีภาระวัณโรคสูง โดยมีอุบัติการณ์ 150 ต่อประชากร 100,000 คน และมีอุบัติการณ์ของ MDR-TB ประมาณ 1.7% ในผู้ป่วยรายใหม่และ 10% ในผู้ป่วยที่เคยได้รับการรักษามาก่อน ความหลากหลายทางพันธุกรรมของ Mycobacterium tuberculosis (MTB) ในประเทศไทยประกอบด้วยทั้งสายพันธุ์ปักกิ่งและสายพันธุ์ที่ไม่ใช่ปักกิ่ง โดยสายพันธุ์ปักกิ่งมีความเกี่ยวข้องกับ MDR-TB และวัณโรคที่ดื้อยาขั้นสูง (XDR-TB) การศึกษานี้มีวัตถุประสงค์เพื่อสำรวจการกลายพันธุ์ของยาชั้นแรกที่เกี่ยวข้องกับการดื้อยาในสายพันธุ์ปักกิ่ง และสรุปข้อมูลเกี่ยวกับการแพร่ระบาด โปรไฟล์การกลายพันธุ์ การกลายพันธุ์ใหม่ และผลกระทบต่อการจัดการวัณโรคตามพันธุกรรมของ MTB ข้อมูลระบาดวิทยาระดับโมเลกุลของ MDR-TB มีความสำคัญอย่างยิ่งต่อกลยุทธ์ด้านสาธารณสุข ช่วยในการติดตามการกระจายทางภูมิศาสตร์และการแพร่เชื้อของโคลน MTB ที่ดื้อต่อยา

การศึกษาครั้งนี้นี้ได้ทำการค้นคว้าเอกสารอย่างเป็นระบบโดยใช้ฐานข้อมูล เช่น PubMed, Scopus และ Web of Science เน้นการศึกษาเกี่ยวกับระบาดวิทยาระดับโมเลกุลของวัณโรคในประเทศไทยที่ตีพิมพ์ระหว่างปี 2000 ถึง 2023 ผลการทบทวนพบว่าสายพันธุ์ปักกิ่งมีการแพร่กระจาย

ในประเทศไทยมากที่สุด มีความเกี่ยวข้องกับอัตราการแพร่เชื้อสูงและการดื้อยา รวมถึงพบการกลายพันธุ์เฉพาะ เช่น H526P, Q513P, และ H526C ในยีน rpoB การทำความเข้าใจเกี่ยวกับการกลายพันธุ์เหล่านี้และผลกระทบต่อการดื้อยามีความสำคัญต่อการพัฒนากลยุทธ์การควบคุมและการรักษาวัณโรคที่มีประสิทธิภาพในประเทศไทยและพื้นที่ที่มีภาระสูงอื่น ๆ
คำสำคัญ : ระบาดวิทยาระดับโมเลกุล, ประเทศไทย, โรคอุบัติซ้ำ, การดื้อต่อยา, ไมโคแบคทีเรียมทูเบอร์คูโลซิส

Abstract

Tuberculosis (TB) remains a leading cause of death globally, with an estimated 10.0 million cases and 1.5 million deaths in 2022. Of these, approximately 500,000 were new cases of multidrug-resistant TB (MDR-TB), significantly impacting TB control and transmission interventions. Thailand ranks among the top 30 high TB burden countries, with a prevalence of 150 per 100,000 population and an estimated MDR-TB prevalence of 1.7% in new cases and 10% in previously treated cases. In Thailand, the genotypic diversity of Mycobacterium tuberculosis (MTB) includes both Beijing and non-Beijing strains, with the Beijing strain being particularly associated with MDR-TB and extensively drug-resistant (XDR-TB) strains. This review aims to explore the gene mutations related to first-line drug resistance in Beijing genotypes and summarize the prevalence, mutation profiles, and implications for TB management based on MTB genetics. Molecular epidemiology data of MDR-TB are crucial for public health strategies, aiding in tracking the geographic distribution and transmission of drug-resistant MTB clones. A systematic literature search using databases like PubMed, Scopus, and Web of Science was conducted, focusing on studies related to the molecular epidemiology of TB in Thailand published between 2000 and 2023. The results highlight the predominance of the Beijing lineage in Thailand, its association with high transmission rates and drug resistance, and the presence of unique mutations such as H526P, Q513P, and H526C in the rpoB gene. Understanding these genetic mutations and their contribution to drug resistance is vital for developing effective TB control strategies and treatments in Thailand and other high-burden settings.
Keywords : Molecular Epidemiology, Thailand, Re-emerging, Drug Resistance, Mycobacterium tuberculosis

Introduction

Tuberculosis (TB) continued to be the leading cause of death, contributing to public health challenges globally. In 2022, the global TB burden was reported to be 10.0 million cases with 1.5 million deaths approximately. 500 thousand of these were newly reported cases of multidrug-resistant tuberculosis (MDR-TB), impacting TB control and transmission intervention.[1]

In 2019, with a prevalence of 150 per 100,000 and an estimated MDR-TB of 1.7% in new TB cases and 10% in previously treated TB, respectively, Thailand is ranked among 30 of the highest TB burden countries.[1] The genotypic diversity of MTB in Thailand is characterized by the presence of both Beijing and non-Beijing strains. The Beijing strain is known for its high virulence and association with MDR-TB and extensively drug-resistant (XDR) TB strains. Several studies have utilized advanced molecular techniques such as 24-locus Mycobacterial interspersed repetitive unit-variable number tandem repeat (MIRU-VNTR) typing to analyze the genotypic distribution of drug-resistant TB strains to highlight the prevalence of these strains in various parts of Thailand reported a significant presence of Beijing strains associated with higher pathogenicity and resistance to first-line anti-TB drugs.[2-5] Moreover, proteomic and transcriptomic studies have shown that Beijing strains exhibit upregulation of specific genes under stress conditions, which may contribute to their survival and persistence in latent TB infections (LTBI). These strains have been shown to have higher rates of TB recurrence and reinfection in regions with high TB incidence.[6]

This review aims to explore the major gene mutations related to the first line drug for TB resistance in Beijing Genotypes and to and to summarize the prevalence, mutation profiles, new mutations and implications for TB management based on the genetics of MTB.

Molecular epidemiology data of MDR-TB are significant towards public health, applied to tracking of the geographic distribution and transmission of drug-resistant Mycobacterium Tuberculosis (MTB) clones.[7]

Study Methods

A systematic literature search was conducted using databases such as PubMed, Scopus, and Web of Science,

covering studies published between 2000 and 2023. This review included original research articles, reviews, and meta-analyses that focused on the molecular epidemiology of Tuberculosis (TB) in Thailand. Studies were excluded if they did not provide primary molecular data from Thailand or focused solely on clinical aspects without any molecular analysis.

Study Selection and Data Evaluation Process

To ensure comprehensive, reliable, and reproducible results, the study selection process followed a rigorous systematic review framework. This process included the following key steps:

1. Search Strategy: A predefined search strategy was implemented in PubMed, Scopus, and Web of Science to retrieve relevant studies. Search terms focused on TB molecular epidemiology, multidrug-resistant tuberculosis (MDR-TB), and specific gene mutations associated with drug resistance, using keywords such as Mycobacterium Tuberculosis, drug resistance, and Thailand.

2. Inclusion Criteria: Studies were included if they met the following conditions:

2.1 Focused on molecular epidemiology, with an emphasis on genetic mutations related to drug resistance (e.g., rpoB, katG, gyrA, rrs).

2.2 Conducted in Thailand or with data specifically relevant to the Thai population.

2.3 Published between 2000 and 2023.

2.4 Included original data, reviews, or meta-analyses related to molecular analysis.

3. Exclusion Criteria: Studies were excluded if:

3.1 They did not provide primary molecular data from Thailand.

3.2 They focused solely on clinical or epidemiological data without molecular analysis.

3.3 They were editorials, letters, or conference abstracts without original data.

4. Flowchart of Study Selection: A flowchart was created to visually represent the step-by-step selection process, illustrating the number of studies screened, excluded, and finally included. This flowchart can be referenced to follow the systematic approach taken (see figure 1).

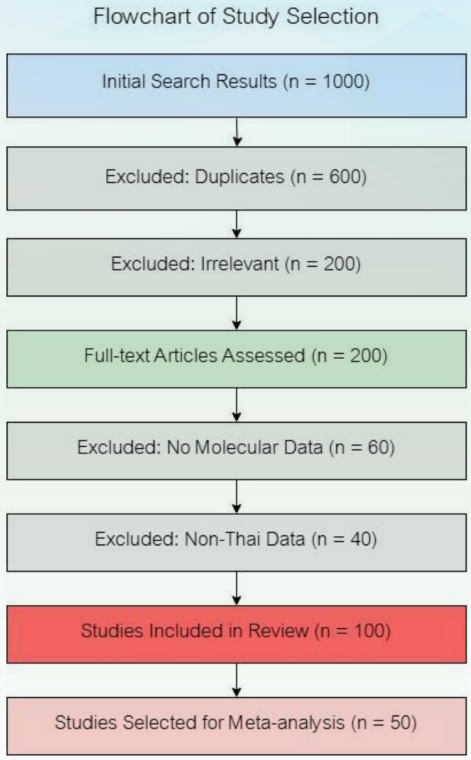

Figure 1 Flowchart of Study Selection

Risk of Bias Assessment

To assess the quality and reliability of the included studies, the Newcastle-Ottawa Scale (NOS) was employed. This scale evaluated studies on three criteria:

1. Selection - How studies were chosen and the population included.
2. Comparability - How comparable study groups were based on design or analysis.
3. Outcome - The objectivity of outcome measures, focusing on molecular data analysis.

The risk of bias was thoroughly evaluated to minimize systematic errors. Overall, the studies included in the review demonstrated a high level of robustness, with minimal risk of bias, supporting the reliability of the data for conclusions drawn on the molecular epidemiology of TB in Thailand.

Mutation Profiles and Data Analysis

A detailed data analysis was performed on mutation profiles from the selected studies, with a particular focus on:

- rpoB gene mutations: H526P, Q513P, and H526C, particularly in the Beijing genotype, which is associated with rifampicin resistance.
- katG gene mutations: Contributing to isoniazid resistance.
- gyrA and rrs gene mutations: Leading to resistance against fluoroquinolones and aminoglycosides.

The data analysis revealed geographic variability in mutation frequencies across Thailand. For example, novel mutations such as H526P and H526C in the rpoB gene were identified in specific regions like Chiang Rai, while the clonal expansion of the Beijing strain, especially in provinces with XDR-TB, was also noted.

Further Data Analysis for Identifying Research Gaps

To enhance the reliability of the conclusions, the expanded analysis allowed the identification of several research gaps:

- Need for continuous monitoring of novel mutations and their potential impact on drug resistance patterns.
- Regional disparities in mutation distribution, especially in high-risk border regions where cross-border transmission may occur.
- Lack of standardized genotyping approaches across provinces, which could hinder the development of uniform and effective TB control strategies across Thailand.

These findings emphasize the importance of continuing research into the evolving mutation landscape of Mycobacterium tuberculosis in Thailand to inform public health management and treatment strategies.

Genotypic Characteristics and Clonal Expansion

The predominant MTB genotype in Thailand is the Beijing lineage, which is associated with high transmission rates and drug resistance. A whole genome sequencing (WGS) analysis study analyzing 37 clinical isolates including 579 drug-resistant MTB isolates collected between 2014 and 2017 revealed significant clustering of the proto-Beijing genotype (L2.1) and found a high prevalence of XDR-TB cases (32.4%) with evidence of clonal expansion across multiple provinces. This clonal expansion is supported by the presence of identical drug-resistance mutations and low pairwise SNP distances, indicating recent transmission events.[8] In addition, a notable case study reported the cases of XDR-TB and pre-XDR-TB in Tak province, near the Thailand-Myanmar

border. These cases were characterized by Beijing genotypes, along with a variety of mutations in the rpoB, katG, gyrA, and rrs genes.[9,12] These studies reveal the Beijing is a recent clonal expansion of MTB in Thailand.

Mutations

Mycobacterium Tuberculosis infections can cause a range of medical conditions like active Pulmonary and extrapulmonary (EP) disease. Pulmonary TB is frequently the clinical form of the disease and majorly contributes to TB cases recorded globally. EP TB infects outside of the lungs, still causing a significant figure in mortality and morbidity in populations.[16] Among the 30 highest tb burden countries, Thailand has a prevalence of 150 per 100000, 1.7% and 10% of which are MDR TB, in both new TB cases and previously treated, respectively in 2019.[17]

Mutations of genes like rpoB, gyrA, rrs, katG promoter and inhA Promoter are all associated with drug resistance genes and MTB. The rpoB gene encodes the beta subunit of RNA polymerase in bacteria, which is crucial for the transcription of DNA into RNA. Mutations in specific regions of rpoB can alter the binding site, preventing rifampicin from effectively inhibiting the enzyme, thereby leading to drug resistance. The rpoB gene mutations are critical markers for rifampicin resistance, a key indicator of MDR-TB. The most common mutation observed is at codon 531 (S531L).[2] Nine different rpoB mutation patterns were identified in northern Thailand, with notable diversity in Chiang Rai, Chiang Mai, and Lampang provinces. Unique mutations such as H526P, Q513P, and H526C were detected in Chiang Rai, highlighting regional variations.[4]

GyrA is a subunit of DNA gyrase, an enzyme essential for DNA replication in bacteria. Mutations in the gyrA gene often lead to resistance to fluoroquinolones, a class of antibiotics that target DNA gyrase. These mutations typically occur in the quinolone resistance-determining region (QRDR) of GyrA, with common mutations found at codons 83 and 87 in many bacterial species. The result is a structural change in DNA gyrase that reduces the binding affinity of Fluoroquinolones, rendering them less effective or ineffective leading to resistance to Fluoroquinolones and injectable MTB second-line drugs, respectively. The RRS gene encodes the 16S rRNA, a component of the bacterial ribosome. Mutation in the RRS gene are associated with resistance to aminoglycosides, another antibiotic class that binds to the bacterial ribosome and disrupt protein synthesis. Common mutations

associated with resistance occur at positions 1408 and 1409 in the RRS gene.[18] These mutations alter the ribosomal binding site, preventing aminoglycosides from binding effectively, thereby leading to antibiotic resistance. Both mutations are critical in the context of bacterial resistance and are significant in treatment strategies for bacterial infections.[4]

MDR TB is caused by mycobacterium tuberculosis strains that display resistance to treatment and contains two primary anti-tuberculosis medications: Isoniazid and Rifampicin.[19] The mechanism behind drug resistance of mycobacterium tuberculosis is genetic mutations in the resistance of drugs, medications or treatments like INH and RFP. The occurrence of drug-resistant TB is categorized into primary and secondary drug resistance. While primary drug resistance is due to a drug resistance MTB infection, secondary drug resistance is caused by a development of resistance in later stages of drug-susceptible.[20] Hence how MDR TB can be developed is reliant on treatment with at least two first-line mentioned drugs. In the cases of resistance may also include the development of extensively drug-resistant TB (XDR-TB), specifically resistant to second-line drugs and one of the Fluoroquinolones: Amikacin, Kanamycin, or Capreomycin.[21] Totally drug-resistant (TDR) has also consistently been emerging.[17]

Despite MTB having a relatively low mutation rate,[22] drug resistance has increased significantly worldwide. Specifically, through chromosomal mutations, genes that are associated with first-line drugs exhibit a biological cost due to biological functions that the drug targets.[23] For instance: *rpoB* mutations for Rifampin resistance, *katG* and *inhA* mutations for Isoniazid resistance, *embB* mutations for Ethambutol resistance, and *pncA* mutations for Pyrazinamide resistance.[24] Isoniazid traits infection by inhibiting NADH-dependent enoyl-ACP reductase encoded by inhA and prevents cholic acid synthesis. Additionally, acting as a prodrug requires mycobacterium tuberculosis catalase-peroxidase enzyme katG activation.[23] While the katG gene mutation accounts for 30-75% of INH resistance, regulatory regions of inhA gene mutation or increased expression of this gene can cause low-level resistance to INH. unhA gene encodes for an enzyme involved in mycolic acid biosynthesis. More specifically, the most frequent mutation in the katG gene is Ser315Thr. Additionally, point mutation in the regulatory region of inhA promote may also contribute to INH resistance (6-30%).[25-26]

Mutations of these genes cause resistance to the drug isoniazid. Some associated is katG, inhA promoter, kasA, ndh, and oxyR-ahpC.[27]

On the other hand, Rifampicin-resistant strains only carry mutations in certain areas of the gene that encodes for DNA-dependent RNA polymerase beta subunit known as the rpoB gene. The mutation of this gene causes 90-96% of RIF resistance.[26, 28] Treatment for infection uses a combination of Isoniazid, Rifampicin and Pyrazinamide, in the case that the strain is fully drug-susceptible.[29] However, not complying to treatment or adequate medication can contribute to the development of drug resistance against all antibiotics relevant to the condition.[30]

MTB strains identified in Thailand have also included novel mutations of the strain like H526P, Q513P, and H526C Mutations, which are relatively rare mutations of the rpoB gene. Isolates from Chiang Rai that include this mutation were found, indicating the genetic diversity of MDR-TB strains.[2, 4] Moreover, it has been concluded and reported that the S315T mutation in the katG gene is the most prevalent mutation associated with Isoniazid resistance. This mutation was found in about 52.94% of MDR-TB isolates in Thailand.[9] Furthermore, Proto-Beijing Genotype (L2.1), a rare genotype, showed high prevalence of XDR-TB cases with evidence of clonal expansion across multiple provinces.[2]

Incidence and genotyping methods applied in the Thai population

A study was coducted in Thailand, using collected clinical samples associated with MDR-TB, sourced from hospitals from 7 different provinces in upper southern Thailand. Concluded that during the years 2020-2022, samples with TB decreased overtime. Furthermore, the highest average incidence of TB was found in Phuket province, a moderate to high-density population. On the other hand, Phang Nga province has the lowest incidence.[10]

Additionally, since the study was conducted during the COVID-19 pandemic, the incidence results revealed to have decreased over time.[11] Kanchanaburi province has one of the highest incidences of MDR-TB. Thamaka district, in particular, has been recorded as a hotspot, with continuous outbreaks of MDR-TB within their community in 2002 until 2010.[12]

Using various genotyping methods like spoligotyping to differentiate MTB strains, provides comprehensive genetic information a piece of comprehensive genetic information and typing MTB. Whole genome sequencing characterizes MTB,

determining the factors that affect transmission and investigating the possible links between TB patients, outbreaks, and infections from reactivation in relapse cases.[13]

Spoligotyping is a genotyping method that detects polymorphisms, utilizing the precence or absence of 43 unique spacer sequences in direct repeat regions as an identifier.[14] This method has been applied to categorize MTB strains into families like the Beijing, East African Indian, Central Asian, Latin American Mediterranean, unclassified, and T family(s).[15] A combination of spoligotyping and analysis of mycobacterial interspersed repetitive unit-variable-number tandem repeat is widely used as a tool to get clear identification of MTB strains.[31]

Beijing genotype strain with MDR is the most prevalent MTB strain that causes consistent transmission of tb in Thailand. This dominant strain was virulent and resistant to INH and RIF is still not eliminated from areas in Thailand. Most isolates showed Beijing spoligointernational type 1 was predominant with 52.8%, the remaining being non-beijing sublineages. Most Beijing isolates were of the modern type.[12] Application of spoligotyping and 15-MIRU-VNTR analysis in characterizing and discriminating MTB strains. Tools and methods applied to Thai-specific studies can be found in the paper of Drug-resistant Mycobacterium tuberculosis and its genotypes isolated from an outbreak in western Thailand.[12,33]

Thai provinces with the highest incidence of TB are Bangkok, Samut Sakhon, Tak, Chiang Rai, and Chiang Mai. Two of which are in upper northern Thailand. This is discussed to be affected by the frequent movement of immigrant workers and inadequate treatment due to the lack of resources combined with tourists visiting.[32] The borders of Thailand are yet to conduct genotyping routinely.[12]

Studies using Whole Genome Sequencing (WGS) have identified high transmission clusters, particularly in urban areas. These clusters are often associated with the Beijing lineage, indicating its role in the spread of TB. Thailand's geographical location and extensive border with several countries facilitate cross-border transmission of TB. Molecular studies have shown genetic similarities between strains in Thailand and neighboring countries, highlighting the need for regional collaboration in TB control.[8] Therefore, epidemiological investigations are necessary to control TB transmission in the epidemic area, providing not only development for proper strategies and rapid response and hence effective treatments.[12]

Conclusion

The reemergence of tuberculosis (TB) in Thailand, specifically the surge of multidrug-resistant and extensively drug-resistant strains poses a significant challenge for TB control. Understanding the importance of molecular epidemiology in strain diversity, transmission dynamics, and genetic mutations associated with the MTB in Thailand. Concluding that Beijing genotype is the most prominent and dominant in the country overall, identified by the application of molecular techniques like MIRU-VNTR typing and other tools. Revealing high incidence and prevalence at specific clusters like border areas. Genetic mutations include rpoB, katG, gyrA, and rrs genes and other novel mutations further emphasize the urge for tb management strategies. Further research should address the challenges in transmission and the appropriate genotypic surveillance for such matters.

แนะนำการอ้างอิงสำหรับบทความนี้

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