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GENETIC VARIATIONS OF MYCOBACTERIUM TUBERCULOSIS AND THEIR IMPACT ON DRUG RESISTANCE

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Annotation: Mycobacterium tuberculosis (M. tuberculosis) remains a serious global threat to public health. Particularly, the emergence of drug-resistant forms — multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains — complicates treatment outcomes. This article analyzes the genetic variations of M. tuberculosis, especially single nucleotide polymorphisms (SNPs) and other mutations, and their influence on drug resistance. The methodology is based on a systematic review of scientific literature, genomic research, and knowledge of genetic diversification. The main section discusses the common molecular mechanisms of drug resistance across major gene groups (e.g., rpoB, katG, inhA, gyrA, embB, and others), as well as the clinical implications of these mutations and their relevance within Uzbekistan's diagnostic and treatment context. The study concludes that a deeper understanding of the genetic basis of drug resistance in M. tuberculosis is essential for improving tuberculosis control strategies and advancing personalized therapeutic approaches. The article aims to provide an analytical perspective useful for researchers and to serve as a foundation for future studies.

Keywords: Mycobacterium tuberculosis, genetic variation, nucleotide polymorphism, drug resistance, multidrug resistance, rpoB, katG, inhA, gene mutation diagnostics.

Introduction

Tuberculosis (TB) is an infectious disease that primarily affects the lungs and is caused by bacteria belonging to the Mycobacterium tuberculosis (MTB) complex. According to the World Health Organization (WHO), millions of new TB cases are diagnosed each year, and a significant proportion involve drug-resistant forms. Drug resistance complicates treatment regimens, increases the burden on healthcare systems, and worsens patient outcomes. Therefore, understanding the genetic characteristics of M. tuberculosis — particularly its mutations and genetic diversification — is crucial for effective disease control and treatment. Genetic variation refers to changes within the bacterial genome, such as nucleotide substitutions, insertions or deletions (indels), and recombination events, which can alter the bacterium's susceptibility to drugs. For example, several studies have demonstrated that mutations in the rpoB gene are responsible for rifampicin resistance, while mutations in katG and inhA are associated with isoniazid resistance. Advances in genomic analysis and whole-genome sequencing (WGS) have expanded the spectrum of known mutations and improved molecular diagnostic tools. In Uzbekistan, active measures are being taken to strengthen TB control and

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diagnostics, including the introduction of molecular genetic analyzers. However, locally published research on the genetic mechanisms of drug resistance remains limited. Therefore, studying genetic variations and their contribution to drug resistance is of high relevance. The purpose of this paper is to systematically analyze M. tuberculosis genetic variations and their association with drug resistance based on current literature, draw evidence-based conclusions, and highlight challenges specific to the Uzbek context. To achieve this, the paper defines its methodology, reviews key research findings on the genetic basis of drug resistance, and presents analytical results and conclusions.

Methodology

This article is a qualitative, literature-based study consisting of the following stages:

Literature search: Research articles on M. tuberculosis genetic mutations and drug resistance were retrieved from international and local scientific journals using keywords such as "Mycobacterium tuberculosis," "genetic variation," "drug resistance," and "mutation rpoB katG inhA."

Example: "Evolution of drug resistance in Mycobacterium tuberculosis: a review on the molecular determinants of resistance and implications for personalized care."

Selection criteria: Studies that explored associations between genetic variations (SNPs, indels, or gene rearrangements) and drug resistance were included. Relevant publications on TB diagnostics and control in Uzbekistan were also considered (e.g., "Tuberkulyoz kasalligiga bakteriologik tashxis qo'yish usullari").

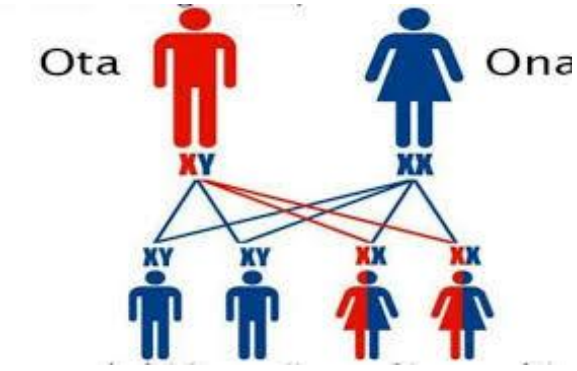
Data compilation: Extracted data were categorized according to mutation type, related drug group, epidemiological context, laboratory methodology, and clinical outcomes.

Analytical approach: The relationships between mutations and levels of drug resistance were systematically analyzed.

Local context analysis: Particular emphasis was placed on Uzbekistan's diagnostic and control capacities, including available genetic testing resources and their limitations. Through this methodology, the article aims to provide a synthesized understanding of the current state of knowledge regarding the genetic basis of TB drug resistance.

Main discussion

1. Mutation mechanisms and genetic diversification



Drug resistance in M. tuberculosis primarily arises from genetic mutations. These mutations generate new variants that may survive under selective drug pressure. Whole-genome sequencing has enabled in-depth exploration of these variations, revealing significant genetic diversification among resistant strains. The most frequently studied variations include single nucleotide polymorphisms (SNPs), insertions/deletions (indels), and transposable elements such as IS6110. The "fitness-cost" hypothesis suggests that resistance-conferring mutations can reduce bacterial growth; however, compensatory mutations — particularly in Lineage 2 (Beijing strains) — can restore fitness. Lineage-specific differences are thus crucial to understanding the evolution and spread of drug resistance.

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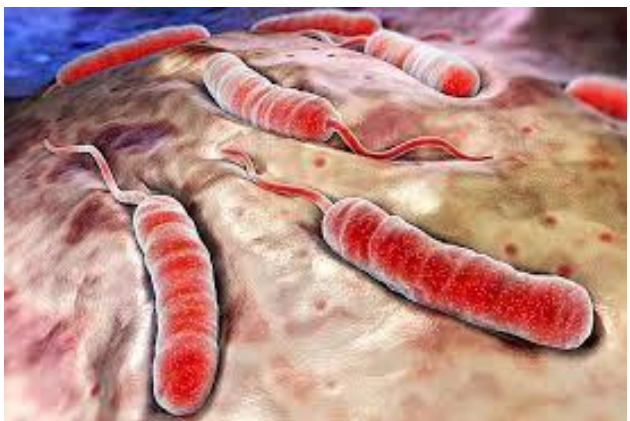
2. Key genes and mutations

- rpoB gene: Confers resistance to rifampicin (RIF). Mutations typically occur within the 81-bp rifampicin resistance-determining region (RRDR; codons 507–533). Common mutations include G516V, D516V, and S531L.
- katG gene: Associated with isoniazid (INH) resistance; the katG315 (Ser→Thr) mutation is one of the most prevalent worldwide.
- inhA gene and promoter region: Linked to low-level INH resistance, particularly through mutations affecting the enzyme's regulatory pathway.
- embB gene: Plays a major role in ethambutol (EMB) resistance, with embB306 being the most studied mutation.
- gyrA / gyrB genes: Associated with fluoroquinolone (FQ) resistance, with common mutations at gyrA90 and gyrA94.
- Other contributing genes: Efflux pump–related genes (e.g., Rv0191, Rv1410c) are also implicated in multidrug and fluoroquinolone resistance. Drug resistance often results from a combination of mutations across multiple genes, creating complex multidrug-resistant profiles.

3. Clinical impact of genetic variation

Mutations directly influence the clinical drug-resistance profile. For example, strains harboring katG315 mutations often display high-level INH resistance and poorer treatment outcomes. Longitudinal WGS studies (e.g., in Japan) have tracked M. tuberculosis isolates within a single patient over nine years, demonstrating stepwise accumulation of mutations leading to XDR-TB. Additionally, genetic clustering — where isolates share highly similar genomes — indicates ongoing transmission. In Sichuan, China, high clustering rates were observed among Lineage 2 strains with the katG S315T mutation, correlating with MDR/RR-TB cases. This shows that genetic variation affects not only resistance but also epidemiological spread.



4. Diagnostics, control, and the situation in Uzbekistan

Detecting genetic mutations is essential for rapid TB diagnosis and treatment optimization. Identifying mutations in rpoB, katG, and inhA allows clinicians to tailor

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drug regimens more effectively. In Uzbekistan, recent advancements include the implementation of molecular diagnostic platforms enabling faster detection of resistance-associated mutations. Nevertheless, the capacity for advanced genomic testing remains limited. Local literature highlights the scarcity of comprehensive analyses linking genetic variation with clinical resistance patterns. Expanding molecular laboratory capacity and integrating genomic surveillance into national TB programs are therefore vital.

5. Challenges and recommendations

Key challenges include limited laboratory resources, high costs of genomic technologies, and difficulties in data interpretation. Moreover, not all resistance mechanisms are fully understood — some mutations remain undetected by standard diagnostic panels.

To address these issues, Uzbekistan should:

✓ Standardize molecular testing methods,

✓ Develop a national genetic database of TB strains,

✓ Train laboratory specialists in genomic analysis, and

✓ Map the geographic distribution of M. tuberculosis lineages and mutations.

Analysis and results

The analysis reveals that genetic mutations play a central role in the development of drug resistance in M. tuberculosis. Genes such as rpoB, katG, inhA, embB, and gyrA are of particular importance. Lineage background (e.g., Beijing/Lineage 2) interacts with specific mutations, shaping both resistance levels and transmission potential. In Uzbekistan, the limited availability of genomic testing constrains individualized treatment approaches. Incomplete mutation detection and the absence of a national mutation database can result in "undetermined" resistance patterns, complicating drug selection. Overall, integrating genetic monitoring into TB control programs — through improved laboratory infrastructure, data management, and clinical-genetic correlation — is critical for enhancing disease surveillance and treatment outcomes.

Conclusion

This study comprehensively examined the genetic variations of Mycobacterium tuberculosis and their impact on drug resistance. Mutations in genes such as rpoB, katG, and inhA are key determinants of resistant phenotypes. Genetic lineages and evolutionary processes further contribute to the persistence and spread of resistance. For diagnostics and treatment, identifying these mutations allows for personalized therapy and improved control of TB transmission. In Uzbekistan, expanding genomic research, developing local mutation databases, training specialists, and strengthening laboratory capacity are necessary steps toward effective TB control. Future genetic approaches will be instrumental in optimizing treatment regimens, enabling individualized therapy, and improving national and global TB control strategies.

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References:

1. Coll, F., et al. (2018). GWAS and functional studies suggest a role for altered DNA repair in the evolution of drug resistance in Mycobacterium tuberculosis. eLife, 7. Retrieved from https://elifesciences.org/articles/75860
2. Cohen, K. A., et al. (2019). The evolving biology of Mycobacterium tuberculosis drug resistance. Frontiers in Cellular and Infection Microbiology, 12, 1027394. https://doi.org/10.3389/fcimb.2022.1027394
3. Hou, K., Jabeen, R., & Wei, J. (2024). How do Mutations of Mycobacterium Genes Cause Drug Resistance in Tuberculosis? Current Pharmaceutical Biotechnology, 25(6), 724–736. Retrieved from https://rjsocmed.com/1389-2010/article/view/644873
4. Sattarov, A., & Turobova, Y. (2024). Tuberkulyoz kasalligiga bakteriologik tashxis qo‘yish usullari. ACUMEN: International Journal of Multidisciplinary Research. Retrieved from https://www.universalpublishings.com/index.php/aijmr/article/view/11523
5. Abdurahmonov, P. S. (2024). Improving epidemiological control of tuberculosis in Uzbekistan. Tadqiqotlar.UZ. Retrieved from https://scientific-jl.org/tad/article/view/166