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Association Between Treatment Failure Cases and Individual Genetic Background in Patients With Drug-Resistant Tuberculosis

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Abstract This study explored the association between treatment failure and individual genetic background in patients with drug-resistant tuberculosis, aiming to reveal the role of host genetic factors in the treatment outcomes of drug-resistant tuberculosis (DR-TB). The study included tuberculosis patients with multidrug-resistant (MDR) and extensively drug-resistant (XDR) confirmed by drug sensitivity tests. By combining whole-genome sequencing (WGS), targeted gene analysis and clinical follow-up data, the relationship between host gene polymorphisms and drug metabolism, immune response and treatment outcomes was systematically evaluated. The results showed that the polymorphisms of drug metabolism genes (*NAT2*, *CYP2E1*, *CYP3A4*), drug transport genes (*ABCG2*, *SLCO1B1*), and immune regulatory genes (*PDCD1*, *VDR*, *PI3K/AKT*) significantly affected drug exposure levels, efficacy, and adverse reactions. Patients with slowly acetylated NAT2 are more prone to hepatotoxicity, while those with rapidly acetylated NAT2 have an increased risk of recurrence due to insufficient drug exposure. ABCG2 and VDR variations are associated with delayed sputum conversion to negative and adverse reactions. In addition, immune gene polymorphisms may affect the host's immune clearance ability, leading to persistent positivities or relapses in some patients even under the standard protocol. Based on this, this study proposes genotype-guided individualized treatment strategies, including drug selection and dosage optimization, dynamic monitoring of high-risk genotypes, and a comprehensive "gene-clinical-pharmacokinetic" evaluation model. Although pharmacogenomics is still limited by cost and validation in the clinical application of drug-resistant tuberculosis, it has great potential in precision treatment. In the future, through multi-omics integration and intelligent analysis, pharmacogenomics is expected to increase the cure rate, reduce toxicity and curb the spread of drug resistance.

Keywords Drug-resistant tuberculosis; Pharmacogenomics; Host genetic polymorphism; Treatment failure; Individualized treatment

1 Introduction

Drug-resistant tuberculosis (DR-TB) remains a major problem in the field of global health to this day. It not only makes the problem of antibiotics being ineffective more serious, but also slows down the pace of tuberculosis prevention, control and eradication. The latest data shows that in 2022, 410 000 cases of multidrug-resistant tuberculosis (MDR/DR-TB) or rifampicin-resistant tuberculosis were reported worldwide. At present, the pressure brought by multidrug-resistant and extensively drug-resistant tuberculosis (XDR-TB) is still increasing, and this problem is particularly prominent in regions with average economic conditions and among adolescents and young people (Gao et al., 2024). Insufficient medical resources, untimely diagnosis and the gap in economic conditions have made the burden brought by diseases even heavier. Some models predict that if there is no effective intervention, the number of cases and deaths of drug-resistant tuberculosis may still increase in the coming decades (Lü et al., 2024; Guo et al., 2025; Cui et al., 2025). In addition, drug-resistant strains can not only be directly transmitted among humans but also gradually change within patients' bodies. This implies that we urgently need more comprehensive public health strategies, such as rapid diagnosis, contact tracing, and targeted preventive measures (Liebenberg et al., 2022; Farhat et al., 2024).

With the emergence of new drugs and the application of short-term all-oral regimens (such as bedaquinolin-centered regimens), the treatment options for multidrug-resistant tuberculosis are increasing day by day. Compared with traditional long-term regimences, these new regimences usually bring a higher probability of cure and can reduce patient mortality (Fekadu et al., 2025; Michalik et al., 2025). The treatment outcome for