3.3 Immune response-related genes and their impact on pathogen clearance

Host immune response is an important determinant of the treatment outcome of tuberculosis, and polymorphisms of immune-related genes can change the pathogen clearance ability and the probability of treatment success or failure by influencing the anti-tuberculosis immune effect and the intensity of inflammatory response. At present, the genes that have been studied more mainly focus on cytokine signaling and immune regulatory networks, such as *IL6*, *STAT3*, *PDCD1 (PD-1)*, *CTLA4*, *HAVCR2 (TIM-3)*, *mTOR* and *VDR (vitamin D receptor)*. During the treatment process, variations related to the IL-6/STAT3 pathway were associated with changes in cytokine responses and susceptibility to drug-induced hepatotoxicity. Meanwhile, the polymorphisms of mTOR and PI3K/AKT pathway genes involved in macrophage activation and bacterial clearance are also associated with increased susceptibility to tuberculosis and differences in treatment response (Wu et al., 2023)

The differences in immune-related genes can affect the efficacy of immunotherapy for tuberculosis. Genes like *PD-1, CTLA-4* and *TIM-3* are different and may affect the working state of T cells and the strength of immune responses, thereby influencing a person's ability to resist tuberculosis and control the condition. Studies have found that changes in the rs7568402 locus of the PDCD1 gene and the rs13170556 locus of the *HAVCR2* gene are both associated with the risk of tuberculosis, and this relationship may be different between men and women (Wang et al., 2021; Liu et al., 2024). Meanwhile, variations at the FokI locus of the *VDR* gene have also been proven to increase the risk of tuberculosis, indicating that the immune regulation involved in vitamin D is very important for controlling infection (Yadav et al., 2021). These genetic differences related to immunity may further alter patients' responses to treatment by influencing the body's ability to clear bacteria.

4 Case Study Design and Data Sources

4.1 Inclusion and exclusion criteria

This study adopted a case-control design to evaluate the association between genetic background and treatment failure in patients with drug-resistant tuberculosis (DR-TB). The included subjects were adults aged 18 years and above with tuberculosis who were confirmed to be multidrug-resistant (MDR) or extensively drug-resistant (XDR) by molecular or phenotypic drug sensitivity tests: MDR was defined as resistance to at least rifampicin and isoniazid, and XDR was defined as additional resistance to any fluoroquinolone drug and at least one second-line injection drug (such as amicacin or capreomycin) on this basis. Those WHO meet the conditions need to complete the standardized second-line treatment protocol as recommended by the WHO and be managed under direct observation treatment. The treatment plan usually includes the combination of bedaquiline, linezolid, levofloxacin and cycloserine, etc. To reduce confounding effects, patients with incomplete treatment records, co-infection with HIV, severe liver dysfunction or other chronic infectious diseases were excluded.

After the treatment commences, the patient will be followed up for 24 months, mainly to observe the negative sputum culture, disease recurrence and death. If the sputum culture remains positive after 6 months of treatment, or if it recurs within 1 year after the end of treatment, or if the patient dies of tuberculosis, it is regarded as treatment failure. The basic information, clinical data and microbiological test results of the patients mainly come from the national tuberculosis surveillance system and hospital databases. The inclusion criteria of this study were consistent with those of the relevant cohort studies in China and South Korea. Both used similar criteria to evaluate the relationship between genetic factors and treatment effects (Che et al., 2021).

4.2 Collect clinical data, follow-up records and laboratory test results

Clinical and laboratory information is collected through the standardized electronic medical record system of the designated tuberculosis hospital. Baseline variables include age, gender, smoking history, nutritional status, comorbidities, previous tuberculosis treatment history and drug resistance spectrum, etc. At the same time, record the treatment plan, compliance rate, adverse events and culture results, and extract them at the predetermined frequency (once a month during the intensive period and once every quarter thereafter). Sputum specimens were collected at both the baseline and follow-up stages for smear, culture and GeneXpert MTB/RIF detection. First-line and second-line drug sensitivity tests (DST) were performed using the proportional method on Lowenstein-Jensen medium. Meanwhile, combined with molecular line probe method (LPAs) for rapid detection of drug resistance-related mutations.