Some studies use whole-genome sequencing to identify genetic changes related to drug resistance and thereby determine the types of bacterial branches. When conducting the analysis, researchers not only focus on drug resistance genes, but also take into account the variations of compensation genes such as rpoA, rpoC, and gyrA. This can more comprehensively explain the connection between different bacterial characteristics and therapeutic effects (Figure 2) (Song et al., 2023). During the follow-up process, doctors will record the time when sputum bacteria turn negative (bacteria disappear), whether there is a recurrence, and changes in clinical scores. The death and recurrence of patients will be verified through the National tuberculosis Registry system. All data collection adheres to ethical requirements and has been approved by the institutional review board.

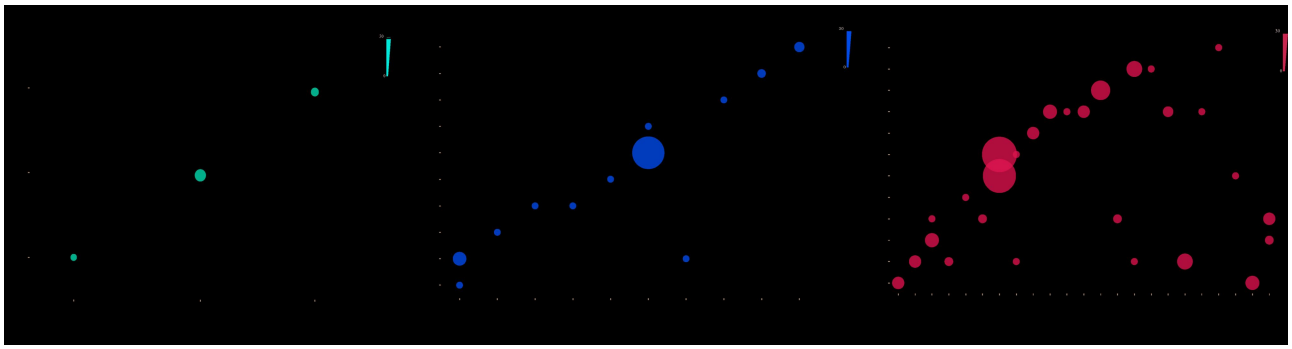

Figure 2 Putative compensatory mutations in the rpoA, rpoB, and rpoC genes were identified in this study (Adopted from Song et al., 2023)

Image caption: Each putative compensatory mutation was supported by at least two independent evolution events on the phylogenetic tree (Adopted from Song et al., 2023)

4.3 Overall framework of genetic testing and statistical analysis methods

Some studies have combined whole-genome sequencing with targeted sequencing and also used bioinformatics technology to identify genetic changes that may be related to therapeutic effects. Whole genome sequencing was performed on the Illumina HiS1eq platform, with an average sequencing depth of over 100×. Researchers compared the data obtained from sequencing with the reference genome of *H37Rv.* GATK is used to identify single nucleotide polymorphisms, that is, situations where a single base on a gene is altered. Researchers used the PhyloTB and TB-Profiler tools to jointly analyze the branch types and genetic characteristics of the strains. This research process is consistent with the commonly used genomic monitoring methods at home and abroad (He et al., 2022; Liang et al., 2023). Next, an in-depth analysis of the known drug-resistant genes will be conducted, with a focus on common genetic variations and potential new variations.

Statistical analysis was conducted using SPSS and R: descriptive statistics were used to summarize clinical features, and chi-square test and t-test were used to compare the classification and continuous variable differences between the successful treatment group and the failed treatment group. Logistic regression was used to evaluate the association between host genetic polymorphism and treatment outcomes, and confounding factors such as age, gender, comorbidities and drug resistance patterns were adjusted. The sputum transformation time and mortality risk were estimated by Kaplan-Meier and Cox proportional hazards models, and the methods were consistent with the designs of recent genomic and cohort studies. Genome-wide association analysis was conducted using tools such as PLINK and admix, and error detection rate correction was adopted to control multiple comparisons. The result interpretation emphasizes the significance at the functional pathway level and its potential value for precise anti-tuberculosis treatment strategies.

5 Review of Cases of Failed Treatment for Drug-Resistant Tuberculosis

5.1 Basic case information, drug resistance overview and initial treatment plan

This study focuses on patients with drug-resistant tuberculosis. Multidrug-resistant tuberculosis usually refers to tuberculosis that is resistant to both isoniazid and rifampicin. On this basis, extensively drug-resistant tuberculosis may also be resistant to fluoroquinolones and at least one second-line injection drug. Among our group of patients, the majority are aged between 25 and 60, and the proportion of men is also higher. This is the same as the