Incorporating these related genetic differences into pharmacogenomic screening is expected to help formulate more precise medication management and monitoring plans, reduce the drug toxicity burden on patients with drug-resistant tuberculosis, and lower the risk of treatment failure.

### 3.2 Genes related to drug transport and excretion

Efflux transporters are one of the key factors influencing the absorption and utilization of anti-tuberculosis drugs in the body, their distribution in tissues, and the risk of treatment failure. Members of the ATP-binding cassette (ABC) transporter family (such as ABCB1 [also known as P-glycoprotein] and ABCG2) can regulate the concentrations of various anti-tuberculosis drugs within cells. When the activity of these transport proteins is too high or there are functional genetic differences, the effective drug concentration at the lesion site may decrease, thereby affecting the treatment outcome and increasing the probability of treatment failure. Research has found that among Chinese people, differences in the *ABCG2* gene (especially at the rs2622605 locus) are associated with an increased risk of liver damage caused by anti-tuberculosis drugs, indicating that differences in transporter genes not only affect the metabolic process of drugs in the body It will also make people more prone to drug toxicity reactions. Therefore, the genetic differences of transporters not only relate to the therapeutic effect but also affect the safety of medication, having a dual significance of "efficacy and safety", and deserve special attention when conducting risk assessment.

In addition, the drug efflux mechanism also intersects with cellular signaling and immune regulation processes: the activation of pathogen efflux pumps can directly contribute to bacterial resistance, while variations in host efflux related genes may further weaken drug efficacy. Changes in the activity of ABC transporters can affect the disposal process of key drugs such as rifampicin and bedaquinoline, and may alter the intracellular drug accumulation levels of drug-resistant strains, thereby influencing the treatment response (Figure 1) (He et al., 2022). Given that extraining-related genetic factors can simultaneously act on the host pharmacodynamic environment and bacterial resistance phenotypes, a systematic understanding of their effects is helpful for optimizing protocol design and reducing the risk of further expansion of drug resistance.

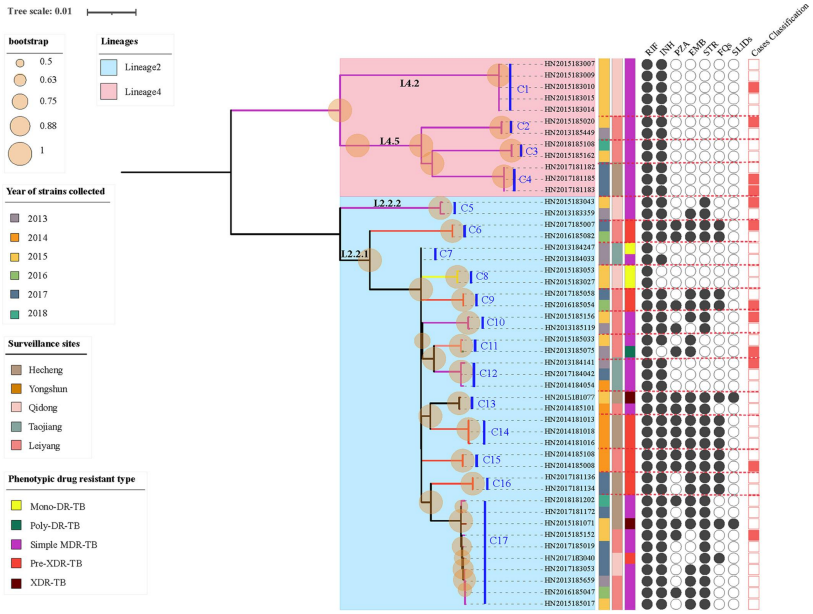


Figure 1 Maximum-likelihood tree of 44 rifampicin-resistant tuberculosis strains within 17 clusters and their phenotypic drug-resistant profiles (Adopted from He et al., 2022)

Image caption: The red dotted lines indicate boundaries of individual clusters; Cluster 1–17 was labeled as C1-C17; RIF, rifampicin; INH, isoniazid; PZA, pyrazinamide; EMB, ethambutol; STR, streptomycin; FQs, fluoroquinolones, including moxifloxacin and ofloxacin in this study; SLIDs, second-line anti-TB drugs, including kanamycin and amikacin in this study; Circles filled with black indicate drug-resistant strains, while empty circles indicate drug-susceptible strains; Rectangle filled with red indicate strains collected from cases with previously treatment history, while empty rectangles indicate strains collected from new cases; Scale bar indicates the genetic distance proportional to the total number of single nucleotide polymorphisms (Adopted from He et al., 2022)