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Role of pharmacogenomics in Tuberculosis

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ABSTRACT
Tuberculosis (TB) continues to be a global health burden, with millions of new cases and deaths each year. Despite standardized treatment regimens, there is considerable interindividual variability in both therapeutic outcomes and adverse effects. Pharmacogenomics, the study of how genetic variation in patients influences drug response, promises to tailor anti-TB therapy for improved efficacy and safety. In this review, we examine the current knowledge of pharmacogenomic determinants for first-line and some second-line TB drugs; assess evidence linking genetic polymorphisms (e.g. in NAT2, SLCO1B1, PXR, ABCB1, etc.) to drug levels, toxicity, and treatment outcomes; consider assay development; and outline the barriers and future directions for integrating pharmacogenomics into TB care. Available evidence strongly supports that NAT2 slow acetylator genotypes increase risk of isoniazid-induced hepatotoxicity, that SLCO1B1 variants influence rifampicin pharmacokinetics (though not all studies show consistent effects), and that resistance in M. tuberculosis (e.g. via pncA, katG/inahA) further interacts with treatment response. To realize the promise of precision medicine in TB, there is a need for large, diverse cohorts, cost-effective assays, regulatory and implementation frameworks, and consideration of population diversity.
Keywords: TB, Pharmacogenomics, resistance, genetic variation

I. INTRODUCTION

Tuberculosis (TB), caused by Mycobacterium tuberculosis, remains one of the leading causes of morbidity and mortality worldwide. Globally, millions of new TB cases are reported annually, and despite the availability of effective drug regimens, cure rates are compromised by treatment failure, relapse, and adverse drug reactions. The WHO's End TB Strategy aims for large reductions in incidence and mortality by 2035, but to achieve this, improvements are needed in diagnostics, drug regimens, adherence, and also in how individual variations in drug response are addressed.

While TB treatment guidelines typically assume a "one-size-fits-all" drug regimen, there is ample evidence that genetic differences among patients influence drug absorption, distribution, metabolism, excretion (pharmacokinetics, PK) and drug-target interactions (pharmacodynamics, PD). Differences in genetic variants can lead to subtherapeutic drug concentrations (leading to treatment failure or emergence of resistance) or elevated concentrations (leading to toxicity) (e.g., hepatotoxicity with isoniazid, etc.).

Pharmacogenomics refers to the systematic study of genetic variation (often single nucleotide polymorphisms, SNPs, or other kinds of variants) and how these affect drug response. In TB, pharmacogenomics can contribute at several levels:

1. Host pharmacogenomics, i.e. human genetic variation that affects drug metabolism or transport.
2. Microbial genomics, i.e. variations in M. tuberculosis that confer drug resistance or alter drug sensitivity.
3. Combined host-pathogen dynamics, where host variation in metabolism affects exposure to drugs, which (especially under suboptimal PK) can facilitate resistance emergence.

In this review, we focus mainly on host pharmacogenomic variation (though microbial resistance is also discussed where relevant) with respect to first-line TB drugs (isoniazid, rifampicin, pyrazinamide, ethambutol) and selected second-line drugs; summarize what is known, gaps, and how to move toward clinical implementation.

II. KEY GENETIC DETERMINANTS AFFECTING FIRST-LINE TB DRUGS

2.1 NAT2 (N-acetyltransferase 2) and Isoniazid

2.1.1 Role of NAT2 in Isoniazid Metabolism

Isoniazid (INH) is metabolized in the liver by N-acetyltransferase 2 (NAT2). Polymorphisms in the NAT2 gene lead to different acetylator phenotypes: slow, intermediate, and fast acetylators. These phenotypes influence both the

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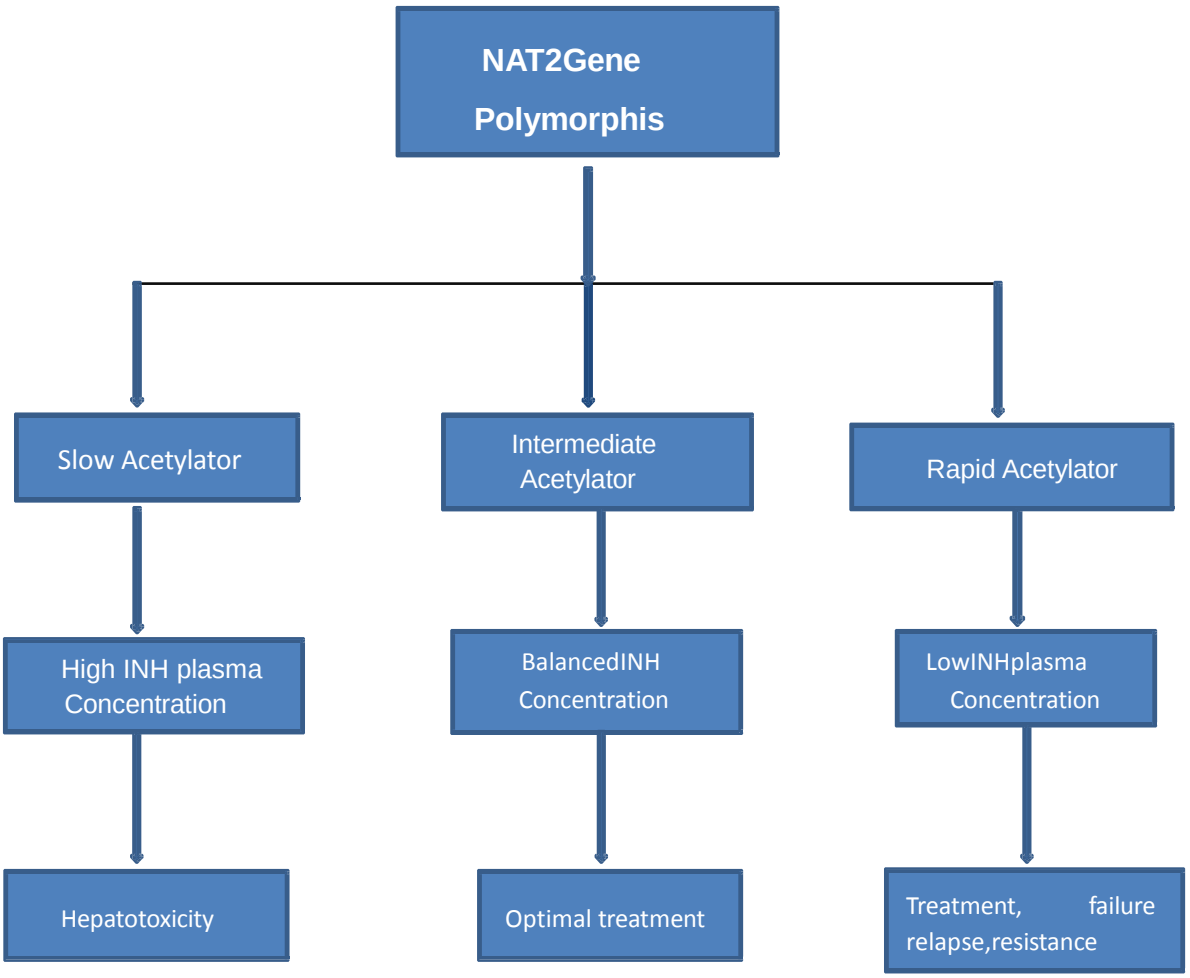
rate at which isoniazid is cleared and the risk of accumulation-associated toxicity (especially hepatotoxicity) as well as possibly affecting efficacy.



2.1.2 Evidence Linking NAT2 Variants to Adverse Effects

A recent systematic review and meta-analysis (2024) confirms that individuals with slow NAT2 acetylator genotypes have significantly greater risk of anti-tuberculosis drug-related hepatotoxicity (ATDH). Specifically, the overall odds ratio (OR) for ATDH in slow acetylators vs other acetylator phenotypes was approximately 2.52 (95% CI: 1.95–3.27; $p < 0.001$) across 24 studies. Among specific slow acetylator genotypes NAT25/7, *5/6, and *6/6, the risk was further elevated.[1]

Other studies show that in South African patients, for example, rapid and intermediate acetylators had 2.3- and 1.6-times faster isoniazid clearance respectively, compared to slow acetylators.**[2]**

Also, in a Cameroonian cohort of TB/HIV co-infected patients, NAT2*5 was paradoxically associated with decreased risk of drug-induced hepatotoxicity (DIH), while NAT26 was associated with increased risk (OR ~4.2) in that population. This suggests population-specific variant effects and possibly differences in allele frequencies, co-morbidities (like HIV), dosing, or other factors. [3]

2.1.3 Clinical Assay and Predictive Tools

One recent development is a cartridge-based multiplex qPCR assay (on the GeneXpert platform) for NAT2 genotyping. In a study of 48 TB patients, predicted acetylator types (slow, intermediate, and rapid) using a 5-SNP model correlated with measured INH clearance: slow acetylators had lowest clearance, fast acetylators highest. The assay could detect allele patterns from small whole blood volumes (25 µl). This kind of tool is promising for point-of-care implementation. [3]

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2.1.4 Gaps / Uncertainties

- Not all variants are equally predictive across ethnic groups; allele frequencies of NAT2 variants (*5, *6, *7, etc.) vary by region.
- Some studies differ in defining "slow" phenotype (how many SNPs genotyped, which reference alleles, etc.).
- The clinical significance of moderate elevations in drug levels (in intermediate acetylators) in terms of patient-oriented outcomes (e.g. toxicity, relapse) is less well quantified.

2.2 SLCO1B1 and Rifampicin

2.2.1 Role of SLCO1B1 in Drug Transport

SLCO1B1 encodes OATP1B1 (organic anion transporting polypeptide 1B1), which mediates hepatic uptake of several drugs, potentially including rifampicin (RIF). Genetic variants in SLCO1B1 (e.g. *rs4149056, rs2306283, etc.) may alter transporter function. Rifampicin exposure is important because both under- and overexposure can lead to bad outcomes (resistance, toxicity).

2.2.2 Population PK Studies and Variant Effects

- In a large study of 879 TB patients in Korea, SLCO1B1 rs4149056 genotype was one of the most significant covariates of rifampicin clearance (CL/F). Wild-type individuals had ~16.6% higher clearance than variant carriers, which resulted in lower drug exposure among them. The investigators proposed adjusted rifampicin dosing by weight bands, in addition to genotype, to achieve target exposures.[4]
- However, in South India, three SLCO1B1 polymorphisms (rs11045819, rs4149032, rs4149033) did not show significant effect on 2-hour post-dose rifampicin levels among 256 patients. [5]
- In Uganda, a study comparing rifampicin resistant vs susceptible TB patients found that SLCO1B1 genotypes (including rs4149032, *1B, *5) did not significantly influence rifampicin pharmacokinetics or rifampicin-TB sensitivity status, though a substantial fraction of patients had subtherapeutic rifampicin concentrations. [6]

2.2.3 Broader Reviews

A systematic review examining genetic polymorphisms of drug transporters and metabolizing enzymes affecting rifamycins (including rifampicin) indicates that SLCO1B1, ABCB1, AADAC (arylacetamide deacetylase), CES2, among others, contribute partially to pharmacokinetic variability. However, effect sizes are often modest, and findings are inconsistent across populations. [2]

2.3 Other Genes & First-Line Drugs

2.3.1 PXR, ABCB1, UGT1A

- PXR (pregnane X receptor) regulates expression of drug-metabolizing enzymes and transporters; variants have been explored for associations with rifampicin and other drug exposures. In some studies in South Africa, PXR, ABCB1, and UGT1A genotypes were tested for associations with rifampicin PK, but no strong associations emerged in that cohort. [2]
- ABCB1 (P-glycoprotein) variants have been studied, with some early reports suggesting modest effects on drug disposition, but overall results are mixed and less consistent than with NAT2 or SLCO1B1. [6]

2.3.2 Pyrazinamide and Ethambutol

Data for pyrazinamide (PZA) and ethambutol (EMB) pharmacogenomics are more limited.

- Regarding PZA, microbial resistance (i.e. in M. tuberculosis) via pncA gene and other mutations is well established. For example, in MDR/XDR TB isolates in South Africa and Georgia, ~70-96% had pncA polymorphisms associated with PZA resistance. [8]
- There are fewer studies on human host genomic variation affecting PZA pharmacokinetics or toxicity; this is a gap.
- For EMB, even less is known about host genetic variation impacting its PK or toxicity.

III. CLINICAL IMPLICATIONS: TREATMENT OUTCOMES, TOXICITY, AND DRUG RESISTANCE

3.1 Treatment Outcomes

- Drug exposure: Several studies show that lower drug exposure (e.g. measures like Cmax, AUC) of rifampicin correlates with slower bacteriological conversion of sputum, worse radiographic improvements, and possibly higher risk of failure or resistance. For example, Korean studies have shown that higher rifampicin exposure is associated with improved chest radiograph changes, though in the same study, SLCO1B1 genotype did not

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significantly alter time to culture conversion. [2]
- Isoniazid clearance: Faster acetylators clear drug more rapidly, which might lead to lower drug levels; whether this contributes to relapse in some settings is suggested but not conclusively proven in many populations.

3.2 Adverse Drug Reactions
- Isoniazid-induced hepatotoxicity is one of the most studied ADRs. Strong association exists between slow NAT2 genotype and risk of ATDH. Meta-analyses confirm this across many ethnicities. [6]
- Other ADRs such as peripheral neuropathy are also related to isoniazid dose and possibly accumulation; intracellular toxic metabolites may also play a role depending on metabolism.
- Drug-induced hepatotoxicity in co-infected patients (TB & HIV) appears to be higher, potentially due to interactions, comorbid liver stress, and variation in NAT2 alleles. As noted, in Cameroonian TB/HIV patients, NAT2*6 was associated with increased risk of hepatotoxicity. [7]

3.3 Drug Resistance
- Microbial resistance: Mutations in M. tuberculosis genes such as katG, inhA, pncA are primary causes of resistance to isoniazid, ethionamide and PZA. These drive failure in standard regimens. For example, pncA mutations are frequent in MDR/XDR TB isolates, making PZA less effective in many resistant cases. [8]
- Role of host pharmacogenomics: If host metabolism leads to low drug exposure (due to fast acetylation, poor uptake, or elevated clearance), there is a concern of subtherapeutic levels that allow bacteria to persist and potentially develop resistance. While direct prospective data is less abundant, the hypothesis is biologically plausible and supported by pharmacokinetic modeling. For example, Korean studies adjusting rifampicin dose based on SLCO1B1 genotype and weight are motivated by trying to avoid subtherapeutic exposures. [4]

IV. ASSAYS, GENOTYPING, AND STRATEGIES FOR IMPLEMENTATION

4.1 Genotyping Tools
- The assay built on GeneXpert for NAT2 discussed above represents a good example of translating research into practical bedside or point-of-care tools. It uses a 5-SNP model which (in that cohort) showed full accuracy in genotype prediction (100%) in out-of-sample data for acetylator status. [2]
- Many studies use TaqMan SNP assays, Sanger sequencing, or other genotyping platforms for NAT2, SLCO1B1, etc. These are effective in research settings but may be costly or less accessible in high TB burden countries.

4.2 Dose Adjustment Strategies
- For isoniazid, adjusting dose based on NAT2 acetylator status could reduce toxicity in slow acetylators and possibly improve efficacy in fast acetylators. However, there is no yet consensus guideline with dose adjustments in many countries.
- For rifampicin, dose escalation strategies are being explored. Studies suggest that patients with SLCO1B1 alleles associated with higher clearance may benefit from higher rifampicin doses; some modeling studies propose weight-banded increases. [9]

4.3 Integration into Clinical Trials and Practice
To make pharmacogenomics a part of standard TB care, several components are needed:
- Large-scale, multi-ethnic cohort studies that measure genotype, drug levels, exposures, clinical outcomes (e.g. cure, relapse, culture conversion).
- Standardization in defining phenotypes (e.g. what thresholds of drug concentrations matter, what defines hepatotoxicity, etc.).
- Cost-effectiveness studies showing that genotyping plus dose adjustment improves outcomes or reduces overall costs (by avoiding toxicity, reducing treatment duration, avoiding resistance).
- Regulatory and guideline support, especially in high TB burden, low and middle income countries.

V. CHALLENGES AND GAPS

5.1 Heterogeneity Among Studies
- Differences in genotyping panels (which SNPs are included), allele definitions, and reference alleles.
- Differences in drug dosing, formulations, patient adherence, nutritional status, comorbidities (e.g. HIV, liver disease), age,

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pregnancy—all can influence the pharmacokinetics independent of genetics.
- Variation across ethnic groups: allele frequencies differ substantially; some variants may have strong effects in one population and weak or no effects in another. For example, the frequency of SNPS in SLCO1B1 differ, and some studies show no association in certain populations (e.g. South India) while others show effect (e.g. Korea).[2]

5.2 Technical and Operational Barriers
- Cost of genotyping assays and setting up infrastructure in resource-poor settings.
- Turnaround time: genotype needs to be available early enough to influence treatment decisions (ideally before or very early in therapy).
- Regulatory, ethical, and logistical issues: quality control, training, data privacy.
- Limited data for certain drugs (e.g. ethambutol, pyrazinamide acutely from host side), and for second-line drugs.

5.3 Clinical Relevance and Acceptability
- How much drug exposure difference matters: what are cutoff values for Cmax, AUC, etc., that impact outcomes?
- Risk vs benefit: raising doses to overcome fast metabolism or low transporter activity may increase risk of toxicity in some patients.
- Patients' adherence, food effects, drug interactions may overshadow genetic effects in many settings if not addressed.

VI. RECENT ADVANCES AND FUTURE DIRECTIONS

6.1 Novel Assays and Predictive Models
- The GeneXpert-based NAT2 assay (5-SNP) is a promising prototype for point-of-care pharmacogenomics, potentially allowing genotype to guide dosing. [2]
- Population PK modeling incorporating weight, genotype (e.g. SLCO1B1), demographic and clinical covariates (e.g. in Korea) is helping to define suggested dosing regimens that could mitigate risk of underexposure. [4]

6.2 Expanding Evidence Base
- There is growing evidence from different geographies (Africa, Asia, South America) about NAT2 and SLCO1B1 effects. These help understand population-specific variant frequencies and clinical effects. For example, the Ghanaian children study showed minimal clinical utility at population level for some genotypes but flagged possible individual-level utility. [2]
- More work is needed on second-line TB drugs (linezolid, bedaquiline, etc.), co-morbid patient populations (HIV, diabetes, pregnancy), pediatric populations, and elderly.

6.3 Implementation Science
- Pilot implementation studies to test genotype-guided dosing protocols.
- Health economic evaluations: are the upfront costs of genotyping offset by reductions in toxicity, shorter hospitalizations, fewer treatment failures, less emergence of resistance?
- Policy, regulatory, guideline incorporation – inclusion by WHO, national TB programs of pharmacogenomic considerations**.**

6.4 Ethical, Equity, and Access Considerations
- Ensuring that populations in high burden countries are represented in genetic studies, so that genotyping panels capture variants relevant to those populations.
- Avoiding exacerbation of health disparities: if pharmacogenomic tools are only available in richer settings, inequities may increase.

VII. CONCLUSION

Pharmacogenomics has matured to the point where its relevance to TB therapy is well supported in multiple areas. The strongest evidence exists for NAT2 variation affecting isoniazid metabolism and hepatotoxicity; there is encouraging but mixed evidence for SLCO1B1 variation and rifampicin pharmacokinetics; for drugs such as pyrazinamide and ethambutol, and for most second-line agents, host pharmacogenomic data remain sparse.

Moving forward, it will be essential to build large, diverse, well-phenotyped cohorts; develop robust, inexpensive, rapid genotyping assays; define actionable thresholds for drug exposure and toxicity; integrate genotype info into TB treatment guidelines; and implement clinical trials of genotype-guided dosing. If successful, pharmacogenomics can enhance efficacy, reduce adverse events, and contribute substantially to global TB control and ultimately the goals set out by the WHO's End TB Strategy.

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