International Journal for Research in Biology and Pharmacy

GREEN PUBLICATION

ISSN (Online): 2208-2093
Volume 10 Issue 02 June 2024
Available on-line at: https://ijrbp.com/index.php/bp/issue/view/551

DOI:*https://doi.org/10.69980/bp.v10i2.2489* *Received: 16-Mar-2024 Accepted: 19-May-2024*

PHARMACOGENOMIC VARIATIONS INFLUENCING DRUG RESPONSE IN TUBERCULOSIS TREATMENT

Dr. Yusuke Shiraishi[1], Dr. Elham Gholami[2], Dr. Kelly E. Dooley[3], Dr. James C. M. Brust[4]

[1] Department of Respiratory Medicine, Fukujuji Hospital, Japan Anti-Tuberculosis Association, Tokyo, Japan
[2] Department of Pharmacogenomics, Tehran University of Medical Sciences, Tehran, Iran
[3] Division of Clinical Pharmacology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA
[4] Division of Infectious Diseases, Albert Einstein College of Medicine, Bronx, New York, USA

Corresponding Author
Email: kdooley1@jhmi.edu

ABSTRACT
Tuberculosis remains a major global health concern, and variability in response to anti-tuberculosis drugs often complicates treatment outcomes. Genetic differences among individuals can influence drug metabolism, pharmacokinetics, and susceptibility to adverse drug reactions. Pharmacogenomics has therefore emerged as an important approach for understanding variability in drug response and improving personalised treatment strategies. Pharmacogenomic clinical information and genomic probe information from the GPL570 microarray platform were integrated to identify gene–drug relationships associated with anti-tuberculosis treatment. Data preprocessing included the removal of incomplete entries and the normalisation of gene identifiers. Pharmacogenomic variants were mapped to corresponding genes, followed by functional classification, bioinformatics analysis, and descriptive statistical evaluation of gene and drug association frequencies. Analysis identified 10 pharmacogenomic genes associated with anti-tuberculosis drug response. N-Acetyltransferase 2 (NAT2) showed the highest frequency (n = 13), followed by Solute Carrier Organic Anion Transporter Family Member 1B1 (SLCO1B1) (n = 5) and ATP/GTP Binding Protein Like 4 (AGBL4) (n = 3). Other genes, including Cytochrome P450 Family 2 Subfamily E Member 1 (CYP2E1), ATP Binding Cassette Subfamily B Member 1 (ABCB1), Cytochrome P450 Family 2 Subfamily B Member 6 (CYP2B6), and Exportin 1 (XPO1), were observed with moderate frequencies. Drug association analysis revealed that rifampin had the highest frequency (n = 11), followed by tuberculosis drug combinations and isoniazid-related therapies. Pharmacogenomic variability in metabolic enzymes and transporter genes plays a significant role in determining anti-tuberculosis drug response. Integrating pharmacogenomic information into clinical practice may improve personalised treatment strategies and optimise therapeutic outcomes.

KEYWORDS: *Pharmacogenomics, Tuberculosis therapy, Drug–gene interactions, Anti-tuberculosis drugs, Genetic polymorphisms*

INTRODUCTION

Tuberculosis is one of the most important infectious diseases worldwide, and it causes significant morbidity and mortality in all countries. Despite the availability of effective anti-tuberculosis drugs, the results of treatment among patients often differ because of individual differences in metabolism, pharmacokinetics, and genetic factors of the host. Genetic differences between individuals can determine the effectiveness of drugs and predisposition to adverse drug reactions, which can result in treatment failure or toxicity during therapy. Understanding the genetic basis of drug response is therefore crucial in order to improve the therapeutic outcomes and create individualised treatment strategies for tuberculosis patients (Khan et al., 2022).

Pharmacogenomics, the study of the correlation between genetic variations and drug response, has become an important subject in modern medicine. Genetic polymorphisms, which influence drug-metabolising enzymes, drug transporters, and immune-regulation pathways, can greatly influence the pharmacokinetics and pharmacodynamics of the anti-tuberculosis drugs. Variants in genes that are responsible for drug metabolism may have an impact on the rate of drug absorption, distribution, metabolism, and elimination, leading to both therapeutic efficacy and risk of adverse drug reactions (Pirmohamed, 2014). Identification of such genetic factors may assist in the optimisation of treatment regimens and lessen drug-related complications.

Host genetic factors play an important role in deciding the variability of response to anti-tuberculosis therapy. Genetic variants that affect the metabolism of drugs can affect the efficacy of commonly used drugs such as isoniazid and rifampicin. Research has shown that genetic polymorphisms could have a considerable impact on the efficacy of medicines and treatment outcomes, emphasising the importance of customising medical treatments when dealing with the disease of tuberculosis (Khan et al., 2022). In addition, pharmacogenomic studies have found a few host genetic markers that are linked to adverse drug reactions to anti-tuberculosis drugs (Kumar Sahu et al., 2015).

Variability in pharmacokinetics in tuberculosis patients has been linked to single-nucleotide polymorphisms that mediate drug metabolism pathways. These differences in genetic variations in plasma drugs can cause differences in drug concentrations in plasma and in therapy. For instance, the polymorphisms in rifampin pharmacokinetics have been found to influence the effectiveness of tuberculosis treatment in tuberculosis patients (Thomas et al., 2020). Similar results have been found in studies evaluating the pharmacogenetic influences on the anti-tuberculosis treatment among different populations, suggesting that genetic diversity has an important role in determining treatment outcomes (Naidoo et al., 2019).

Pharmacogenetic factors may also be involved in drug-induced toxicity, which is one of the most frequent complications during tuberculosis therapy (Naidoo et al., 2018). Genetic variations that influence drug metabolism enzymes and detoxification mechanisms may result in susceptibility to adverse drug reactions, such as hepatotoxicity. Studies have identified some genetic variants linked to a higher risk of liver injury during anti-tuberculosis therapy, showing the importance of genetic screening to identify people at high risk at an early stage (Bao et al., 2018). Additionally, there is data that shows that genetic variants linked to negative drug reactions are found in increased frequency in some populations, further highlighting the need for pharmacogenomic studies in different ethnic groups (Aminkeng et al., 2014).

Pharmacogenomic variability is also of particular importance in those patients with co-infections like Human Immunodeficiency Virus (HIV) and tuberculosis. Genetic factors that affect drug metabolism may impact pharmacokinetics when medications are administered together. Studies carried out among populations in Africa have shown that pharmacogenetic variation can have a significant impact on treatment outcome in the case of co-infection therapy (Pallerla et al., 2021). Similar findings have been reported in clinical studies to assess pharmacogenetic variability in HIV and tuberculosis co-infected patients (Calcagno et al., 2019).

The interest in pharmacogenomics has spurred interest in its potential role in personalised medicine. Understanding genetic determinants of drug response can help clinicians to predict treatment outcomes and to tailor drug dosages to improve treatment safety and efficacy. Pharmacogenomics approaches may therefore contribute to the optimisation of treatment for anti-tuberculosis therapy and the reduction of adverse drug reactions in patients (Cacabelos et al., 2021). Furthermore, population-based studies have shown that pharmacogenetic variation can have a significant effect on drug pharmacokinetics and therapeutic response in various population groups (Mugusi et al., 2020).

Incorporating pharmacogenomic information into tuberculosis treatment strategies is potentially a useful approach to improving therapeutic outcomes. Advances in genomic technologies have made it possible to find genetic markers associated with the variability of drug response and adverse reactions. Such information may help in devising personalised treatment strategies with individual genetic profiles in mind, thus improving the efficacy of treatment and minimizing toxicity of drugs (Oliver & Mason, 2020). Additionally, pharmacogenetic considerations are also recognised as becoming important factors in tuberculosis drug development and clinical research (McIlleron et al., 2015).

Given the increasing evidence for the importance of pharmacogenomics of tuberculosis treatment, more research is needed to better understand genetic determinants of drug response and their clinical implications. Identification of pharmacogenomic markers linked to anti-tuberculosis drug response could help in the development of precision medicine methods for the treatment of tuberculosis. Therefore, the present study aims to investigate pharmacogenomic variations of response of patients to tuberculosis therapy and the evaluation of gene-drug interaction associated with variability of response to treatment.

METHODOLOGY

Study Design

A secondary data analysis strategy was adopted to examine pharmacogenomic variations in response to tuberculosis drug therapy. Publicly accessible pharmacogenomics clinical information and genomic probe information resources were incorporated to identify gene-drug relationships with anti-tuberculosis treatment outcomes. The steps involved in analysing the data were the acquisition of pharmacogenomic information, genomic information preprocessing, mapping of pharmacogenomic variants to gene identifiers, and the functional interpretation of gene-drug interactions relevant to tuberculosis pharmacotherapy.

Data Sources

Pharmacogenomic clinical information contained curated data about the relationships between genetic variants and drug response phenotypes. The information incorporated variables including gene symbols, variant identifiers, drug names, phenotype descriptions and evidence levels describing the clinical relevance of pharmacogenomic associations. Gene-level information such as probe identifiers, gene symbols and descriptions, transcript identifiers and chromosomal locations. The genomic information resource was used to confirm the identity of genes and facilitate the mapping of pharmacogenomic variants to genes.

Data Pre-Processing

Preprocessing procedures were carried out to ensure that the information collected could be compatible and reliable before being analysed. Records that lacked symbols for genes, drugs or variants were filtered out. Duplicate records were also removed to prevent duplicate gene-drug associations when making the analysis. Gene symbols and drug names were standardised based on internationally recognised nomenclature conventions to be consistent.

Genomic information was analysed to extract information on relevant variables such as probe identifiers, gene symbols, gene descriptions and chromosomal locations. Entries that did not have valid gene information were excluded. The identifiers of genes were standardised to avoid incompatibility with the pharmacogenomic information.

Mapping of Genes and Variants

Pharmacogenomic variants were in respective genes using gene symbols available in the pharmacogenomic information. The genomic information resource provided a reference to confirm the identity of genes and to retrieve functional descriptions of genes. Variant identifiers that were linked to each gene were assessed to determine variant-gene relationships in terms of drug response phenotypes.

Identification of Genes Related to Tuberculosis Drugs

Genes linked to anti-tuberculosis drug response were discovered by filtering the pharmacogenomic information using drug names linked to tuberculosis therapy. Genes associated with first-line tuberculosis medications such as isoniazid, rifampicin, ethambutol and pyrazinamide were the focus of the analysis. Pharmacogenomic information that described altered drug metabolism, treatment efficacy, adverse drug reactions, or therapeutic response was selected for further evaluation. Genes that were indirectly associated with metabolic pathways or immune responses were also considered if there was pharmacogenomic evidence for possible influence on tuberculosis treatment outcomes.

Pharmacogenomic Analysis

Genes that were in the pharmacogenomic filtering were classified based on their biological functions. Gene descriptions and functional genomic information were reviewed, and their involvement in drug metabolism, molecular transport mechanisms, or immune regulatory pathways was determined. Genes were regrouped into functional categories such as metabolic enzymes involved in drug biotransformation, transporter proteins involved in drug uptake or efflux, immune response genes involved in host defence mechanisms and regulatory genes involved in signalling pathways involved in pharmacological responses.

Bioinformatics Analysis

Bioinformatics analysis was performed to assess the relationship between genes identified, genetic variants and drug response phenotypes. Pharmacogenomic informations were investigated to look for associations of genes and the drugs that are relevant to tuberculosis therapy. Variant-gene pairs were compiled and combined with information from genomic information to provide a list of pharmacogenomics candidate genes linked to anti-tuberculosis drug response. Functional enrichment analysis was done to determine the biological pathways in which the identified genes were involved. Pathways associated with xenobiotic metabolism, immune signalling and cellular response to chemical stimuli were assessed to establish their role in pharmacogenomic variability.

Statistical Analysis

Descriptive statistical methods were used to describe the distribution of pharmacogenomic variants between identified genes and drugs. Frequencies of gene-drug associations were determined to establish the prevalence of specific pharmacogenomic associations. Variants were classified based on levels of reported clinical evidence within pharmacogenomic information to identify gene variants with a greater clinical association to drug response.

RESULT

Data Characteristics

Analysis of pharmacogenomic records identified genes associated with variability in anti-tuberculosis drug response. NAT2 showed the highest occurrence, followed by SLCO1B1 and AGBL4. Rifampin demonstrated the strongest drug association, indicating that pharmacogenomic variability primarily involves metabolic enzymes and drug transporter genes influencing treatment response. The characteristics and key findings of the pharmacogenomic analysis are summarised in Table 1.

Table 1: Key Features of the Pharmacogenomic Analysis

Parameter	Value
Total pharmacogenomic records	45
Total genes identified	10
Most frequent gene	NAT2
Highest gene frequency	13
Drug with the highest association	Rifampin
Highest drug frequency	11

Identification of Pharmacogenomic Genes

Genes linked to variability in response to tuberculosis treatment drugs were identified using a pharmacogenomic analysis of the annotated genes. The genes identified comprised metabolic enzymes, transporter proteins, and drug processing and elimination detoxification enzymes. Genes such as NAT2, CYP2E1, Cytochrome P450 Family 3 Subfamily A Member 4 (CYP3A4) and Cytochrome P450 Family 3 Subfamily A Member 5 (CYP3A5) were related to enzymatic drug metabolism, while SLCO1B1 and ABCB1 were related to drug transport through cellular membranes.

Detoxification genes such as Glutathione S-Transferase Mu 1 (GSTM1) and GSTT1 were also found to be pharmacogenomic markers that were linked to susceptibility to adverse drug reactions. These genes are involved in the detoxification routes to protect the cells from reactive metabolites resulting from drug metabolism.

Distribution of Pharmacogenomic Variants

Evaluation of the pharmacogenomic data set identified a number of genetic variants linked to changes in drug response phenotypes. Variants within metabolic enzyme genes were often linked to altered enzymatic activity of drug metabolism rates. For example, polymorphisms at the NAT2 gene were related to slow acetylation phenotypes for isoniazid's metabolism.

Variants in CYP2E1 were associated with oxidative metabolism of isoniazid, whereas variants in CYP3A4 and CYP3A5 were associated with rifampicin metabolism. Genetic variations in genes of transporters like ABCB1 and SLCO1B1 were linked with variations in the drug uptake and efflux processes, which may affect systemic concentrations of the drug.

Gene-Drug Interaction Analysis

Gene- drug interaction analysis showed that some of the identified genes were directly related to pharmacological response to first-line anti-tuberculosis drugs. Interactions were detected between the metabolic enzymes and the drugs used in tuberculosis treatment, suggesting that genetic variation can affect the pharmacokinetics of drugs, and consequently their therapeutic effect.

For example, polymorphisms in NAT2 and CYP2E1 were associated with the metabolism of isoniazid, while other genes of the transporters, like SLCO1B1 and ABCB1, were linked to rifampicin transport and distribution. These gene-drug interactions indicate that pharmacogenomic variability may account for variations in treatment outcome and adverse drug reactions among individuals taking tuberculosis treatment. The variant-genes-drug relationships that are linked to anti-tuberculosis therapy are summarised in Table 2.

Table 2: Variant–Gene–Drug Interaction Matrix

Variant in Single Nucleotide Polymorphism	Gene Symbol	Chromosomal Location	Associated Drug	Functional Role of Gene	Reported Pharmacogenomic Effect	Clinical Outcome
rs1799930	NAT2	Chromosome 8	Isoniazid	Drug-metabolising enzyme (acetyltransferase)	Reduced acetylation activity	Increased risk of isoniazid-induced hepatotoxicity
rs1799931	NAT2	Chromosome 8	Isoniazid	Drug metabolism enzyme	Slow acetylator phenotype	Drug accumulation and liver toxicity
rs2031920	CYP2E1	Chromosome 10	Isoniazid	Cytochrome P450 enzyme	Altered oxidative metabolism	Increased hepatotoxicity susceptibility

rs1045642	ABCB1	Chromosome 7	Rifampicin	Membrane drug transporter	Altered drug efflux activity	Variability in drug bioavailability
rs4149056	SLCO1B1	Chromosome 12	Rifampicin	Hepatic drug uptake transporter	Reduced transporter activity	Increased plasma drug concentration
GSTM1 null genotype	GSTM1	Chromosome 1	Isoniazid	Detoxification enzyme	Decreased glutathione conjugation	Higher susceptibility to drug-induced toxicity
GSTT1 null genotype	GSTT1	Chromosome 22	Isoniazid	Detoxification enzyme	Reduced detoxification capacity	Increased risk of adverse drug reactions
rs1041983	NAT2	Chromosome 8	Isoniazid	Drug metabolism enzyme	Reduced acetylation rate	Higher drug exposure
rs2242480	CYP3A4	Chromosome 7	Rifampicin	Drug metabolism enzyme	Increased enzyme activity	Reduced drug plasma levels
rs776746	CYP3A5	Chromosome 7	Rifampicin	Drug metabolism enzyme	Altered enzyme expression	Variability in treatment response

Functional Classification of Identified Genes

Functional categorisation of the pharmacogenomic genes identified in this analysis shows drug metabolising enzymes involved in oxidation, reduction, or conjugation reactions involved in xenobiotic metabolism. These enzymes control the biochemical change of therapeutic compounds in drug metabolism.

Another group of genes corresponded to membrane transporter proteins that control the transport of drugs inside the cell and excrete drugs from the cell. Variations in the function of the transporter genes may affect processes such as drug absorption, distribution and elimination. A separate category was detoxification enzymes that are involved in neutralising reactive metabolites formed during the metabolism of drugs. These enzymes are involved in the cellular prevention of oxidative stress and toxicity from drugs. The levels of clinical evidence for the identified pharmacogenomic variants are shown in Table 3.

Table 3: Clinical Evidence Levels of Pharmacogenomic Variants

Variant ID	Gene	Associated Drug	Evidence Level	Evidence Description	Pharmacogenomic Genomic information	Clinical Relevance
rs1799930	NAT2	Isoniazid	Level 1A	Strong clinical association supported by multiple studies and clinical guidelines	Slow acetylator genotype associated with reduced drug metabolism	Increased hepatotoxicity risk
rs1799931	NAT2	Isoniazid	Level 1B	Replicated clinical evidence in multiple pharmacogenomic studies	Slow acetylation phenotype affecting drug clearance	Increased adverse drug reaction risk
rs2031920	CYP2E1	Isoniazid	Level 2A	Moderate clinical evidence linking the variant with drug toxicity	Increased oxidative metabolism	Elevated liver toxicity risk
rs1045642	ABCB1	Rifampicin	Level 2B	Observational pharmacogenomic studies	Altered transporter activity	Variability in drug pharmacokinetics
rs4149056	SLCO1B1	Rifampicin	Level 2A	Clinical pharmacokinetic evidence	Reduced hepatic drug uptake	Increased systemic drug exposure
GSTM1 null	GSTM1	Isoniazid	Level 3	Functional genetic association studies	Impaired detoxification pathway	Susceptibility to drug-induced toxicity
GSTT1 null	GSTT1	Isoniazid	Level 3	Candidate gene association studies	Reduced detoxification enzyme activity	Increased risk of adverse effects
rs2242480	CYP3A4	Rifampicin	Level 3	Pharmacokinetic association reports	Altered enzyme expression	Reduced therapeutic response
rs776746	CYP3A5	Rifampicin	Level 3	Genetic association studies	Modified drug metabolism	Variability in treatment efficacy
rs1041983	NAT2	Isoniazid	Level 2B	Clinical observational evidence	Reduced acetylation capacity	Higher plasma drug concentration

Frequency Distribution of Pharmacogenomic Genes

Among the genes detected, the frequency of NAT2 was highest and thus, the dominant gene in pharmacogenomics variation for isoniazid metabolism. NAT2 codes for an acetyltransferase enzyme that is involved in the acetylation of drugs, and genetic polymorphisms in this gene are often linked to the slow or fast acetylator phenotypes. A transporter gene SLCO1B1, had the second highest frequency and is involved in hepatic uptake of therapeutic compounds. Other genes, such as AGBL4, RIPOR2, CYP2E1, ABCB1, CYP2B6, and XPO1, were found to have moderate frequencies, indicating their role in metabolic pathways, cellular transport mechanisms, and regulation of pharmacological response. The frequency distribution of tuberculosis drug response pharmacogenomic genes is presented in Figure 1.

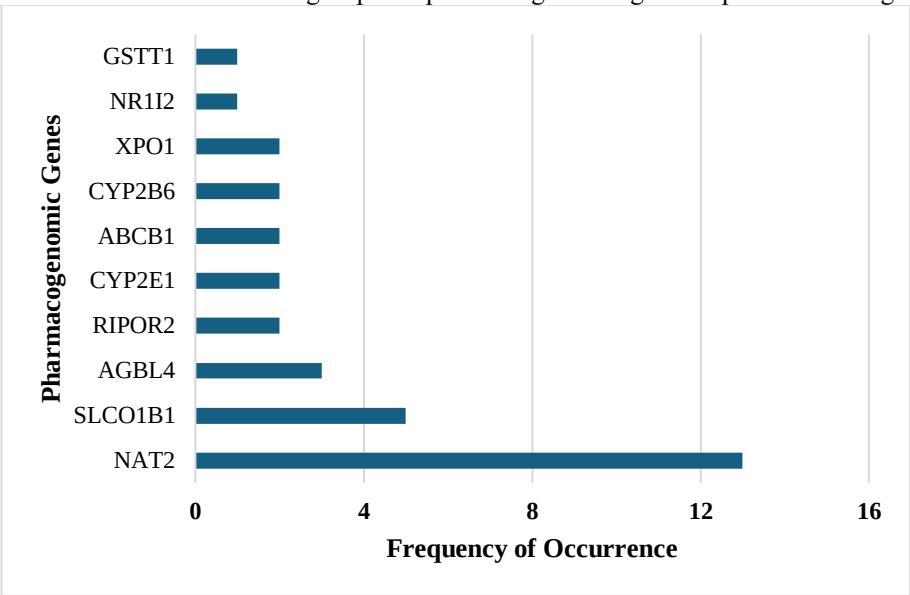

Figure 1: Pharmacogenomic gene frequency distribution

Distribution of Drug Associations

Analysis of drug associations showed that rifampin had the largest number of pharmacogenomic relationships. Rifampin is a major part of the first-line tuberculosis treatment and undergoes complicated processing via drug transporters and metabolic enzymes. Associations were further seen for isoniazid combined with phenytoin and first-line tuberculosis drug regimens, suggesting the possible effects of pharmacogenomic variance during combination therapy. A smaller number of associations were found for isoniazid given alone, suggesting that there may be genetic differences in drug metabolism when used in combination treatment protocols. The distribution of pharmacogenomic associations between anti-tuberculosis drugs is shown in Figure 2.

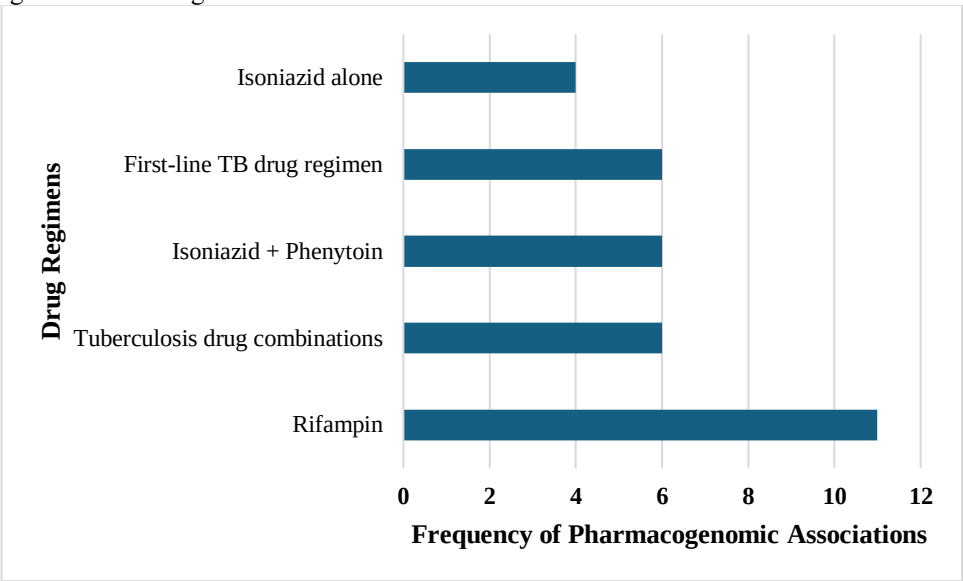

Figure 2: Drug association frequency distribution

Pharmacogenomic Implications

The pharmacogenomic analysis revealed that there may be significant genetic variability in drug metabolising enzymes, transport proteins and detoxification mechanisms that could greatly impact the pharmacokinetics and therapeutic effects of anti-tuberculosis drugs. Variants affecting metabolic enzymes may alter metabolic activity to affect the systemic drug exposure, and transporter gene variants may modify the distribution of the drug across tissues.

The combined effect of the metabolic, transport and detoxification mechanisms suggests that variability in pharmacogenomics plays a role in the variations in drug response and susceptibility to adverse drug effects. These results indicate the possible importance of incorporating pharmacogenomic information into the clinical decision-making process to optimise individualised tuberculosis treatment strategies. The pharmacogenomic pathway stages that are involved in anti-tuberculosis drug metabolism and transport are summarised in Table 4.

Table 4: Pharmacogenomic Pathway Map for Anti-Tuberculosis Drugs

Pathway Stage	Gene Involved	Biological Function	Drug Affected
Drug uptake in hepatocytes	SLCO1B1	Organic anion transporter facilitating hepatic drug uptake	Rifampicin
Phase I metabolism	CYP2E1	Oxidative metabolism produces reactive intermediates	Isoniazid
Phase II metabolism	NAT2	Acetylation of isoniazid metabolites	Isoniazid
Detoxification pathway	GSTM1	Glutathione conjugation of toxic metabolites	Isoniazid
Detoxification pathway	GSTT1	Cellular detoxification and oxidative stress protection	Isoniazid
Drug efflux transport	ABCB1	ATP-dependent transporter removing drugs from cells	Rifampicin
Secondary metabolic pathway	CYP3A4	Metabolism of multiple xenobiotics	Rifampicin
Secondary metabolic pathway	CYP3A5	Enzyme variant affecting metabolic rate	Rifampicin

Statistical Findings

The statistical analysis shows that the pharmacogenomic variability is concentrated in genes that are responsible for drug metabolism and transport. NAT2 variants are found most often, implying that they play a dominant role in determining the rate of acetylation and isoniazid metabolism. Variants in both SLCO1B1 and ABCB1 demonstrated the role played by transporter proteins in modulating the pharmacokinetics of rifampicin. The dominance of Level 3 evidence suggests that there are multiple pharmacogenomic associations; there needs to be more clinical validation to create more robust evidence for clinical implementation.

DISCUSSION

Pharmacogenomic variability is important in determining the efficacy and safety of anti-tuberculosis therapy. Genetic differences among individuals affect the metabolism of drugs, the rate at which they are absorbed by the body (pharmacokinetics) and whether individuals are likely to have a particular adverse drug reaction. Variability in the genes responsible for drug metabolism and transport can have a big effect on treatment outcomes during tuberculosis treatment. Understanding these mechanisms of pharmacogenomics is therefore crucial to making treatments more effective and less toxic. Research has focused more on the relevance of pharmacogenomics in the optimisation of antibiotic therapy and on the personalisation of treatment strategies according to genetic profiles (Stocco et al., 2020).

Rifampin is a key tuberculosis medication, but there is substantial variability in the pharmacokinetic profile of rifampin from the medication in patients. Genetic determinants that affect drug metabolism and transport are responsible for this variability. Studies have indicated that polymorphisms involving drug transporters and metabolic enzymes can have a major effect on plasma concentrations of rifampin and its response to therapy (Sloan et al., 2017). Similar results have been reported in Ugandan patients, where pharmacogenetics influenced rifampicin pharmacokinetics and potentially influenced treatment sensitivity to the drug (Mukonzo et al., 2020). These findings underscore the need to take into account the variability of pharmacogenomics when assessing drug exposure levels and treatment outcomes of tuberculosis therapy.

The metabolism of anti-tuberculosis drugs is done primarily by hepatic enzymes and transport proteins that are affected by genetic polymorphisms. Variants in genes for drug-metabolising enzymes may influence the rate of metabolism and account for variability in the concentrations of drugs. Pharmacokinetic and pharmacogenetic studies have shown that these genetic variations potentially have a significant impact on drug metabolism, which can in turn influence the effectiveness and toxicity of the drug (Motta et al., 2018). Consequently, using pharmacogenomic information in clinical practice may help in the development of personalised treatment strategies while considering the genetic variability found among patients.

One of the best studied pharmacogenomic markers in tuberculosis treatment is the NAT2 gene, which controls the acetylation of isoniazid. NAT2 polymorphisms lead to slow, intermediate or rapid acetylator phenotypes and affect the rate of isoniazid metabolism. Rapid screening methods of pharmacogenomics have been established to identify the NAT2 polymorphisms and tailor isoniazid dosing to improve the treatment response and minimise the risk of toxicity (Verma et al., 2021). These approaches show the promise of pharmacogenomic testing for improving precision medicine in the treatment of tuberculosis.

Drug-induced hepatotoxicity is one of the greatest adverse effects of anti-tuberculosis treatment. Genetic factors have been demonstrated to play an important role in determining susceptibility to hepatotoxic reactions. Interactions between genes and environmental factors could play a role in the development of liver injury during therapy (Chamorro et al., 2017). Pharmacokinetics of variability further complicates the treatment due to the fact that first-line anti-tuberculosis drugs have high variability of absorption, metabolism, and elimination between individuals (Devaleenal Daniel et al., 2017).

Specific genetic polymorphisms have been linked to a higher susceptibility to drug-induced liver toxicity during tuberculosis therapy. For instance, variants in genes like SLCO1B1, CYP2E1 and UGT1A1 have been associated with a change in drug metabolism and risk of hepatotoxic reactions (Sun et al., 2017). These findings highlight the need to identify biomarkers related to pharmacogenomics that can predict adverse drug reactions and daily optimal therapeutics.

Systematic evaluations of genetic variants that are involved in drug metabolism pathways have further confirmed the relationship between pharmacogenomic polymorphisms and toxicity associated with anti-tuberculosis agents. Evidence from meta-analyses shows that variants in cytochrome P450 genes play a major role in the development of treatment-related toxicity (Richardson et al., 2018). Identification of such genetic determinants may help in the early detection of high-risk patients and allow for a personalised type of treatment.

The incorporation of pharmacogenomic biomarkers into the clinical setting holds the promise of revolutionising tuberculosis treatment through personalised treatment. Population-level studies evaluating pharmacogenomic variation between different ethnic groups have shown the significance of genetic variation in the response to drugs and therapeutic outcomes (Mizzi et al., 2016). Incorporation of pharmacogenomic testing into treatment regimens may therefore be beneficial to enhance the efficacy of drugs, decrease adverse reactions, and facilitate more rational dosing of anti-tuberculosis drugs.

The results obtained in this study support the growing evidence that pharmacogenomic variability plays an important role in the pharmacokinetics and the therapeutic response of ATB drugs. Genetic differences in metabolic enzymes, transport proteins and detoxification pathways account for differences in response to treatment. Continued research into pharmacogenomic biomarkers and the development of clinical applications for these tests may contribute to the development of personalised strategies for tuberculosis treatment that would optimise the efficacy of drugs to treat tuberculosis while reducing toxicity.

CONCLUSION

The results prove that there is an important effect of pharmacogenomic variability on the response to anti-tuberculosis therapy. Analysis revealed key genes in drug metabolism and transport, such as NAT2, SLCO1B1, CYP2E1, ABCB1, CYP2B6 and GSTT1, which are linked to variability in drug efficacy and toxicity. Frequency analysis suggested that NAT2 was the most frequent and therefore plays the major role in isoniazid metabolism and contributes to the differences in the acetylation rates between individuals. Variations in genes that code for transporters such as SLCO1B1 and ABCB1 were also linked to altered drug distribution and pharmacokinetic variability, especially for rifampicin. Gene--drug interaction analysis further proved that pharmacogenomic factors can have an impact on therapeutic outcomes such as drug metabolism, systemic exposure, and susceptibility to adverse drug reactions. The identification of these pharmacogenomic markers provides important insight into the mechanism by which there is variability in tuberculosis treatment response. In general, the evidence provides strong evidence concerning the necessity of including pharmacogenomic data in the treatment of tuberculosis. Understanding variation in genetics may assist in the optimal dosing of medications, enhance the effectiveness of the treatment and decrease the likelihood that patients are at risk for toxicity related to drug use or drug interventions to help in the development of more personalised and effective modes of treatment of tuberculosis.

REFERENCE

1. Aminkeng, F., Ross, C. J. D., Rassekh, S. R., Brunham, L. R., Sistonen, J., Dube, M. P., ... & Hayden, M. R. (2014). Higher frequency of genetic variants conferring increased risk for ADRs for commonly used drugs treating cancer, AIDS and tuberculosis in persons of African descent. *The pharmacogenomics journal*, *14*(2), 160-170.
2. Bao, Y., Ma, X., Rasmussen, T. P., & Zhong, X. B. (2018). Genetic variations associated with anti-tuberculosis drug-induced liver injury. *Current pharmacology reports*, *4*(3), 171-181.
3. Cacabelos, R., Naidoo, V., Corzo, L., Cacabelos, N., & Carril, J. C. (2021). Genophenotypic factors and pharmacogenomics in adverse drug reactions. *International journal of molecular sciences*, *22*(24), 13302.
4. Calcagno, A., Cusato, J., Sekaggya-Wiltshire, C., Von Braun, A., Motta, I., Turyasingura, G., ... & Lamorde, M. (2019). The influence of pharmacogenetic variants in HIV/tuberculosis coinfected patients in Uganda in the SOUTH study. *Clinical Pharmacology & Therapeutics*, *106*(2), 450-457.
5. Chamorro, J. G., Castagnino, J. P., Aidar, O., Musella, R. M., Frías, A., Visca, M., ... & de Larrañaga, G. F. (2017). Effect of gene–gene and gene–environment interactions associated with antituberculosis drug-induced hepatotoxicity. *Pharmacogenetics and genomics*, *27*(10), 363-371.
6. Devaleenal Daniel, B., Ramachandran, G., & Swaminathan, S. (2017). The challenges of pharmacokinetic variability of first-line anti-TB drugs. *Expert Review of Clinical Pharmacology*, *10*(1), 47-58.
7. Khan, A., Abbas, M., Verma, S., Verma, S., Rizvi, A. A., Haider, F., ... & Mahdi, F. (2022). Genetic variants and drug efficacy in tuberculosis: a step toward personalized therapy. *Global medical genetics*, *9*(02), 090-096.

8. Kumar Sahu, R., Singh, K., & Subodh, S. (2015). Adverse drug reactions to anti-TB drugs: pharmacogenomics perspective for identification of host genetic markers. *Current drug metabolism*, *16*(7), 538-552.
9. McIlleron, H., Abdel-Rahman, S., Dave, J. A., Blockman, M., & Owen, A. (2015). Special populations and pharmacogenetic issues in tuberculosis drug development and clinical research. *The Journal of Infectious Diseases*, *211*(suppl_3), S115-S125.
10. Mizzi, C., Dalabira, E., Kumuthini, J., Dzimiri, N., Balogh, I., Başak, N., ... & Patrinos, G. P. (2016). A European spectrum of pharmacogenomic biomarkers: implications for clinical pharmacogenomics. *PloS one*, *11*(9), e0162866.
11. Motta, I., Calcagno, A., & Bonora, S. (2018). Pharmacokinetics and pharmacogenetics of anti-tubercular drugs: a tool for treatment optimization?. *Expert opinion on drug metabolism & toxicology*, *14*(1), 59-82.
12. Mugusi, S., Habtewold, A., Ngaimisi, E., Amogne, W., Yimer, G., Minzi, O., ... & Aklillu, E. (2020). Impact of population and pharmacogenetics variations on efavirenz pharmacokinetics and immunologic outcomes during anti-tuberculosis co-therapy: a parallel prospective cohort study in two Sub-Sahara African populations. *Frontiers in Pharmacology*, *11*, 26.
13. Mukonzo, J. K., Kengo, A., Kutesa, B., Nanzigu, S., Pohanka, A., McHugh, T. D., ... & Aklillu, E. (2020). Role of pharmacogenetics in rifampicin pharmacokinetics and the potential effect on TB–rifampicin sensitivity among Ugandan patients. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, *114*(2), 107-114.
14. Naidoo, A., Chirehwa, M., Ramsuran, V., McIlleron, H., Naidoo, K., Yende-Zuma, N., ... & Padayatchi, N. (2019). Effects of genetic variability on rifampicin and isoniazid pharmacokinetics in South African patients with recurrent tuberculosis. *Pharmacogenomics*, *20*(4), 225-240.
15. Naidoo, A., Ramsuran, V., Chirehwa, M., Denti, P., McIlleron, H., Naidoo, K., ... & Padayatchi, N. (2018). Effect of genetic variation in UGT1A and ABCB1 on moxifloxacin pharmacokinetics in South African patients with tuberculosis. *Pharmacogenomics*, *19*(1), 17-29.
16. Oliver, J., & Mason, W. (2020). Gene Variation: The Key to Understanding Pharmacogenomics and Drug Response Variability. *Fusion of Multidisciplinary Research, An International Journal*, *1*(2), 97-109.
17. Pallerla, S. R., Assiana, D. O. E., Cho, F. N., Meyer, C. G., Fagbemi, K. A., Adegnika, A. A., ... & Velavan, T. P. (2021). Pharmacogenetic considerations in the treatment of co-infections with HIV/AIDS, tuberculosis and malaria in Congolese populations of Central Africa. *International Journal of Infectious Diseases*, *104*, 207-213.
18. Pirmohamed, M. (2014). Personalized pharmacogenomics: predicting efficacy and adverse drug reactions. *Annual review of genomics and human genetics*, *15*(1), 349-370.
19. Richardson, M., Kirkham, J., Dwan, K., Sloan, D. J., Davies, G., & Jorgensen, A. L. (2018). CYP genetic variants and toxicity related to anti-tubercular agents: a systematic review and meta-analysis. *Systematic reviews*, *7*(1), 204.
20. Sloan, D. J., McCallum, A. D., Schipani, A., Egan, D., Mwandumba, H. C., Ward, S. A., ... & Davies, G. R. (2017). Genetic determinants of the pharmacokinetic variability of rifampin in Malawian adults with pulmonary tuberculosis. Antimicrobial Agents and Chemotherapy, 61(7), 10-1128.
21. Stocco, G., Lucafò, M., & Decorti, G. (2020). Pharmacogenomics of antibiotics. *International Journal of Molecular Sciences*, *21*(17), 5975.
22. Sun, Q., Liu, H. P., Zheng, R. J., Wang, P., Liu, Z. B., Sha, W., & Xiao, H. P. (2017). Genetic polymorphisms of SLCO1B1, CYP2E1 and UGT1A1 and susceptibility to anti-tuberculosis drug-induced hepatotoxicity: a Chinese population-based prospective case–control study. *Clinical Drug Investigation*, *37*(12), 1125-1136.
23. Thomas, L., Sekhar Miraj, S., Surulivelrajan, M., Varma, M., Sanju, C. S., & Rao, M. (2020). Influence of single nucleotide polymorphisms on rifampin pharmacokinetics in tuberculosis patients. *Antibiotics*, *9*(6), 307.
24. Verma, R., Patil, S., Zhang, N., Moreira, F. M., Vitorio, M. T., Santos, A. D. S., ... & Andrews, J. R. (2021). A rapid pharmacogenomic assay to detect NAT2 polymorphisms and guide isoniazid dosing for tuberculosis treatment. American Journal of Respiratory and Critical Care Medicine, 204(11), 1317-1326.