CORRELATION OF GENETIC POLYMORPHISM IN UGT1A1, SLC01B1, NAT2, AND CYP2E1 WITH HEPATOTOXICITY

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ABSTRACT

Tuberculosis (TB) has been identified as one of the most highly infectious diseases in the world. Tuberculosis can be identified as pulmonary or extrapulmonary. Therapy for TB is a combination of several drugs in one treatment. The effectiveness and toxicity of TB therapy may differ in each patient because of some risk factors, especially genetic variations. This review describes several genes that can affect the effectiveness and toxicity of antituberculosis drugs, namely UGT1A1, SLC01B1, NAT2, and CYP2E1. This review was conducted utilizing the PubMed database, with keywords used as follows: polymorphism, antituberculosis, and tuberculosis. The presence of polymorphisms in these genes can result in hepatotoxicity and decreased drug bioavailability. Therefore, polymorphisms in these genes can determine the effectiveness of TB therapy.

Keywords: Antituberculosis drugs, Genetic polymorphism, Tuberculosis

INTRODUCTION

Between a quarter and a third of the world’s population have been identified to be latently infected with Mycobacterium tuberculosis [1]. Approximately 1.2 million (around 1.1–1.3 million) tuberculosis (TB) deaths were recorded among Human Immunodeficiency Virus (HIV)-negative people in 2018 (a 27% reduction from 1.7 million in 2000) and an additional 251,000 deaths (around 223,000–281,000) [2]. Most TB cases in 2018 are in the Southeast Asian region (44%), Africa (24%), and the Western Pacific (18%), while smaller percentages are determined to be in the Eastern Mediterranean (8%), America (3%), and Europe (3%). Eight countries accounted for two-thirds of the global total, namely India (27%), China (9%), Indonesia (8%), Philippines (6%), Pakistan (6%), Nigeria (4%), Bangladesh (4%), and South Africa (3%) [3]. The effectiveness of antituberculosis drugs can differ in each patient. At some point, these drugs can cause adverse reactions [4]. Some adverse reactions to antituberculosis drugs affect the outcomes of treatment and probably cause treatment failure. The predominant of adverse reactions were gastrointestinal disorders, drug-induced hepatotoxicity [5], musculoskeletal disorders, central and peripheral nervous system disorders, and less vision disorder [6]. Some risk factors for decreased liver function are malnutrition, alcohol consumption [7], and genetics factor [8]. Genetics factors that cause drug effects such as the presence of gene polymorphisms in patients. Genetic factors in patients can cause poor therapeutic outcomes as well as an increased risk of drug resistance [9].

A single nucleotide mutation, referred to as single nucleotide polymorphisms (SNPs), can cause such variations in drug response. SNPs occur when a nucleotide is substituted erroneously within an allele, which may be unique or common to many individuals in the human population. SNPs occur in a variety of DNA [10]. Based on current literature, genes that can affect the responses of drugs in TB patients are UDP-glucuronosyltransferase 1A1 (UGT1A1), solute carrier organic anion transporter family member 1B1 (SLCO1B1), N-acetyltransferase 2 (NAT2), and cytochrome P450 2E1 (CYP2E1). UGT1A1 has been identified as a phase II drug metabolism enzyme that is important in conjugation and elimination of xenobiotics, carcinogens, and drugs [11–13]. The presence of polymorphisms in UGT1A1 causes a decrease in enzyme activity, resulting in pharmacokinetic differences from drugs [14]. SLC01B1 is a gene that encodes transporters with a role in drug metabolism, specifically organic anion transporting polypeptide (OATP). Genetic variations of this gene can change the activity of transporters, leading to changes in pharmacokinetics and drug efficacy [15, 16]. NAT2 is a gene that codes for enzymes that activate and deactivate drugs. The polymorphism in this gene has been identified to be related to the N-acetylation polymorphism, which determines fast, medium, and slow acetylator phenotypes. Polymorphisms in this gene are also associated with high drug toxicity [17]. CYP2E1 is a gene that codes for the cytochrome P450 enzyme, which catalyzes reactions in drug metabolism [18].

Methods

This review included studies published in PubMed obtained using the keywords "polymorphism," "antituberculosis," and "tuberculosis." Additionally, annual reports released by the World Health Organization were included. However, reviews, non-English studies, and non-human studies were excluded. Of the 179 studies, we included 17 studies that focused on the relationship between gene polymorphisms and antituberculosis drugs, namely UGT1A1, SLC01B1, NAT2, and CYP2E1 (Fig. 1).

Fig. 1: Flowchart of the literature search process
DISCUSSION

The varying efficacy and toxicity of drugs are still identified to be a problem, causing harm to patients who are struggling to recover from their illness. Identifying the genetic differences in each patient can help the clinician adjust dosing and improve the results of therapy. This review further describes the influence of several genes, such as UGT1A1, SLCO1B1, NAT2, and CYP2E1, which might be associated with antituberculosis drug response (table 1). However, the results obtained from each population may be different.

### Table 1: Association gene polymorphisms with the responses of antituberculosis drugs

| Gene   | Polymorphism | Study population | Discussion | Ref |
|--------|--------------|------------------|------------|-----|
| **UGT1A1** | UGT1A1*27 ([686C>A] rs2070672) | 98 Taiwanese | There is an association between gene polymorphism and elevated antituberculosis drug-induced hepatotoxicity risk | [19] |
|        | UGT1A1*28 ([TA]→[TA']) rs2070673 | 927 Chinese | Gene polymorphism with A/A genotype significantly could reduce antituberculosis drug-induced hepatotoxicity risk | [20] |
|        | rs4148323 A/A | 445 Chinese | No significant association between gene polymorphism and antituberculosis drug-induced hepatotoxicity risk | [21] |
|        | rs4148223 | 445 Chinese | Patient with one haplotype of SLCO1B1*15 could have a higher risk of antituberculosis drug-induced hepatotoxicity than others with SLCO1B1*1a or SLCO1B1*1b | [22] |
|        | rs8330 | 445 Chinese | Patients with rs4149034 G/A, rs1564370 G/C, and rs2900478 T/A polymorphism could have a lower risk of antituberculosis drug-induced hepatotoxicity. While a patient with rs2417957 T/T and rs4149063 T/T polymorphism could have a higher risk of antituberculosis drug-induced hepatotoxicity | [20] |
| **SLCO1B1** | SLCO1B1*15 | 226 Korean | No association between gene polymorphism with the development of antituberculosis drug-induced hepatotoxicity risk | [23] |
|        | rs4149034 G/A | 927 Chinese | Gene polymorphism could higher development of antituberculosis drug-induced hepatotoxicity | [26] |
|        | rs1564370 G/C | 241 Indonesian | Gene polymorphism could higher development of antituberculosis drug-induced hepatotoxicity | [27] |
|        | rs2900478 T/A | 408 Indian | Gene polymorphism could higher development of antituberculosis drug-induced hepatotoxicity | [28] |
|        | rs2417957 T/T | 2244 Uyghur | There is an association between genetic polymorphism and antituberculosis drug-induced hepatotoxicity higher in a patient with CT genotype than CC genotype | [29] |
|        | rs4149063 T/T | 208 Chinese | Gene polymorphism could higher development of antituberculosis drug-induced hepatotoxicity | [26] |
|        | rs4149014 | 241 Indonesian | Gene polymorphism could higher development of antituberculosis drug-induced hepatotoxicity | [27] |
|        | rs2306283, rs4149056 | 174 Black African | Did not explain variability in AUCCmax of rifampin | [24] |
|        | rs4149032, rs11045819 | 113 Ghanaian | Patients with homozgyous *1b variants (AA genotype) significantly decreased Cmax and AUCCmax of rifampicin compared to wildtype (GG genotype) | [25] |
| **NAT2** | rs1041983 (282TT) | 208 Chinese | Gene polymorphism could higher development of antituberculosis drug-induced hepatotoxicity | [26] |
|        | rs1799930 (590AA) | 241 Indonesian | Gene polymorphism could higher development of antituberculosis drug-induced hepatotoxicity | [27] |
|        | rs1799931 (857Ga) | 408 Indian | Gene polymorphism could higher development of antituberculosis drug-induced hepatotoxicity | [28] |
|        | rs1799930 | 2244 Uyghur | There is an association between genetic polymorphism and antituberculosis drug-induced hepatotoxicity higher in a patient with CT genotype than CC genotype | [29] |
|        | rs1799931 | 66 Tunisian | Polymorphism of rs1799929 (CC genotype) and rs1799930 (GG genotype) associated with decreasing antituberculosis drug-induced hepatotoxicity, while rs1799929 (TT genotype) and rs1799930 (AA genotype) associated with a higher risk of antituberculosis drug-induced hepatotoxicity | [30] |
|        | rs1801279 | 113 Ghanaian | Isoniazid doses and slow NAT2 genotype associated with Cmax and AUCCmax of isoniazid. Twelve patients recorded Cmax of isoniazid values >3 g/ml (low) and 49 recorded participants had Cmax values >6 g/ml (high). Of the 12 patients with low Cmax, only 1 had a rapid NAT2 genotype (wildtype homozygote) and 2 had a slow NAT2 genotype (variants homozygote), of the 49 patients with high isoniazid, 26 had a slow NAT2 genotype (variants homozygote) | [25] |
|        | rs1041983 | 241 Indonesian | Gene polymorphism could higher development of antituberculosis drug-induced hepatotoxicity | [27] |
|        | rs1801280 | 241 Indonesian | Gene polymorphism could higher development of antituberculosis drug-induced hepatotoxicity | [27] |
|        | rs1799929 | 241 Indonesian | Gene polymorphism could higher development of antituberculosis drug-induced hepatotoxicity | [27] |
|        | rs1799930 | 241 Indonesian | Gene polymorphism could higher development of antituberculosis drug-induced hepatotoxicity | [27] |
|        | rs1208 | 241 Indonesian | Gene polymorphism could higher development of antituberculosis drug-induced hepatotoxicity | [27] |
|        | rs1799931 | 241 Indonesian | Gene polymorphism could higher development of antituberculosis drug-induced hepatotoxicity | [27] |
| **NAT2** | **4** | 30 Venezuelan | AUCCmax and t1/2 of isoniazid are statistically higher in slow acetylators (NAT2*4, *6, *7, *14) compared to genotypically rapid (NAT2*4, *12, *13) acetylators. Whereas the clearance was significantly lower in the slow acetylators compared with the rapid acetylators | [31] |
| **NAT2** | **5** | 30 Venezuelan | AUCCmax and t1/2 of isoniazid are statistically higher in slow acetylators (NAT2*4, *6, *7, *14) compared to genotypically rapid (NAT2*4, *12, *13) acetylators. Whereas the clearance was significantly lower in the slow acetylators compared with the rapid acetylators | [31] |
| **NAT2** | **6** | 30 Venezuelan | AUCCmax and t1/2 of isoniazid are statistically higher in slow acetylators (NAT2*4, *6, *7, *14) compared to genotypically rapid (NAT2*4, *12, *13) acetylators. Whereas the clearance was significantly lower in the slow acetylators compared with the rapid acetylators | [31] |
| **NAT2** | **7** | 30 Venezuelan | AUCCmax and t1/2 of isoniazid are statistically higher in slow acetylators (NAT2*4, *6, *7, *14) compared to genotypically rapid (NAT2*4, *12, *13) acetylators. Whereas the clearance was significantly lower in the slow acetylators compared with the rapid acetylators | [31] |
| **NAT2** | **12** | 30 Venezuelan | AUCCmax and t1/2 of isoniazid are statistically higher in slow acetylators (NAT2*4, *6, *7, *14) compared to genotypically rapid (NAT2*4, *12, *13) acetylators. Whereas the clearance was significantly lower in the slow acetylators compared with the rapid acetylators | [31] |
| **NAT2** | **13** | 30 Venezuelan | AUCCmax and t1/2 of isoniazid are statistically higher in slow acetylators (NAT2*4, *6, *7, *14) compared to genotypically rapid (NAT2*4, *12, *13) acetylators. Whereas the clearance was significantly lower in the slow acetylators compared with the rapid acetylators | [31] |
| **NAT2** | **14** | 30 Venezuelan | AUCCmax and t1/2 of isoniazid are statistically higher in slow acetylators (NAT2*4, *6, *7, *14) compared to genotypically rapid (NAT2*4, *12, *13) acetylators. Whereas the clearance was significantly lower in the slow acetylators compared with the rapid acetylators | [31] |
| **CYP2E1** | rs4646244, rs4646267 | 221 Korean | No association between NAT2 polymorphism with the antituberculosis drug-induced maculopapular eruption | [32] |
|        | rs1799930, rs1799931 | 221 Korean | No association between NAT2 polymorphism with the antituberculosis drug-induced maculopapular eruption | [32] |
|        | rs2031920 | 408 Indian | Could have the risk of antituberculosis drug-induced hepatotoxicity development | [28] |
|        | rs2031920 | 2244 Uyghur | No significant association between polymorphism and development of antituberculosis drug-induced hepatotoxicity risk | [29] |
|        | rs6413432 | 445 Chinese | No significant association between polymorphism and development of antituberculosis drug-induced hepatotoxicity risk | [33] |
|        | rs2031920, rs2070672 | 445 Chinese | No significant association between polymorphism and development of antituberculosis drug-induced hepatotoxicity risk | [34] |
|        | rs915908, rs8192775 | 221 Korean | No association between CYP2E1 polymorphism with the antituberculosis drug-induced maculopapular eruption | [32] |
|        | rs2515641, rs2515644 | 314 Indian | No association between CYP2E1 polymorphism with the antituberculosis drug-induced maculopapular eruption | [32] |
UGT1A1

UGT1A1, a gene in the UGT1A family, has been determined to code for UDP-glucuronosyltransferase. This enzyme catalyzes glucuronidation during phase II of drug metabolism, specifically conjugation. With it, various substances are processed, including estrogen, bilirubin, carcinogens, xenobiotics, and medications [11–13]. UGT1A1 is located on chromosome 2 at position 37.1 [36] (fig. 2).

The presence of UGT1A1 polymorphism causes a decrease in enzyme activity, resulting in pharmacokinetic differences from drugs [1–4]. In Taipei, Taiwan, the UGT1A1 gene polymorphisms UGT1A1*27 (686C>A) and UGT1A1*28 (TA3→TA7) are associated with antituberculosis drug-induced hepatotoxicity (ATDIH) [19]. In Shanghai, China, polymorphisms in rs4148323 A/A genotypes significantly reduce the risk of developing ATDIH [20]. However, in other populations in China, studies located outside Shanghai found that polymorphisms at rs4148323 and rs8330 had no significant effect on the risk of developing ATDIH [21].

SLCO1B1

SLC (solute carrier family) is a transporter family that includes OATP [22, 23, 38]. This protein in hepatocytes facilitates hepatic uptake of compounds from the blood to be excreted [36]. In addition to transporting bile acids and other endogenous substances, OATP is also involved in the transportation of drugs [22, 23, 38]. OATP1B1 is an essential member of the OATP family and is found in the basolateral membrane of hepatocytes. Various drugs, including the first line anti TB drugs, rifampicin and rifabutin, are absorbed and transported via the hepatic portal system for uptake by OATP1B1, after which they will be metabolized and eliminated [38–40]. SLCO1B1, one of the genes that encode for the transporter, is situated in chromosome 12, in position 12.1 [36] (fig. 3).

Genetic variations of this gene can change the activity of transporters, leading to drug pharmacokinetic changes [15, 16]. Gene variations from the haplotype analysis show that patients who have at least one SLCO1B1*15 haplotype have a higher risk of developing ATDIH compared to those who have a SLCO1B1*1a or SLCO1B1*1b haplotype in populations in Zhejiang, Guangxi, Chongqing, Hainan, China [22]. Other results have shown that patients with SLCO1B1 polymorphisms rs4149034 G/A and rs2900478 T/A have a lower risk of ATDIH. On the other hand, patients in Shanghai, China, with rs2417957 T/T and rs4149063 T/T have an increased risk of developing ATDIH [20]. In Korea, polymorphisms at rs4149013, rs4149014, rs2306283 and rs4149056 did not show an association with the risk of developing ATDIH [23]. In Ghanaian populations, patients with homozygous *1b variants (rs2306283) (AA genotype) significantly decreased the Cmax and AUCC∞ of rifampin compared to the wildtype (GG genotype) [25]. Another study showed that rs4149034 G/A and rs11045819 on Black African populations did not explain any variability in the AUCC∞ and AUC0–∞ of rifampin [24].

NAT2

NAT2 codes for enzymes that activate and deactivate drugs [17]. N-acetylationtransferase is identified to be an enzyme mainly found in the liver to detoxify large amounts of chemical compounds. NAT2 has more than 23 variations to current knowledge [42]. The polymorphism of this gene determines N-acetylation polymorphism, which can lead to fast, medium, and slow acetylator phenotypes. Polymorphism in this gene is also determined to be associated with cancer and higher drug toxicity [17]. NAT2 is on chromosome 8 at position 22 [43] (fig. 4).

Based on several studies, polymorphisms of this gene are associated with the risk of developing ATDIH in TB patients. A polymorphism in rs1799930 in a TB patient has been found to be associated with an increased risk of developing ATDIH in Beijing [26], Indonesia [27].
CONCLUSION

There are several differences in gene polymorphisms in each population. Some genes that can affect the effectiveness and toxicity of antituberculosis drugs are UGT1A1, SLC01B1, NAT2, and CYP2E1. Polymorphisms in these genes can cause harm to TB patients. In UGT1A1, polymorphisms at rs414832 and rs8330 have no significant association with ATDIH; rs414832 A/A could reduce ATDIH risk; rs414832 A/A was associated with a lower risk of ATDIH; rs3813867 G/C and rs2900478 T/A were associated with a lower risk of ATDIH. In SLC01B1 polymorphisms at rs4149034 G/A, rs1564370 G/C, and rs2900478 T/A are associated with a low Cmax of isoniazid; rs2419757 T/T, rs4149063 T/T, and SLC01B1/*15 are related to a higher risk of ATDIH; rs4149013, rs4149014, rs2306283, rs4149056, and rs4149033 have no significant association with ATDIH; rs2306283 A/A is significantly decreased Cmax and AUCm of isoniazid; rs11045819 and rs149093 did not have a relationship with rifampicin’s AUCm. In NAT2, polymorphisms at rs1801280, rs1799930, and rs1799931 were associated with an increased risk of ATDIH; rs1801280, rs1799930, and rs1799931 were observed variations in Cmax and AUC values of rifampicin. In CYP2E1, polymorphisms at rs3813867, rs2031920, rs2070672, and rs2070673 had no association with antituberculosis drug-induced maculopapular eruption in Korean populations [32]. In India, rs2031920 showed that significantly higher in antituberculosis drug-induced hepatotoxicity than in the non-antituberculosis drug-induced hepatotoxicity group [48].

In many of the studies above, genetic polymorphisms had an association with various anti TB drug responses, such as clearance, the risk of ATDIH, and the bioavailability of drugs (fig. 5), and can further lead to adverse outcomes.

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CYP2E1

The CYP450 protein is a monoxygenase that catalyzes many of the reactions involved in drug metabolism. These enzymes metabolize endogenous or exogenous substrates [18]. CYP2E1 is one of the crucial enzymes in the metabolism of anti TB drugs, especially isoniazid. Several new studies were published regarding the relationship between CYP2E1 polymorphisms and ATDIH [26, 33, 44-46]. One of these studies describes how gene polymorphism coding for CYP2E1 can affect enzyme activity as well as susceptibility to hepatitis induced by anti-TB drugs [47].

In India, polymorphisms at rs2031920 have a significant associated risk of developing ATDIH [28]. In China, there were no significant relationships between rs2031920 [29, 33], rs2070672, rs915908, rs192775, rs2515641, rs2515644 [34], and rs6413432 [33] with the risk of developing ATDIH. Another study showed that CYP2E1 polymorphism at rs2031920, rs2070672, and rs2070673 had no association with antituberculosis drug-induced maculopapular eruption in Korean populations [32]. In India, rs2031920 showed that significantly higher in antituberculosis drug-induced hepatotoxicity than in the non-antituberculosis drug-induced hepatotoxicity group [48].

In many of the studies above, genetic polymorphisms had an association with various anti TB drug responses, such as clearance, the risk of ATDIH, and the bioavailability of drugs (fig. 5), and can further lead to adverse outcomes.
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