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Review Article

CORRELATION OF GENETIC POLYMORPHISM IN *UGT1A1*, *SLCO1B1*, *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*, *SLCO1B1*, *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

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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 dan peripheral nervous system disorders, and less vision disorder [6]. Some risk factors for decreased liver function are malnutrition, alcohol consumptions [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]. *SLCO1B1* 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*, *SLCO1B1*, *NAT2*, and *CYP2E1* (fig. 1).

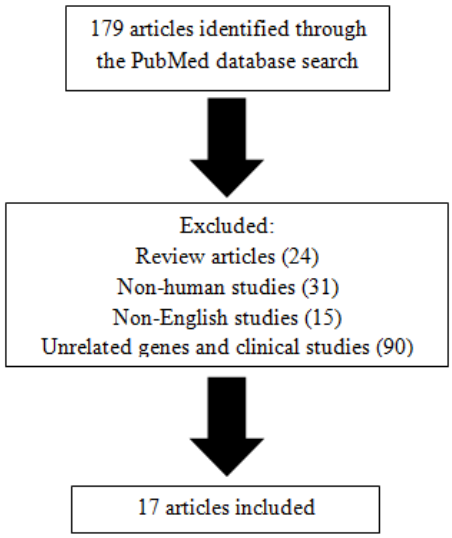

Fig. 1: Flowchart of the literature search process

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
		Number	Ethnic		
UGT1A1	*UGT1A1**27 (686C>A) *UGT1A1**28 [$(TA)_6 \rightarrow (TA)_7$]	98	Taiwanese	There is an association between gene polymorphism and elevated antituberculosis drug-induced hepatotoxicity risk	[19]
	rs4148323 A/A	927	Chinese	Gene polymorphism with A/A genotype significantly could reduce antituberculosis drug-induced hepatotoxicity risk	[20]
	rs4148323 rs8330	445	Chinese	No significant association between gene polymorphism and antituberculosis drug-induced hepatotoxicity risk	[21]
SLCO1B1	*SLCO1B1**15	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]
	rs4149034 G/A rs1564370 G/C rs2900478 T/A rs2417957 T/T rs4149063 T/T	927	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]
	rs4149013, rs4149014 rs2306283, rs4149056	226	Korean	No association between gene polymorphism with the development of antituberculosis drug-induced hepatotoxicity risk	[23]
	rs4149032 rs11045819	174	Black African	Did not explain variability in $AUC_{0-\infty}$ of rifampin	[24]
	rs2306283	113	Ghanaian	Patients with homozygous *1b variants (AA genotype) significantly decreased Cmax and AUC_{0-8h} of rifampicin compared to wildtype (GG genotype)	[25]
NAT2	rs1041983 (282TT) rs1799930 (590AA) rs1799931 (857GA)	208	Chinese	Gene polymorphism could higher development of antituberculosis drug-induced hepatotoxicity	[26]
	rs1799930 (*NAT2**6A)	241	Indonesian	Gene polymorphism could higher development of antituberculosis drug-induced hepatotoxicity	[27]
	rs1799929 rs1799930 rs1799931	408	Indian	Gene polymorphism could higher development of antituberculosis drug-induced hepatotoxicity	[28]
	rs1799929	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]
	rs1799929 rs1799930	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 rs1041983 rs1801280 rs1799929 rs1799930 rs1208 rs1799931	113	Ghanaian	Isoniazid doses and slow *NAT2* genotype associated with Cmax and AUC_{0-8h} of isoniazid. Twelve patients recorded Cmax 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]
	*NAT2**4 *NAT2**5 *NAT2**6 *NAT2**7 *NAT2**12 *NAT2**13 *NAT2**14	30	Venezuelan	AUC_{0-24} and $t_{1/2}$ of isoniazid are statistically higher in slow acetylators (*NAT2**5, *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]
	rs4646244, rs4646267 rs1799930, rs1799931	221	Korean	No association between *NAT2* polymorphism with the antituberculosis drug-induced maculopapular eruption	[32]
CYP2E1	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	[29]
	rs2031920 rs6413432	445	Chinese	No significant association between polymorphism and development of antituberculosis drug-induced hepatotoxicity	[33]
	rs2031920, rs2070672 rs915908, rs8192775 rs2515641, rs2515644	445	Chinese	No significant association between polymorphism and development of antituberculosis drug-induced hepatotoxicity	[34]
	rs2031920, rs2070672 rs2070673	221	Korean	No association between *CYP2E1* polymorphism with the antituberculosis drug-induced maculopapular eruption	[32]
	rs2031920	314	Indian	Genotypic distribution of rs2031920 significantly higher in antituberculosis drug-induced hepatotoxicity than in the non-antituberculosis drug-induced hepatotoxicity group	[35]

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).

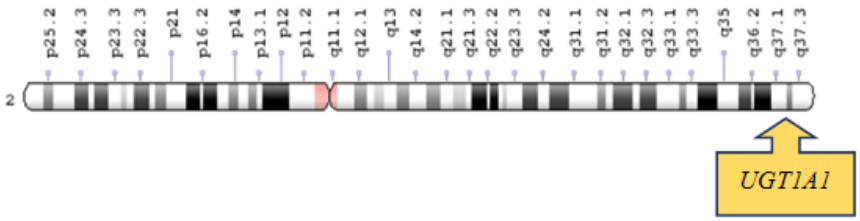

Fig. 1: Cytogenetic location of *UGT1A1* [37]

The presence of *UGT1A1* polymorphism causes a decrease in enzyme activity, resulting in pharmacokinetic differences from drugs [14]. In Taipei, Taiwan, the *UGT1A1* gene polymorphisms *UGT1A1**27 (686C>A) and *UGT1A1**28 [(TA)6↔(TA)7] 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, Jilin, China [22]. Other results have shown that patients with *SCLO1B1* 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 C_{max} and AUC_{0-8h} of rifampicin compared to the wildtype (GG genotype) [25]. Another study showed that rs4149032 and rs11045819 on Black African populations did not explain any variability in the $AUC_{0-\infty}$ of rifampin [24].

NAT2

NAT2 codes for enzymes that activate and deactivate drugs [17]. N-acetyltransferase 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 [42s]. 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).

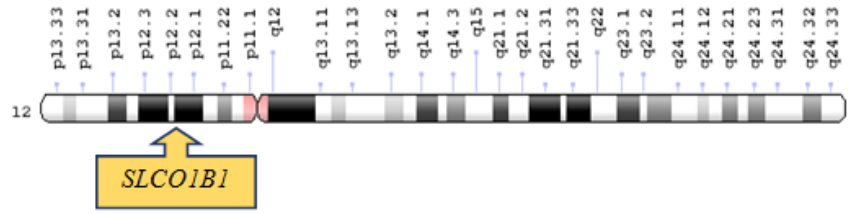

Fig. 2: Cytogenetic location of *SLCO1B1* [41]

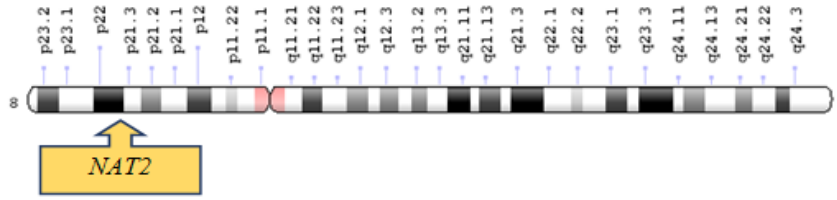

Fig. 3: Cytogenetic location of *NAT2* [43]

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],

India [28], and Tunisia (AA genotype) [30]. In Tunisia, the GG genotype is associated with a decreased risk of ATDIH [30]. The rs1799931 gene polymorphism is associated with ATDIH in Beijing [26] and India [28]. Other polymorphisms at rs1041983 are associated with an increased risk of developing ATDIH in Beijing [26]. The rs1799929 gene polymorphism is associated with an increased risk of ATDIH in Indian [28], Tunisian (TT genotype) [30], and Xinjiang populations [29], while in Tunisian populations, the CC genotype was associated with a decreased risk of ATDIH [30]. Another study showed that rs1801279, rs1041983, rs1801280, rs1799929, rs1799930, rs1208, and rs1799931 were associated with changes in the C_{max} and $AUC_{(0-8h)}$ of isoniazid. Twelve patients recorded C_{max} isoniazid values<3 g/ml (low), and 49 recorded participants had C_{max} values>6 g/ml (high). Of the 12 patients with a low C_{max}, only 1 was identified to have a rapid *NAT2* genotype (wildtype homozygote), while 2 had a slow *NAT2* genotype (variants homozygote). Of the 49 patients with high isoniazid C_{max}, only 26 were determined to have a slow *NAT2* genotype (variant homozygote) [25]. Meanwhile, in Venezuelan populations with the genotypes *NAT2**4, *5, *6, *7, *12, *13, and *14, the AUC_{0-24} and $t_{1/2}$ of isoniazid were statistically higher in slow acetylators (*NAT2**5, *6, *7, *14) compared to genotypically rapid (*NAT2**4, *12, *13) acetylators. Conversely, the clearance was significantly lower in the slow acetylators compared with the rapid acetylators [31]. In Korea, the *NAT2* polymorphisms at rs4646244, rs4646267, rs1799930, and rs1799931 had no association with antituberculosis drug-induced maculopapular eruption [32].

CYP2E1

The CYP450 protein is a monooxygenase 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, rs8192775, 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.

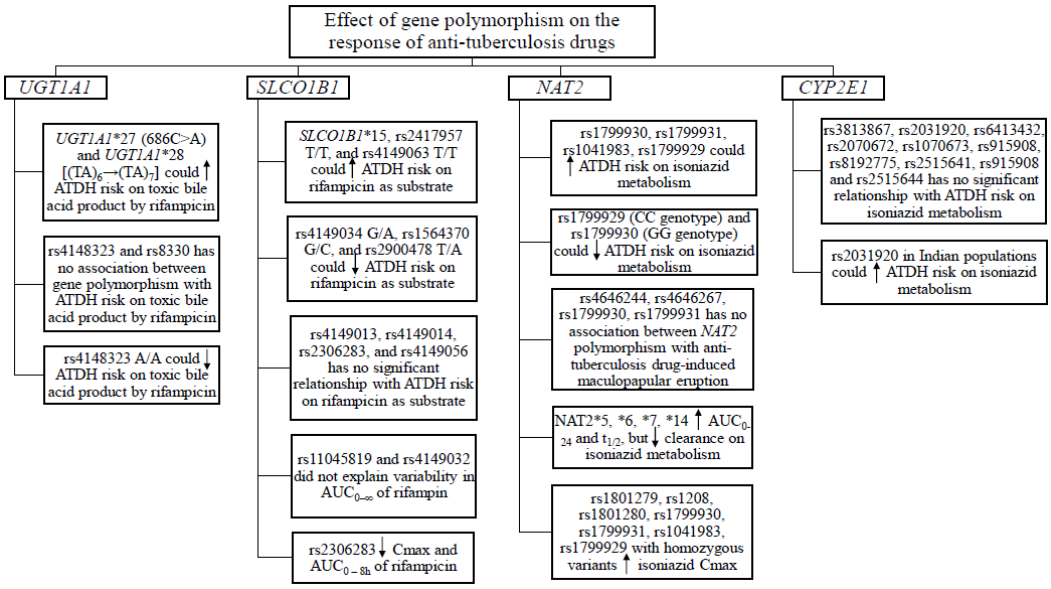

Fig. 4: Effect of gene polymorphisms on the responses of antituberculosis drugs

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*, *SLCO1B1*, *NAT2*, and *CYP2E1*. Polymorphisms in these genes can cause harm to TB patients. In *UGT1A1*, polymorphisms at rs4148323 and rs8330 have no significant association with ATDIH; rs4148323 A/A could reduce ATDIH risk; *UGT1A1**27 (686C>A) and *UGT1A1**28 [(TA)6→(TA)7] could elevate ATDIH risk. In *SLCO1B1*, polymorphisms at rs4149034 G/A, rs1564370 G/C, and rs2900478 T/A are associated with a lower risk of ATDIH; rs2417957 T/T, rs4149063 T/T, and *SLCO1B1**15 are related to a higher risk of ATDIH; rs4149013, rs4149014, rs2306283, rs4149056, and rs4149033 have no significant association with ATDIH; rs2306283 A/A significantly decreased Cmax and AUC_{0-8h} of rifampicin; rs11045819 and rs414903 did not have a relationship with rifampicin's $AUC_{0-\infty}$. In *NAT2*, polymorphisms at rs1801280, rs1799930, 1799931, rs1041983, and rs1799929 are related to an increased the risk of ATDIH; rs1801279, rs1041983, rs1801280, rs1799929, rs1799930, rs1208, and rs1799931 had observed variations in Cmax and AUC_{0-8h} of isoniazid; rs4646244, rs4646267, rs1799930, and rs1799931 had no association with antituberculosis drug-induced maculopapular eruption. In *CYP2E1*, polymorphisms at rs3813867, rs2031920, rs6413432, rs2070672, rs915908, rs8192775, rs2515641, and rs2515644 had no significant relationship with the risk of developing ATDIH; rs2031920, rs2070672, and rs2070673 revealed no association with antituberculosis drug-induced maculopapular eruption. Therefore, personalized medicine that takes genetic polymorphisms into consideration is recommended in order to reach the optimal therapeutic result in each patient.

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AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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