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Review Article

Recent progress in genetic variation and risk of antituberculosis drug-induced liver injury

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Abstract

Antituberculosis drug-induced liver injury (ATDILI) is the most prevalent hepatotoxicity in many countries. All of the three first-line antituberculosis drugs, isoniazid, rifampicin, and pyrazinamide, may induce hepatic damage, especially isoniazid. The major drug-metabolizing enzyme of isoniazid is *N*-acetyltransferase (NAT). Other possible enzymes are CYP2E1, glutathione *S*-transferase (GST) and manganese superoxide dismutase (MnSOD, SOD2). There is evidence that variations of the genes that encode these enzymes may influence the activity of the corresponding drug-metabolizing enzymes. Recent studies have demonstrated that these genetic variations may be associated with the risk of ATDILI. Among them, NAT acetylation status has been most studied. The proposed risk-associated genotypes are *NAT2* slow acetylator (without wild-type *NAT2*4* allele), *CYP2E1 *1A/*1A* (homozygous wild type), homozygous null *GSTM1* genotype and *MnSOD* mutant C allele. Although the available data in the field are complex and inconsistent, meta-analyses disclosed that *NAT2* slow acetylator status possesses the highest association (odds ratio = 3.18). There are associations of *CYP2E1 *1A/*1A* and homozygous null *GSTM1* genotype with ATDILI by meta-analyses, but the odds ratios were lower than that of *NAT2*. Of note, there was an ethnic difference in this association. The ATDILI in East Asians seems to have a higher correlation with genetic variations of *NAT2*, *CYP2E1* and *GSTM1*. However, the meta-analyses could not validate these associations in Caucasians, although some showed positive correlations. To mitigate the crucial ATDILI, this review article underlines the importance of this pharmacogenetic endeavor to identify high-risk patients.

Keywords: arylamine acetyltransferase; cytochrome P450 2E1; drug-induced liver injury; genetic variation; glutathione *S*-transferase; isoniazid; toxic hepatitis; tuberculosis

1. Introduction

Owing to the increasing prevalence of drug-resistant mycobacterium tuberculosis (TB) strains and patients with acquired immunodeficiency syndrome (AIDS), TB has been a growing public health burden and challenge. The three common first-line drugs for TB are isoniazid, rifampicin and pyrazinamide, which have the potential to induce liver damage.[1] This antituberculosis drug-induced liver injury (ATDILI) ranges from mild to severe forms, and can even be fatal. The incidence of ATDILI depends on different antituberculosis regimens, definitions of liver injury, and ethnic populations. Generally, 10–20% of patients may have elevation of serum aminotransferase during administration of these drugs. Approximately 1% of patients may develop overt hepatitis, defined as symptomatic hepatotoxicity with jaundice, and significant elevation of serum aminotransferase.[1] The mortality rate of patients with overt hepatitis is estimated to be around 10%. ATDILI is the most prevalent drug-induced hepatotoxicity in Taiwan, China, South Africa and many other areas, which may both threaten patients' health and

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hinder the treatment of TB.[2] Attempts to ameliorate this potentially grave drug-induced liver injury (DILI) are crucial.

2. Characteristics of antituberculosis drug-induced liver injury

Among the antituberculosis drugs, isoniazid is the drug which most frequently induces hepatotoxicity.[1] The latent period of ATDILI ranges from 1 week to 12 months, with the median being around 8 weeks.[1] The clinical course may be insidious, without significant symptoms or signs. However, some cases may have nonspecific manifestations, such as anorexia, nausea, vomiting, poor appetite, upper abdominal discomfort, yellowish discoloration of skin and tea-colored urine. Liver tests often revealed typical hepatocellular pattern, with elevated serum aminotransferase levels, but with normal or near-normal serum alkaline phosphatase. Pathology of the liver is characterized by zonal, submassive, or massive necrosis in the hepatic lobules. Recovery usually occurs if drugs are withdrawn before severe liver injury happens. Of note, liver function may resume to normal in some patients with mild liver injury, even though the anti-TB drugs are continuously administered. This is believed to be an "adaptation" of the liver to dispose of the drugs and metabolites more efficiently.[1] Metabolic intermediates of isoniazid are incriminated in induction of liver injury (Fig. 1).[2] The immunological reaction may play a small role in ATDILI.

Rifampicin may induce hepatocellular type liver damage as isoniazid.[1] However, it may also interfere with the uptake and excretion of bilirubin and cause isolated direct or indirect hyperbilirubinemia, without elevation of serum aminotransferase. In addition, rifampicin may augment the activities of amidase and CYP2E1, and enhance the hepatotoxicity of isoniazid (Fig. 1).[2]

Pyrazinamide is known as a dose-dependent hepatotoxin and causes hepatocellular injury like isoniazid.[1] However, little is known about the risk factors and genetic predisposition of pyrazinamide or rifampicin-induced liver injury, because most studies were undertaken with the combination therapy of anti-TB agents.

3. Risk factors of antituberculosis drug-induced liver injury

A better understanding of the risk factors and mechanisms of ATDILI may help us to prevent and mitigate this important adverse drug reaction. Elderly, female, African American, Asian, malnutrition, low body weight, alcoholism, pre-existing liver disease, chronic hepatitis B and C infections, AIDS, pregnancy, co-administration of hepatotoxic agents, abnormal baseline liver function and genetic factors have been reported to increase the risk of ATDILI.[1] Pharmacogenetic or pharmacogenomic approaches to the genetic variations of drug-metabolizing enzymes (DMEs) and immunological reaction have recently gained global attention.[2] Variations of the encoding genes may influence the activity of the corresponding DMEs, and then increase or decrease the susceptibility to ATDILI. Although there have been many reports from different ethnic populations in this field in the past decade, most were small in sample size, and with different definition of DILI.[2] Therefore, the results are intricate and complex, and should be interpreted with caution. Owing to many pharmacogenetic meta-analyses in recent years, we have the chance to re-evaluate the association of genetic factors and ATDILI more objectively.

4. Genetic variation and susceptibility to ATDILI

4.1. N-acetyltransferase

Isoniazid is first metabolized to acetylisoniazid via *N*-acetyltransferase (NAT), followed by hydrolysis to acetylhydrazine (Fig. 1).[3] Acetylhydrazine can be oxidized to many hepatotoxic intermediates by cytochrome P450 2E1 (CYP2E1)[4] or acetylated to nontoxic diacetylhydrazine. Another metabolic pathway to generate toxic metabolites is

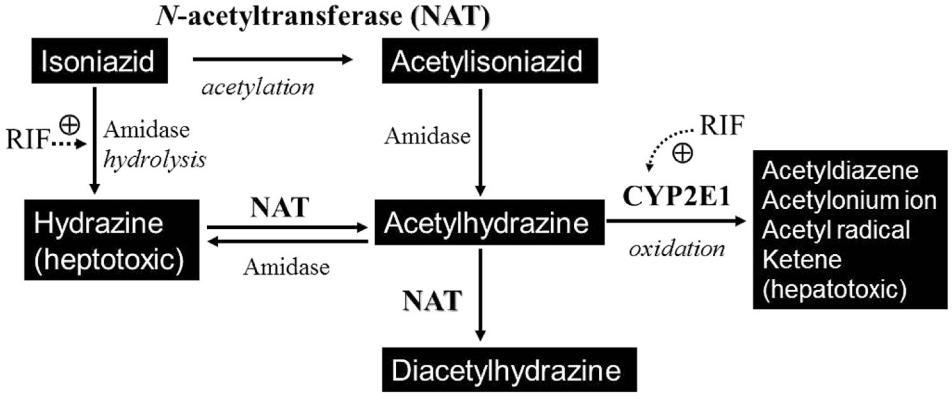

Fig. 1. The metabolic pathway of isoniazid. Isoniazid is first metabolized to acetylisoniazid via *N*-acetyltransferase (NAT), followed by hydrolysis to acetylhydrazine by amidase. Acetylhydrazine can be oxidized to many hepatotoxic intermediates by CYP2E1, or acetylated to nontoxic diacetylhydrazine. Another metabolic pathway to generate toxic metabolites is the direct hydrolysis of isoniazid to toxic hydrazine via amidase. Rifampicin may augment the activities of amidase and CYP2E1, and enhance the hepatotoxicity of isoniazid. CYP = cytochrome; NAT = *N*-acetyltransferase; RIF = rifampicin.

the direct hydrolysis of isoniazid to a potent toxic hydrazine via amidase.[2]

It is speculated that the activity of NAT may affect the detoxification process, and is associated with the susceptibility to ATDILI. People are identified as rapid or slow acetylators, according to the activity of NAT. Mitchell et al[5] first pointed out that rapid acetylators were more vulnerable to ATDILI, because they produced more hepatotoxins via rapid activity of NAT. However, the disposal of acetylhydrazine also depends on further acetylation by NAT to form the nontoxic metabolite, diacetylhydrazine. This crucial detoxification pathway is slower in slow acetylators, which suggests that slow acetylators have a higher risk of ATDILI than rapid acetylators in other studies. Whether rapid or slow acetylator status is related to the risk of ATDILI has been debated for many decades. Acetylator status was determined by measuring metabolites of an index drug catalyzed by NAT in all studies before 2000. This indirect phenotyping method may be influenced by many individual intrinsic factors and has bias. Genotyping *NAT2* is believed to be a more accurate method to differentiate rapid from slow acetylators.

NAT is encoded by *NAT1* and *NAT2* genes. The latter is the main human gene controlling hepatic NAT. Humans have genetic variation in *NAT2*, which has been proven to influence the activity of NAT. The *NAT2*4* is the wild-type allele, which possesses the highest NAT activity compared with the variants (*NAT2*5*, *NAT*6*, *NAT*7*, etc.).[3] Accordingly, the presence of any two variant alleles defines the slow acetylator phenotype; one variant and one wild-type allele, intermediate acetylator; and two wild-type alleles, rapid acetylators. Many researchers merge the intermediate acetylators and rapid acetylators, and simply divide humans into rapid and slow acetylators.

By the application of genotyping methods, slow acetylators were found to have a higher risk of ATDILI than rapid acetylators in recent studies from East Asia.[3,4,6–8] Furthermore, slow acetylators may have more serious liver damage than rapid acetylators in patients with ATDILI.[3] Most studies in Asia and India show similar findings.[6–10] However, some discordant results came from studies of Caucasians.[10,11]

Meta-analyses recruiting recent relevant studies revealed that *NAT2* slow acetylators had a higher risk of ATDILI across different ethnic populations [odds ratio (OR) = 3.18 in total, Table 1].[10,11] However, East Asians had a higher OR than that of Indians (3.32 vs. 2.96).[10] Although some studies of Caucasians possessed a statistically significant association of *NAT2* and ATDILI, the meta-analysis failed to establish this association in Caucasians (Table 1).[10]

4.2. Cytochrome P450 2E1

CYP2E1, a phase 1 enzyme, is involved in the metabolism of many carcinogens and drugs, and is associated with susceptibilities to alcoholic liver disease, nonalcoholic fatty liver disease and many cancers, such as hepatocellular carcinoma.[4] This enzyme also has functional genetic variation in humans. Three restriction enzymes, *Rsa*I, *Pst*I and *Dra*I, are commonly used to detect *CYP2E1* restriction fragment length polymorphism (RFLP). The *Rsa*I and *Pst*I restriction sites are in the transcription regulation region of *CYP2E1*, which has been linked to gene expression.[4]

The three genotypes of *CYP2E1* are classified as c1/c1, c1/c2 and c2/c2 by RFLP using *Rsa*I as the restriction enzyme. The wild-type allele is c1 and the variant allele is c2. According to the new nomenclature for CYP2E1, **1A* is equivalent to c1 and **5* is equivalent to c2.

Huang et al[4] first demonstrated that patients with homozygous wild genotype *CYP2E1 *1A/*1A* had a higher risk of hepatotoxicity (OR = 2.52) than those with mutant allele **5* (*CYP2E1 *1A/*5* or **5/*5*).[4] If *CYP2E1 *1A/*5* or **5/*5* genotype combined with rapid acetylator status was regarded as the reference group, the OR of ATDILI increased from 3.94 for *CYP2E1*1A/*1A* with rapid acetylator status, to 7.43 for *CYP2E1 *1A/*1A* with slow acetylator status. Furthermore, under the administration of isoniazid, individuals with *CYP2E1 *1A/*1A* genotype had higher CYP2E1 activity than those with other genotypes and, hence, may produce more hepatotoxins and increase the risk of ATDILI.

Some studies from East Asia and Europe support the aforementioned study,[10–13] but others disproved it.[14] Recent meta-analyses disclosed that the *CYP2E1 Rsa*I genetic variation was associated with the susceptibility to ATDILI in East Asians, although the OR was not high (OR = 1.35, Table 1).[10,12] However, the meta-analyses could not endorse this association in Indians and Caucasians.[10,12]

4.3. Glutathione S-transferase

Glutathione S-transferase (GST), an important phase 2 detoxification enzyme, can catalyze the conjugation of glutathione to a host of electrophils, including arene oxides, unsaturated carbonyls, organic halides and many other chemicals.[15] The GST supergene family encodes this enzyme and has functional genetic variations, which are correlated with the susceptibility of alcoholic liver disease and many cancers. Individuals with the homozygous "null" mutant genotype of *GSTM1* or *GSTT1* have been found to lose enzymatic activity.

It is reasonable to speculate that individuals with null *GSTM1* or *GSTT1* genotypes may have a higher risk of ATDILI. Roy et al[16] first reported that *GSTM1* null mutation is associated with the susceptibility of this DILI, but *GSTT1* null mutation is not. Other studies may or may not support this finding.[15,17,18] Recent meta-analyses demonstrated that the association of null *GSTM1* genotype and ATDILI existed, although the OR was not high.[10,18] Similar to the finding regarding *CYP2E1*, the association of *GSTM1* null genotype with ATDILI only existed in East Asians, but not in Indians and Caucasians.[10,18] Further, this association for overall ethnicity was statistically significant, although it seemed weak (OR = 1.43, Table 1).[10,18]

Regarding the other important *GST T1* null genotype, only a few small-scale studies suggest an association with ATDILI. The results of recent meta-analyses disproved the

Table 1
Odds ratios of antituberculosis drug-induced liver injury associated with proposed high-risk genetic variations in different ethnic populations.

Genetic variations	Overall	East Asian	Indian	Caucasian	References
Drug-metabolizing enzyme					
—*NAT2* slow acetylator	3.18[a],*	3.32[a],*	2.96[a],*	1.44[a]	3−11
—*CYP2E1 *1A/*1A*	1.28[a]	1.35[a],*	0.56[a]	0.81[a]	4,6−8,10, 12−14
—*GSTM1* null	1.43[a],*	1.55[a],*	1.70[a]	0.73[a]	10,15−18
—*GSTT1* null	1.07[a]	0.96[a]	2.92[a]	2.60[a]	10,15−18
—*MnSOD (SOD2)* variant *c1* allele	—	2.47*	—	—	15
—*UGT1A1* variant*27, *28* allele	—	13.86*	—	—	19
—*NOS2* C/C	—	3.60*	—	—	20
—*BACH1* C/C	—	29.14*	—	—	20
—*MAFK* G/A, A/A	—	5.72*	—	—	20
Immunological reaction					
—*HLA-DQB1*0201*	—	—	1.90*	—	21
—*TNF-α -308* variant *A* allele	—	1.95*	—	—	22

*$p < 0.05$.
BACH = BTB and CNC homology 1; CYP = cytochrome P450; GST = glutathione *S*-transferase; HLA = human leukocyte antigen; MAFK = Maf basic leucine zipper protein; MnSOD = manganese superoxide dismutase; NAT = *N*-acetyltransferase; NOS = nitric oxide synthase; TNF = tumor necrosis factor; UGT = UDP glucuronosyltransferase.
[a] Data derived from meta-analyses.

role of *GSTT1* in ATDILI in all geographical regions studied (Table 1).[10,18]

4.4. Manganese superoxide dismutase

Manganese superoxide dismutase (MnSOD, SOD2) is a crucial phase 2 enzyme with an antioxidative property.[15] A thymine (T)-to-cytosine (C) substitution at position 47 in the human *MnSOD* gene was found, resulting in an alanine-for-valine substitution in the leader amino acid sequence.[15] In turn, this amino acid substitution may modify the helical structure of the mitochondrial targeting sequence, and then augment the import of MnSOD into the mitochondrial matrix. This T/C genetic variation has been associated with an increased risk of many cancers and alcoholic liver disease.[15]

Huang et al[15] found that individuals with a variant C allele (T/C or C/C genotype) of *MnSOD* had a higher risk of ATDILI than did those with *MnSOD* T/T genotype (OR = 2.47, 95% confidence interval = 1.13−5.39, $p = 0.02$). However, this study warrants further research to verify these findings.

4.5. UDP glucuronosyltransferase

UDP glucuronosyltransferase (UGT), an important phase 2 enzyme group, is associated with the conjugation and detoxification of many drugs, xenobiotics and bilirubin.[19] Genetic variations of UGT are associated with drug-induced hyperbilirubinemia, Gilbert's syndrome and many cancers. One report from Taiwan disclosed that individuals with both *UGT1A1* variant*27 and *28* alleles had a very high OR for ATDILI (OR = 13.86, 95% confidence interval = 1.09−177.04, $p = 0.043$).[19] However, the case number was limited in this study. Further studies with a large sample size and with different ethnic populations are warranted to clarify the role of *UGT* genetic variation in the risk of ATDILI.

4.6. Antioxidant pathway proteins

The antioxidation pathway is critical to detoxify many free radicals and toxic chemicals. Many enzymes and transcription factors are involved in this pathway to regulate the antioxidative process. Similarly, genetic variations of the associated regulatory genes may confer different activities on the relevant enzymes. Nitric oxide synthase (NOS), BTB and CNC homology 1 (BACH) and Maf basic leucine zipper protein (MAFK) are important antioxidant enzymes or transcription factors. One recent study from Japan disclosed that a C/C genotype at rs11080344 in *NOS2A*, a C/C genotype at rs2070401 in *BACH1* and a G/A or A/A genotype at rs4720833 in *MAFK* independently conferred ATDILI susceptibility with a very high OR (Table 1).[20] However, the sample size of ATDILI cases in this study was very small ($n = 18$).[20] The association of genotypes of these antioxidant proteins and ATDILI needs large-scale research for confirmation.

4.7. Human leukocyte antigen

Although it is generally believed that genetic variations of DMEs comprise the major pathogenesis of ATDILI, immunological reactions still play some role in this hepatotoxicity.[21,22] Among the immunological reaction, human leukocyte antigen (*HLA*) variation has been well explored in many diseases. Only one available study from India has shown that *HLA-DQB1*0201* genotype is associated with ATDILI.[21] Owing to *HLA* variation in different ethnic populations, the association of *HLA* and ATDILI awaits further confirmation.

5. Conclusion

From the available data and meta-analyses, the possible high-risk genetic variations are *NAT2* slow acetylator (without wild-type *NAT2*4* allele), *CYP2E1 *1A/*1A* (homozygous

wild type), homozygous null *GSTM1* genotype and *MnSOD* mutant C allele. Among them, *NAT2* slow acetylator status possesses the highest association. The correlation of *CYP2E1* and *GSTM1* genotype with ATDILI is low. Of note, ethnic differences exist in this association. ATDILI in East Asians seems to have a significant correlation with genetic variations of *NAT2*, *CYP2E1* and *GST M1*. However, the meta-analysis could not validate these associations in Caucasians, although some studies showed positive correlations.

It is suggested that patients with high-risk genotypes should have regular liver biochemical tests in the first few months following administration of antituberculosis drugs. Tailoring the antituberculosis regimen to patients according to individual genetic profiles is expected in the near future.[23]

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