Cytochrome P450 2E1 Genotype and the Susceptibility to Antituberculosis Drug–Induced Hepatitis

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Most cases with antituberculosis drug–induced hepatitis have been attributed to isoniazid. Isoniazid is metabolized by hepatic *N*-acetyltransferase (NAT) and cytochrome P450 2E1 (CYP2E1) to form hepatotoxins. However, the role of CYP2E1 in this hepatotoxicity has not yet been reported. The aim of this study was to evaluate whether the polymorphism of the *CYP2E1* gene is associated with antituberculosis drug–induced hepatitis. A total of 318 tuberculosis patients who received antituberculosis treatment were followed prospectively. Their *CYP2E1* and *NAT2* genotypes were determined using a polymerase chain reaction with restriction fragment length polymorphism method. Twenty-one healthy volunteers were recruited for CYP2E1 phenotype study using a chlorzoxazone test. Forty-nine (15.4%) patients were diagnosed to have drug-induced hepatotoxicity. Patients with homozygous wild genotype *CYP2E1* c1/c1 had a higher risk of hepatotoxicity (20.0%; odds ratio [OR], 2.52) than those with mutant allele c2 (*CYP2E1* c1/c2 or c2/c2, 9.0%, $P = .009$). If *CYP2E1* c1/c2 or c2/c2 genotype combined with rapid acetylator status was regarded as the reference group, the risk of hepatotoxicity increased from 3.94 for *CYP2E1* c1/c1 with rapid acetylator status to 7.43 for *CYP2E1* c1/c1 with slow acetylator status. After adjustment for acetylator status and age, the *CYP2E1* c1/c1 genotype remained an independent risk factor for hepatotoxicity (OR, 2.38; $P = .017$). Furthermore, under the administration of isoniazid, the volunteers with *CYP2E1* c1/c1 genotype had higher CYP2E1 activity than those with other genotypes had and, hence, might produce more hepatotoxins. In conclusion, *CYP 2E1* genetic polymorphism may be associated with susceptibility to antituberculosis drug–induced hepatitis. (HEPATOLOGY 2003;37:924-930.)

A resurgence of tuberculosis has been recently described in many countries.[1] Despite the availability of effective chemotherapeutic agents to treat tuberculosis, hepatotoxicity resulting from these drugs remains common and may limit the drugs' clinical use.[2-15] The incidence of antituberculosis drug–induced hepatitis ranges from 1% to 36%, depending on different regimens and definitions of hepatic injury.[3-15] This hepatotoxicity is also the most prevalent drug-induced hepatic injury in Taiwan and many other countries, and its associated mortality is not rare.[10,13-17] Alcohol consumption, advanced age, acetylator status, and existing chronic liver disease have been reported to increase the risk of antituberculosis drug–induced hepatitis.[3-15] However, the exact mechanism for this hepatotoxicity remains unclear.

Of the various antituberculosis regimens, isoniazid is the main drug to induce hepatotoxicity.[2-15] Metabolic intermediates of isoniazid, instead of isoniazid *per se*, are incriminated as the cause of hepatotoxicity.[3,4] Therefore, a better understanding of the metabolism of isoniazid may be of help in understanding the mechanisms underlying hepatotoxicity and obviate its occurrence. In the liver, isoniazid first is metabolized into acetylisoniazid via *N*-acetyltransferase (NAT),[5] followed by hydrolysis to acetylhydrazine (Fig. 1). Acetylhydrazine then is oxidized

Abbreviations: NAT, N-acetyltransferase; CYP2E1, cytochrome P450 2E1; RFLP, restriction fragment length polymorphism; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IgM, immunoglobulin M; ULN, upper limit of the normal value; PCR, polymerase chain reaction; CZX, Chlorzoxazone; 6-OH-CZX, 6-hydroxychlorzoxazone; OR, odds ratio.

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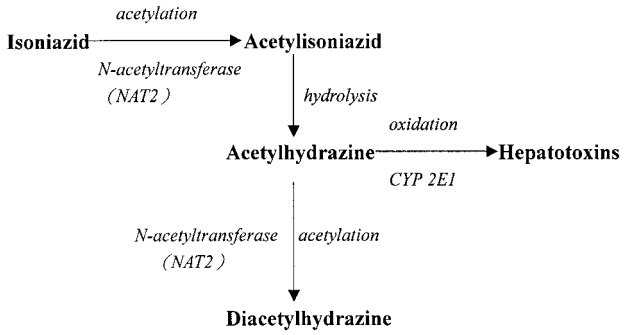

Fig. 1. Metabolism of isoniazid in the liver.

into hepatotoxic intermediaries by cytochrome P450 2E1 (CYP2E1).[3,18] Our previous *NAT2* genotype study suggested that slow acetylators have a higher incidence of antituberculosis drug–induced hepatitis than rapid acetylators,[15] which is consistent with other studies.[7,9,12] However, the impact of CYP2E1, the major catalyzing enzyme in the formation of hepatotoxins, on the risk of developing antituberculosis drug–induced hepatitis has not been studied. CYP2E1 is involved in the metabolism of several carcinogens and drugs and may be associated with susceptibilities to alcoholic liver disease and many cancers, such as hepatocellular carcinoma.[19-23] This enzyme has a genetic polymorphism in humans. Three genotypes of *CYP2E1* are classified as c1/c1, c1/c2, and c2/c2 by restriction fragment length polymorphism (RFLP) using *Rsa*I as the restriction enzyme.[24] Therefore, this study assessed whether the genetic polymorphism of *CYP2E1* influenced susceptibility to antituberculosis drug–induced hepatitis.

Patients and Methods

Study Subjects. A total of 318 Taiwanese patients with incident pulmonary or extrapulmonary tuberculosis diagnosed at Taipei Veterans General Hospital from May 1998 to August 2001 were surveyed consecutively. Their standard daily antituberculosis regimen for the first 2 months included isoniazid (300 mg), rifampin (600 mg or 450 mg if body weight $<$50 kg), pyrazinamide (20 mg/kg body weight), and ethambutol (25 mg/kg body weight). Pyrazinamide was then discontinued, whereas isoniazid, rifampin, and ethambutol (15 mg/kg body weight) were continued for another 4 months. Before the antituberculosis therapy began, serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin were measured. Serum ALT, AST, and bilirubin were then monitored monthly up to the end of the treatment or checked whenever patients had symptoms or signs of hepatitis, such as anorexia, nausea, vomiting, malaise, and jaundice. The serum hepatitis B virus surface antigen, immunoglobulin M (IgM) antibody to hepatitis A virus, and antibody to hepatitis C virus were tested when serum ALT or AST level was elevated. According to the American Thoracic Society and the Centers for Disease Control and Prevention,[25] isoniazid was withdrawn if serum aminotransferase levels exceeded 3 to 5 times the upper limit of the normal value (ULN). Serum ALT, AST, and bilirubin were checked closely thereafter. After normalization of serum aminotransferases and bilirubin levels, isoniazid was rechallenged gradually from low doses to a full dose, and the patients' liver biochemical tests were monitored closely. The exclusion criteria were 1. abnormal serum ALT, AST, or bilirubin before antituberculosis treatment; and 2. refusal of blood sampling or informed written consent.

Antituberculosis drug–induced hepatitis was diagnosed as 1. an increase in serum ALT level greater than twice the ULN during treatment, according to the criteria established by the International Consensus Meeting[26]; 2. negative serum hepatitis B virus surface antigen, IgM antibody to hepatitis A virus, and antibody to hepatitis C virus when ALT or AST is elevated; 3. without any other major hepatic or systemic diseases that may induce elevation of liver biochemical tests, such as alcoholic liver disease, autoimmune hepatitis, congestive heart failure, hypoxia, and bacteremia; and 4. a causality assessment score[27] greater than 5 (when classified as "probable" or "highly probable" drug-induced hepatitis), as derived from the International Consensus Meeting.[26]

The extent of pulmonary tuberculosis was classified as minimal, moderately advanced, or far advanced according to previous classifications.[28] Patient's nutritional status was expressed by body mass index.

For phenotyping study of CYP2E1 using a chlorzoxazone test, 21 healthy volunteers were recruited. The patients with tuberculosis were not included, because the study for basal CYP2E1 activity would delay the antituberculosis treatment. All volunteers, who were within 15% of ideal body weight, were nonsmokers and drank alcohol infrequently or not at all. They were required to refrain from taking any medication or alcohol drinking during the study and for 1 week before the study.

Written informed consent was obtained from each subject before the study. The study protocol was approved by the Institutional Review Board of Taipei Veterans General Hospital.

***Genotyping CYP2E1* and *NAT2*.** DNA was extracted from the patients' peripheral blood white blood cells. Polymerase chain reaction (PCR) with RFLP was used to genotype the *CYP2E1* of patients, as previously reported.[24] Briefly, after an initial amplification with the

primer 5′-TTCATTCTGTCTTCTAACTGG-3′ and 5′-CCAGTCGAGTCTACATTGTCA-3′, the PCR product was digested with the restriction enzyme, *Rsa*I. The wild-type allele of *CYP2E1* is c1, and the mutant is c2. Accordingly, each individual was grouped into one of the three *CYP2E1* genotypes, c1/c1, c1/c2, and c2/c2.

Simultaneously, the acetylator status of the patients were determined from their *NAT2* genotypes with a PCR-RFLP method.[29] After initial amplification, the PCR product was cut separately with three different restriction enzymes, *Kpn*I, *Taq*I, and *BamH*I. Loss of a *Kpn*I restriction site denotes *NAT2*5* allele. Loss of a *Taq*I restriction site means *NAT2*6* allele, whereas loss of a *BamH*I restriction site denotes *NAT2*7* allele. The presence of any two mutant alleles defines the slow acetylator genotype, whereas rapid acetylators have one or two wild-type *NAT2*4* alleles.

Serum liver biochemical tests were measured using an autoanalyzer (Technicon SMAC, Technicon Instruments, Tarrytown, NY). The serum hepatitis B virus surface antigen and IgM antibody to hepatitis A virus were measured by radioimmunoassay with commercially available kits (Abbott Laboratories, Chicago, IL). The serum antibody to hepatitis C virus was measured by a second-generation enzyme immunoassay containing structural and nonstructural hepatitis C viral antigens (Abbott Laboratories, Chicago, IL).

Phenotyping CYP2E1. The Chlorzoxazone (CZX; Veterans Pharmaceutical, Chung-Li, Taiwan) test was used to determine the enzymatic activity of CYP2E1, as previously described by Girre et al.[30] Briefly, after an overnight fasting, healthy volunteers were administered 500 mg of CZX with 200 mL of water. A venous blood sample was drawn 2 hours after drug intake to measure the concentrations of CZX and its metabolite by CYP2E1, 6-hydroxychlorzoxazone (6-OH-CZX), using a high-performance liquid chromatography method as previously described.[30] The serum 6-OH-CZX/CZX concentration ratio has been shown to reflect the rate of CZX hydroxylation and thus represent the CYP2E1 activity.[30-32] To study the effect of isoniazid on the CYP2E1 activity in subjects with different *CYP2E1* genotypes, isoniazid 300 mg daily was administered for 7 days (days 1 to 7). The CZX test was performed 1 day before the administration of isoniazid (day 0) and the last day of isoniazid intake (day 7).

Statistical Methods. Data was expressed as median (range) unless otherwise noted. Odds ratios (ORs) and CI were calculated using a logistic regression analysis. The Student's *t* test, χ^2 test with or without Yates' correction, and Fisher's exact test were used for univariate analysis when appropriate. Multivariate analysis was performed to evaluate the adjusted risk of hepatic injury using a logistic regression analysis. Expected gene frequencies were calculated from respective single allele frequencies according to the Hardy-Weinberg equation:

$$p^2 + 2pq + q^2 = 1$$

where p and q are respective allele frequencies.[33] The observed and expected gene frequencies were compared using a χ^2 goodness-of-fit test to the Hardy-Weinberg proportion. The interaction between the *CYP2E1* genotype and acetylator status for the susceptibility to hepatotoxicity was assessed using a multivariate logistic regression analysis. This assessment was performed to compare the goodness of fit of the model containing an interaction term (*CYP2E1* genotype × acetylator status) with a reduced model containing indicator variables of the main effects of the *CYP2E1* genotype and acetylator status and other confounding factors. The Mann-Whitney *U* test was performed to compare CYP2E1 phenotypes between different *CYP2E1* genotypes. The statistical tests were based on 2-tailed probability. A *P*-value below .05 was considered significant. All analyses were performed using SPSS 10.0 software (SPSS Inc., Chicago, IL).

Results

Forty-nine (15.4%) of 318 patients were diagnosed with antituberculosis drug–induced hepatitis. Compared with those without hepatotoxicity, patients with hepatic injury were older and had a smaller mean body mass index (Table 1). Seven patients (2.2%) had 2 to 3 times ULN of ALT during treatment, and antituberculosis drugs were continuously administered throughout the course uneventfully. Twenty-two patients (6.9%) had more than 3 times the ULN of ALT; thus, isoniazid was discontinued temporarily. After the liver biochemical tests were normalized, isoniazid was rechallenged with gradually increasing doses to these 22 patients safely. However, an elevated serum ALT level greater than 3 times ULN was noted in 19 other patients (6.0%) during their isoniazid rechallenge, so isoniazid was replaced with streptomycin or ofloxacin to prevent further severe hepatic injury. One 73-year-old male patient, a slow acetylator with a *CYP2E1* c1/c1 genotype, was found to have high serum ALT (2,090 U/L), AST (2,260 U/L) and total bilirubin (6.2 mg/dL) levels after 1 month of antituberculosis treatment. Despite discontinuing all antituberculosis drugs, he died of hepatic failure. Antituberculous drugs were incriminated in his hepatic injury.

A total of 185 patients (58.2%) were genotyped as *CYP2E1* c1/c1, 118 patients (37.1%) as *CYP2E1* c1/c2,

Table 1. Characteristics of Patients With or Without Hepatotoxicity

	Hepatotoxicity		
	Present (n = 49)	Absent (n = 269)	P
Age (y)*	70 (37-83)	59 (24-88)	.006
Gender (M/F)	9/40	40/229	.522
Body mass index (kg/m^2)*	21 (17-26)	22 (16-26)	.040
Sites of tuberculosis (lungs/others)	44/5	256/13	.170
Extent of pulmonary tuberculosis (minimal/moderately advanced/far advanced)	11/19/14	55/100/101	.624
Before treatment			
ALT (U/L)*	28 (12-40)	26 (15-40)	.461
AST (U/L)*	32 (18-45)	32 (17-45)	.278
Total bilirubin (mg/dL)*	1.2 (0.8-1.6)	1.1 (0.4-1.6)	.266
During treatment			
Peak ALT (U/L)*	235 (98-2,090)	32 (18-78)	<.001
Peak AST (U/L)*	233 (56-2,260)	39 (18-79)	<.001
Peak total bilirubin (mg/dL)*	1.70 (0.5-20.2)	1.2 (0.3-2.3)	.001

NOTE. Normal interval of ALT: 0 to 40 U/L; AST, 5 to 45 U/L; total bilirubin, 0.2 to 1.6 mg/dL.

*Median (range).

and 15 patients (4.7%) as *CYP2E1* c2/c2. The *CYP2E1* genotype under investigation was in Hardy-Weinberg equilibrium (Table 2). There was a significant difference in 3 genotypes of *CYP2E1* and the susceptibility of hepatotoxicity ($P = .025$; χ^2 test). Patients with homozygous wild genotype *CYP2E1* c1/c1 had a higher risk of hepatotoxicity than those with mutant allele c2 (*CYP2E1* c1/c2 or c2/c2) (20.0% vs. 9.0%; $P = .009$; Table 3). The risk of hepatotoxicity was higher also in slow acetylators than in rapid acetylators (24.7% vs. 12.4%; $P = .011$; Table 3).

There was no statistical difference in the age, gender, body mass index, and pretreatment liver biochemical tests between *CYP2E1* c1/c1 and other genotypes (Table 4). However, patients with the *CYP2E1* c1/c1 genotype had higher posttreatment serum ALT levels than those with *CYP2E1* c1/c2 or c2/c2 had ($P = .009$).

Considering the *CYP2E1* genotype and acetylator status together, the OR for antituberculosis drug–induced hepatitis increased from rapid acetylators with *CYP2E1* c1/c2 or c2/c2 (reference), to 3.94 for rapid acetylators with *CYP2E1* c1/c1, 4.64 for slow acetylators with *CYP2E1* c1/c2 or c2/c2, and 7.43 for slow acetylators with *CYP2E1* c1/c1 (Table 5). The χ^2 test showed there was no significant association between the *CYP2E1* genotype and acetylator status ($P = .759$; $r^2 = 0.002$).

Table 2. Observed Frequencies of *CYP2E1* Genotypes

Genotype	No.	Observed Frequency (%)	Expected Frequency (%)
c1/c1	185	58.2	58.9
c1/c2	118	37.1	35.7
c2/c2	15	4.7	5.4

NOTE. Test for Hardy-Weinberg proportions, $P = .784$.

Table 3. Risk for Antituberculosis Drug–induced Hepatitis in Relation to *CYP2E1* Genotype and Acetylator Status

	Hepatotoxicity			
	Present (n = 49)	Absent (n = 269)	Odds Ratio (95% CI)	P
CYP2E1 genotype				
c2/c2	2 (13.3%)	13 (86.7%)	1.00 (reference)	
c1/c2	10 (8.5%)	108 (91.5%)	0.60 (0.12-3.05)	.540
c1/c1	37 (20.0%)	148 (80.0%)	1.63 (0.35-7.52)	.534
CYP2E1 genotype				
c2/c2 or c1/c2	12 (9.0%)	121 (91.0%)	1.00 (reference)	
c1/c1	37 (20.0%)	148 (80.0%)	2.52 (1.26-5.05)	.009
Acetylator status				
Rapid	30 (12.4%)	211 (87.6%)	1.00 (reference)	
Slow	19 (24.7%)	58 (75.3%)	2.30 (1.21-4.39)	.011

Significant risk factors obtained from univariate analysis, including *CYP2E1* genotype c1/c1, rapid acetylators, age, and body mass index were analyzed further in a multivariate logistic regression model. After adjustment for other possible risk factors, *CYP2E1* c1/c1 genotype remained an independent risk factor for antituberculosis drug–induced hepatitis (OR and 95% CI, 2.38 and 1.17 to 4.85; $P = .017$). Furthermore, the interaction term between the *CYP2E1* c1/c1 genotype and slow acetylator failed to reach statistical significance ($P = .084$), after adjusting for age, body mass index, and main effects of the *CYP2E1* genotype and acetylator status.

There was no statistical difference in the basal CYP2E1 activity between *CYP2E1* genotype c1/c1 and other genotypes (Table 6). Isoniazid had an inhibitory effect on the CYP2E1 activity. However, the CYP2E1 activity was less inhibited by isoniazid in subjects with *CYP2E1* c1/c1

Table 4. Characteristics of Patients, Stratified by *CYP2E1* Genotype

	CYP2E1 genotype		
	c1/c1 (n = 185)	c1/c2 or c2/c2 (n = 133)	P
Age (y)	63 (24-88)	60 (32-88)	.333
Gender (M/F)	155/30	114/19	.754
Body mass index (kg/m^2)	22 (16-26)	22 (17-26)	.122
Before treatment			
ALT (U/L)	26 (12-40)	26 (16-40)	.992
AST (U/L)	31 (17-45)	32 (17-45)	.678
Total bilirubin (mg/dL)	1.1 (0.4-1.6)	1.0 (0.5-1.6)	.280
During treatment			
Peak ALT (U/L)	34 (20-2,090)	32 (18-802)	.009
Peak AST (U/L)	41 (18-2,260)	40 (18-1,148)	.073
Peak bilirubin (mg/dL)	1.2 (0.5-20.2)	1.3 (0.3-7.3)	.140

NOTE. Data expressed as median (range), except where noted.

Table 5. Combined Risk for Antituberculosis Drug–induced Hepatitis Associated With *CYP2E1* Genotype and Acetylator Status

CYP2E1 Genotype	Acetylator Status	No.	Hepatotoxicity*		Odds Ratio (95% CI)	*P*
			Present	Absent		
c2/c2 or c1/c2	Rapid	98	5 (5.1%)	93 (94.9%)	1.0 (reference)	
c1/c1	Rapid	143	25 (17.5%)	118 (82.5%)	3.94 (1.45-10.67)	.007
c2/c2 or c1/c2	Slow	35	7 (20.0%)	28 (80.0%)	4.64 (1.37-15.77)	.014
c1/c1	Slow	42	12 (28.6%)	30 (71.4%)	7.43 (2.42-22.79)	.001

*$P < .001$ (χ^2 test for trend).

genotype than in those with *CYP2E1* c1/c2 or c2/c2 ($P = .029$; Table 6).

Discussion

CYP2E1 is induced by ethanol and is critically important in the metabolic activation of many drugs and carcinogens.[31,34,35] Three restriction enzymes, *Rsa*I, *Pst*I, and *Dra*I, can be used to detect *CYP2E1* RFLP. The *Rsa*I and *Pst*I restriction sites are in the transcription-regulation region of *CYP2E1*, which has been linked with gene expression.[34,36] The polymorphism detected by *Dra*I digestion is located in intron 6, and no functional significance of this polymorphism currently is known.[22] The *CYP2E1* RFLP detected by *Dra*I or *Pst*I was found to be associated closely with the RFLP of *CYP2E1* by *Rsa*I digestion.[20-22] For susceptibility to the hepatic tumor or liver disease, *Pst*I and *Dra*I polymorphism add no more information than *Rsa*I *CYP2E1* genotypes.[20-22] Consequently, only *Rsa*I RFLP was performed in this study.

Earlier reports[21,34,36] showed that the rare mutant allele of *CYP2E1* (c2 allele) that lacks the *Rsa*I restriction site is associated with higher transcriptional activity, protein levels, and enzyme activity than the more common wild type allele (c1 allele). However, recent studies do not show any relationship between *Rsa*I polymorphism and basal CYP2E1 activity,[31,35] which is confirmed by the present study.

Table 6. The Relationship of *CYP2E1* Genotype and Phenotype, Presented by 6-OH-CZX/CZX Ratio in 21 Healthy Volunteers

	CYP2E1 Genotype		
	c1/c1 (n = 12)	c1/c2 or c2/c2 (n = 9)	*P*
Age (y)*	37 (26-52)	38 (31-47)	.455
Gender (M/F)	7/5	6/3	1.000
6-OH-CZX/CZX*			
Before isoniazid	0.38 (0.30-0.42)†	0.36 (0.31-0.40)‡	.521
With isoniazid	0.30 (0.24-0.38)†	0.23 (0.17-0.38)‡	.029

*Median (range).
†$P = .005$.
‡$P = .011$.

Isoniazid is known to have a biphasic effect on CYP2E1 activity, depending on the time course.[37] During the administration of isoniazid, CYP2E1 activity is inhibited,[37-39] which is concordant with the result of our study. However, induction of CYP2E1 occurs after isoniazid is discontinued.[37,40,41] The present study further revealed that subjects with *CYP2E1* c1/c1 genotype had higher CYP2E1 activity than those with *CYP2E1* c1/c2 or c2/c2 genotype, under the inhibitory effect of isoniazid. Therefore, subjects with *CYP2E1* c1/c1 may generate more hepatotoxins and increase their risk for hepatotoxicity.

Yu et al.[22] found that homozygosity for the *CYP2E1* c1/c1 genotype significantly increases the risk of developing hepatocellular carcinoma in cigarette smokers. Maezawa et al. showed that *CYP2E1* c1/c1 homozygotes are more prevalent in the alcoholic fibrotic group than in the nonfibrotic group.[20] Our finding that *CYP2E1* c1/c1 homozygotes have increased risk of hepatotoxicity is consistent with the above studies.[20,22] Although the role of CYP2E1 in the susceptibilities for drug-induced hepatitis, hepatocellular carcinoma, and alcoholic liver disease are not exactly the same, CYP2E1 seems crucial in activating certain procarcinogens and hepatotoxic intermediaries.[19]

The action of NAT in the disposition of isoniazid is followed by CYP2E1.[3,4] An interaction between genetic polymorphisms of *CYP2E1* and *NAT2* is suspected. However, after adjusting for possible confounding factors, the interaction term (*CYP2E1* genotype × acetylator status) failed to reach statistical significance in our study ($P = .084$). Also, the χ^2 test failed to show any significant association between *CYP2E1* genotype and acetylator status. Multivariate logistic regression analysis further showed that the *CYP2E1 c1/c1* genotype was an independent risk factor for antituberculosis drug–induced hepatitis, after adjustment for acetylator status, age, and body mass index. All of these may suggest that *CYP2E1* genetic polymorphism is independently associated with the risk of antituberculosis drug–induced hepatitis. We found a trend for increasing hepatotoxicity in step with adding the *CYP2E1* c1/c1 genotype and slow acetylator status in this

study, which also manifested an independent but additive effect from these 2 genetic factors in hepatotoxicity.

Because of high incidence of hepatotoxicity, high frequency of medicinal use, and reasonable representation of various genotypes, isoniazid-related hepatotoxicity is well suited for exploring pharmacogenetic basis for drug hepatotoxicity. However, this approach may not be applicable to other drug hepatotoxicities, which lack the characteristics of isoniazid-related hepatitis.

From our own previous work[10] and observations from other studies,[3,4,14] chronic hepatitis B infection and chronic alcohol intake are also risk factors for this hepatotoxicity. However, drug-induced hepatitis can be difficult to diagnose in active hepatitis B carriers and alcoholics. To avoid confusion and to make the diagnosis of antituberculosis drug–induced hepatitis more reliable, we excluded patients with alcoholic liver diseases and chronic hepatitis B or C infections in this study. The elderly appear to be vulnerable to antituberculosis drugs.[5,6,12-15] Nevertheless, after adjustment for age, we found that *CYP2E1* remained a significant independent risk factor for antituberculosis drug–induced hepatotoxicity.

We conclude that subjects with homozygous, wild genotype *CYP2E1* c1/c1 may be at increased risk for antituberculosis drug–induced hepatitis. Regular monitoring of liver biochemical tests may be considered in patients with the *CYP2E1* c1/c1 genotype who are subjected to antituberculosis drugs.

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