Int J Clin Exp Med 2019;12(4):4321-4329
www.ijcem.com /ISSN:1940-5901/IJCEM0077134

Original Article

The relationship between metabolic enzyme genetic polymorphisms and anti-tuberculosis drug-induced hepatotoxicity

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Received July 28, 2017; Accepted September 12, 2018; Epub April 15, 2019; Published April 30, 2019

Abstract: This study investigated the correlation between genetic polymorphisms of drug-metabolizing enzymes (cytochrome P450 [CYP450], glutathione S-transferase [GST], and uridine diphosphate [UDP]-glucuronosyltransferase [UGT]) and anti-tuberculosis drug-induced hepatotoxicity (ADIH). We conducted a case control study on 207 cases of tuberculosis (TB) in the Han population who experienced liver injury within 6 months of anti-TB chemotherapy treatment as the case group, and 207 cases of TB patients with no abnormal liver function as the control group. Multivariate logistic regression analysis showed that the mutant genotype at CYP3A4*18B-20232G/A, UGT2B7-268A/G, and UGT2B7 802C/T was the protective genotype of ADIH. The mutant genotype at CYP3A5*3-6986A/G was the risk genotype of ADIH. No CYP1A2 734C/A, CYP2C19 681G/A, GSTA1-69C/T, and GSTM3 deletion mutations were involved in the development of ADIH. Multifactor dimensionality reduction analysis showed that gene-gene interactions between UGT2B7-268A/G, CYP3A4*18B-20232G/A, and CYP3A5*3-6986A/G can increase risk of ADIH. In summary, CYP3A4*18B-20232G/A, UGT2B7-268A/G, and UGT2B7 802C/T wild-type genotypes and CYP3A5*3-6986A/G mutant genotypes are related to the development of ADIH for TB patients receiving anti-TB chemotherapy.

Keywords: Tuberculosis, drug-metabolizing enzymes, genetic polymorphisms, ADIH, CYP450, GST, UGT

Introduction

Tuberculosis (TB) is a common infectious disease in China. Anti-TB treatment mainly requires the combined chemotherapy of isoniazid, rifampicin, pyrazinamide, and other anti-TB drugs. Incidence rate of anti-TB drug-induced hepatotoxicity (ADIH) is high [1], and ranks first among all drug-induced liver injuries [2]. The occurrence of ADIH features distinct individual differences. Genetic polymorphisms cause drugs to present different clearance rates in metabolic processes and thus change their accumulated concentration in vivo. Genetic polymorphisms can cause changes in drug-metabolizing enzyme activity, resulting in different capacities of individuals on drug detoxification [3]. This difference is one of the genetic bases that lead to the increased risk of drug-induced diseases in individuals [4]. Therefore, genetic susceptibility of drug-induced liver injury has become a significant concern in research communities.

Drug action in the body mainly transpires through phase I and II metabolisms. Occurrence of ADIH is considered a result of the accumulation of toxic drug metabolites and imbalance in detoxification. Cytochrome P450 (CYP450) clears more than 60% of drugs. CYP family genes that are involved in drug metabolism include CYP3A4/5, CYP2C9, CYP2D6, CYP1A2, CY2E1, and CY2C19; among which, CYP1A2 and CYP2C19 account for approximately 13% and 20% of liver drug-metabolizing enzymes [5], respectively. Genetic polymorphisms of CYP3A5*3 and CYP3A4*18B may not only be related to drug metabolism but may also exhibit combined effects [6]. CYP1A2 and CYP2C19 genes are associated with liver injury induced by drugs, such as thioacetamide, acetaminophen, and endothelin receptor antagonists

[7-9]. Hence, they may be involved in isoniazid metabolism [10].

Detoxification of drugs in the body occurs through phase II reactions. Up to 40% to 70% of drugs are cleared by metabolism of phase II metabolic enzymes [11]. Glutathione S-transferase (GST) acts as an important phase II metabolic enzyme in in vivo biotransformation and detoxification. Changes in the activity of GST are closely related to drug metabolism [12]. GSTA1 and GSTM3 are key enzymes in the GST-binding reaction. They are abundant and highly specific in liver tissues [13]. Moreover, C-69T mutation of GSTA1 gene and deletion of three bases of GSTM3 intron 6 significantly affect GST activity. The GSTA family can be detected in drug-induced liver injury and GSTM family activity is reduced; however, several studies are inconsistent and thus warrant further studies [14, 15].

Uridine diphosphate (UDP)-glucuronosyltransferase (UGT) serves as an important phase II drug-metabolizing enzyme that catalyzes glucuronidation reaction, thus completing drug detoxification. UGT is divided into two major families: UGT1A and UGT2B. UGT1A6 and UGT1A7 genetic polymorphisms are associated with the occurrence of ADIH. UGT2B7 genetic polymorphism bears significance in pharmacological and toxicological metabolism [16].

Because of the different races of the subjects and different genetic backgrounds, different phenotypic effects were observed for the same mutation. Perhaps, the coexistence of a variety of "susceptible" genotypes plays an important role. However, the correlation between polymorphisms of CYP1A2, CYP3A4, CYP3A5, CYP2C19, GSTA1, GSTM3, and UGT2B7 are not yet reported in China. So, this study aimed to investigate the relationship between these gene site polymorphisms and ADIH; and to guide clinical medication and reduce the occurrence of liver injury.

Subjects and methods

Subjects of the study

This research employed a matching case control study. Research subjects were selected from TB patients who were diagnosed and approved for TB treatment in Tangshan City Tuberculosis Hospital from September 2014 to March 2015.

Case group inclusion criteria were as follows

Prior to TB treatment, all indicators in liver function test were normal. Liver injury patients were recruited 6 months after follow-up visits. The definition of liver injury, in accordance with the "2014 ACG clinical guidelines: the diagnosis and treatment of drug-induced liver injury" developed by the American College of Gastroenterology [17], requires alanine aminotransferase level equal to or more than thrice the upper limit of the normal level. The basic chemotherapy regimen for newly diagnosed patients comprised 2S (E) HRZ4HR (S = streptomycin, E = ethambutol, H = isoniazid, R = rifampin, Z = pyrazinamide; intensive treatment for the first 2 months and consolidation therapy in the following 4 months with daily medication). The basic chemotherapy regimen for the recurrent patients was 2S (E) HRZ4HR (medication on alternate days). The case group included 207 patients.

Control group inclusion criteria

The control group, which was selected on the basis of the same proportions of gender and residence in urban and rural areas, consisted 207 cases of TB patients with no abnormal liver function 6 months after follow-up visits.

Exclusion criteria for case and control groups

① patients with abnormal liver functions before TB treatment; ② patients with other diseases that can cause abnormal liver function, such as viral hepatitis, alcoholic liver disease, autoimmune hepatitis, hypoxia, bacteremia, and congestive heart failure; and ③ patients who received other drugs, such as chloramphenicol, acetaminophen, and chlorpromazine, that can cause abnormal liver functions.

Epidemiological survey

In accordance with requirements of this study, we designed a unified questionnaire to conduct a survey after receiving informed consent. Data included general information (age, gender, height, weight, and marital status), place of residence, smoking and drinking habits, educational attainment, occupation, history of disease and medication, anti-TB chemotherapy

Table 1. Sequences of primers used for RFLP-PCR

Genes	Sense	Antisense
CYP1A2 734C/A	5'-CTACTCCAGCCCCAGAAGTG-3'	5'-GAAGGGAACAGACTGGGACA-3'
CYP3A4*18B-20232G/A	5'-CACCCTGATGTCCAGCAGAAACT-3'	5'-AATAGAAAGCAGATGAACCAGAGAA-3'
CYP3A5*3-6986A/G	5'-CATGACTTAGTAGACAGATGAC-3'	5'-GGTCCAAACAGGGAAGAGATA-3'
CYP2C19 681G/A	5'-CAACCAGAGCTTGGCATATT-3'	5'-TACGCAAGGCAGTCACATAAC-3'
GSTA1-69C/T	5'-TGTTGATTGTTTGCCTGAAATT-3'	5'-GTTAAACGCTGTCACCGTCCT-3'
GSTM3 deletion mutation	5'-ACCCTGCCATCCTCAAGTGAA-3'	5'-ATGCTTAGGTCTGAGGAGTAGTAGCCTGCAGAGATAGAGAAG-3'
UGT2B7-268A/G	5'-TCCAACTGATTGTTATGGTAGAT-3'	5'-GCTGTTCCTTTCTGTCATTTCTC-3'
UGT2B7 802C/T	5'-GACAATGGGGAAAGCTGACG-3'	5'-GTTTGGCAGGTTTGCAGTG-3'

regimens, and previous liver function test results. Anticoagulated venous blood (3 ml) was collected from subjects and stored at -20°C.

Primer design

Primer Premier 5.0 software was used to design primers in accordance with human gene sequence characteristics in the literature and in gene banks. **Table 1** shows the primer sequences.

Genotyping

Whole genomic DNA was extracted by salting out method. Polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) was used to analyze polymorphisms of eight gene loci. Genomic DNA was used as template to establish basic PCR reaction conditions: initial denaturation at 94°C for 5 min; denaturation at 94°C for 30 sec, annealing at 55°C for 45 sec, and extension at 72°C for 30 sec, with a total of 35 cycles; and annealing at 72°C for 5 min. An optimal restriction enzyme system was established. PCR products were analyzed through restriction enzyme digestion. The endonuclease *Apa* I, *Rsa* I, *Ssp* I, *Sma* I, *Hinf* I, *BamH* I, *Bgl* II, and *BseG* I were used to identify the polymorphisms for CYP1A2 734C/A, CYP3A4*18B-20232G/A,CYP3A5*3-6986A/G, CYP2C19 681G/A, GSTA1-69C/T, GSTM3, UGT2B7-268A/G, and UGT2B7 802C/T, respectively. All digested products of genetic polymorphisms were detected by 2% agarose gel electrophoresis.

Statistical analysis

Survey and experimental data were input in Excel 2010 spreadsheets, gathered, and checked. SPSS was used for statistical analysis. Bilateral tests were adopted at test level $\alpha = 0.05$. Hardy-Weinberg genetic balance analysis of genotype distribution used chi-square goodness-of-fit test. The relationship between genetic polymorphism and ADIH was analyzed by univariate and multivariate logistic regression. Interaction between gene-gene single-nucleotide polymorphisms was analyzed by multifactor dimensionality reduction (MDR).

Results

General information of study subjects and balance analysis

Mean age of the study group totaled (46.7 ± 17.5) years old and that of the control group reached (44.8 ± 17.3) years old. No statistical significance was detected between the two groups ($t = 1.214$, $P > 0.05$). Hardy-Weinberg genetic balance test was used to test the genotypes of the control group. Observed values were similar to those of theoretical values. Chi-Square value at CYP1A2 734C/A, CYP3A4*18B-20232G/A, CYP3A5*3-6986A/G, CYP2C19 681G/A, UGT2B7-268A/G, UGT2B7 802C/T, GSTA1-69C/T, and GSTM3 reached 0.108, 2.740, 0.854, 3.534, 3.329, 0.169, 2.286, and 0.403, respectively, at $P > 0.05$ for all variables. Thus, the sample population was balanced and highly representative.

Univariate analysis of the general information on case and control groups

This paper analyzed the relationship between general information and ADIH, excluding the gender and place of residence (urban or rural areas) which. No statistical significance was found in distribution differences between the two groups in terms of marital status, educational attainment, profession, body mass index

Table 2. Analysis of the general information on case and control group (n=207)

Factors		Case	Control	χ^2	*P*
Marital status	Married	176	188	3.451	0.077
	Single	31	19		
Education	Illiterate	14	14	1.583	0.812
	Primary school	45	55		
	Secondary school	120	115		
	College and above	28	23		
Profession	Worker	60	57	0.937	0.919
	Farmer	67	76		
	Office clerk	13	13		
	Others	67	61		
BMI (kg/m^2)*	< 18.5	67	62	1.561	0.435
	18.5~23.9	107	118		
	24.0~26.9	24	21		
	≥ 27	9	6		
Smoking	Yes	43	41	0.060	0.841
	No	164	166		
Drinking	Yes	34	30	0.296	0.580
	No	173	177		

*China reference standard.

(BMI), smoking and drinking habits (**Table 2**). Therefore, the above factors cannot be concluded to be related to the occurrence of ADIH.

Univariate analysis of the relationship between genetic polymorphisms and ADIH

Non-conditional logistics regression analysis was used to study differences in distribution proportion of genetic polymorphisms of the above mentioned genes (loci) in the case and control groups. **Table 3** showed that the mutant genotypes of CYP1A2 734C/A, CYP3A4*18B-20232G/A, UGT2B7-268A/G, and UGT2B7 802C/T were the protective genotypes of ADIH. However, mutant genotypes at CYP3A5*3-6986A/G and GSTA1-69C/T represented risk genotypes of ADIH.

Hence, **Table 4** showed a univariate analysis of alleles of the eight genes. Results showed that except for the alleles of CYP3A4*18B-20232G/A, alleles of the other seven genes corresponded with results in **Table 3**. That was to say, the mutant alleles of CYP1A2 734C/A, UGT2B7-268A/G, and UGT2B7 802C/T were the protective alleles of ADIH, while the mutant alleles of CYP3A5*3-6986A/G and GSTA1 -69C/T were the risk alleles of ADIH.

Multivariate analysis of the relationship between genetic polymorphisms and ADIH

To eliminate mutual interference between research factors and control effects of confounding factors, significant risk factors in the univariate study were introduced into the multivariate unconditional logistic regression model. The dependent variable was whether liver injury occurred after taking anti-TB drugs. The independent variable represented any one kind of genotypes from those eight drugs' metabolic enzyme, and covariates referred to other genotype variables of the rest which were statistically significant in the univariate analysis. Totally eight multivariate unconditional logistic regression models were established successively based on those variables. **Table 5** shows that after adjusting the influence of other genetic polymorphisms, genetic polymorphisms at CYP3A4*18B-20232G/A, CYP3A5*3-6986A/G, UGT2B7-268A/G, and UGT2B7 802C/T remained significantly correlated with the occurrence of anti-TB drug-induced liver injury. Moreover, CYP1A2 734C/A locus was unrelated to the occurrence of ADIH.

Gene-gene interaction analysis using MDR

MDR algorithm was used to analyze the interaction between eight single-nucleotide polymorphisms. The study estimated all interaction models from two to eight factors. When taking two indicators: accuracy of test sample and consistency of cross-validation as measurement criteria, it concluded that the optimal interaction model was the one that comprised three factors, namely, UGT2B7-268A/G, CYP3A4*18B-20232G/A, and CYP3A5*3-6986A/G. As the accuracy of the test sample reached 61.29% and consistency of cross-validation totaled 10/10 in this model. Test difference was statistically significant ($P < 0.05$) after 1,000 displacements. Although, the model which comprised of UGT2B7 802C/T,

Table 3. Univariate analysis of genetic polymorphisms and ADIH (n=207)

Genes	Genotype	Case	Control	χ^2	*P*	*OR* (95% *CI*)
CYP1A2 734C/A	CC	34	49			1.000 (ref.)
	CA	84	99	0.536	0.464	0.818 (0.460-1.425)
	AA	89	59	7.079	0.008	0.460 (0.251-0.811)
CYP3A4*18B-20232G/A	GG	91	116			1.000 (ref.)
	GA	95	69	6.755	0.009	0.570 (0.358-0.866)
	AA	21	14	3.123	0.077	0.523 (0.236-1.077)
CYP3A5*3-6986A/G	AA	51	11			1.000 (ref.)
	AG	72	67	13.548	0.000	4.314 (1.979- 9.378)
	GG	84	129	26.564	0.000	7.120 (3.409-15.356)
CYP2C19 681G/A	GG	71	76			1.000 (ref.)
	GA	104	110	0.003	0.959	0.988 (0.628-1.555)
	AA	32	21	2.069	0.150	0.613 (0.308-1.198)
GSTA1-69C/T	CC	64	42			1.000 (ref.)
	CT	4	4	0.304	0.582	1.524 (0.355-6.347)
	TT	139	161	6.179	0.013	1.765 (1.132-2.855)
GSTM3 deletion mutation	AA	96	91			1.000 (ref.)
	AB	15	12	0.233	0.629	0.844 (0.363-1.847)
	BB	96	104	0.437	0.509	1.143 (0.763-1.727)
UGT2B7-268A/G	AA	73	115			1.000 (ref.)
	AG	119	73	18.891	0.000	0.389 (0.245-0.588)
	GG	15	19	0.331	0.565	0.804 (0.368-1.726)
UGT2B7 802C/T	CC	73	92			1.000 (ref.)
	CT	69	89	0.000	0.996	1.023 (0.638-1.565)
	TT	45	26	6.535	0.011	0.458 (0.254-0.834)

Table 4. Univariate analysis of alleles and ADIH (n=414)

Genes	Allele	Case	Control	χ^2	*P*	*OR* (95% *CI*)
CYP1A2 734C/A	A	152	197	10.029	0.002	0.639 (0.484-0.844)
	C	262	217			
CYP3A4*18B-20232G/A	A	277	301	3.301	0.069	0.759 (0.564-1.022)
	G	137	113			
CYP3A5*3-6986A/G	G	174	89	40.259	0.001	2.647 (1.951-3.592)
	A	240	325			
CYP2C19 681G/A	A	246	262	1.304	0.254	0.849 (0.642-1.124)
	G	168	152			
GSTA1-69C/T	T	132	88	11.984	0.001	1.734 (1.268-2.372)
	C	282	326			
GSTM3 deletion mutation	B	207	194	0.817	0.366	1.134 (0.863-1.490)
	A	207	220			
UGT2B7-268A/G	G	265	303	8.094	0.004	0.651 (0.485-0.876)
	A	149	111			
UGT2B7 802C/T	T	215	273	11.788	0.001	0.558 (0.422-0.738)
	C	199	141			

UGT2B7-268A/G, CYP3A4*18B-20232G, and CYP3A5*3-6986G also had interaction among those four factors, it was not the optimal one. Estimates of the optimal model showed that in

Table 5. Multivariate Logistic analysis of genetic polymorphisms and ADIH (n=207)

Genes	Genotype	*β*	*S.E*	*Wald* χ^2	*P*	*OR* (95% *CI*)
CYP1A2 734C/A	CC					1.000 (ref.)
	CA	-0.411	0.374	1.206	0.272	0.663 (0.318-1.381)
	AA	-0.664	0.386	2.957	0.086	0.515 (0.241-1.097)
CYP3A4*18B-20232G/A	GG					1.000 (ref.)
	GA	-2.425	0.608	15.908	0.000	0.088 (0.027-0.291)
	AA	-1.509	0.462	10.656	0.001	0.221 (0.089-0.547)
CYP3A5*3-6986A/G	AA					1.000 (ref.)
	AG	4.261	0.797	28.543	0.000	70.850 (14.843-338.185)
	GG	3.100	0.524	34.971	0.000	22.200 (7.946-62.025)
CYP2C19 681G/A	GG					1.000 (ref.)
	GA	-0.117	0.294	0.159	0.690	0.889 (0.500-1.582)
	AA	-0.326	0.423	0.594	0.441	0.722 (0.315-1.653)
GSTA1-69C/T	CC					1.000 (ref.)
	CT	0.121	1.135	0.011	0.915	1.129 (0.122-10.439)
	TT	0.101	0.319	0.099	0.753	1.106 (0.591-2.068)
GSTM3 deletion mutation	AA					1.000 (ref.)
	AB	-0.617	0.547	1.272	0.259	0.539 (0.185-1.577)
	BB	0.161	0.281	0.328	0.567	1.174 (0.677-2.036)
UGT2B7-268A/G	AA					1.000 (ref.)
	AG	-1.176	0.299	15.463	0.000	0.309 (0.172-0.555)
	GG	-0.506	0.496	1.041	0.308	0.603 (0.228-1.593)
UGT2B7 802C/T	CC					1.000 (ref.)
	CT	0.347	0.311	1.251	0.263	1.416 (0.770-2.602)
	TT	-1.140	0.401	8.070	0.004	0.320 (0.146-0.702)

Table 6. Gene-gene interaction analysis on ADIH

Model	Training sample test accuracy	Test sample test accuracy	Cross-validation consistency	*P*	*OR* (95% *CI*)
CYP3A5*3-6986G	0.5901	0.5901	10/10	0.041	1.717 (1.061-4.478)
CYP3A4*18B-20232G, CYP3A5*3-6986G	0.5825	0.5882	6/10	0.153	0.541 (0.347-3.069)
UGT2B7-268A/G, CYP3A4*18B-20232G, CYP3A5*3-6986G	0.6136	0.6129	10/10	0.022	2.803 (1.801-5.836)
UGT2B7 802C/T, UGT2B7-268A/G, CYP3A4*18B-20232G, CYP3A5*3-6986G	0.6048	0.5866	7/10	0.012	3.057 (1.914-7.151)

comparison with low-risk genotype combinations, high-risk genotype combinations can significantly increase risk of ADIH. **Table 6** shows the results.

Discussion

Most anti-TB drugs require catalysis of phase I and II metabolic enzymes, such as *N*-acetyltransferase-2, glutathione transferase, CYP-450 enzyme, and UGT, in the liver to accomplish their metabolic transformation. Genetic polymorphism exists in gene expression of all enzymes. Enzyme gene mutation can cause changes in expression activity, thus modifying the efficacy of enzyme metabolism of drugs and diseases.

We observed that genetic polymorphisms of CYP3A4*18B-20232G/A, CYP3A5*3-6986A/G, UGT2B7-268A/G, and UGT2B7 802C/T were associated with the occurrence of ADIH. Carrying mutant genotypes at CYP3A4*18B-20232G/A, UGT2B7-268A/G, and UGT2B7 802C/T may reduce risk of ADIH. On the contrary, carrying mutant genotypes at CYP3A5*3-6986A/G increases risk of ADIH. Further analysis revealed that interaction exists between

genes. The optimal model was the three-factor-interaction model consisting of UGT2B7-268A/G, CYP3A4*18-20232G/A, and CYP3A5*3-6986A/G.

CYP450 is a key enzyme involved in drug metabolism in the liver and may be related to the occurrence of ADIH [18]. CYP1A2 and 2C19 are important oxidoreductases in the human liver. They are influenced by drugs, genes, and other factors. Differences in enzyme activity and expression level of CYP1A2 between different individuals can reach up to 60 times. Moreover, genetic polymorphism plays a decisive role in individual differences. CYP2C19 gene mutation critically affects its enzyme activity. The most common mutation among the Chinese population occurs at the 681G/A locus. However, in this study, no correlation was found between genetic polymorphism at CYP2C19 681G/A locus and occurrence of ADIH. The result is consistent with the research of Tang et al. [19]. Genetic susceptibility at CYP2C19 681G/A locus remains the same for different races. Thus, mutations of drug-metabolizing enzymes at CYP2C19 681G/A locus may feature minimal effects on ADIH.

Aside from CYP1A2 and CYP2C19, CYP3A5 and CYP3A4 subtypes are also important members of the CYP family and play important roles in drug metabolism. Studies show that genetic polymorphisms of CYP3A5*3 and CYP3A4*18B can affect pharmacokinetics. In addition, risk of liver transplantation rejection can be reduced by adjusting dosage of drugs on the basis of CYP3A5 genotypes [20]. This paper is the first to study the relationship between genetic polymorphisms at CYP3A4*18B-20232G/A and CYP3A5*3-6986A/G and ADIH.

GST enzyme is a phase II detoxification enzyme involved in drug metabolism in the liver. With regard to the gene family of this enzyme, domestic and foreign research rarely report GSTM3 and ADIH. However, existing literature on GSTM family of enzymes and ADIH locally and abroad reach different conclusions. Studies in India, Chinese Taipei, and mainland China show that GSTM1 genetic polymorphisms are associated with the occurrence of ADIH [21, 22]. By contrast, studies in South Korea and one in India arrive at opposite assumptions (23). This study fails to conclude that genetic polymorphisms of GSTA1-69C/T and GSTM3 are associated with the occurrence of anti-TB drug-induced liver injury. This result may be due to the influence of various factors related to anti-TB drug-induced liver injury. Such factors include differences between regions and races or insufficient sample size. Therefore, a large sample and multivariate analysis are needed to determine the association of GSTA1-69C/T and GSTM3 with anti-TB drug-induced liver injury.

UGT is the most important metabolic enzyme for biotransformation of exogenous substances in organisms. UGT2B7 is mainly expressed in the liver and is closely related to drug detoxification and metabolism. Studies showed that high genetic polymorphisms exist in coding and promoter regions of UGT2B7. These polymorphisms serve as important basis for determining genetic susceptibility among individuals. We noted that genetic polymorphisms at UGT2B7-268 and 802 loci were significantly associated with the occurrence of anti-TB drug-induced liver injury [23, 24]. Risk of anti-TB drug-induced liver injury for carriers with mutant heterozygous AG at UGT2B7 gene -268 locus and mutant homozygous TT at 802 locus was significantly lower than that for wild-type carriers.

In recent years, studies suggested that the occurrence of diseases involves a combination of genetic polymorphisms at multiple loci. Therefore, gene-gene interactions exist. In 2001, Ritchie et al. introduced MDR to analyze the interaction model between susceptible genes [25]. This method mainly evaluates the intensity of interaction factor by cross-validation and displacement test. Then, the optimal multivariate joint model is selected in accordance with the balance test error of 1/10 of test sample, results of sign test, and accuracy of cross-validation. The optimal MDR joint model obtained in this study is the interaction model of UGT2B7-268A/G, CYP3A4*18B-20232G/A, and CYP3A5*3-6986A/G. Moreover, this research is the first to study the correlation between interactions of the abovementioned genes (loci) and anti-TB drug-induced liver injury in Chinese Han population with TB.

In conclusion, the study of seven genes at eight loci confirmed that carrying CYP3A4*18B-20232G/A, UGT2B7-268A/G, and UGT2B7 802C/T wild-type genotypes and mutant genotypes at CYP3A5*3-6986A/G heightens the

risk of developing ADIH for TB patients receiving anti-TB chemotherapy.

Acknowledgements

This study was supported by National Natural Science Foundation of China (No.: 81041096).

Disclosure of conflict of interest

None.

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