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ORIGINAL RESEARCH ARTICLE

Genetic Polymorphisms of *SLCO1B1*, *CYP2E1* and *UGT1A1* and Susceptibility to Anti-Tuberculosis Drug-Induced Hepatotoxicity: A Chinese Population-Based Prospective Case–Control Study

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Abstract

Background Drug transporters and drug-metabolizing enzymes have been linked to drug-induced hepatotoxicity. Solute carrier organic anion transporter family member 1B1 (*SLCO1B1*), cytochrome P450 2E1 (*CYP2E1*), and UDP glucuronosyltransferase 1A1 (*UGT1A1*) were selected as candidate genes to explore their association with susceptibility to anti-tuberculosis drug-induced hepatotoxicity (ATDH).

Methods Thirty-four tag single nucleotide polymorphisms (tagSNPs) in *SLCO1B1*, *CYP2E1,* and *UGT1A1* with 10-kb expansion up- and down-stream were genotyped in 461 patients with ATDH and 466 patients without ATDH in a prospective 1:1 matched case–control study. The frequencies and distributions of genotypes and haplotypes were compared between the groups using three genetic models (dominant, recessive, and additive) to identify associations with susceptibility to ATDH.

Results Patients with the rs4149034 G/A, rs1564370 G/C, and rs2900478 T/A genotypes of *SLCO1B1* had a significantly lower risk of ATDH, while those carrying the rs2417957 T/T and rs4149063 T/T genotypes had an increased risk. The rs4148323 A/A genotype of *UGT1A1* was found to significantly reduce the risk of ATDH. Haplotype analysis showed the TGTG, TTTC, and GTTC haplotypes of *SLCO1B1* were associated with an increased ATDH risk, whereas the GACC haplotype was related to a reduced risk. The ATG haplotype of *UGT1A1* reduced the risk of ATDH. Moreover, treatment outcomes in tuberculosis patients were further affected by genetic variants of *SLCO1B1*.

Conclusions Genetic polymorphisms of *SLCO1B1* and *UGT1A1* were found to be associated with susceptibility to ATDH. Molecular identification of susceptibility genes provides a theoretical foundation for predicting the likelihood of ATDH and predicting treatment outcomes in tuberculosis patients.

Key Point

This Chinese population-based prospective case–control study revealed significant associations between genetic polymorphisms of *SLCO1B1* and *UGT1A1* genes and susceptibility to anti-tuberculosis drug-induced hepatotoxicity.

The genetic variants of *SLCO1B1* gene have influences on the treatment outcomes in TB patients.

1 Introduction

China has the third largest burden of tuberculosis (TB) in the world with 78.8–106.0 million newly diagnosed TB patients estimated in 2015, contributing to an incidence of 8.83% worldwide [1]. Chemotherapy of TB is critical, but TB drugs are frequently associated with serious adverse

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reactions, such as anti-TB drug-induced hepatotoxicity (ATDH). Our preliminary cohort study discovered that the incidence of ATDH in hospitalized patients treated with first-line anti-TB drugs was approximately 12.9%, leading to decreases in the sputum conversion rate, and closure rate of the lung cavities, and then further significantly increasing the rate of treatment failure [2]. Meanwhile, drug-induced liver injury (DILI) if unresolved for over 1 year will transform into chronic DILI, causing a small group of patients to suffer severe adverse consequences such as early-stage liver cirrhosis and acute liver failure and even to require liver transplantation [3, 4].

The underlying causes of ATDH are multifactorial. Our previous study identified several independent risk factors for ATDH including both HBsAg- and HBeAg-positive hepatitis B, systemic lupus erythematosus (SLE), plasma albumin $\leq$25 g/L, and chronic alcohol abuse. The clinical risk of hepatotoxicity in patients with one or more of these factors was significantly higher after treatment with first-line anti-TB drugs [2], which was consistent with the findings of additional studies [3, 5–8]. Meanwhile, accumulating evidence shows that differences in the adverse effects of anti-TB drugs among individuals and between different races are mainly determined by genetic factors. It has been shown that genetic variants of drug transporters [9, 10] and drug-metabolizing enzymes [11–15] can cause changes in the functions of related substrates, thus affecting drug absorption, distribution, and metabolism in vivo. However, there has been a lack of consistency in the findings for ATDH-susceptible genes even in the studies comparing patients from the same ethnic group due to the following limitations in study design: (1) the numbers of samples in previous studies, in particular, the number in the case group, have been very small, often only a few dozen. A large sample pool is one of the most critical factors in gene single nucleotide polymorphism (SNP) and phenotypic association studies. Theoretically, the results are more reliable with more case data. However, it is apparently difficult to obtain sufficient sample sizes because the incidence of ATDH in clinical practice is low [16]. (2) Only a few SNP loci were included in previous studies, which often selected repeats of a single or a few SNP loci that could not cover a majority of the target gene.

In the present study, the transport protein solute carrier organic anion transporter family member 1B1 (*SLCO1B1*), Phase I DME cytochrome P450 2E1 (*CYP2E1*), and Phase II DME UDP glucuronosyltransferase 1A1 (*UGT1A1*) were selected as candidate genes. A tagSNP is a representative SNP in a region of the genome with high linkage disequilibrium, which enables the full haplotype information to be sufficiently captured by a small fraction of tagSNPs without genotyping every SNP in a chromosomal region. The tagSNP strategy has been proven to be an effective and valuable tool in the study of genetic polymorphisms, with similar power as haplotype data [17]. In the present study, we genotyped all tagSNPs screened from the target candidate genes using bioinformatic tools to identify associations with susceptibility to ATDH and further to determine the effects of positive SNPs on the prognosis of TB patients in a Chinese Han population.

2 Methods

2.1 Ethical Approval

The present study was approved by the Ethics Committees of both Tongji University School of Medicine and Shanghai Pulmonary Hospital. Written informed consent was received from patients.

2.2 Study Design and Case Population

The TB patients enrolled in this prospective one-to-one matched case–control study were aged from 18 to 65 years, receiving directly observed treatment short-course, and hospitalized at Shanghai Pulmonary Hospital between March 2012 and August 2015. Patients with ATDH after anti-TB therapy served as case group and patients without ATDH served as control group. Patients in the control group were selected and matched with patients in the case group by age ($\pm$3 years) and gender. A standard integrated initial therapy with 2–3 months of isoniazid (5 mg/kg), rifampicin (10 mg/kg), ethambutol (15 mg/kg), and pyrazinamide (25 mg/kg) was initiated for all patients, followed by a consolidated treatment with isoniazid, rifampicin, and ethambutol according to the guideline of the Chinese Medical Association. The exclusion criteria were as follows: (1) presence of any basic hepatic diseases such as viral hepatitis, hepatic adipose infiltration, cirrhosis, autoimmune liver disease, and alcoholic liver disease, etc.; (2) had liver dysfunction before anti-TB therapy initiation; (3) confirmed liver injury induced by another drug or unknown cause; (4) having received non-standard treatment regimen initially; (5) drug resistance found in the initial antimicrobial susceptibility test, identification of non-tuberculous mycobacteria, or development of non-liver-related side effects.

During the treatment of TB, patients underwent routine blood examination, and the hepatic enzymes as well as bilirubin levels were evaluated every month. ATDH was diagnosed according to the modified criteria for DILI [18, 19] and the standard diagnostic criteria established by the Chinese Medical Association. The Council for International Organizations of Medical Science (CIOMS)/Roussel Uclaf Causality Assessment Method (RUCAM)

scale was used in causality assessment of liver damage [20]. Briefly, ATDH was defined as: (1) increased serum alanine aminotransferase (ALT) that was greater than 5× the upper limit of normal (ULN) or an alkaline phosphatase (ALP) level greater than 2× ULN; or serum ALT level was more than 3× ULN combined with a total bilirubin (TBIL) level greater than 2× ULN; and (2) a total score on the CIOMS/RUCAM scale of more than 8 points [20].

2.3 Bioinformatic Statistics of tagSNPs Screened from SLCO1B1, CYP2E1 and UGT1A1 Genes

The candidate genes *SLCO1B1*, *CYP2E1* and *UGT1A1* were loaded into the International HapMap Project SNP database (HapMap Data Rel 28 Phase II + III, August 10, on NIBI B36 assembly, dbSNP b126) for screening of SNPs within expansions 10 kb up- and down-stream of the gene region. All the tagSNPs obtained were then introduced into HaploView software version 4.2 (Broad Institute, Cambridge, MA, USA) with criteria for locus quality control as follows: p value for Hardy–Weinberg equilibrium (HWE-p) >0.001, minor genotype >0.75, minor allele frequency >0.1, and $r^2 > 0.8$. Finally, a total of 34 tagSNPs were selected, including 21 from *SLCO1B1*, 9 from *CYP2E1*, and 4 from *UGT1A1* (Table 1).

2.4 DNA Isolation and Genotyping

A whole blood sample was collected from each patient for genomic DNA extraction. DNA was extracted using the QIAGEN DNeasy Blood and Tissue Kit (Qiagen GmbH, Germany) with the standard protocol given in the manufacturer's instructions, and genotyped using a custom-by-design 48-Plex SNPscan^{TM} Kit (Cat#: G0104; Genesky Biotechnologies Inc., Shanghai, China). Briefly, a sample of 100–200 ng DNA was first denatured at 98 °C for 5 min in a 10-μL reaction containing 1 × DNA lysis buffer and then mixed well with 10 μL ligation mix composed of 2 μL 10 × ligase buffer, 0.5 μL ligase, 1 μL probe mixture, and 6.5 μL Milli-Q water. The ligation reaction was carried out in an ABI2720 thermal cycler with the following program: 98 °C for 2 min, 5 cycles at 95 °C for 30 sec and 58 °C for 3 h, 94 °C for 2 min, and finishing at 72 °C. Two 48-plex fluorescence polymerase chain reactions (PCRs) were performed for each ligation product. PCRs were prepared in a 20-μL mixture containing 2 μL 10× Takara PCR buffer, 2.4 μL dNTP mix (2.5 mM), 0.8 μL $MgCl_2$ (25 mM), 0.3 μL primer mix set A or set B, 0.8 U Taq polymerase, and 1 μL ligation product. PCR products were separated and detected by capillary electrophoresis in an ABI3730XL sequencer. Raw data were analyzed according to the information obtained for the labeling dye color and fragment size of the allele-specific ligation-PCR product. Genotyping was conducted with blinding of the case or control status. Repeated genotyping was performed with the same assay in a random selection of 4% of samples to ensure the data quality.

2.5 Follow-up of Treatment Outcomes

All patients were followed up for at least 3 months after completion of anti-TB therapy. The effects of different genotypes of susceptible SNPs we discovered on the prognosis of TB patients were analyzed according to the treatment failure rate and sputum conversion rate. An unsuccessful outcome was defined as death or therapeutic failure, including persistent or relapsed positive sputum smear/culture, development of drug resistance, or exacerbation of lesions during the initial therapy.

2.6 Statistical Analysis

The observed and expected gene frequencies as well as the HWE-p values were estimated using GENEPOP. The distributions of each SNP genotype in the case group and control group were analyzed using binary logistic regression, and odds ratios (ORs); 95% confidence intervals (CIs) were estimated with SPSS 16.0 software (SPSS Inc., Chicago, IL, USA). The frequencies of alleles and genotypes in the two groups were compared using three different genetic models: dominant, recessive, and additive. The linkage disequilibrium profiles of SNPs were mapped using Haploview software version 4.2 (Broad Institute, Cambridge, MA, USA). The differences in the frequencies of haplotypes between the two groups were analyzed by calculating ORs and 95% CIs. The treatment failure rates of patients with different genotypes of susceptible SNPs were compared by chi-square test (χ^2). The sputum conversion rate of patients over time in the different groups was plotted using the Kaplan–Meier method and compared by the Log-Rank test. A two-tailed p value <0.05 was considered statistically significant.

3 Results

3.1 Patient Characteristics

A total of 927 study patients successfully completed peripheral blood sampling for DNA extraction and genotyping and follow-up. The case group contained 461 patients in total with an average age of 38.2 ± 13.7 years, among whom 283 were male and 178 were female. The control group consisted of 466 patients with an average age of 38.9 ± 13.5 years, among whom 287 were male and 179 were female.

Table 1 Information of 34 tagSNPs genotyped from the candidate genes *SLCO1B1*, *CYP2E1* and *UGT1A1*

Gene (chromosome)	Reference SNP ID	Chromosome position	Region	HWE-P	MAF	Alleles
SLCO1B1 (12p)	rs327543	21275451	5′-flanking	0.342	0.128	C:A
	rs852549	21281889	5′-flanking	0.322	0.128	G:T
	rs4149022	21295612	intron2	1.000	0.441	C:T
	rs12580258	21305153	intron2	0.414	0.317	A:G
	rs4149023	21309457	intron2	0.160	0.135	G:T
	rs16923519	21311718	intron2	0.199	0.430	G:A
	rs11045802	21312320	intron2	0.386	0.126	T:G
	rs7138177	21312924	intron2	0.187	0.128	A:G
	rs976754	21315522	intron2	0.805	0.371	A:G
	rs4149028	21315952	intron2	0.730	0.290	T:C
	rs4149034	21317922	intron2	0.115	0.418	A:G
	rs2417957	21323611	intron2	0.999	0.277	C:T
	rs4149045	21330020	intron5	0.560	0.520	A:G
	rs4149047	21330338	intron5	1.000	0.037	C:T
	rs4149050	21330988	intron5	0.508	0.481	C:T
	rs1564370	21335190	intron7	0.939	0.236	C:G
	rs4149063	21350790	intron8	0.466	0.304	G:T
	rs2900478	21368797	intron11	0.926	0.116	T:A
	rs11513225	21386843	intron14	0.694	0.428	C:T
	rs12578392	21389970	intron14	0.414	0.261	C:T
	rs4149085	21392290	3′-UTR	0.976	0.311	T:C
CYP2E1 (10q)	rs10857736	135336514	5′-flanking	0.223	0.412	A:G
	rs3813867	135339605	5′-flanking	0.342	0.227	G:C
	rs915906	135343738	intron2	0.843	0.202	T:C
	rs8192773	135345974	intron4	0.638	0.041	T:C
	rs915908	135346959	intron5	0.277	0.163	G:A
	rs4646976	135347727	intron6	0.979	0.154	A:G
	rs743535	135349367	intron6	0.444	0.266	G:A
	rs2249695	135352168	intron8	0.888	0.395	C:T
	rs1952467	135353499	3′-flanking	0.230	0.417	G:T
	rs4240522	135355557	3′-flanking	0.230	0.417	T: C
UGT1A1 (2q)	rs4148323	234669144	nonsynon_exon1	0.073	0.216	G:A
	rs4148326	234673462	intron1	0.610	0.302	T:C
	rs12479045	234673588	intron1	0.035	0.175	G:C
	rs4148328	234677659	intron4	0.165	0.385	T:C

HWE Hardy–Weinberg equilibrium, *MAF* minor allele frequency, *SNP* single nucleotide polymorphism, *SLCO1B*: solute carrier organic anion transporter family member 1B1, *CYP2E1* cytochrome P450 2E1, *UGT1A1* UDP glucuronosyltransferase 1A1

3.2 Associations of SLCO1B1, CYP2E1, and UGT1A1 Polymorphisms with Susceptibility to ATDH

The allele frequency at each locus was in HWE (Table 1). Five tagSNPs from *SLCO1B1* were detected to be closely related to ATDH susceptibility. Patients with the rs4149034 G/A (OR 0.642, $p = 0.003$), rs1564370 G/C (OR 0.736, $p = 0.029$), and rs2900478 T/A (OR 0.652, $p = 0.012$) genotypes had a significantly lower risk of ATDH, whereas patients carrying the rs2417957 T/T (OR 2.197, $p = 0.002$) and rs4149063 T/T (OR 1.704, $p = 0.032$) genotypes had an increased risk of developing ATDH. In the Dom model, both rs4149034 G/A + G/G (OR 0.728, $p = 0.023$) and rs2900478 T/T + A/A (OR 0.667, $p = 0.014$) genotypes were associated with a decreased risk of ATDH. In the Rec model, the rs2417957 T/T genotype (OR 2.067, $p = 0.003$) was found to increase

the risk of ATDH. In the Add model, alleles of rs2417957 minor T (OR 1.328, $p = 0.006$) and rs4149063 minor T (OR 1.256, $p = 0.023$) were associated with an increased risk of ATDH, whereas the rs2900478 minor A allele (OR 0.712, $p = 0.025$) was related to a reduced risk of ATDH.

The *UGT1A1* gene rs4148323 A/A genotype was found to significantly reduce the risk of ATDH (OR 0.371, $p = 0.020$). The rs4148323 A/A genotype (OR 0.394, $p = 0.023$) in the Rec model and the minor A allele (OR 0.791, $p = 0.040$) in the Add model were significantly associated with a reduced risk of ATDH. No association was observed between any tagSNP of *CYP2E1* and susceptibility of ATDH (Tables 2, 3).

3.3 Associations of Haplotypes of SLCO1B1, CYP2E1, and UGT1A1 Genes with Susceptibility to ATDH

The linkage disequilibrium distributions of 21 loci of *SLCO1B1*, 10 loci of *CYP2E1,* and 4 loci of *UGT1A1* are shown in Fig. 1. Twenty-one loci of *SLCO1B1* were divided into three linkage disequilibrium blocks, with eight SNPs (rs327543, rs852549, rs4149022, rs12580258, rs4149023, rs16923519, rs11045802, and rs7138177) grouped in Block 1, 4 SNPs (rs2417957, rs4149045, rs4149050, and rs1564370) grouped in Block 2, and 4 SNPs (rs4149063, rs2900478, rs11513225, and rs12578392) grouped in Block 3. Ten loci of *CYP2E1* were divided into two linkage disequilibrium blocks, 2 SNPs (rs10857736 and rs3813867) in Block 1 and 6 SNPs (rs915908, rs4646976, rs743535, rs2249695, rs1952467, and rs4240522) in Block 2. Three loci of *UGT1A1*, rs4148323, rs4148326, and rs12479045, were centered in one block.

Haplotypes were assigned according to linkage disequilibrium distribution, and relative distribution frequencies of haplotypes in the case and control groups were analyzed. Four haplotypes of *SLCO1B1* were associated with ATDH susceptibility, and among them TGTG (OR 1.286, $p = 0.015$), TTTC (OR 1.260, $p = 0.022$), and GTTC (OR 2.249, $p = 0.03$) were discovered to increase the risk of ATDH, while GACC (OR 0.708, $p = 0.023$) reduced the risk. Haplotype ATG (OR 0.793, $p = 0.045$) of *UGT1A1* was found to potentially decrease the risk of ATDH. None of the haplotypes of *CYP2E1* was found to be associated with ATDH (Table 4).

3.4 Impact of SLCO1B1, CYP2E1, and UGT1A1 Variants on Treatment Outcomes in TB Patients

In the present study, 91 of 927 cases (9.8%) were labeled as unsuccessful treatment. The treatment failure rate of patients carrying the *SLCO1B1* rs4149034 G/A genotype (7.8%; 36/462) was significantly lower (OR 0.630, $p = 0.039$) than that of patients carrying the A/A + G/G genotypes (11.8%; 55/465). No additional SNP genotype was found to be significantly associated with the treatment failure rate.

Of the 927 cases, 447 patients had positive sputum smear/culture results, and among them 27 (6.04%) remained positive through the end of post-therapy follow-up. The sputum conversion rate and median time in carriers of the *SLCO1B1* rs4149034 G/A genotype were 95.3% (203/213) and 1.5 months (95% CI 1.336–1.664 months), and these values were significantly higher (Log rank $p = 0.033$) than the 92.7% (217/234) and 2.0 months (95% CI 1.799–2.201 months) for those carrying A/A + G/G genotypes (Fig. 2). Moreover, a sputum conversion rate of 90.7% (39/43) among patients carrying the *SLCO1B1* rs2147957 T/T genotype with a median time of 2.5 months (95% CI 1.795–3.205 months) was significantly lower (Log rank $p = 0.026$) than the sputum convesion rate of 94.3% (381/404) among those carrying C/C + T/C genotypes, for whom the median time was 1.5 months (95% CI 1.350–1.650 months; Fig. 3). No other individual SNPs were found to be associated with the sputum conversion rate in TB patients.

4 Discussion

In this present study, we screened and selected all tagSNPs spanning *SLCO1B1*, *CYP2E1,* and *UGT1A1* with 10-kb expansion up- and down-stream by bioinformatic statistical methods and genotyped 927 samples from a Chinese Han population in a prospective 1:1 matched case–control study. We further analyzed the impact of different genotypes of susceptible SNPs on treatment outcomes in TB patients and demonstrated remarkably significant associations of gene polymorphisms of *SLCO1B1* and *UGT1A1* with ATDH susceptibility and the further effects of variants of *SLCO1B1* on treatment outcomes in Chinese TB patients.

Organic anion-transporting polypeptides (OATPs) belong to a large group of uptake membrane transporters from the solute carrier family (SLC). In addition to transport of bile acid and other endogenous substances, OATPs are also involved in transporting of a variety of exogenous substances, particularly drugs, playing a key role in drug absorption, distribution, and elimination [9, 10, 21]. OATP1B1 is an important member of the OATP family, specifically present in the basolateral membrane of hepatocytes. It is currently known that a variety of drugs, including methotrexate, sorafenib, statins, rifampicin and rifabutin among the first-line anti-TB drugs, can be absorbed and transported from the hepatic portal system

Table 2 Frequencies of SNP genotypes of *SLCO1B1*, *CYP2E1* and *UGT1A1* genes in patients with and without ATDH

Gene	tagSNPs Major > minor	Genotype	ATDH $n = 461$		Non-ATDH $n = 466$		OR (95% CI)	p value*
			n	%	n	%		
SLCO1B1	rs327543	C/C	343	74.4	356	76.4	1	
	C>A	C/A	110	32.1	106	22.7	1.077 (0.794–1.461)	0.634
		A/A	8	2.3	4	0.9	2.076 (0.619–6.957)	0.237
	rs852549	G/G	345	74.8	353	75.8	1	
	G>T	T/G	108	23.4	109	23.4	1.014 (0.748–1.375)	0.930
		T/T	8	1.7	4	0.9	2.046 (0.611–2.858)	0.246
	rs4149022	G/G	151	32.8	139	30.2	1	
	G>A	G/A	219	47.5	242	51.9	0.833(0.621–1.118)	0.223
		A/A	91	19.7	85	18.2	0.986 (0.677–1.434)	0.939
	rs12580258	T/T	229	49.7	208	44.6	1	
	T>G	T/G	187	40.6	221	47.4	0.769(0.586–1.007)	0.056
		G/G	45	9.8	37	7.9	1.105 (0.688–1.774)	0.680
	rs4149023	G/G	341	74.0	343	73.6	1	
	G>T	T/G	114	24.7	118	25.3	0.972 (0.721–1.309)	0.851
		T/T	6	1.3	5	1.1	1.207 (0.365–3.992)	0.758
	rs16923519	G/G	141	30.6	143	30.7	1	
	G>A	G/A	233	50.5	246	52.8	0.961 (0.716–1.288)	0.788
		A/A	87	18.9	77	16.5	1.146 (0.780–1.684)	0.488
	rs11045802	T/T	345	74.8	353	75.8	1	
	T>G	T/G	112	24.3	108	23.2	1.061 (0.784–1.437)	0.701
		G/G	4	0.9	5	1.1	0.819 (0.218–3.074)	0.767
	rs7138177	A/A	347	75.3	353	75.8	1	
	A>G	G/A	108	23.4	109	23.4	1.008 (0.743–1.367)	0.959
		G/G	6	1.3	4	0.9	1.526 (0.427–5.454)	0.516
	rs976754	A/A	200	43.4	178	38.2	1	
	A>G	G/A	195	42.3	227	48.7	0.765(0.579–1.010)	0.059
		G/G	66	14.3	61	13.1	0.963 (0.644–1.440)	0.854
	rs4149028	T/T	245	67.5	233	50.0	1	
	T>C	T/C	168	36.4	198	42.5	0.807 (0.614–1.060)	0.123
		C/C	48	10.4	35	7.5	1.304(0.814–2.089)	0.269
	rs4149034	A/A	171	37.1	140	30.0	1	
	A>G	G/A	203	44.0	259	55.6	0.642 (0.481–0.857)	**0.003**
		G/G	87	18.9	67	14.4	1.063 (0.720–1.569)	0.758
	rs2417957	C/C	220	47.7	251	53.9	1	
	C>T	T/C	189	41.0	188	40.3	1.147 (0.875–1.504)	0.322
		T/T	52	11.3	27	5.8	2.197 (1.334–3.619)	**0.002**
	rs4149045	G/G	134	29.1	124	26.6	1	
	G>A	G/A	231	50.1	228	48.9	0.938 (0.691–1.272)	0.679
		A/A	96	20.8	114	24.5	0.779 (0.541–1.123)	0.181
	rs4149047	C/C	427	92.6	432	92.7	1	
	C>T	T/C	31	6.7	32	6.9	0.980 (0.588–1.635)	0.939
		T/T	3	0.7	2	0.4	1.518 (0.252–9.128)	0.649

Table 2 continued

Gene	tagSNPs Major > minor	Genotype	ATDH $n = 461$		Non-ATDH $n = 466$		OR (95% CI)	p value*
			n	%	n	%		
	rs4149050	T/T	136	29.5	124	26.6	1	
	T>C	T/C	233	50.5	225	48.3	0.944 (0.696–1.280)	0.712
		C/C	92	20.0	117	25.1	0.717 (0.497–1.034)	0.075
	rs1564370	C/C	284	61.6	262	56.2	1	
	C>G	G/C	146	31.7	183	39.3	0.736 (0.559–0.969)	**0.029**
		G/G	31	73.8	21	4.5	1.362 (0.763–2.429)	0.296
	rs4149063	G/G	200	43.4	232	49.8	1	
	G>T	T/G	214	46.4	202	43.3	1.229 (0.938–1.609)	0.134
		T/T	47	10.2	32	50.2	1.704 (1.046–2.774)	**0.032**
	rs2900478	T/T	383	83.1	357	76.6	1	
	T>A	T/A	72	15.6	103	22.1	0.652 (0.467–0.910)	**0.012**
		A/A	6	1.3	6	1.3	0.932 (0.298–2.917)	0.904
	rs11513225	T/T	159	34.5	150	33.5	1	
	T>C	T/C	232	50.3	223	47.9	0.981 (0.735–1.310)	0.899
		C/C	70	15.2	93	20.0	0.710 (0.485–1.040)	0.079
	rs12578392	C/C	267	57.9	250	53.6	1	
	C>T	T/C	163	35.4	182	39.1	0.839 (0.638–1.102)	0.206
		T/T	31	42.1	34	7.3	0.854 (0.509–1.431)	0.548
	rs4149085	T/T	205	44.5	224	48.1	1	
	T>C	T/C	214	46.4	196	42.1	1.193 (0.910–1.564)	0.202
		C/C	42	55.5	46	9.9	0.998 (0.630–1.579)	0.992
CYP2E1	rs10857736	A/A	154	33.4	151	32.4	1	
	A>G	G/A	241	52.3	235	50.4	1.006 (0.754–1.341)	0.970
		G/G	66	14.3	80	17.2	0.809 (0.545–1.202)	0.294
	rs3813867	G/G	286	62.0	263	56.5	1	
	G>C	G/C	160	34.7	180	38.6	0.817 (0.623–1.072)	0.145
		C/C	15	3.3	23	4.9	0.600 (0.306–1.174)	0.136
	rs915906	T/T	271	58.8	299	64.2	1	
	T>C	T/C	166	36.0	147	31.5	1.246 (0.945–1.642)	0.119
		C/C	24	5.2	20	4.3	1.324 (0.715–2.451)	0.372
	rs8192773	T/T	417	90.5	431	92.5	1	
	T>G	T/G	42	9.1	34	7.3	1.277 (0.797–2.046)	0.310
		G/G	2	0.4	1	0.2	2.067 (0.187–22.883)	0.554
	rs915908	G/G	310	67.2	327	70.2	1	
	G>A	G/A	135	29.3	131	28.1	1.087 (0.816–1.447)	0.568
		A/A	16	3.5	8	1.7	2.110 (0.890–4.999)	0.090
	rs4646976	A/A	321	69.6	331	71.0	1	
	A>G	G/A	134	29.1	122	26.2	1.133 (0.848–1.513)	0.399
		G/G	6	1.3	13	2.8	0.476 (0.179–1.267)	0.137
	rs743535	G/G	253	54.9	239	51.3	1	
	G>A	G/A	185	40.1	194	41.6	0.901 (0.689–1.178)	0.445
		A/A	23	5.0	33	7.1	0.658 (0.376–1.154)	0.144

Table 2 continued

Gene	tagSNPs Major > minor	Genotype	ATDH $n = 461$		Non-ATDH $n = 466$		OR (95% CI)	p value*
			n	%	n	%		
	rs2249695	C/C	166	36.0	168	36.1	1	
	C>T	T/C	223	48.4	221	47.4	1.021 (0.769–1.357)	0.885
		T/T	72	51.6	77	16.5	0.946 (0.643–1.393)	0.780
	rs1952467	G/G	152	33.0	148	31.8	1	
	G>T	T/G	235	51.0	239	51.3	0.957 (0.717–1.278)	0.768
		T/T	74	16.0	79	16.9	0.912(0.618–1.347)	0.643
	rs4240522	T/T	156	33.8	153	32.8	1	
	T>C	T/C	231	50.1	235	50.4	0.964 (0.723–1.285)	0.803
		C/C	74	16.1	78	16.8	0.930 (0.631–1.372)	0.716
UGT1A1	**rs4148323**	G/G	294	63.8	273	58.6	1	
	G>A	G/A	159	34.5	173	37.1	0.853 (0.651–1.119)	0.252
		A/A	8	1.7	20	4.3	0.371 (0.161–0.857)	**0.020**
	rs4148326	T/T	220	47.7	227	48.7	1	
	T>C	T/C	188	40.8	197	42.3	0.958 (0.750–1.293)	0.912
		C/C	53	11.5	42	9.0	1.302 (0.834–2.033)	0.245
	rs12479045	G/G	306	66.4	331	71.0	1	
	G>C	G/C	137	29.7	114	24.5	1.300 (0.970–1.743)	0.079
		C/C	18	3.9	21	4.5	0.927 (0.485–1.773)	0.819
	rs4148328	T/T	157	34.1	178	38.2	1	
	T>C	T/C	233	50.5	231	49.4	1.144 (0.863–1.515)	0.350
		C/C	71	15.4	57	12.4	1.412 (0.938–2.127)	0.098

ATDH anti-tuberculosis drug-induced hepatotoxicity, *SNP* single nucleotide polymorphism, *SLCO1B1* solute carrier organic anion transporter family member 1B1, *CYP2E1* cytochrome P450 2E1, *UGT1A1* UDP glucuronosyltransferase 1A1, *CI* confidence interval

* p values less than 0.05 were shown in bold type

into the liver cells as a substrate for OATP1B1 to be metabolized and eliminated [21–23]. Therefore, the expression and transport function of OATP1B1 in the liver tissue potentially influence the drug concentration in blood, bioavailability, and side effects. OATP1B1 is encoded by *SLCO1B1* on chromosome 12p. Our study revealed that the risk of ATDH was reduced by genotypes of *SLCO1B1* including rs4149034 G/A, rs1564370 G/C, and rs2900478 T/A, but increased significantly by the rs2147957 T/T and rs4149063 T/T genotypes by up to 2.197- and 1.704-fold, respectively. Although the mechanisms by which different SNP genotypes of *SLCO1B1* alter the risk of ATDH remain unknown, it has already been made clear that rifampicin is a substrate for OATP1B1 that is transported into liver cells for metabolism. As an important anti-TB drug with known hepatotoxicity, rifampicin is also a powerful catalyst that induces a variety of metabolizing enzymes such as cytochrome P450 in the liver. When co-administered with drugs including isoniazid and pyrazinamide, rifampicin will react with intermediate metabolites from the drugs in synergistic action, leading to increased toxicity and damage of liver cells [24]. Weiner et al. [22] found that the *SLCO1B1* c.463 C>A gene polymorphism resulted in a lower rifampicin concentration in blood. Thus, we conclude that different genotypes may result in upregulation or downregulation of *SLCO1B1*, leading to functional changes in OATP1B1 binding and transporting of drugs and therefore altering the blood concentrations and metabolite levels of anti-TB drugs. Decreased expression of *SLCO1B1* may result in the reduced transport capacity of OATP1B1, leading to weakened clearance of rifampicin and its toxic metabolites and thereby causing hepatic injury. Further studies should be conducted to investigate how the variants of the loci affect the transport function of OATP1B1 and the corresponding changes in the concentrations of anti-TB drugs and metabolites that lead to hepatic injury.

The CYP enzyme system is one of the most important Phase I-metabolizing enzymes, metabolizing about 60–70% of clinical drugs. CYP2E1 coded by gene *CYP2E1* on chromosome 10q, is a member of the CYP450 family mainly distributed in the liver. Whether genetic polymorphisms of *CYP2E1* are related to ATDH susceptibility is still controversial. Singla et al. [15] reported that the heterozygous genotype of c1/c2 of *CYP2E1*5B* was associated with ATDH susceptibility (OR 7.47, 95% CI 1.263–34.32, $p = 0.04$, $n = 17$), and Bose [25] found that

Table 3 Comparison of allele and genotype distributions and frequencies in three genetic models between case and control group

Gene	tagSNPs	Dominant model		Recessive model		Additive model	
		OR (95% CI)	*p* value*	OR (95% CI)	*p* value*	OR (95% CI)	*p* value*
SLCO1B1	rs327543	1.113 (0.826–1.502)	0.481	2.040 (0.610–6.821)	0.238	1.136(0.866–1.490)	0.358
	rs852549	1.050 (0.779–1.416)	0.747	2.040 (0.610–6.821)	0.238	1.082(0.826–1.419)	0.567
	rs4149022	0.873 (0.661–1.152)	0.337	1.102 (0.794–1.531)	0.561	0.971(0.809–1.167)	0.757
	rs12580258	0.817 (0.631–1.057)	0.124	1.254 (0.795–1.978)	0.329	0.927(0.761–1.129)	0.453
	rs4149023	0.981 (0.732–1.315)	0.900	1.216 (0.368–4.012)	0.748	0.994 (0.763–1.296)	0.966
	rs16923519	1.005 (0.760–1.328)	0.973	1.175 (0.838–1.648)	0.349	1.051 (0.875–1.263)	0.595
	rs11045802	1.050 (0.779–1.416)	0.747	0.807 (0.215–3.024)	0.750	1.032 (0.786–1.355)	0.820
	rs7138177	1.026 (0.761–1.385)	0.865	1.523 (0.427–5.433)	0.514	1.042 (0.794–1.369)	0.766
	rs976754	0.807 (0.620–1.049)	0.108	1.109 (0.763–1.614)	0.587	0.918 (0.760–1.109)	0.376
	rs4149028	0.882 (0.681–1.141)	0.338	1.431 (0.907–2.258)	0.122	0.994 (0.813–1.216)	0.954
	rs4149034	0.728 (0.554–0.958)	**0.023**	1.385 (0.978–1.963)	0.066	0.949 (0.789–1.141)	0.577
	rs2417957	1.279 (0.988–1.655)	0.062	2.067 (1.274–3.354)	**0.003**	1.328 (1.086–1.625)	**0.006**
	rs4149045	0.885 (0.664–1.179)	0.404	0.812 (0.597–1.106)	0.186	0.885 (0.737–1.062)	0.189
	rs4149047	1.012 (0.617–1.658)	0.963	1.520 (0.253–9.137)	0.685	1.041 (0.652–1.662)	0.868
	rs4149050	0.866 (0.650–1.154)	0.327	0.744 (0.546–1.014)	0.061	0.851 (0.709–1.021)	0.083
	rs1564370	0.800 (0.616–1.040)	0.096	1.528 (0.864–2.700)	0.142	0.915 (0.738–1.135)	0.421
	rs4149063	1.294 (0.999–1.676)	0.051	1.540 (0.963–2.461)	0.070	1.256 (1.031–1.530)	**0.023**
	rs2900478	0.667 (0.482–0.923)	**0.014**	1.011 (0.324–3.158)	0.985	0.712 (0.529–0.959)	**0.025**
	rs11513225	0.902 (0.686–1.185)	0.457	0.718 (0.511–1.010)	0.056	0.865 (0.719–1.040)	0.123
	rs12578392	0.841 (0.649–1.090)	0.191	0.916 (0.553–1.517)	0.733	0.881 (0.715–1.085)	0.233
	rs4149085	1.156 (0.893–1.497)	0.272	0.915 (0.590–1.421)	0.693	1.068 (0.878–1.299)	0.511
CYP2E1	rs10857736	0.956 (0.727–1.257)	0.745	0.806 (0.565–1.150)	0.234	0.924 (0.768–1.111)	0.400
	rs3813867	0.793 (0.610–1.031)	0.083	0.648 (0.334–1.258)	0.197	0.811 (0.651–1.009)	0.060
	rs915906	1.255 (0.963–1.636)	0.092	1.225 (0.667–2.249)	0.513	1.204 (0.965–1.503)	0.100
	rs8192773	1.299 (0.817–2.066)	0.268	2.026 (0.183–22.422)	0.557	1.307 (0.837–2.041)	0.238
	rs915908	1.146 (0.868–1.513)	0.337	2.058 (0.872–4.858)	0.093	1.181 (0.926–1.506)	0.179
	rs4646976	1.069 (0.807–1.418)	0.641	0.460 (0.173–1.220)	0.110	0.997 (0.777–1.279)	0.979
	rs743535	0.866 (0.669–1.121)	0.273	0.689 (0.398–1.193)	0.181	0.864 (0.703–1.062)	0.165
	rs2249695	1.002 (0.766–1.310)	0.989	0.935 (0.658–1.328)	0.707	0.982 (0.816–1.183)	0.850
	rs1952467	0.946 (0.719–1.246)	0.693	0.937 (0.662–1.325)	0.712	0.958 (0.796–1.152)	0.645
	rs4240522	0.928 (0.706–1.220)	0.593	0.951 (0.672–1.347)	0.778	0.953 (0.792–1.146)	0.610
UGT1A1	**rs4148323**	0.803 (0.617–1.047)	0.105	0.394 (0.172–0.903)	**0.023**	0.791 (0.632–0.990)	**0.040**
	rs4148326	1.040 (0.804–1.346)	0.763	1.311 (0.856–2.010)	0.212	1.085 (0.891–1.321)	0.419
	rs12479045	1.242 (0.940–1.640)	0.127	0.861 (0.453–1.638)	0.648	1.149 (0.905–1.458)	0.254
	rs4148328	1.197 (0.915–1.565)	0.189	1.306 (0.898–1.901)	0.162	1.166 (0.968–1.406)	0.106

SLCO1B1 solute carrier organic anion transporter family member 1B1, *CYP2E1* cytochrome P450 2E1, *UGT1A1* UDP glucuronosyltransferase 1A1, *CI* confidence interval

* *p* values less than 0.05 were shown in bold type

the DraI C/D genotype of *CYP2E1* was associated with the occurrence of ATDH (OR 3.22, 95% CI 1.28–8.08, $p = 0.00157$, $n = 41$). Sheng et al. [26] demonstrated an association of the c1/c1 genotype of gene *CYP2E1* with ATDH via meta-analysis. However, several other studies showed no evidence of a relationship between *CYP2E1* and ATDH [12, 13]. In the present study, the frequencies and distributions of certain genotypes and haplotypes of 10 tagSNPs from *CYP2E1* within 10-kb expansion up- and down-stream were verified in a larger sample pool; however, none of the SNPs was found to be associated with ATDH susceptibility.

Uridine 5′-diphospho-glucuronosyl transferase (UGT) is one of the most important Phase II metabolizing enzymes, mainly catalyzing endogenous (bilirubin, steroids, etc.) or exogenous compounds such as drugs and phenols that

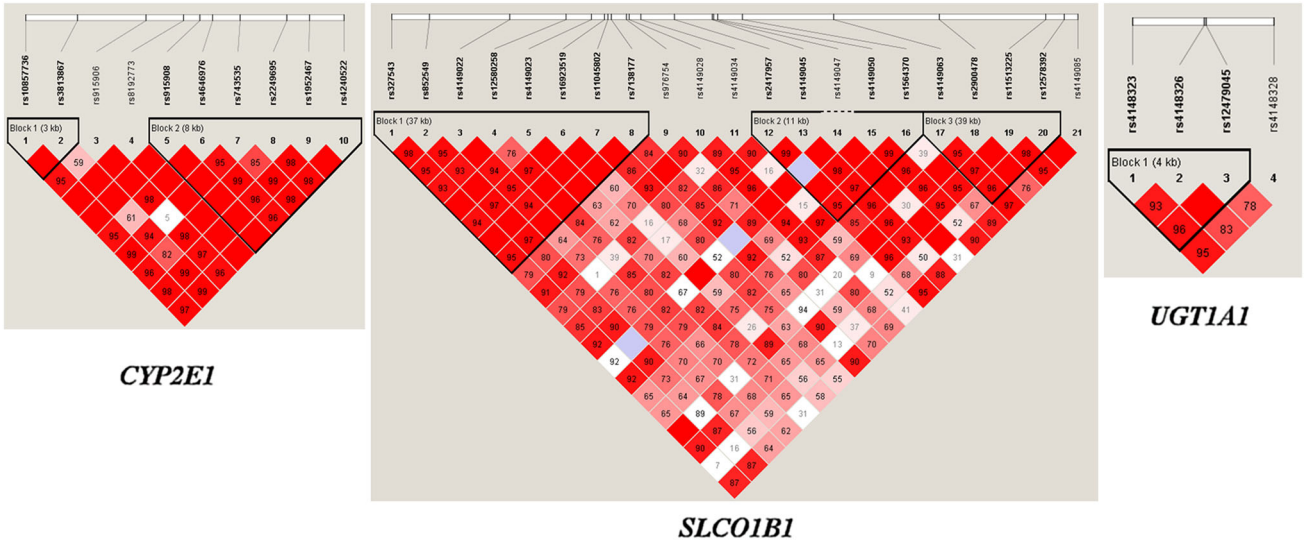

Fig. 1 Linkage disequilibrium structures of SNPs of the candidate genes *SLCO1B1*, *CYP2E1* and *UGT1A1*. *SNP* single nucleotide polymorphism, *SLCO1B1* solute carrier organic anion transporter family member 1B1, *CYP2E1* cytochrome P450 2E1, *UGT1A1* UDP glucuronosyltransferase 1A1

Table 4 Frequencies of haplotypes assigned by SNPs of *SLCO1B1*, *CYP2E1* and *UGT1A1* genes in patients with and without ATDH

Gene	SNPs constituted	Haplotypes	Frequencies		OR (95% CI)	*p* value*
			ATDH	Non-ATDH		
SLCO1B1	rs327543, rs852549, rs4149022, rs12580258, rs4149023, rs16923519, rs11045802, rs7138177	CGGTGATA	0.426	0.422	1.014 (0.843–1.220)	0.897
		CGAGGGTA	0.282	0.303	0.905 (0.740–1.106)	0.329
		CGATTGGA	0.127	0.123	1.033 (0.783–1.361)	0.819
		ATGTGGTG	0.124	0.121	1.033 (0.782–1.365)	0.819
	rs2417957, rs4149045, rs4149050, rs1564370	CACC	0.449	0.486	0.862 (0.718–1.035)	0.111
		TGTC	0.309	0.259	1.286 (1.050–1.575)	**0.015**
		CGTG	0.218	0.238	0.895 (0.720–1.112)	0.315
	rs4149063, rs2900478, rs11513225, rs12578392	GTCC	0.308	0.312	0.982 (0.807–1.196)	0.860
		TTTC	0.332	0.283	1.260 (1.034–1.535)	**0.022**
		GTTT	0.242	0.265	0.887 (0.719–1.094)	0.262
		GACC	0.090	0.123	0.708 (0.525–0.955)	**0.023**
		GTTC	0.024	0.011	2.249 (1.059–4.776)	**0.030**
CYP2E1	rs10857736, rs3813867	AG	0.594	0.576	1.078 (0.896–1.297)	0.427
		GC	0.205	0.242	0.805 (0.647–1.003)	0.053
		GG	0.201	0.181	1.133 (0.899–1.429)	0.290
	rs915908, rs4646976, rs743535, rs2249695, rs1952467, rs4240522	GAGCGT	0.403	0.422	0.924 (0.767–1.113)	0.405
		GAATTC	0.236	0.240	0.978 (0.789–1.212)	0.839
		AAGCGT	0.177	0.150	1.229 (0.960–1.575)	0.102
		GGGTTC	0.158	0.144	1.114 (0.863–1.438)	0.408
		GAACTC	0.017	0.026	0.674 (0.356–1.278)	0.224
UGT1A1	rs4148323, rs4148326, rs12479045	GTG	0.493	0.475	1.076 (0.862–1.224)	0.519
		ATG	0.187	0.223	0.793 (0.633–0.995)	**0.045**
		GCC	0.194	0.165	1.209 (0.953–1.533)	0.118
		GCG	0.123	0.131	0.927 (0.705–1.219)	0.589

ATDH anti-tuberculosis drug-induced hepatotoxicity, *SNP* single nucleotide polymorphism, *SLCO1B1* solute carrier organic anion transporter family member 1B1, *CYP2E1* cytochrome P450 2E1, *UGT1A1* UDP glucuronosyltransferase 1A1, *CI* confidence interval

* *p* values less than 0.05 were shown in bold type

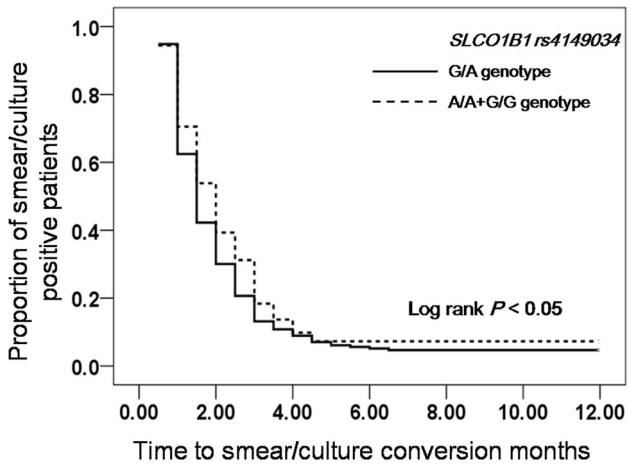

Fig. 2 Comparisons of sputum smear and culture conversion rates in patients carrying different genotypes of the rs4149034 SNP of *SLCO1B1*. *SNP* single nucleotide polymorphism, *SLCO1B1* solute carrier organic anion transporter family member 1B1, *CYP2E1* cytochrome P450 2E1, *UGT1A1* UDP glucuronosyltransferase 1A1

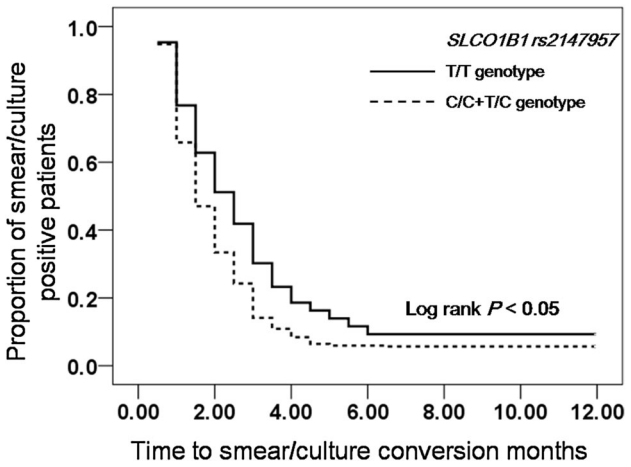

Fig. 3 Comparisons of sputum smear and culture conversion rates in patients carrying different genotypes of the rs2147957 SNP of *SLCO1B1*. *SNP* single nucleotide polymorphism, *SLCO1B1* solute carrier organic anion transporter family member 1B1, *CYP2E1* cytochrome P450 2E1, *UGT1A1* UDP glucuronosyltransferase 1A1

combine with cofactor uridine diphosphate glucuronic acid and increase the heteropolarity of lipophilic substrates, promoting excretion of the compound in urine or bile. Thus, the glucuronidation reaction can reduce the activity or toxicity of the potential compounds while accelerating the elimination of the compounds, playing an important role in metabolic detoxification [23, 27, 28]. As a member of the UGT family, UGT1A1 is an enzyme that is encoded by the *UGT1A1* gene on chromosome 2q and mainly distributed in the liver. A few studies have demonstrated a correlation between *UGT1A1* polymorphisms and ATDH susceptibility. One study in only 17 patients with ATDH showed that *UGT1A1*27* and *UGT1A1*28* were associated with an increased risk of ATDH (OR 13.859; 95% CI 1.085–177.056) [29]. However, Chen [30] found no association between *UGT1A1* and ATDH in a study with only 87 cases. Our study revealed that the *UGT1A1* rs4148323 A/A genotype significantly reduced the risk of ATDH, and its minor A allele significantly decreased the risk of ATDH in the Add model. The ATG haplotype of *UGT1A1* was potentially associated with a decreased risk of ATDH. Therefore, we propose that the presence of mutant A or haplotype ATG might increase the expression of *UGT1A1* to enhance the activity of the UGT1A1 enzyme, resulting in accelerated elimination of toxic metabolites from anti-TB drugs through glucuronidation reaction to protect the liver.

The *SLCO1B1* and *UGT1A1* genes were confirmed to be associated with susceptibility to ATDH in the present study. Our previous cohort study demonstrated the negative impact of ATDH on the treatment failure rate, sputum conversion rate, and closure rate of the lung cavities in TB patients [2]. Therefore, we further investigated the effects of different genotypes of *SLCO1B1* and *UGT1A1* on treatment outcomes in TB patients. The results showed possible impacts of genetic variants of *SLCO1B1* on the prognosis of TB patients. Patients carrying the *SLCO1B1* rs4149034 G/A genotype experienced a significantly lower treatment failure rate, shorter median time to sputum negative conversion, and an increased sputum conversion rate over time. On the other hand, patients carrying the *SLCO1B1* rs2147957 T/T genotype had a longer median time to sputum negative conversion and a significantly decreased sputum conversion rate over time. We can infer that the two polymorphic loci rs4149034 G/A and rs2147957 T/T may have caused a decrease and increase, respectively, in the incidence of ATDILI in TB patients, leading to an impact on the treatment outcomes. These results may be practically beneficial and useful in predicting outcomes of TB treatment after chemotherapy.

5 Conclusion

In conclusion, both genotype and haplotype analysis in the present study revealed that *SLCO1B1* and *UGT1A1* gene polymorphisms were closely related to ATDH susceptibility in a Chinese Han population. Moreover, genetic variants of *SLCO1B1* were associated with the treatment outcomes in TB patients. Molecular identification of susceptibility genes provides a theoretical foundation for planning individualized treatment schemes and better predicting the likelihood of adverse effects in patients. Further studies are needed to better understand the molecular mechanisms by which susceptibility to ATDH is regulated by the expression of ATDH-susceptibility genes and proteins.

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Compliance with Ethical Standards

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Conflict of interest The authors declare no conflict of interest.

Ethics approval The present study was approved by the Ethics Committees of both Tongji University School of Medicine and Shanghai Pulmonary Hospital.

Informed consent Written informed consent was received from patients.

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