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The genetic variants in calcium signaling related genes influence anti-tuberculosis drug induced liver injury

A prospective study

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Abstract

Although many genetic variants related to anti-tuberculosis drug induced liver injury (ATDILI) have been identified, the prediction and personalized treatment of ATDILI have failed to achieve, indicating there remains an area for further exploration. This study aimed to explore the influence of single nucleotide polymorphisms (SNPs) in Bradykinin receptor B2 (*BDKRB2*), Teneurin transmembrane protein 2 (*TENM2*), transforming growth factor beta 2 (*TGFB2*), and solute carrier family 2 member 13 (*SLC2A13*) on the risk of ATDILI.

The subjects comprised 746 Chinese tuberculosis (TB) patients. Custom-by-design 2x48-Plex SNPscanTM kit was employed to genotype 28 selected SNPs. The associations of SNPs with ATDILI risk and clinical phenotypes were analyzed according to the distributions of allelic and genotypic frequencies and different genetic models. The odds ratio (OR) with corresponding 95% confidence interval (CI) was calculated.

Among subjects with successfully genotyped, 107 participants suffered from ATDILI during follow-up. In *BDKRB2*, patients with rs79280755 G allele or rs117806152 C allele were more vulnerable to ATDILI ($P_{\text{Bonferronicorrection}}$ = .002 and .03, respectively). Rs79280755 increased the risk of ATDILI significantly whether in additive (OR = 3.218, 95% CI: 1.686–6.139, $P_{\text{Bonferroni correction}}$ = .003) or dominant model ($P_{\text{Bonferroni correction}}$ = .003), as well as rs117806152 (Additive model: $P_{\text{Bonferroni correction}}$ = .05; dominant model: $P_{\text{Bonferroni correction}}$ = .03). For *TENM2*, rs80003210 G allele contributed to the decreased risk of ATDILI ($P_{\text{Bonferroni correction}}$ = .02), while rs2617972 A allele conferred susceptibility to ATDILI ($P_{\text{Bonferroni correction}}$ = .01). Regarding rs2617972, significant findings were also observed in both additive (OR = 3.203, 95% CI: 1.487–6.896, $P_{\text{Bonferroni correction}}$ = .02) and dominant model ($P_{\text{Bonferroni correction}}$ = .02). Moreover, rs79280755 and rs117806152 in *BDKRB2* significantly affected some laboratory indicators. However, no meaningful SNPs were observed in *TGFB2* and *SLC2A13*.

Our study revealed that both *BDKRB2* and *TENM2* genetic polymorphisms were interrogated in relation to ATDILI susceptibility and some laboratory indicators in the Western Chinese Han population, shedding a new light on exploring novel biomarkers and targets for ATDILI.

Abbreviations: ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, ATDILI = anti-tuberculosis drug induced liver injury, *BDKRB2* = bradykinin receptor B2, BK = bradykinin, CHS = Southern Han Chinese, CI = confidence interval, EPTB = extra pulmonary tuberculosis, Foxa1 = formerly hepatic nuclear factor 3alpha, GGT = gamma glutamyl transpeptidase, HNF1A = hepatocyte nuclear factor 1 alpha, HNF4 = hepatocyte nuclear factor 4, HWE = Hardy–Weinberg equilibrium, LD = linkage disequilibrium, MAF = minor allele frequency, MAPK = mitogen-activated protein kinase, OR = odds ratio, PTB = pulmonary tuberculosis, PTB with EPTB = pulmonary tuberculosis combined with extra pulmonary tuberculosis, *SLC2A13* = solute carrier family 2 member 13, SNPs = single nucleotide polymorphisms, TB = tuberculosis, *TENM2* = teneurin transmembrane

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ML and JZ contributed equally to this work.

This trial was approved by the Ethics Committee of West China Hospital of Sichuan University. All biological samples were obtained from patients and controls that had provided written informed consent in accordance with the tenets of the Declaration of Helsinki. Written informed consents were obtained from all included patients.

All data generated or analyzed during this study are included in this manuscript.

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protein 2, TFBMs = transcription factor binding motifs, *TGFB2* = transforming growth factor beta 2, *TRPM7* = melastatin 7, ULN = upper limit of the normal.

Keywords: ATDILI, calcium signaling, genetic polymorphism, susceptibility

1. Introduction

Anti-tuberculosis (TB) drugs hold the key to thwart the rise and spread of TB. However, the adverse drug reactions (ADRs) caused by these anti-TB drugs have become new problems that cannot be ignored. Among all types of ADRs, anti-tuberculosis drug induced liver injury (ATDILI) has a high prevalence (2–30%[1]) and mortality (22.7%[2]), unpredictable course and adverse impact on anti-TB treatment, thereupon is becoming a mainstream topic for researchers.[3,4] ATDILI is defined as a heterogeneous set of responses triggered by anti-TB drugs,[5] usually manifesting as a decreased liver function.[6–8] A growing body of evidence implicates calcium signaling in mitochondrial dysfunction, oxidative stress, and ensuing ATDILI.[9,10] In addition, an access key role of calcium signaling in some inflammatory processes also supports the involvement of this signaling pathway in the development of ATDILI.[11] Now, risk factors related to calcium signaling have been explored extensively, aiming to identify their value of risk assessment, diagnosis and personalized treatment in ATDILI. Among these factors, genetic factors, especially single nucleotide polymorphisms (SNPs), are considered to play a crucial role due to the unpredictable and non-dose-dependent characteristics of ATDILI.[8]

Bradykinin receptor B2 (*BDKRB2*) encodes a G-protein coupled receptor of bradykinin (BK).[12] Accumulating reports have confirmed that *BDKRB2* is capable of regulating calcium signaling. Through binding to *BDKRB2*, BK allows calcium to enter, leads to calcium-induced calcium release and evokes calcium signaling via upregulating the expression of transient receptor potential melastatin 7 (*TRPM7*).[13–15] Teneurin transmembrane protein 2 (*TENM2*) encodes a type 2 membrane protein, consisting of a cytosolic N-terminus, a single transmembrane region and an extracellular C-terminal domain.[16] Existing researches imply that *TENM2* is inclined to a better interaction with latrophilin-1, and this interaction elicits intracellular calcium signaling.[17] Transforming growth factor beta 2 (*TGFB2*) encodes the transforming growth factor beta family of cytokines which functions in proliferation, differentiation, adhesion, and migration in many cell types.[18] Close relationship between *TGFB2* and calcium signaling has been recognized. *TGFB2* enables to transmit signals via calcium signaling,[19] and thus play roles in some diseases such as cardiomyopathy in mouse models.[20] Solute carrier family 2 member 13 (*SLC2A13*) is responsible for encoding GLUT13, an H^+/myoinositol cotransporter.[21] Ongoing evidence shows that *SLC2A13* participates indirectly in calcium signaling. *SLC2A13* is closely associated with the transport of inositol, while inositol is the key molecule in regulating calcium signaling.[22] Clearly, these 4 genes, *BDKRB2, TENM2, TGFB2*, and *SLC2A13*, are correlated with calcium signaling. Therefore, it seems that these 4 genes influence the individual susceptibility to ATDILI via calcium signaling.

Although the exploration of genetic variants related to ATDILI have never been stopped, it is far from to predict and individualize the treatment of ATDILI based on existing findings. More novel genetic variants in different genes and different populations should be identified to facilitate our understanding of ATDILI. Considering the heavy burden of ATDILI in Southwest China,[23] we conducted this prospective study in Western Chinese Han population to investigate the relationship between ATDILI and genetic variants in *BDKRB2, TENM2, TGFB2*, and *SLC2A13*, aiming to evaluate the potential value of these 4 genes polymorphisms in the risk assessment, pathogenesis, and personalized treatment of ATDILI.

2. Materials and methods

2.1. Study population

From December 2016 and April 2018, this prospective study consecutively recruited TB participants registering in the West China Hospital of Sichuan University. Blood and other specimens were collected from all participants for TB diagnosis and liver function examination. The clear TB evidence and normal liver function before anti-TB treatment were need for all included patients. Once participants suffered from HIV, immunodeficiency diseases or other lung or liver disorders, they would be excluded. After recruitment, all subjects would be treated with a 6-month 4-drug standard treatment (2 months of rifampicin, isoniazid, pyrazinamide, and ethambutol, followed by rifampicin and isoniazid for 4 months) and received liver function examination regularly. Patients would also be excluded if they were treated with analgesics and antipyretics including acetaminophen, hypoglycemic drugs including glitazones, anticonvulsants, and herbal medicines during the 6-month follow-up.

The diagnostic criteria of ATDILI was described by Watkins et al.[24] Specifically, ATDILI was identified based on serum alanine aminotransferase (ALT) $>$ 2 times upper limit of the normal (ULN) or aspartate aminotransferase (AST) $>$ 2 times ULN combined with total bilirubin $>$ 2 times ULN during anti-TB therapy.

This trial was approved by the Ethics Committee of West China Hospital of Sichuan University. The signed written informed consents were collected from all included TB patients.

2.2. Genes genotyping

Peripheral whole blood of each patient was collected for extracting genomic DNA by QIAamp DNA blood mini kit (Qiagen, Germany). After considering minor allele frequency (MAF) ($\geq$0.02) in both Southern Han Chinese and Han Chinese in Beijing, locations, linkage disequilibrium (LD) constant ($r^2 <$ 0.8) and others, 28 SNPs: 8 SNPs in *BDKRB2*, 7 SNPs in *TENM2*, 8 SNPs in *TGFB2*, and 5 SNPs in *SLC2A13* were selected by Haploview version 4.1 (The Broad Institute, Cambridge, MA, USA). All SNPs were genotyped by the custom-by-design 2x48-Plex SNPscanTM kit (Genesky Biotechnologies Inc., Shanghai, China). Approximately 10% samples would be redetected to calculate the concordance for quality assessment.

2.3. Statistical analysis

Continuous variables and categorical variables were compared by Mann–Whitney's *U* test and chi-square test or Fisher's exact

test, respectively. While Hardy–Weinberg equilibrium (HWE), and allelic and genotypic frequencies were evaluated by chi-square analysis or Fisher's exact test. PLINK version 1.07 was applied for identify the relationship between selected SNPs and ATDILI by logistic regression analysis, while SHEsis was employed to perform Linage analysis and haplotype construction (MAF $\geq$ 0.01). Odds ratio (OR) with corresponding 95% confidence interval (CI) was calculated for measuring of relationships. Significance was set at $P \leq .05$. Power and Sample Size Program was used to calculate the power based on the sample size of this work. Furthermore, some online tools were applied to predictive the functions of candidate SNPs.

3. Results

A total of 746 TB patients were enrolled in our study (Fig. 1), nevertheless, 28 selected SNPs were successfully genotyped among 686 participants. Among these 686 subjects, 107 participants suffered from ATDILI during our 6 months follow-up. Significant differences in the incidence of fever ($P=.02$), ALT levels ($P<.001$), AST levels ($P<.001$), alkaline phosphatase (ALP) levels ($P=.03$), gamma glutamyl transpeptidase (GGT) levels ($P=.004$) and uric acid levels ($P=.03$) were identified between the cases and the controls. While there were no meaningful findings in other characteristics (Table 1).

3.1. The relationship between selected SNPs and ATDILI

All genotypes of 28 SNPs did not deviate from the HWE in controls. In *BDKRB2*, rs79280755, and rs117806152 were associated with the risk of ATDILI. The mutant G allele of rs79280755 and C allele of rs117806152 increased the risk of ATDILI significantly ($P_{\text{Bonferroni correction}}=.002$ and .03, respectively). Furthermore, rs79280755 conferred significantly increased risk of ATDILI in both additive (OR = 3.218, 95% CI: 1.686–6.139, $P_{\text{Bonferroni correction}}=.003$) and dominant model (OR = 3.218, 95% CI: 1.686–6.139, $P_{\text{Bonferroni correction}}=.003$), as well as rs117806152 (additive model: OR = 2.424, 95% CI: 1.292–4.548, $P_{\text{Bonferroni correction}}=.05$; dominant model: OR = 2.613, 95% CI: 1.369–4.988, $P_{\text{Bonferroni correction}}=.03$).

In *TENM2*, both rs80003210 and rs2617972 had significant impacts on susceptibility to ATDILI. For rs80003210, patients carrying G allele had the decreased risk of ATDILI with an OR of 0.156 (95% CI: 0.038–0.642, $P_{\text{Bonferroni correction}}=.02$). However, rs80003210 conferred comparable risk of ATDILI based on 3 genetic models. For rs2617972, A allele carriers had 3.083 times (95% CI: 1.455–6.532) higher risk of ATDILI than C allele carriers ($P_{\text{Bonferroni correction}}=.01$). An adverse effect was identified in both additive model (OR = 3.203, 95% CI: 1.487–6.896, $P_{\text{Bonferroni correction}}=.02$) and dominant model (OR = 3.203, 95% CI: 1.487–6.896, $P_{\text{Bonferroni correction}}=.02$).

Whether in *TGFB2* or *SLC2A13*, no meaningful SNPs were found (Tables 2 and 3).

3.2. Subgroup analyses

Age (the threshold: 50 years) and sex have been reported as risk factors of ATDILI,[25] while TB subtypes were also taken into consideration for subgroup analyses.

A total of 31 ATDILI cases and 217 non-ATDILI controls were classified in the elder subgroup (≥50 years), while the remaining

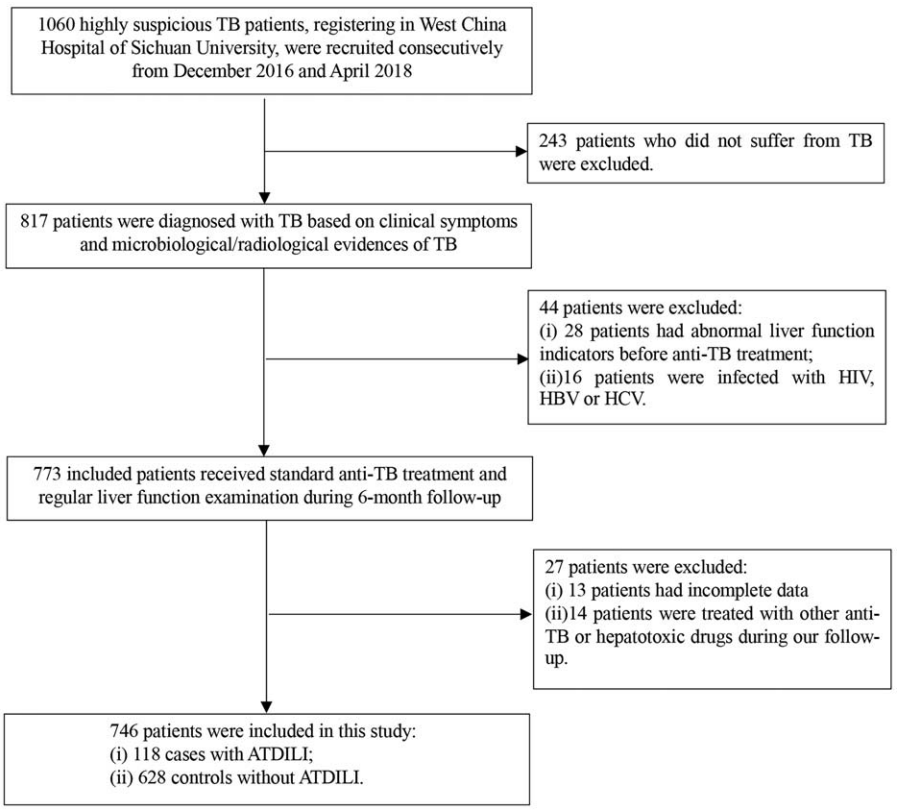

Figure 1. Selection of patients included in this study. ATDILI = anti-tuberculosis drug induced liver injury, TB = tuberculosis.

Table 1

The characteristics of enrolled patients.

Characteristics	Cases* (n = 107)	Controls* (n = 579)	*P*
General data			
Age, mean ± SD,[a] years	42.34 ± 15.53	42.26 ± 17.58	.35
Sex (male/female)	62/45	351/228	.60
Body mass index, mean ± SD (kg/m^2)	20.02 ± 3.47	20.28 ± 3.35	.66
TB[b] subtypes (PTB[c]/EPTB[d]/PTB with EPTB)	68/18/21	406/50/123	.03
Clinical symptoms, n (%)			
Fever	56 (52.34)	232 (40.07)	.02
Night sweat	27 (25.23)	156 (26.94)	.71
Loss weight	31 (28.97)	210 (36.27)	.15
Poor appetite	42 (39.25)	204 (35.23)	.43
Fatigue	27 (25.23)	129 (22.28)	.50
Laboratory data, median ($percent_{25}$–$percent_{75}$)			
WBC[e] (*10^9/L)	6.61 (4.82–7.92)	6.55 (5.19–8.56)	.96
Erythrocyte (*10^{12}/L)	4.34 (4.00–4.73)	4.34 (3.83–4.71)	.31
Platelet (*10^9/L)	235.00 (184.00–315.50)	234.50 (173.00–296.00)	.13
Hemoglobin (g/L)	123.00 (109.00–138.00)	124.00 (107.75–137.00)	.48
Hematocrit (L/L)	0.37 (0.34–0.42)	0.38 (0.32–0.41)	.07
Neutrophil (%)	71.60 (62.60–77.80)	71.80 (62.70–79.20)	.86
Leucocyte (%)	17.10 (13.10–25.90)	17.50 (12.10–25.60)	> .99
Monocyte (%)	8.00 (5.65–9.25)	7.20 (5.90 -8.90)	.09
CRP[f] (mg/L)	8.78 (2.30–33.45)	12.50 (2.56–39.88)	.60
ESR[g] (mm/h)	35.00 (18.50–62.50)	34.00 (15.00–64.25)	.97
Total bilirubin (μmol/L)	10.10 (7.45–13.35)	9.70 (6.30–12.10)	.05
Direct bilirubin (μmol/L)	3.50 (2.30–5.55)	3.40 (2.50–5.40)	.06
Indirect bilirubin (μmol/L)	5.70 (3.75–8.05)	4.80 (3.38–7.00)	.22
ALT[h] (IU/L)	28.00 (16.50–38.00)	14.50 (10.00–21.00)	<.001
AST[i] (IU/L)	28.00 (20.00–34.00)	19.00 (16.00–25.00)	<.001
ALP[j] (IU/L)	88.00 (70.00–109.50)	78.50 (62.75–98.25)	.03
GGT[k] (IU/L)	43.00 (27.50–78.50)	30.00 (18.75–48.25)	.004
Total protein (g/L)	69.80 (63.70–75.10)	69.25 (38.60–109.10)	.39
Albumin (g/L)	37.80 (20.80–53.00)	38.50 (63.18–74.80)	.25
Globulin, g/L	30.20 (26.00–35.50)	30.40 (26.10–34.53)	.98
Glucose (mmol/L)	5.08 (4.62–5.95)	5.13 (4.71–5.82)	.21
Urea (mmol/L)	3.90 (2.90–5.24)	4.00 (3.10–5.32)	.51
Creatinine (μmol/L)	56.40 (48.00–66.50)	60.00 (49.00–74.00)	.72
Cystatin c (mg/L)	0.91 (0.81–1.05)	0.92 (0.79–1.07)	.50
Uric acid (μmol/L)	271.00 (195.95–362.00)	307.00 (228.00–410.00)	.03
Triglyceride (mmol/L)	1.02 (0.82–1.32)	1.06 (0.81–1.44)	.09
Cholesterol (mmol/L)	3.95 (3.16–4.80)	3.80 (3.15–4.56)	.80
HDL-C[l] (mmol/L)	1.12 (0.86–1.46)	1.08 (0.82–1.41)	.76
LDL-C[m] (mmol/L)	2.20 (1.80–2.77)	2.20 (1.68–2.77)	.68

a = standard, b = tuberculosis, c = pulmonary tuberculosis, d = extra pulmonary tuberculosis, e = white blood cell, f = C-reactive protein, g = erythrocyte sedimentation rate, h = alanine aminotransferase, i = aspartate transaminase, j = alkaline phosphatase, k = gamma glutamyl transpeptidase, l = high density lipoprotein cholesterol, m = low density lipoprotein cholesterol.

* The cases and controls referred to patients with and without anti-tuberculosis drug induced liver injury, respectively.

438 patients were in another subgroup. Older patients carrying A allele of *BDKRB2* rs79280755 had 4.671 times (95% CI: 1.477–14.770) higher risk of ATDILI than those with G allele ($P_{\text{Bonferroni correction}} = .03$), whereas comparable risk of ATDILI was identified in 3 genetic models. In the younger subgroup, no meaningful findings were observed.

There were 413 males and 273 females in this trial. In *BDKRB2*, both rs79280755 A allele and rs117806152 C allele conferred susceptibility to ATDILI ($P_{\text{Bonferroni correction}} < .001$ and .009, respectively). The genetic model analyses demonstrated that both rs79280755 and rs117806152 increased the risk of ATDILI whether in dominant model ($P_{\text{Bonferroni correction}} < .001$ and .009, respectively) or additive model ($P_{\text{Bonferroni correction}} < .001$and .02, respectively). While females with C allele of *TENM2* rs2617972 were more susceptible to ATDILI with an OR of 4.000 (95% CI: 1.353–11.820, $P_{\text{Bonferroni correction}} = .05$).

Altogether 474/686, 68/686, and 144/686 subjects were classified into pulmonary TB (PTB) subgroup, extra PTB (EPTB) subgroup and PTB combined with EPTB (PTB with EPTB) subgroup, respectively. The susceptibility to ATDILI for PTB patients were potentially endowed to the mutant alleles of *BDKRB2* rs79280755 and *BDKRB2* rs117806152 ($P_{\text{Bonferroni correction}} = .04$ and .04, respectively). In PTB with EPTB subgroup, the meaningful relationship was identified between *TENM2* rs2617972 and the risk of ATDILI ($P_{\text{Bonferroni correction}} = .009$) (Table 4).

3.3. LD analysis and haplotype construction

Based on the cut-off value of pairwise $r^2 > 0.80$, 2 SNPs of *BDKRB2* (rs76192091 and rs4900312), as well as 2 SNPs of *BDKRB2* (rs4905469 and rs8012552) and 3 SNPs of *TGFB2*

Table 2

The comparison of allelic and genotypic frequency between cases* and controls*.

Genes	SNP[a]	Group	HWE [c]-P	Allele						Genotype				
				1†	2†	OR[d] (95% CI[e])	*P*	*P*‡	Power	11†	12†	22†	*P*	*P*‡
BDKRB2[f]	rs79280755 (A>G)	Cases	>.99	16	198	3.038 (1.626–5.678)	**<.001**	**.002**	.889	0	16	91	NA[g]	
		Controls	>.99	30	1128					0	30	549		
	rs76192091 (A>G)	Cases	>.99	1	213	0.267 (0.036–2.001)	.17			0	1	106	NA	
		Controls	>.99	20	1138					0	20	559		
	rs4900312 (G>A)	Cases	>.99	2	212	0.511 (0.119–2.195)	.36			0	2	105	NA	
		Controls	>.99	21	1137					0	21	558		
	rs117806152 (A>C)	Cases	>.99	15	199	2.419 (1.297–4.511)	**.004**	**.03**	.753	0	15	92	NA	
		Controls	.41	35	1123					1	33	545		
	rs4905469 (A>G)	Cases	.56	106	108	1.183 (0.884–1.584)	.26			28	50	29	.43	
		Controls	> .99	525	633					119	287	173		
	rs8012552 (A>G)	Cases	.56	106	108	1.179 (0.881–1.579)	.27			28	50	29	.43	
		Controls	>.99	526	632					119	288	172		
	rs61193624 (C>A)	Cases	.50	65	149	1.545 (1.119–2.133)	.008			8	49	50	.03	
		Controls	.40	255	903					24	207	348		
	rs4905470 (G>A)	Cases	.21	56	158	1.106 (0.793–1.543)	.55			10	36	61	.58	
		Controls	.37	281	877					38	205	336		
TENM2[h]	rs72645737 (G>A)	Cases	.31	86	128	1.154 (0.857–1.556)	.35			20	46	41	.30	
		Controls	.72	426	732					76	274	229		
	rs75081018 (A>C)	Cases	>.99	83	131	1.093 (0.810–1.475)	.56			16	51	40	.81	
		Controls	.48	425	733					82	261	236		
	rs80003210 (A>G)	Cases	>.99	2	212	0.156 (0.038–0.642)	**.003**	**.02**	.954	0	2	105	NA	
		Controls	>.99	66	1092					1	64	514		
	rs1549211 (A>C)	Cases	.54	18	196	0.707 (0.423–1.185)	.19			1	16	90	.36	
		Controls	.68	133	1025					6	121	452		
	rs5024074 (A>G)	Cases	>.99	20	194	1.056 (0.639–1.746)	.83			1	18	88	.96	
		Controls	>.99	103	1055					4	95	480		
	rs9313396 (A>C)	Cases	.23	89	125	0.967 (0.720–1.300)	.83			15	59	33	.59	
		Controls	.55	491	667					100	291	188		
	rs2617972 (C>A)	Cases	>.99	11	203	3.083 (1.455–6.532)	**.002**	**.01**	.783	0	11	96	NA	
		Controls	>.99	20	1138					0	20	559		
TGFB2[i]	rs2799085 (C>A)	Cases	.236	90	124	0.955 (0.711–1.283)	.761			22	46	39	.67	
		Controls	.499	500	658					112	276	191		
	rs2009112 (G>A)	Cases	.463	34	180	1.204 (0.805–1.803)	.366			1	32	74	.40	
		Controls	.722	157	1001					9	139	431		
	rs4335431 (A>G)	Cases	1.000	22	192	0.973 (0.603–1.572)	.911			1	20	86	.97	
		Controls	.824	122	1036					7	108	464		
	rs17047740 (G>A)	Cases	1.000	27	187	1.249 (0.800–1.950)	.327			1	25	81	.53	
		Controls	1.000	120	1038					6	108	465		
	rs1317681 (A>G)	Cases	.564	103	111	1.055 (0.788–1.412)	.721			23	57	27	.91	
		Controls	.359	542	616					121	300	158		
	rs6657275 (G>A)	Cases	.788	49	165	0.834 (0.591–1.178)	.302			6	37	64	.59	
		Controls	.198	304	854					46	212	321		
	rs10482796 (G>A)	Cases	.425	86	128	0.942 (0.700–1.268)	.695			15	56	36	.82	
		Controls	.393	482	676					95	292	192		
	rs6684205 (G>A)	Cases	1.000	48	166	0.846 (0.598–1.197)	.345			5	38	64	.51	
		Controls	.102	295	863					45	205	329		
SLC2A13[j]	rs75036080 (G>A)	Cases	.243	63	151	1.210 (0.876–1.669)	.247			12	39	56	.43	
		Controls	.192	297	861					44	209	326		
	rs17560847 (G>A)	Cases	.385	69	145	1.349 (0.984–1.849)	.062			13	43	51	.18	
		Controls	.236	302	856					45	212	322		
	rs2404350 (G>A)	Cases	.245	32	182	0.988 (0.656–1.486)	.952			4	24	79	.45	
		Controls	.871	175	983					12	151	416		
	rs7976837 (G>A)	Cases	.252	46	168	0.746 (0.525–1.059)	.101			7	32	68	.20	
		Controls	.397	311	847					46	219	314		
	rs2404574 (G>A)	Cases	1.000	0	214	0 (0-NA)	.047			0	0	107	NA	
		Controls	.169	21	1137					1	19	559		

a = single nucleotide polymorphisms, b = chromosome, c = Hardy–Weinberg equilibrium, d = odd ratio, e = confidence interval, f = Bradykinin receptor B2, g = non available, h = Teneurin transmembrane protein 2, i = transforming growth factor beta 2, j = solute carrier family 2 member 13.

* The cases and controls referred to patients with and without anti-tuberculosis drug induced liver injury, respectively.

† "1" and "2" referred to the mutant allele and wild allele, respectively. While "11," "12," and "22" represented the mutant homozygote, heterozygote, and wild homozygote, respectively.

‡ *P* value after Bonferroni correction.

Table 3

The results of genetic model analyses.

Genes	SNP[a]	Addictive model			Dominant model			Recessive model		
		OR[b] (95% CI[c])	*P*	*P**	OR (95% CI)	*P*	*P**	OR (95% CI)	*P*	*P**
BDKRB2[d]	rs79280755 (A>G)	**3.218 (1.686–6.139)**	**<.001**	**.003**	**3.218 (1.686–6.139)**	**<.001**	**.003**	NA[e]	NA	
	rs76192091 (A>G)	0.264 (0.035–1.986)	.20		0.264 (0.035–1.986)	.20		NA	NA	
	rs4900312 (G>A)	0.506 (0.117–2.191)	.36		0.506 (0.117–2.191)	.36		NA	NA	
	rs117806152 (A>C)	**2.424 (1.292–4.548)**	**.006**	**.05**	**2.613 (1.369–4.988)**	**.004**	**.03**	0 (0-NA)	>.99	
	rs4905469 (A>G)	1.181 (0.883–1.580)	.26		1.146 (0.722–1.819)	.56		1.370 (0.851–2.205)	.20	
	rs8012552 (A>G)	1.178 (0.880–1.576)	.27		1.137 (0.716–1.804)	.59		1.370 (0.851–2.205)	.20	
	rs61193624 (C>A)	1.583 (1.133–2.211)	.01		1.717 (1.135–2.600)	.01		1.869 (0.816–4.278)	.14	
	rs4905470 (G>A)	1.101 (0.796–1.523)	.56		1.043 (0.687–1.582)	.84		1.468 (0.708–3.044)	.30	
TENM2[f]	rs72645737 (G>A)	1.154 (0.857–1.555)	.35		1.053 (0.689–1.609)	.81		1.521 (0.884–2.618)	.13	
	rs75081018 (A>C)	1.090 (0.811–1.466)	.57		1.152 (0.753–1.763)	.51		1.066 (0.596–1.904)	.83	
	rs80003210 (A>G)	0.152 (0.037–0.629)	.009		0.151 (0.036–0.625)	.009		0 (0-NA)	>.99	
	rs1549211 (A>C)	0.703 (0.418–1.183)	.19		0.672 (0.386–1.170)	.16		0.901 (0.107–7.560)	.92	
	rs5024074 (A>G)	1.056 (0.638–1.751)	.83		1.047 (0.610–1.798)	.87		1.356 (0.150–12.250)	.79	
	rs9313396 (A>C)	0.966 (0.714–1.307)	.82		1.078 (0.691–1.684)	.74		0.781 (0.434–1.404)	.41	
	rs2617972 (C>A)	**3.203 (1.487–6.896)**	**.003**	**.02**	**3.203 (1.487–6.896)**	**.003**	**.02**	NA (NA-NA)	NA	
TGFB2[g]	rs2799085 (C>A)	0.957 (0.717–1.278)	.766		0.858 (0.558–1.320)	.486		1.079 (0.647–1.801)	.771	
	rs2009112 (G>A)	1.214 (0.804–1.835)	.357		1.299 (0.827–2.038)	.256		0.598 (0.075–4.765)	.627	
	rs4335431 (A>G)	0.973 (0.604–1.569)	.911		0.985 (0.586–1.655)	.955		0.771 (0.094–6.330)	.809	
	rs17047740 (G>A)	1.253 (0.800–1.964)	.325		1.309 (0.805–2.131)	.278		0.901 (0.107–7.560)	.923	
	rs1317681 (A>G)	1.057 (0.784–1.425)	.715		1.112 (0.693–1.785)	.660		1.036 (0.627–1.714)	.889	
	rs6657275 (G>A)	0.841 (0.601–1.179)	.315		0.836 (0.549–1.272)	.403		0.688 (0.286–1.654)	.404	
	rs10482796 (G>A)	0.940 (0.693–1.274)	.688		0.979 (0.632–1.514)	.922		0.831 (0.461–1.496)	.537	
	rs6684205 (G>A)	0.853 (0.608–1.197)	.358		0.884 (0.581–1.346)	.566		0.582 (0.225–1.501)	.263	
SLC2A13[h]	rs75036080 (G>A)	1.195 (0.875–1.633)	.263		1.173 (0.776–1.774)	.448		1.536 (0.782–3.015)	.213	
	rs17560847 (G>A)	1.327 (0.976–1.804)	.071		1.376 (0.910–2.080)	.130		1.641 (0.853–3.159)	.138	
	rs2404350 (G>A)	0.988 (0.657–1.485)	.953		0.905 (0.567–1.444)	.674		1.835 (0.581–5.800)	.301	
	rs7976837 (G>A)	0.755 (0.535–1.066)	.110		0.680 (0.444–1.041)	.076		0.811 (0.356–1.848)	.618	
	rs2404574 (G>A)	0 (0-NA)	.997		0 (0-NA)	.997		0 (0-NA)	.999	

a = single nucleotide polymorphisms, b = odd ratio, c = confidence interval, d = Bradykinin receptor B2, e = non available, f = Teneurin transmembrane protein 2, g = Transforming growth factor beta 2, h = Solute carrier family 2 member 13.

* *P* value after Bonferroni correction.

(rs6657275, rs10482796, and rs6684205) were in a LD block, respectively (Fig. 2). Nevertheless, no haplotypes, which were constructed based on these SNPs, reached statistically significant (Table 5).

3.4. The association of SNPs and clinical phenotypes

Based on dominant or recessive model, the potential influence of meaningful SNPs in *BDKRB2* (rs79280755 and rs117806152) and *TENM2* (rs80003210 and rs2617972) on clinical characteristics was investigated further. For *BDKRB2* rs79280755, G allele-containing genotypes indicated significantly higher platelet counts ($P = .003$), percentage of monocyte ($P = .02$) and erythrocyte sedimentation rate ($P = .02$). Regarding *BDKRB2* rs117806152, patients carrying C allele-containing genotypes showed higher platelet counts ($P = .009$) and erythrocyte sedimentation rate ($P = .04$) than those with AA genotype. No significant findings on the relationship between *TENM2* gene polymorphisms and clinical characteristics were observed (Fig. 3).

4. Discussion

This present study found *BDKRB2* and *TENM2* gene polymorphisms, but not *TGFB2* and *SLC2A13*, had influence on the risk of AIDILI. The mutant alleles of *BDKRB2* rs79280755, *BDKRB2* rs117806152, and *TENM2* rs2617972 were the adverse elements of ATDILI, while a decreased risk of ATDILI was associated with the mutant allele of *TENM2* rs80003210. Subgroup analyses identified the relationships between 3 SNPs (*BDKRB2* rs79280755, *BDKRB2* rs117806152, and *TENM2* rs2617972) and the risk of ATDILI for patients with different ages, genders, and TB subtypes. Moreover, the influence of these meaningful SNPs on laboratory indicators was also explored. These findings provided experimental evidence for some new ATDILI-related targets, which promoted the development of ATDILI related research to some extent.

As we described above, *BDKRB2* acts though participating in calcium signaling pathway, mitogen-activated protein kinase (MAPK), and other signal pathways to affect inflammatory processes, endocrine regulation, and drug response.[26,27] In our study, *BDKRB2* rs79280755 and *BDKRB2* rs117806152 are intron variants which have not been reported thus far. Online tool, HaploReg, suggests that more than 10 transcription factor binding motifs (TFBMs) are altered by rs79280755, and most of changed motifs contribute their share to regulate transcription (https://pubs.broadinstitute.org/mammals/haploreg/detail_v4.1.php?query=&id=rs79280755). Interestingly, *BDKRB2* has been recognized as a transcriptional regulator of specific genes,[28] consistent with the functional predictions provided by HaploReg to some extent. Notably, one of the affected transcription factors, formerly hepatic nuclear factor 3alpha (Foxa1), is known as a pioneer transcription factor and responsible for normal development of liver and lung.[29] Vatamaniuk et al[30] have revealed that

Table 4

The results of subgroup analyses.

				Allele					Genotype					Genetic model								
														Dominant model			Recessive model			Additive model		
Gene	Subgroup	SNP[a]	Cases or controls[*]	1[†]	2[†]	OR[b] (95% CI[c])	*P*	*P*[‡]	11[†]	12[†]	22[†]	*P*	*P*[‡]	OR (95% CI)	*P*	*P*[‡]	OR (95% CI)	*P*	*P*[‡]	OR (95% CI)	*P*	*P*[‡]
BDKRB2[d]	Age: ≥50	rs79280755 (G>A)	Cases (n=31)	5	57	4.671 (1.477–14.770)	.004	.03	0	5	26	NA [e]		5.024 (1.529–16.500)	.008		NA (NA-NA)	NA		5.024 (1.529–16.500)	.008	.06
			Control (n=217)	8	426				0	8	209											
	Sex: male	rs79280755 (G>A)	Cases (n=62)	13	111	4.450 (2.121–9.338)	<.001	<.001	0	13	49	NA		4.908 (2.264–10.640)	<.001	<.001	NA (NA-NA)	NA		4.908 (2.264–10.640)	<.001	<.001
			Control (n=351)	18	684				0	18	333											
		rs117806152 (A>C)	Cases (n=62)	11	113	3.319 (1.549–7.113)	.001	.009	0	11	51	NA		3.769 (1.695–8.379)	.001	.009	NA (0-NA)	>.99		3.254 (1.506–7.029)	.003	.02
			Control (n=351)	20	682				1	18	332											
	TB [f] subtypes: PTB [g]	rs79280755 (G>A)	Cases (n=68)	10	126	2.850 (1.319–6.160)	.006	.04	0	10	58	NA		3.009 (1.356–6.677)	.007		NA (NA-NA)	NA		3.009 (1.356–6.677)	.007	.05
			Control (n=406)	22	790				0	22	384											
		rs117806152 (A>C)	Cases (n=68)	10	126	2.850 (1.319–6.160)	.006	.04	0	10	58	NA		3.161 (1.417–7.049)	.005	.04	NA (0-NA)	>.99		2.779 (1.285–6.007)	.009	.08
			Control (n=406)	22	790				1	20	385											
TENM2[h]	Sex: female	rs2617972 (A>C)	Cases (n=45)	6	84	4.000 (1.353–11.820)	.007	.05	0	6	39	NA		4.231 (1.392–12.860)	.01		NA (NA-NA)	NA		4.231 (1.392–12.860)	.01	.08
			Control (n=228)	8	448				0	8	220											
	TB subtypes: PTB with EPTB	rs2617972 (A>C)	Cases (n=21)	5	37	6.514 (1.798–23.590)	.001	.009	0	5	16	NA		7.375 (1.921–28.310)	.004	.03	NA (NA-NA)	NA		7.375 (1.921–28.310)	.004	.03
			Control (n=123)	5	241				0	5	118											

a=single nucleotide polymorphisms, b=odd ratio, c=confidence interval, d=Bradykinin receptor B2, e=non available, f=tuberculosis, g=pulmonary tuberculosis, h=Teneurin transmembrane protein 2.

[*] The cases and controls referred to patients with and without anti-tuberculosis drug induced liver injury, respectively.

[†] "1" and "2" referred to the mutant allele and wild allele, respectively. While "11," "12" and "22" represented the mutant homozygote, heterozygote, and wild homozygote, respectively.

[‡] *P* value after Bonferroni correction.

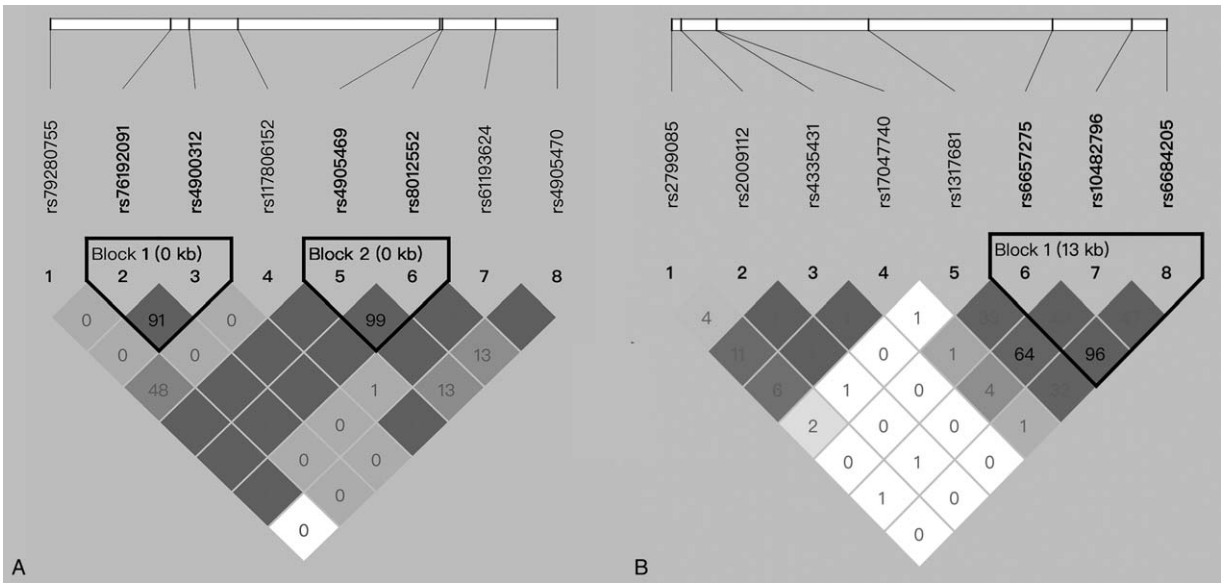

Figure 2. Linkage disequilibrium plots. The threshold was set at pairwise $r^2 > 0.80$. The percentages in diamonds and color of diamonds represent pairwise r^2 values for all pairs of SNPs and the intensity of pairwise r^2, respectively. (A) Linkage disequilibrium plots of 8 single-nucleotide polymorphisms (SNPs) in *BDKRB2*; (B) linkage disequilibrium plots of 8 single-nucleotide polymorphisms (SNPs) in *TGFB2*.

Foxa1 involves in calcium influx and regulation of oxidative phosphorylation. Herein, rs79280755 may lead to significantly different risk of ATDILI via mediating calcium metabolism by affecting the Foxa1.

TENM2, locating on chromosome 5, elicits heterophilic cell–cell adhesion via plasma membrane cell adhesion molecules, calcium signaling, axon guidance, and other pathophysiological processes.[17] Our study testified that *TENM2* rs2617972 and *TENM2* rs80003210 might be the potential pharmacogenetic biomarkers for ATDILI in the Western Chinese Han population. Of the 2 candidate SNPs, rs80003210 is likely to influence the functions of a transcription factor, hepatocyte nuclear factor 4 (HNF4) (https://pubs.broadinstitute.org/mammals/haploreg/detail_v4.1.php?query=&id=rs80003210). Growing investigators have confirmed the relationship between HNF4 and calcium metabolism. Through the animal trials, Niehof et al[31] have demonstrated that the HNF4 acts as a master transcriptional regulator for key genes in calcium signaling. Furthermore, HNF4 is also able to function in the preservation of calcium homeostasis via controlling the expression of hepatocyte nuclear factor 1 alpha (*HNF1A*).[32,33] Obviously, rs80003210 participates in calcium signaling by various ways, and the relationship between rs8000321 and calcium metabolism may explain the role of this variant in the occurrence of ATDILI to some extent.

We first investigated the roles of variants in 4 genes related to calcium signaling in ATDILI, facilitating our understanding of ATDILI etiology and contributing to develop personalized treatment strategies. Unfortunately, our study still suffered from the limitations of sample size and singleness of ethnicity although the power calculation was performed to assess the reliability of our results. Based on some online bioinformatic tools and our results, we predicted the functions of candidate variants in *BDKRB2* and *TENM2*, and functional trials to verify these predictions are warranted urgently.

Table 5

Haplotype constructions of BDKRB2[a] and TGFB2[b] variants related to the risk of ATDILI.[c]

Haplotype	Frequency			OR[d] (95% CI [e])	*P*
	ALL (n = 686)	Cases* (n = 107)	Controls* (n = 579)		
BDKRB2: Rs76192091–rs4900312 haplotype					
GA	0.983	0.991	0.982	1.000 (NA[f]–NA)	NA
AG	0.015	0.005	0.017	0.270 (0.040–2.000)	.20
GG	0.002	0.005	NA	5.310 (0.330–85.630)	.24
BDKRB2: Rs4905469–rs8012552 haplotype					
AA	0.539	0.505	0.546	1.000 (NA–NA)	NA
GG	0.460	0.495	0.453	1.180 (0.880–1.580)	.26
TGFB2: Rs6657275–rs10482796–rs6684205 haplotype					
GGG	0.586	0.598	0.584	1.000 (NA–NA)	NA
AAA	0.250	0.224	0.255	0.870 (0.610–1.240)	.43
GAG	0.157	0.173	0.154	1.100 (.720–1.660)	.67
AAG	0.007	0.005	0.008	0.590 (0.070–4.700)	.61

a = Bradykinin receptor B2, b = Transforming growth factor beta 2, c = anti-tuberculosis drug induced liver injury, d = odd ratio, e = confidence interval, f = non available.
* The cases and controls referred to patients with and without anti-tuberculosis drug induced liver injury, respectively.

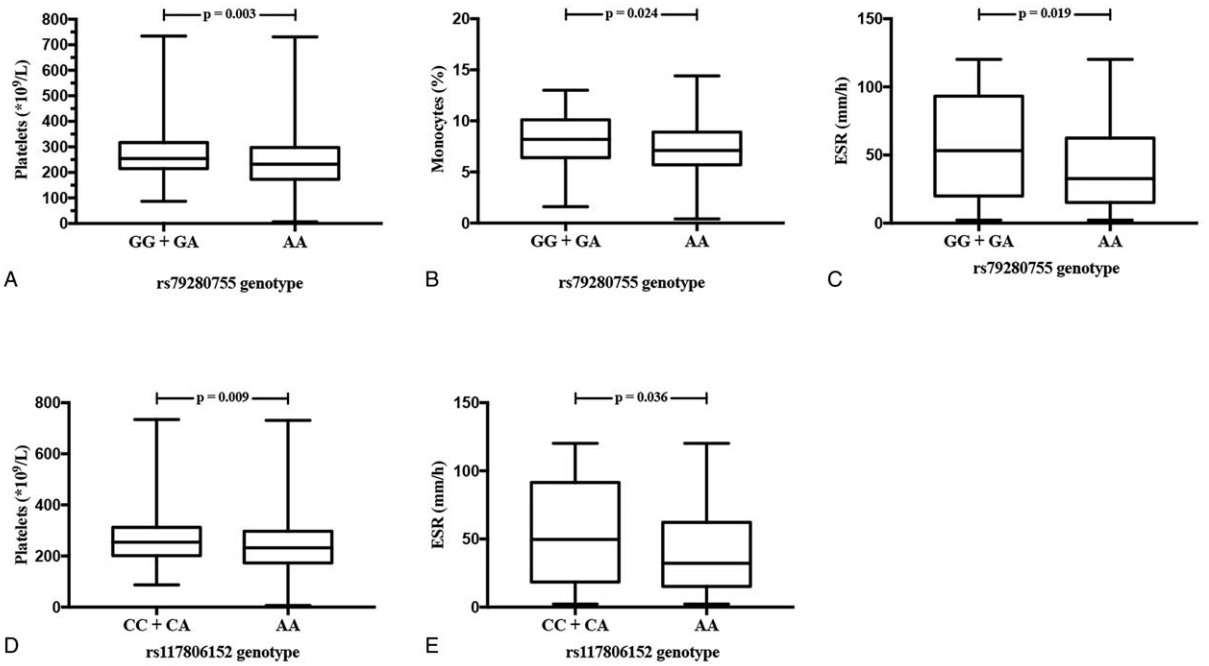

Figure 3. The impact of 2 single-nucleotide polymorphisms (SNPs) in *BDKRB2* on clinical phenotypes. (A) The impact of rs79280755 in dominant model on platelet counts; (B) the impact of rs79280755 in dominant model on percentage of monocyte; (C) the impact of rs79280755 in dominant model on erythrocyte sedimentation rate; (D) the impact of rs117806152 in dominant model on platelet counts; (E) the impact of rs117806152 in dominant model on erythrocyte sedimentation rate. ESR = erythrocyte sedimentation rate.

5. Conclusion

In summary, we explored the roles of some calcium signaling-related genes and their variants played in ATDILI and first demonstrated that *BDKRB2* rs79280755, *BDKRB2* rs117806152, *TENM2* rs80003210, and *TENM2* rs2617972 were in reference to the susceptibility to ATDILI in Western Chinese Han population. The novel biomarkers of ATDILI founded in this work could contribute their share to plot complete genetic map of ATDILI, which could bring benefits to more accurately predict and diagnose the ATDILI. In addition, these new targets may also help researchers to explore the underlying mechanism of this severe disease and develop the effective vaccines or drugs, reducing the heavy disease burden on multiple levels.

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