

World Journal of *Gastroenterology*

World J Gastroenterol 2020 March 28; 26(12): 1231-1381



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INDEXING/ABSTRACTING

The WJG is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, and Scopus. The 2019 edition of Journal Citation Report® cites the 2018 impact factor for WJG as 3.411 (5-year impact factor: 3.579), ranking WJG as 35th among 84 journals in gastroenterology and hepatology (quartile in category Q2). CiteScore (2018): 3.43.

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Yan-Liang Zhang*

Proofing Production Department Director: *Yun-Xiaojuan Wu*

NAME OF JOURNAL

World Journal of Gastroenterology

ISSN

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE

October 1, 1995

FREQUENCY

Weekly

EDITORS-IN-CHIEF

Subrata Ghosh, Andrzej S Tarnawski

EDITORIAL BOARD MEMBERS

<http://www.wjgnet.com/1007-9327/editorialboard.htm>

EDITORIAL OFFICE

Ze-Mao Gong, Director

PUBLICATION DATE

March 28, 2020

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INSTRUCTIONS TO AUTHORS

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<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Case Control Study

Single-nucleotide polymorphisms of *HLA* and *Polygonum multiflorum*-induced liver injury in the Han Chinese population

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Author contributions: Yang WN contributed to data collection, analyses, writing and revision; Pang LL, Zhou JY, Qiu YW, Miao L, Wang SY, Liu XZ, Tan KA and Shi WW contributed to data collection; Hou FQ and Wang GQ contributed to study design and critical revision of the manuscript for important intellectual content; Hou FQ had primary responsibility and all authors approved the final paper.

Supported by the National Natural Science Foundation of China, No. 81470849; and the China Mega-Project for Infectious Diseases, No. 2017ZX10203202.

Institutional review board statement: The study was approved by the Human Research Committee of Peking University First Hospital.

Informed consent statement: All patients gave informed consent.

Conflict-of-interest statement: No

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Abstract

BACKGROUND

Polygonum multiflorum is one of the leading causes of herb-induced liver injury in China. *HLA-B*35:01* is reported to be a potential biomarker of *Polygonum multiflorum*-induced liver injury (PM-DILI). However, little is known about the relationship between single-nucleotide polymorphisms (SNPs) and PM-DILI.

AIM

To identify SNPs that indicate susceptibility to PM-DILI.

METHODS

We conducted a systematic study enrolling 382 participants from four independent hospitals, including 73 PM-DILI patients, 118 patients with other

benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement – checklist of items, and the manuscript was prepared and revised according to the STROBE Statement – checklist of items.

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Manuscript source: Unsolicited manuscript

Received: December 5, 2019

Peer-review started: December 5, 2019

First decision: January 12, 2020

Revised: February 7, 2020

Accepted: February 28, 2020

Article in press: February 28, 2020

Published online: March 28, 2020

P-Reviewer: Ng QX, Kagawa T, Shimizu Y, Tarantino G

S-Editor: Tang JZ

L-Editor: Webster JR

E-Editor: Ma YJ



drug-induced liver injury (other-DILI) and 191 healthy controls. Whole-exome sequencing was performed for 8 PM-DILI patients and 8 healthy controls who were randomly selected from the above subjects. Nineteen SNPs that showed high frequencies in the 8 PM-DILI patients were selected as candidate SNPs and then screened in 65 PM-DILI patients, 118 other-DILI patients and 183 healthy controls using the MassARRAY system. *HLA-B* high-resolution genotyping was performed for the 73 PM-DILI and 118 other-DILI patients. The Han-MHC database was selected as a population control for *HLA-B* analysis. $P < 6.25 \times 10^{-3}$ after Bonferroni correction was considered significant.

RESULTS

The frequencies of rs111686806 in the *HLA-A* gene, rs1055348 in the *HLA-B* gene, and rs202047044 in the *HLA-DRB1* gene were significantly higher in the PM-DILI group than in the control group [27.2% *vs* 11.6%, $P = 1.72 \times 10^{-5}$, odds ratio (OR) = 3.96, 95% confidence interval (CI): 2.21-7.14; 42.5% *vs* 8.6%, $P = 1.72 \times 10^{-19}$, OR = 13.62, 95% CI: 7.16-25.9; 22.9% *vs* 8.1%, $P = 4.64 \times 10^{-6}$, OR = 4.1, 95% CI: 2.25-7.47]. Only rs1055348 showed a significantly higher frequency in the PM-DILI group than in the other-DILI group (42.5% *vs* 13.6%, $P = 1.84 \times 10^{-10}$, OR = 10.06, 95% CI: 5.06-20.0), which suggested that it is a specific risk factor for PM-DILI. rs1055348 may become a tag for *HLA-B*35:01* with 100% sensitivity and 97.7% specificity in the PM-DILI group and 100% sensitivity and 98.1% specificity in the other-DILI group. Furthermore, *HLA-B*35:01* was confirmed to be associated with PM-DILI with a frequency of 41.1% in the PM-DILI group compared with 11.9% ($P = 4.30 \times 10^{-11}$, OR = 11.11, 95% CI: 5.57-22.19) in the other-DILI group and 2.7% ($P = 6.22 \times 10^{-166}$, OR = 62.62, 95% CI: 35.91-109.20) in the Han-MHC database.

CONCLUSION

rs111686806, rs1055348, and rs202047044 are associated with PM-DILI, of which, rs1055348 is specific to PM-DILI. As a tag for *HLA-B*35:01*, rs1055348 may become an alternative predictive biomarker of PM-DILI.

Key words: Drug-induced liver injury; *Polygonum multiflorum*; Single-nucleotide polymorphism; rs111686806; rs1055348; rs202047044; *HLA-B*35:01*

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Core tip: We aimed to identify single-nucleotide polymorphisms that indicate susceptibility to *Polygonum multiflorum*-induced liver injury (PM-DILI). We successfully identified three single-nucleotide polymorphisms, rs111686806 in the *HLA-A* gene, rs1055348 in the *HLA-B* gene and rs202047044 in the *HLA-DRB1* gene that were associated with PM-DILI. Of which, rs1055348 had the strongest effect and was a specific risk factor for PM-DILI. We also validated the association between *HLA-B*35:01* and PM-DILI. Furthermore, we analyzed the correlation between rs1055348 and *HLA-B*35:01*. With 100% sensitivity and > 95% specificity, rs1055348 may serve as a tag for *HLA-B*35:01* and an alternative predictive biomarker of PM-DILI.

Citation: Yang WN, Pang LL, Zhou JY, Qiu YW, Miao L, Wang SY, Liu XZ, Tan KA, Shi WW, Wang GQ, Hou FQ. Single-nucleotide polymorphisms of *HLA* and *Polygonum multiflorum*-induced liver injury in the Han Chinese population. *World J Gastroenterol* 2020; 26(12): 1329-1339

URL: <https://www.wjgnet.com/1007-9327/full/v26/i12/1329.htm>

DOI: <https://dx.doi.org/10.3748/wjg.v26.i12.1329>

INTRODUCTION

Herbs are usually considered to be natural and safe. However, herbs are often major causes of drug-induced liver injury (DILI)^[1]. A previous retrospective study estimated the annual incidence of DILI in the general population at 23.80 per 100000 persons in mainland China, with traditional Chinese medicines, herbal and dietary supplements, and antituberculosis drugs being the leading causes^[2]. Among herbal supplements,

Polygonum multiflorum (PM) has been reported in several studies to be one of the leading causative agents of DILI^[3-5].

PM is a well-known traditional Chinese herbal medicine called *He Shou Wu* in China and East Asia and *Fo-ti* in North America. PM has been used since ancient times as a medical prescription or food supplement for gray hair, hair loss, constipation, and hyperlipemia^[6]. Nonetheless, reports of PM-induced liver injury (PM-DILI) have been increasing in recent years. Indeed, several cases of hepatitis associated with PM have been reported in patients from Australia, China, Italy, Japan, the Netherlands, the United States and Slovakia^[7-11]. In addition, experiments both *in vivo* and *in vitro* have indicated that PM is toxic to the liver^[12-14]. The diagnosis of DILI can be difficult because it relies largely on the exclusion of other potential causes and requires a high index of suspicion, as patients are often asymptomatic^[15]. To improve the safe use of PM, the identification of biomarkers to prevent and diagnose PM-DILI is essential.

Susceptibility to DILI is considered to be genetically determined^[16]. The HLA genotype as well as drug metabolism genes affect susceptibility to DILI due to a range of drugs and correlate with the underlying mechanisms^[16,17]. For example, associations have been found between *HLA-DRB1*15:01* and amoxicillin-clavulanate-DILI^[18], *HLA-A*33:01* and fenofibrate-DILI^[19], and *NAT2*, *GST* and *CYP2E1* polymorphisms and antituberculosis-DILI^[20]. Recently, Li *et al.*^[17] reported an association between *HLA-B*35:01* and PM-DILI.

However, HLA genotyping is time consuming and expensive compared with the detection of single-nucleotide polymorphisms (SNPs). Here, we present a systematic multicenter study that aimed to identify SNP risk factors for PM-DILI.

MATERIALS AND METHODS

Participants

The 73 adult PM-DILI patients involved in our study were recruited at Peking University First Hospital (Beijing, China), the Fifth People's Hospital of Wuxi (Jiangsu, China), the Third Hospital of Qinhuangdao (Hebei, China), and Yantai City Hospital for Infectious Diseases (Shandong, China) from January 2012 to October 2017. An additional 118 adult other drug-induced liver injury (other-DILI) patients and 191 adult healthy controls were recruited at Peking University First Hospital (Beijing, China). The DILI patients met one of the following criteria: Alanine aminotransferase (ALT) levels $\geq 5 \times$ the upper limit of normal (ULN), ALT $\geq 3 \times$ ULN and total bilirubin level (TBil) $\geq 2 \times$ ULN, alkaline phosphatase (ALP) level $\geq 2 \times$ ULN, or pathological diagnosis of DILI. Patients who took both other drugs and single PM or PM preparations were excluded. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Human Research Committee of Peking University First Hospital (approval number, 2015[892]). The participants were Han Chinese and provided written informed consent before donating blood samples. Subjects with viral hepatitis, autoimmune liver diseases, alcoholic liver disease and non-alcoholic fatty liver disease were excluded. The overall study design is shown in Figure 1.

Assessment of causality

The causality of DILI cases was evaluated by a panel of two hepatologists, and all patients had a Roussel Uclaf Causality Assessment Method (RUCAM) score of 3 or greater. RUCAM scores were grouped into likelihood levels of "highly probable" (≥ 9), "probable" (6-8), "possible" (3-5), "unlikely" (1-2), and "excluded" (≤ 0)^[21].

Assessment of clinical patterns of liver injury

According to the Council for International Organizations of Medical Sciences criteria^[22], the clinical pattern of DILI was based on the earliest identified liver biochemistry abnormalities and was defined using the R value. R values > 5 were classified as hepatocellular injury, < 2 as cholestatic injury, and 2-5 as mixed injury, where $R = (\text{ALT} / \text{ULN}) / (\text{ALP} / \text{ULN})$.

DNA preparation

Genomic DNA was extracted from lymphocytes using DNA Blood Mini Kits (QIAGEN, Hilden, Germany) according to the manufacturer's instructions and stored at -80°C in Peking University First Hospital.

Candidate SNP selection and detection

Whole-exome sequencing was carried out for 8 PM-DILI patients and 8 healthy controls who were randomly selected from the 73 PM-DILI patients and 191 healthy

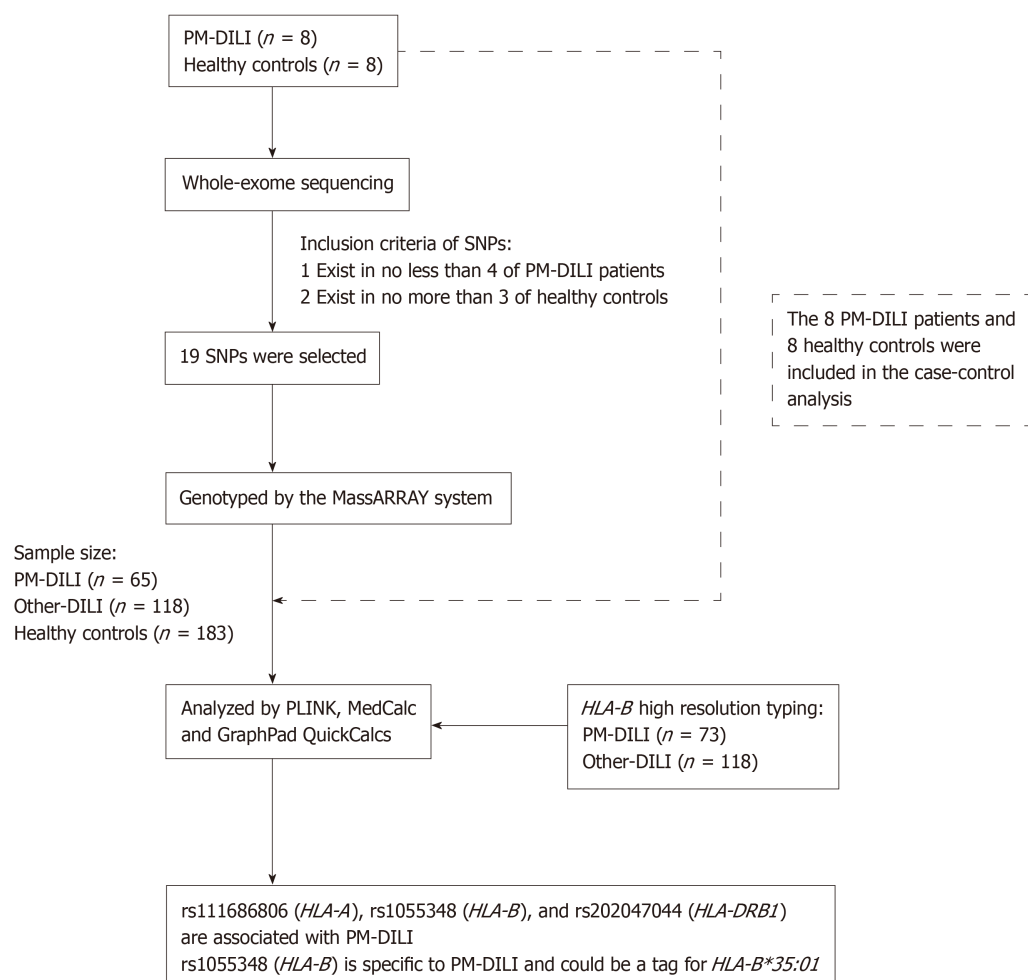


Figure 1 Flow chart of the study design. SNPs: Single-nucleotide polymorphisms; PM-DILI *Polygonum multiflorum*-induced liver injury; Other-DILI: Other drug-induced liver injury.

controls. Whole-exome sequencing was performed by GENEWIZ, Inc. with a depth of 50-fold and a coverage of 90%. All sequencing data are available through the NCBI Sequence Read Archive under accession number PRJNA564440. A total of 19 candidate SNPs that were found in no less than 4 of the PM-DILI patients and no more than 3 of the healthy controls were selected. Detailed information on the SNPs is shown in Table 1 and can be obtained from the SNP database system of the National Center for Biotechnology Information (<http://www.ncbi.nlm.nih.gov/snp>).

The 19 candidate SNPs were then screened in 65 PM-DILI patients, 118 other-DILI patients and 183 healthy controls using the MassARRAY system which can test up to 40 target-specific DNA fragments in a single reaction. Quality control of the detection data was performed using PLINK software (version 1.07). SNPs with genotype failure rates larger than 5% (2 SNPs), a minor allele frequency less than 5% (1 SNP), or Hardy-Weinberg equilibrium test P values < 0.05 (8 SNPs) were excluded. As a result, 8 SNPs were included in the analysis. Statistical analysis was performed on the 8 SNPs among 73 PM-DILI patients, 118 other-DILI patients and 191 healthy controls.

HLA-B high-resolution genotyping

To investigate the relationship between rs1055348 and HLA-B*35:01, high-resolution genotyping of HLA-B in the 73 PM-DILI patients and 118 other-DILI patients was performed by BFR Gene Diagnostics Co., Ltd. The 10689 healthy individuals from the Han-MHC database were selected as study controls^[23]. Sensitivity, specificity, positive predictive value, negative predictive value and Cohen's kappa coefficient were calculated.

Statistical analysis

A comparison of the clinical features between the PM-DILI group and other-DILI group was performed using SPSS software, version 20.0 (SPSS Inc., Chicago, IL, United States). Quantitative variables were analyzed by Student's t test. Categorical

Table 1 Candidate single-nucleotide polymorphisms selected from whole-exome sequencing of 8 *Polygonum multiflorum*-induced liver injury patients and 8 healthy controls

| SNP ID | Chromosome | Gene | Number of PM-DILI patients with candidate SNP | Number of healthy controls with candidate SNP |
|--------------------------|------------|----------|---|---|
| rs1042597 | 2 | UGT1A8 | 6 | 0 |
| rs3795958 ³ | 2 | DRC1 | 6 | 3 |
| rs111686806 | 6 | HLA-A | 5 | 0 |
| rs2231119 | 6 | HLA-A | 8 | 0 |
| rs1136903 ³ | 6 | HLA-A | 6 | 0 |
| rs115662401 ³ | 6 | HLA-A | 6 | 0 |
| rs117162979 ³ | 6 | HLA-A | 5 | 2 |
| rs1059516 ³ | 6 | HLA-A | 5 | 0 |
| rs1050341 ² | 6 | HLA-B | 5 | 0 |
| rs1055348 | 6 | HLA-B | 5 | 0 |
| rs2308655 ³ | 6 | HLA-B | 6 | 0 |
| rs1050458 ¹ | 6 | HLA-B | 5 | 0 |
| rs1051488 ¹ | 6 | HLA-B | 6 | 0 |
| rs202047044 | 6 | HLA-DRB1 | 4 | 0 |
| rs111534875 | 6 | HLA-DRB1 | 5 | 3 |
| rs78246137 | 6 | HLA-DRB1 | 7 | 0 |
| rs2308768 ³ | 6 | HLA-DRB1 | 5 | 0 |
| rs1799931 ³ | 8 | NAT2 | 4 | 0 |
| rs5747933 | 22 | PRODH | 7 | 3 |

¹Single-nucleotide polymorphism (SNPs) detected in fewer than 95% of individuals (2 SNPs).

²SNPs with minor allele frequency < 5% (1 SNPs).

³SNPs with Hardy-Weinberg equilibrium test *P* values < 0.05 (8 SNPs). PM-DILI: *Polygonum multiflorum*-induced liver injury.

variables were compared using the chi-square or Fisher's exact test, and the results are shown as a number and percentage. Results were considered statistically significant at $P < 0.05$ (2-tailed).

PLINK (version 1.07) software was used to compare allele frequencies between groups. We used the chi-square or Fisher's exact test to compare allele frequencies between groups. Logistic regression was applied to investigate independent risk factors for PM-DILI. We set a threshold of $P < 6.25 \times 10^{-3}$ by Bonferroni correction for SNPs and *HLA-B* alleles.

Sensitivity, specificity, and positive and negative predictive values were analyzed by MedCalc for Windows, version 15.2 (MedCalc Software, Ostend, Belgium). Cohen's kappa coefficient was calculated using GraphPad QuickCalcs (GraphPad Software Inc., La Jolla, CA, United States).

RESULTS

Clinical features

Of the 73 PM-DILI patients recruited, disease was caused in 11 patients by PM alone and in 58 patients by PM preparations; 4 patients were rechallenged with PM preparations. Of the 118 other-DILI patients, 65 cases were mainly induced by Chinese herbal medicines and 53 by Western medicines. The top 6 causative agents in the other-DILI group were antibiotics (18), *Radix Bupleuri* (16), statins (11), *Fructus Psoraleae* (10), *Cortex Dictamnii* (8), and methimazole (4). There were more female and younger patients in the PM-DILI group ($P < 0.05$). ALT, aspartate aminotransferase (AST) and TBil levels were higher in the PM-DILI group ($P < 0.05$), although body mass index, ALP level, distribution of injury type and RUCAM scores were not significantly different between the two groups (Table 2).

Association between SNPs and PM-DILI

The frequencies of rs111686806 in the *HLA-A* gene, rs1055348 in the *HLA-B* gene and rs202047044 in the *HLA-DRB1* gene were significantly higher in the PM-DILI group than in the control group ($P < 6.25 \times 10^{-3}$); no significant difference was found for the

Table 2 Demographic and clinical features of *Polygonum multiflorum*-induced liver injury patients and other drug-induced liver injury patients

| Characteristics | PM-DILI (n = 73) | Other-DILI (n = 118) | P |
|----------------------------------|--------------------|----------------------|---------|
| Mean age, yr | 47.7 ± 15.8 | 52.3 ± 14.2 | 0.045 |
| Female, n (%) | 56 (76.7) | 74 (62.7) | 0.044 |
| BMI | 23.6 ± 3.2 | 24.0 ± 3.7 | 0.447 |
| Medication time ¹ , d | 30 (45) | 30 (60.8) | 0.097 |
| ALT (U/L) | 1105.0 ± 679.9 | 626.3 ± 670.1 | < 0.001 |
| AST (U/L), n | 797.7 ± 557.3 (65) | 485.6 ± 596.5 (118) | 0.001 |
| ALP (U/L), n | 148.5 ± 58.4 (59) | 160.5 ± 212.3 (105) | 0.673 |
| TBil (mg/dL), n | 112.9 ± 107.2 (61) | 76.9 ± 92.5 (99) | 0.026 |
| Injury type | n = 59 | n = 105 | 0.917 |
| Hepatocellular | 57 | 82 | |
| Cholestatic | 1 | 12 | |
| Mixed | 1 | 11 | |
| RUCAM score | | | 0.319 |
| 3-5 (Possible) | 7 | 20 | |
| 6-8 (Probable) | 53 | 82 | |
| ≥ 9 (Highly probable) | 13 | 16 | |

¹A variable is expressed as the median (interquartile range). Other variables are expressed as the mean ± standard deviation (SD). BMI: Body mass index; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; TBil: Total bilirubin level; RUCAM: Roussel Uclaf causality assessment method; Other-DILI: Other drug-induced liver injury; PM-DILI: *Polygonum multiflorum*-induced liver injury.

other 5 SNPs (Table 3). Logistic regression analysis showed that rs111686806, rs1055348, and rs202047044 were risk factors for PM-DILI compared with the control group.

Notably, only rs1055348 in the *HLA-B* gene exhibited a significantly different distribution between the PM-DILI group and the other-DILI group. The frequency of rs1055348 was 42.5% in the PM-DILI group and 13.6% in the other-DILI group, a difference that was significant ($P = 1.84 \times 10^{-10}$). A logistic regression model showed that rs1055348 was a risk factor for increased susceptibility to PM-DILI compared with other-DILI [Odds ratio (OR) = 10.06, 95% confidence interval (CI): 5.06-20.0] and healthy controls (OR = 13.62, 95%CI: 7.16-25.9).

Moreover, in the PM-DILI group, 10 of 11 (90.91%) PM-DILI patients whose disease was caused by PM alone, 4 of 4 (100%) PM-DILI patients who were rechallenged with PM preparations and 44 of 58 (75.86%) PM-DILI patients whose disease was caused by PM preparations carried the rs1055348 G allele. No significant difference was found between the three subgroups ($P = 0.305$).

Furthermore, we compared biochemical characteristics between patients with the rs1055348 G allele and those without the rs1055348 G allele (Table 4). In both the PM-DILI and other-DILI groups, patients with the rs1055348 G allele had higher ALT and AST levels than did patients without the rs1055348 G allele ($P < 0.05$). No significant difference in the TBil level was found.

Association between *HLA-B* alleles and PM-DILI

HLA-B alleles showed considerable variability. A total of 48 alleles were identified in the 73 PM-DILI patients and 118 other-DILI patients, and the distribution of alleles with frequencies > 1% is shown in Figure 2 and Figure 3. The frequency of *HLA-B**35:01 was 41.1% in the PM-DILI group compared with 11.9% ($P = 4.30 \times 10^{-11}$, OR = 11.11, 95%CI: 5.57-22.19) in the other-DILI group and 2.7% ($P = 6.22 \times 10^{-166}$, OR = 62.62, 95%CI: 35.91-109.20) in the Han-MHC database of 10689 healthy control subjects^[23]. These results validated the previous conclusion that *HLA-B**35:01 is a genetic risk factor for PM-DILI^[17].

Association between the *HLA-B**35:01 allele and rs1055348 in the *HLA-B* gene

The sensitivity, specificity, positive predictive value, negative predictive value and Cohen's kappa coefficient of the rs1055348 G allele for *HLA-B**35:01 are shown in Table 5. Both in the PM-DILI group and the other-DILI group, the rs1055348 G allele had 100% sensitivity and > 95% specificity for *HLA-B**35:01, which indicated that

Table 3 Association between the 8 single-nucleotide polymorphisms and *Polygonum multiflorum*-induced liver injury

| SNP ID | Chromosome (Gene) | Minor allele | Minor allele frequency (%) | | | PM-DILI vs control | | PM-DILI vs Other-DILI | |
|-------------|-----------------------|--------------|----------------------------|----------------------|-------------------|-------------------------|-------------------|-------------------------|------------------|
| | | | PM-DILI (n = 73) | Other-DILI (n = 118) | Control (n = 191) | P value | OR (95%CI) | P value | OR (95%CI) |
| rs1055348 | 6 (<i>HLA-B</i>) | G | 42.5% | 13.6% | 8.6% | 1.72×10^{-19a} | 13.62 (7.16-25.9) | 1.84×10^{-10a} | 10.06 (5.06-20) |
| rs202047044 | 6 (<i>HLA-DRB1</i>) | C | 22.9% | 17.5% | 8.1% | 4.64×10^{-6a} | 4.1 (2.25-7.47) | 0.212 | 1.53 (0.84-2.76) |
| rs111686806 | 6 (<i>HLA-A</i>) | T | 27.2% | 27.6% | 11.6% | 1.72×10^{-5a} | 3.96 (2.21-7.1) | 0.937 | 0.97 (0.53-1.77) |
| rs2231119 | 6 (<i>HLA-A</i>) | A | 26.0% | 24.4% | 36.8% | 0.020 | 0.57 (0.36-0.90) | 0.714 | 1.11 (0.66-1.85) |
| rs111534875 | 6 (<i>HLA-DRB1</i>) | A | 29.6% | 32.0% | 20.1% | 0.022 | 1.64 (1.06-2.55) | 0.622 | 0.89 (0.57-1.40) |
| rs1042597 | 2 (<i>UGT1A8</i>) | G | 42.1% | 44.0% | 51.0% | 0.071 | 0.71 (0.48-1.04) | 0.723 | 0.93 (0.61-1.41) |
| rs78246137 | 6 (<i>HLA-DRB1</i>) | T | 29.5% | 31.6% | 22.5% | 0.095 | 1.45 (0.94-2.25) | 0.656 | 0.9 (0.57-1.43) |
| rs5747933 | 22 (<i>PRODH</i>) | T | 13.6% | 16.7% | 10.2% | 0.279 | 1.35 (0.77-2.39) | 0.424 | 0.8 (0.45-1.42) |

^aP value that reached the threshold of $P < 6.25 \times 10^{-3}$ by Bonferroni correction. Other-DILI: Other drug-induced liver injury; SNP: Single-nucleotide polymorphisms; PM-DILI: *Polygonum multiflorum*-induced liver injury; OR: Odd ratio; CI: Confidence interval.

*HLA-B*35:01* could be tagged by rs1055348. And a nearly perfect agreement was found between the rs1055348 G allele and *HLA-B*35:01* with $\kappa = 0.959$ in the PM-DILI group and $\kappa = 0.911$ in the other-DILI group.

DISCUSSION

It is difficult to assess the relationship between PM and liver injury or to predict PM-DILI. In China, the use of PM is often combined with Western drugs. Identification of a specific genetic biomarker of PM-DILI is helpful for the diagnosis or prediction of PM-DILI. We successfully identified three SNPs, rs111686806 in the *HLA-A* gene, rs1055348 in the *HLA-B* gene and rs202047044 in the *HLA-DRB1* gene, to be risk factors for PM-DILI compared with the control group. *HLA-A* and *HLA-B* are *HLA* class I alleles associated with cytotoxic CD8⁺ T cell-mediated liver injury, while *HLA-DRB1* is an *HLA* class II allele involved in the interaction between antigen-presenting cells and CD4⁺ T cells, which leads to liver injury^[24]. These results indicate that the adaptive immunity response may play an important role in the pathogenesis of PM-DILI.

Notably, when compared with that in the other-DILI group, rs1055348 in the *HLA-B* gene was the only potential genetic risk factor, which suggests that rs1055348 in the *HLA-B* gene is specific to PM-DILI and may help strengthen the diagnosis of PM-DILI, particularly in distinguishing PM-DILI from other-DILI.

rs1055348 is a T > G or T > C mutation in the 3'-untranslated region of the *HLA-B* gene. The 3'-untranslated region of a gene is best known for regulating mRNA expression, including localization, translation, and degradation^[25]. Thus, rs1055348 in the *HLA-B* gene may increase susceptibility to PM-DILI by regulating expression of the *HLA-B* gene.

On the other hand, *HLA*-associated DILI is normally correlated with *HLA* genotyping which has different amino acid sequences, but not the untranslated region. Therefore, another mechanism may be that rs1055348 in the *HLA-B* gene may be a tag for one *HLA-B* genotype. *HLA-B*35:01* was reported to be a genetic risk factor for PM-DILI and a potential biomarker for predicting PM-DILI^[17]. The clinical performance of rs1055348 in the *HLA-B* gene to become a tag for *HLA-B*35:01* has been evaluated in African, Ad Mixed American, East Asian and European populations from the 1000 Genomes Dataset^[26], and it was concluded that rs1055348 may not be suitable due to a low specificity of 80.22%.

Regardless, in the current study, we evaluated the potential for the rs1055348 G allele in the *HLA-B* gene to become a tag for *HLA-B*35:01*. In both the PM-DILI group and the other-DILI group, the sensitivity was 100%, and the specificity was > 95%.

Table 4 Biochemical characteristics between patients with the rs1055348 G allele and those without the rs1055348 G allele

| Variables | PM-DILI | | | Other-DILI | | |
|----------------------------------|--------------------------------------|---|----------|--------------------------------------|---|---------|
| | With the rs1055348 G allele (n = 58) | Without the rs1055348 G allele (n = 15) | P value | With the rs1055348 G allele (n = 32) | Without the rs1055348 G allele (n = 86) | P value |
| Age, mean \pm SD, yr | 46.7 \pm 15.1 | 51.2 \pm 16.2 | 0.317 | 49.2 \pm 14.4 | 53.4 \pm 14.0 | 0.152 |
| Female, n (%) | 42 (72.4) | 14 (93.3) | 0.167 | 22 (68.8) | 52 (60.5) | 0.408 |
| BMI | 23.7 \pm 2.9 | 23.0 \pm 3.0 | 0.407 | 23.8 \pm 3.0 | 24.0 \pm 3.9 | 0.774 |
| Medication time ¹ , d | 30 (40.8) | 30 (22) | 0.533 | 46.5 (63.5) | 30 (54) | 0.269 |
| ALT (U/L) | 1234.8 \pm 609.5 | 603.2 \pm 517.0 | < 0.0001 | 936.7 \pm 866.7 | 510.8 \pm 532.7 | 0.013 |
| AST (U/L), n | 876.9 \pm 537.8 (51) | 509.2 \pm 507.6 (14) | 0.025 | 712.8 \pm 691.5 (32) | 401.0 \pm 513.4 (86) | 0.009 |
| ALP (U/L), n | 155.8 \pm 59.8 (48) | 116.7 \pm 40.0 (11) | 0.044 | 140.3 \pm 99.4 (28) | 167.8 \pm 240.8 (77) | 0.559 |
| Tbil (mg/dL), n | 123.9 \pm 110.5 (48) | 70.7 \pm 84.9 (13) | 0.113 | 85.7 \pm 104.8 (29) | 73.3 \pm 87.4 (70) | 0.547 |

¹A variable is expressed as the median (interquartile range). Variables are expressed as the mean \pm SD. PM-DILI: *Polygonum multiflorum*-induced liver injury; Other-DILI: Other drug-induced liver injury; BMI: Body mass index; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; Tbil: Total bilirubin level.

The 100% sensitivity and > 95% specificity were considered sufficient for the clinical utility of tagging SNPs in a previous study^[27]. Thus, the rs1055348 G allele in the *HLA-B* gene may serve as a tag for *HLA-B*35:01* in PM-DILI patients and other-DILI patients in the Han Chinese population.

Furthermore, compared with *HLA-B*35:01* typing, testing of rs1055348, a tag SNP, is cost-effective and time efficient. In fact, real-world experience demonstrated that using tag SNP rs116488202 to screen for axial spondyloarthritis can yield a 94% reduction in costs relative to cases in which all patients were assessed with *HLA-B*27*^[28], which suggests that screening for tag SNP rs1055348 before consuming PM would produce considerable economic benefits.

Studies on the biochemical characteristics of traditional Chinese medicines and Western medicines are controversial^[4,5,29]. In the current study, the distribution of gender, age, ALT level, AST level and Tbil level were significantly different between the PM-DILI and other-DILI groups ($P < 0.05$). Patients with the rs1055348 G allele showed higher levels of ALT and AST than did those without the rs1055348 G allele in both groups, which indicates that immune factors are involved not only in the onset of DILI but also in the process of inflammation. In addition, the higher frequency of rs1055348 may be another reason for the higher levels of ALT and AST in the PM-DILI group. However, the causative agents in the other DILI group consisted of multiple types of drugs, including both Chinese herbal medicines and Western medicines. More cases are needed to further compare the clinical features of PM-DILI with other-DILI.

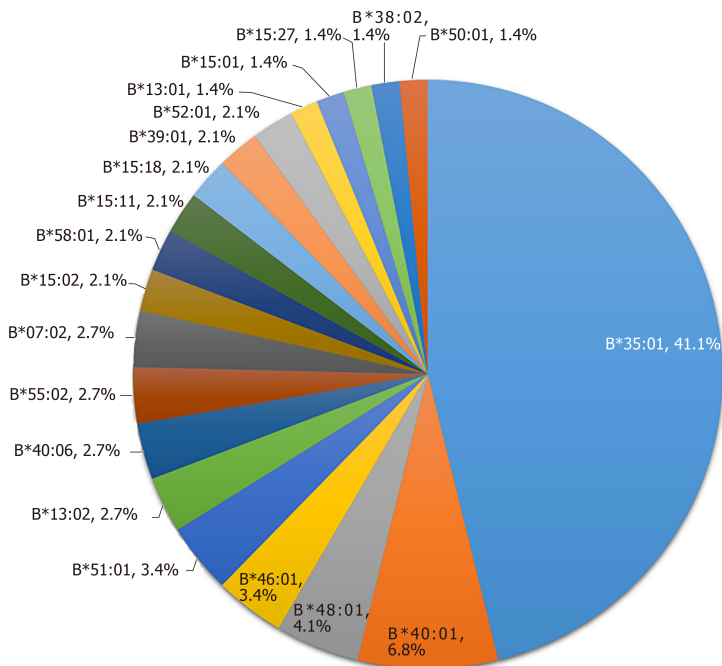
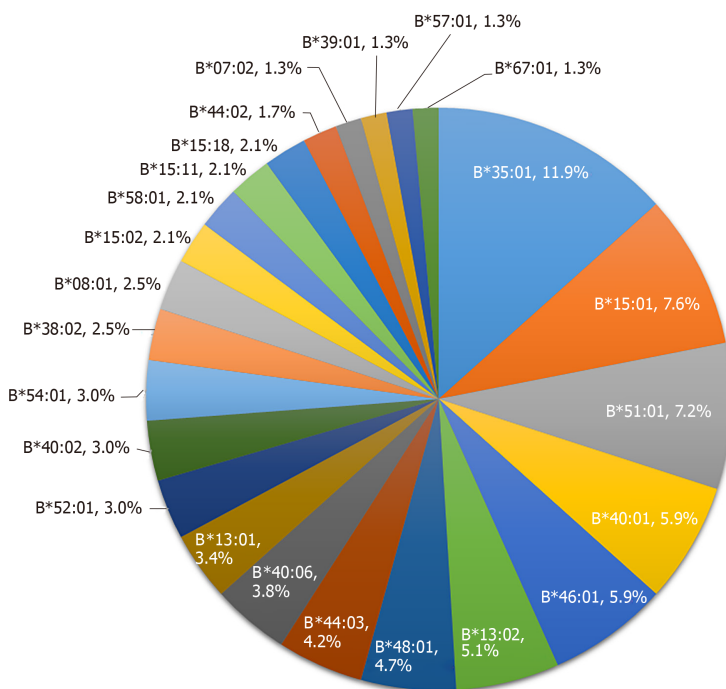
The limitations of this study include the small sample size and number of patients taking PM only. A prospective study with a larger sample size of patients taking PM only is needed to further evaluate the role of rs1055348 in the *HLA-B* gene in PM-DILI.

In summary, our systematic study identified rs111686806 in the *HLA-A* gene, rs1055348 in the *HLA-B* gene, and rs202047044 in the *HLA-DRB1* gene as genetic risk factors for PM-DILI, of which, rs1055348 in the *HLA-B* gene was specific to PM-DILI compared to other drugs. As a tag for *HLA-B*35:01*, rs1055348 in the *HLA-B* gene may become an alternative predictive biomarker of PM-DILI. Further study to explore the mechanisms of rs1055348 in PM-DILI is needed.

Table 5 Performance of the rs1055348 G allele for HLA-B*35:01 in the *Polygonum multiflorum*-induced liver injury group (*n* = 73) and the other drug-induced liver injury group (*n* = 78)

| Group | TP | TN | FP | FN | Sensitivity (95%CI) | Specificity (95%CI) | PPV (95%CI) | NPV (95%CI) | κ (95%CI) |
|------------|----|-----|----|----|---------------------|---------------------|------------------|--------------------|---------------------|
| PM-DILI | 60 | 84 | 2 | 0 | 100.0 (94.0-100.0) | 97.7 (91.9-99.7) | 96.8 (88.8-99.6) | 100.0 (95.7-100.0) | 0.959 (0.879-1.000) |
| Other-DILI | 28 | 204 | 4 | 0 | 100.0 (87.7-100.0) | 98.1 (95.1-99.5) | 87.5 (71.0-96.5) | 100.0 (98.2-100.0) | 0.911 (0.825-0.996) |

TP: True positive; TN: True negative; FP: False positive; FN: False negative; PPV: Positive predictive value; NPV: Negative predictive value; Other-DILI: Other drug-induced liver injury; PM-DILI: *Polygonum multiflorum*-induced liver injury; CI: Confidence interval.

**Figure 2** Distribution of HLA-B alleles with frequencies > 1% in the *Polygonum multiflorum*-induced liver injury group (*n* = 73).**Figure 3** Distribution of HLA-B alleles with frequencies > 1% in the other drug-induced liver injury group (*n* = 118).

ARTICLE HIGHLIGHTS

Research background

Polygonum multiflorum (PM) is a well-known traditional Chinese herbal medicine. However, reports of PM-induced liver injury (PM-DILI) have been increasing in recent years. To increase the safe use of PM, the identification of biomarkers to prevent and diagnose PM-DILI is essential.

Research motivation

Susceptibility to DILI is considered to be genetically determined. Recently, an association between *HLA-B*35:01* and PM-DILI was reported. However, *HLA* genotyping is time consuming and expensive compared with the detection of single-nucleotide polymorphisms (SNPs). The identification of SNPs which could serve as biomarkers of PM-DILI would improve the application of PM and produce considerable economic benefits.

Research objectives

The objective of this study was to identify SNPs that indicate susceptibility to PM-DILI.

Research methods

The study enrolled 73 PM-DILI patients, 118 other drug-induced liver injury (other-DILI) patients and 191 healthy controls. Whole-exome sequencing was performed on 8 PM-DILI patients and 8 healthy controls who were randomly selected from 73 PM-DILI patients and 191 healthy controls. Nineteen SNPs which were selected from previous whole-exome sequencing were screened in the remaining subjects using the MassARRAY system. *HLA-B* high-resolution genotyping was performed for 73 PM-DILI patients and 118 other-DILI patients. The Han-MHC database was selected as a population control for *HLA-B* analysis. SPSS (version 20.0, SPSS Inc., Chicago, IL, United States), PLINK software (version 1.07), MedCalc for Windows (version 15.2, MedCalc Software, Ostend, Belgium), and GraphPad QuickCalcs (GraphPad Software Inc., La Jolla, CA, United States) were used for statistical analyses.

Research results

Compared with the control group, three SNPs, rs111686806 in the *HLA-B* gene, rs1055348 in the *HLA-B* gene, and rs202047044 in the *HLA-DRB1* gene were associated with PM-DILI. Only rs1055348 had a significantly higher frequency in the PM-DILI group than in the other-DILI group ($P = 1.84 \times 10^{-10}$), which suggested that rs1055348 was a specific risk factor for PM-DILI. *HLA-B*35:01* was confirmed to be associated with PM-DILI. Furthermore, rs1055348 may serve as a tag for *HLA-B*35:01* with 100% sensitivity and > 95% specificity.

Research conclusions

rs111686806, rs1055348 and rs202047044 are associated with PM-DILI, and rs1055348 is specific to PM-DILI. As a tag for *HLA-B*35:01*, rs1055348 may be used as an alternative predictive biomarker of PM-DILI.

Research perspectives

Screening for tag rs1055348 before consuming PM would improve the safe use of PM and produce considerable economic benefits. A prospective study with a larger sample size of patients taking PM only is needed to further evaluate the role of rs1055348 in the *HLA-B* gene in PM-DILI.

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