The roles of transmembrane 6 superfamily member 2 rs58542926 polymorphism in chronic liver disease: A meta-analysis of 24,147 subjects

Xinpei Chen | Pengcheng Zhou | De Luo | Bo Li | Song Su

Abstract

Background: Some genetic association studies tried to investigate potential associations of transmembrane 6 superfamily member 2 (TM6SF2) polymorphisms with chronic liver disease. However, the results of these studies were not consistent. Thus, we performed the present meta-analysis to explore associations between TM6SF2 polymorphisms and chronic liver disease in a larger pooled population.

Methods: Systematic literature research of PubMed, Web of Science, Embase, and CNKI was performed to identify eligible studies for pooled analyses. I² statistics were employed to assess between-study heterogeneities. If I² was greater than 50%, random-effect models (REMs) would be used to pool the data. Otherwise, fixed-effect models (FEMs) would be applied for synthetic analyses.

Results: Totally 28 studies were included for analyses (13,137 cases and 11,010 controls). The pooled analyses showed that rs58542926 polymorphism was significantly associated with chronic liver disease in overall population (dominant model: \( p < 0.0001, \text{OR} = 0.70, 95\% \text{CI} = 0.64-0.76, \text{I}^2 = 47\% \)); recessive model: \( p < 0.0001, \text{OR} = 2.94, 95\% \text{CI} = 2.05-4.20, \text{I}^2 = 0\% \); over-dominant model: \( p < 0.0001, \text{OR} = 1.34, 95\% \text{CI} = 1.23-1.47, \text{I}^2 = 0\% \); allele model: \( p < 0.0001, \text{OR} = 0.68, 95\% \text{CI} = 0.63-0.73, \text{I}^2 = 47\% \)), and these significant findings were further confirmed in both Asians and Caucasians. Stratified analyses by type of disease revealed similar positive results in hepatocellular carcinoma (HCC), cirrhosis, alcoholic liver disease (ALD) and NAFLD (Nonalcoholic fatty liver disease), but not in chronic hepatitis B infection (CHB) and chronic hepatitis C infection (CHC).

Conclusions: These results suggested that TM6SF2 rs58542926 could be used to identify individuals at higher susceptibility to chronic liver disease, especially for HCC, cirrhosis, ALD, and NAFLD.

Keywords

chronic liver disease, meta-analysis, rs58542926 polymorphisms, transmembrane 6 superfamily member 2 (TM6SF2)
1 | INTRODUCTION

Chronic liver disease is a major global health threat and it currently accounts for approximately 3.5% of all deaths worldwide (Asrani, Devarbhavi, Eaton, & Kamath, 2019). Cirrhosis and hepatocellular carcinoma (HCC) are the two leading causes of liver-related deaths. Annually, cirrhosis causes 1.16 million deaths, and HCC causes 788,000 deaths, making them the 11th and 16th most common causes of death respectively (Marcellin & Kutala, 2018; Peery et al., 2019). The etiologies of chronic liver disease are highly complex. Although excessive alcohol intake, obesity, and chronic viral infection were already verified to be pathogenic factors of different types of chronic liver disease (Lee et al., 2012; Saracco et al., 2016), the fact that the likelihoods of developing chronic liver disease in these exposed to above mentioned etiological factors were quite different suggested that genetic factors also played crucial parts in the pathogenesis of chronic liver disease.

The transmembrane 6 superfamily 2 (TM6SF2) gene is responsible for regulating lipid metabolism in the liver. Previous experimental studies demonstrated that TM6SF2 siRNA inhibition was associated with a reduced secretion of triglyceride-rich lipoproteins and an increased triglyceride aggregation in hepatocytes, whereas TM6SF2 overexpression was associated with reduced liver cell steatosis (Li et al., 2018; Mahdessian et al., 2014). Recently, two genome-wide association studies conducted by Kozlitina et al. (2014) and Liu et al. (2014) found that the transmembrane 6 superfamily member 2 (TM6SF2) rs58542926 polymorphism (a functional variant that was associated with altered gene expression levels) was not only associated with higher liver fat levels, but also associated with elevated serum levels of alanine transaminase and advanced liver fibrosis, supporting that this polymorphism might play crucial roles in the development of different types of liver diseases. Since then, several genetic association studies were performed in diverse populations to estimate potential associations between rs58542926 polymorphism and chronic liver disease, with inconsistent results (Bale et al., 2017; Krawczyk et al., 2017; Manchiero et al., 2017; Milano et al., 2015). Therefore, we conducted a meta-analysis of all relevant studies to more comprehensively analyze the effects of TM6SF2 polymorphisms on individual susceptibility to chronic liver disease in a larger pooled population.

2 | MATERIALS AND METHODS

We reported this meta-analysis as suggested by the Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline (Moher, Liberati, Tetzlaff, Altman, & PRISMA group, 2009).
If $I^2$ was greater than 50%, random-effect models (REMs) would be used to pool the data on account of significant heterogeneities. Otherwise, fixed-effect models (FEMs) would be used for synthetic analyses. Subgroup analyses by ethnicity of participants and type of disease were performed. Stabilities of synthetic results were evaluated with sensitivity analyses, and publication biases were evaluated with funnel plots.

3 | RESULTS

3.1 | Characteristics of included studies

The initial literature search found 263 potential relevant articles. Among these articles, totally 28 studies met the inclusion criteria and thus were included for pooled analyses (see Figure 1). The NOS score of eligible articles ranged from 7 to 8, which indicated that all included studies were of high quality. Baseline characteristics of included studies were shown in Table 1.

3.2 | Overall and subgroup analyses

The results of overall and subgroup analyses were summarized in Table 1. To be brief, 13,137 cases and 11,010 controls were eligible for analyses, the pooled analyses showed that rs58542926 polymorphism was significantly associated with chronic liver disease in overall population (dominant model: $p < 0.0001$, $OR = 0.70$, 95% CI = 0.64–0.76, $I^2 = 47%$; recessive model: $p < 0.0001$, $OR = 2.94$, 95% CI = 2.05–4.20, $I^2 = 0%$; over-dominant model: $p < 0.0001$, $OR = 1.34$, 95% CI = 1.23–1.47, $I^2 = 0%$; allele model: $p < 0.0001$, $OR = 0.68$, 95% CI = 0.63–0.73, $I^2 = 47%$), and these significant findings were also confirmed in both Asians (dominant, recessive, over-dominant, and allele models) and Caucasians (dominant, recessive, over-dominant, and allele models). Further stratified analyses by type of disease revealed similar positive results in hepatocellular carcinoma (HCC), cirrhosis, alcoholic liver disease (ALD), and NAFLD (Nonalcoholic fatty liver disease), but not in chronic hepatitis B infection (CHB) and chronic hepatitis C infection (CHC) (see Table 2).

3.3 | Sensitivity analyses

We performed sensitivity analyses to test the effects of individual study on pooled results. No any altered results were observed in overall and subgroup comparisons, which indicated that our findings were statistically robust.

3.4 | Publication biases

We used funnel plots to assess publication biases. We did not find obvious asymmetry of funnel plots in any comparisons, which suggested that our findings were unlikely to be impacted by severe publication biases (see Figure S1).

4 | DISCUSSION

As far as we know, this is to date the first meta-analysis on associations of TM6SF2 polymorphisms with chronic liver disease, and our pooled analyses suggested that rs58542926 polymorphism was significantly associated with chronic liver disease in both Asians and Caucasians. Further stratified analyses revealed similar positive results in HCC, cirrhosis, ALD and NAFLD, but not in CHB and CHC.

There are several notable points about this meta-analysis. Firstly, although several different types of chronic liver disease were combined for analyses, between-study heterogeneities in overall analyses were only mild, which suggested that pool the results of these studies was feasible. Secondly, subgroup analyses by type of disease suggested that the positive results were mainly driven by HCC, cirrhosis, ALD, and NAFLD, but not in CHB and CHC.

Considering that the sample sizes of pooled analyses with regard to the ALD, CHB, and CHC were still relatively small. It is possible that our study was still not statistically adequate
to detect the actual associations between rs58542926 polymorphism and these liver diseases. Therefore, further studies with larger sample sizes still need to test the associations between rs58542926 polymorphism and chronic liver disease, especially for ALD, CHB and CHC. Thirdly, the pathogenesis of chronic liver disease is extremely complex, and therefore the probability that a specific genetic polymorphism could significantly contribute to its development is low, and

**TABLE 1** The characteristics of included studies for *TM6SF2* rs58542926 polymorphism and chronic liver disease

| First author (year) | Country | Ethnicity | Type of disease | Sample size | Genotype distribution | P-value for HWENOS score | NOS score |
|---------------------|---------|-----------|-----------------|-------------|-----------------------|------------------------|-----------|
| Bale (2017)         | India   | Mixed     | NAFLD           | 250/232     | 171/66/13             | 0.947                  | 8         |
| Buch (2015)         | Germany | Caucasian | ALD             | 712/1426    | NA                    | NA                     | NA        |
| Coppola (2015)      | Italy   | Caucasian | Cirrhosis       | 101/47      | 85/16/0               | 0.882                  | 7         |
| Donati (2017)       | Italy   | Caucasian | HCC             | 132/633     | 109/19/4              | 0.121                  | 8         |
| Eslam (2016)        | Australia | Caucasian | CHB             | 507/228     | 450/55/2              | 0.901                  | 8         |
| Eslam (2016)        | Australia | Caucasian | CHC             | 2023/228    | 1778/235/10           | 0.901                  | 8         |
| Eslam (2016)        | Australia | Caucasian | NAFLD           | 502/228     | 391/100/11            | 0.901                  | 8         |
| Falleti (2016)      | Italy   | Caucasian | Cirrhosis       | 511/228     | 443/66/2              | 0.381                  | 8         |
| Falleti (2016)      | Italy   | Caucasian | CHB + CHC       | 285/228     | 255/30/0              | 0.381                  | 8         |
| Falleti (2016)      | Italy   | Caucasian | ALD             | 226/228     | 188/36/2              | 0.381                  | 8         |
| Falleti (2016)      | Italy   | Caucasian | NAFLD           | 150/228     | 123/26/1              | 0.381                  | 8         |
| Goffredo (2016)     | Italy   | Caucasian | NAFLD           | 158/296     | 135/22/1              | 0.429                  | 7         |
| Grove (2018)        | UK      | Caucasian | NAFLD           | 186/439     | NA                    | NA                     | NA        |
| Jiang (2018)        | China   | Asian     | CHB             | 288/106     | 254/33/1              | 0.610                  | 8         |
| Koo (2018)          | Korea   | Asian     | NAFLD           | 365/96      | 306/57/2              | 0.630                  | 7         |
| Krawczyk (2016)     | Germany | Caucasian | NAFLD           | 143/180     | 110/30/3              | 0.258                  | 8         |
| Krawczyk (2016)     | Germany | Caucasian | Cirrhosis       | 90/205      | 68/20/2               | 0.641                  | 8         |
| Kruk (2018)         | Poland  | Caucasian | Cirrhosis       | 55/123      | 50/5/0                | 0.440                  | 7         |
| Li (2019)           | China   | Asian     | NAFLD           | 201/239     | 188/13/0              | 0.870                  | 8         |
| Liu (2014)          | UK      | Caucasian | NAFLD           | 349/379     | 271/70/8              | 0.908                  | 8         |
| Manchiero (2017)    | Brazil  | Mixed     | Cirrhosis       | 58/232      | 46/12/0               | 0.562                  | 7         |
| Milano (2015)       | Italy   | Caucasian | CHC             | 815/231     | 746/69/0              | 0.966                  | 8         |
| Musso (2017)        | Italy   | Caucasian | NAFLD           | 60/60       | 37/21/2               | 0.121                  | 7         |
| Raksayot (2019)     | Thailand | Asian     | CHB             | 270/105     | 218/51/1              | 0.682                  | 8         |
| Raksayot (2019)     | Thailand | Asian     | CHC             | 131/105     | 101/29/1              | 0.682                  | 8         |
| Raksayot (2019)     | Thailand | Asian     | HCC             | 132/105     | 78/46/8               | 0.682                  | 8         |
| Sagnelli (2016)     | Italy   | Caucasian | Cirrhosis       | 31/136      | 26/5/0                | 0.590                  | 7         |
| Sookoian (2015)     | Argentina | Mixed    | NAFLD           | 226/135     | 184/37/5              | 0.494                  | 8         |
| Stickel (2018)      | Switzerland | Caucasian | HCC             | 751/1165    | 558/164/29            | 0.143                  | 7         |
| Teng (2018)         | China   | Asian     | CHB             | 160/179     | 142/18/0              | 0.479                  | 8         |
| Teng (2018)         | China   | Asian     | Cirrhosis       | 239/179     | 209/29/1              | 0.479                  | 8         |
| Wang (2018)         | China   | Asian     | NAFLD           | 367/366     | 302/65/0              | 0.366                  | 8         |
| Wang (2016)         | China   | Asian     | CHB             | 683/364     | 608/73/2              | 0.365                  | 8         |
| Wang (2016)         | China   | Asian     | Cirrhosis       | 677/364     | 602/74/1              | 0.365                  | 8         |
| Wang (2016)         | China   | Asian     | HCC             | 418/364     | 363/55/0              | 0.365                  | 8         |
| Xu (2018)           | China   | Asian     | CHB             | 260/156     | 229/30/1              | 0.500                  | 8         |
| Yue (2018)          | China   | Asian     | NAFLD           | 118/122     | 111/7/0               | 0.708                  | 7         |
| Zhang (2018)        | China   | Asian     | ALD             | 507/645     | 435/65/7              | 0.966                  | 8         |

Abbreviations: TM6SF2, Transmembrane 6 superfamily 2; HCC, Hepatocellular carcinoma; NAFLD, Nonalcoholic fatty liver disease; ALD, Alcoholic liver disease; CHB, Chronic hepatitis B infection; CHC, Chronic hepatitis C infection; HW, Hardy–Weinberg equilibrium; NOS, Newcastle-Ottawa scale; NA, Not available.
**Table 2** Results of pooled analyses for TM6SF2 rs58542926 polymorphism and chronic liver disease

| Population     | Sample size | Dominant comparison | Recessive comparison | Overdominant comparison | Allele comparison |
|----------------|-------------|---------------------|----------------------|-------------------------|-------------------|
|                |             | p value  | OR (95%CI) | I² statistic | p value  | OR (95%CI) | I² statistic | p value  | OR (95%CI) | I² statistic |
| Overall        | 13137/11010 | <0.0001 | 0.70 (0.64-0.76) | 47% | <0.0001 | 2.94 (2.05-4.20) | 0% | <0.0001 | 1.34 (1.23-1.47) | 0% | <0.0001 | 0.68 (0.63-0.73) | 47% |
| Asian          | 4816/3495   | <0.0001 | 0.69 (0.60-0.79) | 34% | 0.03    | 2.29 (1.07-4.87) | 0% | <0.0001 | 1.41 (1.22-1.63) | 28% | <0.0001 | 0.69 (0.60-0.79) | 28% |
| Caucasian      | 7787/6916   | 0.004   | 0.77 (0.64-0.92) | 52% | <0.0001 | 2.85 (1.85-4.37) | 0% | 0.0002  | 1.25 (1.11-1.40) | 39% | <0.0001 | 0.74 (0.63-0.86) | 54% |
| HCC            | 1433/2267   | 0.003   | 0.58 (0.40-0.83) | 65% | <0.0001 | 3.29 (1.92-5.66) | 0% | 0.01    | 1.55 (1.10-2.18) | 59% | 0.0007  | 0.58 (0.42-0.79) | 62% |
| Cirrhosis      | 1762/1514   | 0.006   | 0.72 (0.57-0.91) | 25% | 0.37    | 1.79 (0.50-6.37) | 0% | 0.01    | 1.36 (1.08-1.71) | 27% | 0.004   | 0.73 (0.58-0.90) | 18% |
| NAFLD          | 3075/3000   | <0.0001 | 0.54 (0.46-0.64) | 0% | <0.0001 | 5.20 (2.43-11.13) | 0% | <0.0001 | 1.69 (1.44-1.98) | 0% | <0.0001 | 0.55 (0.48-0.63) | 0% |
| ALD            | 1445/2299   | 0.18    | 0.82 (0.62-1.10) | 40% | 0.06    | 3.33 (0.97-11.44) | 0% | 0.41    | 1.13 (0.84-1.51) | 42% | <0.0001 | 0.71 (0.60-0.84) | 26% |
| CHB            | 2168/1138   | 0.34    | 0.89 (0.71-1.12) | 0% | 0.84    | 1.14 (0.33-3.92) | 0% | 0.38    | 1.11 (0.88-1.40) | 0% | 0.31    | 0.89 (0.72-1.11) | 0% |
| CHC            | 2969/564    | 0.44    | 0.60 (0.16-2.19) | 65% | 0.71    | 1.10 (0.68-1.77) | 0% | 0.75    | 0.93 (0.58-1.49) | 63% | 0.65    | 0.90 (0.57-1.41) | 64% |

*Note:* The values in bold represent there is statistically significant differences between cases and controls.

*Abbreviations:* HCC, Hepatocellular carcinoma; ALD, Alcoholic liver disease; NAFLD, Nonalcoholic fatty liver disease; CHB, Chronic hepatitis B infection; CHC, Chronic hepatitis C infection; OR, Odds ratio; CI, Confidence interval; NA, Not available.
we strongly recommend further studies to perform haplotype analyses and explore potential gene-gene interactions. Fourthly, to more precisely measure the effects of certain endogenous/exogenous factors on disease occurrence and development, molecular pathologic epidemiology (MPE) analyses should be adopted. However, since included studies only focused on the effects of rs58542926 polymorphism on individual susceptibility to chronic liver disease, such analyses were not applicable in the current meta-analysis. But to better elucidate the underlying pathogenesis mechanisms of chronic liver disease, future studies should try to investigate the interaction of rs58542926 polymorphism (as endogenous factors) with potential pathogenic environmental factors (as exogenous factors) as an MPE approach (Nishi et al., 2016). Fifthly, the present meta-analysis aimed to explore associations between all TM6SF2 polymorphisms and chronic liver disease. However, only rs58542926 polymorphism could be analyzed in the current study because no any other TM6SF2 polymorphisms were investigated by at least two different genetic association studies.

Like all meta-analysis, this study certainly has some limitations. First, due to lack of raw data, adjusted analyses were inapplicable, and we have to admit that failure to perform further adjusted analyses for potential confounding factors might impact the reliability of our findings (Zhang, Guo, Qin, & Li, 2016; Zhang, Zhu, Huo, Qin, & Yuan, 2016). Second, associations between rs58542926 polymorphisms and chronic liver disease might also be modified by gene-environmental interactions. However, we could not perform relevant analyses accordingly since most of studies did not investigate these associations (Abdel-Hamed, Ghattas, Mesbah, Saleh, & Abo-Elmatty, 2017; Zhang, Guo, et al., 2016; Zhang, Zhu, et al., 2016). Third, gray literatures that were not formally published in academic journals were not considered to be eligible for analyses in this meta-analysis since it is hard to determine their quality. However, since gray literatures were not analyzed, although funnel plots suggested that severe publication biases were unlikely, it is still possible that our findings may be impacted by potential publication biases (Kapil et al., 2016). On account of above mentioned limitations, our findings should be cautiously interpreted.

In conclusion, our meta-analysis suggested that TM6SF2 rs58542926 polymorphism might affect individual susceptibility to chronic liver disease in both Asians and Caucasians. Further stratified analyses revealed similar positive results in HCC, cirrhosis and NAFLD, but not in ALD, CHB, and CHC. These results suggested that this polymorphism could be used to identify individuals at higher susceptibility to chronic liver disease, especially for HCC, cirrhosis, and NAFLD. Future investigations are warranted to explore potential roles of other TM6SF2 polymorphisms in the development of chronic liver disease.

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None.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHORS’ CONTRIBUTIONS

Xinpei Chen, Pengcheng Zhou, De Luo, and Song Su conceived of the study, participated in its design. Xinpei Chen, Pengcheng Zhou, and De Luo conducted the systematic literature review. Bo Li performed data analyses. Xinpei Chen, Pengcheng Zhou, De Luo, and Song Su drafted the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

ORCID

Song Su https://orcid.org/0000-0002-9729-3975

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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