Int J Clin Exp Med 2016;9(12):22969-22975
www.ijcem.com /ISSN:1940-5901/IJCEM0035176

Review Article

Association between transforming growth factor-β1 polymorphisms and liver cirrhosis: a meta-analysis in a single ethnic group

Shao-Lei Han, Qian Wang, Xiao-Qing Wang, Zhuang-Bo Mu

Department of Liver Diseases, Jinan Infectious Disease Hospital, Jinan, China

Received July 6, 2016; Accepted October 19, 2016; Epub December 15, 2016; Published December 30, 2016

Abstract: In this study, a meta-analysis was conducted to assess the effects of transforming growth factor-β1 (TGF-β1) polymorphisms on the risk for development of liver fibrosis in the Chinese population. Studies were identified using PubMed and Chinese databases through March 2016. This meta-analysis identified 7 studies, including 874 liver cirrhosis cases and 889 controls. In the overall analysis, a non-significant association between the TGF-β1 polymorphisms and liver fibrosis was found in the Chinese population. In the analyses based on consistency with Hardy-Weinberg equilibrium (HWE) for controls, significantly increased risks for liver cirrhosis in association with TGF-β1 -509C/T variants were found. Furthermore, a significantly increased risk of TGF-β1 +869T/C variants was found in the population-based studies. Our meta-analysis showed that TGF-β1 -509C/T and +869T/C variants appear to influence the risk for liver cirrhosis in Chinese individuals. Studies with larger sample sizes and wider population spectra are warranted to verify this finding.

Keywords: Meta-analysis, transforming growth factor-β1, polymorphism, liver fibrosis

Introduction

Liver cirrhosis is defined as a diffuse process characterised by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules [1], representing an advanced stage of chronic liver diseases [2]. It is a major public health problem in the world, with around 1.5 million deaths per year [3]. Liver cirrhosis is a multi-factorial disease, involving chronic viral hepatitis [4], alcohol consumption [5] and other causes such as autoimmune diseases [6], fatty liver diseases [7], or inherited metabolic disorders [7]. Increasing evidence indicates that genetic factors determine the progression rate of liver fibrosis [8]. In recent years, many candidate genes have been identified as potential periodontitis susceptibility loci. An important one is transforming growth factor-β (TGF-β) gene, which is encoded by three different genes-TGF-β1, TGF-β2, and TGF-β3. The TGF-β1 single nucleotide polymorphism has been extensively studied with liver cirrhosis. Of the identified TGF-β1 polymorphisms, two ones (-509C/T [rs1800469] and +869T/C [rs1800470]) have been mostly investigated. In 2000, Bathgate et al. conducted the first ever study investigating the relationship between TGF +869T/C polymorphism and liver cirrhosis in a Caucasian population [9]. As a consequence, many studies have attempted to clarify this relationship, but there has been no definite consensus to date. Differences in findings may be due to race and clinical heterogeneity in patients who have been studied, as well as a limited number of patients in each study. Meta-analysis is one way to overcome the problems of small sample size and and inadequate statistical power. For addressing the association between TGF-β1 polymorphism and liver cirrhosis risk, we performed a meta-analysis of all eligible studies in the Chinese population to lessen the influence of different genetic background. We also performed a subgroup analysis, to explore the possible effects of gene environment interaction on the risk of liver cirrhosis.

Material and methods

Search strategy and selection criteria

Eligible studies were retrieved by searching the PubMed and Chinese databases for relevant

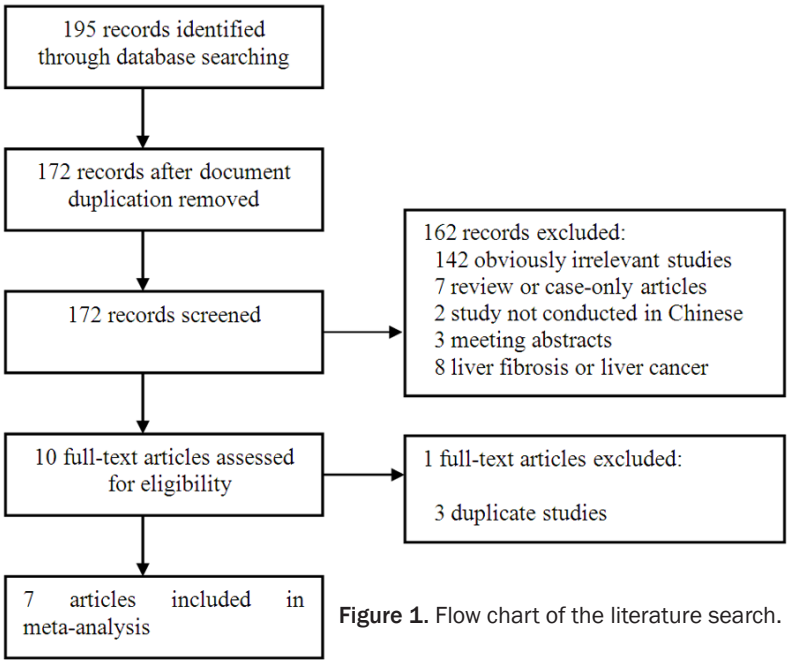

Figure 1. Flow chart of the literature search.

reports published before March 2016. The following search terms were used: liver cirrhosis and (TGF-β1 or transforming growth factor-β1) and (China or Chinese) and gene. The search was conducted on human without language limitation. The reference lists and relevant reviews were also screened to identify eligible studies.

Inclusion criteria: (1) they must be case-control studies describing the associations between TGF-β1 -509C/T and +869T/C polymorphisms and risk of liver cirrhosis, (2) they provided the genetypes in cases and controls, (3) participants were Chinese population, (4) if more than one study used same data series, the latest published study or study with more useful information for this meta-analysis was prior to be selected. Exclusion criteria: (1) letter, abstract, comment or editorial, (2) incomplete data, (3) case-only articles, (4) review articles.

Data extraction

Two authors independently extracted the data by a standard form, and disagreements were resolved by discussion. Titles and abstracts of all identified studies were screened firstly. Full articles were scrutinized if the title and abstract were ambiguous. The following data were collected for pooled analyses: the name of first author, year of publication, sources of controls, geographic areas, sample size, and number of subjects with TGF-β1 -509C/T and +869T/C genotypes. Hardy-Weinberg equilibrium (HWE) in controls were calculated from corresponding genotype distributions. According to sources of controls, all case-control studies were divided into two groups, i.e., population-based or hospital-based studies (PB or HB).

Statistical analysis

Statistical analysis was conducted using the version 10 STATA statistical package (STATA, College Station, TX, USA). Odds ratio (OR) and corresponding 95% confidence interval (95% CI) were used to present the strength of the associations. The statistical significance of pooled ORs was examined by the Z-test. The genetic comparisons included allele, homozygotes, recessive, and dominant models. The χ^2-test was used for determining the Hardy-Weinberg equilibrium (HWE) of genotypes and the heterogeneity of rare allele frequencies in the control groups of each study reviewed. Depending on the results of the heterogeneity test among individual studies, the fixed-effect model (Mantel-Haenszel) or random-effect model (DerSimonian and Laird) was selected to summarize the combined ORs and their 95% CIs. Sensitivity analysis was evaluated by comparing the results of fixed-effects model and random-effects model. In order to keep clinical homogeneity, subgroup analyses were conducted according to sources of controls, and goodness-in-fitness of HWE. All the *P* values less than 0.05 was considered to be statistically significant.

Results

Description of included studies

Figure 1 illustrates the literature search process in the form of a flow chart. We identified 172 articles that examined the association between TGF-β1 polymorphisms and risk of

Table 1. Characteristics of studies included in the meta-analysis

References	Source of controls	Geographic areas	Case number	Control number	Cases			Controls			HWE	
TGF-β1 -509C/T					CC	CT	TT	CC	CT	TT	χ^2	*P*
Yang 2005	PB	Shanghai	134	92	57	0	77	31	0	61	92.00	0.000
Li 2007	PB	Fujian	102	106	30	54	18	5	71	30	18.57	0.000
Wang 2008	PB	Shanghai	118	104	31	53	34	29	50	25	0.14	0.706
Jiang 2009	PB	Shanghai	169	119	38	79	52	39	52	28	1.67	0.196
Luo 2010	PB	Guangxi	155	170	29	79	47	51	83	36	0.04	0.836
Shi 2011	PB	Zhejiang	42	52	10	26	6	7	39	6	13.03	0.000
Shi 2011	HB	Zhejiang	42	131	10	26	6	15	91	25	20.69	0.000
TGF-β1 +869T/C					TT	TC	CC	TT	TC	CC	χ^2	*P*
Yang 2005	PB	Shanghai	134	92	32	60	42	29	45	18	0.01	0.942
Zhu 2006	PB	Zhejiang	56	50	9	33	14	15	30	5	3.13	0.077
Zhu 2006	HB	Zhejiang	56	65	9	33	14	8	39	18	3.41	0.065
Wang 2008	PB	Shanghai	118	104	31	53	34	29	49	26	0.34	0.562
Luo 2010	PB	Guangxi	155	170	34	78	43	46	84	40	0.02	0.891
Shi 2011	PB	Zhejiang	42	52	20	13	9	10	26	16	0.01	0.922
Shi 2011	HB	Zhejiang	42	131	20	13	9	33	75	23	3.02	0.082

Table 2. Association of TGF-β1 -509C/T polymorphism and risk for liver cirrhosis

Analysis model		n	Orr (95% CI)	ORf (95% CI)	P_h
T versus C	Total analysis	7	0.92 (0.66-1.28)	0.98 (0.85-1.14)	0.000
	In HWE	3	1.37 (1.13-1.66)	1.37 (1.13-1.66)	0.502
	Population-based	6	0.95 (0.66-1.38)	1.02 (0.87-1.18)	0.000
TT versus CC	Total analysis	7	0.79 (0.39-1.60)	0.96 (0.73-1.27)	0.000
	In HWE	3	1.82 (1.25-2.67)	1.82 (1.25-2.67)	0.576
	Population-based	6	0.88 (0.41-1.87)	1.02 (0.77-1.35)	0.000
TT versus CC+CT	Total analysis	7	1.03 (0.73-1.45)	1.06 (0.84-1.34)	0.075
	In HWE	3	1.46 (1.07-2.00)	1.46 (1.07-2.00)	0.839
	Population-based	6	1.06 (0.73-1.55)	1.09 (0.85-1.38)	0.057
TT+CT versus CC	Total analysis	7	0.73 (0.39-1.34)	0.91 (0.72-1.15)	0.000
	In HWE	3	1.54 (1.11-2.13)	1.54 (1.11-2.13)	0.376
	Population-based	6	0.79 (0.41-1.52)	0.96 (0.75-1.22)	0.000

ORr: Odd ratio for random-effect model; ORf: Odd ratio for fixed-effect model; P_h *P* value for heterogeneity test.

liver cirrhosis in various databases. After screening the titles and abstracts, 162 articles were excluded according to the exclusion criteria described. Then we reviewed all of the remaining full-articles [10-19], three [10-12] were excluded due to duplicate studies. Finally, 7 articles [13-19] met the inclusion criteria. The publication year of involved studies ranged from 2005 to 2011. In total, 874 liver cirrhosis cases and 889 controls were included in this meta-analysis. The source of controls was mainly population-based. Characteristics of included studies are summarized in **Table 1**.

Meta-analysis

Comparison between TGF-β1 -509C/T and liver cirrhosis: We compared TGF-β1 -509C/T polymorphism and liver cirrhosis. Results indicated a non-significant association between the TGF-β1 -509C/T polymorphism and liver cirrhosis in all variants of -509C/T in the overall analysis: T versus C (OR, 0.92; 95% CI, 0.66-1.28), TT versus CC (OR, 0.79; 95% CI, 0.39-1.60), TT + CT versus CC (OR, 0.73; 95% CI, 0.39-1.34), and TT versus CC + CT (OR, 1.06; 95% CI, 0.84-1.34) (**Table 2**; **Figure 2**). Stratified analyses

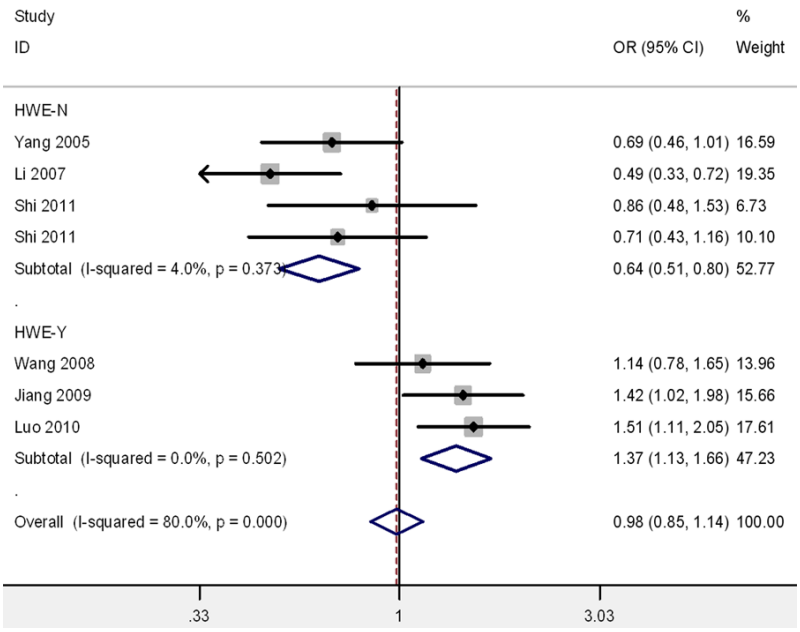

Figure 2. Forest plot for allele contrasts of TGF-β1 -509C/T polymorphism in overall and subgroup analyses by HWE.

based on sources of controls revealed non-significant results for population-based studies. However, a significantly elevated risk for liver cirrhosis was found in the analyses based on consistency with HWE for controls: T versus C (OR, 1.37; 95% CI, 1.13-1.66), TT versus CC (OR, 1.82; 95% CI, 1.25-2.67), TT versus CC + CT (OR, 1.46; 95% CI, 1.07-2.00), and TT + CT versus CC (OR, 1.54, 95% CI, 1.11-2.13) (**Table 2**; **Figure 2**).

Comparison between TGF-β1 +869T/C and liver cirrhosis: We compared TGF-β1 +869T/C polymorphism and liver cirrhosis. Overall, a non-significant elevated risk of liver cirrhosis was associated with all variants of +869T/C: C versus T (OR, 1.03; 95% CI, 0.77-1.38), CC versus TT (OR, 1.14; 95% CI, 0.66-1.97), CC+TC versus TT (OR, 0.88; 95% CI, 0.53-1.47), and CC versus TT+TC (OR, 1.29; 95% CI, 0.99-1.67) (**Table 3**; **Figure 2**). In the subgroup analyses stratified by sources of controls, it revealed the significant results in population-based studies (CC versus TT+TC: OR, 1.36; 95% CI, 1.01-1.82), and in hospital-based studies (CC+TC versus TT: OR, 0.47; 95% CI, 0.26-0.85) (**Table 3**; **Figure 3**).

Sensitivity analysis

For comparison of differences and evaluation of sensitivity, we used fixed- and random-effect models to evaluate meta-analysis stability. All the significant pooled ORs did not materially alter except the recessive model for TGF-β1 +869T/C, suggesting that the results of this meta-analysis are stable (**Tables 2**, **3**).

Discussion

TGF is a pluripotent cytokine in regulation of inflammation and immune response, and thus play a central role in process of organic injury, wound healing as well as fibrosis and cirrhosis [20, 21]. The relationship between TGF-β1 polymorphisms and liver cirrhosis risk attracted the attention of both doctors and researchers. Since the first study for TGF-β1 +869T/C polymorphism and liver cirrhosis was reported in a Caucasian population [9], many studies have been undertaken to explore the association. However, results of individual studies were inconclusive. Regional and racial differences are one likely reason for the conflicting results. Therefore, we performed this meta-analysis to assess the effect of TGF-β1 polymorphisms on risk for liver cirrhosis in a single ethnic group, in order to reduce the impact of genetic background.

Our meta-analysis included 7 case-control studies with 874 liver cirrhosis cases and 889 controls. Results showed a non-significant association between the TGF-β1 -509C/T and +869T/C polymorphisms with liver cirrhosis in the overall analyses. The controls of three [13, 14, 18] of the cohorts were not in Hardy Weinberg equilibrium (P<0.05), which contributes about 50% of the controls included in the study for TGF-β1 -509C/T. Therefore, we further performed the analyses based on consistency with HWE for controls, the results showed a significant association between TGF-β1 -509C/T polymorphism and liver cirrhosis risk in all the models. As for TGF-β1 +869T/C, the significantly results were found both in population-based and hospital-based studies. The hospital-based studies may have some biases because such controls are not representative of the general population.

Table 3. Association of TGF-β1 +869T/C polymorphism and risk for liver cirrhosis

Analysis model		n	Orr (95% CI)	ORf (95% CI)	P_h
C versus T	Total analysis	7	1.03 (0.77-1.38)	1.08 (0.92-1.27)	0.006
	Population-based	5	1.14 (0.81-1.61)	1.18 (0.99-1.41)	0.009
	Hospital-based	2	0.77 (0.54-1.11)	0.77 (0.54-1.10)	0.491
CC versus TT	Total analysis	7	1.14 (0.66-1.97)	1.21 (0.88-1.65)	0.016
	Population-based	5	1.36 (0.70-2.67)	1.38 (0.98-1.96)	0.014
	Hospital-based	2	0.66 (0.32-1.39)	0.66 (0.32-1.39)	0.930
CC versus TT+TC	Total analysis	7	1.28 (0.95-1.71)	1.29 (0.99-1.67)	0.327
	Population-based	5	1.36 (0.93-1.98)	1.36 (1.01-1.82)	0.202
	Hospital-based	2	1.04 (0.58-1.89)	1.04 (0.57-1.88)	0.523
CC+TC versus TT	Total analysis	7	0.88 (0.53-1.47)	0.97 (0.75-1.25)	0.002
	Population-based	5	1.08 (0.63-1.87)	1.14 (0.86-1.52)	0.012
	Hospital-based	2	0.47 (0.25-0.89)	0.47 (0.26-0.85)	0.287

ORr: Odd ratio for random-effect model; ORf: Odd ratio for fixed-effect model; P_h *P* value for heterogeneity test.

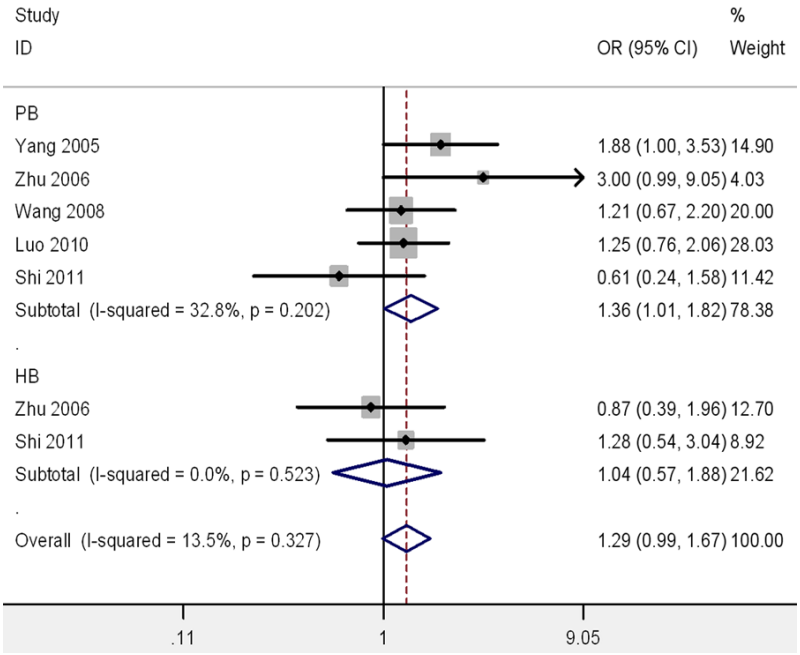

Figure 3. Forest plot for recessive contrasts of TGF-β1 +869T/C polymorphism in overall and subgroup analyses by sources of controls.

Due to this point, the significant result for TGF-β1 +869T/C polymorphism and liver cirrhosis from hospital-based studies should be interpreted with caution.

As compared to a previous meta-analysis by Wu et al. [22], it only included a smaller number of studies which were conducted in Chinese populations, and did not calculate pooled ORs for all studies in Chinese populations. This current meta-analysis is strengthened by investigating the association only in a Chinese ethnicity. The effects of deviation from HWE and sources for controls were determined by subgroup analyses. We were able to explore the association between TGF-β1 polymorphisms and liver cirrhosis may not be influenced by genetic backgrounds and living environment. Therefore, our results indicated that TGF-β1 polymorphisms are associated with liver cirrhosis in individuals from China.

Several limitations of this study should be figured out. First, this ethnic-specific meta-analysis only included data from Chinese patients, and thus, our results are only applicable to this ethnic group. Second, since this meta-analysis was based primarily on unadjusted effect estimates and CIs, confounding factors were not controlled. Adjusting analysis would lead to a more precise result, which can be conducted if individual data were available. Third, although we devised a comprehensive search strategy, the number of included studies is remains relatively small. This might be the low incidence of liver cirrhosis, especially for Eastern countries, and subsequently it was difficult to include many studies. Finally, due to the limitations of funnel plotting, which requires a range of stud-

ies, we did not evaluate publication bias in this meta-analysis.

In conclusion, this meta-analysis indicates that TGF-β1 -509C/T and +869T/C polymorphisms were associated with the risk of liver cirrhosis in the Chinese population. Ethnicity seems to play a role in the genetic association of the disease. Due to the limited number of available studies, further studies are required to explore the broader role of these polymorphisms which play in the pathogenesis of liver cirrhosis.

Disclosure of conflict of interest

None.

Address correspondence to: Zhuang-Bo Mu, Department of Liver Diseases, Jinan Infectious Disease Hospital, No. 22029 Jingshi Road, Jinan 250021, China. Tel: +86 531 87930851; Fax: +86 531 87930851; E-mail: jnmuzb2003@126.com

References

[1] Anthony PP, Ishak KG, Nayak NC, Poulsen HE, Scheuer PJ, Sobin LH. The morphology of cirrhosis: definition, nomenclature, and classification. Bull World Health Organ 1977; 55: 521-40.

[2] Hytiroglou P, Snover DC, Alves V, Balabaud C, Bhathal PS, Bioulac-Sage P, Crawford JM, Dhillon AP, Ferrell L, Guido M, Nakanuma Y, Paradis V, Quaglia A, Theise ND, Thung SN, Tsui WM, van Leeuwen DJ. Beyond "cirrhosis": a proposal from the international liver pathology study group. Am J Clin Pathol 2012; 137: 5-9.

[3] Lim YS and Kim WR. The global impact of hepatic fibrosis and end-stage liver disease. Clin Liver Dis 2008; 12: 733-46.

[4] Perz JF, Armstrong GL, Farrington LA, Hutin YJ, Bell BP. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. J Hepatol 2006; 45: 529-38.

[5] Dufour MC. Alcoholic liver disease. In: Talley NJ, Locke GR III, Saito YA, editors. GI epidemiology. 1st edition. Massachusetts: Blackwell Publishing, Inc.; 2007. pp. 231-7.

[6] Selmi C, Bowlus CL, Gershwin ME, Coppel RL. Primary biliary cirrhosis. Lancet 2011; 377: 1600-9.

[7] Brunt EM. Non-alcohol fatty liver disease. In: Burt AD, Portmann BC, Ferrell LD, editors. MacSween's Pathology of the Liver. 5th edtion. Philadelphia, PA: Churchill Livingstone; 2007. pp. 367-97.

[8] Bataller R, North KE, Brenner DA. Genetic polymorphisms and the progression of liver fibrosis: a critical appraisal. Hepatology 2003; 37: 493-503.

[9] Bathgate AJ, Pravica V, Perrey C, Hayes PC, Hutchinson IV. Polymorphisms in tumour necrosis factor alpha, interleukin-10 and transforming growth factor beta1 genes and end-stage liver disease. Eur J Gastroenterol Hepatol 2000; 12: 1329-1333.

[10] Li H. The effects of the rennin angiotensin system related gene polymorphisms on the HBV-induced liver cirrhosis. Doctor's Thesis of Shandong University, China 2005.

[11] Yang ZX. Association of single nucleotide polymorphisms of transforming growth factor β1 gene with liver cirrhosis induced by HBV. Master's Thesis of The Second Military Medical University, China 2005.

[12] Yang ZX, Wang H, Wan MB, Wang XJ, Gao CF. A association of polymorphisms of the transforming growth factor β1 gene with HBV-induced liver cirrhosis. Chin J Clin Lab 2005; 23: 168-171.

[13] Yang ZX, Wang H, Gao CF, Xu LL, Zhao WP. Effect of polymorphism of transforming growth factor b1 gene on HBV induced liver cirrhosis. Zhong Hua Yi Xue Za Zhi 2005; 85: 1021-1026.

[14] Li H, Wu HL, Lv H, Wei HS, Wang HB, Wang PL. The association of TGFb1and AT1R gene polymorphisms with hereditary susceptibility and clinical phenotype of HBV-induced liver cirrhosis. Zhong Hua Yi Xue Yi Chuan Xue Za Zhi 2007; 24: 298-301.

[15] Wang H, Zhao YP, Gao CF, Ji Q, Gressner AM, Yang ZX, Weiskirchen R. Transforming growth factor beta 1 gene variants increase transcription and are associated with liver cirrhosis in Chinese. Cytokine 2008; 43: 20-25.

[16] Jiang ZL, Zhang W, Zhang H, Liu YBL, Su SB. Relationship between TNF-a, TGF-b1 and IL-10 genetic polymorphisms and posthepatitis B cirrhosis. Hua Ren Xiao Hua Za Zhi 2009; 17: 3263-3268.

[17] Luo B, Wang JL, Huang CM, Qin HJ. Single nucleotide polymorphisms of transforming growth factor β1 gene in patients with liver cirrhosis resulting from chronic hepatitis B. Chin J Nosocomiol 2010; 20: 1389-1392.

[18] Shi W, Guo J, Chen Q, Wang Y, Xun Y, Shi J, Lou G. Association between TGF-n gene polymorphism and hepatocirrhosis in Chinese patients with chronic HBV infection. Yi Xue Yan Jiu Za Zhi 2011; 40:93-96.

[19] Zhu JS, He ZB, Chen Z, Zeng WX, Zhu M, Wang GG, Chen HZ, Fang H. A association of polymorphisms of the transforming growth factor β1 gene with liver fibrosis. Chin J Infect Dis 2006; 24: 410-413.

[20] Seki E, De Minicis S, Osterreicher CH, Kluwe J, Osawa Y, Brenner DA, Schwabe RF. TLR4 enhances TGF-beta signaling and hepatic fibrosis. Nat Med 2007; 13: 1324-1332.
[21] Dooley S, Ten Dijke P. TGF-beta in progression of liver disease. Cell Tissue Res 2011; 347: 245-256.
[22] Wu XD, Zeng K, Gong CS, Chen J, Chen YQ. Transforming growth factor-β genetic polymorphisms on development of liver cirrhosis in a meta-analysis. Mol Biol Rep 2013; 40: 535-43.