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*Original Article*

# IL-17A G197A gene polymorphism contributes to susceptibility for liver cirrhosis development from patients with chronic hepatitis B infection in Chinese population

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**Abstract:** Background: IL-17A G197A and IL-17F A7488G gene polymorphisms are found to be associated with the risk of several diseases, however few studies have focused on their correlation with risk of liver cirrhosis (LC). Aims: The aim of this study was to assess the impact of IL-17A G197A and IL-17F A7488G gene polymorphisms on development of LC from chronic hepatitis B (CHB) in Chinese patients. Methods: A total of 163 HBV-related LC patients and 168 CHB patients were enrolled in the present study. IL-17A and IL-17F gene polymorphisms were analyzed using a polymerase chain reaction (PCR) restriction fragment length polymorphism assay (PCR-RFLP). Results: Frequencies of IL-17A G197A genotype AA and allele A were significantly higher in LC patients compared with that in CHB patients (AA 42.33% *vs* 27.98%, *P* = 0.032; A 56.34% *vs* 46.15%, *P*=0.011, respectively); While no significant difference in frequencies of genotypes and alleles of IL-17F A7488G was found between the two groups. The AA genotype of IL-17A G197A significantly increased LC risk (OR 4.186, 95% CI: 1.479-11.844), while A allele carriers were also associated with an increased LC risk (OR 1.856, 95% CI: 1.161-2.967). Conclusion: IL-17A G197A is a candidate gene that confers the genetic susceptibility for LC development from CHB in Chinese population.

**Keywords:** IL-17, liver cirrhosis, gene polymorphisms

## Introduction

Liver cirrhosis (LC) is a severe end-stage liver disease usually caused by HBV infection in China [1]. Patients with LC possess a significantly reduced life expectancy in contrast with non-cirrhotic ones. Optimal treatment of LC requires better understanding of its pathogenetic mechanism. According to current knowledge, the most important pathogenetic mechanism of liver cirrhosis is chronic inflammation [3, 4]. Immune response induced by HBV could cause progression of liver disease from mild inflammation to severe fibrosis and liver cirrhosis.

A series of cytokines are involved in the inflammation of hepatocytes which could cause activation of hepatic stellate cells (HSCs), the latter are considered to be responsible for the excess deposition of extra-cellular matrix (ECM) during liver fibrosis [5, 6]. According to previous studies, IL-17A and IL-17F produced by Th17 cells have been considered to play an important role in process of inflammation, autoimmune diseases [7-9]. A study on HepG2 cells found that IL-17 could induce fibrogenesis through periostin mediated collagen deposition, especially combined with TNF-α [10]. In addition, a recent study demonstrated that exogenous IL-17 could promote the activation of

**Table 1.** PCR primers and restriction enzymes for genotype assays

| SNP | Primer sequence | Restriction enzyme | Genotypes | Fragment size |
|---|---|---|---|---|
| IL-17A G197A | F 5'-AACAAGTAAGAATG AAAAGAGGACATGGT-3' | XagI | GG | 68 and 34 bp |
| | | | AA | 102 bp |
| | R 5'-CCCCCAATGA GGTCATAGAAGAATC-3' | | AG | 102, 68 and 34 bp |
| IL-17F T7488C | F 5'-GTTCCCATC CAGCAAGAGAC-3' | NlaIII | AA | 288 and 124 bp |
| | | | GG | 412 bp |
| | R 5'-AGCTGGGAA TGCAAACAAAC-3' | | GA | 412, 288 and 124 bp |

SNP: single nucleotide polymorphisms.

**Table 2.** Demographic and Clinical characteristics of CHB patients and LC patients

| Variables | CHB patients | LC patients | *P* value |
|---|---|---|---|
| number of subjects | 168 | 163 | |
| mean age ± SD (year) | 30.56 ± 6.05 | 45.06 ± 6.38 | < 0.01 |
| female/male | 50/118 | 54/109 | 0.554 |
| ALT, IU/L | 87 (38-507) | 104 (35-667) | 0.02 |
| AST, IU/L | 65 (31-352) | 70 (31-720) | 0.03 |
| TBIL, μmol/L | 21.7 (11.1-425) | 31.9 (11.3-428.9) | < 0.01 |
| PTA (%) | 97 (50-117) | 93 (36-128) | < 0.01 |

stellate cells and aggravated liver fibrosis [11]. According to another study based on liver tissue, IL-17A was found to be increased in fibrotic livers compared with nonfibrotic livers which suggested that IL-17A play a role in fibrotic process [12].

At present, IL-17A and IL-17F gene polymorphisms were found to be associated with a series of diseases. Wang, et al demonstrated that IL-17 G197A (rs2275913) A allele and rs3748067 C allele were associated with an increased gastric cancer risk in contrast with normal controls, which suggest that some IL-17 gene polymorphisms significantly increase gastric cancer risk [13]. Another recent study on cervical cancer patients revealed that IL17A G197A gene polymorphism was associated with the susceptibility of the cancer in Chinese women [14]. A His-to-Arg substitution at amino acid 161 (H161R) caused by IL-17F A7488G (rs763780) polymorphism could influence the function of wild-type IL-17F and the risk of asthma in Japanese [15]. Moreover, other researchers have recently reported that IL-17A rs2275913 and IL-17F (rs763780) polymorphisms were associated with the susceptibility to rheumatoid arthritis and ulcerative colitis [16, 17]. However, few studies have focused on their correlation with risk of LC.

Genetic factors have also been suspected to play a role in development of LC. Whether genetic polymorphisms in IL-17A and IL-17F could influence the risk of liver cirrhosis remains unknown. In the present study, we examined IL-17A G197A and IL-17F A7488G gene polymorphisms in LC and CHB patients to assess the impact of IL-17A G197A and IL-17F A7488G gene polymorphisms on development of LC from CHB.

## Materials and methods

### *Subjects*

A total of 168 CHB patients and 163 LC patients who attended Provincial Hospital affiliated to Shandong University from September 2013 to December 2014 were enrolled in the current study. Diagnose of CHB was based on the Guideline of CHB Treatment published by Asia-Pacific Associations for the Study of Liver Disease [18]. Clinical manifestation, such as esophageal varices and ascites combined with imaging findings on ultrasonography, computed tomography and magnetic resonance imaging were employed to diagnose LC. Exclusion criteria included any coexisting chronic liver disease, other types of hepatitis virus infection or human immunodeficiency virus, and immunosuppressive therapy. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), albumin, and globulin, prothrombin activity (PTA), HBV-DNA concentrations were obtained from examination at admission. Written informed consent was obtained from

**Table 3.** Distribution of the genotypes and alleles frequencies of IL-17A and IL-17F in all subjects

| | CHB (%) | LC (%) | *P* value | *P* value/OR[1] (95% CI) |
|---|---|---|---|---|
| IL-17A genotypes | | | | |
| GG | 31 (18.45) | 22 (13.50) | | 1 |
| AA | 47 (27.98) | 69 (42.33) | 0.032 | 0.007/4.186 (1.479-11.844) |
| AG | 90 (53.57) | 72 (44.17) | 0.71 | 0.05/2.761 (1.002-7.612) |
| AA+AG | 137 (81.55) | 141 | 0.22 | 0.865/0.932 (0.412-2.106) |
| Alleles | | | | |
| G | 152 (53.85) | 116 (43.66) | | 1 |
| A | 184 (46.15) | 210 (56.34) | 0.011 | 0.10/1.856 (1.161-2.967) |
| IL-17F genotypes | | | | |
| AA | 91 (54.17) | 78 (47.85) | | 1 |
| GG | 10 (5.95) | 13 (7.98) | 0.35 | 0.802/1.175 (0.33-4.15) |
| GA | 67 (39.88) | 72 (44.17) | 0.09 | 0.09/0.553 (0.279-1.098) |
| GG+GA | 77 (45.83) | 85 (52.15) | 0.25 | 0.157/0.626 (0.327-1.198) |
| Alleles | | | | |
| A | 249 (84.9) | 228 (81.0) | | 1 |
| G | 87 (15.1) | 98 (19.0) | 0.23 | 0.394/0.803 (0.484-1.331) |

CI, confidence interval; OR, odds ratio; 1, Adjusted for age and gender.

each subject. The study protocol was approved by the local Ethics Committee of Provincial Hospital affiliated to Shandong University.

*DNA extraction*

DNA of all subjects was separated from 2 ml peripheral blood with QIAamp DNA Mini Kit (Qiagen, Hilden, Germany) and the DNA was resuspended in RNAse/DNAse-Free Distilled water.

*IL-17A and IL-17F genotyping*

IL-17A and IL-17F gene polymorphisms were analyzed using a polymerase chain reaction-restriction fragment length polymorphism assay (PCR-RFLP). Primer sequences and restriction enzymes for them are demonstrated in **Table 1**. The PCR amplification was performed in a total volume of 25 ul mixtures containing 50-150 ng of genomic DNA, 10 pM of each primer and Premix Taq (Takara, Dalian, China). For IL-17A G197A PCR amplification, an initial denaturation at 94°C for 5 min was followed by 38 cycles at 94°C for 45 s, 58°C for 45 s, at 72°C for 1 min, and a final extension at 72°C for 10 min. For IL-17F A7488G PCR amplification, an initial denaturation at 94°C for 5 min was followed by 36 cycles at 94°C for 45 s, 60°C for 45 s, at 72°C for 1 min, and a final extension at 72°C for 10 min.

The PCR products of IL-17A G197A and IL-17F T7488C were digested with XagI (Fermentas, Lithuania) and NlaIII (New England Biolabs, Ipswich, MA, USA) at 37°C for 5 minutes, respectively. The products were then analyzed in 2% agarose gel stained with ethidium bromide and visualized under UV light (**Figure 1**).

*Statistical analysis*

Hardy-Weinberg equilibrium of genotypes was evaluated with chi-square test. Differences of demographic and clinical characteristics and genotype distribution between CHB patients and LC patients were compared using the Student's t-test, Mann-Whitney U test or chi-square test. Oddsratios (ORs) and 95% confidence intervals (CIs) for LC in association with genotypes were calculated with unconditional logistic regression adjusted by age and gender. All data were analyzed using the statistical package SPSS version 17.0 (SPSS, Chicago, IL). *P* values < 0.05 were considered to be statistically significant.

## Results

*Subjects characteristic and Hardy-Weinberg equilibrium*

A total of 168 CHB patients and 163 LC patients were enrolled in this study. Genotype distribu-

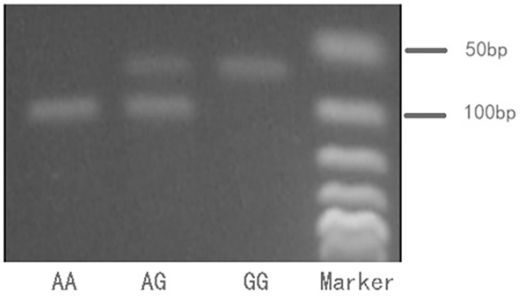


**Figure 1.** Genotyping analysis of IL-17A G197A polymorphism by PCR-RFLP. Product of polymerase chain reaction-based restriction analysis of IL-17A G197A. AG: heterozygote, 102 bp, 68 bp and 34 bp (too short to be detected) GG: homozygote, 102 bp AA: homozygote, 68 bp and 34 bp.

tion of IL-17A G197A and IL-17F A7488G were in Hardy-Weinberg equilibrium ($P > 0.05$). Demographic and clinical characteristics of subjects are shown in **Table 2**. In brief, significantly higher levels of ALT, AST, TBIL and PTA were found in LC patients than in CHB patients.

*Frequencies of IL-17A G197A genotype AA and allele A were significantly higher in LC patients than CHB patients*

In order to study the impact of IL-17A G197A and IL-17F A7488G polymorphisms on development of LC from CHB, we employed PCR-RFLP to assess the distribution of the genotypes in all subjects. The results demonstrated that frequencies of IL-17A G197A genotype AA and allele A were significantly higher in LC patients compared with that in CHB patients (AA 42.33% *vs* 27.98%, $P = 0.032$; A 56.34% *vs* 46.15%, $P = 0.011$); While no significant difference in frequencies of IL-17F A7488G genotypes and alleles was found between the two groups. Frequencies of the two polymorphisms in CHB patients and LC patients are summarized in **Table 3**. This result suggested that IL-17A may play a role in the development of LC from CHB.

*AA genotype of IL-17A G197A significantly increased risk of LC development from CHB*

To assess whether IL-17A G197A polymorphism was associated with the risk of LC developed from CHB, we analyzed their relationship with unconditional logistic regression. We found that compared with GG genotype, the AA genotype of IL-17A G197A significantly increased LC risk with OR of 4.186 (95% CI: 1.479-11.844), while A allele carriers were also associated with an increased LC risk when compared with G allele carriers (OR 1.856, 95% CI: 1.161-2.967) (**Table 3**). The above suggested that A allele and AA genotype of IL-17A G197A carriers possess a higher risk of LC development.

## Discussion

As a life-threatening health problem, liver cirrhosis is characterized by regenerated nodule development due to chronic inflammation. Hepatitis B virus (HBV) infection is considered to be the most important etiology of LC in China. The mechanism of development of LC from CHB is still undefined. In the present study, we identified correlations between polymorphisms of IL-17A and IL-17F genes and LC development from CHB patients. Our results revealed that IL-17A 197AA genotype and A allele were associated with higher LC risk, while no significant differences in IL-17F A7488G distribution was found between CHB patients and LC patients. It suggested that IL-17A may play a role in the development of LC from CHB.

In line with our findings, a recent study demonstrated that IL-17A G197A (rs2275913) GA and AA genotypes were related with an increased risk for the severity of the gastric mucosal atrophy in comparatively younger subjects, while A allele was associated with an increased risk for a peptic ulcer [19]. The above researchers also demonstrated that G197A minor homozygote (AA) carriers had an increased risk of the development of ulcerative colitis [20]. Another study on gastric cancer revealed that IL-17A G197A AA genotype was significantly higher in gastric cancer patients in contrast to controls [21]. Other polymorphisms of IL-17A were also found to be associated with some diseases. For example, Wang, et al reported that polymorphism of IL17A rs8193036 in promoter was in the association with pediatric asthma in Taiwanese population [22]. Our results in LC were consistent with these studies emphasizing that IL-17A polymorphisms were associated with susceptibility of several diseases.

The mechanism involved in the above findings may be that IL-17A plays a role in inflammation by inducing release of proinflammatory and neutrophil-mobilizing cytokines [23]. IL-17 plasma levels were found to be significantly

increased in a series of inflammation-related diseases, such as asthma [24], systemic lupus erythematosus [25], allergic rhinitis [26] and HBV-related liver cirrhosis [11]. Some researchers also demonstrated that IL-17 together with IL-17-activated monocytes could promote the activation of stellate cells, which aggravated liver fibrosis and the inflammatory response [11]. In addition, Du et al, also found that serum IL-17 levels in LC patients were significantly higher compared to CHB and PHC patients, which suggested that IL-17 takes part in development of LC [27]. The mechanisms of LC development from CHB remains unclear, genetic factors may be involved, as a variety of gene polymorphisms are involved in the process. For instance, Jin, et al reported that IL-10 -592A/C gene polymorphism could enhance the risk for liver cirrhosis [28]. A recent meta-analysis revealed that T/T genotype of IL-28B gene rs12979860 significantly more frequent in LC patients than in chronic hepatitis patients [29]. In combined with our findings, we suggested that genetic factor of IL-17A G197A gene polymorphism play a role in development of LC from CHB.

Both IL-17A and IL-17F are produced by Th17 cells and lie immediately adjacent to one another on human chromosome 6 [30, 31]. However, our investigation suggests that IL-17A, but not IL-17F, contributes to susceptibility of LC development from CHB. We speculated that different ethnic groups or relative small numbers of our subjects contribute to the results. Furthermore researches should be carried out on more subjects and diseases. In brief, we suggested that IL-17A G197A is a candidate gene that confers the genetic susceptibility for LC development from CHB in Chinese population. Further investigations should be conducted to understand the functions and mechanisms of the associated SNPs in regulating IL17A expression.

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## Disclosure of conflict of interest

None.

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