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

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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 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
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 genotypes 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 χ²-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 liver cirrhosis.
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Table 1. Characteristics of studies included in the meta-analysis

<table>
<thead>
<tr>
<th>References</th>
<th>Source of controls</th>
<th>Geographic areas</th>
<th>Case number</th>
<th>Control number</th>
<th>Cases</th>
<th>Controls</th>
<th>HWE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yang 2005</td>
<td>PB Shanghai</td>
<td>134</td>
<td>92</td>
<td>57</td>
<td>77</td>
<td>31</td>
<td>61</td>
</tr>
<tr>
<td>Li 2007</td>
<td>PB Fujian</td>
<td>102</td>
<td>106</td>
<td>30</td>
<td>54</td>
<td>18</td>
<td>5</td>
</tr>
<tr>
<td>Wang 2008</td>
<td>PB Shanghai</td>
<td>118</td>
<td>104</td>
<td>31</td>
<td>53</td>
<td>34</td>
<td>29</td>
</tr>
<tr>
<td>Jiang 2009</td>
<td>PB Shanghai</td>
<td>169</td>
<td>119</td>
<td>38</td>
<td>79</td>
<td>52</td>
<td>39</td>
</tr>
<tr>
<td>Luo 2010</td>
<td>PB Guangxi</td>
<td>155</td>
<td>170</td>
<td>29</td>
<td>79</td>
<td>47</td>
<td>51</td>
</tr>
<tr>
<td>Shi 2011</td>
<td>PB Zhejiang</td>
<td>42</td>
<td>52</td>
<td>10</td>
<td>26</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Shi 2011</td>
<td>HB Zhejiang</td>
<td>42</td>
<td>131</td>
<td>10</td>
<td>26</td>
<td>6</td>
<td>15</td>
</tr>
</tbody>
</table>

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

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

ORr: Odd ratio for random-effect model; ORf: Odd ratio for fixed-effect model; 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...
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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.
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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 ethnic-

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-
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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.

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References


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