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The common genetic variants in *IL-1B* and *IL-1RN* may have no predisposition to alcoholic liver disease: A meta-analysis

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ABSTRACT

Background: Interleukin-1β (IL-1β) has been demonstrated to play critical roles in the development of alcoholic liver disease (ALD). However, the association studies about functional polymorphisms of *interleukin-1β* gene (*IL-1B*) and *interleukin-1 receptor antagonist* gene (*IL-1RN*) and individual susceptibility to ALD produced conflicting results. Thus, a systematic review and meta-analysis was performed to investigate the associations between *IL-1B* and *IL1RN* polymorphisms and ALD risks.

Methods: Relevant studies were retrieved from six database including PubMed, Web of Science, Scopus, China Biology Medical literature database (CBM), Database of Chinese Scientific and Technical Periodicals (VIP), and Wanfang Data. Pooled odds ratio (OR) and 95% confidence interval (95%CI) were calculated by random-effects model.

Results: A total of 10 studies (including 825 ALD patients, 470 alcoholics without ALD and 743 health controls) were identified and included in the meta-analysis. The combined results showed that there were no significant associations between *IL-1B* ($-511C > T$ and $+3953T > C$) polymorphisms and ALD susceptibility, or between *IL-1RN VNTR* polymorphism and ALD susceptibility. Moderate to higher heterogeneity was detected in most comparisons. No obvious publication bias was observed in all the genetic models.

Conclusion: The common genetic variants in *IL-1B* and *IL-1RN* may have no predisposition to ALD. Large and well-designed epidemiological studies are needed to confirm these results.

1. Introduction

Alcoholic liver disease (ALD) represents a progressively aggravated liver disease that range from fatty liver to hepatic inflammation, fibrosis, and cirrhosis (Gramenzi et al., 2006). Although the majority of long-term heavy drinkers develop fatty liver, only 10%–35% of them develop hepatitis and 8%–20% of them will progress to cirrhosis (O'Shea et al., 2010). Accumulating evidences indicate that genetic factors may play essential roles in the pathogenesis and progression of ALD (Zeng et al., 2013). In this regards, the common genetic variants in endotoxin/lipopolysaccharide (LPS) signaling pathway have gained great interest due to the important roles of endotoxin/LPS and Kupffer cells (KCs) in the pathogenesis of ALD (Gao, 2012).

Innate immunity response to ethanol has been demonstrated to play predominant roles in the pathogenesis of ALD (Gao, 2012; Zeng et al., 2016). Excessive alcohol consumption enhances the gut permeability, resulting in increased translocation of gut-sourced endotoxin/LPS to liver (Rao, 1998; Basuroy et al., 2005; Zeng et al., 2016). LPS combines with Toll-like receptor 4 (TLR-4), cluster of differentiation 14 (CD14), and myeloid differentiation factor 2 (MD-2), leading to the activation of KCs (Szabo and Bala, 2010; Zeng et al., 2016). The activated KCs can release a large amount of reactive oxygen species (ROS) and pro-inflammatory cytokines including interleukin 1β (IL-1β), which has been demonstrated to play critical roles in the pathogenesis of ALD (Ceni et al., 2014). The serum levels of IL-1β in ALD patients and chronic ethanol-intoxicated rats were significantly increased (Tilg et al., 1992; Valles et al., 2003). Importantly, physiological doses of IL-1β induced steatosis, inflammatory and pro-steatotic chemokine MCP-1 in hepatocytes, while recombinant interleukin-1 receptor antagonist (IL-1Ra) blocked IL-1 signaling and markedly attenuated ALD (Petrasek et al., 2012). Results of these studies suggest that IL-1β plays critical roles in the pathogenesis of ALD and inhibition of IL-1 signaling may be

Abbreviations: ALD, alcoholic liver disease; AWLD, alcoholics without liver disease; ALC, alcoholic liver cirrhosis; CD14, cluster of differentiation 14; CIs, confidence intervals; HCs, healthy controls; IL-1β, interleukin-1β; IL1-Ra, interleukin-1 receptor antagonist; KCs, Kupffer cells; LPS, lipopolysaccharide; MD-2, myeloid differentiation factor 2; ORs, odds ratios; PCR-RELP, polymerase chain reaction-restriction fragment length polymorphism; ROS, reactive oxygen species; TLR-4, toll-like receptor 4; TNF-α, tumor necrosis factor α; VNTR, variable number tandem repeat

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beneficial for various stage of ALD, including fatty liver, steatohepatitis, and fibrosis (Mathews and Gao, 2013).

IL-1β and IL-1Ra are encoded by *IL-1B* and *IL-1RN* genes, respectively, which share the same region of chromosome 2q12-21(Mao et al., 2000). Several functionally relevant genetic variants in these genes have been identified. Three polymorphic loci in *IL-1B* gene, i.e. $-511C > T$ in the promoter, $+3953T > C$ in exon 5 and $-31C > T$ in the promoter, have been reported to regulate the secretion of IL-1β (Pociot et al., 1992; Santtila et al., 1998). The *IL-1RN* gene contains an 86 bp variable number tandem repeat (*VNTR*) polymorphism in intron 2. As previous epidemiological studies about the associations between these polymorphisms and ALD risks provided conflicting results, a systematic review and meta-analysis was performed.

2. Methods

2.1. Literature and search strategy

Relevant studies were retrieved from six databases including PubMed, ISI Web of Science, Scopus, China Biology Medical literature database (CBM), Database of Chinese Scientific and Technical Periodicals (VIP), and Wanfang Data. The following keywords were jointly used to identify the potentially relevant studies: “gene polymorphism or variation or mutation”, “alcoholic liver disease or alcoholic liver cirrhosis or alcoholic hepatitis or alcoholic liver fibrosis” and “cytokine or interleukin-1β or IL-1β, or interleukin-1 receptor antagonist, or IL-1Ra”. The reference lists and cited literatures of selected studies were manually examined for other potentially eligible studies. There was no restriction on time period, population, sample size, or language. The literature search was updated to 20 July 2015.

2.2. Inclusion and exclusion criteria

Studies included in this meta-analysis must meet the following criteria: (1) case-control design; (2) definite diagnose of ALD; (3) evaluating the associations between ALD susceptibility and *IL-1B* polymorphisms ($-511C > T$, and/or $+3953T > C$, and/or $-31T > C$), or between ALD susceptibility and *IL-1RN VNTR* polymorphism; (4) numbers of individuals with each genotype were reported; (5) if more than on article was published using the same case series, only the study with largest sample size was selected.

2.3. Data extraction

The following information was extracted from each study: (1) name of the first author; (2) publication year; (3) country of origin; (4) age and sex of enrolled participants; (5) genotyping method; (6) genotype and allele distribution; and (7) detailed definition of case and control in each study.

2.4. Assessment of the methodological quality of included studies

The methodological quality of included studies was assessed using the Newcastle-Ottawa Scale (NOS) as previously reported (Thelma Beatriz et al., 2014; Wu et al., 2015). The quality of each study was evaluated based on 8 items that assess patient selection, study comparability and exposure (Wells et al., n.d.). A score of 6 will be considered as the cut-off point to distinguish higher quality studies from lower ones (Thelma Beatriz et al., 2014).

2.5. Statistical analysis

Deviation from Hardy-Weinberg equilibrium (HWE) for genotype distribution in the control group was analyzed using χ^2 test. The associations between *IL-1B*, *IL-1RN* polymorphisms and ALD susceptibility were evaluated by the crude odds ratios (ORs) with 95% confidence intervals (CIs). The comparisons were made between ALD patients and alcoholics without liver disease (AWLD), and also between ALD patients and healthy controls (HCs). Meta-analyses were not performed when there were < 3 studies available. The pooled ORs were calculated using a random-effect model, and the statistical significance was determined by the *Z*-test. The statistical heterogeneity among studies was estimated by Cochran's Q test and the I^2 statistic. Sensitivity analysis was performed to assess the effects of individual study on pooled results by removing one single study once a time to check whether the polled ORs were stable (Tobias, 1999). The publication bias was detected with Begg's funnel plot and Egger's linear regression method. Probability < 0.05 was judged to be significant. All statistical analyses were carried out using Stata software (version 11.0; StataCorp 2P, College Station, Texas, USA).

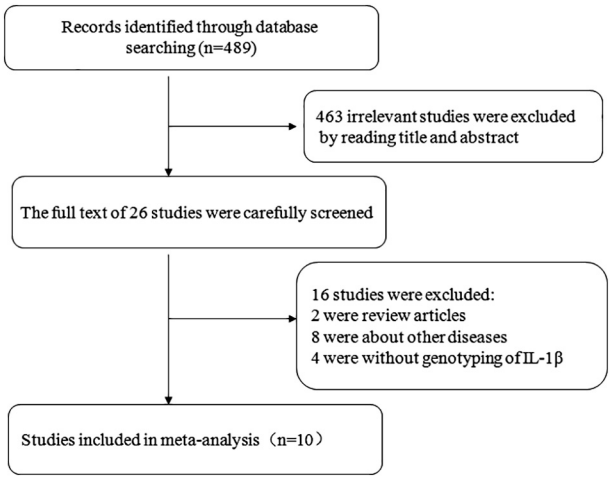

Fig. 1. The flow chart of study selection based on the inclusion and exclusion criteria.

3. Result

3.1. Characteristics of studies included in the meta-analysis

The flow chart of literature search was shown in Fig. 1. A total of 489 potentially relevant articles were identified in the literature search, and 463 irrelevant papers were excluded by reading the titles and abstracts. Another 16 studies were excluded as they were review articles, not about ALD, etc. Finally, 10 eligible studies (8 about the associations between *IL-1B* polymorphisms and ALD susceptibility, 4 about *IL-1RN VNTR* polymorphism and ALD susceptibility) were included in the meta-analyses (Pastor et al., 2000; Takamatsu et al., 2000; Kim et al., 2004; Chen et al., 2005; Pastor et al., 2005; Gleeson et al., 2008; Petrasek et al., 2009; Roy et al., 2012; Dutta, 2013; Yang et al., 2014). For the studies about *IL-1B* polymorphisms, 6 studies investigated the associations between $-511C > T$ polymorphism and ALD susceptibility, while 3 studies and 1 study were between $+3953T > C$ polymorphism and ALD susceptibility and between $-31T > C$ polymorphism and ALD susceptibility, respectively. The genotype distributions in controls of all studies were consistent with HWE. All ALD patients had definite diagnose and excluded other causes of liver disease. Most of included studies used peripheral blood for DNA extraction and polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) methods for genotyping. The characteristics of selected studies were summarized in Table 1 and Table 2. The detailed criteria for the selection of cases and controls in the included studies were provided in Supplementary Table 1s.