Association of HSD17B13 rs72613567: TA Allelic Variant With Liver Disease: Review and Meta-Analysis

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Abstract

AIM: To assess the association of HSD17B13 rs7261356:TA allelic variant with liver disease, we performed the current review and meta-analysis.

METHODS: 5 studies were identified by a search of CNKI,CBM,MEDLINE, PubMed, EMBASE, and CENTRAL databases from inception to April 2020. Odds ratios (ORs) with 95% confidence interval (CI) were calculated using random effects model or fixed effects model based on the between-study heterogeneity. The Stata 12.0 software was employed for data analysis.

RESULTS: Statistical analysis showed that the HSD17B13 rs7261356:TA allelic variant was associated with HCC compared with CLD (TA vs T OR=0.766, 95% CI=0.682-0.860, P=0.000) or healthy controls (TA vs T OR=0.649, 95% CI=0.431-0.977, P=0.038). But the HSD17B13 rs7261356:TA allelic variant was not associated with NAFLD compared with non-NAFLD (TA vs T OR=0.749, 95% CI=0.517-1.804, P=0.126). Egger's test revealed no significant publication bias.

Conclusion: The present findings suggest HSD17B13 rs7261356:TA allelic variant was association with HCC risk in the entire population studied.

Introduction

Chronic liver disease (CLD) is a common and expensive condition, and studies of CLD-related hospitalizations have underestimated the true burden of disease^[1]. Chronic liver disease (CLD) in the world is currently the fourth leading cause of death among persons aged 45 to 64 years^[2]. Given significant advances in treatment of viral hepatitis, the burden of liver disease is shifting toward alcoholic liver disease (ALD) and nonalcoholic fatty liver disease (NAFLD)^[3]. The prevalence of NAFLD is estimated to be 10–40% in adults worldwide, and it is the most common liver disease in children and adolescents in developed countries^[4]. Hepatocellular carcinoma is life-threatening co-morbidities of both NAFL and NASH^[5]. From 1999 to 2016 in the US annual deaths from hepatocellular carcinoma doubled to 11073^[6]. Therefore, assessing the genetic factors of HCC and NAFLD for early diagnosis of the disease represents the key to reducing the high mortality rate. Previous case-control studies investigating the association between the HSD17B13 rs7261356: TA allelic variant and liver disease have given controversial results due to differences in population samples, detection methods and diagnostic criteria^[7, 8]. In order to unify these differences, a meta-analysis of published research was conducted to comprehensively assess the relationship between HSD17B13 rs7261356: TA allelic variant and liver disease.

Methods And Materials

The current meta-analysis complied with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (PROSPERO CRD42020178246)^[9].

Search strategy

Relevant publications were identified through searching PubMed (Medline), China National Knowledge Infrastructure (CNKI), CBM, EMBASE and CENTRAL web databases using the following search terms: "Hydroxysteroid 17- β dehydrogenase 13" and "Liver Diseases". What is more, we also checked the references of relevant articles to find any other potentially relevant papers. Table 1 summarizes the search strategy for PubMed, and it was also employed for all databases. The last literature search in the above databases was completed on July 2, 2020.

Table 1
PubMed search strategy

Number	Search items
#1	"Hydroxysteroid 17- β dehydrogenase 13" OR "Hydroxysteroid 17-BETA dehydrogenase 13" OR "17-beta-hydroxysteroid dehydrogenase 13" OR "17- β -hydroxysteroid dehydrogenase 13" OR HSD17B13 OR rs72613567 OR rs6834314 OR rs62305723
#2	"Liver Diseases"[Mesh] OR Liver* OR hepatoma* OR Intrahepatic* OR Hepatic* OR Hepatis* OR hepatocellular* OR hepatitis* OR cirrhosis* OR HBV OR HCV OR HCC OR fibrosis* OR ALD OR NAFLD OR Hepatolenticular* OR Hepatomegaly* OR Hepatopulmonary* OR Hepatorenal*
#3	#1 AND #2

Inclusion and exclusion criteria of the literature

Inclusion criteria: (1) involving the associations between HSD17B13 rs7261356: TA allelic variant and liver disease; (2) case-control studies; (3) if two (or more) studies included the same cohort, the most recent was included to avoid repeated statistics; (4) providing complete data on genotype frequencies. **Exclusion criteria:** (1) no clear diagnostic criteria for liver disease described; (2) not reported the genotype frequencies; (3) the OR values and 95% CI were not available by calculation; (4) no-case-control study; (5) in vitro or animal studies.

Data extraction

The information extracted by two independent investigators from each study included: the first author's surname, publication year, country in which the study was conducted, total numbers of patients in the case and control groups, sex ratio, as well as the numbers of cases and controls with the TA and T genotypes. Any disagreement was resolved by discussing with the third author until we reached a group consensus.

Statistical analysis

All the statistical analyses were performed with STATA 12.0 software, with probability value of < 0.05 considered to be statistically significant. Summary odds ratio (ORs) and 95% confidence intervals (CIs) were calculated to evaluate the association of the TA/T polymorphism in the HSD17B13 gene with liver disease under allele genetic contrast. Heterogeneity was measured by Cochran's Chi square-based Q test and I^2 -statistic for all qualified studies. If $P < 0.05$ or $I^2 > 50\%$, indicating significant heterogeneity, the random-effects model was applied to calculate pooled ORs. otherwise, the fixed-effects model was utilized. We also performed sensitivity analysis to explore the effect of a single study on overall results by removing one study sequentially. The Egger's test was employed to assess publication bias, with $P < 0.05$ considered to present statistical significance.

Results

Study characteristics

Figure 1 depicted the flow diagram of literature research and selection. Initially, we identified 187 relevant studies in the databases before July 2020. After exclusion of duplicate or irrelevant to this meta-analysis, 44 remaining literature seemed to be eligible for this meta-analysis. The second-round of review was based on careful full-text review of the 44 retained papers. Then, 39 reports were excluded as follows: reviews(3), focusing on basic research(4), abstract poster(17), without control population(6), repeat population(2), research diseases are not NAFLD or HCC(7). Eventually, this meta-analysis included 5 case-control studies. A total of patients with 1384 liver cancer, 2990 patients with chronic liver disease, 4621 healthy controls, 563 patients with NAFLD and 4654 individuals without NAFLD were included. The main characteristics and genotyping data for all studies are summarized in Table 1.

Meta-analysis results

Association between HSD17B13 rs7261356: TA allelic variant and HCC

The main results of the meta-analysis are displayed in Table 2. 5 literatures described the association between HSD17B13 rs7261356: TA allelic variant and susceptibility to HCC compared with chronic liver disease. Using fixed-effect model, we found that there was a significant association for HSD17B13 rs7261356: TA allelic variant and HCC under allelic model: TA vs T OR = 0.766, 95% CI = 0.682–0.860, P = 0.000 (Fig. 2). Besides, this meta-analysis involved 3 articles on the association between HSD17B13 rs7261356: TA allelic variant and susceptibility to HCC compared with healthy controls. The random effects model was employed for pooled ORs since significant heterogeneity was detected. We discovered that the HSD17B13 rs7261356: TA allelic variant was significantly associated with susceptibility to HCC compared with healthy controls: TA vs T OR = 0.649, 95% CI = 0.431–0.977, P = 0.038 (Fig. 3).

Association between HSD17B13 rs7261356: TA allelic variant and NAFLD

3 articles were included in the HSD17B13 rs7261356: TA allelic variant and risk of NAFLD. Using random-effect model, we found no significant association between the HSD17B13 rs7261356: TA allelic variant and NAFLD susceptibility: TA vs T OR = 0.749, 95% CI = 0.517–1.804, P = 0.126 (Fig. 4).

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

study	Cohort characteristics	Country	Total numbers	Gender, (men%)	Study design	Genotyping	allele	
							TA	T
Stickel.F 2019	HCC	Europe	1031	91	case control	TaqMan	365	1697
	CLD		1653	84	study		728	2578
Yang.J 2019 ^[11]	HCC	Europe	178	83	case control	TaqMan	86	270
	CLD		459	68	study		316	602
Fazio.M 2019 ^[12]	HCC	Europe	123	-	case control	TaqMan	52	194
	CLD		241		study		98	384
Abul-Husn.N 2018 ^[13]	HCC	Europe	44	-	case control	TaqMan	12	76
	CLD		435		study		106	764
Scheiner.B 2018 ^[14]	HCC	Europe	8	-	case control	TaqMan	4	12
	CLD		202	74	study		89	315
Abul-Husn.N 2018 ^[13]	HCC	Europe	44	-	case control	TaqMan	12	76
	Healthy controls		4279		study		1172	7386
Yang.J 2019 ^[11]	HCC	Europe	178	83	case control	TaqMan	86	270
	Healthy controls		252	-	study		202	302
Fazio.M 2019	HCC	Europe	123	-	case control	TaqMan	52	194
	Healthy controls		90		study		50	130
Fazio.M 2019 ^[12]	NAFLD	Europe	151	-	case control	TaqMan	48	254
	NON-NAFLD		90		study		50	130
Abul-Husn.N 2018 ^[13]	NAFLD	Europe	210	-	case control	TaqMan	46	374
	NON-NAFLD		4279		study		1172	7386
Scheiner.B 2018 ^[14]	NAFLD	Europe	202	76	case control	TaqMan	89	315
	NON-NAFLD		285	74	study		125	445

Table 2

Meta-analysis of the association of HSD17B13 rs7261356: TA allelic variant and liver disease susceptibility

Liver disease	Relevance test			Heterogeneity test			Publication	
	OR(95% CI)	Z	P _{value}	I ²	Q	P _{het}	P _{egger}	t
HCC compared with CLD	0.766(0.682–0.860)	4.51	0.000	45.8	7.38	0.117	0.378	1.03
HCC compared with healthy controls	0.648(0.429–0.979)	2.06	0.039	62.1	5.28	0.071	0.033	19.01
NAFLD compared with NON-NAFLD	0.749(0.517–1.084)	1.53	0.126	70.1	6.68	0.035	0.274	-2.18

Sensitivity analysis and publication bias

In the meta-analysis, the results of sensitivity analysis showed that no single study impacted the overall ORs qualitatively, confirming the statistical stability of our findings (Supplementary Figs. 1.2.3).

In the meta-analysis of HSD17B13 rs7261356: TA allelic variant and liver disease susceptibility, the Egger regression analysis suggested that obviously publication bias existed in HCC patients compared with healthy controls. (Supplementary Fig. 5). Examination of the pruning method showed that the funnel chart was basically symmetrical after pruning, and the OR difference in the combined effect before pruning was statistically significant (OR = 0.648, 95% CI = 0.429–0.979, $p = 0.039$). The OR difference in the combined effects after trimming was also statistically significant (OR = 0.476, 95% CI = 0.312–0.727, $p = 0.001$), indicating that there was no significant publication offset after trimming, and the results were robust (Supplementary Fig. 6). And no publication bias existed in other groups. (Supplementary Figs. 4,7).

Discussion

HSD17B13 is a member of the short-chain dehydrogenase/reductase family, a group of enzymes involved in the metabolism of steroid hormones, prostaglandins, lipids, xenobiotics, and retinoids^[15]. The HSD17B13 protein is 300 amino acids long and contains an NAD(P)H binding site, a catalytic site, and a lipid droplet binding domain that targets the protein to the surface of hepatic lipid droplets^[16]. The rs72613567 is an indel, of which the predicted functional consequence is a splice donor variant of HSD17B13 gene^[17].

Although the research on the relationship between HSD17B13 rs7261356: TA allelic variant and liver disease has attracted the attention of many researchers, the results vary from study to study. In addition to research on HCC and NAFLD in this meta-analysis, Peter Ferenci^[18] determined HSD17B13:TA (rs72613567) variant by allelic discrimination real-time PCR in 586 Wilson's disease (WD) patients. They get the conclusion that the HSD17B13: TA allele modulates the phenotype and outcome of WD. This allele likely ameliorates hepatic fibrosis and reduces the transition from copper induced hemolysis to fulminant disease in patients with WD. In this study, We use suitable mathematical models to perform quantitative analysis of multiple identical or similar research results, increasing the test efficiency of research results.

We developed a retrieval strategy and conducted literature quality evaluation according to the requirements of the Oxford Critical Appraisal Skill Program (Oxford CASP, 2004)¹⁹. Finally, 5 literatures meeting the requirements were included for data extraction. The fixed effect model was used to conduct combined analysis of the data of HCC compared with chronic liver disease. The random effect model was used to conduct combined analysis of the data of HCC compared with healthy controls and NAFLD compared with non-NAFLD. The results showed that HSD17B13 rs7261356: TA allelic variant was associated with HCC, but was not associated with NAFLD.

In the meantime, there are still some limitations in this article. First, due to the lack of a unified document quality evaluation standard, the included articles are subjectively selected and evaluated, which may affect the stability of the meta-analysis results. Second, since meta-analysis itself is a retrospective study, there is a degree of bias. Thirdly, due to the limited number of articles included, the credibility of the results of the meta-analysis may be impacted. Due to these limitations, we still need to expand the sample size to further and systematically evaluate case-control studies.

In summary, the polymorphism of HSD17B13 rs7261356: TA allelic variant was associated with HCC, but was not associated with NAFLD.

Abbreviations

CLD Chronic liver disease

ALD Alcoholic liver disease

NAFLD Nonalcoholic fatty liver disease

PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses

CNKI China National Knowledge Infrastructure

ORs Odds ratio

CIs Confidence intervals

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

All data generated or analyzed during this study are derived from previously published original research articles. Details are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Author contributions:

ST and JZ contributed equally to this work; ST and JZ designed and wrote the manuscript; TTM and WYZ searched and filtered the literature; HBY and SJZ participated critical revision of the manuscript for important intellectual content and supervised this study. HBY and SJZ were corresponding authors. All authors have read and approved the manuscript.

Conflict-of-interest statement:

The authors have no conflict of interest to declare. There are no financial or other competing interests for principal investigators, the patients included or any trial participant

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Figures

Figure 1

Flow diagram for study selection

Figure 2

Besides, this meta-analysis involved 3 articles on the association between HSD17B13 rs7261356: TA allelic variant and susceptibility to HCC compared with healthy controls.

Figure 3

The random effects model was employed for pooled ORs since significant heterogeneity was detected. We discovered that the HSD17B13 rs7261356: TA allelic variant was significantly associated with susceptibility to HCC compared with healthy controls:TA vs T OR=0.649, 95% CI=0.431-0.977, P=0.038

Figure 4

3 articles were included in the HSD17B13 rs7261356: TA allelic variant and risk of NAFLD. Using random-effect model, we found no significant association between the HSD17B13 rs7261356: TA allelic variant and NAFLD susceptibility:TA vs T OR=0.749, 95% CI=0.517-1.804, P=0.126

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