European Review for Medical and Pharmacological Sciences 2020; 24: 8997-9007

HSD17B13 rs72613567 protects against liver diseases and histological progression of nonalcoholic fatty liver disease: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: The authors performed a systematic review and meta-analysis to investigate the role of rs72613567 within *hydroxysteroid 17-beta dehydrogenase 13 (HSD17B13)* in liver diseases.

MATERIALS AND METHODS: Relevant studies on the effects of *HSD17B13* rs72613567 on liver diseases were found using the PubMed, Web of Science, and Embase databases, up to March 2020. The keywords "*HSD17B13*", "polymorphism", "variant" and "rs72613567" were used. Odds ratios (OR) and 95% confidence interval (CI) were extracted or estimated from each eligible study. A random-effects model was applied to pool results.

RESULTS: We included a large population for the assessment of any liver disease (n=564702), cirrhosis (n=559834), and hepatocellular carcinoma (HCC) (n=183179), respectively. The results demonstrated that the TA allele of *HSD17B13* rs72613567 could provide substantial protection from these disorders (any liver diseases: pooled OR=0.73, 95% CI=0.61-0.87; liver cirrhosis: pooled OR=0.81, 95% CI=0.76-0.88; HCC: pooled OR=0.64, 95% CI=0.53-0.77). In addition, four studies were summarized based on the histological features of nonalcoholic fatty liver disease (NAFLD). *HSD17B13* rs72613567 showed a tendency towards decreased inflammation, reduced fibrosis, and milder disease severity in NAFLD.

CONCLUSIONS: Our study highlights that *HSD17B13* rs72613567 is an important protective factor in multiple categories of liver diseases.

Key Words:
Hydroxysteroid 17-beta dehydrogenase 13 (*HSD17B13*), Rs72613567, Liver diseases, Nonalcoholic fatty liver disease (NAFLD), Risk.

Introduction

Liver diseases are highly prevalent and account for nearly two million deaths each year around the world. One million of these deaths are attributed to liver cirrhosis and the remaining million deaths are due to hepatitis and hepatocellular carcinoma (HCC)[1]. Cirrhosis is the 11th leading cause of global death and within the top 20 causes of disability[1]. As the sixth most common cancer, HCC incidence has risen faster than other cancers in recent years[2,3]. Other liver diseases, such as alcoholic liver disease (ALD) and nonalcoholic fatty liver disease (NAFLD), also represent a heavy health and economic burden to the affected individuals and society. The prevention of these diseases is becoming an urgent issue, with the identification of potential factors as the first step.

Previous studies[4,5] have confirmed several environmental risk factors that contribute to liver diseases, including viral infection, alcohol and obesity. Increasing researches[6,7] have further revealed that genetic factors also play a crucial role in liver diseases. In particular, genome-wide association studies (GWAS) have identified several contributing loci, such as rs738409 (p.I148M) within patatin like phospholipase domain containing 3 (PNPLA3) and rs58542926 (p.E167K) within transmembrane 6 superfamily member 2 (TM6SF2)[8,9]. In 2018, a new variant, rs72613567 within hydroxysteroid 17-beta dehydrogenase 13 (HSD17B13) was first reported to likely provide substantial protection against liver diseases[10]. HSD17B13 rs72613567 is a protein-truncating

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variant with an insertion of A allele adjacent to the splice site of exon 6. Subsequent studies[10-16] have investigated its role in different types or pathological process of liver diseases, but the results are conflicting. Therefore, we performed this systematic review and meta-analysis to assess the effect of *HSD17B13* rs72613567 on the risk and progression of liver diseases.

Materials and Methods

This study was carried out in accordance with the statement of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[17].

Data Searches and Study Selection

PubMed, Embase, and Web of Science were searched for relevant records without any restrictions (up to March 2020). The search items included "*HSD17B13*", "polymorphism", "variant", and "rs72613567". We also conducted manual search by careful review of reference lists of identified publications.

A study was eligible for inclusion if it met all the following criteria: (1) it was a case-control or cohort study on the association between *HSD17B13* rs72613567 and the risk or progression of liver diseases; (2) it provided the odds ratio (OR) and 95% confidence interval (CI), and/or reported allele frequency or genotypes. The exclusion criteria included: (1) review, meta-analysis, conference abstract or experimental studies; (2) missing controls or having overlapped data with other studies. If two studies have an overlapped population, we kept the one with the larger and detailed data. Two independent authors (PW and CW) performed these procedures. In case of disagreement, consensus was resolved by discussion. All data were double checked by another author (YL).

Data Extraction and Quality Evaluation

The following items were extracted from each eligible study: the first author, publication year, country, ethnicity, genotyping methods, age, sex, body mass index (BMI), and study features. ORs and 95% CIs, genotype distribution and allele frequency were also recorded. The quality of the included studies was assessed using the Newcastle-Ottawa scale (NOS)[18]. Three authors participated in the aforementioned work (WP, CW and YL).

Statistical Analysis

The Hardy-Weinberg equilibrium (HWE) was examined in controls using a χ^2-test. The strength of the association was measured by ORs and 95% CIs. Multivariate-adjusted ORs and 95% CIs were preferentially recorded from each study. If they were not available, unadjusted ORs and 95% CIs were calculated based on allelic data. Between-study heterogeneity was assessed using the Cochran's Q test and I^2 statistics. $p<0.10$ or $I^2>50$ % indicated significant heterogeneity[19]. A random-effects model was used to pool the results. In addition, one-way sensitivity analysis was used to evaluate the stability of the pooled results. Begg's and Egger's tests were used to examine the publication bias[20,21]. If not specified, a two-sided $p\leq0.05$ was considered as statistically significant. This meta-analysis was conducted by STATA 13.0 (StataCorp LLC, College Station, TX, USA).

Results

Identification of Eligible Studies

A flow chart of literature search and study selection is shown in Figure 1. Initially, we retrieved a total of 113 records. After removing duplicates and reviewing title and abstract, 23 relevant articles were selected for full-text evaluation. We further excluded 16 articles due to the following reasons: (1) they were not relevant to the association between *HSD17B13* rs72613567 and liver diseases risk or histological features (n = 9)[22-30]; (2) they had overlapped data with other studies (n = 3)[31-33]; (3) they did not provide the allelic data of *HSD17B13* rs72613567 (n = 2)[34,35]; (4) they focused on specific populations, such as people with Wilson's Disease[36] or obese children[37] (n = 2) . Ultimately, seven eligible studies[10-16] met all the inclusion criteria.

Characteristics of Included Studies

Study characteristics are summarized in Table I and Table II. As shown in Table I, five studies[10-14] were included for the meta-analysis of the association of *HSD17B13* rs72613567 with the risk of liver diseases. The first study was published in 2018, which comprised three cohorts[10]. All included studies were population-based and high-quality (NOS score ≥ 6).

Due to the insufficient number of studies for meta-analysis, we summarized relevant studies on the role of *HSD17B13* rs72613567 in NA-

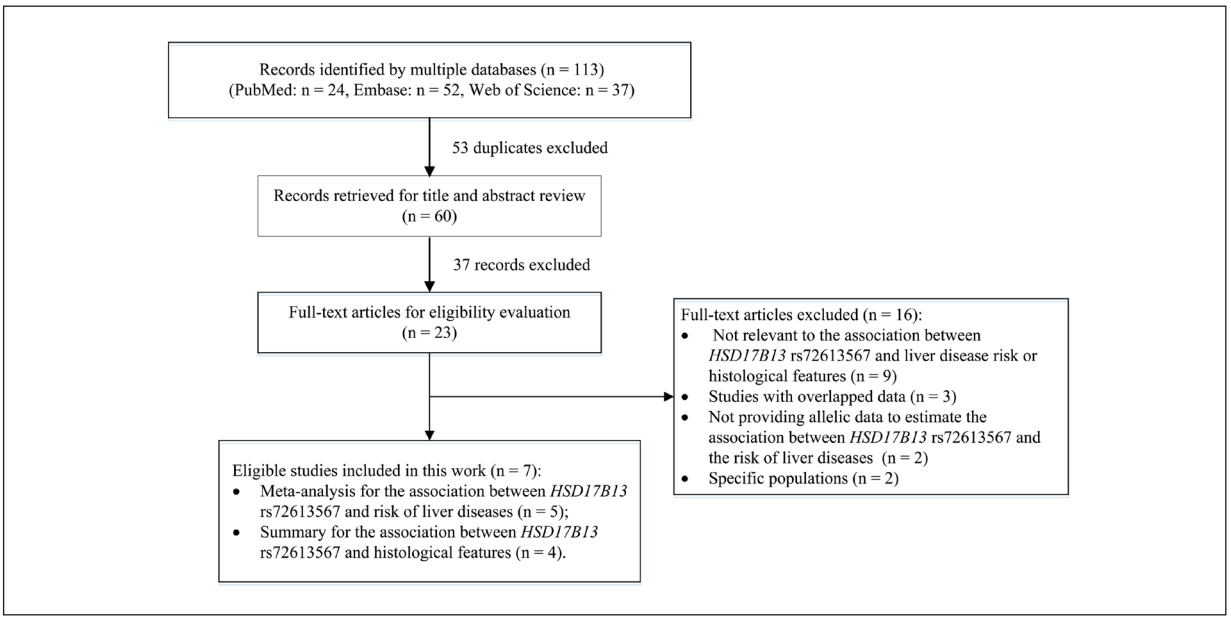

Figure 1. A flow chart of literature search and study selection.

FLD-histological features[10,11,15,16]. Features included steatosis, inflammation, hepatocyte ballooning, NAFLD activity score (NAS), fibrosis, and disease severity. Multivariate-adjusted ORs and 95% CIs, genetic models and adjustment were also demonstrated in Table II.

The Association Between HSD17B13 rs72613567 and Risk of Liver Diseases

We applied a random-effects model based on allelic data to pool the results, as summarized in Figure 2.

Any Liver Disease

The estimation of any liver disease was analyzed in five studies including 564702 individuals[10-14]. The results suggested that the mutant TA allele of *HSD17B13* rs72613567 conferred a protective effect on any liver disease (pooled OR = 0.73, 95% CI = 0.61-0.87, $p_{heterogeneity} < 0.001$, I^2 = 89.4%, Figure 2), with no significant publication bias ($p_{Egger} = 0.057$, $p_{Begg} = 0.707$). The sensitivity analysis suggested that the results were stable (**Supplementary Figure S1a**). We further assessed the role of *HSD17B13* rs72613567 in alcoholic liver disease. Compared with the wild allele, the mutant TA allele demonstrated a significant protection against alcoholic liver disease with low heterogeneity (pooled OR = 0.82, 95% CI = 0.74-0.90, $p_{heterogeneity} = 0.211$, $I^2 = 31.6\%$, Figure 2). No publication bias was observed ($p_{Egger} = 0.128$, $p_{Begg} = 0.086$). The sensitivity analysis also showed the result was stable (**Supplementary Figure S1b**). Despite an insufficient number of studies[10,13,15] for the meta-analysis of nonalcoholic liver disease, existing publications supported the protective effect of *HSD17B13* rs72613567.

Liver Cirrhosis

The estimation of liver cirrhosis was performed in four studies including 559834 individuals[10-12,14]. *HSD17B13* rs72613567 was significantly associated with a lower risk of liver cirrhosis (pooled OR = 0.81, 95% CI = 0.76-0.88, $p_{heterogeneity} = 0.294$, I^2 = 19.0%, Figure 2). The sensitivity analysis showed that the result was stable (**Supplementary Figure S1c**). No publication bias was found ($p_{Egger} = 0.967$, $p_{Begg} = 0.806$). A stable association was also observed in alcoholic cirrhosis (pooled OR = 0.77, 95% CI = 0.65-0.90, $p_{heterogeneity} = 0.105$, $I^2 = 51.2\%$, Figure 2 and **Supplementary Figure S1d**). No publication bias was observed ($p_{Egger} = 0.099$, $p_{Begg} = 0.089$). In addition, the results from Abul-Husn NS showed that *HSD17B13* rs72613567 also had a protection from nonalcoholic cirrhosis[10].

HCC

A total of 183179 individuals from four studies[10,12-14] were included. A stable result revealed

Table I. Characteristics of the included studies on the association between HSD17B13 rs72613567 and the risk of liver diseases.

First author	Year	Country	Ethnicity	Genotyping method and HWE	Age (median [IQR] or mean ± SD, years)	Female, n (%)	BMI (median [IQR] or mean ± SD, kg/m²)	Study features	NOS score
Abul-Husn et al[10]	2018	USA	GHS cohort: European Americans	Whole-exome sequencing; genotypes were in HWE by our calculation.	GHS cohort: 63 (50-74)	GHS cohort: 26875 (58)	GHS cohort: 30 (25-45)	**1.** ALD vs. normal (cases = 190, controls = 29928); **2.** NALD vs. normal (cases = 1857, controls = 29928); **3.** AC vs. normal (cases = 124, controls = 29928); **4.** NAC vs. normal (cases = 374, controls = 29928); **5.** HCC *vs.* normal (cases = 75, controls = 29928).	9
			DLS cohort: African American, European American and Hispanic American	TaqMan assay; genotypes were not in HWE by our calculation	DLS cases: 55 (48-60); DLS controls: 44 (36-53)	DLS cases: 277 (54); DLS controls: 2494 (58)	DLS cases: 30 (27-35); DLS controls: 30 (26-35).	**1.** Any liver disease *vs.* normal (cases = 517, controls = 4279); **2.** ALD *vs.* normal (cases = 223, controls = 4279); **3.** NALD *vs.* normal (cases = 212, controls = 4279); **4.** AC *vs.* normal (cases = 215, controls = 4279); **5.** NAC *vs.* normal (cases = 100, controls = 4279); **6.** HCC *vs.* normal (cases = 44, controls = 4279).	
			DPLS cohort: Hispanic American	TaqMan assay; authors did not report HWE testing and genotypes were not available by providing data	DPLS cases: 12 (10-15); DPLS controls: 12 (11-14)	DPLS cases: 63 (31); DPLS controls: 118 (50)	DPLS cases: 30 (27-34); DPLS controls: 31 (28-35).	Any liver disease *vs.* normal (cases = 205, controls = 234)	
Ma et al[11]	2019	USA	Mixed	Sequenom MassARRAY iPLEX Gold platform; authors did not report HWE testing and genotypes were not available by providing data	66.9 ± 8	221052 (54)	27.4 ± 4.8	**1.** Any liver disease *vs.* normal (cases = 4095, controls = 404056); **2.** ALD *vs.* normal (cases = 810, controls = 408151); **3.** Cirrhosis *vs.* normal (cases = 809, controls = 408152)	8

Table continued

Table I *(Continued)*. Characteristics of the included studies on the association between HSD17B13 rs72613567 and the risk of liver diseases.

First author	Year	Country	Ethnicity	Genotyping method and HWE	Age (median [IQR] or mean ± SD, years)	Female, n (%)	BMI (median [IQR] or mean ± SD, kg/m²)	Study features	NOS score
Stickel et al[12]	2019	Multiple centers	European	TaqMan assay; genotypes were reported to be in HWE	HCC: 62 ± 10; AC: 55 ± 10; Controls: 48 ± 10	HCC: 93 (9); AC: 463 (28); Controls: 414 (16).	HCC: 27.8 ± 4.8; AC: 25.9 ± 4.9; Controls: 24.7 ± 4.1.	**1.** AC vs. normal (cases = 1653, controls = 2588); **2.** HCC vs. normal (cases = 1031, controls = 2588).	7
Yang et al[13]	2019	Multiple centers	European	TaqMan assay; genotypes were reported to be in HWE. The control group was 33337 healthy European individuals from the Exome Aggregation Consortium	Patients with CLD without HCC (n=2206): 55±11; HCC patients Exploratory cohort (n=285): 64.8 ± 11.1; HCC Patients n Validatio cohort (n=824): 63±11	Patients with CLD without HCC (n=2206): 693 (31); HCC patients Exploratory cohort (n=285): 53 (19); HCC Patients Validation cohort (n=824): 140 (17).	NA	HCC vs. normal (cases = 285, controls = 33337)	6
Gellert-Kristensen et al[14]	2020	Denmark	Danish	TaqMan assay; genotypes were reported to be in HWE	58 (48-68)	61542 (55)	26 (23-28)	**1.** Cirrhosis and/or HCC *vs.* normal (cases = 566, controls = 111046); **2.** Cirrhosis vs. normal (cases = 497, controls = 111115); **3.** AC vs. normal (cases = 294, controls = 111318); **4.** HCC vs. normal (cases = 113, controls = 111499).	8

Table II. Studies on the role of *HSD17B13* rs72613567 in NAFLD-histological features.

	Study	Phenotype	Subjects	OR (95% CI)	Genetic model	Adjustments
Steatosis	Ma et al[11]	At least moderate steatosis (≥ 33% *vs.* <33%)	735	1.36 (1.04-1.77)	Additive	Age, gender and BMI
Inflammation						
	Ma et al[11]	Significant inflammation (combined portal and lobular inflammatory score ≥ 3 *vs.* <3)	735	0.74 (0.57-0.96)	Additive	Age, gender and BMI
	Pirola et al[15]	Lobular inflammation (yes *vs.* no)	609	0.45 (0.26-0.77)	Additive	Sex, age, BMI (body mass index), HOMA-IR and rs738409 (PNPLA3)
Hepatocyte Ballooning	Ma et al[11]	Significant ballooning (many cells *vs.* none or few)	735	0.78 (0.60-1.03)	Additive	Age, gender and BMI
	Pirola et al[15]	Ballooning degeneration (yes *vs.* no)	609	0.47 (0.28-0.82)	Additive	Sex, age, BMI (body mass index), HOMA-IR and rs738409 (PNPLA3)
NAS	Pirola et al[15]	NAS score ≥ 5 *vs.* NAS score < 5	356	0.37 (0.15-0.89)	Additive	BMI
Fibrosis	Ma et al[11]	Significant fibrosis (bridging fibrosis *vs.* less)	699	0.77 (0.58-1.03)	Additive	Age, gender, and BMI
	Pirola et al[15]	Fibrosis (yes *vs.* no)	609	0.42 (0.17-1.00)	Additive	Sex, age, BMI (body mass index), HOMA-IR and rs738409 (PNPLA3)
Disease severity	Abul-Husn et al[10]	Simple steatosis *vs.* normal	1328	1.11 (0.94–1.32)	Allelic	Age, age squared, sex, BMI, and the first four principal components of ancestry
	Abul-Husn et al[10]	NASH *vs.* normal	1489	0.86 (0.72–1.02)	Allelic	Age, age squared, sex, BMI, and the first four principal components of ancestry
	Abul-Husn et al[10]	NASH *vs.* simple steatosis	1735	0.77 (0.66-0.90)	Allelic	Age, age squared, sex, BMI, and the first four principal components of ancestry
	Pirola et al[15]	NASH *vs.* NAFL	356	0.64 (0.40-1.00)	Additive	Sex, age, BMI (body mass index), HOMA-IR and rs738409 (PNPLA3)
	Koo et al[16]	NASH *vs.* NAFL	430	0.84 (0.63-1.13)	Additive	No
	Abul-Husn et al[10]	NASH with fibrosis *vs.* simple steatosis	1435	0.74 (0.62–0.88)	Allelic	Age, age squared, sex, BMI, and the first four principal components of ancestry

that *HSD17B13* rs72613567 could reduce the susceptibility of HCC (pooled OR = 0.64, 95% CI = 0.53-0.77, $p_{heterogeneity}$ = 0.236, I^2 = 27.9%, Figure 2 and **Supplementary Figure S1d-e**), with no publication bias (p_{Egger} = 0.741, p_{Begg} = 0.806).

NAFLD-Histological Features

Four eligible studies are summarized in Table II according to histological features[10,11,15,16]. The sample size of these studies ranged from 356 subjects to 1735 subjects. Overall, *HSD17B13* rs72613567 was associated with decreased inflammation and lower NAS scores, and tended towards reduced ballooning and fibrosis. For disease severity, *HSD17B13* rs72613567 was not associated with steatosis or nonalcoholic steatohepatitis (NASH), but was associated with a decreased risk of progression.

Discussion

This systematic review and meta-analysis evaluated the role of *HSD17B13* rs72613567 in the risk of liver diseases and histological progression. Our major findings are as follows: (1) *HSD17B13* rs72613567 provided significant protection against several liver diseases, including alcohol liver disease, cirrhosis, and HCC; (2)

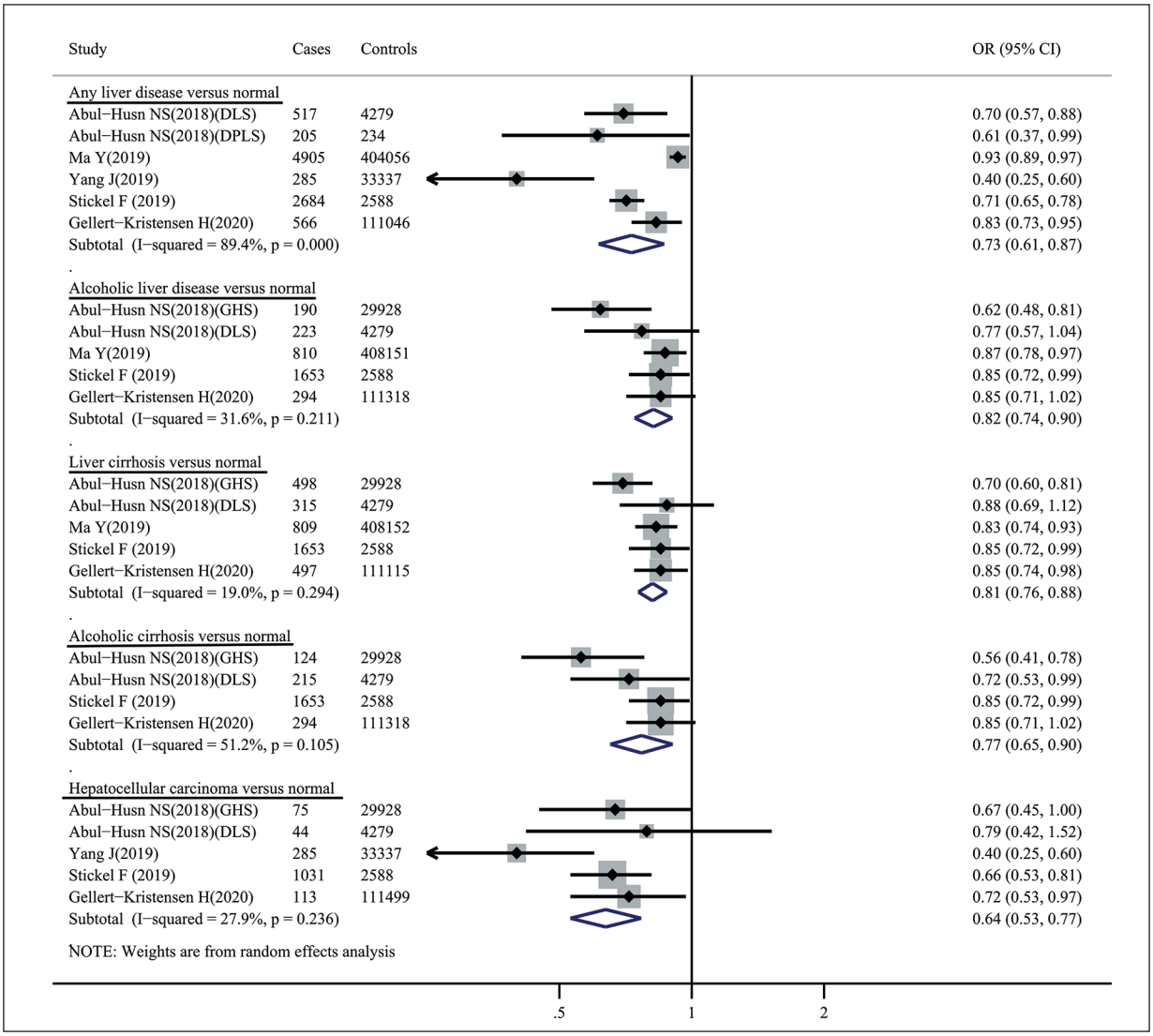

Figure 2. Forest plots of the association between *HSD17B13* rs72613567 and the risk of liver diseases.

HSD17B13 rs72613567 may be associated with a milder histological progression of NAFLD, with reduced inflammation, lower NAS scores, and less ballooning and fibrosis.

HSD17B13 encodes a pivotal lipid-droplet enzyme, which is predominantly expressed in the cytoplasm of hepatocytes, and its aberrant expression has been reported in fatty liver, cirrhosis and HCC[38-40]. More recently, Abul-Husn integrated the exome-sequence data of a large collaborative cohort in a population study. They revealed that *HSD17B13* rs72613567 conferred a protective effect on chronic liver disease and mitigation against progressive NASH[10]. This variant disturbed mRNA splicing and led to a prematurely truncated protein, the TA allele of which was associated with decreased or absent HSD17B13 expression in an allele-dose-dependent manner[10,15].

HSD17B13 rs72613567 provides protection in patients with ALD, NAFLD, cirrhosis, and even HCC[10,12-14,32]. In particular, each TA allele may reduce the risk of cirrhosis and HCC by 15% and 28%, respectively. Moreover, the TA allele was associated with a lower liver-related mortality rate of 33% in a general population[14]. By pooling the available data from eligible studies, our meta-analysis confirmed the protective role of *HSD17B13* rs72613567 in liver diseases, ranging from ALD to HCC.

For NAFLD-histological progression, since we did not identify enough studies for meta-analysis, we summarized the existing data according to progression features instead. All the studies were adjusted for confounding factors. Overall, *HSD17B13* rs72613567 was found to have a tendency to mitigate the progression of NAFLD. HSD17B13 is a liver-specific enzyme that regulates liver lipid homeostasis, and its aberrant expression and high enzyme activity have been confirmed to promote the development of NAFLD[40]. As such, a likely explanation is that *HSD17B13* rs72613567 results in a loss-of-function truncated protein, thus attenuating the progression of NAFLD.

Furthermore, *HSD17B13* rs72613567 may be associated with reduced serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT)[10,14,15]. These results were also in agreement with our conclusion that *HSD17B13* rs72613567 could be a protective factor against liver diseases.

To the best of our knowledge, it was the first comprehensive systematic review and meta-analysis of the effects of *HSD17B13* rs72613567 on the risk of liver diseases and histological progression. Different types of liver diseases and multiple histological features were summarized to delineate the protective role of this variant.

However, several limitations should be noted. First, only four eligible studies were initially included for the meta-analysis of the association between *HSD17B13* rs72613567 and liver disease risk. The limited number of studies hampered the subgroup analysis, and most likely led to the unstable pooled results (e.g., any liver diseased vs. normal, alcohol cirrhosis vs. normal). Second, meta-analysis on the effect of *HSD17B13* rs72613567 on histological progression was also not possible due to the small number of eligible studies. Instead, we chose to summarize existing studies based on histological features. Last but not least, our results did not cover Asian data because of the lack of such studies in Asian populations. The minor allele frequency of *HSD17B13* rs72613567 is known to range from 5% in African populations to 34% in East Asian populations (http://asia.ensembl.org/index.html). These dramatic differences need to be investigated in future researches using different ethnic populations in order to validate our results.

Conclusions

Our study highlights that *HSD17B13* rs72613567 exhibits significant protection against multiple categories of liver disease, and consistently, is associated with a milder progression of NAFLD. In terms of treatment, our results support the view that individuals at high risk of liver diseases may be benefit from HSD17B13 inhibition. Further studies, particularly in Asian populations, will be needed to validate our results.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Funding Acknowledgements

This work was support by National Natural Science Foundation of China (No. 81601839 to NS).

Availability of Data and Materials

The datasets during this study are available from the corresponding author on reasonable request.

Ethics Statement

Ethic approval was not applicable for systematic review and meta-analysis.

Authors' Contribution

NS conceived and supervised the study. PW, CW and YL performed literature search, study selection and data extraction. PW and CW conducted statistical analysis. CW prepared tables and figures. PW drafted the manuscript. All these authors completely consented with all the data in the study and approved the final manuscript. NS had the primary responsibility for final manuscript.

References

1) Asrani SK, Devarbhavi H, Eaton J, Kamath PS. Burden of liver diseases in the world. J Hepatol 2019; 70: 151-171.
2) Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019; 69: 7-34.
3) Cronin KA, Lake AJ, Scott S, Sherman RL, Noone AM, Howlader N, Henley SJ, Anderson RN, Firth AU, Ma J, Kohler BA, Jemal A. Annual Report to the Nation on the Status of Cancer, part I: national cancer statistics. Cancer 2018; 124: 2785-2800.
4) Dyson J, Jaques B, Chattopadyhay D, Lochan R, Graham J, Das D, Aslam T, Patanwala I, Gaggar S, Cole M, Sumpter K, Stewart S, Rose J, Hudson M, Manas D, Reeves HL. Hepatocellular cancer: the impact of obesity, type 2 diabetes and a multidisciplinary team. J Hepatol 2014; 60: 110-117.
5) Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, Adair T, Aggarwal R, Ahn SY, Alvarado M, Anderson HR, Anderson LM, Andrews KG, Atkinson C, Baddour LM, Barker-Collo S, Bartels DH, Bell ML, Benjamin EJ, Bennett D, Bhalla K, Bikbov B, Bin Abdulhak A, Birbeck G, Blyth F, Bolliger I, Boufous S, Bucello C, Burch M, Burney P, Carapetis J, Chen H, Chou D, Chugh SS, Coffeng LE, Colan SD, Colquhoun S, Colson KE, Condon J, Connor MD, Cooper LT, Corriere M, Cortinovis M, de Vaccaro KC, Couser W, Cowie BC, Criqui MH, Cross M, Dabhadkar KC, Dahodwala N, De Leo D, Degenhardt L, Delossantos A, Denenberg J, Des Jarlais DC, Dharmaratne SD, Dorsey ER, Driscoll T, Duber H, Ebel B, Erwin PJ, Espindola P, Ezzati M, Feigin V, Flaxman AD, Forouzanfar MH, Fowkes FG, Franklin R, Fransen M, Freeman MK, Gabriel SE, Gakidou E, Gaspari F, Gillum RF, Gonzalez-Medina D, Halasa YA, Haring D, Harrison JE, Havmoeller R, Hay RJ, Hoen B, Hotez PJ, Hoy D, Jacobsen KH, James SL, Jasrasaria R, Jayaraman S, Johns N, Karthikeyan G, Kassebaum N, Keren A, Khoo JP, Knowlton LM, Kobusingye O, Koranteng A, Krishnamurthi R, Lipnick M, Lipshultz SE, Ohno SL, Mabweijano J, MacIntyre MF, Mallinger L, March L, Marks GB, Marks R, Matsumori A, Matzopoulos R, Mayosi BM, McAnulty JH, McDermott MM, McGrath J, Mensah GA, Merriman TR, Michaud C, Miller M, Miller TR, Mock C, Mocumbi AO, Mokdad AA, Moran A, Mulholland K, Nair MN, Naldi L, Narayan KM, Nasseri K, Norman P, O'Donnell M, Omer SB, Ortblad K, Osborne R, Ozgediz D, Pahari B, Pandian JD, Rivero AP, Padilla RP, Perez-Ruiz F, Perico N, Phillips D, Pierce K, Pope CA, 3rd, Porrini E, Pourmalek F, Raju M, Ranganathan D, Rehm JT, Rein DB, Remuzzi G, Rivara FP, Roberts T, De Leon FR, Rosenfeld LC, Rushton L, Sacco RL, Salomon JA, Sampson U, Sanman E, Schwebel DC, Segui-Gomez M, Shepard DS, Singh D, Singleton J, Sliwa K, Smith E, Steer A, Taylor JA, Thomas B, Tleyjeh IM, Towbin JA, Truelsen T, Undurraga EA, Venketasubramanian N, Vijayakumar L, Vos T, Wagner GR, Wang M, Wang W, Watt K, Weinstock MA, Weintraub R, Wilkinson JD, Woolf AD, Wulf S, Yeh PH, Yip P, Zabetian A, Zheng ZJ, Lopez AD, Murray CJ, AlMazroa MA, Memish ZA. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012; 380: 2095-2128.
6) Danford CJ, Yao ZM, Jiang ZG. Non-alcoholic fatty liver disease: a narrative review of genetics. J Biomed Res 2018; 32: 389-400.
7) Khemlina G, Ikeda S, Kurzrock R. The biology of hepatocellular carcinoma: implications for genomic and immune therapies. Mol Cancer 2017; 16: 149.
8) Buch S, Stickel F, Trepo E, Way M, Herrmann A, Nischalke HD, Brosch M, Rosendahl J, Berg T, Ridinger M, Rietschel M, McQuillin A, Frank J, Kiefer F, Schreiber S, Lieb W, Soyka M, Semmo N, Aigner E, Datz C, Schmelz R, Bruckner S, Zeissig S, Stephan AM, Wodarz N, Deviere J, Clumeck N, Sarrazin C, Lammert F, Gustot T, Deltenre P, Volzke H, Lerch MM, Mayerle J, Eyer F, Schafmayer C, Cichon S, Nothen MM, Nothnagel M, Ellinghaus D, Huse K, Franke A, Zopf S, Hellerbrand C, Moreno C, Franchimont D, Morgan MY, Hampe J. A genome-wide association study confirms PNPLA3 and identifies TM6SF2 and MBOAT7 as risk loci for alcohol-related cirrhosis. Nat Genet 2015; 47: 1443-1448.
9) Young KA, Palmer ND, Fingerlin TE, Langefeld CD, Norris JM, Wang N, Xiang AH, Guo X, Williams AH, Chen YI, Taylor KD, Rotter JI, Raffel LJ, Goodarzi MO, Watanabe RM, Wagenknecht LE. Genome-wide association study identifies loci for liver enzyme concentrations in Mexican Americans: the GUARDIAN Consortium. Obesity (Silver Spring) 2019; 27: 1331-1337.
10) Abul-Husn NS, Cheng X, Li AH, Xin Y, Schurmann C, Stevis P, Liu Y, Kozlitina J, Stender S, Wood GC, Stepanchick AN, Still MD, McCarthy S, O'Dushlaine C, Packer JS, Balasubramanian S, Gosalia N, Esopi D, Kim SY, Mukherjee S, Lopez AE, Fuller ED, Penn J, Chu X, Luo JZ, Mirshahi UL, Carey DJ, Still CD, Feldman MD, Small A, Damrauer SM, Rader DJ, Zambrowicz B, Olson W, Murphy AJ, Borecki IB, Shuldiner AR, Reid JG, Overton JD, Yancopoulos GD, Hobbs HH, Cohen JC, Gottesman O, Teslovich TM, Baras A, Mirshahi T, Gromada J, Dewey FE. A protein-truncating HSD17B13 variant and protection from chronic liver disease. N Engl J Med 2018; 378: 1096-1106.
11) Ma Y, Belyaeva OV, Brown PM, Fujita K, Valles K, Karki S, de Boer YS, Koh C, Chen Y, Du X, Handel-

man SK, Chen V, Speliotes EK, Nestlerode C, Thomas E, Kleiner DE, Zmuda JM, Sanyal AJ, Kedishvili NY, Liang TJ, Rotman Y. 17-beta hydroxysteroid dehydrogenase 13 is a hepatic retinol dehydrogenase associated with histological features of nonalcoholic fatty liver disease. Hepatology 2019; 69: 1504-1519.

12) Stickel F, Lutz P, Buch S, Nischalke HD, Silva I, Rausch V, Fischer J, Weiss KH, Gotthardt D, Rosendahl J, Marot A, Elamly M, Krawczyk M, Casper M, Lammert F, Buckley TW, McQuillin A, Spengler U, Eyer F, Vogel A, Marhenke S, von Felden J, Wege H, Sharma R, Atkinson S, Franke A, Nehring S, Moser V, Schafmayer C, Spahr L, Lackner C, Stauber RE, Canbay A, Link A, Valenti L, Grove JI, Aithal GP, Marquardt JU, Fateen W, Zopf S, Dufour JF, Trebicka J, Datz C, Deltenre P, Mueller S, Berg T, Hampe J, Morgan MY. Genetic variation in HSD17B13 reduces the risk of developing cirrhosis and hepatocellular carcinoma in alcohol misusers. Hepatology 2019; 72: 88-102.

13) Yang J, Trepo E, Nahon P, Cao Q, Moreno C, Letouze E, Imbeaud S, Bayard Q, Gustot T, Deviere J, Bioulac-Sage P, Calderaro J, Ganne-Carrie N, Laurent A, Blanc JF, Guyot E, Sutton A, Ziol M, Zucman-Rossi J, Nault JC. A 17-beta-hydroxysteroid dehydrogenase 13 variant protects from hepatocellular carcinoma development in alcoholic liver disease. Hepatology 2019; 70: 231-240.

14) Gellert-Kristensen H, Nordestgaard BG, Tybjaerg-Hansen A, Stender S. High risk of fatty liver disease amplifies the alanine transaminase-lowering effect of a HSD17B13 variant. Hepatology 2020; 71: 56-66.

15) Pirola CJ, Garaycoechea M, Flichman D, Arrese M, San Martino J, Gazzi C, Castano GO, Sookoian S. Splice variant rs72613567 prevents worst histologic outcomes in patients with nonalcoholic fatty liver disease. J Lipid Res 2019; 60: 176-185.

16) Koo BK, Joo SK, Kim D, Lee S, Bae JM, Park JH, Kim JH, Chang MS, Kim W. Development and validation of a scoring system, based on genetic and clinical factors, to determine risk of steatohepatitis in asian patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2020; doi: https://doi.org/10.1016/j.cgh.2020.02.011.

17) Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009; 6: e1000097.

18) Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010; 25: 603-605.

19) Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21: 1539-1558.

20) Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-634.

21) Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994; 50: 1088-1101.

22) Rotman Y, Fujita K, Koh C, Maeder DL, Kleiner DE, Zmuda JM, O'Brien TR, Sanyal AJ, Liang TJ. Identification of HSD17B13 and RORA as genes involved in pathogenesis of nonalcoholic fatty liver disease. Hepatology 2012; 56: 265A-265A.

23) Kitamoto A, Kitamoto T, Nakamura T, Ogawa Y, Yoneda M, Hyogo H, Ochi H, Mizusawa S, Ueno T, Nakao K, Sekine A, Chayama K, Nakajima A, Hotta K. Association of polymorphisms in GCKR and TRIB1 with nonalcoholic fatty liver disease and metabolic syndrome traits. Endocr J 2014; 61: 683-689.

24) Ghanbari M, Franco OH, de Looper HW, Hofman A, Erkeland SJ, Dehghan A. Genetic variations in microRNA-binding sites affect microrna-mediated regulation of several genes associated with cardio-metabolic phenotypes. Circ Cardiovasc Genet 2015; 8: 473-486.

25) Xu L, Jiang CQ, Lam TH, Zhang WS, Zhu F, Jin YL, Thomas GN, Cheng KK, Schooling CM. Mendelian randomization estimates of alanine aminotransferase with cardiovascular disease: Guangzhou Biobank Cohort study. Hum Mol Genet 2017; 26: 430-437.

26) Kozlitina J, Stender S, Hobbs HH, Cohen JC. HSD17B13 and chronic liver disease in blacks and hispanics. N Engl J Med 2018; 379: 1876-1877.

27) McClain CJ. Biomarkers for alcoholic hepatitis: implications for diagnosis and therapy. Alcohol Clin Exp Res 2018; 42: 125A-125A.

28) Rotroff DM, Pijut SS, Marvel SW, Jack JR, Havener TM, Pujol A, Schluter A, Graf GA, Ginsberg HN, Shah HS, Gao H, Morieri ML, Doria A, Mychaleckyi JC, McLeod HL, Buse JB, Wagner MJ, Motsinger-Reif AA. Genetic variants in HSD17B3, SMAD3, and IPO11 impact circulating lipids in response to fenofibrate in individuals with Type 2 diabetes. Clin Pharmacol Ther 2018; 103: 712-721.

29) Whitfield JB, Zhu G, Madden PAF, Montgomery GW, Heath AC, Martin NG. Biomarker and genomic risk factors for liver function test abnormality in hazardous drinkers. Alcohol Clin Exp Res 2019; 43: 473-482.

30) Chen VL, Chen Y, Du X, Handelman SK, Speliotes EK. Genetic variants that associate with cirrhosis have pleiotropic effects on human traits. Liver Int 2020; 40: 405-415.

31) Stickel F, Lutz P, Buch S, Fischer J, Rausch V, Silva I, Rosendahl J, Nischalke HD, Krawczyk M, Lammert F, Casper M, Zopf S, Marhenke S, Vogel A, Eyer F, von Felden J, Gotthardt D, Weiss KH, Spengler U, Mueller S, Canbay A, Baselli GA, Valenti L, McQuillin A, Berg T, Hampe J, Morgan M. HSD17B13 rs72613567 TA is associated with a reduced risk for developing hepatocellular carcinoma in patients with alcohol-related cirrhosis. J Hepatol 2019; 70: E109-E110.

32) Stickel F, Lutz P, Buch S, Rausch V, Silva L, Fischer J, Nischalke HD, Rosendahl J, Krawczyk M, Casper M, Zopf S, Marhenke S, Lammert F, Vogel A, Datz

C, Sharma R, Eyer F, Spengler U, Von Felden J, Zeissig S, Canbay A, Grove J, Aithal G, McQuillin A, Valenti L, Weiss KH, Mueller S, Morgan MY, Gotthardt D, Berg T, Hampe J. Carriage of HSD17B13 rs72613567TA is associated with a reduced risk for developing hepatocellular carcinoma in patients with alcohol-related cirrhosis. Z Gastroenterol 2019; 57: e25.

33) Gellert-Kristensen H, Richardson TG, Davey Smith G, Nordestgaard BG, Tybjaerg-Hansen A, Stender S. Combined effect of PNPLA3, TM6SF2, and HSD17B13 variants on risk of cirrhosis and hepatocellular carcinoma in the general population. Hepatology 2020. doi: 10.1002/hep.31238. Online ahead of print.

34) Kallwitz E, Tayo BO, Kuniholm MH, Daviglus M, Zeng D, Isasi CR, Cotler SJ. Association of HSD17B13 rs72613567:TA with non-alcoholic fatty liver disease in Hispanics/Latinos. Liver Int 2020.

35) Luukkonen PK, Tukiainen T, Juuti A, Sammalkorpi H, Haridas PAN, Niemela O, Arola J, Orho-Melander M, Hakkarainen A, Kovanen PT, Dwivedi O, Groop L, Hodson L, Gastaldelli A, Hyotylainen T, Oresic M, Yki-Jarvinen H. Hydroxysteroid 17-beta dehydrogenase 13 variant increases phospholipids and protects against fibrosis in nonalcoholic fatty liver disease. JCI insight 2020; 5: e132158.

36) Ferenci P, Pfeiffenberger J, Stattermayer AF, Stauber RE, Willheim C, Weiss KH, Munda-Steindl P, Trauner M, Schilsky M, Zoller H. HSD17B13 truncated variant is associated with a mild hepatic phenotype in Wilson's Disease. JHEP Rep 2019; 1: 2-8.

37) Di Sessa A, Umano GR, Cirillo G, Marzuillo P, Arienzo MR, Pedulla M, Miraglia Del Giudice E. The rs72613567: TA Variant in the hydroxysteroid 17-beta dehydrogenase 13 gene reduces liver damage in obese children. J Pediatr Gastroenterol Nutr 2020; 70: 371-374.

38) Su W, Wang Y, Jia X, Wu W, Li L, Tian X, Li S, Wang C, Xu H, Cao J, Han Q, Xu S, Chen Y, Zhong Y, Zhang X, Liu P, Gustafsson JA, Guan Y. Comparative proteomic study reveals 17beta-HSD13 as a pathogenic protein in nonalcoholic fatty liver disease. Proc Natl Acad Sci U S A 2014; 111: 11437-11442.

39) Chen J, Zhuo JY, Yang F, Liu ZK, Zhou L, Xie HY, Xu X, Zheng SS. 17-beta-hydroxysteroid dehydrogenase 13 inhibits the progression and recurrence of hepatocellular carcinoma. Hepatobiliary & pancreatic diseases international : HBPD INT 2018; 17: 220-226.

40) Su W, Mao Z, Liu YA, Zhang XY, Zhang WZ, Gustafsson JA, Guan YF. Role of HSD17B13 in the liver physiology and pathophysiology. Mol Cell Endocrinol 2019; 489: 119-125.