

# World Journal of *Gastroenterology*

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## ABOUT COVER

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## Observational Study

Pediatric non-alcoholic fatty liver disease and kidney function: Effect of *HSD17B13* variant

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## Abstract

## BACKGROUND

Growing evidence supports a genetic link between non-alcoholic fatty liver disease (NAFLD) and chronic kidney disease (CKD). Interesting data demonstrated that both the major NAFLD risk polymorphisms such as the I148M polymorphism in the *patatin like phospholipase containing domain 3* (PNPLA3) and the E167K allele in the *transmembrane 6 superfamily member 2* gene (TM6SF2) affect renal function. Recently the *hydroxysteroid 17-beta dehydrogenase 13* (HSD17B13) gene has been recognized as a novel genetic variant involved in NAFLD pathophysiology. In particular, it has been showed the protective effect of the *rs72613567:TA* variant of this gene against liver damage both in adults and children.

## AIM

To investigate the impact of the *rs72613567:TA* variant of the *HSD17B13* gene on estimated glomerular filtration rate (eGFR) in obese children.

## METHODS

We enrolled 684 obese children (mean age  $10.56 \pm 2.94$  years; mean BMI-SDS  $2.98 \pm 0.78$ ) consecutively attending our Obesity Clinic. All the patients underwent a careful clinical assessment and a comprehensive biochemical evaluation. To detect hepatic steatosis, a liver ultrasound was performed. NAFLD was defined by ultrasound detected liver steatosis and/or alanine aminotransferase (ALT) levels



are appropriately investigated and resolved.

#### Institutional review board

**statement:** The study was approved by the Institutional Review Board of Università degli Studi della Campania Luigi Vanvitelli.

#### Informed consent statement:

Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

#### Conflict-of-interest statement:

Nothing to declare.

#### Data sharing statement:

Datasets generated during analyses are available on request.

#### STROBE statement:

The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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> 40 IU/L. The study population was divided on the basis of the NAFLD presence. Genotyping for the *rs72613567:TA* variant of the *HSD17B13* gene in all the enrolled subjects was also made.

## RESULTS

Patients carrying the *HSD17B13* rare A allele showed higher eGFR levels compared with homozygous patients both among subjects with and without NAFLD. A general linear model confirmed a direct and significant association of eGFR values with *HSD17B13* genotype independently of *PNPLA3* and *TM6SF2* polymorphisms both in patients with and without NAFLD. A comparison of regression line confirmed the influence of *HSD17B13* genotype on the relationship between eGFR and age both among patients with and without NAFLD. *H* omozygous patients for *HSD17B13* genotype with NAFLD showed a significantly higher decline of eGFR with the increase of the age compared with the patients with NAFLD carrying the *HSD17B13* rare A allele (*P* value for intercepts = 0.005; *P* value for slopes = 0.94). The same effect was observed among patients without NAFLD (*P* value for intercepts = 0.0012; *P* value for slopes = 0.87).

## CONCLUSION

Carriers of the *HSD17B13* rare A allele showed higher eGFR levels than homozygous subjects both among subjects with and without NAFLD and independently of *PNPLA3* I148M and *TM6SF2* E167K polymorphisms.

**Key Words:** Hydroxysteroid; Dehydrogenase; Fatty; Liver; Renal; Function; Obese; Children

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**Core Tip:** Compelling evidence supports a genetic link between non-alcoholic fatty liver disease (NAFLD) and chronic kidney disease. In particular, both the major NAFLD risk polymorphisms such as the I148M polymorphism in the *PNPLA3* and the E167K allele in the *TM6SF2* gene affect renal function. Recently the *rs72613567* variant in the *HSD17B13* gene has been recognized as a novel genetic protective variant in the NAFLD scenario. We aimed to evaluate the effect of this variant on renal function in obese children.

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## INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) and chronic kidney disease (CKD) represent worldwide public health concerns affecting up to 25%-30% and up to 10%-15% of the general population, respectively<sup>[1]</sup>. Both diseases are progressive chronic conditions representing a spectrum of diseases ranging from mild to severe disease with end-stage organ injury and sharing several pathogenic factors<sup>[1,2]</sup>.

In childhood, NAFLD has been recognized as the most common chronic liver disease, with a prevalence of 8% in the general pediatric population and up to 34.2% among obese children<sup>[3]</sup>.

To date, several studies demonstrated that NAFLD has been associated with increased prevalence of chronic kidney disease CKD (defined as sustained reduction in estimated glomerular filtration rate (eGFR) or evidence of structural or functional abnormalities of the kidneys on urinalysis, imaging or biopsy)<sup>[1,2,4,5]</sup>. In addition, it has been also showed that renal impairment obesity-related might occur already in childhood with a potential genetic influence<sup>[6-8]</sup>.

Recent data added novel pieces in the knowledge of the intriguing link between NAFLD and renal function<sup>[1,9,10]</sup>. Compelling evidence showed that the major genetic NAFLD risk factors such as the I148M polymorphism in the *patatin like phospholipase*

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containing domain 3 (PNPLA3) and the E167K allele in the *transmembrane 6 superfamily member 2* (TM6SF2) gene exert an effect on estimated glomerular filtration rate (eGFR) both in adults and children<sup>[1,5,9-12]</sup>. In particular, our group previously showed that children with obesity and homozygous for PNPLA3 rare allele had lower eGFR levels compared to other genotypes both among patients with and without NAFLD, with a major effect of this polymorphism in NAFLD context<sup>[10]</sup>. In addition, we demonstrated that obese children carrying the TM6SF2 E167K allele showed higher eGFR levels compared with the homozygous subjects for the TM6SF2 E167 allele, irrespective of presence of NAFLD<sup>[9]</sup>.

In the NAFLD susceptibility gene variants scenario, the role of the hepatic lipid droplet protein *hydroxysteroid 17-beta dehydrogenase 13* (HSD17B13) gene in NAFLD has been recently studied<sup>[3,13,14]</sup>. A growing body of evidence shows the role of the rs72613567 HSD17B13 polymorphism in protecting against liver damage both in adults and children<sup>[3,13-15]</sup>. This variant represents a splice region characterized by an adenine (A) insertion in the coding region adjacent to the donor splice site of exon 6, leading to a frame-shift and premature truncation of HSD17B13 protein<sup>[3]</sup>.

To date, there are no studies evaluating the effect of the rs72613567 HSD17B13 polymorphism on eGFR in obese children and adolescents. Considering the evidence of the data both in adulthood and childhood supporting a genetic link between NAFLD and CKD<sup>[5,8-11]</sup>, we hypothesized that this variant, as demonstrated on NAFLD, could show the same protective effect on renal function in obese children and adolescents. We aimed to investigate the role of the rs72613567 HSD17B13 polymorphism on eGFR levels in obese children with and without NAFLD and without known primary kidney disease.

## MATERIALS AND METHODS

### Study population

We recruited 684 obese children consecutively attending our Obesity Clinic from February 1, 2017 to January 31, 2019. Both Body Mass Index (BMI) > 95<sup>th</sup> percentile according to reference values and normal renal function (eGFR > 90 mL/min/1.73 m<sup>2</sup>)<sup>[6,16]</sup> were considered as inclusion criteria. Secondary forms of NAFLD or obesity, consumption of medications, eGFR < 90 mL/min/1.73 m<sup>2</sup>, presence of proteinuria or hematuria at urine dipstick on urine samples<sup>[17]</sup>, missing eGFR levels, or denied consent for diagnostic procedures represented exclusion criteria. Patients presenting possible signs of underlining primary kidney disease (decreased eGFR and proteinuria/hematuria) were also excluded to avoid potential affection of our analysis. The ethical committee of University of Study of Campania “Luigi Vanvitelli” approved the study. A written informed consent was obtained before any procedure. Clinical parameters including pubertal stage and blood pressure were obtained as described<sup>[18]</sup>. Evaluation of patients’ growth charts was made to calculate duration of obesity.

### Laboratory and ultrasound evaluation

Biochemical parameters were assayed and homeostasis model assessment (HOMA-IR) calculated<sup>[18]</sup>. Alanine transaminase (ALT) levels greater than 40 IU/L were considered as elevated. The Jaffè method was used to serum creatinine (mg/dL) measurement and the eGFR was calculated through the Schwartz equation<sup>[6,19]</sup>. The eGFR to the ideal body weight-derived body surface area was normalized.

A trained radiologist performed liver ultrasound imaging in order to detect the presence of steatosis. Liver steatosis was assessed as present or absent given the abnormally intense, high-level echoes arising from the hepatic parenchyma and liver-kidney differences in echo amplitude. NAFLD was defined by the presence of ultrasound detected liver steatosis and/or ALT levels > 40 IU/L.

### Genotyping

At diagnosis, informed consent was collected for DNA extraction from peripheral whole blood.

Genomic DNA was extracted from peripheral whole blood with a DNA extraction kit (Promega, Madison WI, United States). All recruited subjects were genotyped for the single nucleotide polymorphism (SNP) rs72613567: TA allele of the HSD17B13 gene using a TaqMan allelic discrimination custom assay (ID: ANNKVTJ) (Applied Biosystems, United States) on ABI 7900HT Real Time PCR system. Patients were also genotyped for PNPLA3 I48M and TM6SF2 E167K polymorphisms<sup>[3]</sup>.

### Statistical analysis

A Chi Square test was used to verify whether the genotypes were in Hardy-Weinberg equilibrium and to compare categorical variables. We classified the population according to the presence/absence of NAFLD and we compared eGFR levels in these two groups (with and without NAFLD) on the basis of *HSD17B13* polymorphism.

Differences for continuous variables were analyzed using ANOVA if normally distributed, or the Kruskal-Wallis test if non-normally distributed. Not-normally distributed variables were log-transformed before the analysis, but raw means are shown.

The genotype was coded with an additive model of inheritance. It was coded 0 or 1 corresponding to the subjects homozygous for the wild type allele and carrying the A rare allele, respectively.

A general linear model (GLM) for eGFR variance including gender, duration of obesity, *HSD17B13*, *PNPLA3*, and *TM6SF2* genotypes, BMI-SDS, HOMA, LDL, and triglycerides was made both in patients with and without NAFLD. The non-normally distributed variables were log transformed for this analysis.

A comparison of regression lines by ANOVA was performed to examine the influence of *HSD17B13* genotype on the relationship between eGFR and age both among patients with and without NAFLD.

The IBM SPSS Statistics software, Version 24 (IBM, Armonk, NY, United States) was used for all statistical analyses with the exception of the comparison of regression lines made by Stat-Graph XVII software for Windows. Data were expressed as means  $\pm$  SD. *P*-values less than 0.05 were considered statistically significant.

## RESULTS

We enrolled 684 obese patients with mean age of  $10.56 \pm 2.94$  years and mean BMI-SDS of  $2.98 \pm 0.78$ . The frequency of the *HSD17B13* polymorphism distribution was in Hardy Weinberg equilibrium ( $P > 0.05$ ).

Patients carrying the *HSD17B13* rare A allele showed higher eGFR levels compared with homozygous patients both among subjects with and without NAFLD (Table 1 and 2). As expected, ALT and aspartate transaminase (AST) levels were significantly lower in subjects carrying the *HSD17B13* rare A allele in both groups (Table 1 and 2). A general linear model for eGFR variance including gender, duration of obesity, *HSD17B13*, *PNPLA3*, and *TM6SF2* genotypes, BMI-SDS, HOMA, ALT and triglycerides confirmed a direct and significant association of eGFR values with *HSD17B13* genotype both in patients with and without NAFLD (Table 3).

A comparison of regression line slopes was performed to examine the influence of *HSD17B13* genotype on the relationship between eGFR and age both among patients with and without NAFLD. Homozygous patients for *HSD17B13* genotype with NAFLD showed a significantly higher decline of eGFR with the increase of the age compared with the patients with NAFLD carrying the *HSD17B13* rare A allele (*P* value for intercepts = 0.005; *P* value for slopes = 0.94) (Figure 1). We also confirmed this effect among patients without NAFLD (*P* value for intercepts = 0.0012; *P* value for slopes = 0.87) (Figure 2).

## DISCUSSION

The novel finding of our study was the association between the rs72613567 *HSD17B13* polymorphism and higher eGFR levels in obese children and adolescents without evidence of primary kidney disease. We confirmed these results both in patients with and without NAFLD and independently of rs738409 *PNPLA3* and *TM6SF2* E167K polymorphisms. Notably, carriers of the *HSD17B13* rare A allele both with and without NAFLD maintained significant higher eGFR levels increasing the age. Taken together, these results corroborate the protective role of the *HSD17B13* gene in both NAFLD and CKD.

Emerging evidence suggests a potential influence of the major NAFLD susceptibility gene variants such as *PNPLA3* I148M and *TM6SF2* 167K on CKD<sup>[9,10]</sup>. In fact, previous studies showed that both in adults and children with and without NAFLD the *PNPLA3* I148M variant was associated with lower eGFR levels<sup>[1,5,10,11]</sup>. Interestingly, the *PNPLA3* GG genotype was associated not only with higher risk of early glomerular injury but also tubular damage in NAFLD patients with persistently



**Table 1** Main features in patients with non-alcoholic fatty liver disease according to *HSD17B13* genotypes

	<i>HSD17B13</i> TT (n = 218)	<i>HSD17B13</i> TA/AA (n = 100)	P value
Age, yr	10.72 ± 2.88	10.60 ± 2.80	0.67
BMI-SDS	2.98 ± 0.73	3.00 ± 0.75	0.85
Duration of obesity, yr	4.65 ± 1.93	4.64 ± 2.17	0.60
Sex (male), %	53.3	51.2	0.82
SBP-SDS	1.00 ± 1.15	1.12 ± 1.14	0.33
DBP-SDS	0.25 ± 0.89	0.30 ± 0.91	0.54
W/Hr	0.62 ± 0.05	0.63 ± 0.06	0.04
ALT, U/L	35.45 ± 21.69	30.60 ± 21.52	0.02
AST, U/L	26.86 ± 10.18	24.49 ± 8.86	0.01
GGT, U/L	20.42 ± 9.73	19.70 ± 9.49	0.45
Total-Cholesterol, mg/dL	160.13 ± 33.85	158.19 ± 30.80	0.55
LDL, mg/dL	95.84 ± 29.31	93.38 ± 23.93	0.40
HDL, mg/dL	44.07 ± 10.68	45.30 ± 11.24	0.67
Triglycerides, mg/dL	101.21 ± 51.36	99.92 ± 47.62	0.79
Glycaemia, mg/dL	83.05 ± 9.10	81.80 ± 8.44	0.14
HOMA-IR	6.19 ± 5.35	5.94 ± 3.86	0.62
eGFR, mL/min/1.73m <sup>2</sup>	186.71 ± 36.55	197.45 ± 34.92	0.01

ALT: Alanine transaminase; AST: Aspartate transaminase; BMI: Body mass index; DBP: Diastolic blood pressure; eGFR: Estimated glomerular filtration rate; GLM: General linear model; HDL-C: High-density lipoprotein cholesterol; HOMA: Homeostasis model assessment; LDL-C: Low density lipoprotein cholesterol; SBP: Systolic blood pressure; SDS: Standard deviation score; W/Hr: Waist to height ratio.

normal ALT levels<sup>[12]</sup>. Further researches investigating the role of the *TM6SF2* 167K allele on renal function showed a protective role of this variant on eGFR both in adults and children also regardless the presence of NAFLD<sup>[5,8,9]</sup>.

The *HSD17B13* gene encodes the hepatic lipid droplet protein hydroxyl-steroid 17-beta dehydrogenase 13, an uncharacterized member of the hydroxysteroid 17-beta dehydrogenase family involved in sex hormone and mainly in fatty acid metabolism<sup>[13]</sup>. The rs72613567 *HSD17B13* splice variant alters m-RNA splicing resulting in a truncated protein with reduced enzymatic activity against several proinflammatory lipid species<sup>[13,14]</sup>. The mechanism linking *HSD17B13* to liver disease is not referred to hepatic fat accumulation, but directly involves modulation of inflammation and fibrogenesis through an involvement in retinol metabolism<sup>[20]</sup>. Taken together, these findings support the beneficial influence of this *loss-of-function* against risk of chronic liver disease and hepatocellular carcinoma as well<sup>[14,20]</sup>.

To date, the exact pathophysiologic function remains still poorly elucidated, but the protective role of the rs72613567 *HSD17B13* variant in NAFLD development and progression has been confirmed both in adults and children<sup>[3,13,15]</sup>. As observed in the liver context, we could speculate that the rs72613567 *HSD17B13* variant might exert a “protective” role on renal function through its role in retinol metabolism by modulating both inflammation and fibrogenesis.

Recent data showed a significant association between NAFLD and the long-term risk of incident CKD<sup>[1,2]</sup>. Moreover, it should be noted that NAFLD is closely linked to an increased risk of cardiovascular disease (CVD), independent of the coexistence of common cardiometabolic risk factors<sup>[21]</sup>. In addition, it has been well established that CKD represents a major risk factor for end-stage renal disease, CVD and premature death<sup>[2]</sup>. Despite several newer hypotheses (including gut microbiota, platelet activation, and dietary changes) the major pathogenic link underlying these chronic diseases is represented by the activation of the shared proinflammatory and profibrotic factors<sup>[1]</sup>. In this context, the role of the *HSD17B13* gene in retinol metabolism leading to lack of hepatic stellate cells activation might contribute to explain its protective effect on renal function<sup>[3]</sup>. Given that, this intriguing “vicious circle” among NAFLD, CVD and CKD represents a challenging field for clinicians that

**Table 2** Main features in patients without non-alcoholic fatty liver disease according to *HSD17B13* genotypes

	<i>HSD17B13</i> TT (n = 199)	<i>HSD17B13</i> TA/AA (n = 167)	P value
Age, yr	10.36 ± 2.98	10.36 ± 3.20	0.89
Duration of obesity	2.96 ± 0.79	2.95 ± 0.96	0.94
BMI-SDS	4.41 ± 1.84	4.88 ± 2.51	0.24
Sex (male), %	50.5	55.5	0.68
SBP-SDS	1.08 ± 1.24	0.79 ± 1.20	0.09
DBP-SDS	0.18 ± 0.75	1.03 ± 1.15	0.64
W/Hr	0.61 ± 0.05	0.60 ± 0.05	0.21
ALT, U/L	22.95 ± 6.90	20.30 ± 6.56	0.003
AST, U/L	23.03 ± 4.92	21.35 ± 6.07	0.004
GGT, U/L	16.70 ± 5.80	17.38 ± 4.34	0.33
Total-Cholesterol, mg/dL	160.66 ± 27.11	161.84 ± 33.11	0.76
LDL-C, mg/dL	93.74 ± 24.59	98.10 ± 28.27	0.36
HDL-C, mg/dL	48.18 ± 15.28	45.96 ± 8.97	0.50
Triglycerides, mg/dL	96.90 ± 59.74	95.77 ± 38.79	0.87
Glycaemia, mg/dL	79.95 ± 7.34	80.52 ± 7.66	0.08
HOMA-IR	4.63 ± 3.16	5.16 ± 3.75	0.27
eGFR, mL/min/1.73 m <sup>2</sup>	187.34 ± 37.76	197.82 ± 39.78	0.007

ALT: Alanine transaminase; AST: Aspartate transaminase; BMI: Body mass index; DBP: Diastolic blood pressure; eGFR: Estimated glomerular filtration rate; HDL-C: High-density lipoprotein cholesterol; HOMA: Homeostasis model assessment; LDL-C: Low density lipoprotein cholesterol; SBP: Systolic blood pressure; SDS: Standard deviation score; W/Hr: Waist to height ratio.

should be carefully evaluated. In fact, these findings emphasize the importance of an early detection of NAFLD diagnosis in order to potentially counteract the risk of both CKD and CVD. Beyond the established contribute in identifying subjects with greater susceptibility to NAFLD, a better NAFLD genetic characterization might be also helpful to individuate patients with NAFLD who may be at higher risk of chronic diseases such as CKD and CVD.

Our study has some limitations that deserve mention. First, there is a lack of a more accurate method to measure glomerular filtration rate (*i.e.*, by cystatin C). NAFLD diagnosis has been performed by ultrasound and ALT levels and not by liver biopsy or magnetic resonance. Moreover, this is only a pathophysiological study evaluating only children with normal renal function, and as future perspective could be interesting to evaluate the effect of the *rs72613567 HSD17B13* polymorphism on proteinuria.

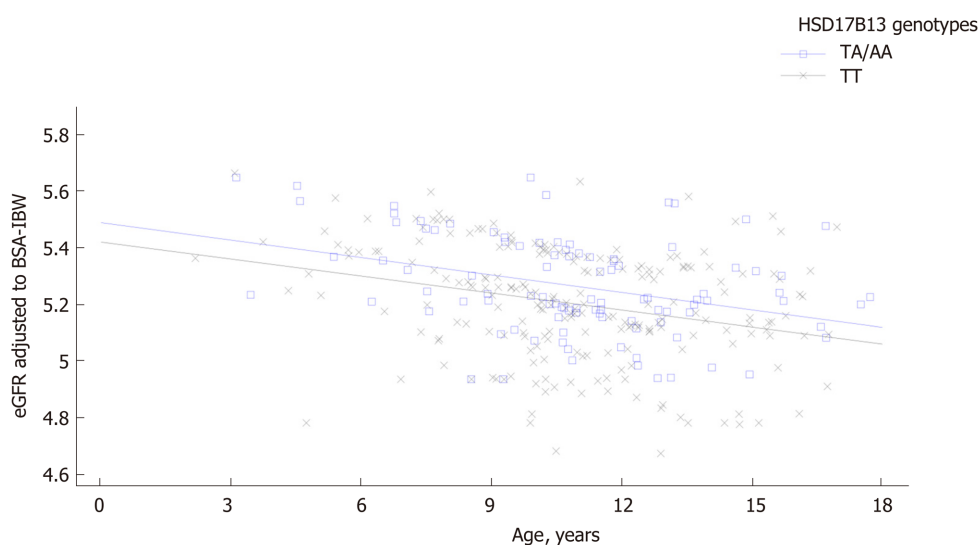
## CONCLUSION

In conclusion, for the first time in literature, we showed that the *rs72613567 HSD17B13* polymorphism is associated with higher eGFR levels in obese children. This effect on renal function is confirmed in patients with and without NAFLD and independently of *PNPLA3* I148M and *TM6SF6* E167K polymorphisms. Of note, this variant exerts a protective role against renal function decline increasing the age both in patients with and without NAFLD. Given these results, we added to the existing knowledge of the role of genetics on the association between NAFLD and renal function already in childhood. Collectively, these findings might also have significant clinical implications in improving both prevention and treatment strategies of obese patients with NAFLD.

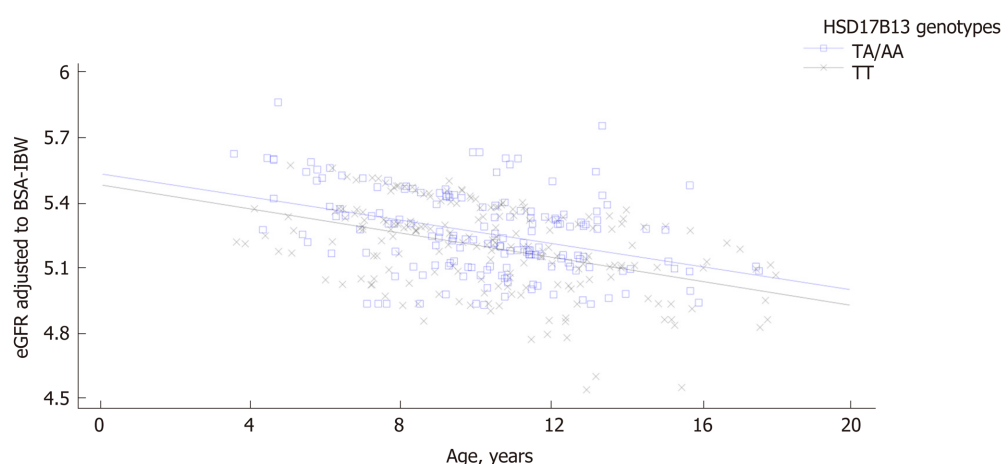
**Table 3** General linear model for analysis of variance of estimated glomerular filtration rate both among patients with and without non-alcoholic fatty liver disease

Source	Patients with NAFLD			Patients without NAFLD		
	Coefficient	F-ratio	P value	Coefficient	F-ratio	P value
Model		6.24	< 0.0001		3.30	0.001
Gender	-0.78	0.62	0.43	0.31	0.09	0.75
Duration of obesity	-2.48	6.17	0.01	-0.47	0.22	0.63
<i>HSD17B13</i> genotype	1.89	42.58	< 0.0001	4.63	21.49	< 0.0001
<i>PNPLA3</i> genotype	-3.80	11.19	0.001	-0.90	0.81	0.36
<i>TM6SF2</i> genotype	1.13	11.82	0.001	1.40	1.97	0.16
BMI-SDS	0.62	0.38	0.53	0.51	0.26	0.61
HOMA-IR	-1.20	1.44	0.23	0.63	0.40	0.52
Triglycerides	-0.94	0.89	0.34	0.95	0.90	0.34
LDL-Cholesterol	0.69	0.47	0.49	0.23	0.05	0.81

NAFLD: Model  $r^2$  0.39, adjusted  $r^2$  0.33; Non NAFLD: Model  $r^2$  0.16, adjusted  $r^2$  0.11. ALT: Alanine transaminase; BMI: Body mass index; eGFR: Estimated glomerular filtration rate; GLM: General linear model; HOMA: Homeostasis model assessment; LDL: Low density lipoprotein; SDS: Standard deviation score.



**Figure 1** Regression analysis describing the relationship between estimated glomerular filtration rate and age according to *HSD17B13* genotype in patients with non-alcoholic fatty liver disease. The regression is described by the equation  $y = 5.49596 - 0.0205849x - 0.0688943 \times (\text{hsd17b13} = 1) + 0.00054199x \times (\text{hsd17b13} = 1)$ . *P* value for intercepts is 0.005 while for slopes is 0.94.



**Figure 2** Regression analysis describing the relationship between estimated glomerular filtration rate and age according to *HSD17B13* genotype in patients without non-alcoholic fatty liver disease. The regression is described by the equation  $y = 5.54093 - 0.0266856x - 0.0508993 \times (\text{hsd17b13}=1) - 0.00105742x \times (\text{hsd17b13}=1)$ . *P* value for intercepts is 0.0012 while for slopes is 0.87.

## ARTICLE HIGHLIGHTS

### Research background

Accumulating data supports a genetic link between non-alcoholic fatty liver disease (NAFLD) and chronic kidney disease (CKD), mostly sustained by both the major NAFLD risk polymorphisms such as the I148M polymorphism in the *patatin like phospholipase containing domain 3* (*PNPLA3*) and the E167K allele in the *transmembrane 6 superfamily member 2* gene (*TM6SF2*). Recently the *hydroxysteroid 17-beta dehydrogenase 13* (*HSD17B13*) gene has been recognized as a novel genetic variant involved in NAFLD pathophysiology with a protective role against liver damage both in adults and children.

### Research motivation

Despite a growing interest regarding the potential genetic link between NAFLD and CKD, available literature data showed no studies investigating the effect of the *rs72613567:TA* variant of the *HSD17B13* gene on estimated glomerular filtration rate (eGFR) in obese children.

### Research objectives

In this study we aimed to evaluate the impact of the *rs72613567:TA* variant of the *HSD17B13* gene on estimated glomerular filtration rate (eGFR) in obese children.

### Research methods

Anthropometric, laboratory, and instrumental evaluations were conducted in all the enrolled 684 obese children. NAFLD was defined by ultrasound detected liver steatosis and/or alanine aminotransferase (ALT) levels > 40 IU/L. Genotyping for the *rs72613567:TA* variant of the *HSD17B13* gene in all the enrolled subjects was also performed.

### Research results

Patients carrying the *HSD17B13* rare A allele had higher eGFR levels than homozygous patients both among subjects with and without NAFLD. This association was independent of *PNPLA3* and *TM6SF2* polymorphisms both in patients with and without NAFLD. The eGFR decline in homozygous subjects for *HSD17B13* genotype with and without NAFLD was more markedly with the increase of the age than in carriers the *HSD17B13* rare A allele.

### Research conclusions

In line with the beneficial effect against NAFLD risk, the *rs72613567:TA* variant of the *HSD17B13* gene exerts a protective role also on renal function in obese children with and without NAFLD and independently of *PNPLA3* I148M and *TM6SF2* E167K polymorphisms.



## Research perspectives

Findings from this study highlight the importance of a better NAFLD genetic assessment as possible clinical tool for improved strategies to identify patients at higher cardiometabolic risk already in childhood.

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