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OPINION REVIEW

- 3693 Approach to medical therapy in perianal Crohn's disease
Vasudevan A, Bruining DH, Loftus EV Jr, Faubion W, Ehman EC, Raffals L

REVIEW

- 3705 Incorporating mucosal-associated invariant T cells into the pathogenesis of chronic liver disease
Czaja AJ
- 3734 Artificial intelligence in small intestinal diseases: Application and prospects
Yang Y, Li YX, Yao RQ, Du XH, Ren C
- 3748 Impact of the COVID-19 pandemic on inflammatory bowel disease patients: A review of the current evidence
Kumric M, Ticinovic Kurir T, Martinovic D, Zivkovic PM, Bozic J
- 3762 Management of hepatitis B virus infection in patients with inflammatory bowel disease under immunosuppressive treatment
Axiaris G, Zampeli E, Michopoulos S, Bamias G

MINIREVIEWS

- 3780 Worldwide management of hepatocellular carcinoma during the COVID-19 pandemic
Inchingolo R, Acquafredda F, Tedeschi M, Laera L, Surico G, Surgo A, Fiorentino A, Spiliopoulos S, de'Angelis N, Memeo R
- 3790 Human immune repertoire in hepatitis B virus infection
Zhan Q, Xu JH, Yu YY, Lo KK E, Felicianna, El-Nezami H, Zeng Z
- 3802 Emerging applications of radiomics in rectal cancer: State of the art and future perspectives
Hou M, Sun JH
- 3815 Advances in paediatric nonalcoholic fatty liver disease: Role of lipidomics
Di Sessa A, Riccio S, Pirozzi E, Verde M, Passaro AP, Umano GR, Guarino S, Miraglia del Giudice E, Marzuillo P
- 3825 Autoimmune pancreatitis and pancreatic cancer: Epidemiological aspects and immunological considerations
Poddighe D
- 3837 Gut microbiota in obesity
Liu BN, Liu XT, Liang ZH, Wang JH

ORIGINAL ARTICLE**Basic Study**

- 3851 Zinc oxide nanoparticles reduce the chemoresistance of gastric cancer by inhibiting autophagy
Miao YH, Mao LP, Cai XJ, Mo XY, Zhu QQ, Yang FT, Wang MH

- 3863 PPARGC1A rs8192678 G>A polymorphism affects the severity of hepatic histological features and nonalcoholic steatohepatitis in patients with nonalcoholic fatty liver disease
Zhang RN, Shen F, Pan Q, Cao HX, Chen GY, Fan JG

Retrospective Cohort Study

- 3877 Does endoscopic intervention prevent subsequent gastrointestinal bleeding in patients with left ventricular assist devices? A retrospective study
Palchoudhuri S, Dhawan I, Parsikia A, Birati EY, Wald J, Siddique SM, Fisher LR

Retrospective Study

- 3888 Diverse expression patterns of mucin 2 in colorectal cancer indicates its mechanism related to the intestinal mucosal barrier
Gan GL, Wu HT, Chen WJ, Li CL, Ye QQ, Zheng YF, Liu J
- 3901 Clinical characteristics of patients in their forties who underwent surgical resection for colorectal cancer in Korea
Lee CS, Baek SJ, Kwak JM, Kim J, Kim SH

Observational Study

- 3913 Effect of gastric microbiota on quadruple *Helicobacter pylori* eradication therapy containing bismuth
Niu ZY, Li SZ, Shi YY, Xue Y

META-ANALYSIS

- 3925 Endoscopic submucosal dissection *vs* endoscopic mucosal resection for colorectal polyps: A meta-analysis and meta-regression with single arm analysis
Lim XC, Nistala KRY, Ng CH, Lin SY, Tan DJH, Ho KY, Chong CS, Muthiah M

CASE REPORT

- 3940 Gastric schwannoma treated by endoscopic full-thickness resection and endoscopic purse-string suture: A case report
Lu ZY, Zhao DY

LETTER TO THE EDITOR

- 3948 Gastrointestinal cytomegalovirus disease secondary to measles in an immunocompetent infant
Hung CM, Lee PH, Lee HM, Chiu CC

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Basic Study

PPARGC1A rs8192678 G>A polymorphism affects the severity of hepatic histological features and nonalcoholic steatohepatitis in patients with nonalcoholic fatty liver disease

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Abstract**BACKGROUND**

The association between PPARGC1A rs8192678 and nonalcoholic fatty liver disease (NAFLD) requires further confirmation. In addition, it is still unknown whether PPARGC1A rs8192678 is associated with hepatic histological features in NAFLD in the Chinese population.

AIM

To investigate the interaction between PPARGC1A rs8192678 and nonalcoholic steatohepatitis (NASH), and whether this polymorphism is associated with hepatic histological features.

METHODS

Fifty-nine patients with liver biopsy-proven NAFLD and 93 healthy controls were recruited to a cohort representing the Chinese Han population. The SAF (steatosis, activity, and fibrosis) scoring system was used for hepatic histopathological evaluation. The polymorphisms of PPARGC1A rs8192678 and patatin-like phospholipase domain-containing protein 3 (PNPLA3) rs738409 were genotyped. The intrahepatic mRNA expression of PPARGC1A was evaluated by real-time polymerase chain reaction.

approved by the institutional review board of Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine.

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RESULTS

Thirty-seven patients with NAFLD had NASH, of which 12 were nonobese. The PPARGC1A rs8192678 risk A allele (carrying GA and AA genotypes) had the lowest *P* value in the dominant model; the odds ratio (OR) for NAFLD was 2.321 [95% confidence interval (CI): 1.121-4.806]. After adjusting for age, sex, and the PNPLA3 rs738409 risk G allele, the PPARGC1A rs8192678 A allele was a risk factor for NAFLD (OR 2.202, 95%CI: 1.030-4.705, *P* = 0.042). The genetic analysis showed that patients with NAFLD, moderate-to-severe steatosis (S2-3), and Activity 2-4 (*A* ≥ 2) were more likely to carry A in PPARGC1A rs8192678 (OR 5.000, 95%CI: 1.343-18.620, *P* = 0.012; and OR 4.071, 95%CI: 1.076-15.402, *P* = 0.031). The multivariate logistic regression analysis showed that PPARGC1A rs8192678 risk A allele was also independently associated with S2-3, *A* ≥ 2, and NASH (OR 6.190, 95%CI: 1.508-25.410, *P* = 0.011; OR 4.506, 95%CI 1.070-18.978, *P* = 0.040; and OR 6.337, 95%CI: 1.135-35.392, *P* = 0.035, respectively) after adjusting for age, sex, body mass index, and PNPLA3 rs738409 risk G allele. The results also showed that this polymorphism was associated with nonobese NASH (OR 22.000, 95%CI: 1.540-314.292, *P* = 0.021). The intrahepatic expression of PPARGC1A mRNA was significantly lower in the group of patients who carried the risk A allele (*P* = 0.014).

CONCLUSION

The PPARGC1A rs8192678 risk A allele is associated with NAFLD, and with S2-3, *A* ≥ 2 and NASH in NAFLD patients, independent of PNPLA3 rs738409, and may be associated with nonobese NASH.

Key Words: Nonalcoholic fatty liver disease; Nonalcoholic steatohepatitis; PPARGC1A rs8192678 polymorphism; Steatosis; Activity

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Core Tip: The PPARGC1A rs8192678 A allele was found to be a risk factor for liver biopsy-proven nonalcoholic fatty liver disease (NAFLD) after adjusting for age, sex, and patatin-like phospholipase domain-containing protein 3 rs738409 polymorphism. The multivariate logistic regression analysis showed that the PPARGC1A rs8192678 risk A allele was also independently associated with the severity of hepatic histological features (S2-3 and *A* ≥ 2) and nonalcoholic steatohepatitis (NASH), and might also be associated with nonobese NASH, indicating that the PPARGC1A rs8192678 risk A allele was associated with NAFLD in the Chinese Han adult population. Also, the intrahepatic expression of PPARGC1A mRNA was significantly lower in the patients who carried the risk A allele, implying that it might be a genetic contribution to the pathogenesis of NAFLD.

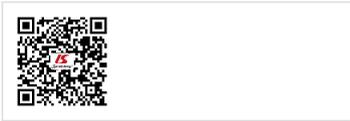
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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) has become one of the most common forms of chronic liver diseases worldwide. The overall global prevalence of NAFLD is about 25%. The clinical spectrum of NAFLD ranges from nonalcoholic fatty liver (NAFL), nonalcoholic steatohepatitis (NASH), liver fibrosis and cirrhosis, and finally hepatocellular carcinoma. NAFLD also has high risk and is associated with multisystem diseases, such as obesity, type 2 diabetes mellitus (T2DM), cardiovascular diseases, chronic kidney disease, and malignancy[1,2].



The pathogenesis of NAFLD is multifactorial and strongly associated with obesity, insulin resistance, T2DM, and metabolic syndrome. Although NAFLD has a high prevalence in obese patients, nonobese patients and even lean patients, were recently found to have NAFLD as well. The anthropometric data on body mass index (BMI) was used to define nonobese or lean. The BMI values of 25 and 30 kg/m² are the thresholds to define overweight and obese participants, respectively, as recommended by the World Health Organization. In Asia, BMI < 25 kg/m² is defined as nonobese, whereas BMI < 23 kg/m² is defined as lean[3]. A meta-analysis was carried out to estimate the overall prevalence of NAFLD in nonobese and lean populations (15.7% and 10.2%, respectively)[4].

The differences in prevalence, clinical profile, hepatic histology severity, and outcomes of NAFLD among different ethnic groups suggested that both environmental and genetic factors influenced susceptibility to NAFLD in individuals[5]. Genetic factors have been implicated in the occurrence and development of NAFLD; the gene of peroxisome proliferator-activated receptor- γ coactivator-1 α (PGC-1 α), encoded by PPARGC1A, is also a susceptibility candidate gene for NAFLD[6-8]. PGC-1 α is a transcriptional coactivator with a crucial impact on multiple aspects of cellular energy metabolism including mitochondrial biogenesis and cellular respiration, regulation of adaptive thermogenesis, adipocyte cell development, and lipid and glucose metabolism. A number of genetic variants have been identified in PPARGC1A, and the Gly482Ser polymorphism (a G-to-A transition that predicted a glycine (G) to serine (S) substitution at amino acid position 482 in exon 8, rs8192678) is the most common variant, which was associated with T2DM, obesity, and hypertension in several studies[9-13]. However, the results were controversial in the Chinese Han adult population, which require further confirmation[14,15]. Whether this polymorphism is associated with the severity of hepatic histological features [steatosis, activity (hepatocyte ballooning and lobular inflammation), and fibrosis] and with NASH or nonobese NASH needs further investigation.

The present study aimed to determine the relationship between polymorphism rs8192678 of PPARGC1A gene and the risk of NAFLD, especially in NASH, in a Chinese Han population, and to investigate the association between PPARGC1A rs8192678 G>A polymorphism and the severity of hepatic histological features.

MATERIALS AND METHODS

Study populations

A total of 152 unrelated adult participants (18-70 years old) were recruited between March 2012 and March 2013. Patients with NAFLD were enrolled from Xinhua Hospital, Shanghai, China. All participants were Han Chinese in origin. Each patient had undergone an ultrasound-guided percutaneous liver biopsy and met the diagnostic criteria for NAFLD. The liver stiffness measurement (LSM) and controlled attenuation parameter (CAP) values were tested using FibroScan 502 (Echosens, Paris, France) by previously described methods.

The exclusion criteria were as follows: (1) excessive alcohol consumption (> 30 g/d for men and > 20 g/d for women); other diseases that led to fatty liver, such as chronic hepatitis C, drug-induced liver injury, Wilson's disease, total parenteral nutrition, and autoimmune hepatitis; (2) previous liver transplantation; (3) other end-stage diseases or malignancies; and (4) contraindications to FibroScan examination (*e.g.*, ascites, implanted pacemakers, nonhealing wounds in the upper-right quadrant of the abdomen, and pregnancy) or unreliable measurement of LSM and CAP values.

All control participants were confirmed to be free of liver diseases by both B-mode ultrasound and FibroScan 502 examination (CAP \leq 240 dB/m and LSM values < 7.0 kPa)[16]; they all had normal liver function test results and lacked evidence of etiologies of liver injury. The study protocol was approved by the Ethics Committees of Xinhua Hospital, and the study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Clinical and laboratory evaluation

Demographic information, such as age and sex, was collected. Venous blood samples were obtained from the participants after overnight fasting (12 h) to measure the levels of alanine transaminase (ALT), alkaline phosphatase (ALP), γ -glutamyl transpeptidase (GGT), total bilirubin, directed bilirubin, fasting blood glucose (FBG), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and uric acid (UA). All laboratory biochemical

parameters were measured in a conventional automated analyzer (Hitachi 7600, Tokyo, Japan).

Hepatic histopathologic assessment

Liver biopsy specimens were fixed with 10% buffered formalin, embedded in paraffin, sliced, and stained with hematoxylin & eosin (HE), reticulin, and Masson trichrome. A minimum 15-mm biopsy specimen or the presence of at least 10 complete portal tracts was required. For each liver biopsy, the steatosis, activity, and fibrosis (SAF) score summarizing the main histological lesions was defined. The SAF score was designed by the fatty liver inhibition of progression Pathology Consortium. The steatosis (0-3) was categorized as follows: S0: < 5%; S1: 5%-33%; S2: 34%-66%; and S3: ≥ 67%. The grade of hepatic inflammatory activity (A, from 0 to 4) was calculated by adding together the grades for hepatocyte ballooning (0-2) and lobular inflammation (0-2). Liver fibrosis was staged as follows: F0, none; F1, perisinusoidal or portal fibrosis; F2, perisinusoidal and periportal fibrosis without bridging; F3, bridging fibrosis; and F4, cirrhosis. A case presenting with at least grade 1 of each of the three features (steatosis, ballooning, and lobular inflammation) was classified as NASH; other cases were diagnosed as NAFL.

DNA preparation and single-nucleotide polymorphism genotyping

Polymorphism genotyping of genomic DNA was prepared from each blood sample using the QiAamp DNA Mini Kit (Qiagen, Hilden, Germany). The custom Ion AmpliSeq panel (Life Technologies, MA, United States) of PPARGC1A and patatin-like phospholipase domain-containing protein 3 (PNPLA3) was designed. The polymerase chain reaction (PCR) of the template was performed using the Ion OneTouch 2 System (Life Technologies, MA, United States) following the manufacturer's instructions. PPARGC1A and PNPLA3 variants were genotyped by DNA sequencing using the Ion 318 Chip (Life Technologies, United States) following the Ion PGM 200 Sequencing kit protocol. Negative controls were introduced for each run to ensure genotyping quality. Samples giving discordant results were reanalyzed.

Real-time PCR for measuring PPARGCA1 mRNA expression

Total RNA was isolated from samples of liver biopsy specimens using the TRIzol reagent (Takara, Dalian, China) and reverse transcribed using the PrimeScript RT Reagent Kit (Takara, Dalian, China). The mRNA expression of PPARGC1A and β -actin was measured by real-time PCR (RT-PCR) using the SYBR Premix Ex Taq Kit (Takara, Dalian, China) and an ABI 7500 RT-PCR System (Applied Biosystems, United States). Target mRNA levels were normalized to β -actin expression levels. The following primers were used: PPARGC1A (F: 5'-GAGTGACATCGAGTGTGCTG-3'; R: 5'-GGGCAATCCGTCTTCATCCA-3'); β -actin (F: 5'-TCCTTCCTGGGCATGGAGT-3'; R: 5'-CAGGAGGAGCAATGATCTTGAT-3'). A duplicate of this experiment was performed for the same reaction. The $2^{-\Delta\Delta Ct}$ method was used to calculate the relative expression levels of each gene. Thermal cycling was performed as follows: Initial denaturation at 95°C for 5 min, followed by 40 cycles of 95°C for 15 s and 60°C for 34 s.

Statistical analysis

Continuous variables were expressed as mean \pm SD, median and interquartile range for those with a skewed distribution and categorical variables as the frequency or percentage. The *t* test and chi-squared test were used where appropriate. Multiple logistic regression models were used to assess the factors independently associated with the severity of histological parameters. In the dominant model, the frequencies of the participants with the allele 1 (allele 1 homozygote and heterozygote) were compared with the participants homozygous for the allele 2 using a 2 \times 2 contingency table. The odds ratio (OR) and the 95% confidence interval (CI) were calculated using Woolf's method. In all analyses, GA and AA for PPARGC1A rs8192678 was considered when choosing a dominant model of inheritance. Analyses were performed using SPSS 23.0 (SPSS Inc., IL, United States). A two-sided *P* < 0.05 indicated a statistically significant difference.

RESULTS

Anthropometric and clinical data

The clinical characteristics of 152 participants (59 patients with NAFLD and 93

controls) are listed in [Table 1](#). Age, BMI, ALT, GGT, TC, TG, LDL-C, UA, CAP, and LSM values were significantly higher in the NAFLD group. No differences in sex, ALP, HDL-C, and FBG were observed between the two groups. Among the patients with NAFLD, 37 (62.71%) had NASH, and 22 (37.29%) had NAFL. Furthermore, 69.49% (41/59) were obese, and 30.51% (18/59) were nonobese. Patients with NAFLD also showed a significantly higher frequency of hypertension and T2DM. The ALT, GGT, CAP, and LSM levels were significantly higher in patients with NASH compared to patients with NAFL, with no significant difference in the frequency of obesity, hypertension, and T2DM ([Tables 1 and 2](#)).

PPARGC1A rs8192678 polymorphism genotypes and allele frequencies and the risk of NAFLD between different groups

The percentage of PPARGC1A rs8192678 GA genotype was significantly higher in the NAFLD group than in the control group (62.71% *vs* 39.78%), suggesting that carriers of this genotype had a significantly increased risk of NAFLD (OR 2.786, 95%CI: 1.300-5.962, $P = 0.008$) ([Table 3](#)). The carriers of the homozygous AA genotype had no significantly increased risk of NAFLD compared to participants with GG homozygous alleles ($P = 0.609$). The close association was further revealed in the dominant model (combined GA and AA genotypes, GA + AA *vs* GG, OR 2.321, 95%CI: 1.121-4.806, $P = 0.022$) ([Tables 3 and 4](#)).

The percentage of the PNPLA3 rs738409 GG genotype was also significantly higher in patients with NAFLD than in controls (33.90% *vs* 16.13%, $P = 0.004$). The OR of NAFLD was 3.889-fold (95%CI: 1.534-9.926, $P = 0.004$) higher in participants with the GG genotype than in those with the CC genotype; and the participants carrying G allele also had a high risk of NAFLD (GG + GC *vs* CC, OR 2.364, 95%CI: 1.105-5.055, $P = 0.025$) ([Table 3](#)). The multiple logistic regression analysis revealed that the PPARGC1A rs8192678 A allele was a risk factor for NAFLD (OR 2.202, 95%CI: 1.030-4.705, $P = 0.042$) independent of age, sex, and PNPLA3 rs738409 polymorphism ([Table 5](#)).

Association between PPARGC1A rs8192678 polymorphism and hepatic histological features

The hepatic histological features, including steatosis, activity (lobular inflammation and ballooning), and fibrosis, were assessed in patients with NAFLD. The frequencies of PPARGC1A rs8192678 GA + AA genotypes were remarkably higher in patients with moderate-to-severe steatosis (S2-3) and activity 2-4 ($A \geq 2$) compared with those with mild steatosis (S1) and activity 0-1 ($A < 2$). Also, the carriers with risk A allele (carrying GA and AA genotypes) had a significantly increased risk in NAFLD patients with S2-3 and $A \geq 2$ (OR 5.000, 95%CI: 1.343-18.620, $P = 0.012$ and OR 4.071, 95%CI: 1.076-15.402, $P = 0.031$). The multivariate analysis showed that PPARGC1A rs8192678 A allele was also significantly associated with S2-3 and $A \geq 2$ (OR 6.190, 95%CI: 1.508-25.410, $P = 0.011$ and OR 4.506, 95%CI: 1.070-18.978, $P = 0.040$) after adjusting for age, sex, BMI, and PNPLA3 rs738409 risk G allele. However, no significant differences were found in significant fibrosis 2-4 (F2-4) and advanced fibrosis 3-4 (F3-4) compared with F0-1 and F0-2 ($P = 0.186$ and $P = 0.426$) ([Figure 1A-E](#) and [Table 6](#)).

The patients with NASH carrying PPARGC1A rs8192678 GA + AA genotypes had an OR of 4.431 (95%CI: 1.245-15.763, $P = 0.017$) when compared with NAFL ([Table 4](#)). The multivariate analysis also showed that PPARGC1A rs8192678 risk A allele was independently associated with NASH after adjusting for age, sex, BMI, and PNPLA3 rs738409 risk G allele in patients with NAFLD (OR 6.337, 95%CI: 1.135-35.392, $P = 0.035$) ([Table 6](#)).

PPARGC1A rs8192678 genotype is associated with nonobese NASH patients

The GA + AA genotypes were not associated with obese NAFLD, obese NASH, and obese NAFL in the dominant model compared with nonobese NAFLD, nonobese NASH, and nonobese NAFL, respectively. Genetic analysis also showed no significant difference in the patients carrying A allele in PPARGC1A rs8192678 between obese NASH and obese NAFL groups ([Table 4](#)).

The remaining anthropometric values, biochemical test values, and PNPLA3 polymorphism did not show any significant differences between the two groups, apart from a trend in a higher level of GGT ($P = 0.068$) and CAP ($P = 0.056$) in nonobese NASH. However, genetic analysis showed that the proportion of PPARGC1A rs8192678 GA + AA genotypes was significantly higher in the patients with nonobese NASH compared with patients with nonobese NAFL, which was significantly associated with nonobese NASH (OR 22.000, 95%CI: 1.540-341.292, $P = 0.021$) ([Tables 4](#)

Table 1 Clinical characteristics of patients with nonalcoholic fatty liver disease and controls

Variables	NAFLD (n = 59)	Controls (n = 93)	P value
Sex (M/F)	43/16	59/34	0.227
Age (year)	38.20 ± 13.78	42.20 ± 11.05	0.039
BMI (kg/m ²)	27.31 ± 3.31	23.06 ± 2.74	< 0.0001
ALT (U/L)	70.56 ± 47.6	24.98 ± 16.07	< 0.0001
GGT (U/L)	72.75 ± 55.22	25.94 ± 18.17	< 0.0001
ALP (U/L)	97.07 ± 44.73	96.50 ± 32.54	0.347
TC (mmol/L)	4.86 ± 0.86	4.39 ± 0.89	0.001
TG (mmol/L)	1.99 ± 1.25	1.14 ± 0.74	< 0.0001
HDL-C (mmol/L)	1.20 ± 0.28	1.23 ± 0.28	0.177
LDL-C (mmol/L)	2.83 ± 0.7	2.24 ± 0.50	< 0.0001
FBG (mmol/L)	5.93 ± 2.62	5.31 ± 0.79	0.941
UA (μmol/L)	361.32 ± 105.78	274.25 ± 76.53	< 0.0001
CAP (dB/m)	313 (277-351)	212 (172-232)	< 0.0001
LSM (kPa)	7.7 (5.6-12)	5.25 (4.1-7.0)	< 0.0001
Hypertension, n (%)	22 (37.29%)	15 (16.13%)	0.003
T2DM, n (%)	7 (11.86%)	1 (1.08%)	0.005
Obesity, n (%)	41 (69.49%)	19 (20.43%)	< 0.0001
Steatosis (S, n)			
S1/S2/S3	25/25/9	/	/
Activity (A, n)			
A0/A1/A2/A3/A4	1/12/16/22/8	/	/
Fibrosis (F, n)			
F0/F1/F2/F3/F4	11/29/8/7/4	/	/

The data are expressed as mean ± SD, or as *n* (%) for normally distributed variables and as median (interquartile range) when distribution of the variable was skewed. NAFLD: Nonalcoholic fatty liver disease; BMI: Body mass index; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; GGT: γ-glutamyl transpeptidase; TC: Total cholesterol; TG: Triglycerides; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; FBG: Fasting blood glucose; UA: Uric acid; LSM: Liver stiffness measurement; CAP: Controlled attenuation parameter; T2DM: Type 2 diabetes mellitus.

and 7).

mRNA expression of PPARGC1A in the liver of patients with NAFLD

The expression of PPARGC1A mRNA in the liver biopsy specimens of patients with NAFLD was evaluated by RT-PCR. The results obtained by RT-PCR in the GA or AA group (*n* = 5) were compared with the results in the GG group (*n* = 5) at PPARGC1A rs8192678. As shown in **Figure 1F**, the expression of PPARGC1A mRNA transcripts in the liver was significantly lower in the GA or AA group than in the GG group (*P* = 0.014).

DISCUSSION

Genetic factors may be important in the development of NAFLD, in either obese or nonobese patients. The present study further indicated that PPARGC1A rs8192678 risk A allele was associated with liver biopsy-proven NAFLD susceptibility in a Chinese Han adult population, and it was especially associated with NASH compared with NAFL. The PPARGC1A rs8192678 risk A allele was also associated with nonobese NASH in patients with nonobese NAFLD. In addition, this polymorphism was

Table 2 Clinical characteristics of patients with nonalcoholic steatohepatitis and nonalcoholic fatty liver among patients with nonalcoholic fatty liver disease

Variable	NAFL (<i>n</i> = 22)	NASH (<i>n</i> = 37)	<i>P</i> value
Sex (M/F)	17/5	26/11	0.559
Age (year)	37.23 ± 13.64	38.78 ± 14.01	0.605
BMI (kg/m ²)	27.07 ± 3.69	27.38 ± 3.17	0.675
ALP (U/L)	102.96 ± 52.34	93.56 ± 39.91	0.982
GGT (U/L)	38.00 (23.80-69.03)	69.70 (39.00-85.50)	0.023
ALT (U/L)	46.00 (30.33-64.95)	71.40 (46.9-111.70)	0.006
TC (mmol/L)	5.03 ± 1.04	4.76 ± 0.72	0.801
TG (mmol/L)	1.91 ± 0.74	2.04 ± 1.48	0.532
HDL-C (mmol/L)	1.21 ± 0.28	1.19 ± 0.28	0.903
LDL-C (mmol/L)	2.97 ± 0.91	2.72 ± 0.49	0.444
FBG (mmol/L)	6.43 ± 3.59	5.62 ± 1.77	0.318
UA (μmol/L)	360.91 ± 107.80	361.62 ± 106.22	0.482
CAP (dB/m)	295.50 (249.25-345.00)	333.00 (296.25-356.25)	0.038
LSM (kPa)	6.20 (4.55-9.95)	9.60 (6.50-12.85)	0.008
Obesity, <i>n</i> (%)	16 (72.73)	25 (60.97)	0.677
Hypertension, <i>n</i> (%)	8 (36.36)	14 (37.84)	0.910
T2DM, <i>n</i> (%)	3 (13.64)	4 (10.81)	0.746

The data are expressed as mean ± SD, or as *n* (%) for normally distributed variables and as median (interquartile range) when distribution of the variable was skewed. NAFL: Nonalcoholic fatty liver; NASH: Nonalcoholic steatohepatitis; BMI: Body mass index; ALP: Alkaline phosphatase; GGT: γ-glutamyl transpeptidase; ALT: Alanine aminotransferase; TC: Total cholesterol; TG: Triglycerides; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; FBG: Fasting blood glucose; UA: Uric acid; LSM: Liver stiffness measurement; CAP: Controlled attenuation parameter; T2DM: Type 2 diabetes mellitus.

Table 3 Genotype distribution of PPARGC1A rs8192678 and patatin-like phospholipase domain-containing protein 3 rs738409 in patients with nonalcoholic fatty liver disease and controls

Genotype	NAFLD (<i>n</i> = 59)	Controls (<i>n</i> = 93)	χ ²	<i>P</i> value	OR (95%CI)
PPARGC1A rs8192678					
GG	14 (23.73%)	39 (41.94%)			
GA	37 (62.71%)	37 (39.78%)	7.148	0.008	2.786 (1.300-5.962)
AA	8 (13.56%)	17 (18.28%)	0.262	0.609	1.311 (0.464-3.704)
GA+AA	45 (76.27%)	54 (58.06%)	5.269	0.022	2.321 (1.121-4.806)
PNPLA3 rs738409					
CC	12 (20.34%)	35 (37.63%)			
CG	27 (45.76%)	43 (46.24%)	2.152	0.142	1.831 (0.812-4.131)
GG	20 (33.90%)	15 (16.13%)	8.423	0.004	3.889 (1.524-9.926)
CG + GG	47 (79.56%)	58 (62.37%)	5.055	0.025	2.364 (1.105-5.055)

OR: Odds ratio; CI: Confidence interval; PNPLA3: Patatin-like phospholipase domain-containing protein 3; NAFLD: Nonalcoholic fatty liver disease.

associated with moderate-to-severe steatosis and higher histological activity, but not with significant and advanced fibrosis.

PPARGC1A/PGC-1α is a coactivator for a number of transcription factors, including the peroxisome proliferator-activated receptor. PGC-1α is a critical regulator

Table 4 Association tests of PPARGC1A rs8192678 polymorphism between different groups

PPARGC1A rs8192678	Case			Control			Dominant model		
	GG	GA	AA	GG	GA	AA	χ^2	P value	OR (95%CI)
NAFLD <i>vs</i> Control	14	37	8	39	37	17	5.269	0.022	2.321 (1.121-4.806)
NASH <i>vs</i> Control	5	28	4	39	37	17	9.550	0.002	4.622 (1.653-12.929)
NASH <i>vs</i> NAFL	5	28	4	9	9	4	5.721	0.017	4.431 (1.245-15.763)
Obese <i>vs</i> nonobese participants	17	33	10	36	41	15	1.864	0.172	1.626 (0.807-3.276)
Obese NAFLD <i>vs</i> nonobese NAFLD	9	27	5	5	10	3	0.235	0.628	1.368 (0.384-4.865)
Obese NASH <i>vs</i> nonobese NASH	4	19	2	1	9	2	0.408	0.348	0.477 (0.047-4.806)
Obese NAFL <i>vs</i> nonobese NAFL	5	8	3	4	1	1	2.264	0.132	4.400 (0.596-32.501)
Obese NASH <i>vs</i> obese NAFL	4	19	2	5	8	3	1.324	0.250	2.386 (0.531-10.734)
Nonobese NASH <i>vs</i> nonobese NAFL	1	9	2	4	1	1	6.785	0.021	22.000 (1.540-314.292)

NAFL: Nonalcoholic fatty liver; NASH: Nonalcoholic steatohepatitis; NAFLD: Nonalcoholic fatty liver disease; OR: Odds ratio; CI: Confidence interval.

Table 5 Multiple logistic regression analysis of predictive factors for nonalcoholic fatty liver disease

Variables	B	S.E.	Wald	OR (95%CI)	P value
Age (year)	-0.031	0.015	4.236	0.970 (0.942-0.999)	0.040
Sex (Male)	-0.233	0.385	0.365	0.793 (0.373-1.686)	0.546
PPARGC1A rs8192678 A allele	0.789	0.388	4.148	2.202 (1.030-4.705)	0.042
PNPLA3 rs738409 G allele	0.857	0.403	4.524	2.356 (1.070-5.191)	0.033

OR: Odds ratio; CI: Confidence interval; PNPLA3: Patatin-like phospholipase domain-containing protein 3.

Table 6 Association of the PPARGC1A genotypes with steatosis, activity, and fibrosis in patients with nonalcoholic fatty liver disease

Histological features		Genotypes		Dominant model		Multivariate analysis ¹	
		GG (n = 14)	GA + AA (n = 45)	P value	OR (95%CI)	P value	OR (95%CI)
Steatosis (S)	S1	10 (71.43%)	15 (33.33%)	0.012	5.000 (1.343-18.620)	0.011	6.190 (1.508-25.410)
	S2-3	4 (28.57%)	30 (66.67%)				
Activity (A)	A < 2	6 (42.86%)	7 (15.56%)	0.031	4.071 (1.076-15.402)	0.040	4.506 (1.070-18.978)
	A ≥ 2	8 (57.14%)	38 (84.44%)				
Significant fibrosis	F0-1	12 (85.71%)	28 (62.22%)	0.100	3.643 (0.726-18.292)	0.186	3.449 (0.551-21.598)
	F2-4	2 (14.29%)	17 (37.78%)				
Advanced fibrosis	F0-2	13 (92.86%)	35 (77.78%)	0.206	3.714 (0.432-31.949)	0.426	2.549 (0.255-25.490)
	F3-4	1 (7.14%)	10 (22.22%)				
NASH	NAFL	9 (64.28%)	13 (28.89%)	0.017	4.431 (1.245-15.763)	0.035	6.337 (1.135-35.392)
	NASH	5 (35.71%)	32 (71.11%)				

¹Multivariate analysis adjusted for age, sex, body mass index, and patatin-like phospholipase domain-containing protein 3 rs738409 risk G allele. NAFL: Nonalcoholic fatty liver; NASH: Nonalcoholic steatohepatitis; OR: Odds ratio; CI: Confidence interval.

of adaptive thermogenesis, cellular respiration, and energy metabolism[17]. Recent studies suggested that PGC-1 α also regulates lipid metabolism, PGC-1 α stimulates the expression of farnesoid X receptor (FXR) target genes in hepatic cells and reduces TG secretion by enhancing FXR activity[18]. In addition, PGC-1 α can transactivate the

Table 7 Biochemical and genetic characteristics of patients with nonobese nonalcoholic fatty liver disease

Variables	NAFL (<i>n</i> = 6)	NASH (<i>n</i> = 12)	<i>P</i> value
Sex (M/F)	4/2	10/2	0.569
Age (year)	35.33 ± 18.44	39.67 ± 4.80	0.452
BMI (kg/m ²)	22.83 ± 1.61	23.69 ± 0.90	0.122
ALP (U/L)	123.32 ± 77.62	84.25 ± 23.28	0.426
GGT (U/L)	28.50 (21.18-85.00)	73.25 (54.75-99.25)	0.068
ALT (U/L)	42.00 (21.78-78.50)	71.15 (41.10-115.25)	0.325
TC (mmol/L)	5.11 ± 0.55	4.96 ± 1.02	0.606
TG (mmol/L)	2.00 ± 0.43	1.77 ± 0.95	0.371
HDL-C (mmol/L)	1.10 ± 0.16	1.24 ± 0.44	0.943
LDL-C (mmol/L)	3.16 ± 0.46	2.82 ± 0.80	0.524
FBG (mmol/L)	5.03 ± 0.94	5.24 ± 0.85	0.587
UA (μmol/L)	360.86 ± 167.34	354.17 ± 67.43	0.684
CAP (dB/m)	257.00 ± 57.03	316.73 ± 43.48	0.056
LSM (kPa)	6.95 ± 4.07	6.79 ± 2.06	0.421
PPARGC1A rs8162678			
GG, <i>n</i> (%)	4 (66.67)	1 (8.33)	
GA + AA, <i>n</i> (%)	2 (33.33)	11 (91.67)	0.021
PNPLA3 rs738409			
CC, <i>n</i> (%)	2 (33.33)	1 (8.33)	
CG + GC, <i>n</i> (%)	4 (66.67)	11 (91.67)	0.245

The data are expressed as mean ± SD, or as *n* (%) for normally distributed variables and as median (interquartile range) when distribution of the variable was skewed. NAFL: Nonalcoholic fatty liver; NASH: Nonalcoholic steatohepatitis; BMI: Body mass index; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; GGT: γ -glutamyl transpeptidase; TC: Total cholesterol; TG: Total triglycerides; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; FBG: Fasting blood glucose; UA: Uric acid; LSM: Liver stiffness measurement; CAP: Controlled attenuation parameter; PNPLA3: Patatin-like phospholipase domain-containing protein 3.

hepatocyte nuclear factor 4 α -dependent human hepatic lipase gene promoter to increase the production of hepatic lipase. The PGC-1 α is also highly expressed in the liver and coordinates the induction of fatty acid oxidation when fasting. Multiple studies showed that decreased PGC-1 α expression might be the mechanism underlying metabolic diseases. Tissue-specific reduction of PGC-1 α expression in adipose, liver, and muscle reduced glucose tolerance and insulin sensitivity in mice[19, 20], supporting the hypothesis that decreased PGC-1 α expression in insulin-sensitive tissues might contribute to a higher risk of T2DM. PPARGC1A mRNA expression decreased in muscle and adipose tissue of human participants with T2DM[21], and a correlation existed between adipose PGC-1 α protein levels and decreased insulin sensitivity[22]. T2DM was also a risk factor for NAFLD. Another reported PPARGC1A polymorphism rs2290602 also decreased the expression of PPARGC1A in patients with NAFLD[6]. Therefore, genetic factors that alter the expression of PGC-1 α might participate in the pathogenesis of NAFLD. The present study also indicated that the expression of PPARGC1A was significantly lower in patients who carried the A allele, which supported the hypothesis that decreased PGC-1 α expression in steatosis liver tissues might contribute to a higher risk of NAFLD.

Recently, the association between different single nucleotide polymorphisms (SNPs) and metabolic diseases, such as NAFLD, was reported[23]. Therefore, different polymorphisms of PPARGC1A associated with different metabolic diseases were investigated. Iglseder *et al*[24] showed that the -3974T/C (rs2970865) polymorphism of the PPARGC1A gene was associated with the severity of carotid atherosclerosis. The variations in rs2290602 in the PPARGC1A gene was expected to affect lipid and glucose metabolism and result in the development of NAFLD and NASH[6]. Another

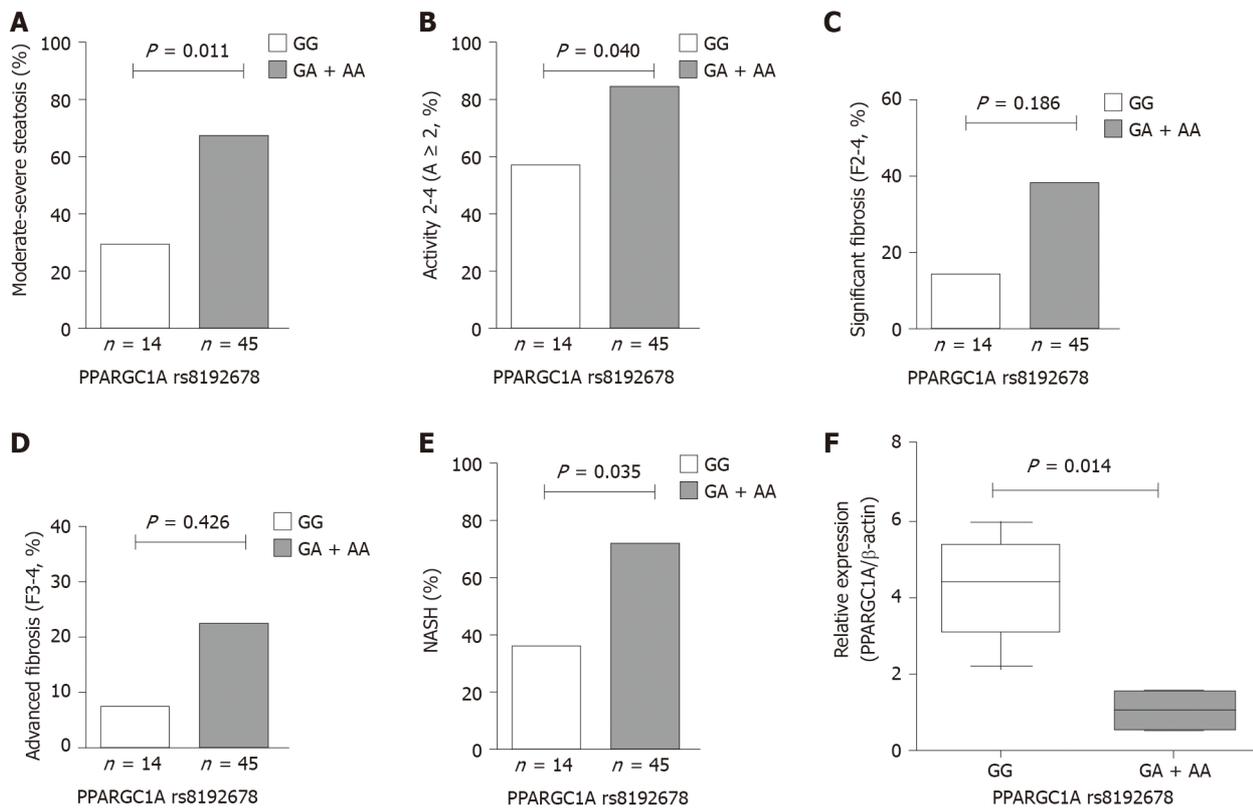


Figure 1 Comparison of various quantitative phenotypes (hepatic histological features and mRNA expression) in patients with nonalcoholic fatty liver disease at the PPARGC1A rs8192678 polymorphism. A-E: Prevalence of moderate-severe steatosis (S2-3), activity 2-4 (A ≥ 2), significant fibrosis (F2-4), advanced fibrosis (F3-4), and nonalcoholic steatohepatitis according to the PPARGC1A rs8192678 polymorphism in 59 patients with nonalcoholic fatty liver disease. The reference genotype for the PPARGC1A rs8192678 polymorphism was GG, and a mode of dominant inheritance was used; F: The intrahepatic mRNA expression of PPARGC1A between the GG group (n = 5) and the GA or AA group (n = 5) at PPARGC1A rs8192678. NASH: Nonalcoholic steatohepatitis.

common PPARGC1A rs8192678 polymorphism might contribute to the risk of coronary artery disease in the Chinese population[9,24], and was also associated with obesity, hypertension, and T2DM. This polymorphism in PPARGC1A was also reported to be related to the susceptibility of NAFLD in different populations and ethnicities. The present study showed that the variation of PPARGC1A rs8192678 GA genotype was significantly higher in patients with NAFLD, but PPARGC1A rs8192678 AA genotype showed no difference between NAFLD and control groups, and the percentage of AA genotype was only 13.56% (8/59) in NAFLD patients, which was consistent with the findings of Lin *et al*[7] in obese children in Taiwan. The explanation of this finding in Lin *et al*[7] concluded two probable reasons. First, the number with PPARGC1A rs8192678 AA genotype was relatively small, because of the sample variation and inadequate statistical power, the role of AA genotype in NAFLD was not presented. Second, the cellular effects of PGC-1α were complicated, and the mechanism by which PGC-1α influenced the pathogenesis of NAFLD was still unclear [7]. However, a comparison between GA + AA and GG genotypes revealed that the participants who carried the PPARGC1A rs8192678 A allele were found to be significantly associated with not only liver biopsy-proven NAFLD but also NASH, independent of age, sex, BMI, and PNPLA3 rs738409 risk G allele in the dominant model. No study analyzed the association between the PPARGC1A rs8192678 A allele and hepatic histological features in NAFLD. Significant associations of PPARGC1A rs8192678 risk A allele with moderate-to-severe steatosis and higher histological activity in patients with NAFLD were found in this study. However, significant fibrosis and advanced fibrosis were not associated with PPARGC1A rs8192678 risk A allele. This suggested that PPARGC1A rs8192678 risk A allele was associated with steatosis and liver damage, contributing to the occurrence of NASH.

Several studies reported that PPARGC1A rs8192678 was significantly associated with obesity; this polymorphism conferred a higher risk of obesity in certain populations[25,26]. The patients who carried PPARGC1A rs8192678 AA genotype benefited more from interventions aimed at weight loss, including caloric restriction,

bariatric surgery, and acarbose treatment[27,28]. The prevalence of lean NAFLD and nonobese NAFLD has increased in eastern and western countries in recent years. The genetic, metabolic, microbiome, metabolomics, and inflammatory factors may also be the causes of NAFLD in lean or nonobese individuals. Genetic factors may also be important in the occurrence and development of nonobese NAFLD. IFNL3 rs12979860 polymorphism has been shown to be associated with hepatic inflammation and fibrosis in patients with nonobese NAFLD[29]. Two SNPs rs12447924 and rs12597002 of the cholesteryl ester transfer protein gene were reported to be associated with a risk of steatosis in nonobese individuals[30]. Wang *et al*[31] found a significantly higher prevalence of advanced fibrosis ($F \geq 3$) and LSM values in patients with nonobese NASH compared with obese NASH; also, a higher prevalence of TM6SF2 T allele was observed in patients with nonobese NASH, indicating that patients with nonobese NASH had more severe hepatic histological changes and genetic susceptibility in the Chinese population[31]. The present study found that the PPARGC1A rs8192678 A allele was not significantly closely associated with obese participants, patients with obese NAFLD, and patients with obese NASH. However, the PPARGC1A rs8192678 A allele was relatively more common in patients with nonobese NASH compared with patients with obese NASH. The results also showed that the PPARGC1A rs8192678 GA + AA genotypes were remarkably associated with nonobese NASH, indicating that the PPARGC1A rs8192678 A allele was associated with a high risk of NASH. This, especially, increased the risk of nonobese NASH, and the PPARGC1A rs8192678 polymorphism might be the pathogenesis of nonobese NASH. Despite no significant difference in TC, TG, ALT, GGT, FBG, UA, and CAP values and PNAPL3 rs738409 between the nonobese NAFL and NASH groups, the levels of GGT ($P = 0.068$) and CAP ($P = 0.056$) followed an increasing trend in nonobese NASH. This suggested that genetic background might also be a risk factor for nonobese NASH. The influence of metabolic factors, such as lipid and glucose, needs further exploration using a large sample.

The association between PPARGC1A rs8192678 and NAFLD in the Asian population is controversial. Hui *et al*[15] and Zhou *et al*[14] reported no association between the PPARGC1A rs8192678 variant and ultrasound-defined NAFLD in Chinese adults[14,15]. However, Tai *et al*[8] reported that the PPARGC1A variant rs8192678 was associated with liver biopsy-proven NASH in severely obese Taiwanese patients[8]. Saremi *et al*[32] also indicated that the AA genotype and A allele of PPARGC1A increased in Iranian patients with liver biopsy-proven NAFLD[32]. The frequency of the PPARGC1A rs8192678 A allele was 0.453 in Han Chinese, 0.350 in Europeans, and 0.040 in Africans according to the National Center for Biotechnology Information human SNP database, which inferred that the PPARGC1A rs8192678 risk A allele conferred a higher genetic susceptibility to NAFLD in Asians than in Europeans and Africans[7]. Also, the PPARGC1A rs8192678 was associated with NAFLD, especially NASH, in the Chinese Han adult population with liver biopsy-proven NAFLD. This contradictory conclusion might be due to the different criteria used for the definition of NAFLD; ultrasonography or liver biopsy was carried out in different studies. In the present study, the gold diagnostic standard for NAFLD, liver histopathology, was used to avoid the potential image bias in Chinese Han patients with NAFLD.

However, this study also had limitations. First, obtaining liver biopsies was difficult, and hence patients with NAFLD were relatively few, especially those with nonobese NAFLD. Consequently, no statistically significant differences were identified. Second, the risk factors such as hypertension and diabetes, which might influence obese/nonobese NAFLD, were not mentioned in this study. Therefore, a large number of patients with liver biopsy-proven NAFLD should be included in further studies, and well-designed case-control studies should be performed to confirm and support these findings.

CONCLUSION

In conclusion, the present study showed that PPARGC1A rs8192678 risk A allele was associated with liver biopsy-proven NAFLD/NASH, which also had an effect on the severity of hepatic histological features ($S2-3$ and $A \geq 2$), and might also be associated with nonobese NASH in the Chinese Han adult population. These findings also suggested that PPARGC1A polymorphism rs8192678 risk A allele and lower expression of PPARGC1A mRNA might contribute to the etiology of NAFLD. Further studies with large samples are required to confirm these findings.

ARTICLE HIGHLIGHTS

Research background

Nonalcoholic fatty liver disease (NAFLD) has become the most common chronic liver disease and is a significant global burden worldwide. It is also common in obese and nonobese populations. Although the mechanism of NAFLD is unclear, genetic susceptibility plays a vital role in NAFLD. The association between PPARGC1A rs8192678 polymorphism and NAFLD has been reported in several studies, but it is controversial in the Asian population. Whether PPARGC1A rs8192678 is associated with hepatic histological features in NAFLD in the Chinese population is unknown.

Research motivation

The association between PPARGC1A rs8192678 polymorphism and NAFLD requires further investigation, and the association with hepatic histological features and nonobese NAFLD in the Chinese population is unknown.

Research objectives

The aim was to investigate the association between PPARGC1A rs8192678 polymorphism and nonalcoholic steatohepatitis (NASH) and to determine whether PPARGC1A rs8192678 is associated with the hepatic histological features of NASH.

Research methods

Patients with NAFLD and healthy controls were recruited to a cohort representing the Chinese Han population. Patients with NAFLD were proven by liver biopsy. The SAF (Steatosis, activity, and fibrosis) scoring system was used for histopathological evaluation. The polymorphisms of PPARGC1A rs8192678 and patatin-like phospholipase domain-containing protein 3 (PNPLA3) rs738409 were genotyped. The intrahepatic mRNA expression of PPARGC1A was evaluated by real-time polymerase chain reaction.

Research results

In NAFLD patients, 37 patients had NASH, of which 12 were nonobese NASH. The PPARGC1A rs8192678 risk A allele (carrying GA and AA genotypes) increased the risk of NAFLD in the dominant model. The PPARGC1A rs8192678 A allele was also found to be a risk factor for NAFLD after adjusting for age, sex, and PNPLA3 rs738409 polymorphism. In the hepatic histological features of NAFLD patients, moderate-to-severe steatosis (S2-3), and Activity 2-4 ($A \geq 2$) were more likely to carry PPARGC1A rs8192678 risk A allele. After adjusting for age, sex, body mass index, and PNPLA3 rs738409 risk G allele, the PPARGC1A rs8192678 risk A allele was also independently associated with S2-3, $A \geq 2$, and NASH. The results also showed that this polymorphism was associated with nonobese NASH. In the group of patients who carried A allele (GA or AA genotypes), the intrahepatic expression of PPARGC1A mRNA was significantly lower than that in patients with GG genotype.

Research conclusions

The PPARGC1A rs8192678 A allele is a risk factor for NAFLD, and is associated with the severity of hepatic histological features (S2-3 and $A \geq 2$) and NASH in NAFLD patients, independent of PNPLA3 rs738409, and might be associated with nonobese NASH.

Research perspectives

The result that PPARGC1A rs8192678 was associated with liver biopsy-proven NASH and had an additive effect on the severity of hepatic histological features was further confirmed in the Chinese Han adult population. PPARGC1A rs8192678 might contribute to the etiology of NAFLD. PPARGC1A rs8192678 might be a useful tool for diagnosing NASH and predicting the severity of the hepatic histological features of NAFLD.

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