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PNPLA3 rs738409 underlies treatment response in nonalcoholic fatty liver disease

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Abstract

Non-alcoholic fatty liver disease (NAFLD) has now become the leading cause of chronic liver disease with its growing incidence worldwide. Patatin-like phospholipase domain-containing protein 3 (PNPLA3) rs738409 C > G reflects one of the critical genetic factors that confers high-risk to NAFLD. However, the role of PNPLA3 polymorphism in NAFLD treatment remains uncertain. Here, the present review reveals that NAFLD patients with G-allele at PNPLA3 rs738409 (PNPLA3 148M variant) are sensitive to therapies of lifestyle modification, dipeptidyl peptidase-4 inhibitors, and bariatric surgery. They exhibit much significant reduction of liver fat content, in concurrence with weight loss and abolished insulin resistance, as compared to those of C-allele carriers. In contrast, patients bearing PNPLA3 rs738409 C-allele (PNPLA3 148I variant), instead of G-allele, demonstrate greater beneficial effects by omega-3 poly-unsaturated fatty acids and statin intervention. Improved adipose tissue-liver interaction and decrease in intrahepatic triglyceride efflux may contribute to the PNPLA3 rs738409 related diversities in therapeutic efficacy. Therefore, PNPLA3 rs738409 underlies the response to a variety of treatments, which warrants a personalized, precise medicine in NAFLD on the basis of genotype stratification.

Key words: Non-alcoholic fatty liver disease; Patatin-like phospholipase domain-containing protein 3; Treatment; Lifestyle; Pharmacotherapy; Surgery; Polymorphism

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Core tip: Patatin-like phospholipase domain-containing protein 3 (PNPLA3) rs738409 imposes universal, yet distinctly different, impact on various therapies in nonalcoholic fatty liver disease (NAFLD) patients. As compared to those with C-allele, patients with PNPLA3 rs738409 G-allele (PNPLA3 148M variant) show grater improvement in response to lifestyle modification, dipeptidyl peptidase-4 inhibitor ingestion, and bariatric surgery. In contrast, NAFLD patients carrying PNPLA3 rs738409 C-allele (PNPLA3 148I variant) are much sensitive to both omega-3 poly-unsaturated fatty acids and statin intervention. These diversities in treatment response warrant a personalized, precise medicine in NAFLD by stratification of PNPLA3 rs738409 genotype.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD), a metabolic stress-induced chronic liver disease, has undergone a dramatic increase in prevalence worldwide over the last few decades with a morbidity rate of 15%-40%^[1,2]. Over 20% of NAFLD patients progress from simple steatosis to non-alcoholic steatohepatitis (NASH)^[3,4], which has a >10% chance of developing into liver fibrosis/cirrhosis and even hepatocellular carcinoma^[5]. Due to the considerable burden of NAFLD on public health, it has become an emergent target for clinical intervention.

In addition to a sedentary lifestyle and Western diet, genetic polymorphism of various genes is considered as the other important factor in NAFLD predisposition^[6]. In a genome-wide association scan (GWAS) of nonsynonymous sequence variations ($n = 9229$), patatin-like phospholipase domain-containing protein 3 (PNPLA3) rs738409 C > G (PNPLA3 I148M) was identified as a risk factor for NAFLD in Hispanic, African American and European Americans^[7]. Further studies in multiple ethnic populations confirmed the effect of PNPLA3 I148M on NAFLD susceptibility, with a spectrum ranging from steatosis, NASH, to liver fibrosis^[8-11]. PNPLA3 encodes the adiponutrin which is sited in the endoplasmic reticulum and on lipid droplets in hepatocytes. Possessing a patatin-like domain at the N-terminal, PNPLA3 shows hydrolase activity against glycerolipids (triacylglycerol, diacylglycerol, and monoacylglycerol), and has a crucial role in the homeostasis of lipid metabolism^[12,13]. However, PNPLA3 148M functions in a "loss-of-function" way and leads to low levels of glycerolipid hydrolysis

in the liver and inhibition of lipid outflow to peripheral adipose tissues^[12,13]. Therefore, the PNPLA3 148M variant contributes to hepatic steatosis and related disorders depending on its interference with lipometabolic balance.

Current therapeutic approaches for NAFLD include lifestyle modification (e.g., diet therapy and physical activity)^[14,15], pharmacotherapy [e.g., omega-3 fatty acids, statins, and dipeptidyl peptidase-4 (DPP-4) inhibitors]^[16], and bariatric surgery (e.g., nonadjustable or adjustable banding, vertical banded gastroplasty, and gastric bypass)^[17]. It is rational to propose that PNPLA3 rs738409 C > G (PNPLA3 148M) may affect the efficacy of NAFLD therapy due to the disturbance of glycerolipid-metabolic homeostasis. In this review, we summarize the therapeutic outcomes in NAFLD patients with different genetic backgrounds in order to highlight the interaction between PNPLA3 genotypes and treatment response.

LIFESTYLE MODIFICATION

Lifestyle modification, including a hypocaloric diet and/or increased physical activity, has been recommended as first-line therapy by the Diagnosis and Management of NAFLD practice guideline^[18]. To test the effects of PNPLA3 polymorphism on treatment response to lifestyle modification, a randomized controlled trial was conducted in 154 adult Hong Kong residents with NAFLD^[19]. Following equal randomization into the intervention and control group, respectively, 77 NAFLD patients received dietary consultation sessions that encouraged an individual-designed menu with emphasis on fruit and vegetables, and moderate-carbohydrate, low-fat, low-glycemic index, and low-caloric products in appropriate portions according to the recommendations of the American Dietetic Association. In addition, the patients were instructed to develop a routine exercise habit (30 min every day). Evaluation of these patients using proton magnetic resonance spectroscopy (¹H-MRS) showed that NAFLD patients carrying the G-allele at PNPLA3 rs738409 demonstrated a greater reduction in intrahepatic triglyceride content (IHTG) (GG: 11.3 ± 8.8%) compared to those with the C-allele (CC: 3.7 ± 5.2%, CG: 6.5 ± 3.6%) at the end of the 12-mo treatment. A greater decrease in body weight, waist-to-hip ratio (WHR), total cholesterol (TC), and low-density lipoprotein (LDL) cholesterol was also confirmed in the G-allele, but not the C-allele carriers with the exception of biochemical and liver stiffness measurements. The reduction in hepatic fat was parallel with the decrease in body weight and improvement in LDL cholesterol and TC. Multivariate analysis showed that PNPLA3 genotype and body mass index (BMI) change were the only factors correlated with IHTG reduction in the intervention group. In contrast, no correlations between PNPLA3 rs738409 and changes in IHTG or other measured parameters were found in the control group.

Eight subjects with a homozygous PNPLA3 rs738409

G-allele (PNPLA3-148MM) and 10 with a homozygous PNPLA3 rs738409 C-allele (PNPLA3-148II) were recruited for a further 6-d trial of a hypocaloric (1000-kcal deficit/d), low-carbohydrate diet (< 30 g/d)^[20]. Despite a similar percentage of liver fat as shown by 1H-MRS on day 0, the PNPLA3-148MM group experienced a significantly greater reduction in liver fat than the PNPLA3-148II group (day 6, PNPLA3-148MM vs PNPLA3-148II: $10.2 \pm 1.8\%$ vs $11.9 \pm 2.1\%$) independent of a comparable weight loss. In this study, no statistical differences were found in plasma alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), γ -glutamyltransferase (GGT), and free fatty acid (FFA) concentrations between the two groups. It is necessary for individuals with NAFLD to achieve amelioration of steatosis by a 3%-5% weight loss, and to achieve an improvement in necroinflammation of up to 10%^[18,21]. Thus, the incomplete response to diet therapy may be due to an inadequate weight reduction ($-3.7 \pm 0.5\%$ in the PNPLA3-148MM group, $-3.3 \pm 0.3\%$ in the PNPLA3-148II group). In addition, 143 Caucasian Polish patients with NAFLD were prospectively enrolled in a dietary intervention^[22]. All overweight or obese individuals received a 500 kcal restriction diet, whereas patients with normal weight were permitted a dietary intake that was consistent with physiological needs. The total fat content, including mono- and polyunsaturated fats, was reduced to an energy intake of 25%. Additionally, daily cholesterol consumption was less than 300 mg. After 4 mo of the intervention, individuals with the MM genotype of PNPLA3 exhibited a greater improvement in WHR compared to those with the II genotype. In support of the close correlation between WHR and hepatic steatosis^[23], decreased WHR facilitates the amelioration of NAFLD on the basis of attenuated abdominal obesity.

Peripheral lipolysis has been identified as the major source of intrahepatocellular triglycerides^[24,25], one of the dominant lipid components responsible for hepatic steatosis. Based on the significant correlation between extrahepatic lipolysis and the change in liver fat content^[24], the decrease in liver fat following lifestyle modification is attributed to a change in peripheral lipolysis and then FFA delivery to the liver. Using [²H₅] glycerol, whole-body lipolysis can be analyzed by the rate of appearance (Ra) of glycerol^[20]. Enhanced percentage suppression of glycerol Ra increased the anti-lipolytic effect of insulin by the ketogenic diet^[20]. PNPLA3-148MM, but not PNPLA3-148II, significantly promoted the suppression of glycerol Ra ($37 \pm 5\%$ before and $51 \pm 4\%$ after the ketogenic diet)^[20]. These findings suggest that a greater improvement in the insulin sensitivity of individuals with PNPLA3 148MM compared to those with PNPLA3 148II could have contributed to the greater reduction in liver fat following lifestyle modification.

PHARMACOTHERAPY

NAFLD, with the hallmark of excessive triglyceride ac-

cumulation, is considered the hepatic manifestation of the metabolic syndrome (MetS). The co-existence of other MetS components (e.g., dysglycemia, decreased HDL cholesterol and arterial hypertension^[26]) can also be risk factors for NAFLD severity^[27]. Thus, medications associated with glycolipid metabolism (e.g., omega-3 fatty acids, statins, and DPP-4 inhibitors) have been used in the management of NAFLD-related hepatic disorders ranging from steatosis and steatohepatitis to liver fibrosis.

Omega-3 fatty acids

One hundred and three subjects from six hospitals in the south of England were enrolled in a multi-center, double-blind, placebo-controlled clinical trial, "the WELCOME trial", which was performed to test the polymorphism-based therapeutic effects of high-dose omega-3 fatty acids on NAFLD^[28]. The primary outcomes were a decrease in percentage liver fat and improvement in liver fibrosis scores. A total of 51 participants block randomized to omega-3 fatty acid ethyl esters, received Omacor® 4 g/d [4 \times 1000-mg capsules of 460 mg eicosapentaenoic acid (EPA) and 380 mg docosahexaenoic acid (DHA)] for 15-18 mo. The remaining 52 NAFLD patients were treated with a placebo of isocaloric olive oil (4 g/d) containing approximately 67% oleic acid, 15% linoleic acid, 15% palmitic acid, 2% stearic acid, and 1% alpha linolenic acid. According to the 1H-MRS results, both PNPLA3 148I/I and 148I/M carriers demonstrated an adjusted mean decrease in liver fat percentage (148I/I: -7.05% , 148I/M: -7.30%) following the DHA+EPA intervention, whereas the PNPLA3 148M/M group had a slight increase in liver fat percentage (2.75%). Moreover, regression modeling demonstrated that the PNPLA3 148 M/M genotype was independently associated with the end-of-study liver fat percentage.

Similar findings were obtained in a randomized controlled trial of DHA supplementation (250 mg/d or 500 mg/d) in obese Italian children with ultrasound-diagnosed NAFLD^[29]. As assessed by the combined DHA 250 mg/d and 500 mg/d groups versus placebo group, the 24-mo DHA trial resulted in a decreased probability of severe liver steatosis, with an independent effect of PNPLA3 polymorphism on the response to DHA. Somers' D model of liver fat evaluation revealed that the 148M allele of PNPLA3 predisposes carriers to low treatment response, with a 50% higher probability of more severe steatosis at the end of the trial. In contrast, a greater response to DHA was detected in those who were homozygous for the 148I allele in comparison with heterozygotes. An association between dietary N-6/N-3 polyunsaturated fatty acids (PUFA) ratio and hepatic fat content, and even serum ALT, was previously shown in multiethnic obese children who were homozygous for the 148M PNPLA3 allele^[30]. The PNPLA3 148M/M genotype minimizes the secretion of both large TG-rich very-low-density lipoprotein particles and apoB100, and partially decreases lipolytic activity and lysophosphatidic

acid acyl-CoA transferase activity^[31]. Furthermore, it contributes to the distorted fatty acid composition of liver lipid droplets by facilitating the differential incorporation of various types of fatty acids^[32,33]. As a result, human PNPLA3 I148M is thought to be responsible for the abnormal efflux and remodeling, but not the influx of hepatic lipid. Omega-3 PUFAs (N3-PUFAs), including EPA and DHA, exert their pharmaceutical activity on liver fat reduction mainly by inhibiting de novo lipogenesis through SREBP-1c and ChREBP downregulation^[34]. Therefore, the PNPLA3 148M allele counteracts the benefit of N3-PUFAs treatment via the limited outflow of liver fat.

Statins

With the exception of PUFAs, the interaction between statin use and PNPLA3 genotype on the risk of NASH was investigated in a multicenter cohort ($n = 107$) of European descent from Italy and Finland^[35]. Each subject underwent liver biopsy due to increased liver enzymes, ultrasonographic evidence of steatosis and risk factors, or routine examination during bariatric surgery. Following different types and different intensities of treatment (49% on simvastatin, 27% on rosuvastatin, 17% on atorvastatin, 4% on pravastatin, and 2% on fluvastatin; 15% on high-intensity, 73% on moderate-intensity, and 12% on low-intensity treatment), statins demonstrated dose-dependent protective effect on steatosis, steatohepatitis, and liver fibrosis for at least 6 mo. In support of the findings in the N3-PUFAs intervention, individuals carrying PNPLA3 I148M alleles were susceptible to the full spectrum of liver damage. Statin use was negatively associated with steatohepatitis in patients without PNPLA3 148M variant diagnosed with NAFLD activity score. NASH is characterized by the excessive accumulation of hepatic free cholesterol on the basis of activated 3-hydroxy-3-methyl-glutaryl coenzyme-A reductase (HMGCR), which acts as the rate-limiting enzyme in cholesterol biosynthesis^[36-38]. As HMGCR inhibitors, statins have been linked to a reduced risk of NAFLD in epidemiological studies^[39]. Therefore, down-regulation of cholesterol synthesis is thought to underlie the therapeutic effects of statins on NAFLD/NASH. In contrast, PNPLA3 I148M inhibits lipid efflux to abolish the statin-dependent decrease in the hepatic cholesterol pool. This may provide a rational explanation for the blunted benefit of statin treatment in patients with the PNPLA3 148M allele.

DPP-4 inhibitors

A 33.1-mo study determined the efficacy of alogliptin (25 mg/d), a selective DPP-4 inhibitor, in 41 biopsy-proven Japanese NAFLD patients with type 2 diabetes mellitus (DM)^[40]. Of the metabolic and biochemical parameters measured, patients with the G-allele at PNPLA3 rs738409 (genotype CG/GG) showed a positive correlation between improvements in hemoglobin A1c (Δ HbA1c) levels and changes in aminotransferases

(Δ ALT and Δ AST). It is also worth noting that patients with the CG/GG genotype, instead of the CC genotype, exhibited significantly greater improvements in TC, TG and hyaluronic acid after their intentional weight loss. As effective medications for glucose metabolism, DPP-4 inhibitors (*i.e.*, sitagliptin, alogliptin) have a beneficial impact on HbA1c which depends on the prolonged half-life of glucagon-like peptide 1^[41,42]. The serum level of ALT has been proved to be significantly correlated with increased fasting plasma glucose (FPG), a consequence of abnormal HbA1c^[43]. The decrease in HbA1c following DPP-4 inhibitor treatment, especially in patients with high HbA1c ($\geq 7.5\%$), is positively associated with amelioration of AST and ALT levels^[44]. Thus, DPP-4 inhibitors are thought to prevent liver injury, including inflammation and hepatocyte ballooning in NAFLD patients with glucolipid dysmetabolism^[45,46].

BARIATRIC SURGERY

Bariatric surgery is currently recommended in NAFLD patients with a BMI ≥ 40 kg/m², or BMI ≥ 35 kg/m² with comorbidities and limited efficacy of diet therapy and/or physical activity^[47-50]. In addition to its effect on weight loss^[51,52] and metabolic parameters^[53,54], bariatric surgery has been demonstrated to improve the pathologic features of NAFLD^[55,56]. Notably, the PNPLA3 polymorphism has an influence on the response of individuals to therapy.

Bariatric surgery, including gastric bypass surgery in 43 individuals and gastric sleeve surgery in 41, was performed in obese adult Caucasian subjects (BMI 35-64 kg/m²)^[57]. Compared with that at baseline, carriers of the PNPLA3 I148M allele M exhibited a higher median weight loss (47 kg, 36.1% of total) than those with genotype II (38 kg, 32.3% of total) 12 mo after bariatric surgery. Consistent with this weight loss, the magnetic resonance imaging-based estimation of the Folch value^[58] revealed a significantly higher decrease in liver fat in patients carrying allele M rather than allele I, with up to 65.5%, 70.7%, and 85.5% of their initial fat content in the II, IM and MM genotypes, respectively. Fifty-seven percent of the study population was diagnosed with moderate-to-severe hepatic steatosis (grade 2 or 3) before surgery^[57], and the improvements in body weight and liver fat led to a diminished percentage of patients with steatosis at the end point. Patients with the MM genotype showed a percentage change higher than those with the II genotype. Multivariate regression analysis further indicated that the PNPLA3 polymorphism and the initial grade of steatosis were the strongest independent predictors of surgical efficacy in non-alcoholic fatty liver. The PNPLA3 polymorphism had no effect on serum ALT activity, which may be attributed to the recruitment of patients in the early stages of NAFLD.

The prospective, controlled Swedish Obese Subjects study, "the SOS study", enrolled individuals (men: BMI ≥ 34 , women: ≥ 38) for bariatric surgery (surgery

Table 1 Effect of Patatin-like phospholipase domain-containing protein 3 rs738409 C > G p.1148M on therapeutic response in nonalcoholic fatty liver disease

Study	Country	Duration	Number	Intervention	Results
Sevastianova <i>et al</i> ^[20] (2011)	Finland, Italy	6 d	18 (all in intervention group)	Hypocaloric (1000-kcal deficit/d), low-carbohydrate diet (< 30 g/d)	Δliver fat ^a
Shen <i>et al</i> ^[19] (2015)	China	12 mo	Intervention group (<i>n</i> = 77), control group (<i>n</i> = 77)	Exercise and limitation on caloric intake	ΔIHTG ^d , ΔBody weight ^c , ΔWC ^c , ΔWHR ^c , ΔTC ^c , ΔHDL-C ^d , ΔWHR ^c
Milkiewicz <i>et al</i> ^[22] (2016)	Poland	4 mo	323 (143 in intervention group; 180 in control group)	Diet with 500 kcal restriction for subjects (BMI > 25); maintenance of body weight for subjects (BMI ≤ 25)	Δliver fat ^e
Scorletti <i>et al</i> ^[28] (2015)	United States	15-18 mo	Omacor [®] : <i>n</i> = 51; placebo: <i>n</i> = 52	Omacor [®] , 4 g/d (460 mg EPA + 380 mg DHA for 1 g Omacor)	Δliver fat ^e
Nobili <i>et al</i> ^[29] (2013)	Italy	24 mo	DHA 250 mg/d (<i>n</i> = 20), DHA 500 mg/d (<i>n</i> = 20), placebo group (<i>n</i> = 20)	DHA 250 mg/d, DHA 500 mg/d, or placebo	Severe steatosis ^{e,h} , TG ⁱ ALT ⁱ
Dongiovanni <i>et al</i> ^[35] (2015)	Italy, Finland	6 mo	107 (all in intervention group)	Drug: simvastatin (49%), rosuvastatin (27%), atorvastatin (17%), pravastatin (4%), fluvastatin (2%) Intensity: high (15%), moderate (73%), low (12%)	Risk of NASH ^k
Kan <i>et al</i> ^[40] (2016)	Japan	33.1 mo	41 (all in alogliptin group)	Alogliptin, 25 mg/d	ΔALT, ΔAST, ΔHbA1c ^m
Krawczyk <i>et al</i> ^[57] (2016)	Spain	12 mo	84 (all in surgery group)	Gastic bypass surgery; gastric sleeve surgery	Δweight ^f , Δliver fat ^o
Palmer <i>et al</i> ^[59] (2012)	Sweden	2 yr; 10 yr	3473 (2 nd year: 1624 in surgery group; 10 th year: 1355 in surgery group)	nonadjustable or adjustable banding; vertical banded gastroplasty; gastric bypass	ΔHOMA-IR ^q , Δserum TG ^q , ΔALT ^s

^a*P* < 0.05, PNPLA3 148M/M *vs* PNPLA3 148I/I; ^c*P* < 0.05, ^d*P* < 0.01, among PNPLA3 148I/I, 148I/M, and 148M/M in intervention group; ^e*P* < 0.05 PNPLA3 148I/I + 148I/M *vs* PNPLA3 148M/M; ^h*P* < 0.001, PNPLA3 148M/M *vs* PNPLA3 148I/I and ⁱ*P* < 0.05, PNPLA3 148I/M *vs* PNPLA3 148I/I; ^j*P* < 0.05, PNPLA3 148M/M *vs* 148I/M; ^k*P* < 0.001, PNPLA3 148I/I *vs* 148I/M or PNPLA3 148I/I *vs* 148M/M; ^mΔHbA1c correlates to ΔALT (*P* = 0.001) and ΔAST (*P* = 0.014) in patients with PNPLA3 rs738409 C/G+G/G; ^o*P* < 0.05, ^p*P* < 0.01, PNPLA3 148I/I *vs* PNPLA3 148I/M+148M/M; ^q*P* < 0.05, among PNPLA3 148I/I, 148I/M, and 148M/M in surgery group (2nd, 10th year); ^s*P* < 0.001, among PNPLA3 148I/I, 148I/M, and 148M/M in surgery group (2nd year). ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; IHTG: Intrahepatic triglyceride content; HbA1c: Hemoglobin A1c; HDL-C: High-density lipoprotein-cholesterol; HOMA-IR: Homeostasis model assessment-insulin resistance; TC: Total cholesterol; TG: Triglycerides; WC: Waist circumference; WHR: Waist-to-hip ratio.

group) or conventional treatment (matched control group)^[59]. In contrast to the matched control group who underwent nonsurgical treatment (sophisticated lifestyle intervention and behavior modification), the surgery group received one surgical procedure (nonadjustable or adjustable banding, vertical banded gastroplasty, or gastric bypass) at baseline^[60]. Weight losses of 25 ± 11%, 16 ± 11%, and 14 ± 14% were documented for gastric bypass, vertical-banded gastroplasty, and banding, respectively, after a 10-year follow-up^[60]. PNPLA3 148M carriers showed a greater reduction in homeostasis model assessment-insulin resistance (HOMA-IR) and plasma ALT, together with a lower reduction in triglyceride levels, in comparison with PNPLA3 148I carriers. The prevalence of biopsy-proven hepatic steatosis increased up to 70% in an obese population (BMI ≥ 30)^[61], and even reached 91% in another ultrasound-based study^[62]. Multivariate analysis provided deeper insight into the significant association between obese-related steatosis and impairment in both insulin sensitivity (e.g., fasting insulin, HOMA-IR)

and glucose metabolism (e.g., FBG)^[59]. Moreover, the occurrence of steatohepatitis markedly increased with grade of obesity, and was approximately 3% in the lean population, 19% in the obese population, and 50% in the morbidly obese population^[63]. Augmentation of serum aminotransferases reflected hepatocyte injury with high sensitivity in these patients with steatohepatitis^[64]. In contrast, according to the Diagnosis and Management of NAFLD guideline, weight reduction leads to the amelioration of NAFLD with steatosis resolution, improved HOMA-IR, and normalization of ALT^[18].

An interesting common result in the two above-mentioned studies^[57,59] was the association between PNPLA3 148M and some measured parameters (e.g., liver fat content) which was abolished after weight loss induced by surgery. Marked weight reduction was achieved in both studies (over 30% weight loss after 12 mo in the former^[57]; 20%-32% weight loss after 1 - 2 years and 14%-25% weight loss after 10 yr in the latter^[60]), and no NAFLD occurred in the majority of the subjects at the end of the follow-up.

CONCLUSION

Taken together, these results show that PNPLA3 rs738409 has a universal, yet distinctly different, impact on the response to various therapies in NAFLD patients independent of age, gender, and ethnic background.

Although the G-allele at PNPLA3 rs738409 (PNPLA3 148M variant) is associated with more severe NAFLD than the C-allele (148I variant), it results in a greater reduction in liver fat following lifestyle modification, bariatric surgery, and pharmacotherapy with DPP-4 inhibitors. The concurrence of weight loss, improved systemic glycolipid metabolism (WHR, TC, TG, LDL, and HbA1c) and decreased intrahepatic fat content highlight an interaction between peripheral adipose tissue and the liver on the actions of the PNPLA3 polymorphism (Table 1). Enhanced systemic insulin sensitivity (*e.g.*, lowered HOMA-IR) with an anti-lipolytic effect and inhibition of periphery-to-liver delivery of FFAs are thought to underlie the benefits of the PNPLA3 rs738409 G-allele over the C-allele. Nevertheless, the hepatoprotective effect, with down-regulated biomarkers of plasma ALT, AST, ALP, and GGT, may not be necessary for the beneficial acquisition.

The risk allele of PNPLA3 rs738409 C > G (PNPLA3 I148M) predisposes NAFLD patients to a poor treatment response to pharmacotherapy (*e.g.*, N3-PUFAs and statins), with increased liver fat percentage and a higher probability of NASH, compared with wild-type PNPLA3 (PNPLA3 148I variant) (Table 1). Both N3-PUFAs, including EPA and DHA, and statins prevent *de novo* lipogenesis. However, the PNPLA3 148M allele inactivates hepatic glycerolipid hydrolysis due to its "loss-of-function" phenotype and minimizes lipid efflux from the liver to peripheral adipose tissues. This may result in a counteracting mechanism to limit the beneficial effect of pharmacotherapy.

NAFLD is well described to be a complex disease with polymorphic association to multiple genes^[6]. Limited number of PNPLA3 variant (*e.g.*, rs738409) among these ones has a significant contribution, whereas variants in TM6SF2^[65], MBOAT7^[66] and GCKR^[67] show the moderate-size effects. Besides, large number of variants in APOB^[68], APOC3^[69], LYPLAL1^[70], MTP^[68], LPIN1^[71], SOD2^[72], UCP2^[73], ENPP1^[74], IRS1^[74], IL28B^[75], KLF6^[76], MERTK^[77], and Irisin^[78] action in a low-effect manner. Effect of any risk variant of NAFLD is unlikely to be clinically meaningful. Nonetheless, the variant-dependent difference in treatment response provides prospect for the personalized risk algorithms and therapeutic strategy of NAFLD.

Given the close association of PNPLA3 polymorphism and NAFLD, patients with the G-allele at PNPLA3 rs738409 are thought to benefit from lifestyle modification, DPP-4 inhibitors, and bariatric surgery, which are characterized by weight loss and improved insulin resistance. NAFLD patients carrying the C-allele demonstrate sensitivity to N3-PUFAs and statin treatment. Therefore, stratification of the PNPLA3 rs738409 genotype may serve as a poten-

tial approach in the precise treatment of NAFLD.

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