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# Pathogenic gene variations in metabolism related fatty liver disease

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**Abstract.** Metabolism related fatty liver disease (MAFLD), or named nonalcoholic fatty liver disease (NAFLD), is a highly hereditary disease closely related to gene mutations. The incidence rate of MAFLD is increasing due to unhealthy eating habits such as unhealthy living habits, high calorie diet and unreasonable dietary structure, which has been affecting modern life. However, there is currently a lack of approved effective drugs for the treatment. Multiple genes have been found to be related to MAFLD. SNP rs738409 on genes, including phospholipase domain protein 3 (PNPLA3), is closely related to MAFLD, which is expressed in various tissues and has particularly high expression levels in the liver and kidneys. Other SNPs, such as transmembrane 6 superfamily member 2 (TM6SF2) rs58542926 and membrane-bound O-acyltransferase 7 (MBOAT7) rs641738, have also been confirmed to be related to MAFLD. The former can reduce liver lipid accumulation through overexpression, and its expression is adapted to contemporary high-fat eating habits (HFD), while the latter drives lysophosphatidylinositol lipidation to inhibit MAFLD. This article summarizes the mutagenesis of PNPLA3, TM6SF2, and MBOAT7 genes and their relationship to pathogenesis, aiming to provide an explanation of three genes and the mechanisms for future research on therapeutic approaches of MAFLD.

**Keywords:** MAFLD, NAFLD, PNPLA3, TM6SF2, MBOAT7.

## 1. Introduction

The daily state of young office workers is generally characterized by prolonged sitting, staring at the computer, staying up late and working overtime, high work pressure, and facing high-pressure environments. People's dietary habits also choose high calories to compensate for stress and fatigue. These unhealthy lifestyles are slowly eroding the health of the liver. A vicious cycle, accompanied by psychological pressure, can increase an individual's rate of developing cardiovascular disease. Meanwhile, cardiovascular disease risks, such as obesity and hypertension, are closely related to common liver problems, such as non-alcoholic fatty liver disease. Under the dual pressure, people's metabolism is disrupted, exacerbating the incidence of metabolic related fatty liver (MAFLD) [1,2].

MAFLD is mainly characterized Malignant changes of hepatic steatosisand Has become the most well-known and frequently seen among usGlobal Liver Disease, affects 40% of the world's population. The other name of MAFLD is Nonalcoholic fatty liver disease (NAFLD). The complexity of MAFLD, At present, there are no approved drugs in the world that can treat this disease for clinical use.Currently, many studies have shown that lipids, carbohydrates, proteins, and micronutrients are metabolic abnormalities that are crucial for the pathophysiology of MAFLD. Current research indicates that lipids,

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carbohydrates, amino acids, and micronutrients are all metabolic abnormalities crucial for the pathophysiology of MAFLD [1]. Insulin resistance is A common pathophysiology with potential. The The unequal relationship between energies intake and consumption leads to insulin resistance in many Human body parts and changes in Intestinal bacteria, leading to Liver lipids storage. Metabolic dysfunction related categories basically include obesity, type 2 diabetes, hypertension, hyperlipidemia and two metabolic syndromes.The role of genetic factors in liver fat accumulation and fibrosis has also been revealed. During the process of liver fat accumulation, intracellular damage and liver insulin resistance can further exacerbate inflammation, fibrosis, and carcinogenesis. The increased supply of fat-producing substrates from other tissues, liver Irs1 allocation, and other factors play a key role in the increased de novo fat production in MAFLD patients with liver insulin resistance [2].

The mutation now affects the functions of three genes: PNPLA3, TM6SF2, and MBOAT7 [2]. It exists in various organs, but is particularly abundant in the liver and kidneys. Romeo et al. found that one allele of the PNPLA3 gene (rs738409; I148M) is associated with high liver fat content and inflammation in PNPLA3 [3]. The gene (rs738409; I148M) is associated with high levels of liver fat and inflammation [3]. The TM6SF2 mutation is a functional loss mutation that links to hepatic steatosis by reducing VLDL-TG production in the liver. Treating hepatic steatosis by reducing VLDL-TG production in the liver. The MBOAT7 mutation leads to a decrease in the expression of MBOAT7 protein in the liver, which is associated with an increase in liver fat storage by inducing changes in phospholipid remodeling. This results in a decrease in the expression of MBOAT7 protein in the liver and an increase in liver fat storage by inducing changes in phospholipid remodeling [2].

This review explains the pathogenic mechanisms of three functional genes, including PNPLA3, TM6SF2, and MBOAT7, in MAFLD and aims to provide insight into the role of MAFLD-repated pathogenic genes.

## 2. PNPLA3

Research has shown that the PNPLA3 rs738409 C>G polymorphism is related to increased risk of HCC [4]. Replacing I148M may result in loss of PNPLA3 functionality [4]. The PNPLA3 variant leads to be damaged the mobilization effect of lipid droplets on TG, which can easily lead to the progression of a type of liver disease injury associated with fatty liver [2]. Through the evaluation of data from 81003 testers on platforms such as PubMed, it was found that the consistent association between rs738409 polymorphism and blood lipid levels was a significant decrease in triglyceride (TG) and total cholesterol (TC) levels [5]. And its polymorphism is also different in different populations. Generally speaking, the association between TG and TC levels of Caucasians is stronger than that of Asians, the association between TG and TC levels of obese people is stronger than that of type 2 diabetes people, and the association between TG and TC levels of adults is stronger than that of children [5]. The impact of three PNPLA3 I148M (rs738409 C/G) variants on MAFLD and disease severity in different populations. Research has found that rs738409 has a significant impact on liver fat accumulation and susceptibility to more invasive diseases. Compared to CC homozygotes, GG homozygotes have a higher risk. However, carrying two G alleles does not seem to increase the risk of severe histological features, and compared to the CC genotype, the rs738409 GG genotype has elevated serum alanine aminotransferase levels [5].

The mechanism of accumulation of triglycerides (TG) and PNPLA3 in hepatic lipid droplets(LD) was studied by using knock in (KI) mice (PNPLA3 148M/M). Table 1 lists the differences in the phenotype of mice (PNPLA3 148M/M) compared to other mice in the experiment, in order to better understand the role of the mouse PNPLA3 gene in mouse metabolism. Therefore, it can be seen that there is no difference in the synthesis, utilization, or secretion of TG between Pnpla3 148M/M and Pnpla3+/+in mouse liver. This is consistent with the fact that TG accumulation is caused by TG mobilization damage in LD. And sucrose feeding is necessary to induce fatty liver in KI mice. This resulted in a more significant and prolonged increase in PNPLA3 protein in KI mice compared to wild-type (WT) mice. Inhibition of bortezomib did not lead to an increase in PNPLA3 levels in PNPLA3 148M/M mice, and only trace amounts of ubiquitinated PNPLA3 were observed in experimental animals.

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However, if macroautophagy (3-methyladenine) is not inhibited, significantly increased levels of PNPLA3 in wild-type mice can be observed. The 148M variant leads to the disruption of PNPLA3 ubiquitination and degradation of related proteases, the accumulation of PNPLA3-148M can impair TG mobilization in LD [6].

## 3. TM6SF2

Using human experiments to study the E167K variant in TM6SF2, genotyping was performed on the E167K (rs58542926) variant in TM6SF2 and the I148M (rs738409) variant in patatin like phospholipase domain protein 3 (PNPLA3). The plasma lipid profiles of E167K carriers (TM6SF2EK/KK) and non carriers (TM6SF2EE) were compared, as well as the plasma lipid profiles between three groups of NAFLD: (i) carriers of E167K but not carrying the I148M variant in PNPLA3 (TM6SF2 NAFLD), (ii) carriers of I148M but not carrying the E167K variant (PNPLA3). PLA3 NAFLD 'and (iii) carriers who do not carry any risk allele ('risk-free NAFLD'). Insulin sensitivity of liver and adipose tissue was measured using normal blood glucose hyperinsulin clamp technique combined with [3-3H] glucose infusion in 111 subjects. Measure their LFAT using 1H-MRS, measure circulating lipids using UPLC-MS, and measure the sensitivity of liver and fat to insulin. Experimental studies have found that insulin affects LFAT levels in E167K carriers. Comparing three NAFLD groups with similar LFAT, it was found that compared with the "risk-free NAFLD" group, the "TM6SF2 NAFLD" and "PNPLA3 NAFLD" groups had significantly lower triglyceride levels and the most common TAG level. The impact of glucose production and fat breakdown is significantly higher than that of non-carriers. It can be concluded that despite a significant increase in LFAT content, insulin sensitivity is maintained in cases of fat breakdown, hepatic glucose production, and lack of hypertriglyceridemia [7].

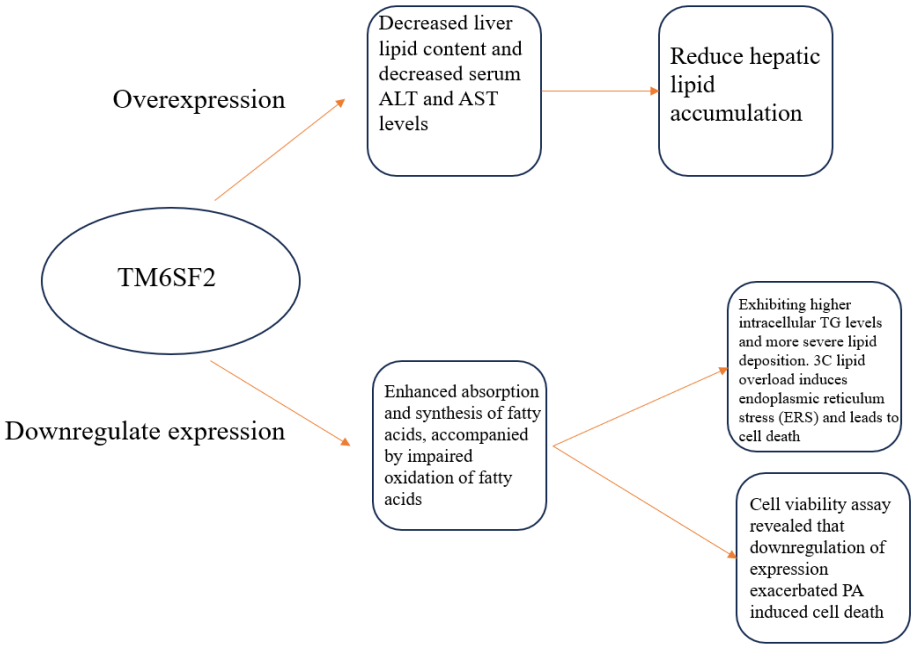


**Figure 1.** TM6SF2 overexpression and downregulation in MAFLD disease. Figure credit: original.

Using a mouse model of NAFLD and 80 samples of human liver, evaluate the expression of TM6SF2 through Western blotting and other methods [8]. RNA sequencing data is obtained from a comprehensive gene expression database and is often used in this experiment to determine whether TM6SF2 has been overexpressed. This can reduce the error in response after TM6SF2 is knocked out or overexpressed.MK-4074 was also employed as a treatment intervention to assess its effectiveness in treating NAFLD induced by TM6SF2 deficiency. Figure 1 shows differential overexpression and downregulation of TM6SF2 in MAFLD disease. The key conclusion is that substituting I148M in

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PNPLA3 does not cause hepatic steatosis by boosting TG production or decreasing TG treatment via fatty acid oxidation or VLDL-TG release. The 148M variation can change the post-translational modifications of PNPLA3. Bortezomib, a proteasome inhibitor, elevated liver PNPLA3-WT levels by almost 15 times in mice, indicating protein polyubiquitination. The findings revealed that liver TM6SF2 levels were higher in NAFLD patients and mice models. Overexpressing TM6SF2 can minimise hepatic lipid buildup, which is favourable for the high-fat diet (HFD). In the simulated TM6SF2 E167K mutation state, there is an imbalance in fatty acid metabolism, which increases after downregulation, resulting in intracellular lipid accumulation. There is a correction phenomenon of NAFLD phenotype caused by TM6SF2 deficiency, which occurs after the use of acetyl CoA carboxylase inhibitor (MK-4074) [8].

## 4. MBOAT7

Membrane bound O-acyltransferase 7 (MBOAT7) and transmembrane 6 superfamily member 2 (TM6SF2) have been found to be associated with lipid metabolism. Research has found that a range of liver diseases, including NAFLD, are associated with mutations rs641738 on MBOAT7 and rs58542926 on TM6SF2. According to relevant research retrieved from databases such as Pubmed and CNKI, analysis shows that except for the allele model, Asians exhibit this reduced risk of NAFLD in all other genetic models, and also in heterozygous and dominant models. Researchers have found that among all inherited individuals and their genes, MBOAT7 rs641738 has been shown to have no association with NAFLD risk. The variant TM6SF2 rs58542926 locus has a lower risk of NAFLD in homozygous, heterozygous, dominant, and recessive models, while MBOAT7 rs641738 is not associated with NAFLD risk in all genetic variants. Generally speaking, the CC genotype of TM6SF2 rs58542926, but MBOAT7 rs641738 and NAFLD are irrelevant to the risk of NAFLD [9].

The relationship between SNPs around the MBOAT7 gene and advanced liver disease has been discovered through genome-wide association studies (GWAS). It has also been found that non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease (ALD), and liver fibrosis are associated with common variations in the MBATA7 gene (rs641738) that lead to decreased expression of MBOAT7.MBOAT7-mediated lysophosphatidylinositol lipidation is an important mechanism for slowing the course of MAFLD. In comparison to the healthy control group, individuals who drank frequently had significantly lower circulating levels of MBOAT7 metabolites.Experiments revealed that, According to genetic studies linking the mutated MBOAT7 to alcohol-related liver cirrhosis, such as phosphophosphatidylinositol containing arachidonic acid and eicosapentaenoic acid, than age-matched healthy controls. It is emphasized that among the heavy drinkers studied, it is found that only a part of the population has reduced MBOAT7 products containing polyunsaturated fatty acids, but the PI of all other types of molecules has not changed. Researchers also investigated the circulating levels of LPI substrates in MBOAT7 and were surprised to find no substantial difference between the control group and alcoholics. Thus, there is a phenomenon related to excessive alcohol consumption in the low blood lipid levels of MBOAT7 products. In addition, liver cells (Mboat7 HSKO) do not have bone marrow specificity, and the lack of Mboat7 can exacerbate liver damage, which is only related to ethanol induced injury and has not been studied elsewhere. In addition, the loss of MBOAT7 function caused by ALD is promoted by the lipid homeostasis of recombinant lysosomes. In MBOAT7-HSKO mice exposed to ethanol, there is usually an imbalance between autophagic flux and lysosomal biosynthesis, which is found to be related to the damage of lysosomal biosynthesis and autophagic volume accumulation caused by transcription factor EB. In this study, the mechanism underlying the imbalance of autophagic flux through lysosomal biosynthesis of large MBOAT7 and ALD processes was extensively explored, emphasizing that ethanol induced liver injury is the primary factor contributing to liver cell specific MBOAT7 deficiency [10].

Although there are multiple gene variants in MAFLD, summarized in Table 1, future research is required to identify other pathgenic gene variants and the potential mechanisms.

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**Table 1.** Gene variants in MAFLD.

| Genes | Mechanisms | Effects | References |
|---|---|---|---|
| PNPLA3 | There is no difference in TG synthesis, utilization, or secretion in the liver of mice | The ubiquitination and proteasomal degradation of PNPLA3 were disrupted by the 148M variant, resulting in the accumulation of PNPLA3-148M and damage to the mobilization of TG in LD. Insulin sensitivity is maintained during periods of fat breakdown, hepatic glucose production, and hypertriglyceridemia deficiency | [6] |
| TM6SF2 | The effect of insulin on glucose production and fat breakdown in the E167K carrier group of TM6SF2 is significantly higher than that in the non carrier group | The ubiquitination and proteasomal degradation of PNPLA3 were disrupted by the 148M variant, resulting in the accumulation of PNPLA3-148M and damage to the mobilization of TG in LD. Insulin sensitivity is maintained during periods of fat breakdown, hepatic glucose production, and hypertriglyceridemia deficiency | [7] |
| MBOAT7 | Loss of MBOAT7 function promotes ALD through recombinant lysosomal lipid homeostasis | Liver cell specific MBOAT7 deficiency is the main driving factor for ethanol induced liver injury | [10] |

## 5. Conclusion

The number of MAFLD patients has continued to increase in high-pressure social environments. Thus, it is critical to understand its pathogenesis. This review aims to understand the pathogenesis of MAFLD from a genetic perspective through the proposed PNPLA3, TM6SF2, and MBOAT7 genes. Firstly, PNPLA3 mutation can damage the mobilization of TG in lipid droplets, which can easily lead to the occurrence of a wide range of liver injury diseases related to fatty liver. The second related gene is TM6SF2, which is a gene responsible for the loss of related functions due to the secretion of liver fat caused by the reduction of VLDL-TG in the liver. The third type is MBOAT7, whose variation leads to a decrease in MBOAT7 protein expression in the liver, which is associated with an increase in liver fat content by inducing changes in phospholipid remodeling. The variation of three genes can indirectly or indirectly induce MAFLD in the human body. Therefore, future studies are required to better understand its pathogenesis, aiming to develop drugs and treatment plans.

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