OPEN ACCESS

**Saudi Journal of Medical and Pharmaceutical Sciences**

Abbreviated Key Title: Saudi J Med Pharm Sci
ISSN 2413-4929 (Print) | ISSN 2413-4910 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

**Original Research Article** **Hepatology**

# Role of Genetic Polymorphism in the Development of Metabolic Associated Fatty Liver Disease among the Family Members of Metabolic Associated Steatohepatitis Cirrhosis Patients

Saiful Islam[1*], SKM Nazmul Hasan[2], Tanvir Ahmad[3], Md. Mahabubul Alam[4], Asma Helen Khan[5], Md. Shahinul Alam[6]

[1]Research Assistant, Department of Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh
[2]Assistant Professor, Department of Hepatology, Shahid Syed Nazrul Islam Medical College, Kishoreganj, Bangladesh
[3]Consultant, Kurmitola General Hospital, Dhaka, Bangladesh
[4]Medical Officer, Department of Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh
[5]Medical Officer, Department of Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh
[6]Professor, Department of Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh

**DOI:** 10.36348/sjmps.2023.v09i12.017 | **Received:** 08.11.2023 | **Accepted:** 21.12.2023 | **Published:** 30.12.2023

***Corresponding author:** Dr. Saiful Islam
Research Assistant, Department of Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh

## Abstract

***Introduction:*** Metabolic associated fatty liver disease (MAFLD) is one of the most common liver diseases worldwide. NAFLD is associated with metabolic syndrome, which consists of obesity, hypertension, diabetes, and hyperlipidemia. This study aimed to identify the role of Genetic polymorphism in the development of metabolic-associated fatty liver disease among the family members of metabolic-associated steatohepatitis cirrhosis patients. ***Methods:*** This was a cross-sectional observational study conducted in the Department of Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh, from January 2015 to December 2016. In this study, 50 patients with NASH cirrhosis attended Hepatology OPD or were admitted to the inpatient department within the study period, and 81 first-degree family members were included after considering inclusion and exclusion criteria. ***Result:*** The mean age was 35.34 ± 10.29 years, and the mean BMI was 25.59 ± 4.28. Serum lipid profiles showed mean HDL at 36.91 ± 7.49 mg/dL and triglycerides at 161.23 ± 59.76 mg/dL. Male predominance (54.32%) was observed among family members. A total of 78% of families had 1st-degree relatives affected by fatty liver. Fatty liver was present in 47 family members (58%), with 36 (76.6%) showing PNPLA3 polymorphism (C/G), compared to 19 (55.9%) in the non-fatty liver group (P=0.033). Comparing metabolic syndrome components, fatty liver family members showed significantly higher serum triglycerides (>150 mg/dL, P=0.001), fasting glucose (>5.6 mmol/L, P=0.003), and HDL <40 mg/dL for males or <50 mg/dL for females. ***Conclusion:*** This study showed that family members of MASH cirrhosis patients show a high prevalence of fatty liver, metabolic abnormalities, and PNPLA3 polymorphism, especially in 1st-degree relatives.

**Keywords:** Genetic polymorphism, Metabolic syndrome, Fatty liver, Steatohepatitis cirrhosis.



## INTRODUCTION

Metabolic associated fatty liver disease (MAFLD) is the present term for NAFLD (Non-Alcoholic Fatty Liver Disease) which is one of the most common liver diseases worldwide. A significant Japanese cohort study found that 29.7% of persons have NAFLD. [1] NAFLD is associated with metabolic syndrome, which consists of obesity, hypertension, diabetes, and hyperlipidemia. [2, 3] For this reason, NAFLD is considered a part of the metabolic syndrome. Non-alcoholic fatty liver disease (NAFL) encompasses a wide range of disorders, including cirrhosis, fibrosis, hepatocellular carcinoma (HCC), non-alcoholic steatohepatitis (NASH), and non-alcoholic fatty liver (NAFL). [3,4,5] It has been determined that several environmental factors, such as lifestyle and enteral environment, affect the development of MASH. However, the disease state in MAFLD is different in individuals with any body mass index or visceral fat. Moreover, twin studies have suggested that NAFLD is inherited. [6] In individuals without symptoms of alcohol abuse or viral hepatitis, twin studies revealed that alanine transaminase (ALT) levels, which mainly indicated the

buildup of liver fat, were a heritable characteristic, with genetic factors explaining more than 60% of the variability.[7] Overall, evidence indicates that about half of steatosis variability, determined by biochemical indices or noninvasive assessment of liver fat, is inherited. [8] Therefore, several hypothesis-driven studies tried to evaluate the role of candidate genetic variants in the susceptibility to NAFLD and progressive NASH, to identify disease markers or potential drug targets, but with inconsistent results.[8]

PNPLA3, alternatively referred to as adiponutrin, encodes a 481 amino acid protein that is highly expressed in the liver and plays a role in the hydrolysis of triglycerides. [9,10]

The rs738409 single-nucleotide polymorphism (SNP) in the PNPLA3 gene is a missense variation, in particular isoleucine to methionine substitution at amino acid 148 (I148) that results in the abolishment of triglyceride lipase activity, which interferes with hepatic triglyceride hydrolysis, leading to decreased incorporation into very low-density lipoprotein (VLDL) and increased intracellular triglyceride content. [11,12]

A genome-wide association study also revealed that the rs738409 SNP in patatin-like phospholipase domain-containing 3 (PNPLA3) is strongly associated with hepatic fat content. [5] Recently, Kumari et al. (2012) showed that PNPLA3 I148 substitution increases TG synthesis by converting lysophosphatidic acid (LPA) into phosphatidic acid, leading to hepatic steatosis.[13]

NAFLD has a strong association with insulin resistance and other components of metabolic syndrome (MS), like Type 2 DM, central obesity, hyperlipidemia as well as hypertension. The etiology of severe non-alcoholic fatty liver disease (NAFLD) is complicated and involves metabolic, genetic, and environmental factors. Nearly 90.0% and 33.0% of NAFLD patients have a four to eleven times higher risk and are less likely to remit when MS is present. At least one MS feature and all MS characteristics were present in NAFLD individuals, respectively. The majority of NAFLD patients are obese, which increases their risk of steatosis by around five times. Those with impaired fasting glucose have a considerable risk of non-alcoholic fatty liver disease (NAFLD), even if their risk is smaller than that of type 2 diabetes mellitus (T2DM).
Therefore, in this study, we aimed to identify the role of Genetic polymorphism in the development of metabolic-associated fatty liver disease among the family members of metabolic-associated steatohepatitis cirrhosis patients.

## METHODOLOGY AND MATERIALS

This was a prospective observational study conducted in the Department of Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh, from January 2015 to December 2016. In this study, 50 patients with MASH cirrhosis attended Hepatology OPD or were admitted to the inpatient department within the study period, and 81 first-degree family members were included after considering inclusion and exclusion criteria.

These are the following criteria to be eligible for enrollment as our study participants: a) Patients aged from 18 years to 70 years; b)Patients with biopsy-proven cirrhosis; c) Patients with coarse hepatic parenchyma on ultrasonogram with esophageal varices in endoscopy; d) Patients with liver stiffness measurement of greater than 14 Kpa; e) Patients with the chronic liver disease having signs of decompensation; f) First-degree relative of the index patients who were willing to participate were also included in the study And a) Patient with significant alcohol intake (more than 30 gm/day in case of male and more than 20 gm/day in case of female); b) Patients receiving drugs that may cause fatty liver (i.e. tamoxifen, valproate, amiodarone and methotrexate); c) Patients with any other liver diseases i.e (Chronic viral hepatitis, Wilson's disease, Autoimmune liver diseases, Hemochromatosis); d) Patients with Pregnancy, hypothyroidism & liver cirrhosis other than MASH; e) Patients with any history of acute illness (e.g., renal or pancreatic diseases, ischemic heart disease, asthma, COPD, etc.); f) Patients who were not willing to participate were excluded from our study.

**Statistical Analysis**

All data were recorded systematically in preformed data collection form. Quantitative data was expressed as mean and standard deviation and qualitative data was expressed as frequency distribution and percentage. The differences between groups were analyzed by unpaired t-test and chi-square ($X^2$) test. A p-value <0.05 was considered as significant. Statistical analysis was performed by using SPSS 20 (Statistical Package for Social Sciences) for Windows version 10. Ethical approval was taken from the Institutional Review Board (IRB) of Bangabandhu Sheikh Mujib Medical University.

## RESULTS

**Table 1: Baseline characteristics of the family members.**

| Parameter | Family members (Mean±SD) |
|---|---|
| Age (year) | 35.34±10.29 |
| Waist circumference (cm) | 91.18±8.21 |
| Systolic BP (mm of Hg) | 112.59±9.84 |
| Diastolic BP (mm of Hg) | 73.82±6.23 |
| BMI (Kg/m$^2$) | 25.59±4.28 |
| Fasting blood sugar (mmol/L) | 5.28±2.14 |
| Total cholesterol (mg/dl) | 187.10±33.66 |
| LDL (mg/dl) | 114.92±21.45 |
| HDL (mg/dl) | 36.91±7.49 |
| TG (mg/dl) | 142.03±60.41 |
| AST (U/L) | 35.53±21.98 |
| ALT (U/L) | 36.81±35.40 |

Table 1 shows the baseline characteristics of the family member's mean age was 35.34±10.29. The mean waist circumference was 91.18±8.21, which is above the metabolic range. Mean systolic BP and diastolic BP were 112.59±9.84 and 73.82±6.23 mmHg respectively. The mean BMI was 25.59±4.28 kg/m$^2$, which is at the obese level. Mean fasting blood sugar 5.28±2.14 mmol/L. The serum lipid profile of family members shows that mean total cholesterol was 187.10±33.66 mg/dL, mean LDL 114.92±21.45 mg/dL, mean HDL 36.91±7.49 mg/dL, and mean triglyceride was 36.91±7.49 mg/dL. Regarding liver enzymes, the mean AST was 35.53±21.98 U/L, and the mean ALT was 36.81±35.40 U/L. It was observed that family members were relatively younger, had high BMI and waist circumference was above metabolic range.

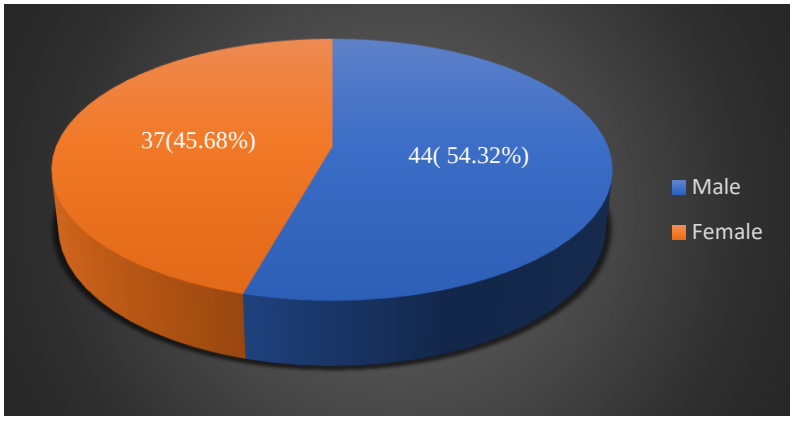


**Figure 1: Sex distribution of family member groups**

The pie chart shows that among the 81 family members evaluated 44 (54.32%) were male and 37 (45.68%) were female. A male predominance was observed.

**Table 2: Affected number of families with fatty liver and PNPLA3 Genotype (n=50)**

| Fatty liver on USG | Frequency | Percent |
|---|---|---|
| Fatty change in liver | 39 | 78 |
| No fatty change in the liver | 11 | 22 |
| Total no of family | 50 | 100.0 |
| PNPLA3 Genotype | **Frequency** | **Percent** |
| C/G + G/G | 39 | 78 |
| C/C | 11 | 22 |
| Total | 50 | 100.0 |

Table 2 shows the number of affected families in whom fatty liver was found in either siblings or the next generation. A maximum number of families (78%) had affected 1st-degree relatives. The number of affected families in whom PNPLA3 polymorphism either in the form of C/G or G/G in siblings or the next generation. The maximum number of families (78%) had affected 1st-degree relatives.

**Table 3: Relationship between PNPLA3 genotyping with and without fatty liver**

| Genotype | With fatty liver (n=47) | | Without fatty liver (n=34) | | P-value |
|---|---|---|---|---|---|
| | No | % | No | % | |
| C/C | 09 | 19.1 | 15 | 44.1 | 0.033 |
| C/G | 36 | 76.6 | 19 | 55.9 | |
| G/G | 02 | 4.3 | 00 | 00 | |

Table 3 shows the relationship between the PNPLA3 genotyping with and without fatty liver. Among 47 family members with fatty liver, 36 (76.6%) of them had PNPLA3 polymorphism variety C/G and 02 (4.3%) of them had PNPLA3 polymorphism variety G/G. Among 34 family members without fatty liver, 19 (55.9%) of them had PNPLA3 polymorphism variety C/G and 15 (44.1%) of them had PNPLA3 polymorphism variety C/C. The difference between the two groups is statistically significant (P=0.033). It was observed that the frequency of genetic polymorphism was significantly higher among the fatty liver groups.

**Table 4: Pattern of Fatty liver, PNPLA3 polymorphism among family members**

| PNPLA3 | Son (n=38) | | Daughter (n=31) | | Brother (n=06) | | Sister (n=06) | |
|---|---|---|---|---|---|---|---|---|
| | FL n=22 (57.89%) | Normal n = 16 (42.10%) | FL n =16 (51.6%) | Normal n =15 (48.4%) | FL n = 05 (83.3%) | Normal n=01 (16.7%) | FL n=04 (66.7%) | Normal n=02 (33.3%) |
| C/C | 06(27.27%) | 06(37.5%) | 02(12.5%) | 05(33.3%) | 02(40%) | 01(100%) | 01(25%) | 01(50%) |
| C/G | 14(63.63%) | 10(62.5%) | 14(87.5%) | 10(66.7%) | 03(60%) | | 03(75%) | 01(50%) |
| G/G | 02(9.09%) | 00 | | | | | | |

Table 4 shows that among the 81 family members we evaluated, 38 were sons, 31 were daughters, 06 brothers, and 06 sisters of the MASH cirrhosis patients. Out of 38 sons, 22(57.89%) have fatty liver on ultrasonogram and 16(42.10%) have normal liver on ultrasonogram. Of these 22 fatty liver son PNPLA3 polymorphism was found in 16 person, 02(9.09%) with G/G and 14(63.63%) with C/G. Among 31 daughters, fatty liver was found in 16 (51.6%) daughters, and 14(87.5%) of them had PNPLA3 polymorphism with C/G. 15(48.4%) daughters found normal on ultrasonogram and 10(66.7%) of them had PNPLA3 polymorphism with C/G. A total of 06 brothers were evaluated among 05(83.3%) who were found fatty livers and 03(60%) of them had PNPLA3 polymorphism with C/G. A total of 06 sisters were evaluated among 04 (66.7%) who were found fatty livers and 03(75%) of these 04 sisters had PNPLA3 polymorphism with C/G. So, it was observed that sons and daughters are equally affected by fatty liver but the rate of genetic polymorphism was relatively higher in daughters.

**Table 5: Distribution of MASH Cirrhosis patients according to metabolic syndrome**

| Metabolic syndrome | Frequency | Percent % |
|---|---|---|
| DM<br>FBS (≥110 mg/dl) | 38 | 76 |
| Waist circumference (cm)<br>>80 for female, >90 for male | 47 | 94 |
| Dyslipidemia<br>TG>150mg/dl, HDL (M<40 mg/dl, F<50 mg/dl), | 44 | 88 |
| HTN<br>BP (>130/>85 mmHg) | 28 | 56 |

Table 5 shows the distribution of MASH cirrhosis patients according to components of metabolic syndrome. Among 50 MASH cirrhosis patients 38(76%) had diabetes mellitus, dyslipidemia characterized by raised Triglyceride (>150 mg/dl), reduced HDL cholesterol (M<40 mg/dl, F<50 mg/dl) found in 44(88%) of patients. Waist circumference above the metabolic range was found in 47(94%) of patients. Hypertension was also common and found in 28(56%) patients. Most of the patients showed at least two or more components of metabolic syndrome.

**Table 6: Comparison of metabolic syndrome between two groups of family members with or without fatty liver.**

| Variables | With fatty liver (n=47) | | Without fatty liver (n=34) | | P-value |
|---|---|---|---|---|---|
| | No | % | No | % | |
| Waist circumference (cm) >80 for female, 90 for male | 36 | 80.0 | 23 | 63.9 | 0.105 |
| Serum triglycerides >150 mg/dl | 24 | 54.5 | 6 | 16.7 | 0.001 |
| Fasting blood glucose >5.6 mmol/L | 13 | 28.9 | 1 | 2.9 | 0.003 |
| HDL (mg/dl) <40 for males <50 for female | 10 | 22.7 | 10 | 27.8 | 0.606 |
| Blood pressure (mmHg) >130 SBP, 85 DBP | 2 | 4.4 | 0 | 00 | 0.203 |

Table 6 shows the distribution of metabolic syndrome in family members. Comparison of different components of metabolic syndrome of these two groups showed Waist circumference (cm) (>80 for females, >90 for males), 36 (80.0%) in the fatty liver group and 23(63.9%) in the without fatty liver group. Serum triglycerides > 150(mg/dl) are found in 24 (54.5%) in the fatty liver group and 06 (16.7%) in the without fatty liver group. The difference is statistically significant (P = 0.001) between the two groups. Fasting blood glucose >5.6 mmol/L is found 13 (28.9%) in the fatty liver group and 01 (2.9%) in the without fatty liver group. The difference is statistically significant (P = 0.003) between the two. HDL <40 mg/dl for males and <50 mg/dl for females was found 34 (77.3%) in the fatty liver group and 26 (72.2%) in the without fatty liver group.

## DISCUSSION

This study comprised 50 MASH cirrhosis patients and their 81 1st degree relatives to identify the role of Genetic polymorphism in the development of metabolic-associated fatty liver disease among the family members of metabolic-associated steatohepatitis cirrhosis patients.

MAFLD has an association with serious cardiometabolic abnormalities, including type -2 diabetes mellitus, metabolic syndrome, and coronary heart disease. With the increasing prevalence of obesity, diabetes, and metabolic syndrome in the general population, metabolic associated fatty liver disease (MAFLD) has become the most common cause of chronic liver disease in Western countries as well as lower BMI areas such as in regions of Asia.

In the present study, the mean age of the family members was 35.34±10.29 years with a range from 18-66 years. The mean age of the participants in the study by Alam et al. (2013) was 40.8 ± 10.2 years. [1] Of the patients with MASH cirrhosis in this research, 28 (56%) of them were female. A similar female majority (57%) was seen in other studies. [1, 14] There is growing evidence that both hereditary and environmental factors have a role in the development of NAFLD. [15] In recent years, genetic determinants of steatosis have been revealed using genome-wide association studies,[5] among which PNPLA3 gene polymorphism has been identified as a major genetic determinant for the predisposition to NAFLD in different ethnic populations.

NAFLD is strongly associated with insulin resistance and other components of the metabolic syndrome, like Type 2 DM, central obesity, hyperlipidemia, and hypertension.[16] The occurrence of NAFLD is reported to range from 60–95% in obese patients, 28–55% in Type 2 DM patients, and 27–92% in hyperlipidemic patients. [17] Some investigations have previously reported an association between increased abdominal obesity and hepatic steatosis.[18] Obesity is the condition most often reported in association with MAFLD. In morbidly obese patients (BMI >35 kg/m$^2$), the frequency of NAFLD is as high as 90%, with advanced disease (i.e. NASH) seen in 9% to 40%. [19]

Regarding PNPLA3 polymorphism 85% of MASH cirrhosis patients had genetic polymorphism either in the form of C/G or G/G. These findings are similar to previous studies done by Xu et al, 2015.[20] Strong evidence of an association was detected between the PNPLA3 polymorphism and MASH risk under the additive model.

Based on ultrasonographic findings of the hepatobiliary system, we found 47 (58.02%) family members in the group with fatty liver and 34(41.98%) family members in the group without fatty liver. The estimated prevalence of NAFLD is 20–30% and for NASH it is estimated at 3.5–5%.[21] The probable reason behind this is that genetic predisposition is triggered by several other environmental factors like insulin resistance, DM, metabolic syndrome, sedentary lifestyle, etc.

The present study successfully replicated the findings of an association of the PNPLA3 variant with NAFLD in the population as was observed in several studies, where they showed a positive association between genetic polymorphism in the PNPLA3 gene particularly those having the G allele with the development of NAFLD. [22-24]

The maximum number of families (78%) had affected 1st degree relatives by fatty liver and genetic polymorphism. To explore the pattern of involvement of fatty liver among the family members and distribution of genotype frequency we further subdivided the 1st degree relatives for better analysis. 38 were sons, 31 were daughters, 06 brothers and 06 sisters of MASH cirrhosis patients. It was observed that sons and daughters are equally affected by fatty liver, but the rate of polymorphism was found more among the daughters and sisters.

A comparison of different components of metabolic syndrome between two groups of family members shows BMI, serum triglyceride, total cholesterol, fasting blood sugar, AST, and ALT levels are significantly higher in the fatty liver group. This result is similar to a previous study done by Bajaj et al. 2007, where they found significantly higher values of BMI, fasting blood sugar, total cholesterol, and triglyceride levels in the NAFLD group in comparison to the healthy group. [25]

The majority of people with metabolic associated fatty liver disease (MAFLD) have several risk factors, including central obesity, type 2 diabetes mellitus, and hyperlipidemia, while some affected individuals may not have all recognized risk factors. The risk and severity of MAFLD increase with the number of metabolic syndrome components. [26]

**Limitations of the study**

Our study was a single-center study. The sample size was small due to our short study period. After evaluating those patients and their family members, we did not follow up with them for the long term and did not know of other possible interference that may happen in the long term with these patients.

## CONCLUSION AND RECOMMENDATIONS

This study's findings show that PNPLA3, a genetic polymorphism, is a significant contributor to the development of metabolic-associated fatty liver disease among family members of patients with metabolic-associated steatohepatitis cirrhosis. People with fatty liver were shown to have a higher prevalence of the PNPLA3 polymorphism, namely the C/G genotype, than those without it. Significant metabolic abnormalities were also observed in family members with fatty livers, including higher fasting glucose levels, reduced HDL cholesterol, increased waist circumference, and elevated triglycerides—all key components of metabolic syndrome.

So further study with a prospective and longitudinal study design including a larger sample size needs to be done to validate the findings of our study.

***Funding:*** *No funding sources*
***Conflict of interest:*** *None declared*
***Ethical approval:*** *This study was approved by the ethical review committee*

## REFERENCES

1. Alam S, Noor EASM, Chowdhury ZR, Alam M, Kabir J. Nonalcoholic steatohepatitis in nonalcoholic fatty liver disease patients of Bangladesh. World J Hepatol. 2013 May 27;5(5):281-7.
2. Ruhl C, Everhart J. Determinants of the association of overweight with elevated serum alanine aminotransferase activity in the United States. Gastroenterology. 2003 Jan;124(1):71-9.
3. Amarapurkar D, Kamani P, Patel N, Gupte P, Kumar P, Agal S, et al. Prevalence of non-alcoholic fatty liver disease: population-based study. Ann Hepatol. 2007 Jul-Sep;6(3):161-3.
4. Clark JM. Epidemiology of Non-alcoholic Fatty Liver Disease in Adults. J Clin Gastroenterol. 2006 Jan;40(1 Suppl):S5-10.
5. Romeo S, Kozlitina J, Xing C, Pertsemlidis A, Cox D, Pennacchio LA, et al. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. Nat Genet. 2008 Dec;40(12):1461-5.
6. Baulande S, Lasnier F, Lucas M, Pairault J. Adiponutrin, a transmembrane protein corresponding to a novel dietary-and obesity-linked mRNA specifically expressed in the adipose lineage. J Biol Chem. 2001 Sep 28;276(36):33336-44.
7. Makkonen J, Pietiläinen KH, Rissanen A, Kaprio J, Yki-Järvinen H. Genetic factors contribute to variation in serum alanine aminotransferase activity independent of obesity and alcohol: A study in monozygotic and dizygotic twins. J Hepatol. 2009 May;50(5):1035-42.
8. Dongiovanni P, Anstee QM, Valenti L. Genetic predisposition in NAFLD and NASH: impact on severity of liver disease and response to treatment. Curr Pharm Des. 2013;19(29):5219-38.
9. Baulande S, Lasnier F, Lucas M, Pairault J. Adiponutrin, a transmembrane protein corresponding to a novel dietary- and obesity-linked mRNA specifically expressed in the adipose lineage. J Biol Chem. 2001 Sep 28;276(36):33336-44.
10. Lake AC, Sun Y, Li JL, Kim JE, Johnson JW, Li D. Expression, regulation, and triglyceride hydrolase activity of Adiponutrin family members. J Lipid Res. 2005 Nov;46(11):2477-87.
11. He S, McPhaul C, Li JZ. A sequence variation (I148M) in PNPLA3 associated with nonalcoholic fatty liver disease disrupts triglyceride hydrolysis. J Biol Chem. 2010 Mar 5;285(9):6706-15.
12. Pirazzi C, Adiels M, Burza MA, Mancina RM, Levin M, Ståhlman M, et al. Patatin-like phospholipase domain-containing 3 (PNPLA3) I148M (rs738409) affects hepatic VLDL secretion

in humans and in vitro. J Hepatol. 2012 Dec;57(6):1276-82.
13. Kumari M, Schoiswohl G, Chitraju C, Paar M, Cornaciu I, Rangrez AY, et al. Adiponutrin Functions as a Nutritionally Regulated Lysophosphatidic Acid Acyltransferase. Cell Metab. 2012 May 2;15(5):691-702.
14. Mohan V, Farooq S, Deepa M, Ravikumar R, Pitchumoni CS. Prevalence of non-alcoholic fatty liver disease in urban south Indians in relation to different grades of glucose intolerance and metabolic syndrome. Diabetes Res Clin Pract. 2009 Jan;84(1):84-91.
15. Day CP. From fat to inflammation. Gastroenterology. 2006 Jan;130(1):207-10.
16. Clark JM, Brancati FL, Diehl AM. The prevalence and etiology of elevated aminotransferase levels in the United States. Am J Gastroenterol. 2003 May;98(5):960-7.
17. Angulo P, Hui JM, Marchesini G , Bugianesi E, George J, Farrell G, et al. The NAFLD fibrosis score: A noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology. 2007 Apr;45(4):846-54.
18. Pang Q, Zhang JY, Song SD, Qu K, Xu X, Liu SS, Liu C. Central obesity and nonalcoholic fatty liver disease risk after adjusting for body mass index. World J Gastroenterol. 2014 Feb 28;21(5):1650-62.
19. Dixon J, Bhathal P, O'Brien P. Nonalcoholic Fatty Liver Disease: Predictors of Nonalcoholic Steatohepatitis and Liver Fibrosis in the Severely Obese. Gastroenterology. 2001 Jul;121(1):91-100.
20. Xu R, Tao A, Zhang S, Deng Y, Chen G. Association Between Patatin-Like Phospholipase Domain Containing 3 Gene (PNPLA3) Polymorphisms and Nonalcoholic Fatty Liver Disease: A Huge Review and Meta-Analysis. Sci Rep. 2015;5:9284.
21. Browning JD, Szczepaniak LS, Dobbins RL, Nuremberg P, Horton JD, Cohen JC, et al. Prevalence of hepatic steatosis in an urban population in the United States: Impact of ethnicity. Hepatology. 2004 Dec;40(6):1387-95.
22. Hotta K, Yoneda M, Hyogo H, Ochi H, Mizusawa S, Ueno T, et al. Association of the rs38409 polymorphism in PNPLA3 with liver damage and the development of nonalcoholic fatty liver disease. BMC Med Genet. 2010;11:172.
23. Rotman Y, Koh C, Zmuda J, Kleiner DE, Liang TJ. The association of genetic variability in patatin-like phospholipase domain-containing protein 3 (PNPLA3) with histological severity of nonalcoholic fatty liver disease. Hepatology. 2010 Sep;52(3):894-903.
24. Sookoian S, Pirola CJ. Meta-analysis of the influence of I148M variant of patatin-like phospholipase domain containing 3 gene (PNPLA3) on the susceptibility and histological severity of nonalcoholic fatty liver disease. Hepatology. 2011 Jun;53(6):1883-94.
25. Bajaj S, Nigam P, Luthra A, Pandey RM, Kondal D, Bhatt SP, et al. A case-control study on insulin resistance, metabolic co-variates & prediction score in non alcoholic fatty liver disease. Indian J Med Res. 2009 Mar;129(3):285-92.
26. Marchesini G, Bugianesi E, Forlani G, Cerrelli F, Lenzi M, Manini R, et al. Nonalcoholic fatty liver, steatohepatitis and the metabolic syndrome. Hepatology. 2003 Apr;37(4):917-23.