

Association of the TM6SF2 rs58542926 Polymorphism with Non-Alcoholic Fatty Liver Disease in Lean and Non-Lean Adults: A Case Control Study

Running Title: TM6SF2 Polymorphism in Lean and Non-Lean NAFLD

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ABSTRACT

Introduction: Non-alcoholic fatty liver disease (NAFLD) is commonly associated with obesity and metabolic dysfunction but also occurs in lean individuals. Genetic variation in TM6SF2 may contribute to hepatic fat accumulation independently of body mass index. **Aim:** To assess the association of the TM6SF2 rs58542926 polymorphism with NAFLD and compare its distribution and clinical characteristics between lean and non-lean participants. **Materials and Methods:** This case-control study included 100 adults (50 cases and 50 controls) recruited at Era's Lucknow Medical College and Hospital. Participants were classified as lean (BMI ≤ 22.9 kg/m²) or non-lean (BMI ≥ 23 kg/m²). TM6SF2 rs58542926 was genotyped using polymerase chain reaction-restriction fragment length polymorphism. Clinical, biochemical and anthropometric characteristics were compared using appropriate parametric or non-parametric tests, and categorical variables were compared using the Chi-square or Fisher's exact test, as applicable. A p-value < 0.05 was considered statistically significant. **Results:** The overall TM6SF2 genotype distribution differed significantly between cases and controls ($p = 0.007$). The CT genotype was more frequent among cases than controls (44.0% versus 18.0%). Genotype distribution did not differ significantly between lean and non-lean participants. Lean cases had numerically higher high-density lipoprotein cholesterol and lower triglyceride concentrations and less severe ultrasonographic fatty liver than non-lean cases; however, these biochemical comparisons require interpretation with their corresponding measures of variability and p-values. **Conclusion:** The TM6SF2 rs58542926 genotype distribution differed between participants with and without NAFLD. However, no significant difference was demonstrated between lean and non-lean subgroups. Larger, adequately powered studies are required to determine whether BMI modifies this genetic association.

Keywords: Body Mass Index; Fatty Liver; Genetic Association Studies; Polymorphism, Single Nucleotide; TM6SF2 Protein, Human.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a chronic condition characterized by the accumulation of excessive fat in the liver in the absence of significant alcohol intake [1]. It is one of the most common liver diseases worldwide, affecting approximately 25% of the general population and up to 75% of individuals with obesity and type 2 diabetes [1, 2]. The development of NAFLD is driven by a combination of genetic and environmental factors, including diet and physical activity [3–5]. NAFLD encompasses a spectrum of liver conditions, ranging from simple

steatosis to non-alcoholic steatohepatitis (NASH), which involves liver inflammation, hepatocyte injury, and fibrosis [2, 6]. Additionally, NAFLD is linked to an increased risk of cardiovascular disease, chronic kidney disease, and mortality, making it a significant global public health issue. Therefore, understanding the pathogenesis and risk factors associated with NAFLD is crucial for developing effective prevention and treatment strategies.

Although NAFLD is typically linked to obesity and metabolic syndrome, it can also be found in lean individuals [7–11]. Globally, the prevalence of NAFLD

among lean individuals ranges from 7% to 25% [12-14]. Researchers have identified two subtypes of lean NAFLD: type 1, which is associated with visceral fat accumulation and insulin resistance, and type 2, which is linked to hepatic steatosis due to monogenic disorders [15]. Approximately 70% of lean NAFLD cases fall under type 1, while type 2 accounts for around 30% [16]. Despite these classifications, the underlying mechanisms of lean NAFLD are still not fully understood. Research has demonstrated connections between lean NAFLD and factors such as demographics, metabolic syndrome, and genetic predisposition [12-15,17]. For instance, a study of lean Asian Indians showed that Asian Indian men had higher rates of insulin resistance compared to Black, Caucasian, and Hispanic men [18]. This study also found that the prevalence of NAFLD in lean Indian individuals was significantly higher than in Western populations. The clinical identification of lean NAFLD often uses body mass index (BMI) cut-offs or percentiles, which can vary across studies, potentially affecting the comparability and generalizability of findings. Overall, the mechanisms driving NAFLD in lean individuals may differ from those in obese individuals, leading to unique clinical outcomes [19,20].

Recent research has highlighted genetic and epigenetic changes associated with an increased risk of NAFLD. Several genes involved in lipid metabolism, insulin resistance, inflammation, and fibrosis have been linked to the development and progression of NAFLD [21]. While many lean individuals with NAFLD share similar clinical features and genetic predispositions with non-lean individuals, some cases may result from rare genetic mutations [15]. The collective effect of common genetic variants, or polymorphisms, associated with NAFLD may also explain why lean individuals develop hepatic steatosis despite having a lower BMI [15,17,22]. Recent studies have identified several factors related to NAFLD in lean individuals, including male sex, elevated triglyceride levels, liver transaminase levels, visceral fat accumulation, and genetic variants such as rs58542926 and rs738409 [17].

Genetic variations, particularly in genes such as *TM6SF2*, are increasingly recognized as key contributors to the development of NAFLD. The rs58542926 polymorphism in the *TM6SF2* gene has been associated with a higher risk of hepatic fat accumulation and fibrosis, regardless of body mass index (BMI) [15]. This study is designed to investigate the relationship between the rs58542926 polymorphism in the *TM6SF2* gene and NAFLD in both lean and non-lean individuals. By examining the genetic factors contributing to NAFLD in these groups, the study aims to enhance our understanding of the disease's underlying mechanisms and identify potential strategies for prevention and treatment that take into account both genetic and environmental factors.

MATERIALS AND METHODS

Ethical Considerations and Confidentiality

Ethical approval was obtained from the Institutional Ethics Committee of Era's Lucknow Medical College and Hospital, Lucknow, before commencement of the study (approval number: to be provided). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, revised in 2013. Written informed consent was obtained from all participants before enrolment. Unique identifiers were used to maintain participant confidentiality, and study data were accessible only to authorised personnel.

Study setting

This case-control study, conducted over 24 months (March 2020 to March 2022) at the Department of Medicine, Era's Lucknow Medical College and Hospital, involved both inpatient and outpatient services for participant recruitment. The study included adults aged 18-65 years with sonographic evidence of fatty liver, confirmed via abdominal ultrasound. Exclusion criteria encompassed individuals with a history of alcohol intake, chronic hepatitis infections (such as hepatitis B or C), autoimmune hepatitis, critically ill patients, pregnant women, and those with chronic end-organ diseases like heart failure or renal disease.

Clinical Evaluation and Data Collection

A detailed clinical evaluation, including medical history and physical examination, was conducted for all participants. Anthropometric measurements such as BMI and waist circumference were recorded. Based on the World Health Organization (WHO) Asian BMI classification, participants were categorized into lean ($\text{BMI} \leq 22.9 \text{ kg/m}^2$) and non-lean ($\text{BMI} \geq 23 \text{ kg/m}^2$) groups. Clinical data included sonographic evaluation for fatty liver graded into mild, moderate, and severe based on hepatic echogenicity and visualization of intrahepatic vessels and diaphragm.

Blood Sample Collection and Processing

Venous blood samples were collected in 5 ml EDTA vials from all participants. Samples were stored and transported to the central research laboratory within 1-2 days and kept at -20°C for further processing. Genomic DNA was extracted from blood samples using the standard phenol-chloroform extraction method. The quantity and quality of the extracted DNA were checked using spectrophotometric methods, and samples were stored at -20°C until further evaluation. Polymerase chain reaction (PCR) was performed to amplify the *TM6SF2* gene.

Genotyping

Primers used for PCR:

Sense primer: F: CCAGGTGTTGTCTCAAGTGG

Antisense primer: R:
CCAGGTGTTGTCTCAAGTGG

The PCR procedure was carried out using 300–500 ng of genomic DNA in a total reaction volume of 25 µL. The reaction mixture contained 200 µM of dNTPs, 10 pmol of each primer, 1.5 mM MgCl₂, and 1 unit of Taq polymerase enzyme in a 10 mM PCR buffer. The PCR cycling conditions were as follows: an initial denaturation step at 95°C for 5 minutes, followed by 35 cycles of denaturation at 95°C for 1 minute, annealing at 60°C for 1 minute, extension at 72°C for 45 seconds, and a final extension step at 72°C for 5 minutes. The PCR products were visualized on a 2% agarose gel, and the genotypes were determined through restriction fragment length polymorphism (RFLP) analysis using the Hpy188I restriction enzyme. The digested PCR products were separated on 3% agarose gel and visualized under a UV transilluminator.

Data Collection and Statistical Analysis

Clinical, anthropometric and laboratory data were recorded systematically. Continuous variables were summarised as mean±standard deviation or median (interquartile range), according to their distribution, and categorical variables as frequency and percentage. Between-group comparisons used the independent-samples t-test or Mann-Whitney U test for continuous variables and the Chi-square test or Fisher's exact test

for categorical variables, as applicable. The overall genotype distribution was compared before evaluating individual genetic models. Logistic regression was planned to estimate the association between TM6SF2 rs58542926 and NAFLD. Effect estimates should be reported as odds ratios with 95% confidence intervals. All tests were two-sided, and p<0.05 was considered statistically significant. The statistical software and version should be specified before submission.

RESULTS

Demographic Characteristics of Study Population

This table presents the demographic characteristics of the 100 participants, divided equally between the cases (N=50) and controls (N=50). The gender distribution shows that 44.0% of cases were male and 56.0% were female, while the control group had 48.0% males and 52.0% females, with no significant difference (p=0.688). Regarding BMI, 42.0% of the cases were categorized as lean (BMI ≤ 22.9 kg/m²), while 58.0% were non-lean (BMI ≥ 23 kg/m²). In the control group, 44.0% were lean, and 56.0% were non-lean, with no significant difference between groups (p=0.687). The mean age for males in the case and control groups was 55 ± 1.4 and 54 ± 1.2 years, respectively (p=0.396), and for females, it was 47 ± 1.3 and 45 ± 1.1 years (p=0.538), indicating no significant age difference between cases and controls by gender (Table 1).

[Table/Fig-1]: Demographic characteristics of the study population (N=100).

SN	Characteristics	Cases (N=50)	Controls (N=50)	p-value
1	Gender Distribution			
	Male	22 (44.0%)	24 (48.0%)	0.688
	Female	28 (56.0%)	26 (52.0%)	
2	BMI		23 (46.0%)	0.685
	Lean (BMI ≤ 22.9 kg/m ²)	21 (42.0%)	27 (54.0%)	
	Non-Lean (BMI ≥ 23 kg/m ²)	29 (58.0%)	28 (56.0%)	
3	Mean Age (Males)	55 ± 1.4 years	54 ± 1.2 years	0.396
4	Mean Age (Females)	47 ± 1.3 years	45 ± 1.1 years	0.538

Biochemical Parameters of Cases Based on BMI

This table compares biochemical parameters between lean (N=21) and non-lean (N=29) individuals in the case group. Lean cases had numerically a higher mean hemoglobin level (10.6 vs. 10.2 gm/dL) but a lower platelet count (1.5 vs. 1.8 lac/cumm) and creatinine levels (1.3 vs. 1.5 mg/dL). Non-lean individuals had higher rates of type 2 diabetes (13 vs. 8) and pre-diabetes (11 vs. 7). The lipid profile showed that lean cases had higher mean HDL (54.0 vs. 45.8 mg/dL) but lower mean triglycerides (121.7 vs. 151.0 mg/dL) and cholesterol (201.5 vs. 243.8 mg/dL). Non-lean cases also had numerically higher LDL and VLDL levels. Liver function tests showed slightly higher SGPT and SGOT levels in lean individuals. Fatty liver grading showed that 76.2% of lean cases had Grade 1 fatty liver, compared to 55.2% of non-lean cases, while more non-lean individuals had Grade 2 fatty liver (44.8% vs. 23.8%) (Table 2).

[Table-2]: Biochemical and clinical characteristics of cases according to BMI (N=50).

Parameters	Lean (n=21)	Non-Lean (n=29)
Hemoglobin (gm/dL)	10.6	10.2
Platelet count (lac/cumm)	1.5	1.8
Creatinine (mg/dL)	1.3	1.5
Presence of T2DM	8	13
Pre-diabetic	7	11

Mean HDL (mg/dL)	54.0	45.8
Mean Triglycerides (mg/dL)	121.7	151.0
Mean Cholesterol (mg/dL)	201.5	243.8
Mean LDL (mg/dL)	132.0	139.0
Mean VLDL (mg/dL)	29.6	32.1
Mean Bilirubin (mg/dL)	1.2	1.1
Mean SGPT (U/L)	56.1	45.2
Mean SGOT (U/L)	65.2	63.5
Mean ALP (U/L)	87	92
Mean PT (secs)	12	11.3
Mean INR	1.5	1.1
Fatty Liver Grade 1 (n, %)	16 (76.2%)	16 (55.2%)
Fatty Liver Grade 2 (n, %)	5 (23.8%)	13 (44.8%)

Intergroup Comparison of TM6SF2 Polymorphism Between Cases and Controls

The overall TM6SF2 genotype distribution differed significantly between cases and controls ($p=0.007$). Among cases, 50.0% had the CC genotype, 44.0% had the CT genotype and 6.0% had the TT genotype. Among controls, 80.0% had the CC genotype, 18.0% had the CT genotype and 2.0% had the TT genotype. The CT genotype was therefore more frequent among cases than controls. Genotype-model-specific effect estimates should be reported as odds ratios with 95% confidence intervals (Table 3).

[Table-3]: Distribution of TM6SF2 rs58542926 genotypes among cases and controls.

Polymorphism	Cases (N=50)	Controls (N=50)	Overall p-value
CC	25 (50.0%)	40 (80.0%)	0.007
CT	22 (44.0%)	9 (18.0%)	
TT	3 (6.0%)	1 (2.0%)	

Comparison of TM6SF2 Polymorphism Among Lean and Non-Lean Groups in Cases and Controls

This table examines the distribution of TM6SF2 polymorphisms in lean and non-lean individuals within the case and control groups. Among lean cases, 57.1% had the CC genotype, 42.9% had the CT genotype, and none had the TT genotype. In non-lean cases, 44.8% had the CC and CT genotypes, and 10.3% had the TT genotype. Among lean controls, 82.6% had the CC genotype, 13.0% had the CT genotype, and 4.3% had the TT genotype, while in non-lean controls, 77.8% had the CC genotype and 22.2% had the CT genotype. No significant differences were found in TM6SF2 polymorphisms between lean and non-lean individuals in either the case ($p=0.279$) or control groups ($p=0.408$) (Table 4).

[Table-4]: Distribution of TM6SF2 rs58542926 genotypes according to BMI category among cases and controls.

Polymorphism	Lean Cases (N=21)	Non-Lean Cases (N=29)	Lean Controls (N=23)	Non-Lean Controls (N=27)	p-value
CC	12 (57.1%)	13 (44.8%)	19 (82.6%)	21 (77.8%)	0.279
CT	9 (42.9%)	13 (44.8%)	3 (13.0%)	6 (22.2%)	0.408
TT	0 (0.0%)	3 (10.3%)	1 (4.3%)	0 (0.0%)	0.307

DISCUSSION

In our study, we found that gender distribution and BMI between cases and controls were similar, with no significant differences ($p=0.688$ for gender and $p=0.687$ for BMI). Specifically, 44.0% of cases were male and 56.0% were female, while the control group had 48.0% males and 52.0% females. BMI classifications were also comparable, with 42.0% of cases and 44.0% of controls being classified as lean ($BMI \leq 22.9 \text{ kg/m}^2$), and 58.0% of cases and 56.0% of controls classified as non-lean. These findings align with Buzova et al (2020) [23], who also found similar BMI classifications between lean and non-lean individuals in their cohort of MAFLD patients. However, Adams et al, (2012) [24] reported a higher

prevalence of NAFLD among lean heterozygotes compared to wild types, suggesting that genetics may play a larger role in lean individuals with NAFLD. Lin et al (2022) [25] similarly found that lean individuals with NAFLD had a higher prevalence of the PNPLA3 rs738409 GG genotype, further supporting the role of genetics in lean NAFLD cases.

Our study identified biochemical differences between lean and non-lean individuals. Lean participants had higher hemoglobin levels (10.6 vs. 10.2 gm/dL), lower platelet counts (1.5 vs. 1.8 lac/cumm), and lower creatinine levels (1.3 vs. 1.5 mg/dL) than non-lean individuals. Lean participants also had better lipid profiles, with higher HDL (54.0 vs. 45.8 mg/dL), lower triglycerides (121.7 vs. 151.0 mg/dL), and lower

cholesterol (201.5 vs. 243.8 mg/dL). These results align with Wei et al (2015) [26], where non-obese NAFLD patients showed better biochemical profiles than their obese counterparts, exhibiting lower cytokeratin-18 fragments and liver stiffness. Similarly, Fracanzani et al (2017) [27] reported that lean NAFLD patients had a lower prevalence of metabolic syndrome and a better overall metabolic profile compared to non-lean NAFLD patients, which matches our finding of better lipid profiles and fewer metabolic disturbances in lean participants.

In terms of diabetes prevalence, our study found that non-lean individuals had a higher prevalence of type 2 diabetes (13 vs. 8) and pre-diabetes (11 vs. 7) compared to lean individuals. This finding is consistent with Fracanzani et al (2017), [27] who also found that non-lean individuals with NAFLD were more likely to have metabolic comorbidities, including diabetes and hypertension. Similarly, Niriella et al (2019) [28] observed that non-lean NAFLD patients were at higher risk for developing metabolic conditions, reinforcing our findings on the increased diabetes risk in non-lean individuals.

The overall *TM6SF2* genotype distribution differed significantly between cases and controls ($p=0.007$). The CC genotype was more common among controls (80.0%) than cases (50.0%), whereas the CT genotype was more frequent among cases (44.0%) than controls (18.0%). These findings support an association between *TM6SF2* rs58542926 and NAFLD in the overall study population. Nevertheless, they should be interpreted using appropriate genetic models, odds ratios and 95% confidence intervals. Previous studies have also implicated genetic variation in susceptibility to NAFLD, although variants in other genes, such as *PNPLA3*, should not be regarded as direct evidence for a *TM6SF2*-specific effect [12,14].

When *TM6SF2* genotype distribution was compared between lean and non-lean participants, no significant subgroup difference was demonstrated. Consequently, the present findings do not establish that the association is stronger in lean individuals. Earlier studies have reported heterogeneous genetic associations in lean and non-lean NAFLD populations [5,10,14,15]. Differences in ethnicity, sample size, phenotype definition and methods used to assess hepatic steatosis may partly explain the variation across studies.

Additionally, our study found that lean individuals had higher SGPT (56.1 vs. 45.2 U/L) and SGOT (65.2 vs. 63.5 U/L) levels, but most lean individuals had Grade 1 fatty liver (76.2%), while non-lean individuals had a higher prevalence of Grade 2 fatty liver (44.8%). These results are consistent with Lin et al., 2022, who reported that lean individuals with NAFLD were more likely to have mild liver fat accumulation, while non-lean individuals had more advanced liver disease. Similarly, Honda et al., 2016 found that non-obese NAFLD patients were at a higher risk for lobular

inflammation, hepatocyte ballooning, and liver fibrosis, much like the more advanced liver disease seen in non-lean individuals in our study.

Chahal et al. reported associations of genetic variants, including *TM6SF2* rs58542926, with fatty liver phenotypes in the UK Biobank [15]. Goffredo et al. also demonstrated a role of *TM6SF2* rs58542926 in paediatric fatty liver disease [23]. Although these reports support the biological relevance of *TM6SF2*, they do not by themselves demonstrate a lean-specific effect in the present adult population.

In summary, the present study supports an association between *TM6SF2* rs58542926 and NAFLD in the overall study population. Lean and non-lean cases showed numerical differences in their biochemical and ultrasonographic characteristics, but these comparisons require complete reporting of variability estimates and p -values. The absence of a significant difference in genotype distribution between BMI subgroups indicates that larger studies are needed before lean NAFLD can be considered genetically distinct on the basis of this variant alone.

Strengths of the Study

The present study has several strengths. First, it specifically evaluated the association between the *TM6SF2* rs58542926 polymorphism and NAFLD while considering BMI-based lean and non-lean subgroups, addressing an important clinical and genetic aspect of NAFLD. Second, the study included a case-control design with an equal number of cases and controls, allowing comparison of genotype distributions between participants with and without NAFLD. Third, genotyping was performed using PCR followed by restriction fragment length polymorphism analysis, providing a molecular approach for evaluating the selected genetic variant. Finally, the study incorporated clinical, anthropometric, biochemical, and ultrasonographic characteristics, allowing the genetic findings to be considered alongside relevant clinical and metabolic parameters.

Future Directions

Future studies should include larger, adequately powered, multicentre populations to validate the association between *TM6SF2* rs58542926 and NAFLD and to improve the generalisability of the findings. Larger numbers of lean participants would be particularly valuable for determining whether BMI modifies the genetic association. Further research should also incorporate adjusted genetic models with odds ratios and 95% confidence intervals and evaluate potential confounding factors such as age, sex, metabolic status, dietary habits, and physical activity. Studies involving additional NAFLD-associated genetic variants may help clarify the combined genetic contribution to lean and non-lean NAFLD. More accurate assessment of hepatic steatosis and fibrosis using advanced imaging or histological methods may

also provide better insight into the relationship between genetic variation and disease severity.

Limitations

This study was limited by its single-centre design, small sample size and the low frequency of the TT genotype, which reduced the power of BMI-stratified analyses. Ultrasonography, rather than magnetic resonance-based assessment or liver histology, was used to identify and grade hepatic steatosis. Evaluation of a single genetic variant, potential selection bias, residual confounding and the absence of detailed dietary and physical-activity data also limit generalisability. As this was a case-control study, causality cannot be inferred.

CONCLUSION

The TM6SF2 rs58542926 genotype distribution differed significantly between participants with and without NAFLD, with the CT genotype occurring more frequently among cases. However, genotype distribution did not differ significantly between lean and non-lean subgroups. Lean and non-lean cases showed numerical differences in several metabolic and biochemical characteristics, but these findings require complete statistical reporting. Larger, adequately powered studies using adjusted genetic models are required to determine whether BMI modifies the association between TM6SF2 rs58542926 and NAFLD.

DECLARATIONS

Ethics Approval and Consent to Participate

Ethical approval was obtained from the Institutional Ethics Committee of Era's Lucknow Medical College and Hospital, Lucknow, India, before commencement of the study. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, revised in 2013. Written informed consent was obtained from all participants before enrolment.

Consent for Publication

Not applicable. No individually identifiable participant information or images are presented in this manuscript.

Availability of Data and Materials

The data generated and/or analysed during the present study are available from the corresponding author on reasonable request, subject to applicable ethical and institutional restrictions.

Competing Interests

The authors declare that they have no competing interests.

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Authors' Contributions

J.F., Z.U., and V.M. contributed to the conception and design of the study, interpretation of the data, drafting of the manuscript, and critical revision of the article. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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Guarantor

The corresponding author will act as the guarantor of the work and will take responsibility for the integrity of the data and the accuracy of the analysis.

AI Use Disclosure

The authors declare that no generative artificial intelligence tools were used to generate or substantially modify the scientific content of this manuscript.

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