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ORIGINAL RESEARCH

Association Between FAM134B and Diabetic Peripheral Neuropathy in Type 2 Diabetes: A Double-Center Case-Control Study

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Purpose: The role of FAM134B in neurological diseases has received significant attention; however, its role in diabetic peripheral neuropathy (DPN) remains unexplored. This study investigated the association between plasma FAM134B levels and DPN while assessing its diagnostic value.

Methods: The study included 128 inpatients with type 2 diabetes divided into DPN (n = 68) and non-DPN (n = 60) groups. FAM134B expression was determined via qRT-PCR analysis of plasma FAM134B mRNA level. All clinical data were retrieved from the Hospital Information System. SPSS and R were used for statistical analyses.

Results: Plasma FAM134B mRNA levels were significantly higher in the DPN than in the non-DPN group ($p < 0.001$). Increased FAM134B mRNA levels were strongly linked to increased odds of DPN, with the highest quartile showing a significant risk elevation (Odds Ratio [OR] = 21.42, 95% Confidence Interval: 4.86–96.46, $p < 0.001$). Restricted cubic spline analysis confirmed a non-linear relationship, thereby identifying a critical threshold of FAM134B mRNA levels at 2.53, above which the risk sharply increased (adjusted OR = 3.11, $p = 0.006$). Subgroup analysis showed consistent associations across most subgroups, with a notable difference in males ($p = 0.038$). The diagnostic performance was moderate (Area Under the Curve [AUC] = 0.756). While adding FAM134B mRNA to the model did not dramatically improve the AUC, it significantly enhanced reclassification metrics (Net Reclassification Improvement = 0.165, Integrated Discrimination Improvement = 0.095, $p < 0.05$), thereby highlighting its clinical value.

Conclusion: Increased FAM134B expression positively correlated with the odds of DPN, and may act as a promising target for diagnostic and therapeutic interventions.

Plain Language Summary:

- Diabetic peripheral neuropathy (DPN) is a common diabetic complication without effective treatment to block or reverse its progression currently. FAM134B is thought to be closely linked with neurological disease in previous studies, potentially playing a pivotal role in DPN.
- Plasma FAM134B mRNA levels were significantly increased in individuals with DPN and markedly associated with increased odds of DPN. Different statistical models demonstrated that FAM134B had an excellent diagnostic predictive value for DPN.
- Our findings provide a theoretical foundation for the development of FAM134B as a potential target for diagnostic and therapeutic interventions of DPN.

Keywords: FAM134B, type 2 diabetes, diabetic peripheral neuropathy, clinical value

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Introduction

In 2021, the International Diabetes Federation's 10th edition of the Global Diabetes Atlas, revealed that 537 million adults aged 20–79 years (10.5% of the worldwide population within this age range) have diabetes mellitus. Projections estimate a rise to 643 million (11.3%) by 2030 and up to 783 million (12.2%) by 2045.[1] Diabetic neuropathy, most prevalent chronic complication of diabetes, affects more than half of individuals with diabetes.

The predominant form of diabetic neuropathy, peripheral sensorimotor neuropathy, typically presents with tingling, numbness, and pain, especially in the lower extremities.[2] Individuals with diabetic peripheral neuropathy (DPN) are at a higher risk of falls and fractures due to impaired limb sensation,[3] and difficult-to-heal foot ulcers, which can lead to Charcot neuroarthropathy and poor prognosis in the context of hyperglycemia. The high incidence and disability rates of DPN severely compromise patients' quality of life and impose significant financial and psychological burdens on families and society.[4]

The precise pathogenesis of DPN remains unclear. However, several risk factors have been identified, including hyperglycemia, hypertension, hyperlipidemia, smoking, and certain nonmodifiable factors such as age and race. FAM134B, also known as RETREG1 (JK-1), is a member of the family with sequence similarity 134. FAM134B primarily expressed in sensory and autonomic nerves. Evidence suggests that FAM134B mutations and aberrant expression are closely linked to hereditary sensory and autonomic neuropathy (HSAN) type IIB.[5] HSAN type IIB is primarily characterized by sensory neuropathy, with clinical features including progressive hyperalgesia and hyperesthesia, and peripheral nerve demyelination—hallmarks closely resembling DPN. Our previous studies demonstrated that FAM134B-knockout mice exhibit dysmyelination, hypomyelination, and demyelination phenotypes that mirror those observed in wild-type diabetic mice.[6] The expression of FAM134B may be a critical initiating factor in DPN, potentially contributing to its onset and progression.

This study evaluated plasma FAM134B mRNA levels in individuals with type 2 diabetes, comparing those with DPN to those without (non-DPN). Additionally, we explored the potential relationship between plasma FAM134B levels and DPN, and constructed statistical models to assess the diagnostic value of FAM134B in identifying DPN in type 2 diabetes.

Methods

Study Design and Participants

This double-center case-control study was approved by the ethics committees of the participating hospitals (Approval No. SYSKY-2022-042-03). Between September 2022 and May 2024, a total of 128 inpatients with type 2 diabetes mellitus, diagnosed according to the latest Chinese clinical guidelines[7] and who had previously provided informed consent for voluntary participation, were screened by the Department of Endocrinology at Sun Yat-sen Memorial Hospital and Shenzhen Longhua District Central Hospital. The exclusion criteria included: (1) acquired inflammatory demyelinating peripheral neuropathy, including Guillain–Barré Syndrome; (2) peripheral neuropathy from non-diabetic causes, such as tumors, connective tissue disease, alcohol abuse, or drug use; (3) inability to perform nerve conduction tests (NCT) due to diabetic foot, gouty arthritis, or mental disease; and (4) pregnancy or lactation.

Data Collection

Each patient underwent a comprehensive clinical assessment, with clinical data retrieved from the Hospital Information System (HIS) at Sun Yat-sen Memorial Hospital and Shenzhen Longhua District Central Hospital. The collected data included demographic data, metabolic indicators, liver and kidney function, cardiac evaluation, and diabetes related history (details in Table 1). FAM134B expression was measured using quantitative real-time polymerase chain reaction (qRT-PCR) to express plasma FAM134B mRNA levels. The detailed procedure of qRT-PCR and the primer sequences for target genes were presented in Appendix 1. β-Actin served as the housekeeping reference gene for normalization.

Table 1 Baseline Characteristics of All Participants with and without DPN

Characteristic	Total N = 128	Non-DPN N = 60	DPN N = 68	*p value*
Sex[a], n (%)				0.146
Male	81(63.3)	34(56.7)	47(69.1)	
Female	47(36.7)	26(43.3)	21(30.9)	
Age (years, mean ± SD)	53.5 ± 8.0	52.6 ± 7.8	54.3 ± 8.1	0.223
BMI (kg/cm^2, mean ± SD)	24.5 ± 3.8	24.8 ± 3.7	24.2 ± 3.8	0.342
Smoking[a], n (%)	30(23.4)	10(16.7)	20(29.4)	0.091
Duration (years, mean ± SD)	10.2 ± 5.4	9.7 ± 4.6	10.7 ± 6.1	0.261
Chronic complication excluded DPN[a], n (%)	88(68.8)	31(51.7)	57(83.8)	0.000**
HbA1c (%)	8.8 ± 2.2	8.4 ± 1.8	9.2 ± 2.3	0.044*
FBG (mmol/L)	7.1 ± 2.1	7.0 ± 1.9	7.1 ± 2.2	0.684
TG (mmol/L)	2.1 ± 1.8	2.2 ± 1.6	2.0 ± 2.0	0.512
TC (mmol/L)	4.7 ± 1.3	4.7 ± 1.1	4.6 ± 1.5	0.845
LDL-c (mmol/L)	2.6 ± 1.0	2.7 ± 0.9	2.6 ± 1.1	0.886
HDL-c (mmol/L)	1.2 ± 0.4	1.2 ± 0.5	1.1 ± 0.3	0.392
Crea (umol/L)	82.2 ± 35.3	75.9 ± 24.5	87.7 ± 42.0	0.053
eGFR (mL/min/1.73m^2)	88.4 ± 29.2	91.5 ± 28.1	85.7 ± 30.1	0.258
ALT (U/L)	27.3 ± 22.4	26.9 ± 22.2	27.6 ± 22.8	0.848
AST (U/L)	24.2 ± 19.6	22.0 ± 10.1	26.2 ± 24.8	0.218
TBIL (umol/L)	10.6 ± 7.4	10.1 ± 5.2	11.1 ± 9.0	0.502
ALB (g/L)	41.3 ± 4.6	41.9 ± 5.2	40.8 ± 4.0	0.180
CK-MB (U/L)	12.2 ± 5.0	12.3 ± 4.4	12.1 ± 5.5	0.813
LVEF (%)	67.8 ± 5.2	68.4 ± 4.5	67.2 ± 5.7	0.200

Notes: *p<0.05, **p<0.001. [a]Mann–Whitney *U*-test. Other quantitative variates were analyzed by Student's *t*-test.
Abbreviations: DPN, diabetic peripheral neuropathy; Non-DPN, individuals with diabetes without DPN; N, number of cases; SD, standard deviation; BMI, body mass index, calculated as weight (kg) divided by height (m2); HbA1c, glycated hemoglobin; FBG, fasting blood glucose; TG, triglyceride; TC, total cholesterol; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; Crea, Creatinine; eGFR, estimated glomerular filtration rate, calculated using the Modification of Diet in Renal Disease (MDRD) formula; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; ALB, albumin; CK-MB, creatine kinase-MB; LVEF, left ventricular ejection fraction, from cardiac ultrasound.

Assessment and Definition of Diabetic Peripheral Neuropathy

Owing to the lack of unified diagnostic criteria for DPN, NCT abnormalities served a the primary objective measure for this condition.[8] In this study, DPN was defined based on NCT values from both upper and lower extremities, including assessments of the median, ulnar, sural, peroneal, and superficial peroneal nerves. DPN was confirmed electrophysiologically based on the presence of abnormalities in any nerve conduction index of at least two separate nerves.[9] The Toronto Clinical Scoring System (TCSS) was utilized for evaluating the clinical features of DPN based on clinical signs and symptoms. Participants were assessed using the TCSS, which includes a six-item symptom score evaluating lower extremity symptoms (numbness, tingling, pain, weakness, imbalance) and any upper extremity symptoms; a five-item physical examination score assessing light touch, temperature sensation, pinprick sensation, vibration, and positional sensation; and an eight-item reflex score examining ankle, knee, and bilateral reflexes, each graded as absent, diminished, or normal. The combined total score has a maximum of 19 points.[10]

Statistical Analysis

Statistical analyses were performed using SPSS version 18.0 and R version 4.4.1. Demographic data, clinical features, and plasma FAM134B mRNA levels were compared using Student's *t*-test or the Mann–Whitney *U*-test for continuous and categorical data, respectively. Pearson's correlation analysis was performed to evaluate the relevance of plasma FAM134B mRNA levels to the TCSS score and the different indices of NCT. The association between plasma FAM134B mRNA levels and DPN risk was assessed using logistic regression models. Subgroup analyses were also performed to

investigate potential effect modifications by various demographic and clinical factors. A two-piecewise linear regression model was employed to investigate the relationship between plasma FAM134B mRNA levels and DPN risk. Various statistical models and algorithms were applied to evaluate the diagnostic effectiveness of FAM134B mRNA in predicting DPN in multiple dimensions. Statistical significance was defined as $p < 0.05$ in all analyses. The specifics of statistical methodologies are presented in Appendix 2.

Results

Baseline Characteristics of Participants

The elementary characteristics of all participants are shown in Table 1. Overall, 128 individuals with type 2 diabetes mellitus were enrolled, with 68 (53%) diagnosed with DPN. The DPN group exhibited a higher mean glycated hemoglobin (HbA1c) level (9.2 ± 2.3% vs 8.4 ± 1.8%, $p = 0.044$) and a greater prevalence of chronic diabetic complications history (excluding DPN) compared to the non-DPN group (83.8% vs 51.7%, $p < 0.001$). Differences in sex, age, body mass index (BMI), smoking history, diabetes duration, fasting blood glucose, blood lipid, liver function, kidney function, and cardiac indicators across the groups were not statistically significant.

Plasma FAM134B mRNA Level Between DPN and Non-DPN Group

The data on plasma FAM134B mRNA levels were consistent with non-normal distribution. Mann–Whitney *U*-test showed that the median plasma FAM134B mRNA level in the DPN group was markedly higher than that in the non-DPN control group (3.09 ± 3.56 vs 1.76 ± 1.57, $p < 0.001$) (Figure 1A). All participants were divided into four groups based on the quartiles of plasma FAM134B mRNA levels. Chi-square test results showed that the proportion of DPN increased progressively with higher plasma FAM134B mRNA levels ($p < 0.001$) (Figure 1B).

Correlation of Plasma FAM134B mRNA Level with TCSS Score

The TCSS score represents the typical clinical signs and symptoms of DPN. Pearson's correlation coefficient test showed a statistically significant positive correlation between plasma FAM134B mRNA levels and TCSS scores ($r = 0.182$, $p = 0.041$) (Figure 2A). Similarly, all participants were divided into four groups based on the quartiles of plasma FAM134B mRNA levels, and the one-way analysis of variance (ANOVA) results indicated that the TCSS score in F4 group (the highest quartile) was markedly higher than that in F1 group (the lowest quartile) ($p = 0.021$) (Figure 2B).

Correlation of Plasma FAM134B mRNA Level with NCT

The NCT values for the median, ulnar, sural, peroneal, and superficial peroneal nerves, including conduction velocity, distal latency, and amplitude, are presented in Table 2. The heatmap directly displayed a general trend of decreasing conduction velocity and amplitude accompanied by increasing levels of plasma FAM134B mRNA, while distal latency increased (Figure 3).

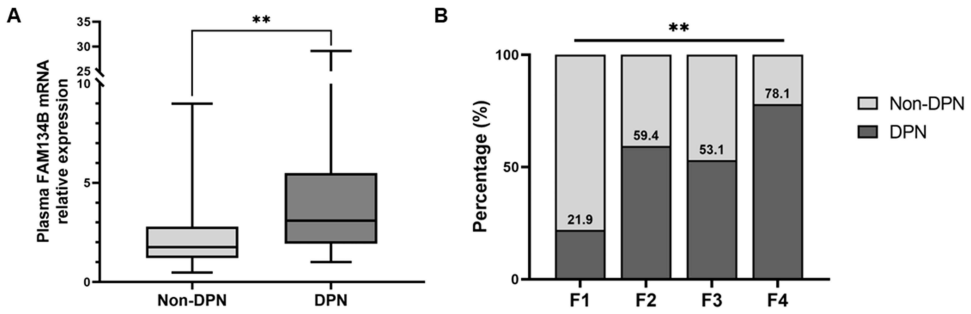

Figure 1 (**A**) Differential expression of plasma FAM134B mRNA between the non-DPN group and DPN group. (**B**) Percentage of DPN across plasma FAM134B mRNA levels. All participants were divided into four groups according to quartiles of plasma FAM134B mRNA level (F1 [first quartile]: <1.507; F2 [second quartile]: 1.507–2.326; F3 [third quartile]: 2.326–3.977; F4 [4th quartile]: ≥3.977). $^{**}p < 0.001$.

Abbreviations: DPN, diabetic peripheral neuropathy; Non-DPN, individuals with diabetes without DPN.

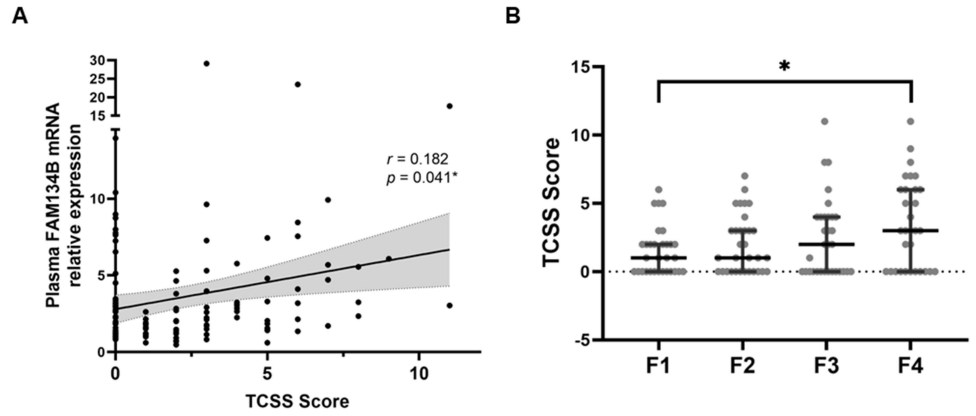

Figure 2 (**A**) Correlation between plasma FAM134B mRNA level and TCSS score. (**B**) Comparison of TCSS scores across plasma FAM134B mRNA levels. All participants were divided into four groups according to quartiles of plasma FAM134B mRNA level (F1 [first quartile]: < 1.507; F2 [second quartile]: 1.507–2.326; F3 [third quartile]: 2.326–3.977; F4 [fourth quartile]: ≥ 3.977). *p < 0.05. r represents Pearson correlation coefficients.
Abbreviation: TCSS, Toronto clinical scoring system.

We further performed a Pearson's correlation coefficient test to explore the relationship between plasma FAM134B mRNA levels and different NCT indices. The results showed significant negative correlations between plasma FAM134B mRNA levels and conduction velocities of the median (sensory and motor branches), ulnar (sensory), peroneal (motor), and superficial peroneal (sensory) nerves. Additionally, the amplitude of the sural nerve (sensory branch) was negatively correlated with plasma FAM134B mRNA levels. A statistically significant positive correlation was identified between

Table 2 Values of Nerve Conduction Tests

Examined Nerve		Values of Nerve Conduction Tests		*p value*
		Non-DPN (N=60)	DPN (N=68)	
Sensory nerve				
Median nerve	Conduction velocity (m/s)	57.0 ± 6.0	47.8 ± 7.5	< 0.001**
	Amplitude (uV)	25.6 ± 12.5	11.5 ± 8.4	< 0.001**
	Latency (ms)	2.3 ± 0.4	2.9 ± 0.7	< 0.001**
Ulnar nerve	Conduction velocity (m/s)	55.6 ± 4.7	50.0 ± 5.1	< 0.001**
	Amplitude (uV)	14.1 ± 5.0	7.9 ± 4.8	< 0.001**
	Latency (ms)	1.9 ± 0.2	2.2 ± 0.3	< 0.001**
Sural nerve	Conduction velocity (m/s)	56.1 ± 6.8	50.0 ± 8.1	< 0.001**
	Amplitude (uV)	16.1 ± 7.2	7.4 ± 5.2	< 0.001**
	Latency (ms)	2.2 ± 0.3	2.5 ± 0.4	< 0.001**
Superficial peroneal nerve	Conduction velocity (m/s)	54.0 ± 6.7	47.0 ± 6.4	< 0.001**
	Amplitude (uV)	8.9 ± 5.6	3.6 ± 3.0	< 0.001**
	Latency (ms)	3.1 ± 1.4	4.1 ± 2.3	0.016*
Motor nerve				
Median nerve	Conduction velocity (m/s)	55.2 ± 3.3	51.0 ± 4.1	< 0.001**
	Amplitude (uV)	8.9 ± 1.8	7.3 ± 2.5	< 0.001**
	Latency (ms)	3.1 ± 0.4	3.8 ± 0.8	< 0.001**
Ulnar nerve	Conduction velocity (m/s)	58.1 ± 4.6	51.4 ± 6.9	< 0.001**
	Amplitude (uV)	9.6 ± 2.3	8.1 ± 3.0	0.003*
	Latency (ms)	2.4 ± 0.3	2.8 ± 0.6	< 0.001**
Peroneal nerve	Conduction velocity (m/s)	47.6 ± 3.0	41.1 ± 5.4	< 0.001**
	Amplitude (uV)	5.7 ± 2.2	3.2 ± 1.6	< 0.001**
	Latency (ms)	3.4 ± 0.7	3.9 ±1.1	0.002*

Notes: *p < 0.05, **p < 0.001.
Abbreviations: DPN, diabetic peripheral neuropathy; Non-DPN, individuals with diabetes without DPN; N, number of cases.

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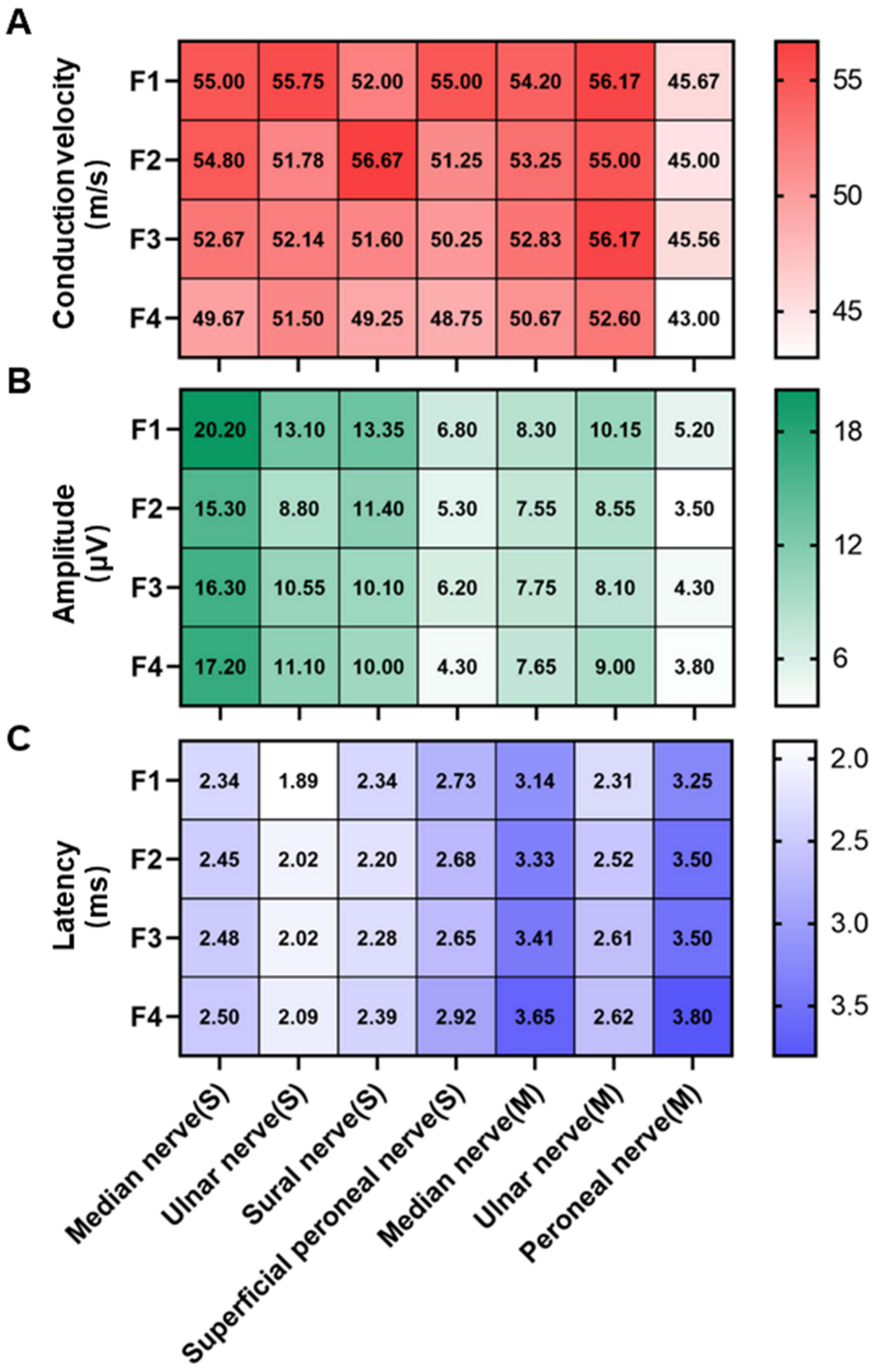

Figure 3 Descriptive analysis of nerve conduction tests across different plasma FAM134B mRNA levels. (**A**) Conduction velocity heatmap. (**B**) Amplitude heatmap. (**C**) Latency heatmap. All participants were divided into four groups according to quartiles of plasma FAM134B mRNA level (F1 [first quartile]: < 1.507; F2 [second quartile]: 1.507 ~ 2.326; F3 [third quartile]: 2.326 ~ 3.977; F4 [fourth quartile]: ≥ 3.977).
Abbreviations: S, sensory nerve; M, motor nerve.

plasma FAM134B mRNA levels and the distal latencies of the median nerve (motor branch), sensory nerve (sensory and motor branches), and common peroneal nerve (motor branch). Other NCT indices showed weak or no correlation with plasma FAM134B mRNA levels (Figure 4).

Multivariate-Adjusted Odds Ratio (OR) for the Association Between Plasma FAM134B mRNA Levels and DPN Risk

In the multivariate analysis, the relationship between plasma FAM134B mRNA levels and the prevalence of DPN was evaluated across the three models (Figure 5). Higher plasma FAM134B mRNA levels were consistently associated with increased odds of developing DPN. In Model 1, participants in the highest quartile of plasma FAM134B mRNA levels (F4, ≥3.977) had a markedly elevated risk of DPN (OR = 12.76, 95% CI: 3.90–41.73) than those in the reference group (F1, <1.507). This association strengthened in Models 2 and 3, with Model 3 showing an OR of 21.42 (95% CI: 4.86–96.46), highlighting the robustness of this relationship across different model adjustments. The p-trend across all models was statistically significant ($p < 0.001$), indicating a clear dose-response relationship between increasing plasma FAM134B mRNA levels and DPN risk.

These findings were further supported by the restricted cubic spline (RCS) analysis, which demonstrated a significant non-linear relationship between plasma FAM134B mRNA levels and DPN risk ($p < 0.05$, Figure 6), revealing a sharp increase in the odds of developing DPN when FAM134B mRNA levels exceeded 2.53, corroborating the threshold effect identified in the two-piecewise model (Table 3). Below this threshold, the adjusted OR for DPN was substantially higher (adjusted OR = 3.11, 95% CI: 1.42–7.28, $p = 0.006$). In contrast, above 2.53, the risk increase was less pronounced (adjusted OR = 1.21, 95% CI: 0.99–1.56, $p = 0.113$). The two-piecewise model demonstrated a better fit than the linear model ($p = 0.040$).

Further subgroup analyses (Figure 7) clarified the effects of various demographic and clinical factors on the relationship between FAM134B mRNA levels and DPN. This association remained consistent across subgroups. Notably, the association was stronger in males (OR = 2.23, 95% CI: 1.35–3.67, p-interaction = 0.038), indicating a potential sex-specific vulnerability. Other factors, including age, smoking status, BMI, HbA1c level, and diabetes duration, did not significantly affect this relationship ($p > 0.05$).

Diagnostic Value of Plasma FAM134B mRNA Level in Detecting DPN

Receiver operating characteristic (ROC) curves showed plasma FAM134B mRNA levels exhibited moderate diagnostic performance for DPN, with the area under the curve (AUC) of 0.756 (95% CI: 0.549–0.822) (Figure 8A). When incorporated into the multivariate model, the AUC increased to 0.82; however, this improvement did not achieve statistical significance (p = 0.156) (Figure 8B). Boruta feature selection (Figure 8C) highlighted plasma FAM134B mRNA as the most influential factor, surpassing traditional clinical variables, such as comorbidities and HbA1c. The decision curve analysis (DCA) (Figure 8D) demonstrated that the inclusion of FAM134B mRNA provided a greater net benefit across various thresholds. Calibration plots (Figure 8E) confirmed that the FAM134B-enhanced model showed better alignment between predicted and observed risks. While the incorporation of FAM134B mRNA resulted in only a marginal increase in the C-index (from 0.772 to 0.816, $p = 0.156$), it significantly enhanced the reclassification measures, with notable gains in both integrated discrimination improvement (IDI = 0.095, $p < 0.001$) and net reclassification improvement (NRI = 0.165, $p = 0.022$) (Figure 8F).

Discussion

In this study, FAM134B mRNA expression levels were significantly higher in type 2 diabetes individuals with DPN than in those without peripheral neuropathy, which may highlight the critical role of FAM134B in the pathophysiology of DPN. The human FAM134B gene, located at position 15.1 on the short arm of chromosome 5, encodes a 479-amino acid protein whose function remains unclear.[11] Initially, FAM134B was reported to be associated with esophageal and colon cancers.[11,12] Since the identification of nonsense mutations in FAM134B as a primary trigger for HSAN IIB in 2009,[13] its function has received widespread attention in neurological diseases such as vascular dementia,[14] epilepsy,[15] and

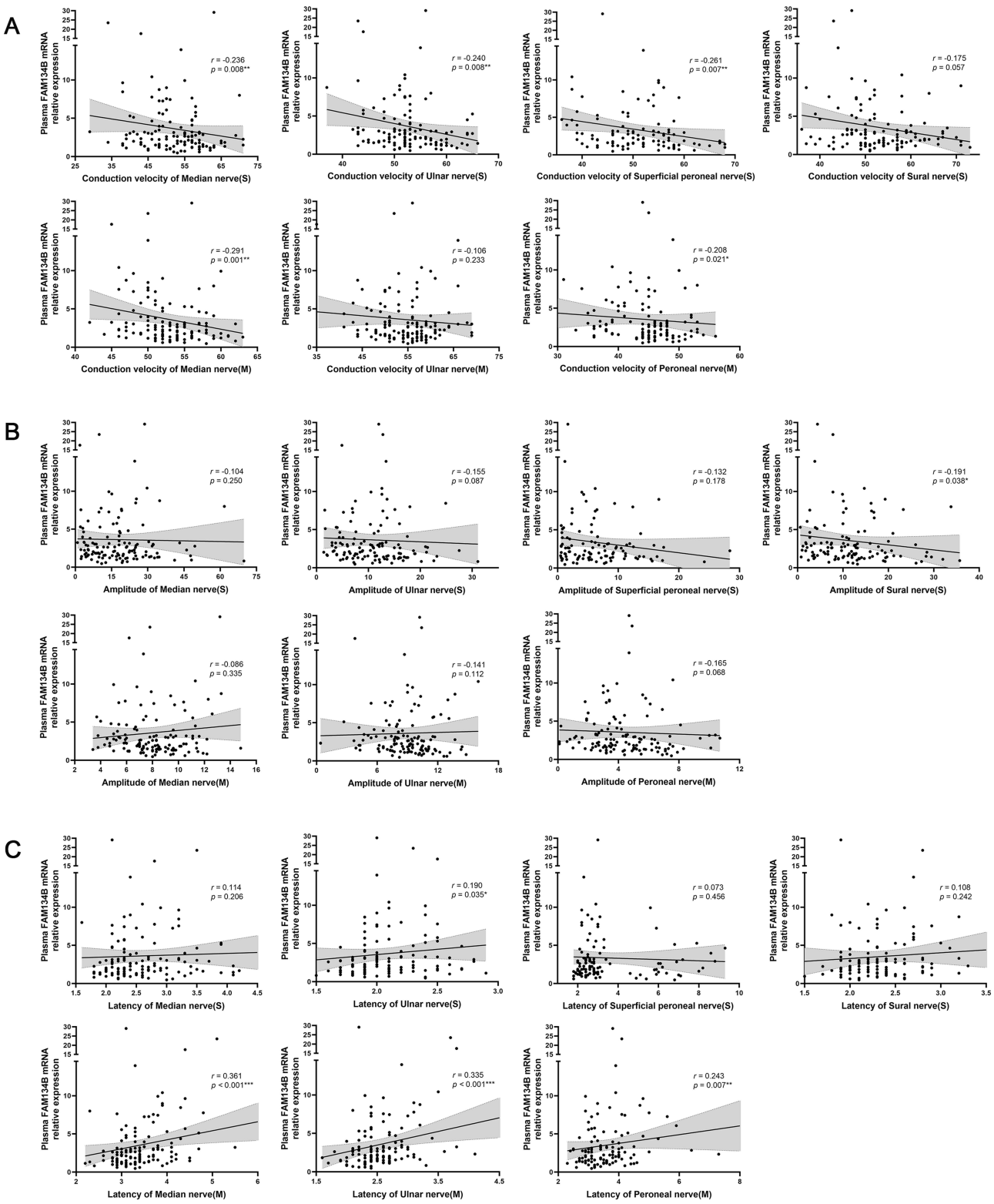

Figure 4 Correlation between plasma FAM134B mRNA level and conduction velocity (**A**), amplitude (**B**), and distal latency (**C**) of peripheral sensory and motor nerves. *$p < 0.05$. *r* represents Pearson correlation coefficients. Unit: conduction velocity: m/s; amplitude: uV; distal latency: ms.

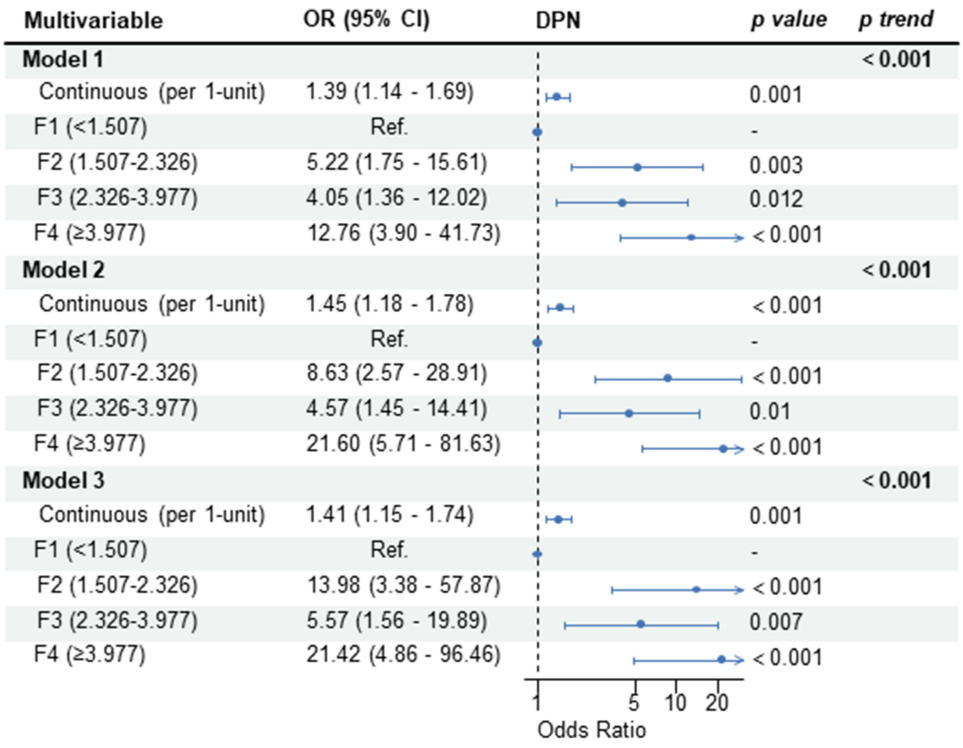

Figure 5 Forest plot of the binary logistic regression analysis for plasma FAM134B mRNA level as a risk factor for DPN in individuals with diabetes. Model 1 was unadjusted; Model 2 was adjusted by Model 1+ age + sex + BMI; Model 3 was adjusted by Model 2+ smoking + diabetes duration + chronic complication excluded DPN + HbA1c. (F1 [first quartile]: < 1.507; F2 [second quartile]: 1.507–2.326; F3 [third quartile]: 2.326–3.977; F4 [fourth quartile]: ≥ 3.977).
Abbreviations: DPN, diabetic peripheral neuropathy; BMI, body mass index; HbA1c, glycosylated hemoglobin; OR, odds ratio; CI, confidence interval.

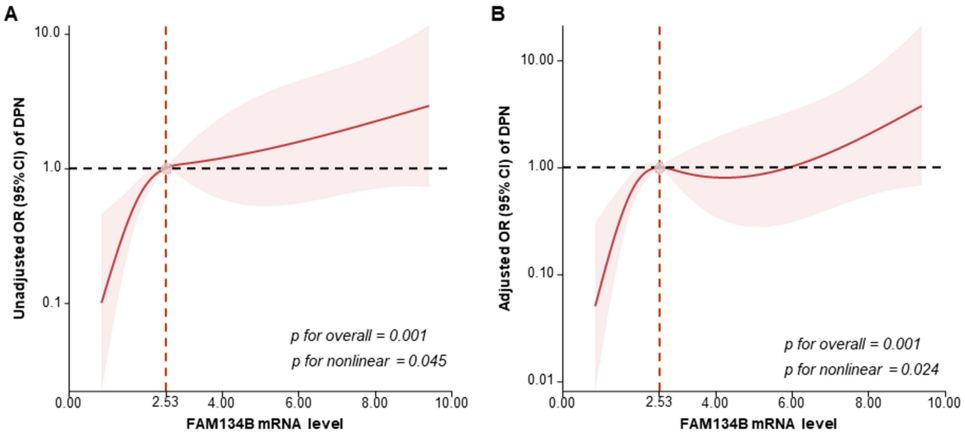

Figure 6 Association between plasma FAM134B mRNA levels and DPN using unadjusted (**A**) and adjusted (**B**) restricted cubic spline regression model. Adjusted for sex, age, smoking, diabetes duration, and chronic complication excluded DPN, HbA1c, and BMI. Data were analyzed using a logistic regression model, with four knots at the 5th, 35th, 65th, and 95th percentiles of FAM134B. The reference value, based on the inflection point of the curve, was set at 2.53. Solid lines represent odds ratios (OR), while shaded areas denote 95% confidence intervals (CI).
Abbreviations: DPN, diabetic peripheral neuropathy; HbA1c, glycosylated hemoglobin; BMI, body mass index.

Parkinson's disease.[16] Our findings suggest that FAM134B may be an important independent influencing factor for DPN, which has not been extensively investigated in the existing literature.

Clinical signs and symptoms are the primary criteria used for assessing peripheral neuropathy. Various rating scales, such as the TCSS, MNSI, and NSC, have been widely applied in clinical evaluations. The TCSS is a comprehensive scoring system based on the clinical characteristics of DPN, which assesses the function of myelinated and tiny unmyelinated nerve fibers. Owing to its simplicity and comprehensiveness, it is suitable for clinical screening for

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Table 3 Segmented Regression Analysis

	Event/N	Unadjusted OR (95% CI)	*p-value*	Adjusted[a] OR (95% CI)	*p-value*
FAM134B mRNA level					
Total	68/128	1.39 (1.16–1.73)	0.001*	1.41 (1.66–1.78)	0.001*
Fitting by two-piecewise linear model					
Inflection point		2.53		2.53	
<2.53 ≥2.53	27/65 41/63	3.28 (2.72–3.97) 1.27 (1.22–1.33)	0.004* 0.132	3.11 (1.42–7.28) 1.21 (0.99–1.56)	0.006* 0.113
p for Log-likelihood ratio			0.036*		0.040*

Notes: *$p<0.05$. [a]Adjusted by age, sex, BMI, smoking, diabetes duration, chronic complication excluded DPN, HbA1c.
Abbreviations: N, number of cases; OR, odds ratio; CI, confidence interval.

DPN and for conducting large-scale epidemiological investigations. In our study, we observed statistically significant positive correlations between TCSS score and plasma FAM134B levels, although the strength of these associations was weak. This may be attributable to the limited sample size and the inherent subjectivity of the TCSS rating scale.

Electrophysiology can be regarded as an extension of clinical neurological measurement. Owing to the objective nature of its measurements and independence from the individual subjective responses, electrophysiological techniques currently represent the most reliable assessment of peripheral neuromuscular function.

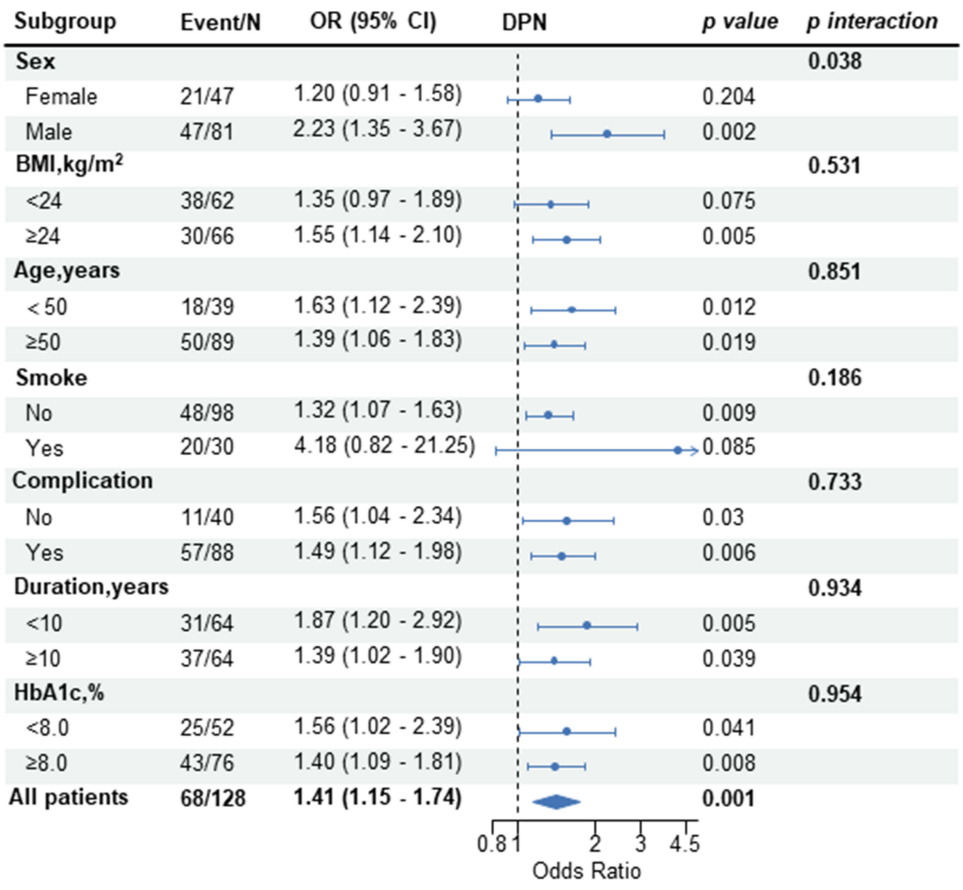

Figure 7 Subgroup analysis of plasma FAM134B mRNA levels with DPN. Adjusted by sex, BMI, age, smoking, chronic complication (excluding DPN), diabetes duration, and HbA1c.
Abbreviations: DPN, diabetic peripheral neuropathy; BMI, body mass index; HbA1c, glycosylated hemoglobin; OR, odds ratio; CI, confidence interval.

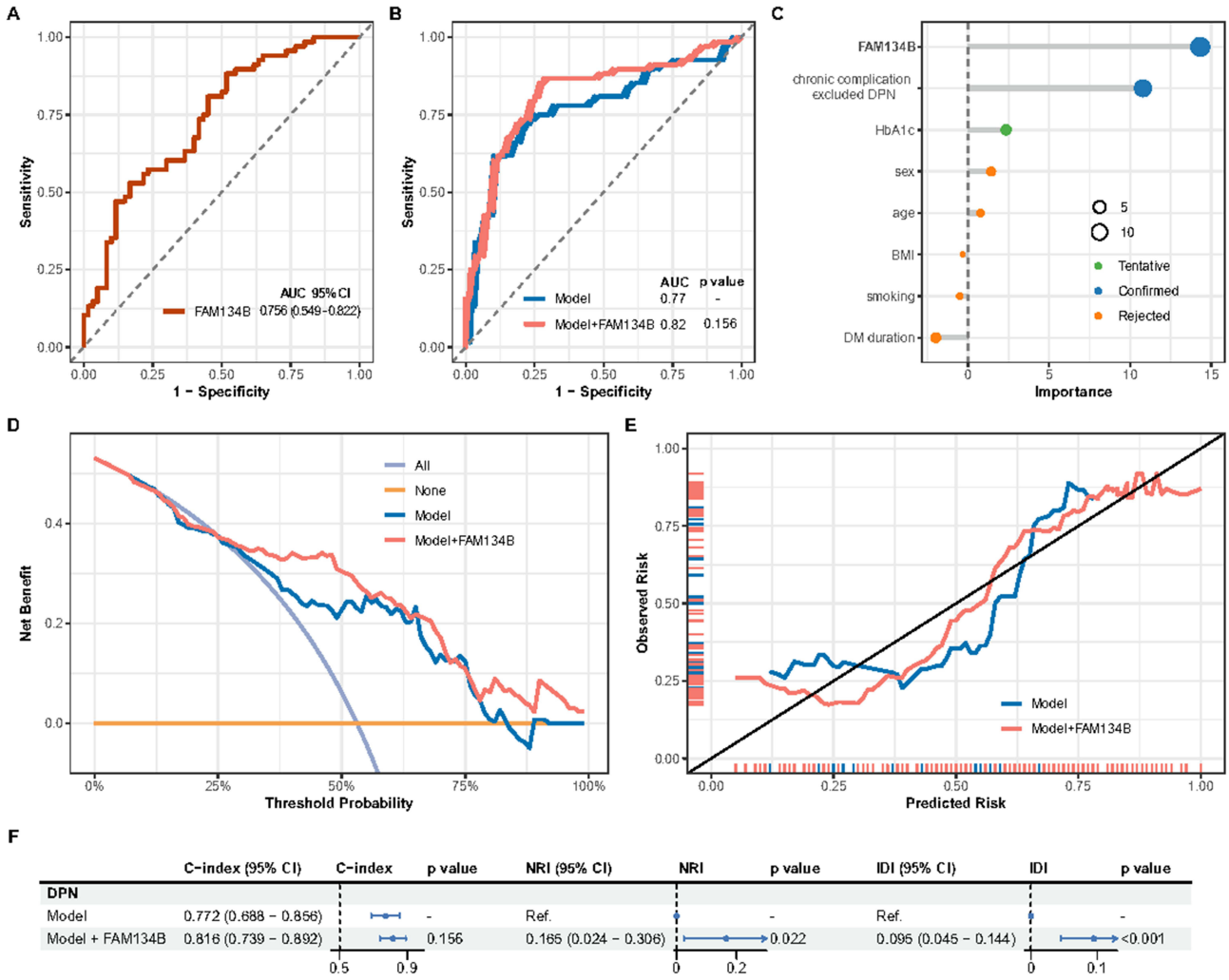

Figure 8 (**A**) ROC curve for plasma FAM134B mRNA levels to indicate DPN among individuals with type 2 diabetes mellitus. (**B**) ROC curve comparison for the model with or without FAM134B. (**C**) Feature importance assessment via Boruta analysis for clinical variables associated with DPN. (**D**) Decision curve analysis for the model with or without FAM134B. (**E**) Calibration curve analysis for the model with or without FAM134B. (**F**) Evaluation of model improvement with and without FAM134B for the diagnostic prediction of DPN. The model includes age, sex, BMI, smoking, diabetes duration, chronic complication excluded DPN, and HbA1c.

Abbreviations: DPN, diabetic peripheral neuropathy; ROC, Receiver operating characteristic; BMI, body mass index; HbA1c, glycosylated hemoglobin; Ref, reference; C index, Harrell's concordance statistic; NRI, net reclassification improvement; IDI, integrated discrimination improvement.

The NCT, a classical electrophysiological examination, is the gold standard for identifying peripheral neuropathy. It can differentiate neuropathy from mimics (radiculopathy and distal myopathy), assess disease severity, reveal subclinical involvement of neurons and fibers in the absence of clinical manifestations, and identify major pathophysiological alterations (axonal vs demyelinating).[17] In contrast to axonal neuropathies, which show a loss of amplitude and relative preservation of conduction velocity, demyelinating polyneuropathies show a decline in nerve conduction velocity while maintaining nerve potential amplitudes.[18] The findings of the present study show that increased FAM134B levels correlate strongly with slowed conduction velocity, prolonged distal latency, and flattened amplitude of the peripheral sensory and motor nerves. All these indicators are critical measures for evaluating myelinated axonal function of peripheral nerves. These data indicate that FAM134B may be involved in the pathological changes associated with peripheral neuropathy, especially demyelination.

Currently, NCT is a universally accepted diagnostic criterion for DPN;[19] however, its application in primary healthcare settings is limited due to being time-consuming, labor-intensive, and expensive. Although TCSS can be used for early detection of DPN, its accuracy is implicitly limited by its subjectivity. Therefore, a relatively easy-to-

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perform and objective examination is urgently needed to identify early DPN. FAM134B expression in peripheral blood could serve as an objective outcome to address deficiency.

Previous studies have suggested that risk factors such as age, sex, BMI, smoking, diabetes duration, and HbA1c are demonstrably associated with DPN.[20–23] In this study, after adjusting for confounding factors using binary logistic regression analysis, FAM134B was identified as an independent risk indicator for DPN. Notably, subgroup and interaction analyses showed that FAM134B had a stronger impact on DPN in males. However, no similar studies have been conducted to date. These sex differences may be linked to the protective benefit of estrogen in females, which could be counteracted by the negative effects of FAM134B. Male sex is considered a risk factor for DPN; however, it should be noted that the study cohort had an imbalanced sex ratio (male: female ≈ 2:1), which may affect the objectivity of the statistical analysis. The interaction between sex and increased expression of FAM134B in diabetic populations, especially those with DPN, remains unclear and warrants further investigation. Nevertheless, this finding supports our hypothesis that FAM134B might be a significant risk factor influencing the occurrence and progression of DPN.

Most studies have shown that FAM134B contributes to the development, survival, and repair of the nervous system; however, the definite mechanisms involved in DPN remain incompletely elucidated. The increased expression of FAM134B in our study suggests that its role in the pathogenesis of DPN is different from that in HSAN type IIB.

A report published in *Nature* indicates that FAM134B functions as an autophagy receptor for the endoplasmic reticulum (ER), promoting ER fragmentation and facilitating its entry into the autophagosome to ensure the decomposition and removal of damaged ER components.[5]

Appropriate autophagy is crucial for cell homeostasis; however, dysregulated autophagy can lead to various disease presentations, including inflammation, metabolic disturbances, and neurodegenerative alterations.[24] Numerous studies indicate that severe toxicity of glucose and oxidative stress can result in dysregulated autophagy.[25–27] Furthermore, excessive autophagy may contribute to the excessive degradation of myelin-associated proteins and the death of glial cells. Therefore, the driving effect of FAM134B on DPN progression may be mediated through the modulation of ER-phagy.

ROC curve analysis suggested that plasma FAM134B mRNA levels have diagnostic value for DPN. Furthermore, our study showed that adding FAM134B expression to the diagnostic model enhanced the identification of DPN. The Plus model exhibited satisfactory clinical value across different indices, such as Boruta feature importance, IDI, and NRI. These findings indicate the necessity of further mechanistic research into the pathogenic effects of FAM134B and its role in the formation and advancement of DPN.

This study had several limitations. As this study was retrospective and cross-sectional, determining a causal relationship between the expression of FAM134B and the risk of developing DPN could not be established. Additionally, no commercial kit exists for detecting FAM134B protein expression in peripheral blood; therefore, we could only detect mRNA levels via PCR to indirectly reflect FAM134B expression. The cutoff values derived from the Jordon index represent relative expression values applied to the current study population; nonetheless, these shortcomings could be addressed by employing standardized controls if future clinical applications are pursued. Finally, the study included only individuals with type 2 diabetes and lacked non-diabetic control data, making it difficult to confirm the association between FAM134B expression levels and DPN across populations.

Conclusion

This study revealed that plasma FAM134B mRNA levels were significantly elevated in individuals with DPN in the type 2 diabetes mellitus population and were an independent factor influencing the presence of DPN. Additionally, different statistical models demonstrated that FAM134B had significant diagnostic predictive value for DPN. To our best knowledge, this is the first study to comprehensively assess the association between FAM134B and DPN. Further well-designed prospective longitudinal studies are needed to validate these findings and clarify the precise role of FAM134B in the etiology of DPN. Thus, FAM134B may emerge as a promising target for both diagnostic and therapeutic management strategies for DPN.

Data Sharing Statement

All data are available on reasonable request from corresponding authors.

Ethics Approval and Informed Consent

This study was conducted in accordance with the declaration of Helsinki and approved by the Ethics Committee of Sun Yat-sen Memorial Hospital, Sun Yat-sen University (Approval No. SYSKY-2022-042-03). All participants have signed the informed consent.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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