

Intelectin-1 (*ITLN1*) Val109Asp (rs2274907) polymorphism: Association with circulating Omentin-1 Levels and Metaflammation in Men with Type 2 Diabetes

Saiaia Ikkurthi

AIIMS, Mangalagiri <https://orcid.org/0000-0002-9148-2628>

Srinivasan Raghavan Abu

raghavan.drvars2000@gmail.com

Mahatma Gandhi Medical College and Research Institute <https://orcid.org/0000-0001-5775-272X>

Suresh Vaikkakara

AIIMS, Mangalagiri <https://orcid.org/0000-0002-9563-6874>

Jayanthi Rajendran

Mahatma Gandhi Medical College and Research Institute <https://orcid.org/0000-0002-4795-2696>

Desai Vidya Sripad

AIIMS, Mangalagiri <https://orcid.org/0000-0002-4085-6351>

M.Rajeswari

A IIMS, Mangalagiri <https://orcid.org/0000-0003-1620-7359>

Research Article

Keywords: ITLN1 Val109Asp, Omentin-1, Insulin resistance, Type 2 diabetes mellitus, Metaflammation, Obesity

Posted Date: October 5th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11229523/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.
[Read Full License](#)

Additional Declarations: The authors declare no competing interests.

Abstract

Aim

Omentin-1 is an adipokine associated with insulin sensitivity and inflammatory processes, while the ITLN1 Val109Asp (rs2274907) variant has been implicated in metabolic phenotypes. We investigated its association with circulating omentin-1 and a metaflammatory phenotype in men with type 2 diabetes mellitus (T2DM).

Methods

In this cross-sectional study, 225 men with T2DM were genotyped for ITLN1 Val109Asp (TT, AT, and AA). Anthropometric, glycaemic, insulin-resistance, lipid, inflammatory, and haematological parameters were compared across genotypes. Associations between circulating omentin-1 and metabolic, inflammatory, and haematological parameters were assessed using Spearman correlation. Logistic regression evaluated associations between the variant and obesity under dominant, recessive, and additive models. Receiver operating characteristic analysis assessed discrimination of low circulating omentin-1.

Results

Omentin-1 concentrations decreased progressively from TT to AT to AA genotypes [749.6, 627.9, and 483.2 ng/L, respectively; $P < 0.001$], whereas BMI, HOMA-IR, METS-IR, lipid abnormalities, and inflammatory markers showed less favourable profiles in the AA group. Genotype and allele distributions differed across BMI phenotypes ($P = 0.027$ and $P = 0.002$, respectively). Omentin-1 was inversely correlated with BMI, WHR, HOMA-IR, and METS-IR and positively correlated with QUICKI across genotype groups. Each additional A allele was associated with higher odds of obesity (age-adjusted OR 1.97, 95% CI 1.27–3.05; $P = 0.002$). IL-8 showed the highest discrimination for low omentin-1 (AUC 0.976, 95% CI 0.959–0.992).

Conclusion

ITLN1 Val109Asp was associated with circulating omentin-1 concentrations and a metaflammatory phenotype in men with T2DM, linking genetic variation with a metabolic–inflammatory profile.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a heterogeneous metabolic disorder characterised by impaired insulin action and dysregulated glucose homeostasis, with insulin resistance as a fundamental component of its pathophysiology [1]. Excess adiposity, particularly visceral adiposity, is closely linked to insulin resistance and chronic low-grade inflammation [2, 3]. This persistent, metabolically associated inflammatory state, often referred to as metaflammation, can arise in the context of metabolic excess and adipose tissue dysfunction. Altered adipokine secretion and inflammatory signalling may therefore contribute to the metabolic dysfunction characteristic of T2DM [2, 3].

Adipose tissue is an active endocrine organ that secretes adipokines involved in glucose and lipid metabolism, insulin sensitivity, and inflammatory regulation [4, 5]. Omentin-1, encoded by *ITLN1*, is predominantly expressed in the stromal vascular fraction of visceral adipose tissue and is the major circulating isoform of omentin [4, 6]. It enhances insulin-stimulated glucose uptake, whereas circulating concentrations are reduced in obesity [4–6].

Circulating omentin-1 has also been linked to insulin resistance, T2DM, and inflammation. A systematic review and meta-analysis reported lower circulating omentin-1 concentrations in individuals with T2DM than in non-diabetic controls [7]. In patients with impaired glucose regulation or newly diagnosed T2DM, omentin-1 was inversely associated with BMI, HOMA-IR, fasting insulin, TNF- α , and IL-6 [8]. Similarly, higher omentin-1 concentrations were associated with lower fasting insulin, IL-6, and TNF- α in individuals with obesity [9]. Experimental evidence suggests that omentin-1 can attenuate TNF- α -induced inflammatory signalling in human endothelial cells [10].

ITLN1 variation may contribute to inter-individual metabolic differences. The *ITLN1* Val109Asp (A326T; rs2274907) missense variant has been associated with insulin resistance and obesity-related traits, although findings have not been uniform. In Iranian individuals with newly diagnosed T2DM, rs2274907 was associated with higher HOMA-IR, particularly among overweight or obese participants [11]. In a Central-European cohort, the variant differed in distribution between obese and morbidly obese groups and was associated with daily energy intake [12]. In a large Asian Indian cohort, the A allele was associated with lower circulating adiponectin concentrations, with its association with cardiometabolic health attenuated after adjustment for adiponectin [13].

Despite these findings, the relationship between *ITLN1* Val109Asp and circulating omentin-1 in established T2DM remains insufficiently characterised, particularly in relation to metaflammation. We examined associations of this variant with circulating omentin-1, adiposity, insulin-resistance-related indices, and inflammatory markers in men with T2DM. We also evaluated obesity associations under different genetic models and the capacity of metabolic and inflammatory markers to discriminate low circulating omentin-1

2. Methods

2.1 Study design and participants

This cross-sectional study was conducted at a tertiary care teaching hospital in South India from September 2020 to December 2024. The study protocol was approved by the Institutional Ethics Committee (Approval No. AIIMS/MG/IEC/2020-21/57; approved on 19 September 2020), and written informed consent was obtained from all participants. The study was conducted in accordance with the principles of the Declaration of Helsinki [14].

Sample size was calculated using OpenEpi 3.01 based on reported DV genotype frequencies of 49.4% in individuals with diabetes and 27.1% in controls [11]. With $\alpha = 0.05$ and 80% power, the minimum sample

size was 75. We recruited 225 men with T2DM, 75 per BMI category.

Participants were classified according to Asia-Pacific BMI cut-offs as non-obese (18.5–22.9 kg/m²), overweight (23.0–27.5 kg/m²), or obese (> 27.5 kg/m²) [15]. Men aged 18–60 years with T2DM duration < 5 years were included.

Participants with type 1 diabetes mellitus or hepatic, renal, cardiovascular, thyroid, neuromuscular, malignant, inflammatory, or other endocrine disorders were excluded. Medication use, including glucose-lowering, lipid-lowering, and antihypertensive therapies, was recorded and considered when interpreting metabolic and inflammatory measurements.

2.2 Anthropometric and clinical measurements

Height, weight, waist and hip circumference were measured using standardised procedures; BMI and WHR were calculated using standard definitions.

Blood pressure was measured after at least 5 min of seated rest using a calibrated automated sphygmomanometer. Three measurements were obtained at 2-min intervals, and their mean was used for analysis [16]. Mean arterial pressure (MAP) was calculated as diastolic blood pressure plus one-third of the pulse pressure.

2.3 Blood collection and biochemical measurements

After an overnight fast of 8–10 h, venous blood was collected for biochemical, haematological, and molecular analyses; serum and plasma were separated, aliquoted, and stored at – 80°C until analysis.

Fasting plasma glucose, total cholesterol, triglycerides, and HDL-C were measured by enzymatic methods using an automated biochemical analyser (AU 780; Beckman Coulter, Brea, CA, USA). LDL-C was calculated using the Friedewald equation because triglyceride concentrations were < 400 mg/dL in all participants [17]. HbA1c was measured by high-performance liquid chromatography using the Tosoh G8 analyser and reported in NGSP (%) and IFCC (mmol/mol) units. Serum insulin was measured using the GENLISA™ Human Insulin ELISA kit (catalogue no. KBH0010; Krishgen Biosystems Pvt. Ltd., Mumbai, India), according to the manufacturer's instructions. Samples were analysed in duplicate.

2.4 Omentin-1 and inflammatory biomarker measurements

Serum omentin-1, TNF-α, IL-6, and IL-8 were measured using commercial ELISA kits (Krishgen Biosystems, Mumbai, India; catalogue numbers KBH3770, KB1145, KB1068, and KB1070, respectively) according to the manufacturers' instructions. All measurements were performed in duplicate.

Serum CRP was measured by an immunoturbidimetric method using the AU 780 automated biochemical analyser (Beckman Coulter, Brea, CA, USA), according to the manufacturer's instructions. ESR was measured in EDTA-anticoagulated whole blood using the CUBE 30 Touch ESR analyser (Diesse Diagnostica Senese S.p.A., Monteriggioni, Italy), based on a modified Westergren method [18]. Complete blood count parameters, including total leukocyte, neutrophil, lymphocyte, and monocyte counts, were

measured using a Sysmex XN-1000 automated haematology analyser (Sysmex Corporation, Kobe, Japan).

2.5 Derived metabolic and inflammatory indices

Insulin resistance and metabolic indices were calculated from fasting biochemical and anthropometric measurements.

HOMA-IR was calculated as:

$$\text{HOMA-IR} = [\text{fasting insulin (mIU/L)} \times \text{fasting glucose (mg/dL)}] / 405 [19].$$

QUICKI was calculated as:

$$\text{QUICKI} = 1 / [\ln(\text{fasting insulin [mIU/L]}) + \ln(\text{fasting glucose [mg/dL]})] [20].$$

METS-IR was calculated as:

$$\text{METS-IR} = \{\ln[2 \times \text{fasting glucose (mg/dL)} + \text{triglycerides (mg/dL)}] \times \text{BMI (kg/m}^2)\} / \ln[\text{HDL-C (mg/dL)}] [21].$$

AIP was calculated as:

$$\text{AIP} = \log_{10}[\text{triglycerides (mg/dL)} / \text{HDL-C (mg/dL)}] [22].$$

MLR was calculated as the absolute monocyte count divided by the absolute lymphocyte count.

Systemic Inflammation Response Index (SIRI) was calculated as the product of the absolute neutrophil and monocyte counts divided by the absolute lymphocyte count [23].

2.6 DNA extraction and *ITLN1* genotyping

Genomic DNA was extracted from peripheral whole blood collected in EDTA-containing vacutainer tubes using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany), according to the manufacturer's instructions. DNA concentration and purity were assessed spectrophotometrically, and samples were stored at -20°C until genotyping.

The *ITLN1* Val109Asp (A326T; rs2274907) missense polymorphism was genotyped using a pre-designed TaqMan™ SNP Genotyping Assay (Assay ID C__16183152_10; SNP ID rs2274907; Thermo Fisher Scientific/Applied Biosystems, Waltham, MA, USA) with TaqMan™ Genotyping Master Mix (catalogue no. 4371353) on a QuantStudio™ 5 Dx Real-Time PCR System, according to the manufacturer's protocol. Genotypes were determined by allelic discrimination using QuantStudio™ Design and Analysis Software. Positive and no-template controls were included in each assay run. Samples were assigned as TT, AT, or AA according to their allelic-discrimination clusters.

2.7 Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 31.0 (IBM Corp., Armonk, NY, USA). Continuous-variable distributions were assessed using the Shapiro–Wilk test and are presented as median (interquartile range [IQR]); categorical variables are presented as frequencies and percentages. There were no missing data for variables included in the final analyses. Continuous variables were compared among *ITLN1* Val109Asp (rs2274907) genotype groups (The TT genotype was considered the wild-type genotype, AT the heterozygous genotype, and AA the homozygous variant genotype) using the Kruskal–Wallis test followed by Dunn–Bonferroni post hoc comparisons where appropriate. Genotype and allele frequencies across BMI phenotype groups were compared using Pearson's χ^2 test.

Associations between circulating omentin-1 and anthropometric, glycaemic, metabolic, lipid, inflammatory, and haematological parameters were assessed using Spearman's rank correlation coefficient separately within the TT, AT, and AA genotype groups. Overall, Spearman correlations across all 225 participants were calculated for relationships presented in Fig. 2B–D

Binary logistic regression was used to evaluate the association between the *ITLN1* Val109Asp (rs2274907) polymorphism and obesity. Obesity was defined as BMI > 27.5 kg/m², with BMI ≤ 27.5 kg/m² classified as non-obese. For the dominant model, TT was compared with AT + AA; for the recessive model, TT + AT was compared with AA; and for the additive model, genotypes were coded as TT = 0, AT = 1, and AA = 2. Crude and age-adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were estimated; in the additive model, the OR represented the change in odds of obesity per additional A allele.

Receiver operating characteristic (ROC) curve analysis assessed the discriminatory performance of selected anthropometric, metabolic, and inflammatory markers for low circulating omentin-1. Low circulating omentin-1 was defined as ≤ 560.45 ng/L using a study-derived threshold based on its observed distribution across the three BMI groups. AUCs with 95% CIs were calculated, and optimal marker cut-offs were determined using Youden's index, with corresponding sensitivity and specificity. For QUICKI, classification direction was reversed because lower values were associated with a greater likelihood of low circulating omentin-1. All tests were two-sided, with $P < 0.05$ considered statistically significant.

3 Results

3.1 Genotype-related differences in anthropometric, metabolic, and inflammatory characteristics

Among the 225 participants, 57 (25.3%) had the TT genotype, 89 (39.6%) the AT genotype, and 79 (35.1%) the AA genotype. Genotype groups differed in anthropometric, glycaemic, insulin-resistance, lipid, inflammatory, and haematological parameters (Table 1). Circulating omentin-1 decreased progressively from TT to AT to AA [749.6 (668.7–775.6), 627.9 (528.9–665.8), and 483.2 (398.7–552.7)

ng/L, respectively; $P < 0.001$]. HOMA-IR increased and QUICKI decreased across genotype groups, while the AA genotype showed the most adverse lipid and inflammatory profiles. MLR and SIRI did not differ significantly ($P = 0.199$ and 0.120 , respectively). Dunn–Bonferroni pairwise comparisons are in **Supplementary Table S2**

Table 1

Anthropometric, glycaemic, metabolic, lipid, inflammatory, and haematological characteristics according to ITLN1 Val109Asp (rs2274907) genotype in adult men with type 2 diabetes mellitus

Variable	TT genotype (n = 57)	AT genotype (n = 89)	AA genotype (n = 79)	P-value
Anthropometric characteristics				
Body mass index (kg/m ²)	26.366 (22.724–32.007)	27.239 (22.790–33.090)	30.408 (26.449–33.854)	0.005
Waist-to-hip ratio (WHR)	1.113 (0.878–1.196)	1.135 (0.898–1.204)	1.180 (1.103–1.206)	0.02
Glycaemic and insulin-resistance parameters				
Fasting plasma glucose (mg/dL)	126 (121–129)	146 (137–152)	183 (173–202)	< 0.001
Glycated haemoglobin (HbA1c), % (mmol/mol)	6.10 (5.90–6.30) [43 (41–45)]	7.10 (6.70–7.60) [54 (50–60)]	9.60 (8.25–10.65) [81 (67–93)]	< 0.001
Fasting plasma insulin (mIU/L)	16.50 (14.90–18.70)	19.80 (17.80–21.30)	24.50 (23.15–26.70)	< 0.001
Homeostasis model assessment of insulin resistance (HOMA-IR)	5.111 (4.672–5.818)	6.967 (6.345–7.836)	10.970 (9.636–13.379)	< 0.001
Quantitative insulin sensitivity check index (QUICKI)	0.302 (0.297–0.305)	0.290 (0.286–0.293)	0.274 (0.268–0.278)	< 0.001
Metabolic score for insulin resistance (METS-IR)	44.739 (37.444–53.312)	48.331 (40.487–60.551)	59.507 (51.116–67.793)	< 0.001
Lipid parameters				
Total cholesterol (mg/dL)	201 (192–220)	250 (229–271)	290 (276–301)	< 0.001
Triglycerides (mg/dL)	145 (132–153)	173 (165–187)	242 (220–256.5)	< 0.001
HDL-C (mg/dL)	36 (35–38)	31 (30–32)	27 (26–29)	< 0.001
Data are presented as median (IQR). <i>P</i> values were obtained using the Kruskal–Wallis test. BMI, body mass index; WHR, waist-to-hip ratio; HOMA-IR, Homeostasis model assessment of insulin resistance; QUICKI, quantitative insulin sensitivity check index; METS-IR, metabolic score for insulin resistance; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; AIP, atherogenic index of plasma; TNF- α , tumour necrosis factor- α ; IL-6, interleukin-6; IL-8, interleukin-8; CRP, C-reactive protein; WBC, white blood cell; ESR, erythrocyte sedimentation rate; MLR, monocyte-to-lymphocyte ratio; SIRI, systemic inflammation response index.				

Variable	TT genotype (n = 57)	AT genotype (n = 89)	AA genotype (n = 79)	P-value
Anthropometric characteristics				
LDL-C (mg/dL)	135.2 (127.6–155.0)	184.4 (165.4–205.0)	214.2 (203.4–225.9)	< 0.001
Atherogenic index of plasma (AIP)	0.605 (0.534–0.640)	0.742 (0.712–0.785)	0.944 (0.890–0.982)	< 0.001
Adipokine and inflammatory markers				
Omentin-1 (ng/L)	749.6 (668.7–775.6)	627.9 (528.9–665.8)	483.2 (398.7–552.7)	< 0.001
Tumour necrosis factor- α (TNF- α) (pg/mL)	10.90 (9.60–12.40)	13.30 (11.50–20.10)	21.10 (17.20–23.55)	< 0.001
Interleukin-6 (IL-6) (pg/mL)	10.10 (8.90–10.90)	12.70 (11.20–14.30)	17.20 (14.55–19.20)	< 0.001
Interleukin-8 (IL-8) (pg/mL)	17.80 (16.10–20.60)	23.60 (21.10–28.90)	33.10 (28.10–38.80)	< 0.001
C-reactive protein (CRP) (mg/L)	9.10 (8.60–9.90)	10.80 (10.20–12.10)	14.10 (13.10–14.75)	< 0.001
Haematological and systemic inflammatory indices				
White blood cell count (WBC) ($\times 10^3/\mu\text{L}$)	10.10 (9.80–10.60)	11.10 (10.90–11.30)	12.10 (11.70–12.50)	< 0.001
Erythrocyte sedimentation rate (ESR) (mm/h)	10 (9–10)	13 (12–13)	16 (15–16)	< 0.001
Monocyte-to-lymphocyte ratio (MLR)	0.255 (0.227–0.291)	0.257 (0.221–0.307)	0.278 (0.223–0.337)	0.199
Systemic inflammation response index (SIRI)	2.284 (1.900–2.509)	2.192 (1.783–2.547)	2.455 (1.925–2.917)	0.12
Data are presented as median (IQR). <i>P</i> values were obtained using the Kruskal–Wallis test. BMI, body mass index; WHR, waist-to-hip ratio; HOMA-IR, Homeostasis model assessment of insulin resistance; QUICKI, quantitative insulin sensitivity check index; METS-IR, metabolic score for insulin resistance; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; AIP, atherogenic index of plasma; TNF- α , tumour necrosis factor- α ; IL-6, interleukin-6; IL-8, interleukin-8; CRP, C-reactive protein; WBC, white blood cell; ESR, erythrocyte sedimentation rate; MLR, monocyte-to-lymphocyte ratio; SIRI, systemic inflammation response index.				

3.2 Distribution of *ITLN1* Val109Asp genotypes and alleles across BMI phenotypes

ITLN1 Val109Asp (rs2274907) genotype distributions differed significantly across BMI phenotype groups ($P = 0.027$; Table 2). TT frequency decreased from 34.7% (26/75) in non-obese participants to 22.7% (17/75) in overweight and 18.7% (14/75) in obese participants. Conversely, AA frequency increased from 22.7% (17/75) to 36.0% (27/75) and 46.7% (35/75), respectively. Allele frequencies also differed significantly ($P = 0.002$), with A increasing from 44.0% in non-obese participants to 56.7% in overweight and 64.0% in obese participants, with a corresponding decrease in T (Table 2).

Table 2

Distribution of *ITLN1* Val109Asp (rs2274907) genotype and allele frequencies according to body mass index phenotype in adult men with type 2 diabetes

Genotype/allele	Non-Obese (n = 75)	Overweight (n = 75)	Obese (n = 75)	P-value
Genotype, n (%)				
TT	26 (34.7)	17 (22.7)	14 (18.7)	0.027
AT	32 (42.7)	31 (41.3)	26 (34.7)	
AA	17 (22.7)	27 (36.0)	35 (46.7)	
Allele frequency, n (%)				
A	66 (44.0)	85 (56.7)	96 (64.0)	0.002
T	84 (56.0)	65 (43.3)	54 (36.0)	

Data are presented as number (%). Genotype and allele frequencies were compared among BMI phenotype groups using Pearson's χ^2 test. Allele frequencies were calculated assuming two alleles per participant (150 alleles per group). All tests were two-sided, and a P value < 0.05 was considered statistically significant.

3.3 Genotype-stratified associations of circulating omentin-1 with metabolic and inflammatory parameters

Omentin-1 showed genotype-stratified correlations with metabolic, lipid, inflammatory, and haematological parameters (Table 3). In all three genotype groups, omentin-1 was inversely correlated with BMI, WHR, HOMA-IR, and METS-IR and positively correlated with QUICKI (all $P < 0.001$). Omentin-1 was also inversely correlated with total cholesterol, triglycerides, LDL-C, and AIP and positively correlated with HDL-C across the genotype groups (all $P < 0.01$).

Table 3

Spearman correlation of circulating omentin-1 with anthropometric, glycaemic, metabolic, lipid, inflammatory, and haematological parameters according to *ITLN1* Val109Asp (rs2274907) genotype

Variables	TT genotype (n = 57)		AT genotype (n = 89)		AA genotype (n = 79)	
	ρ	P	ρ	P	ρ	P
Anthropometric characteristics						
Body mass index (kg/m ²)	-0.792	< 0.001	-0.840	< 0.001	-0.680	< 0.001
Waist-to-hip ratio (WHR)	-0.814	< 0.001	-0.892	< 0.001	-0.803	< 0.001
Glycaemic and insulin-resistance parameters						
Fasting plasma glucose (mg/dL)	0.039	0.775	-0.382	< 0.001	-0.252	0.025
Glycated haemoglobin (HbA1c), % (mmol/mol)	-0.390	0.003	-0.643	< 0.001	-0.649	< 0.001
Fasting plasma insulin (mIU/L)	-0.641	< 0.001	-0.696	< 0.001	-0.647	< 0.001
HOMA-IR	-0.586	< 0.001	-0.683	< 0.001	-0.536	< 0.001
QUICKI	0.586	< 0.001	0.683	< 0.001	0.536	< 0.001
METS-IR	-0.848	< 0.001	-0.870	< 0.001	-0.775	< 0.001
Lipid parameters						
Total cholesterol (mg/dL)	-0.585	< 0.001	-0.678	< 0.001	-0.693	< 0.001
Triglycerides (mg/dL)	-0.385	0.003	-0.617	< 0.001	-0.419	< 0.001
HDL-C (mg/dL)	0.895	< 0.001	0.88	< 0.001	0.81	< 0.001
LDL-C (mg/dL)	-0.662	< 0.001	-0.711	< 0.001	-0.775	< 0.001

Data are presented as Spearman's rank correlation coefficient (ρ) and corresponding P values. Correlation analyses were performed separately within each *ITLN1* Val109Asp (rs2274907) genotype group (TT, AT, and AA) to assess the correlation between circulating omentin-1 concentration and the parameters shown. All tests were two-sided. A P value < 0.05 was considered statistically significant.

Variables	TT genotype (n = 57)		AT genotype (n = 89)		AA genotype (n = 79)	
	ρ	<i>P</i>	ρ	<i>P</i>	ρ	<i>P</i>
Anthropometric characteristics						
Atherogenic index of plasma (AIP)	-0.649	< 0.001	-0.843	< 0.001	-0.666	< 0.001
Adipokine and inflammatory markers						
Tumour necrosis factor- α (TNF- α) (pg/mL)	-0.814	< 0.001	-0.877	< 0.001	-0.771	< 0.001
Interleukin-6 (IL-6) (pg/mL)	-0.783	< 0.001	-0.846	< 0.001	-0.777	< 0.001
Interleukin-8 (IL-8) (pg/mL)	-0.766	< 0.001	-0.841	< 0.001	-0.804	< 0.001
C-reactive protein (CRP) (mg/L)	-0.630	< 0.001	-0.747	< 0.001	-0.626	< 0.001
Haematological and systemic inflammatory indices						
White blood cell count (WBC) ($\times 10^3/\mu\text{L}$)	-0.635	< 0.001	-0.507	< 0.001	-0.680	< 0.001
Erythrocyte sedimentation rate (ESR) (mm/h)	-0.527	< 0.001	-0.533	< 0.001	-0.558	< 0.001
Monocyte-to-lymphocyte ratio (MLR)	-0.340	0.01	-0.500	< 0.001	-0.445	< 0.001
Systemic inflammation response index (SIRI)	-0.399	0.002	-0.550	< 0.001	-0.467	< 0.001
Data are presented as Spearman's rank correlation coefficient (ρ) and corresponding <i>P</i> values. Correlation analyses were performed separately within each ITLN1 Val109Asp (rs2274907) genotype group (TT, AT, and AA) to assess the correlation between circulating omentin-1 concentration and the parameters shown. All tests were two-sided. A <i>P</i> value < 0.05 was considered statistically significant.						

Inflammatory markers, including TNF- α , IL-6, IL-8, and CRP, showed significant inverse correlations with omentin-1 in all three genotype groups (all *P* < 0.001). WBC count and ESR also showed significant inverse correlations, as did the inflammatory indices MLR and SIRI (all *P* $\leq$ 0.01) (Table 3). Fasting plasma glucose was not significantly correlated with omentin-1 in the TT genotype group (ρ = 0.039, *P* = 0.775), whereas significant inverse correlations were observed in the AT (ρ = -0.382, *P* < 0.001) and AA (ρ = -0.252, *P* = 0.025) genotype groups. In the overall study population, circulating omentin-1 was

inversely correlated with WHR ($\rho = -0.706$, $P < 0.001$), HOMA-IR ($\rho = -0.838$, $P < 0.001$), and TNF- α ($\rho = -0.931$, $P < 0.001$) (Fig. 2B–D).

3.4 Association of *ITLN1* Val109Asp with obesity under genetic models

Binary logistic regression showed significant associations between *ITLN1* Val109Asp (rs2274907) and obesity under dominant, recessive, and additive models (Table 4). Under the dominant model, AT or AA genotypes had higher odds of obesity than TT (crude OR 2.31, 95% CI 1.09–4.90; $P = 0.029$; age-adjusted OR 2.28, 95% CI 1.08–4.84; $P = 0.032$). Under the recessive model, AA had higher odds of obesity than TT or AT (crude OR 2.99, 95% CI 1.47–6.05; $P = 0.002$; age-adjusted OR 2.96, 95% CI 1.46–5.99; $P = 0.003$). In the additive model, each additional A allele was associated with higher odds of obesity (crude OR 1.98, 95% CI 1.28–3.07; $P = 0.002$), with a similar age-adjusted association (OR 1.97, 95% CI 1.27–3.05; $P = 0.002$). The corresponding crude allelic association is provided in **Supplementary Table S3**.

Table 4

Binary logistic regression analysis of the association between the *ITLN1* Val109Asp (rs2274907) polymorphism and obesity in adult men with type 2 diabetes mellitus

Genetic model	Genotype comparison	Crude OR (95% CI)	P-value	Age-adjusted OR† (95% CI)	P-value
Dominant	TT vs AT + AA	2.31 (1.09–4.90)	0.029	2.28 (1.08–4.84)	0.032
Recessive	TT + AT vs AA	2.99 (1.47–6.05)	0.002	2.96 (1.46–5.99)	0.003
Additive	Per additional A allele	1.98 (1.28–3.07)	0.002	1.97 (1.27–3.05)	0.002

Data were analysed using binary logistic regression with obesity status (obese vs non-obese) as the dependent variable. Crude ORs were estimated using univariable logistic regression. †Age-adjusted models were adjusted for age (years). Reference categories were TT for the dominant model and TT + AT for the recessive model. For the additive model, genotypes were coded as TT = 0, AT = 1, and AA = 2; the OR represents the change in odds of obesity associated with each additional A allele. ORs are presented with 95% CIs. All tests were two-sided, and $P < 0.05$ was considered statistically significant.

3.5 ROC analysis of markers for low circulating omentin-1

Receiver operating characteristic (ROC) analysis assessed the discriminatory performance of anthropometric, metabolic, and inflammatory markers for identifying participants with low circulating omentin-1 (≤ 560.45 ng/L; $n = 89$) (Fig. 1; **Supplementary Table S1**). All evaluated markers had areas under the curve (AUCs) significantly greater than 0.50 ($P < 0.001$). IL-8 showed the highest AUC (0.976, 95% CI 0.959–0.992), followed by TNF- α (0.968, 95% CI 0.949–0.988) and IL-6 (0.960, 95% CI 0.937–0.983). METS-IR also showed high discriminatory performance (AUC 0.928, 95% CI 0.894–0.961), followed by CRP (AUC 0.922, 95% CI 0.887–0.956), QUICKI and HOMA-IR (both AUC 0.914, 95% CI 0.876–0.951), WHR (AUC 0.863, 95% CI 0.813–0.914), BMI (AUC 0.854, 95% CI 0.803–0.906), and SIRI

(AUC 0.771, 95% CI 0.707–0.835). Youden index-derived cut-offs were > 27.100 for IL-8 (sensitivity 94.4%, specificity 93.4%), > 17.200 pg/mL for TNF- α (93.3%, 88.2%), > 14.300 pg/mL for IL-6 (88.8%, 91.2%), and > 49.968 for METS-IR (96.6%, 75.7%). Corresponding thresholds and classification characteristics for the remaining markers are provided in **Supplementary Table S1**.

4 Discussion

In this cross-sectional study of 225 men with T2DM, *ITLN1* Val109Asp (rs2274907) was associated with circulating omentin-1 and a broader metaflammatory phenotype. Omentin-1 decreased across TT, AT, and AA genotypes, while the AA genotype and A allele were associated with adverse obesity-related and metabolic–inflammatory features. Omentin-1 also showed inverse associations with adiposity, insulin-resistance-related indices, lipids, and inflammatory markers. The study integrates genetic variation, circulating omentin-1, and metabolic and inflammatory measures.

Previous studies had linked rs2274907 to metabolic phenotypes. In Iranian individuals with newly diagnosed type 2 diabetes, the variant was associated with higher HOMA-IR, particularly among those who were overweight or obese [11]. An Indian study reported an association between the AT genotype and higher BMI among individuals with type 2 diabetes, although no association with type 2 diabetes susceptibility was observed [24]. In contrast, an earlier study in a Caucasian population found no significant differences in Val109Asp allele frequencies or genotype distributions between individuals with type 2 diabetes and non-diabetic controls [27]. Taken together, the present findings extend previous work on *ITLN1* Val109Asp by connecting the variant not only with metabolic traits but also with circulating omentin-1 and a broader metaflammatory profile. This integrated association between genotype, circulating protein concentration, metabolic dysfunction, and inflammatory status represents a principal contribution of the present study.

The male-specific design is also relevant because adipose tissue biology and circulating adipokine profiles may exhibit sex-related differences. By examining a male T2DM cohort without pooling male and female participants, the present study provides evidence on the relationship between *ITLN1* variation, circulating omentin-1, and the associated metabolic–inflammatory phenotype. Whether these associations are similar in women with T2DM remains to be established.

Omentin-1 was inversely correlated with BMI, WHR, HOMA-IR, and METS-IR and positively correlated with QUICKI across all three genotype groups. Overall analyses showed inverse associations with WHR, HOMA-IR, and TNF- α (Fig. 2). Previous studies have reported inverse relationships between circulating omentin-1 and BMI, HOMA-IR, fasting insulin, and metabolic measures [8, 25, 28]. A meta-analysis of 42 studies also demonstrated lower circulating omentin-1 concentrations in T2DM than in controls [7].

Circulating omentin-1 was also inversely correlated with TNF- α , IL-6, IL-8, and CRP across all three genotype groups. This finding is consistent with previous clinical evidence linking lower omentin-1 concentrations with inflammatory markers [8, 9]. Experimental studies have shown that omentin can attenuate TNF- α -induced inflammatory signalling in human endothelial cells [10]. However, given the

cross-sectional design, these findings demonstrate associations but cannot establish temporal directionality or causality.

The association of *ITLN1* Val109Asp with obesity was supported by BMI-stratified genotype and allele distributions and genetic-model analyses. The A allele was associated with higher odds of obesity under dominant, recessive, and additive models, with similar estimates after adjustment for age. Previous studies have also linked rs2274907 with obesity-related phenotypes, including higher HOMA-IR in Iranian individuals with type 2 diabetes [11], differences in genotype distribution between obese and morbidly obese individuals in a Central European cohort [12], and higher BMI associated with the AT genotype in an Indian population with type 2 diabetes [24]. Our findings extend these observations by demonstrating a genotype-related gradient in circulating omentin-1.

The biological basis of this genotype–phenotype pattern remains uncertain. Val109Asp is a missense variant in *ITLN1*, and omentin-1 has been shown experimentally to enhance insulin-stimulated glucose uptake and Akt phosphorylation and to exert anti-inflammatory effects [4, 6, 9, 10]. However, functional investigation of the V109D variant did not demonstrate alterations in *ITLN1* protein abundance in intestinal tissue, glycan binding, or protein oligomerisation [26]. Thus, the present findings do not establish that the amino acid substitution directly alters omentin-1 biology. The observed genotype–omentin-1 association may instead involve tissue-specific expression, secretion, protein processing, or other regulatory mechanisms that require further investigation.

ROC analysis showed that inflammatory and metabolic markers discriminated participants with low circulating omentin-1. However, the threshold for low omentin-1 and marker-specific cut-offs were derived from the same population; therefore, these findings represent internal discriminatory performance rather than validated diagnostic thresholds and require external validation.

5. Conclusions

The *ITLN1* Val109Asp (rs2274907) polymorphism was associated with circulating omentin-1 concentrations and a broader metaflammatory phenotype in men with type 2 diabetes. The AA genotype was associated with lower circulating omentin-1 concentrations and more adverse adiposity, insulin-resistance-related, lipid, and inflammatory profiles, while the A allele was associated with higher odds of obesity. The observed relationships integrate genetic variation with a circulating adipokine and multiple metabolic and inflammatory features, highlighting an association between *ITLN1* variation and the metabolic–inflammatory milieu of T2DM. These findings require confirmation in larger, sex-diverse populations and functional studies.

Declarations

CRedit authorship contribution statement

Conceptualization: Abu R. Srinivasan, Saidaiah Ikkurthi

Methodology: Abu R. Srinivasan, Saidaiah Ikkurthi, M Rajeswari

Data curation: Saidaiah Ikkurthi

Formal analysis: Saidaiah Ikkurthi, M Rajeswari

Investigation: Saidaiah Ikkurthi, Suresh Vaikkakara

Validation: Abu R. Srinivasan, Saidaiah Ikkurthi

Writing – original draft: Saidaiah Ikkurthi

Writing – review & editing: Abu R. Srinivasan, Jayanthi Rajendran, Desai Vidya Sripad

Supervision: Abu R. Srinivasan

Final approval of the manuscript: All authors

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethics approval and informed consent

The study protocol was approved by the Institutional Ethics Committee of All India Institute of Medical Sciences (AIIMS), Mangalagiri, Andhra Pradesh, India (Ref. No. AIIMS/MG/IEC/2020-21/57). The study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants before enrolment.

Data availability statement

The datasets generated and/or analysed during the current study are not publicly available because they contain participant-level clinical data and are subject to institutional and ethical restrictions. De-identified data may be made available by the corresponding author upon reasonable request and subject to appropriate institutional and ethical approvals.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this manuscript, the authors used ChatGPT (OpenAI) solely for language editing, grammar correction, manuscript organisation, and improvement of readability. All scientific content, data interpretation, analyses, conclusions, and final editorial decisions were independently

reviewed, verified, and approved by the authors. The authors accept full responsibility for the accuracy, originality, and integrity of the manuscript.

Acknowledgements

The authors gratefully acknowledge all participants for their valuable contribution to this study. The authors also thank Sri Balaji Vidyapeeth (Deemed to be University), Puducherry, for academic guidance, and the All-India Institute of Medical Sciences (AIIMS), Mangalagiri, Andhra Pradesh, India, for providing the laboratory and research facilities required for this work.

References

1. Accili D, Deng Z, Liu Q (2025) Insulin resistance in type 2 diabetes mellitus. *Nat Rev Endocrinol* 21(7):413–426. <https://doi.org/10.1038/s41574-025-01114-y>
2. Burhans MS, Hagman DK, Kuzma JN, Schmidt KA, Kratz M (2019) Contribution of adipose tissue inflammation to the development of type 2 diabetes mellitus. *Compr Physiol* 9(1):1–58. <https://doi.org/10.1002/cphy.c170040>
3. Zatterale F, Longo M, Naderi J, Raciti GA, Desiderio A, Miele C et al (2020) Chronic adipose tissue inflammation linking obesity to insulin resistance and type 2 diabetes. *Front Physiol* 10:1607. <https://doi.org/10.3389/fphys.2019.01607>
4. Yang RZ, Lee MJ, Hu H, Pray J, Wu HB, Hansen BC, Shuldiner AR, Fried SK, McLenithan JC, Gong DW (2006) Identification of omentin as a novel depot-specific adipokine in human adipose tissue: possible role in modulating insulin action. *Am J Physiol Endocrinol Metab* 290(6):E1253–E1261. <https://doi.org/10.1152/ajpendo.00572.2004>
5. de Souza Batista CM, Yang RZ, Lee MJ, Glynn NM, Yu DZ, Pray J, Ndubuizu K, Patil S, Schwartz A, Kligman M, Fried SK, Gong DW, Shuldiner AR, Pollin TI, McLenithan JC (2007) Omentin plasma levels and gene expression are decreased in obesity. *Diabetes* 56(6):1655–1661. [10.2337/db06-1506](https://doi.org/10.2337/db06-1506)
6. Watanabe T, Watanabe-Kominato K, Takahashi Y, Kojima M, Watanabe R (2017) Adipose tissue-derived omentin-1 function and regulation. *Compr Physiol* 7(3):765–781. <https://doi.org/10.1002/cphy.c160043>
7. Pan X, Kaminga AC, Wen SW, Acheampong K, Liu A (2019) Omentin-1 in diabetes mellitus: a systematic review and meta-analysis. *PLoS ONE* 14(12):e0226292. <https://doi.org/10.1371/journal.pone.0226292>
8. Pan HY, Guo L, Li Q (2010) Changes of serum omentin-1 levels in normal subjects and in patients with impaired glucose regulation and with newly diagnosed and untreated type 2 diabetes. *Diabetes Res Clin Pract* 88(1):29–33. <https://doi.org/10.1016/j.diabres.2010.01.013>
9. Zabetian-Targhi F, Mirzaei K, Keshavarz SA, Hossein-Nezhad A (2016) Modulatory role of omentin-1 in inflammation: cytokines and dietary intake. *J Am Coll Nutr* 35(8):670–678. <https://doi.org/10.1080/07315724.2015.1126207>

10. Yamawaki H, Kuramoto J, Kameshima S, Usui T, Okada M, Hara Y (2011) Omentin, a novel adipocytokine inhibits TNF-induced vascular inflammation in human endothelial cells. *Biochem Biophys Res Commun* 408(2):339–343. <https://doi.org/10.1016/j.bbrc.2011.04.039>
11. Khoshi A, Bajestani MK, Shakeri H, Goodarzi G, Azizi F (2019) Association of Omentin rs2274907 and FTO rs9939609 gene polymorphisms with insulin resistance in Iranian individuals with newly diagnosed type 2 diabetes. *Lipids Health Dis* 18(1):142. <https://doi.org/10.1186/s12944-019-1085-5>
12. Splichal Z, Bienertova-Vasku J, Novak J, Zlamal F, Tomandl J, Tomandlova M, Forejt M, Havlenova S, Jackowska A, Vasku A (2015) The common polymorphism Val109Asp in the omentin gene is associated with daily energy intake in the Central-European population. *Nutr Neurosci* 18(1):41–48. <https://doi.org/10.1179/1476830513Y.0000000100>
13. Vimalleswaran KS, Bodhini D, Jiang J, Ramya K, Mohan D, Shanthi Rani CS et al (2021) Circulating adiponectin mediates the association between omentin gene polymorphism and cardiometabolic health in Asian Indians. *PLoS ONE* 16(5):e0238555. <https://doi.org/10.1371/journal.pone.0238555>
14. World Medical Association (2013) World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 310(20):2191–2194. <https://doi.org/10.1001/jama.2013.281053>
15. WHO Expert Consultation (2004) Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* 363(9403):157–163. [https://doi.org/10.1016/S0140-6736\(03\)15268-3](https://doi.org/10.1016/S0140-6736(03)15268-3)
16. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D et al (2020) 2020 International Society of Hypertension Global Hypertension Practice Guidelines. *Hypertension* 75(6):1334–1357. <https://doi.org/10.1161/HYPERTENSIONAHA.120.15026>
17. Friedewald WT, Levy RI, Fredrickson DS (1972) Estimation of the concentration of low-density-lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 18(6):499–502. <https://doi.org/10.1093/clinchem/18.6.499>
18. Lapić I, Rade A, Kraljević A, Miloš M, Coen Herak D, Daskijević L, Cerovac P, Rogić D (2023) Analytical validation of the modified Westergren method on the automated erythrocyte sedimentation rate analyser CUBE 30 touch. *Clin Chem Lab Med* 61(8):1463–1469. <https://doi.org/10.1515/cclm-2023-0033>
19. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC (1985) Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28(7):412–419. <https://doi.org/10.1007/BF00280883>
20. Katz A, Nambi SS, Mather K, Baron AD, Follmann DA, Sullivan G, Quon MJ (2000) Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. *J Clin Endocrinol Metab* 85(7):2402–2410. <https://doi.org/10.1210/jcem.85.7.6661>
21. Bello-Chavolla OY, Almeda-Valdes P, Gomez-Velasco D, Viveros-Ruiz T, Cruz-Bautista I, Romo-Romo A et al (2018) METS-IR, a novel score to evaluate insulin sensitivity, is predictive of visceral adiposity

- and incident type 2 diabetes. *Eur J Endocrinol* 178(5):533–544. <https://doi.org/10.1530/EJE-17-0883>
22. Dobiášová M, Frohlich J (2001) The plasma parameter log (TG/HDL-C) as an atherogenic index: correlation with lipoprotein particle size and esterification rate in apoB-lipoprotein-depleted plasma (FERHDL). *Clin Biochem* 34(7):583–588. [https://doi.org/10.1016/S0009-9120\(01\)00263-6](https://doi.org/10.1016/S0009-9120(01)00263-6)
23. Qi Q, Zhuang L, Shen Y et al (2016) A novel systemic inflammation response index (SIRI) for predicting the survival of patients with pancreatic cancer after chemotherapy. *Cancer* 122(14):2151–2160. <https://doi.org/10.1002/cncr.30057>
24. Rathwa N, Patel R, Palit SP, Jadeja SD, Narwaria M, Ramachandran AV, Begum R (2019) Circulatory Omentin-1 levels but not genetic variants influence the pathophysiology of type 2 diabetes. *Cytokine* 119:144–151. <https://doi.org/10.1016/j.cyto.2019.03.011>
25. Zhang Q, Zhu L, Zheng M, Fan C, Li Y, Zhang D et al (2014) Changes of serum omentin-1 levels in normal subjects, type 2 diabetes and type 2 diabetes with overweight and obesity in Chinese adults. *Ann Endocrinol (Paris)* 75(3):171–175. <https://doi.org/10.1016/j.ando.2014.04.013>
26. Nonnecke EB, Castillo PA, Dugan AE, Almalki F, Underwood MA, De La Motte CA et al (2021) Human intelectin-1 (*ITLN1*) genetic variation and intestinal expression. *Sci Rep* 11(1):12889. <https://doi.org/10.1038/s41598-021-92198-9>
27. Schäffler A, Zeitoun M, Wobser H, Buechler C, Aslanidis C, Herfarth H (2007) Frequency and significance of the novel single nucleotide missense polymorphism Val109Asp in the human gene encoding omentin in Caucasian patients with type 2 diabetes mellitus or chronic inflammatory bowel diseases. *Cardiovasc Diabetol* 6:3. <https://doi.org/10.1186/1475-2840-6-3>
28. Yan P, Liu D, Long M, Ren Y, Pang J, Li R (2011) Changes of serum omentin levels and relationship between omentin and adiponectin concentrations in type 2 diabetes mellitus. *Exp Clin Endocrinol Diabetes* 119(4):257–263. <https://doi.org/10.1055/s-0030-1269912>

Figures

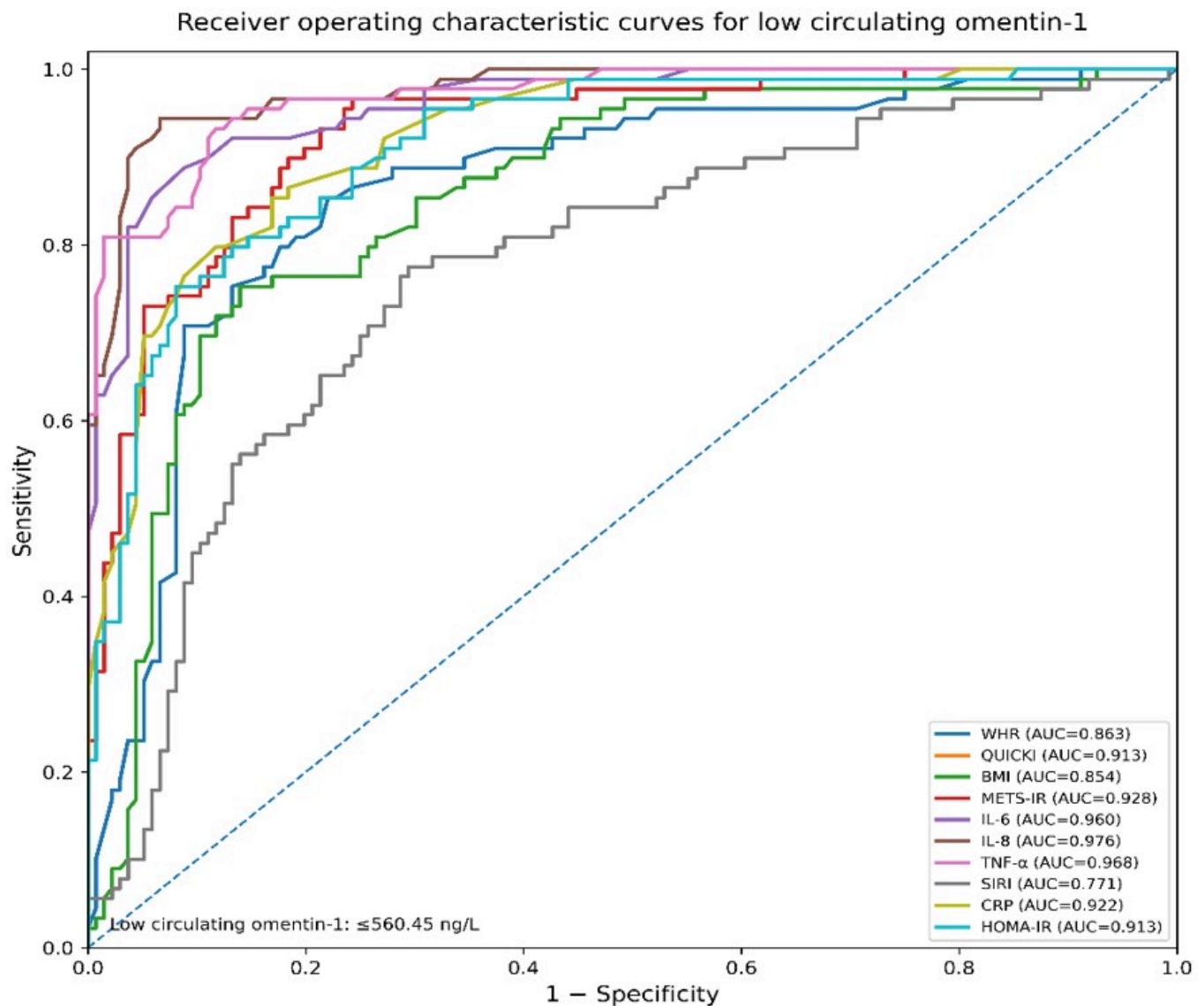


Figure 1

Receiver operating characteristic curves of selected anthropometric, metabolic, and inflammatory markers for discrimination of low circulating omentin-1 concentrations.

Low circulating omentin-1 was defined as ≤ 560.45 ng/L. AUC, area under the curve; BMI, body mass index; CRP, C-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance; IL-6, interleukin-6; IL-8, interleukin-8; METS-IR, metabolic score for insulin resistance; QUICKI, quantitative insulin sensitivity check index; SIRS, systemic inflammation response index; TNF- α , tumour necrosis factor- α ; WHR, waist-to-hip ratio.

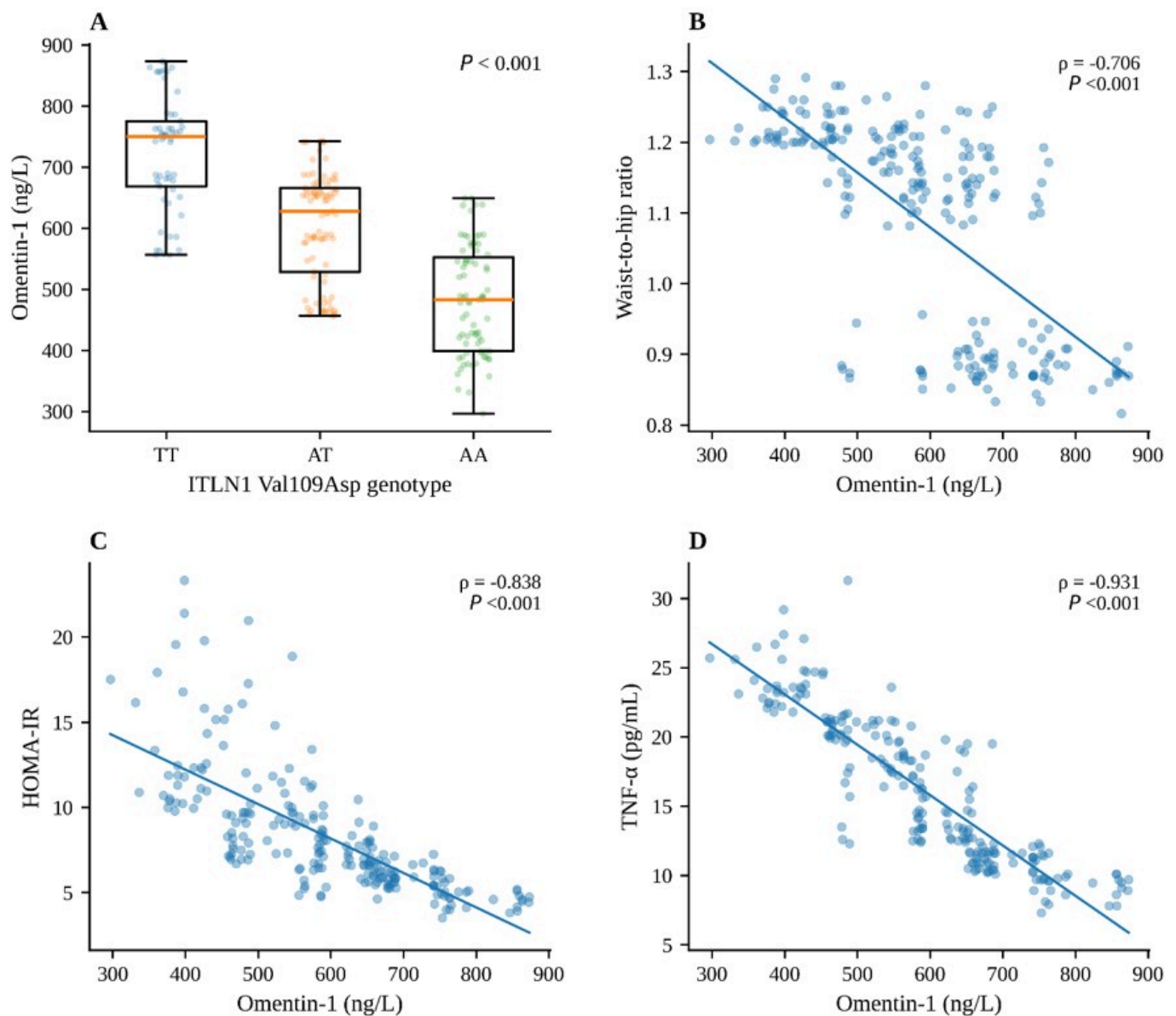


Figure 2

Association of *ITLN1*Val109Asp genotype and circulating omentin-1 with adiposity, insulin resistance, and inflammation in men with type 2 diabetes.

(A) Circulating omentin-1 concentrations according to *ITLN1* Val109Asp (rs2274907) genotype (TT, AT, and AA). (B–D) Spearman correlations of circulating omentin-1 with waist-to-hip ratio (WHR), HOMA-IR, and TNF- α , respectively. The P value in panel A represents the Kruskal–Wallis test across genotype groups. Correlation coefficients (ρ) and corresponding P values in panels B–D are based on Spearman correlation analysis using all 225 participants. HOMA-IR, homeostasis model assessment of insulin resistance; TNF- α , tumour necrosis factor- α ; WHR, waist-to-hip ratio.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryTableS1S31.docx](#)