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Integrative Genetic Analysis of DPP4-Related Variants Reveals Risk Patterns for Type 2 Diabetes and Cardiometabolic Comorbidities

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Background: Hypertension (HTN) and dyslipidemia (DYS) frequently complicate type 2 diabetes mellitus (T2DM), increasing cardiovascular risk. Genetic variation within the *DPP4–ABCC8–INSR–IGF1* axis may underlie this clustering.

Methods: A total of 444 T2DM patients were stratified into T2DM (n = 256), T2DM with HTN (T2MH, n = 134), and T2DM with HTN and DYS (T2MH-DYS, n = 54). Six single nucleotide polymorphisms (SNPs) were genotyped, and associations were assessed by logistic regression and haplotype analysis with Bonferroni correction.

Results: Clinical profiling showed higher C-reactive protein (CRP) and adrenocorticotropic hormone (ACTH) in T2MH and more severe metabolic derangements in T2MH-DYS. DPP4 rs3788979 was strongly linked to hypertension: CT (adjusted OR = 0.370, P = 0.001) and CC (adjusted OR = 0.424, P = 0.001) were protective versus TT, while in the T2MH vs T2MH-DYS comparison, the same CT and CC genotypes conferred increased dyslipidemia risk (adjusted OR = 5.418, P = 0.001; OR = 5.620, P = 0.002). In the comparison between T2DM and T2MH-DYS, the same genotypes also increase the susceptibility risk. IGF1 rs972936 TC genotype also reduced T2MH risk (adjusted OR = 0.460, P = 0.006). Haplotype analysis identified GAATGT as protective against hypertension (OR = 0.312, P = 0.0014) and GACCGT as a risk haplotype for dyslipidemia (OR = 4.113, P = 0.0021); both remained significant after Bonferroni correction.

Conclusion: Variants within the DPP4 axis influence susceptibility to HTN and DYS in T2DM, with GAATGT and GACCGT emerging as robust haplotype markers. Notably, the risk conferred by DPP4 rs3788979 genotypes was modulated by lipid status: CT/CC were protective against hypertension alone but became risk factors when dyslipidemia co-occurred.

Keywords: DPP4 axis, polymorphism, haplotype, type 2 diabetes, hypertension, dyslipidemia

Introduction

The global prevalence of type 2 diabetes mellitus (T2DM) has escalated dramatically over recent decades, and hypertension (HTN) and dyslipidemia (DYS) are among the most frequent cardiometabolic comorbidities in these patients. In large-scale cohorts, hypertension affects 45–60% of people with T2DM, while dyslipidemia (particularly hyperlipidemia or hypertriglyceridemia) is observed in 40–50% of such individuals.[1–3] The coexistence of T2DM with HTN or DYS substantially increases cardiovascular disease risk. T2DM patients with hypertension have approximately 2- to 3-fold greater risk of cardiovascular events compared to T2DM alone.[4,5] From a public health perspective, unraveling the genetic underpinnings of this cardiometabolic clustering is critical for enabling precision prevention and early intervention.

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Insulin secretion and signaling constitute the central pathological axis of T2DM and its cardiometabolic complications.[6] Dipeptidyl peptidase 4 (DPP4) regulates the availability of incretin hormones such as glucagon-likepeptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP), thereby influencing postprandial insulin release.[7,8] Downstream, ATP-binding cassette subfamily C member 8 (ABCC8), encoding the sulfonylurea receptor subunit of the β-cell KATP channel, serves as the molecular switch for glucose-stimulated depolarization and insulin exocytosis.[9,10] Secreted insulin subsequently binds to its receptor encoded by insulin receptor (INSR), initiating the IRS1/PI3K/Akt cascade to promote glucose uptake and maintain metabolic balance.[11,12] In parallel, insulin-like growth factor 1 (IGF1), which shares structural homology and receptor crosstalk with insulin, enhances insulin sensitivity and supports metabolic regulation.[13] Collectively, these four genes form an "incretin–secretion–signaling–sensitivity" pathway. Genetic polymorphisms across this pathway may exert synergistic effects, producing a "double-hit" of impaired insulin secretion and signaling resistance, ultimately amplifying susceptibility to T2DM and its comorbid HTN and DYS. Identifying genetic markers along key physiological pathways could significantly impact clinical practice by improving early risk prediction, guiding individualized treatment decisions, and enabling monitoring of high-risk patients with T2DM.

Although numerous studies have reported associations between individual *DPP4*,[14–16] *ABCC8*,[17–24] *INSR*,[25] and *IGF1*[26–30] polymorphisms and T2DM or complications, the combined effects of these genes along a unified biological axis have not been systematically investigated. Unlike the conventional genetic studies that focus on single variant or gene in isolation, this study employs an integrated pathway-based approach to examine synergistic effects across the incretin–secretion–signaling–sensitivity axis. In particular, the joint genetic contribution of *DPP4* and its downstream secretion–signaling partners to the development of T2DM with HTN and DYS remains largely unexplored. Therefore, the present study aimed to comprehensively evaluate the associations of common polymorphisms in *DPP4, ABCC8, INSR*, and *IGF1* with the risk of T2DM accompanied by HTN and/or DYS. We hypothesize that a combined genetic profile across this pathway will be more strongly associated with cardiometabolic comorbidity patterns than any single variant, and that gene–gene interactions within the axis may further modulate disease risk. We further sought to investigate potential gene–gene interactions within this pathway, in order to elucidate the genetic architecture underlying secretion–signaling defects and provide a theoretical basis for precision prevention of cardiometabolic comorbidities in T2DM populations.

Materials and Methods

Study Cohort and Eligibility

Between September 2021 and January 2022, a total of 650 patients with T2DM were initially enrolled from the Department of Endocrinology at the First Affiliated Hospital of Guilin Medical University. Strict exclusion criteria were applied to obtain a homogenous study cohort. Patients were excluded if they had any of the following: (1) severe comorbid conditions: this included recent acute cardiovascular events (within the past 6 months, eg myocardial infarction or valvular heart disease requiring surgery), advanced chronic kidney disease (stage 4–5 with eGFR < 30 mL/min/1.73 m^2), or decompensated liver cirrhosis (Child-Pugh class B or C); (2) confounding diabetes classifications: patients with type 1 diabetes were excluded (confirmed by negative GAD65 autoantibodies and preserved C-peptide levels). Additionally, those with active severe microvascular complications, such as proliferative diabetic retinopathy or macroalbuminuric diabetic nephropathy, were not included; (3) other systemic conditions: patients were excluded if they had systemic autoimmune diseases (eg systemic lupus erythematosus), a recent history of malignancy (diagnosed within the last 5 years), any inherited metabolic disorder, pregnancy, or significant cognitive impairment.

T2DM diagnostic criteria: the diagnosis of type 2 diabetes was confirmed according to the 2021 American Diabetes Association (ADA) guidelines.[31,32] Specifically, T2DM was defined by a fasting plasma glucose ≥ 7.0 mmol/L, a 2-hour oral glucose tolerance test (OGTT) plasma glucose ≥ 11.1 mmol/L, or a glycosylated hemoglobin (HbA1c) ≥ 6.5%.

HTN was defined and categorized based on the American Heart Association and Chinese hypertension management guidelines.[33,34] Blood pressure was measured using a validated Omron HEM-7136 oscillometric device after the patient had been seated at rest for 5 minutes. Three measurements were taken at 1–2 minute intervals and averaged. DYS was diagnosed according to the Chinese guidelines for prevention of adult dyslipidemia.[35] DYS was defined by the presence of any of the

following criteria: total cholesterol ≥ 5.2 mmol/L, low-density lipoprotein cholesterol (LDL-C) ≥ 3.4 mmol/L, high-density lipoprotein cholesterol (HDL-C) < 1.0 mmol/L in men or < 1.3 mmol/L in women, or triglycerides ≥ 1.7 mmol/L.

After applying all exclusion criteria and ensuring completeness of key data, a final cohort of 444 T2DM patients remained. These patients were stratified into three study groups: a T2DM group (n = 256, T2DM without accompanying hypertension or dyslipidemia), a T2MH group (n = 134, T2DM with hypertension), and a T2MH-DYS group (n = 54, T2DM with both hypertension and dyslipidemia). The three groups were comparable in age and sex distribution (median age: 61.0 [53.0–66.0] vs 59.73 ± 7.41 vs 59.20 ± 8.21 years, $P > 0.05$ across all comparisons; male/female: 156/100 vs 78/56 vs 33/21, $P > 0.05$). This study was approved by the Institutional Review Board of Guilin Medical University and was conducted in accordance with the Declaration of Helsinki (Approval No. 2023QTLL-37). Written informed consent was obtained from all participants, and all subjects confirmed no biological kinship with one another to ensure the independence of samples.

Clinical and Biochemical Assessments

Baseline data collection encompassed a broad range of clinical and biochemical parameters for each patient. Demographic characteristics (age, sex, and weight) were recorded alongside key metabolic measures such as blood pressure (SBP/DBP), HbA1c, and fasting plasma glucose. Markers of renal function, including plasma urea and creatinine, were measured, as well as a full lipid profile (triglycerides, total cholesterol, HDL-C, and LDL-C) and an inflammatory marker (C-reactive protein). In addition, the presence of islet autoantibodies (anti-GAD65 and insulin autoantibodies) was assessed, and levels of selected neuroendocrine hormones were measured (adrenocorticotropic hormone [ACTH], angiotensin II, aldosterone, and renin).

All blood samples were analyzed in the ISO 15189-accredited clinical laboratory of Guilin Medical University (Certification No. ML00036). Key biochemical assays were performed using a Cobas e701 automatic analyzer. HbA1c was measured by high-performance liquid chromatography (Bio-Rad D-100 system; reference range 4.0–6.0%) with intra-assay and inter-assay coefficients of variation (CV) ≤ 1.8% and ≤ 2.3%, respectively. Fasting plasma glucose was determined by the enzymatic hexokinase method (CV < 2.1%). LDL-C values were calculated using the Friedewald equation (applicable only when triglycerides ≤ 4.5 mmol/L).[36] Neuroendocrine hormone levels were measured with an AutoLumo A6000 chemiluminescent analyzer. The ACTH assay had a sensitivity of 1.0 pg/mL with a CV < 5.2%. Angiotensin II and aldosterone were quantified using a solid-phase extraction followed by chemiluminescent detection, with dynamic ranges of 5–2000 pg/mL for angiotensin II and 25–1600 pg/mL for aldosterone. Islet autoantibodies were measured by chemiluminescence immunoassay, using positivity cut-off values of ≥ 5 IU/mL for GAD65 antibodies and ≥ 0.4 nU/mL for insulin autoantibodies.

Genotyping of Candidate Polymorphisms

Genotyping of candidate polymorphisms was performed using a locus-specific, ligation-dependent PCR method. Genomic DNA was first prepared by thermal lysis at 98 °C for 5 minutes. Locus-specific probes targeting each single nucleotide polymorphism (SNP) were then hybridized to the DNA in the presence of a DNA ligase at 58 °C for 4 hours (with a ligase-to-probe volume ratio of 0.5 μL:1 μL). After this ligation step, a multiplex touchdown PCR was carried out, during which the annealing temperature was gradually lowered from 62 °C to 57 °C through successive cycles (using a primer mix ratio of 10:1). The PCR amplification products were diluted 1:10 (v/v) and analyzed by capillary electrophoresis on an ABI 3730XL DNA Analyzer, using a Liz600 size standard for allele sizing. The resulting electropherograms were interpreted with GeneMapper version 4.1 to discriminate alleles and assign genotypes (Supplementary Figure 1). The specific primer sequences used for PCR amplification are listed in Supplementary Table 1.

Candidate SNPs were selected through a two-step filtering strategy. First, a functional/regulatory prioritization was applied: we focused on non-synonymous variants predicted to be damaging, variants located in key regulatory regions (promoters or enhancers), and any SNPs with experimental evidence of affecting gene expression or protein function (for example, expression quantitative trait loci identified in GTEx or variants reported in functional studies). Second, a population-based filter was used: we included only variants with a minor allele frequency (MAF) > 5% in East Asian populations (based on NCBI dbSNP data), and we excluded variants that had not been previously associated with metabolic traits in the literature.

Statistical Analysis

Statistical analyses were performed using SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA) and the SHEsis online platform for genetic data analysis. The Kolmogorov–Smirnov test was used to assess whether continuous variables followed a normal distribution. Continuous data that were approximately normally distributed are presented as mean ± standard deviation (SD) and were compared between groups using independent-samples t tests. Continuous data with a non-normal distribution are presented as median and interquartile range and were compared using the Mann–Whitney *U*-test. Categorical variables were summarized as counts (percentages) and compared using the chi-square (χ^2) test. Genotype frequencies were tested for Hardy-Weinberg equilibrium using a χ^2 goodness-of-fit test. Haplotype construction and analysis were performed using the SHEsis software (http://analysis.bio-x.cn).[37] For comparisons involving more than two groups, one-way analysis of variance (ANOVA) was employed, followed by Tukey's Honestly Significant Difference (HSD) post hoc test for pairwise comparisons. A P value < 0.05 was considered statistically significant.

Results

Hemodynamic, Metabolic, and Inflammatory Features in T2DM with Comorbidities

As expected, systolic blood pressure was significantly higher in both the T2MH and T2MH-DYS groups compared with T2DM patients (145.35 ± 22.97 vs 138.65 ± 20.82 vs.133.87 ± 19.36 mmHg, $P^4 < 0.001$, Table 1), confirming HTN status. The T2MH-DYS subgroup exhibited the greatest metabolic disturbances, with significantly elevated fasting plasma glucose (10.81 [6.43–16.52] vs 7.87 [6.11–11.43] mmol/L, $P = 0.017$), triglycerides (2.38 [1.53–5.19] vs 1.68 [1.05–2.71] mmol/L, $P < 0.001$), total cholesterol (5.20 ± 1.71 vs 4.58 ± 1.30 mmol/L, $P = 0.003$), and LDL-C (3.17 [2.28–3.95] vs 2.87 ± 0.99 mmol/L, $P = 0.009$), indicating pronounced dyslipidaemia and poorer glycaemic control. Inflammatory and endocrine markers were also perturbed. CRP was elevated in the T2MH group compared with T2DM (2.85 vs 1.79 mg/L, $P = 0.007$), consistent with chronic low-grade inflammation, while ACTH levels were significantly higher in T2MH group (20.07 vs 13.24 pg/mL, $P = 0.009$), suggesting neuroendocrine activation. By contrast, GAD65 autoantibodies were reduced in the T2MH-DYS group ($P < 0.001$). Overall, HTN in T2DM was associated with inflammatory and endocrine dysregulation, whereas the coexistence of DYS further aggravated metabolic imbalance (Table 1).

Genetic Variants in the DPP4 Axis Across Clinical Subgroups

All examined loci were in Hardy–Weinberg equilibrium ($P > 0.05$). In the three-group comparisons (T2DM, T2MH, and T2MH-DYS), significant distributional differences were identified within the DPP4 axis (Table 2). The most striking finding was for DPP4 rs3788979, where genotype frequencies varied significantly among the three groups (TT vs CT vs CC: $\chi^2 = 21.193$, $P < 0.001$). The recessive model further confirmed this association, with TT carriers showing divergent distributions across subgroups (TT vs CT+CC: $\chi^2 = 20.831$, $P < 0.001$). At the allelic level, the T versus C contrast also reached high significance ($\chi^2 = 16.152$, $P < 0.001$). For IGF1 rs5742632, overall genotype distributions differed (AA vs AG vs GG: $\chi^2 = 9.820$, $P = 0.044$), and a recessive comparison demonstrated that GG homozygotes were unevenly distributed (GG vs AA+AG: $\chi^2 = 7.177$, $P = 0.028$). Similarly, IGF1 rs972936 displayed significant variation across groups (TT vs TC vs CC: $\chi^2 = 10.372$, $P = 0.035$), with further evidence from dominant (TT vs TC+CC: $\chi^2 = 6.137$, $P = 0.046$) and heterozygote (TC vs TT+CC: $\chi^2 = 7.205$, $P = 0.027$) contrasts. In contrast, INSR rs1799817 and ABCC8 rs1799854/rs757110 did not show significant genotype or allele frequency differences (all $P > 0.05$).

T2DM vs T2MH: Hypertension-Linked Associations within the DPP4 Axis

Pairwise χ^2 comparisons demonstrated significant differences in the DPP4 rs3788979 locus between T2DM and T2MH (TT vs CT vs CC: $\chi^2 = 14.419$, $P = 0.001$; T vs C: $\chi^2 = 11.968$, $P = 0.001$; Table 3). Logistic regression confirmed that, relative to TT homozygotes, both CT (OR = 0.373, 95% CI = 0.210–0.663, $P = 0.001$) and CC carriers (OR = 0.427, 95% CI = 0.255–0.715, $P = 0.001$) were associated with lower odds of hypertension, with results persisting after adjustment for age and gender (Figure 1). At the allele level, C allele carriers also had a reduced risk of T2MH (adj OR = 0.593, 95% CI = 0.440–0.799, $P = 0.001$). For IGF1 rs972936, χ^2 testing revealed significant contrasts (TT vs TC+CC: $\chi^2 = 5.943$,

Table 1 Clinical Characteristics of the Study Subjects

Variables	Total	T2DM Sufferers	T2MH Sufferers	T2MH-DYS Sufferers	P^1 value	P^2 value	P^3 value	P^4 value
N	444	256	134	54	-	-	-	-
Age (years)	59.57±9.04	61.00(53.00–66.00)	59.73±7.41	59.20±8.21	0.868	0.539	0.669	0.807
M:F	267/177	156/100	78/56	33/21	0.601	0.981	0.714	0.862
Weight (kg)	64.18±13.17	63.14±12.39	63.35±11.97	67.00(60.00–74.00)	0.890	0.064	0.054	0.128
SBP (mmHg)	138.86±21.564	133.87±19.362	145.35±22.97	138.65±20.82	<0.001	0.136	0.075	<0.001
DBP (mmHg)	86.08±13.870	84.60±14.443	86.69±13.39	89.06±12.87	0.223	0.052	0.288	0.116
HbA1c (%)	8.30(6.80–10.20)	8.15(6.90–10.175)	8.30(6.70–10.20)	8.97±2.57	0.763	0.546	0.480	0.761
FPG (mmol/L)	6.54(6.12–12.66)	7.87(6.11–11.43)	9.48(5.95–13.21)	10.81(6.43–16.52)	0.114	0.008	0.129	0.017
Urea (mmol/L)	5.40(4.30–6.95)	5.39(4.31–6.66)	5.80(4.35–8.66)	4.90(4.10–6.08)	0.037	0.168	0.019	0.024
Cr (μmol/L)	74.00(62.25–91.00)	73.00(63.00–89.00)	84.00(65.00–109.50)	70.00(58.75–80.25)	0.004	0.098	0.002	0.001
TG (mmol/L)	1.69(1.08–2.72)	1.68(1.05–2.71)	1.51(1.05–2.23)	2.38(1.53–5.19)	0.233	<0.001	<0.001	<0.001
TC (mmol/L)	4.59(3.76–5.39)	4.58±1.30	4.40±1.07	5.20±1.71	0.166	0.003	<0.001	0.001
HDL-C (mmol/L)	1.00(0.85–1.22)	1.01(0.85–1.22)	1.00(0.82–1.23)	1.01(0.85–1.19)	0.561	0.806	0.846	0.838
LDL-C (mmol/L)	2.81(2.11–3.45)	2.87±0.99	2.65(2.04–3.23)	3.17(2.28–3.95)	0.038	0.136	0.009	0.016
CRP (mg/L)	2.10(0.91–4.70)	1.79(0.79–4.17)	2.85(1.18–6.88)	2.13(0.91–4.09)	0.007	0.745	0.097	0.022
GAD65 (IU/mL)	6.95(6.12–8.54)	7.00(6.16–9.11)	7.28(6.18–8.57)	6.25(5.80–7.00)	0.922	<0.001	<0.001	<0.001
IAA (nU/mL)	7.21(6.12–8.52)	7.25(6.14–8.51)	7.34(6.02–9.31)	6.83(6.08–7.69)	0.388	0.088	0.049	0.115
ACTH (pg/mL)	15.01(5.98–28.36)	13.24(4.29–28.23)	20.07(7.56–35.52)	15.82(6.40–25.41)	0.009	0.559	0.186	0.032
Ang II (pg/mL)	118.82(101.60–148.47)	118.02(101.28–160.18)	121.21(102.09–163.61)	120.41(104.31–174.05)	0.537	0.413	0.731	0.654
ALD (pg/mL)	15.71(8.35–31.23)	15.18(8.32–28.49)	14.58(7.95–31.71)	22.63(9.20–37.63)	0.714	0.042	0.050	0.098
Ren (pg/mL)	136.44(107.00–186.30)	137.29(109.17–185.10)	130.29(102.07–177.20)	137.75(107.43–198.47)	0.309	0.682	0.326	0.487
GH (ng/mL)	14.15(10.63–18.01)	13.52(10.34–17.44)	15.12(11.87–18.13)	15.23±6.54	0.072	0.161	0.822	0.122
IGF-1 (μg/L)	0.78(0.26–1.90)	0.78(0.25–2.06)	0.90(0.29–1.75)	0.59(0.19–1.58)	0.733	0.313	0.219	0.479
Cor (nmol/L)	142.63(101.55–178.86)	143.81±56.52	138.71±62.18	147.18(104.23–182.97)	0.462	0.366	0.145	0.344

Notes: All variables were calculated by Kolmogorov–Smirnov test, data with normal distribution was indicated by mean ± standard deviation (SD), otherwise, it was presented by median (inter-quartile range, P25-P75). P^1:T2DM vs T2MH; P^2: T2DM vs T2MH-DYS; P^3: T2MH vs T2MH-DYS; P^4: T2DM vs T2MH vs T2MH-DYS.

Abbreviations: T2DM, type 2 diabetes mellitus; T2MH, type 2 diabetes mellitus with hypertension; T2MH-DYS, type 2 diabetes mellitus with hypertension and dyslipidemia; M:F, male to female ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; FPG, fasting plasma glucose; Cr, creatinine; TG, triglycerides; TC, total cholesterol; H/LDL-C, high/low-density lipoprotein cholesterol; CRP, C-reactive protein; GAD65, glutamic acid decarboxylase 65; IAA, insulin autoantibodies; ACTH, adrenocorticotropic hormone; Ang II, angiotensin II; ALD, aldosterone; Ren renin; GH, growth hormone; IGF-1, insulin like growth factor 1; Cor, Cortisol.

Table 2 Genotype Distributions of DPP4 Related Polymorphisms in T2DM, T2MH, and T2MH-DYS Groups

Genotype and Allele		Total	T2DM	T2MH	T2MH-DYS	Comparison	χ^2	P value
INSR	AA	64	40(15.6)	19(14.2)	5(9.3)	AA vs GA+GG	1.473	0.479
rs1799817	GA	253	138(53.9)	78(58.2)	37(68.5)	GA vs AA+GA	4.002	0.135
	GG	127	78(30.5)	37(27.6)	12(22.2)	GG vs AA+GG	1.577	0.454
	Total	444	256(100.0)	134(100.0)	54(100.0)	AA vs GA vs GG	4.109	0.391
	A	381	218(42.6)	116(43.3)	47(43.5)	A vs G	0.055	0.973
	G	507	294(57.4)	152(56.7)	61(56.5)			
ABCC8	AA	125	75(29.3)	32(23.9)	18(33.3)	AA vs GA+GG	2.091	0.351
rs1799854	GA	229	132(51.6)	71(53.0)	26(48.1)	GA vs AA+GG	0.361	0.835
	GG	90	49(19.1)	31(23.1)	10(18.5)	GG vs GA+AA	0.985	0.611
	Total	444	256(100)	134(100)	54(100)	AA vs GA vs GG	2.462	0.651
	A	479	282(55.1)	135(50.4)	62(57.4)	A vs G	2.162	0.339
	G	409	230(44.9)	133(49.6)	46(42.6)			
ABCC8	AA	194	114(44.5)	54(40.3)	26(48.1)	AA vs CA+CC	1.136	0.567
rs757110	CA	188	112(43.8)	54(40.3)	22(40.7)	CA vs AA+CC	0.494	0.781
	CC	62	30(11.7)	26(19.4)	6(11.1)	CC vs AA+CA	4.740	0.094
	Total	444	256(100)	134(100)	54(100)	AA vs CA vs CC	5.002	0.287
	A	576	340(66.4)	162(60.4)	74(68.5)	A vs C	3.461	0.177
	C	312	172(33.6)	106(39.6)	34(31.5)			
DPP4	TT	98	46(18.0)	47(35.1)	5(9.3)	TT vs CT+CC	20.831	**<0.001**
rs3788979	CT	212	126(49.2)	55(41.0)	31(57.4)	CT vs TT+CC	4.655	0.098
	CC	134	84(32.8)	32(23.9)	18(33.3)	CC vs TT+CT	3.620	0.164
	Total	444	256(100.0)	134(100.0)	54(100.0)	TT vs CT vs CC	21.193	**<0.001**
	T	408	218(46.7)	149(55.6)	41(33.9)	T vs C	16.152	**<0.001**
	C	448	294(53.3)	119(44.4)	80(66.1)			
IGF-1	AA	137	76(29.7)	40(29.9)	21(38.9)	AA vs AG+GG	1.861	0.394
rs5742632	AG	227	143(55.9)	60(44.8)	24(44.4)	AG vs AA+GG	5.423	0.066
	GG	80	37(14.5)	34(25.4)	9(16.7)	GG vs AA+AG	7.177	**0.028**
	Total	444	256(100.0)	134(100.0)	54(100.0)	AA vs AG vs GG	9.820	**0.044**
	A	465	295(54.4)	140(52.2)	66(61.1)	A vs G	2.456	0.293
	G	387	217(45.6)	128(47.8)	42(38.9)			
IGF-1	TT	82	39(15.2)	34(25.4)	9(16.7)	TT vs TC+CC	6.137	**0.046**
rs972936	TC	229	146(57.0)	59(44.0)	24(44.4)	TC vs TT+CC	7.205	**0.027**
	CC	133	71(27.7)	41(30.6)	21(38.9)	CC vs TT+TC	2.682	0.262
	Total	444	256(100.0)	134(100.0)	54(100.0)	TT vs TC vs CC	10.372	**0.035**
	T	393	224(43.8)	127(47.4)	42(38.9)	T vs C	2.380	0.304
	C	495	288(56.2)	141(52.6)	66(61.1)			

Notes: Dates are shown as n(percent). The *P* values were calculated by chi-square test. Bold value indicates statistical significance.
Abbreviations: T2DM, type 2 diabetes mellitus; T2MH, type 2 diabetes mellitus with hypertension; T2MH-DYS, type 2 diabetes mellitus with hypertension and dyslipidemia; INSR, insulin receptor; ABCC8, ATP Binding Cassette Subfamily C Member 8; DPP4, Dipeptidyl Peptidase 4; IGF-1, insulin like growth factor 1.

P = 0.015; TC vs TT+CC: χ^2 = 5.963, P = 0.015; TT vs TC vs CC: χ^2 = 7.910, P = 0.019), and logistic regression indicated a protective effect of the TC genotype (OR = 0.464, 95% CI = 0.267–0.804, P = 0.006), stable after adjustment. For IGF1 rs5742632, although χ^2 analyses suggested an excess of GG genotypes in T2MH (GG vs AA+AG: χ^2 = 7.044, P = 0.008; overall χ^2 = 7.838, P = 0.020), logistic regression only showed a non-significant trend toward increased risk (adjusted OR = 1.769, 95% CI = 0.966–3.240, P = 0.065). No significant associations were detected for INSR rs1799817 or ABCC8 rs1799854/rs757110.

Table 3 Pairwise Comparisons of Significantly Associated DPP4–ABCC8–INSR–IGF1 Axis Gene Polymorphisms

SNP	Genotype and Allele	χ^2	P^1 value	χ^2	P^2 value	χ^2	P^3 value
INSR	AA vs GA+GG	0.143	0.705	1.456	0.228	0.837	0.360
rs1799817	GA vs AA+GG	0.659	0.417	3.873	**0.049**	1.722	0.189
	GG vs AA+GA	0.345	0.557	1.472	0.225	0.580	0.446
	AA vs GA vs GG	0.659	0.719	3.976	0.137	1.828	0.401
	A vs G	0.036	0.850	0.032	0.858	0.002	0.967
ABCC8	AA vs GA+GG	1.296	0.255	0.346	0.556	1.762	0.184
rs1799854	GA vs AA+GG	0.071	0.789	0.208	0.648	0.361	0.548
	GG vs AA+GA	0.860	0.354	0.011	0.916	0.481	0.488
	AA vs GA vs GG	1.659	0.436	0.353	0.838	1.844	0.398
	A vs G	1.565	0.211	0.196	0.658	1.527	0.217
ABCC8	AA vs CA+CC	0.643	0.423	0.236	0.627	0.970	0.325
rs757110	CA vs AA+CC	0.429	0.513	0.165	0.685	0.003	0.955
	CC vs AA+CA	4.224	**0.040**	0.016	0.899	1.874	0.171
	AA vs CA vs CC	4.229	0.121	0.237	0.888	2.114	0.348
	A vs C	2.723	0.099	0.179	0.672	2.146	0.143
DPP4	TT vs CT+CC	3.358	0.067	0.005	0.941	1.762	0.184
rs3788979	CT vs TT+CC	1.950	0.163	1.196	0.274	3.776	0.052
	CC vs TT+CT	3.358	0.067	0.005	0.941	1.762	0.184
	TT vs CT vs CC	14.419	**0.001**	2.650	0.266	12.820	**0.002**
	T vs C	11.968	**0.001**	13.597	**<0.001**	8.598	**0.003**
IGF-1	AA vs AG+GG	0.001	0.973	1.756	0.185	1.434	0.231
rs5742632	AG vs AA+GG	4.329	**0.037**	2.338	0.126	0.002	0.967
	GG vs AA+AG	7.044	**0.008**	0.173	0.678	1.654	0.198
	AA vs AG vs GG	7.838	**0.020**	2.432	0.296	2.246	0.325
	A vs G	2.063	0.151	0.448	0.503	2.446	0.118
IGF-1	TT vs TC+CC	5.943	**0.015**	0.070	0.791	1.654	0.198
rs972936	TC vs TT+CC	5.963	**0.015**	2.853	0.091	0.003	0.959
	CC vs TT+TC	0.352	0.553	2.659	0.103	1.197	0.274
	TT vs TC vs CC	7.910	**0.019**	3.217	0.200	2.080	0.354
	T vs C	0.941	0.332	0.860	0.354	2.247	0.134

Notes: P^1:T2DM vs T2MH; P^2: T2DM vs T2MH-DYS; P^3: T2MH vs T2MH-DYS. Bold value indicates statistical significance.
Abbreviations: T2DM, type 2 diabetes mellitus; T2MH, type 2 diabetes mellitus with hypertension; T2MH-DYS, type 2 diabetes mellitus with hypertension and dyslipidemia; INSR, insulin receptor; ABCC8, ATP Binding Cassette Subfamily C Member 8; DPP4, Dipeptidyl Peptidase 4; IGF-1, insulin like growth factor 1.

T2DM vs T2MH-DYS: Convergence of Hypertension and Dyslipidaemia within the DPP4 Axis

In the comparison between T2DM and T2MH-DYS, DPP4 rs3788979 showed robust allelic divergence (Table 3 and Figure 2). χ^2 analysis confirmed significance (T vs C: $\chi^2 = 13.597$, $P < 0.001$), and logistic regression demonstrated that the C allele was overrepresented in T2MH-DYS, conferring higher odds relative to T2DM (OR = 2.204, 95% CI = 1.439–3.375, $P < 0.001$), consistent after adjustment. At the genotype level, no models retained significance in regression analysis despite nominal χ^2 signals. For IGF1 rs5742632 and rs972936, χ^2 analyses did not reveal strong differences (all $P > 0.05$), and regression models were similarly non-significant. INSR rs1799817 and ABCC8 rs1799854/rs757110 likewise showed no evidence of association.

T2MH vs T2MH-DYS: Stratification within Hypertensive Diabetes

Among patients with hypertension, further stratification by dyslipidaemia status revealed striking genotype-specific differences at DPP4 rs3788979 (Table 3 and Figure 3). χ^2 testing identified significant overall distributional shifts (TT vs CT vs CC: $\chi^2 = 12.820$, $P = 0.002$; T vs C: $\chi^2 = 8.598$, $P = 0.003$). Logistic regression indicated that, compared with

Genotype and allele	OR(95%CI)	P	OR(95%CI)	P*
INSR rs1799817				
AA	Reference		Reference	
GA	1.001(0.511−1.960)	0.997	0.980(0.497−1.933)	0.954
GG	1.192(0.737−1.925)	0.474	1.181(0.730−1.912)	0.497
A	Reference		Reference	
G	1.029(0.764−1.387)	0.85	1.021(0.756−1.378)	0.893
ABCC8 rs1799854				
AA	Reference		Reference	
GA	0.674(0.366−1.243)	0.207	0.682(0.369−1.261)	0.222
GG	0.850(0.498−1.451)	0.552	0.854(0.500−1.458)	0.563
A	Reference		Reference	
G	0.828(0.616−1.113)	0.211	0.833(0.619−1.121)	0.229
ABCC8 rs757110				
AA	Reference		Reference	
CA	0.547(0.295−1.013)	0.055	0.549(0.296−1.018)	0.057
CC	0.556(0.300−1.032)	0.063	0.556(0.300−1.033)	0.063
A	Reference		Reference	
C	0.773(0.569−1.050)	0.099	0.775(0.571−1.053)	0.103
DPP4 rs3788979				
TT	**Reference**		**Reference**	
CT	**0.373(0.210−0.663)**	**0.001**	**0.370(0.208−0.659)**	**0.001**
CC	**0.427(0.255−0.715)**	**0.001**	**0.424(0.253−0.710)**	**0.001**
T	**Reference**			
C	**0.592(0.440−0.798)**	**0.001**	**0.593(0.440−0.799)**	**0.001**
IGF−1 rs5742632				
AA	Reference		Reference	
AG	0.797(0.490−1.298)	0.362	0.807(0.495−1.317)	0.391
GG	1.746(0.955−3.190)	0.07	1.769(0.966−3.240)	0.065
A	Reference		Reference	
G	1.243(0.924−1.673)	0.151	1.252(0.930−1.686)	0.139
IGF−1 rs972936				
TT	**Reference**		**Reference**	
TC	**0.464(0.267−0.804)**	**0.006**	**0.460(0.265−0.799)**	**0.006**
CC	0.662(0.364−1.206)	0.178	1.130(0.732−1.743)	0.582
T	Reference		Reference	
C	0.864(0.642−1.162)	0.332	0.857(0.637−1.154)	0.309

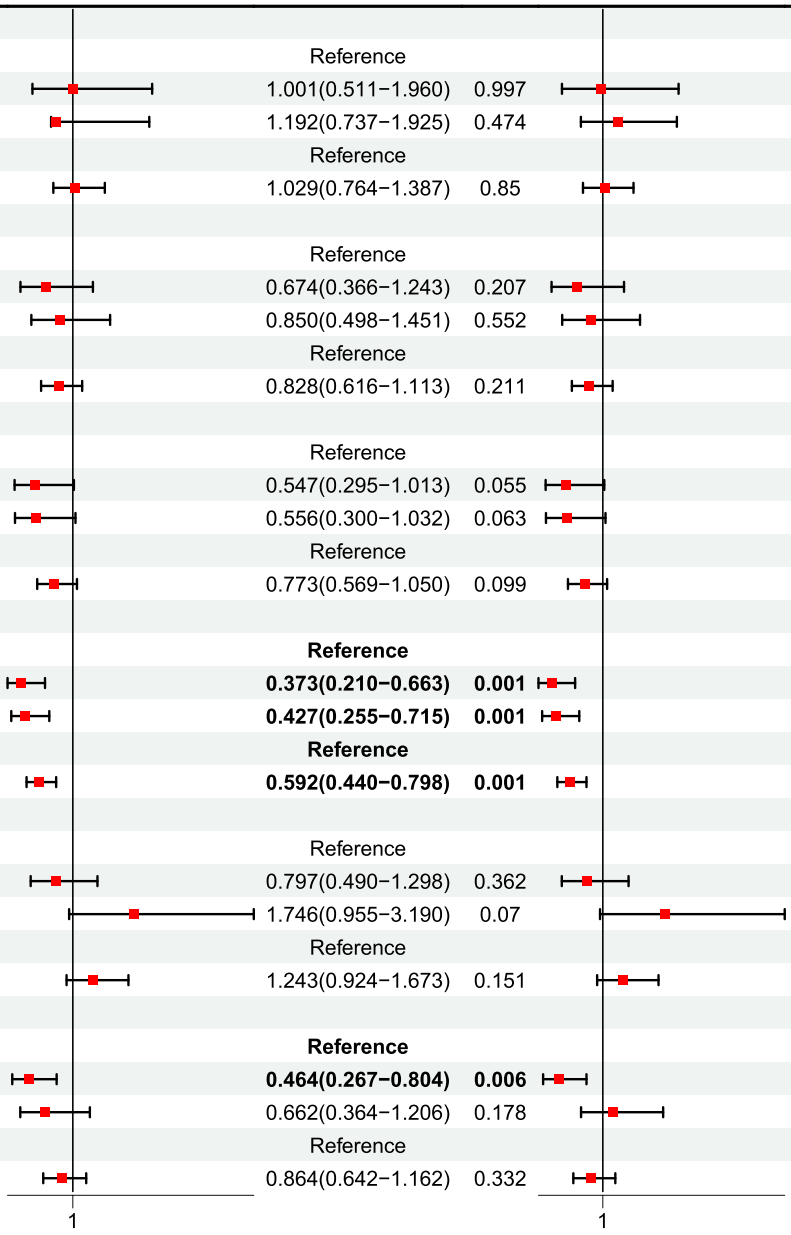

Figure 1 Analysis of regression (T2DM vs T2MH). *P** value was adjusted by age, gender. Bold value indicates statistical significance.

TT homozygotes, both CT (OR = 5.289, 95% CI = 1.907–14.717, $P = 0.001$; adjusted OR = 5.418, $P = 0.001$) and CC carriers (OR = 5.287, 95% CI = 1.782–15.693, $P = 0.003$; adjusted OR = 5.620, $P = 0.002$) were associated with markedly increased odds of belonging to the T2MH subgroup rather than T2MH-DYS. Allele analysis confirmed that the C allele was also beneficial for the occurrence of T2MH-DYS (odds ratio = 1.968, 95% confidence interval = 1.247–3.104, $P = 0.004$; adjusted odds ratio = 1.967, 95% confidence interval = 1.246–3.104, $P = 0.004$), indicating that the C allele was relatively enriched in T2MH-DYS. No significant associations were detected for IGF1 rs5742632/rs972936, INSR rs1799817, or ABCC8 rs1799854/rs757110 in this within-hypertension comparison.

Lipid Profiles Stratified by DPP4 rs3788979 Genotype

To elucidate the metabolic phenotype associated with the DPP4 rs3788979 risk allele, we stratified the lipid profiles by genotype and clinical subgroup. The results demonstrated that serum triglyceride (TG) levels were significantly higher in

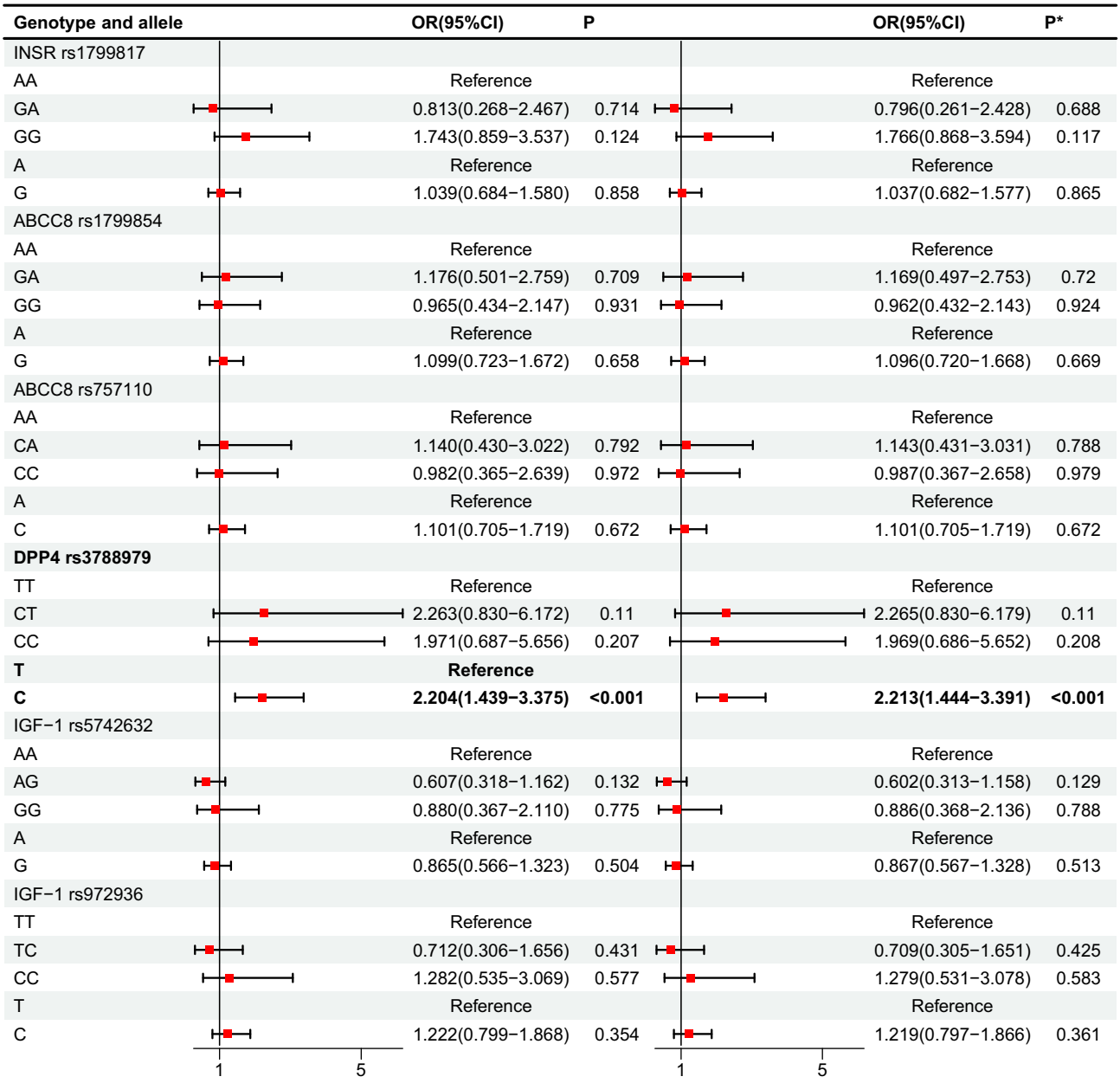

Figure 2 Analysis of regression (T2DM vs T2MH-DYS). *P** value was adjusted by age, gender. Bold value indicates statistical significance.

the T2MH-DYS group than in both the T2DM and T2MH groups, regardless of whether individuals carried the CC, CT, or TT genotype (all $P < 0.05$, Figure 4A–C). However, no significant differences were observed for other lipid parameters across genotype subgroups. These findings indicate that the dyslipidemia risk conferred by the DPP4 rs3788979 C allele is manifested primarily as significantly elevated TG levels in the presence of concomitant hypertension, rather than a comprehensive alteration of the lipid profile.

Synergistic Haplotype Effects within the DPP4 Axis

Haplotype analysis of INSR, ABCC8, DPP4, and IGF1 variants was conducted to explore polygenic interactions underlying diabetic comorbidities (Table 4 and Table 5; Supplementary Table 2). In the T2DM vs T2MH comparison, multiple haplotypes showed significant associations with hypertension risk. The GAATGT haplotype was markedly underrepresented in T2MH (3.2% vs 8.8%), indicating a protective effect (OR = 0.312, 95% CI: 0.147–0.661, *P* =

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Genotype and allele	OR(95%CI)	P	OR(95%CI)	P*
INSR rs1799817				
AA	Reference		Reference	
GA	0.813(0.268−2.467)	0.714	0.796(0.261−2.428)	0.688
GG	1.743(0.859−3.537)	0.124	1.766(0.868−3.594)	0.117
A	Reference		Reference	
G	1.039(0.684−1.580)	0.858	1.037(0.682−1.577)	0.865
ABCC8 rs1799854				
AA	Reference		Reference	
GA	1.176(0.501−2.759)	0.709	1.169(0.497−2.753)	0.72
GG	0.965(0.434−2.147)	0.931	0.962(0.432−2.143)	0.924
A	Reference		Reference	
G	1.099(0.723−1.672)	0.658	1.096(0.720−1.668)	0.669
ABCC8 rs757110				
AA	Reference		Reference	
CA	1.140(0.430−3.022)	0.792	1.143(0.431−3.031)	0.788
CC	0.982(0.365−2.639)	0.972	0.987(0.367−2.658)	0.979
A	Reference		Reference	
C	1.101(0.705−1.719)	0.672	1.101(0.705−1.719)	0.672
DPP4 rs3788979				
TT	Reference		Reference	
CT	2.263(0.830−6.172)	0.11	2.265(0.830−6.179)	0.11
CC	1.971(0.687−5.656)	0.207	1.969(0.686−5.652)	0.208
T	**Reference**			
C	**2.204(1.439−3.375)**	**<0.001**	**2.213(1.444−3.391)**	**<0.001**
IGF−1 rs5742632				
AA	Reference		Reference	
AG	0.607(0.318−1.162)	0.132	0.602(0.313−1.158)	0.129
GG	0.880(0.367−2.110)	0.775	0.886(0.368−2.136)	0.788
A	Reference		Reference	
G	0.865(0.566−1.323)	0.504	0.867(0.567−1.328)	0.513
IGF−1 rs972936				
TT	Reference		Reference	
TC	0.712(0.306−1.656)	0.431	0.709(0.305−1.651)	0.425
CC	1.282(0.535−3.069)	0.577	1.279(0.531−3.078)	0.583
T	Reference		Reference	
C	1.222(0.799−1.868)	0.354	1.219(0.797−1.866)	0.361

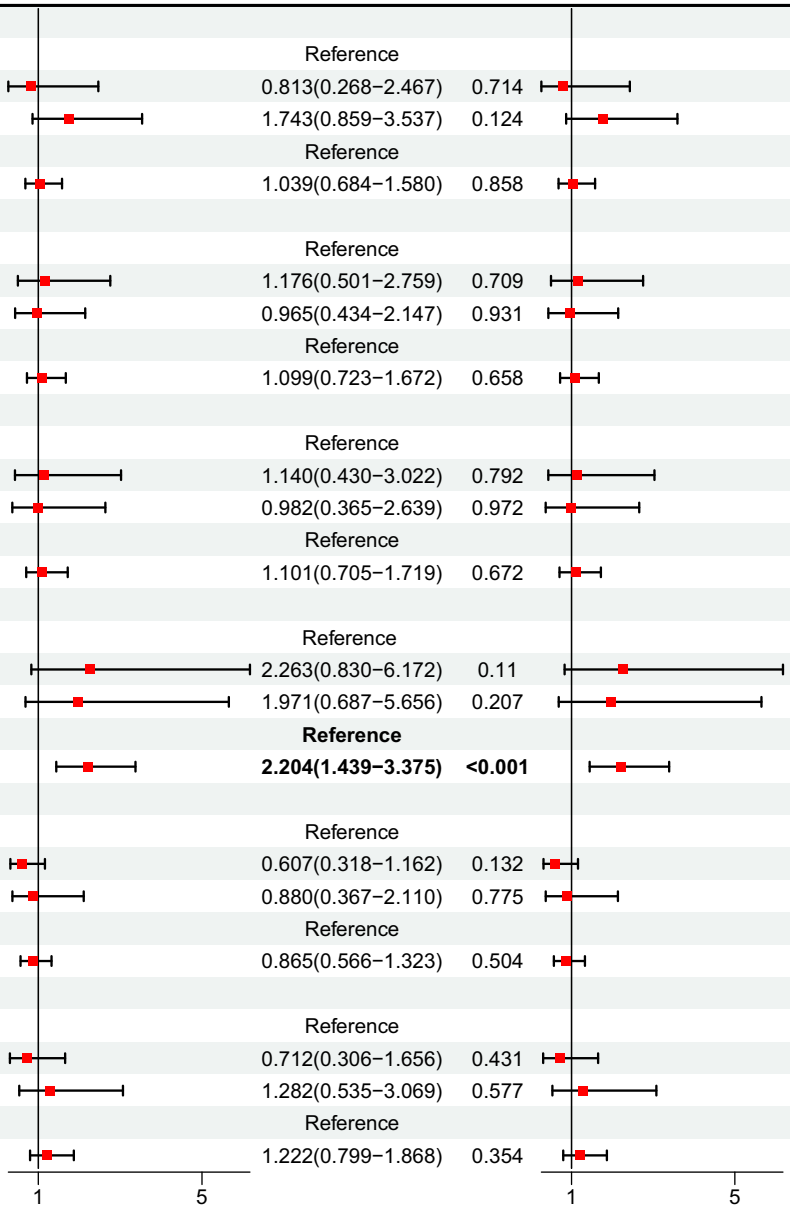

Figure 3 Analysis of regression (T2MH vs T2MH-DYS). *P** value was adjusted by age, gender. Bold value indicates statistical significance.

0.0014). By contrast, AACTAC (OR = 5.925, 95% CI: 1.511–23.233, $P = 0.0040$) and GGACGT (OR = 4.205, 95% CI: 1.277–13.849, $P = 0.0106$) were enriched in T2MH. The global haplotype test was highly significant ($\chi^2 = 71.803$, $P = 4.60 \times 10^{-8}$). After Bonferroni correction ($\alpha = 0.0025$), only GAATGT remained statistically significant, whereas AACTAC and GGACGT exhibited nominal associations. For T2DM vs T2MH-DYS, the haplotypes GACCGT (OR = 4.113, 95% CI: 1.563–10.826, $P = 0.0021$) and AGCTAC (OR = 4.298, 95% CI: 1.439–12.843, $P = 0.0047$) were more frequent in T2MH-DYS patients. The global haplotype distribution was significant ($\chi^2 = 59.580$, $P = 2.39 \times 10^{-6}$). Following Bonferroni correction ($\alpha = 0.0036$), GACCGT retained significance, while AGCTAC did not withstand correction. In the T2MH vs T2MH-DYS contrast, AAACAC was enriched in T2MH-DYS (5.9% vs 0.9%; OR =

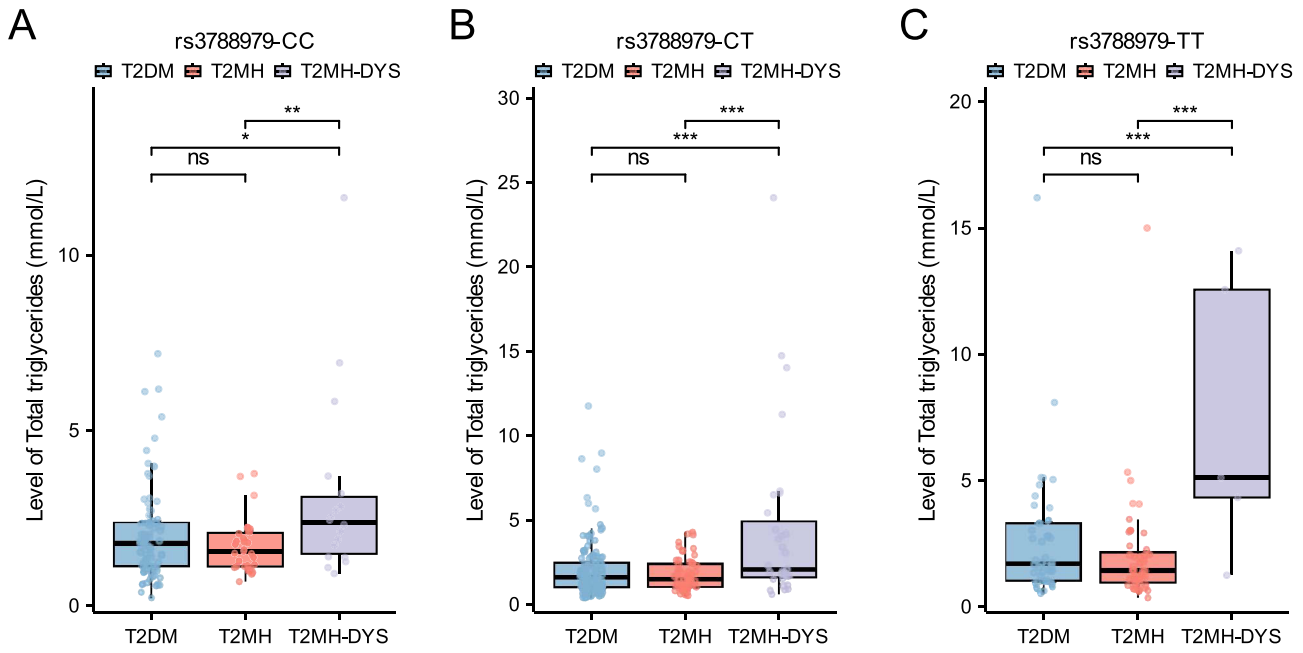

Figure 4 Serum triglyceride levels across clinical subgroups stratified by DPP4 rs3788979 genotype. (**A**) CC homozygotes, (**B**) CT heterozygotes, and (**C**) TT homozygotes. *P < 0.05, **P < 0.01, ***P < 0.001.

6.369, 95% CI: 1.401–28.960, P = 0.0065), whereas GAATGT was less frequent (3.2% vs 11.1%; OR = 0.361, 95% CI: 0.095–1.374, P = 0.0057). Although the global test was significant (χ^2 = 73.730, $P = 4.43 \times 10^{-8}$), neither haplotype remained significant after Bonferroni correction (α = 0.0036), indicating only nominal evidence of association.

Table 4 Haplotype Association Analysis with Global Tests (T2DM vs T2MH)

Haplotype	T2MH Freq	T2DM Freq	χ^2	P value	OR (95% CI)
AAATAC	0.033	0.061	3.546	0.0597	0.487 (0.228–1.044)
AAATGT	0.030	0.007	6.187	0.0129	4.385 (1.235~15.575)
AACCAC	0.015	0.033	2.708	0.0998	0.405 (0.133–1.230)
AACCGT	0.018	0.042	3.670	0.0555	0.390 (0.144–1.056)
AACTAC	0.033	0.005	8.312	0.0040	5.925 (1.511–23.233)
AGACAC	0.032	0.060	3.428	0.0642	0.490 (0.227–1.057)
AGACGT	0.046	0.077	3.703	0.0543	0.527 (0.272–1.021)
AGATAC	0.070	0.031	5.312	0.0212	2.208 (1.109–4.397)
AGCTGT	0.054	0.023	4.703	0.0302	2.335 (1.063–5.127)
GAACAC	0.076	0.075	0.039	0.8444	0.945 (0.540–1.657)
GAACGT	0.027	0.043	1.564	0.2111	0.585 (0.250–1.368)
GAATAG	0.057	0.032	2.138	0.1438	1.696 (0.830~3.465)
GAATGT	0.032	0.088	10.191	**0.0014***	0.312 (0.147–0.661)
GACCGT	0.043	0.017	3.986	0.0459	2.408 (0.991–5.850)
GACTAC	0.054	0.033	1.679	0.1950	1.605 (0.780–3.302)
GGACAC	0.051	0.072	1.871	0.1713	0.641 (0.338–1.217)
GGACGT	0.033	0.008	6.539	0.0106	4.205 (1.277–13.849)
GGATGT	0.056	0.023	4.932	0.0263	2.363 (1.084–5.148)
GGCCAC	0.030	0.021	0.399	0.5277	1.343 (0.536–3.363)
GGCTGT	0.050	0.037	0.425	0.5143	1.269 (0.619–2.603)
Global test	—	—	71.803	**4.60×10^{-8}**	—

Notes: Only haplotypes with frequency ≥3% in either group are shown. Total alleles: T2DM=512, T2MH=268. Variant order: rs1799817 → rs1799854 → rs757110 → rs3788979 → rs5742632 → rs972936. Bonferroni correction, α = 0.0025. *Multiple tests corrected for haplotype analysis P values are still significant. Bold value indicates statistical significance.

Abbreviations: T2DM, type 2 diabetes mellitus; T2MH, type 2 diabetes mellitus with hypertension.

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Table 5 Haplotype Association Analysis with Global Tests (T2DM vs T2MH-DYS)

Haplotype	T2MH-DYS Freq	T2DM Freq	χ^2	P value	OR (95% CI)
AAACAC	0.059	0.024	2.724	0.0988	2.240 (0.840–5.973)
AACCAC	0.045	0.033	0.132	0.7166	1.208 (0.434–3.364)
AACTAC	0.034	0.005	5.812	0.0159	5.637 (1.163–27.333)
AGACAC	0.058	0.060	0.172	0.6783	0.830 (0.343–2.006)
AGACGT	0.104	0.077	0.244	0.6214	1.192 (0.594–2.392)
AGATAC	0.056	0.031	0.919	0.3377	1.593 (0.610–4.158)
AGCTAC	0.061	0.013	7.985	0.0047	4.298 (1.439–12.843)
GAACAC	0.118	0.075	1.040	0.3078	1.415 (0.724–2.767)
GAATAC	0.041	0.032	0.036	0.8492	1.109 (0.383–3.214)
GAATGT	0.111	0.088	0.079	0.7783	1.102 (0.561–2.164)
GACCGT	0.077	0.017	9.481	**0.0021***	4.113 (1.563–10.826)
GGACAC	0.060	0.072	0.694	0.4047	0.695 (0.294–1.643)
GGACGT	0.032	0.008	3.582	0.0584	3.707 (0.869–15.818)
Global test	—	—	59.58	**2.39×10^{-6}**	—

Notes: Only haplotypes with frequency ≥ 3% in either group are shown. Total alleles: T2DM=512, T2MH=268. Variant order: rs1799817 → rs1799854 → rs757110 → rs3788979 → rs5742632 → rs972936. Bonferroni correction, α = 0.0036. *Multiple tests corrected for haplotype analysis *P* values are still significant. Bold value indicates statistical significance.

Abbreviations: T2DM, type 2 diabetes mellitus; T2MH-DYS, type 2 diabetes mellitus with hypertension and dyslipidemia.

Discussion

In this study, we provide the first evidence that genetic polymorphisms within the *DPP4–ABCC8–INSR–IGF1* axis are dynamically associated with the coexistence of HTN and/or DYS in patients with T2DM. Among these, DPP4 rs3788979 displayed a lipid-modulated effect: CT and CC genotypes were protective against hypertension when considered alone, yet shifted to risk alleles in the presence of dyslipidemia. Haplotype-based analysis further revealed distinct combinatorial effects: GAATGT exerted a strong protective influence against hypertension (OR = 0.312, P = 0.0014), whereas GACCGT synergistically increased dyslipidemia risk more than fourfold (OR = 4.113, P = 0.0021). These findings underscore a polygenic cooperative mechanism, where genetic effects are reshaped by metabolic context, transcending the limitations of conventional single-locus studies and establishing a novel composite panel of genetic markers with potential utility for precision prediction of cardiometabolic comorbidities in T2DM.

Beyond the established roles of insulin resistance and chronic low-grade inflammation in driving comorbid HTN and DYS in T2DM, increasing attention has turned to the genetic determinants of the insulin secretion–signaling cascade.[18] The *DPP4–ABCC8–INSR–IGF1* axis represents a critical pathway that links incretin degradation, β-cell excitability, insulin receptor activation, and insulin sensitivity.[38,39] Dysregulation along this axis may therefore create a dual burden of impaired insulin release and attenuated signaling responsiveness, predisposing to cardiometabolic clustering.[7,40,41] Systematic investigation of polymorphisms within this axis provides a rational framework for elucidating the molecular underpinnings of T2DM with comorbid HTN and DYS, and for identifying genetic signatures predictive of high-risk phenotypes.

The role of the DPP4 rs3788979 polymorphism in cardiovascular disease has been contentious, with studies reporting both protective[14] and risk[42,43] associations, underscoring the complexity of its function. To resolve these discrepancies, we investigated its role in the sequential development of cardiometabolic comorbidities within T2DM. Our analysis revealed a critical, context-dependent risk reversal: the CT/CC genotypes were protective against incident hypertension in normolipidemic individuals (T2DM vs T2MH) but became risk factors for dyslipidemia in T2MH patients, as triglyceride (TG) levels were highest in the T2MH-DYS group across all genotypes—a finding corroborated by Xing[44]—indicating that the risk conferred by the C allele is specifically manifested through elevated TG. We hypothesize that a plausible, though currently speculative, mechanism for this risk transition could involve tissue-specific DPP-4 activity,[15,45] potentially amplified by the pro-inflammatory microenvironment of hypertension. We hypothesize that the C allele may promote heightened DPP-4 activity in key tissues like the vascular endothelium and adipose tissue, an effect

not fully captured by systemic levels. In the setting of hypertension, this genetically primed, elevated local activity could be exacerbated, leading to intensified degradation of GLP-1, impaired clearance of TG-rich lipoproteins, and aggravated endothelial insulin resistance, thereby shifting the allele's net effect from systemic protection to localized pro-dyslipidemic action.[46,47] This proposed mechanism remains a hypothesis requiring direct experimental validation.

Similarly, while genetic investigations of IGF1 have predominantly focused on susceptibility to T2DM itself, evidence regarding its role in cardiometabolic complications is emerging yet less consolidated. For instance, the IGF1 rs5742632 polymorphism has been linked to an increased risk of retinopathy in Pakistani T2DM patients,[26] whereas rs972936 was not associated with mild cognitive impairment in a Chinese cohort,[48] highlighting the pleiotropic and context-dependent nature of this gene. Extending this narrative to cardiometabolic comorbidities, our analysis revealed that the TC genotype of IGF1 rs972936 exerted a significant protective effect against hypertension (adjusted OR = 0.464, P = 0.006). In contrast, the GG genotype of rs5742632 showed only a non-significant trend toward increased risk (adjusted OR = 1.769, P = 0.065). These findings suggest that IGF1 variants, particularly rs972936, contribute to the genetic architecture of hypertension risk in T2DM, possibly by modulating insulin-like growth factor signaling pathways that influence vascular function and metabolic homeostasis. The weaker association of rs5742632 underscores the complexity of these relationships. Collectively, the associations uncovered within both DPP4 and IGF1 reinforce the concept that the entire "incretin-secretion-signaling-sensitivity" axis represents a concerted genetic determinant shaping the clinical heterogeneity of T2DM. Haplotype analysis, which captures the combined effect of alleles co-inherited on the same chromosome, often provides greater power than single-locus analysis for detecting associations with complex diseases, as it more accurately reflects genomic architecture and linkage disequilibrium patterns.[49,50] Our study identified several key haplotypes within the DPP4 axis that exert synergistic effects on cardiometabolic comorbidity risk. Most notably, the GAATGT haplotype demonstrated a potent protective effect against hypertension, reducing the odds by nearly 70% (OR = 0.312, P = 0.0014) in T2DM patients. Conversely, the GACCGT haplotype emerged as a major risk factor, increasing the susceptibility to dyslipidemia by over fourfold (OR = 4.113, P = 0.0021). The identification of these haplotypes, which remained significant after stringent Bonferroni correction, underscores a polygenic cooperative mechanism where the combined allelic status across the *INSR-ABCC8-DPP4-IGF1* pathway dictates clinical outcomes. The effect sizes of these haplotype blocks exceeded those observed for individual SNPs, strongly supporting the cumulative genetic burden theory in complex trait etiology. This coordinated polygenic interaction not only reframes the genetic architecture of cardiometabolic clustering in T2DM but also mechanistically pinpoints these specific haplotype combinations as strategic nodes within the "incretin-secretion-signaling-sensitivity" axis. Precise targeting of these synergistic functional modules may pave the way for therapeutic breakthroughs in disrupting the progression cascade of diabetic complications. Such a tool may help stratify T2DM patients at diagnosis for more vigilant monitoring or early, targeted interventions to prevent hypertension and dyslipidemia.

Several limitations of this study warrant acknowledged. First, its single-center, cross-sectional design precludes causal inference. Second, the modest size of the T2MH-DYS subgroup may affect the precision and stability of some odds ratio estimates, necessitating caution in their interpretation. These results should be validated in larger, multi-center, prospective cohorts Third, the lack of comprehensive data on potential confounders such as body mass index, detailed medication history (especially DPP4 inhibitors), diabetes duration, and lifestyle factors limits our ability to fully adjust for residual confounding; these factors may interact with genetic susceptibility and should be prioritized in future prospective studies.

Conclusion

Variants within the DPP4 axis influence susceptibility to HTN and DYS in T2DM, with GAATGT and GACCGT emerging as robust haplotype markers. These findings highlight polygenic mechanisms underlying cardiometabolic clustering and may guide precision management.

Abbreviations

ABCC8, ATP Binding Cassette Subfamily C Member 8; ACTH, Adrenocorticotropic Hormone; ADA, American Diabetes Association; AHA, American Heart Association; ALD, Aldosterone; Ang II, Angiotensin II; Cr, Plasma

creatinine; CRP, C-Reactive Protein; CV, Coefficients of variation; DPP4, Dipeptidyl Peptidase 4; DBP, Diastolic Blood Pressure; DYS, Dyslipidemia; FFAs, Free Fatty Acids; FPG, Fasting Plasma Glucose; GAD65, Glutamic Acid Decarboxylase 65; GSIS, Glucose-Stimulated Insulin Secretion; GLP-1, Glucagon-Likepeptide-1; GIP, Gastric Inhibitory Polypeptide; HbA1c, Glycated Hemoglobin; HDL-C, High-Density Lipoprotein Cholesterol; HTN, Hypertension; IAA, Insulin Autoantibodies; INSR, Insulin Receptor; IGF1, Insulin Like Growth Factor 1; LDL-C, Low-Density Lipoprotein Cholesterol; M:F, Male to Female Ratio; MAF, Minor Allele Frequency; Ren, Renin; SBP, Systolic Blood Pressure; SNPs, Single Nucleotide Polymorphisms; T1DM, Type 1 Diabetes Mellitus; T2DM, Type 2 Diabetes Mellitus; T2MH, Type 2 Diabetes Mellitus patients with Hypertension; T2MH-DYS, Type 2 Diabetes Mellitus patients with comorbid Hypertension and dyslipidemia; TC, Total Cholesterol; TG, Triglycerides; Urea, Plasma urea.

Data Sharing Statement

All data associated with this study are available in the main text or the supplementary materials. The original data analyzed in this study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

According to the relevant regulations in the field of biomedical research in China, all protocols of this study were approved by the Clinical Research Ethics Committee of the First Affiliated Hospital of Guilin Medical University (No. 2023QTLL-37). The study was conducted after the Declaration of Helsinki. Informed consent was obtained from all subjects involved in the study. Prior to signing the informed consent, all participants were informed of the procedure and purpose of the study. In addition, patient data confidentiality and privacy are protected in accordance with the provisions of the law.

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Author Contributions

Q.X.: Conceptualization, Supervision, Writing – Review & Editing;
N.Z.: Conceptualization, Supervision, Writing – Review & Editing;
Y.Q.: Resources, Data curation, Writing – Review & Editing;
S.W.: Methodology, Investigation, Validation, Writing – Original Draft;
C.Z.: Methodology, Investigation, Visualization, Writing – Original Draft;
C.B.: Formal Analysis, Resources, Writing – original draft;
Q.C.: Formal Analysis, Resources, Writing – original draft.

All authors 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 declare no conflict of interest.

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