Original Article

Althea Medical Journal
ISSN Online: 2337-4330
https://doi.org/10.15850/amj.v12n4.4448

PPAR-γ, but not KCNJ11, Is Associated with Type 2 Diabetes Mellitus Progression among First-Generation Offspring of Lembak Ethnicity in Bengkulu, Indonesia

Diah Ayu Aguspa Dita,[1] Elvira Yunita,[2] Debie Rizqoh,[3] Hesty Rhauda Ashan,[4] Dita Fahira[5]

[1]Department of Medical Physiology, Faculty of Medicine and Health Sciences, University of Bengkulu, Bengkulu, Indonesia
[2]Department of Biochemistry, Faculty of Medicine and Health Sciences, University of Bengkulu, Bengkulu, Indonesia
[3]Department of Microbiology, Faculty of Medicine and Health Sciences, University of Bengkulu, Bengkulu, Indonesia
[4]Department of Clinical Pathology, Faculty of Medicine and Health Sciences, University of Bengkulu, Bengkulu, Indonesia
[5]Faculty of Medicine and Health Sciences, University of Bengkulu, Bengkulu, Indonesia

Abstract

Background: Genetic and environmental factors influence the onset and progression of type 2 diabetes mellitus (T2DM). Variants affecting peroxisome proliferator activated-receptor gamma (PPAR-γ) and potassium, inwardly rectifying channel subfamily J member 11 (KCNJ11) may alter insulin secretion and sensitivity. This study investigated the association between PPAR-γ and KCNJ11 gene expression and the risk of T2DM among first-generation (F1) offspring of T2DM patients of Lembak ethnicity in Bengkulu, Indonesia.

Methods: A cross-sectional observational study was conducted from July to September 2024, recruiting 60 unrelated participants aged 18–40 years, all of whom were exposed to the *neron* tradition (high-sugar consumption). Gene expression of PPAR-γ and KCNJ11 was determined using real-time quantitative PCR (qRT-PCR).

Results: F1 offspring of T2DM patients (n=30) had significantly ($p<0.05$) higher body weight (66.89±15.62 kg; p=0.008), body mass index (BMI) (23.55±3.46 kg/m^2), HbA1C (6.55±1.25), random blood glucose levels (median 131 [75–371] mg/dl), and duration of *neron* consumption (median 3 [1–12] years) compared with controls (n=30). PPAR-γ expression differed significantly between group (1.60±2.91 vs 4.23±8.54; p=0.009), whereas KCNJ11 expression did not (0.79±0.76 vs 1.37±0.89; p=0.124). Multivariate analysis revealed no correlation between gene expression and the patients characteristic ($p>0.05$). Linear regression showed 30.4% of PPAR-γ and 45.8% of KCNJ11 variability.

Conclusions: PPAR-γ expression is associated with T2DM onset among Lembak F1 offspring, whilst KCNJ11 expression is not. Multiple genetic and environmental factors likely contribute to disease progression. Screening for PPAR-γ expression may support interventions targeting insulin sensitivity and lipid metabolism.

Keywords: F1 offspring, gene expression, KCNJ11, PPAR-γ, type 2 diabetes mellitus

Althea Medical Journal.
2025;12(4):239–246

Received: August 22, 2025
Accepted: December 1, 2025
Published: December 31, 2025

Correspondence:
Diah Ayu Aguspa Dita, Department of Medical Physiology, Faculty of Medicine and Health Sciences, University of Bengkulu, Bengkulu, Indonesia

E-mail:
diahayuaguspadita@unib.ac.id

Introduction

Type 2 diabetes mellitus (T2DM) is a major global health challenge, affecting 10.5% of the global population and ranking Indonesia consistently among the top ten countries with the highest disease burden.[1] In Bengkulu Province, the prevalence of T2DM has risen more than threefold in the past five years, underscoring a rapidly growing public health concern.[2,3] T2DM is a complex metabolic disorder characterized by elevated blood

glucose levels due to impaired insulin function.[4]

The development of T2DM is determined by various environmental and genetic factors. Psychosocial and lifestyle influences, poor dietary habits, family history, age, ethnicity, and genetic predispositions are linked to T2DM and blood sugar regulation.[5] Understanding the mechanisms underlying the interactions between environmental exposures such as diet, physical inactivity, and psychosocial stress and inherited genetic susceptibility is crucial, especially in population with unique cultural or lifestyle patterns.

Genome-wide association studies have identified several genetic variants associated with susceptibility of T2DM, including peroxisomal proliferator-activating receptor gamma (PPAR-γ) and potassium inwardly rectifying channel subfamily J member 11 (KCNJ11).[6,7] PPAR-γ is a nuclear transcription factor regulating insulin sensitivity, glucose utilization and lipid metabolism. Dysregulation of its expression has been implicated in impaired insulin signaling and T2DM pathogenesis.[8] Meanwhile, KCNJ11 gene, positioned at 11p15.1, comprises a single exon encoding the Kir6.2 protein, which is the inner segment of the adenosine triphosphate-sensitive potassium ion channel (KATP) in pancreatic beta cells, where it is crucial for the regulation of insulin secretion.[9] Variants or altered expression of KCNJ11 can reduce channel sensitivity and impair insulin release, contributing to hyperglycemia.[10] Although numerous studies report associations between PPAR-γ or KCNJ11 polymorphisms such as rs5219 and T2DM, findings vary widely across ethnic group, with several populations showing no significant correlation.[11–14] This inconsistencies highlight the influence of ethnic-specific genetic backgrounds and lifestyle factors.[15,16]

Despite evidence linking these genes to T2DM, no previous studies have evaluated PPAR-γ and KCNJ11 gene expression among the Lembak ethnic group in Bengkulu, Indonesia, a population with distinctive high-sugar dietary tradition (*neron*). This population presents a unique model for studying gene-environment interactions. This study aimed to investigate the differential association of PPAR-γ and KCNJ11 gene expression with the risk and progression of T2DM among first generation (F1) offspring of T2DM patients within the Lembak ethnicity in Bengkulu, Indonesia.

Methods

This analytical observational study used cross-sectional design and was conducted from July to September 2024. A total of 60 participants of Lembak ethnicity in Bengkulu, aged 18–40 years, were included and categorized into two primary groups. The first group comprised 30 individuals (15 female and 15 male) who were F1 offspring of patients with T2DM, and possessed a neron. The second group consisted of 30 individuals (17 female and 13 male) who were F1 offspring of non-T2DM parents, had normal random glucose levels, and served as controls. All participants in both groups practiced *neron*, a traditional dietary habit of the Lembak ethnic group characterized by high sugar consumption. This practice involved adding sugar in a greater quantity than tea or coffee powder, at an approximate ratio of 2:1, with consumption occurring two or three times. daily in the morning, afternoon and evening.

Exclusion criteria included pregnant and breastfeeding women, individuals diagnosed with metabolic disorders such as T2DM, metabolic syndrome, or type 1 diabetes mellitus (T1DM), cancer, active infections, and congenital diseases.

Demographic data, including age, sex, sugar intake, *neron* duration, and *neron* consumption frequency, were collected directly using a brief questionnaire.

Table 1 Real-Time Quantitative PCR Primers Sequences

Genes	Primer Sequences	Sequence
PPAR-γ	Forward	5'-CGAGGACACCGGAGAGGG-3'
	Reverse	5'-TGTGGTTTAGTGTTGGCTTCTT-3'
KCNJ11	Forward	5′- ATCCAGGGTGTTACAAGGCA-3
	Reverse	5′-TTTCAGGGACCAAGTAGAGCTG-3′
GADPH	Forward	5′-AGGTCGGTGTGAACGGATTTG-3′
	Reverse	5′-TGTAGACCATGTAGTTGAGGTCA-3′

Note: PPAR-γ= peroxisomal proliferator-activating receptor gamma, KCNJ11= potassium inwardly rectifying channel subfamily J member 11, GADPH= glyceraldehyde 3-Phosphate dehydrogenase

Anthropometric measurements included body weight, height, and waist circumference. Body weight was measured using a calibrated digital scale with participants barefoot, while height was measured using a stadiometer with participants standing upright. Body mass index (BMI) was calculated using the standard formula (weight in kilograms divided by height in meters squared). Waist circumference was measured using a flexible measuring tape positioned at the between the lowest rib margin and the iliac crest along the mid-axillary line.

Blood samples were collected immediately after anthropometric measurements. Serum samples were obtained using EDTA tubes supplemented with RNA shield and stored at −80°C until analysis. Plasma glucose and hemoglobin A1c (HbA1c) levels were measured using enzymatic methods with commercially available reagents.

For gene expression analysis, total RNA was isolated from 500 µl of serum using the using the Geneaid Total RNA Mini Kit (Blood) QAIC/TW/50077 (Geneaid, Taiwan), following the manufacturer's instructions. The quality of total RNA was verified by agarose gel electrophoresis and A260/280 absorbance ratios, while RNA concentration and purity were measured using a Four E Micro Volume Spectrophotometer. Because of the variability in concentration across samples, RNA concentrations were normalized to 25 ng/µl prior to analysis. Reverse transcription was performed using 1 µg of total RNA to synthesize complementary DNA (cDNA). The primer sequences are listed in Table 1.

Expression level of PPAR-γ and KCNJ11 were determined using real-time quantitative reverse transcription chain reaction (qRT-PCR) with glyceraldehyde 3-Phosphate dehydrogenase (GAPDH) as the housekeeping genes. Relative genes expression was calculated using the ΔCT method, and expression ratios were determined using the equation 2^(CT reference−CT target), as previously described.[17–18]

All participants provided written informed consent after receiving a full explanation of the study procedures and potential risks. The study adhered to the guidelines of the principles of Declaration of Helsinki and was approved by the Health Research Ethics Committee of the Faculty of Medicine and Health Science Universitas Bengkulu (no. 157/UN30.14.9/LT/2024).

Numerical data were presented as mean ± standard deviation (SD), while non-normally distributed variables were presented as median (minimum–maximum). Data normality was assessed using the Kolmogorov-Smirnov test. Independent t-test or Mann-Whitney U test were used to compare variables between groups as appropriate. Multivariate linear regression analysis was used to examine relationship between participants characteristics and mRNA expression levels of PPAR-γ and KCNJ11 genes. Statistical analyses were conducted using SPSS version 26 for Mac (SPSS, Chicago, IL, USA). A p-value <0.05 was considered statistically significant.

Results

Participants who were F1 offspring of patients with T2DM had significantly higher body weight and BMI compared with F1 offspring of non-T2DM parents (66.89±15.62 kg vs 57.87±8.85 kg, p=0.008; and 23.55±3.46 kg/m^2 vs 21.68±3.00 kg/m^2, p=0.011, respectively).

Table 2 Baseline Clinical and Biochemical Characteristics of the Study Population

Variables	F1 of T2DM (n=30)	F1 of Non-T2DM (n=30)	p value
Age (years)	22 (18–39)	21 (18–39)	0.211
Gender (male/female)	15/15	13/17	0.608
Body weight (kg)	66.89±15.62	57.87±8.85	0.008**
Height (cm)	164.53±8.10	163.37±7.48	0.564
BMI (kg/m^2)	23.55±3.46	21.68±3.00	0.011*
Waist circumference (cm)	88.73±12.72	83.00±12.47	0.083
HbA1c (%)	6.55±1.25)	5.69±0.57	0.001**
Glucose ad Random (mg/dl)	131 (75–371)	108 (73–182)	0.002**
Sugar intake (tablespoon/day)	2 (1–3)	1.75 (1–3)	0.053
Neron duration (year)	3 (1–12)	2 (1–13)	0.039*
Neron frequency (day)	2 (1–6)	2.2 (1–5)	0.380

Note: Data are presented as mean ± SD or median (min–max) *p<0.05; *p<0.01, BMI= body mass indeks; HbA1c= hemoglobin A1c

Table 3 RNA Concentration and Purity

Variables	F1 of T2DM subjects (n=30)	F1 of Non-T2DM subjects (n=30)
RNA Concentration (ng/µl)	56.45±22.17	59.67 (29.67–126.98)
RNA Purity (A260/280)	1.97 (1.82–2.06)	1.98±0.05

Note: Data are presented as mean ± SD or median (min–max)

Table 4 PPAR-γ and KCNJ11 mRNA Expression Levels (2^(-ΔΔCt))

Genes	Group	Mean±SD	p value
PPAR-γ	F1 of T2DM	1.60±2.91	0.009**
	F1 of non-T2DM	4.23±8.54	
KCNJ11	F1 of T2DM	0.79±0.76	0.124
	F1 of non-T2DM	1.37±0.89	

Note: Data are presented as mean ± SD; **p<0.01

Additionally, the duration of practicing the *Neron* tradition was also significantly longer in the F1 T2DM group than in the non-T2DM group (median 3 (1–12) years vs. 2 (1–13) years; p=0.039) (Table 2).

Furthermore, biochemical parameters showed that HbA1c levels were significantly higher in the F1 T2DM group compared with the non-T2DM group (6.55±1.25% vs 5.69±0.57%, p=0.001). Random blood glucose levels were also significantly elevated in the F1 T2DM group (median 131 (75–371) mg/dL) compared with controls (108 (73–182) mg/dL), p=0.002). No significant differences were observed between groups with respect to age, gender distribution, height, waist circumference, daily sugar intake, or neron consumption frequency (Table 2).

RNA concentration and purity did not differ significantly between groups. The F1 non-T2DM group showed a non-significant trend toward higher RNA concentration and purity compared with the F1 T2DM group (59.67 (29.67–126.98) ng/µl; 1.98±0.05 vs

Table 5 Multivariate Linear Regression Analysis of PPAR-γ and KCNJ11 Gene Expression

Genes	Variable	PPAR-γ mRNA Expression (n=60)			
		p-value	95% CI For Exp(B)		r^2
			Lower	Upper	
PPAR-γ	Age (years)	0.686	−0.412	0.273	0.304
	Gender (male/female)	0.844	−1.754	2.138	0.304
	Body weight (kg)	0.782	−1.767	1.338	0.304
	Height (cm)	0.769	−5.975	4.444	0.304
	BMI (kg/m^2)	0.544	−0.156	0.292	0.304
	Waist circumference (cm)	0.977	−1.922	1.979	0.304
	HbA1c (%)	0.570	−0.060	0.033	0.304
	Glucose ad random (mg/dl)	0.496	−1.894	3.855	0.304
	Sugar intake (tablespoon/day)	0.356	−1.147	0.420	0.304
	Neron duration (year)	0.376	−2.406	0.925	0.304
KCNJ11	Age (years)	0.778	−0.049	0.037	0.458
	Gender (male/female)	0.801	−0.277	0.215	0.458
	Body weight (kg)	0.802	−0.172	0.221	0.458
	Height (cm)	0.865	−0.603	0.716	0.458
	BMI (kg/m^2)	0.967	−0.027	0.029	0.458
	Waist circumference (cm)	0.130	−0.436	0.058	0.458
	HbA1c (%)	0.886	−0.005	0.006	0.458
	Glucose ad random (mg/dl)	0.962	−0.337	0.355	0.458
	Sugar intake (tablespoon/day)	0.522	−0.067	0.131	0.458
	Neron duration (year)	0.097	−0.388	0.033	0.458

56.45±22.17 ng/µl; 1.97 (1.82–2.06) (Table 3).

Analysis of gene expression demonstrated that PPAR-γ mRNA expression was significantly higher in the F1 of non-T2DM group than in the F1 of T2DM group (4.23±8.54 vs 1.60±2.91, p=0.009). Conversely, there was no significant difference in KCNJ11 gene expression between the two groups (0.79±0.76 vs 1.37±0.89, p=0.124) (Table 4).

Multivariate linear regression analysis revealed no significant associations between expression levels of PPAR-γ or KCNJ11 and patient characteristic variables, such as age, BMI, waist circumference, HbA1c, and current blood sugar levels (all p>0.05). The regression model yielded 30.4% of the variance in PPAR-γ expression (r^2=0.304) and 45.8% of the variance in KCNJ11 expression (r^2=0.458) suggesting that a substantial proportion of gene expression variability may be influenced by factors not evaluated in this study (Table 5).

Discussion

The progression of T2DM is influenced by the expression of multiple genes involved in metabolic regulation, inflammation, and the cellular stress response. Among these, PPAR-γ and KCNJ11 play distinct roles, and accumulating evidence underscoring differences in their gene expression patterns during T2DM progression.[10,19] PPAR-γ functions as a nuclear receptor regulating adipogenesis, lipid metabolism, and insulin sensitivity. Genetic variations can alter PPAR-γ binding affinity to DNA and transcriptional activity, thereby contributing to interindividual differences in diabetes risk.[20] Meanwhile, KCNJ11 plays a critical role in insulin secretion through its regulation of ATP-sensitive potassium channels in pancreatic β-cells. Alteration in KCNJ11 expression or pathogenic variants may disrupt β-cell membrane depolarization, impair insulin secretion, and contribute to hyperglicemia.[21]

This study investigated gene expression profiles associated with T2DM progression among F1 offspring of T2DM patients within the Lembak ethnic population. This population is characterized by distinct cultural practices, dietary habits, and lifestyles behaviors, which may interact with genetic factors and influence disease susceptibility. In this study, PPAR-γ mRNA expression was significantly higher in F1 non-T2DM individuals compared with F1 T2DM subjects. Conversely, although KCNJ11 mRNA expression showed an increased trend in the F1 offspring of the non-T2DM group, there was no statistically significant difference between the F1 offspring of non-T2DM and T2DM individuals, suggesting a potentially limited role of altered KCNJ11 expression in early-stage disease progression in this ethnic context.

PPAR-γ gene expression plays an important role in T2DM pathogenesis, and its effects appear to vary across ethnic groups due to genetic, epigenetic, and environmental influences.[8,16] Polymorphisms in PPAR-γ, particularly Pro12Ala, have been consistently associated with T2DM risk and metabolic syndrome in multiple populations, including Asian cohorts, underscoring their impact on insulin resistance mechanisms.[15,22] A study in another ethnic population, such as Pakistani Pashtun group, has also revealed association between PPAR-γ variants and T2DM risk, suggesting that both expression patterns and functional consequences of PPAR-γ may differ depending on ethnic genetic background.[23] The findings of our study align with previous genomic studies conducted in diverse population.[24,25] Variability in PPAR-γ expression and function may affect the rate of insulin resistance development, thereby influencing T2DM progression across different ethnic groups.

Although KCNJ11 polymorphisms have been associated with T2DM susceptibility, this study provides limited evidence for altered KCNJ11 gene expression in the progression of T2DM.[10] In contrast to PPARγ, changes in KCNJ11 expression have not been prominently reported as dynamic markers of T2DM progression or responses to metabolic stress.[14] The E23K (rs5219) polymorphism in KCNJ11 has been linked to increased T2DM risk in several ethnic groups, including Chinese Han and Polish populations.[26,27] These effects appear to be more closely associated with β-cell dysfunction than insulin resistance.[12,26] However, the predictive value of KCNJ11 variants varies across populations and may be less pronounced in certain ethnic groups. Strong associations have been reported in South and East Asian populations,[28,29] whereas other groups, including the Lembak ethnicity in Bengkulu, Indonesia may show weak or no association with KCNJ11 variants.[30]

This variability may be attributed to differences in allele frequency, gene-gene interactions, environmental exposure, lifestyle factors, sample size limitations. Our study included a relatively small number of participants, which may have reduced the statistical power to detect association

involving KCNJ11 expression. In contrast, several large-scale studies included more than 500 participants, thereby the likelihood to identifying significant association.[28,29]

Several limitations should be acknowledged. The cross-sectional design precludes the assessment of temporal changes in gene expression and limits causal inference. The study population was limited to a single ethnic group, potentially limiting generalizability. Furthermore, detailed quantitative assessments of dietary intake and physical activity were not conducted, preventing a more in-depth evaluation of lifestyle-gene interactions. Future longitudinal and multi-ethnic studies with larger sample sizes are needed to further elucidate the dynamic roles of PPAR-γ and KCNJ11 in T2DM progression.

In conclusion, this study demonstrates that PPAR-γ, but not KCNJ11, is significantly associated with the progression of T2DM as among F1 offspring of T2DM patients in the Lembak ethnic group. These findings suggests that PPAR-γ may serve as a more relevant molecular marker for early metabolic dysfunction in this population. Understanding population-specific genetic influences may support the development of targeted preventive strategies aimed at improving insulin sensitivity and metabolic health.

Acknowledgments
The authors acknowledge the Institute of Research and Community Service (IRCS), University of Bengkulu, for its assistance in facilitating the preparation and implementation of the research proposal.

Authors' Contributions
DAAD contributed to study conceptualization and design, methodology, participant recruitment, RT-PCR analysis, data analysis, manuscript drafting and revision, supervision, and funding acquisition. EY contributed to resources provision, including RNA extraction and RT-PCR analysis, validation, and manuscript review and editing. DR contributed to statistical and multivariate analyses, investigation, and project administration, including ethical approval processes in Bengkulu. HRA contributed to methodological procedures, including HbA1c measurement, random blood glucose testing, RNA purity and concentration analysis, and manuscript review and editing. DF contributed to participant recruitment and laboratory resources, including RNA extraction and RT-PCR analysis.

Funding
This study was supported by the Directorate General of Higher Education, Research, and Technology, Ministry of Education, Culture, Research, and Technology, Indonesia.

Conflict of Interest
The authors declare no financial or personal conflicts of interest that could have influenced the results or interpretation of this study.

References

1. Magliano DJ, Boyko EJ. IDF Diabetes Atlas, 10th Ed. Brussels, Belgium: International Diabetes Federation; 2021.
2. Badan Penelitian dan Pengembangan Kesehatan Kementerian Kesehatan Republik Indonesia. Laporan Hasil Riset Kesehatan Dasar (Riskesdas) Indonesia Tahun 2018. Jakarta: Lembaga Penerbit Badan Penelitian dan Pengembangan Kesehatan; 2019.
3. Dinas Kesehatan Provinsi Bengkulu. Profil Kesehatan Provinsi Bengkulu Tahun 2022. Bengkulu: Dinas Kesehatan Provinsi Bengkulu; 2023. Available from: https://ppid.kemendagri.go.id/storage/dokumen/62KW9RpJMDOTF2TUUNMEyZtIUjaS1WYACXlvrm03.pdf.
4. Geng T, Huang T. Gene-environment interactions and type 2 diabetes. Asia Pac J Clin Nutr. 2020;29(2):220–6. doi: 10.6133/apjcn.202007_29(2).0002.
5. Liu X, Collister JA, Clifton L, Hunter DJ, Littlejohns TJ. Polygenic risk of prediabetes, undiagnosed diabetes, and incident type 2 diabetes stratified by diabetes risk factors. J Endocr Soc. 2023;7(4):bvad020. doi: 10.1210/jendso/bvad020.
6. Vujkovic M, Keaton JM, Lynch JA, Miller DR, Zhou J, Tcheandjieu C, et al. Discovery of 318 new risk loci for type 2 diabetes and related vascular outcomes among 1.4 million participants in a multi-ancestry meta-analysis. Nat Genet. 2020;52(7):680–91. doi: 10.1038/s41588-020-0637-y.
7. Salasa RA, Rahman H, Andiani A. Faktor risiko diabetes mellitus tipe 2 pada populasi Asia: a systematic review. Jurnal Biosainstek. 2019;1(1):95–107. doi: 10.52046/biosainstek.v1i01.306.
8. Cataldi S, Costa V, Ciccodicola A, Aprile M. PPARγ and diabetes: beyond the genome and towards personalized medicine. Curr Diab Rep. 2021;21(6):18. doi: 10.1007/s11892-021-01385-5.
9. Rasheed MA, Kantoush N, Abd El-

Ghaffar N, Farouk H, Kamel S, Ibrahim AA, et al. Expression of JAZF1, ABCC8, KCNJ11and Notch2 genes and vitamin D receptor polymorphisms in type 2 diabetes, and their association with microvascular complications. Ther Adv Endocrinol Metab. 2017;8(6):97–108. doi: 10.1177/2042018817708910.
10. Alqadri N. Independent case-control study in KCNJ11 gene polymorphism with Type 2 diabetes Mellitus. Saudi J Biol Sci. 2022;29(4):2794–9. doi: 10.1016/j.sjbs.2022.01.008.
11. Makhzoom O, Kabalan Y, Al-Quobail F. Association of KCNJ11 rs5219 gene polymorphism with type 2 diabetes mellitus in a population of Syria: a case-control study. BMC Med Genet. 2019;20(1):107. doi: 10.1186/s12881-019-0846-3.
12. Bhowmik A, Rokeya B, Kabir Y. KCNJ11 rs5219 gene polymorphism is associated with T2DM in a population of Bangladesh: a case-control study. Int J Endocrinol. 2025;2025:5834412. doi: 10.1155/ije/5834412.
13. Alidoust L, Ajamian F, Abbaspour S, Sharafshah A, Keshavarz P. The E23K polymorphism of KCNJ11 and diabetic retinopathy in Northern Iran. Br J Biomed Sci. 2022;79:10245. doi: 10.3389/bjbs.2021.10245.
14. Moazzam-Jazi M, Najd-Hassan-Bonab L, Masjoudi S, Tohidi M, Hedayati M, Azizi F, et al. Risk of type 2 diabetes and KCNJ11 gene polymorphisms: a nested case-control study and meta-analysis. Sci Rep. 2022;12(1):20709. doi: 10.1038/s41598-022-24931-x.
15. Bage IJ, Kamalanathan S, Selvarajan S, Sahoo J, Mathaiyan J, Naik D. Peroxisome proliferator-activated receptor α and γ gene polymorphisms among South Indian patients with diabetic dyslipidaemia. Indian J Endocrinol Metab. 2023;27(2):118–26. doi: 10.4103/ijem.ijem_451_22.
16. Gouda HN, Sagoo GS, Harding A-H, Yates J, Sandhu MS, Higgins JPT. The association between the peroxisome proliferator-activated receptor-γ2 (PPARG2) Pro12Ala gene variant and type 2 diabetes mellitus: a HuGE review and meta-analysis. Am J Epidemiol. 2010;171(6):645–55. doi: 10.1093/aje/kwp450.
17. Varkonyi-Gasic E, Hellens RP. Quantitative stem-loop RT-PCR for detection of microRNAs. Methods Mol Biol. 2011;744:145–57. doi: 10.1007/978-1-61779-123-9_10.
18. Livak KJ, Schmittgen TD. Analysis of relative gene expression data using real-time quantitative PCR and the 2(-Delta Delta C(T)) Method. Methods. 2001;25(4):402–8. doi: 10.1006/meth.2001.1262.
19. Sarhangi N, Sharifi F, Hashemian L, Hassani Doabsari M, Heshmatzad K, Rahbaran M, et al. PPARG (Pro12Ala) genetic variant and risk of T2DM: a systematic review and meta-analysis. Sci Rep. 2020;10(1):12764. doi: 10.1038/s41598-020-69363-7.
20. Soccio RE, Chen ER, Rajapurkar SR, Safabakhsh P, Marinis JM, Dispirito JR, et al. Genetic variation determines PPARγ function and anti-diabetic drug response in vivo. Cell. 2015;162(1):33–44. doi: 10.1016/j.cell.2015.06.025.
21. Oduori OS, Murao N, Shimomura K, Takahashi H, Zhang Q, Dou H, et al. Gs/Gq signaling switch in β cells defines incretin effectiveness in diabetes. J Clin Invest. 2020;130(12):6639–55. doi: 10.1172/jci140046.
22. Syed R, Jamil K, Asimuddin M, Alqahtani MS, Alshehri M, Mateen A, et al. Molecular & biochemical analysis of Pro12Ala variant of PPAR-γ2 gene in type 2 diabetes mellitus. Saudi J Biol Sci. 2020;27(9):2439–43. doi: 10.1016/j.sjbs.2020.06.046.
23. Jan A, Zakiullah, Ali S, Muhammad B, Arshad A, Shah Y, et al. Decoding type 2 diabetes mellitus genetic risk variants in Pakistani Pashtun ethnic population using the nascent whole exome sequencing and MassARRAY genotyping: a case-control association study. PLoS One. 2023;18(1):e0281070. doi: 10.1371/journal.pone.0281070.
24. Regine I, Husain R, Aswathi RP, Reddy DR, Ahmed S, Ramakrishnan V. Association between PPARγrs1801282 polymorphism with diabetic nephropathy and type-2 diabetes mellitus susceptibility in south India and a meta-analysis. Nefrologia (Engl Ed). 2020;40(3):287–98. doi:10.1016/j.nefro.2020.01.005.
25. Vergotine Z, Yako YY, Kengne AP, Erasmus RT, Matsha TE. Proliferator-activated receptor gamma Pro12Ala interacts with the insulin receptor substrate 1 Gly972Arg and increase the risk of insulin resistance and diabetes in the mixed ancestry population from South Africa. BMC Genet. 2014;15:10. doi:10.1186/1471-2156-15-10.
26. Liu NJ, Wu HH, Li YL, Yang Z, Tao XM, Du YP, et al. An analysis of the association between a polymorphism of KCNJ11 and

diabetic retinopathy in a Chinese Han population. Eur J Med Res. 2015;20(1):3. doi:10.1186/s40001-014-0075-3.
27. Buraczynska M, Boczkowska S, Zaluska W. Association of KCNJ11 E23K/rs5219 gene polymorphism with type 2 diabetes and diabetes-related cardiovascular disease. Diabetes Metab Syndr Obes. 2025;18:653–61. doi:10.2147/DMSO.S506639.
28. Kozárová M, Javorský M, Stančáková A, Dobríková M, Habalová V, Klimčáková L, et al. Relationship of five type 2 diabetes candidate gene polymorphisms to the age at diagnosis of diabetes in the Slovakian population. Bratislavske Lek Listy. 2010;111(3):150–2.
29. Chauhan G, Spurgeon CJ, Tabassum R, Bhaskar S, Kulkarni SR, Mahajan A, et al. Impact of common variants of PPARG, KCNJ11, TCF7L2, SLC30A8, HHEX, CDKN2A, IGF2BP2, and CDKAL1 on the risk of type 2 diabetes in 5,164 Indians. Diabetes. 2010;59(8):2068–74. doi: 10.2337/db09-1386.
30. Yunita E, Dita DAA, Indrian A, Putri CE, Umar LA, Ashan HR, et al. Polymorphism of the KCNJ11 E23K (rs5219) gene and HbA1c concentration in first derivatives of diabetes mellitus ethnic Lembak, Bengkulu. African Journal of Biological Sciences. 2024;6(15):8176–91. doi: 10.48047/afjbs.6.15.2024.8175-8191.