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The Impact of Genetic Factors on the Development of Type 2 Diabetes and Possible Pathways for its Correction

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Abstract. ***Aim*:** The aim of this study was to investigate the impact of genetic factors on the development of type 2 diabetes in the population of the Republic of Kazakhstan.

***Materials and methods*:** The methodology included collection of demographic data, analysis of biochemical parameters, and application of polymerase chain reaction genotyping for single-nucleotide polymorphisms in genes associated with type 2 diabetes.

***Results*:** The main results of the study demonstrated that patients with type 2 diabetes had a 20% higher body mass index (29.5±4.2 kg/m^2 versus 24.3±3.1 kg/m^2) and showed 29% lower physical activity (3.2±1.5 hours per week versus 4.5±2.0 hours per week) compared with the control group. Biochemical parameters showed a 50% higher glucose level (7.8±2.1 mmol/L versus 5.2 ± 0.8 mmol/L), insulin levels by 76% (15.3±5.2 microunits per millilitre versus 8.7±2.5 microunits per millilitre), and glycated haemoglobin by 42% (7.5±1.2% versus 5.3±0.5%) in patients with type 2 diabetes. Genetic analysis revealed substantial associations between type 2 diabetes and risk alleles in the *TCF7L2* (*rs7903146*), *KCNJ11* (*rs5219*), *FTO* (*rs9939609*), *PPARG* (*rs1801282*), and *ADIPOQ* (*rs1501299*) genes, which were linked to compromised insulin secretion and metabolic anomalies in the study population.

***Conclusions*:** The practical significance of the study lies in the potential application of these findings and development of personalised approaches for the prevention and treatment of type 2 diabetes, including lifestyle modification, the use of modern pharmaceuticals, and anti-inflammatory drugs to improve glucose control in patients.

Keywords: polymorphisms, insulin resistance, biochemical parameters, glycated haemoglobin, changes in microbiota composition.

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Genetinių veiksnių įtaka 2 tipo cukriniam diabetui išsivystyti ir galimi jo koregavimo būdai

Santrauka. ***Tikslas:*** Šio tyrimo tikslas buvo ištirti genetinių veiksnių įtaką 2 tipo cukriniam diabetui išsivystyti Kazachstano gyventojų populiacijoje.

Medžiaga ir metodai: Tyrimo metodika apėmė demografinių duomenų rinkimą, biocheminių rodiklių analizę ir polimerazės grandininės reakcijos (PGR) metodą, naudotą genotipavimui nustatyti vieno nukleotido polimorfizmams genuose, susijusiuose su 2 tipo cukriniu diabetu.

Rezultatai: Pagrindiniai tyrimo rezultatai parodė, kad pacientai, sergantys 2 tipo cukriniu diabetu, turėjo 20 % didesnį kūno masės indeksą (29,5 ± 4,2 kg/m², palyginti su 24,3 ± 3,1 kg/m²), ir 29 % mažesnį fizinį aktyvumą (3,2 ± 1,5 valandos per savaitę, palyginti su 4,5 ± 2,0 valandos per savaitę), palyginti su kontroline grupe. Biocheminiai rodikliai parodė 50 % didesnį gliukozės lygį (7,8 ± 2,1 mmol/l, palyginti su 5,2 ± 0,8 mmol/l), 76 % didesnį insulino lygį (15,3 ± 5,2 mikrovienetų mililitre, palyginti su 8,7 ± 2,5 mikrovienetų mililitre), o glikozilinto hemoglobino – 42 % (7,5 ± 1,2 %, palyginti su 5,3 ± 0,5 %) pacientams, sergantiems 2 tipo cukriniu diabetu. Genetinė analizė atskleidė reikšmingą ryšį tarp 2 tipo diabeto ir rizikos alelių TCF7L2 (rs7903146), KCNJ11 (rs5219), FTO (rs9939609), PPARG (rs1801282) ir ADIPOQ (rs1501299) genuose, kurie buvo susiję su sutrikusiu insulino išsiskyrimu ir medžiagų apykaitos anomalijomis tiriamojoje populiacijoje.

Išvados: Tyrimo praktinė reikšmė yra ta, kad šiuos rezultatus galima pritaikyti kuriant individualius 2 tipo cukrinio diabeto prevencijos ir gydymo metodus, įskaitant gyvenimo būdo keitimą, šiuolaikinių vaistų vartojimą ir priešuždegiminių vaistų skyrimą, siekiant pagerinti pacientų gliukozės kontrolę.

Raktažodžiai: genų polimorfizmai, atsparumas insulinui, biocheminiai rodikliai, glikozilintas hemoglobinas, mikrobiotos sudėties pokyčiai.

Introduction

Type 2 diabetes is one of the most common chronic diseases, characterised by impaired glucose metabolism and insulin resistance. This condition is of particular concern due to its high prevalence and serious complications, including cardiovascular disease, stroke, kidney failure, and blindness. Research on this disease is especially relevant in developing countries such as Kazakhstan, where the demographic factors and lifestyle patterns contribute to the rising incidence of diabetes. A study by H. Lee et al. [1] found that the incidence of type 2 diabetes was 29.6% among the participants with a high genetic risk, which indicates that genetic predisposition plays a significant role in the development of this disease.

Several factors contribute to the development of type 2 diabetes, encompassing both external and internal influences. External factors include poor diet, a sedentary lifestyle, and stress. Internal factors include genetic predisposition, which plays a key role in the development of the disease [2]. The challenge in this field lies in the limited understanding of the role of genetic factors in the development of type 2 diabetes, as well as the lack of comprehensive studies linking genetic predisposition to specific diseases and their progression at different stages. Interest in these issues has increased in recent years following the discovery of new genetic markers, yet their impact on disease development in different populations has not been fully explored yet. A major limitation of existing research is that most studies focus on homogeneous groups of patients, while leaving the role of genetic factors in the context of ethnicity and other social determinants incompletely understood.

To date, numerous discoveries have been made in the field of genetic predisposition to type 2 diabetes. For example, N. Chaudhary et al. [3] investigated the association between the *FTO* and *TCF7L2* genes and the development of diabetes, finding that these markers can significantly increase disease risk in individuals with the corresponding genetic predispositions.

Other studies, such as those by V. Mannar et al. [4] and M. Laakso and L. F. Silva [5], extended this analysis to the relationship between epigenetic factors and type 2 diabetes, emphasising the

importance of external influences such as the diet, stress, and lifestyle in combination with genetic predisposition. An important step in this direction is the identification of multifactorial models that can more accurately predict the development of the disease by considering both genetic and environmental factors.

There is a need for further research into the genetics of diabetes, particularly in relation to different ethnic groups and socioeconomic conditions. Studies such as that by F. F. Rahim et al. [6] highlight the importance of a comprehensive approach, on the grounds of incorporating analysis of diverse clinical and laboratory data to identify significant risk factors and develop predictive models. This study, in particular, identified abdominal obesity, a family history of diabetes, and hypertension as risk factors, while an older age and poor nutrition were associated with prediabetes.

In this context, the study of epigenetic changes that may influence disease development also warrants further attention. For example, research by R. A. Kowluru and G. Mohammad [7] emphasises the potential of epigenetic studies to provide new insights into genetic predisposition to diabetes.

The researchers examined genotyping data from a sample of 1,800 Kazakhstanis and found that the frequency of the minor allele for the rs1801282 variant in the *PPARG* gene was 13.78%. By comparison, the frequency of the minor allele for the *rs7903146* variant in the *TCF7L2* gene was slightly higher, at 15.21%. Analysis showed that the frequency of the minor allele G for the *rs1801282* variant in the *PPARG* gene among Kazakhs is comparable to that observed in European populations, but significantly higher than in East Asian populations. This suggests that the Kazakh population has unique genetic characteristics that may influence susceptibility to prediabetes [8].

The study also revealed significant correlations between certain *ADIPOQ* gene variants and susceptibility to type 2 diabetes mellitus and obesity, as well as their impact on the fasting glucose levels and the body mass index among individuals of Kazakh ethnicity. Specifically, the *rs266729* variant was strongly associated with type 2 diabetes and obesity in this demographic group. In contrast, the other studied variants (*rs1501299*, *rs2241766*, and *rs17846866*) did not show significant associations. These results suggest that variations in the ADIPOQ gene may influence risk factors related to type 2 diabetes, thereby underscoring the critical role of genetic factors in disease progression [9].

Thus, despite the substantial body of research in the field of type 2 diabetes genetics, significant knowledge gaps remain nevertheless. Specifically, there is a lack of comprehensive studies linking genetic predisposition to specific disease progression stages within diverse populations, such as that of Kazakhstan. Furthermore, the role of social determinants and ethnicity remains incompletely understood, as most research focuses on homogeneous groups, while leaving the potential for personalized diagnostic and treatment models based on individual genetic markers and environmental factors largely unexplored. This underscores the importance of further research aimed at developing more accurate models for the diagnosis and treatment of diabetes, taking into account individual patient characteristics.

The aim of this study was to analyse the genetic factors influencing the development of type 2 diabetes in the Kazakh population and to create more accurate prediction models by considering individual characteristics and risk factors. The study's objectives were to analyse existing data, identify genetic markers playing a key role in diabetes predisposition, and develop recommendations for improving prevention and treatment based on these findings and the scientific literature.

Materials and Methods

The study involved 400 participants, comprising patients diagnosed with type 2 diabetes mellitus (T2DM) (n=200) and a control group without signs of diabetes (n=200). The inclusion criteria for the main group were: age over 40 years, diagnosis of T2DM confirmed by an endocrinologist, and the absence of other severe chronic diseases that could influence the study results.

The control group was matched to the main group by gender and age but showed no signs of diabetes or prediabetes. The exclusion criteria included pregnancy, cancer, hereditary syndromes affecting glucose metabolism, and refusal to participate. Demographic data (age, gender, *Body Mass Index* (BMI), family history, and lifestyle) were collected from all participants, together with information on their dietary habits and physical activity, as these factors may influence predisposition to diabetes [10].

To investigate the role of genetic factors in the development of T2DM, all participants underwent PCR genotyping of *Single-Nucleotide Polymorphisms* (SNPs) in the *TCF7L2, KCNJ11, PPARG, FTO, ADIPOQ, ADIPOR1,* and *ADIPOR2* genes, which have previously been associated with susceptibility to T2DM [11].

The selection of specific *Single-Nucleotide Polymorphisms* (SNPs) in these genes was based on their well-established functional roles in the pathogenesis of type 2 diabetes, as confirmed by numerous international investigations. These markers were prioritized over broader GWAS catalog variants because they directly regulate critical metabolic processes: for instance, *TCF7L2* and *KCNJ11* are vital for the pancreatic *β*-cell function and insulin secretion, while *PPARG* and *ADIPOQ* govern insulin sensitivity and lipid metabolism. Furthermore, these specific loci, such as the *rs7903146* and *rs9939609* variants, have consistently demonstrated high effect sizes and reproducibility across diverse ethnic cohorts, including East Asian and European populations, making them the most scientifically justified candidates for investigating genetic predisposition within the Kazakhstani population.

Deoxyribonucleic acid (DNA) was isolated from fasting venous blood samples by using the *QIAamp DNA Blood Mini Kit* (*QIAGEN*, Germany) in accordance with the manufacturer's protocol [12]. The concentration and purity of the extracted DNA were assessed with a *NanoDrop 2000* spectrophotometer (*Thermo Fisher Scientific*, USA) at a wavelength ratio of 260/280 nm.

SNP genotyping was performed by real-time PCR (qPCR) using *TaqMan* probes (*Thermo Fisher Scientific*, USA) on a *QuantStudio 5* Real-Time PCR System. Genotype distribution was analysed by using SNPStats software and assessed with the χ^2 test.

To assess diabetes-related biochemical parameters, the following analyses were performed for all participants. Plasma glucose was measured by using the glucose oxidase method on a *Cobas 6000* automated analyser (*Roche Diagnostics*, Switzerland) [13]. Insulin levels were determined by enzyme-linked immunosorbent assay (ELISA) with the *Human Insulin ELISA Kit* (*Abcam*, UK). Glycated haemoglobin (HbA1c) was measured by *High-Performance Liquid Chromatography* (HPLC) using a Bio-Rad Variant II analyser (*Bio-Rad*, USA) [14].

Adiponectin and leptin concentrations were determined by ELISA using commercially available kits (*R&D Systems*, USA). Biological samples were collected and processed in accordance with international laboratory quality standards.

All data were analysed by using *SPSS Statistics 26.0* (*IBM*, USA). To assess the differences between groups, Student's t-test for independent samples was applied to normally distributed data, while the Mann–Whitney U-test was used for non-normally distributed data. One-way analysis of variance (ANOVA) was employed with the objective to assess differences across multiple groups, and logistic regression was performed to examine associations between genotypes and the risk of developing T2DM. For multiple comparisons, the Bonferroni correction was applied to minimise the likelihood of false-positive results [15-17]. The study was reviewed and approved by the Local Ethics Committee of the Non-Profit Joint-Stock Company (NJSC) Astana Medical University, Astana, Kazakhstan (Decision No. 8, 25 November 2022). All participants provided written informed consent for participation, including genetic analysis and biological data collection. The study complied with the principles of the WMA Declaration of Helsinki [18].

Results

Based on the stated aim of the study, the primary focus was to analyse the influence of genetic factors on the development of type 2 diabetes in the Kazakhstani population. Several key genes associated with diabetes were selected for genotyping and subsequent analysis of their association with the disease.

To assess genetic predisposition to type 2 diabetes, genes previously linked to this condition in international studies were chosen. All of these genes play an important role in the pathogenesis of diabetes, and their involvement in the regulation of carbohydrate and lipid metabolism, as well as tissue sensitivity to insulin, has been confirmed by numerous scientific investigations.

The *TCF7L2* gene encodes a transcription factor playing a crucial role in regulating pancreatic secretory activity and carbohydrate metabolism. The *rs7903146* genotype is the most extensively studied variant in relation to type 2 diabetes, and numerous studies have confirmed its association with disease risk in various populations, including European and Asian cohorts [19-21].

The *KCNJ11* gene encodes a protein that constitutes a key component of the potassium channels of pancreatic β-islet cells. The *rs5219* polymorphism in this gene is associated with type 2 diabetes through its effects on insulin secretion and tissue sensitivity to insulin [22,23].

The *FTO* gene is involved in body weight regulation and is therefore important in the pathogenesis of type 2 diabetes, given that obesity is one of the principal risk factors for the disease. The *rs9939609* polymorphism has been identified as a factor that increases susceptibility to both obesity and type 2 diabetes [24].

The *PPARG* gene (peroxisome proliferator-activated receptor γ) regulates carbohydrate and lipid metabolism, as well as insulin sensitivity. The *rs1801282* polymorphism is significantly associated with an improved glucose control in patients with type 2 diabetes [25-27].

The *ADIPOQ* gene encodes adiponectin, a hormone that enhances insulin sensitivity. Recent studies have suggested that its *rs1501299* polymorphism may be associated with type 2 diabetes [28].

The *ADIPOR1* gene encodes the adiponectin receptor, which is essential for maintaining insulin sensitivity and metabolism. The *rs1342387* polymorphism has been linked to altered adiponectin levels and an increased risk of developing type 2 diabetes [29,30].

Genetic and biochemical factors of type 2 diabetes

This study analysed demographic, biochemical, and genetic data from participants so that to identify factors associated with the development of type 2 diabetes. Particular emphasis was placed on the analysis of genetic polymorphisms that may contribute to an increased risk of the disease. Demographic differences are quantitatively summarised in Table 1.

Table 1. Demographic data of study participants

Group	Age (years old)	Gender (M/F)	BMI (kg/m^2)	Family history of T2DM (%)	Physical activity (hours/week)
Patients with type 2 diabetes	55±10	120/130	29.5±4.2	65	3.2±1.5
Control group	54±9	125/125	24.3±3.1	10	4.5±2.0

Source: compiled by the authors.

Table 1 shows that patients with type 2 diabetes had a higher BMI and lower levels of physical activity compared with the control group. They also reported a higher prevalence of family history of type 2 diabetes. These findings suggest that both genetic predisposition and lifestyle factors play a significant role in the development of the disease.

Biochemical parameters also demonstrated significant differences between patients with type 2 diabetes and the control group. These variations highlight the metabolic disturbances associated with type 2 diabetes and are quantitatively summarised in Table 2.

Table 2. Biochemical characteristics of study participants

Group	Glucose (mmol/L)	Insulin (μU/ml)	HbA1c (%)	Adiponectin (μg/ml)	Leptin (ng/ml)
Patients with type 2 diabetes	7.8±2.1	15.3±5.2	7.5±1.2	4.2±1.8	12.5±4.3
Control group	5.2±0.8	8.7±2.5	5.3±0.5	8.5±3.2	6.8±2.7

Source: compiled by the authors.

Analysis of biochemical parameters in the study participants revealed significant differences between patients with type 2 diabetes and the control group. Patients with diabetes exhibited higher glucose and insulin levels, which indicates insulin resistance. This was further confirmed by elevated glycated haemoglobin values, reflecting long-term hyperglycaemia.

In addition, patients with diabetes had decreased adiponectin levels, which may be associated with a worsened metabolic profile and an increased risk of cardiovascular disease. Conversely, leptin levels were elevated in these patients, potentially reflecting an increased fat mass and related metabolic disturbances.

Logistic regression analysis of genetic associations with type 2 diabetes demonstrated significant differences in the frequency of risk alleles between the diabetes and control groups. Specifically, risk alleles in the *TCF7L2*, *KCNJ11*, *FTO*, *PPARG*, and *ADIPOQ* genes were significantly more frequent in patients with type 2 diabetes compared with controls. These findings are quantitatively supported by the data presented in Table 3.

Table 3. Genetic associations with type 2 diabetes

Gene	Polymorphism	Risk allele	Risk allele frequency in the type 2 diabetes group (%)	Risk allele frequency in the control group (%)	*p*-value
TCF7L2	*rs7903146*	T	63	45	<0.001
KCNJ11	*rs5219*	G	57	45	0.02
FTO	*rs9939609*	A	59	45	<0.01
PPARG	*rs1801282*	C	40	30	0.05
ADIPOQ	*rs1501299*	G	50	35	0.03

Source: compiled by the authors.

When analysing quantitative parameters under the assumption of a non-normal data distribution, the statistical significance of group differences was assessed by using non-parametric tests, such as the Mann-Whitney U test, with the subsequent Bonferroni correction of *p*-values. The study demonstrated that genetic variants associated with metabolic regulation and insulin secretion were more common among individuals with diabetes. The strongest correlations were observed for polymorphisms in genes with key roles in glucose and lipid metabolism, thereby indicating their potential involvement in the development of diabetes. Furthermore, variations in genes linked to insulin sensitivity and adipose tissue regulation also showed significant differences in the frequency of risk alleles.

Analysis of the influence of genetic markers on biochemical parameters revealed significant differences between the carriers of risk alleles and the carriers of alternative alleles. Specifically, the carriers of risk alleles exhibited higher fasting glucose levels and elevated glucose concentrations

two hours post-exercise, thus indicating impaired carbohydrate metabolism. These differences in biochemical parameters highlight the importance of genetic factors in metabolic regulation and are quantitatively summarised in Table 4.

Table 4. Influence of genetic markers on biochemical parameters

Gene	Polymorphism	Biochemical indicator	Significance in carriers of the risk allele	Significance in carriers of other alleles	*p*-value
TCF7L2	*rs7903146*	Fasting glucose (mmol/L)	7.5	6.2	<0.001
KCNJ11	*rs5219*	Glucose after 2 hours (mmol/L)	10.2	8.4	0.02
FTO	*rs9939609*	Homeostatic model assessment for insulin resistance (HOMA-IR)	2.2	1.5	<0.01
PPARG	*rs1801282*	HbA1c (%)	6.5	7.2	0.05
ADIPOQ	*rs1501299*	Adiponectin (µg/ml)	3.8	5.2	0.03

Source: compiled by the authors.

To assess the statistical significance of differences between groups for non-normally distributed quantitative data, the Mann-Whitney U test was applied, and the resulting *p*-values were adjusted by using the Bonferroni correction. Adjustment of *p*-values (p_{adj}) accounted for multiple testing and increased the reliability of statistical inferences. After applying the Bonferroni correction, significant associations remained for the following polymorphisms: *rs7903146* of the *TCF7L2* gene (*p*_{adj}<0.001), *rs5219* of the *KCNJ11* gene (*p*_{adj}=0.02), *rs9939609* of the *FTO* gene (*p*_{adj}<0.01), *rs1801282* of the *PPARG* gene (*p*_{adj}=0.05), and *rs1501299* of the *ADIPOQ* gene (*p*_{adj}=0.03).

The carriers of risk alleles exhibited higher levels of insulin resistance, as evidenced by elevated HOMA-IR values. Notably, the carriers of risk alleles also showed lower adiponectin levels, which may be associated with a worsened metabolic profile and an increased risk of cardiovascular disease. At the same time, they demonstrated lower HbA1c levels, which may indicate better long-term blood glucose control.

This conclusion agrees with the unique functional role of the PPARG gene, which is a crucial regulator of insulin sensitivity and glucose metabolism. Certain variations may elevate the overall risk of developing type 2 diabetes; however, they may paradoxically improve the glycemic profile in individuals already afflicted by the condition by augmenting insulin efficacy. This finding is particularly notable as this polymorphism is associated with an improved glucose control, contrasting with other risk alleles like those in the TCF7L2 and FTO genes that correlate with an impaired carbohydrate metabolism and a higher insulin resistance.

Prospects for the prevention and treatment of type 2 diabetes

Smoking is a significant risk factor for the development of type 2 diabetes, acting through both direct and indirect mechanisms. Human studies have shown that smokers have a 73% higher risk of developing type 2 diabetes compared with non-smokers (HR: 1.73, 95% CI: 1.54–1.94), with approximately 38.3% of this risk attributable to metabolic changes such as elevated *VLDL* triglyceride levels and an impaired lipid distribution. Smoking cessation may temporarily worsen the blood glucose control and contribute to weight gain; however, in the long term, it reduces the risk of type 2 diabetes and improves insulin sensitivity [31,32].

Patients with diabetes also demonstrate changes in the composition of the microbiota, notably, a reduction in bacteria involved in the synthesis of short-chain fatty acids, which exert anti-

inflammatory effects and enhance insulin sensitivity. In this context, probiotics, prebiotics, and even faecal transplants are being explored as potential approaches for the prevention and management of T2DM. Furthermore, several incretin-based pharmaceuticals have been developed that show promise in both prevention and treatment of type 2 diabetes. Drugs that harness gut hormones such as glucagon-like peptide-1 (*GLP-1*) and glucose-dependent insulinotropic polypeptide (GIP) enhance postprandial insulin release. These agents not only lower the blood glucose levels but also promote weight loss, improve lipid profiles, and reduce cardiovascular risk. Owing to their multifaceted metabolic effects, incretin-based therapies are emerging as a key focus in the management of T2DM [33,34].

Chronic Low-Grade Inflammation (CLGI), characterised by elevated levels of inflammatory markers such as *C-Reactive Protein* (CRP), *IL-6*, and *TNF-α*, plays an important role in the development of insulin resistance and metabolic syndrome. *Hydroxychloroquine* (HCQ) has been shown to reduce the risk of developing diabetes by 77% when used for more than four years, and to improve insulin sensitivity by 26%. In addition, HCQ reduced *HbA1c* levels by 1.18% after 12 weeks and improved lipid profiles, including reductions in total cholesterol and triglycerides. These findings highlight the potential anti-inflammatory and antidiabetic benefits of *HCQ* in the management of T2DM [35,36].

Looking ahead, the use of nutraceuticals that improve insulin sensitivity, lower the blood glucose levels, and reduce inflammation should be considered. Evidence suggests that nutraceuticals such as cinnamon, bitter gourd, fennel, turmeric, and berberine can significantly improve glucose control and lipid profiles in patients with T2DM. For example, cinnamon supplementation reduces fasting glucose and improves lipid profiles, while berberine activates *AMP-activated protein kinase* (AMPK), thereby enhancing cellular energy metabolism [37-39]. Similarly, omega-3 fatty acids reduce insulin resistance and triglyceride levels, whereas alpha-lipoic acid decreases oxidative stress and improves insulin sensitivity. These findings highlight the potential role of nutraceuticals in the comprehensive management of T2DM, offering safer and more natural adjuncts to conventional treatment strategies [40,41].

Taken together, these data underscore the importance of a comprehensive approach to the management of T2DM, incorporating lifestyle modification, modern pharmacological therapies, and nutraceuticals.

Discussion

The results of this study confirm the importance of genetic predisposition in the development of type 2 diabetes, which is consistent with findings from numerous international studies. Genetic markers such as *FTO*, *TCF7L2*, *SLC30A8*, and *KCNJ11* have demonstrated associations with an increased disease risk. For example, a study by T. Bego et al. [42] showed that the A allele of the *FTO* gene (*rs8050136*) is associated with higher levels of HbA1c, insulin, HOMA-IR index, diastolic blood pressure, and inflammatory markers such as fibrinogen and leukocytes. In addition, it correlates with elevated obesity markers. Similarly, T. Q. Binh et al. [43] reported that the *FTO-rs9939609* polymorphism is a significant predictor of future type 2 diabetes, with each A allele increasing the risk by 35% (HR=1.35, 95% CI 1.02–1.78, p=0.036). The study by L. Del Bosque-Plata et al. [19] emphasised that *TCF7L2* is the strongest risk locus for type 2 diabetes, and its impact on the response to hypoglycaemic drugs such as sulfonylureas requires further investigation. Whereas, W. Ding et al. [44], in a meta-analysis, demonstrated a significant association between the *rs7903146* polymorphism and type 2 diabetes across various ethnic groups, including Caucasians, East Asians, and South Asians, with differing inheritance patterns. Meanwhile, F. S. Mitu et al. [45] found that *SLC30A8 rs13266634* was significantly associated with type 2 diabetes, but not with cardiovascular disease or hypertension. In this context, M. Buraczynska et al. [46] showed that the T allele and TT

genotype of the *KCNJ11* rs5219/E23K polymorphism are associated with an increased risk of both type 2 diabetes and cardiovascular disease, with the TT genotype conferring almost a sixfold higher risk of cardiovascular disease. Collectively, these findings suggest that genetic predisposition plays a key role not only in the development of T2DM but also in influencing the disease progression and therapeutic response. Identifying such genetic markers may therefore prove valuable for predicting the disease risk, guiding early intervention, and enabling a more personalised therapy, including prediction of response to hypoglycaemic agents.

Located on chromosome 10q25.3, the *TCF7L2* gene is critical for regulating the expression of genes involved in glucose and lipid metabolism, as well as pancreatic β-cell function. In a study by N. Gunavathy et al. [47], the *rs7903146* and *rs12255372* polymorphisms of this gene were investigated in relation to lipid metabolism disorders in individuals with type 2 diabetes mellitus. Triglyceride levels in patients with T2DM were significantly elevated compared with the controls (205.2±145.7 mg/dL versus 106.4±27.4 mg/dL), and the mean HbA1c level was 9.7±2.1%. The CT/TT genotype for *rs7903146* and the GT/TT genotype for *rs12255372* were significantly associated with hypertriglyceridaemia (OR: 4.89, p=0.0105; and OR: 5.23, p=0.0101, respectively), suggesting that these SNPs may contribute to the development of an atherogenic profile in individuals with T2DM. These findings emphasise the importance of *TCF7L2* not only in glucose regulation but also in lipid metabolism. In contrast, the present study revealed associations of *TCF7L2* primarily with glucose levels and insulin resistance, whereas the earlier study demonstrated a stronger link with hypertriglyceridaemia.

The findings of this study regarding significant increases in glucose, insulin, and HbA1c levels in patients with T2DM compared with the controls are supported by the results of V. V. Benberin et al. [48], also conducted in the Republic of Kazakhstan. Both studies demonstrated similar trends, thereby indicating the reproducibility of biochemical differences between groups and underscoring the universality of the metabolic disturbances associated with type 2 diabetes. In addition, V. V. Benberin et al. reported pronounced changes in lipid profiles: triglycerides (2.32±0.38 mmol/L versus 1.37±0.12 mmol/L), total cholesterol (5.02±1.88 mmol/L versus 4.93±0.77 mmol/L), HDL (1.25±0.15 mmol/L versus 2.92±0.38 mmol/L), and LDL (3.19±0.70 mmol/L versus 1.93±0.15 mmol/L). Taken together with hyperglycaemia and hyperinsulinaemia, these findings confirm the systemic nature of metabolic disturbances in type 2 diabetes. Furthermore, while the study by V. V. Benberin et al. identified significant associations between certain SNPs and glucose levels, BMI, and lipid profiles, the present study established a broader link, encompassing impaired carbohydrate and lipid metabolism, insulin resistance, and reduced adiponectin levels.

The present study, together with the work of L. Dilworth et al. [49], highlights the importance of a comprehensive understanding of the pathogenesis of T2DM, combining data on the influence of the lifestyle, metabolic changes, and hormonal regulation. Within the framework of the current study, it was found that patients with T2DM had a higher body mass index, maintained a lower physical activity, showed elevated levels of glucose, insulin, and glycated haemoglobin, as well as reduced levels of adiponectin, thus indicating the presence of severe metabolic disturbances. These results are consistent with the findings of L. Dilworth et al., who emphasised the functional role of white adipose tissue as a source of adipokines – particularly leptin and adiponectin – that regulate energy metabolism and insulin sensitivity. The data obtained in this study complement the concept proposed by L. Dilworth et al., confirming that changes in the hormonal activity of the adipose tissue, in combination with lifestyle factors, play a central role in the pathogenesis of T2DM, and that they can be considered potential targets for prevention and therapy. While the authors underlined the role of white adipose tissue and adipokines in regulating energy metabolism and insulin sensitivity, the present study identified specific metabolic disturbances in patients with type 2 diabetes.

Furthermore, a study by Y. T. Wondmkun [50] expands on these findings by elucidating the molecular and inflammatory pathways leading to insulin resistance. It was demonstrated that obesity contributes to the development of insulin resistance through multiple mechanisms, including inflammatory processes, mitochondrial dysfunction, endocrine disturbances, and lipid accumulation. In particular, the study emphasised the role of inflammatory cytokines such as *TNF-α* and *IL-6* in the development of insulin resistance. Taken together, these studies provide a holistic picture: lifestyle and genetics contribute to obesity and metabolic disorders; adipose tissue functions as an endocrine organ influencing insulin resistance; and the inflammatory and cellular mechanisms described by Y. T. Wondmkun and others explain how these processes culminate in the development of T2DM. While Y. T. Wondmkun emphasised obesity and associated physiological factors in the development of insulin resistance, the current study identified specific genetic and biochemical markers associated with type 2 diabetes, including gene polymorphisms and alterations in the adiponectin and leptin levels.

This study focused on the analysis of genetic polymorphisms and their associations with biochemical parameters, while applying the Bonferroni correction to minimise the risk of false positives. Significant associations were identified for several genetic markers. These polymorphisms influence key components of metabolic regulation: for instance, the *rs7903146* variant in *TCF7L2* is associated with impaired insulin secretion and elevated fasting glucose levels; the *rs9939609* polymorphism in *FTO* is linked to increased insulin resistance, as evidenced by elevated HOMA-IR values; and the *rs1501299* variant in *ADIPOQ* is associated with reduced adiponectin levels, which decrease tissue sensitivity to insulin and promote inflammatory processes [51,52]. In the study by I. Cicek et al. [53], machine learning methods such as *Logistic Regression* (LR) and *Artificial Neural Networks* (ANN) were employed to classify data and assess the risk of developing T2DM. Despite methodological differences, the research objectives were similar: to improve the early diagnosis and prevention of T2DM. The findings of I. Cicek et al. complement the current study by identifying variables with the greatest prognostic value, thereby providing a more complete and clinically applicable picture. Integration of the results of both studies enables not only the identification of biological determinants of T2DM but also the accurate prediction of its development, which can enhance personalised prevention and treatment. However, while I. Cicek et al. did not focus on genetic predisposition, while emphasising instead risk factors such as LDL and HDL, the present study identified specific genetic polymorphisms associated with an increased risk of type 2 diabetes. This underscores the importance of a multidisciplinary approach to diabetes research.

Together with previous research, this study has confirmed the significant role of metabolic, behavioural, and genetic factors in the development of T2DM and contributed to a deeper understanding of specific genetic polymorphisms. A clear association was identified between the risk alleles in the *TCF7L2*, *KCNJ11*, *FTO*, *PPARG*, and *ADIPOQ* genes and increased rates of insulin resistance, hyperglycaemia, and abnormal lipid profiles. Furthermore, on the grounds of broadening the scope of research within the Kazakhstani population, a quantitative relationship was demonstrated between these genetic markers and biochemical abnormalities associated with T2DM, including decreased adiponectin levels and increased HOMA-IR. These findings clarify the pathogenetic mechanisms of the disease and strengthen the evidence for the role of polymorphisms in disorders of carbohydrate and lipid metabolism.

The practical significance of these results lies in their potential application for early risk stratification for T2DM based on an individual's genetic profile, as well as for the development of more personalised approaches to disease prevention and treatment. The findings of this study represent an important step towards multifactorial, personalised, and preventive medicine for T2DM.

Conclusions

The study concludes that the development of type 2 diabetes (T2DM) should be viewed not as a result of isolated genetic predisposition, but as a multifactorial process involving the interaction of hereditary, metabolic, behavioural, and inflammatory mechanisms. The identified associations between specific genetic polymorphisms and diabetes-related metabolic disturbances suggest that genetic screening may have practical value for early risk stratification, especially when integrated with biochemical and lifestyle markers. These findings underscore the relevance of a personalized approach to T2DM prevention and treatment. Such an approach should extend beyond correcting hyperglycaemia to account for insulin sensitivity, adipose tissue dysfunction, inflammatory status, weight regulation, and individual behavioural risks. In this context, lifestyle modification remains the fundamental preventive strategy, while pharmacological, nutraceutical, and microbiological interventions represent supplementary directions requiring further clinical validation.

Furthermore, the study demonstrates the importance of population-specific research, as genetic markers may vary in frequency and clinical significance across different ethnic and regional groups. Thus, the data obtained contribute to the development of more precise diagnostic and preventive models tailored to the characteristics of the population under study. At the same time, the findings should be interpreted with caution due to the modest sample size and ethnic specificity of the results. Key directions for future research include expanding the cohort, conducting in-depth studies of genetic markers, exploring the role of the microbiota and the potential of probiotics, and evaluating the impact of nutraceuticals and dietary interventions on glucose control. Additionally, the efficacy and safety of anti-inflammatory drugs in the management of T2DM warrant more rigorous investigation.

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Conflicts of interest

The authors declare no conflicts of interest.

Author contributions

Z. S.: conceptualization, methodology, supervision, project administration, writing – review and editing.
O. I.: investigation, data curation, methodology, writing – original draft preparation.
D. T.: formal analysis, validation, visualization, writing – original draft preparation.
A. Z.: investigation, resources, data curation, writing – review and editing.
A. I.: methodology, formal analysis, writing – original draft, writing – review and editing.

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