



Межгенные взаимодействия и вклад полиморфных локусов генов *KCNJ11*, *ADIPOQ*, оментина, лептина, *TCF7L2* и *PPARG* в развитие сахарного диабета 2-го типа в кыргызской популяции: предварительные результаты исследования по типу случай—контроль с использованием MDR-анализа

© Ж.Т. Исакова^{1*}, Э.Т. Талайбекова¹, Б.Ж. Жыргалбекова¹, Э.М. Миррахимов², Н.М. Алдашева^{1,3}, А.А. Алдашев¹

¹НИИ молекулярной биологии и медицины, Бишкек, Кыргызская Республика; ²Национальный центр кардиологии и терапии, Бишкек, Кыргызская Республика; ³Кыргызско-Российский Славянский Университет, Бишкек, Кыргызская Республика

Обоснование. Выявлено множество генетических локусов, ассоциированных с сахарным диабетом 2-го типа (СД2), причем в разных популяциях развитие СД2 может быть обусловлено эффектами разных генетических локусов.

Цель исследования — изучить межгенные взаимодействия и вклад полиморфных локусов генов *KCNJ11*, *ADIPOQ*, оментина, лептина, *TCF7L2* и *PPARG* в развитие СД2 в кыргызской популяции с использованием MDR-анализа.

Материал и методы. В исследование включены 223 пациента кыргызской национальности, из них 114 — больные СД2 (53 женщины и 61 мужчина, средний возраст 54±7,4 года) и 109 — условно-здоровые лица (48 женщин и 61 мужчина, средний возраст 50±8,4 года) без нарушений углеводного обмена (группа контроля). Методом рестрикционного анализа исследовались полиморфные локусы Glu23Lys гена *KCNJ11*, G276T гена адипонектина, Val109Asp гена оментина, G2548A гена лептина, IVS3C/T гена *TCF7L2* и Pro12Ala гена *PPARG*.

Результаты. Среди изученных полиморфных локусов указанных генов наибольший вклад в развитие СД2 в кыргызской популяции вносят полиморфные локусы генов *ADIPOQ* (2,17%) и *KCNJ11* (2,01%). Маркерами повышенного риска развития СД2 в кыргызской популяции являются аллель 276T (OR=1,68, CI 95% 1,09—2,60; $p=0,025$), гетерозиготный генотип G276T (OR=1,79, CI 95% 1,05—3,05; $p=0,036$) гена *ADIPOQ*, а также аллель 23Lys гена *KCNJ11* (OR=1,62, CI 95% 1,10—2,38; $p=0,019$). Полиморфные локусы Val109Asp гена оментина, G2548A гена лептина, IVS3C/T гена *TCF7L2* и Pro12Ala гена *PPARG* по отдельности на развитие СД2 не оказывают столь существенного влияния и в фенотипической реализации СД2 они участвуют преимущественно за счет ген-генных комбинаций.

Заключение. В популяции кыргызов полиморфные локусы Glu23Lys гена *KCNJ11* и G276T гена *ADIPOQ* ассоциированы с СД2. Локусы G2548A гена лептина, Val109Asp гена оментина, IVS3C/T гена *TCF7L2* и Pro12Ala гена *PPARG* вносят вклад в фенотипическую реализацию СД2 не по одиночке, а преимущественно за счет ген-генных взаимодействий.

Ключевые слова: ген, *KCNJ11*, *ADIPOQ*, оментин, лептин, *TCF7L2*, *PPARG*, СД2, кыргызская популяция.

Gene-gene interactions and the contribution of polymorphic loci of the *KCNJ11*, *ADIPOQ*, omentin, leptin, *TCF7L2* and *PPARG* genes to the development of type 2 diabetes mellitus in the Kyrgyz population: a case-control genetic association study using MDR analysis

© Zhainagul T. Isakova^{1*}, Elnura T. Talaibekova¹, Baktygue Zh. Zhyrgalbekova¹, Erkin M. Mirрахимов², Nazira M. Aldasheva^{1,3}, Alemaz A. Aldashev¹

¹Research Institute of Molecular Biology and Medicine, Bishkek, Kyrgyz Republic; ²National Center of Cardiology and Internal Medicine, Bishkek, Kyrgyz Republic; ³Kyrgyz-Russian Slavic University, Bishkek, Kyrgyz Republic

There are many genetic loci associated with type 2 diabetes mellitus (T2DM). The genetic factors involved in the development of the T2DM can depend on the nature of genetic variation within and across different ethnic groups.

Aims — the aim of this study was to investigate the gene-gene interactions and to determine the role of the *KCNJ11* (Glu23Lys), *ADIPOQ* (G276T), omentin (Val109Asp), leptin (G2548A), *TCF7L2* (IVS3C/T), *PPARG* (Pro12Ala) genes in the development of type 2 diabetes mellitus (T2DM) in the Kyrgyz population using MDR analysis.

Material and methods. We examined 114 patients (53 females and 61 males; mean age, 54±7.4) with T2DM and 109 apparently healthy controls (48 females and 61 males; mean age, 50±8.4). Polymorphisms of the *KCNJ11* (Glu23Lys), *ADIPOQ* (G276T), omentin (Val109Asp), leptin (G2548A), *TCF7L2* (IVS3C/T), *PPARG* (Pro12Ala) genes were defined by PCR-RFLP assay.

Results. Among the six genes (*KCNJ11*, *ADIPOQ*, omentin, leptin, *TCF7L2*, *PPARG*) included in this study, the most significant contribution to the development of T2DM in the Kyrgyz population was detected for the *ADIPOQ* (2.17%) and *KCNJ11* genes (2.01%).

The heterozygous genotype G276T (OR=1.79 CI 95% 1.05—3.05; $p=0.036$) and the 276T allele (OR=1.68 CI 95% 1.09—2.60; $p=0.025$) of the *ADIPOQ* gene were associated with a high risk of developing T2DM in the Kyrgyz population. The 23Lys allele of the *KCNJ11* gene was significantly associated with T2DM in the Kyrgyz population (OR=1.62 CI 95% 1.10—2.38; $p=0.019$). The allele and genotype frequencies of the omentin (Val109Asp), leptin (G2548A), *TCF7L2* (IVS3C/T), *PPARG* (Pro12Ala) genes did not differ between the studied groups ($p>0.05$).

Conclusions. In Kyrgyz population, the polymorphic loci Glu23Lys of the *KCNJ11* gene, the 276T allele and genotype G276T of *ADIPOQ* are associated with T2DM. The omentin (Val109Asp), leptin (G2548A), *TCF7L2* (IVS3C/T), and *PPARG* (Pro12Ala) genes alone do not have such a significant impact on the development of type 2 diabetes; they contribute to the phenotypic development of T2DM mainly due to gene-gene interactions.

Keywords: gene, *KCNJ11*, *ADIPOQ*, omentin, leptin, *TCF7L2*, *PPARG*, T2DM, kyrgyz population.

In recent years, an increase in the number of patients with type 2 diabetes mellitus (T2DM) has been observed in various population and age groups [1].

According to the State Register of Diabetes Mellitus (DM), 5,011 new DM cases were registered in Kyrgyzstan in 2016; of these, new-onset T2DM was diagnosed in 72 children and in 146 adults and adolescents, and new-onset T2DM was diagnosed in 5,533 adults and 1 child. The incidence rate of T1DM was 3.96 and 3.53 per 100,000 population in children and adults, respectively. Especially high incidence rates, as in all other countries, were revealed for T2DM (129.4 per 100,000 population), which confirms the epidemic nature of this type of diabetes [2].

Currently, research is increasingly focused on genetic risk factors for the pathogenesis of T2DM [3,4]. The predisposition to T2DM is controlled by the structural and functional states of numerous genes, including *KCNJ11* (ATP-dependent potassium channel), *ADIPOQ* (adiponectin), omentin, leptin, *TCF7L2* (transcription factor 7-like 2), and *PPAR γ* (peroxisome proliferator-activated receptor gamma) genes whose products participate in various stages of carbohydrate and fat metabolism and affect the sensitivity of tissues to insulin and the functioning of pancreatic β -cells [3,4].

KCNJ11, *ADIPOQ*, omentin, leptin, *TCF7L2*, and *PPAR γ* genes, like most other genes, have polymorphic regions due to nucleotide substitutions in the primary nucleotide DNA sequence [4, 5]. According to the results of clinical and experimental studies, different variants of polymorphic loci Glu23Lys (*KIPNJ11*), G276T (*ADIPOQ*), Val109Asp (omentin gene), G2548A (leptin gene), IVS3C/T (*TCF7L2*), and Pro12Ala (*PPAR γ*) may underlie inter-individual differences in the hereditary predisposition to T2DM [4–6].

Each population is known to have its own specific set of genotypes and alleles and be also characterized by a certain type of diet and lifestyle. In this regard, results of molecular genetic studies on the association between polymorphic loci and multifactorial diseases, which are obtained in one population, are not always consistent with data obtained in other ethnic groups. To identify genetic markers of an increased risk of T2DM, each population should be studied separately. In addition, predisposition to T2DM as a genetically heterogeneous disease arises due to a combined effect of several genes; therefore, gene-gene interactions should be considered when predicting the risk of T2DM.

AIM — the study aim was to investigate gene-gene interactions and the effect of polymorphic loci of *KCNJ11*, *ADIPOQ*, omentin, leptin, *TCF7L2*, and *PPAR γ* genes on development of T2DM in the Kyrgyz population.

Material and methods

The study included 223 patients of Kyrgyz ethnicity; of these, there were 114 T2DM patients (53 females and 61 males; mean age, 54 ± 7.4 years) who underwent inpa-

tient treatment at the Department of General Medicine of the Bishkek National Center of Cardiology and Internal Medicine (Kyrgyz Republic) in the period between 2014 and 2015. T2DM was diagnosed in accordance with the WHO criteria (1999). The control group consisted of 109 apparently healthy subjects (48 females and 61 males; mean age, 50 ± 8.4 years). All participants signed informed consent for participation in molecular genetic studies. The study was approved by the Local Ethical Committee of the Bishkek Institute of Molecular Biology and Medicine.

DNA was isolated from peripheral blood leukocytes using standard phenol-chloroform extraction. Polymorphic loci were genotyped by PCR-RFLP analysis. Amplification and restriction products were analyzed using electrophoresis in a 3% agarose gel and a gel-documentation system (GelDoc-IT, UVP).

To amplify the polymorphic locus Glu23Lys of the *KCNJ11* gene, 5'-GACTCTGCAGTGAGGCCCTA-3' and 5'-ACGTTGCAGTTGCCTTTCTT-3' primers were used. PCR amplification products were treated with Ban II endonuclease (Fig. 1).

To amplify the polymorphic locus G276T of the *ADIPOQ* gene, 5'-GGCCTCTTTCATCACAGACC-3' and 5'-AGATGCAGCAAAGCCAAAGT-3' primers and the BsmI restriction enzyme (Fig. 2) were used.

Genotypes of the omentin gene Val109Asp polymorphism were identified using direct 5'-GAGCCTTTAGGC-CATGTCTCT-3' and inverse 5'-CTCTCCTTCTTCTC-CAGCCCAT-3' primers. To identify genotypes, PCR amplification products were treated with AccI endonuclease (Fig. 3).

The leptin gene G2548A polymorphism was amplified using direct 5'-TTTCCTGTAATTTTCCCGTGAG-3' and inverse 5'-AAAGCAAAGACAGGCATA-AAAA-3' primers. To identify genotypes, PCR amplification products were treated with CfoI endonuclease (Fig. 4).

Genotypes of the *TCF7L2* gene IVS3C/T polymorphism were identified using direct 5'-ACAATTAGAGAGCTAAGCACTTTTAAATA-3' and reverse 5'-CTAACCTTTTTCCTAGTTATCTGACATTG-3' primers. PCR amplification products were treated with SspI endonuclease (Fig. 5).

Direct 5'-GCCAATTCAAGCCCAGTC-3' and reverse 5'-GATATGTTTGCAGACAGTGTATCAGTGAAGGAATCGCTTTCCG-3' primers were used to amplify the *PPAR γ* gene Pro12Ala polymorphism. PCR amplification products were treated with BstUI endonuclease (Fig. 6).

Statistical analysis

Statistical processing of the data was carried out using the GraphPad Prism v5 software package [<http://www.graphpad.com/>]. The occurrence frequency (in percent) was calculated for qualitative data. To find the differences between qualitative indicators, we used the χ^2 method with Yates' continuity correction on contingency tables.

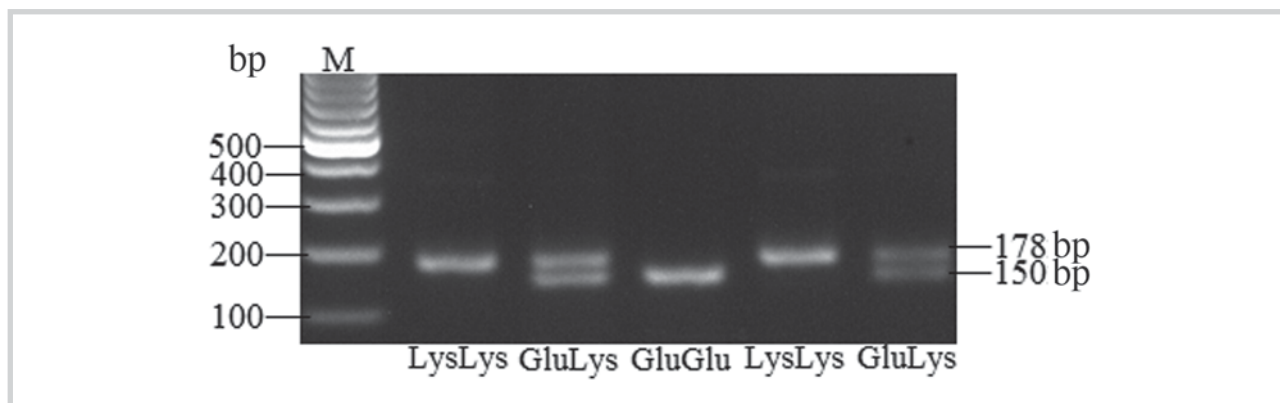


Fig. 1. Agarose gel electrophoresis image of the *KCNJ11* gene Glu23Lys polymorphism.

Glu/Glu genotype — 150+32+28 bp; Lys/Lys genotype — 178+32 bp; Glu/Lys genotype — 178+150+32+28 bp. 32 and 28 bp fragments are not seen due to low molecular weight. M — a DNA molecular weight marker.

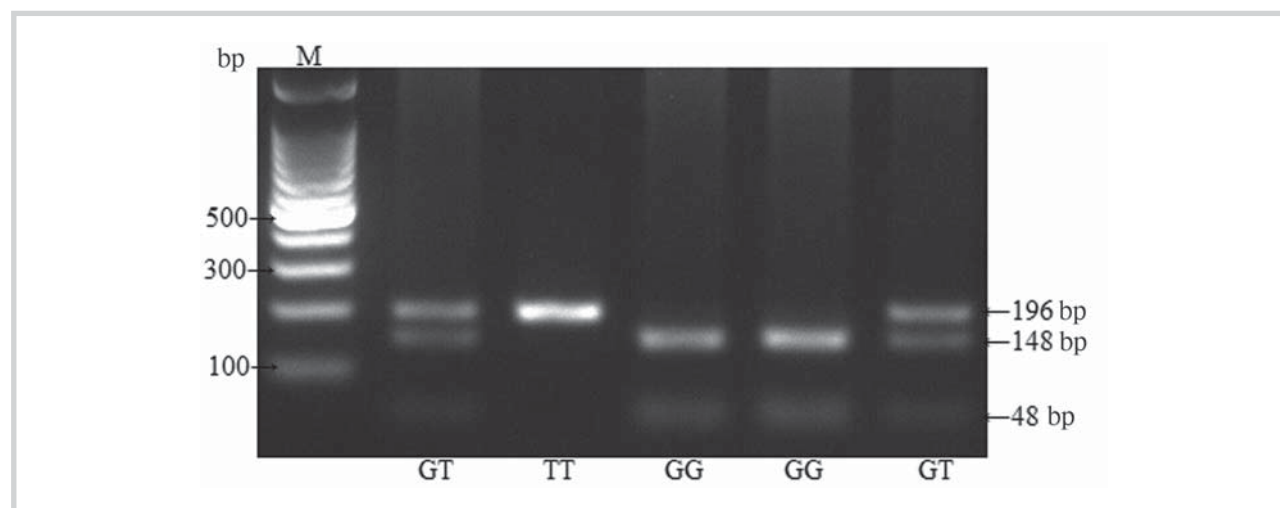


Fig. 2. Agarose gel electrophoresis image of the *ADIPOQ* gene G276T polymorphism.

GG genotype — 148 and 48 bp DNA fragments; heterozygous GT genotype — 196, 648, and 48 bp; TT genotype — 196 bp.

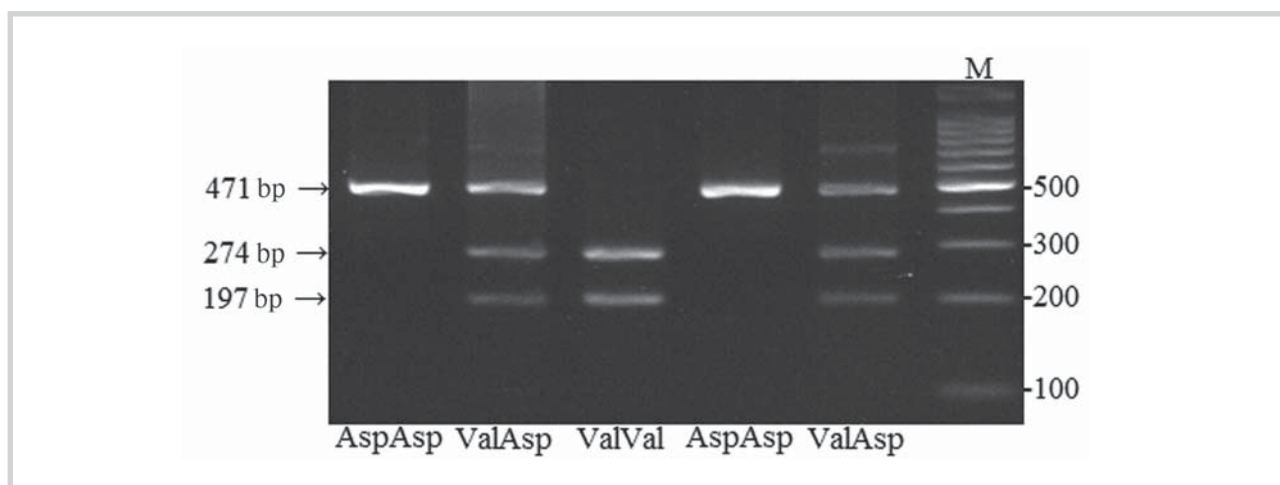


Fig. 3. Agarose gel electrophoresis image of the omentin gene Val109Asp polymorphism.

Val/Val genotype — 274 and 197 bp; Asp/Asp genotype — 471 bp; heterozygous Val/Asp genotype — 471, 274, and 197 bp. M — a DNA molecular weight marker.

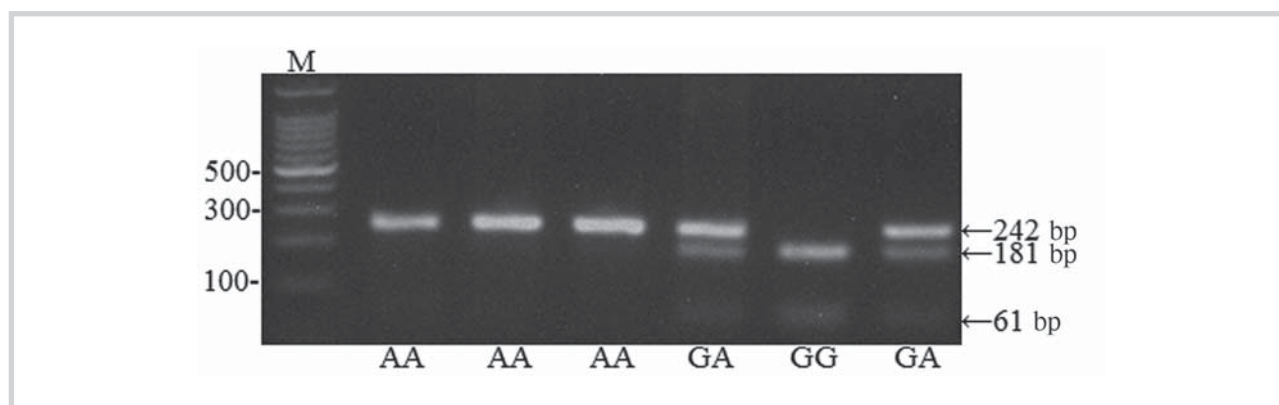


Fig. 4. Agarose gel electrophoresis image of the leptin gene G2548A locus.

GG genotype — 181 and 61 bp; AA genotype — 242 bp; heterozygous GA genotype — 242, 181, and 61 bp. M — a DNA molecular weight marker.

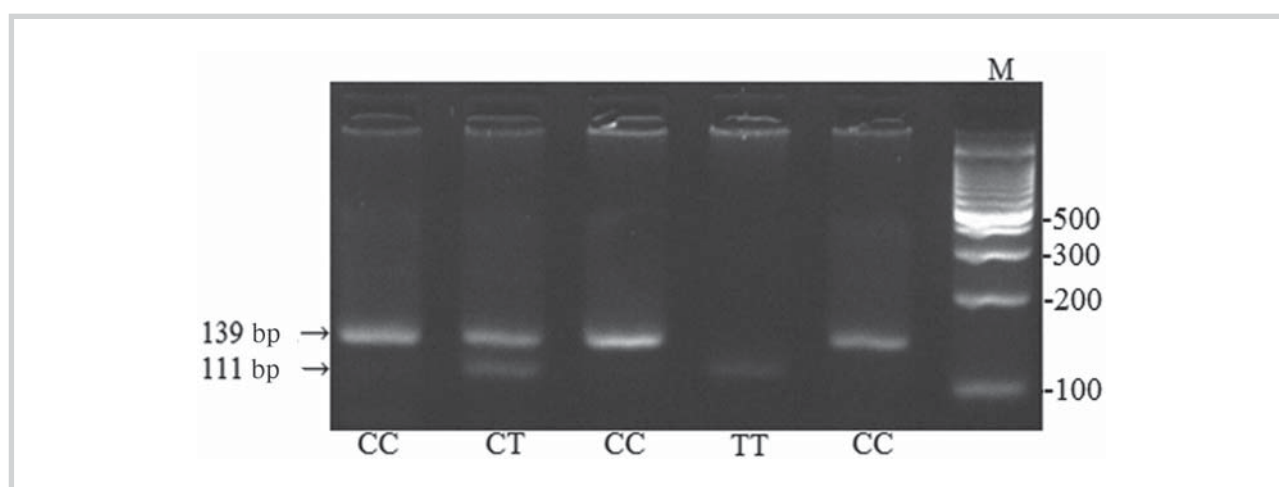


Fig. 5. Electrophoretic separation of genotypes of the *TCF7L2* gene IVS3C/T polymorphic locus after restriction.

CC — homozygous wild type, 139 bp; CT — heterozygous genotype, 139+111 bp; TT — homozygous mutant type, 111 bp.

The strength of association was expressed as the odds ratio (OR) and 95% confidence interval (95% CI). Association was regarded as negative for $OR < 1$ (stability factor), neutral (absent) for $OR = 1$, and positive for $OR > 1$ (risk factor).

Gene-gene interactions were studied using the Multifactor Dimensionality Reduction (MDR 3.0.2) method and its modified version, Generalized Multifactor Dimensionality Reduction (GMDR). A model with the smallest prediction error and the highest reproducibility was chosen among all multilocus models. The critical level of statistical significance was set at $p < 0.05$.

Results

To date, many genetic loci associated with T2DM have been identified; in this case, the development of T2DM in different populations may be associated with effects of different genetic loci. We selected loci of *KCNJ11*, *ADIPOQ*, omentin, leptin, *TCF7L2*, and *PPARG* genes that

demonstrated a statistically significant association with T2DM in some populations [5–7]. Table 1 presents the allele and genotype distribution of studied gene polymorphisms in the group of T2DM patients and the control group.

An analysis of the genotype and allele distribution of the *KCNJ11* gene Glu23Lys polymorphism revealed a higher occurrence frequency of the 23Lys allele in the group of T2DM patients (44%) compared to that in the control group (33%; $\chi^2 = 5.54$; $p = 0.019$). The risk of T2DM in carriers of the 23Lys allele was 1.62-fold higher than that in carriers of the Glu23 allele ($OR = 1.62$, CI 95% 1.10–2.38; $p = 0.019$). Thus, the *KCNJ11* gene 23Lys allele in the Kyrgyz population is a T2DM risk allele, and the Glu23 allele and Glu23Glu genotype, on contrary, have a protective effect.

The *ADIPOQ* gene encodes the adiponectin protein that actively participates in many metabolic processes in the body, including carbohydrate metabolism. Adiponectin maintains glucose levels in the skeletal muscles and liv-

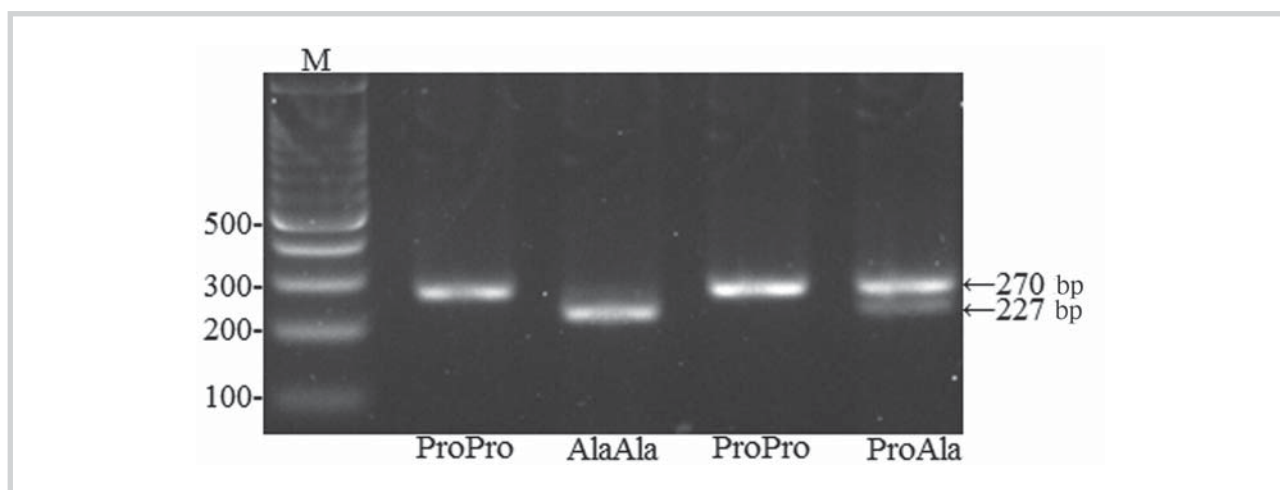


Fig. 6. Electrophoretic separation of genotypes of the *PPARγ* gene Pro12Ala polymorphism after restriction.

Pro/Pro — homozygous wild type, 270 bp; Pro/Ala — heterozygous genotype, 270 and 227 bp; Ala/Ala — homozygous mutant type, 227 bp.

Table 1. Genotype and allele frequency distribution of polymorphisms Glu23Lys (*KCNJ11*), G276T (*ADIPOQ*), Val109Asp (omentin gene), G2548A (leptin gene), IVS3C/T (*TCF7L2*), and Pro12Ala (*PPARγ*) in T2DM patients and controls

| Locus | Alleles and genotypes | T2DM, n=114 (%) | Control, n=109 (%) | χ^2 | p | OR | 95% CI |
|--|-----------------------|-----------------|--------------------|------------|-------|------|--------------|
| Glu23Lys <i>KCNJ11</i> gene rs5219 | Allele Glu23 | 128 (0.56) | 147 (0.67) | 5.54 | 0.019 | 0.62 | (0.42–0.91) |
| | Allele 23Lys | 100 (0.44) | 71 (0.33) | | | 1.62 | (1.10–2.38) |
| | Glu23Glu | 37 (32.4) | 53 (49) | 6.20 | 0.045 | 0.51 | (0.29–0.87) |
| | Glu23Lys | 54 (47.4) | 41 (38) | | | 1.49 | (0.87–2.55) |
| | Lys 23Lys | 23 (20.2) | 15 (14) | | | 1.58 | (0.78–3.23) |
| G276T <i>ADIPOQ</i> gene rs1501299 | Allele G276 | 160 (0.70) | 174 (0.80) | 5.008 | 0.025 | 0.59 | (0.38–0.92) |
| | Allele 276T | 68 (0.30) | 44 (0.20) | | | 1.68 | (1.09–2.60) |
| | G276G | 51 (45) | 67 (61) | 6.65 | 0.036 | 0.51 | (0.30–0.86) |
| | G276T | 58 (51) | 40 (37) | | | 1.79 | (1.05–3.05) |
| | T276T | 5 (4) | 2 (2) | | | 2.45 | (0.46–12.93) |
| Val109Asp Omentin gene rs2274907 | Allele Val109 | 69 (0.30) | 65 (0.30) | 2.146e–007 | 0.990 | 1.02 | (0.68–1.53) |
| | Allele 109Asp | 159 (0.70) | 153 (0.70) | | | 0.98 | (0.65–1.47) |
| | Val109Val | 8 (7) | 4 (4) | 1.62 | 0.450 | 1.98 | (0.58–6.78) |
| | Val109Asp | 53 (46.5) | 57 (52) | | | 0.79 | (0.47–1.34) |
| | Asp 109Asp | 53 (46.5) | 48 (44) | | | 1.10 | (0.65–1.87) |
| G2548A <i>LEP</i> gene rs7799039 | Allele G2548 | 79 (0.35) | 67 (0.31) | 0.61 | 0.433 | 1.19 | (0.80–1.78) |
| | Allele 2548A | 149 (0.65) | 151 (0.69) | | | 0.84 | (0.56–1.24) |
| | G2548 G | 14 (12) | 9 (8) | 1.06 | 0.590 | 1.56 | (0.64–3.76) |
| | G2548A | 51 (45) | 49 (45) | | | 0.99 | (0.58–1.68) |
| | A 2548A | 49 (43) | 51 (47) | | | 0.86 | (0.50–1.45) |
| IVS3C>T <i>TCF7L2</i> gene rs7903146 | Allele C | 202 (0.89) | 194 (0.89) | 0.00033 | 0.980 | 0.96 | (0.53–1.73) |
| | Allele T | 26 (0.11) | 24 (0.11) | | | 1.04 | (0.58–1.87) |
| | CC | 91 (79.5) | 89 (82) | 0.50 | 0.784 | 0.89 | (0.46–1.73) |
| | CT | 20 (17.5) | 16 (15) | | | 1.24 | (0.60–2.53) |
| | TT | 3 (3) | 4 (4) | | | 0.71 | (0.15–3.25) |
| Pro12Ala <i>PPARγ</i> gene rs1801282 | Allele Pro12 | 205 (0.90) | 190 (0.87) | 0.59 | 0.440 | 1.31 | (0.73–2.36) |
| | Allele 12Ala | 23 (0.10) | 28 (0.13) | | | 0.76 | (0.42–1.37) |
| | Pro12Pro | 92 (81) | 83 (76) | 0.88 | 0.642 | 1.31 | (0.69–2.49) |
| | Pro12Ala | 21 (18) | 24 (22) | | | 0.80 | (0.51–1.54) |
| | Ala12Ala | 1 (1) | 2 (2) | | | 0.47 | (0.04–5.30) |

er by increasing the sensitivity of tissues to insulin [6]. A study of the *ADIPOQ* gene G276T polymorphism revealed the association of the heterozygous G276T genotype ($\chi^2=6.65$; $p=0.036$) and 276T allele with an increased risk

of T2DM ($\chi^2=5.008$; $p=0.025$). The risk of T2DM is increased 1.79-fold in the presence of the heterozygous G276T genotype (OR=1.79, CI 95% 1.05–3.05; $p=0.036$) and 1.68-fold in the presence of the 276T allele (OR=1.68,

Table 2. Significant models of gene-gene interactions of *KCNJ11*, *ADIPOQ*, omentin, leptin, *TCF7L2*, and *PPARg* genes in T2DM calculated with the GMDR software using a selective search algorithm

| Number of loci in a model | Combinations of loci in a model (most significant 2-, 3-, 4-, 5-, and 6-locus combinations of studied gene polymorphisms) | Prediction accuracy | Value, <i>p</i> | Model reproducibility | Prediction error |
|---------------------------|---|---------------------|-----------------|-----------------------|------------------|
| 2 | <i>ADIPOQ</i> , <i>LEP</i> | 0.606 | 9 (0.010) | 10/10 | 0.393 |
| 3 | <i>ADIPOQ</i> , <i>KCNJ11</i> , <i>TCF7L2</i> | 0.650 | 9 (0.010) | 10/10 | 0.349 |
| 3 | <i>ADIPOQ</i> , <i>KCNJ11</i> , <i>PPARg</i> | 0.635 | 9 (0.010) | 10/10 | 0.364 |
| 3 | <i>ADIPOQ</i> , Omentin, <i>PPARg</i> | 0.608 | 9 (0.010) | 10/10 | 0.391 |
| 4 | <i>ADIPOQ</i> , <i>KCNJ11</i> , <i>TCF7L2</i> , <i>PPARg</i> | 0.682 | 9 (0.010) | 10/10 | 0.317 |
| 5 | <i>ADIPOQ</i> , Omentin, <i>LEP</i> , <i>TCF7L2</i> , <i>PPARg</i> | 0.725 | 10 (0.001) | 10/10 | 0.274 |
| 6 | <i>ADIPOQ</i> , <i>KCNJ11</i> , Omentin, <i>LEP</i> , <i>TCF7L2</i> , <i>PPARg</i> | 0.796 | 10 (0.001) | 10/10 | 0.203 |

CI 95% 1.09—2.60; $p=0.025$). Therefore, in the Kyrgyz population, the heterozygous G276T genotype and 276T allele of the *ADIPOQ* gene G276T polymorphism may be defined as genetic predictors, while the common G276G genotype and G276 allele may be defined as preventers of T2DM.

Regarding Val109Asp (omentin gene), G2548A (leptin gene), IVS3C/T (*TCF7L2* gene), and Pro12Ala (*PPARg* gene) polymorphisms, there was no statistically significant difference in the frequency of genotypes and alleles of the studied polymorphisms between the T2DM group and the control group. Therefore, these gene polymorphisms were not individually associated with T2DM in the Kyrgyz population.

Given that the phenotype of T2DM as a genetically heterogeneous disease is determined not by a single gene but by certain combinations of genotypes and alleles of different genes, we analyzed gene-gene interactions to identify the most significant ones. The analysis included all polymorphic variants of the studied genes, regardless of previously found or missing associations. The reason for using this strategy was that simultaneous analysis of the contribution of two or more polymorphic variants to the development of T2DM may reveal a previously unidentified pattern, whereas an individual contribution of single nucleotide polymorphisms may not be of decisive importance. Gene-gene interactions were analyzed using the MDR software (<http://www.multifactorialdimensionalityreduction.org/>) and its modified version GMDR (www.healthsystem.virginia.edu/internet/addictiongenomics/Software). Exhaustive and forced search algorithms were used. The exhaustive search algorithm evaluated all possible genotype combinations related to the risk of developing T2DM. In cases where the algorithm was not able to reveal statistically significant interactions of loci, we generated *n*-locus marker combinations with the Forced algorithm that was used to manually select gene loci whose involvement in the development of T2DM was found during preceding analysis steps (Table 1).

We identified seven statistically significant two-, three-, four-, five-, and six-locus models with 100% reproducibility (cross validation consistency (10/10), which controlled predisposition to T2DM in the Kyrgyz popu-

lation (Table 2). All models of gene-gene interactions involve the *ADIPOQ* gene whose product directly increases the sensitivity of tissues to insulin [5,6], which indicates the importance of insulin resistance as a key component in the pathogenesis of T2DM and a clear contribution of the *ADIPOQ* gene to the development of this disease.

Among all *n*-locus models, the most accurate prediction (79%) and smallest prediction error (0.203) are provided by a six-locus model that includes all analyzed polymorphic variants of the studied genes. The MDR software was used to generate a radial diagram for the six-locus model (Fig. 7). The diagram reflected the contribution of each gene polymorphism, either individual or in combination with others, to the development of T2DM. Diagram nodes present informational values of individual genes, and diagram edges present the informational value of gene pair interaction.

An analysis of informational values for each gene separately demonstrated that polymorphic variants of the studied genes unequally affected the phenotypic expression of T2DM. For example, *ADIPOQ* (2.17%) and *KCNJ11* (2.01%) genes make the greatest contribution to the development of T2DM. Regarding studied polymorphisms of other genes, their individual contribution to the development of T2DM was not so significant and ranged from 0.53 to 0.16%. Therefore, omentin, leptin, *TCF7L2*, and *PPARg* genes have a low prognostic potential for the risk of developing T2DM in the Kyrgyz population. The obtained data are in agreement with the results of a monolocus analysis that demonstrated an individual association of *ADIPOQ* and *KCNJ11* genes with T2DM.

Discussion

Investigation of the genetic component is important for identification of genetic predictors of T2DM. Potential candidates are *KCNJ11*, *ADIPOQ*, omentin, leptin, *TCF7L2*, and *PPARg* genes whose products are involved in carbohydrate and lipid metabolism, enhancement of tissue insulin sensitivity, and functioning of pancreatic β -cells [5, 7, 8].

The *KCNJ11* gene is located on chromosome 11 in the p15.1 region and encodes the Kir6.2 protein that is part of

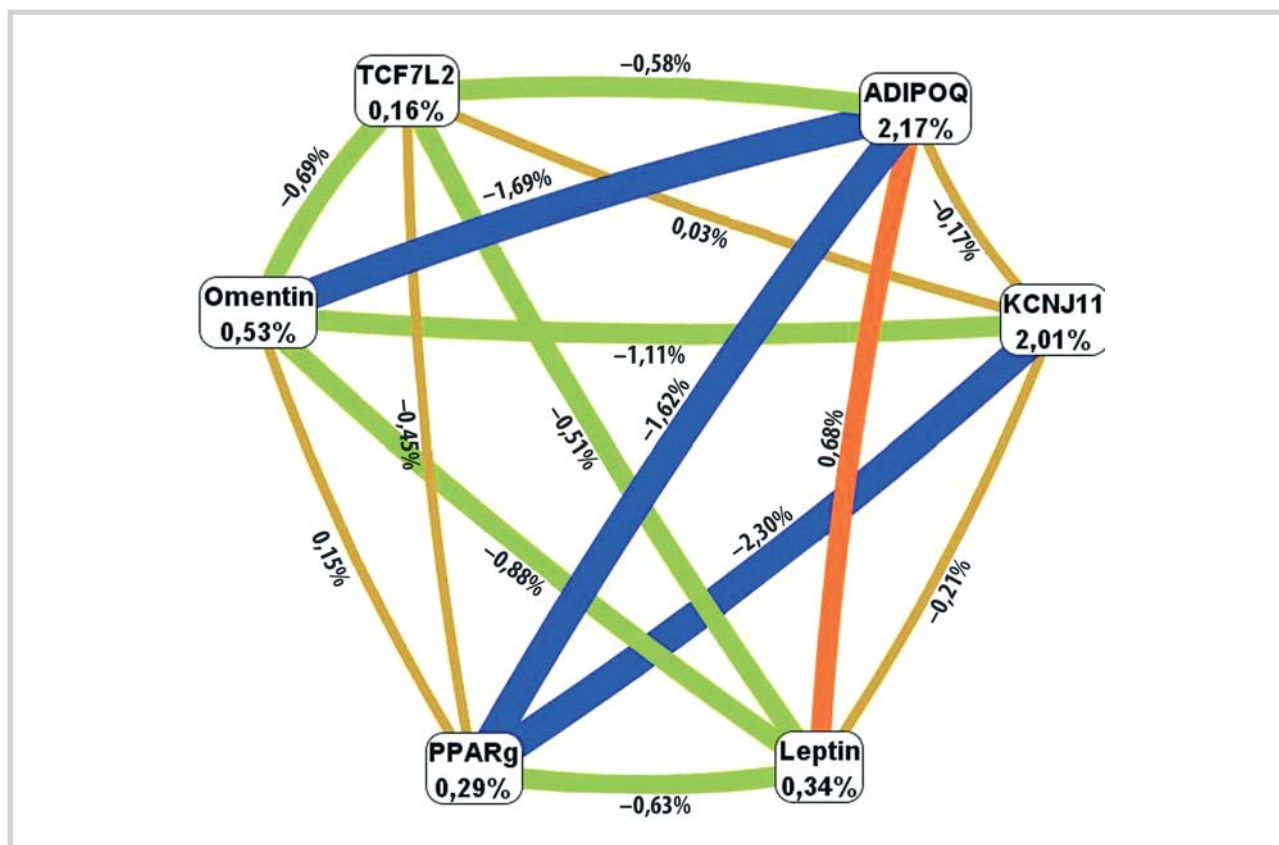


Fig. 7. Gene-gene interactions of polymorphisms of *KCNJ11* (Glu23Lys), *ADIPOQ* (G276T), omentin (Val109Asp), leptin (G2548A), *TCF7L2* (IVS3C/T), and *PPARg* (Pro12Ala) genes involved in predisposition of the Kyrgyz population to T2DM.

Red color denotes a high degree of synergistic interaction; orange color denotes a lower degree of the interaction; brown color denotes an intermediate stage between joint actions and antagonism (lack of communication or independent effects of individual loci); green and blue colors denote some antagonistic effects.

the ATP-dependent K^+ -channel of β -cells [8]. Several polymorphic regions have been identified in the *KCNJ11* gene [8]. The Glu23Lys polymorphism has been studied most fully, and its allelic variant 23Lys, according to the literature, is associated with T2DM in Chinese [9], Japanese [10], Koreans [11], Russians [12], English [13], Tunisians [14], Taiwanese [15], and Iranians [16].

In the Kyrgyz population, the occurrence frequency of the *KCNJ11* gene 23Lys allele in T2DM patients was elevated ($\chi^2 = 5.54$, $p = 0.019$), thereby increasing the risk of this pathology 1.62-fold. Thus, the *KCNJ11* gene 23Lys allele is a predictor of T2DM in both Asian and European populations. The association of the *KCNJ11* gene 23Lys polymorphic marker with T2DM is related to the fact that replacement of a glutamic acid residue by lysine at position 23 of the Kir 6.2 protein leads to reduced insulin secretion due to an increase in activity of the ATP-dependent ion channel, a change in the membrane potential, and a decrease in the concentration of intracellular calcium that initiates secretion of insulin [9, 10, 13].

The *ADIPOQ* gene is mapped on chromosome 3q27 and encodes the adiponectin protein [17]. One of the main functions of adiponectin is to reduce insulin resistance by increasing the sensitivity of skeletal muscles and hepatic tissue to insulin via stimulation of tyrosine (insulin recep-

tor) phosphorylation [17, 18]. The *ADIPOQ* gene consists of 3 exons and 2 introns. The second intron of this gene contains a polymorphic region G276T that is associated with T2DM in several ethnic groups [5, 6, 17, 18]. In our study, the *ADIPOQ* gene G276T locus was also associated with T2DM. In the Kyrgyz population, the heterozygous genotype G276T ($\chi^2 = 6.65$, $p = 0.036$) and 276T allele ($\chi^2 = 5.008$, $p = 0.025$) of the *ADIPOQ* gene are markers of an increased risk of T2DM. Based on adiponectin functions, we may suppose that the association of the *ADIPOQ* gene G276T polymorphism with T2DM is related to impaired sensitivity of tissues to insulin [5, 17, 18].

The omentin gene is localized on chromosome 1 in the 1q22-q23 locus and encodes a protein that is predominantly expressed by adipose tissue and involved in many metabolic processes, including carbohydrate and lipid metabolism [19, 20]. The literature lacks data on the association of the omentin gene Val109Asp polymorphism with T2DM. There are reports of the association of a rare genotype Val109Val of this gene with abdominal obesity [21] and coronary heart disease [22] as well as the association of the Val109 allele with breast cancer [23]. According to our study, the omentin gene Val109Asp polymorphism is not associated with T2DM because its contribution to the development of T2DM is only 0.53%. At the same time,

this gene is included in 3-, 5-, and 6-locus models of gene-gene interactions that predispose to T2DM.

The leptin gene located on chromosome 7 in the 31.3 segment encodes a multifunctional protein, leptin, that is mainly synthesized by cells of white adipose tissue. Most leptin functions are related to the regulation mechanisms of food intake and energy expenditure [24]. G2548A is the most studied polymorphic locus of the leptin gene. The polymorphism is associated with a variety of phenotypes, including obesity, hyperlipidemia [25], insulin resistance [26], and T2DM [27]. No association of the leptin gene G2548A polymorphism with T2DM was found in Egyptians [28]. In our study, the contribution of this locus to the development of T2DM was low (0.34%); however, we found a moderate synergistic effect of the leptin and *ADIPOQ* genes on the risk of developing T2DM (0.68%). This may be due to the fact that leptin and adiponectin are proteins specific for adipose tissue, whereas omentin, which is also expressed by adipose tissue, is not specific for it [20].

The T-cell transcription factor 4 encoded by the *TCF7L2* gene is involved in the Wnt signaling pathway that plays an important role in division and differentiation of pancreatic β -cells and is associated with insulin secretion [29, 30]. The most well-studied *TCF7L2* gene polymorphism is IVS3C>T rs7903146 [30]. The IVS3-T allelic variant of the *TCF7L2* gene IVS3C/T polymorphism is known to be a significant risk factor of T2DM in European populations [30–32]. Asian and European populations significantly differ in the occurrence frequency of the IVS3-T allele of the *TCF7L2* gene IVS3C/T polymorphism. In Asian populations, the occurrence of this allele is lower (5–15%) than in European populations (36–46%). In African populations, the occurrence reaches 50% [33]. In the Kyrgyz population, the frequency of the IVS3-T allele of the *TCF7L2* gene IVS3C/T polymorphism was 11%, which is not significantly different from this indicator in other Asian populations [34, 35].

Unlike Europeans, the *TCF7L2* gene of IVS3C/T polymorphism in Asian populations is either individually weakly associated with T2DM or not associated with it at all [34, 36, 37]. This is most likely due to differences in the occurrence frequency of the IVS3-T allele in Asian and European populations as well as ethnic specificity of the hereditary architecture of T2DM and gene-gene and/or gene-environment interactions of a hereditary component of T2DM in these populations.

The *PPARG* gene located on chromosome 3 (3p25) encodes an intracellular transcription factor that regulates expression of genes whose products are involved in fat accumulation, adipocyte differentiation, and tissue sensitivity to insulin [38]. The most studied T2DM-associated polymorphism in this gene is Pro12Ala [39, 40]. A previously found association of the *PPARG* gene Pro12Ala poly-

morphism with T2DM was not confirmed in our sample of patients from the Kyrgyz population. Similar results were obtained in studies of other populations. For example, M. Fu and co-authors found no association of this polymorphic locus with T2DM in Chinese [41]. In Indians, the *PPARG* gene Pro12Ala polymorphism was also not associated with T2DM [42].

Conclusion

Among the studied six genes, the greatest contribution to the development of T2DM is made by the *ADIPOQ* gene G276T polymorphism (2.17%) and *KCNJ11* gene Glu23Lys polymorphism (2.01%). The markers of an increased risk of T2DM in the Kyrgyz population are the 276T allele and G276T heterozygous genotype of the *ADIPOQ* gene as well as the 23Lys allele of the *KCNJ11* gene.

The individual contribution of polymorphic loci of omentin (Val109Asp), leptin (G2548A), *TCF7L2* (IVS3C/T), and *PPARG* (Pro12Ala) genes to the development of T2DM is not significant, and their involvement in phenotypic expression of T2DM is mediated by gene-gene interactions. An analysis of gene-gene interactions has revealed statistically significant two-locus (*ADIPOQ*, leptin), three-locus (*ADIPOQ*, *KCNJ11*, *TCF7L2*; *ADIPOQ*, *KCNJ11*, *PPARG*; *ADIPOQ*, omentin, *PPARG*), four-locus (*ADIPOQ*, *KCNJ11*, *TCF7L2*, *PPARG*), five-locus (*ADIPOQ*, omentin, leptin, *TCF7L2*, *PPARG*), and six-locus (*ADIPOQ*, *KCNJ11*, omentin, leptin, *TCF7L2*, *PPARG*) models of gene-gene interactions, which predispose to T2DM in the Kyrgyz population. An analysis of the role of each gene, individually and in combination with other genes, indicates a significant role of the *ADIPOQ* gene in increasing the risk for T2DM in the Kyrgyz population.

Identification of genetic predictors of T2DM development, with allowance for ethnicity, is important for screening individuals at increased risk of this disease in order to timely conduct preventive measures to reduce the incidence of diabetes both in families with a diabetes history and in the general population.

ADDITIONAL INFORMATION

Funding. The study was supported by the Ministry of Education and Science of the Kyrgyz Republic (state registry number 0007164 of March 13, 2015).

Conflict of interest. The authors declare no obvious and potential conflicts of interest related to the publication of this article.

Authors' contribution: A.A. Aldashev and E.M. Mirrakhimov — study conception and design; E.T. Talaipekova and B.Zh. Zhyrgalbekova — genotyping; Zh.T. Isakova — data analysis and manuscript preparation; N.M. Aldasheva — manuscript editing. All authors have read and approved the final version of the manuscript before submission.

ЛИТЕРАТУРА | REFERENCES

- Дедов И.И., Шестакова М.В., Андреева Е.Н., и др. *Сахарный диабет: диагностика, лечение, профилактика.* / Под ред. Дедова И.И., Шестаковой М.В. — М.: Медицинское Информационное Агентство; 2011. [Dedov II, Shestakova MV, Andreeva EN, et al. *Sakharnyy Diabet: Diagnostika, Lechenie, Profilaktika.* Moscow: Meditsinskoe Informatsionnoe Agentstvo; 2011. (In Russ.)].
- Султаналиева Р.Б., Сагындова С.К., Албакова А.О., и др. Эпидемиологические аспекты сахарного диабета в Кыргызстане (по данным государственного регистра сахарного диабета в разрезе 2015 г.). // *Вестник КРСУ.* — 2016. — Т. 16. — № 11. — С. 140—144. [Sultanaliyeva RB, Sagynova SK, Albakova AO, et al. Epidemiological facts of diabetes mellitus in Kyrgyzstan (the data of the National register of diabetes during 2015 Year). *Vestnik KRSU.* 2016;16(11):140-144. (In Russ.)].
- Бондарь И.А., Шабельникова О.Ю. Генетические основы сахарного диабета 2-го типа. // *Сахарный диабет.* — 2013. — Т. 16. — № 4. — С. 11—16. [Bondar' IA, Shabel'nikova OYu. Genetic framework of type 2 diabetes mellitus. *Diabetes Mellitus.* 2013;16(4):11-16. (In Russ.)]. doi: 10.14341/Dm2013411—16
- Singh S. Genetics of type 2 diabetes: advances and future prospect. *J Diabetes Metab.* 2015;6(4):518. doi:10.4172/2155—6156.1000518
- Ходырев Д.С., Никитин А.Г., Бровкин А.Н., и др. Анализ ассоциации полиморфных маркеров генов *ADIPOQ*, *ADIPOI* и *ADIPO2* с сахарным диабетом 2-го типа. // *Сахарный диабет.* — 2015. — Т. 18. — № 2. — С. 5—11. [Khodyrev DS, Nikitin AG, Brovkin AN, et al. Association of polymorphisms of the *ADIPOQ*, *ADIPOI* and *ADIPO2* genes with type 2 diabetes mellitus. *Diabetes Mellitus.* 2015;18(2):5-11. (In Russ.)]. doi: 10.14341/Dm201525—11
- Potapov VA, Chistiakov DA, Dubinina A, et al. Adiponectin and Adiponectin receptor gene variants in relation to type 2 diabetes and insulin resistance—related phenotypes. *Rev Diabet Stud.* 2008; 5(1):28-37. doi: 10.1900/Rds.2008.5.28
- Li Q, Chen M, Zhang R, et al. KCNJ11 E23K variant is associated with the therapeutic effect of sulphonylureas in chinese type 2 diabetic patients. *Clin Exp Pharmacol Physiol.* 2014;41(10):748-754. doi: 10.1111/1440—1681.12280
- Schwanstecher C, Meyer U, Schwanstecher M. Kir6.2 polymorphism predisposes to type 2 diabetes by inducing overactivity of pancreatic — cell Atp—Sensitive K⁺ Channels. *Diabetes.* 2002;51(3):875-879. doi: 10.2337/Diabetes.51.3.875
- Zhou D, Zhang D, Liu Y, et al. The E23K variation in the KCNJ11 gene is associated with type 2 diabetes in Chinese and East Asian population. *J Hum Genet.* 2009;54(7):433-435. doi: 10.1038/Jhg.2009.54
- Sakamoto Y, Inoue H, Keshavarz P, et al. SNPs in the KCNJ11—ABCC8 gene locus are associated with type 2 diabetes and blood pressure levels in the Japanese population. *J Hum Genet.* 2007;52(10):781-793. doi: 10.1007/S10038—007—0190—X
- Koo BK, Cho YM, Park BL, et al. Polymorphisms of KCNJ11 (Kir6.2 gene) are associated with type 2 diabetes and hypertension in the Korean population. *Diabet Med.* 2007;24(2):178-186. doi: 10.1111/J.1464—5491.2006.02050.X
- Потапов В.А. *Поиск генетических маркеров, определяющих предрасположенность к сахарному диабету 2-го типа:* Дис. ... канд. биол. наук. — М. 2010. [Potapov VA. *Poisk geneticheskikh markerov, opredelyayushchikh predraspolozhennost' k sakharnomu diabetu 2 tipa:* Diss. Moscow. 2010. (In Russ.)].
- Gloyn AL, Weedon MN, Owen KR, et al. Large-scale association studies of variants in genes encoding the pancreatic — cell KATP channel subunits Kir 6.2 (KCNJ11) and Sur1 (ABCC8) confirm that the KCNJ11 E23K variant is associated with type 2 diabetes. *Diabetes.* 2003;52(2):568-572. doi: 10.2337/Diabetes.52.2.568
- Ezzidi I, Mtiraoui N, Cauchi S, et al. Contribution of type 2 diabetes associated loci in the Arabic population from Tunisia: a case control study. *BMC Med Genet.* 2009;10:33. doi: 10.1186/1471—2350—10—33
- Jiang YD, Chuang LM, Pei D, et al. Genetic variations in the Kir6.2 subunit (KCNJ11) of pancreatic ATP—Sensitive potassium channel gene are associated with insulin response to glucose loading and early onset of type 2 diabetes in childhood and adolescence in Taiwan. *Int J Endocrinol.* 2014;2014:983016. doi: 10.1155/2014/983016
- Rastegari A, Rabbani M, Sadeghi HM, et al. Association of KCNJ11 (E23K) gene polymorphism with susceptibility to type 2 diabetes in Iranian patients. *Adv Biomed Res.* 2015;4:1. doi: 10.4103/2277—9175.148256
- Gu HF, Abulaiti A, Ostenson CG, et al. Single nucleotide polymorphisms in the proximal promoter region of the adiponectin (APM1) gene are associated with type 2 diabetes in Swedish caucasians. *Diabetes.* 2004;53(Supplement 1):S31-S35. doi: 10.2337/diabetes.53.2007.S31
- Hara K, Boutin P, Mori Y, et al. Genetic variation in the gene encoding adiponectin is associated with an increased risk of type 2 diabetes in the Japanese population. *Diabetes.* 2002;51(2):536-540. doi: 10.2337/diabetes.51.2.536
- Schaffler A, Zeitoun M, Wobser H, et al. Frequency and significance of the novel single nucleotide missense polymorphism Val109Asp in the human gene encoding omentin in caucasian patients with type 2 diabetes mellitus or chronic inflammatory bowel diseases. *Cardiovasc Diabetol.* 2007;6:3. doi: 10.1186/1475—2840—6—3
- Pan HY, Guo L, Li Q. Changes of serum omentin-1 levels in normal subjects and in patients with impaired glucose regulation and with newly diagnosed and untreated type 2 diabetes. *Diabetes Res Clin Pract.* 2010;88(1):29-33. doi: 10.1016/j.diabres.2010.01.013
- Исакова Ж.Т., Талайбекова Э.Т., Асамбаева Д.А., и др. Ассоциация полиморфного маркера Val109Asp гена оментина с абдоминальным ожирением в кыргызской популяции. // *Проблемы эндокринологии.* — 2016. — Т. 62. — № 3. — С. 4—8. [Isakova ZT, Talaibekova ET, Asambaeva DA, et al. A polymorphic marker Val109Asp in the omentin gene are associated with abdominal obesity in the kyrgyz population. *Problems of endocrinology.* 2016;62(3):4-8. (In Russ.)]. doi: 10.14341/probl20166234—8
- Yoruk U, Yaykasli KO, Ozhan H, et al. Association of omentin Val109Asp polymorphism with coronary artery disease. *Anadolu Kardiyol Derg.* 2014;14(6):511-514. doi: 10.5152/akd.2013.4932
- Bahadori M, Kohan L, Farzan M, et al. An increased risk of breast cancer associated with Val109Asp polymorphism in omentin gene. *Int J Biosci.* 2014;5(1):429-434. doi: 10.12692/ijb/5.1.429—434
- Zhang Y, Proenca R, Maffei M, et al. Positional cloning of the mouse obese gene and its human homologue. *Nature.* 1994; 372(6505):425-432. doi: 10.1038/372425a0
- Trakovická A, Moravčíková N, Candráková K, Kasarda R. Associations between LEP G2548A polymorphisms and lipids metabolism. *Acta fytotechn zootechn.* 2016;19(Special issue):75-79. doi: 10.15414/afz.2016.19.si.75—79
- Cao L, Mou S, Fang W, et al. Correlational studies on insulin resistance and leptin gene polymorphisms in peritoneal dialysis patients. *Iran J Basic Med Sci.* 2015;18(9):878-886.
- Kohan L, Nasiri M, Habib A, Bolhasani A. Association of G-2548A polymorphism in the promoter of leptin gene with plasma leptin level and risk of type 2 diabetes. *JSSU.* 2013;21(1):70-77.

28. Motawi T, Salman T, Shaker O, Abdelhamid A. Association of polymorphism in adiponectin (+45 T/G) and leptin (–2548 G/A) genes with type 2 diabetes mellitus in male Egyptians. *Arch Med Sci.* 2015;11(5):937–944. doi: 10.5114/aoms.2015.54848
29. Loder MK, da Silva Xavier G, McDonald A, Rutter GA. TCF7L2 controls insulin gene expression and insulin secretion in mature pancreatic β -cells. *Biochem Soc Trans.* 2008;36(Pt 3):357–359. doi: 10.1042/BST0360357
30. Cauchi S, El Achhab Y, Choquet H, et al. TCF7L2 is reproducibly associated with type 2 diabetes in various ethnic groups: a global metaanalysis. *J Mol Med (Berl).* 2007;85(7):777–782. doi: 10.1007/s00109–007–0203–4
31. Никитин А.Г., Потапов В.А., Бровкин А.Н., и др. Ассоциация полиморфных маркеров гена *TCF7L2* с сахарным диабетом 2-го типа. // *Клиническая практика.* — 2014. — № 1. — С. 4–11. [Nikitin AG, Potapov VA, Brovkin AN, et al. Association of the polymorphisms of the *TCF7L2* genes with type 2 diabetes. *Klinicheskaya Praktika.* 2014;(1):4–11. (In Russ.)].
32. Peng S, Zhu Y, Lu B, et al. TCF7L2 gene polymorphisms and type 2 diabetes risk: a comprehensive and updated metaanalysis involving 121,174 subjects. *Mutagenesis.* 2013;28(1):25–37. doi: 10.1093/mutage/ges048
33. Guinan KJ. Worldwide distribution of type ii diabetes associated TCF7L2 SNPs: evidence for stratification in Europe. *Biochem Genet.* 2012;50(3–4):159–179. doi: 10.1007/s10528–011–9456–2
34. Dou H, Ma E, Yin L, et al. The association between gene polymorphism of TCF7L2 and type 2 diabetes in Chinese HAN population: a metaanalysis. *PLoS One.* 2013;8(3):e59495. doi: 10.1371/journal.pone.0059495
35. Wang J, Hu F, Feng T, et al. Metaanalysis of associations between TCF7L2 polymorphisms and risk of type 2 diabetes mellitus in the Chinese population. *BMC Med Genet.* 2013;14:8. doi: 10.1186/1471–2350–14–8
36. Guo T, Hanson RL, Traurig M, et al. TCF7L2 is not a major susceptibility gene for type 2 diabetes in pima indians: analysis of 3,501 individuals. *Diabetes.* 2007;56(12):3082–3088. doi: 10.2337/db07–0621
37. Alsmadi O, Al-Rubeaan K, Mohamed G, et al. Weak or no association of TCF7L2 variants with type 2 diabetes risk in an Arab population. *BMC Med Genet.* 2008;9:72. doi: 10.1186/1471–2350–9–72
38. Vaccaro O, Lapice E, Monticelli A, et al. Pro12Ala PPARgamma2 locus modulates the relationship between energy intake and body weight in type 2 diabetic patients. *Diabetes Care.* 2007;30(5):1156–1161. doi: 10.2337/dc06–1153
39. Tripathi AK, Shukla S, Dwivedi Mk, et al. Type 2 diabetes in a central indian population: association with PPAR2 P121A allele but not ENPP1 K121Q. *Adv Genomics Genet.* 2013;1. doi: 10.2147/agg.s42936
40. Бондарь И.А., Филипенко М.Л., Шабельникова О.Ю., Соколова Е.А. Ассоциация полиморфных маркеров Rs7903146 гена *TCF7L2* и Rs1801282 гена *PPARG* (*Pro12Ala*) с сахарным диабетом 2 типа в Новосибирской области. // *Сахарный диабет.* — 2013. — Т. 16. — № 4. — С. 17–22. [Bondar' IA, Filipenko ML, Shabel'nikova OYu, Sokolova EA. Rs7903146 variant of TCF7L2 gene and rs1801282 variant of *PPARG2* gene (Pro12Ala) are associated with type 2 diabetes mellitus in novosibirsk population. *Diabetes mellitus.* 2013;16(4):17–22. (In Russ.)] doi: 10.14341/DM2013417–22
41. Fu M, Chen H, Li X, et al. Association of Pro12Ala variant in peroxisome proliferator — activated receptor — gamma2 gene with type 2 diabetes mellitus. *Zhonghua Yi Xue Yi Chuan Xue Za Zhi.* 2002;19(3):234–238.
42. Pattanayak AK, Bankura B, Balmiki N, et al. Role of peroxisome proliferator—activated receptor gamma gene polymorphisms in type 2 diabetes mellitus patients of West Bengal (India). *J Diabetes Invest.* 2014;5(2):188–191. doi: 10.1111/jdi.12130

ИНФОРМАЦИЯ ОБ АВТОРАХ

*Исакова Жайнагуль Толоновна — д.м.н. [Zhainagul T. Isakova, MD, PhD]; адрес: Кыргызская Республика, 720040, Бишкек, ул. Тоголок Молдо, 3 [address: 3 Togolok Moldo street, Bishkek, 720040, Kyrgyz Republic]; ORCID: <http://orcid.org/0000-0002-3681-6939>; eLibrary SPIN: 2489-8031; e-mail: jainagul@mail.ru

Талайбекова Эльнура Талайбековна — [Elnura T. Talaibekova]; ORCID: <http://orcid.org/0000-0002-4619-1928>; eLibrary SPIN: 5722-1198; e-mail: elya-1209@mail.ru

Жыргалбекова Бактыгуль Жыргалбековна — [Baktygul Zh. Zhyrgalbekova]; ORCID: <http://orcid.org/0000-0003-0855-9450>; eLibrary SPIN: 6738-1297; e-mail: happyflower7@mail.ru

Миррахимов Эркин Мирсаидович — д.м.н., проф. [Erkin M. Mirрахимov, MD, PhD, Professor]; ORCID: <http://orcid.org/0000-0003-2982-6108>; e-mail: erkmirr@gmail.com

Алдашева Назира Мирсаидовна — д.м.н. [Nazira M. Aldasheva, MD, PhD]; ORCID: <http://orcid.org/0000-0002-0356-9118>; eLibrary SPIN: 2633-7587; e-mail: aldashev@gmail.com

Алдашев Алмаз Абдулхаевич — д.б.н., акад. НАН КР [Almaz A. Aldashev, MD, PhD, Professor]; ORCID: <http://orcid.org/0000-0002-4793-2206>; e-mail: aldashev@gmail.com

ИНФОРМАЦИЯ

Рукопись получена: 21.02.2017. Одобрена к публикации: 26.03.2018.

КАК ЦИТИРОВАТЬ:

Исакова Ж.Т., Талайбекова Э.Т., Жыргалбекова Б.Ж., Миррахимов Э.М., Алдашева Н.М., Алдашев А.А. Межгенные взаимодействия и вклад полиморфных локусов генов *KCNJ11*, *ADIPOQ*, оментина, лептина, *TCF7L2* и *PPARG* в развитие сахарного диабета 2-го типа в кыргызской популяции: исследование по типу случай—контроль с использованием MDR-анализа. // *Проблемы эндокринологии.* — 2018. — Т. 64. — № 4. — С. 216–225. doi: 10.14341/probl8344

TO CITE THIS ARTICLE:

Isakova ZhT, Talaibekova ET, Zhyrgalbekova BZh, Mirрахимov EM, Aldasheva NM, Aldashev AA. Gene-gene interaction and the contribution of polymorphic loci of *KCNJ11*, *ADIPOQ*, omentin, leptin, *TCF7L2* and *PPARG* genes in the development of type 2 diabetes mellitus in the Kyrgyz population: a case-control genetic association study using MDR-analysis. *Problems of Endocrinology.* 2018;64(4):216–225. doi: 10.14341/probl8344