# SEARCH FOR POLYMORPHIC VARIANTS OF GENES ASSOCIATED WITH TYPE 2 DIABETES IN INDIVIDUALS OF THE KAZAKH POPULATION

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**Abstract:** The association of single nucleotide polymorphisms (SNPs) with type 2 diabetes mellitus (T2DM) has been the subject of numerous genetic studies in European, some Asian and African American populations. The present study was performed to find out polymorphic variants of genes associated with type 2 diabetes in individuals of the Kazakh population. SNP candidates were genotyped in 139 patients with type 2 diabetes and 100 healthy controls with no evidence of the disease. Of the 25 previously tested SNPs, eight rs17584499 rs7903146 rs7756992 rs7754840 rs 2237892 rs4712524 ($P < 0.001$), rs1333051 and rs7901695 ($P < 0.01$) statistically significant polymorphic genetic variants were identified. Besides, seven of the tested SNPs had an odds ratio (OR) 1.7 - 2.6, ($P < 0.05$), suggesting that these variants could potentially be used in the Kazakh population for prognostic T2DM testing.

**Keywords:** Type 2 diabetes mellitus, SNP, genotyping.

## Introduction

In recent years, the incidence of type 2 diabetes has significantly increased. [1,2]. The increasing prevalence of diabetes stresses the urgent need for proactive strategies to prevent and control T2DM. [3]. A fairly large number of works show that T2DM is a complex metabolic disease caused by lifestyle, environment, and genetic factors [4]. Thus, the study of a genetic predisposition to diabetes is of great importance. At the same time, one of the most effective methods, besides genome-wide researches, is the use of polymorphic markers of various candidate genes, i.e., those genes, protein products of which (enzymes, regulatory proteins and peptides, structural proteins) can be potentially involved in the development of this disease [ 5]. The study of genetic markers of type 2 diabetes association is relevant worldwide. The incidence rate varies depending on many factors, in particular the ethnicity of the population.

A review of published data shows that the study of the genetic contribution to the formation of T2DM was carried out in residents of some countries in Europe, Asia, Africa and America. Numerous studies of the genetic aspects of T2DM, many dozens of polymorphic variants of genes have been identified in many world populations. This is an important step towards a deeper understanding of the mechanisms of T2DM occurrence. Some studies have shown a connection between single nucleotide polymorphisms of UBE2E2 (rs 6780569, rs 7612463, rs 9812056) and the risk of T2DM developing in Japanese and Koreans, however, statistically significant relationship ($p > 0.05$) between these gene polymorphisms and T2DM was not found in Europeans [6]. Meta-analysis showed a significant contribution of the rs4402960 and rs1470579 polymorphisms of the IGF2BP2 gene in T2DM in Asian populations [7].

Studies have confirmed the association of type 2 diabetes with single nucleotide polymorphisms rs2237897 KCNQ1 and rs1333051 CDKN2 reported in European, Mexican, Chinese, Japanese and Mongolian populations [8]. The results of ethnic studies in the Russian [9], European, Asian, Afro-Caribbean and African-American populations confirmed a significant association of polymorphisms (rs12255372 and rs7903146) in the TCF7L2 gene with T2DM [9]. In Arabs, the association between the TCF7L2 variants and T2DM varied, while a significant association was demonstrated in Tunisians, Moroccans, Omanis [10] and Palestinians, with little or no association in the United Arab Emirates or Saudi Arabs [11]. In European populations, a significant connection between the rs1501299 variant of the adiponectin gene (ADIPOQ) and T2DM was revealed [12]. Association with T2DM was established in the Japanese population and Hispanic Americans, and was not detected in the Pima Indians and African Americans [13].

Numerous studies have been performed to stress the importance of ethnicity in the association between genetic variation and T2DM. To date, more than 100 genes for predisposition to T2DM have been identified (http://www.genome.gov/gwastudies/). The genetic architecture underlying T2DM is significantly different in different ethnic groups [14], each population has its own unique set of allelic gene variants and extrapolation of the results is not possible. **The aim of the study** was to find genetic markers associated with the development of diabetes mellitus 2 in individuals in the Kazakh population.

## Materials and methods

Object of study

The study involved 139 patients with type 2 diabetes. The established by WHO diagnostic criteria were used to diagnose type 2 diabetes. The control group was a random sample of 100 patients with no signs of the disease. The samples were ethnically homogeneous and consisted from individuals of the Kazakh population. Data on ethnicity were made using questionnaires. All patients gave written informed consent. The study was approved by the Local Ethics Commission of the Hospital of the Medical Center of the Presidential Administration of the Republic of Kazakhstan No. 5 of September 27, 2017.

## Genomic DNA Isolation

Genomic DNA samples extracted from the peripheral blood of the subjects using the PurLink Genomic DNA Mini Kit reagent kit (Invitrogen, USA) in accordance with the manufacturer's protocol, were used as a material for the study.

**Genotyping of markers associated with the risk of T2DM on the basis PCR in real-time (25 SNP).**

Despite advances in sequencing and post-genomic technologies, SNPs point-wise genotyping remains the most popular approach in medical genetics. Today, the most common method for SNP genotyping in laboratory and research practice is real-time PCR using fluorescence-labeled probes (TaqMan probes) [15]. In all examined patients' identification of 25 single nucleotide polymorphisms (SNP) associated with T2DM in other populations was made. SNP selection was based on the GWAS catalog. Genotyping of an expanded number of candidate gene polymorphisms was performed on a new generation QuantStudio 12K Flex instrument, Life Technologies. The new generation technology used is real-time microfluidic PCR technology (QuantStudio 12K Flex, Life Technologies). The total volume of the reaction mixture was 5 µl, in which 3 µl 2 × OppenArray Real-time master mix and 2 µl DNA concentration 50 ng / µl. Temperature condition was 10 min at 93C; cycling - 45 sec at 93, 13 sec at 94C, 2.14 min at 53.5 C - 50 cycles; incubation at 25C for 2 minutes Data analysis was performed using the online tools of the Termo Fisher Cloud service (Figure 1). According to the results of bioinformation analysis, the subjects were classified as homozygotes by the major allele (genotype of the wild type), homozygotes by the minor (mutant) allele and heterozygotes.

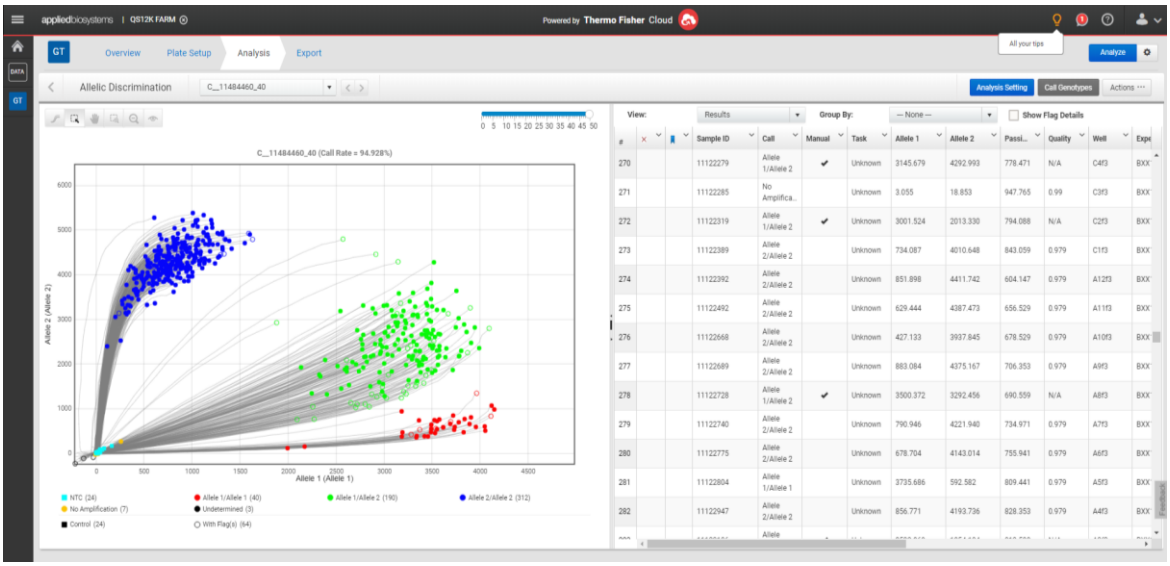


Fig.1 Analysis of data using cloud service Termo Fisher Cloud.

**Statistical analysis**

Statistical processing of the results was performed using the Statistica for Windows 7.0 software package for statistical data processing (StatSoft, USA). To assess the differences in quantitative indicators between the samples, Mann – Whitney method was used. The significance of differences between the qualitative indicators of the compared groups was determined using the $\chi 2$ criterion. Differences were considered significant at $p < 0.05$. To describe the relative risk of developing the disease, the odds ratio (OR), (OR odds ratio) was calculated. OR = 1 was considered as a lack of association, OR> 1 as a positive association, OR < 1 was considered as a negative association of an allele or genotype with a disease (reduced risk of pathology). Confidence Interval (CI) is an interval of values within which the expected OR value is located with a 95% probability.

## Results

### Frequency distribution of alleles and genotypes of the studied polymorphic markers in patients with type 2 diabetes mellitus and in the control group

In our study, we analyzed the relationship of 25 SNPs previously identified in different European and Asian populations, with a risk of developing T2DM, in the Kazakh population. Then for each of the identified polymorphic markers, the frequencies and genotypes associated with the increased and decreased risk of T2DM were determined. (Table 1).

Table 1: Frequency of genotypes and alleles SNP in patients with diabetes mellitus and healthy controls

| Genes | Rs | Alleles | Homozygous wild variant | | Heterozygous variant | | Homozygous mutant variant | |
|---|---|---|---|---|---|---|---|---|
| | | | Studied group (139) | Control group (100) | Studied group (139) | Control group (100) | Studied group (139) | Control group (100) |
| | | | n/% | n/% | n/% | n/% | n/% | n/% |
| TCF7L2 | rs7901695 | T;C | 23/17 | 34/34 | 20/14 | 21/21 | 96/69 | 45/45 |
| | rs7903146 | C;T | 34/24 | 65/65 | 73/53 | 34/34 | 32/23 | 1/1 |
| CD81 | rs1049549 | T;C | 135/97 | 99/99 | 4/3 | 1/1 | -/- | -/- |
| LPIN2 | rs10460009 | C;T | 74/53 | 53/53 | 54/39 | 42/42 | 11/8 | 5/5 |
| IDE | rs6583826 | G;A | 67/46 | 55/55 | 62/45 | 43/43 | 10/9 | 2/2 |
| PTPRD | rs17584499 | C;T | 77/55 | 79/79 | 47/34 | 18/18 | 15/11 | 3/3 |
| CDKAL1 | rs9295474 | C;G | 59/42 | 34/34 | 67/47 | 57/57 | 13/11 | 9/9 |
| | rs7756992 | A;G | 45/32 | 59/59 | 80/58 | 38/38 | 14/10 | 3/3 |
| | rs7754840 | G;T | 36/26 | 46/46 | 62/45 | 50/50 | 41/29 | 4/4 |
| | rs4712524 | A;G | 44/27 | 52/52 | 69/43 | 37/37 | 26/30 | 11/11 |
| | rs4712523 | A;G | 57/41 | 53/53 | 64/46 | 42/42 | 18/13 | 5/5 |
| KCNQ1 | rs8181588 | T;C | 7/5 | 10/10 | 59/42 | 37/37 | 73/53 | 53/53 |
| | rs2237896 | G;A | 23/17 | 34/34 | 59/42 | 38/38 | 57/41 | 28/28 |
| | rs2237892 | C;T | 58/41 | 61/61 | 62/45 | 36/36 | 19/14 | 3/3 |
| | rs163184 | T;G | 68/49 | 62/62 | 49/35 | 31/31 | 22/16 | 7/7 |
| | rs2237897 | C;T | 36/26 | 46/46 | 74/53 | 43/43 | 29/21 | 11/11 |
| CDKN2B-AS1 | rs2383208 | A;G | 67/48 | 62/62 | 63/46 | 33/33 | 9/6 | 5/5 |
| | rs1333051 | A;T | 50/36 | 53/53 | 67/48 | 42/42 | 22/16 | 5/5 |
| DMRTA1 | rs1575972 | T;A | 47/34 | 49/49 | 71/51 | 40/40 | 21/15 | 11/11 |
| IGF2BP2 | rs4402960 | G;T | 57/41 | 57/57 | 65/47 | 38/38 | 17/12 | 5/5 |
| | rs1470579 | A;C | 44/32 | 52/52 | 74/53 | 38/38 | 21/15 | 10/10 |
| NAP1L4 | rs3888647 | G;A | 18/13 | 13/13 | 49/35 | 32/32 | 72/52 | 55/55 |
| FTO | rs8050136 | C;A | 29/21 | 26/26 | 58/42 | 43/43 | 52/37 | 31/31 |
| | rs11642841 | C;A | 68/47 | 41/41 | 1/1 | 1/1 | 70/52 | 58/58 |
| PLS1 | rs3773506 | G;C | 15/11 | 11/11 | 7/5 | 1/1 | 117/84 | 88/88 |

**Statistically significant allele and genotype associations with T2DM**

Of the 25 previously tested SNPs, eight statistically significant polymorphic genetic variants were identified (Table 2). Table 2 shows that six SNPs had high statistical values, p <0.001. The calculation of the odds ratio for alleles and genotypes of polymorphic markers rs17584499 rs7903146 rs7756992 rs7754840 with an OR variation between 2.53 (CI 1.49 –4.31) and 5.73 (CI 3.26 –10.08) allows SNP data attribute to genetic markers of increased risk of type 2 diabetes developing in the Kazakh population. Besides, there was a significant association between type 2 diabetes and rs polymorphisms (p <0.01). The odds ratio was 2.18 (CI 1.29 –3.69) and 2.01 (CI 1.19–3.39), respectively.

Table 2: Allele and genotype associations with T2DM, reaching statistical significance P <0.001

| Rs | Genotypes | Genotype frequency | | OR | ρ | 95% CI |
|---|---|---|---|---|---|---|
| | | СД 2, n = 139 | контроль, n = 100 | | | |
| rs7901695 | T/T | 41 | 56 | | | |
| | T/C+C/C | 98 | 44 | 3.04 | <0.001 | 1.78-5.21 |
| rs17584499 | C/C | 77 | 79 | | | |
| | C/T+T/T | 62 | 21 | 3.03 | <0.001 | 1.69-5.4 |
| rs7903146 | C/C | 34 | 65 | | | |
| | C/T+T/T | 105 | 35 | 5.73 | <0.001 | 3.26-10.08 |
| rs2237892 | C/C | 58 | 61 | | | |
| | C/T+T/T | 81 | 39 | 2.18 | <0.01 | 1.29-3.69 |
| rs4712524 | A/A | 44 | 54 | | | |
| | A/G + G/G | 95 | 46 | 2.53 | <0.001 | 1.49-4.31 |
| rs7756992 | A/A | 45 | 59 | | | |
| | A/G+G/G | 94 | 41 | 3.01 | <0.001 | 1.76-5.13 |
| rs7754840 | G/G | 36 | 49 | | | |
| | G/T +T/T | 103 | 51 | 2.75 | <0.001 | 1.59-4.74 |
| rs1333051 | A/A | 59 | 34 | | | |
| | A/T+ T/T | 80 | 66 | 2.01 | <0.01 | 1.19-3.39 |

Of the 25 previously tested SNPs, seven polymorphic genetic variants showed a nominal association with T2DM, p <0.05. The association trend was observed with SNP rs 2237896, which was in equilibrium linkage with rs 2237897, OR 2.6 (CI 1.41-4.78) and 2.01 (CI 1.41-4.21), respectively. Genotype distribution rs2383208, OR 1.75 (CI 1.04-2.69), rs1575972, OR 1.88 (CI 1.11-3.18), rs4402960, OR 1.91 (CI 1.13-3.21), rs1470579, OR 1.99 (CI 1.17-3.39), rs163184 OR 1.7 (CI 1.01-2.87) contrasted between groups with T2DM and healthy control, but without significant changes (Table 3).

3.3 Nominal allele and genotypic associations with T2DM

| Rs | Genotypes | Genotype frequency | | OR | ρ | 95% CI |
|---|---|---|---|---|---|---|
| | | T2DM, n = 139 | Control, n = 100 | | | |
| rs2237896 | G/G | 23 | 34 | | | |
| | G/A+A/A | 116 | 66 | 2.6 | <0.05 | 1.41-4.78 |
| rs2383208 | A/A | 67 | 62 | | | |
| | A/G+G/G | 72 | 38 | 1.75 | <0.05 | 1.04-2.69 |
| rs1575972 | T/T | 47 | 49 | | | |
| | T/A+A/A | 92 | 51 | 1.88 | <0.05 | 1.11-3.18 |
| rs4402960 | G/G | 57 | 57 | | | |
| | G/T+T/T | 82 | 43 | 1.91 | <0.05 | 1.13-3.21 |
| rs1470579 | A/A | 44 | 52 | | | |
| | A/C+C/C | 95 | 48 | 1.99 | <0.05 | 1.17-3.39 |
| rs163184 | T/T | 68 | 62 | | | |
| | T/G+G/G | 71 | 38 | 1,7 | <0.05 | 1.01-2,87 |
| rs2237897 | C/C | 36 | 46 | | | |
| | C/T+T/T | 103 | 54 | 2.44 | <0.05 | 1.41-4.21 |

**Allele and genotype variants not associated with T2DM**

It should be specially stressed that part of the studied polymorphic genetic markers did not demonstrate any connection with T2DM (Table 4). Besides, in statistical analysis there was no difference in distribution of genotypes between patients with T2DM and the control group, P> 0.05. The odds ratio varied between 0.7-2.93, CI (0.41-1.19 to 0.77-5.71) (Table 4).

Table 4. Significant allele and genotype associations with T2DM P> 0.05

| Rs | Genotypes | Genotype frequency | | OR | ρ | 95% CI |
|---|---|---|---|---|---|---|
| | | T2DM, n = 139 | Control, n = 100 | | | |
| rs10460009 | C/C | 74 | 53 | | | |
| | C/T+T/T | 65 | 47 | 0.99 | >0.05 | 0.59-1.66 |
| rs6583826 | G/G | 67 | 55 | | | |
| | G/A+A/A | 72 | 45 | 1.31 | >0.05 | 0.78-2.2 |
| rs9295474 | C/C | 59 | 34 | | | |
| | C/G+G/G | 80 | 66 | 0.7 | >0.05 | 0.41-1.19 |
| rs8181588 | T/T | 7 | 10 | | | |
| | T/C+C/C | 132 | 90 | 2.1 | >0.05 | 0.77-5.71 |
| rs3888647 | G/G | 18 | 13 | | | |
| | G/A+A/A | 121 | 87 | 1.0 | >0.05 | 0.47-2.16 |

| | | | | | | |
|---|---|---|---|---|---|---|
| rs8050136 | C/C | 29 | 26 | | | |
| | C/A+A/A | 110 | 74 | 1.33 | >0.05 | 0.73-2.44 |
| rs4712523 | A/A | 57 | 53 | | | |
| | A/G + G/G | 82 | 47 | 1.62 | >0.05 | 0.97-2.72 |
| rs3773506 | G/G | 15 | 11 | | | |
| | G/C+ C/C | 124 | 89 | 1.02 | >0.05 | 0.45-2.33 |
| rs1049549 | T/T | 135 | 99 | | | |
| | T/C+C/C | 4 | 1 | 2.93 | >0.05 | 0.32-26.65 |
| rs11642841 | C/C | 68 | 41 | | | |
| | C/A + A/A | 71 | 59 | 0.73 | >0.05 | 0.43-1.22 |

## Discussion

The study of the association of genetic markers with the risk of developing T2DM has been widely studied in various populations [16, 17]. However, studies in different ethnic groups showed contradictory results, while some replication studies have confirmed this relationship, other studies did not find a significant relationship, suggesting ethnic variation [18]. Significant genetic heterogeneity between different populations is noted, thus allowing to suggest that the study of genes for predisposition to T2DM in additional populations can provide a significant understanding of the etiology of the disease [19].

In our study, we decided to study the connection of 25 GWAS SNPs previously detected in populations of Europe and East Asia with a predisposition to T2DM in the Kazakh sample. According to the results of our data, most of the polymorphic variants associated with T2DM in European and East Asian populations are also associated in representatives of the Kazakh population. Of the 25 SNPs tested, 8 loci showed high static significance (P <0.001), 7 others were nominally significant, and 10 variants did not show association with T2DM. According to previous studies in Europe and Asia, our results state a statistically significant connection between the TCF7L2 rs7901695 and rs7903146 variants with T2DM in the Kazakh population. This connection is confirmed by statistical data in which OR = 3.640, 95% CI 1.78–5.21 and OR = 5.73, 95% CI 3.26–10.08, respectively.

It should be noted that TCF7L2 rs7903146 is one of the most sequentially replicated loci for T2DM development of in several populations. High association of the polymorphic marker rs7903146 of the TCF7L2c gene of T2DM was found in Africans (p = 1.61 × 10 -8) [20], in the European population [21]. It is noteworthy that in our study, rs7903146 has a high OR assessment range (5.7395% CI 3.26–10.08,) indicating a potentially more excellent effect of the variant in the Kazakh sample. Variants of the TCF7L2 gene were replicated in many ethnic groups; a significant association of polymorphisms 7756992 and 7754840 and rs4712524 with T2DM was found in European and many subgroups of Asia (P <0.05), while no significant association was found in the African population. [22] (P> 0.05). For example, in the TCF7L2 study, the strongest risk variant associated with type 2 diabetes was found in many European populations in the T allele rs7903146 at the 5'-end of the gene [23]. However, the frequency of the T allele rs7903146 in Asian representatives was rather rare (low allele frequency 2–2.5%) [24].

Our results extend the list of populations in which CDKAL1 rs7756992, rs7754840 and rs4712524 are associated with T2DM. We were able to reproduce the connection of rs7756992 (OR = 3.01 [1.76-5.13], 7754840 (OR = 2.75 [1.59-4.74] and rs4712524 (OR = 2.53 [1.49-4.31] with T2DM in our patients. However, variants rs9295474 and rs4712523 CDKAL1 for T2DM were not statistically significant in the Kazakh population (P> 0.05). The data obtained are consistent with the results of genetic studies in European, Russian and Asian populations [25]. The association of polymorphic markers rs2237892 and rs1333051 with T2DM was registered in the studies of the Mongolian population [26]. In the Kazakh population, polymorphic genetic markers rs2237892 and rs1333051 were demonstrated with statistically significant association with T2DM (OR> 2). This shows that our research could reproduce the results obtained in populations with a similar ethnic origin, and extended replication of several other loci in the Asian population.

As for polymorphic variants rs10460009, rs6583826, rs9295474, rs8181588, rs3888647, rs8050136, rs4712523, rs3773506, we did not find a significant difference in the genotype frequencies between the groups with T2DM and the healthy control in the Kazakh population (P <0.05), the ratio was different (p <0.05) 7-2.6, 95% CI 1.01-4.78. It should be noted that these data are preliminary and require further confirmation. Statistically, the nominal connection in our study may have been related to ethnicity and a small sample size. Therefore, this assumption needs further research with a larger sample in the Kazakh population. Of particular interest is the fact that ten of the tested loci (rs11642841, rs10460009, rs6583826, rs9295474, rs8181588, rs3888647, rs8050136, rs4712523, rs3773506, rs1049549) were not associated with T2DM risk in the Kazakh population. However, lack of the association may also be connected with true genetic diversity. It should be noted that the interaction of food traditions, environment, and hereditary characteristics of metabolism determined the distribution of the most adaptive gene variants in the population. Future studies aimed at a larger sample size and a larger selection of SNPs will overcome the existing limitations and enable the genetic characterization of predisposition to T2DM in the Kazakh population.

## Conclusions

In this work, for the first time, a replicative analysis of 25 single nucleotide markers associated with type 2 diabetes according to the results of wide-genome studies (GWAS) in a sample of Kazakhs was performed. Our associative study confirmed the connection of several previously identified genetic markers with T2DM. Of the 25 previously tested SNPs, we identified eight statistically significant polymorphic genetic variants (p <0.001), seven polymorphic genetic variants showed a nominal association with T2DM, p <0.05, but at the same time 8 SNPs showed no statistical significance with T2DM (P > 0.05), which can be explained by its dependence on other risk factors and actually determines the need for further studies. Thus, the results of this study represent a preliminary understanding of the genetic variants of T2DM in Kazakhs. Study of the basics of the genetic architecture of type 2 diabetes in a given population can improve our understanding of the pathogenesis of this disease and help develop new, effective preventative measures to reduce its risk.

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