Short Communication
Volume 14:4, 2020
DOI: 10.37421/jmgm.2020.14.464

Journal of Molecular and Genetic Medicine

ISSN: 1747-0862 **Open Access**

Analysis of Polymorphisms Associated with type 2 Diabetes in the Kazakh Population

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Abstract

The increasing prevalence of type 2 diabetes (T2D) underlines the urgent need for proactive strategies to prevent and control T2D. A fairly large number of studies show that T2D is a complex metabolic disease caused by lifestyle, environment and genetic factors. 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. The study of genetic markers of type 2 diabetes association is relevant worldwide. The aim of this study was to search for genetic markers associated with the development of T2D in individuals of the Kazakh population.

Keywords: Type 2 Diabetes • Post-genomic technologies • Gene polymorphisms • Genetic

Introduction

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 [1]. 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). 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). Data analysis was performed using the online tools of the Termo Fisher Cloud service. 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 [2].

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 [3,4].

Results and Discussion

We analyzed the relationship of 25 SNPs previously identified in different European and Asian populations with the risk of developing T2D in the Kazakh population and determined the frequencies and genotypes associated with an high and low risk of T2D. Of the 25 previously tested SNPs, eight statistically significant polymorphic genetic variants were identified. 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. 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. It should be specially stressed that part of the studied polymorphic genetic markers did not demonstrate any connection with T2DM. 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)

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Received 05 August 2020; **Accepted** 07 September 2020; **Published** 14 September 2020

Conclusion

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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How to cite this article: Benberin V, Voshchenkova T, Abildinova G and Borovikova A, et al. "Analysis of Polymorphisms Associated with type 2 Diabetes in the Kazakh Population." *J Mol Genet Med* 14 (2020): 464 doi: 10.37421/jmgm.2020.14.464