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Genetic aspects of type 2 diabetes mellitus associated with chronic heart failure.

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Summary

Introduction. Today, the prevalence of type 2 diabetes mellitus (T2DM) has reached "pandemic" proportions. Diabetes is the most significant problem of modern healthcare, as it is characterized by high disability and mortality. FABP2 plays a key role in the absorption and intracellular transport of dietary long-chain fatty acids. Since glucose and fatty acid metabolism are interrelated phenomena, FABP2 soon became an important candidate

gene for T2DM.
The aim of the study was to study the polymorphism of the *FABP2 gene* in patients with T2DM associated with CHF.
Methods and materials. To achieve this goal, a genetic study was conducted in 125 patients diagnosed with type 2 diabetes with and without CHF, treated in the endocrinology and cardiology departments of clinics of the Andijan State Medical Institute. Testing of the FABP2 rs 1799883 polymorphism was carried out by allele-specific PCR in Real-Time format on a Rotor-Gene Q device (Quagen , Germany) using a commercial test kit from Syntol LLC (Russia) in accordance with the manufacturer's instructions.
Results. In patients with type 2 diabetes without CHF, the presence of the allele Thr increased the risk of developing isolated type 2 diabetes by 1.9 times (25.7% versus 15.4%; $\chi 2=3.8$; p=0.05; OR=1.9; 95%CI: 0.99 - 3.66 respectively).
Conclusion. A significant relationship was identified between the carriage of an unfavorable allelic variant 54Thr of the FABP2 gene, associated with increased metabolism of fats in the body and the risk of developing type 2 diabetes, but without CHF.

Key words : *FABP2* , type 2 diabetes mellitus, chronicheart failure.

Today, the prevalence of type 2 diabetes mellitus (T2DM) has reached "pandemic" proportions. Diabetes is the most significant problem of modern healthcare, as it is characterized by high disability and mortality. The number of patients with diabetes in Uzbekistan, as well as throughout the world, is growing every year; over the past 18 years, the number of patients with diabetes in the republic has increased by 2.4 times [1]. Large costs associated primarily with disability and mortality lead to the organization of a system for recording and monitoring clinical and epidemiological information about this disease [2]. The results of genetic studies accumulated to date allow us to say with confidence that the genetic component plays an important role in the formation of carbohydrate metabolism disorders and amounts to 50 or more in the human population. Type 2 diabetes mellitus develops as a result of a complex interaction between unfavorable environmental components and certain genetic factors. Several risk factors, including common, easily measurable phenotypic traits (such as obesity,

hypertension, low high-density lipids, elevated triglycerides, impaired fasting glucose), as well as family history of T2DM, are already effectively used as predictors of T2DM development. Currently, several hundred candidate genes are known to be associated with the development of various disorders of carbohydrate metabolism, such as T2DM, impaired glucose tolerance, and impaired fasting glycemia. Due to the fact that there are many variants of genetic polymorphisms that create the basis of predisposition to T2DM, this determines the polygenic nature of the development of this disease [2, 3].

However, T2DM is one of those complex diseases for which genetic contributions are well accepted. Identification of the genetic components of T2DM is the most important area of diabetes research, as the elucidation of diabetes genes (alleles) will influence all efforts to mechanistically understand the disease, its complications, treatment, management and prevention [5] . In general, many genes have key regulatory functions in the development of T2DM, which is a polygenic disorder with many genes located on different chromosomes contributing to its susceptibility. The analysis of genetic factors associated with T2DM is further complicated by the fact that various environmental factors interact with these genes to cause the disorder. Thus, the identification and characterization of gene variants among a specific ethnic group that play a significant role in T2DM is one of the most important areas of diabetes research, as it will impact all efforts to mechanistically understand disease complications, treatment, cure, and prevention.

Today, genes that are responsible for the most important links in the pathogenesis of T2DM – insulin resistance (IR) and genetic defects of pancreatic β-cells – are being actively studied. There are two main hereditary causes in the formation of carbohydrate metabolism disorders: genetic defects in β-cell function and genetic defects in insulin action.

FABP2 plays a key role in the absorption and intracellular transport of dietary long-chain fatty acids. Since glucose and fatty acid metabolism are interrelated phenomena, FABP2 soon became an important candidate gene for T2DM. The FABP4 gene plays an important role in the regulation of inflammation and lipid metabolism, as well as insulin sensitivity [6].

The aim of the study was to study the polymorphism of the FABP2 gene in patients with T2DM with or without CHF.

Materials and methods: to achieve this goal, a genetic study was conducted in 125 patients diagnosed with type 2 diabetes with and without CHF, treated in the endocrinology and cardiology departments of clinics of the Andijan State Medical Institute.

The control group consisted of 101 healthy individuals of the corresponding middle age. Disease diagnoses were established in accordance with the latest clinical guidelines for diabetes and heart failure.

Isolation of DNA from peripheral blood was carried out using a commercial set of reagents "AmpliPrime RIBO- prep" (Interlabservice LLC , Russia), according to the manufacturer's instructions. Testing of the FABP2 rs 1799883 polymorphism was carried out by allele-specific PCR in Real-Time format on a Rotor-Gene Q device (Quagen , Germany) using a commercial test kit from Syntol LLC (Russia) in accordance with the manufacturer's instructions. Statistical processing of the results was performed using the standard OpenEpi V.9.2 application package.

The distribution of alleles and genotypes corresponded to the Hardy-Weinberg distribution law (HW). The odds ratio (OR) was calculated to describe the relative risk of developing the disease. OR>1 was considered as a positive association (predisposition) of an allele or genotype with a disease, and OR<1 ($p<0.05$) as a negative association.

Results and discussions: when studying the frequency of alleles and genotypes of the Ala 54 Thr gene polymorphism of the FABP 2 gene in all patients with type 2 diabetes without CHF, the distribution was as follows: Ala - 74.3% versus 84.6%; Thr - 25.7% versus 15.4%; Ala / Ala -57.1% versus 77.3%; Ala / Thr - 34.3% vs. 23.8% and Thr / Thr -8.6% vs. 3.9%. Analyzes of frequency distribution of unfavorable genotypes Ala / Thr and Thr / Thr showed a tendency to increase the risk of developing type 2 diabetes by 1.8 and 2.3 times, respectively. (Table 1.). In patients with type 2 diabetes without CHF, the presence of the allele Thr increased the risk of developing isolated type 2 diabetes by 1.9 times (25.7% versus 15.4%; $\chi 2=3.8$; $p=0.05$; OR=1.9; 95%CI: 0.99 - 3.66 respectively).

Table 1.

Distribution frequency of alleles and genotypes of the Ala 54 Thr polymorphism of the FABP 2 gene rs 799883 in the group of patients with type 2 diabetes and controls.

Alleles and genotypes	Number of alleles and genotypes examined				χ^2	p	OR	95%CI
	DM type 2		Control group					
	n	%	n	%				
Ala	52	74.3	171	84.6	3.8	0.05	0.5	0.27 - 1.00
Thr	18	25.7	31	15.4	3.8	0.05	1.9	0.99 - 3.66
Ala / Ala	20	57.1	74	73.3	3.2	0.08	0.5	0.22 - 1.08
Ala / Thr	12	34.3	23	22.8	1.8	0.18	1.8	0.77 - 4.07

Thr / Thr	3	8.6	4	3.9	1.1	0.29	2.3	0.50 -10.32

Analyzes of frequency distribution of unfavorable genotypes Ala / Thr and Thr / Thr also showed a tendency to increase the risk of developing type 2 diabetes by 1.8 and 2.3 times, respectively. (Table 1.).

Differences in the frequency of allelic and genotypic variants of the Ala 54 Thr polymorphism of the FABP 2 rs 799883 gene in the group of type 2 diabetes with CHF and control: when analyzing the distribution of alleles of the studied marker of the FABP2 gene, significant differences were revealed between the group of type 2 diabetes + CHF and the control group. Thus, carriage of a favorable allele Ala and the associated wild genotype Ala / Ala had a protective effect on the risk of developing type 2 diabetes + CHF (70.2% versus 84.6%; χ^2 =7.8; p=0.001; OR=0.4; 95%CI:0.24-0.78 and 52.4% versus 73.3%; χ^2 =7.8; p=0.002; OR=0.4; 95%CI:0.19-0.84, respectively). (Table 6.2). In turn, carriage of an unfavorable allele Thr gene FABP2 increased the risk of developing type 2 diabetes in patients with CHF by 2.3 times (29.8% versus 15.4%; χ^2 =7.8; p=0.001; OR=2.3; 95%CI:1.29-4.24).

Table 2.

Frequency distribution of alleles and genotypes of the Ala 54 Thr polymorphism of the FABP 2 gene rs 799883 in the group of patients with type 2 diabetes with CHF and controls .

Alleles and genotypes	Number of alleles and genotypes examined				χ^2	p	OR	95%CI
	DM+CHF		Control group					
	n	%	n	%				
Ala	59	70.2	171	84.6	7.8	0.001	0.4	0.24 - 0.78
Thr	25	29.8	31	15.4	7.8	0.001	2.3	1.29 - 4.24
Ala / Ala	22	52.4	74	73.3	5.9	0.02	0.4	0.19 - 0.84
Ala / Thr	15	35.7	23	22.8	2.5	0.11	1.9	0.86 - 4.10
Thr / Thr	5	11.9	4	3.9	3.2	0.08	3.3	0.89 -12.09

Statistics have shown that when an unfavorable Ala / Thr genotype is detected FABP2 gene tended to increase the risk of developing type 2 diabetes in patients with CHF by 1.9 times (35.2% versus 27.8%; χ^2 =2.5; p=0.01; OR=1.9; 95%CI:0.86-4.10, respectively). (Table 2). In turn, carriage of the mutant Thr / Thr genotype increased the risk of developing type 2 diabetes in patients with CHF by 3.3 times (11.9% versus 3.9%; χ^2 =3.2; p=0.008; OR=3.3; 95%CI:0.89-12.09 accordingly).

Numerous studies have evaluated FABP2 gene variants and their association with insulin resistance and T2DM. The most studied variant is the Ala54Thr variant at codon 54, an error variant that has some effects on the primary structure of the protein and affects its fatty acid binding properties. Previous studies have found a significant association between FABP2 genotype and the occurrence of T2DM or decreased insulin sensitivity. In Pima Indians, FABP2 genotypes have been shown to be associated with increased fatty acid binding, increased fat oxidation, and insulin resistance [4]. On the other hand, in Finnish participants without diabetes and NIDDM [7.]. A HuGE review and meta-analysis was conducted to more accurately assess this relationship. The PubMed and CNKI databases were searched for case-control studies published up to April 2014. Ultimately, 13 studies were included, including 2020 T2DM cases and 2910 controls. The studies were searched in the electronic databases PubMed and CNKI (China National Knowledge Infrastructure). In this meta-analysis , ethnic stratification of differences was found between Asians and Caucasians. This meta-analysis showed that Ala54Thr polymorphisms in FABP2 are associated with increased susceptibility to T2DM risk among Asians, but not Caucasians. [9; c.1336–1341].

Our research is consistent with the results of a number of studies [10; eleven; 12]. the Ala54Thr polymorphism of the FABP2 gene did not affect insulin sensitivity.

Conclusions: A significant relationship was identified between the carriage of an unfavorable allelic variant 54Thr of the FABP2 gene, associated with increased metabolism of fats in the body and the risk of developing type 2 diabetes, but without CHF. The risk of developing type 2 diabetes when carrying this allelic variant significantly increases by more than 1.9 times (OR=1.9; $\chi 2$=3.8; p=0.05); on the contrary, the wild genotypic variant Ala54 of the FABP2 gene is associated with a reduced risk of developing type 2 diabetes.

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