SEARCH FOR ASSOCIATIONS OF MITOCHONDRIAL GENOME POLYMORPHISMS WITH TYPE 2 DIABETES MELLITUS IN THE SAKHA (YAKUT) POPULATION

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Abstract. The Republic of Sakha (Yakutia), located in the northeastern part of Russia, is characterized by an extremely cold climate, to which the indigenous people is adapted. Over the past decades, there has been a significant increase of the incidence of type 2 diabetes mellitus (T2DM) among the indigenous population. It is known that polymorphisms of the mitochondrial genome, in particular, the 16189C variant of hypervariable segment I (HVS-I), may contribute to the development of T2DM. The aim of the study was to assess the association of mitochondrial DNA (mtDNA) HVS-I polymorphisms with the type 2 diabetes mellitus in the Sakha (Yakut) population. Sequencing of HVS-I mtDNA in 102 patients with T2DM and 101 non-diabetic controls revealed 67 haplotypes and 64 SNP variants. There was no statistically significant difference in the frequencies of detected HVS-I polymorphisms and haplotypes between the two groups, which indicates the absence of a close association between HVS-I polymorphisms and T2DM in the Sakha population.

Keywords: type 2 diabetes mellitus, Sakha (Yakut) population, mitochondrial genome, HVS-I.

List of Abbreviations

RS (Y) – Republic of Sakha (Yakutia)
T2DM – type 2 diabetes mellitus
mtDNA – mitochondrial DNA
HVS-I – hypervariable segment I

Introduction

The prevalence of type 2 diabetes mellitus (T2DM) is on the rise globally with recent estimates of registered cases of 437.9 million [402.0-477.0 million] in 2019 (Nanda *et al.*, 2022). In the Republic of Sakha (Yakutia) (RS(Y)) over the past decades, there has been a significant increase in the incidence of type 2 diabetes. According to the official data of the Yakut Republican Information and Analytical Center (YARMIAC), the T2DM primary incidence in 2000 was 0.5 cases per 1000 adult population of the RS(Y), while at the end of 2022 – 1.9 cases per 1000 population. At the dispensary observation 6.2 per 1000 of the population of the RS(Y) were registered at the end of 2000, and to the end of 2022, that indicator had increased to 26.2 per 1000.

The main reason for the increase in T2DM morbidity of the indigenous people of RS(Y) is a radical change in the lifestyle, primarily diet type, to which peoples of the North are not adapted metabolically. At present, the evolutionarily established protein-lipid nature of the North ethnic nutrition diet has been transformed towards the lipid-carbohydrate «European» of «Western» type (Tikhonov *et al.*, 2009). An assessment of modern diet and eating habits of the indigenous people of RS(Y) revealed an increased consumption of sugar and confectionery, an extremely insufficient consumption of dairy, fish, and meat products. In the structure of the energy value, the proportion of carbohydrates is 60%, proteins and fats are 20% each, respectively (Lebedeva & Abramov, 2015). According to our epidemiological screening data in the Berdigestyakh village – traditional agricultural area with a predominantly indigenous population, only 27% of women and 41% of men have physical activity, there is the gradual loss of traditional activities of the indigenous population (Fedorov *et al.*, 2015).

It is possible that the genome of the indigenous population that contributed to survival in extreme environmental conditions, in changed living conditions (diet transformation, reduced physical activity, reduced time spent in the cold, the emergence of new stress factors) predispose to the development of metabolic disorders (Sivtseva *et al.,* 2021). Genetic variants that determine predisposition to T2DM in northern populations may have their own characteristics due to the evolutionary selection of polymorphisms that affect the adaptation of metabolism to environmental conditions. Previous studies of the nuclear genome revealed an association of T2DM in the Sakha (Yakut) population with 4 genes: rs320 of the *LPL* gene, rs1799859 of the *ABCC8* gene, rs1800796 and rs2234683 of the *IL6* gene, rs34861192 and rs32119177 of the *RSTN* gene (Osakovsky *et al.,* 2010). Given the key role of the mitochondrial genome in maintaining energy and heat metabolism, it seems very interesting to study the contribution of mitochondrial DNA (mtDNA) variants to the development of type 2 diabetes mellitus in the cold climate of Yakutia.

The control region of the mitochondrial genome is represented by non-coding hypervariable segments, one of which is hypervariable segment I (HVS-I), 350 nucleotides long (located between positions 16024-16365 of the mtDNA sequence). The polycytosine tract with a single T nucleotide at position 16189 is localized in the mtDNA HVS-I region within 16184-16193. The replacement of T nucleotide to C at position 16189 is considered to negatively affect the replication and regulation of the mtDNA copy number. There are a number of studies of the role of the polycytosine tract, including the 16189C variant of the mitochondrial genome in the development of diabetes mellitus (Bhat *et al.,* 2007; Park *et al.,* 2008; Kumari *et al.,* 2018), however, some researchers question whether this polymorphism is strongly associated with diabetes mellitus among East Asian populations (Zhong *et al*., 2014). The role of mtDNA among patients with type 2 diabetes mellitus in the Sakha population has not been previously studied.

The aim of the study was to evaluate the association of polymorphisms (single nucleotide variants) of mtDNA hypervariable segment I with the development of type 2 diabetes mellitus in the Sakha (Yakut) population.

Materials and Methods

The hypervariable segment I (HVS-I) sequencing of the mitochondrial genome was performed in 102 patients with T2DM and 101 apparently healthy non-diabetic controls. All participants in the study were of Sakha ethnicity with an updated pedigree up to the third generation. The distribution by gender and age of the studied groups are shown in Table 1. The study was performed in accordance with the Declaration of Helsinki (2013) and approved by the local ethics committee at the M.K. Ammosov North-Eastern Federal University.

Sequencing of mtDNA was carried out in the Research Institute of Genetics of the Tomsk Scientific Research Center of the Russian Academy of Sciences. Haplogroups were determined manually based on mtDNA tree Build 17 (Feb 18, 2016) (van Oven & Kayser, 2009) and MTree 1.02.19804 (May 23, 2023) (https: //www.yfull.com/mtree/ accessed 05/25/2023) in comparison with previously published population data on the structure of the mitochondrial gene pool of the Sakha people (Fedorova *et al.,* 2013).

The association of mtDNA polymorphisms with T2DM was calculated using Pearson's $\chi 2$ test or Fisher's exact test at polymorphism frequencies less than 10, along with odds ratio (OR) and 95% confidence interval (CI). The critical value of the level of statistical significance (p) was taken equal to 5%.

Results

The sequencing of mtDNA HVS-I revealed 64 SNP polymorphisms, most of which occur at a frequency of less than 5% in both groups of patients. The figure 1 shows the frequency of the most common polymorphisms in comparison between the T2DM and the control groups (polymorphisms with a frequency of less than 2% are not shown). The most common polymorphism is 16223T with a frequency of 85.3%

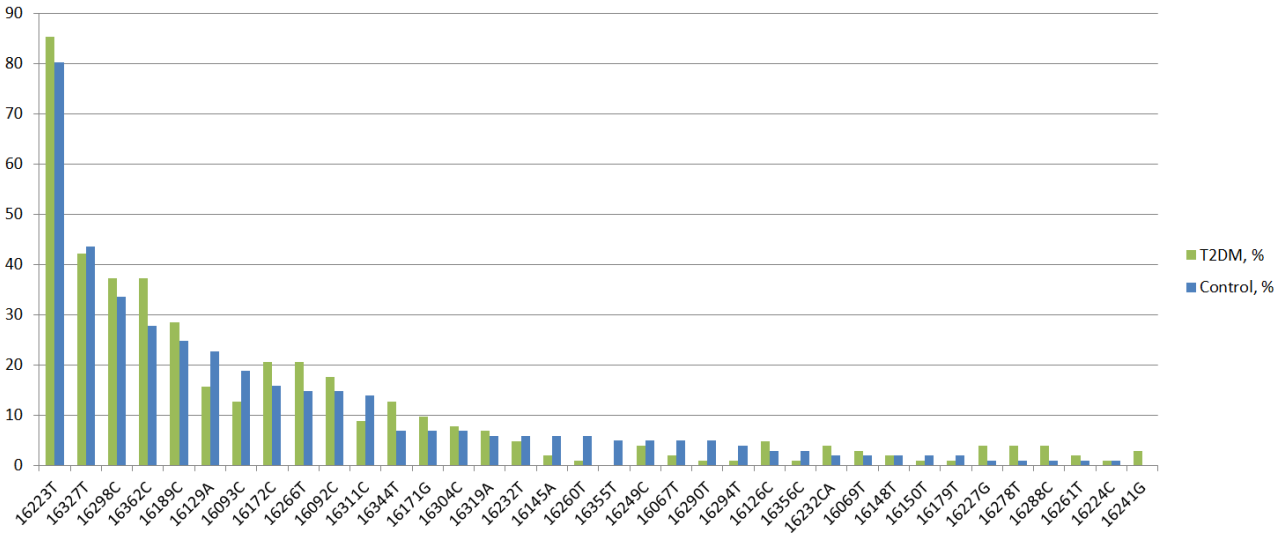

Fig. 1. The frequency of HVS-I polymorphisms in groups of patients with type 2 diabetes mellitus and non-diabetic controls of the studied Sakha population (polymorphisms with a frequency of less than 2% are not shown). None of the polymorphisms has a statistically significant association with T2DM (OR (95%CI), $p > 0.05$)

Table 1

The distribution by gender and age of patients with T2DM and the control group

Age groups	Male		Female		Total	
	T2DM	Non-diabetic control	T2DM	Non-diabetic control	T2DM	Non-diabetic control
Under 44 years old	14	6	11	11	25	17
45-59 years old	14	8	16	28	31	36
Over 60 years old	18	9	29	41	55	48
Total	46	23	56	80	102	101

in patients with T2DM and 80.2% in control group. Other common polymorphisms are 16327T (frequency: 42.2% – T2DM and 43.6% – control), 16298C (frequency: 37.3% – T2DM and 33.7% – control), and 16362C (frequency: 37.3% – T2DM and 27.7% – control). Polymorphism 16189C was detected with a frequency of 28.4% in patients with T2DM and 24.8% in controls. There are no statistically significant differences in the frequencies of all identified polymorphisms between the groups.

The results of sequencing allow us identified 67 haplotypes in the examined patients (Table 2). Of these, 46 haplotypes were found in patients with T2DM, while among the non-diabetic control group – 41 haplotypes (Table 2). The most common haplotypes, both in patients and in the control group, are D5a2a2, C, C4a1, C4a2a, which is consistent with the population frequency previously identified (Fedorova *et al.*, 2013). No statistically significant difference in haplotype frequencies between the groups of patients and controls was found.

According to these results, none of the HVS-I polymorphisms of mtDNA genome is associated with the development of type 2 diabetes mellitus in Sakha population.

Discussion

In this paper, the results of a pilot study of the association of mitochondrial HVS-I polymorphisms with the development of type 2 diabetes mellitus in the Sakha population is presented. We failed to identify a statistically significant association of haplotypes and polymorphisms of the HVS-I mitochondrial genome

Table 2

HVS-I haplotypes and their occurrence in groups of patients with type 2 diabetes mellitus and controls of the studied Sakha population

	HVS-I haplotypes	SNPs position in HVS-I	T2DM, n	Non-diabetic control, n	OR (95%CI)	P value
1	U4	356	–	1		
2	A12a (A4b)	039-189-223-290-319-356-362	–	1		
3	D4m2a	042-093-214-223-362	–	1		
4	A8a1a	066-223-242-290-319	–	1		
5	HV1b2a	067-189	2	–		
6	HV1a1a	067-260-355	–	5		
7	J (J1c5)	069-126	1	2	0.49 (0.04–5.49)	> 0.05
8	J2a2b	069-126-241	2	–		
90	C4a1d	086-129-150-223-298-327	–	1		
10	C4b1a	086-223-259.1A-294-298-327	–	1		
11	D2 (D2b1)	092-129-223-271-362	–	1		
12	D5a2a2	092-172-189-223-266-362	15	14	1.07 (0.49–2.35)	> 0.05
13	F1b1b	092-172-189-232CA-249-304-311-266	1	–		
14	F2 (F2b1)	092TA-245-291-304	1	–		
15	C4a1a3d (C4a1c)	093-129-223-298-327	1	6	0.16 (0.02–1.33)	> 0.05
16	C4a1c	093-129-223-327	9	10	0.88 (0.34–2.27)	> 0.05
17	D4o2a	093-192-223-232-362	1	–		
18	D4o2a	093-223-232-362	1	1	0.99 (0.06–16.04)	> 0.05
19	C5a (C5a2*)	093-223-261-288-298	1	–		
20	U4a1e	093-311-356	–	1		
21	B5b2	111-140-189-234-243	–	1		
22	Y1a	126-231-266-342	1	1	0.99 (0.06–16.04)	> 0.05
23	T2	126-294-296-362	1	–		
24	C4a1a4a (C4a1d)	129-150-223-298-327	1	1	0.99 (0.06–16.04)	> 0.05
25	D2 (D5b1d)	129-189-223-362	–	1		
26	M7b1a1	129-192-223-241-297	1	–		
27	M7b1a1	129-192-223-297	1	–		
28	C4a1*	129-223-298-327	1	2	0.49 (0.04–5.49)	> 0.05

Continuation of the table 2

	HVS-I haplotypes	SNPs position in HVS-I	T2DM, n	Non-diabetic control, n	OR (95%CI)	P value
29	C4a1c	129-223-327	1			
30	R1b	129-224-265-291-311-390	1	1	0.99 (0.06–16.04)	> 0.05
31	M13a1b	145-148-188-189-223-381	–	2		
32	D4l2a1	145-223-274-311-362-368	–	1		
33	D4l2a1	145-223-311-362-368	–	1		
34	M7c1a1b1	145-223-295-304	2	2	0.99 (0.14–7.17)	> 0.05
35	C5b1b	148-164-223-288-298-327	2	–		
36	C4a2a	171-223-256-298-327-344-357	–	1		
37	C4a2a	171-223-298-327-344-357	10	6	1.72 (0.60–4.93)	> 0.05
38	D5a2a2	172-189-223-266-362	2	–		
39	F1b1b	172-189-232CA-249-304	1	–		
40	F1b1b	172-189-232CA-249-304-311	–	2		
41	D4h1 (D4j8)	174-223-362	1			
42	A15 (A4*)	179-223-290-311-319-362	1	1	0.99 (0.06–16.04)	> 0.05
43	A15 (A4*)	179-223-260-290-311-319-362	–	1		
44	Z3*	185-223-260-274-298	1	–		
45	B4	189-217	1	–		
46	C7a2 (C4b1*)	189-223-298-327	1	–		
47	F1b	189-232CA-249-304-311	2	3	0.65 (0.11–3.99)	> 0.05
48	U4d2	189-356	1	–		
49	D4c1b1	223-224-245-292-362	1	–		
50	G2a*	223-227-274-278-362	1	–		
51	G2a*	223-227-278-362	3	1	3.03 (0.31–29.63)	> 0.05
52	D4c2	223-245-362	1	–		
53	C4b1a	223-259.1A-298-327	–	1		
54	C5a1	223-261-288-298	1	1	0.99 (0.06–16.04)	> 0.05
55	C	223-272-298-327	1			
56	G2a	223-278-362	1	–		
67	C4b3a	223-291-298-327-352	–	1		
58	W	223-292	–	1		
59	D4i2	223-294-362	3	4	0.74 (0.16–3.37)	> 0.05
60	C	223-298-304-311-327	1	–		

End of table 2

	HVS-I haplotypes	SNPs position in HVS-I	T2DM, n	Non-diabetic control, n	OR (95%CI)	P value
61	C (C4b*)	223-298-311-327	3	3	0.99 (0.20–5.08)	> 0.05
62	C	223-298-327	9	10	0.88 (0.34–2.27)	> 0.05
63	C4a2	223-298-327-344-357	3	–		
64	D (D4b1*)	223-319-320-362	1	–		
65	D (D4b1*)	223-319-362	4	2	2.02 (0.36–11.29)	> 0.05
66	C	223-398-327	–	1		
67	H	CRS	1	3	0.32 (0.03–3.16)	> 0.05
			102	101		

Note: MtDNA haplotype affiliations according to Fedorova *et al.*, 2013 are given in parentheses.

with type 2 diabetes mellitus in the Sakha population. Previously published data on the high frequency of 16189C variant (Bhat *et al.*, 2007; Park *et al.*, 2008; Weng *et al.*, 2005; Poulton *et al.*, 2002; Soini *et al.*, 2012) and 16093C (Jiang *et al.*, 2019) among patients with type 2 diabetes mellitus compared with the control group in various ethnic groups, was not confirmed in the studied samples.

It should be noted that 16189C and 16093C are the most frequent mtDNA HVS-I variants found in many haplogroups of both Asian and European origin. Earlier, in the Yakutian population, polymorphism 16189C was detected in A4b, B4*, C4a1c, C4b1*, C5a2a, D4e4a1, D5a2a2, D5b1d, F1b, G2a5, M7d, M13a1b, U4d2, U5b1b1a, Y1a haplogroups, and 16093C – in C4a1c, C4b8, C5a2*, C5d1, D4m2, D4o2, G1b, U4a1 haplogroups, which indicates a high frequency of the occurrence of a mutation at these mtDNA HVS-I positions (Fedorova *et al.*, 2013).

In Asian populations (Japanese, Chinese, Uighurs of China), according to various studies of the informative region of the mtDNA genome, single nucleotide variants associated with type 2 diabetes are detected: 1438G, 2706G, 4833G, 5178A, 8414G, 10398G, 12026G (Tawata *et al.*, 1998; Jiang *et al.*, 2017; Ohkubo *et al.*, 2000; Wang *et al.*, 2001; Liao *et al.*, 2008; Saha *et al.*, 2019).

In cold climates, evolutionary selection probably contributed to the dominance of mitochondria with a relatively high level of uncoupling of oxidation and phosphorylation. Thus, it was found that mitochondria with 16223T, 489C, 8701G, and 10400T mtDNA variants have a relatively high level of uncoupling of oxidation and phosphorylation processes compared to CRS (Tikhonov *et al.*, 2022). The 16223T variant is a marker of Asian populations that separates the N and R macrohaplogroups. In our study, this variant are probably signs of the adaptation process, since they were present both in diabetic patients and in the control group with a frequency of 80-85%.

Based on these data, it can be supposed that in Asian populations generally there is a quite high prevalence of mtDNA polymorphisms that can contribute to the development of diabetes mellitus.

Conclusion

We have not found an association of polymorphisms and haplotypes of mtDNA HVS-I with type 2 diabetes mellitus in the Sakha population (representatives of the Yakut ethnic group). The data of other authors on the high frequency of 16189C and 16093C among T2DM patients of different ethnic groups compared with the control group were not confirmed in our study. Further, sequencing of the whole mtDNA genome of Sakha representatives will provide a more complete picture of the role of the mitochondrial genome in diabetes mellitus in an isolated Asian population living in the extreme conditions of the North.

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