ORIGINAL STUDY

HLA-гаплотипы и риск развития сахарного диабета 1 типа в популяции коренного населения Ненецкого автономного округа

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Ненцы – самодийский народ, в антропологическом плане относится к уральской контактной малой расе, для представителей которой свойственно сочетание антропологических признаков, присущих как европеоидам, так и монголоидам. В данной популяции не зафиксировано ни одного случая развития сахарного диабета 1 типа (СД1) за 50-летний период.

***Цель**. Изучить частоту встречаемости HLA-гаплотипов в ненецкой популяции в сравнении с русской.*

***Материалы и методы**. Проведено HLA-типирование у 61 здорового индивидуума ненецкой популяции, проживающих в Архангельской области, 327 здоровых индивидуумов русской популяции, проживающих в г. Москве, и 79 коренных русских в Вологодской области.*

***Результаты**. Частота встречаемости высокопредрасполагающего HLA-гаплотипа DRB1*04-DQA1*0301-DQB1*0302 практически не различалась в ненецкой, московской и вологодской популяциях, составив 11,5%, 8,5% и 11,6% соответственно ($p>0,05$). При этом частота встречаемости второго по значимости высокопредрасполагающего гаплотипа DRB1*17(03)-DQA1*0501-DQB1*0202 была достоверно ниже в ненецкой популяции – 1,6% по сравнению с 10%, 7,4% соответственно в московской и вологодской популяциях (($p_{1,2}=0,03$ ($x^2=4,42$); $p_{1,3}=0,12$ ($x^2=2,46$)). Частота специфического для двух российских популяций гаплотипа DRB1*01-DQA1*0101-DQB1*0501 была также достоверно ниже в ненецкой популяции 3,3% против 11% и 12,4% (($p_{1,2}<0,05$ ($x^2=3,34$); $p_{1,3}<0,05$ ($x^2=3,85$)).*

*Частота защитных гаплотипов (DRB1*11-DQA1*0501-DQB1*0301; DRB1*13-DQA1*0102-DQB1*0602/8/DRB1*13-DQA1*0103-DQB1*0602/8 была достоверно выше в ненецкой этнической группе по сравнению с московской и вологодской популяциями – 32,8% против 12,5% и 9,1% соответственно (($p_{1,2}<0,001$ ($x^2=13,48$); $p_{1,3}<0,001$ ($x^2=17,3$)); 16,4% против 8,5% и 11,1% соответственно (($p_{1,2}=0,07$ ($x^2=3,14$); $p_{1,3}=0,3$ ($x^2=0,97$)). Частота встречаемости ряда нейтральных гаплотипов была также достоверно выше в ненецкой этнической группе по сравнению с русской популяцией: гаплотип DRB1*12-DQA1*0501-DQB1*0301 определялся в ненецкой популяции в 29,5% по сравнению с 2,5% и 1,2% в московской и вологодской популяциях соответственно (($p_{1,2}<0,001$ ($x^2=42,43$); $p_{1,3}<0,001$ ($x^2=37,66$)); гаплотип DRB1*09-DQA1*0301-DQB1*0303 встречался в 14,8% по сравнению с 1% и 2,5% в соответствующих популяциях (($p_{1,2}<0,001$ ($x^2=21,9$); $p_{1,3}<0,001$ ($x^2=10,04$)).*

***Заключение**. По предварительным данным, в ненецкой популяции по сравнению с двумя русскими популяциями выявляется более низкая частота встречаемости двух предрасполагающих гаплотипов и более высокая частота встречаемости двух защитных гаплотипов, что, вероятно, вносит свой вклад в низкую подверженность СД1 у ненцев.*

***Ключевые слова:** HLA-гаплотипы; ненецкая этническая группа; русская популяция*

HLA-haplotypes and the risk of developing type 1 diabetes mellitus in the native population of the Nenets Autonomous district

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Nenets are Samoyedic people belonging to Ural contact minor race, with combined anthropological signs of both Caucasoid and Mongoloid races. In this population, the occurrences of type 1 diabetes mellitus (T1DM) were registered during 30 years.

***Aim**. The study aimed to investigate the incidence of human leucocyte antigen (HLA)-haplotypes in Nenets compared with those in the Russian population.*

Received: 24.06.2016. Accepted: 25.02.2017.

Materials and Methods. *HLA-typing was performed in 61 healthy Nenets subjects residing in the Arkhangelsk district, 341 Russian subjects from Moscow and natives from the Vologda district.*
Results. *DRB1*04-DQA1*0301-DQB1*0302 was similar in all the three study populations: 11.5%, 8.5% and 11.6% for Nenets, Moscow and Vologda populations, respectively ($p > 0.05$). However, the incidence of the second most important high predisposed haplotype DRB1*17(03)-DQA1*0501-DQB1*0202 was significantly lower in Nenets (1.6%) than in the Moscow and Vologda populations (10% and 7.4%, respectively) [($p1.2 = 0.03$ ($x^2 = 4.42$); $p1.3 = 0.12$ ($x^2 = 2.46$)]. The incidence of DRB1*01-DQA1*0101-DQB1*0501 haplotype specific for both Russian populations was also significantly lower in Nenets (3.3%) than in the Moscow and Vologda populations (11% and 12.4%, respectively) [($p1.2 < 0.05$ ($x^2 = 3.34$); $p1.3 < 0.05$ ($x^2 = 3.85$)]. The incidence of protected haplotypes (DRB1*11-DQA1*0501-DQB1*0301 and DRB1*13-DQA1*0102-DQB1*0602/8/DRB1*13-DQA1*0103-DQB1*0602) was significantly higher in Nenets than in the Moscow and Vologda populations: 32.8% versus 12.5% and 9.1%, respectively [($p1.2 < 0.001$ ($x^2 = 13.48$); $p1.3 < 0.001$ ($x^2 = 17.3$)] and 16.4% versus 8.5% and 11.1%, respectively [($p1.2 = 0.07$ ($x^2 = 3.14$); $p1.3 = 0.3$ ($x^2 = 0.97$)]. The incidence of some neutral haplotypes was also significantly higher in Nenets: haplotype DRB1*12-DQA1*0501-DQB1*0301 was detected in 29.5% of Nenets compared with 2.5% and 1.2% of the Moscow and Vologda populations, respectively [($p1.2 < 0.001$ ($x^2 = 42.43$); $p1.3 < 0.001$ ($x^2 = 37.66$)]; haplotype DRB1*09-DQA1*0301-DQB1*0303 was detected in 14.8% of Nenets compared with 1% and 2.5% of the Moscow and Vologda populations, respectively [($p1.2 < 0.001$ ($x^2 = 21.9$); $p1.3 < 0.001$ ($x^2 = 10.04$)].*
Conclusions. *According to preliminary evidence, the incidence of predisposed haplotypes was significantly lower and that of protected haplotypes was significantly higher in Nenets than in the Moscow and Vologda populations, which probably play a role in the very low incidence of T1DM in Nenets.*
Key words: *HLA-haplotypes; Nenets ethnic group; Russian population*

Regional variation in the incidence of type 1 diabetes mellitus (T1DM) can be explained by genetic differences in populations and environmental factors [1, 2]. Population and genetic studies allow the evaluation of the impact of genetic factors on the disease incidence in various human populations, as well as to predict its dynamics in response to environmental changes [3]. Although multiple genes are implicated in the vulnerability to T1DM, the main components of genetic predisposition in all studied populations are the polymorphic alleles of HLA class II genes (*DRB1*, DQA1*, DQB1**). They contain about 60% of the genes involved in disease development [4]. Both predisposing and protective alleles and their combinations (forming DRB1–DQ haplotypes and genotypes) have been identified. Some authors demonstrated that the maximum diabetogenicity of the HLA class II locus is determined by the haplotype and genotype [4, 5]. The analysis of genetic predisposition to T1DM in different population requires an investigation of haplotypes and genotypes.

The results of a multicenter European study indicate that geographic differences in the incidence of T1DM in Europe are partially caused by variations in the frequencies of two main predisposing HLA genotypes: the *DR4-DQA1*0301-DQB1*0302* and the *DR3-DQA1*0501-DQB1*0201* [6]. The highest prevalence of these genotypes was observed in Northern Europe, where the incidence of T1DM is also high, while in Southern Europe their prevalence (as well as T1DM incidence) was lower.

The frequency of the HLA predisposing haplotypes (the *DRB1*03-DQB1*02* and the *DQB1*0302*) was also explored in the populations with minimum and maximum T1DM incidence in Europe: in Romania (3–4 per 100,000 children) and in Sardinia (35 per 100,000). It was found that the frequency of these haplotypes was significantly lower in Romania (15.8%) compared to Sardinia (31.3%) [7].

The most diabetogenic and protective HLA haplotypes specific for Caucasians and Orientals have been identified [8]. There is a substantial inter-ethnic and even inter-populational difference both in the spectrum of diabetogenic polymorphisms, and the degree of their association with the disease. The *DQA1*0501-DQB1*0201* and the *DQA1*0301-DQB1*0302* haplotypes are known as highly predisposing among people from Europe and Russia, whereas it is the *DRB1*07-DQA1*0301-DQB1*0201* haplotype in Afro-Americans. In the Japanese, the *DRB1*09-DQA1*0301-DQB1*0303* haplotype is key, while in China, it is the *DRB1*04-DQA1*0401-DQB1*0302*. The *DRB1*15-DQA1*0602-DQB1*0102* haplotype is protective in most of the populations [9].

Low T1DM incidence in Japan and in South-East Asia was tightly connected to the absence of the *DRB1*03-DQB1*020*1 and the *DRB1*04-DQB1*0302* haplotypes, which are strongly associated with T1DM in European populations [10]. The main predisposing HLA haplotypes in the Japanese and Korean populations were the *DRB1*0405-DQB1*0401* and the *DRB1*0901-DQB1*0303* [11].

The prevalence of T1DM among people of the Mongoloid race is low and accounts for approximately 0.01%–0.02% [8, 12, 13]. It is 10–30 times lower than its prevalence among people of the Caucasian race. According to T.P. Bardymova, Mongoloid populations in the Russian Federation are also characterised by a low incidence and prevalence of T1DM: 0.73 and 24 per 100,000, respectively [14].

As the members of Mongoloid group, the Nenets are characterised by a low incidence of T1DM. They live along the Eurasian coast of the Arctic Ocean, from the Kola

Peninsula to Taimyr. Modern Nenets originate from the Samoyed tribes of the Sayan highlands and aboriginal tribes of the circumpolar zone, which inhabited the territory of the Ob-Yenisei basin. The Nenets belong to the Ural race, members of which have anthropological features of both Europeoids and Mongoloids. Due to the dispersed settlement, Nenets are divided into several groups, demonstrating a trend for decreased Mongoloidity from East to West.

The European Nenets live in the Nenets Autonomous Area located in Arkhangelsk region, whereas the Siberian Nenets live in the Yamalo-Nenets Autonomous Area in the Tyumen region and in the Taimyr Dolgan-Nenets Autonomous Area of the Krasnoyarsk region. Small groups of Nenets reside in the Khanty-Mansi Autonomous Area, in the Murmansk and Arkhangelsk regions, and the Komi Republic.

The Nenets represent the most numerous group of indigenous peoples of the Russian North [15]. According to the 2002 Census data, 41,302 Nenets live in Russia. Currently, 8,302 ethnic Nenets live in the Nenets Autonomous Area (NAA), with a total population of 41,657 people. Four hundred and eighty two Nenets reside in the municipal unit 'Timanskiy' (includes settlements 'Indiga' and 'Vyucheyskiy'), where we arranged the collection of biomaterial.

Aim

To assess the frequency of HLA haplotypes in the population of Nenets living in the NAA compared to the Russian population.

Materials and methods

Between 1981 and 2014, 4,080 Nenets were born in the NAA. Long-term observations show that no cases of T1DM have been registered in the Nenets population from the NAA (both children and adults) during the last 50 years.

Molecular genetic testing was done on 61 healthy people from the Nenets population (living in Indiga and Vyucheyskiy settlements, NAA, Arkhangelsk region), 327 healthy people from the Russian population (living in Moscow), and 79 native Russians (inhabitants of the Vologda region for three generations)

Genomic DNA was extracted from the lymphocytes of peripheral blood using a phenol-chloroform extraction technique after initial treatment with proteinase K. Multi-primer allele-specific polymerase chain reaction (using the kits produced by 'DNA-Technology', Russia) was used for HLA-typing. HLA polymorphisms were defined in accordance with a generally accepted nomenclature [12]. The relative risk was calculated using the formula from J.M. Bland [13]. All participants gave their informed consent prior to inclusion in the study. The study was approved by the Local Ethic Committee of the Endocrinology Research Centre (2013).

Results and discussion

Calculation of epidemiological indices

It is known that 4,080 Nenets children were born in the NAA between 1981 and 2014 (during 23 years, an average 177,4 newborns per year). Presuming that the number of births per year did not vary significantly during the 50 years of observation, we can assume that 8,869.6 Nenets children were born during this period. In the case of 100% survival until 18 years of age (childhood and adolescence), the child population should comprise $8,869.6 \times 17 = 150,783$. Since no cases of T1DM were observed in the Nenets during the 50 years of observation, we can assume that the incidence and prevalence of the disease is 0 per more than 100,000 children.

In the Russian Federation, the average incidence of T1DM in children is 12 per 100,000, with a prevalence of 72.8 per 100,000. In adolescents the incidence and prevalence are 15.26 and 92.6 per 100,000, respectively, although the rates vary significantly between the regions (Fig. 1). In the Northwestern region of the country (where both the NAA and Vologda region are located),

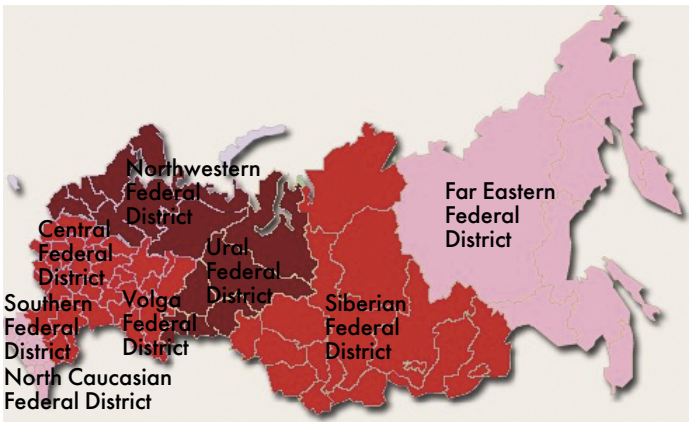

Fig. 1. Incidence of T1DM in children in different regions of the Russian Federation.

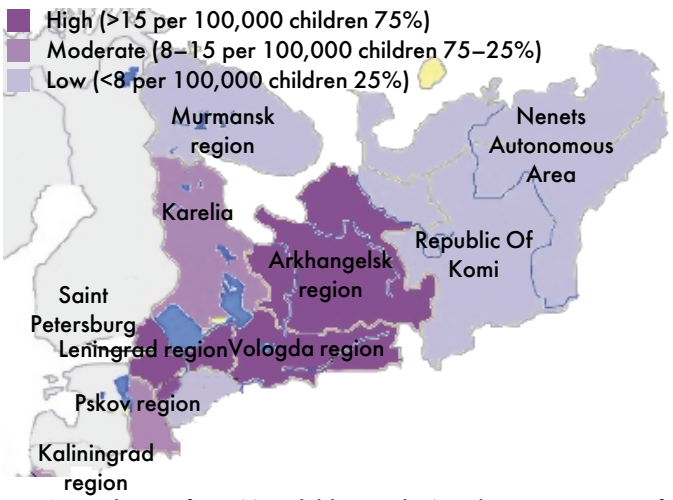

Fig. 2. Incidence of T1DM in children in the Northwestern region of the Russian Federation.

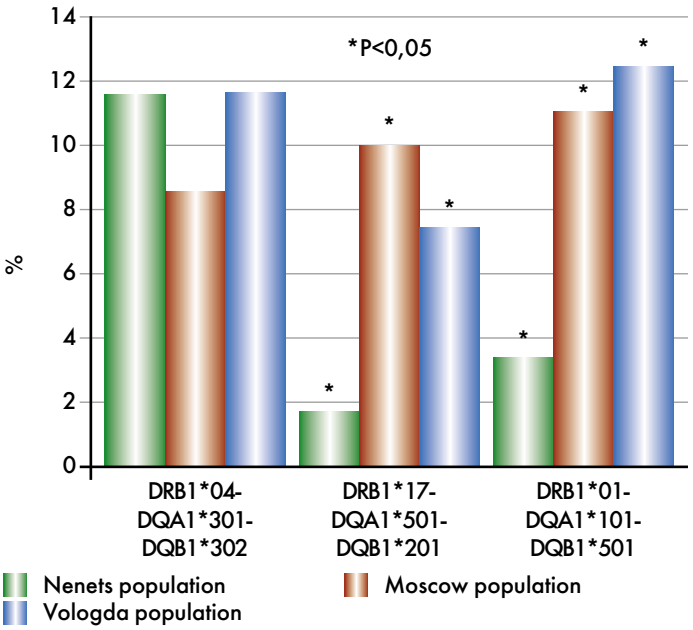

Fig. 3. Frequency of some of the predisposing HLA haplotypes in the population of Nenets compared to the Russian populations.

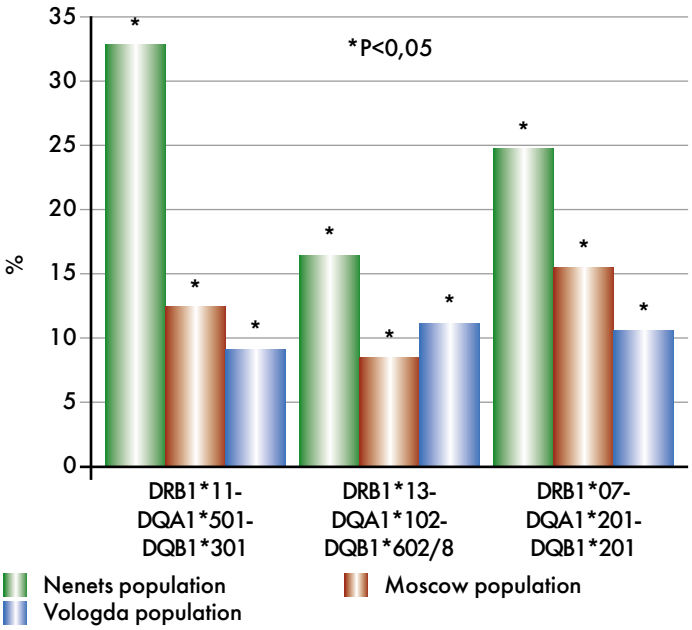

Fig. 4. Frequency of some of the protective HLA haplotypes in the population of Nenets compared to the Russian populations.

the incidence is 15 per 100,000 children [13]. There are variations of the parameters within the area with the maximum incidence (reaching 30 per 100,000) in Saint Petersburg, Arkhangelsk and the Vologda regions (Fig. 2). The NAA has a low T1DM incidence, likely due to the Nenets population.

Molecular genetic analysis

We have assessed the frequency of predisposing and protective HLA-alleles and haplotypes in the population of the ethnic Nenets and in two Russian populations.

The frequency of the highly-predisposing haplotype *DRB1*04-DQA1*0301-DQB1*0302* did not vary significantly between the Nenets, Moscow, and the Vologda populations, and comprised 11.5%, 8.5% and 11.6%, respectively ($p > 0.05$). The frequency of the second most important predisposing haplotype *DRB1*17(03)-DQA1*0501-DQB1*0202* was significantly lower among the Nenets (1.6%) compared to the participants from Moscow (10.0%) and Vologda (7.4%) ($p1,2 = 0.03$ ($\chi^2 = 4.42$); $p1,3 = 0.12$ ($\chi^2 = 2.46$)) (Fig. 3). The frequency of the *DRB1*01-DQA1*0101-DQB1*0501* haplotype (specific for the two Russian populations) was also lower in the Nenets group (3.3%) versus the Moscow (11.0%) and the Vologda (12.4%) groups ($p1,2 < 0.05$ ($\chi^2 = 3.34$); $p1,3 < 0.05$ ($\chi^2 = 3.85$)).

The analysis of the protective haplotypes showed that two (the *DRB1*11-DQA1*0501-DQB1*0301* and the *DRB1*13-DQA1*0102-DQB1*0602/8/DRB1*13-DQA1*0103-DQB1*0602/8*) were significantly more frequent in the Nenets ethnic group compared to the Moscow and Vologda populations (the frequency of the first haplotype was 32.8%, 12.5% and 9.1%, respectively ($p1,2 < 0.001$ ($\chi^2 = 13,48$); $p1,3 < 0.001$ ($\chi^2 = 17.3$)). The frequency of the second haplotype was 16.4%, 8.5% and 11.1%, respectively (($p1,2 = 0.07$ ($\chi^2 = 3.14$); $p1,3 = 0.3$ ($\chi^2 = 0.97$)) (Fig. 4).

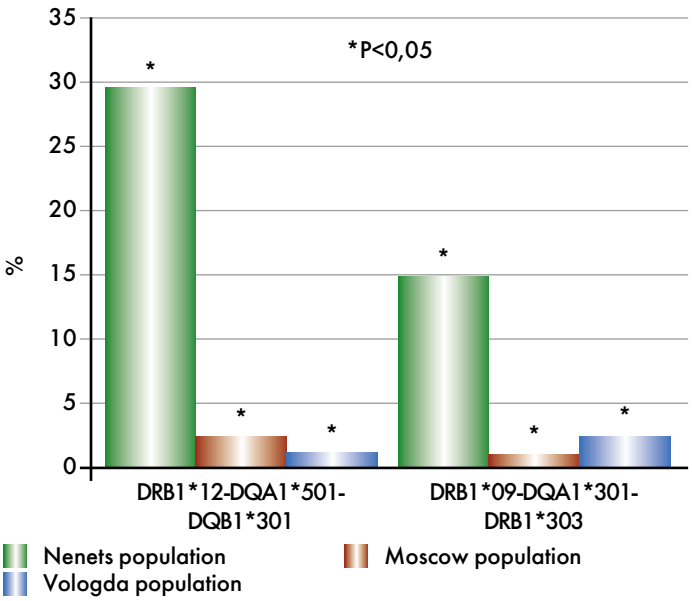

Fig. 5. Frequency of some of the neutral HLA haplotypes in the population of Nenets compared to the Russian populations.

The frequency of neutral haplotypes was also significantly higher in the Nenets compared to the Russians. The neutral haplotype *DRB1*12-DQA1*0501-DQB1*0301* was detected in 29.5% of cases in the Nenets population vs. 2.5% and 1.2% of cases in the Moscow and Vologda populations, respectively (($p1,2 < 0.001$ ($\chi^2 = 42.43$); $p1,3 < 0.001$ ($\chi^2 = 37.66$)). The second neutral haplotype *DRB1*09-DQA1*0301-DQB1*0303* was found in 14.8% of Nenets, 1.0% and 2.5% of the participants from Moscow and Vologda, respectively (($p1,2 < 0.001$ ($\chi^2 = 21.9$); $p1,3 < 0.001$ ($\chi^2 = 10.04$)) (Fig. 5).

The Nenets ethnic group residing in the NAA geographically and genetically belongs to the Mongoloid race. No cases of T1DM were registered in this population during the 50 years of observation.

Preliminary data suggest a lower frequency of the two predisposing haplotypes and a higher frequency of the majority of the protective and neutral haplotypes in the Nenets population compared to the Russian populations. This phenomenon likely contributes to the Nenets' low susceptibility to T1DM. The first results of HLA-typing in Northern peoples (Nenets, Pomors and Saami) and the comparative analysis of these ethnic groups were published in 2002 [18].

Significant genetic variations in some ethnic groups with different incidence of the disease were observed in the Russian Federation [19–22]. They are reflected in the presence of HLA specificity of separate predisposing or protective haplotypes, as well as their characteristics of relative risk.

These variations were detected within a single population: a mixed Russian population living in the European part of Russia, and ethnic Russians living in the Vologda region (for at least three generations). They were characterised by having the highest incidence of T1DM in the country. The new haplotype *DRB1*04-DQA1*301-DQB1*304* was associated with the disease in both groups with a RR of 4.0 for the Moscow population and 9.22 for the Vologda population. The RR for the *DRB1*04-DQA1*0301-DQB1*0302* haplotype was 5.99 and 4.26 in the Moscow and Vologda populations, respectively. The RR for the *DRB1*017(3)-DQA1*0501-DQB1*0201* haplotype was 4.01 and 4.21 in the Moscow and Vologda populations, respectively. The *DRB1*04-DQA1*301-DQB1*304* haplotype is a strong and specific marker of T1DM in Russians. This haplotype was not found in participants from the Nenets population; however, a larger sample is needed to get more accurate results, particularly since the haplotype was quite rare in both Russian groups (observed in 0.17% of cases in the Moscow population (n = 327) and 0% of cases in the Vologda population (n = 79)).

HLA typing of the Moscow and Vologda populations showed an increased frequency of the main predisposing haplotype *DRB1*04-DQA1*0301-DQB1*0302* in the Vologda population (11.6% vs 8.3% in the Moscow population) and a decreased frequency of the protective haplotype *DRB1*11-DQA1*0501-DQB1*0301* (9.1% vs 14.3%). Individuals within Vologda population have greater degree of genetic predisposition to T1DM, with a lower level of protection compared to the Moscow population. Our data correlates with the results of population studies on the assessment of HLA-haplotype distribution, where the Arkhangelsk and Vologda regions (characterised by high T1DM incidence) were integrated into a single cluster with Finland (known as a country with the highest incidence of T1DM in the world), and central regions of Russia combined with central regions of Europe (were incidence levels are also similar) [19, 21].

One of the possible explanations may be the variation in the genetic backgrounds in the populations. The differences in the background frequencies of HLA Class II alleles/haplotypes can be affected by several factors, including strong selective pressure on some HLA genes at the population level and a consolidation of population specific haplotypes as a result of rare episodes of recombination within HLA Class II locus during the evolution of different races (populations) [9, 22].

In Caucasoid populations, the frequency of the highly predisposing haplotypes *DRB1*0301-DQB1*0201 and DRB1*0401-DQB1*0302* reaches 11% and 6.3%, respectively, while their frequency does not exceed 1% in Asian populations. The strongest predisposing haplotypes in Asians are the *DRB1*0405-DQB1*0401* and the *DRB1*0901-DQB1*0303* observed in 12% and 4.5% of people, respectively. Their frequency does not exceed 1% in Caucasoids [8, 19]. In Asian populations, the linkage of HLA Class II genes is organised as follows: the HLA-DR4 alleles considered to be protective in Caucasoids (*DRB1*0403* or **0406*) is linked to the predisposing DQ allele (*DQB1*0302*) and the highly predisposing DR4 alleles (*DRB1*0401, *0402, *0405*) are linked to the neutral/protective DQ allele (*DQB1*0401*). Some authors suggest that the linkage of the predisposing *DRB1** alleles to protective *DQB1** alleles, and vice versa, explains the low incidence and prevalence of T1DM in Asian populations [21].

Some immunological factors may also contribute to the low incidence of diabetes mellitus in the Nenets ethnic group. Investigation of the immune system in separate northern populations revealed a low absolute number of T-cells in these people. T-lymphocytes play an important role in the destruction of the pancreatic β-cells and the development of T1DM. The population in the Arctic regions has the most severe T-cell deficiency. The Nenets are not an exception, and they demonstrate very low absolute and relative concentrations of T-cells [23].

Additionally, the indigenous people of the North have very different living conditions, lifestyle and nutrition. The main occupation is reindeer herding, hunting and fishing. There is no industrial activity in the Timan tundra. An oil terminal is currently under construction and a pipeline is planned.

Most of the population is engaged in traditional activities, although their role has slightly decreased over time (Fig. 6). The traditional household activity and its products ensure survival for the majority of the Timan tundra inhabitants. Approximately 40%–70% of the reindeer herders' diet is composed of reindeer meat and fish, with 10%–25% fowl and wild berries. The total amount of consumed reindeer meat varies between 50 and 250 kg per person per year (150 kg on average). Fish is served 2–7 times per week (depending upon the season), with the amount reaching 1 kg per day (approximately 200 kg per year). On average, each person consumes 10 litres of berries. Eggs and the meat of wild birds are eaten seasonally [24].

Fig. 6. Nenets' traditional lifestyle.

The traditional diet plays an important role in the life of the indigenous people and reflects their high vulnerability to deprivation of their traditional sources of food. Multiple factors can influence their lifestyle: deterioration of pastures, hunting and fishing areas, and a loss of the area used for plants and berries collection (due to industrial development). The replacement of traditional food by purchased foods significantly affects the overall health of the indigenous population. The traditional lifestyle and nutrition of the Nenets are currently changing. This may neutralise the protective effect of the genetic factors, resulting in the occurrence of the first cases of T1DM. According to multiple epidemiological studies, the incidence of T1DM dramatically increases with population migration from the low incidence regions to high incidence regions. This effect appears in the second and third generations of migrants [25, 26].

The preservation of the dietary habits and food behaviour in Nenets (and especially in children) should be considered as a primary measure for T1DM prevention in this population.

Conclusion

Compared to the Russian population, the Nenets have a decreased frequency of predisposing HLA haplotypes and an increased frequency of protective HLA haplotypes. These findings show the importance of genetic factors to provide a low susceptibility to T1DM in the Nenets. The effect of genetic factors is not constant and can be changed due to altered environmental factors. Lifestyle changes in the Nenets population, observed in recent years, may lead to the occurrence of the first cases of T1DM. Investigations on the relationship between T1DM and different environmental factors may expand our knowledge on the triggers for autoimmune destruction of β-cells.

The present study was conducted on a relatively small sample population. The results are preliminary, even though the differences were significant. The authors will continue the research by expanding the sampling of Nenets and the number of loci investigated (testing of additional loci associated with T1DM in the Russian population).

Additional information

Funding

The study was funded in the framework of the research projects approved by the Endocrinology Research Centre, Ministry of Health of Russia.

Conflict of interest

The authors declare no apparent or potential conflict of interest related to current article.

Authors contribution

T.L. Kuraeva–development of a research concept, data analysis, drafting the manuscript; L.A. Zubov–collection of the biomaterial in the Nenets population, drafting the manuscript; E.V. Titovich–processing of biomaterial, data analysis, drafting the manuscript; E.N. Sibileva–development of the study design, collection of epidemiological data for Nenets, drafting the manuscript; O.N. Ivanova–molecular genetic testing; T.Yu. Shiryaeva–epidemiological studies in the Russian Federation; V.A. Peterkova–development of a research concept and study design; I.I. Dedov–organisation and scientific management of the study.

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Цитировать:

Кураева Т.Л., Зубов Л.А., Титович Е.В., Сибилева Е.Н., Иванова О.Н., Ширяева Т.Ю., Петеркова В.А., Дедов И.И. *HLA*-гаплотипы и риск развития сахарного диабета 1 типа в популяции коренного населения Ненецкого автономного округа // Сахарный диабет. — 2017. — Т. 20. — №1. — С. 51-58. doi: 10.14341/DM7954

To cite this article:

Kuraeva TL, Zubov LA, Titovich EV, Sibileva EN, Ivanova ON, Shiryeva TY, Peterkova VA, Dedov II. *HLA*-haplotypes and the risk of developing type 1 diabetes mellitus in the native population of the Nenets Autonomous district. *Diabetes mellitus.* 2017;20(1):51-58. doi: 10.14341/DM7954