Genetic Testing for Hereditary Diseases with Autosomal -Recessive Type of Inheritance in the Republic of Sakha (Yakutia)

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ABSTRACT

Prevalence of some autosomal - recessive diseases in the Republic of Sakha (Yakutia) for genetic testing has been estimated. Among the Yakuts no widespread monogenic diseases such as phenilketonuria and mucoviscidos have been noted. However, there was accumulation of such rare syndromes as 3M and methhemoglobinemia type 1 with major mutation. To decrease a rate of the monogenic diseases in the republic genetic testing system of autosomal-recessive diseases has been elaborated.

Keywords: autosomal-recessive diseases at population of the world, Yakutia, DNA research, phenilketonuria, mucoviscidosis, methhemoglobinemia type 1, 3M syndrome.

INTRODUCTION

Monogenic hereditary diseases are conditionally subdivided on rare, i.e. less than one case per 10 000 newborns, and frequent – more than one case per 10 000 births. Diseases with prevalence of 1 per 6 000 newborns and more can be referred to very frequent monogenic states. As a rule, such diseases have autosomal-recessive type of inheritance. Prevalence of heterozygotic carriage of such diseases in population was noted at 1 per 35-40 the people. For the majority of territories of Russia there are four very frequent monogenic diseases: phenilketonuria, mucoviscidosis, spinal amyotrophy, neurosensor relative deafness. Approximately every tenth person of the population at least is considered as a carrier of one of them. And each person is a heterozygotic carrier of 3-10 mutant genes of autosomal-recessive diseases. In the developed countries of Europe and the USA the screening of all population at reproductive age on carriage of these diseases is carried out (Table).

In the Republic of Sakha (Yakutia) methhemoglobinemia, 3M syndrome, nanizm with optic nerves subatrophy and pelgerovsky anomaly of leukocytes, neurosensor deafness type 1A are frequent monogenic diseases with autosomal-recessive type of inheritance at Yakuts. At Slavic and other nationalities more than 46% of the population of the republic often suffers from phenylketonuria and mucoviscidosis.

Hereditary methemoglobinemy (MGE) caused by deficiency of methemoglobin reductase (Methhemoglobinemia, NADH-Cytocromeb5 Reductase Deficiency, Diaphorase Deficiency, DIA1, MIM 250800) is the autosomal-recessive disease, followed by cyanosis of integuments, mental retardation of various severity degree, a higher level of methhemoglobin and insufficiency of methemoglobin reductase in blood. Vives-Corrons with coauthors [abst. 2] allocated 2 forms of deficiency of methemoglobin reductase. At MGE type 1 there are only symptoms of MGE, fermental defect is limited by erythrocyte soluble cytochrome-b5-reductase. At MGE type 2 mental retardation is manifested, and fermental defect is generalized and affects both soluble, and a microsomal cytochrome-b5-reductase in erythrocytes and leukocytes. Shirabe [abst. 2] noted that missens -mutations at MGE type 2 are located close from the catalytic center of enzyme, it causing high decrease in its catalytic activity while mutations at MGE type 1 affect marginal part of enzyme which influences only on its stability [11].

The first research of hereditary enzymopenic methhemoglobinemia (HEM) was conducted by Zakharova F.A. in Yakutia in 1982. Among the surveyed 120 people (patients and relatives) there were 48 homozygotes, 45 heterozygotic (i.e. HEM patients) (23 of them revealed for the first time) and 12 healthy members of the families living in Yakut Autonomous Soviet Socialist Republic, and also 7 homozygous and 6 heterozygotic ones from other regions of the USSR (Moscow, RSFSR, Ukraine and Uzbekistan). Homo-and heterozygotic HEM patients were identified on the basis of determination of methemoglobin reductase activity (MGR) and MetHb content in erythrocytes, as well as data of family and clinical inspection. Heterozygotic patients had no clinical symptoms of the disease though their MHR activity was reduced on 40-50% in comparison with the norm. The main clinical manifestation of homozygote patients was cyanosis of integuments. The expressiveness of symptoms depended on the MetHb level of "valent hybrids" in blood. The general state of the surveyed was satisfactory that didn't correspond to the expressed cyanosis at some of them. In blood analyses the initial MetHb level fluctuated from 10 to 44%. No MHR activity was noted almost at all (0) [4].

Banshchikova E.S. studied 50 children with HEM who were treated in hematologic department of RH No. 1-NCM of Yakutsk [1]. All children were the Yakuts (Sakha); the greatest number of children lived in the central part of Yakutia and the Viluysky group. At all children HEM type 1 was diagnosed. For the senior age group of children complaints to fast fatigue (31.25%), headache (28.1%) were characteristic. Complaints to heartaches had direct dependence on methemoglobin level in blood, heartbeat, dyspnea (37.5%). A large number of degenerate forms of erythrocytes were detected that could testify to accelerated ageing of

erythrocytes. Among the children with HEM, a higher rate of lipids peroxide oxidation was noted with considerable weakness of antioxidant systems that can promote the prevalence of organ and fabrics hypoxia. The HEM patients underwent the treatment by means of ascorbic acid according to their age. Due to the carried-out therapy the state of children improved: the weakness and heartaches disappeared, the cyanosis decreased. The hemogram didn't change significantly, the level of methemoglobin raised up to 10-12%, but further the data didn't change and the indicators of peroxide oxidation rose moderately. Such moderate increase of peroxide oxidation atHEM patients while treated with ascorbic acid is possibly connected to the increased concentration of ascorbic acid that can cause the pro-oxidant effect and lead to undesirable effects. The children suffering from HEM are subject to dispensary supervision through the whole period of the childhood then transferred to adult network [1].

The identification of methhemoglobinemia mutation at Yakuts was carried out in laboratories of MSSC of Russian Academy of Medical Sciences (Moscow). Samples of genomic DNA of 16 patients and 8 healthy relatives from 16 Yakut families with HEM type 1 were applied for the survey. The diagnosis was verified in the Scientific Institute of Medical Genetics RAMS (Tomsk). Also samples of blood of 9 patients from 8 families suffering from methhemoglobinemia having been sent for DNA diagnostics to the laboratory of MSSC RAMS during the period from 2006 to 2012 were used. For detecting CYB5R3 gene malformation a method of direct automatic sequencing was conducted in order to study all coding area and locations of exonic-intron links of this gene of one genomic DNA proband sample, homozygous on haplotype D22S276 – D22S1178 – D22S418 – D22S1179: 4 – 4 – 1 – 5 . As the result of that survey in exone 9 a change of c.806 C>T mutation in homozygous state was detected for the first time.

The prevalence of heterozygous carriage of c.806C>T mutation among the Yakuts amounted to 55:1000. Using a Hardy-Weinberg's equation as well as basing on experimental data 2pq = 0,055 the prevalence of mutant allele in the population was determined. The calculating prevalence of the disease is equal to 1:1250 in Yakutia. The prevalence of heterozygous carriage of c.806C>T mutation was analyzed in samples of two geographically close Yakut nationalities – the Koryaks (64 chromosomes) and the Chukchi (98 chromosomes). In these samples the mutation wasn’t detected. Considering the geographical and historical neighborhood, and data about prevalence of methhemoglobinemia type 1 among the Eskimos of Alaska, a DNA of representatives of the Canadian Eskimos (78 chromosomes) was investigated. In this sample c.806>T mutation wasn’t found as well [2, 10].

Since 2006 research associates of the department of molecular genetics of YSC CMP SB RAMS optimized a PCR-method in diagnosing HEM and transferred to the laboratory of practical medicine of MGC RH №1-NCM. In total the research of Pro269Leu mutation was carried out at 522 people by the PCR method, where the homozygous state (patients with a clinical picture) was noted at 56 people while the heterozygous one being 59 relatives (parents and sibs)and no mutation being found among the rest 407 people [12].

3-M syndrome (MIM 273750) is a rare autosomal-recessive disease called by initial letters of three authors' surnames (Miller, McKusick, Malvaux), for the first time they described the syndrome in 1975. The disease is characterized by facial dismorphy, pre-and a post-natal hypoplasia of extremities and bodies with normal sizes of a head and normal intelligence, and radiological changes in bones. CUL7 gene (Cullin) causing 3-M syndrome is mapped and identified in 2005 by a group of scientists of several countries of the world. At present patients with 3-M syndrome from 29 families of various nationalities have 25 mutations in CUL7 gene. The prevalence rate of the disease in the world is unknown as only 50 clinical cases and only one case of ultrasonic diagnostics of 3-M syndrome at a fetus has been described for the last 30 years.

In the Yakut population the 3-M syndrome prevalence is high and makes about 1 case per 8600 Yakuts. Molecular and genetic research of absolute haploid genome screening, genetic mapping of a gene, identification of the 3-M syndrome mutation were carried out during 2004 to 2006 together with Japanese colleagues in the Scientific Institute of brain of the University Niigata (Japan) (the head of department of molecular neuroscience Osama Onoder). This project was approved by ethical committee of the University Niigata. We described 43 Yakut patients with the confirmed molecular and genetic diagnosis 3-M syndrome. All patients had the same 458insT nonsense mutation in 25-coding exone of Cullin 7(CUL7) gene. The only mutation and the revealed haplotype testify to effect of the founder. Among the populations of Evenks, Yukaghirs, Evens, Buryats of Buryatia, Russians of the Tomsk region no heterozygous carriers of 4582insT mutation in *CUL7* gene were revealed [8]. The method of DNA diagnostics of 3-M syndrome in the Yakut population (the patent for invention RF№2315310) was devised. Growth inhibition mechanisms at 3-M syndrome are unknown. A fetus placenta with 3-M syndrome was characterized by dissociated maturation of chorionic villae with a large number of cynsytial kidneys. At 41.9% of the Yakut patients at birth asphyxia and a respiratory distress syndrome were noted, 25,6% newborns needed neonatal emergency care because of respiration disturbance. The histologic researches of lungs manifested cartilaginous tissue hypoplasia in

bronchial medium and large caliber with villous space narrowing [13]. The Patent for the invention RF №2315310 "A method of 3-M syndrome diagnostics in the Yakut population" (date of registration of 20.01.2008) has been issued. The research associates of the department of molecular genetics YCS CMP SB RAMS developed and introduced PCR-diagnostics of 3-M syndrome in applied medicine. By appointment of a doctor geneticist in the laboratory of MGC RH№1-NCM the 3M-syndrome DNA diagnostics at nanous patients is carried out. In total 1668 people were investigated by PCR method from 2006 to 2013, 4582insTy mutation being found at 37 patients in the homozygous state (with a clinical picture), at 135 relatives (parents and sibs) in the heterozygous one, no mutation registered at 1496 people. When pregnant women suspected on 3-M syndrome in fetus ultrasonography and both spouses detected as 458insT mutation carriers, they are registered in MGC, as genetic risk of a fetus with 3-M syndrome is estimated at 25%. If a family is cooperative, the prenatal diagnostics is carried out. In a case when the fetus is homozygous, with the consent of a family fetus elimination is performed. By 2013 within the MGC RH№1-NCM the prenatal DNA diagnostics on carriage of 3M-syndrome mutation had been performed at 40 pregnant women, 11 cases of them with homozygous carriage diagnosed, 7 heterozygous carriers of 3M-syndrome revealed. In 8 cases when a fetus was homozygous on mutation, with the consent of parents it was eliminated. In 3 cases parents decided to prolong pregnancy. In 7 cases when the fetus was heterozygous, all pregnancies were preserve and continued [12].

The hereditary diseases with autosomal-recessive type of inheritance, frequent in other regions of the Russian Federation (phenylketonuria, mucoviscidosis), are included there in the list of mass neonatal screening. Phenylketonuria (PKU) is a group of the diseases, being characterized by metabolic imbalance of irreplaceable amino acid xenylamine, coming through a human body with protein food. The developed clinical picture of the disease includes mental retardation, behavioral disorder, pigmentation defect, convulsive syndrome and dermatitis. The prevalence rate considerably varies depending on the population: 1:4370 in Turkey (Ozalp Y. et al. [abst. on 2]), 1:80500 in Japan (ShigematsuY.et al. [abst. on 2]). The prevalence PKU is 1:7 697 in the Russian Federation, 1: 8 376 in Krasnodar Kray.

In MGC RY№1-NCM, according to the Republican genetic register 12 patients with phenylketonuria from 11 families with healthy parents of Slavic and other nationalities are registered. Among the Yakuts no patients with phenylketonuria has been revealed. Of 11 families 6 ones live in Yakutsk, 5 families with 6 patients in other settlements of the republic. One of the parents in all families is a native of other regions of the Russian Federation. In 2012

direct diagnostics for identifying 8 frequent mutations (*IVS10-11G>A, R261Q, R252W, R408W, IVS12+1G>A, R158Q, P281L, IVS4+5S>T)* in *PAH*gene – xenylamine hydroxylase (PKU) was introduced. DNA testing was carried out at 53 patients, as the result 18 heterozygous carriers, 3 patients with *R408W, R158Q, R408W/R408W*mutations in homozygous state were revealed.

Mucoviscidosis (cystous fibrosis; MV) is a frequent monogenic autosomal-recessive disease, being characterized by defeat of excretory glands and vital systems both having severe acute disease and prediction. The prevalence of MV varies in different European populations from 1:600 till 1:12000 (on the average 1:5000) newborns. Mucoviscidosis in the Russian Federation is 1:11 585, in Krasnodar Kray is 1:11 425 [9].

In the genetic register of MGC RH№1-NCM 6 patients with mucoviscidosis are included. In 2011 the direct DNA diagnostics of probands and parents for identification of 16 frequent mutations *Del 21kb, L138ins,3944delTG, delF508, DelI507, 1677delTA, 2143delT, 2184insA, 394delTT, 3821delT, 604insA, 3849+10kbC>T, N1303K, R334W, G542X, W1282X)* in *CFTR* gene with mucoviscidosis (MV) has started. Of 246 DNA investigated by multiplex PCR and visualized by 10% polyacrylamide gel *F508del/N* mutation in heterozygous state was detected in 11 cases, , *del21Kb/W128X* in 1, *F508del*/*F508del* in homozygous state at 3 patients.

The aim of the study is to identify heterozygotic gene carriers of frequent hereditary diseases with autosomal-recessive type of inheritance among the population in the Republic of Sakha (Yakutia).

MATERIALS AND RESEARCH METHODS

For the DNA diagnostics of hereditary enzymopenic methhemoglobinemia type 1 venous blood is used as a material of the research, as for DNA diagnostics of 3-M syndrome venous blood and fetus chorion are applied. Patients' blood collection has been carried out by filling in a questionnaire and signing an informed consent. The DNA has been extracted from leukocytes of peripheral blood by a standard method with proteinase K and subsequent phenol - chloroform extraction. Molecular and genetic diagnostics of Pro269Leu mutation in *DIA1* gene was carried out by the PCR method with original oligoprimers by means of electrophoresis in 2% agarose gel. In norm fragments of 340 and 87 base pairs have to be formed, in case of the homozygous state fragments with length 245, 95 and 87b.p. are formed. In case of the heterozygous carriage of mutation (a healthy carrier) the lengths of fragments will be 340, 245, 95 and 87 b.p.

The molecular and genetic diagnostics of 4582 insT mutation in *CUL7* gene was carried out by the PCR method with original oligoprimer by means of electrophoresis in 3% agarose gel. In norm fragments 125, 115 b.p. have to be formed, in case of the homozygous state (patient)

instead of fragments 125 and 115 a fragment with length of 240b.p. is formed. In case of the heterozygous carriage (a healthy carrier) lengths of fragments will be 240, 125, 115p.n.

As a material for the research the venous blood of 282 students at the age of 21-26 years has been tested. All students from a random sample of the Medical institute NEFU of M. K. Ammosov by Yakut nationality, were engaged in the voluntary testing, they having been informed before about the aim and tasks of this research and filled in an informed consent.

To study phenylketonuria and mucoviscidosis outcomes of neonatal screening have been taken. The neonatal screening in the republic for 2006-2013 covers 99.7%.

RESULTS AND DISCUSSION

The questionnaire results and the analysis of genealogical students have shown that no close relatives with HEM and 3-M syndrome have been revealed. Other hereditary and hereditarily liable diseases have been revealed at relatives of the first and second familial relationship: autosomal-dominant type of inheritance, cardiovascular pathology, diabetes, tuberculosis of lungs, bronchial asthma, hypertension, etc. Testing for the heterozygous carriage of methemoglobinemy was held by the PCR method while studying Pro269Leu mutation. From 282 students 13 people were diagnosed with heterozygous mutation on HEM. The prevalence of the HEM in heterozygous carriers of the Yakut population at reproductive age is 46: 1000 people, or 1 HEM heterozygous carrier: 22 people.

When studying the second hereditary disease of 3-M syndrome at students the heterozygous carriage was found out at 9 people. The prevalence of carriage of 3-M syndrome at population Sakha at reproductive age is rated at 31.3 per 1000, or 1 heterozygotic carrier of 3M syndrome on 32 people.

According to statistical data there are about 8 thousand marriages in a year all over the republic, i.e. 16 thousand men and women marry. Of them 50%, i.e. 8 thousand men and women are representatives of the Yakut nationality, who should be examined by the genetic testing for revealing heterozygous carriers of autosomal-recessive pathology [3].

For 8 thousand people of the Yakut nationality 386 people are supposed to be heterozygous carriers with HEM, and 250 heterozygotes being with 3-M syndrome. At marriage occurring by chance it is rather possible to be a heterozygous couple with identical disease as among the Yakuts there are demographic distinctive features of marriage structure, this issue having been investigated in the republic (Picture).

When studying causes of the accumulation of monogenic diseases in the republic, we have noted that remoteness of settlements with small population from each other, bad transport

network, a high level of birth rate, assortative marriage by nationalities raise conditions for the marriage of heterozygous carriers with identical recessive diseases [6,7].

The data of neonatal screening for 2006-2013 have been investigated for performance of the frequent hereditary diseases, including phenylketonuria and mucoviscidosis which are already conducted at marriage in some countries.

Of 124019 newborns who were born in the republic from 2006 to 2013, 5 patients with phenylketonuria were revealed, no Sakha patient were among them. The prevalence of phenylketonuria in the republic is 1:24803 [12]. The ethnic origin of parents in forms isn't noted. According to demographic sources [5], in the republic about 46% of the population (i.e. 57 048 newborns) concern to the Slavic and other nationalities and the prevalence of PKU among them is comparable to other regions of the Russian Federation. Thus, the PKU prevalence among newborns with the disease (the Slavs and others, except theSakha) is 1:11 404.

For 2006-2013 112164 newborns were screened for mucoviscidosis, 4 patients are revealed, all children being of the Slavic nationality, no patients of Sakha noted. The prevalence of mucoviscidosis in the republic is 1:28041 among all newborns, approximately 1:14020 among the Slavs and others [13].

The prevalence of phenylketonuria and mucoviscidosis in the republic is lower than 1: 10000, and due to a higher degree of genetic heterogeneity at phenylketonuria and mucoviscidosis it is difficult to conduct mass preventive research on heterozygous carriage of these diseases among couples. Parents of sick children with PKU and mucoviscidosis are studied for the detection of heterozygous carriage, in more complicated cases they are sent to federal centers for the purpose of prenatal diagnostics.

Taking into account that no phenylketonuria and mucoviscidosis are noted among the Yakuts, they being frequent hereditary diseases among other nationalities of the Russian Federation, it is necessary to conduct researches on heterozygous carriage in the nearer future.

CONCLUSION

The heterozygous carriage of 2 frequent hereditary diseases in the population of reproductive age has been studied. The prevalence of HEM and 3M syndrome is comparable at students of Sakha with the prevalence of population studies in the Republic of Sakha (Yakutia), carried out earlier by other researchers.

It has been revealed that:

– The accumulation of hereditarymethemoglobinemy type 1 and 3M syndrome in the republic is related to major mutations that makes easier to conduct molecular diagnostics at homo and heterozygous carriers;

- The development of the effective diagnostic testing system of frequent monogenic diseases in the Republic of Sakha (Yakutia) for definition homo-and heterozygous carriers, including HEM type 1 and 3M syndrome is recommended;

– Phenylketonuria and mucoviscidosis in populations of Europe, the USA and the Russian Federation are frequent hereditary pathology and are recommended for the genetic testing for preventive measures. The prevalence of phenylketonuria and mucoviscidosis at newborns in the Republic of Sakha (Yakutia) is lower than in other regions of the Russian Federation and in Europe.

-In accordance with the preliminary molecular researches of parents and probands with phenylketonuria the high degree of genetic polymorphism of *PAH* gene mutation is observed that complicates the planning of prenatal preventive diagnostics of this serious illness;

– The prevalence of mucoviscidosis the republic among the Slavic and other nationalities according to the preliminary data is lower than in other regions of the Russian Federation and Europe; the genetic heterogeneity is observed;

Thus, the introduction of the diagnostics of monogenic diseases into applied medicine in the Republic of Sakha (Yakutia) is carried out by research associates of YSC CMP SD RAMS, further laboratory geneticists of MGC in association with doctors geneticists carry out DNA diagnostics of patients, members of families, prenatal diagnostics at families with high genetic risk on the budgetary basis. The wide application of DNA diagnostics at frequent monogenic diseases has great social and economic value for Yakutia as the remote region of the Russian Federation. If an effective test system of heterozygous and homozygous carriage of frequent monogenic diseases for the diagnostics of marrying people is elaborated thoroughly, it will be possible to lower the rate of hereditary diseases in the republic.

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table

Prevalence of heterozygous carriage of monogenic diseases in world populations

Population	Disease	Prevalence rate
Afro-Americans	Sickle cell anemia	1:10
	Mucoviscidosis	1:65
	Beta-Talassemia	1:75
Jewish andAshkenazi	Goshe disease	1:15
	Mucoviscidosis	1:26-29
	Tay Sacksdisease	1:30
	Disautonomy	1:32
	Cana-Van disease	1:40
Asia	Alpha-Talassemia	1:20
	Beta-Talassemia	1:50
America, Europe	Mucoviscidosis	1:25-29
French-Canadian	Tay Sacksdisease	1:30
Spaniards	Mucoviscidosis	1:46
	Beta-Talassemia	1:30-50
Mediterranean	Beta-Talassemia	1:25
	Mucoviscidosis	1:29
	Sickle cell anemia	1:40
Yakuts	SOPHsyndrome	1:100
	3-M syndrome	1:33
	Hereditary enzymopenic methemoglobinemia	1:25
	APcongenital deafnessIA	1:20