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MEDICAL-GENETIC SERVICE OF THE POPULATION REPUBLIC OF SAKHA (YAKUTIA)

A.N. Nogovisyna[1,2], N.R. Maximova[1,3], A.L. Sukhomyasova[1,2],
L.I. Verbiskaya[4], T.Y. Pavlova[4]
Yakut Scientific Center of Complex Medical Problems of SD RAMS[1]
Republican Hospital № 1-National Center of Medicine of MH RS (Y) [2]
Northeast Federal University named after M. K. Ammosov[3]
Ministry of Health of the Republic of Sakha (Yakutia) [4]

Medical-genetic consultation RH№1-NCM

The main objective of the medical-genetic service (MGS) is prevention of hereditary and congenital diseases, decrease of mortality rate and disability. The medical-genetic assistance to the population represents prevention, diagnostics and treatment of hereditary pathology.

As the first structural unit in practical health care of the republic an office of medical genetics within the City Clinical hospital named after S. Ordzhonikidze was established in 1989 by the order of the minister of MH RS(Y) Mestnikov I.I. and by initiative of the Chief pediatrician Grigoryeva A.N.

Since 1993 the medical-genetic consultation (MGC) joined the Maternal health care centre (the head Nogovisyna Anna Nikolaevna), since 1998 it became the subdivision of the National center of medicine, with modern equipment for development of all types of laboratory diagnostics of hereditary pathology. Since 1999 invasive methods of prenatal diagnostics, since 2000 DNA diagnostics of monogenic hereditary diseases were elaborated. In 2000 a group of monitoring of congenital developmental anomalies was founded, the Republican register of congenital and hereditary pathology of RS(Ya) was introduced. The order of Ministry of Health of RS (Y) № 01-8/4-112 of 28.03.2001 was issued. "About further development of medical-genetic service in RS (Y)".

In the following years the consulting assistance to the population, laboratory diagnostics was actively developed (biochemical, cytogenetic, molecular and genetic), monitoring of congenital defect in the republic was introduced, the department of prenatal diagnostics (the head Sukhomyasova Aytalina Lukichna) was founded. Within the priority national Health projects expanded mass inspection of newborns on five hereditary diseases (phenylketonuria, congenital

hypothyrosis, adrenogenital syndrome, mucoviscidosis, galactosemia) were realized since 2006, prenatal diagnostics of developmental disorder on the basis of a new algorithm since 2011.

In 2010 the staff structure of MGC was expanded to 47,5 units. Within the framework of the National project and the Modernization of health care of RS(Y) the MGC facilities were improved significantly (expert ultrasonic equipment, sets for cytogenetic researches, molecular and genetic technologies.

Close work with the Scientific research institute of medical genetics of Tomsk Scientific Center SD RAMS since 1993 as well as appropriate personnel training allowed to create the MGC at a high professional level.

Now the MGC is a structure of the Prenatal center of the State Budgetary Institution RS (Y) "Republican hospital №1 - National center of medicine". The MGC incorporates a medical-genetic consulting department, a prenatal diagnostics department, an in-patient department, a group of monitoring of congenital developmental disorders, laboratories of molecular genetics, prenatal diagnostics, biochemical and cytogenetic laboratories.

The principle of organizing the medical-genetic assistance in RS (Ya) is based on its availibility to all inhabitants of the republic, co-operating with other services, first of all pediatric, obstetric and gynecologic, therapeutic, neurologic, etc. One of important forms of rendering the medico-genetic assistance in the republic is mobile consulting service together with research associates of the department of molecular genetics of CMP SD RAMS to the regions of Yakutia for the purpose of active identification of the patients needing the specialized aid. This type of the medical-genetic consultation was effective if considering the huge territory of Yakutia, accumulation of hereditary pathology in certain areas. In total over the last 10 years 79335 people (67155 families) have been examined in MGC including 37220 (47,0) rural inhabitants. In 1748 (2,6%) cases the consultations were conducted during the mobile departures to the areas of accumulation of hereditary pathology. The families burdened with monogenic hereditary pathology have been recommended to undergo thorough examination in the medico-genetic consultation.

Annually more than 3 thousand patients address to MGC for clarifying the diagnosis, 2 thousand pregnant women of risk group for forecasting health of their future posterity. In total for 2004-2013 37286 patients were examined. Among them children amounted to 20,7%. 38,7% were presented by the group of the women who had addressed to MGK for the purpose of prenatal diagnostics. Identification of congenital defect of a fetus, ultrasonic markers of

chromosomal anomalies, congenital and hereditary pathology in a family are considered the most frequent causes of addressing pregnant women.

The majority of patients addressed for the medical-genetic consultation have been directed by other experts for clarifying the congenital and hereditary pathology. The great number of patients (14699 people (39,4%) were directed from departments RH№1-NCM. 2879 people addressed for prospective consultation and for clarifying the diagnosis. The active medical-genetic consultation was carried out at 1878 people (5,0%) from the group of high risk.

The MGK formation in the structure of a leading multi-faceted medical institution of the republic provides high level of rendering medical assistance. Consultations of a geneticist and medical-genetic methods of laboratory diagnostics are conducted not only to patients and families addressed to MGC, but also to in-patients and patients from consultative departments of State Budgetary Institution RS (Ya) RH№1-NCM, it amounting to 39,4% addresses.

The medical-genetic consultation is up-dated by introduction of the automated Republican register of congenital and hereditary pathology, foundation of automated workplaces for doctors geneticists.

Modern methods of laboratory diagnostics of congenital and hereditary pathology are joined together in MGC. The technologies of genetic analyses installed in MGC are subject to all population of the republic that increase the efficiency of medical-genetic consultation. When selecting methods and types of diagnostics a range of the most frequent pathology in the region , its remoteness from the Federal centers is considered.

Now the MGC has the following equipment: a ScanRI scanner microchip (Perkin Elmer, Finland), AxioScop research class luminescent microscopes (Carl Zeiss, Germany), (Japan) with the software for cytogenetic and molecular and cytogenetic researches (G-banding, FISH, CGH) (Applied Spectral Imaging, the USA), light microscopes for cytogenetic researches, DNK-amplifiers (Bio-Rad, the USA), an amplifier for PCR in real time (Bio-Rad, the USA), registration system of images, centrifuges, microcentrifuges, thermostats, a nanospectrophotometer, a spectrophotometer, an equipment for neonatal screening, an automatic biochemical analyzer.

The opening of the Department of molecular genetics of the Yakut scientific center RAMS and RS(Ya) Government (at present YSC CMP RAMS) with laboratories of hereditary pathology, molecular and population genetics in 2002 became a significant stage in the MGC development in Yakutia. The practical help of research associates DMG in consultation is invaluable in cases difficult for diagnostics.

In 2013 the new division as a part of the Clinic NEFU named after M. K. Ammosov - Laboratory of genomic medicine (the head Maximova Nadezhda Romanovna) was established, that has made great contribution for further scientific development in practical health care for the purpose of improvement of the medical-genetic help to the population of Yakutia.

Main findings of scientific work of the department of molecular genetics YSC CMP SD RAMS for 2002 - 2013.

Genetic-demographic researches showed that for the majority of ethnic groups of the Republic of Sakha (Yakutia) positive marriage assortativity regarding birthplaces and couple's nationality is characteristic, while international marriages are widespread in settlements, mainly between indigenous people. Characteristics of vital indicators at women of the Yakut nationality in three age groups are given. Temporal variations of vital parameters and components of differential mortality and fertility are shown. For the age groups studied in this research in the content of total selection the greatest contribution is made by the component, connected with differential fertility (over 72%). The decrease in a share of differential mortality in the content of natural selection along with development of medicine can result in accumulation and fixing of negative genes in the population, i.e. increase in genetic burden (Kucher, etc., 2010).

The clinic, epidemiology and molecular reasons of autosomal - dominant myotonic dystrophy in Yakutia have been investigated. The introduction of molecular and genetic methods (PCR) in practice of medical-genetic consultation in RS (Y) has allowed not only to diagnose MD1 in informative families, but to carry out differential diagnostics with diseases with a similar phenotype as well. At present (till 2013) in the Republican genetic register of hereditary and congenital pathology of RS (Y) 202 patients with MD1 are registered, 185 patients have been consulted. (Sukhomyasova, 2005).

According to the republican Register of hereditary and congenital pathology the whole range of monogenic pathology amounts 104 nozologies including 46 diseases with AD t.n., AR pathology of 34 nozologies, 12 nozologies of X-linked-recessive and 10 X-linked dominant pathologies, 10 nozologies of syndromes with unknown t.n. The hereditary tainted and congenital pathology has been estimated, the monitoring of genetic health of the populations of the Republic of Sakha (Yakutia) has been carried out. When comparing hereditary tainted city and rural populations, higher indices on all types of inheritance are noted at rural people. Basic frequency of congenital defect of the central nervous system and chromosomal pathology at newborns of the Republic of Sakha (Yakutia) has been detected, the average frequency of

chromosomal pathology in the republic not exceeding the all-Russian. In industrial regions (Aldan, Lensk, Neryungrinsky, Mirninsky) the prevalence of Down syndrome moderately exceeds the average indices all over the republic as well as the high prevalence of this disease is revealed (in 2-3 times) in agricultural areas: Ust-Aldansky, Churapchinsky, Vilyuisky (Nogovisyna, etc., 2007).

The screening of entire haploid genome at 39 Yakut patients and 39 their relatives from 33 unrelated families has been carried out. Huber with coauthors in 2005 described 25 various mutations in *CUL7* gene at patients with 3-M syndrome from countries of the Mediterranean and Europe, but among Yakut patients it was caused by the only mutation not described earlier in *CUL7* gene. The population prevalence of the mutation 4582insT in *CUL7* gene in the Yakut population amounted to 1,5%, and the prevalence of heterozygotic carriage was 3%. The carriage of the mutation 4582insT in *CUL7* gene at Evens, Evenks, Yukaghirs from RS(Ya), Buryats from Buryatia, Russians from the Tomsk region was carried out, the mutation wasn't found among them. The patent of RF №2315310 "A way of diagnostics of 3-M a syndrome in the Yakut population" was obtained . Date of registration was 20.01.2008. The method of DNA diagnostics, algorithm of medical-genetic consultation and prenatal diagnostics is elaborated. 3M syndrome at Yakuts is as a synonym with the number #273750 *yakut short stature syndrome* in the international base of the National scientific biotechnology institute of the USA (NCBI) in the section OMIM (Online Mendelian Inheritance in Men) (Maximova, etc., 2007, 2008, 2010)

The clinical-genealogical description of a new syndrome of idiopathic short stature with cone dysfunction, atrophy of optic nerve atrophy and Pelger-Huet anomaly at the Yakuts has been presented and its prevalence in the Yakut population has been studied. This gene has been mapped for the first time and the mutation causing the syndrome of idiopathic short stature with cone dysfunction, atrophy of optic nerves and Pelger-Huet anomaly of leukocytes has been identified. The new syndrome was named SOPH syndrome (Short stature, Optic nerve atro syndrome with Cone dysfunction, Optic atrophy and Pelger-Huet anomaly). The SOPH syndrome is included into the international base of National scientific biotechnology institute of the USA (NCBI) in the section OMIM (Online Mendelian Inheritance in Men) with number #614800.

Mechanisms of accumulation of ethnospecific hereditary disease forms (syndrome OPMD, YSN, SCOP) in populations of Yakutia on the basis of haplotype construction in gene loci of the studied diseases by means of microsatellite markers have been considered. The age of

the identified mutations in CUL7 and NAG genes in the Yakut population (Maximova, etc., 2010) has been estimated.

For the first time 5 ethnospecific Yakut hereditary diseases (YHD) by two criteria determined: spinal cerebral ataxia type 1, ocular pharyngeal myodistrophy, myotonic dystrophy, methemoglobinemy, 3M-syndrome (the Yakut nanizm). First, their prevalence is much higher than in the world population, and two diseases - spinal cerebral ataxia type 1 and enzymopenic methemoglobinemy have been referred to the world centers of accumulation of hereditary diseases. Secondly, for each of them the characteristics of molecular nature have been revealed distinguishing them from similar phenotypes in other populations, the latter ones noted incomparably rarely (Puzyrev, 2008).

For the first time in the population of Yakuts by means of the disbalance analysis on coupling and the SSCP analysis with subsequent sequencing of samples with modified flexibility the molecular and genetic reason of the hereditary congenital deafness which is caused by a mutation of splicing donor site IVS1+1G>A of GJB2 (Cx26) gene and, according to the international OMIM catalog (Online Mendelian Inheritance in Men) it is classified as allelic option of autosomal-recessive deafness type 1A (ARG 1A). The prevalence of ARG 1A amounted to 16,2 per 100000 Yakut population, and the frequency of heterozygous carriage of the mutation IVS1+1G>A varies from 3,8 to 11,7% among indigenous people of Yakutia (Evens, Evenks, Dolgans, Yakuts). The findings of the research testify to the local accumulation of the mutation of splicing site of GJB2 (Cx26) gene and characterize the region of Eastern Siberia as the largest in the world "endemic center" of IVS1+1G>A distribution (Barashkov, 2010).

The DNA diagnostics has been introduced by employees DMG in practice of health care of medical-genetic consultation RH№1-NCM:

1. The new PCR method of 3-M syndrome diagnostics has been elaborated, in 2008 the patent RF "The method of 3-M syndrome diagnostics in the Yakut population" by №2315310 from January 20, 2008 was obtained. This method of DNA diagnostics is introduced into the practice of medico-genetic consultation, the prenatal diagnostics is carried out, the register of patients with 3M syndrome is created.

2. For the purpose of fast molecular and genetic diagnostics of ocular pharyngeal myodistrophy the method of direct DNA diagnostics of OPMD by means of amplification of trinucleotide gene locus by the PCR method and the electrophoresis in 8% polyacrylamide gel

(PAAG) has been introduced. The republican register of patients and members of families with OFMD is created.

3. The method of direct DNA diagnostics of Kennedy disease by means of amplification of trinucleotide site of AR gene by the PCR method and the electrophoresis in 1% agarose gel in practical health care in the laboratory of medico-genetic consultation of Republican hospital №1-NCM has been introduced. The DNA direct method of diagnostics allows to clarify the clinical diagnosis, to carry out differential and pre-symptomatic diagnostics, to reveal the heterozygous carriage among women for the purpose of early prevention and prenatal diagnostics of the disease in the burdened families and at the population level.

Monographs:

1 . Fedorova S. A. Genetic portraits of indigenous people of the Republic of Sakha (Yakutia): analysis line of mitochondrial DNA and Y-chromosome//YSC Publishing house of the Siberian Department of the Russian Academy of Science.- P. 235.

2 . Fedorova S. A. Yakuts: comparison of genetic and historical reconstruction / under the editorship of P. B. Konovalov//Ethnogenesis and culturogenesis in the Baikalsk region. 2011 . - Ulan-Ude: Publishing house of BNTs of the Siberian Branch of the Russian Academy of Science. – P.151-176.

3 . Genomic and health in the developing world. Collection. Ed. by D. Kumar. N. - Y. University Press Press, 2012. :

- Kononova S.K. Bioethical aspects of genetics and genomics in Yakut (Siberia) of in Genomics and Health in the Developing World edited by D.Kumar/S.K. Kononova, S.A.Fedorova, and Elza K. Khusnutdinova//Chapter 120, Oxford University Press: New York, P.1426-1430.

- Maximova N, Nogovisina A. Heriditary disease among the Yakuts//Collection Genomic variation and genetic disorders of developing countries Ed. by D. Kumar. N. - Y. : Oxford University Press, 2012. P.1314-1322.

- Fedorova S. Khusnutdinova E. Villems R. MtDNA and Y-chromosomal variation in populations of Sakha (Yakutia)//Collection Genomic and health in the developing world. Ed. by D. Kumar. N. - Y. University Press Press, 2012. P.1269-1280.

A list of the patents, useful models obtained by research associates DMG:

1 . The patent for invention of RF №2315310 "The method of 3-M syndrome diagnostics in the Yakut population". Maximova N. R., Nogovisyna A.N. Sukhomyasova A.L. Date of registration 20.01.2008

2 . The patent for invention No. 244863 "The way of detecting 17 mutations of GJB2 b GJB6 genes at hereditary non-syndrome deafness. Barashkov, etc. Date of registration 20.04.2012 of SI: URAN Institute of biochemistry and genetics of the Ufa Russian Academy of Sciences scientific center, URAMS the Yakut scientific center of complex medical problems SD RAMS.