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INTRODUCTION OF GENETIC TECHNOLOGIES INTO THE PRACTICAL HEALTHCARE OF YAKUTIA ON THE EXAMPLE OF SPINOCEREBELLAR ATAXIA TYPE 1 IN THE CONTEXT OF TRANSLATIONAL MEDICINE

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The article summarizes the history of scientific research translation into the practical healthcare in the Republic of Sakha (Yakutia) on the example of spinocerebellar ataxia type 1, the most common hereditary disease in the Yakut population.

In the duration of twenty years, translational medicine has developed in Yakutia, approaches to personalized medicine are being developed and the use of genomic technologies has become a reality of our time.

Keywords: spinocerebellar ataxia type 1, DNA diagnostics, genomic technologies, translational medicine.

Introduction. Undoubtedly, the most important of the many discoveries in the field of genetics at the end of the 20th century, anticipating the entry of mankind into the genomic era, are the following: DNA – the main universal molecule of the genome of living systems - was artificially altered using vector viruses and plasmids, as a result, recombinant DNA was obtained for the first time; in the 80s, a revolutionary method was discovered - polymerase chain reaction (PCR), which accelerated the development of technologies that made it possible to decipher the genome of living organisms and humans, to understand many molecular genetic mechanisms of transmission of genetic information [3.25]. Since 1999, sequencing (decoding) of the human genome has been accelerated by the use of a large number of simultaneously operating robotic installations of a company called "Celera", and in 2001 the nucleotide sequence of the human genome was fully read, systematized and made available to researchers in the field of genetics [24].

Thus, general and medical genetics received powerful research tools in the field of human molecular genetics, especially in finding out the causes (gene mutations) of hereditary diseases. Researchers began to use the genotypes of individuals as a kind of mechanism on the principle of "divide" and "study" [32]. To date, a huge number of genes responsible for many monogenic and multifactorial human diseases have been identified in the world, the structures of these genes have been fully deciphered, and they themselves have been cloned [20,27].

Genomic research has challenged society and has become the object of increased public interest in genetics in countries with different state systems, religion and culture, and, in this regard, there is a danger of misconceptions or inflated expectations from the use of genetic technologies. International public organizations (UN, UNESCO, WHO, WMA) have paid close attention to the use of genetic technologies in medical practice with the requirements to respect human rights and prevent abuse in this area of science. Bioethical research began to be conducted within one of the three general directions of the Human Genome program ELSI (Ethical, Legal and Social Implications) [18,21].

Currently, new terms related to the integration of molecular genetics and medicine have entered medical practice: molecular medicine, genomic medicine, pharmacogenetics, oncogenetics, etc., in addition, modern directions "translational

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medicine", "personalized medicine" have emerged [28,30]. In parallel, the transformation of traditional medical ethics into bioethics took place. This was due to the use of the latest medical technologies and the search for solutions to moral dilemmas that affected the basic principles of biomedical ethics: the principle of "do no harm", "do good", the principle of respect for individual autonomy, the principle of justice [19].

Translational medicine (TM) is a direction in medical science that studies the mechanisms and principles of the introduction of modern achievements (methods) of fundamental science, such as molecular genetics, cellular technologies, reproductive technologies, etc. into medical practice. Predictive and personalized medicine are closely related to translational medicine – current areas of modern medicine. For example, predictive medicine significantly reduces health care costs, and personalized medicine implies such technologies of diagnosis and treatment of the patient, in which the quality of life of the patient improves, the period of working capacity lengthens and life expectancy, as well as satisfaction with the quality of medical care provided, increases. TM is multidisciplinary in nature, closely related to biology, biomedicine and social sciences. Translational medicine has several stages of research: fundamental research; the introduction of the results of fundamental research into clinical practice, the search for more effective ways (methods) and ensuring the safety of a particular technology and/or drug treatment; evaluation of the effectiveness of a new technology introduced into medical practice and its economic output [12,16,22].

In the early 2000s, methods of molecular genetic diagnostics (DNA diagnostics) of monogenic diseases were introduced for the first time in the Republic of Sakha (Yakutia). The purpose of this article is to summarize the history of translation of molecular genetic technologies into the medical practice of Yakutia over a 20-year period by the example of the most common hereditary disease in the Yakut population - spinocerebellar ataxia type 1.

Translation of genomic technologies into clinical practice in Yakutia on the example of spinocerebellar ataxia type 1 (SCAI)

1. Fundamental epidemiological, population and molecular genetic studies of SCA1 have been carried out, geno-phenotypic characteristics of the disease have been established.

Hereditary cerebellar ataxia (HCA), classified as one of the clinical forms of Vilyuisk encephalomyelitis, was isolated into an independent nosology as a neurodegenerative hereditary disease in the 70s of the last century [4,7]. In 1992, an in-depth study of HCA began within the framework of the state research program "Biology of Vilyui encephalomyelitis". Joint project of the Neurogenetics Department of the National Institute of Nervous Diseases (NINDS/NIH) of The United States and the research and practical center for Vilyuisk encephalomyelitis of the Republic of Sakha was named: "Identification of genes and genetic mechanisms that cause hereditary neurological diseases". In 1993 , the work of Dr. H. Orr et al on identification of the Spinocerebellar ataxia type 1 (*SCA1*) gene was published [33], and in 1994 - the results of the molecular-genetic study of HCA in the Yakut population was published as well, which revealed an allelic association of highly informative markers D6S274 and D6S89 flanking the locus of the *SCA1* gene on the 6th chromosome, with HCA. A strong association was observed in the case of the microsatellite D6S274, whereas coupling with the marker D6S89 was observed only in 2 families, suggesting a possible historical recombination and the far-off time of mutation in the population [29]. Population studies and the propagation frequency of the disease have established HCA as the largest Siberian focus of accumulation of the disease known in the world and identified it as Spinocerebellar ataxia type 1 (SCA1) [23]. According to F.A. Platonova (2003) the prevalence of SCA1 in the Yakut population is 38.6 per 100,000. The detection of homozygotes by the mutant allele of the SCA1 gene confirms the extremely wide propagation of the disease for hereditary dominant pathologies of the central nervous system [14,15].

2. Approaches to the use of DNA diagnostics of SCA1 have been studied

For the first time in 1999, preparations were made for the introduction of DNA diagnostics of SCA1 in the molecular genetic department of the clinical laboratory of Medical Genetic Consultation (MGC) of the Republican Hospital No. 1 (National Center of Medicine). Regulatory documents, orders and instructions of the Ministry of Health of the Russian Federation on the molecular genetic diagnosis of hereditary diseases were not developed at that time, respectively, we adopted our own algorithm for DNA diagnostics of SCA1 as a routine clinical analysis: referral of the patient for DNA analysis, the stages of the method of DNA isolation from peripheral blood lymphocytes, PCR and electrophoresis of amplification products, documentation of the results and its issuing to the clinical department of MGC. The duties of a medical laboratory doctor/biologist, laboratory assistant and orderlies of the molecular genetic department of the MGC were differentiated [2,8].

3. The method of direct DNA diagnostics of SCA1 has been introduced into the practice of medical and genetic consultation of the Republican Hospital No. 1.

Spinocerebellar ataxia type 1 belongs to the group of hereditary neurodegenerative diseases with dynamic mutations and late manifestation. The mutation is an uncontrolled increase in CAG repeats in the coding part of the SCA1 *gene*. Normally, the number of repeats is 25-33, pathological alleles contain 39-72 repeats.

Currently, according to the Republican Genetic Register of Hereditary and Congenital Pathology of the Republic of Sakha (Yakutia), 401 patients with SCA1 have been registered[5,13].

The detection of a mutation in the *SCA1* gene was carried out by direct DNA diagnostics by PCR with subsequent visualization of DNA fragments in agarose gel. Fig. 1

According to published data, from 2000 to 2013, at the MGC of the Republican Hospital No.1 - DNA testing was performed in 1,841 patients, a dynamic mutation in the SCA1 gene *was* detected in 606 patients (33%)[6].

4. Prenatal DNA diagnostics (PD) of SCA1 has been introduced into the clinical practice of the MGC.

We analyzed the demand for PD technology for burdened families (n =36 people) from 2002 to 2008 [10,11]. There were 46 referrals in total, of which 7 women underwent prenatal DNA testing several times (4 women – twice and 3 women – 3 times). There were more refusals from PD than consents, so 25 PD procedures were carried out over 6 years, of which in 12 cases a mutation of SCA1 was detected in fetuses: 10 pregnancies with a positive result (the presence of a mutation) were terminated with the consent of the families, 2 pregnancies were preserved. Table 1.

5. Ethical rules of DNA testing have been introduced into the practice of the MGC

The final third phase of the translation of genomic technologies into the healthcare system, according to researchers, is the revision and development of legal and bioethical norms, taking into account the use of molecular genetic diagnostics, as well as the establishment of recommendations for the effective and safe use

of new medical technologies in order to satisfy the patient with the process of providing medical care [12].

Introduced for the first time in the Republic in the year 2000. DNA diagnostics of SCA1 immediately acquired the status of routine clinical analysis, at the same time there was a need to develop bioethical rules for the use of genetic technologies in the medical practice of the MGC. This was the beginning of scientific research on applied bioethics in the Republic of Sakha (Yakutia).

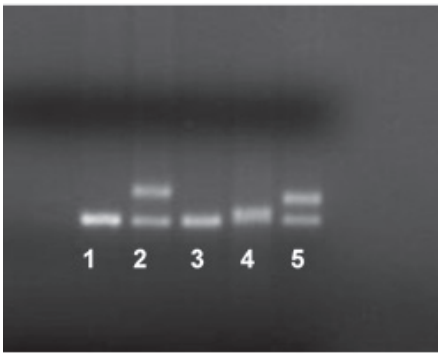
Thus, for the first time, we have developed and implemented bioethical rules for genetic counseling, DNA testing and prenatal diagnosis of SCA1[1,17,26] in the practice of medical and genetic counseling of the Republican Hospital No. 1.

6. The Center for Neurodegenerative Diseases was organized in the clinic of the Yakut Scientific Center for Complex Medical Problems (YSC CMP).

SCA1 is a disease with a progressive neurodegenerative process that leads the patient to disability and social maladaptation. Patients with SCA1 need medical examination, psychological, social assistance and hospital treatment at least twice a year. A study conducted in 2019 showed an insufficient number of inpatient beds that would meet the needs of patients with neurodegenerative diseases (NDD) in the Republic[9]. In this regard, in pursuance of the order of the Ministry of Health of the Russian Federation "On approval of the procedure for providing medical care to adults with diseases of the nervous system" (No. 926n dated 11/15/2011), the Ministry of Health of the Republic issued an order "On the procedure for routing neurological patients suffering from neurodegenerative diseases at the outpatient and inpatient stages" (No. 01-07/184 dated 02/14/2019). Thus, the specialized Center for Neurodegenerative Diseases opened in 2019 at the YSC CMP with a personalized approach to patients is an improved model of providing medical care to patients with NDDs and an example of successful consolidation of medical science and practical healthcare in the Republic[9].

7. The Association of patients with SCA1 and other neurodegenerative diseases has been established

The Association was established to provide medical, social and psychological assistance to patients with NDDs and their relatives. The objectives of the organization are to consolidate the support of social partners to overcome the problems of NDDs in the Republic, informing patients, relatives and society, legal protection of patients with NDDs. On January 17, 2020, a Certificate of state registration of a non-profit organization of the regional public organization "Association of Patients with spinocerebellar ataxia type 1 and other neurodegenerative diseases in the Republic of Sakha (Yakutia)", registration number 1201400000757 was received. With the support of the Presidential Grants Foundation of the Russian Federation and the grant of the Head of the Republic of Sakha (Yakutia), the necessary medical equipment and consumables were purchased, scientific and practical medical expeditions are conducted to assess the health of patients in the areas of the greatest accumulation of NDDs, as well as lectures, seminars, radio and television appearances, publications in the press.



Direct DNA diagnostics of SCA1 in 2% agarose gel: 1, 3, 4 – healthy patients, 2 – a patient with a known number of CAG repeats of 30/50; 5 – a patient with an elongated allele of the SCA1 gene

8. The NDD Center develops methods of physical rehabilitation of patients with SCA1

Patients suffering from NDZ have low motivation to engage in physical education, because firstly, there are many external obstacles, primarily the lack of an accessible environment for recreational activities; secondly, patients have psychological problems (fear, embarrassment, disappointment); thirdly, patients are demotivated by physical ailments (muscle weakness, stiffness, unsteadiness of gait, etc.). At the same time, studies have proved that the targeted use of physical exercises improves the impaired functions of the body, and has a general healing effect[31]. Currently, scientifically based approaches to the physical rehabilitation of patients with SCA1 are being developed using modern methods such as stabilometry.

Conclusion. An example of successful translation of scientific studies of spinocerebellar ataxia type 1, the most common hereditary disease in the Yakut population, into practical healthcare of the Republic of Sakha (Yakutia) is presented. Population-genotypic studies of SCA1 were carried out, the DNA diagnostic method was introduced into the practice of medical genetic counseling at the Republican Hospital No. 1 of the National Center of Medicine, prenatal DNA testing of SCA1 is used, bioethical rules of medical genetic counseling are applied, the Center for Neurodegenerative Diseases and the Association of Patients with SCA1 and Other NDDs were creat-

Prenatal diagnosis of spinocerebellar ataxia type 1

Medical and social characteristics	Results of PD SCA1 (n=36)
Age	19 -40 лет
Education: higher(%)/secondary (%)	22 (61) / 8 (22)
Accommodation: city (%)/village (%)	11 (30) / 25 (69)
Burdened inheritance by line: mother(%)/father(%)/ husband(%)	10 (28) / 10 (28) / 11 (30)
Presence of clinical manifestations of the disease: yes (%)/no (%)	1 (3) / 24 (96)
The family's decision on the proposed PD: consent(%)/ rejection(%)	16 (44) / 20 (56)
Number of PD requests: total (%) / repeated(%)	46 (100) / 7 (15)
The term of pregnancy when applying: 1st trimester(%)/2nd trimester(%)	26 (57) / 20 (43)
The number of PD performed invasively	25
Prenatal DNA testing results: negative(%)/positive(%)	13 (52) / 12 (48)
Pregnancy outcome in the presence of fetal mutation: preservation (%)/termination(%)	2 (17) / 10 (83)
Terms of termination of pregnancy in the presence of a mutation in the fetus: 1st trimester (%) / 2nd trimester (%)	5 (50) / 5 (50)

ed. Approaches to the development of predictive and personalized medicine are being studied. As we can see, transition of research from the laboratory to the clinic does not happen quickly, translational medicine has been developing in Yakutia for twenty years, molecular genetic diagnostic methods are becoming routine, but at the same time it is necessary to continue research on the problems of using genomic technologies in practical medicine.

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