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DNA DIAGNOSTICS IN CLINICAL PRACTICE APPLIED TO TRANSLATIONAL MEDICINE

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The review presents examples of the translation of genomic studies into practical medicine of two common European hereditary diseases - autosomal recessive cystic fibrosis and autosomal dominant Huntington's chorea. With the development of genetic technologies in the Republic Sakha (Yakutia), translational medicine is becoming a reality, and it is necessary to outline the approaches and problems in this field of research using the examples of type 1 spinocerebellar ataxia and type 1A autosomal recessive deafness which are frequent in the republic.

Keywords: translational medicine, hereditary diseases, DNA diagnostics, patient.

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Introduction. So-called translational studies are becoming increasingly more developed as of lately. Translational medicine is a modern multidisciplinary science that will have a leading role in the development of genomic medicine. Translational medicine can be considered as a process involving the transfer of discoveries made as a result of fundamental research in biomedicine into medical practice in order to improve diagnosis and treatment [11, 38].

The National Institutes of Health (USA) proposed the following definition of translational medicine: "translational research includes two areas of translation, the first of which is to bring the results of discoveries made in laboratories and preclinical studies to the stage of clinical research and human studies; the second area of translation is associated with research aimed at increasing the efficiency of introducing advanced technologies into wide medical practice"[22]. In accordance with this definition, translational studies are part of a unidirectional continuum in which research results move from the experimenter's laboratory table to the patient's bed and to society as a whole [17].

In turn, translational genomic research can be included in translational medicine. Translational genomic research is centered around the development of evidence-based guidelines [32]. The whole process includes at least three phases. The first phase is fundamental genomic research carried out by qualified specialists in specialized molecular genetic laboratories at research centers or universities. The second phase is the translation of the discoveries and achievements of genomic research and the development of approaches to the application of the results of genetic research in practical medicine, the assessment of their effectiveness and safety, as a rule, is done with the help of clinical trials conducted in specialized medical centers associated with research institutions [36]. The third phase is the conclusive step for the implementation of translational genomic research into the healthcare system, and, very importantly, this process also includes the revision and development of legal and bioethical norms, taking the application of genomic technologies in practice into account. The final stage establishes adequate recommendations for the optimal, safe and efficient use of new medical technologies in order to improve public health [12].

In this review, we **aim** to display examples of the translation of genomic studies into practical medicine of two common European hereditary diseases - autosomal recessive cystic fibrosis (CF) and autosomal dominant Huntington's chorea (HC). With the development of genetic technologies in the Republic of Sakha (Yakutia), translational medicine is becoming a reality, and it is necessary to outline the approaches and problems in this field of research using the examples of type 1 spinocerebellar ataxia (SCA1) and type 1A autosomal recessive deafness (DFNB1A) which are frequent in the republic.

Cystic fibrosis (CF). In European populations, cystic fibrosis occurs with a frequency of 1: 2500, while in Asian populations it is equal to 1: 90,000. If a frequent monogenic disease acquires social significance, a need for a number of measures to prevent the hereditary disease from spreading appears. A spectrum of more than 1900 different mutations of the *CFTR* gene has been described in 25394 patients from 23 European countries [40]. A permanent European Cystic Fibrosis Society Patient Register (ECFSPR) has been created that collects, quantifies and compares data on CF patients living in Europe and neighboring countries who agree to be included in the registry. This is done in order to better understand CF, develop new European standards for care and treatment, conduct research and treatment (https://www.ecfs.eu/projects) [45]. The CF gene is mapped on the long arm of chromosome 7 (7q31.1) in 1985. At the end of 1989, the CF gene itself was identified. The protein product of this gene was characterized, which was called the "Cystic Fibrosis Transmembrane conductance Regulator" (*CFTR)* and the most frequent mutation was revealed — a deletion of phenylalanine at the 508 position of the amino acid sequence of the protein (delF508), leading to the disease [28,29]. In addition to deletions, many other mutations have been detected in the CFTR gene. Unlike delF508, the vast majority of them are represented by sporadic cases, that is, they are quite rare. By the end of 2006, more than 1,500 point mutations, several deletions and duplications were identified in the *CFTR* gene.

The neonatal screening protocol for CF in the Russian Federation includes 4 stages: determination of immunoreactive trypsin (IRT1), re-determination of immunoreactive trypsin (IRT), sweat test and DNA diagnostics, and only the first three stages are mandatory in the national protocol and are provided by the state. Therefore, DNA diagnostics in many cases are limited. The availability of DNA diagnostics is limited by the high cost and the small number of laboratories capable of conducting this analysis [9,14]. DNA testing of CF is carried out using diagnostic panels, for example, in the "RCMG" a panel is used that includes the most frequent mutations in the world: F508del, CFTRdele2.3 (21kb), 3849 + 10kbC> T, W1282X, 2143delT, 2184insA, 1677delTA , N1303K, G542X, R334W, E92K, L138ins, 394delTT, 3821delT, S1196X, 2789 + 5G> A, G85E, 2183AA> G, 604insA, 621 + 1G> T, R117H, R347P, R553X, 3667insTCA17, 557171TCA17, 55717TCA17, 55717TCA17, 55717TCA17, 55717 -1G> A, 2184delA. Thus, using a specially designed panel that includes 28 mutations, it is possible to detect only about 82.5% of the mutant alleles in the total sample of examined CF patients. Almost 20% of patients with CF need an additional examination to detect rarer mutations or polymorphisms, including the ones which require the usage of the sequencing method, which is not yet routinely used in the Russian Federation [14].

Huntington's chorea (HC) is a progressive autosomal dominant neuromuscular disease characterized by the development of choreic hyperkinesis and dementia. Symptoms of the disease are caused by atrophy of the putamen and the caudate nucleus in the brain of patients, associated with premature selective death of neurons. In most Russian populations, the prevalence of HC is 1 in 10,000. Significant differences are noted in relation to the age of onset and severity of the disease. Moreover, even within individual families, pronounced clinical heterogeneity is observed. When HC is inherited on the paternal side, the effect of anticipation is sometimes manifested — an increase in the severity and a decrease in the age of onset of the disease in a number of generations [6].

The *IT15* gene, in which dynamic mutations lead to the development of HC, is expressed in many types of cells and encodes a protein with a molecular mass of 348 kDa, called huntingtin. In the *IT15* coding region, at a distance of 18 codons downstream from the start of the translation, a polymorphic trinucleotide repeat (CAG)n is localized. The number of CAG repeats in the *IT15* gene normally varies from 9 to 37, while the mutant alleles of patients with HC carry 36 to 121 triplets. An inverse correlation was found between the length of the CAG repeat and the age of onset of the disease and a direct correlation with the rate of progression of clinical symptoms. The change in the length of the repeat during transmission to the offspring explains the majority of cases of anticipation [25].

Mutant alleles in the range of 36–40 triplets are characterized by incomplete penetrance. A significant number of patients with HC with a similar number of repetitions on the mutant allele have been described, and at the same time, clinically healthy individuals older than 70 can be found in the same pedigrees. Alleles with a number of CAG repeats ≥ 40 are always associated with the development of the disease. The study of the state of CAG repeats by PCR in high-risk families allows direct molecular diagnostics of the disease at any stage of ontogenesis, including the pre-symptomatic period [7]. At the same time, it is important to note that genetic counseling in families with HC (as in the case of other diseases with late manifestation) is fraught with ethical difficulties. Given the dominant type of inheritance, the risk of obtaining a mutant gene for children and siblings of a patient with HC is 50%. Naturally, the exclusion of carriage, of course, should have a positive impact on the mental state of people at risk. On the other hand, given the lack of effective methods of treatment for HC, the identification of an allele in a patient with expansion is almost the same as a death sentence. At present, it is customary to conduct a pre-symptomatic examination exclusively of adults from the risk group when they directly seek advice. A serious argument in favor of a pre-symptomatic examination of relatives of patients is the possibility of preventing the disease in high-risk families by conducting prenatal diagnosis. But if we are talking about prenatal DNA testing as a method of preventing hereditary diseases with late onset, which include HC, we cannot ignore the complex moral and ethical aspects that inevitably arise during prenatal medical and genetic counseling [18, 43].

Therefore, as shown by the practice of DNA diagnosis of HC in different countries, a very small number of burdened families agree to prenatal diagnosis. For example, in Portugal, over 5 years of research, 158 families burdened with HC conducted 338 genetic tests, of which 234 were for diagnosis, 96 for pre-symptomatic and only 4 for prenatal DNA testing [34]. In Canada, 1061 pre-symptomatic DNA tests of HC and 636 diagnostic tests were performed over 14 years, of which 15 burdened families agreed to prenatal testing [37]. In Greece, DNA testing of HC was performed in 461 people with clinical symptoms and 256 people for pre-symptomatic diagnosis. Mutation (allele extension) was confirmed in 278 individuals. Prenatal diagnosis was carried out in 6 cases [27]. The authors note that the main reasons for rejecting prenatal diagnosis are the hope of developing treatment for HC and the reluctance to terminate the pregnancy for psychological reasons [24].

Spinocerebellar ataxia of the 1st type belongs to the group of neurodegenerative diseases with late manifestation. Inheritance is characterized by a high degree of penetrance, the phenomenon of anticipation. The mutation of the *SCA1* gene located on the short arm of the 6th

chromosome consists in an uncontrolled increase in the number of trinucleotide CAG repeats in the coding region of the gene. The clinical manifestations of the disease are very diverse, the main ones are: a slow progressive loss of coordination of movements and speech, the presence of the cerebellar-pyramidal syndrome, various degrees of damage to the cerebellum and its pathways [8].

In the 1970s Pierre-Marie cerebellar ataxia was first differentiated from the clinical forms of Vilyui encephalomyelitis (VE), previously this disease was attributed to one of the forms of chronic VE [3]. A comprehensive study of hereditary cerebellar ataxia (HCA) in Yakutia was launched in 1992 during the implementation of the scientific program "Biology of Vilyuisky Encephalomyelitis". Molecular genetic studies of HCA were carried out as part of the scientific project "Identification of genes and genetic mechanisms that cause hereditary neurological diseases", developed by the Department of Neurogenetics of the National Institute of Neurological Disorders and Stroke (NINDS / NIH) in the USA. In 1993, the research work of Dr. H. Orr et al. for the isolation of the Spinocerebellar ataxia type 1 *(SCA1)* gene was accomplished [23]. In 1994, the first work on the molecular genetic study of HCA in the Yakut population was published. A. Lunkes et al. (1994) revealed an allelic association of highly informative markers D6S274 and D6S89 flanking the SCA1 locus on chromosome 6 with HCA disease. The association was absolute in the case of D6S274 microsatellite, while for D6S89 allelic substitution was recorded only in two families, which gave rise to the assumption of historical recombination and date of the spread of the disease in the Yakut population [19]. In 1996, the results of a joint project by Yakut and American researchers were published, in which hereditary cerebellar ataxia, common in Yakutia, was identified as Spinocerebellar ataxia type 1 (SCA1). In these studies, the Siberian site of disease accumulation is defined as the largest known in the world, prone to further increase [41].

The molecular genetic methods of DNA testing of SCA1 were introduced in 1999 in the medical practice of the medical and genetic consultation of the Republican Hospital No. 1 - the National Center of Medicine of the Ministry of Health of the Republic of Sakha (Yakutia) and acquired the status of routine clinical analyzes, despite the absence of relevant instructions and orders for DNA diagnostics of hereditary diseases in clinical diagnostic laboratories. For the first time, DNA testing and prenatal DNA diagnostics work algorithms and bioethical rules for medical and genetic counseling for patients from burdened families were developed [2,4].

Hereditary deafness. Studies have shown that about 50-60% of congenital hearing loss are hereditary. The most common of the hereditary forms is sensorineural hearing loss, which is caused by mutations in the *GJB2* gene encoding the connexin 26 protein, currently there are more than 150 of them [21]. This form of hereditary hearing loss is detected in 1 out of 2,000 newborns, which is twice as often as cystic fibrosis and five times as often as phenylketonuria. Usually the parents of a deaf child have normal hearing, because they are heterozygous carriers of the mutation [5].

Around the world, the spectrum of the main pathological mutations that cause hearing impairment is wide and diverse. So, in various ethnic groups: Europeans, Indians, Jews, Arabs, Bedouins, Pakistanis, etc., the mutation c.35delG was found, among Ashkenazi Jews, the mutation c.167delT is the most common, in Asian populations - the mutation c.235delC [26,35]. Among Yakuts, the population frequency of c35delG is extremely low (0.2%), which may indicate the non-specificity of this deletion for the Yakut population or be single cases of crossbreeding [1]. In the Yakut population, the main cause of congenital hearing loss is a mutation in the donor site of splicing of c.-23+1G>A gene *GJB2 (Cx26)* and, according to the international OMIM catalog (Online Mendelian Inheritance in Men), is classified as an allelic variant of autosomal recessive deafness type 1A (ARD1A) [44].

According to N.A. Barashkov (2011), the prevalence of ARD1A is 16.2 per 100,000 of the Yakut population, and the frequency of heterozygous carriage of the mutation c.-23+1G>A varies from 3.8 to 11.7% among the indigenous population of Yakutia (Evens, Evenks, Dolgans, Yakuts). The results of the study of the *GJB2 (Cx26*) mutation gene splicing site indicate the existence of the world's largest "endemic focus" of c.-23+1G>A accumulation in Eastern Siberia [20].

The high frequency of deafness mutations c.35delG (22.3%) in patients of Caucasian origin in the Republic of Sakha (Yakutia) suggests the possibility of direct DNA diagnostics, differential and prenatal diagnosis, as well as screening of hereditary forms of deafness among wide groups of people, because approximately 50% of the inhabitants of Yakutia are Caucasians [31].

According to V.G. Pshennikova (2017), the proportion of pathogenic variants of the *GJB2* gene was 51.10% of the number of chromosomes studied in 393 unrelated patients. Among them, the three most common (allelic frequency >1%) pathogenic variants were identified: c.-23+1G>A (42.3%), c.35delG (5.9%) and c.109G>A (1,9%). When distributing unrelated patients by ethnicity: among the Yakut patients, the most frequent pathogenic variant is c.-23+1G>A (51.8%), the second most frequent is c.109G>A (2.4%), and the third is c.35delG (1.6%). Among Russian patients, c.35delG (22.3%) and c.-23+1G>A (5.3%) were most frequently encountered [13]. Given the identified spectrum and frequency features of pathogenic variants in the *GJB2* gene in patients with hereditary hearing impairment in Yakutia, a routine DNA diagnostic algorithm for autosomal recessive deafness type 1A was developed. The algorithm is based on a sequential search for the most common variants of the *GJB2* gene (c.-23+1G>A, c.35delG and c.109G>A), followed by resequencing of the protein-non-coding (exon1) and protein-coding regions (exon 2) of the *GJB2* gene, as well as the search for an extended deletion of c.del (GJB6-D13S1830), which allows to detect up to 99% of pathogenic variants responsible for ARD1A in Yakutia [15].

DNA testing of hearing impaired/deaf people involves many organizational and ethical issues. When communicating with deaf people, it must be borne in mind that they are members of a socially isolated community of the "world of the deaf" with their own language, culture and habits [39]. The number of assorted marriages among the deaf is growing, sometimes spouses may express a desire to have a deaf child, despite the unfairness of such a decision in relation to the child.

In any case, comparing themselves to hearing people, most deaf people consider themselves to be flawed and socially deprived [42]. The use of DNA testing to detect mutations responsible for the development of deafness can pose a risk of psychological stress and exacerbate the sense of inferiority in the individual. Therefore, it is necessary to create special conditions for genetic counseling and obtaining informed consent among the deaf [10].

Conclusion. It is impossible to overestimate the importance of translational medicine for solving practical problems of healthcare, because such an approach has already led to the transfer of the role and place of a practical doctor to a different plane, where they operate with fun-

damentally new technologies. Moreover, the ever-increasing distance between practical health care and the accumulating information in the field of fundamental biomedicine dictates the need for direct professional contact between clinicians and research scientists. Moreover, this kind of contact is required to cover not only biological and medical sciences, but also a number of related disciplines that generate facts of strategic importance, which, in turn, need active transfer (translation) to the field of medical practice, and, accordingly, to the real and effective care for a particular patient [16].

According to P. Lunt (2010), the common features of the organization of clinical molecular genetic laboratories are:

- limited contingent for which the diagnosis is intended, these are mainly families burdened by a hereditary disease and their relatives;
- mandatory patient follow-up with counseling and psychological assistance by a trained clinical geneticist;
- a small amount of conductible research; higher price of both the means invested in the laboratory and the cost of analyzes;
- the difficulty of interpreting the results of the study, the long duration of waiting for the results of the analysis;
- the existence of moral and ethical aspects of genomic analyzes [33].

Molecular genetic studies of hereditary diseases in Yakutia open up great opportunities in the field of translational medicine, namely the introduction of the results of scientific research into medical practice in the form of routine DNA diagnostics. On the other hand, modern personalized medicine using genomic technology requires the mandatory consideration of the bioethical, psychological and social aspects of translational medicine.

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HEALTHY LIFESTYLE. PREVENTION

L.D. Starostina

COMPARATIVE ANALYSIS OF HEALTH-SAVING BEHAVIOUR OF STUDENTS OF COMPREHENSIVE SCHOOLS AND UNIVERSITY IN YAKUTSK

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This research compares the behaviour components defining the attitude of the person to his health at comprehensive schools and university in Yakutsk. So, distinctions in value-required, cognitive, emotional and behavioural components have been found. Individual peculiarities, consciousness and attitude to health-saving behaviour have been revealed. Health-saving set and readiness for actions in this area are insufficiently generated in both groups. We should rely on youth high aspirations to self-assertion and self-development when we work with them in the field of health-saving consciousness and behavior.

Keywords: *healthy lifestyle, health-saving behavior, teenage age, student's age, attitude to health, consciousness.*

Introduction. Formation of health-saving behaviour is an important part of education. The researchers mark close interrelation between health, health-saving behaviour and potential development of the person. Many scientists have been studying the attitude to health, formation factors of health-saving behaviour at the teenager age. For instance, R.A. Berezovskaya's researched the problem of the attitude to health and developed the questionnaire for assessment of health-saving behaviour [2]. Ya.V.Ushakova devoted her works to self-saving behaviour, health control of the youth and its formation factors [8, 12, 13]. N.N.Avdeeva, I.I.Ashmarina, G.B.Stepanova researched the human potential of students and factors, promoting its realisation [1]. Youth health as object of social policy was considered by I.V.Zhuravleva, N.V.Lakomova [3]. G.Y. Kozina studied the youth attitude to healthy lifestyle factors [4, 6]. L.G.Rozenfild has described major risk factors of health disorders of students and Y.G.Mironova – self-saving behaviour of student's youth [7, 9]. Researches on the yielded subjects were made also among teenagers [5, 11].

Formation of health-saving behaviour and responsibility for your health should

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