S.K. Kononova

ISSUES OF TRANSLATIONAL MEDICINE IN THE FIELD OF MOLECULAR GENETIC RESEARCH IN YAKUTIA

DOI 10.25789/YMJ.2022.79.23

УДК 613.292

The issues of translational medicine in implementation of the results of molecular genetic research into the practical medicine of Yakutia are discussed. The process of gradual implementation of its main directions is noted: 'Discovery', 'Population studies', 'DNA diagnostics', 'Bioethical research', 'State programs for the prevention of hereditary diseases'. The translation of scientific achievements into clinical practice is a long process, as it turned out, in the conditions of the Sakha Republic, it lasted for about 20 years. On the one hand, the use of new technologies has raised the healthcare of the Republic of Sakha (Yakutia) to a qualitatively new level, on the other hand, it has brought many intractable problems of an ethical, legal and informational nature. It is necessary to raise the issue of the importance of implementing state programs for the prevention and treatment of hereditary diseases in the Republic of Sakha (Yakutia).

Keywords: translational medicine, molecular genetics, DNA diagnostics, bioethics.

Introduction. The concept of translational medicine (TM) implies the implementation of the latest achievements of fundamental science and biotechnology into clinical practice. In many cases, this is due to the use of modern methods in the field of genomics, gene therapy and transcriptomics, bioinformatics and proteomics, the introduction of biobanks and repositories of large clinical databases. It is an integration between researchers, clinicians and health care providers. At the same time, the "old" models of medical care are being improved in areas such as oncology, surgery, therapy, obstetrics and gynecology, pediatrics, etc. The patient receives standard or experimental therapy, the boundaries between experiment and treatment are blurred [9.10, 28.32].

Particularly important and breakthrough discoveries have occurred in the field of molecular genetics and molecular medicine, and research already touched upon the subtle regulatory mechanisms of genes, for example, the study of the effect of variation in the number of copies of DNA sites and methylation of regulatory sites of genes, as well as the search for approaches to identify new regulators and mechanisms in the cellular nuclear organization, regulation of gene transcription, spatio-temporal genome development and assembly [29, 35,36].

Despite the impressive discoveries of recent years, experts note a number of significant problems and disappointments from the expectations of translational medicine. The main ones are the speed of introduction of scientific achievements into clinical practice, bioethical problems and the need for significant financial support not only for research, but also for the process of effective application of scientific achievements by the healthcare system of states and, ultimately, improving the life and health of the patient. The study by Ioannidis et al, 2004 analyzed the publications of fundamental works from 1979 to 1983 in leading journals (Science, Nature, Cell, Journal of Biological Chemistry, Journal of Experimental Medicine and Journal of Clinical Investigation). He showed that at least 101 articles made clear promises of clinical application of the results, but only after 20 years 5 of these published results were licensed. The authors also conclude that the development of simpler, more practical and safer interventions may be an equally important goal for translational research, and the profit motive is unlikely to be sufficient to advance biomedical research to genuine progress [13,18].

The purpose of the article is to discuss the problems of translational medicine in implementation of the results of molecular genetic research in the practical medicine of Yakutia.

Let's consider our proposed scheme of translational medicine in the field of research of hereditary diseases (HD) and describe some aspects of the practical implementation of its stages in Yakutia Fig. 1.

I. The first stage of translational medicine is "Discovery". For example, the discovery of a mutation of the gene responsible for the development of the disease or polymorphisms of the genome regions responsible for the high risk of developing the disease. The clinical and translational discovery turns the decoding of the sequence, structure and function of DNA into a clinical application for predicting and diagnosing specific symptoms of human diseases.

Molecular genetic research in Yakutia began in 1993 as part of an international scientific program to study Vilyuisk encephalomyelitis and spinocerebellar ataxia type 1 (SCA1), the most common autosomal dominant disease in the Yakut population [20]. This was the first discovery in the field of molecular genetics and quite naturally, SCA1 became the most studied hereditary pathology and the first genomic technology introduced into clinical practice[2]. Over the next 20 years, a number of studies were carried out to detect genes that are the cause of other frequent hereditary diseases in Yakuts Table 1.

II. The second stage of TM molecular research includes the study of the population characteristics of HD and the frequency of heterozygous carriage of autosomal recessive diseases, which is of great importance for the organization of preventive measures in medical practice.

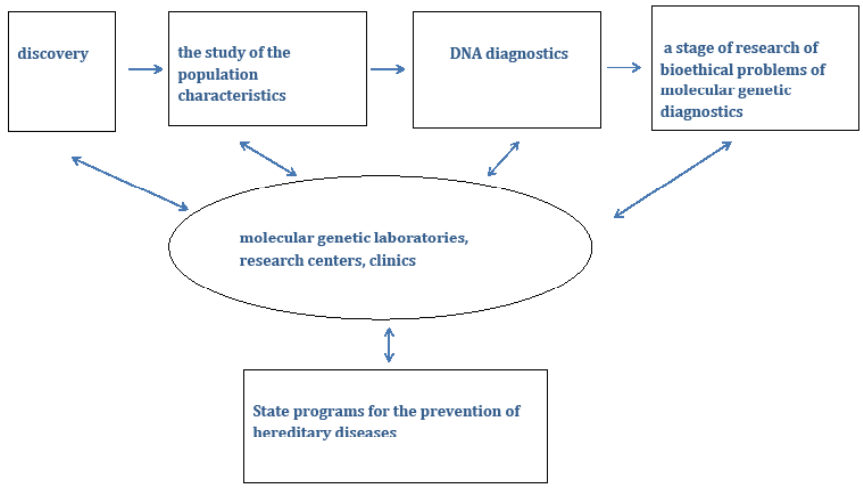
As is known, established populations are characterized by differences in the total burden of hereditary diseases, the sum of the frequencies of autosomal dominant, autosomal recessive and X-linked diseases can vary from 1.5 to 3.5 per 1000 people. For example, the number of patients with phenylketonuria and cystic fibrosis, frequent for the European population, is significantly lower in Yakutia [1,4]. The frequency of certain forms of hereditary diseases due to population reasons may vary more in cases of ethnospecific diseases [3,6]. Such diseases in Yakutia as SCA1, myotonic dystrophy, 3 M syndrome, etc. are ten times more frequently diagnosed than around the world. The accumulation of some nosologies of HD in Yakutia occurred for population reasons, the main of which

KONONOVA Sardana K. – PhD in Biology, chief researcher, head of the Department of Molecular Genetics of the Yakut Scientific Center for Complex Medical Problems, Yakutsk, Russia, konsard@rambler.ru

are the founder effect, gene drift and the passage of the population through the "bottleneck" due to wars, epidemics, famine [7,25].

III. The third stage of TM is the development of algorithms for DNA diagnostics of HD based on molecular genetic studies and the introduction of DNA testing of patients from burdened families into practical medicine. Currently, more than 30 different nosologies of hereditary diseases are available for DNA diagnostics in the Republic of Sakha (Yakutia).

Molecular genetic methods (DNA diagnostics) are a diverse group of methods that allow detecting violations and/or variations in the structure of a DNA molecule, up to the decoding of its nucleotide sequence (sequencing). The simplest to perform in routine clinical practice are direct and indirect (indirect) methods of DNA diagnostics based on the search for pathological mutations leading to the disease or on the analysis of polymorphic markers closely linked to the pathological gene. Direct methods of DNA diagnostics are the most informative, can be used to confirm a clinical diagnosis, for asymptomatic and differential diagnosis. In the Republic of Sakha (Yakutia), direct DNA diagnostics is used for spinocerebellar ataxia type 1, Charcot-Marie-Tutt type 1A neural amyotrophy, Duchene-Becker myodystrophy, oculopharyngeal myodystrophy, etc.; direct method using PCR-RFLP is used for DNA diagnostics of 3M syndrome, autosomal recessive deafness type 1A, a congenital autosomal recessive form of cataract. Indirect DNA diagnostics based on marker alleles linked to a damaged gene is used for such hereditary diseases as hemophilia A, B [2,11,12,19,21,22].



The fluorescent signal accumulation of the amplification of DNA fragments isolated from plasma: a - amplification of a DNA fragment encoding human beta-globin, b - encoding HPV L1 protein

The main problems of using DNA diagnostics of HD as a routine analysis in clinical practice are:

- confidence in the clinical diagnosis and a clear justification for the molecular genetic diagnosis of HD, since the search for a mutation without a diagnosis can turn into a useless procedure with the expense of costly reagents;
- availability of the necessary family members for analysis, and, as a rule, proband genetic material is required for research;
- increasing the personal responsibility of persons involved in the process of molecular genetic diagnosis of HD, responsible for the reliability of the results of the examination, as well as the qualification of a laboratory assistant performing the actual analysis;

IV. Translational medicine provides a stage of research of bioethical problems of molecular genetic diagnostics of HD.

Differences in the manifestation of phenogenotypic signs of HD cause differences in the medical and social consequences of HD. Ethical issues are resolved through the adoption of laws and regulations concerning the use of genetic information of an individual/family. For example, presymptomatic testing for incurable NC raises a number of ethical and psychosocial problems, including possible discrimination of carriers of a pathological gene, deterioration of the quality of life of a person who received such information, etc. The most acute of the existing problems is the possibility of severe emotional trauma with a positive result of DNA testing at the preclinical stage without psychological preparation of the patient. This means that a person may be doomed to an incurable disease that gradually destroys his personality, leading to deep disability and inevitable death in 10-15 years from its onset [8].

Frequent hereditary diseases in the Yakut population

Hereditary disease	frequency in the Yakut population	Gene (OMIM)	Frequency of heterozygous carrier	citation
* Spinocerebellar ataxia Type 1	38,6 : 100000	*SCA1* (164400)	* Autosomal dominant	Lunkes A., Goldfarb L.G., Platonov F.A. et al.,1994 [20]
Short stature syndrome 3 M syndrome	12,72 : 100000	*CUL7* (273750)	3%	Maksimova N, Hara K, Miyashia A et al.,2007 [21]
Short stature syndrome characterised by optic nerve atrophy and Pelger-Huët anomaly (SCOP)	9,95 : 100000	*NAG* (614800)	1%	Maksimova N, Hara K, Nikolaeva I et al.,2010 [22]
Autosomal recessive deafness 1A (DFNB1A)	16,2 : 100000	*GJB2* (220290)	11,7%	Barashkov NA, Dzhemileva LU, Fedorova SA et al., 2011 [11]
A new type of mucopolysaccharidosis with severe systemic symptoms	8,3 : 100000	*VPS33A* (617303)	2,1%	Kondo H, Maksimova N, Otomo T et al.,2017 [19]
Autosomal recessive cataract (CTRCT18)	3,0 : 100000	*FYCO1* (610019)	7,9%	Barashkov NA, Konovalov FA, Borisova TV et al.,2021[12]

The articles describe cases of affective behavior and suicidal attempts in similar situations [15,33]. For example, Huntington's chorea (HC), as well as SCA1, refers to HD with dynamic mutations and late onset of clinical signs. Studies of the issue of patients' attitude to the presymptomatic and prenatal DNA testing of Huntington's Chorea showed a low percentage (5-20%) of those wishing to undergo such a survey [23,24,34].

No less controversial ethical issues are contained in the prenatal diagnosis (PD) of late-manifesting diseases, such as HC and SCA1. There is no consensus on which hereditary disease should be considered serious enough for PD. Some experts believe that the late onset of the disease after a long period of healthy and fulfilling life may make it possible to attribute the condition to frivolous for the decision to terminate the pregnancy of a fetus with a mutation [14,26].

Organizational and bioethical approaches to the prevention of socially significant hereditary diseases remain undeveloped in the healthcare system of Yakutia. Approaches to solving ethical problems in different countries are related to the cultural and religious characteristics of peoples, there are differences in the regulatory documents of the organization of medical and genetic services. The generalized nature of international guidelines on ethical problems of medical and genetic counseling requires concretization taking into account national characteristics [5].

Bioethical problems associated with the latest methods of correction of hearing defects are widely developed by foreign authors. In particular, the dilemma of the acceptability of the modern method of cochlear implantation (a new generation of hearing aids implanted in early childhood) for hearing correction is discussed. The main bioethical problem in this case is obtaining the consent of both parents, because cases are described in families when both parents who are deaf do not want their child to be able to hear. This fact is associated by many researchers with a well-developed social security system and a sufficiently developed system of public organizations for hearing-impaired people in Western countries who do not consider lack of hearing a serious defect and are ready to raise a deaf child [16,17,30,31]. In Russia, the attitude of persons with impaired sound perception to cochlear implantation and DNA diagnostics has not been studied. Molecular genetic studies of hereditary non-syndromic forms of deafness in Russia are at an early stage, the needs of the population for DNA testing have not been determined. In Yakutia, with a high frequency of this disease, there is a gap between the results of scientific developments and their application in practice due to extremely low awareness of the population about genetic technologies [27].

When developing the ethical aspects of TM for the prevention of HD, it is necessary to emphasize the following aspects:

- late -manifesting character;
- vital prognosis depending on nosology;
-methods of introducing genetic analysis and the consequences of using DNA testing;
- public perception of applied genetic technologies;
- the need of burdened families for prenatal diagnosis;
- ethnic characteristics in the area of the study, etc.

V. The fifth stage of TM is the involvement of the state in the process of introducing and applying scientific achievements in practical medicine to improve the quality of medical care provided to the population with the greatest coverage of all those in need and a fair distribution of financial resources to improve the health and quality of life of patients. As a rule, this is the adoption of state programs for the prevention of diseases. For example, genetic screening programs are implemented by government programs taking into account the needs of populations in need of a particular type of screening. The main evaluation of screening is the effectiveness of the proposed methods of prevention and treatment of hereditary diseases.

An example of the successful implementation of the Republican target Program "Development of human genodiagnostics in the Republic of Sakha (Yakutia) for 2001-2005, adopted by the Decree of the Government of the Republic of Sakha (Yakutia) dated May 11, 2001 No. 277, is the introduction of the results of molecular genetic studies and prenatal diagnostics of HD into practical healthcare of the Republic, as well as the expansion of the scope of complex preventive measures for the diagnosis of hereditary diseases in general. During the implementation of this program, the material and technical base of the first molecular genetic laboratory was modernized, specialists in molecular genetics for the Republic of Sakha (Yakutia) were trained in leading federal genetic centers.

Conclusion. In the Republic of Sakha (Yakutia), a new direction in science - translational medicine - has been developed in the field of molecular genetics research of hereditary diseases. The process of gradual implementation of its main directions is noted: "Discovery", "Population studies", "DNA diagnostics", "Bioethical research", "State programs for the prevention of hereditary diseases". The translation of scientific achievements into clinical practice is a long process, as it turned out, in the conditions of the Republic, it lasted for about 20 years. On the one hand, the use of new technologies has raised the healthcare of the Republic of Sakha (Yakutia) to a qualitatively new level, on the other hand, it has brought many intractable problems of an ethical, legal and informational nature. The main problems of TM are medical, social, organizational and financial. In the field of medical and social problems, bioethical ones stand out, since with the existing differences in the clinical and social effects of hereditary diseases common in Yakutia, differentiated approaches are required in the development of ethical rules for DNA testing and the study of public opinion on the genomic technologies used. Organizational problems include the issues of training laboratory doctors for molecular genetic laboratories, equipping laboratories with equipment and reagents for genetic research. Economic problems are specific to our republic, due to the remoteness of the region from Central Russia, so it is necessary to raise the issue of the importance of implementing state programs for the prevention and treatment of hereditary diseases in the Republic of Sakha (Yakutia).

Reference

1. Matulevich S A Zinchenko L V Golikhina T A [et al.] Analiz mutatsii gena FAG u bolnykh fenilketonuriei v Krasnodarskom krae [Analysis of PAH gene mutations in patients with phenylketonuria in Krasnodar Krai]. Medicinskaya genetika [Medical genetics. 2004; 3(10): 466-469 (In Russ.).]

2. Fedorova S.A., Kononova S.K., Sukhomyasova A.L. [et al.] Vnedrenie molekuliarno-geneticheskikh metodov diagnostiki nasledstvennykh boleznei v prakticheskoe zdravo-okhranenie RS (Ya) [Introduction of molecular genetic methods for the diagnosis of hereditary diseases in the practical healthcare of the RS Ya]. Voprosy formirovaniia zdorovia i patologii cheloveka na Severe fakty problemy i perspektivy. Mater nauch -prakt konf [Issues on the formation of human health and pathology in the North facts problems and prospects. Materials of scientific konf. Yakutsk. 2002; 276-279 (In Russ.).]

3. Geneticheskaia struktura i nasledstvennye bolezni chuvashskoi populiatsii [Genetic structure and hereditary diseases of the Chuvash population. Edit. Gintera E.K. Cheboksary. Publ. house Pegas. 2006; 232 (In Russ.).]

4. DNK-diagnostika i profilaktika nasledstvennoi patologii v Respublike Bashkortostan [DNA diagnostics and prevention of hereditary pathology

in the Republic of Bashkortostan]. Edit. prof E. K. Khusnutdinova. Ufa. Kitap. 2005; 204 (In Russ.).]

5. Izhevskaya V.L. Mediko-geneticheskoe konsultirovanie eticheskie printsipy [Medical and genetic counseling ethical principles]. Medicinskaya genetika [Medical genetics. 2003; 2(8): 354-366 (In Russ.).]

6. Puzyrev V.P., Nazarenko L.P. Genetikoepidemiologicheskoe issledovanie nasledstvennoi patologii v Zapadnoi Sibiri [Genetic and epidemiological study of hereditary pathology in Western Siberia. Tomsk. STT. 2000; 192 (In Russ.).]

7. Fedorova S.A Geneticheskie portrety narodov Respubliki Sakha IAkutiia analiz linii mitokhondrialnoi DNK i Y-khromosomy [Genetic portraits of the peoples of the Republic of Sakha Yakutia Analysis of mitochondrial DNA and Y-chromosome lines]. Yakutsk. Publishing House 'Yakutsk'. YSC SD RAS. 2008; 235 (In Russ.).]

8. Klyushnikov S.A. Ivanova-Smolenskaya I.A. [et al.] Eticheskie problemy mediko-geneticheskogo konsultirovaniia na primere KHorei Gentingtona [Ethical problems of medical and genetic counseling on the example of Huntington's Chorea]. Russian Medical Journal. 2000; 2: 32-36. (In Russ.).]

9. Abraham E, Marincola FM, Chen Z, Wang X. Clinical and translational medicine: Integrative and practical science. Clin Transl Med. 2012;1(1):1. doi: 10.1186/2001-1326-1-1.

10. Asiimwe R, Lam S, Leung S et al. From biobank and data silos into a data commons: convergence to support translational medicine. J Transl Med. 2021 Dec 4;19(1):493. doi: 10.1186/s12967-021-03147-z.

11. Barashkov NA, Dzhemileva LU, Fedorova SA, et al. Autosomal recessive deafness 1A (DFNB1A) in Yakut population isolate in Eastern Siberia: extensive accumulation of the splice site mutation IVS1+1G>A in GJB2 gene as a result of founder effect. J Hum Genet. 2011;56(9):631-9. doi: 10.1038/jhg.2011.72.

12. Barashkov NA, Konovalov FA, Borisova TV,et al. Autosomal recessive cataract (CTRCT18) in the Yakut population isolate of Eastern Siberia: a novel founder variant in the FYCO1 gene. Eur J Hum Genet. 2021;29(6):965-976. doi: 10.1038/s41431-021-00833-w.

13. Contopoulos-Ioannidis DG, Ntzani E, Ioannidis JP: Translation of highly promising basic science research into clinical applications. Am J Med 2003;114:477-484.

14. Creighton S, Almqvist EW, MacGregor D. et al. Predictive, pre-natal and diagnostic genetic testing for Huntington's disease: the experience in Canada from 1987 to 2000 . Clin. Genet. 2003; 63(6):462–475.

15. Farrer L. Suicide and attempted suicide in Huntington's disease: implication for preclinical testing of personal at risk.Am.J.Med.Genet.1986;.24:305-311.

16. Fellinger J, Holzinger D, Dobner U,et al. Mental distress and quality of life in a deaf population. Soc Psychiatry Psychiatr Epidemiol. 2005;40(9):737-42. doi: 10.1007/s00127-005-0936-8.

17. Fellinger J, Holzinger D, Dobner U,et al. An innovative and reliable way of measuring health-related quality of life and mental distress in the deaf community. Soc Psychiatry Psychiatr Epidemiol. 2005;40(3):245-50. doi: 10.1007/s00127-005-0862-9.

18. Ioannidis JP. Materializing research promises: opportunities, priorities and conflicts in translational medicine. J Transl Med. 2004;2(1):5. doi: 10.1186/1479-5876-2-5.

19. Kondo H, Maksimova N, Otomo T, et al. Mutation in VPS33A affects metabolism of glycosaminoglycans: a new type of mucopolysaccharidosis with severe systemic symptoms. Hum Mol Genet. 2017;26(1):173-183. doi: 10.1093/hmg/ddw377.

20. Lunkes A., Goldfarb L.G., Platonov F.A. et al. Autosomal dominant spinocerebellar ataxia (SCA) in a Siberian Founder Population: assignment to the SCA1 locus. Experimental neurology.1994;126:310-312.

21. Maksimova N, Hara K, Miyashia A, et al. Clinical, molecular and histopathological features of short stature syndrome with novel CUL7 mutation in Yakuts: new population isolate in Asia. J Med Genet. 2007;44(12):772-8. doi: 10.1136/jmg.2007.051979.

22. Maksimova N, Hara K, Nikolaeva I,et al. Neuroblastoma amplified sequence gene is associated with a novel short stature syndrome characterised by optic nerve atrophy and Pelger-Huët anomaly. J Med Genet. 2010 ;47(8):538-48. doi: 10.1136/jmg.2009.074815.

23. Markel DS, Young AB, Penney JB At-risk persons' attitudes toward presymptomatic and prenatal testing of Huntington disease in Michigan// Am J Med Genet. 1987;26(2):295-305

24. Mastromauro C, Myers RH, Berkman B. Attitudes toward presymptomatic testing in Huntington disease . Clinical Genetics. 2003; 63: 462

25. Puzyrev VP, Maksimova NR. Hereditary diseases among Yakuts. Genetika. 2008 ;44(10):1317-24.

26. Powledge T.M., Fletcher J.C. Guidelines for ethical, legal and social issues in prenatal diagnosis.N.Eng.J.Med.1987;300:168.

27. Solovyev AV, Dzhemileva LU, Posukh OL, et al. Opinions of hearing parents about the causes of hearing impairment of their children with biallelic GJB2 mutations. J Community Genet. 2017;8(3):167-171. doi: 10.1007/s12687-017-0299-3.

28. Sonntag KC. Implementations of translational medicine. J Transl Med. 2005;3:33. doi: 10.1186/1479-5876-3-33.

29. Seisenberger S, Peat JR, Hore TA, Santos F, Dean W, Reik W. Reprogramming DNA methylation in the mammalian life cycle: building and breaking epigenetic barriers. Philos Trans R Soc Lond B Biol Sci. 2013;368(1609):20110330. doi: 10.1098/rstb.2011.0330.

30. Stebnicki J.A., Coeling H.V. The culture of the deaf. J Transcult Nurs. 1999; 10(4):350-7.

31. Smeijers AS, Ens-Dokkum MH, van den Bogaerde B, Oudesluys-Murphy AM. Clinical practice: The approach to the deaf or hard-of-hearing paediatric patient. Eur J Pediatr. 2011; 170(11):1359-63. doi: 10.1007/s00431-011-1530-6.

32. Wang DC, Wang X. Discovery in clinical and translational medicine. Clin Transl Med. 2021 ;11(10):e568. doi: 10.1002/ctm2.568.

33. Wahlin T B. R., Bäckman L. et al. High suicidal ideation in persons testing for Huntington's disease . Acta Neurologica Scandinavica. 2000;102 :150

34. Williams JK, Schutte DL, Evers CA, Forcucci C. Adults seeking presymptomatic gene testing for Huntington disease. Image J. Nurs. Sch. 1999; 31(2):109–114.

35. Yap EL, Greenberg ME. Activity-Regulated Transcription: Bridging the Gap between Neural Activity and Behavior. Neuron. 2018 ;100(2):330-348. doi: 10.1016/j.neuron.2018.10.013.

36. Zarrei M, MacDonald JR, Merico D, Scherer SW. A copy number variation map of the human genome. Nat Rev Genet. 2015 ;16(3):172-83. doi: 10.1038/nrg3871.