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GENETIC TESTING AND INFORMED CONSENT FOR SPINOCEREBELLAR ATAXIA TYPE I, THE MOST COMMON HEREDITARY DISEASE IN THE YAKUT POPULATION

ABSTRACT

The article discusses the issues of informed consent for DNA testing at type 1 spinocerebellar ataxia, the most common hereditary disease with late onset of manifestation in the Yakut population. Different stages of obtaining informed consent in medical genetic counseling and in scientific research are described. The expediency of using the bioethical principle of non-disclosure of genetic information for a participant in a scientific study on the research of hereditary diseases with late manifestation is established.

Keywords: DNA testing, hereditary diseases, informed consent, type I spinocerebellar ataxia.

INTRODUCTION

Since 70th years of last century the works about cloning of human DNA developed in high gear and accomplished with the successful Human Genome project of the full interpretation of the DNA nucleotide sequence, and it offered great opportunities for development of new fields of science and practice, including molecular genetics, ethnogenomics, molecular medicine etc.

In the world there are about 7000 nosologies of monogenic diseases, which are detected in 3-6% of newborns, and in structure of the child mortality total rate of under-fives it is 10-14% [13]. There is a conditional separation of monogenic diseases on orphan diseases with a frequency of 1:100000 (lysosomal storage disorders, etc.) and common hereditary diseases - 1:10000 (a mucoviscidosis, a phenylketonuria, etc.). Frequency of monogenic diseases in various populations of the world can differ considerably. It depends on evolutionary features of formation of a genetic pool of the people. In some populations, however, this or that mutation which is the reason of monogenic pathology owing to evolutionary and genetic features becomes frequent and can be called "ethno-specific". For example, so-called "Finnish" hereditary diseases, generally autosomal and recessive which frequency of Finns is much higher, than in any other populations are known

long ago [11,16]. The phenomenon of accumulation of monogenic diseases at Finns is bound to drift of genes, long-term isolation of population and high coefficient of an inbreeding. On the same population mechanisms there was probably also an accumulation of some hereditary diseases of Ashkenazi Jews, and the highest frequency is Tay-Sachs disease and cerebroside lipidosis (Gaucher's disease) type 1 [6,12]. In the European populations the mucoviscidosis meets with a frequency of 1:2500, whereas in the Asian populations – 1:90000.

Around the world problems of use of genetic testing of hereditary diseases in applied medicine are relevant, especially standardization and improvement of quality of molecular and genetic analyses.

In 1999 the working group on genetic testing (the Task Force on Genetic Testing) defined genetic test as: "the analysis of DNA, RNA, chromosomes and proteins to define the hereditary genotypes, mutations, phenotypes or karyotypes bound to illnesses for the clinical purposes. These purposes include clinical diagnostics and forecasts, identification of carriers of hereditary diseases, presymptomatic and prenatal diagnostics and also neonatal screening" [14].

Recently the increasing value in activity of medicogenetic consultation of the Republic of Sakha (Yakutia) gets a DNA testing as one of the main diagnostic methods of hereditary diseases. Human DNA researches are innovative for applied medicine, because modern molecular and genetic laboratory methods begin to be applied for the first time in health care of Yakutia. Genetic testing allows to detect and form risk groups of the examined patients more intensively, to hold predictive events in the preclinical stage, to use programs for the disease development risk reduction. At the same time the DNA testing has also controversial issues, and first of it are all moral aspects and psychological risks for the individuals who are exposed to genetic testing [8,9,10,17].

One of topical issues of legal adjustment of medicine is the problem of the informed consent (IC). The attention of a legislator became the instance of IC importance. Today there is a majority of the federal normative legal acts in a health care field concerning both the general, and single questions of medicine, contain regulations about the informed consent. Each person has the right to freedom of choice in many areas of the public relations. In a health care field for the patient (a person who asked for a medical care) there is a possibility of the choice of diagnostic methods and treatment. Thereby the importance of equal participation of the patient in the course of treatment of the disease is emphasized [4]. However, as practice shows, doctors and researchers don't pay sufficient attention to the informed consent giving formal character to such an important bioethical principle that can have very negative consequences for the patient who asked for the medicogenetic help.

In our article there are discussed the features of using IC in a medicogenetic consultation (MGC) and a DNA testing of the most widespread monogenic hereditary disease in the Yakut population: spinocerebellar ataxia of the I type (SCA1). In clinical researches of Platonov in 2003 and other described about the accumulation reasons, clinical and molecular and genetic characteristics of SCA1 in most details. [5].

The main way of prophylaxis of SCA1 is the prenatal diagnostics (PD) of this disease. Bioethical aspects of the DNA testing and PD of late symptomatic monogenic illness with a dynamic mutation are described in early published works [3].

Now the medicogenetic consultation seeks to achieve psychological and educational aims referred on social adaptation of a family to the genetic risk or child birth with a hereditary disease [1]. The main task of a geneticist consists not in surely to recommend molecular and genetic diagnostics, but correctly help the patient to understand sense of the informed consent and, without imposing the opinion, to help him to make the adequate decision about the DNA testing.

MATERIALS AND METHODS

Information from republican genetic register about hereditary and congenital diseases were used in the article. According to the genetic register, 252 patients with the diagnosis a spinocerebellar ataxia of the I type [7] stayed on the registry in MGC. The method of direct DNA Diagnostics by the PCR method with the specific nucleotide primers was used for the Routine DNA Diagnostics of SCA1 as described in Orr et al (1993) with further detection pathologically extended allele in 2% agarose gel [15]. Determination of number of repetitions in a gene of SCA1 was carried out by method of a capillary electrophoresis on the automatic ABIPrism3130 (AppliedBiosystems) DNA analyzer [2].

RESULTS AND DISCUSSION

SCA1 IC for clinical practice

For the first time DNA Diagnostics of SCA1 was carried out in the medicogenetic consultation of the Republican Hospital № 1 National Center of Medicine in 2000. According to the latest published materials in 14 years it was tested 1841 persons; existence of the mutation of SCA1 was confirmed at 606 people from whom 354 (58%) asymptomatic persons was agreed to carry out a predictive DNA testing. 132 individuals were tested averagely in a year. The detectability of the mutation was 33% [2].

As mentioned above, more than a half of patients (58%) of the burdened families underwent presymptomatic DNA testing. It means that by the time of the request for the medicogenetic consultation these individuals had no clinically expressed SCA1 disease symptoms. In this case there is a question: is the asymptomatic individual (SCA1 mutation carrier) a patient in full sense of this concept? On the one hand, he makes the decision about DNA testing independently, being absolutely healthy, realizing the fact that there is a risk group, and on the other hand, learned the genetic status, perhaps, the individual won't address for medicogenetic consultation during the long time.

There are several general stages of the medicogenetic consultation of the patients bound to DNA Diagnostics:

1) pre-testing MGC;

2) DNA testing;

3) post-testing MGC with psychological follow-up.

From among addressed for the medicogenetic consultation on SCA1 it is possible to allocate at least four groups:

1. group of the patients having clinical implications of SCA1 by the time of visiting a doctor;

2. group of the asymptomatic mutation carriers of SCA1 detected by the DNA testing;

3. group of healthy individuals with negative result on SCA1 mutation

carriage;

4. group of persons interested to carry out a SCA1 PD.

At the first MGC pre-testing stage the greatest importance has the bioethical "principle of the informed consent" - each individual has the right to be informed on the forthcoming diagnostic method, in particular DNA diagnostics of SCA1. It is possible to assume that in a case with the DNA testing of SCA1 the patient is already ready for DNA testing as it had time to consider this important decision, but the medical adviser-geneticist shouldn't convince the patient by all means to undergo the DNA testing in the very first day of visiting, because it can be a consequence of an emotional rush or a special psychological make-up. It is necessary to lead a quiet discussion, to disclose all possible psychological risks of receiving a positive take of a presymptomatic testing, to be convinced that the decision on DNA diagnostics is made it is weighed. During the consultation, the geneticist has to pay attention to the patient age and his educational level.

There are described the necessary stages of receiving IC for SCA1.

1) an advising geneticist opens all known information about SCA1 disease (hereditary nature, the molecular reasons, anticipation effect, clinical symptoms);

2) discloses advantages of DNA testing to the individual (to learn the genetic status for planning a family and, in general, the main priorities in life). This stage is very important for the patient that he could take measures about the important decision making, without having felt compulsoriness from the doctor;

3) discloses possible psychological risks after obtaining results of DNA testing (psychological trauma, frustration, depression, etc);

4) shows possible ways out from a difficult psychological situation (remoteness of the SCA first symptoms expression; it is also possible to explain that there is a set of other diseases which are suffered by other people; to give hope for search and development of more effective methods of stopping symptoms or SCA1 treatment);

5) opens IC alternatives (to sign the document at once, to receive time for considering, to refuse DNA - testing).

SCA1 IC for scientific research

The informed consent for scientific research differs from IC for DNA testing and the medicogenetic consultation of patients from the risk group. In scientific research the individual is an alleged participant of a research work. It is important to a researcher received IC togive emphasis to the next moments:

1) to explain that this work is scientific research and participation in it is a voluntary decision of a participant; the explanation has to be provided with understandable terms for the participant, without using difficult medical or genetic terms.

2) to explain a research object;

3) to give confidentiality guarantees at all investigation phases;

4) before signing of IC to discuss results of a scientific research as in this case there are only two options with the participant: either the participant will want to learn the genetic status or not. But SCA1 features, especially moral and psychological problems, give the reasons for recommending to the researchers to make it clear for the participant about an inexpediency of the obtaining information about the participant genetic status.

CONCLUSION

The informed consent is an important and necessary condition of providing any medical service or a scientific research with participation of a person. It is a legal condition. The advising doctors need to avoid formalistic approach in informing patients, especially when the problem is bound to DNA testing of late symptomatic hereditary diseases. Obtaining negative information about patient health status and dismal prognosis of the disease can have moral injury and the long-term mental implications. The quality and efficiency of the medicogenetic help to the patient with SCA1 are not about the convincing the patient to undergo DNA testing but helping him to make the decision independently about testing based on comprehensive informing and offering various alternatives. On the assumption of bioethical principle of hurting, genetic information about

Информированное согласие
на проведение ДНК-тестирования спиноцеребеллярной атаксии 1-го типа

Настоящее добровольное согласие составлено в соответствии Федеральным законом от 21.11.2011 N323-ФЗ (ред. от 13.07.2015, с изм. от 30.09.2015) "Об основах охраны здоровья граждан в Российской Федерации" (с изм. и доп., вступ. в силу с 24.07.2015)

Мне _____

разъяснены цели теста, манипуляции по забору материала, преимущества и риски ДНК-тестирования.

• Я полностью информирован врачом-генетиком о заболевании, его особенностях, прогнозе и течении.

• При моем желании, мне дается время подумать о необходимости прохождения ДНК – тестирования.

• Мое решение принято мною добровольно, без всякого давления со стороны врача, родственников и/или супруга(и).

• Мне предоставляются альтернативные варианты прохождения ДНК-диагностики:

• Какое бы решение Вы не приняли, это не отразится на предоставлении Вам медицинской помощи.

Варианты решения	Подпись пациента
Я прохожу ДНК-тестирование и узнаю о результатах сразу после выполнения анализа	
Я сдаю кровь в Банк ДНК и узнаю о результатах позже, когда я буду готов психологически (через месяц, год, два и т.д.)	
Я сдаю кровь в Банк ДНК и могу не узнавать о результатах ДНК-тестирования	
Я не сдаю кровь и отказываюсь от ДНК-тестирования	

• Какое бы решение Вы не приняли, это не отразится на предоставлении Вам медицинской помощи.

Подпись врача-генетика Дата

Форма информированного согласия для спиноцеребеллярной атаксии 1-го типа

existence/lack of SCA1 mutation has to be closed for the participant of the research that surely taken in an oral or written form of the informed consent.

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