Никонова Маргарита Александровна
Тюменский государственный университет
Институт Биологии
Кафедра иностранных языков и межкультурной
профессиональной коммуникации
Студент специалитета 26БиБс186
stud0000216762@study.utmn.ru
Гаркуша Надежда Анатольевна
Тюменский государственный университет
Институт Социально-Гуманитарных наук
Кафедра иностранных языков и межкультурной
профессиональной коммуникации
Доцент, канд. пед. наук
n.a.garkusha@utmn.ru

ВОЗРАСТ – КАК ФАКТОР ВЛИЯНИЯ НА МУТАЦИИ

Nikonova Margarita Alexandrovna
University of Tyumen
Institute of Biology
Foreign Languages and Intercultural
Professional Communication Department
Student of 26BiBs186
stud0000216762@study.utmn.ru
Garkusha Nadezhda Anatolievna
University of Tyumen
Institute of Social Sciences
Foreign Languages and Intercultural
Professional Communication Department
Associate Professor, Candidate of Pedagogic Sciences
n.a.garkusha@utmn.ru

AGE AS A FACTOR IN INFLUENCING MUTATIONS

Аннотация. Данная статья посвящена влиянию возраста на геномные и хромосомные мутации. В статье представлена информация об изменениях клеточных структур в половой системе человеческого организма в процессе старения. Основная цель статьи это рассмотреть и изучить влияние возраста на частоту геномных и хромосомных мутаций.

Ключевые слова. Мутация, геномы, хромосомы, возраст, ДНК.

Abstract. This article is devoted to the influence of age on genomic and chromosomal mutations. The article presents information about changes in cellular structures in the sexual system of the human body in the process of aging. The main purpose of the article is to consider and study the influence of age on the frequency of genomic and chromosomal mutations.

Key words. Mutation, genomes, chromosomes, age, DNA.

Introduction

I chose this topic because I think it is very relevant nowadays. Nowadays most people live their careers, and the idea of creating a family comes after 30 years of age, but just after that age the probability of giving birth to a fully healthy child is significantly reduced. Icelandic geneticists have conducted an unprecedented study of mutagenesis in modern humans, analyzing the complete genomes of 1548 "triplets", including a couple of parents and their offspring. It turned out that every newborn child receives an average of 70 new mutations, which parents did not have. Rapid growth of number of new mutations with age of the father was confirmed: each year of life of the father adds to his posterity on the average 1,5 mutations.

Distribution of "maternal" mutations by genome turned out to be non-uniform: the frequency of their occurrence is sharply increased in several areas. Apparently, this is due to the fact that chromosomes in aging oocytes are most often torn in these areas.

Mutation (lat. mutatio - change) - stable genotype transformation occurring under the influence of external or internal environment.

The age of the woman

Approximately 95% of chromosomal syndromes are due to an erroneous distribution of chromosomes in the formation of the ovum. Everyone is always likely to make such an error, because one of the normal properties of DNA is to make mistakes. It is only a matter of probability. I would like to emphasize that the quality of chromosomes is not significantly affected by lifestyle or habit, the only significant factor is the age of the woman. The figures will speak for themselves: the probability of chromosomal anomaly for 20- to 25-year-olds 1:1300, for 30-year-olds 1:750, for 35-year-olds 1:300, for 40-year-olds 1:80, for 45-year-olds 1:5.

Only a fraction of these mistakes will lead to the birth of a child with the syndrome, most pregnancies will be spontaneously terminated. But neither result can be called desirable. However, no one is in control of their chromosomes. It is not for nothing that the supply of eggs is limited (from 400 to 500 for life), and with it and the reproductive age of women. Here, by the way, it would be useful to remind about the possibility to detect chromosomal abnormalities during pregnancy due to screening and prenatal diagnosis.

It is known that aneuploidy is mainly a consequence of abnormal chromosome segregation in oogenesis. The main number of aneuploids is the result of chromosomal nonconformities in the 1st meiosis division. What is the meaning and what are the biological mechanisms of "aging of the ovum" with the age of the woman remains unclear. Several hypotheses have been put forward to explain this phenomenon. Let's consider some of them.

The "limited pool" hypothesis is based on the assumption that as the body ages, the oocyte pool is depleted and the average number of anthralic follicles decreases in each cycle. However, chromosomes in the "overripe" oocytes of older women are more susceptible to indistinction. These processes are not directly related to the chronological age of the woman, although in many ways are peculiar to the aging body. This hypothesis is indirectly confirmed by experimental data and some clinical observations. Thus, an increase in the level of aneuploid oocytes in mice with one

remote ovary, as well as the birth of children with an aneuploid karyotype in patients with Turner's syndrome, who have partial dysgenesis of gonads.

The "productive line" hypothesis has not lost its significance today. It is based on the assumption that in the mammalian embryonic ovary there is a certain order of entry of ogonias into meiosis: the primary sex cells, which first reached the rudiments of gonads, are the first to enter meiosis and then the first to ovulate. They are characterized by a high frequency of chromosomal recombinations (hiasms), as opposed to gonads, which later entered meiosis. Due to differences in the frequency of chiasma formation, early oocytes are characterized by a low number of univalents and, consequently, a low frequency of chromosome non-divergence in the first division of meiosis, while oocytes ovulating later have an increased frequency of univalents and, consequently, a higher frequency of aneuploidy.

The age of a man

Men are able to keep their fertility until they're old. Unless, of course, they spoil the very gift of nature because male sex cells are very sensitive to external influences. Unlike eggs, sperm cells are formed in huge amounts (about 20 million in 1 ml of semen) and this provides competition between them. It is because of this competition that a sperm with an excess chromosome has virtually no chance of fertilization, as it is heavier and slower than normal. For a long time, it was believed that the age of a man does not affect the genetic material of sperm cells transmitted to descendants. But a number of studies in recent decades suggest otherwise.

The frequency of spontaneous abortions in women younger than 30 is twice as high for men over 40 as for men aged 25-30. This can be explained by chromosomal anomalies caused by spermatozoa with a lack of chromosomes. In addition, DNA spontaneously changes not only at the chromosome level, but also at the gene level. This determines the occurrence of de novo mutations, that is, those that the parent does not have, but they appeared in his germline and will be in the offspring. So, the vast majority (about 90%) of de novo mutations occur in sperm cells of men over 35 years old. If the new mutation is recessive, it will add to the "silent" genetic burden, which only under a certain number of circumstances may appear in the next

generations. But if there is a dominant mutation, it will manifest itself in the child. There are a lot of such monogenic dominant diseases, their genes are well studied and allow to determine the exact origin of the mutation. The overall risk of giving birth to a child with a dominant mutation is 0.001-0.004%, and for men over the age of 40 it is two orders of magnitude higher: 0.1-0.4%.

And there is also a group of diseases in the development of which the genetic component is important, but it is not yet known exactly. These are, for example, oncology in children, schizophrenia, autism. It turned out that there is a direct link between the risk of these diseases and the age of parents. Especially the age of fathers.

Chromosomal indistinctness and parents' age

The older the parents, the more likely they are to have a child with Down syndrome2.

The ages of mothers and fathers usually correlate: the older the wife, the older their husbands are. In the case of Down syndrome, the increase in risk, as shown in 1933 by Penrose, is due to an increase in the age of the mother. Based on data from 150 cases in which both the mother's age and the father's age are known, he obtained the following specific correlation coefficients:

a) The particular correlation between the age of mothers and the frequency of children with Down syndrome at a constant age of fathers r = +0.221;

b) a particular correlation between the age of fathers and the frequency of Down syndrome in their children r = - 0.011.

Calculation of partial correlations allows us to estimate the correlations between the two variables, excluding the influence of the third one. Penrose analyzed the same data using the regression method and obtained almost the same result.

The effect of the mother's age was recognized and repeatedly confirmed for 50 years. However, several years ago, data were published showing some influence of the father's age, which complements the influence of the mother's age. This involved the study of 224 patients with Down's syndrome born in Denmark between 1960 and 1971, 176 of whom were identified by cytogenetic methods as trisomycs from the

21st chromosome. This sample was compared with a control sample of 6053 randomly selected individuals born in the same country and at the same time, as well as samples described in the literature.

The following results were obtained:

1) The risk of having children with Down syndrome is significantly increased for men aged 55 and over;

2) In almost all large samples studied in published studies, this trisomy is associated with cases where the father's age is much higher than that of the mother.

3) When comparing patients and monitoring privately by age group, it was found that the proportion of fathers of children with Down's syndrome increased, albeit slightly, with an increase in the age of fathers. This finding has been subjected to new and new checks, leading to abrasive results.

Conclusion

Thus, there is no doubt that the formation of aneuploid gametes depends on age and sex, but the mechanisms of these phenomena, despite the presence of many hypotheses, remain unclear. Accordingly, possible ways of preventing the formation of chromosomal anomalies in the process of gametogenesis are not clear. The only real way to prevent chromosomal diseases in the offspring at the present time is prenatal, including preimplantation diagnostics.

Human chromosomes reveal a constant level of individual variability for many generations, also known as heteromorphism. Everyone is responsible for the hereditary well-being of their children, and an important factor is their biological education, as knowledge of anomaly, physiology, genetics will warn people against making mistakes.

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