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MtDNA polymorphism and its role in adaptation to environmental conditions and predisposition to diseases

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Objective: analysis of the role of population polymorphism of human mtDNA in the formation of hereditary adaptation to extreme environmental conditions and predisposition to diseases.

Materials and methods. Genotyping of mitochondrial DNA (mtDNA) is carried out by using various methods, including modern high-performance sequencing technologies. Phylogeographic studies make it possible to reconstruct the family tree of human mtDNA and assess the prevalence of characteristic haplotypes in various populations. Studies of the associations of mtDNA polymorphism with diseases are based on a comparison of the prevalence of haplotypes and individual mtDNA variants in patient groups with ethnically relevant control samples.

Results. The results of studies of mtDNA polymorphism in human populations from different geographical regions indicate that some haplotypes and individual variants of mtDNA can play a role in adaptation of the population to high altitude conditions. Studies of the associations of mtDNA polymorphism with multifactorial diseases have revealed haplogroups and individual mtDNA polymorphisms that affect the risk of developing diseases and their complications depending on the population.

Cunclusion. The study of mitochondrial genome polymorphism is important for the purposes of population, evolutionary and medical genetics. In addition, these studies are of interest to specialists in the history of ethnic groups and cultures and have an interdisciplinary importance.

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Keywords: mitochondrial DNA; genetic adaptation; hereditary predisposition to disease

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Mitochondrial DNA (mtDNA) is a small but important part of our genome. It encoded information on 13 subunits of mitochondrial respiratory chain complexes.

Compared to nuclear genes, mtDNA has several distinctive features: maternal inheritance, lack of recombination in meiosis, and high mutation rate (approximately 10 times higher than in nuclear genes). As in the Y chromosome, new mutations are added to existing ones, forming haplotypes that are unchanged in a number of generations, each of which can be described by a sequence of substitutions with respect to the ancestral sequence (MRCA - the most recent common ancestor) or to a reference sequence mtDNA (rCRS - revised Cambridge Reference Sequence). Mitochondrial DNA is today perhaps the most studied

part of the human genome. The number of sequenced individual mtDNA sequences amounts to tens of thousands; human populations in all regions of the globe have been studied. Detailed phylogeny of mtDNA haplotypes has been created, which reflects the "family ties" of all nucleotide substitutions that have arisen during microevolution. Large clusters in this phylogeny can be divided into “African”, “European” (West Eurasian) and “Asian” (East Eurasian), in accordance with the place of their origin and predominant distribution (Figure 1).

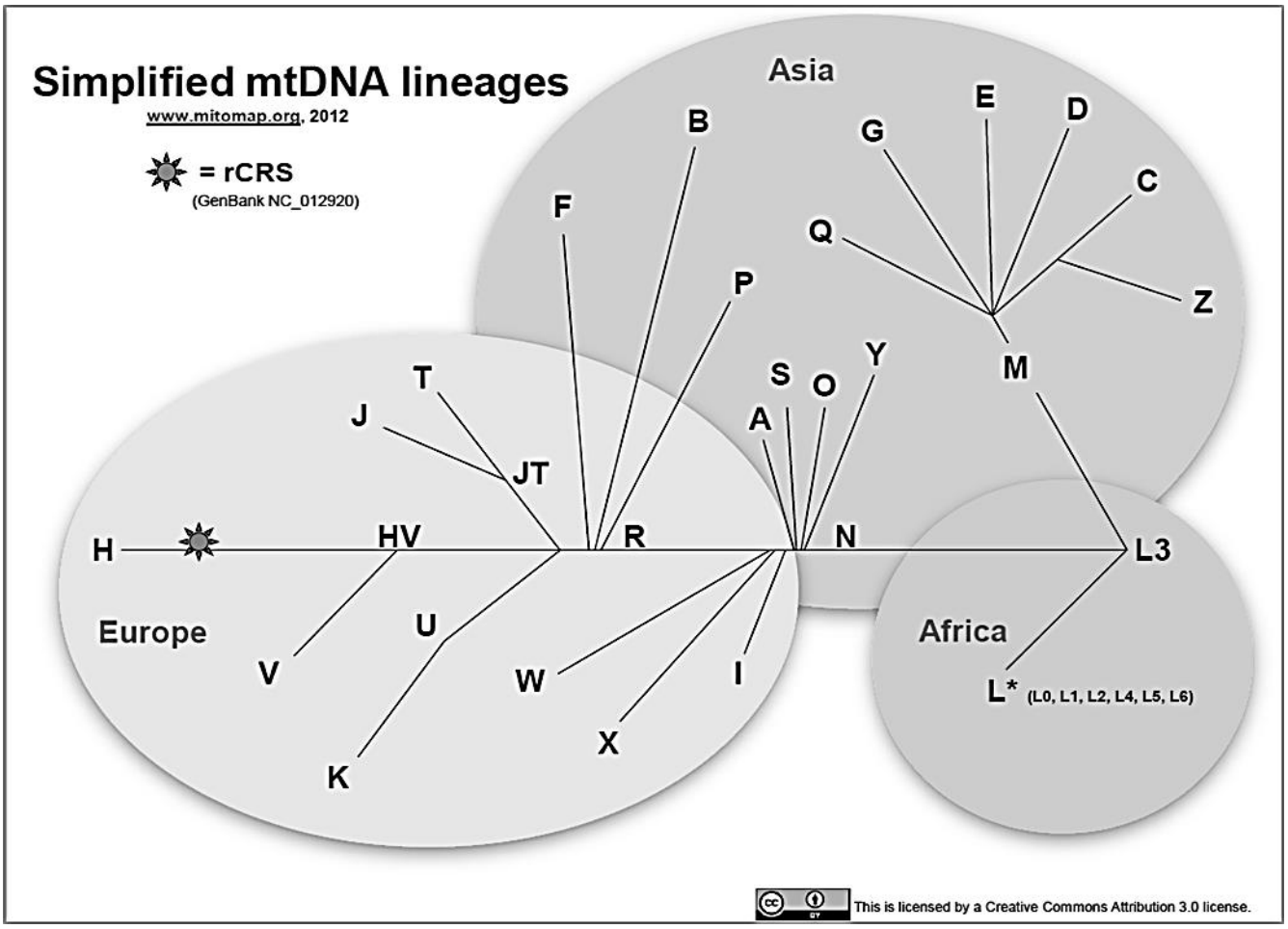

Figure 1. Scheme of the pedigree tree of human mitochondrial DNA (from website www.mitomap.or).

This geographical differentiation can be caused, on the one hand, by the peculiarities of migration processes, as well as by “drift of genes” - a random, non-directional change in gene frequencies in populations of small numbers. On the other hand, the distribution of individual haplogroups and mtDNA haplotypes in some populations living in extreme conditions (for example, in the highlands or in the Far North) may be the result of the selection of locally adaptive combinations of polymorphisms.

On this pedigree tree, there are also variants leading to amino acid substitutions, and mutations in the genes of transport and ribosomal ribonucleic acid (RNA), as well as reverse and second mutations. Since mtDNA encodes mitochondrial respiratory chain proteins, that is, it is involved in the vital functions of the cell, it is logical to assume that the resulting mtDNA mutations may be subject to selection. The results of numerous studies of the associations of mtDNA polymorphism with susceptibility to various diseases indicate the functional significance of population polymorphism. However, these results are often contradictory - it is possible because the qualitative and quantitative composition of mtDNA population gene pools is “region-specific”.

Adaptive and functional role of mtDNA polymorphism

Mitochondrial DNA encodes the vital proteins involved in the synthesis of Adenosintriphosphate (ATP), as well as the ribosomal and transport RNA required for their translation. Although mtDNA polymorphism has been one of the main DNA tools of human population and evolutionary genetics for many years, the neutrality of this polymorphism is not indisputable, and the question of the effect of selection on the mtDNA polymorphism pattern in human populations has long been raised. In some cases, it was really possible to identify this effect. For example, an analysis of the ratio of synonymous and non-synonymous substitutions in European mtDNA haplogroups revealed traces of the action of selection in several lines [5]. As has been shown, for climate adaptation, substitutions in the genes of cytochrome B and ATP synthase are of particular importance. As a result of comparison of synonymous and nonsynonymous substitutions in the phylogeny of human mtDNA, it was shown that haplogroup J mtDNA is under the influence of selection and that the influence of selection in mitochondrial lines should be taken into account when assessing the age of coalescence of haplogroups [20].

It is known that haplogroups H and J of mtDNA differ in the efficiency of oxidative phosphorylation and production of reactive oxygen species: H is characterized by higher values of these indicators, and J - lower. This was demonstrated using cybrids, cell lines that have the same nuclear genome but differ in mtDNA genotype. Comparison of the haplo group H and the African super haplogroup L revealed differences in the production of ATP and ROS, as well as in the expression level of some nuclear genes [12]. Cell lines with haplogroup T were more resistant to oxidative stress [16], while cybrid lines with haplogroup J had a higher growth rate and higher survival rate at sublethal doses of ultraviolet radiation [13]. In patients with asthenozoospermia with haplogroup T, when studying the activity of oxidative phosphorylation, a decrease in the efficiency of the first complex was found to be reduced by 23%, and the fourth complex - by 29%, compared with haplogroup H [21]. In the highlands, the oxygen content in the air is reduced, and the body experiences oxygen starvation (at an altitude of more than 1800 m above sea level). Under these conditions, mtDNA lines that provide the most efficient operation of the electron transport chain of mitochondria can have an advantage. In particular, among the Sherpas in the high mountain populations of Tibet, the predominance of haplogroups C4a3b1 and A4e3a was revealed [11]. In another study, the “risky” effect of haplogroup B and the “protective” effect of haplogroup D4 in the Chinese were revealed in relation to the development of pulmonary edema induced by hypoxia [14]. A comparison of the highland and lowland populations of Dagestan revealed differentiation according to several variants of nuclear genes, apparently providing adaptation to altitudinal hypoxia, however, mtDNA was not studied in this work [19]. Associations of mtDNA polymorphism with longevity and multifactorial diseases.

The hypothesis of “free-radical aging” of Harman is widely known [8], according to which the aging of the body is largely determined by increasing mitochondrial dysfunction (and, accordingly, an increase in the production of free radicals). Mitochondrial dysfunction, in turn, can be caused by mtDNA damage that accumulates over the course of a lifetime. If mtDNA polymorphism also affects the conjugation / uncoupling of oxidative phosphorylation, then this may affect individual “starting conditions” for aging processes and the possibility of long-term life.

The results of the studies indicate a possible role of the mtDNA polymorphism in the formation of a predisposition to longevity, however, the identified associations in most cases are population-specific. For example, haplogroup J was associated with increased chances of surviving to a hundred years of age in Northern Italy and Finland [7, 17]. In Japan, similar associations are shown for several branches of haplogroup D [18], and in France for haplogroup U-K [10]. Thus, although each population has its own mtDNA lines associated with longevity, we can assume that there are common features between them: for exam-

ple, repeating variants in certain genes or in mtDNA expression/replication regulation sites. To study this issue, it is necessary to study new populations. In this regard, various regions of the Caucasus are of particular interest, which are characterized by both a significant number of centenarians and a diverse ethnic composition, i.e. in the same territory with similar climatic conditions, several isolated gene pools coexist.

MtDNA polymorphism can also be associated with diseases of the central nervous system - in particular, with Alzheimer's disease. As for longevity, in different populations, the association was revealed for different mtDNA haplogroups. For example, in the Italian population, the risk factor for Alzheimer's disease was haplogroup H5 [22], and in the Polish population, haplogroup HV [15]. When analyzing the associations of mtDNA polymorphism and Parkinson's disease, it was demonstrated that mitochondrial haplogroups K and J had a protective effect, reducing the risk of developing the disease by almost 50% [23].

Cardiovascular disease is one of the leading causes of death in the modern world. Studies of associations of mtDNA polymorphism with various diseases and phenotypes of the cardiovascular system indicate the role of mtDNA variants in forming the risk of development of cardiovascular diseases and their complications. In particular, we have shown that haplogroup H1 is associated with early death from cardiovascular disease [4]. The same adverse effect for haplogroup H1 was also revealed with respect to the risk of developing repeated cardiovascular catastrophes (myocardial infarction, ischemic strokes, progression of heart failure) within a year after the first myocardial infarction. The risk factor for early myocardial infarction (up to 55 years) was the haplogroup U2e and the replacement of T16189C [2]. Analysis of mtDNA polymorphism in arterial hypertension showed that haplo group T increased the risk of developing left ventricular hypertrophy of the heart, and haplogroup H had a protective effect on heart hypertrophy [1]. Haplogroup J was more common in older people without clinically pronounced atherosclerosis of the carotid arteries and other cardiovascular diseases, compared with patients whose carotid artery stenosis was more than 50% [3]. Associations of polymorphism mtDNA with quantitative character variability were also detected: for example, haplogroup H and variant 16519C were associated with body mass index in patients with acute coronary syndrome, and in patients with type 2 diabetes mellitus, haplogroup H has been associated with higher fasting blood glucose values; an association of haplogroup U with the thickness of the intima-media complex of the carotid arteries was revealed, an association of haplogroup H with cholesterol level and glucose values in the blood of individuals upon admission to hospital was found [6].

Thus, we can say that the effect of mtDNA polymorphism at the level of the phenotype of the cardiovascular system is more often not in predisposition to cardiovascular diseases as a whole, but in modulating the risk of complications and comorbid phenotypes in the limits of the cardiovascular continuum.

The role of mtDNA polymorphism in the manifestation of hereditary mitochondrial diseases

Perhaps the most famous example of the influence of the genetic background on the phenotypic expression of mtDNA mutations is the fact that in European populations Lebera ophthalmopathy (LHON) mutations are more often manifested against the background of haplogroup J. For example, in the German population the frequency of this haplogroup is about 7%, but among patients with LHON - 60% [9]. This effect of haplogroup J is associated with a large number of amino acid substitutions in the genes of subunits of NADH-dehydrogenase (the first complex of the respiratory chain). The significance of the background genotype for LHON mutations was also shown in the Mongoloid population: in Chinese, these mutations are more likely to appear against the background of haplogroup M7b and less often against haplogroup F [24].

Another “frequent”, repeatedly occurring mtDNA mutation in humans, leading to mitochondrial diseases, is the replacement of

A3243G in one of the two leucine transport RNA genes, usually associated with MELAS syndrome - Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (mitochondrial encephalopathy, lactic acidosis, stroke-like seizures). In a study conducted in the Finnish population (a total of 245 201 people were examined), 11 individuals with symptoms of mitochondrial diseases had this mutation, and in half of them, mtDNA belonged to haplogroup U, which is determined by A12308G polymorphism in another transfer RNA gene leucine. In general, in the Finnish population, haplogroup U is found with a much lower frequency - about 25%. In France, in patients with the A3243G mutation, a statistically significant "protective" effect of haplogroup J was found: it was less frequently recorded in the patient sample compared to the population [20]. Interestingly, the U2e haplogroup, which is found in the French with a very low frequency (no more than 1%, according to various publications), was represented in 5 patients with A3243G in patients with different HVSI haplotypes (3.65%; differences with a population are not statistically significant).

The data presented indicate that in hereditary diseases the "genetic background" of the locus in which the mutation occurred can affect its phenotypic manifestation.

Conclusion

The study of the mitochondrial genome in human populations plays an important role in the development of population, evolutionary, and medical genetics. In addition, these studies have interdisciplinary significance, since their results complement and refine the picture of the history of ethnic groups, which is the subject of study of the humanities. The structure of the gene pool of the population of multinational Dagestan is unique, and its study is relevant both for phylogeographic studies and for the search for possible adaptive options and a description of the patterns of mtDNA microevolution.

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The authors declare no apparent and potential conflicts of interest related to the publication of this article.

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