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DISEASES CAUSED BY MITOCHONDRIAL DNA MUTATIONS

V. Matiiuk ORCID 0000-0002-2286-6337

Institute of Pig Breeding and Agro-Industrial Production of the National Academy of Agrarian Sciences of Ukraine, 1 Shvedska Mohyla St., Poltava, 36000, Ukraine
E-mail: kaleriya200600@gmail.com

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This article highlights data on diseases caused by mitochondrial DNA mutations. The purpose of the review was to reveal existing diseases that arise as a result of mtDNA mutations. Mitochondrial diseases are diseases that are most often caused by genetically determined structural and functional disorders of mitochondria, and as a result, the energy supply of cells is disrupted. All mitochondrial diseases are transmitted through the maternal line, so if mutations are detected in time, they can be blocked and the further inheritance will be stopped. It is suggested that the role of mitochondrial DNA in certain diseases began to develop rapidly in 1988 when the first mutations in mitochondrial DNA were discovered. To understand the course and development of mitochondrial DNA, it is necessary to understand the structure and functional properties of the mitochondrial cell. MtDNA is a circular DNA molecule and is localized in mitochondria. Such organelles can replicate, transcribe, and translate their own DNA independently of nuclear DNA. Mitochondrial DNA can mutate more than 10 times more often than nuclear DNA. MtDNA has no protective functions against the phenomena of mutations. A mitochondrial cell can contain both mutant DNA and normal DNA. In genetics, such a condition is called heteroplasmy, which allows the survival of a lethal mutation. Single deletions, large deletions, and multiple deletions that are transmitted autosomally and have different phenotypic manifestations are the primary cause of the development of mitochondrial diseases. Scientists also identify systemic manifestations of mitochondrial DNA mutations. they include endocrine manifestations (diabetes), neurological diseases, gastrointestinal manifestations (acid-alkaline imbalance), and pulmonary manifestations (myoclonic epilepsy, hypoventilation abnormalities). Several main principles of treatment of mitochondropathies are distinguished: following a diet; additional introduction of cofactors involved in enzymatic reactions of energy metabolism (thiamine, riboflavin, nicotinamide, lipoic acid, biotin, carnitine); prescription of drugs, capable of carrying out the function of transferring electrons in the respiratory chain (vitamins K1 and K3, ascorbic acid).

***Keywords**: mitochondrial DNA, diseases, mutations, diseases, genes, cells, mitochondria.*

ХВОРОБИ, СПРИЧИНЕНІ МУТАЦІЯМИ МІТОХОНДРІАЛЬНОЇ ДНК

В. В. Матіюк
Інститут свинарства і агропромислового виробництва НААН, м. Полтава, Україна

Ця стаття висвітлює дані щодо хвороб, спричинених мутаціями мітохондріальної ДНК. Метою огляду було розкрити наявні хвороби, які виникають внаслідок мутацій мтДНК. Мітохондріальні хвороби – це захворювання, які найчастіше зумовлені генетично обумовленими структурними та функціональними порушеннями мітохондрій, внаслідок чого порушується енергетичне забезпечення клітин. Усі мітохондріальні хвороби передаються по материнській лінії, тому, якщо мутації вчасно виявити, їх можна заблокувати і подальше успадковування буде припинено. Є припущення, що роль мітохондріальної ДНК у певних захворюваннях розпочала швидко розвиватися з 1988 року, коли були виявлені перші мутації в мітохондріальній ДНК. Для усвідомлення перебігу та розвитку

мітохондріальної ДНК потрібно розуміти будову та функціональні властивості мітохондріальної клітини. МтДНК є кільцевою молекуло ДНК і локалізована в мітохондрії. Такі органели мають змогу реплікувати, транскрибувати та транслювати свою власну ДНК незалежно від ядерної ДНК. Мітохондріальна ДНК може мутувати бчльш ніж у 10 разів частіше, ніж ядерна ДНК. МтДНК не має захисних функцій від явищ мутацій. Мітохондріальна клітина може містити водночас як мутантну ДНК, так і нормальну ДНК. У генетиці такий стан називають гетероплазмія, що дозволяє зберегтися летальній мутації. Першопричиною розвитку мітохондріальних захворювань є поодинокі делеції, великі делеції, множинні делеції, що передаються аутосомно та мають різні фенотипові прояви. Вчені виділяють і системні прояви мутацій мітохондріальної ДНК. Вони включають: ендокринні прояви (цукровий діабет), неврологічні захворювання, шлунково-кишкові прояви (порушення кислотно-лужного балансу), легеневі прояви (міоклонічна епілепсія, гіповентиляційні аномалії). Виокремлюють декілька головних принципів лікування мітохондропатій: дотримання дієти; додаткові введення кофакторів, що беруть участь в ензимних реакціях енергетичного обміну (тіамін, рибофлавін, нікотинамід, ліпоєва кислота, біотин, карнітин); призначення препаратів, здатних здійснювати функцію перенесення електронів у дихальному ланцюзі (вітаміни К1 і К3, аскорбінова кислота).

***Ключові слова**: мітохондріальна ДНК, хвороби, мутації, захворювання, гени, клітини, мітохондрії.*

Mitochondrial encephalomyopathy is a diverse group of disorders resulting from structural, biochemical, or genetic abnormalities of mitochondria (Fig. 1) [1]. Despite the amazing array of clinical manifestations (ophthalmoplegia, stroke, convulsions, myoclonus, optic neuropathy, myopathy, fatigue and exercise intolerance, elevated cerebrospinal fluid protein, sensorineural hearing loss, ataxia, dementia) and variations in the development, course and progression of the disease, many mitochondrial disorders have clear systemic effects (cardiac conduction disorders, cardiomyopathy, diabetes, short stature, hypoparathyroidism, retinopathy pigmentosa, cataracts, lactic acidosis, hearing loss, proximal spinal cord dysfunction, glomerulopathy, intestinal pseudoobstruction, psychiatric disorders) that contribute to their morbidity.

It can be assumed that the role of mitochondrial DNA in certain diseases began to develop rapidly since 1988, when the first mutations in mitochondrial DNA were discovered [2, 3]. Such mutations have subsequently been identified in various diseases, [4-7] and the pathogenic role of cumulative mitochondrial DNA damage is being investigated in many common diseases that develop in late life and even in the aging process itself.

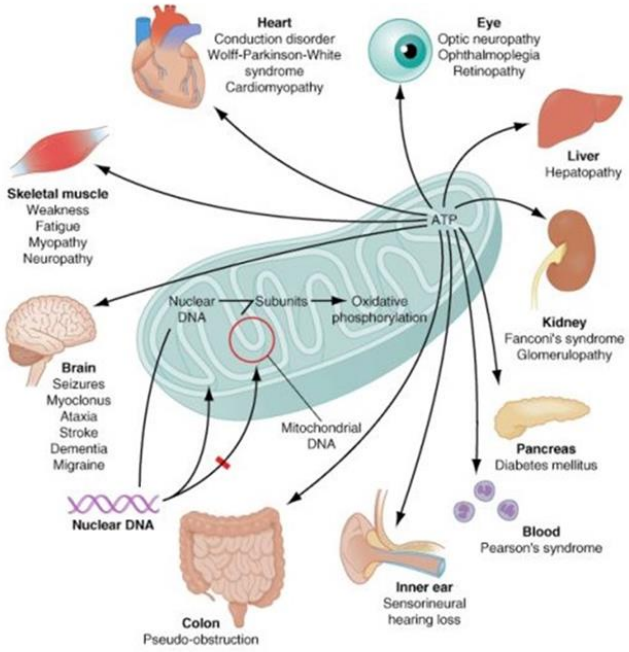

Fig. 1. Interaction between genes encoded by nuclear DNA and genes encoded by mitochondrial DNA during oxidative phosphorylation.
Source: [1].

To understand mitochondrial disease, one must first study the unique features of mitochondrial DNA. Mitochondria are cellular organelles that generate energy for cellular processes by producing ATP through oxidative phosphorylation. These organelles contain their own extrachromosomal DNA, which differs from the DNA in the nucleus [8]. Mitochondrial DNA or mtDNA is a circular DNA molecule localized in mitochondria, cytoplasmic organelles of most eukaryotic cells, which have the appearance of filamentous or granular formations. The localization of mtDNA differs from the localization of most DNA of eukaryotes, which is located in the nuclei of cells. It is a double-stranded circular molecule that encodes 13 protein subunits, 4 biochemical complexes, and 24 structural RNAs (2 ribosomal RNAs [rRNAs] and 22 transport RNAs [tRNAs]) that are required for intramitochondrial translation of protein-coding units [9]. Mitochondrial DNA mutations were detected in each type of mitochondrial gene (Fig. 2).

Mitochondria, which probably evolved from independent organisms that became part of the cell, are capable of replicating, transcribing, and translating their DNA independently of nuclear DNA. However, cell function and mitochondrial function are interdependent [10]. Nuclear DNA encodes protein subunits for oxidative phosphorylation and numerous macromolecular compounds required for mitochondrial structure and function (eg, replication, transcription, and translation). Proteins encoded by nuclear DNA must be imported from the cytoplasm to the correct position in the mitochondria [8].

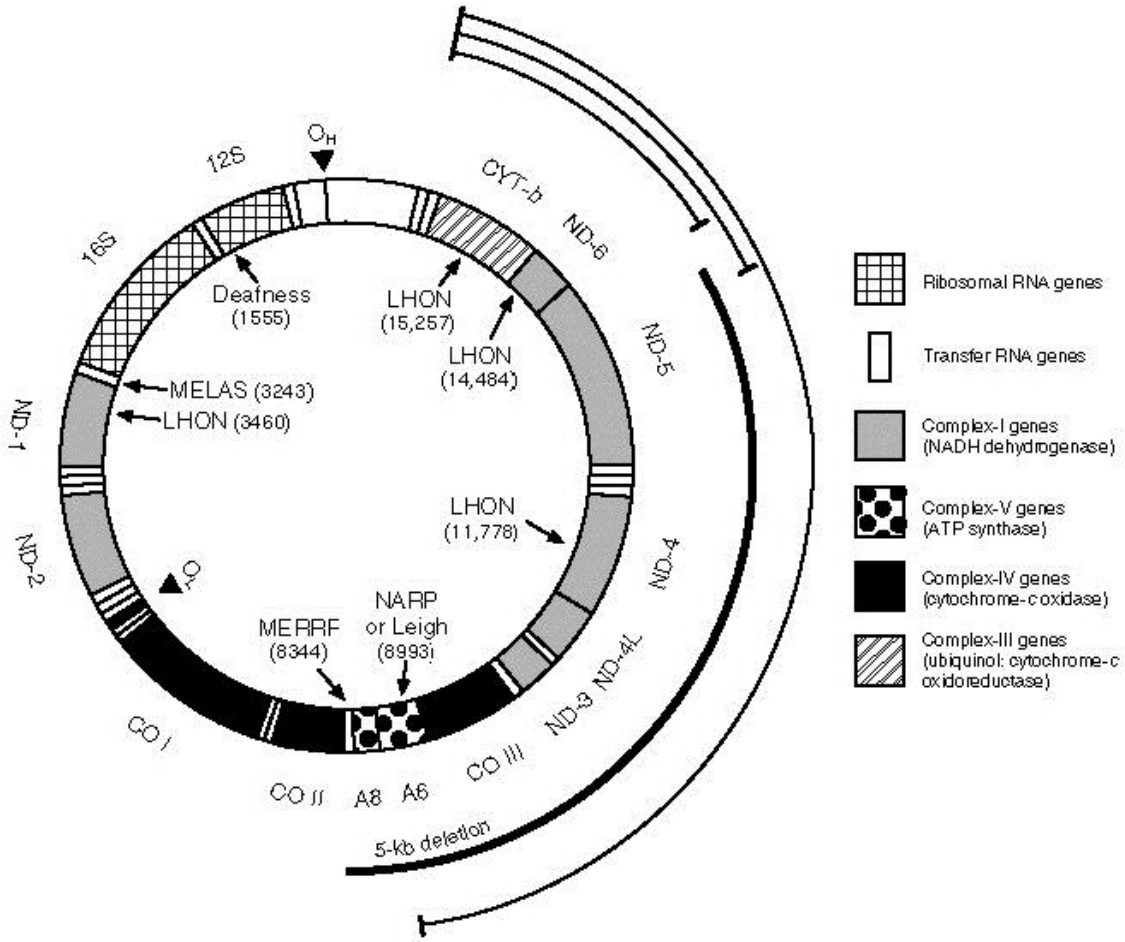

Fig. 2. Diagram of mitochondrial DNA and the most common associated pathogenetic mutations.
Source: [1].

During oxidative phosphorylation, energy is derived from intermediate metabolites to produce ATP via an electrochemical gradient. This biochemical process depends on tRNAs encoded by mitochondrial DNA, which cleave multigene transcripts into individual matrix RNAs and tRNAs [10].

Several features of mitochondrial DNA may account for its frequent association with disease. Mitochondrial DNA mutates more than 10 times more often than nuclear DNA and has no introns, so a random mutation usually affects the coding sequence of the DNA. In addition, mitochondrial DNA has

neither protective histones nor an effective repair system, and it is exposed to free oxygen radicals produced as a result of oxidative phosphorylation.

Mitochondrial DNA is inherited through the maternal line and does not recombine; mutations thus accumulate sequentially through the maternal line. Each mitochondrion contains between 2 and 10 DNA molecules, and each cell contains several mitochondria. Thus, normal and mutant mitochondrial DNA can coexist in the same cell. This condition, known as heteroplasmy, allows the lethal mutation to persist. Homoplasmy is the presence of either completely normal or completely mutant mitochondrial DNA. Thus, the principles of population genetics, not the principles of Mendelian genetics, govern mitochondrial DNA. Selection pressure occurs at the molecular and cellular levels, as well as at the level of the organism itself.

The classic mitochondrial phenotypes described below are caused by gross structural rearrangements (single deletions, multiple deletions, or duplications) or point mutations in mitochondrial DNA. Mutations that can potentially cause lethal disruption of oxidative phosphorylation (gross structural defects or point mutations in critical regions) are viable only if they are heteroplasmic. Most of the milder, missense mutations in protein-coding genes are homoplasmic.

Until 1988, when the first abnormal mitochondrial DNA was identified, many diseases were provisionally classified as mitochondrial disorders due to abnormal morphological or biochemical features of mitochondria or patterns of maternal inheritance. The first direct evidence that mitochondrial DNA was involved in the disease came from two observations: the detection of large deletions in mitochondrial DNA with mitochondrial myopathy [2] and the detection of a missense mutation in mitochondrial DNA with Leber's hereditary optic neuropathy [3]. Over the next few years, the molecular genetic basis of classic mitochondrial encephalomyopathies was clarified [4-7]. These disorders are relatively rare, but they were the first molecularly defined examples of many cardinal neurological diseases, including stroke (mitochondrial encephalomyopathy syndrome, mammary acidosis and stroke-like episodes [MELAS]), seizures (MELAS syndrome and myoclonic epilepsy with irregular red fibers) and optic neuropathy (Leber's hereditary optic neuropathy).

Among these diseases, there is also a syndrome of multiple deletions that is transmitted autosomally and has various phenotypic manifestations in mitochondrial DNA, most of which are variants of chronic progressive external ophthalmoplegia [12, 13, 18, 19]. Multiple deletions differ from single deletions in their mode of inheritance, location in the mitochondrial genome, and molecular structure. Unlike single deletions, which are almost always sporadic, multiple deletions can be transmitted in autosomal dominant and autosomal recessive patterns [18]. The model of autosomal inheritance suggests the existence of a gene encoded by nuclear DNA that affects the structure of normal DNA.

There are also systemic manifestations of mitochondrial DNA mutations. Virtually all tissues in the body depend to some extent on oxidative metabolism and therefore can be affected by mitochondrial DNA mutations. Non-syndromal deafness, which is also transmitted from the mother and due to the known effect of aminoglycosides on bacterial ribosomes, has a negative effect, which causes the development of deafness [11].

Endocrine manifestations are frequent, and the incidence of diabetes is relatively high. Pancreatic islet cells are extremely active metabolically and, therefore, are sensitive to impaired oxidative phosphorylation. Diabetes mellitus associated with mitochondrial DNA mutations is mainly caused by a defect in insulin secretion. The disorder has been associated with a heteroplasmic point mutation in the tRNALeu (UUR) gene at nucleotide position 3243, usually associated with sensorineural hearing loss [11,20]. Other neurological features associated with this mutation, such as MELAS syndrome or nondeletional chronic progressive external ophthalmoplegia. Diabetes mellitus, which is a treatable feature of a number of mitochondrial diseases, may thus be the predominant manifestation of a mitochondrial DNA mutation.

Gastrointestinal manifestations of mitochondrial DNA mutations include colonic pseudo-obstruction, [19] hepatopathy and weight loss. The most pronounced renal manifestation is a type of nonselective dysfunction of the proximal nephron with aminoaciduria, phosphaturia, and glucosuria, reminiscent of Fanconi syndrome. Lactic acidosis and acid-base imbalance or glomerulopathy may attract the attention of nephrologists. Pearson syndrome of pancreatic exocrine dysfunction, sideroblastic hypoproliferative anemia, and pancytopenia occur in association with large single deletions in mitochondrial DNA. Other forms of sideroblastic anemia or aplastic anemia may also be associated with acquired or inherited mitochondrial DNA mutations. Multiple symmetrical lipomas with a characteristic location on the chest in the form of a collar arise in connection with a mutation of mitochondrial DNA at the position of nucleotide 8344.22,23

The most prominent pulmonary manifestations of mitochondrial DNA mutations are the central hypoventilatory abnormalities of Leigh disease and severe cases of myoclonic epilepsy with ragged red fibers. A mildly elevated creatine kinase, along with muscle fatigue, poor endurance, and poor endurance,

may draw the attention of rheumatologists to patients with mitochondrial disease, possibly leading to the evaluation of inflammatory myopathy. Psychiatric manifestations, especially depression, have been noted in association with multiple mitochondrial DNA deletions [37].

Among the main principles of treatment of mitochondropathies: following a diet; additional introduction of cofactors involved in enzymatic reactions of energy metabolism (thiamine, riboflavin, nicotinamide, lipoic acid, biotin, carnitine); the appointment of drugs capable of carrying out the function of electron transfer in the respiratory chain (vitamins K1 and K3, ascorbic acid); reduction of lactic acidosis by stimulating the activity of mitochondrial enzymes (dichloroacetate, 2-chloropropionate); prevention of oxygen radical damage to mitochondrial membranes (ascorbic acid, vitamin E); symptomatic treatment (artificial lung ventilation, hemotransfusion, intravenous administration of soda solutions, etc.) [49].

Conclusions

The analysis of general data, which were highlighted in a number of scientific works, proves the need to continue studying the mechanisms of mitochondrial DNA influence on the body. The relevance of the chosen topic lies in the detailed consideration of diseases, solving problems with morbidity caused by mtDNA and methods of treatment. Mitochondrial DNA is inherited through the maternal line and does not recombine further, so mutations thus accumulate sequentially through the maternal line. Each mitochondrion can contain between 2 and 10 DNA molecules, and each cell contains several mitochondria. Normal and mutant mitochondrial DNA can coexist in the same cell. This condition, known as heteroplasmy, allows the lethal mutation to persist. Each mitochondrial disorder is amenable to treatment or blocking of further mutations in the maternal line of the organism.

Prospects for further research. Further research of possible and existing mitochondrial DNA mutations and measures to prevent the creation of new ones remains a promising direction; improving the principles of treatment of mitochondrial disorders. Detailed studies of mitochondrial diseases also provide insight into fundamental biological processes such as oxidative phosphorylation and aging.

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