Animal Models of Mitochondrial Diseases Associated with Nuclear Gene Mutations

O. A. Averina[1,2,3], S. A. Kuznetsova[1*], O. A. Permyakov[1,3], P. V. Sergiev[1,2,3]
[1]Institute of Functional Genomics, Lomonosov Moscow State University, Moscow, 119991 Russian Federation
[2]Belozersky Institute of Physico-Chemical Biology, Lomonosov Moscow State University, Moscow, 119991 Russian Federation
[3]Department of Chemistry, Lomonosov Moscow State University, Moscow, 119991 Russian Federation
*E-mail: svetlana@belozersky.msu.ru
Received: August 25, 2023; in final form, October 05, 2023
DOI: 10.32607/actanaturae.25442

ABSTRACT **Mitochondrial diseases (MDs) associated with nuclear gene mutations are part of a large group of inherited diseases caused by the suppression of energy metabolism. These diseases are of particular interest, because nuclear genes encode not only most of the structural proteins of the oxidative phosphorylation system (OXPHOS), but also all the proteins involved in the OXPHOS protein import from the cytoplasm and their assembly in mitochondria. Defects in any of these proteins can lead to functional impairment of the respiratory chain, including dysfunction of complex I that plays a central role in cellular respiration and oxidative phosphorylation, which is the most common cause of mitopathologies. Mitochondrial diseases are characterized by an early age of onset and a progressive course and affect primarily energy-consuming tissues and organs. The treatment of MDs should be initiated as soon as possible, but the diagnosis of mitopathologies is extremely difficult because of their heterogeneity and overlapping clinical features. The molecular pathogenesis of mitochondrial diseases is investigated using animal models: i.e. animals carrying mutations causing MD symptoms in humans. The use of mutant animal models opens new opportunities in the study of genes encoding mitochondrial proteins, as well as the molecular mechanisms of mitopathology development, which is necessary for improving diagnosis and developing approaches to drug therapy. In this review, we present the most recent information on mitochondrial diseases associated with nuclear gene mutations and animal models developed to investigate them.**

KEYWORDS **mitochondrial diseases, nDNA, mutations, animal models.**

ABBREVIATIONS **MD – mitochondrial disease; mtDNA – mitochondrial DNA; nDNA – nuclear DNA; OXPHOS – oxidative phosphorylation; NADH – reduced form of nicotinamide adenine dinucleotide; FGF – fibroblast growth factor.**

INTRODUCTION

Mitochondrial diseases (MDs), which are caused by nuclear gene mutations, are a heterogeneous group of inherited diseases affecting all mitochondrial processes. Nuclear DNA (nDNA) encodes not only most of the structural proteins of the oxidative phosphorylation (OXPHOS, approximately 80 proteins) system, but also all the proteins necessary for OXPHOS protein import from the cytoplasm and their assembly in mitochondria. Defects in any of these proteins can lead to functional impairment of the respiratory chain and, therefrom, the development of MDs. Similar negative effects can also be induced by dysfunction in the proteins that control the stability and/or integrity of mitochondrial DNA (mtDNA). MDs are also caused by some disorders associated with the dysfunction of proteins from other organelles, such as WFS1, in the endoplasmic reticulum, or EIF2S3, in the cytoplasm [1, 2].

nDNA mutations associated with MDs are autosomal-dominant or recessive and can be located on the X chromosome as well. They are found in more

than 300 genes, which accounts for 78.5% of the total number of genes whose mutations are associated with MDs [3, 4].

Oxidative phosphorylation provides energy to most mammalian cells and tissues. The OXPHOS system includes five multisubunit protein complexes comprising more than 80 nDNA-encoded proteins and 13 mtDNA-encoded subunits. Mutations in the individual components of OXPHOS result in a heterogeneous group of inborn errors of metabolism – primary MDs.

The most common cause of MDs is a dysfunction in complex I, the largest OXPHOS enzyme complex, which plays a central role in cellular respiration and oxidative phosphorylation [5]. Complex I deficiency symptoms most often manifest in childhood: approximately 75% of patients do not survive beyond the age of 10 years, and almost 50% of them die before the age of 2 years [6]. The first report of a mutation in an nDNA-encoded complex I subunit, causing Leigh syndrome, happened in 1998 [7]. Leigh syndrome is diagnosed in almost 80% of children with complex I deficiency, and approximately 70% of these are associated with nDNA mutations. Leigh syndrome patients experience encephalopathy, hypotonia, developmental retardation, psychomotor dysfunction, dystonia, seizures, dysphagia, respiratory dysfunction, and early mortality [8]. Complex I (NADH:ubiquinone oxidoreductase) is a 1 MDa L-shaped multiprotein complex comprising 45 different subunits arranged into six modules (N, Q, ND1, ND2, ND4, and ND5) located on hydrophobic and hydrophilic (peripheral) arms. Mutations in 39 different nuclear genes are associated with MDs caused by complex I deficiency. Most nuclear gene mutations associated with MDs are located in the NADH dehydrogenase subunit and hydrophilic arm Q-module genes. Mutations have been found both in the main catalytic subunits (NDUFV1, NDUFV2, NDUFS1, NDUFS2, NDUFS3, NDUFS7, and NDUFS8) and in the subunits responsible for complex I assembly and stability (NDUFS4, NDUFS6, NDUFA2, NDUFA12, NDUFA13, NDUFA1, NDUFA6, NDUFA8, NDUFA9, NDUFA10, NDUFA11, NDUFB3, NDUFB8, NDUFB9, NDUFB10, NDUFB11, and NDUFC2), which cumulatively are responsible for NADH:ubiquinone oxidoreductase deficiency. Destabilization of complex I also leads to several additional defects, including changes in the mitochondrial network morphology, membrane potential, and intracellular calcium homeostasis, as well as overproduction of reactive oxygen species. Data on mutations in 13 genes associated with MDs, *NDUFA5*, *NDUFAB1*, *NDUFS5*, NDUFB4, *NDUFV3*, *NDUFC1*, *NDUFB1*, *NDUFB2*, *NDUFB5*, *NDUFB6*, *NDUFAF7*, *ECSIT*, and *NDUFA3* have not yet been obtained and/or reported. However, due to the increasing application of exome or whole-genome sequencing, new pathological mutations may be identified in the near future [3, 5].

Diagnosis of MD, which includes the assessment of serum lactate, alanine, glucose, and FGF levels, electron microscopic and histochemical analysis of mitochondrial ultrastructure, and evaluation of the enzymatic activity of OXPHOS components, is a complex task. The heterogeneous clinical manifestations of MDs complicate the achievement of a correct diagnosis and choice of an appropriate therapy. Many MD symptoms share the features of other hereditary diseases, such as diabetes mellitus, stroke, or cardiomyopathy [4]. These issues can be addressed by using animal MD models. Mutant animal models may shed light on the mechanisms that underlay MD development and the functions of the genes that encode mitochondrial proteins. Highly conserved mitochondrial proteins offer a wide array of choices of models that can be tapped to study the consequences of mutations in humans.

ANIMAL MODELS OF MITOCHONDRIAL DISEASES

The choice of an animal MD model is always a matter of much debate. No model is inherently "good" or "bad"; the value of a particular model may only be assessed in the context of a specific project. The choice of the species, sex, and genetic properties of a model animal is based on the direction and aims of the research to achieve the most adequate transfer of the results obtained in animals to humans. It is also necessary to evaluate the possibility of using organisms from a lower step on the evolution ladder to obtain representative results without compromising their quality. The choice of a model animal should account for the factors of its availability, ease of manipulation, cost of research, ease of maintenance, and genetic and physiological homology. Genetic divergence between humans and other mammals is about 90 million years. For example, this divergence between humans and model animals such as dwarf pigs (*Porcula salvania*) and sheep (*Ovis aries*) or rabbits (*Oryctolagus cuniculus*) and rats (*Rattus norvegicus*) amounts to 94 and 87 million years, respectively [9]. For this reason, the genomes of all mammals are considered relatively similar. However, it is the laboratory mouse (*Mus musculus*) that has remained the quintessential model animal used to study human genetic MDs for many years. In general, mice and humans have almost the same set of genes. The protein-coding regions of the mouse and human genomes are approximately 85% identical. Almost every gene found in one species is identified as a closely related form in the other; in this case,

some genes are 99% identical, while others are only 60% identical [10].

The first genetic studies in mice were based not on changes in the disease-modeling genotype, but on the disease-resembling phenotypes resulting from random spontaneous mutations or exposure to mutagenic factors. The advent of mouse genome editing techniques has eliminated the need to select the appropriate phenotype after random mutagenesis and enabled the generation of specific mutations in the mouse genome and the investigation of their consequences. Thus, mouse models are extremely important for elucidating the functions of genes and studying the pathological processes associated with mutations in these genes [11].

Mice with altered genomes, which model more than 50% of MDs associated with nuclear gene mutations, have been generated. However, complete inactivation of the gene under study leads to 50% embryonic lethality, although this pathological mutation can cause death at an early age [3–5, 12]. To overcome this obstacle in disease modeling, animals with heterozygous mutations in the gene of interest are examined. While some heterozygous mutants do not display a pathological phenotype, others become model animals; e.g., heterozygous *Risp*$^{+/P224S}$ mice exhibit obviously reduced activity of mitochondrial complex III [13], and *Tfam*$^{+/-}$ mice are characterized by mtDNA depletion syndrome (severe decrease in mtDNA content) characteristic of people with a mutation in this gene [14]. Another approach to the investigation of vital genes is the generation of conditional tissue-specific knockouts of these genes. These knockouts have been developed for almost all lethal mutations in the nuclear genes of MDs in the tissues and organs that are most affected by each specific mutation [3–5, 12]. In the case of embryonic lethality, the ideal study object is the eggs of the *Danio rerio* fish and the *Xenopus laevis* amphibian and their fry and tadpoles, respectively [15–17]. These models have recommended themselves well in genome editing studies [18]. At early developmental stages, *D. rerio* and *X. laevis* are translucent, which enables continuous, real-time assessment and monitoring of the development of major internal organs. In this case, *D. rerio* and *X. laevis* develop independently of the parent organism and are available for direct exposure to agents at different embryogenesis stages [19]. In addition, a battery of behavioral tests has been developed to analyze neurodegenerative disorders in these animals [20, 21].

Unfortunately, there are situations when the mouse genome manipulations that should lead to MD development do not reflect the clinical picture associated with the pathological mutation in humans [22]. On the one hand, such results are associated with a higher resistance of mice to MDs [23], and on the other, some mutations in humans can manifest themselves in combination with more complex factors, such as lifestyle and concomitant diseases [24]. In these cases, a solution may be to use another animal model. For example, people carrying a mutation in the gene encoding a mitochondrial protein involved in cytochrome *c* oxidase assembly are diagnosed with Leigh syndrome, but constitutive *SURF1*$^{-/-}$ knockout mice do not reproduce the severity of the clinical phenotype in humans. In this case, *SURF1*$^{-/-}$ mutant pigs characterized by failure to thrive, muscle weakness, delayed central nervous system development in newborn piglets, and highly reduced life span become appropriate model animals [25].

It is worth noting the contribution of alternative research objects to the modeling of basic mitochondrial processes and some aspects of human pathologies:

The zebrafish *D. rerio* is considered an optimal alternative to mice. It can be used to model Leigh syndrome, in particular with liver dysfunction, and MDs involving the nervous, immune, and cardiovascular systems. Also, as mentioned above, there exist behavioral tests to assess motor and sensory response impairments typical of clinical MD manifestations [26].

The *Caenorhabditis elegans* nematode and *Drosophila melanogaster* fruit fly, despite their significant divergence from humans (686 million years [9]), have emerged as powerful genetic MD models, with great potential in early high-throughput screening for therapeutic agents [27, 28].

Microorganisms are also used to study MDs. For example, mitochondrial functions in humans and *Saccharomyces cerevisiae* (yeast) are highly similar. Yeast can be used to reproduce pathogenic mutations leading to mitochondrial dysfunction in humans. Yeast is a good alternative model for studying MDs [29] and screening therapeutic agents [30].

Therefore, the generation of reliable animal models enables us to study the functions of mitochondrial protein-encoding genes and the molecular mechanisms of MD development, which is necessary to improve diagnostics and develop approaches to drug therapy.

ANIMAL MODELS OF HUMAN MITOCHONDRIAL DISEASES ASSOCIATED WITH NUCLEAR GENE MUTATIONS (SUMMARY TABLE)

Based on an analysis of publications devoted to various MDs [4, 5] and information gleaned from the periodically updated resources Genomics England PanelApp [3] and Online Mendelian Inheritance in Man [12], we prepared a table that summarizes the most recent data on MDs associated with nuclear

gene mutations. The data are correlated to the corresponding animal models. The table provides information about clinical MD manifestations, the specific nuclear gene mutations that cause certain MDs, inheritance modes, and detailed descriptions of the animal models corresponding to these MDs. This summary table may be useful both for planning and analyzing exploratory and clinical studies and for writing scientific papers and publications.

CONCLUSION

Mitochondrial diseases are some of the most common genetic diseases. They arise at birth or develop throughout life. The genetic mutations that cause these diseases are diverse. So, researchers describing the phenotypic effect of a certain mutation have faced the problem that the mutation consequences can be mapped on a wide range of clinical manifestations. Therefore, researchers face a challenge in describing the phenotypes of mitochondrial mutations and identifying the mechanisms through which certain mutations in mitochondrial protein-coding genes manifest themselves at the level of the organism. This problem may be addressed using modeling of MDs in animals. Manipulations with the genome of model animals, in particular mice, are often able to accurately reproduce the clinical picture of human MDs, providing the opportunity to study the molecular mechanisms of pathological processes, test drugs, predict their efficacy, and select new treatment modalities. ●

Conflict of interest. The authors declare no conflict of interest.

This study was supported by a grant of the Russian Science Foundation No. 17-75-30027 and partially financed from the budget of the Institute of Functional Genomics, Lomonosov Moscow State University.

Animal models of human mitochondrial diseases associated with nuclear gene mutations

Gene	Clinical picture	Inheritance mode
Mitochondrial complex I deficiency		
ACAD9 acyl-CoA dehydrogenase family, member 9	• hypertrophic cardiomyopathy, • reduced exercise tolerance, • mild beta oxidation deficiency	Autosomal recessive
Acad9 knockout mice [31]: • complete *Acad9* inactivation leads to embryonic lethality; • cardiac-specific *Acad9* knockout is associated with the lack of expression of *Acadvl* (encodes long-chain acyl-CoA dehydrogenase) and *Ecsit* (encodes a protein involved in complex I assembly) genes in cardiac tissue; expression of *Acadm*, encoding medium-chain acyl-CoA dehydrogenase, is reduced; complex I dysfunction; cardiomyopathy with atrial and ventricular thickening is diagnosed by day 14 of life; • muscle tissue-specific *Acad9* knockout is associated with reduced exercise tolerance and lactic acidosis.		

NDUFS1 NADH-ubiquinone oxidoreductase Fe-S protein 1	• Leigh syndrome • cavitating leukoencephalopathy	Autosomal recessive
Homozygous *Ndufs1* knockout in mice is lethal [32].		
NDUFS4 NADH-ubiquinone oxidoreductase Fe-S protein 4	• combined complex I and III deficiency, • Leigh syndrome, • hypertrophic cardiomyopathy	Autosomal recessive
Complete *Ndufs4* knockout mice [33–35]: • Leigh-like syndrome, • ataxia, neurological disorders, • developmental delay, • development of blindness by day 21 of life, • early mortality. Tissue-specific *Ndufs4* knockout targeting neurons and glia [36]: • progressive lethal encephalopathy, • reactive glial cell phenotype, neuronal loss, ataxia; • respiratory disturbance. • Cardiac-specific *Ndufs4* knockout [37, 38]: • hypertrophic cardiomyopathy. *Ndufs4* point mutation [39]: • embryonic lethality of homozygous *Ndufs4*$^{-/-}$ mice, • reduced activity of complex I in heterozygous mice upon stable activity of complex II. reduced activity of complex I in heterozygous mice upon stable activity of complex II.		
NDUFS6 NADH-ubiquinone oxido-reductase Fe-S protein 6	• lactic acidosis with fatal outcome in the neonatal period, • mitochondrial encephalomyopathy, • Leigh syndrome	Autosomal recessive
Ndufs6 knockdown mice [40, 41]: • cardiomyopathy, systolic dysfunction, • renal disease associated with ultrastructural changes.		
NDUFV1 NADH-ubiquinone oxido-reductase flavo protein 1	• mitochondrial encephalomyopathy, • cerebral ataxia, • Leigh syndrome	Autosomal recessive
Transgenic *Caenorhabditis elegans* (soil nematode) strain with mutations in the *Nuo-1* gene, the *Ndufv1* homolog [42]: • lactic acidosis, • decreased NADH-dependent mitochondrial respiration, • hypersensitivity to exogenous oxidative stress.		
NUBPL nucleotide-binding protein-like protein	• leukoencephalopathy	Autosomal recessive
Homozygous *Nubp1* knockout in mice is lethal [32].		
NDUFAF7 NADH dehydrogenase (ubiquinone) complex I, assembly factor 7	• pathological myopia	
Lethality of homozygous *Ndufaf7* knockout mice [15]. Morpholino-mediated *Ndufaf7* knockdown in *D. rerio* [15]: • delayed hatching time, • morphological abnormalities, • decreased complex I activity.		
NDUFS7 NADH-ubiquinone oxido-reductase Fe-S protein 7	• Leigh syndrome	Autosomal recessive
Homozygous *Ndufs7* knockout in mice is lethal [32].		
NDUFA1 NADH-ubiquinone oxidoreductase subunit a1	• Leigh syndrome	X-linked recessive
Mutant mice with targeted destruction of complex I subunit mRNA, Ndufa1 [43]: • complex I deficiency, increased levels of reactive oxygen species, • optic nerve and retinal lesions.		

NDUFA13 NADH-ubiquinone oxidoreductase subunit a13 or *GRIM19* gene associated with retinoid- & interferon-induced mortality 19	• encephalopathy associated with sensory deprivation, • Leigh syndrome, • thyroid cancer	Autosomal recessive
Mutant mice deficient in Grim19 [44]: • Grim19$^{-/-}$ embryos die by day 9.5 of embryonic development, • delayed and abnormal development of Grim19$^{-/-}$ blastocysts associated with abnormal mitochondrial structure and defective complex I (GRIM-19 physically resides in complex I and is responsible for its assembly), • heterozygous Grim19$^{+/-}$ mice lack physiological or phenotypic abnormalities.		
NDUFA8 NADH-ubiquinone oxidoreductase subunit a8	• developmental delay, • microcephaly, • epilepsy, • weight loss and failure to thrive, • speech development defects	Autosomal recessive
Homozygous *Ndufa8* knockout in mice is lethal [32].		
NDUFB11 NADH-ubiquinone oxidoreductase 1 beta subcomplex, 11	• multiple congenital malformations, • microphthalmia with linear skin defects (MLS syndrome), • embryonic male lethality, • lactic acidosis, • histiocytoid cardiomyopathy, • microphthalmia, • skin defects	X-linked
Ndufb11 knockdown in *Drosophila* [45]: • reduced life span, • decreased metabolic rate, • complex I assembly defects, • increased lactate and pyruvate levels.		
Mitochondrial electron transport chain defects; OXPHOS disturbance		
UCP2 uncoupling protein 2	• obesity	Not found
Ucp2 knockout mice [46, 47]: • no obesity, normal response to cold or a high-fat diet, • resistant to *Toxoplasma gondii* infection (forms brain cysts) thanks to an increased level of reactive oxygen species in macrophages, • glucose-induced insulin secretion increases, typical of type II diabetes mellitus. Mutant mice with increased Ucp2 expression in hypocretin (orexin) neurons [48]: • these mutant mice have increased temperature of the hypothalamus, which leads to an overall decrease in body temperature by 0.3–0.5°C, • these mutants have increased energy efficiency and a longer average life span. *Ucp1* knockout mice [49]: • sensitive to cold, which indicates impaired thermoregulation, • accumulate excess fat in brown adipose tissue, but do not become fat, • *Ucp1* knockout is compensated by *Ucp2* that is expressed in brown epididymal fat. *Ucp3* knockout mice [50]: • *Ucp3* inactivation is associated with *Ucp1* and *Ucp2* upregulation in brown adipose tissue, • in skeletal muscles, an increased state 3/state 4 ratio due to proton leak, • in skeletal muscles, increased production of reactive oxygen species and decreased mitochondrial aconitase.		
PDHA1 pyruvate dehydrogenase, alpha-1	• impaired glycolysis–tricarboxylic acid cycle relationship, • Leigh syndrome, • deficiency of pyruvate dehydrogenase E1-alpha, • neurological dysfunction, • lactic acidosis, • growth retardation, • early mortality	X-linked dominant
Inactivation of the mouse pyruvate dehydrogenase *Pdha1* gene is embryonic-lethal [51]. *D. rerio* mutants with visual function defects – no optokinetic response a (noa) – are deficient in dihydrolipoamide-S-acetyltransferase (Dlat), the PDH E2 subunit [16]: • a phenotype similar to pyruvate dehydrogenase complex deficiency syndrome in humans (neurological dysfunction, lactic acidosis, growth retardation, early death).		

PDSS2 renyl diphosphate synthase, subunit 2	• defect in ubiquinone (CoQ10) synthesis, • encephalomyopathy, • tubulopathy, • ataxia	Autosomal recessive
Embryonic lethality of *Pdss2* knockout mice [52]. Tissue-specific *Pdss2* knockout targeting glomerular podocytes [52]: • nephrotic syndrome without changes in the coenzyme Q level in kidney homogenates. Tissue-specific *Pdss2* knockout targeting hepatocytes [52]: • coenzyme Q depletion in liver homogenates, • mitochondrial respiratory chain dysfunction, • disruption of basic metabolic processes. Tissue-specific *Pdss2* knockout targeting the kidney ($Pdss2^{kd/kd}$) [53]: • mitochondrial renal ultrastructural abnormalities, renal CoQ deficiency, decreased respiratory chain activity, increased oxidative stress, • development of nephropathy and proteinuria, up to fatal renal failure, • cerebellar abnormalities.		
COQ9 coenzyme Q9	Coenzyme Q10 (ubiquinone) deficiency	Autosomal recessive
Mice with a truncating R239X mutation in the *Coq9* gene [54]: • impaired mitochondrial respiration with loss of ATP and complex I activity, • encephalomyopathy, • neuronal death, demyelination, vacuolization, spongiform degeneration, and astrogliosis, • cardiac fibrosis, • impaired locomotor activity and progressive paralysis, • early mortality.		
CYCS cytochrome C somatic isoform	• thrombocytopenia	Autosomal dominant
Cyt *c* deficiency in mice causes embryonic lethality and attenuates stress-induced apoptosis [55]. Mice expressing mutant cyt *c* (KA allele) that retains the electron transfer function, but is incapable of Apaf-1 activation [56]: • exencephaly and hydrocephalus, • cachexia, • lymphopenia.		
COQ2 coenzyme Q2, polyprenyltransferase	• encephalomyopathy, • tubulopathy, • ataxia	Autosomal recessive
	• tendency to multiple system atrophy	Autosomal recessive/ dominant
Homozygous *Coq2* knockout in mice is lethal [32].		
Mitochondrial complex II deficiency		
SDHD succinate dehydrogenase complex, subunit D, integral membrane protein	• paraganglioma and gastric stromal sarcoma, • pheochromocytoma	Autosomal recessive/ dominant
Homozygous *Sdhd* knockout in mice is lethal [57, 58].		
SDHA succinate dehydrogenase complex, subunit A, flavo protein	• Leigh syndrome, • cardiomyopathy	Autosomal recessive
	• neurodegeneration and ataxia, • optic nerve atrophy, • paraganglioma	Autosomal dominant
Homozygous *Sdha* knockout in mice is lethal [32].		

Mitochondrial complex III deficiency		
BCS1L BCS1 homolog, ubiquinol-cytochrome c reductase complex chaperone	• encephalopathy, • tubulopathy, • liver dysfunction, • Bjornstad syndrome, • GRACILE syndrome	Autosomal recessive
Mice with a homozygous *Bcs1l* mutation [59]: • mouse model of GRACILE syndrome – neonatal MD involving the liver and kidneys, • growth retardation and short life span, • hepatic glycogen depletion, steatosis, fibrosis, cirrhosis, tubulopathy, • lactic acidosis, • complex III deficiency in the liver, heart, and kidneys.		
UQCRFS1 ubiquinol-cytochrome *c* reductase, rieske iron-sulfur or *RISP* Rieske iron-sulfur protein	• hypertrophic cardiomyopathy, • thrombocytopenia, • hypotonia, • increased serum lactate and alanine levels, • slightly impaired motor skills and reduced muscle strength	Autosomal recessive
Homozygous *Risp* mutation is lethal in mice [13]. Heterozygous *Risp*$^{+/P224S}$ mutant mice [13]: • reduced complex III activity associated with a decreased level of the iron-sulfur protein RISP, • decreased overall metabolic rate and life span in males, but not females. Conditional knockout (cKO) of the *Risp* gene in mouse neurons using the Cre-loxP system [60]: • short life span, • sudden death with minimal behavioral changes, • weight loss, • cyclic hyperactivity, • decreased performance, • extensive oxidative stress, • neurodegenerative diseases, neuronal death, piriform and somatosensory cortex damage associated with a CIII defect. Mutant mice with *Risp* inactivation in Treg cells [61]: • Treg-specific deficiency of complex III, • early lethal inflammatory disease, • loss of the ability to suppress T cells without changing Treg cells proliferation and survival, • increased DNA methylation.		
Mitochondrial complex IV deficiency		
COX4I2 or *COX4-2* cytochrome C oxidase, subunit 4i2/IV, isoform 2	• exocrine pancreatic insufficiency, • dyserythropoietic anemia, • calvarial hyperostosis, • lung-specific Cox4 CIV subunit isoform	Autosomal recessive
Mutant mice with *Cox4I2* gene inactivation [62]: • pulmonary pathology with inflammation and Charcot-Leyden crystal formation (in sputum in bronchial asthma).		
COX6A2 cytochrome *C* oxidase, subunit 6a2	• early hypotonia, • weakness of the facial muscles and limbs, • high palatal vault, • respiratory distress, • cardiomyopathy, • impaired mental development	Autosomal recessive
Mutant *Cox6a2*$^{-/-}$ mice [63]: • stable, abnormally low weight even upon a high-fat diet due to ineffective energy metabolism, increased energy expenditure, and adaptive thermogenesis, • high Ucp1 and 2 expression levels in the heart and adipose tissue, • increased size of muscle mitochondria, • enhanced glucose tolerance and insulin sensitivity, which is associated with increased phosphorylation and constitutive Ampk activation.		

COX10 cytochrome *C* oxidase assembly factor	• mitocomplex IV deficiency, • ataxia, • acidosis, • hypoglycemia, • hypotonia, • mitochondrial encephalopathy, • muscle weakness, • droopy upper eyelid, • pyramidal syndrome, • proximal tubulopathy, • epileptic clouded state, • cardiomyopathy, • hypotrophy, • lactic acidosis, • Leigh syndrome	Autosomal recessive
Mice with muscle tissue-specific *Cox10* gene inactivation [64]: • regressive myopathy and weakness, • early death, • progressive decrease in COX activity and increase in SDH activity in muscles, • neuromuscular pathology, histologically proven signs of torn red fibers, • abnormal mitochondria. Mice with neuronal tissue-specific *Cox10* gene inactivation [65]: • decreased COX activity in the cerebral cortex and hippocampus, • early mortality, • decreased size and density of forebrain cells, • behavioral defects. Mice with liver tissue-specific *Cox10* gene inactivation [66]: • early mortality, • mitochondrial hepatopathy, • reduced body weight and general activity, • severe liver dysfunction, • decreased COX activity and increased SDH activity, • increased mitochondrial proliferation and decreased ATP levels, • lipid accumulation and glycogen depletion. A conditional *Cox10* knockout is characterized by dysfunction of oligodendrocytes and Schwann cells to form COX [67]: • severe neuropathy with demyelination, abnormal Remak bundles in the peripheral nervous system, • muscle atrophy, palsy, • impaired mitochondrial respiration.		
SURF1 surfeit 1	Leigh syndrome, Charcot–Marie–Tooth amyotrophy	Autosomal recessive
Mice with inactivation of the *Surf1* gene encoding the complex IV (COX) assembly factor. *Neo*$^{-/-}$ mutants (replacement of exons 5–7 by a neomycin-resistance cassette) [68]: • 90% embryonic lethality (presumably not due to Surf1 inactivation, but due to the neo cassette or deletions of regulatory elements), • reduced life span, • decreased motor activity, coordination, muscle strength, and endurance without obvious brain morphology abnormalities or neurological symptoms, • suppressed fertility in both sexes, • histochemical analysis of the skeletal muscles and liver revealed decreased COX activity and increased SDH activity, • a drop in COX activity to 23–40% of normal values in various tissues. *Surf1loxp*$^{-/-}$ mutants (insertion of the loxP sequence into exon 7 generating a stop codon at position 225 and elimination of 81 C-terminal amino acids) [69]: • no embryonic lethality, • increased life span, • histochemical analysis of skeletal muscles revealed decreased COX activity and increased SDH activity, • reduction in COX activity by 50–70% in various tissues, • there are no neurological defects, but there is resistance to Ca^{2+}-mediated damage to isolated neurons and the whole brain, • mitochondria retain normal morphology and membrane potential. *SURF1*$^{-/-}$ mutant pigs[25]: • overall developmental delay, • delay in central nervous system development in newborns, • muscle weakness, • short life span, • cytochrome *c*-oxidase deficiency in the jejunum villi (histochemical analysis).		

SCO2 SCO cytochrome C oxidase assembly protein 2	• Leigh syndrome, • hypertrophic cardiomyopathy, • neuropathy	Autosomal recessive
	• myopia	Autosomal dominant
The *Sco2*$^{-/-}$ knockout mouse model is embryonic-lethal [70]. Homozygous mice with an insertion in the *Sco2* gene or a mutation in the compound heterozygous state are viable and exhibit respiratory chain failure, defects in complex IV assembly, decreased mitochondrial copper content, and overall muscle weakness [70].		
COX15 cytochrome C oxidase assembly factor	• Leigh syndrome, • hypertrophic cardiomyopathy	Autosomal recessive
Homozygous *Cox15*$^{-/-}$ knockout mice are embryonic-lethal [71]. Mice with a skeletal muscle tissue-specific mutation develop severe myopathy [71].		
Mitochondrial complex V (ATP synthase) deficiency		
ATP synthase defects are most often associated with mtDNA mutations. Regarding nuclear gene mutations, there are five genes associated with human MDs. Three of them – *ATP5A1*, *ATP5D*, and *ATP5E* – encode structural α-, δ-, and ε-subunits of the enzyme, respectively, and the other two, *ATPAF2* and *TMEM70*, encode specific auxiliary factors that facilitate ATP synthase biogenesis. All of these defects have a similar phenotype that is characterized by a pronounced generalized decrease in the ATP synthase complex level: • neonatal hypotension, • lactic acidosis, • hyperammonemia, • hypertrophic cardiomyopathy, • 3-methylglutaconic aciduria. Mutations in the *ATP5A1*, *ATP5D*, *ATP5E*, and *ATPAF2* genes are very rare, and animal models with these mutations are mostly lethal. In contrast, *TMEM70* gene mutations are the most common cause of ATP synthase deficiency.		
TMEM70 transmembrane protein 70	• encephalopathy, • facial dysmorphism, • hypertrophic cardiomyopathy, • lactic acidosis	Autosomal recessive
Tmem70$^{-/-}$ homozygous knockout mice [72]: • embryonic-lethality, • embryos are characterized by delayed cardiovascular system development and impairment of the myocardial mitochondrial ultrastructure with an irregular crista structure. *Tmem70*$^{+/-}$ heterozygous knockout mice [72]: • viable, • normal postnatal growth and development of the mitochondrial OXPHOS system, • mild deterioration in cardiac function. *Tmem70* knockout rats generated using the SHR strain genetic background and under the control of the universal EF-1α promoter [73]: • viable model, • genetic complementation restored Tmem70 expression in various tissues, • to complete restore the physiological function of mitochondria biochemical complement of ATP synthase biogenesis in the liver, 20% of the TMEM70 protein and single-allelic Tmem70 are sufficient, and in the heart at least 40% of TMEM70 and both transgenic alleles.		
Depletion (decrease in content) of mtDNA		
TYMP thymidine phosphorylase	• mtDNA depletion syndrome, • mitochondrial neurogastrointestinal encephalomyopathy	Autosomal recessive
Upp1/Tymp double knockout mice [74, 75]: • critical Tymp deficiency, increased thymidine and deoxyuridine levels in tissues, high levels of mitochondrial deoxythymidine triphosphate, • partial mtDNA depletion, respiratory chain complex deficiency, and encephalopathy, • intense brain damage due to increased plasma pyrimidine levels and subsequent axonal swelling.		

ANT1 adenine nucleotide translocator 1	• mtDNA depletion syndrome	Autosomal dominant/ recessive
	• hypertrophic cardiomyopathy, • hypotonia	Autosomal recessive
	• progressive external ophthalmoplegia	Autosomal dominant
Ant1 gene inactivation in mice [76, 77]: • mitochondrial myopathy, hypertrophic cardiomyopathy, metabolic acidosis, • mitochondrial proliferation in the skeletal muscles and heart, • inhibition of complexes I, III, and IV of the mitochondrial respiratory chain, oxidative stress in muscle and heart tissues, • accumulation of multiple mtDNA deletions, mtDNA destabilization. *Ant4* gene inactivation in mice [78]: • spermatogenesis defect, male infertility. Simultaneous *Ant1* and *Ant2* inactivation in the mouse liver [79]: • complex IV activity and COI and cytochrome *c* levels are increased to compensate for OXPHOS ATP deficiency, • Ca^{2+} excess is required for mtPTP activation, and pores cannot be regulated by Ant ligands, including adenine nucleotides, • hepatocytes are able to respond to induction of cell death, • liver mitochondria exhibit an increase in the respiration rate and no response to ADP addition and an increase in the membrane potential.		
TWNK twinkle mtDNA helicase	• mtDNA depletion (sharp decrease in content) syndrome, • Alpers syndrome/progressive infantile poliodystrophy, • Perrault syndrome (a type of female hypogonadism), • infantile spinocerebellar ataxia	Autosomal recessive
	• progressive external ophthalmoplegia	Autosomal dominant
Mutant mice with Twinkle overexpression [80]: • abnormal increase in the mtDNA copy number in the muscles and heart. Mice with a PEO-associated mutation, carrying a substitution of threonine for alanine at position 360 of the mouse Twinkle protein ($Twinkle^{AT}$) [81]: • mild myopathy phenotype. Deletor mice with a PEO-associated mutation, carrying an in-frame duplication of amino acids 353–365 ($Twinkle^{dup}$) [81, 82]: • mitochondrial myopathy; the myofibrillar structure is replaced by large mitochondria with concentric cristae and proliferation, • mitochondrial proliferation in cerebellar Purkinje cells, hippocampal pyramidal neurons, and neurons of the indusium griseum (a gray matter layer covering the superior surface of the corpus callosum), • reduced mtDNA levels in the brain (but not in the muscles and heart), • lipid metabolism disorders, • gene expression profiles in skeletal muscle with mitochondrial myopathy revealed induction of several transcripts involved in the response to amino acid and lipid starvation and activation of the Akt and fibroblast growth factor-21 (starvation hormone) signaling.		
POLG polymerase, DNA, gamma	• progressive external ophthalmoplegia, • SANDO syndrome – a systemic disease characterized by ataxia, balance disturbance, and nerve disorders, such as sensory ataxia, neuropathy, dysarthria, and ophthalmoparesis, • parkinsonism	Autosomal dominant/ recessive
	• mtDNA depletion (sharp decrease in content) syndrome, • Alpers syndrome/progressive infantile poliodystrophy, • mitochondrial neurogastrointestinal encephalomyopathy	Autosomal recessive
D257A (proofreading-deficient PolgA) mice [83–88]: • increased levels of mtDNA point and somatic mutations, induction of apoptotic markers, • reduced life span, decreased subcutaneous fat, alopecia, kyphosis, osteoporosis, anemia, decreased fertility, enlarged heart, anemia, loss of intestinal crypt cells, weight, and hearing, sarcopenia, • PolgA deficiency in mouse embryos causes early developmental arrest.		

TK2 thymidine kinase, mitochondrial	• myopathy, • mtDNA depletion (sharp decrease in content) syndrome, • progressive external ophthalmoplegia	Autosomal recessive
Tk2$^{-/-}$ with a his126-to-asn (H126N) mutation in the *Tk2* gene [89, 90]: • growth retardation, decreased activity, generalized gross tremor, and gait disturbance, • mortality at 2 weeks of age, • mtDNA depletion, most remarkable in the brain, • decreased activity of mitochondrial respiratory chain enzymes, ATP levels, and ATP/ADP ratio in the brain, • degeneration and dysfunction of certain types of neurons, • abnormal vacuolar changes in spinal cord neurons, • activated glial cells in the spinal white matter and cerebral cortex, rapidly progressive encephalomyelopathy.		
DGUOK deoxyguanosine kinase	• mtDNA depletion (sharp decrease in content) syndrome, • Alpers syndrome/progressive infantile poliodystrophy, • non-cirrhotic portal hypertension/Banti's syndrome, • progressive external ophthalmoplegia	Autosomal recessive
Dguok$^{-/-}$ mutant mice [91]: • weight loss, reduced adipose tissue, • mtDNA deficiency in the liver, brain, heart, and skeletal muscles, • lipofuscin accumulation in liver tissues and increased oxidative stress, • increased catabolic lipid metabolism, • increased relative weight of the liver, kidneys, and heart, • abnormal fur pigmentation (lightening).		
MPV17 mitochondrial inner membrane protein	• mtDNA depletion (sharp decrease in content) syndrome, • Alpers syndrome/progressive infantile poliodystrophy, • peroneal muscular atrophy (Charcot–Marie–Tooth disease)	Autosomal recessive
Mpv17$^{-/-}$ mutant mice [92]: mtDNA depletion in the liver associated with an increased transcription rate, mtDNA depletionin in skeletal muscles, moderate decrease in the enzymatic activity of the mitochondrial respiratory chain and mild changes in cytoarchitecture in the liver, abnormal fur pigmentation (lightening), cochlear sensory epithelium degeneration, focal segmental glomerulosclerosis with massive proteinuria, short life span.		

TFAM mitochondrial transcription factor A	• mtDNA depletion (sharp decrease in content) syndrome	Autosomal recessive
Homozygous *Tfam*$^{-/-}$ mice [14]: • embryonically lethal depletion of mtDNA. Heterozygous Tfam$^{+/-}$ mice [14]: • reduced mtDNA copy number and mitochondrial respiratory chain activity in the heart. Heart and muscle tissue-specific *Tfam* knockout [93]: • early mortality associated with mosaic cardiac-specific progressive respiratory chain deficiency, dilated cardiomyopathy, and atrioventricular blockage, • depletion of mtDNA and Tfam protein, complex I and IV deficiency in the heart and muscles. Skeletal muscle tissue-specific *Tfam* knockout in mice [94, 95]: • progressive myopathy, decreased muscle strength associated with increased levels of mitochondrial Ca^{2+} and decreased release of Ca^{2+} from the sarcoplasmic reticulum, • enlarged mitochondria with deformed cristae, • decreased mtDNA and mitochondrial transcript levels, respiratory chain function, and ATP production. Midbrain dopamine neuron-specific *Tfam* knockout in mice (MitoPark) [96]: • parkinsonian-like phenotype with behavioral disturbances, loss of dopamine neurons, and the presence of Lewy bodies, • decreased mtDNA expression and respiratory chain deficiency in midbrain dopamine neurons. T cell-specific *Tfam* knockout in mice [97]: • premature signs of aging, including metabolic, cognitive, physical, and cardiovascular changes, • a cytokine storm was an inducer of senescence, • early mortality. Pancreatic β-cell tissue-specific *Tfam* knockout in mice [98]: • mitochondrial diabetes, • elevated glucose levels, a gradual decrease in the β-cell mass and pancreatic endo/exocrine tissue ratio, • mutant β-cells exhibit reduced COX activity, normal SDH activity, and abnormally large mitochondria. Neocortical neuron-specific *Tfam* knockout in mice [99]: • mouse model of mitochondrial neurodegeneration (MILON) with late onset (around 4–6 months), • reduced respiratory chain activity and mtDNA and mtRNA levels in neurons, • increased vulnerability to excitotoxic stress, • short life span at the final stage, progressive neurodegeneration, and massive cell death in the hippocampus and neocortex. P1 artificial chromosome (PAC) mutant mice expressing human TFAM in the setting of stable expression of mouse TFAM [100]: • net TFAM overexpression, • increased mtDNA copy number upon normal respiratory chain capacity and total mitochondrial mass, • combination of mice with TFAM overexpression and TFAM knockout demonstrated that the mtDNA copy number is directly proportional to the total TFAM protein levels.		
Iron metabolism disorders		
ABCB7 ATP-binding cassette, subfamily b, member 7	• sideroblastic anemia with ataxia	X-linked recessive
• the lethality of a complete A*bcb7* knockout is associated with a defect in the extra-embryonic visceral endoderm that predominantly contains the X-chromosome as an active allele [101], • X-inactivations and tissue-specific deletions revealed that *Abcb7* is essential for the development of all tissues except hepatocytes and endothelial cells [101], • loss of *Abcb7* in the liver caused mild mitochondrial damage, impaired cytosolic Fe-S cluster assembly, and altered iron sensing, but was not fatal [101].		

FXN frataxin or *FRDA*	• Friedreich ataxia	Autosomal recessive
Mutant mice with a *Frda* exon 4 deletion [102]: • homozygous $Frda^{-/-}$ model is embryonic-lethal, • embryonic mortality is not associated with abnormal iron accumulation. A viable line of tissue-specific frataxin deficient mice was generated by breeding of conditional *Frda* allele homozygotes and *Frda* exon 4 deletion heterozygotes supplemented with the *Cre/Lox* excision system under the control of the muscle creatine kinase promoter (MCK mutant mouse line) or neuron-specific enolase (NSE mutant mouse line) [103, 104]: • NSE mutants had no obvious signs of pathology, and post-mortem studies revealed no iron deposits, • early deficiency of complexes I–III and aconitase activity in the hearts of mutant MCK mice (day 7 of life), • MCK mutant mice develop gradual mitochondrial degeneration from 4 weeks of age, • lipid and protein oxidation levels in the hearts of MCK mutant mice decrease from 7 weeks of age, • intramitochondrial iron deposits in MCK mutant mice form at the terminal stage (10–12 weeks of life) after inactivation of Fe/S enzymes (4 weeks of life) and the development of cardiac dilatation, with left ventricular hypertrophy (5 weeks of life). Tissue-specific *Frda* knockout in mouse hepatocytes [105]: • high level of oxidative stress in the liver, • impaired mitochondrial respiration, decreased ATP levels and Fe/S enzyme activity, • reduced OXPHOS, • multiple liver tumors, • decreased life span. Double heterozygous mutants generated by breeding of mice with a GAA repeat insertion in the *Frda* gene (in humans, intronic expansion of GAA triplets in the *FXN* gene causes frataxin deficiency and, as a consequence, Friedreich ataxia) and mice with a frataxin gene knockout [106–108]: • GAA repeat length controls the age of onset of somatic instability and the mutation rate and magnitude, • $Frda^{-/^{230}GAA}$ mice are viable and do not exhibit a pronounced pathological phenotype, • this model demonstrates that dysregulation of the peroxisome proliferator-activated receptor gamma (PPARγ) pathway underlies the increased lipogenesis in skeletal muscle and changes in cardiac fiber composition, which are consistent with insulin resistance and cardiomyopathy. *Drosophila* with inactivation of the *Dfh* gene, a homologue of frataxin [109, 110]: • prolonged larval stage and reduced life span of adult animals, • increased size of larvae, • impaired expression of ferritin only in adults, • H_2O_2 is an important pathological substrate underlying the phenotypes resulting from frataxin deficiency in *Drosophila*.		
Mutations in nuclear antioxidant defense genes		
SOD1 superoxide dismutase 1	• amyotrophic lateral sclerosis, • spastic tetraplegia, • axial hypotonia	Autosomal recessive/ dominant
Mutant mice overexpressing *Sod1* are a basic model of amyotrophic lateral sclerosis. There are several transgenic mouse strains with different forms of *Sod1* mutations overexpressed at different levels. Mice with the SOD1G93A mutation are the most commonly used model of amyotrophic lateral sclerosis [111–113]. Mice with Cu/ZnSOD deficiency and a *Sod1* knockout [114, 115]: • increased amounts of mitochondria and lipofuscin granules in hepatocytes, • widespread oxidative damage, • hepatocarcinogenesis, • retinal dysfunction, • short life span.		

SOD2 superoxide dismutase 2	• microangiopathy in diabetes mellitus	Not determined
Mice with MnSOD deficiency, *Sod2* knockout, generated on the genetic background of a C57BL6/J2 inbred line [116]: • severe anemia, neuronal degeneration in the basal ganglia and brain stem, • progressive motor disorders associated with weakness, fatigue, and rotational behavior, • extensive mitochondrial damage in degenerating neurons and cardiac myocytes, • increased susceptibility to oxidative mitochondrial damage. Mice with MnSOD deficiency, *Sod2* knockout, generated on the genetic background of a CD1 outbred line [117, 118]: • short life span, • dilated cardiomyopathy, • accumulation of lipids in the liver and skeletal muscles, • metabolic acidosis, • iron-sulfur center, aconitase, citrate synthase, and complex II and I deficiency in the heart and brain, • accumulation of oxidative DNA damages, • organic aciduria. Heterozygous $Sod2^{+/-}$ mice [119]: • model of the free radical aging theory – chronic oxidative damage to tissues and cells, • chronic oxidative damage to lipids of the inner mitomembrane in middle-aged mice increases proton output, • middle-aged and elderly mice have highly sensitized mtPTP, which is associated with a threefold increase in apoptotic hepatocytes, • decreased mitochondrial function accompanied by an increased activity of respiratory chain enzymes.		
GPX1 glutathione peroxidase 1	• hemolytic anemia due to glutathione peroxidase deficiency	Autosomal recessive
Inactivation of the *GPx1* gene in mice revealed [120–122]: • GPx1 is highly expressed in the liver, brain, and renal cortex, but very weakly in the heart and skeletal muscle, • Gpx1 plays a critical role in oxidative stress protection and antioxidant defense mechanisms, • $GPx1^{-/-}$ mice are viable, but they have reduced body weight and chronic growth retardation, • $GPx1^{-/-}$ mitochondria release 4-fold more H_2O_2 in the liver, but not in the heart, which is presumably due to catalase in cardiac mitochondria. Overexpression of *GPx1* in the heart of myocardial infarction model mice (left coronary artery ligation) resulted in better indicators and survival compared with those in wild-type mice [123].		
Mutations in nuclear genes of mitochondrial dynamics		
MFN2 mitofusin 2	• axonal Charcot–Marie–Tooth disease	Autosomal dominant/ recessive
	• hereditary motor sensory neuropathy	Autosomal dominant
Cerebellar tissue-specific inactivation of the *Mfn2* gene in mice [124, 125]: • model of neurodegeneration caused by loss of mitochondrial fusion, • 50% mortality in litter; destruction of the giant cell layer of the placental trophoblast in embryos; fragmented mitochondria in embryonic fibroblasts, • $Mfn2^{-/-}$ Purkinje cells have abnormal morphology, short, thin, and less branched dendritic trees with a reduced number of spines; and changes in the morphology, ultrastructure, and distribution of mitochondria with decreased activity of complexes I and IV and increased activity of complex II, • survived mice possess 75% cerebellar atrophy due to a decreased number and quality of Purkinje cells; dystaxia. Tissue-specific inactivation of the *Mfn2* gene in peripheral motor neurons [126]: • homozygous animals lack the ability to flex their hind legs with atrophy of the anterior calf muscles; shortened, deformed tails with bends and thickenings; • $Mfn2^{-/-}$ motor axons are less numerous and have mitochondrial distribution abnormalities (formation of dense clusters).		

OPA1 OPA1 mitochondrial dynamin-like GTPase	• optic nerve atrophy	Autosomal dominant
	• Behr syndrome, • mtDNA depletion syndrome	Autosomal recessive
	• tendency to develop glaucoma	Not determined
Mice with a mutation in the *Opa1* gene encoding nuclear dynamin-related GTPase occurring in mitochondria [127, 128]: • 50% decrease in the Opa1 protein level, • homozygous mutation is embryonic-lethal, • heterozygous animals exhibit age-related degeneration of retinal ganglion cells and decreased visual function, • the number of axons in *Opa1*$^{+/-}$ optic nerves is reduced; the remaining axons have an abnormal shape, irregular myelination, decreased number of neurofibrils, and morphologically abnormal mitochondria with disorganized cristae, • morphological changes in *Opa1*$^{+/-}$ fibroblasts, increased mitochondrial fission and fragmentation.		
Defects in mitochondrial and peroxisomal fission		
DNM1L dynamin 1-like	• encephalopathy, • microcephaly, • optic nerve atrophy, • lactic acidosis	Autosomal dominant/ recessive
Homozygous *Drp1* knockout in mice is lethal [129]: • *Drp1*$^{-/-}$ embryos exhibit impaired heart and liver development, depletion of the neural tube cell layer, and enlarged mitochondria, • asymmetric cytokinesis in *Drp1*$^{-/-}$ fibroblasts, • neuronal cells are highly sensitive to Ca2+-dependent apoptosis. Mice with a neural cell-specific *Drp1* deletion (*NS-Drp1*$^{-/-}$) [129]: • infant mortality due to hypoplasia and apoptosis of the brain, • analysis of primary *NS-Drp1*$^{-/-}$ forebrain culture revealed that aggregated mitochondria were not properly distributed in nerve cell processes, • neuronal cells are highly sensitive to Ca^{2+}-dependent apoptosis. Heterozygous *Dnm1l* knockdown in mice causes elongation of the mitochondrial network of retinal ganglion cells, but not axonal degeneration in the optic nerve [130].		
Mitochondrial enzyme cofactor deficiency		
SLC19A2 solute carrier family 19 (thiamine transporter), member 2	• thiamine (vitamin B1)-responsive megaloblastic anemia (TRMA)	Autosomal recessive
Mutant mice with inactivation of the *Slc19a2* gene encoding the high-affinity thiamine transporter Thtr-1 [131, 132]: • lack of a high-affinity component of thiamine transport, • diabetes mellitus with decreased insulin secretion and increased response to insulin, • sensorineural deafness, loss of inner hair cells in the cochlea, • abnormal bone marrow with megaloblastosis.		

REFERENCES

1. Dogan S.A., Trifunovic A. // Physiol. Res. 2011. V. 60. № SUPPL. 1.
2. Mayr J.A., Haack T.B., Freisinger P., Karall D., Makowski C., Koch J., Feichtinger R.G., Zimmermann F.A., Rolinski B., Ahting U., et al. // J. Inherit. Metab. Dis. 2015. V. 38. № 4. P. 629–640.
3. Martin A.R., Williams E., Foulger R.E., Leigh S., Daugherty L.C., Niblock O., Leong I.U.S., Smith K.R., Gerasimenko O., Haraldsdottir E., et al. // Nat. Genet. 2019. V. 51. № 11. P. 1560–1565.
4. Rambani V., Hromnikova D., Gasperikova D., Skopkova M. // Endocr. Regul. 2022. V. 56. № 3. P. 232–248.
5. Fernandez-Vizarra E., Zeviani M. // FEBS Lett. 2021. V. 595. № 8. P. 1062–1106.
6. Koene S., Rodenburg R.J., van der Knaap M.S., Willemsen M.A.A.P., Sperl W., Laugel V., Ostergaard E., Tarnopolsky M., Martin M.A., Nesbitt V., et al. // J. Inherit. Metab. Dis. 2012. V. 35. № 5. P. 737–747.
7. Loeffen J., Smeitink J.A.M., Triepels R., Smeets R., Schuelke M., Sengers R., Trijbels F., Hamel B., Mullaart R., van den Heuvel L. // Am. J. Hum. Genet. 1998. V. 63. № 6. P. 1598–1608.
8. Chang X., Wu Y., Zhou J., Meng H., Zhang W., Guo J. // Medicine. 2020. V. 99. № 5. P. e18634.
9. Kumar S., Suleski M., Craig J.M., Kasprowicz A.E., Sanderford M., Li M., Stecher G., Hedges S.B. // Mol. Biol. 2022. V. 39. № 8. P. 1–6.
10. Law M., Shaw D.R. // Methods Mol. Biol. 2018. V. 1757. P. 141–161.
11. Gurumurthy C.B., Kent Lloyd K.C. // DMM Disease Models and Mechanisms. 2019. V. 12. № 1. P. dmm029462
12. Amberger J.S., Bocchini C.A., Scott A.F., Hamosh A. // Nucl. Acids Res. 2019. V. 47. № D1. P. D1038–D1043.
13. Hughes B.G., Hekimi S. // PLoS One. 2011. V. 6. № 10. P. e26116.
14. Larsson N.G., Wang J., Wilhelmsson H., Oldfors A., Rustin P., Lewandoski M., Barsh G.S., Clayton D.A. // Nat. Genet. 1998. V. 18. № 3. P. 231–236.
15. Zurita Rendón O., Silva Neiva L., Sasarman F., Shoubridge E.A. // Hum. Mol. Genet. 2014. V. 23. № 19. P. 5159–5170.
16. Taylor M.R., Hurley J.B., van Epps H.A., Brockerhoff S.E. // Proc. Natl. Acad. Sci. USA. 2004. V. 101. № 13. P. 4584–4589.
17. Nenni M.J., Fisher M.E., James-Zorn C., Pells T.J., Ponferrada V., Chu S., Fortriede J.D., Burns K.A., Wang Y., Lotay V.S., et al. // Front. Physiol. 2019. V. 10. № 26. P. 154.
18. Naert T., Vleminckx K. // Drug. Discov. Today Technol. England. 2018. V. 28. P. 41–52.
19. Menegola E., Battistoni M., Metruccio F., Di Renzo F. // Curr. Opin. Toxicol. 2023. V. 34. P. 100387.
20. Zeng S.L., Sudlow L.C., Berezin M.Y. // Expert. Opin. Drug Discov. 2020. V. 15. № 1. P. 39–52.
21. Langova V., Vales K., Horka P., Horacek J. // Front. Psychiatry. 2020. V. 11. P. 1–22.
22. Ruzzenente B., Rötig A., Metodiev M.D. // Hum. Mol. Genet. 2016. V. 25. № R2. P. R115–R122.
23. Wallace D.C. // Am. J. Med. Genet. 2001. V. 106. № 1. P. 71–93.
24. Ishikawa K., Nakada K. // Biochim. Biophys. Acta Gen. Subj. 2021. V. 1865. № 3. P. 129835.
25. Quadalti C., Brunetti D., Lagutina I., Duchi R., Perota A., Lazzari G., Cerutti R., Di Meo I., Johnson M., Bottani E., et al. // Biochim. Biophys. Acta Mol. Basis Dis. 2018. V. 1864. № 6 Pt A. P. 2131–2142.
26. Steele S.L., Prykhozhij S.V., Berman J.N. // Transl. Res. 2014. V. 163. № 2. P. 79–98.
27. Maglioni S., Ventura N. // Mitochondrion. 2016. V. 30. P. 117–125.
28. Sen A., Cox R.T. // Curr. Top. Dev. Biol. 2017. V. 121. P. 1–27.
29. Baile M.G., Claypool S.M. // Front. Biosci. 2013. V. 18. № 1. P. 241–278.
30. Garrido-Maraver J., Cordero M.D., Moñino I.D., Pereira-Arenas S., Lechuga-Vieco A.V., Cotán D., De la Mata M., Oropesa-Ávila M., De Miguel M., Bautista Lorite J., et al. // Br. J. Pharmacol. 2012. V. 167. № 6. P. 1311–1328.
31. Sinsheimer A., Mohsen A.-W., Bloom K., Karunanidhi A., Bharathi S., Wu Y.L., Schiff M., Wang Y., Goetzman E.S., Ghaloul-Gonzalez L., et al. // Mol. Genet. Metab. 2021. V. 134. № 1–2. P. 156–163.
32. Dickinson M.E., Flenniken A.M., Ji X., Teboul L., Wong M.D., White J.K., Meehan T.F., Weninger W.J., Westerberg H., Adissu H., et al. // Nature. 2016. V. 537. № 7621. P. 508–514.
33. Kruse S.E., Watt W.C., Marcinek D.J., Kapur R.P., Schenkman K.A., Palmiter R.D. // Cell Metab. 2008. V. 7. № 4. P. 312–320.
34. Leong D.W., Komen J.C., Hewitt C.A., Arnaud E., McKenzie M., Phipson B., Bahlo M., Laskowski A., Kinkel S.A., Davey G.M., et al. // J. Biol. Chem. 2012. V. 287. № 24. P. 20652–20663.
35. van de Wal M.A.E., Adjobo-Hermans M.J.W., Keijer J., Schirris T.J.J., Homberg J.R., Wieckowski M.R., Grefte S., van Schothorst E.M., van Karnebeek C., Quintana A., et al. // Brain. 2022. V. 145. № 1. P. 45–63.
36. Quintana A., Zanella S., Koch H., Kruse S.E., Lee D., Ramirez J.M., Palmiter R.D. // J. Clin. Invest. 2012. V. 122. № 7. P. 2359–2368.
37. Sterky F.H., Hoffman A.F., Milenkovic D., Bao B., Paganelli A., Edgar D., Wibom R., Lupica C.R., Olson L., Larsson N.-G. // Hum. Mol. Genet. 2012. V. 21. № 5. P. 1078–1089.
38. Karamanlidis G., Lee C.F., Garcia-Menendez L., Kolwicz S.C., Suthammarak W., Gong G., Sedensky M.M., Morgan P.G., Wang W., Tian R. // Cell Metab. 2013. V. 18. № 2. P. 239–250.
39. Ingraham C.A., Burwell L.S., Skalska J., Brookes P.S., Howell R.L., Sheu S.S., Pinkert C.A. // Mitochondrion. 2009. V. 9. № 3. P. 204–210.
40. Ke B.X., Pepe S., Grubb D.R., Komen J.C., Laskowski A., Rodda F.A., Hardman B.M., Pitt J.J., Ryan M.T., Lazarou M., et al. // Proc. Natl. Acad. Sci. USA. 2012. V. 109. № 16. P. 6165–6170.
41. Forbes J.M., Ke B.X., Nguyen T.V., Henstridge D.C., Penfold S.A., Laskowski A., Sourris K.C., Groschner L.N., Cooper M.E., Thorburn D.R., et al. // Antioxid. Redox Signal. 2013. V. 19. № 4. P. 331–343.
42. Grad L.I., Lemire B.D. // Hum. Mol. Genet. 2004. V. 13. № 3. P. 303–314.
43. Qi X., Lewin A.S., Sun L., Hauswirth W.W., Guy J. // Ann. Neurol. United States. 2004. V. 56. № 2. P. 182–191.
44. Huang G., Lu H., Hao A., Ng D.C.H., Ponniah S., Guo K., Lufei C., Zeng Q., Cao X. // Mol. Cell. Biol. 2004. V. 24. № 19. P. 8447–8456.
45. Kohda M., Tokuzawa Y., Kishita Y., Nyuzuki H., Moriyama Y., Mizuno Y., Hirata T., Yatsuka Y., Yamashita-Sugahara Y., Nakachi Y., et al. // PLoS Genet. 2016. V. 12. № 1. P. e1005679.
46. Arsenijevic D., Onuma H., Pecqueur C., Raimbault S., Manning B.S., Miroux B., Couplan E., Alves-Guerra M.C., Goubern M., Surwit R., et al. // Nat. Genet. 2000. V. 26. № 4. P. 435–439.
47. Zhang C.Y., Baffy G., Perret P., Krauss S., Peroni O., Grujic D., Hagen T., Vidal-Puig A.J., Boss O., Kim Y.B., et al. // Cell. 2001. V. 105. № 6. P. 745–755.

48. Conti B., Sanchez-Alavez M., Winsky-Sommerer R., Morale M.C., Lucero J., Brownell S., Fabre V., Huitron-Resendiz S., Henriksen S., Zorrilla E.P., et al. // Science. 2006. V. 314. № 5800. P. 825–828.
49. Enerbäck S., Jacobsson A., Simpson E.M., Guerra C., Yamashita H., Harper M.E., Kozak L.P. // Nature. 1997. V. 387. № 6628. P. 90–94.
50. Vidal-Puig A.J., Grujic D., Zhang C.Y., Hagen T., Boss O., Ido Y., Szczepanik A., Wade J., Mootha V., Cortright R., et al. // J. Biol. Chem. 2000. V. 275. № 21. P. 16258–16266.
51. Johnson M.T., Mahmood S., Hyatt S.L., Yang H.S., Soloway P.D., Hanson R.W., Patel M.S. // Mol. Genet. Metab. 2001. V. 74. № 3. P. 293–302.
52. Peng M., Falk M.J., Haase V.H., King R., Polyak E., Selak M., Yudkoff M., Hancock W.W., Meade R., Saiki R., et al. // PLoS Genet. 2008. V. 4. № 4. P. e1000061.
53. Quinzii C.M., Garone C., Emmanuele V., Tadesse S., Krishna S., Dorado B., Hirano M. // FASEB J. 2013. V. 27. № 2. P. 612–621.
54. García-Corzo L., Luna-Sánchez M., Doerrier C., García J.A., Guarás A., Acín-Pérez R., Bullejos-Peregrín J., López A., Escames G., Enríquez J.A., et al. // Hum. Mol. Genet. 2013. V. 22. № 6. P. 1233–1248.
55. Li K., Li Y., Shelton J.M., Richardson J.A., Spencer E., Chen Z.J., Wang X., Williams R.S. // Cell. 2000. V. 101. № 4. P. 389–399.
56. Hao Z., Duncan G.S., Chang C.C., Elia A., Fang M., Wakeham A., Okada H., Calzascia T., Jang Y., You-Ten A., et al. // Cell. 2005. V. 121. № 4. P. 579–591.
57. Piruat J.I., Pintado C.O., Ortega-Sáenz P., Roche M., López-Barneo J. // Mol. Cell Biol. 2004. V. 24. № 24. P. 10933–10940.
58. Bayley J.P., van Minderhout I., Hogendoorn P.C.W., Cornelisse C.J., van der Wal A., Prins F.A., Teppema L., Dahan A., Devilee P., Taschner P.E.M. // PLoS One. 2009. V. 4. № 11. P. 1–7.
59. Levéen P., Kotarsky H., Mörgelin M., Karikoski R., Elmér E., Fellman V. // Hepatology. 2011. V. 53. № 2. P. 437–447.
60. Diaz F., Garcia S., Padgett K.R., Moraes C.T. // Hum. Mol. Genet. 2012. V. 21. № 23. P. 5066–5077.
61. Weinberg S.E., Singer B.D., Steinert E.M., Martinez C.A., Mehta M.M., Martínez-Reyes I., Gao P., Helmin K.A., Abdala-Valencia H., Sena L.A., et al. // Nature. 2019. V. 565. № 7740. P. 495–499.
62. Hüttemann M., Lee I., Gao X., Pecina P., Pecinova A., Liu J., Aras S., Sommer N., Sanderson T.H., Tost M., et al. // FASEB J. 2012. V. 26. № 9. P. 3916–3930.
63. Quintens R., Singh S., Lemaire K., De Bock K., Granvik M., Schraenen A., Vroegrijk I.O.C.M., Costa V., van Noten P., Lambrechts D., et al. // PLoS One. 2013. V. 8. № 2. P. e56719.
64. Diaz F., Thomas C.K., Garcia S., Hernandez D., Moraes C.T. // Hum. Mol. Genet. 2005. V. 14. № 18. P. 2737–2748.
65. Fukui H., Diaz F., Garcia S., Moraes C.T. // Proc. Natl. Acad. Sci. USA. 2007. V. 104. № 35. P. 14163–14168.
66. Diaz F., Garcia S., Hernandez D., Regev A., Rebelo A., Oca-Cossio J., Moraes C.T. // Gut. 2008. V. 57. № 2. P. 232–242.
67. Fünfschilling U., Supplie L.M., Mahad D., Boretius S., Saab A.S., Edgar J., Brinkmann B.G., Kassmann C.M., Tzvetanova I.D., Möbius W., et al. // Nature. 2012. V. 485. № 7399. P. 517–521.
68. Agostino A., Invernizzi F., Tiveron C., Fagiolari G., Prelle A., Lamantea E., Giavazzi A., Battaglia G., Tatangelo L., Tiranti V., et al. // Hum. Mol. Genet. 2003. V. 12. № 4. P. 399–413.
69. Dell'Agnello C., Leo S., Agostino A., Szabadkai G., Tiveron C.C., Zulian A.A., Prelle A., Roubertoux P., Rizzuto R., Zeviani M. // Hum. Mol. Genet. 2007. V. 16. № 4. P. 431–444.
70. Yang H., Brosel S., Acin-Perez R., Slavkovich V., Nishino I., Khan R., Goldberg I.J., Graziano J., Manfredi G., Schon E.A. // Hum. Mol. Genet. 2009. V. 19. № 1. P. 170–180.
71. Viscomi C., Bottani E., Civiletto G., Cerutti R., Moggio M., Fagiolari G., Schon E.A., Lamperti C., Zeviani M. // Cell. Metab. 2011. V. 14. № 1. P. 80–90.
72. Vrbacký M., Kovalčíková J., Chawengsaksophak K., Beck I.M., Mráček T., Nůsková H., Sedmera D., Papoušek F., Kolář F., Sobol M., et al. // Hum. Mol. Genet. 2016. V. 25. № 21. P. 4674–4685.
73. Markovič A., Tauchmannová K., Šimáková M., Mlejnek P., Kaplanová V., Pecina P., Pecinová A., Papoušek F., Liška F., Šilhavý J., et al. // Biomedicines. 2022. V. 10. № 2. P. 276.
74. Haraguchi M., Tsujimoto H., Fukushima M., Higuchi I., Kuribayashi H., Utsumi H., Nakayama A., Hashizume Y., Hirato J., Yoshida H., et al. // Mol. Cell. Biol. 2002. V. 22. № 14. P. 5212–5221.
75. López L.C., Akman H.O., García-Cazorla Á., Dorado B., Martí R., Nishino I., Tadesse S., Pizzorno G., Shungu D., Bonilla E., et al. // Hum. Mol. Genet. 2009. V. 18. № 4. P. 714–722.
76. Graham B.H., Waymire K.G., Cottrell B., Trounce I.A., MacGregor G.R., Wallace D.C. // Nat. Genet. 1997. V. 16. № 3. P. 226–234.
77. Esposito L.A., Melov S., Panov A., Cottrell B.A., Wallace D.C. // Proc. Natl. Acad. Sci. USA. 1999. V. 96. № 9. P. 4820–4825.
78. Brower J.V., Rodic N., Seki T., Jorgensen M., Fliess N., Yachnis A.T., McCarrey J.R., Oh S.P., Terada N. // J. Biol. Chem. 2007. V. 282. № 40. P. 29658–29666.
79. Kokoszka J.E., Waymire K.G., Levy S.E., Sligh J.E., Cai J., Jones D.P., MacGregor G.R., Wallace D.C. // Nature. 2004. V. 427. № 6973. P. 461–465.
80. Tyynismaa H., Sembongi H., Bokori-Brown M., Granycome C., Ashley N., Poulton J., Jalanko A., Spelbrink J.N., Holt I.J., Suomalainen A. // Hum. Mol. Genet. 2004. V. 13. № 24. P. 3219–3227.
81. Tyynismaa H., Mjosund K.P., Wanrooij S., Lappalainen I., Ylikallio E., Jalanko A., Spelbrink J.N., Paetau A., Suomalainen A. // Proc. Natl. Acad. Sci. USA. 2005. V. 102. № 49. P. 17687–17692.
82. Tyynismaa H., Carroll C.J., Raimundo N., Ahola-Erkkilä S., Wenz T., Ruhanen H., Guse K., Hemminki A., Peltola-Mjøsund K.E., Tulkki V., et al. // Hum. Mol. Genet. 2010. V. 19. № 20. P. 3948–3958.
83. Trifunovic A., Wredenberg A., Falkenberg M., Spelbrink J.N., Rovio A.T., Bruder C.E., Bohlooly-Y M., Gidlöf S., Oldfors A., Wibom R., et al. // Nature. 2004. V. 429. № 6990. P. 417–423.
84. Kujoth C.C., Hiona A., Pugh T.D., Someya S., Panzer K., Wohlgemuth S.E., Hofer T., Seo A.Y., Sullivan R., Jobling W.A., et al. // Science. 2005. V. 309. № 5733. P. 481–484.
85. Miller R.A. // Science. 2005. V. 310. № 5747. P. 441–443.
86. Hance N., Ekstrand M.I., Trifunovic A. // Hum. Mol. Genet. 2005. V. 14. № 13. P. 1775–1783.
87. Vermulst M., Wanagat J., Kujoth G.C., Bielas J.H., Rabinovitch P.S., Prolla T.A., Loeb L.A. // Nat. Genet. 2008. V. 40. № 4. P. 392–394.
88. Ross J.M., Stewart J.B., Hagström E., Brené S., Mourier A., Coppotelli G., Freyer C., Lagouge M., Hoffer B.J., Olson L., et al. // Nature. 2013. V. 501. № 7467. P. 412–415.
89. Akman H.O., Dorado B., López L.C., García-Cazorla Á., Vilà M.R., Tanabe L.M., Dauer W.T., Bonilla E., Tanji K., Hirano M. // Hum. Mol. Genet. 2008. V. 17. № 16. P. 2433–2440.

90. Bartesaghi S., Betts-Henderson J., Cain K., Dinsdale D., Zhou X., Karlsson A., Salomoni P., Nicotera P. // Hum. Mol. Genet. 2010. V. 19. № 9. P. 1669–1677.
91. Zhou X., Curbo S., Zhao Q., Krishnan S., Kuiper R., Karlsson A. // Hum. Mol. Genet. 2019. V. 28. № 17. P. 2874–2884.
92. Viscomi C., Spinazzola A., Maggioni M., Fernandez-Vizarra E., Massa V., Pagano C., Vettor R., Mora M., Zeviani M. // Hum. Mol. Genet. 2009. V. 18. № 1. P. 12–26.
93. Wang J., Wilhelmsson H., Graff C., Li H., Oldfors A., Rustin P., Brüning J.C., Kahn C.R., Clayton D.A., Barsh G.S., et al. // Nat. Genet. 1999. V. 21. № 1. P. 133–137.
94. Wredenberg A., Wibom R., Wilhelmsson H., Graff C., Wiener H.H., Burden S.J., Oldfors A., Westerblad H., Larsson N.G. // Proc. Natl. Acad. Sci. USA. 2002. V. 99. № 23. P. 15066–15071.
95. Aydin J., Andersson D.C., Hänninen S.L., Wredenberg A., Tavi P., Park C.B., Nils-Göran L., Bruton J.D., Westerblad H. // Hum. Mol. Genet. 2009. V. 18. № 2. P. 278–288.
96. Ekstrand M.I., Terzioglu M., Galter D., Zhu S., Hofstetter C., Lindqvist E., Thams S., Bergstrand A., Hansson F.S., Trifunovic A., et al. // Proc. Natl. Acad. Sci. USA. 2007. V. 104. № 4. P. 1325–1330.
97. Desdín-Micó G., Soto-Heredero G., Aranda J.F., Oller J., Carrasco E., Gabandé-Rodríguez E., Blanco E.M., Alfranca A., Cussó L., Desco M., et al. // Science. 2020. V. 368. № 6497. P. 1371–1376.
98. Silva J.P., Köhler M., Graff C., Oldfors A., Magnuson M.A., Berggren P.O., Larsson N.G. // Nat. Genet. 2000. V. 26. № 3. P. 336–340.
99. Sörensen L., Ekstrand M., Silva J.P., Lindqvist E., Xu B., Rustin P., Olson L., Larsson N.G. // J. Neurosci. 2001. V. 21. № 20. P. 8082–8090.
100. Ekstrand M.I., Falkenberg M., Rantanen A., Park C.B., Gaspari M., Hultenby K., Rustin P., Gustafsson C.M., Larsson N.G. // Hum. Mol. Genet. 2004. V. 13. № 9. P. 935–944.
101. Pondarré C., Antiochos B.B., Campagna D.R., Clarke S.L., Greer E.L., Deck K.M., McDonald A., Han A.-P., Medlock A., Kutok J.L., et al. // Hum. Mol. Genet. 2006. V. 15. № 6. P. 953–964.
102. Cossée M., Puccio H., Gansmuller A., Koutnikova H., Dierich A., LeMeur M., Fischbeck K., Dollé P., Koenig M. // Hum. Mol. Genet. 2000. V. 9. № 8. P. 1219–1226.
103. Puccio H., Simon D., Cossée M., Criqui-Filipe P., Tiziano F., Melki J., Hindelang C., Matyas R., Rustin P., Koenig M. // Nat. Genet. 2001. V. 27. № 2. P. 181–186.
104. Seznec H., Simon D., Monassier L., Criqui-Filipe P., Gansmuller A., Rustin P., Koenig M., Puccio H. // Hum. Mol. Genet. 2004. V. 13. № 10. P. 1017–1024.
105. Thierbach R., Schulz T.J., Isken F., Voigt A., Mietzner B., Drewes G., von Kleist-Retzow J.-C., Wiesner R.J., Magnuson M.A., Puccio H., et al. // Hum. Mol. Genet. 2005. V. 14. № 24. P. 3857–3864.
106. Miranda C.J., Santos M.M., Ohshima K., Smith J., Li L., Bunting M., Cossée M., Koenig M., Sequeiros J., Kaplan J., et al. // FEBS Lett. 2002. V. 512. № 1–3. P. 291–297.
107. Clark R.M., De Biase I., Malykhina A.P., Al-Mahdawi S., Pook M., Bidichandani S.I. // Hum. Genet. 2007. V. 120. № 5. P. 633–640.
108. Coppola G., Marmolino D., Lu D., Wang Q., Cnop M., Rai M., Acquaviva F., Cocozza S., Pandolfo M., Geschwind D.H. // Hum. Mol. Genet. 2009. V. 18. № 13. P. 2452–2461.
109. Anderson P.R., Kirby K., Hilliker A.J., Phillips J.P. // Hum. Mol. Genet. 2005. V. 14. № 22. P. 3397–3405.
110. Anderson P.R., Kirby K., Orr W.C., Hilliker A.J., Phillips J.P. // Proc. Natl. Acad. Sci. USA. 2008. V. 105. № 2. P. 611–616.
111. Swarup V., Julien J.-P. // Prog. Neuropsychopharmacol Biol. Psychiatry. 2011. V. 35. № 2. P. 363–369.
112. Kreilaus F., Guerra S., Masanetz R., Menne V., Yerbury J., Karl T. // Genes Brain Behav. 2020. V. 19. № 2. P. 1–14.
113. Riboldi G., Nizzardo M., Simone C., Falcone M., Bresolin N., Comi G.P., Corti S. // Prog. Neurobiol. 2011. V. 95. № 2. P. 133–148.
114. Elchuri S., Oberley T.D., Qi W., Eisenstein R.S., Roberts L.J., van Remmen H., Epstein C.J., Huang T.T. // Oncogene. 2005. V. 24. № 3. P. 367–380.
115. Hashizume K., Hirasawa M., Imamura Y., Noda S., Shimizu T., Shinoda K., Kurihara T., Noda K., Ozawa Y., Ishida S., et al. // Am. J. Pathol. 2008. V. 172. № 5. P. 1325–1331.
116. Lebovitz R.M., Zhang H., Vogel H., Cartwright J., Dionne L., Lu N., Huang S., Matzuk M.M. // Proc. Natl. Acad. Sci. USA. 1996. V. 93. № 18. P. 9782–9787.
117. Li Y., Huang T.T., Carlson E.J., Melov S., Ursell P.C., Olson J.L., Noble L.J., Yoshimura M.P., Berger C., Chan P.H., et al. // Nat. Genet. 1995. V. 11. № 4. P. 376–381.
118. Melov S., Coskun P., Patel M., Tuinstra R., Cottrell B., Jun A.S., Zastawny T.H., Dizdaroglu M., Goodman S.I., Huang T.T., et al. // Proc. Natl. Acad. Sci. USA. 1999. V. 96. № 3. P. 846–851.
119. Kokoszka J.E., Coskun P., Esposito L.A., Wallace D.C. // Proc. Natl. Acad. Sci. USA. 2001. V. 98. № 5. P. 2278–2283.
120. Esposito L.A., Kokoszka J.E., Waymire K.G., Cottrell B., MacGregor G.R., Wallace D.C. // Free Radic. Biol Med. 2000. V. 28. № 5. P. 754–766.
121. Reddy V.N., Giblin F.J., Lin L.R., Dang L., Unakar N.J., Musch D.C., Boyle D.L., Takemoto L.J., Ho Y.S., Knoernschild T., et al. // Invest. Ophthalmol. Vis. Sci. 2001. V. 42. № 13. P. 3247–3255.
122. De Haan J.B., Bladier C., Griffiths P., Kelner M., O'Shea R.D., Cheung N.S., Bronson R.T., Silvestro M.J., Wild S., Zheng S.S., et al. // J. Biol. Chem. 1998. V. 273. № 35. P. 22528–22536.
123. Shiomi T., Tsutsui H., Matsusaka H., Murakami K., Hayashidani S., Ikeuchi M., Wen J., Kubota T., Utsumi H., Takeshita A. // Circulation. 2004. V. 109. № 4. P. 544–549.
124. Chen H., Detmer S.A., Ewald A.J., Griffin E.E., Fraser S.E., Chan D.C. // J. Cell Biol. 2003. V. 160. № 2. P. 189–200.
125. Chen H., McCaffery J.M., Chan D.C. // Cell. 2007. V. 130. № 3. P. 548–562.
126. Detmer S.A., Velde C. Vande, Cleveland D.W., Chan D.C. // Hum. Mol. Genet. 2008. V. 17. № 3. P. 367–375.
127. Alavi M.V., Bette S., Schimpf S., Schuettauf F., Schraermeyer U., Wehrl H.F., Ruttiger L., Beck S.C., Tonagel F., Pichler B.J., et al. // Brain. 2007. V. 130. № 4. P. 1029–1042.
128. Davies V.J., Hollins A.J., Piechota M.J., Yip W., Davies J.R., White K.E., Nicols P.P., Boulton M.E., Votruba M. // Hum. Mol. Genet. 2007. V. 16. № 11. P. 1307–1318.
129. Ishihara N., Nomura M., Jofuku A., Kato H., Suzuki S.O., Masuda K., Otera H., Nakanishi Y., Nonaka I., Goto Y.I., et al. // Nat. Cell. Biol. 2009. V. 11. № 8. P. 958–966.
130. Gerber S., Charif M., Chevrollier A., Chaumette T., Angebault C., Kane M.S., Paris A., Alban J., Quiles M., Delettre C., et al. // Brain. 2017. V. 140. № 10. P. 2586–2596.
131. Oishi K., Hofmann S., Diaz G.A., Brown T., Manwani D., Ng L., Young R., Vlassara H., Ioannou Y.A., Forrest D., et al. // Hum. Mol. Genet. 2002. V. 11. № 23. P. 2951–2960.
132. Liberman M.C., Tartaglini E., Fleming J.C., Neufeld E.J. // J. Assoc. Res. Otolaryngol. 2006. V. 7. № 3. P. 211–217.