Review Article

Mitochondrial Disorders

Thomas Klopstock, Claudia Priglinger, Ali Yilmaz, Cornelia Kornblum, Felix Distelmaier, Holger Prokisch

Friedrich-Baur-Institute, Department of Neurology, LMU Ludwig Maximilians University of Munich; German Center for Neurodegenerative Diseases (DZNE) Munich; Munich Cluster for Systems Neurology (SyNergy): Prof. Dr. med. Thomas Klopstock, FEAN

Department of Ophthalmology, University Hospital, LMU Munich: PD Dr. med. Claudia Priglinger

Department of Cardiology and Angiology, University Hospital Münster: Prof. Dr. med. Ali Yilmaz

Department of Neurology, University Hospital Bonn: Prof. Dr. med. Cornelia Kornblum

Department of General Pediatrics, Neonatology and Pediatric Cardiology, University Hospital Düsseldorf: Prof. Dr. med. Felix Distelmaier

Institute of Neurogenomics, Helmholtz Zentrum Munich; Institute of Human Genetics, Klinikum rechts der Isar, Technische Universität München (TUM): Dr. rer. nat. Holger Prokisch

Summary

Background: Mitochondrial disorders are among the most common heritable diseases, with an overall lifetime risk of approximately one in 1500. Nonetheless, their diagnosis is often missed because of their extreme phenotypic and genotypic heterogeneity.

Methods: This review is based on publications retrieved by a selective literature search on the clinical features, genetics, pathogenesis, diagnosis, and treatment of mitochondrial diseases.

Results: Pathogenic defects of energy metabolism have been described to date in over 400 genes. Only a small number of these genes lie in the mitochondrial DNA; the corresponding diseases are either maternally inherited or of sporadic distribution. The remaining disease-associated genes are coded in nuclear DNA and cause diseases that are inherited according to Mendelian rules, mostly autosomal recessive. The most severely involved organs are generally those with the highest energy requirements, including the brain, the sensory epithelia, and the extraocular, cardiac, and skeletal musculature. Typical manifestations include epileptic seizures, stroke-like episodes, hearing loss, retinopathy, external ophthalmoparesis, exercise intolerance, and diabetes mellitus. More than two manifestations of these types should arouse suspicion of a disease of energy metabolism. The severity of mitochondrial disorders ranges from very severe disease, already evident in childhood, to relatively mild disease arising in late adulthood. The diagnosis is usually confirmed with molecular-genetic methods. Symptomatic treatment can improve patients' quality of life. The only disease-modifying treatment that has been approved to date is idebenone for the treatment of Leber hereditary optic neuropathy. Intravitreal gene therapy has also been developed for the treatment of this disease; its approval by the European Medicines Agency is pending.

Conclusion: Patients with mitochondrial diseases have highly varied manifestations and can thus present to physicians in practically any branch of medicine. A correct diagnosis is the prerequisite for genetic counseling and for the initiation of personalized treatment.

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Primary mitochondrial disorders (MIDs) form a group of extremely heterogeneous diseases caused by genetic mitochondrial dysfunction. Taken as a whole, they are among the most common heritable diseases.

Consistent with the central importance of mitochondrial energy metabolism, defects can affect any tissue and any organ. Disorders can manifest with any form of symptom and at any age *(Table 1)*. Tissues with high energy requirements, such as brain, sensory epithelia, and extraocular, cardiac, and skeletal musculature, are particularly vulnerable, explaining why patients with an MID present primarily to neurology, neuropediatrics, ophthalmology, and cardiology departments.

The structure and function of mitonchondria are determined by, among others, the interaction of approximately 1500 proteins. Pathogenic defects of energy metabolism have now been attributed to mutations in >400 of the associated 1500 genes. The majority of disorders involve impairment of the main mitochondrial function: aerobic energy production. *eFigure 1* provides an overview of affected genes and their function.

As a relic of their evolutionary past in the form of endosymbiotic bacteria, mitochondria have their own mitochondrial DNA (mtDNA) made up of 16,569 base pairs. This encodes for 13 structural proteins of the respiratory chain, as well as for two ribosomal RNAs (rRNA) and 22 transfer RNAs (tRNA), which are needed for the semi-autonomous transcription and

TABLE 1

Phenotypic spectrum of mitochondrial disorders in children and adults, classified according to categories in the Human Phenotype Ontology (HPO)

Phenotypes	Children (%)*1	Adults (%)*2
Nervous system	79.4	52.1
Metabolism	69.8	21.0
Muscles	53.6	43.8
Heart and circulation	24.2	13.2
Eyes	23.8	62.0
Growth and weight	21.3	4.9
Gastrointestinal tract	17.8	2.9
Facial features	10.8	4.6
Lungs	10.6	2.5
Hearing	10.5	18.6
Blood	9.1	0.3
Urogenital tract	7.0	2.1
Endocrine system	4.3	11.6
Skin	1.5	0.5
Immune system	1.5	0.5
Skeleton	0.9	0.2

*1 In 1234 patients with disease onset < 18 years of age; based on data from mitoNET and the Institute of Human Genetics at the TU Munich, Germany
*2 In 985 patients with disease onset ≥ 18 years of age; based on data from mitoNET

translation of the structural proteins. Pathogenic variants of all these 37 genes have been described.

Oocytes contain hundreds of mitochondria, whereas the few mitochondria that a sperm possesses are eliminated during fertilization. For this reason, mtDNA mutations and the related clinical pictures *(Figure, Table 2)* are inherited only down the maternal line. In most cases, a mixture of mutated and wild-type mtDNA is present (heteroplasmy), which can vary from generation to generation and tissue to tissue, and which determines to a great extent symptom severity *(Figure)*.

The majority of the approximately 1500 mitochondrial proteins, however, are encoded by nuclear DNA (nDNA) in the cell nucleus; the associated messenger RNA is translated on cytoplasmic ribosomes into proteins, which enter the mitochondria via their own protein import mechanism. Accordingly, numerous MIDs follow Mendelian rules of inheritance, mostly autosomal recessive, rarely autosomal dominant or X-chromosomal *(Table 2, Figure)*. Therefore, precise genetic classification of a disorder is of the utmost importance for the genetic counseling of affected families.

With regard to epidemiology, a lifetime risk for developing an autosomal recessive MID of 48.4:100,000 individuals in Europe has been calculated using population genetic methods (1); for mtDNA-related MIDs, population-based data show a lifetime risk of 20.4:100,000 individuals (2). Together, this yields an estimated lifetime risk of 68.8:100,000 individuals. This means that one in 1470 newborns will develop an MID over the course of their lifetime.

General diagnosis

The most important diagnostic step is taken right at the outset: thinking of the possibility of an MID. Specific symptoms or symptom constellations, as well as an unusual combination of multiple organ manifestations, may provide pointers. Laboratory and imaging investigations (for example, elevated lactate in blood and cerebrospinal fluid, pathognomonic findings on cranial magnetic resonance imaging [cMRT]) may strengthen suspicion. Muscle biopsy, as a screening test for morphological (ragged red fibers [RRF]) and biochemical indications of an MID, has recently lost much of its importance. Instead, molecular genetic methods have become established as first-line diagnostics. This was initially in the form of targeted candidate gene sequencing (panel diagnostics), and is now increasingly performed in the form of whole exome sequencing (WES) or whole genome sequencing (WGS), both methods that best address the vast genetic heterogeneity of MIDs.

At up to 50%, WES and WGS achieve significantly higher diagnostic rates compared to panel diagnostics, and also enable the description of novel disease-associated genes (3). The cross-sectoral use of these methods is hampered by regulatory hurdles in the German healthcare system; as a result, they are currently used mainly following an application to the respective health insurance in individual cases or in the context of scientific projects. With the elimination of the application and authorization requirements for sequencing > 25 kb, the first steps have been taken in the direction of routine use of these methods. However, the indication should be made by appropriately qualified physicians, while the sequencing itself should be performed and interpreted by human geneticists. The aim of, among others, the German genome initiative, genomDE, is to establish these methods in routine practice in the sense of knowledge-generating patient care (www.genom.de). In order to further increase the diagnostic yield, multiomics data from transcriptome and proteome analyses are now being used in addition to functional investigations at the cellular level—to date, however, only in the context of scientific projects (4–7). Here, unresolved cases of MID require a skin biopsy to be taken for fibroblast culture in order to generate the necessary data for a molecular diagnosis.

However, the aim of generating is not merely to elucidate the genetic cause and correctly classify the clinical picture. Due to the clinical heterogeneity of MID, comprehensive and regularly repeated phenotyping of all relevant organ systems is recommended, even if in the first instance there are no corresponding

signs (deep phenotyping). This serves to detect hidden or subsequent organ involvement at an early stage and can have important therapeutic ramifications (8). For example, even in the absence of symptoms, we recommend annual cardiac investigations with long-term electrocardiogram (ECG) and echocardiography in order to promptly detect and treat conduction disorders and cardiomyopathy.

General treatment

Although MIDs are undoubtedly challenging to treat and the evidence for current treatment recommendations is mainly low-level, there are no grounds for therapeutic nihilism. Symptom-oriented treatments, such as the administration of antiepileptic drugs and the deployment of cochlear implants or pacemakers, can significantly improve quality of life and disease course. In order to counteract a vicious circle of exercise intolerance, reduced physical activity, and secondary deconditioning, individually tailored endurance and strength training is recommended (9). There is no evidence that taking vitamins and supplements confers any benefit, except in the case of a specific deficiency, for example, coenzyme Q10 deficiency disorders (10). Disease-modifying treatments are under development and include pharmaceuticals (for example, those with antioxidant activity or that promote mitochondrial biogenesis [11]), enzyme replacement therapies, and gene therapies. The only medication authorized to date is idebenone for Leber hereditary optic neuropathy (LHON). For information on the studies currently underway, the reader is referred to www.clinicaltrials.gov.

Registry and natural history studies

The German Network for Mitochondrial Diseases (mitoNET, www.mitoNET.org) has been funded by the German Federal Ministry of Education and Research (*Bundesministerium für Bildung und Forschung*, BMBF) since 2009. It operates, among other things, a patient registry and a biobank, and also conducts studies on the natural history of MIDs. It currently includes the data of > 1700 patients *(eFigure 2)*. As part of the EU-funded project GENOMIT (www.GENOMIT.eu), an internationally harmonized concept for data collection has been developed, and a global MID registry will shortly open.

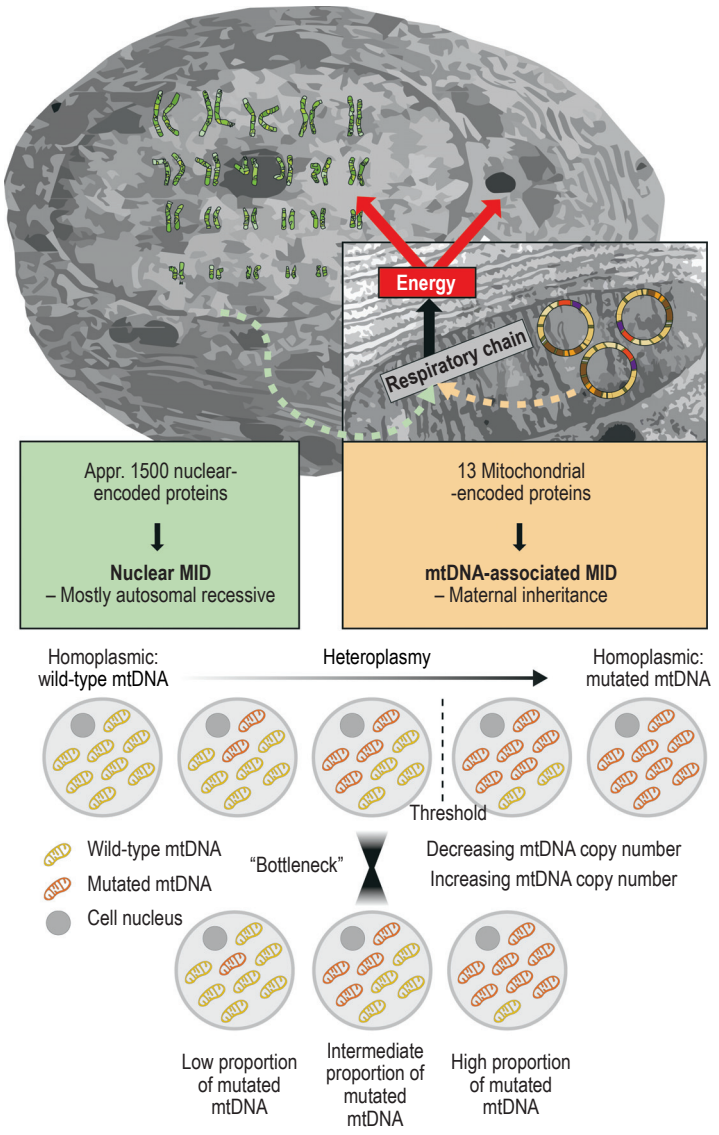
Registries of this kind make it possible to gain new insights into the phenotypic and genotypic spectrum of MIDs thanks to the large number of patients, and to promptly contact suitable patients regarding inclusion in clinical trials (trial readiness). Furthermore, monitoring the natural history of the disease through regular follow-ups is of tremendous importance for the planning of urgently needed randomized treatment studies.

Individual disorders

Leber hereditary optic neuropathy

The retina and optic nerve are among the tissues with particularly high energy demands. For this reason,

FIGURE



Mitochondrial DNA (mtDNA) encodes for only 13 proteins in the mitochondrial respiratory chain. A total of around 1500 proteins, which are primarily encoded in the cell nucleus on the chromosomes, are needed for the structure and function of mitochondria. Accordingly, disorders that are attributed to mutations of nuclear-encoded genes are inherited according to Mendelian rules, mostly in an autosomal recessive pattern. In contrast, disorders caused by mtDNA mutations are maternally inherited. In most cases, not all mtDNA molecules carry the mutation, and a mixture of mutated and wild-type mtDNA is present (heteroplasmy). Cellular dysfunction mostly develops above a threshold of approximately 60% mutated mtDNA. The degree of heteroplasmy can vary from generation to generation due to the decline and subsequent increase in mtDNA copy number in embryogenesis (mitochondrial bottleneck), as well as from tissue to tissue, and plays a major role in determining symptom severity. MID, mitochondrial disorder

TABLE 2

Characteristics of selected mitochondrial disorders

Disorder	Commonest mutations	Characteristics
mtDNA point mutations: maternal inheritance		
LHON	ND4-m.11778, ND1-m.3460, ND6-m.14484	Subacute, high-grade, central visual impairment P: approximately 1:30,000 (12)
MELAS/MIDD	tRNA-Leu- m.3243 > m.3271	Full-blown disease rare; oligosymptomatic disease common, for example, MIDD P: approximately 1:30,000 symptomatic m.3243-mutation carriers, of which approximately 10% have the full set of MELAS symptoms, around 30% MIDD (21)
MERRF	tRNA-Lys- m.8344 > m.8356	Eponymous symptoms not obligatory: myoclonus: 59%, epilepsy: 61%, RRF: 63%; in addition, frequently hearing loss: 72%, ataxia: 70%, psychiatric abnormalities: 54%, multiple lipomas P: approximately 1:500,000 symptomatic m.8344-mutation carriers (2)
NARP/MILS	ATP6- m.8993 > m.9176	55% Leigh syndrome, 8% NARP, other than that, numerous mono- or oligosymptomatic manifestations, primarily ataxia and/or neuropathy → Should be considered in multiple DD (32)
mtDNA deletions: occur mostly sporadically		
CPEO (plus)	Single mtDNA deletion	Chronic progressive ptosis and external ophthalmoplegia, with or without additional non-muscular symptoms; double vision in around 50% of cases (33); usually occurs sporadically, maternally inherited only in exceptional cases (< 5%) (34); study results with elamipretide hitherto inconsistent (35)
KSS	Single mtDNA deletion	Historically defined as CPEO, retinitis pigmentosa, onset before 20 years of age, and additional symptoms
Nuclear gene mutations: autosomal dominant inheritance		
ADOA	*OPA1* > *OPA3*	Slowly progressive loss of central vision (36); idebenone possibly beneficial, but hitherto based only on retrospective analysis of an uncontrolled cohort (37)
adPEO	*POLG1* > ANT1, Twinkle → Secondary multiple mtDNA deletions	Mutations in nuclear-encoded genes cause impaired mtDNA replication, thus multiple mtDNA deletions; clinically, adPEO is indistinguishable from the sporadic form; crucial to genetic counseling: risk of inheritance of 50% in adPEO, < 5% in CPEO
Nuclear gene mutations: X-chromosomal inheritance		
PDH deficiency	PDHA1	Ranging from severe neonatal lactic acidosis to Leigh syndrome and on to later-onset neurological disturbances; exacerbated in the case of intercurrent infections or fever; prognosis mostly poor
Nuclear gene mutations: autosomal recessive inheritance (selection from > 200 defects)		
Leigh syndrome	> 80 Genes including *SURF1*	Subacute necrotizing encephalomyelopathy ([38]; *Figure 1d*) I: approximately 1:40,000 live births (39) Depending on the underlying defect, trial use of the dietary supplements thiamine, coenzyme Q10, and riboflavin (40)
SANDO	*POLG1* → Secondary multiple mtDNA deletions and depletion	Biallelic *POLG1* mutations cause varying combinations of epilepsy, ataxia, neuropathy, myopathy, and ophthalmoplegia
MNGIE	*TYMP1* → Secondary multiple mtDNA deletions and depletion	*TYMP1* defect results in impaired mtDNA synthesis via mitochondrial nucleotide pool imbalances; clinical onset usually in late childhood; CPEO, leukoencephalopathy, peripheral neuropathy; gastrointestinal disorders result in pronounced cachexia, which significantly reduces life expectancy

ADOA, autosomal dominant optic atrophy; adPEO, autosomal dominant progressive external ophthalmoplegia; CPEO, chronic progressive external ophthalmoplegia;
DD, differential diagnosis; I, incidence; KSS, Kearns–Sayre syndrome; LHON, Leber hereditary optic neuropathy;
MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERRF, myoclonic epilepsy with ragged-red fibers;
MIDD, maternally inherited diabetes and deafness; MILS, maternally inherited Leigh syndrome; MNGIE, mitochondrial neurogastrointestinal encephalomyopathy;
NARP, neuropathy, ataxia, retinitis pigmentosa; P, prevalence; PDH, pyruvate dehydrogenase; RRF, ragged red fibers;
SANDO, sensory ataxia, neuropathy, dysarthria, and ophthalmoplegia

visual disorders are a frequent symptom of MID. Visual loss is particularly pronounced in LHON, which is considered the most common MID with a prevalence of approximately 1:30,000 (12). Although LHON can develop at any age, onset is predominantly in adolescence and young adulthood. Males are significantly more frequently affected than are women; a protective effect for estrogen is mooted. Following subacute onset, central vision becomes impaired to a high degree *(Figure 1a)*. Either both eyes are affected simultaneously or, more frequently, initially only one eye, followed some weeks later by the second. In the majority of patients, visual acuity remains at < 0.1 in the long-term course.

The cause in > 90% of cases is one of the three primary LHON mutations, ND4-m.11778, ND6-m.14484, and ND1-m.3460 of the mtDNA, which result in defects of the complex I of the mitochondrial respiratory chain. Penetrance of these

almost always homoplasmic *(Figure)* mutations is incomplete. Only around 50% of male mutation carriers and around 10% of female mutation carriers develop disease, which explains why male patients predominate. Smoking is considered a trigger for the onset of symptoms (13). In the course of pathogenesis, retinal ganglion cell dysfunction develops, while in the chronic course, apoptotic loss of these cells and their axons (optic nerve) occurs.

Establishing the clinical diagnosis is challenging. Initially, there is no optic nerve atrophy, but instead discrete optic nerve swelling and peripapillary telangiectasia. In some cases, the optic disc is normal on fundoscopy and only optical coherence tomography shows discrete thickening of the nerve fiber layers. In the majority of patients, particularly in the case of unilateral onset, optic neuritis is initially suspected, and appropriate neurological diagnosis and treatment are carried out. It is crucial at this point to think of the possibility of LHON and arrange the simple and inexpensive genetic blood test.

Since mtDNA mutations are maternally inherited, all relatives in the maternal line are at risk of developing disease. Therefore, information regarding the harmful effect of smoking needs to be communicated to those at risk. However, as a result of the reduced penetrance, it is not unusual for no further cases to be known within a family.

In symptom-oriented treatment, magnifying visual aids and acoustic aids (for example, via smartphone) are important. Based on the results of a randomized controlled trial (14) and an expanded access program (15), conditional approval was granted in the European Union (EU) in 2015 for the drug idebenone (3 × 300 mg/day) (evidence level Ib, grade A recommendation [8]). Idebenone acts as an intramitochondrial antioxidant and is able to transfer electrons directly to complex III of the respiratory chain while bypassing the defective complex I, thereby producing overall less oxidative damage and more energy. Compared to the natural course, treatment improves the chances that visual acuity that is still good stabilizes (50% of patients) or that visual acuity that is already significantly reduced recovers in a clinically relevant manner (16). Recovery of this kind was observed in 46% of treated patients (versus 31% in a historical, untreated control group). Visual acuity in these patients improved by a mean of > 7 lines on the visual chart (15).

In addition, intravitreal gene therapy has been developed for patients with ND4-m.11778 mutation. Following unilateral injection 6–12 months after symptom onset, visual acuity improved in 37 patients at 96 weeks by a mean of 15 letters in the treated eye and 13 letters in the untreated contralateral eye on the eye chart. The contralateral effect could be explained in primate experiments by transfer of the gene therapy construct via the optic chiasm (17). Unilateral injection < 6 months following symptom onset produced similarly positive results in a further 38 patients (18). Gene therapy approval has been applied for.

Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes

MELAS syndrome (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes) is a mitochondrial multisystem disorder that usually begins in the first to second decade of life *(Table 2)*. In cases of severe disease, the disorder is apparent in childhood through delayed development, short stature, muscle weakness and exercise intolerance, migraines, epileptic seizures, and stroke-like episodes. In the further course, hearing loss, diabetes mellitus, as well as cardiac and gastrointestinal manifestations also develop. Stroke-like episodes were defined in a consensus paper as subacute-onset encephalopathic crises with neurological and psychiatric symptoms (including impaired consciousness, headache, epileptic seizures, visual deficits, visual hallucinations, agitation, and behavioral disturbances) that develop in the setting of epileptic activity (19). On cMRI, they appear as predominantly occipital cortical hyperintensities that are not confined to vascular territories *(Figure 1b)*. They may either completely resolve, together with the clinical symptoms, or develop into cortical laminar necrosis. In the longer course, MELAS patients usually develop marked brain atrophy and dementia. Life expectancy is difficult to estimate in individual cases due to the highly variable course of the disease, but on average it is significantly reduced. Median survival in fully symptomatic patients was 16.9 years from the onset of neurological manifestations, while the average age of death was 34.5 ±19 years (20). The most frequent causes of death are epileptic state and cardiac events.

The cause of MELAS in >80% of cases is the m.3243A>G mutation in mtDNA, which leads to a change in conformation of the tRNA that transfers leucine, thereby resulting in less mitochondrial protein synthesis. In addition to this, numerous other mtDNA mutations are described. The diagnosis is confirmed by detection of the mutation in blood (leukocytes) or, in an even more sensitive manner, in urine sediment. Muscle biopsies are mostly no longer required for diagnostic purposes.

Disease severity correlates with the proportion of mutated mtDNA versus wild-type mtDNA. The full clinical picture of MELAS develops in only around 10% of m.3243-mutation carriers. More frequently, patients exhibit a combination of only diabetes and hearing loss (maternally inherited diabetes and deafness [MIDD], 30%), as well as other symptom constellations that do not meet the MELAS criteria (21). Heteroplasmy level and phenotype can also vary widely within a family.

In symptomatic treatment, consistent antiepileptic therapy is particularly important for the suppression and secondary prevention of seizures and stroke-like episodes. Primarily newer antiepileptic drugs such as levetiracetam, lamotrigine, and lacosamide are recommended, whereas older antiepileptic drugs may

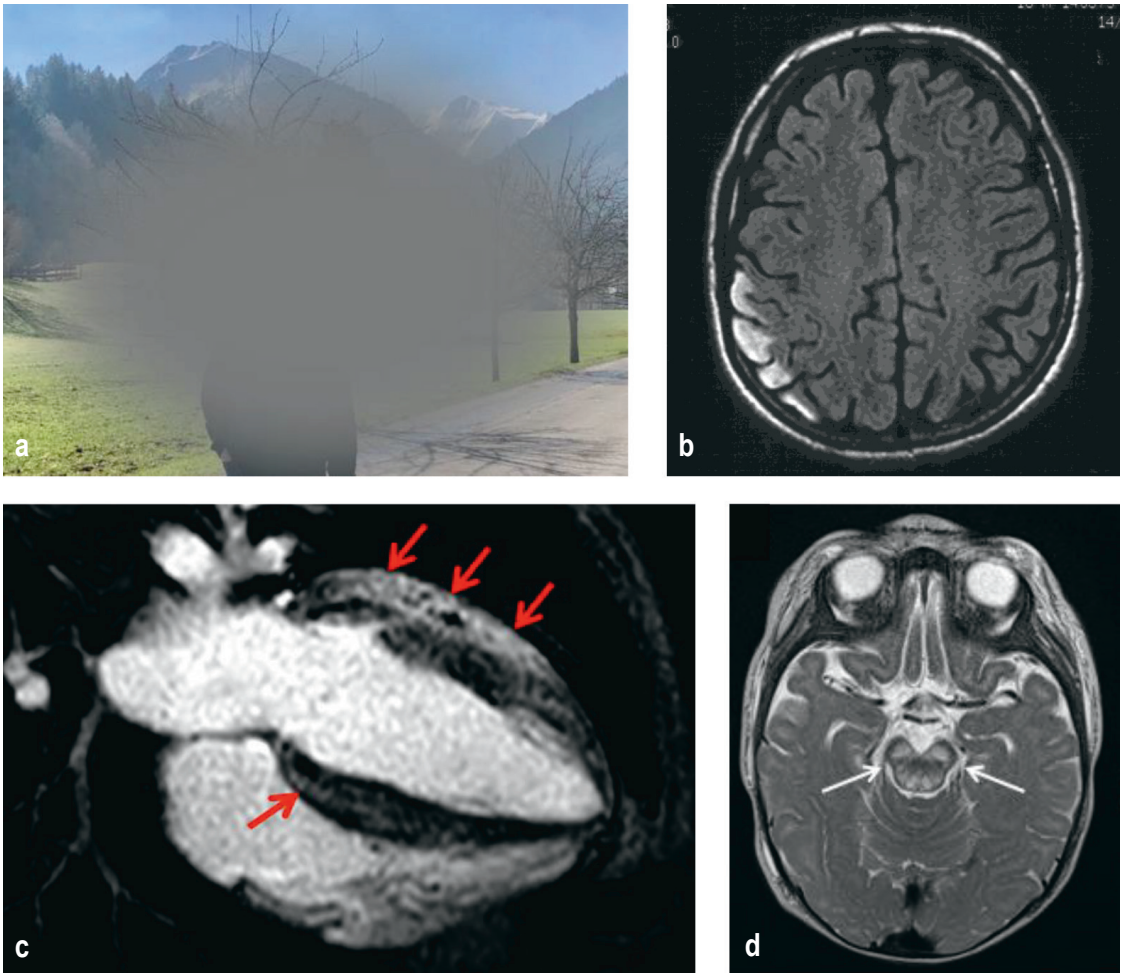


Figure 1: Pathognomic findings in mitochondrial disorders
a) LHON: central scotoma from the patient's perspective
b) MELAS: cortical T2 hyperintensity on cMRT in the case of fresh stroke-like episode
c) MELAS: cardiac involvement; the four-chamber view shows marked concentric left ventricular hypertrophy with contrast uptake (red arrows) consistent with myocardial fibrosis
d) Leigh syndrome: symmetrical signal changes in the brainstem
cMRT, cranial magnetic resonance imaging; LHON, Leber hereditary optic neuropathy; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes

have mitochondrial toxicity, and valproate in particular is even contraindicated. The use of L-arginine is the subject of controversy and, in the absence of sufficient evidence, is not recommended in the consensus paper (19). To date, there are no specific treatments that positively affect disease course. A randomized controlled trial with dichloroacetate failed to demonstrate an effect and even had to be discontinued due to adverse effects (toxic neuropathy) (22).

Other important MIDs are presented in the *eSupplement* and in *Table 2*.

Special aspects

Cardiac involvement

Due to their high energy consumption, cardiomyocytes are particularly susceptible to impaired mitochondrial energy metabolism. In our cohort, cardiovascular symptoms were observed in 24% of patients with disease onset <18 years of age and in 13% of patients with onset ≥18 years of age *(Table 1)*. In the heart, both the myocardium (cardiomyopathy) and the cardiac conduction system can be affected (23). For example, hypertrophic cardiomyopathy in MELAS is characteristic *(Figure 1c)* with a typical pattern of scarring. From a clinical perspective, this cardiac disease causes exercise dyspnea and heart failure; the myocardial scarring can be the starting point for ventricular arrythmias (in some cases even sudden cardiac death) (24).

On the other hand, patients with chronic progressive external ophthalmoplegia (CPEO), and in particular Kearns–Sayre syndrome (KSS), are more likely to exhibit conduction disturbances (in the form of bundle branch or AV block) and circumscribed textural disturbances in the left ventricular myocardium

(with systolic heart function often still preserved). As a result of primary bradycardic arrhythmias, these patients are also predisposed to sudden cardiac death (25), which has been reported as the cause of death in up to 20% of patients with KSS (26). As early on as at initial diagnosis of MID, a cardiac work-up with ECG and echocardiography is recommended, additionally including cardiac MRI if necessary. Regular long-term ECG follow-up is of central importance for treatment decisions (for example, whether or not a pacemaker or defibrillator is required).

Anesthesia

The organ systems particularly affected by MID (central nervous system, heart, muscles) are also target organs for anesthesia drugs. This often results in increased sensitivity to these drugs. Therefore, careful selection and dosage are required. Due to the heterogeneity of MID as well as limited evidence, anesthesia needs to be individually tailored to each patient. To this end, comprehensive preoperative assessment and patient information are needed. In principle, any anesthetic is capable of suppressing mitochondrial function. Before, during, and after anesthesia, it is essential to ensure that disturbances in glucose metabolism, body temperature, electrolytes, and fluid balance are kept to a minimum in patients with MID. Postoperatively, monitoring on an intensive care unit is indicated (27, 28).

Vaccinations

Infectious diseases pose a particular risk for MID patients. An inflammatory reaction, especially fever, can trigger a clinical exacerbation, in some cases with fatal consequences. Since there is no scientific evidence of a negative effect for vaccinations in MID, both the US Center for Disease Control and Prevention and the World Health Organization recommend the same vaccinations for MID patients as for the healthy population (29, 30).

COVID-19

As an infectious disease, COVID-19 may pose a particular risk to MID patients, for example, when diabetes mellitus, cardiomyopathy, or respiratory failure are present in the setting of MID. There is also experimental evidence showing that mitochondrial dysfunction may promote a severe COVID-19 course (31). Therefore, MID patients should take particular precautions to avoid infection and also get vaccinated against COVID-19.

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Conflict of interest statement

Prof. Klopstock received third-party funding to conduct clinical trials from Santhera Pharmaceuticals, GenSight Biologics, Khondrion, and Stealth BioTherapeutics. He is chairman of the non-profit association *Deutsches mitoNET e. V.*, which received donations from Santhera Pharmaceuticals and GenSight Biologics. He received consulting fees from Santhera Pharmaceuticals, GenSight Biologics, Chiesi GmbH, and Pretzel Therapeutics. For lectures he received speaker's fees from Santhera Pharmaceuticals, GenSight Biologics, and Chiesi GmbH. In addition, the abovementioned companies partially reimbursed congress fees as well as travel and accommodation costs.

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Prof. Yilmaz received speaker's and consulting fees from Alnylam Therapeutics GmbH, Pfizer Pharma GmbH, and Akcea Therapeutics GmbH; he also has scientific collaborations with Philips and Circle Cardiovascular Imaging Inc.

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Dr. Prokisch declares that no conflict of interest exists.

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Corresponding author
Prof. Dr. med. Thomas Klopstock, FEAN
Friedrich-Baur-Institut an der Neurologischen Klinik
LMU Klinikum, Ludwig-Maximilians-Universität München
Ziemssenstraße 1, 80336 München, Germany
tklopsto@med.LMU.de

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► **Supplementary material**

eSupplement, eBox, eFigures:
www.aerzteblatt-international.de/m2021.0251

Questions on the article in issue 44/2021:

Mitochondrial Disorders

cme plus+

The submission deadline is 4 November 2022. Only one answer is possible per question.
Please select the answer that is most appropriate.

Question 1

Which pattern of inheritance do genetic mutations in mitochondrial DNA (mtDNA) follow?

a) Autosomal dominant
b) Autosomal recessive
c) Down the father's line (paternal)
d) Down the mother's line (maternal)
e) Intermediate autosomal

Question 2

Approximately how high is the lifetime risk for mitochondrial disorders?

a) 10:100 000 Persons
b) 20:100 000 Persons
c) 50:100 000 Persons
d) 70:100 000 Persons
e) 90:100 000 Persons

Question 3

Which organ systems are most frequently affected in adults with mitochondrial disorders (and disease onset ≥ 18 years of age) according to data from mitoNET?

a) Eyes, nervous system, and muscles
b) Hearing, eyes, and immune system
c) Endocrine system, muscles, and cardiovascular system
d) Metabolism, hearing, and immune system
e) Urogenital tract, muscles, and hearing

Question 4

How many mitochondrial respiratory chain proteins are encoded in mitochondrial DNA (mtDNA)?

a) Three proteins
b) 13 Proteins
c) 30 Proteins
d) 1000 Proteins
e) 1500 Proteins

Question 5

To date, there is an approved disease-modifying pharmacological therapy for only one mitochondrial disorder. Which disorder is this?

a) Chronic progressive external ophthalmoplegia (CPEO)
b) Leigh syndrome
c) Leber hereditary optic neuropathy (LHON)
d) Kearns–Sayre syndrome (KSS)
e) Myoclonic epilepsy with ragged-red fibers (MERRF)

Question 6

What does the abbreviation MELAS stand for?

a) Mitochondrial epilepsy, lactic acidosis, and sleepless episodes
b) Myocarditis, encephalomyopathy, lactic acidosis, and sight loss
c) Myocarditis, epilepsy, lung edema, acidosis, and stroke
d) Muscle weakness, encephalomyopathy, lactic acidosis, and stroke-like episodes
e) Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes

Question 7

Which antiepileptic drug is contraindicated for the treatment of epileptic seizures in the setting of a mitochondrial disorder?

a) Levetiracetam
b) Gabapentin
c) Valproate
d) Lamotrigine
e) Lacosamide

Question 8

Which of the following disorders/syndromes are caused exclusively by nuclear gene mutations?

a) PDH (pyruvate dehydrogenase) deficiency
b) LHON (Leber hereditary optic neuropathy)
c) NARP (neuropathy, ataxia, retinitis pigmentosa)
d) KSS (Kearns–Sayre syndrome)
e) MIDD (maternally inherited diabetes and deafness)

Question 9

Which of the following statements applies to vaccinations for patients with mitochondrial disorders?

a) Due to stronger vaccination side effects, only the most essential vaccinations should be performed.
b) The same vaccinations as in the general population are recommended.
c) Patients with mitochondrial disorders are not allowed to receive any vaccinations.
d) Vaccinations should only be administered in an inpatient setting with patient monitoring.
e) The intervals between vaccinations in the basic immunization schedule should be halved in each case, since the immune response is weaker.

Question 10

Which term describes the presence of a mixture of mutated and wild-type mtDNA (mtDNA, mitochondrial DNA) in a tissue/cell?

a) Homoplasmy
b) Haploidy
c) Heteroploidy
d) Heteroplasmy
e) Heterozygosity

Supplementary material to:

Mitochondrial Disorders

by Thomas Klopstock, Claudia Priglinger, Ali Yilmaz, Cornelia Kornblum, Felix Distelmaier, and Holger Prokisch

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eSUPPLEMENT

Additional individual disorders

Autosomal dominant optic atrophy

Autosomal dominant optic atrophy (ADOA) begins almost unnoticed at pre-school age with symmetrical, slowly progressive visual loss. As a result, the diagnosis is often not made until a routine examination is carried out upon starting school or in adulthood as part of family check-ups. Approximately 40% of patients retain vision of ≥ 0.32 and 15% ≥ 0.5. In around 20% of cases, extraocular symptoms manifest (ADOA plus), in particular hearing loss (63%), ocular motility disturbances (46%), myopathy (36%), ataxia (30%), and neuropathy (30 %).

The cause of ADOA in approximately 70% of cases is a mutation in the nuclear gene *OPA1*, which encodes for a mitochondrial dynamin-like GTPase. Other genes are affected in the remaining cases, for example *OPA3* (36). Here again, as in Leber hereditary optic neuropathy (LHON), the retinal ganglion cells and their axons (optic nerve) are particularly vulnerable. Since it is primarily the papillomacular bundles that are affected, central or paracentral scotomas develop, while the peripheral visual field mostly remains well preserved.

Symptomatic therapy is the same as in LHON. There are also early indications that idebenone may confer a benefit, but these are based to date only on retrospective analysis of an uncontrolled cohort (37).

Chronic progressive external ophthalmoplegia and Kearns–Sayre syndrome

Chronic progressive external ophthalmoplegia (CPEO) is one of the most common MIDs. Slowly progressive bilateral ptosis and increasingly limited eye movements in all directions of view are typical and associated with double vision in approximately 50% of patients (33). Proximal muscle weakness as well as muscular dysphagia and dysarthria may also develop. Since the transition from pure CPEO to mitochondrial multisystem disorders (CPEO plus) is fluid, a comprehensive neurological and internal medicine work-up should always be carried out. The most severe manifestation in this continuum is Kearns–Sayre syndrome (KSS), which, historically, is defined as a combination of CPEO, pigmentary retinopathy, onset before the age of 20, as well as one of the following additional symptoms: ataxia, elevated cerebrospinal fluid protein, or cardiac conduction disturbances.

These disorders can be caused by different gene defects, the precise classification of which is important for genetic counseling. Most commonly, they are due to single mtDNA deletions, which usually occur sporadically and are inherited through the maternal line only in exceptional cases (<5%) (34). In other cases, a nuclear gene mutation (for example, in the *POLG1* gene, which codes for the mitochondrial DNA polymerase) causes multiple mtDNA deletions that are inherited in an

autosomal dominant manner. More rarely, one finds mtDNA point mutations that are maternally inherited.

To confirm this diagnosis, it is still usually necessary to perform a muscle biopsy, since the mtDNA deletions can only be reliably detected there. Morphological demonstration of ragged red fibers (RRF) and cytochrome c oxidase (COX)-negative fibers also underpins the diagnosis.

As part of symptomatic treatment, surgical lid elevation is medically indicated if the eyelid covers the pupil. Disturbing double vision can be corrected with prism glasses, if necessary also with strabismus surgery. Early implantation of a cardiac pacemaker or defibrillator in the case of relevant arrhythmias can be life-saving. To date, there are no specific treatments that positively affect disease course. Positive effects seen in a phase-2 trial with elamipretide (35) were not confirmed in a phase-3 trial.

Leigh syndrome

Leigh syndrome *(Table 2)*, a typical and relatively common (approximately 1:40,000 live births) form of childhood MID, is defined as a combination of clinical and laboratory signs of mitochondrial dysfunction associated with symmetrical lesions in the basal ganglia and/or brainstem (38; *Figure 1d*). As such, rather than a unified clinical picture, Leigh syndrome is an umbrella term for >80 syndromes attributable to various genetic defects, with autosomal recessive mutations in the *SURF1* gene or mutations at position m.8993 of the mtDNA being the most frequent (39). The same mtDNA mutation can also cause much milder disease with juvenile or adult onset and symptom constellations consisting primarily of ataxia, cognitive impairment, and neuropathy *(Table 2)*, as well as in rare cases full-blown NARP (neuropathy, ataxia, retinitis pigmentosa) syndrome (32). Contrary to previous assumptions, the degree of heteroplasmy of the m.8993 mutation does not correlate well with the severity of disease. Thus, there must be other unknown modifying factors. Due to the wide clinical and genetic heterogeneity of Leigh syndrome, prognosis is challenging and affected families can only be adequately counseled if they are aware of the underlying genetic abnormalities. However, it must be stressed that early-childhood Leigh syndrome very often follows an unfavorable course and that therapeutic intervention can be undertaken in only very few cases. Treatable causes of Leigh syndrome primarily include impaired thiamine metabolism and defects in coenzyme Q10 biosynthesis. In rare cases, riboflavin-responsive disorders (for example, ACAD9 deficiency) may also be present. Therefore, the dietary supplements thiamine, coenzyme Q10, and riboflavin, which have low side-effect profiles, should be given on a low-threshold trial basis in equivocal cases of Leigh syndrome (31). It is also important to avoid catabolic states (for example, in the case of refusal to eat, gastroenteritis, and bacterial infections). The parents of affected children need to be advised that such situations should be regarded as emergencies and that low-threshold hospital admission (for example, for rehydration, glucose administration, and, where necessary, antibiotic treatment) is indicated.

eBOX

Legend to eFigure 1: Gene defects in mitochondrial disorders

An association with mitochondrial disorders has been reported for 413 genes. The genes have been grouped into subcategories according to their function:

(1) OXPHOS subunits (SU), assembly factors (AF), and electron carriers (112 of 413 genes)
(2) Mitochondrial DNA replication and expression (104 of 413 genes)
(3) Mitochondrial dynamics, homeostasis, and quality control (55 of 413 genes)
(4) Metabolism of substrates (57 of 413 genes)
(5) Metabolism of cofactors (49 of 413 genes)
(6) Metabolism of toxic compounds (10 of 413 genes)
(7) Other or unknown functions (26 of 413 genes).

The mode of inheritance is indicated by color. Some genes (n = 13) have different functions within these categories (indicated by *).
Of the 413 genes, 141 are not in the core set of all four publications (indicated by ⊗). Genes encoding proteins that are not localized in the mitochondria according to MitoCarta2.0 are highlighted with an underscore (54 of 413 genes).

Gene defects in mitochondrial disorders (legend see *eBox1*)

autosomal recessive; autosomal dominant; autosomal recessive and autosomal dominant; maternal; x-chromosomal recessive; x-chromosomal dominant; unknown

1. OXPHOS subunits, assembly factors, and electron carriers

CI UE
MT-ND1
MT-ND2
MT-ND3
MT-ND4
MT-ND4L
MT-ND5
MT-ND6
NDUFA1
NDUFA10
NDUFA12
NDUFA13
NDUFA2
⊗ NDUFA6
⊗ NDUFA8
NDUFA9
NDUFB10
NDUFB11
NDUFB3
⊗ NDUFB8
NDUFB9
NDUFS1
NDUFS2
NDUFS3
NDUFS4
NDUFS6
NDUFS7
NDUFS8
NDUFV1
NDUFV2

CI AF
ACAD9
⊗ ECSIT
FOXRED1
NDUFA11
NDUFAF1
NDUFAF2
NDUFAF3
NDUFAF4
NDUFAF5
NDUFAF6
⊗ NDUFAF7
⊗ NDUFAF8
NUBPL*
TIMMDC1
⊗ TMEM126A
TMEM126B

CII UE
SDHA
SDHB
⊗ SDHC
SDHD

CII AF
SDHAF1
⊗ SDHAF2

CIII UE
CYC1
MT-CYB
UQCRB
UQCRC2
⊗ UQCRFS1
UQCRQ

CIII AF
BCS1L
LYRM7
TTC19
UQCC2
UQCC3

Coenzym Q10
COQ2
COQ4
COQ5
COQ6
COQ7
COQ8A
COQ8B
COQ9
PDSS1
PDSS2

Cytochrome C
CYCS*
HCCS*

other
RTN4IP1

CIV UE
COX4I1
COX4I2
COX5A
COX6A1
⊗ COX6A2
COX6B1
COX7B
COX8A
MT-CO1
MT-CO2
⊗ MT-CO3
NDUFA4

CIV AF
CEP89
COA3
COA5
COA6*
COA7
COX10*
COX14
COX15*
COX20
FASTKD2
⊗ OXA1L*
PET100
PET117
SCO1*
SCO2*
SURF1
TACO1

CV UE
ATP5F1A
⊗ ATP5F1D
ATP5F1E
MT-ATP6
MT-ATP8

CV AF
⊗ ATP5MD
ATPAF2
⊗ OXA1L*
TMEM70

2. Mitochondrial DNA replication and expression

tRNAs
MT-TA
MT-TC
MT-TD
MT-TE
MT-TF
MT-TG
MT-TH
MT-TI
MT-TK
MT-TL1
MT-TL2
MT-TM
MT-TN
MT-TP
MT-TQ
MT-TR
MT-TS1
MT-TS2
MT-TT
MT-TV
MT-TW
MT-TY

Replication and transcription
DNA2
MGME1
POLG
POLG2
⊗ POLRMT
RNASEH1
⊗ SSBP1
⊗ TFAM
⊗ TOP3A
TWNK

DNA repair
⊗ APTX
⊗ XRCC4

tRNA synthetases
AARS2
CARS2
DARS2
EARS2
FARS2
GARS
⊗ GATB
⊗ GATC
HARS2
IARS2
KARS
LARS2
MARS2
MTFMT
NARS2
PARS2
QRSL1
RARS2
SARS2
TARS2
VARS2
WARS2
YARS2

Ribosomes
MRPL12
⊗ MRPL24
MRPL3
MRPL44
⊗ MRPS14
MRPS16
⊗ MRPS2
MRPS22
MRPS23
⊗ MRPS25
⊗ MRPS28
MRPS34
MRPS7
MT-RNR1
⊗ MT-RNR2
⊗ PTCD3

RNA processing
ELAC2
ERAL1
GTPBP3
HSD17B10
LRPPRC
MRM2
MTO1
MTPAP
NSUN3
⊗ PDE12
PNPT1
PUS1
⊗ THG1L
TRIT1
TRMT10C
TRMT5
TRMU
TRNT1

Translational regulation
C12orf65
C1QBP
GFM1
GFM2
⊗ GUF1
RMND1
TSFM
TUFM

Nucleotide pool repair
DGUOK
RRM2B
SAMHD1
TK2
TYMP

3. Mitochondrial dynamics, homeostasis, and quality control

Morphology
⊗ MIEF2
MSTO1
OPA1
YME1L1

Phospholipid and import machinery
AGK
AIFM1
⊗ CHKB
DNAJC19
GFER
OPA3
⊗ PAM16
PISD
PMPCA
⊗ PNPLA8
SERAC1
TAZ
⊗ TIMM22
TIMM50
TIMM8A
⊗ TOMM70
⊗ XPNPEP3

Quality control
AFG3L2
ATAD3A
CLPB
CLPP
⊗ CLPX
⊗ HSPA9
HSPD1
⊗ HSPE1
HTRA2
LONP1
MIPEP
⊗ PINK1
⊗ PITRM1
⊗ PMPCB
⊗ PRKN
SACS
SPG7
⊗ TRAP1

Defective apoptosis
APOPT1
⊗ DIABLO
⊗ PTRH2

Cleavage
DNM1L
GDAP1
MFF
SLC25A46*
STAT2

Fusion
MFN2
⊗ NME3

Ca^{2+} homeostasis
C19orf70*
⊗ CYP24A1
MICU1
MICU2

MICOS-complex
C19orf70*
CHCHD10
⊗ CHCHD2
SLC25A46*

4. Metabolism of substrates

Mitochondrial carrier
MPC1
SLC25A4
⊗ SLC25A10
⊗ SLC25A11
SLC25A12
⊗ SLC25A15
⊗ SLC25A21
⊗ SLC25A22
⊗ SLC25A24
SLC25A26
SLC25A3

Pyruvate metabolism
DLAT
DLD*
PDHA1
PDHB
PDHX
PDK3
PDP1
⊗ PDPR

Fatty acid oxidation
⊗ ACADM
⊗ ACADS
⊗ ACADSB
⊗ ACADVL
⊗ CPT1A
⊗ CPT2
⊗ CRAT
⊗ ETFA
⊗ ETFB
⊗ ETFDH
⊗ FA2H
⊗ HADH
⊗ HADHA
⊗ HADHB
⊗ PYCR1
⊗ SLC22A5
⊗ SLC25A20

Keton bodies
⊗ ACAT1
⊗ HMGCL
⊗ HMGCS2
⊗ OXCT1

Redox carrier
⊗ GOT2
⊗ MDH1
SLC25A1
⊗ SLC25A13

Tricarboxylic acid cycle
ACO2
⊗ ALDH18A1
⊗ DLST
FH
IDH3A
IDH3B
MDH2
⊗ OGDH
PPA2
SUCLA2
SUCLG1

Anaplerosis
⊗ CA5A
⊗ PC*

5. Metabolism of cofactors

Heme biosynthesis
⊗ ABCB6
⊗ ALAS2
COX10*
COX15*
CYCS*
HCCS*
⊗ PPOX
SFXN4
⊗ SLC25A38

CoA metabolism
COASY
PANK2
⊗ PPCS
SLC25A42
⊗ SLC33A1

NADPH metabolism
⊗ HAAO
⊗ KYNU
NADK2
⊗ NAXD
NAXE
⊗ NMNAT1
⊗ NNT

Iron-sulfur cluster biosynthesis
⊗ ABCB7
BOLA3
FDX1L
FDXR
FXN
GLRX5
IBA57
⊗ ISCA1
ISCA2
ISCU
LYRM4
NFS1
NFU1
NUBPL*

Selenocysteine metabolism
⊗ SECISBP2
⊗ SEPSECS

Copper metabolism
⊗ CCS
COA6*
SCO1*
SCO2*

Lipoic acid biosynthesis
DLD*
LIAS
LIPT1
LIPT2
⊗ MCAT
MECR

Riboflavin metabolism
FLAD1
SLC25A32
⊗ SLC52A1
⊗ SLC52A2
⊗ SLC52A3

Thiamine metabolism
⊗ SLC19A2
SLC19A3
SLC25A19
TPK1

Biotin metabolism
⊗ BTD
⊗ HLCS
⊗ PC*

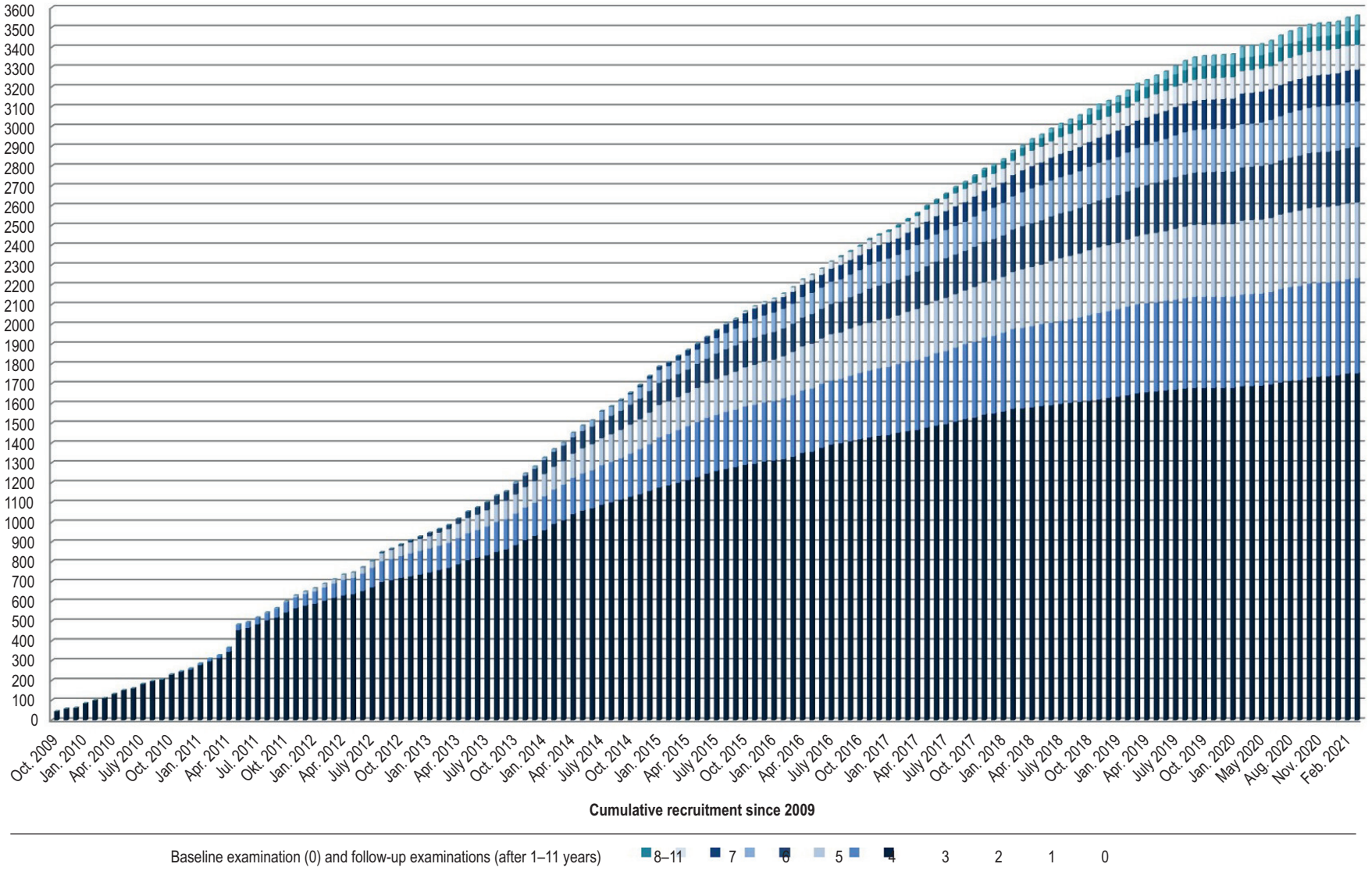
6. Metabolism of toxic compounds

⊗ D2HGDH
ECHS1
ETHE1
HIBCH
⊗ HTT
⊗ IDH2
⊗ L2HGDH
⊗ SQOR
TXN2
⊗ TXNIP

7. Other or unknown functions

ABAT
⊗ ANO10
⊗ C19orf12
⊗ CISD2
⊗ CTBP1
⊗ DCC
⊗ DIAPH1
⊗ EMC1
⊗ EXOSC3
FBXL4
⊗ FGF12
⊗ KIF5A
MPV17
⊗ PLA2G6
⊗ PNPLA4
⊗ POP1
⊗ ROBO3
⊗ SLC39A8
⊗ SPART
⊗ SPATA5
⊗ STXBP1
⊗ TANGO2
TMEM65
⊗ TRAK1
⊗ VPS13C
⊗ WFS1

eFIGURE 2



History of recruitment in the mitoNET registry. Between October 2009 and February 2021, 1753 patients with mitochondrial disorders (confirmed or highly suspected) were included in the mitoNET registry (0 = baseline examination). In addition, follow-up examinations (at 1 year, 2 years, etc. up to 11-year follow-up) are shown, from which it is possible to reconstruct the natural history of disorders.