Mitochondrial Disease
Guide for Health Professionals

Reviewed by:
Professor John Christodoulou AM, MBBS PhD FRACP
Dr Shanti Balasubramaniam MBBS FRACP
Dr Christine Wools MBBS FRACP
Dr Isabel Lopez Sanchez BSc PhD
April 2023

mito FOUNDATION
Hope for mitochondrial disease

mito.org.au

About the Mito Foundation

The Mito Foundation supports people affected by mitochondrial disease; funds essential research into the prevention, diagnosis, treatment, and cures of mitochondrial disorders; and increases disease awareness and education.

Mito Foundation is the peak body for the Australian mitochondrial disease community. Further information about Mito Foundation can be accessed at **mito.org.au**

About this guide

This guide has been developed to assist health professionals with the diagnosis and management of Australian patients with mitochondrial disease. This guide provides an overview of mitochondrial disease and the ***Patient Care Standards for primary mitochondrial disease in Australia***.[1] The standards were developed by a multidisciplinary team and build on international recommendations, with an emphasis on clinical management in the Australian setting.

Acknowledgements

In addition to our expert reviewers, Mito Foundation would like to acknowledge Mint Health, WriteSource Medical and Lightbulb Design for their contribution to the development of this resource.

Mito Foundation would like to thank Dr Karen Crawley, Professor Carolyn Sue, Professor David Thorburn and Professor John Christodoulou for their voluntary contributions to the development of educational information for medical practitioners, printed and published on Mito Foundation's website as early as 2010.

mito FOUNDATION
Hope for mitochondrial disease

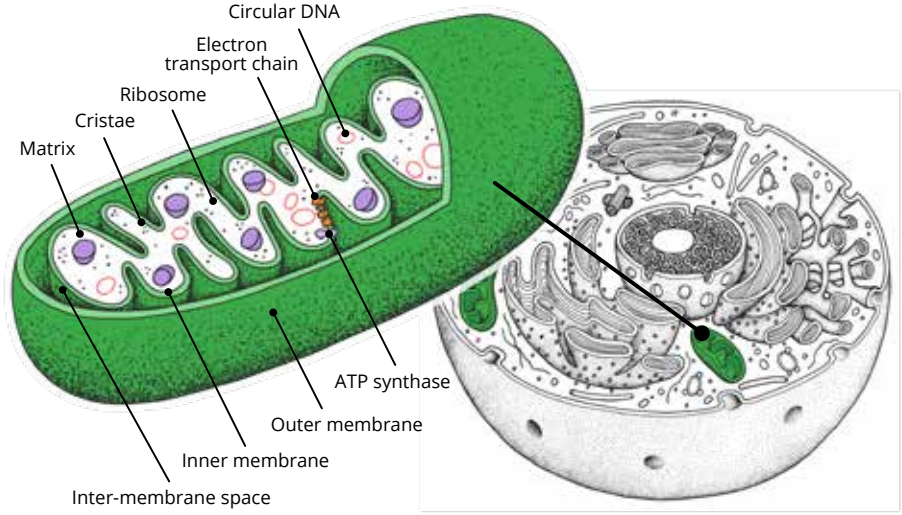
Version 1.0 April 2023

What is the mitochondrion?

Mitochondria play a key role in the human body, producing energy vital for sustaining life, supporting growth and functioning. Other functions include storage of calcium for cell signalling, and mediating cell growth and death.[2]

Mitochondria are double-membrane-bound organelles found in the cytoplasm of most eukaryotic cells (Figure 1)[3]. The breakdown products of carbohydrates and fats form the substrates of oxidative phosphorylation (OXPHOS) which produces the energy source adenosine triphosphate (ATP).[3] This cellular respiration (aerobic metabolism) produces approximately 90% of the energy needed by the human body (Figure 2).[4]

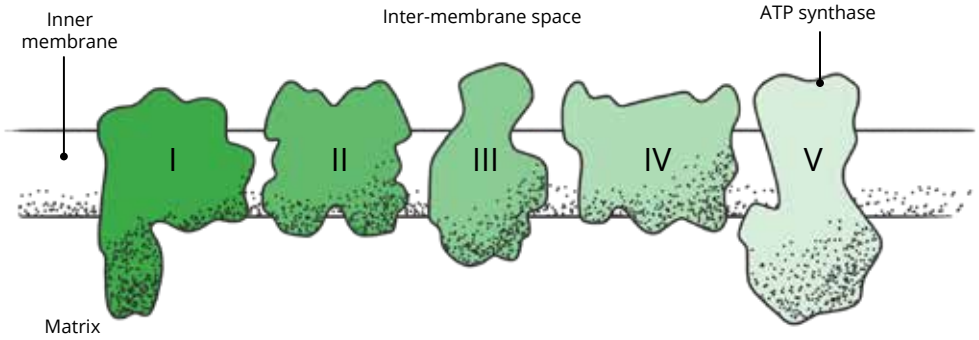
Figure 1 The Mitochondrion structure



Human cell

There are five protein complexes that interact on the inner mitochondrial membrane. These make up the mitochondrial respiratory chain complex and allow OXPHOS to occur (Figure 2).[3] Glucose and other energy sources are metabolised in the cell cytoplasm before being imported by proteins at the start of the mitochondrial respiratory chain.[3] During respiration, some oxygen is converted to reactive oxygen species such as superoxide, which play a role in cell signalling. However, they can be toxic if overproduced.[5]

Figure 2 The respiratory chain



Mitochondria are the only cellular organelles known to have a small amount of their own deoxynucleic acid (DNA), called mitochondrial DNA or mtDNA. This is in addition to the DNA found in the chromosomes within the cell nucleus, called nuclear DNA or nDNA.[6]

MtDNA contains only 37 genes, all of which are essential for energy production via OXPHOS. In addition to these genes, mitochondria rely on approximately 1,500 nuclear genes that are involved in the production, assembly and support of the five OXPHOS complexes (I-V) and ancillary mitochondrial processes.[7]

Unlike most nDNA genes, which are present in two copies in each cell (one from each parent), mtDNA is present in hundreds to thousands of copies in each cell.[8] This means that each cell can contain a mixture of healthy mtDNA and variant mtDNA, which can generate a variety of phenotypes.[8] All mitochondria of the embryo originate from the mother's ovum and therefore mtDNA is transmitted maternally.[7]

Defective mitochondria cause a cell to become deprived of ATP, and the cell accumulates unused energy precursors and oxygen. The mechanism is ineffective and results in the production of lactic acid and reactive oxygen species. This results in the metabolic consequences of OXPHOS disorders.[5]


Maeve

What is mitochondrial disease?

Mitochondrial disease is an umbrella term like 'cancer'. It is a heterogeneous group of disorders that are caused by a dysfunction in the structure and function of the mitochondria, including energy production.[9] The first genetic cause of mitochondrial disease was identified in 1988 and disease-causing variants (or changes) in over 350 genes are now known to cause mitochondrial disease.[10,11] Mitochondrial disease can result from genetic variants in either mtDNA or nDNA.[12]

Mitochondrial disease most often affects tissues and organs that depend on aerobic metabolism, like the brain and skeletal muscle.[6]

mtDNA variants are more commonly seen in adult patients while nDNA variants account for the majority of paediatric-onset mitochondrial patients.[13] Some mtDNA related mitochondrial diseases, such as Maternally Inherited Leigh Syndrome (MILS) and Mitochondrial Encephalopathy, Lactic Acidosis and Stroke-like Episodes (MELAS), can present early and may result in early death.[13]

For mitochondrial disease caused by mtDNA variants, the proportion of variant mtDNA must exceed a critical threshold, 'the threshold effect', before the cell develops an abnormality in the mitochondrial OXPHOS complex.[7,14] The threshold may vary in the organs and tissues of an individual, and also amongst people within the same family.[7,14] Therefore, the symptomatic expression of mitochondrial disease may vary according to the individual's specific mtDNA variant, and their genetic background.

Individuals with mitochondrial disease resulting from mtDNA variations may have a mixture of variant and healthy mtDNA within each cell (heteroplasmy).[6] Retrospective studies have demonstrated that the mtDNA level of heteroplasmy correlates with disease severity, however this may not be the sole contributing factor in the patient's presentation.[13]

Some mitochondrial diseases, such as Leber Hereditary Optic Neuropathy (LHON), may usually affect only one organ, e.g. the eye; however most presentations involve multiple organ systems with prominent neurologic and myopathic features (Figure 4).[6,7]

Affected individuals may present with a cluster of features that fall into a discrete clinical syndrome, such as Mitochondrial Encephalopathy with Lactic Acidosis and Stroke-like episodes (MELAS) or Myoclonic Epilepsy with Ragged-Red Fibres (MERRF).[7] Additional information on the organ systems and red flags associated with mitochondrial disease are presented in Figure 3, and common mitochondrial disease presentations are shown in Figure 4.

Clinical Point

Tissues that need a lot of energy have the greatest number of mitochondria. These tissues are often the most affected in mitochondrial disease. The tissues most often damaged are skeletal muscle, brain, heart, liver, gastrointestinal tract, ears, and eyes.[6,7]

Figure 3 Maybe it's mito?

1 Any symptom

A 'common' disease with 'atypical' features

Diagnosing primary mitochondrial disease or 'mito' can be challenging due to the wide variety of symptoms and sub-groups.[1] It is often known as the 'notorious masquerader' because it mimics many different illnesses.

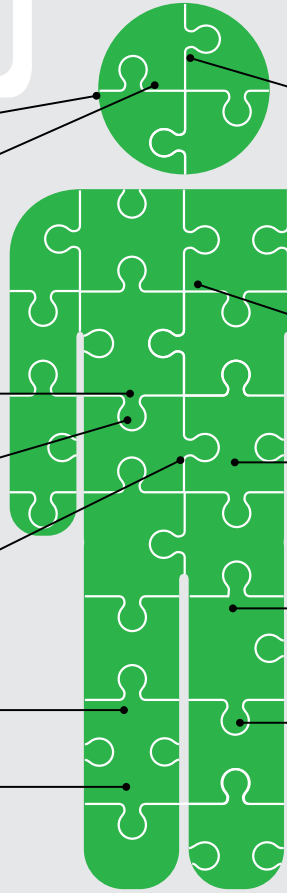
2 Any organ

Involves at least three organ systems and/or any 'red flag' symptom[1,2]

3 Any age

Recurrent setbacks/flare ups with infections

As a result, people with mito may experience profound and prolonged fatigue, as well as worsening of existing symptoms, in response to infection.[4]



Ears

Aminoglycoside-induced hearing loss

Eyes

Visual loss/blindness, optic atrophy disorders of extra-ocular muscles, ptosis, retinal degeneration with signs of night blindness, colour-vision deficits, pigmentary retinal changes such as retinitis pigmentosa or 'salt and pepper' retinopathy.

Liver

Hypoglycaemia, unexplained liver failure, valproate-induced liver failure.

Pancreas

Diabetes and exocrine pancreatic failure (inability to make digestive enzymes).

Digestive

Gastro-oesophageal reflux, delayed gastric emptying, constipation, pseudo-obstruction, chronic or recurrent vomiting.

Skin

Symmetrical lipomatosis.

Blood

Sideroblastic anaemia.

Brain & nerves

Developmental delay, intellectual disability/regression, stroke-like episodes, seizures, coma, neuro-psychiatric disturbances, atypical cerebral palsy, myoclonus, movement disorders, ataxia, migraines, strokes, weakness (which may be intermittent), neuropathy, absent or excessive sweating resulting from temperature regulation problems, dementia.

Heart

Conduction defects (e.g. heart blocks, WPW), cardiomyopathy.

Kidneys

Proximal renal tubular wasting causing the loss of protein, magnesium, phosphorous, calcium and other electrolytes, aminoaciduria, nephrotic syndrome, renal failure.

Muscles

Weakness, hypotonia, cramping, muscle pain, recurrent rhabdomyolysis.

Systemic - whole body

Exercise intolerance which is not proportional to weakness, fatigue, short stature, respiratory problems including dyspnoea, hypersensitive to general anaesthetics.

Red flag symptoms are symptoms that should prompt futher investigation, considering the possibility of mito.
A PDF version of this graphic is available on the Mito Foundation webpage **mito.org.au/maybe-its-mito-gp**

References: Figure 3: Maybe It's Mito, red flag symptoms noted[15,16]

Figure 4 Common mitochondrial disease presentations

Type	Typical Onset	Disease Characteristics	Inheritance
MELAS Mitochondrial Encephalopathy, Lactic Acidosis and Stroke-like episodes*	Usually between 2 years and 40 years (can be any age).	Lactic acidosis and stroke-like episodes with seizures, dementia, muscle weakness, sensorineural hearing loss, blindness, migraines, myopathy, cardiomyopathy, diabetes, ataxia and short stature.	Maternal
MERRF Myoclonic Epilepsy and Ragged-Red Fibres	Usually late adolescence to adulthood.	Stimulus sensitive myoclonus, seizures, cardiomyopathy, sensorineural hearing loss, ataxia, dementia, weakness, and short stature.	Maternal
KSS Kearns-Sayre Syndrome	Before age 20.	PEO**, ptosis, pigmentary retinopathy, heart block, cardiomyopathy and dysphagia, most commonly associated with sensorineural hearing loss, ataxia, dementia, diabetes mellitus and other endocrine abnormalities, hearing loss.	Sporadic
MILS Maternally inherited Leigh Syndrome Subacute necrotizing encephalomyopathy	Infancy.	Motor and intellectual regression, with ataxia, dystonia, seizures, visual loss, and cardiomyopathy.	Maternal or Nuclear
NARP Neurogenic weakness with Ataxia and Retinitis Pigmentosa	Infancy or childhood.	Pigmentary retinopathy causing vision loss, ataxia, weakness, and seizures.	Maternal
CPEO Chronic Progressive External Ophthalmoplegia	More severe with younger onset (can be any age).	Impaired eye movements with ptosis, and muscle weakness.	Maternal or Nuclear
LHON Leber Hereditary Optic Neuropathy	Male predominance, median age of onset 24 years.	Bilateral vision loss, and less commonly, preexcitation cardiac syndromes and dystonia.	Maternal

* The most common type of mitochondrial encephalopathy. **PEO: Progressive External Ophthalmoplegia

Why achieving a mito diagnosis is challenging

Most general practitioners (GPs) will at some stage care for a patient with mitochondrial disease and can play a role in the diagnostic process. Research estimates that 1 in 200 people carry a genetic variant that may cause mitochondrial disease,[17] therefore in a practice with 2,000 patients, ten patients will have a variant that may cause mitochondrial disease.

A survey of 215 patients found that the average number of doctors consulted prior to a mitochondrial disease diagnosis was 8.19 (median = 5); a majority of participants (54.6%) received one or more non-mitochondrial diagnoses before their final diagnosis.[18]

Mitochondrial disease can be very difficult to diagnose. This may be for several reasons including:

- Individuals with mitochondrial disease have varied presentations with onset at any age, from before birth (intrauterine growth restriction), to late adult life.[13,19,20]
- Mitochondrial disease presents in a highly variable manner.
- Many patients with a genetic change conferring risk for mitochondrial disease are asymptomatic or oligosymptomatic.
- Genetic testing is complex and can be expensive when not funded publicly.
- When a genetic test does not find a pathogenic variant, this does not rule out mitochondrial disease.[21]

Research continues to explore mitochondrial disease, with the number of known disease-causing genes continuing to expand.[10]

Clinical Point

Patients with mitochondrial disease may present with any symptom, in any organ, at any age, and with any mode of inheritance.

The referral pathway

The diagnostic workup for suspected mitochondrial disease involves multiple steps. The increasing availability and reduced cost of genetic testing is likely to decrease the need for invasive tests (such as biopsies) and increase the number of people diagnosed through genetic testing.

Step 1

A comprehensive patient history is required.[16]

Step 2

Clinicians should consider the more common mitochondrial syndromes e.g. MELAS or MERRF (see Figure 4). A specialist in mitochondrial disease may request additional testing including:

- blood and urine tests
- electrophysiology studies
- imaging of the brain and other organs
- audiometry and cardiac investigations
- tissue biopsy of the muscle, skin, or liver

Some patients may not show any biochemical, histological, or imaging abnormalities. For example, a normal electromyography finding may support a clinical diagnosis of mitochondrial myopathy as many other forms of non-mitochondrial myopathy have diagnostic abnormalities.[1,16,22]

Step 3

If the clinical assessment in steps 1 and 2 suggests mitochondrial disease, genetic testing is recommended.

In instances where an individual has received a genetic diagnosis through cascade testing, the diagnostic pathway may differ.

To find a mitochondrial disease specialist, please refer to the Mito Clinics Directory at **mito.org.au/clinics-directory**

Mitochondrial disease genetics and genetic testing

Research shows that one in 4,300 will develop mitochondrial disease.[23] Furthermore it is estimated one in 200 Australians has a genetic variant that puts them at risk of mitochondrial disease during their lifetime.[17] Not all of these individuals will develop symptoms, and many may develop subtle symptoms that go unnoticed during their lifetime.

nDNA variants can be inherited from either or both parents (Mendelian pattern), with most severe phenotypes caused by autosomal recessive variants.[20] mtDNA variants are usually inherited from the mother but they can also occur sporadically.[6,13] During conception the sperm's small number of mitochondria and its mtDNA are destroyed, and so paternal transmission of mtDNA is not seen in humans.[14]

Research in Australia is currently focused on preventing known mitochondrial genetic variants continuing through a family line. Prenatal diagnosis (PND) and pre-implantation genetic testing (PGT) may be available for families with an identified pathogenic genetic variant. Referral to a clinical genetics service for preconception genetic counselling will allow families to explore their available options.[1] In March 2022, the Australian Parliament passed the Mitochondrial Donation Law Reform (Maeve's Law) Bill, which allows eligible Australian women carrying a mtDNA variant to access mitochondrial donation under clinical trial conditions.[24] Further information about the clinical trial is available at **monash.edu/medicine/mitohope**.

Mitochondrial donation is a technique that replaces the variant mtDNA with healthy mtDNA (from donor oocytes) through pronuclear transfer, or maternal spindle transfer.[25] These techniques offer women the chance of having genetically related children with a reduced risk of transmitting mtDNA diseases.[26] The processes allow the retention of unique genetic information, while eliminating the variant mtDNA, thereby reducing the risk of their offspring having mtDNA diseases.[26]

Clinical Point

- Identifying a mtDNA or nDNA abnormality is 'gold standard' for the diagnosis of mitochondrial disease.
- Presence of a number of suggestive clinical features (Figure 3) should raise the question of a diagnosis of mitochondrial disease but further diagnostic workup is recommended
- Where there is a suspicion of mitochondrial disease, clinicians should refer the patient to a mitochondrial specialist.
  To find a specialist visit **mito.org.au/clinics-directory**

Sally

Patient care standards

The Patient care standards for primary mitochondrial disease in Australia: an Australian adaptation of the Mitochondrial Medicine Society recommendations[1] provide consensus-based recommendations on the management of patients with mitochondrial disease. Detailed recommendations specific to Australian clinical practice are symptom based, and provide a brief overview of each subject within the patient care standards.

More information about the Patient Care Standards is available at **mito.org.au/care-standards-for-mito/**

Audiology

Hearing loss can be progressive, and regular monitoring is required.[1] Individuals with certain mtDNA mutations are at risk of sensorineural deafness if exposed to aminogylcoside antibiotics.

Cardiology

Baseline cardiology and regular monitoring is required in both adult and paediatric patients; thereafter annual echocardiograms are recommended and repeat echocardiograms are recommended at intervals determined by baseline echocardiogram findings and other patient factors such as a family history or evidence of cardiac abnormalities.[1]

Endocrinology

Patients should be regularly monitored for diabetes and insulin resistance; other endocrinological manifestations can occur in patients with mitochondrial disease.[1]

Gastroenterology

Patients with mitochondrial disease may experience gastroenterological concerns; the patient care standards closely follows Australian clinical practice.[1]

Haematology

Haematological involvement is infrequent in patients with mitochondrial disease, however annual monitoring is recommended.[1]

Immunology

Patients with mitochondrial disease are at greater risk of sepsis and can take longer to recover from infections. There are no contraindications for vaccinations, including live vaccinations, in patients with mitochondrial disease.[1]

Nephrology

Asymptomatic kidney disease has been associated with mitochondrial disease. Mitochondrial disease may play a significant role in the development or acceleration of pre-existing renal disease; therefore regular monitoring is recommended.[1]

Neurology

Patients with mitochondrial disease may present with a wide spectrum of neurological manifestations, some of which may be life-threatening.[1]

Ophthalmology

Progressive or sudden visual loss can occur in some mitochondrial disease phenotypes. Recommendations for the management of ophthalmological manifestations of mitochondrial disease are included in the patient care standards.[1]

Psychiatry

Depression and anxiety are common in adults with mitochondrial disease. It is recommended that screening be undertaken using validated tools.[2]

Respiratory

Respiratory function may be impaired in patients with mitochondrial disease; symptoms should be screened for routinely.[1]

Additional care considerations

Critical care

Patients with mitochondrial disease are at risk of decompensation and worsening symptoms during intercurrent illnesses. Specific recommendations for monitoring during critical care presentations are included.[1]

Care coordination

Care coordination should incorporate social support for patients and their families, and is best undertaken as part of a multidisciplinary team.[1]

Orthopaedics and rehabilitation medicine

Annual evaluation of musculoskeletal complications should be undertaken in collaboration with allied health professionals.[1]

Pre-, peri- and post-operative care

The stress of surgery and anaesthesia may lead to unexpected complications and specific recommendations on pre-, peri- and post-operative care are made in the patient care standards.[1]

Pregnancy

Pregnancy in patients with mitochondrial disease should be managed in consultation with a specialist experienced in mitochondrial disease. During pregnancy, patients should be referred to the high-risk pregnancy unit and a specialised mitochondrial disease clinic or clinician.[1]

Other considerations

Altitude

There is no anecdotal evidence of patients with mitochondrial disease experiencing high-altitude sickness although it may be reasonable to suspect that they are at higher risk of complications when cardiopulmonary manifestations are present.[1]

Fatigue and exercise

Fatigue is a common symptom for patients with mitochondrial disease; graded exercise therapy is an important treatment option.[1]

Supplements and nutrition

Patients should be encouraged to eat a healthy and nutritious diet. There is limited evidence for specific diets in adult patients with mitochondrial disease, although a high-fat, high-protein diet may be useful in children. There are anecdotal reports that supplements may be beneficial. In many cases there is insufficient evidence to prove benefit.[1]

Timmy

More information on mitochondrial disease

Mito Foundation offers a range of support services for patients and carers including peer support activities, educational events and help with accessing health services and the NDIS. For a list of resources and services for mitochondrial disease patients and their carers, please visit the Mito Foundation website **mito.org.au**

If you or a patient would like further information about mitochondrial disease or Mito Foundation's support services, please contact the Mito Foundation Helpline on 1300 977 180 (choose option 1) or email helpline@mito.org.au.

Mito Foundation has developed several resources to support clinicians, patients, and carers on the following topics:

- find a mito-aware health professional
- genetics and mito
- important information about medicines and mito
- tailored newly diagnosed information and support
- nutrition and mito
- exercise and mito

These and other resources can be found in the Resource Hub on the Mito Foundation's webpage.

For more information on current clinical trials in mitochondrial disease see **clinicaltrials.gov** (US) or the **Australian New Zealand Clinical Trials Registry**.

References

1. Sue CM, Balasubramaniam S, Bratkovic D, et al. Patient care standards for primary mitochondrial disease in Australia: an Australian adaptation of the Mitochondrial Medicine Society recommendations. Internal Medicine Journal 2022;52:110-20.
2. Duchen MR. Mitochondria and calcium: from cell signalling to cell death. J Physiol 2000;529 Pt 1:57-68.
3. Cooper GM. The cell : a molecular approach / Geoffrey M. Cooper. Second edition. ed. Washington, D.C: ASM Press; 2000.
4. Javadov S, Kozlov AV, Camara AKS. Mitochondria in Health and Diseases. Cells 2020;9.
5. Smeitink JA, Zeviani M, Turnbull DM, Jacobs HT. Mitochondrial medicine: a metabolic perspective on the pathology of oxidative phosphorylation disorders. Cell Metab 2006;3:9-13.
6. Ng YS, Turnbull DM. Mitochondrial disease: genetics and management. J Neurol 2016;263:179-91.
7. DiMauro S, Davidzon G. Mitochondrial DNA and disease. Annals of Medicine 2005;37:222-32.
8. Miko I. Non-nuclear genes and their inheritance. Nature Education 2008;1.
9. Taylor RW, Turnbull DM. Mitochondrial DNA mutations in human disease. Nat Rev Genet 2005;6:389-402.
10. Ng YS, Bindoff LA, Gorman GS, et al. Mitochondrial disease in adults: recent advances and future promise. Lancet Neurol 2021;20:573-84.
11. Wallace DC, Singh G, Lott MT, et al. Mitochondrial DNA mutation associated with Leber's hereditary optic neuropathy. Science 1988;242:1427-30.
12. Chial HC, J. mtDNA and mitochondrial diseases. Nature Education 1(1):217. Nature Education 2008.
13. Gorman GS, Chinnery PF, DiMauro S, et al. Mitochondrial diseases. Nature Reviews Disease Primers 2016;2:16080.
14. Wei W, Chinnery PF. Inheritance of mitochondrial DNA in humans: implications for rare and common diseases. J Intern Med 2020;287:634-44.
15. Haas RH, Parikh S, Falk MJ, et al. Mitochondrial disease: a practical approach for primary care physicians. Pediatrics 2007;120:1326-33.
16. Keogh MJ, Chinnery PF. How to spot mitochondrial disease in adults. Clin Med (Lond) 2013;13:87-92.
17. Elliott HR, Samuels DC, Eden JA, Relton CL, Chinnery PF. Pathogenic mitochondrial DNA mutations are common in the general population. Am J Hum Genet 2008;83:254-60.
18. Grier J, Hirano M, Karaa A, Shepard E, Thompson JLP. Diagnostic odyssey of patients with mitochondrial disease: Results of a survey. Neurol Genet 2018;4:e230.
19. Rahman S. Mitochondrial disease in children. J Intern Med 2020;287:609-33.
20. 2Alston CL, Rocha MC, Lax NZ, Turnbull DM, Taylor RW. The genetics and pathology of mitochondrial disease. J Pathol 2017;241:236-50.
21. Niyazov DM, Kahler SG, Frye RE. Primary Mitochondrial Disease and Secondary Mitochondrial Dysfunction: Importance of Distinction for Diagnosis and Treatment. Mol Syndromol 2016;7:122-37.
22. Chinnery PF. Primary Mitochondrial Disorders Overview. In: Adam MP, Mirzaa GM, Pagon RA, et al., eds. GeneReviews(®). Seattle (WA): University of Washington, Seattle. Copyright © 1993-2023, University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved.; 1993.
23. Gorman GS, Schaefer AM, Ng Y, et al. Prevalence of nuclear and mitochondrial DNA mutations related to adult mitochondrial disease. Ann Neurol 2015;77:753-9.
24. Commonwealth of Australia. Mitochondrial Donation Law Reform (Maeve's Law) Bill 2021. In: Parliament of Australia, ed. Bills Digest, No 65, 2020-2021. Canberra: Commonwealth of Australia; 2021.
25. Dziadek MA, Sue CM. Mitochondrial donation: is Australia ready? Med J Aust 2022;216:118-21.
26. Richardson J, Irving L, Hyslop LA, et al. Concise reviews: Assisted reproductive technologies to prevent transmission of mitochondrial DNA disease. Stem Cells 2015;33:639-45.

mito FOUNDATION
Hope for mitochondrial disease

To learn more about Mito Foundation's work and read the stories of those who have generously allowed us to feature their photos in this report, please visit:

mito.org.au

Mito Foundation, Suite 804, Level 8, 28 Foveaux Street, Surry Hills, NSW, 2010
02 8033 4113 info@mito.org.au ABN: 84 135 324 391

Helpline: 1300 977 180