# Natural history of mitochondrial disorders: a systematic review

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**ABSTRACT**

The natural history of a disease defines the age of onset, presenting features, clinical phenotype, morbidity and mortality outcomes of disease that is unmodified by treatments. A clear understanding of the natural history of mitochondrial disorders is essential for establishing genotype-phenotype-prognosis correlations. We performed a systematic review of the reported natural history of mitochondrial disease by searching the literature for all published natural history studies containing at least 20 individuals. We defined a phenotype as 'common' if it was observed in ≥30% of cases in a study, thereby highlighting common and uncommon phenotypes for each disorder. Thirty-seven natural history studies were identified encompassing 29 mitochondrial disease entities. Fifty-nine percent of disorders had an onset before 18m and 81% before 18y. Most disorders had multisystemic involvement and most often affected were the central nervous system, eyes, gastrointestinal system, skeletal muscle, auditory system and the heart. Less frequent involvement was seen for respiratory, renal, endocrine, hepatic, haematological, and genitourinary systems. Elevated lactate was the most frequent biochemical abnormality, seen in 72% of disorders. Age of death was <1y in 13% of disorders, <5y in 57%, and <10y in 74%. Disorders with high mortality rates were generally associated with earlier deaths. The most robust indicators of poor prognosis were early presentation of disease and truncating mutations. A thorough knowledge of natural history has helped to redefine diagnostic criteria for classical clinical syndromes and to establish a clinical baseline for comparison in single-arm clinical trials of novel therapies.

**KEY POINTS**

1. A majority (81%) of mitochondrial disorders present in childhood
2. Multisystemic involvement is almost universal, and elevated lactate is the commonest biochemical abnormality
3. Prognosis is poor with age of death <10y in 74% of disorders
4. Poor prognosis is often indicated by earlier presentation and in individuals with mutations resulting in truncated protein
5. Natural history studies are useful diagnostic tools and are needed to ensure that clinical diagnostic criteria are kept up-to-date
6. Natural histories are essential for establishing genotype-phenotype–prognosis correlations which enable accurate provision of prognostic information to affected families, and the development of targeted surveillance programmes to monitor for known complications

7. Clinical data from natural history studies may be utilised when designing single-arm clinical trials

## INTRODUCTION

### Primary mitochondrial diseases

Mitochondria are the site of oxidative phosphorylation (OXPHOS) within eukaryotic cells. The five complexes of the OXPHOS system are the site of a series of redox reactions that lead to the generation of adenosine triphosphate (ATP) (1). Mitochondria contain their own circular genome (mtDNA) that is integral to mitochondrial function (2). In addition several hundred nuclear genes also control mitochondrial function (3)**.** Complexes I, III, IV and V all contain protein subunits that are encoded by both mtDNA and nuclear genes, whilst complex II subunits are encoded entirely by nuclear genes.

Mitochondrial diseases are a group of genetic disorders that are characterized by defects in OXPHOS caused by mutations in genes that encode proteins involved in mitochondrial function (4, 5). They are individually rare but have a collective prevalence of 1:4300-1:5000 (6, 7). They are often multisystemic and present with varying degrees of severity. The most severe presentations often occur in early childhood. Systemic involvement affecting nearly every organ has been described, leading to an immense variation in clinical phenotype which poses an enormous diagnostic challenge. Clear definitions for the classification of clinical phenotypes and formulation of diagnostic pathways are needed to guide clinicians. The situation becomes more complicated with the realisation that a single gene defect may give rise to a multitude of different recognisable clinical syndromes/ phenotypes and that sometimes affected siblings who share the same mutation may present differently, suggesting a role for other genetic and/or environmental modifiers. Even more puzzlingly, unrelated individuals with pathogenic mutations in different genes may share the same clinical phenotype (8). This presents a diagnostic challenge in the clinic when assessing an individual with suspected disease who may present with clinical features that are not specific enough to indicate a single gene defect or clinical syndrome, and also when faced with the task of having to deliver accurate prognostic information to affected individuals and families (9).

### Natural History Studies

An understanding of the natural history of the disease is essential in order to address these challenges, as well as to inform future clinical trials of novel therapeutic agents. A natural history study is a longitudinal study of the evolution of the complete clinical phenotype including disease morbidity and mortality that is unmodified by any therapeutic interventions in a large homogeneous cohort of individuals with a single disease entity (10). Such studies are important to be able to:

1. Establish a knowledgebase of the phenotypic and genotypic spectrum of disease and identify any genotype-phenotype correlations (8)

2. Facilitate earlier diagnosis by identification of a recognisable clinical syndrome (11)
3. Update existing diagnostic criteria for established clinical syndromes based on prevalence of clinical features or the discovery of new phenotypes (12, 13)
4. Develop a comprehensive programme of surveillance for known disease complications
5. Establish clinical, biochemical and genetic prognostic indicators of disease (14)
6. Provide up-to-date prognostic information to families including during prenatal genetic counselling
7. Define a clinical baseline for comparative analysis in clinical trials of novel therapies and determine indicators of when therapeutic interventions are most likely to be beneficial
8. Inform the planning of healthcare services and their delivery in tertiary centres particularly with respect to the formation of a comprehensive multidisciplinary team to provide input that matches the spectrum of multisystemic disease (12).

Natural history studies also present several challenges and limitations:

1. Recruitment of patients to a study requires the clear definition of inclusion and exclusion criteria, which is made difficult by the clinical, biochemical and genetic heterogeneity inherent to mitochondrial disease.
2. Many patients do not have a genetic diagnosis, which limits the value of natural history studies of a particular clinical or biochemical phenotype.
3. Studies of defined genetic disorders with wide phenotypic variability reduces the number of patients within each phenotypic subgroup and therefore makes it more difficult to make meaningful comparisons (12).
4. In prospective studies, death and disability reduces the number of assessments made and therefore the power of longitudinal data.
5. In retrospective studies there is variable data quality, and there may be a survival bias if only subjects who are alive at the time of study enrolment are recruited.
6. Where an effective therapy is available, it may be unethical to withhold treatment to allow a natural history study to be performed prior to conducting a clinical trial.
7. Where no therapy is available, patients may not be motivated to participate, owing to a lack of personal benefit (15).
8. Rare disorders require national/multinational collaboration in order to recruit sufficient patients.
9. Differing methodologies limit the depth of detail and uniformity of data. For example, the use of different severity scales or making assessments at different time points may make meta-analysis difficult and may lead to conflicting conclusions.

## METHODS

### Search Terms:

The following search terms were input to PubMed (last performed on 21/3/18):

1. Mitochondrial disease AND natural history [Text Word]

This yielded 195 publications of which 16 met our definition of natural history studies, as described above.

2. Mitochondrial disease AND phenotype

This yielded 4921 publications of which a further 14 met our definition.

3. Survival AND natural history [Title] AND outcome

This yielded 606 publications of which another publication met our definition.

4. Survival AND clinical course AND phenotype

This yielded 706 publications of which a further two met our definition

5. Mitochondrial AND disease AND study AND (phenotype OR phenotypes)

This yielded 1460 publications of which a further two met our definition

The natural history of TK2 deficiency was communicated to us by Garone *et al* in advance of publication (16).

### Exclusion Criteria:

The following were excluded: case reports, studies with fewer than 20 patients, and studies limited to a single family/pedigree. In addition, studies focussing on a single specific phenotype of a multisystemic disorder were not included where there were other studies that assessed the complete phenotype of the disease. Studies assessing involvement of a single organ system in mitochondrial disorders were not included if they did not define a single disease entity. Studies not published in English and those where the full text was not available were also excluded.

## RESULTS

Thirty-seven studies were identified that met our criteria as natural history studies for mitochondrial disorders, encompassing 29 disease entities and 3730 patients. Thirty-two of these 37 studies had a retrospective study design and 5/37 had a prospective study design. The studies were divided into the following groups:

I. **Clinical phenotype-based studies**

- 1 study – 1 disease entity - Leigh syndrome (11)

II. **Biochemical profile-based studies**

- 2 studies - 2 disease entities - Complex I and Complex II deficiency (14, 17)

III. **Gene based studies – mtDNA mutations**

- 7 studies, 5 disease entities – single large-scale mtDNA deletions (SLSMDs) (12, 13), mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS, m.3243A>G) (15, 18), maternally inherited diabetes and deafness (MIDD, m.3243A>G) (19), myoclonic epilepsy ragged red fibres (MERFF, m.8344A>G) (20), and Leber hereditary optic neuropathy (LHON) (21)

IV. **Gene based studies - nuclear gene mutations**

- 27 studies, 21 disease entities – mutations of *SURF1* (22), *LRPPRC* (23), *SCO2* (24), *TMEM70* (25), *POLG* (26, 27), *TWNK* (28, 29), *TK2* (16), *MPV17* (30), *SUCLA2* (31), *SUCLG1* (31), *TYMP* (32), *FBXL4* (33), *MTO1* (34), *DARS2* (35),*RMND1* (36), *SERAC1* (37), *TAZ* (38, 39), *CLPB* (40), *OPA1* (41) and *FXN* (42-44) and PDHc deficiency (45, 46)

Figure 1 shows the age of onset (expressed as either mean or median because of varying data reporting methods) of the 27 disorders for which this information was available. Data for *MPV17* and *TMEM70* mutations were not available. Fifty-nine percent (16/27) of disorders had an onset before 18 months and the majority (22/27, 81%) had an onset before 18 years. Disorders which had predominant adult onset disease included SLSMDs, LHON, MERRF (m.8344A>G), MIDD (m.3243A>G), and *TWNK* (previously known as *PEO1*) mutations. For the reported ranges and standard deviations from the mean/median, where applicable, see Table 1.

Mitochondrial disorders are multisystemic, apart from LHON and *OPA1*-related optic atrophy which only affected the eye in the vast majority of cases for which natural history data were reported (21, 41). Natural history data were not available for the multisystem presentation of OPA1 deficiency. Features were taken to be 'common' if they were observed in at least 30% of patients in studies. Based on this definition, the central nervous system was seen to be commonly involved in 25/29 (86%) of disorders, whilst eye manifestations were common in 21/29 (72%) of disorders, gastrointestinal involvement was a common feature in 20/29 (69%) of disorders, muscle involvement was a common feature in 15/29 52%) of disorders, sensorineural hearing loss was common in 12/29 (41%) and the heart was commonly involved in 7/29 (24%) of disorders. Less frequent involvement was seen for respiratory, renal, endocrine, haematological, hepatic and genitourinary systems which were common in ≤ 5 disorders as shown in Figure 2. It should be noted that the full spectrum of each disorder however is far more multisystemic and is expanded upon in Table 1.

In 21/29 (72%) of disorders elevated lactate was a common feature. Elevated levels of plasma alanine and urinary Krebs cycle intermediates and 3-methylglutaconate were common features in 6 disorders each (see Table 1). Other biochemical abnormalities common to ≤4 disorders included hypo/hyperglycaemia, elevated creatine kinase, hyperammonaemia, deranged liver function, methylmalonic aciduria, hyperuricaemia and ketonuria (Table 1). Results of OXPHOS analyses varied considerably and are detailed in Table 1.

On neuroimaging, basal ganglia involvement was commonly seen in 14/29 (48%) of disorders. Brainstem, cerebral, white matter,cerebellar and spinal cord abnormalities were common features in 12, 10, 10  10 and 4 disorders respectively (see Table 1 for details). Thalamus and midbrain involvement was a common feature in 2 disorders each.

Figure 3 shows the age of death (mean/median) in patients who died for 23 disorders for which this information was available. It should be noted that disease related mortality was not seen in LHON, *OPA1*-related optic atrophy and MIDD (19, 21, 28, 41). Age of death was not available for Friedreich ataxia, *DARS2* mutations or *TMEM70* mutations.  Age of death was <1 year in 3/23 (13%) of disorders, <5 years in 13/23 (57%) of disorders, and <10 years in 17/23 (74%) of disorders. Disorders with survival to beyond 10 years age included *POLG* mutations (26, 27)*SUCLA2* mutations (31), MERRF caused by the m.8344 A>G mutation (20), MELAS associated with the m.3243 A>G mutation (15, 18) and MNGIE caused by *TYMP* mutations (32). Reported ranges of age of death and mortality rates are included in Table 1, together with the cause of death.

Overall mortality rates are shown in Figure 4 for 25 out of 29 disorders expressed as a percentage of the cohort. Ten disorders had a mortality of at least 50% during the period of follow up. Seven of these (*CLPB, MPV17, RMND1, SCO2, LRPPRC, SUCLG1* mutations and Complex I deficiency) were also among the 10 disorders with worst outcomes according to age at death data (see Figure 1). This demonstrates that disorders with high overall mortality were generally associated with earlier death.
In SLSMDs, most deaths were seen in early presenting patients, who make up the minority of the natural history cohort, while few late presenting patients died during the duration of follow up (12, 13). This also accounts for the mean age of death reported as lower than the overall mean age of onset.

**DISCUSSION**

**Identification of a recognisable clinical phenotype**

The identification of a classical mitochondrial phenotype/syndrome may make the diagnosis clear to the clinician, and confirmation may be possible with a single-gene test. This reduces the lag time between presentation and diagnosis and improves the ability to monitor complications. For example, MIDD should be suspected when diabetes mellitus is seen in a young patient of low/normal body mass index who later develops hearing loss, especially in the presence of positive family history (19). This may lead to targeted testing for m.3243A>G that enables an earlier diagnosis, and patients to be monitored closely for renal, cardiac, neuromuscular and psychiatric complications that present later.

More commonly, however, the recognition of a defined mitochondrial disease phenotype may aid the clinician in formulating a diagnostic hypothesis which can be tested with appropriate genetic investigations. For example an infant presenting with encephalopathy and liver disease with low mtDNA copy number will usually be investigated with a targeted gene panel for hepatocerebral mtDNA depletion syndrome, first starting with *POLG* and then extended to other genes e.g. *DGUOK* and *MPV17* if needed.

On the other hand, some phenotypes appear to overlap with one another and may even be on a continuum. For example, patients diagnosed with MERRF may develop stroke-like episodes that are phenotypically similar to MELAS (20). A single patient may partially match more than one phenotype or may have a phenotype that cannot be classified by existing criteria, e.g. some patients with SLSMDs (12, 13). In such cases the approach to genetic investigations may need to be broader. For nuclear gene defects, whole exome and whole genome sequencing are increasingly being adopted as first-line genetic investigations in suspected mitochondrial disease (5).

**Clarification of classical phenotypes**

Natural history studies may shed further light on the characteristics of known and well established clinical syndromes. For example in a multinational study of paediatric POLG deficiency it was noted that only children with an Alpers phenotype develop seizures; children with myocerebrohepatopathy spectrum (MCHS) do not (27). Conversely only children with an MCHS phenotype develop renal disease; those with Alpers syndrome do not. This may help discriminate between the two groups, which has important prognostic implications (27).

In succinyl-CoA ligase deficiency, associated with encephalomyopathic mtDNA depletion syndrome, hepatopathy and cardiomyopathy were observed only in patients with mutations in *SUCLG1* but not in *SUCLA2*. This may also discriminate between the two and is important since the two genetic disorders have different prognoses (31). Another example is in Complex IV deficient Leigh syndrome: Debray *et al* noted that LRPPRC deficiency (French Canadian Leigh syndrome) is marked by recurrent

metabolic decompensations and neurological crises which carry negative implications for prognosis and are absent in SURF1 deficiency; this may at least partially explain the relatively better survival of the latter group (22, 23).

Natural history studies are essential to ensure that existing definitions/classifications are kept up-to-date by reassessing the incidence of certain manifestations in a given disease. For example, Altmann *et al* noted in their prospective study of a cohort of patients diagnosed with MERRF caused by m.8344A>G, that the canonical features of myoclonus, seizures, ataxia and ragged red fibres were only present in 59, 61, 70 and 63% of patients (20). Conversely, patients had high incidences of other features: hearing loss (72%), psychiatric abnormalities (54%) and migraine (52%). The authors questioned whether the canonical definition captures the phenotype of disease adequately and support the revision of diagnostic criteria for MERRF in view of the expanding clinical phenotype (20).

Similarly, in a series of children with SLSMDs, only four of 11 patients diagnosed with Pearson syndrome met the classical diagnostic criteria of sideroblastic anaemia with pancreatic exocrine dysfunction – indeed, while all 11 were anaemic, only 7 had ringed sideroblasts and only 4 had low faecal elastase and chronic diarrhoea (12). The authors therefore suggested that pancreatic dysfunction not be considered an essential diagnostic criterion for Pearson syndrome. Conversely there was a high number of patients who developed ptosis, endocrine and renal disease (especially tubulopathy) in patients with SLSMDs, thereby expanding the spectrum of phenotypes of disease (12). Another study proposed updated diagnostic criteria for KSS, noting that in a large cohort of patients with SLSMDs, few patients met classical KSS criteria (13). A new definition of patients entitled 'KSS spectrum' was proposed, removing age of onset <20y and retinopathy as essential criteria, maintaining ptosis and ophthalmoplegia as essential criteria and including at least one of retinopathy, ataxia, cardiac conduction defects, hearing loss, FTT, cognitive involvement, tremor and cardiomyopathy as an additional criterion (13).

**Correlating clinical phenotype to prognosis**

Even where there is no clear genotype-phenotype correlation, natural history studies may reveal a correlation between certain clinical phenotypes and adverse outcomes. An important recurring correlation across many disorders is that early presentation is associated with a worse prognosis. Other correlations are summarised in Table 2.

**Identification of genotype-phenotype correlation**

Ideally, a patient affected by a single gene defect (caused by a single mutation) would present with a defined and unique phenotype with an expected prognosis. This linear paradigm of correlation, where applicable, may simplify the diagnostic process for the clinician. In mitochondrial disease, however, this paradigm is often not applicable as a genotype-phenotype correlation may be difficult to establish for the following reasons:

1. For disorders due to mtDNA mutations, the degree of heteroplasmy/mutation load in individual organs influences which tissues are affected. Unaffected/asymptomatic carriers may have lower mutation loads than affected individuals. On the other hand, previously defined 'carriers' may become symptomatic at a later stage, as demonstrated in MELAS (15, 18)**.** Therefore, having a confirmed pathogenic mtDNA mutation does not necessarily predict the presence of disease in a given individual.
2. For disorders associated with a large number of known gene defects such as Complex I deficiency and pyruvate dehydrogenase complex deficiency, it may be difficult to find a clear genotype-phenotype correlation, because the number of published cases of patients affected by a specific gene defect may actually be too few to identify a clear correlation.
3. Even in a very genetically homogenous cohort of patients, e.g. LRPPRC deficiency for which nearly all affected cases had the same common mutation, there were widely varied outcomes (23), suggesting a role for other genetic modifiers and/or environmental factors in influencing severity of disease.
4. A single mutation may present with multiple phenotypes, e.g. m.3243A>G in the *MT-TL1* gene is associated with MELAS, MIDD and a range of other phenotypes (47). On the other hand, defects in different genes may present with a common phenotype, for example more than 89 mtDNA and nuclear genes have been linked to Leigh syndrome (8). This leads to a major diagnostic challenge for the clinician.

Despite these caveats, clear genotype-phenotype/ prognosis correlations are seen in some cases. Truncating mutations are likely to be more severe than missense mutations in a number of disorders. These and other correlations are summarised in Table 3.

**The value of multicentre collaboration**

Multicentre collaboration is essential for recruitment and study of large national or international cohorts. This is essential to increase the power of statistical comparisons, and to eliminate geographical skew of data that may be related to founder effects and environmental modifiers, for example in a large multicentre cohort of SURF1 deficiency seizures were mainly observed in Australian

patients (22). It also enables the standardisation of research methodology and data collection which is essential for designing high quality prospective studies.

Examples of where this has been applied in natural history studies include the retrospective recruitment of patients with Leigh syndrome under the auspices of the Mitochondrial Clinical and Research Network (MCRN) which encompasses clinicians in 9 different mitochondrial centres in 7 European countries (11). The German Network for Mitochondrial disorders (MitoNET) comprises a total of 18 specialist centres, and its 'MitoNET registry' was used to recruit patients to a prospective study of MERRF (20). For LHON, an international meeting of experts from 20 centres from 7 countries in North America and Europe was held to review the literature, define the natural history of disease, formulate guidelines for management of the disorder and to define a target population for treatment with idebenone (48). The Barth syndrome registry encompasses data from 8 countries, allowing the clinical description of the largest known cohort of affected patients with Barth syndrome (38). In France, a national retrospective cohort of patients with Barth syndrome was set up by collaboration between healthcare professionals of different disciplines including cardiologists, geneticists, haematologists, metabolic physicians and by referring to national archives containing death certificates that list the disorder as a contributory cause of death (39). For Friedreich ataxia, the European Friedreich Ataxia Consortium for Translational Studies (EFACTS) comprising 11 centres from 6 countries was able to recruit a large number of patients for a prospective study and helped define potential endpoints and sample sizes that could be utilised for clinical trials (44). The Italian Collaborative Network of Mitochondrial Diseases registry of patients was interrogated retrospectively to study a SLSMDs cohort (13).

**Define a clinical baseline for comparative use in single-arm clinical trials**

For rare diseases with high mortality and no known effective treatments, for which a novel therapeutic agent is to be trialled, the natural history of disease may be useful in assessing therapeutic effectiveness. This is particularly true for a trial drug that is known to have a good safety profile and where preliminary phase 1 data suggests that it may be an effective treatment. In such cases, it may be difficult/unethical to recruit patients to the control arm of the trial, especially if the overall number of patients eligible for recruitment is low. This approach cannot be used in disorders for which an effective treatment already exists and the aim of the trial is to demonstrate non-inferiority or superiority to an existing therapy.

Martinelli *et al* described a single-arm Phase 2A study to assess safety and efficacy of a trial drug EPI-743 in 10 children with 7 different gene defects causing Leigh syndrome (49). Ten children received the treatment enterally for 6 months. The children were required to stop any coenzyme $Q_{10}$ or other antioxidant treatments. The Newcastle Paediatric Mitochondrial Disease Scale (NPMDS), Gross Motor Function Measure (GMFM) and a quality of life measure (PedsQL Neuromuscular Module) were used to as primary endpoints. The response was compared to baseline patient scores at the start of the trial and to the natural history of disease reported in the literature in children with the same genetic causes of Leigh syndrome. When compared to baseline scores, all 9 patients who completed the treatment course of 6 months showed improvements in all indices. In comparison, 99.4% of all children identified from natural history studies demonstrated either disease progression or death, with only one patient showing some spontaneous improvement. By virtue of this, the authors concluded a positive treatment effect.

Sadun *et al* used similar methodology and applied EPI-743 to LHON in a small single arm trial (50). Five patients with genetically confirmed LHON with 3 different mtDNA mutations were recruited to the trial within 90 days of presentation with visual loss, and administered EPI-743 orally over a period of 18 months. Primary endpoints included assessments of visual acuity, retinal nerve fibre layer thickness, visual fields and colour vision. The response was compared to the natural history of LHON from the literature. Four of the 5 patients experienced reversal of visual loss with 2 having total recovery of visual acuity. When compared to the natural history which demonstrated that visual loss is irreversible, EPI-743 appeared to be effective (50).

The limitations of this type of approach are that assessors are not blinded as there is no placebo control arm, introducing the possibility of assessment bias, and that quantitative comparisons using measured indices are not possible when comparing to natural history data that do not contain measurable outcomes. As such, it was not possible to quantify the degree of improvement seen compared to the natural history data in either of these EPI-743 trials. Clearly, randomised placebo controlled clinical trials are superior but for preliminary studies utilising a small number of patients in rare diseases, a single-arm approach using comparative data from natural history studies may be beneficial before proceeding to recruit patients to randomised placebo controlled clinical trials as necessary.

**Limitations of this study**

In our literature search we excluded case reports and studies with fewer than 20 patients. While this may preserve to some extent the standardisation of data between patients, a major drawback is a reduction in the number of cases included in meta-analyses. Furthermore, most papers reported retrospective analyses, with associated limitations of lack of data standardisation, incomplete data sets and loss of patients during follow up. Studies of disorders for which there is a 'founder effect' are likely to skew data due to a lack of publications concerning mutations seen in other populations worldwide. Indeed, the majority of studies included concerned European cohorts which may not be genotypically representative of mitochondrial disorders elsewhere in the world. In reporting mortality and survival data, a limitation of using of age of death as an indicator of prognosis is that for disorders where early presenting patients make up the majority of deaths but the minority of the natural history cohort, e.g. SLSMDs, the mean/median age at death may not accurately reflect the overall prognosis of the disorder. The overall mortality needs to be taken into account in this respect. Unfortunately, owing to differences in data reporting between studies, prospective mortality data (e.g. 10 or 20 year mortality) were not available for many disorders. It is clear that more prospective studies are needed.

**CONCLUSION**

An understanding of the natural history of mitochondrial disorders is essential for defining the spectrum of disease. Establishment of a known recognisable pattern of disease may sometimes lead to a specific genetic diagnosis, but more often is likely to generate a panel of further investigations in order to test or refute diagnostic hypotheses. There is considerable overlap between disorders of varying genetic aetiology and considerable variability in severity of disease for a specific genotype. Certain disorders have specific genotypic and phenotypic predictors of disease severity and prognosis. Multicentre collaboration is essential if large prospective cohorts are to be studied, to ensure significant power of analyses. The use of standardised scales to measure disease severity ensures uniformity of data collection. The input of patients and carers themselves is essential to ensure completeness of data. Natural histories may be beneficial in providing comparative data for use in single-arm clinical trials.

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**FIGURE LEGENDS**

**Figure 1 Age of onset (median/mean) in years for mitochondrial disorders**

Age of onset in years for mitochondrial disorders expressed as either mean or median. The Y axis indicates the number of mitochondrial disorders; data for 27 disorders are shown. Data were not available for 2 disorders (MPV17 and TMEM70 deficiencies). Where a single disorder had more than one natural history study, e.g. Barth Syndrome, PDHc deficiency, Friedrich ataxia, *POLG* mutations, *TWNK* mutations, MELAS and SLSMDs, the mean age of onset was calculated by meta-analysis of raw data.

**Figure 2 Common involvement of organ systems in 29 mitochondrial disorders**

Common involvement of organ systems, as defined as affecting at least 30% of cases. The Y axis indicates the number of mitochondrial disorders (total 29).

**Figure 3 Age of death (median/mean) in years for mitochondrial disorders**

Age of death in years for mitochondrial disorders expressed as either a mean or median. Data were not available for TMEM70 deficiency. LHON*, OPA1* mutations*, TWNK* mutations, Friedreich ataxia and MIDD were excluded as no death was reported due to these disorders in the natural history studies captured by the systematic review. Age of death data was combined in meta-analysis of different studies for *POLG* mutations, PDHc deficiency, Barth syndrome and MELAS.

**Figure 4 Mortality rates for mitochondrial disorders**

The mortality rates are expressed as a percentage of deaths over the duration of follow up as a proportion of total number of cases included in the study. Mortality rates were not available for *TYMP* and *TMEM70* mutations, SLSMDs and Friedreich ataxia.

**Table 1 Natural history studies of mitochondrial disease**

| EXISTING NATURAL HISTORY STUDIES OF MITOCHONDRIAL DISEASE | | | | | | | | | | | |
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| | **Disease** | **Reference** | **No. cases** | **Study design** | **Age onset** | **Initial features** | **Overall phenotype** | **Biochemistry** | **Neuro-radiology** | **Muscle Biopsy** | **Age of death/ Prognosis** |
| **CLINICAL PHENOTYPE BASED STUDIES** | | | | | | | | | | | |
| 1 | Leigh syndrome | (11) | 130 | Retrospective multinational study | 3-12m (median 7m) | Common: abnormal motor findings<br>Uncommon: ocular abnormalities, feeding difficulty, seizures, FTT | Common: motor delay, mental retardation, progressive cognitive decline, hypotonia, dyskinesia, ataxia, dystonia, dysphagia, seizures, ocular abnormalities.<br><br>Uncommon: respiratory, cardiac/liver/GI/renal involvement, deafness, autonomic dysregulation and cytopaenias. | Lactic acidosis | Bilateral lesions in thalamus, basal ganglia, brainstem, posterior columns of spinal cord, cerebellum | Multiple complexes affected | 39% died<br>Median 2.4y<br>Death due to respiratory complications, neurological progression or sepsis |
| **BIOCHEMISTRY BASED STUDIES** | | | | | | | | | | | |
| 2 | Complex I deficiency | (14) | 130 | Retrospective literature review | 0-9y (median 4m) | If <6m: hypotonia, FTT, encephalopathy, epilepsy, eye movement disturbances.<br>If >6m: psychomotor retardation/ regression, pyramidal signs, FTT, optic atrophy, dystonia, epilepsy | Common: Leigh syndrome, optic atrophy.<br><br>Uncommon: micro/macrocephaly, dysmorphic features, cardiac/renal/hepatic involvement, infective exacerbations. | Lactic acidosis, elevated alanine, elevated Krebs cycle intermediates | Hyperintense lesions in basal ganglia, thalamus, midbrain, brainstem, cerebellum, spinal cord. | Complex I deficiency | 75% died<br>Median 10m<br>Death due to cardiorespiratory failure, lactic acidosis, central hypoventilation |

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| 3 | Complex II deficiency | (17) | 37 | Retrospective literature review | 1d-46y (median 11m) | See overall phenotype | Common: neurological involvement (hypotonia, spasticity, ataxia, seizures, irritability), DD, cardiac involvement (HCM, DCM, conduction defects), muscle and eye involvement (ptosis, PEO, pigmentary retinopathy, optic atrophy, nystagmus), FTT. | Elevated lactate | Leuko-encephalopathy and features of Leigh syndrome<br>Uncommon: normal, cerebellar atrophy | Complex II deficiency | 21% died at median 18m (5m-31y) |
| **GENE BASED STUDES – mtDNA MUTATIONS** | | | | | | | | | | | |
| 4 | Single large-scale mtDNA deletions | (12) | 34 | Retrospective multicentre study | 0-15y (mean 4.3y, median 1w for patients with Pearson syndrome and 6y for other phenotypes) | Common: ptosis, cytopaenias<br>Uncommon: FTT, tremor, endocrine and renal involvement | Common: Pearson syndrome, KSS, PEO/PEO plus. Renal, cardiac, deafness, neurological, endocrine involvement.<br><br>Uncommon: No classifiable phenotype, GI involvement. | Elevated lactate, alanine, ketonuria, low CSF 5MTHF | Basal ganglia and white matter abnormalities | Common: Complex IV deficiency<br><br>Uncommon: Normal/ reduced complex I and III | 32% died, mean 6.7y ( median for Pearson: 2y6m and Non-Pearson: 13y9m) |
| 5 | Single large-scale mtDNA deletions | (13) | 228 | Retrospective multicentre study | Mean 22.6± 14.6y | Common: ptosis, ophthalmoplegia<br><br>Uncommon: muscle weakness/wasting/ pain, hearing loss, ataxia, hypotonia, neuropathy, tremor, cognitive impairment, FTT, DM, retinopathy, cardiac conduction defects, | Common: PEO, no classifiable phenotype, muscle weakness.<br><br>Uncommon: Pearson syndrome, KSS, hearing loss, retinopathy, DM, cardiac involvement. | Elevated lactate<br><br>Uncommon: elevated CK, deranged liver function | Common: Normal, basal ganglia, white matter and brainstem abnormalities<br><br>Uncommon: cortical/ cerebellar atrophy, thalamic/ subthalamic | Common: RRF, COX negative fibres<br><br>Uncommon: Lipid storage | NS |

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| | | | | | | liver/respiratory involvement | | | nucleus involvement | | |
| 6 | MELAS m.3243A>G | (15) | 31 | Prospective single centre cohort study | 90% before 30y. Median NS. | <6y: developmental delay<br>6-10y: myalgia<br>20-30y: deafness | Common: seizures, SLEs, exercise intolerance, abdominal discomfort, constipation, deafness.<br><br>Uncommon: ptosis, night blindness, DM, hirsutism. | Lactic acidosis | Cerebral lesions, MRS shows elevated lactate peak | Not measured | 67% died<br>Mean 34.5y<br>Death due to neurological events including seizures, and SLEs, GI pseudo-obstruction |
| 7 | MELAS m.3243A>G | (18) | 33 | Retrospective study | 1m–47y (mean 17.4 ± 12.9 y) | Common: myopathy, ptosis, PEO, SNHL<br><br>Uncommon: DM, FTT, seizures, depression | Common: seizures, migraines, SLEs, myopathy, SNHL, PEO, ptosis, cognitive impairment, DM, GI dysmotility, short stature.<br><br>Uncommon: peripheral neuropathy, cerebellar symptoms, dysphagia, visual loss, optic atrophy, pigmentary retinopathy, WPW, CM, thyroid disease, depression. | Common: Elevated lactate, alanine, CK, deranged liver function<br><br>Uncommon: elevated creatinine | Common: cerebral ischaemic lesions(parietal and occipital), cerebellar atrophy<br><br>Uncommon: cortical atrophy, BG calcifications, BG lesions | Multiple complexes affected<br><br>RRF, COX negative fibres | 33% died at a mean of 34.5y ± 16.2 due to heart failure, CM, infection, suicide |
| 8 | MIDD m.3243A>G | (19) | 54 | Prospective multicentre study | Presenting with DM: 12-67y (mean 38.8y); Presenting with deafness: 2-61y | Deafness, DM | Common: Deafness, DM (may or may not be insulin dependent), low BMI, macular dystrophy, muscle weakness, myalgia, hypertension, renal impairment.<br><br>Uncommon: hypertrophic cardiomyopathy, WPW, AF, coronary heart disease, | Hyper-glycaemia | Uncommon: cerebral/cerebellar atrophy | NS | NS |

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| | | | | | (mean 34.6y) | | ophthalmoplegia, ataxia, psychiatric disorder. | | | | |
| 9 | MERRF m.8344A>G | (20) | 34 | Retrospective multicentre national study | 6-48y (mean 24.5y) | See overall phenotype | Common: deafness, muscle weakness, fatigue, myalgia, seizures, cerebellar ataxia, myoclonus, migraine, psychiatric disorders, respiratory insufficiency, GI symptoms, dysphagia<br><br>Uncommon: hyperthyroidism, cardiac involvement, IDDM, ptosis, eye involvement, SLEs | Elevated lactate, elevated CK | Common: Cerebral/ cerebellar atrophy<br><br>Uncommon: white matter abnormalities | COX deficient fibres, RRF | 2 (6%) patients died, mean 27y (14-40y) |
| 10 | LHON | (21) | 44 | Retrospective and prospective study | 4-61y (mean 23.9y) | Common: loss of retinal ganglion cells resulting in loss of visual acuity, visual fields and deterioration in ERG | Common: stable visual acuity, visual fields and ERG<br>Uncommon: improvement in visual acuity over a mean of 27.5m. | NA | NA | NA | No mortality<br>68% of patients had stable visual loss |
| **GENE BASED STUDIES – NUCLEAR GENE MUTATIONS** | | | | | | | | | | | |
| 11 | SURF1 deficiency | (22) | 44 | Retrospective multinational study | 0-5y (median 9.5m) | Common: poor feeding, vomiting, FTT, hypotonia<br><br>Uncommon: developmental regression | Common: poor weight gain, hypotonia, vomiting, developmental regression precipitated by infective decompensations, hypertrichosis, nystagmus, ophthalmoplegia, movement disorder<br><br>Uncommon: seizures, optic atrophy, encephalopathy, hypertrophic cardiomyopathy | Elevated lactate, metabolic acidosis | Common: symmetrical hyperintense lesions in brainstem and basal ganglia<br><br>Uncommon: normal, white matter involvement, | Complex IV deficiency | 82% died<br>Median 5.4y<br>Cause of death: central respiratory failure |

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| | | | | | | | | | cerebellar atrophy | | |
| 12 | French Canadian Leigh syndrome (*LRPPRC* mutations) | (23) | 56 | Retrospective multicentre study | 0-24m (median 5m) | Common: neonatal distress, psychomotor delay, hypotonia, FTT, ataxia, acute metabolic acidosis | Common: mild facial dysmorphism, global DD, hypotonia, weakness, ataxia, tremors, strabismus, recurrent metabolic crises<br><br>Uncommon: seizures, neurological crises, Leigh syndrome, stroke like episodes | Elevated lactate, metabolic acidosis especially during crises, elevated Krebs cycle intermediates | Common: hyperintense lesions in brainstem, periaqueductal grey<br><br>Uncommon: lesions in cerebellar white matter, thalamus, basal ganglia | Complex IV deficiency | 82% died<br>Median 1.6y<br>Cause of death: central respiratory failure, multiorgan failure |
| 13 | SCO2 deficiency | (24) | 36 | Retrospective study and literature review | S1 0m<br>S2 4m<br>S3 >12m<br><br>Mean 5.26m (0-16m) | S1 CM<br>S2/S3: hypotonia, psychomotor retardation, infective episode causing neurological regression. | S1 'cardiomyopathic'<br>Cardiomyopathy, no motor development<br>S2 'SMA-like/Leigh like'<br>Delayed development, respiratory failure, cardiomyopathy<br>S3 'Milder encephalopathic type'<br>Delayed development, uncommon: cardiomyopathy<br><br>S1, S2, S3: weakness, muscular hypo/hypertonia, ptosis, tremors, ataxia, dystonia, strabismus, nystagmus, stridor | Elevated lactate, increased Krebs cycle intermediates, low free carnitine, increased phosphor-creatine | Common: Progressive atrophy of cerebrum and cerebellum, Leigh-like changes<br>Uncommon: white matter involvement | Complex IV deficiency | 64% died<br>S1 1-2.5m<br>S2 6-16.5m<br>S3 24-48m<br>Mean 15m (2.7-60) |
| 14 | TMEM70 deficiency | (25) | 48 | Retrospective multinational | Early onset: 1d-1m | Early onset disease: Common: oligo/ anhydramnios, | Common: facial dysmorphism, ptosis, congenital cardiac defects, HCM, hypospadias, FTT, | Elevated lactate, ammonia, | Common: white matter changes | Common: Complex V deficiency | Number of deaths and mean age of death NS. |

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| | | | | questionnaire based survey | Later onset 1m – 2y<br><br>Mean NS | IUGR, poor condition at birth, respiratory failure requiring ventilation, metabolic acidosis, high lactate, hyperammonaemia.<br>Uncommon: HCM antenatally detected, heart failure, hypo/hyper-glycaemia, PPHN.<br><br>Later onset disease:<br>Common: poor feeding, faltering growth, hypotonia, CM, DD, lactic acidosis.<br>Uncommon: hyperammonaemia, hypoglycaemic seizures | short stature, microcephaly, hypotonia, DD, recurrent vomiting, renal disease, metabolic crises followed by developmental regression<br><br>Uncommon: hernias, epispadias, syndactyly, polydactyly, congenital clubfoot, multiple flexion contractures, ataxia, epilepsy, WPW, cataracts, strabismus, pigmentary retinopathy, hypopigmented retina, amblyopia, hearing impairment, intestinal pseudo obstruction, endocrine disease | alanine, urate, 3MGA and 2-hydroxy-glutarate in urine seen at onset / during metabolic crises.<br>Hypo/hyperglycaemia and hyponatraemia seen | especially hypo-myelination<br><br>Uncommon: PV cysts, callosal agenesis/hypoplasia, cortical and ponto-cerebellar atrophy, normal | Less common: Complex I and IV deficiency | Higher risk of death for early onset disease<br><br>No deaths in later onset disease<br><br>63% survival at 10y |
| 15 | *POLG* mutations in adults and children | (26) | 38 | Retrospective multinational study | 0.5- 63y (mean 23.1y)<br><br>Alpers: mean 1.8y (0.5-7y) | Common phenotypic groups: PEO with additional features, Alpers (hepato-encephalopathy)<br><br>Uncommon: encephalopathy | Common:<br>Liver disease especially induced by valproate, encephalopathy, PEO, myopathy, ataxia, dysphagia, neuropathy<br><br>Uncommon: cardiomyopathy, stroke like episodes, myoclonus, diabetes, thyroid disease, | NS | NS | NS | 18% died, mean age at death 7.85y(1-41y)<br><br>In the hepato-encephalopathy group 40% died by age 2y |

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| | | | | | | without liver disease, unclassified phenotype | hearing loss, psychosis, dementia, cardiac conduction defects | | | | |
| 16 | *POLG* biallelic mutations in childhood | (27) | 27 | Retrospective multinational study | 0.6-80.6m (mean 12.3m) | Common: seizures, hypotonia, FTT, vomiting, chronic diarrhoea, liver dysfunction<br><br>Uncommon: SLEs, deafness, optic atrophy, cataracts, nystagmus, renal tubular dysfunction, endocrine disease | Classical phenotypes 'Alpers' 'MCHS', 'MNGIE'<br><br>Common: seizures, hypotonia, FTT, vomiting, chronic diarrhoea, liver dysfunction<br><br>Uncommon: SLEs, ataxia, dystonia, hearing impairment, cataracts, optic atrophy, nystagmus, hypoparathyroidism, hypothyroidism | Common: elevated lactate, low albumin, deranged liver function, hypoglycaemia<br><br>Uncommon: elevated CK | Common: focal cortical lesions, white matter lesions<br><br>Uncommon: generalised cerebral/ cerebellar atrophy, thalamic lesions | Common: multiple enzyme complex deficiency, normal<br><br>Uncommon: isolated complex I and IV deficiency | 81% died, mean 20.4m (1.03m – 8.75y)<br>Cause of death: liver failure, sepsis, status epilepticus |
| 17 | *TWNK* (Twinkle/ *PEO1*) dominant mutations | (28) | 33 | Retrospective study | 8-65y (mean 42y) | See overall phenotype | Common: Ptosis, PEO, fatigue<br><br>Uncommon: proximal muscle weakness, myalgia, dysphagia, ventricular hypertrophy, arrhythmia, ECG abnormalities, endocrine disease, visual impairment, GI symptoms, hearing loss, cataracts, epilepsy. | NS | NS | COX deficient/ negative fibres, RRF | NS |
| 18 | *TWNK (Twinkle/ PEO1) recessive mutations* | (29) | 23 | Prospective study | 0.8-1.5y (mean 1.15y in 19 patients) | Ataxia, muscle hypotonia, athetoid movements, areflexia. | Common: Ophthalmoplegia, SNHL, sensory axonal neuropathy, female hypergonadotrophic hypogonadism, learning difficulties, cognitive impairment, epilepsy, psychiatric symptoms, migraines. | Uncommon: elevated lactate in CSF and plasma, elevated α fetoprotein, elevated liver transaminases | Atrophy of brainstem, cerebellum, dorsal roots, posterior columns, posterior spinocerebellar | Uncommon: COX deficiency | 35% died, mean 18.5y (4.5 -30y)<br>Cause of death: status epilepticus |

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| | | | | | | | | | tracts, stroke-like lesions | | |
| 19 | Thymidine kinase 2 deficiency | (16) | 92 | Multinational retrospective study and literature review | 5-35y (mean 17.9y)<br><br>Infantile onset: (<1y)<br><br>Childhood onset >1y and <12y<br><br>Late onset ≥12y | Proximal myopathy | Common: myopathy, delayed motor development and impaired motor function, respiratory compromise, especially in infantile onset cases, ptosis.<br><br>Uncommon: myoglobinuria, rhabdomyolysis, peripheral neuropathy, PEO, dysphagia, dysarthria, dysphonia, facial weakness, CNS involvement including seizures, encephalopathy, hearing loss, | Elevated CK | Uncommon: cerebral or cerebellar atrophy, immature myelination, lissencephaly | Common: multiple complex deficiencies, RRF, COX deficient fibres<br><br>Uncommon: Isolated Complex III, IV deficiency, elevated CS<br><br>mtDNA depletion/ deletions | Infantile onset: median survival 1y.<br><br>Childhood/late onset: median survival 23y<br><br>Overall mortality 86%, mean 6.24y (0.15-50y) Deterioration in motor function leading to disability, ventilator dependence and/or death due to respiratory failure in infantile and childhood onset |
| 20 | Succinate CoA ligase deficiency (*SUCLA2* mutations) | (31) | 50 | Retrospective questionnaire-based review (20 cases) and literature review (30) | Median 2m (0-6y) | See overall phenotype | Common: hypotonia, DD, dystonia, SNHL, feeding problems, FTT<br><br>Uncommon: epilepsy | Elevated plasma MMA, lactate, CSF lactate, 3MGA, MC, 3OHV, Krebs cycle intermediates | Common: basal ganglia lesions, cerebral atrophy<br><br>Uncommon: leukoencephalopathy, normal | Common: Complex I, III and IV deficiency, mtDNA depletion | 31% died Median 20y (12% survival ≥20y) |

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| | | | | | | | | Uncommon: elevated urine MMA | | Uncommon: Isolated Complex I deficiency, normal mtDNA copy number | |
| 21 | Succinate CoA ligase deficiency (*SUCLG1* mutations) | (31) | 21 | Retrospective questionnaire-based review (5 cases) and literature review (16) | Median birth (birth-1.5y) | See overall phenotype | Common: hypotonia, DD, hepatopathy, feeding problems, dystonia, SNHL<br><br>Uncommon: epilepsy, CM | Elevated plasma MMA, lactate, CSF lactate, Krebs cycle intermediates<br><br>Uncommon: elevated urine MMA | Common: basal ganglia lesions, cerebral atrophy<br><br>Uncommon: leukoencephalopathy, normal | Common: Complex I, III and IV deficiency, mtDNA depletion<br><br>Uncommon: Isolated Complex I deficiency, normal mtDNA copy number | 67% died. Median 20m (10% survival ≥20y) |
| 22 | *MPV17* mutations | (30) | 29 | Retrospective study and literature review | 0-8m Median NS | See overall phenotype | Common: hepatomegaly, liver failure/cirrhosis, DD, muscular weakness, hypotonia, FTT<br><br>Uncommon: peripheral neuropathy, ataxia, myoclonus, hepatocellular carcinoma, microcephaly, renal tubulopathy, hypoparathyroidism, pancreatitis, reflux, scoliosis, | Lactic acidosis, hypoglycaemia | Common: white matter abnormalities | Multiple enzyme deficiencies (especially I,II,IV)<br><br>mtDNA depletion | Death in 75%, median age 11m (3m-20y) due to liver failure, sepsis<br>34% received liver transplant |

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| | | | | | | | neutropaenia, pigmentary retinopathy, nephrolithiasis | | | | |
| 23 | MNGIE (*TYMP* mutations) | (32) | 102 | Retrospective study and literature review | 5m-35y (mean 17.9y) | Common: GI symptoms<br><br>Uncommon: ocular symptoms, peripheral neuropathy, hearing loss, tinnitus, myopathy | Common: GI symptoms (weight loss, abdominal pain, vomiting, nausea, diarrhoea, pseudo-obstruction), ocular symptoms (ptosis, PEO), neurological symptoms (demyelinating peripheral neuropathy, absent reflexes, foot drop), hearing loss<br><br>Uncommon: GI symptoms: gastroparesis, dysphagia, diverticulosis, aspiration, constipation, malabsorption, malnutrition.<br>Diabetes, pancreatic insufficiency, short stature, prolonged QT, pigmentary retinopathy, psoriasis, hepatopathy | Elevated lactate and CSF protein | Common: leukoencephalopathy | Deficiencies in Complex I,III,IV or normal<br><br>COX deficient fibres and RRF or normal | Mean age of death 35y (15-54)y, due to pneumonia, intestinal rupture, sepsis, suicide, electrolyte imbalance, malignant melanoma, arrhythmia, metabolic acidosis, cardiorespiratory arrest, variceal bleed of oesophagus<br><br>High mortality between 20-40y |
| 24 | *FBXL4* mutations | (33) | 87 | Retrospective multinational study and literature review | Mean 6m (0-13y) | See overall phenotype | Common: FTT, short stature, microcephaly, DD, hypotonia, feeding difficulty, facial dysmorphism<br><br>Uncommon: seizures, movement disorders, cerebellar ataxia, stroke like episodes, HCM, arrhythmias, pulmonary HTN, strabismus, nystagmus, optic | Lactic acidosis, hyper-ammonaemia,<br><br>Uncommon: elevated liver transaminases | Common: white matter abnormalities, cerebral atrophy, basal ganglia abnormalities, elevated lactate peak on MRS | Multiple complexes deficient (I-V)<br><br>mtDNA depletion | Death in 20% of cases, median age of death 2y, due to sepsis, acidosis, pneumonia, cardiorespiratory failure |

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| | | | | | | | atrophy, cataracts, SNHL, undescended testes, hypospadias, renal impairment/tubular acidosis, neutropaenia, recurrent infections | | Uncommon: hydrocephalus, enlarged cisterna magna, thin CC, cerebellar atrophy, periventricular/ arachnoid cysts, brainstem abnormalities | | |
| 25 | *MTO1* mutations | (34) | 35 | Retrospective study and literature review | Mean 10.2m (1d-8y) | Common: HCM<br><br>Uncommon: hypotonia, ataxia | Common: HCM, hypotonia, GDD, FTT, optic atrophy<br><br>Uncommon: PEO, ptosis, cataract, seizures, ataxia, hepatic and renal dysfunction, hypoglycaemia | Elevated lactate, alanine, UOA showed 3MGA, tyrosine metabolites, Krebs cycle intermediates | Basal ganglia, cerebellar peduncle abnormalities, hypoplasia of CC, normal, elevated lactate peak on MRS | Common: Complex I,IV deficiency<br><br>Uncommon: Complex I,III,IV deficiency | 34% died at a mean of 2.67y (1w – 23y) |
| 26 | *DARS2* mutations | (35) | 66 | Retrospective study | 0.4-40y (mean 8y) | Cerebellar ataxia, hypotonia | Common: cerebellar ataxia, difficulty walking with deteriorating motor function<br><br>Uncommon: Impaired cognitive function, delayed development | NS | Leuko-encephalopathy, signal abnormalities in medulla, corticospinal tracts, cerebellum. Elevated lactate on MRS. | NS | 2 patients (3%) died under 2y age. No other deaths reported. Unable to report mean survival accurately as number of deaths is low. |

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| 27 | *RMND1* mutations | (36) | 32 | Multinational retrospective study and literature review | Median 29d (birth-18m) | See overall phenotype | Common: hypotonia, DD, SNHL, seizures, abnormal EEG, microcephaly, CKD, HTN, RTA, FTT, dysphagia,<br><br>Uncommon: peripheral spasticity, strabismus, dysplastic kidneys, anaemia, pancreatitis, diarrhoea, abdominal pain, HCM, DCM, cardiac conduction defects, other congenital cardiac defects, dysmorphic features | Elevated lactate, metabolic acidosis | Common: White matter abnormalities<br><br>Uncommon: cysts in cerebrum, basal ganglia calcification, acute infarcts, normal | Common: Complex I,III,IV deficiency, Complex I and IV or isolated complex IV deficiency | 63% died at median of 1.03y (0-6.67y) |
| 28 | *SERAC1* mutations causing MEGDEL syndrome | (37) | 67 | Multinational retrospective study and literature review | Median 6m | Common: neonatal sepsis, recurrent hypoglycaemia, muscular hypotonia, delayed motor development<br><br>Uncommon: liver dysfunction, respiratory insufficiency | Common: developmental regression, spasticity, dystonia, dysphagia, drooling, epilepsy, cognitive impairment, DD, scoliosis, SNHL, visual loss, severe liver dysfunction/failure, recurrent pneumonia, FTT<br><br>Uncommon: pigmentary retinopathy, optic atrophy, renal tubulopathy, cardiac abnormalities | Hyper-ammonaemia, jaundice, deranged liver function, 3MGA, lactic acidosis | Progression of disease in 5 stages: pallidal abnormality, swelling of caudate and putamen, with sparing of the dorsal putamen, 'putaminal eye', progressive atrophy of basal ganglia | Multiple complexes deficient | 24% died at a median age of 9y (5d-16y) due to respiratory infection, multiorgan failure |
| 29 | Barth syndrome (*TAZ* mutations) | (38) | 73 | Patient registry (self report and medical record abstracted data) | Mean 0.76±1.6y | Common: CM and cardiac failure, neutropaenia, growth delay, FTT | Common: CM, poor growth, neutropaenia, recurrent mouth ulcers, DD especially motor, FTT, pneumonia | NS | NA | NS | 5 deaths: mean age 15.5y (5.8-25.4y) due to congestive cardiac failure, sepsis, and |

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| | | | | | | | Uncommon: scoliosis, delayed bone age | | | | gastric erosion associated with use of gastrostomy |
| 30 | Barth syndrome (*TAZ* mutations) | (39) | 22 | Retrospective study | Mean 0.24y (0-1.7y) | Common: CM, infection<br><br>Uncommon: hypoglycaemia, growth delay | Common: symptomatic CM (91%), neutropaenia, skeletal myopathy | Elevated 3MGA, decreased cardiolipin and low/normal arginine | NA | Lipid storage myopathy in 6/7 patients biopsied | Mean 0.69y (0.1-2.56y), 11 deaths related to CM/ sepsis. |
| 31 | *CLPB* mutations | (40) | 31 | Multinational retrospective study and literature review | From birth or antenatally | Antenatal scans showing polyhydramnios and contractures, abnormal fetal movements. | Common: cataracts, swallowing problems, respiratory insufficiency, abnormal EEG (burst suppression), hyperekplexia, absent voluntary movements, generalised muscular hypertonia/hypotonia, contractures, dystonia, jitteriness, unresponsiveness to pain, neutropaenia<br><br>Uncommon: seizures | UOA showing 3MGA | Brain atrophy | NS | 58% died at median age 2.6m (1d – 3.9y) |
| 32 | *OPA1*-related autosomal dominant optic atrophy | (41) | 69 | Retrospective study | Mean 10.2y SD 10.1 | See overall phenotype | Visual impairment (84%), asymptomatic (16%) | NA | NA | NA | In mean 9.6y FU BCVA improved by >2 logMAR lines in 10%, unchanged in 62%, worsened by ≥2 logMAR lines in 28% |
| 33 | Friedreich ataxia | (42) | 80 | Single centre retrospective study | Mean 11.6 ±4.5y | Common: ataxia | Common: ataxia, areflexia, dysmetria, scoliosis, absent reflexes, hypotonia, dysarthria, | NA | Cerebellar/cerebral/ brainstem atrophy | NA | Progression of disease severity and impairment |

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| | | | | | | Uncommon: lower limb weakness, clumsiness, dysarthria, tremor, vertigo, cardiac symptoms | pes cavus, dysautonomia, muscle wasting, abnormal ECG<br><br>Uncommon: dysphagia, nystagmus, ptosis, hyperacusis, dysphoria, urinary urgency, DM, HCM, tachycardia, EEG abnormalities | | | | of central pathways with worsening pyramidal and cerebellar signs |
| 34 | Friedreich ataxia | (43) | 812 | Prospective study | Mean 13.7 ±9.9y | See overall phenotype | Common: ataxia, dysarthria, impaired vision and hearing, scoliosis, cardiomyopathy<br><br>Uncommon: DM | NA | NA | NA | Progression in severity of all neurological scores and vision scores over a 5 y period. No mortality reported |
| 35 | Friedreich ataxia | (44) | 605 | Prospective study | Mean 15.5 ±10.4y | NS | Ataxia, impaired verbal fluency, cognitive ability and activities of daily living, ophthalmological signs | NA | NA | NA | Progression of severity of all outcome measures over 2y period. No mortality |
| 36 | Pyruvate dehydrogenase complex (PDHc) deficiency | (45) | 371 | Retrospective literature review | Mean 8± 15.9m | Common: neonatal acidotic decompensation associated with respiratory distress | Common: DD, hypo/hypertonia, seizures<br><br>Uncommon: microcephaly, ataxia, facial dysmorphism, spasticity, peripheral neuropathy, optic atrophy, nystagmus, ptosis, choreoathetosis, strabismus | Elevated lactate, pyruvate, alanine in blood and lactate/ pyruvate ratio <20<br><br>Elevated CSF lactate | Ventriculo-megaly CC hypo/agenesis, radiological features of Leigh syndrome | NA | 36% died Mean 2.7y (0.1-35y) |

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| 37 | Pyruvate dehydrogenase complex (PDHc) deficiency | (46) | 59 | Retrospective analysis of cases including questionnaires | NS | NS | Common: hypo/hypertonia, seizures, ventriculomegaly, callosal agenesis/hypoplasia, microcephaly, visual and hearing impairment.<br><br>Uncommon: ataxia, dystonia, peripheral neuropathy | NS | Ventriculo-megaly, CC hypo/agenesis, radiological features of Leigh syndrome | NA | 39% died<br>Median survival not stated. 61% died by 1y, 91% by 4y. Causes of death included severe lactic acidosis, respiratory failure, infection, neurological progression |

**Key:** 3MGA 3-methylglutaconate, 3OHV 3-hydroxyvalerate, 5MTHF 5-methyltetrahydrofolate, AF atrial fibrillation, BCVA best corrected visual acuity, BMI body mass index, CC corpus callosum, CK creatine kinase, CKD chronic kidney disease, CM cardiomyopathy, COX cytochrome *c* oxidase, CS citrate synthase, CSF cerebrospinal fluid, d days, DCM dilated cardiomyopathy, DD developmental delay, DM diabetes mellitus, ECG electrocardiogram, EEG electroencephalogram, ERG electroretinogram, FTT Failure to thrive, FU follow up, GI gastrointestinal, HCM hypertrophic cardiomyopathy, HTN hypertension, IDDM insulin dependent diabetes mellitus, IUGR intrauterine growth restriction, KSS Kearns-Sayre Syndrome, logMAR logarithm of the minimum angle of resolution, m months, MC methylcitrate, MCHS myocerebrohepatopathy spectrum, MMA methylmalonic acid, MNGIE mitochondrial neurogastrointestinal encephalopathy, MRS magnetic resonance spectroscopy, NA not applicable, NS not stated, PEO progressive external ophthalmoplegia, PPHN persistent pulmonary hypertension, PV periventricular, RRF ragged red fibres, RTA renal tubular acidosis, S1-S3 three commonest genotypes of SCO2 deficiency, SD standard deviation, SLEs stroke-like episodes, SMA spinal muscular atrophy, SNHL sensorineural hearing loss, UOA urinary organic acids, w weeks, WPW Wolff Parkinson White Syndrome, y years

**Table 2 Clinical indicators of poor prognosis**

| STUDY | CLINICAL POOR PROGNOSIS INDICATORS | REFERENCES |
|---|---|---|
| Leigh syndrome | Elevated CSF lactate, acute infective exacerbations, presentation <6m, failure to thrive, brainstem involvement, ITU admission, presence of epilepsy | (11) |
| Complex I deficiency | Early presentation | (14) |
| MELAS | Elevated lactate peak on MRS<br>Early presentation | (15)<br>(18) |
| *LRPPRC* mutations | Hyperglycaemia and deranged liver transaminases during metabolic decompensations | (23) |
| *TMEM70* mutations | Early presentation | (25) |
| *POLG* disorders | Alpers phenotype and the presence of seizures | (27) |
| *TK2* mutations | Earlier presentation, which also correlates with presence of CNS involvement/encephalopathy and mtDNA depletion | (16) |
| *MTO1* mutations | Earlier presentation | (34) |
| *DARS2* mutations | Early presentation | (35) |
| *RMND1* mutations | Earlier presentation, presence of renal disease is associated with a better outcome | (36) |
| Barth syndrome | Severity of neutropenia at the first blood test | (39) |
| *CLPB* mutations | Antenatal features including abnormal fetal movements, polyhydramnios | (40) |
| Friedreich ataxia | Earlier presentation, worse initial baseline scores<br>Male sex | (44)<br>(43) |
| Pyruvate dehydrogenase complex deficiency | High lactates, early presentation, younger patients, lower enzyme activity; males were twice as likely to die, surviving females have higher disability | (45)<br>(46) |

**Key:** CSF cerebrospinal fluid; CNS central nervous system; ITU intensive therapy unit; m months; MRS magnetic resonance spectroscopy

**Table 3 Genotype/phenotype correlations in mitochondrial disorders**

| STUDY | GENOTYPE – PHENOTYPE/PROGNOSIS CORRELATION | REFERENCES |
|---|---|---|
| Leigh syndrome | Certain genotypes had a poorer prognosis: m.8993T>G, and mutations in *SLC19A3* and *SURF1*.<br>Prognosis in Leigh syndrome due LRPPRC deficiency is worse than in Complex I deficiency, which is in turn worse than SURF1 deficiency. | (11)<br><br>(22, 23) |
| Complex I deficiency | Nuclear gene defects have a worse prognosis compared to mtDNA mutations. Mutations in genes encoding the 14 'core' subunits of Complex I have a worse prognosis compared to non-core subunits. Certain genes were associated with specific phenotypes e.g. *ACAD9* and *NDFUA11* mutations were associated with cardiomyopathy; *NDUFAF2*, *NDUFS4* and *NDUFS7* mutations were associated with Leigh syndrome; *NDUFA1* mutations were associated with hearing loss; and *NDUFS1* and *NDUFV1* mutations were associated with leukoencephalopathy. | (14) |
| Complex II deficiency | Mutations in *SDHAF1* were associated with leukoencephalopathy and *SDHA* mutations with Leigh syndrome and cerebellar atrophy. | (17) |
| Single large-scale mtDNA deletions | Higher % heteroplasmy for deletions was associated with an earlier age of presentation of disease. Longer deletions were associated with KSS spectrum compared to PEO. | (12)<br>(13) |
| *SCO2* mutations | Patients who had the c.1541G>A *in trans* with a stop codon mutation had the worst prognosis – they presented earlier, with neonatal cardiomyopathy, developed more severe neurological disease and died earlier in comparison to c.1541G>A /c.1541G>A and c.1541G>A /c.1653T>C patients. | (24) |
| *TMEM70* mutations | Homozygotes with the c.317A>G mutation, who were often of Roma ethnicity, had a worse prognosis compared to compound heterozygotes who had milder phenotypes. | (25) |
| *POLG* mutations | Severe early onset disease in childhood was associated with at least one mutation in the linker region and one in the polymerase domain. Exonuclease domain mutations are more commonly found in patients presenting in teenage/adult life with less severe disease. | (26) |
| *TWNK (Twinkle/ PEO1/C10orf2) recessive mutations* | Compound heterozygotes for p.Tyr508Cys and p.Ala318Thr present earlier and progress more quickly than p.Tyr508Cys homozygotes | (29) |
| Succinyl-CoA ligase deficiency | Missense mutations in both *SUCLA2* and *SUCLG1* were associated with longer survival compared to loss-of-function mutations. *SUCLA2* patients had a better prognosis compared to *SUCLG1* patients. | (31) |
| *FBXL4* mutations | Missense mutations have a better prognosis/survival than nonsense/frameshift/splice site/in-frame deletions. | (33) |
| *MTO1* mutations | Compound heterozygotes with a truncating mutation had poorer prognosis; no cases had biallelic truncating mutations implying that this may not be compatible with survival. | (34) |
| *DARS2* mutations | Patients with c.228-21_-20delTTinsC and either c.455 G>T or c.492 + 2 T>C had a milder phenotype | (35) |

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| *CLPB* mutations | Severe phenotypes were indicated by truncating mutations rather than missense mutations which were associated with a milder phenotype. | (40) |
| Friedreich ataxia | Longer trinucleotide repeats correlate with greater neurological dysfunction; greater than 353 GAA repeats have worse prognosis. | (43, 44) |
| Pyruvate dehydrogenase complex deficiency | Patients with missense mutations tended to present later in life; missense mutations more common in boys than frameshift mutations (usually affected girls, present earlier in life).<br>Certain mutations involving amino acid 378 of the *PDHA* gene were associated with a poorer prognosis. Mortality is higher in boys, probably due to a higher number of patients with *PDHA* mutations (X-Linked) than other genetic defects. | (45)<br><br>(46) |

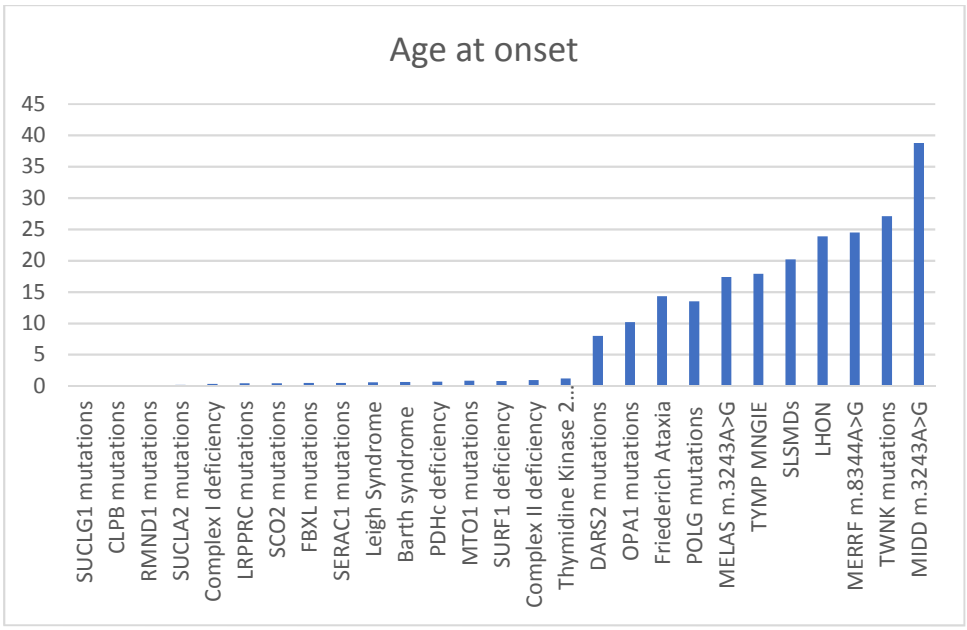


Figure 1 Age of onset(median/mean) in years for mitochondrial disorders

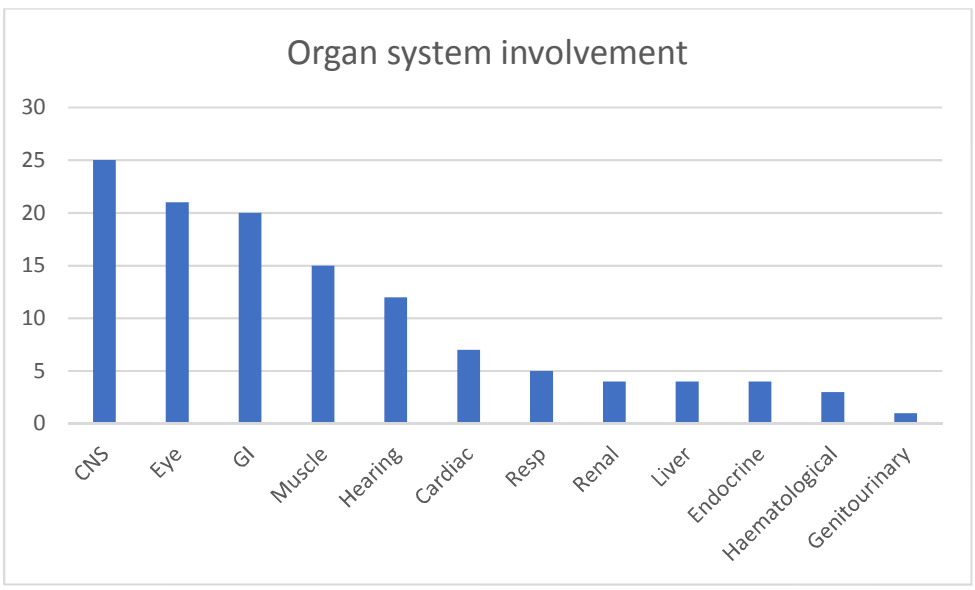


Figure 2 Common involvement of organ systems. Y axis indicates number of mitochondrial disorders (total 29)

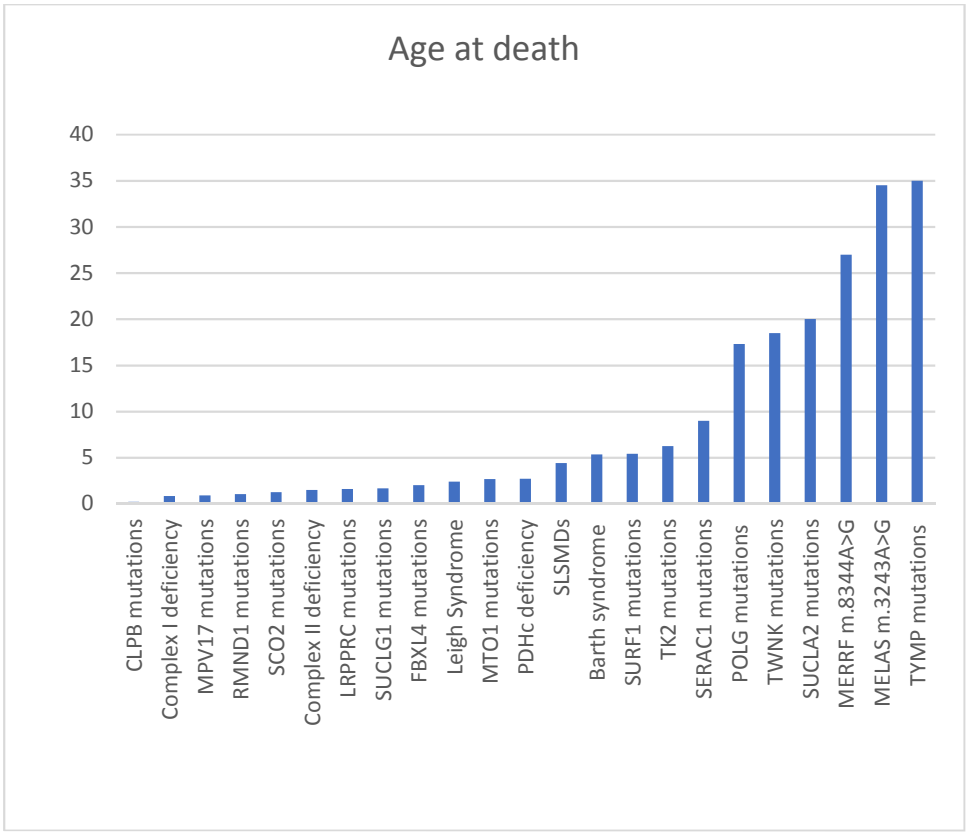


Figure 3 Age of death (median/mean) in years for mitochondrial disorders

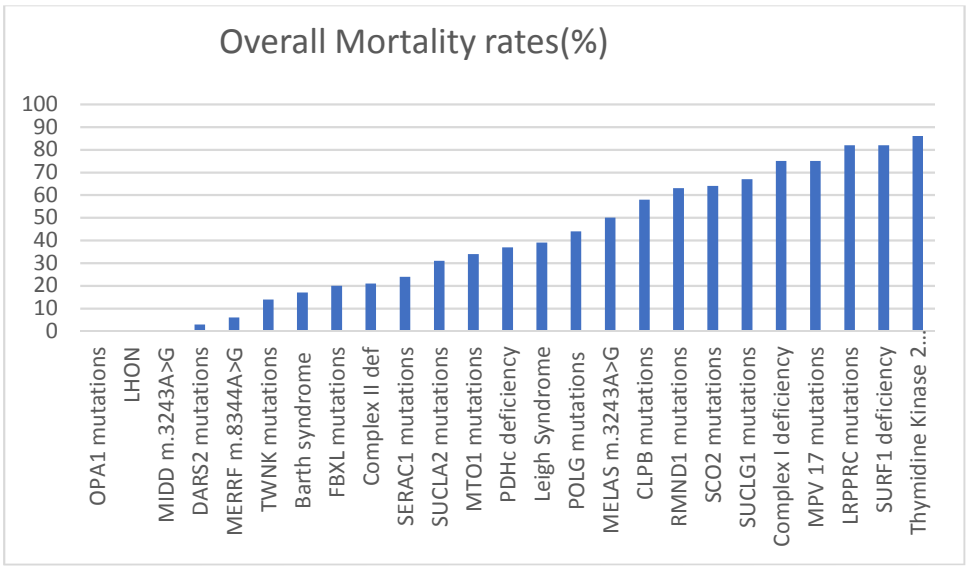


Figure 4 Overall mortality rates (% mortality) for mitochondrial disorders