Systematic review of cognitive deficits in adult mitochondrial disease

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The profile and trajectory of cognitive impairment in mitochondrial disease are poorly defined. This systematic review sought to evaluate the current literature on cognition in mitochondrial disease, and to determine future research directions. A systematic review was conducted, employing PubMed, Medline, Psycinfo, Embase and Web of Science, and 360-degree citation methods. English language papers on adult patients were included. The literature search yielded 2421 articles, of which 167 met inclusion criteria. Case reports and reviews of medical reports of patients yielded broad diagnoses of dementia, cognitive impairment and cognitive decline. In contrast, systematic investigations of cognitive functioning using detailed cognitive batteries identified focal cognitive rather than global deficits. Results were variable, but included visuospatial functioning, memory, attention, processing speed and executive functions. Conclusions from studies have been hampered by small sample sizes, variation in genotype and the breadth and depth of assessments undertaken. Comprehensive cognitive research with concurrent functional neuroimaging and physical correlates of mitochondrial disease in larger samples of well-characterized patients may discern the aetiology and progression of cognitive deficits. These data provide insights into the pattern and trajectory of cognitive impairments, which are invaluable for clinical monitoring, health planning and clinical trial readiness.

Introduction

Mitochondrial diseases are a common group of genetic neuromuscular disorders characterized by genotypic and phenotypic heterogeneity, with a prevalence similar to that of many other genetically determined neurodegenerative diseases [1]. Although there is significant clinical variability, neurological impairment remains a hallmark of mitochondrial disease and cognitive impairment is one of the least understood aspects.

A review of clinical manifestations by El-Hattab and colleagues [2] identified initial symptoms of developmental delay in <10% of patients and impaired mentation in 10–24% of patients referred to as having mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS). Overall, 50–74% featured learning disability or memory impairment and ≥90% experienced dementia. Prevalence rates of cognitive difficulties have ranged from 0 to 90%, depending on genotype and stage of disease [3–10]. These findings would indicate variable cognitive outcomes for patients with mitochondrial disease. Nevertheless, to date, our knowledge of intellectual ability in patients with mitochondrial disease and how this may change with disease progression remains scarce.

The purposes of this systematic review were twofold: (i) to investigate current literature on cognition in mitochondrial disease and (ii) to determine how the field must advance to improve our knowledge of cognition in this group.

Methods

Throughout this systematic review, we have adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for conducting systematic reviews [11].
Search strategy

We independently searched five databases (PubMed, Medline, Psycinfo, Embase and Web of Science) for articles published up to and including 10 June 2019. Search terms related to mitochondrial disease and to cognitive functioning were chosen, based on the individual thesaurus used in each database (full search terms are provided in Tables S1–S5). Papers were further identified through manual search strategies and using 360-degree citation methods to ensure that the breadth of the literature was comprehensively screened (Fig. 1).

Review criteria

Inclusion criteria were English language, human studies of adult patients (≥16 years) with primary mitochondrial disease. Child studies were excluded unless part of a family study. No robust animal models yet exist for the common forms of mitochondrial disease associated with cognitive impairment; thus, animal research was excluded. Papers were considered if they referred to cognitive functioning in the title or abstract, or to discussion of clinical findings. Exclusion criteria were: other diseases/disorders commonly associated with mitochondrial dysfunction (e.g. Creutzfeldt–Jakob disease, Friedreich’s ataxia, Parkinson’s disease, Huntington’s disease), diseases of memory without mitochondrial disease (e.g. Alzheimer’s disease, dementia), psychiatric problems without concurrent cognitive difficulties, unpublished data, conference presentations and abstracts where the full paper was not published.

Data synthesis

Due to substantial methodological and clinical heterogeneity in systematic research studies identified by this literature search (Table 1), we used a narrative approach to synthesize the findings of the included studies, as meta-analysis was deemed inappropriate [12].

Results

The literature search yielded 2421 articles, of which 168 met inclusion criteria. Articles were subdivided into case literature (75% of published articles), reviews of the medical literature (18%) and larger scale, systematic investigations of cognition in mitochondrial disease (7%; Fig. 1), categorized by mutation/phenotype.

Case literature

Many case reports have been published that give a clinical profile of the patient(s) in question, including a statement about cognition (Table 2), without reference to the neuropsychological assessments and/or results obtained (see Table S6 for broader impairments associated with cognitive difficulty and the reference list for both tables). Cognition was reported in 114 patients; 34% showed cognitive impairment, 24% cognitive decline and 15% dementia. Cognitive domains with high reports of impairment were memory (32%) and language (20%). However, to highlight variability in reporting, only 2% identified dementia and memory difficulties, 14% cognitive impairment and memory difficulties, and 7% cognitive decline and memory difficulties (which could constitute a diagnosis of dementia, depending on the extent of impairment).

Comprehensive assessment of 14 patients with MELAS revealed higher VIQ than PIQ, and intellectual decline and dementia [24,25], as well as visuospatial difficulties [25,26], attention difficulties, verbal fluency, set-shifting ability, planning and problem solving (suggestive of executive dysfunction) [26,27], auditory agnosia (inability to process environmental sounds and speech, in the absence of aphasia) [28–32] and understanding of sentences [26]. Magnetic resonance imaging (MRI) of the brain generally revealed generalized atrophy [24–26,28] although electroencephalographic results from one study were suggestive of focal lesions [27]. Cognitive decline was commonly reported in patients with point mutations [33–35]. Wide-ranging difficulties were described, with all reports identifying deficits in visuospatial functioning, memory and attention [33–37], but with variation in impairment in language [33–35], processing speed [36,37], verbal fluency, planning, and initiative and set-shifting (areas of...
executive functioning) [35–37]. Relative strengths varied across patients, with some showing better verbal [37] and some showing better visual [33,34] abilities.

**Reviews of the medical literature**

A number of studies have reviewed different domains of cognitive functioning in patients with mitochondrial disease, often reporting variable frequencies of individuals with dementia, cognitive impairment and cognitive decline (Table 3).

Kartsounis and colleagues [38] reviewed the medical records of 72 patients with undefined mitochondrial disease from 1969 to 1989. General or focal cognitive deficits were observed in 61% of 36 patients who underwent neuropsychological assessment. Moderate to severe general intellectual decline was detected in 36%, defined by a discrepancy between estimated optimal intelligence quotient (IQ) and performance on general intelligence tests of ≥15 IQ points (15–30, moderate; 30+, severe). A total of 16 patients demonstrated memory deficits, 15 demonstrated perception deficits and 12 demonstrated language deficits. Only 28% displayed normal higher cerebral functioning. However, patients were assessed as part of clinical care and it is not known what the cognitive ability of untested individuals was, or whether they might have exhibited subtle cognitive deficits that were unlikely to be detected by initial clinical impression. This study provided neither phenotype/genotype reflecting the pre-genetic era, with only four reporting genotype (Table 3) [39–42].

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**Figure 1** Process implemented to identify papers for this systematic review. [Colour figure can be viewed at wileyonlinelibrary.com]
### Table 1

| Mutation | Author | Sample | Follow-up? | Cognitive assessments | Cognitive domain assessed |
|----------|--------|--------|------------|----------------------|--------------------------|
| m.3243A>G | Majamaa- Voltti et al. [13] | 33 | 3-year follow-up study | WASI-R, WMS-IBenton Visual Retention test, TMT A and B, Letter Fluency task, Finger Tapping test, Reaction Time test (choice reaction) | Verbal and visual intelligence, Verbal memory, Visual memory, Executive function, Motor performance, Motor performance, Visual perception and construction |
|          | Kaufmann et al. [14] | 85 | Single time point | Specific assessment not specified | Pre-morbid (crystalline) intelligence, Visuoperception, visuoconstruction, secondary visual memory, Executive function, Verbal working memory, Verbal working memory, Selective attention, Anxiety and depression |
|          | Kraya et al. [15] | 10 | MRI and cognition single time point | Mehrfachwahl Wortschatz Intelligenztest B, Rey-Osterrieth Complex Figure test, Regensburg Word Fluency Test, Zoo Map task from the Behavioural Assessment of the Dysexecutive Syndrome, Auditory Verbal Learning Test (AVLT), Digit span backwards from WMS-R, Hospital Anxiety and Depression Scale | Pre-morbid (crystalline) intelligence, Visuoperception, visuoconstruction, secondary visual memory, Executive function, Verbal working memory, Verbal working memory, Selective attention, Anxiety and depression |

### Baseline imaging

- MRI: 20 participants
  - No changes in 16 participants
  - EEG: 13 participants
  - Significantly lower mean parietal and occipital EEG alpha waves

- EEG was normal in 67%, mildly abnormal in 21%, and moderately abnormal in 12% of cases

- Most pronounced lesions found in tempo-occipital, occipital and parietal regions

- Loss of grey and white matter: 46%, moderate abnormality: 30%
| Author            | Sample Description                                                                 | Follow-up? | Cognitive assessments                  | Cognitive domain assessed                  | Definition of impairment                                                                 | Baseline imaging |
|-------------------|-------------------------------------------------------------------------------------|------------|----------------------------------------|--------------------------------------------|------------------------------------------------------------------------------------------|------------------|
| Fromont et al. [6] | 11 m.3243A>G = 9 m.14709T>G = 2 9 age-matched, type 1 diabetic controls             | Single time point | Mini Mental State Examination Hamilton test Fear and Cued selective reminding test Rey's Figure Visual memory subtest of the WMS-R Digit Span subtest of the WAIS-R TMT A/B Raven's Progressive Matrixes PM-38 Verbal Fluency Frontal Assessment Battery DO80, a standardized French picture-naming test Rey's Figure | Global cognitive function Depression Episodic memory Immediate and delayed recall Visual memory Executive function Executive function Executive function Executive function Executive function Executive function | Z-score below -1.65SD, standard score below six or percentile below 5% Vermis atrophy: 70% Severe cerebellar atrophy extending into cerebellar hemispheres: 18% Focal white matter lesions: 50% Basal ganglia calcifications: 9% |                 |
| Turconi et al. [7] | 16 CPEO = 9 CPEO = 3 KSS = 3 MERRF = 1 Point mutation (unspecified) = 1 Multiple deletions = 2 Large-scale single deletion = 13 | Single time point | WAIS-R Digit Span subtest of the WAIS-R Memory Assessment Scale Judgment of Line Orientation Rey Figure (A and B) Copy test | VIQ, PQ and FSIQ Verbal short-term memory Global memory, short-term memory, verbal memory and visual memory Visuospatial organization and drawing abilities Perceptual motor skills | FSIQ<70 (2SD from the norm) MRI normal: 81% Diffuse aspecific abnormalities: 13% 2 patients with KSSH1 patients with singlephoton emission computed tomography results: At least one significant asymmetry: 100% Bilateral involvement: 45% CPEO/CPEO+: temporal cortex: 7/8 patients, mesial regions: 5/7 without prevalent laterality, basal ganglia: 4/8, thalamus (3/8) temporal lobes, mesial parieto-occipital: 3/8 KSS: widespread cortical and subcortical hypoperfusion: 1/2, left mesial temporal cortex involvement: 1/2 MERRF: right thalamus involvement: 1/1 |                 |
| Bosbach et al. [17] | 22 CPEO = 16 KSS = 6 Large-scale single deletions = 15 m.1243444dgtG = 2 Unknown = 5 Healthily age-, gender- and education-matched controls | Single time point | Language and visuoconstruction Language/aphasia screening Visual perception Visuospatial organization and visual memory Visuomotor coordination Perceptual speed/visual scanning Sustained attention and visual scanning Vigilance Abstraction/flexibility Abstraction/flexibility Verbal memory Health-related quality of life | Score below the 10th percentile | N/A |
| Author                  | Sample Description                                                                 | Follow-up? | Cognitive Assessments                                                                 | Cognitive Domain Assessed                                                                 | Definition of Impairment | Baseline Imaging |
|------------------------|-------------------------------------------------------------------------------------|------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|--------------------------|-----------------|
| Multiple deletions     | Granstad et al. [18]                                                                 | 3-year follow-up of one patient | WAIS, Norwegian Translations with US norms, WMS-R; Norwegian version Halstead-Reitan Battery, using Norwegian cross-validation data | VIQ, PIQ and FSIQ, General Memory Index, Verbal Memory Index, Visual Memory Index | Not specified | N/A             |
|                        | Gramstad et al. [18]                                                                | Single time point | Neuropsychological battery test, Sensory screening battery | Memory, orientation, non-verbal intelligence, drawing, arithmetic, word list generation, trail making and digit span | Not specified | N/A             |
|                        | Montrisso et al. [20]                                                               | Single time point | WAIS, Halstead-Reitan battery, Norwegian version | Performance, reaction time and brain functioning | Not specified | N/A             |
|                        | Kaufmann et al. [21]                                                                | Single time point | Specific assessments not specified | Intellectual abilities, not otherwise specified | N/A | MRS ventricular lactate rose significantly from asymptomatic through to symptomatic 3243A>G carriers |
|                        | Incalzi-Firkan et al. [22]                                                          | Single time point | WAIS, Rey Auditory Verbal Learning Test, Stroop Color-Word Test, TMT A/B, Verbal Fluency | Intellectual abilities, not otherwise specified | N/A | MRS ventricular lactate rose significantly from asymptomatic through to symptomatic 3243A>G carriers |
|                        | Moore et al. [23]                                                                  | 18-month follow-up | WAIS-IV, Delis-Kaplan executive function system, WMS-IV | FSIQ, verbal comprehension, perceptual reasoning, working memory, processing speed | Z-score > 1, 2 and 3 SD from the normative mean | N/A             |

CPEO, chronic progressive external ophthalmoplegia; EEG, electroencephalographic; FSIQ, full-scale IQ; Fz, Pz, Cz, location of scalp electrodes defined using the international 10-20 system for EEG; IQ, intelligence quotient; KSS, Kearns-Sayre syndrome; MELAS, mitochondrial encephalopathy, lactic acidosis and stroke-like episodes; MERRF, myoclonic epilepsy with ragged red fibers; MIDD, maternally-inherited diabetes and deafness; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; MSCAE, mitochondrial spinocerebellar ataxia and epilepsy; N/A, not applicable; PEO, progressive external ophthalmoplegia; PIQ, performance IQ; TMT, Trail-Making Test; VIQ, verbal IQ; WAIS, Wechsler Adult Intelligence Scale; WAIS-R, Wechsler Adult Intelligence Scale-IV; WMS-I, Wechsler Memory Scale-I; WMS-IV, Wechsler Memory Scale-IV; WMS-IV, Wechsler Adult Intelligence Scale-IV; WAIS-IV, Wechsler Adult Intelligence Scale-IV; WMS-R, Wechsler Memory Scale-Revised.
| Author       | n  | Age (years) | Sex | Genotype/phenotype | No evidence of CI | Developmental delay | Dementia | Cognitive impairment | Cognitive decline | Comprehension | Language | Arithmetic | Memory | Processing speed | Executive function | Visuospatial | Other |
|--------------|----|-------------|-----|--------------------|-------------------|---------------------|----------|----------------------|------------------|--------------|----------|------------|--------|-----------------|-------------------|---------------|-------|
| Mooguin      | 1  | 46          | M   | NK                 |                    |                     |          |                      |                  |              |           |            |        |                 |                   |              |       |
| Hughes et al.| 1  | 48          | F   |                    |                    |                     |          |                      |                  |              |           |            |        |                 |                   |              |       |
| Suzuki et al.| 1  | 31          | M   | NK                 |                    |                     |          |                      |                  |              |           |            |        |                 |                   |              |       |
| Finsterer et al. | 1  | 60          | F   | NK                 |                    |                     |          |                      |                  |              |           |            |        |                 |                   |              |       |
| Lewandowksa et al. | 2  | 36          | F   | NK                 | +                  |                     |          |                      | +                |              |           |            |        |                 |                   |              |       |
| Gopal & Anand | 1  | 20          | F   | NK                 |                    |                     |          |                      | +                |              |           |            |        |                 |                   |              |       |
| Holliday et al. | 3  | 28          | M   | NK                 | +                  |                     |          |                      |                  |              |           |            |        |                 |                   |              |       |
| Majamaa et al.| 4  | 27          | M   | 3241A-G            | +                  |                     |          |                      |                  |              |           |            |        |                 |                   |              |       |
| Suzuki et al. | 3  | 33-70       | M   | 3241A-G            | +                  |                     |          |                      |                  |              |           |            |        |                 |                   |              |       |
| Orandi et al. | 2  | 39          | F   | 3241A-G MELAS      |                    |                     | +        |                      |                  |              |           |            |        |                 |                   |              |       |
| Kishimoto et al. | 1  | 43          | M   | 3241A-G MELAS      |                    |                     | +        |                      |                  |              |           |            |        |                 |                   |              |       |
| Gilchrist et al. | 1  | 46          | F   | 3241A-G MELAS      |                    |                     |          |                      |                  |              |           |            |        |                 |                   |              |       |
| Di Trapani et al. | 1  | 27          | M   | 3241A-G MELAS      |                    |                     | +        |                      |                  |              |           |            |        |                 |                   |              |       |
| Huang et al. | 1  | 28          | M   | 3241A-G MELAS      |                    |                     | +        |                      |                  |              |           |            |        |                 |                   |              |       |
| Komata et al. | 1  | 60          | M   | 3241A-G MELAS      |                    |                     | +        |                      |                  |              |           |            |        |                 |                   |              |       |
| Shafiee et al. | 1  | 55          | F   | 3241A-G MELAS      |                    |                     | +        |                      |                  |              |           |            |        |                 |                   |              |       |
| Perna et al. | 2  | 18          | F   | 3241A-G MELAS      |                    |                     | +        |                      |                  |              |           |            |        |                 |                   |              |       |
| Yamashita et al. | 2  | 57          | F   | 3241A-G MELAS      |                    |                     | +        |                      |                  |              |           |            |        |                 |                   |              |       |
| Hill et al. | 1  | 29          | F   | 3241A-G MELAS      |                    |                     | +        |                      |                  |              |           |            |        |                 |                   |              |       |
| Emmanuclid et al. | 4  | 37          | F   | 3241A-G MELAS      |                    |                     | +        |                      |                  |              |           |            |        |                 |                   |              |       |
| Benning et al. | 1  | 63          | F   | 3241A-G MELAS      |                    |                     | +        |                      |                  |              |           |            |        |                 |                   |              |       |
| Collorone et al. | 1  | 47          | M   | 3241A-G MELAS      |                    |                     | +        |                      |                  |              |           |            |        |                 |                   |              |       |
| Prasad et al. | 1  | 29          | F   | 3241A-G MELAS      |                    |                     | +        |                      |                  |              |           |            |        |                 |                   |              |       |
| Sparacino et al. | 2  | 53          | M   | 3241A-G MELAS      |                    |                     | +        |                      |                  |              |           |            |        |                 |                   |              |       |
| Dubus et al. | 1  | 38          | F   | 3241A-G MELAS      |                    |                     | +        |                      |                  |              |           |            |        |                 |                   |              |       |
| Fang, Zhang & Zhang | 1  | 63          | F   | 3241A-G MELAS      |                    |                     | +        |                      |                  |              |           |            |        |                 |                   |              |       |
| Smith et al. | 1  | 61          | F   | 3241A-G MELAS      |                    |                     | +        |                      |                  |              |           |            |        |                 |                   |              |       |
| Author          | n  | Age (years) | Sex | Genotype/ phenotype | No evidence of CI | Global impairment | Cognitive difficulties | Cognitive domains |
|-----------------|----|-------------|-----|---------------------|------------------|------------------|----------------------|------------------|
| Isozumi et al.  | 1  | 50          | F   | MELAS               | +                | +                | +                    | +                |
| Tsujiya et al.  | 1  | 20          | F   | MELAS               | +                | +                | +                    | +                |
| Abaroni et al.  | 4  | <18         | M   | MELAS               | +                | +                | +                    | +                |
| Kaufman et al.  | 1  | 39          | M   | MELAS               | +                | +                | +                    | +                |
| Koller et al.   | 1  | 37          | M   | MELAS               | +                | +                | +                    | +                |
| Apostolova et al| 1  | 58          | F   | MELAS               | +                | +                | +                    | +                |
| Ducruex et al.  | 1  | 23          | M   | MELAS               | +                | +                | +                    | +                |
| Chu et al.      | 1  | 30          | M   | MELAS               | +                | +                | +                    | +                |
| De Luca et al.  | 1  | 29          | F   | MELAS               | +                | +                | +                    | +                |
| Magnac-         | 1  | 50          | M   | MELAS               | +                | +                | +                    | +                |
| Matis et al.    | 1  | 29          | M   | MELAS               | +                | +                | +                    | +                |
| Seyama et al.   | 1  | 38          | M   | 3243A-G             | +                | +                | +                    | +                |
| Rasenlen et al. | 1  | 37          | M   | 3243A-G             | +                | +                | +                    | +                |
| Dui et al.      | 1  | 60          | F   | 3243A-G             | +                | +                | +                    | +                |
| Dickerson et al.| 1  | 61          | F   | 13513G-A MELAS      | +                | +                | +                    | +                |
| Lindberg et al. | 1  | 44          | F   | 75127-C MELAS       | +                | +                | +                    | +                |
| Coon et al.     | 27 | 4-47        |      | 3260A-G MELAS       | +                | +                | +                    | +                |
| Wang et al.     | 3  | 22          | F   | 13513G-A MELAS      | +                | +                | +                    | +                |
| van den et al.  | 11 | 19-58       |      | 3243A-G MIDD        | +                | +                | +                    | +                |
| Chen et al.     | 1  | 48          | F   | MIDD                | +                | +                | +                    | +                |
| Lien et al.     | 6  | 8-74        |      | MIDD                | +                | +                | +                    | +                |
| Kobayashi et al. | 2  | 41-67       |      | 3243A-G MIDD        | +                | +                | +                    | +                |
| Herce et al.    | 1  | 50          | M   | 5521G-A MELAS/      | +                | +                | +                    | +                |
| Martin et al.   | 1  | 8           | M   | MERRF               | +                | +                | +                    | +                |
| Huang et al.    | 8  | 19-50       |      | MELAS/ MERRF        | +                | +                | +                    | +                |
| Han et al.      | 2  | 38          | F   | 8344A-G             | +                | +                | +                    | +                |
| Larson et al.   | 2  | 21          | M   | MERRF               | +                | +                | +                    | +                |
| Teixe et al.    | 1  | 52          | M   | MERRF               | +                | +                | +                    | +                |
| Taylor et al.   | 1  | 29          | F   | MERRF               | +                | +                | +                    | +                |
| Marques et al.  | 1  | 42          | F   | 611G-A MERRF        | +                | +                | +                    | +                |
| Young et al.    | 1  | 57          | F   | 586G-A              | +                | +                | +                    | +                |
| Morton et al.   | 1  | 31          | F   | 3252A-G             | +                | +                | +                    | +                |
| Aunaiya et al.  | 1  | 29          | M   | 3256C>T             | +                | +                | +                    | +                |
| Jukkoh et al.   | 1  | 55          | M   | MELAS               | +                | +                | +                    | +                |

(continued)
| Author          | n | Age (years) | Sex | Genotype/ phenotype | No evidence of CI | Global impairment | Cognitive impairment | Cognitive decline | Cognitive domains | Other (Table S6) |
|-----------------|---|-------------|-----|---------------------|-------------------|-------------------|---------------------|-------------------|-------------------|-----------------|
| Silvestri et al.| 1 | 36          | F   | 5540G-A             | +                 |                     |                     | +                 |                   |                 |
| Nelson et al.   | 1 | 45          | M   | 5540G-A             | + +               |                     |                     | +                 |                   |                 |
| Djordjevic et al.| 1 | 24          | F   | 5577C-T             | + +               |                     |                     | +                 |                   |                 |
| Scuderi et al.  | 1 | 30          | F   | 5614A-G             | +                 |                     |                     | +                 |                   |                 |
| Bodoki et al.   | 1 | 36          | F   | 5408A-G             | +                 |                     |                     | +                 |                   |                 |
| Koubi et al.    | 1 | 42          | F   | 8296A-G             | +                 |                     |                     | +                 |                   |                 |
| Houssaini et al.| 1 | 48          | F   | 8328G-A             | +                 |                     |                     | +                 |                   |                 |
| Seno et al.     | 1 | 31          | M   | 8367T-C             | + +               |                     |                     | +                 |                   |                 |
| Hanna et al.    | 1 | 36          | F   | 9935G-A             | +                 |                     |                     | +                 |                   |                 |
| Mertik et al.   | 1 | 55          | M   | 10155T-C ND3        | +                 |                     |                     | +                 |                   |                 |
| Taylor et al.   | 1 | 42          | M   | 10191T-C in ND3     | +                 |                     |                     | +                 |                   |                 |
| Deschauer et al.| 1 | 67          | M   | 1177C>A in ND4      | +                 |                     |                     | +                 |                   |                 |
| Coku et al.     | 1 | 35          | F   | 12276G-A            | +                 |                     |                     | +                 |                   |                 |
| Sarek et al.    | 1 | 21          | M   | 13042G-A            | +                 |                     |                     | +                 |                   |                 |
| Schiavello et al.| 1 | 26          | M   | 13042G-A            | +                 |                     |                     | +                 |                   |                 |
| Sikorska et al. | 1 | 17          | M   | 4042T>C & 9035T-C   | +                 |                     |                     | +                 |                   |                 |
| Corona et al.   | 4 | 27-64       |     | 4244G-A             | +                 |                     |                     | +                 |                   |                 |
| Santarelli et al.| 1 | 12          | F   | 8367G-A             | +                 |                     |                     | +                 |                   |                 |
| Virgilio et al. | 7 | 24-44       |     | 8363G-A             | +                 |                     |                     | +                 |                   |                 |
| Tsam et al.     | 14| 6-38        |     | 8997T-G             | +                 |                     |                     | +                 |                   |                 |
| Ateni et al.    | 5 | 27-62       |     | 8296A-G & 8303G-A   | +                 |                     |                     | +                 |                   |                 |
| Wei & Wang      | 1 | 26          | M   | m.9136T>C           | +                 |                     |                     | +                 |                   |                 |
| Shoffner et al. | 1 | 28          | M   | tRNA deletion 3271- | +                 |                     |                     | +                 |                   |                 |
| Debray et al.   | 1 | 18          | F   | 3402delC            | +                 |                     |                     | +                 |                   |                 |
| De Coo et al.   | 1 | 20          | M   | 4-bp deletion at 14737| +                 |                     |                     | +                 |                   |                 |
| Nishihara et al.| 1 | 60          | F   | 2-bp deletion in C12orf6 | +                 |                     |                     | +                 |                   |                 |
| Poci et al.     | 1 | 48          | F   | KSS                 | +                 |                     |                     | +                 |                   |                 |
| Van Goethem et al.| 1 | 18          | M   | POLG                | +                 |                     |                     | +                 |                   |                 |
| Manes et al.    | 1 | 48          | M   | POLG                | +                 |                     |                     | +                 |                   |                 |
| Luoini et al.   | 1 | 44          | F   | POLG                | +                 |                     |                     | +                 |                   |                 |
| Deshauer et al. | 1 | 28          | M   | POLG1               | +                 |                     |                     | +                 |                   |                 |
| Van Hoeve et al.| 1 | 71          | F   | POLG                | +                 |                     |                     | +                 |                   |                 |
| Martikainen et al.| 1 | 64          | F   | c.2993C>T & c.3550G-C in POLG | +     | +                 |                     | +                 |                   |                 |

(continued)
| Author          | n  | Age  | Sex | Genotype/phenotype            | Global impairment | Cognitive domains |
|-----------------|----|------|-----|-------------------------------|-------------------|------------------|
| Synofzik et al. | 2  | 32   | F   | W748S in POLG                 | No evidence of CI | Comprehension ++ |
|                 |    |      |     |                               | Developmental     | Language ++      |
|                 |    |      |     |                               | delay             | +                |
|                 |    |      |     |                               | Dementia          | +                |
|                 |    |      |     |                               | Cognitive        | Arithmetic +      |
|                 |    |      |     |                               | impairment        | Memory +          |
|                 |    |      |     |                               | Cognitive        | Processing       |
|                 |    |      |     |                               | decline           | speed +           |
|                 |    |      |     |                               |                   | Executive        |
|                 |    |      |     |                               |                   | function         |
|                 |    |      |     |                               |                   | Vissuospatial     |
|                 |    |      |     |                               |                   | +                |
| Hakonen et al.  | 2  | 31   | F   | W748S & E1143G in POLG        |                   | +                |
|                 |    |      |     |                               |                   | +                |
|                 |    |      |     |                               |                   | +                |
|                 |    |      |     |                               |                   | +                |
|                 |    |      |     |                               |                   | +                |
| Hansen et al.   | 1  | 23   | F   | p.A467T & p.W748S in POLG     |                   | +                |
|                 |    |      |     |                               |                   | +                |
|                 |    |      |     |                               |                   | +                |
| Hudson et al.   | 2  | 41-74|M     | POLG                          |                   | +                |
|                 |    |      |     |                               |                   | +                |
|                 |    |      |     |                               |                   | +                |
| Melberg et al.  | 2  | 60-61| F   | POLG                          |                   | +                |
|                 |    |      |     |                               |                   | +                |
|                 |    |      |     |                               |                   | +                |
|                 |    |      |     |                               |                   | +                |
| Beu et al.      | 2  | 48   | M   | c.673C>T                      |                   | +                |
|                 |    |      |     |                               |                   | +                |
|                 |    |      |     |                               |                   | +                |
|                 |    |      |     |                               |                   | +                |
| Komulainen et al.| 2  | 78-86| M   | c.3447G>A                     |                   | +                |
|                 |    |      |     |                               |                   | +                |
|                 |    |      |     |                               |                   | +                |
|                 |    |      |     |                               |                   | +                |
|                 |    |      |     |                               |                   | +                |
| Rantamäki et al.| 4  | 19-84| M   | W748S & A467T in POLG         |                   | +                |
|                 |    |      |     |                               |                   | +                |
| Echantier et al.| 2  | 81-82| M   | RG34W in PEO1                  |                   | +                |
|                 |    |      |     |                               |                   | +                |
| Laguma et al.   | 3  | 42-64| M   |                               |                   | +                |
|                 |    |      |     |                               |                   | +                |
| Gebus et al.    | 3  | 58   | M   | W748S & R627Q in POLG         |                   | +                |
|                 |    |      |     |                               |                   | +                |
| Bianco et al.   | 1  | 24   | M   | m.3460G>A                     |                   | +                |
|                 |    |      |     |                               |                   | +                |
| Morimoto et al. | 1  | 37   | F   | LHON                          |                   | +                |
| Hirano et al.   | 1  | 40   | M   | MNGIE                         |                   | +                |
| Carod-Artal et al.| 1 | 35   | M   | MNGIE                         |                   | +                |
| Marti et al.    | 1  | 61   | F   | MNGIE                         |                   | +                |
| Baris et al.    | 1  | 18   | F   | MNGIE                         |                   | +                |
| Spiegler et al. | 4  | 7-20 | F   | MNGIE                         |                   | +                |
| Schuepbach et al.| 3 | 20-22| F   | MNGIE                         |                   | +                |
| Blondon et al.  | 3  |      |     | MNGIE                         |                   | +                |
| Massa et al.    | 1  | 67   | F   | MNGIE                         |                   | +                |

*Family study (+, deficit in ≥1 family member). +, comprehension including ability to follow commands; ++, language, including reading and writing; CI, cognitive impairment; F, female; KSS, Kearns-Sayre syndrome; LHON, Leber's hereditary optic neuropathy; LS, Leigh syndrome; M, male; MELAS, mitochondrial encephalopathy, lactic acidosis and stroke-like episodes; MERRF, myoclonic epilepsy with ragged red fibers; MIDD, maternally-inherited diabetes and deafness; MNGIE, mitochondrial neurogastrointestinal encephalomyopathy; NK, not known; PEO, progressive external ophthalmoplegia.
Larger-scale, systematic investigations of cognition

A total of 12 studies conducted systematic investigations of cognition in mitochondrial disease (Table 1). Three studies investigated cognition in patients with m.3243A>G. At initial assessment, Majamaa-Voltti et al. [13] identified 16 patients as cognitively impaired (50%). In the whole sample, executive dysfunction was commonly observed, with 14 patients (14/32) failing to complete the task. Cognitive progression was rare, although data were not provided to corroborate this.

Kaufmann et al. [14] demonstrated that their fully symptomatic patient group (n = 31) not only performed worse than the asymptomatic/partially symptomatic group but also showed progressively worse cognition over time, whereas the asymptomatic/partially symptomatic group remained stable. However, specific assessments and results of cognitive domains were not reported. Furthermore, high dropout rates were evident between years 1 and 4, limiting the generalizability of results over time.

Kraya et al. [15] found that patients performed significantly worse than controls on measures of visuoconstruction, Trail-Making Test (TMT) visual and divided attention, set-switching/inhibition and verbal fluency, but not on other measures of executive function, working/visual memory. Higher lesion load correlated with worse attention, visuoconstruction, list-learning ability and verbal fluency. Increasing symptom severity (measured by Newcastle Mitochondrial Disease Adult Scale [43] correlated with worsening attention, planning, verbal fluency and list learning.

One study investigating cognition in patients in association with maternally-inherited diabetes and deafness (MIDD) (m.3243A>G:9, m.14709T>G:2) [16] found executive functioning and visual memory deficits. The authors suggested that visual memory impairment may be caused by executive dysfunction, particularly as verbal memory was intact using a task that minimized executive function load. Although cognitive deficits were found in patients with MIDD, no cognitive deficit was severe enough to fit dementia

### Table 3: Prevalence of cognitive difficulties reported by review articles

| Author | Phenotype | n  | Cognitive difficulties |
|--------|-----------|----|-----------------------|
| Goto et al. | MELAS | 40 | 65% showed cognitive impairment |
| Hirano et al. | MELAS | 69 | Dementia reported in 90% of cases Learning disability in 60% of cases |
| Damian et al. | MELAS | 21 | Dementia/cognitive impairment in 5/21 cases |
| Chinnery et al. | MELAS | 111 | 27% of cases presented with dementia |
| Majamaa et al. | MELAS | 11 | 4/11 patients showed cognitive decline |
| Suzuki et al. | m.3243A>G | 113 | 7.1% showed cognitive impairment3.6% presented with dementia |
| Murakami et al. | m.3243A>G | 14 | Current cognitive decline in 6/8 patients with prior diagnosis of diabetes (75%) and 0/6 without prior diagnosis of diabetes |
| Chae et al. | MELAS | 18 | Learning disability reported in 50% of cases |
| Sproule & Kaufmann | MELAS | 45 | Memory problems reported in 71% of cases |
| Lorenzoni et al. | MELAS | 10 | Developmental delay reported in 1/10 patientsDementia present in 5/10 patients |
| Ma et al. | MELAS | 47 | 33/47 probands (70.2%) showed cognitive impairment |
| Hammons et al. | MERRF | 18 | Dementia in 22% of cases |
| Ozawa et al. | MERRF | 10 | Cognitive deterioration in 50% of cases |
| Chinnery et al. | MERRF | 55 | 25% of cases presented with dementia |
| Sinha et al. | MERRF | 10 | Cognitive decline in 7/10 patients |
| Lorenzoni et al. | MERRF | 6 | 6/6 had normal early development. 2/6 presented with of dementia |
| Mancuso et al. | MERRF | 34 | 2/34 presented with cognitive involvement (6%) |
| Pavlikis et al. | MELAS/MERRF/KSS | 97 | 9/11 MELAS, 11/16 MERRF, 34/70 KSS presented with dementia |
| Kambatta et al. | KSS | 35 | 11/35 presented with cognitive decline |
| Wray et al. | KSS | 8 | 4/8 presented with cognitive impairment |
| Van Goethem et al. | Multiple deletions | 8 | Unspecified number with mild cognitive impairment |
| Winterthun et al. | Multiple deletions | 6 | 5/6 patients exhibited cognitive dysfunction |
| Hakonen et al. | Multiple deletions | 6 | Mild to moderate cognitive impairment in 74% of cases |
| Horvath et al. | Multiple deletions | 19 | Early-onset dementia in 11% of cases |
| Tzoulis et al. | Multiple deletions | 26 | Suspected mild cognitive impairment in 8 patients, confirmed mild cognitive impairment in 4 patients |
| Wong et al. | Multiple deletions | 61 | Developmental delay or dementia reported in 66% of patients |
| Van Hove et al. | Multiple deletions | 56 | Memory loss reported in 5% of patients |
| Naimi et al. | Multiple deletions and depletions | 15 | 1/15 presented cognitive impairment |
| Jaksch et al. | Multiple point mutations | 16 | 8/16 patients from 7 families presented with cognitive impairment |

References available in Appendix S1. KSS, Kearns-Sayre syndrome; MELAS, mitochondrial encephalopathy, lactic acidosis and stroke-like episodes; MERRF, myoclonic epilepsy with ragged red fibers.
criteria, as demonstrated by Mini-Mental State Examination scores within the normal range. When compared with type 1 diabetics, patients with MIDD showed worse attention, working memory and abstract reasoning.

Two studies explored cognition in patients with large-scale single mitochondrial DNA deletions. Turconi et al. [7] found no impairment in FSIQ; however, PIQ was lower than VIQ. Specific deficits were also found in short-term memory and visuospatial abilities. Bosbach et al. [17] observed no general intellectual decline or dementia compared with controls (Table 1). However, specific deficits were found in executive function, attention and visual construction. Examination of quality of life demonstrated differences from the norm on a number of measures; however, subjective wellbeing and limitations in social activities did not differ significantly.

Only one study has investigated cognition in patients with POLG-related mitochondrial disease (N:8; mitochondrial spinocerebellar ataxia and epilepsy phenotype). Gramstad et al. [18] found a mean FSIQ of 77.4 (moderate impairment) and all patients showed significantly better VIQ than PIQ. This led the authors to suggest reduced cognitive functioning, although five patients scored within the normal range. Retesting one patient 3 years later showed declines in FSIQ, VIQ and PIQ. A trend of lower IQ with increasing age at assessment and duration of epilepsy was noted, suggesting a profile of progressive cognitive decline. Unfortunately, no statistical analyses were reported to corroborate these claims.

Five systematic investigations of cognition have included patients with variable genotypes. The assessments of Lang et al. [19] showed that patients with KSS performed best and those with MELAS performed worst (PEO, 8; MELAS, 4; KSS, 3). Four out of 15 patients performed within the normal range (KSS, 2; PEO, 2) and seven patients were impaired on more than half of all subtests (PEO, 3; MELAS, 4). Patients showed the highest number of deficits on TMT, suggesting difficulties in tasks tapping executive functions, although patient scores may have been affected on the TMT by ophthalmoplegia or motor speed difficulties (not considered by the authors). Over half of all patients demonstrated memory impairment. Five patients (MELAS, 3; PEO, 2) were diagnosed with dementia. Although patients with MELAS were more severely affected than patients with Kearns-Sayre syndrome KSS or progressive external ophthalmoplegia PEO, there appeared to be no readily identifiable pattern of deficits.

Montirosso et al. [20] demonstrated performance and reaction time for patients (Table 1) and controls on both tasks. However, electroencephalographic activity showed a delayed N2 component, reflecting early slowing of information processing, and reduced P3 amplitude, highlighting dysfunction in post-perceptual resetting and updating of information. These results indicated processing-speed problems at a neural level, in the absence of cognitive impairment.

Kaufmann et al. [21] completed comprehensive neuropsychological testing on 91 individuals from 34 m.3243A>G families and 15 individuals from two m.8344A>G families. They identified progressively worse neuropsychological performance in asymptomatic, oligosymptomatic and symptomatic groups, which correlated with estimates of brain ventricular lactate. Cerebral lactate correlated not only with global cognitive functioning, but also with tests specifically measuring frontal brain regions, which are rarely affected by stroke-like episodes. Furthermore, m.3243A>G probands showed lower neuropsychological test scores than m.8344A>G probands, suggesting genotypic variance in cognitive profiling. Although this study assessed a large group of individuals, information about the specific neuropsychological tests and their results was limited.

Inczedy-Farkas et al. [22] found average FSIQ within normal limits, and lower PIQ than VIQ scores. Pronounced PIQ deficits were observed in processing speed and visuospatial functioning. Despite average FSIQ scores, the authors reported a general pattern of moderate to severe cognitive impairment. Memory performance was variable, with recall being differentially more impaired than encoding/learning and retroactive (but not proactive) interference. Although data from 13 control participants were collected, parametric statistical comparisons were not made with patients due to genetic heterogeneity. Comparisons of effect sizes were used, however, criteria of magnitude were not defined.

Our group [23] showed that patients had mild to moderate pre-morbid cognitive impairment, but substantial impairment in FSIQ, as well as distinct domains of verbal comprehension, perceptual reasoning, working memory, processing speed and memory. It was not clear whether the executive dysfunction reported in this sample was caused by frontal difficulties, or simply slower decision-making. These results were corroborated by significant differences from controls, except for memory, where performance was similar. This suggests that, in this sample, memory was intact when pre-morbid cognition was controlled for. Cognitive decline appeared slow and was unlikely in the short-term when other disease-specific factors remained stable.

**Discussion**

This is the first review to report a systematic search of the literature describing mitochondrial disease and
cognition. Small sample sizes, genotypic variability and the breadth and depth of assessments undertaken introduced significant heterogeneity across studies precluding a meta-analysis, as any interpretation would not be meaningful and could introduce significant bias. As such, our results provide a narrative synthesis of the literature.

Examination of the case literature commonly revealed dementia, cognitive impairment and cognitive decline, as well as other memory problems in patients with mitochondrial disease. Difficulties with language and attention were frequently reported, as well as personality and mood disorders, whereas executive dysfunction was rarely reported, although this was identified more frequently with detailed assessment. Reviews of medical reports provided broad diagnoses of impairment, and dementia, learning disability, cognitive impairment and cognitive decline were reported as common. It is difficult to know whether the identified impairments represent the common difficulties experienced by patients with mitochondrial disease, or a more extreme end of functioning of severely affected individuals who have warranted clinical evaluation and intervention.

Systematic studies that have reported the results of neuropsychological testing are much less indicative of general cognitive impairment and dementia than is suggested by the findings of case reports and review articles. These results instead provide strong support for a profile of focal cognitive deficits, rather than global difficulties, in areas such as visuospatial functioning, memory, attention, processing speed and executive functions. In terms of clinical care, detailed descriptions of focal cognitive difficulties are much more beneficial, as this information can feed into the development of management strategies. Further difficulties arise with understanding the cognitive challenges faced by patients with mitochondrial disease as a group because the literature does not currently apply a uniform classification system for the severity of cognitive deficit. There has also been substantial variability in the range of cognitive assessments used across systematic research studies identified by this review and little discussion about suitability of measures. Consensus on this matter is challenging due to the clinical heterogeneity found within this group of diseases; however, consideration must be given to the physical limitations of the sample in question and how these might affect performance. As an example, performance on standard versions of the TMT [44] might be affected by ocular movements across the test page, ataxia, muscular weakness and fatigue.

Although the evidence is not strong enough to substantiate distinct genotype-specific cognitive profiles, research considering genotypic variation in cognitive functioning has postulated differences [19,21]. However, with the exception of Kaufmann and colleagues [21], most systematic investigations have remained small, and clinical profiles and/or genetic mutations have varied considerably, limiting the ability to generalize these findings to the wider population of patients with mitochondrial disease. Currently, understanding about the aetiology and progression of cognitive dysfunction is limited. Virgilio and colleagues [45] found significantly higher mutation load in patients with a severe clinical phenotype than mild/moderate and asymptomatic phenotypes, but they did not explore the link with cognitive functioning. More recently, our group [23] showed that disease severity (measured by Newcastle Mitochondrial Disease Adult Scale and urinary heteroplasmy), rather than genotype, is a stronger predictor of cognitive abilities. Research has also shown links between severity of other symptoms related to mitochondrial disease (e.g. cerebral lactate, nuclear factors) and general cognitive performance [21,46], but specific cognitive domains have not been robustly investigated. As highlighted in Table 1, neuroimaging findings (where available) vary greatly across studies. The current literature does not clarify whether focal cognitive deficits and general cognitive impairment/dementia are part of a continuum of symptoms varying in severity, and how these relate to focal lesions and generalized atrophy in patients, nor how underlying mutation load accounts for these changes. Unfortunately, neuroimaging data are too scarce at present to determine the association between cognitive difficulties and imaging results. Another important consideration when interpreting cognitive dysfunction is additional disease factors that may exacerbate cognitive performance on any given day (e.g. fatigue, mental health difficulties). Unfortunately, no systematic research to date has addressed this.

Information about prognosis is also currently limited, as most research investigating disease-specific factors related to cognitive impairment has taken measurements at a single time point. Samples in longitudinal studies, to date, remain small and require validation. Kaufmann et al. [14] found worse initial performance and greater progression of general cognitive difficulties over a 4-year period in fully symptomatic vs. asymmetrically partially symptomatic (relatives) patients with m.3243A>G mutations. Conversely, our group showed no change over 18 months when other disease-specific factors remained stable, although decline between premorbid and current cognition over the longer term was predicted by disease severity. Samples in longitudinal research remain small, and greater follow-up duration is required to validate results. This is essential for understanding disease progression and trajectories of change, in order to apply this to clinical monitoring and subsequent health planning.
Conclusions

From this systematic review, patients with mitochondrial disease face high rates of cognitive difficulties, in areas including (but not limited to) visuospatial functioning, memory, attention, processing speed and executive functions. However, there is a great deal of variation in the specific deficits reported, and the pattern and progression are not fully understood. In order to advance this field, larger samples of well-characterized patients should be assessed using comprehensive, systematic measures tapping different domains of cognitive functioning, including real-time functional imaging during assessments.

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Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. OVID Medline electronic search term strategy (1946 to 12 November 2018).

Table S2. PsycINFO electronic search term strategy (1806 to November Week 1 2018).

Table S3. Embase electronic search term strategy (1974 to 12 November 2018).

Table S4. PubMed electronic search term strategy (1970–2018).

Table S5. Web of Knowledge electronic search term strategy (1970–2018).

Table S6. Additional impairments found in patients with mitochondrial disease experience who also experience cognitive difficulties.

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