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# Nuclear Gene-Encoded Leigh Syndrome Spectrum Overview

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## Summary

The purpose of this overview is to increase the awareness of clinicians regarding genetic causes of nuclear gene-encoded Leigh syndrome spectrum (LSS), management, especially treatable disorders, and relevant genetic counseling issues. The following are the goals of this overview.

### Goal 1

Describe the clinical characteristics of nuclear gene-encoded LSS.

### Goal 2

Review the genetic causes of nuclear gene-encoded LSS.

### Goal 3

Provide an evaluation strategy to identify the genetic cause of nuclear gene-encoded LSS in a proband (when possible).

### Goal 4

Review management of nuclear gene-encoded LSS, especially treatable disorders.

### Goal 5

Inform genetic counseling of family members of an individual with nuclear gene-encoded LSS.

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# 1. Clinical Characteristics of Nuclear Gene-Encoded Leigh Syndrome Spectrum

**Clinical manifestations of nuclear gene-encoded Leigh syndrome spectrum.** The term Leigh syndrome spectrum comprises both Leigh syndrome and Leigh-like syndrome.

**Leigh syndrome** (or subacute necrotizing encephalomyelopathy) is characterized by decompensation (often with elevated lactate levels in blood and/or cerebrospinal fluid [CSF]) during an intercurrent illness. It is typically associated with psychomotor retardation or regression, often followed by transient or prolonged stabilization or even improvement, but inevitably resulting in eventual progressive neurologic decline, typically occurring in stepwise decrements.

Neurologic manifestations include hypotonia, spasticity, movement disorders (including chorea), cerebellar ataxia, and peripheral neuropathy.

Extraneurologic manifestations may include hypertrophic cardiomyopathy, hypertrichosis, anemia, renal tubulopathy, liver involvement, ptosis, and muscle weakness.

Onset is typically between ages three and 12 months, frequently following a viral infection. About 50% of affected individuals die by age three years, most often as a result of respiratory or cardiac failure.

Later onset (including in adulthood) and long-term survival may occasionally occur.

Life expectancy and extraneurologic manifestations appear to be related, at least in part, to the underlying genetic defect [Wedatilake et al 2013, Rahman et al 2017].

**"Leigh-like syndrome"** is often used when clinical and other features strongly suggest Leigh syndrome but do not fulfil the stringent diagnostic criteria because of atypical or normal neuroimaging, lack of evidence of abnormal energy metabolism, atypical neuropathology (variation in the distribution or character of lesions or with the additional presence of unusual features such as extensive cortical destruction), and/or incomplete evaluation. The term Leigh syndrome spectrum comprises both Leigh syndrome and Leigh-like syndrome.

**Neuropathologic features of Leigh syndrome.** Leigh syndrome was originally defined in 1951 by characteristic neuropathologic features including multiple focal symmetric necrotic lesions in the basal ganglia, thalamus, brain stem, dentate nuclei, and optic nerves. Histologically, lesions have a spongiform appearance and are characterized by demyelination, gliosis, and vascular proliferation. Although neuronal loss can occur, typically the neurons are relatively spared. The advent of magnetic resonance imaging (MRI) has made it possible to establish the diagnosis by neuroimaging, and thus postmortem examination is now rarely performed outside of a research context.

**Establishing the diagnosis of nuclear gene-encoded Leigh syndrome spectrum** requires the following [Rahman et al 1996, Lake et al 2016]:

- Characteristic clinical presentation
- Bilateral symmetric $T_2$-weighted hyperintensities in the basal ganglia and/or brain stem on brain MRI
- Evidence of abnormal energy metabolism based on one or more of the following:
  - Elevated lactate in blood and/or CSF
  - Other evidence of disturbed oxidative phosphorylation or pyruvate dehydrogenase activity
- Identification of pathogenic variant(s) in a specific nuclear gene (See Section 2.)

**Differential diagnosis of nuclear gene-encoded Leigh syndrome spectrum** includes mitochondrial DNA-associated Leigh syndrome (see Mitochondrial DNA-Associated Leigh Syndrome and NARP and Mitochondrial Disorders Overview), nonmitochondrial genetic causes of bilateral striatal necrosis (e.g., heterozygous

pathogenic variant in *ADAR*, biallelic pathogenic variants in *NUP62*, or heterozygous pathogenic variant in *RANBP2*), and acquired nongenetic causes such as viral encephalopathy.

# 2. Causes of Nuclear Gene-Encoded Leigh Syndrome Spectrum

Pathogenic variants in more than 80 nuclear genes have been associated with autosomal recessive, autosomal dominant, and X-linked nuclear gene-encoded Leigh syndrome spectrum (LSS), as summarized below [Rahman et al 2017].

## Autosomal Recessive Leigh Syndrome Spectrum

Autosomal recessive nuclear gene-encoded LSS (Table 1) includes:

- Pathogenic variants in genes encoding proteins needed for:
  - OXPHOS enzyme activity and assembly;
  - Mitochondrial DNA maintenance (see Mitochondrial DNA Maintenance Defects Overview) and gene expression;
  - Cofactor biosynthesis (lipoic acid and coenzyme $Q_{10}$);
  - Mitochondrial membrane lipid remodeling, quality control, and dynamics;
  - Pyruvate dehydrogenase (see Primary Pyruvate Dehydrogenase Complex Deficiency Overview), biotinidase, and B vitamin transport and metabolism.
- Organic acidemias with accumulation of metabolites leading to secondary OXPHOS dysfunction.

**Table 1.** Autosomal Recessive Leigh Syndrome Spectrum

| Gene | Proportion of AR LSS Caused by Biallelic Variants in Gene | Distinguishing Clinical & Laboratory Features | | | Reference |
|---|---|---|---|---|---|
| | | Neurologic [1] | Other | Laboratory Findings | |
| **Complex I-deficient Leigh syndrome spectrum [2]** | | | | | |
| *NDUFS1* | <5% | Cystic leukoencephalopathy | HCM | Complex I deficiency (mb) | Bénit et al [2001] |
| *NDUFS2* | <5% | | HCM | | Loeffen et al [2001] |
| *NDUFS3* | <5% | | | | Bénit et al [2004] |
| *NDUFS4* | ~5% | | HCM | | Budde et al [2000] |
| *NDUFS7* | <5% | | | | Triepels et al [1999] |
| *NDUFS8* | <5% | Leukodystrophy | HCM | | Loeffen et al [1998] |
| *NDUFV1* | <5% | Cystic leukoencephalopathy | | | Bénit et al [2001] |
| *NDUFV2* | 1 person | Spasticity | Optic atrophy; HCM | | Cameron et al [2015] |
| *NDUFA2* | 1 family | | HCM | | Hoefs et al [2008] |
| *NDUFA9* | 1 family | | | | van den Bosch et al [2012] |
| *NDUFA10* | 1 family | | HCM | | Hoefs et al [2011] |
| *NDUFA12* | 1 family | Severe dystonia | Hypertrichosis | | Ostergaard et al [2011] |

*Table 1. continued from previous page.*

| Gene | Proportion of AR LSS Caused by Biallelic Variants in Gene | Distinguishing Clinical & Laboratory Features | | | Reference |
|---|---|---|---|---|---|
| | | Neurologic [1] | Other | Laboratory Findings | |
| *NDUFAF2* | <5% | MRI: symmetric lesions in mamillothalamic tracts, substantia nigra / medial lemniscus, medial longitudinal fasciculus, & spinothalamic tracts | | | Barghuti et al [2008] |
| *NDUFAF4* | 1 person | Seizures | | Complex I deficiency (fbs) | Baertling et al [2017] |
| *NDUFAF5* (*C20orf7*) | <5% | | FILA (1 person); survival into 20s in 1 family | Complex I deficiency (mb) | Sugiana et al [2008], Gerards et al [2010] |
| *NDUFAF6* (*C8orf38*) | 1 family | | | | Pagliarini et al [2008] |
| *FOXRED1* | <5% | Seizures & myoclonus | Slowly progressive; survival possible into 20s | | Calvo et al [2010], Fassone et al [2010] |
| *NUBPL* | <1% | Characteristic MRI changes: predominant abnormalities of cerebellar cortex, deep cerebral white matter, & corpus callosum | | | Calvo et al [2010] |
| *NDUFAF8* (*C17ORF89*) | 3 persons | Infantile spasms; hypsarrhythmia; periventricular cystic encephalomalacia | | | Floyd et al [2016], Alston et al [2020] |
| *TIMMDC1* | 1 person | Cerebellar syndrome; basal ganglia abnormalities (CT); subsequent MRI unremarkable | | | Kremer et al [2017] |
| **Complex II-deficient Leigh syndrome spectrum [2]** | | | | | |
| *SDHA* | <5% | | Course may be indolent w/survival into adulthood; ±HCM. | Complex II deficiency (mb); succinate peak (brain MRS) | Bourgeron et al [1995], Pagnamenta et al [2006] |
| *SDHAF1* | <5% | Leukoencephalopathy on MRI (1 person w/ neuropathologic LS) | | | Ohlenbusch et al [2012] |
| **Complex III-deficient Leigh syndrome spectrum [2]** | | | | | |

*Table 1. continued from previous page.*

| Gene | Proportion of AR LSS Caused by Biallelic Variants in Gene | Distinguishing Clinical & Laboratory Features | | | Reference |
|---|---|---|---|---|---|
| | | Neurologic [1] | Other | Laboratory Findings | |
| *UQCRQ* | 1 family | | Slowly progressive; survival into 30s | Complex III deficiency (mb) | Barel et al [2008] |
| *TTC19* | <5% | Severe olivopontocerebellar atrophy | Slowly progressive; survival into 20s/30s | | Ghezzi et al [2011] |
| *BCS1L* | <5% | SNHL | Proximal renal tubulopathy, hepatic involvement, pili torti | | de Lonlay et al [2001] |
| **Complex IV-deficient Leigh syndrome spectrum [2]** | | | | | |
| *NDUFA4* | 1 family | Epilepsy; sensory axonal peripheral neuropathy | Slowly progressive; survival into 20s/30s | Complex IV deficiency (mb) | Pitceathly et al [2013] |
| *COX8A* | 1 person | Seizures; hypotonia; spasticity | | | Hallmann et al [2016] |
| *SURF1* | ~50% of complex IV-deficient LS (~10% of all LS) | Developmental regression (71%); nystagmus + ophthalmoplegia (52%); movement disorder (52%) | Hypertrichosis (48%); median survival 5.4 yrs | Complex IV deficiency (more severe fbs than mb) | Wedatilake et al [2013] |
| *COX10* | <5% | SNHL | HCM; anemia (due to defect of mt heme A biosynthesis) | Complex IV deficiency (mb) | Antonicka et al [2003] |
| *COX15* | <5% | Seizures | HCM | | Oquendo et al [2004] |
| *SCO2* | <5% | | HCM | | Joost et al [2010] |
| *LRPPRC* [3] | <5% | Metabolic & neurologic (stroke-like) crises | Survival 5 days - 30 yrs; median age at death 1.6 yrs | | Mootha et al [2003], Debray et al [2011] |
| *TACO1* | <5% | Cognitive dysfunction; dystonia; visual impairment; periventricular white matter lesions | Late onset (4-16 yrs); slowly progressive | | Weraarpachai et al [2009], Oktay et al [2020] |
| *PET100* [4] | <5% | Prominent seizures | Survival to 20s (50%) | | Lim et al [2014] |
| *PET117* | 1 family | | | | Renkema et al [2017] |
| **Complex V-deficient Leigh syndrome [2]** | | | | | |
| *ATP5MD* [5] | <1% | | | ↓ ATP synthesis (fbs) | Barca et al [2018] |
| **Leigh syndrome assoc w/defects of mitochondrial DNA maintenance** | | | | | |

*Table 1. continued from previous page.*

| Gene | Proportion of AR LSS Caused by Biallelic Variants in Gene | Distinguishing Clinical & Laboratory Features | | | Reference |
|---|---|---|---|---|---|
| | | Neurologic [1] | Other | Laboratory Findings | |
| *POLG* | <1% | Roving eye movements; prominent seizures; more often presents as Alpers or other epilepsy syndromes than LSS | Hepatocerebral disease | Multiple RCE deficiencies; isolated complex IV deficiency (rare) | Taanman et al [2009] |
| *SUCLA2* [6] | <5% | Hypotonia; muscle atrophy; hyperkinesia; severe SNHL | Growth retardation | MMA; multiple RCE deficiencies | Elpeleg et al [2005], Ostergaard et al [2007] |
| *SUCLG1* | <1% | Severe myopathy | Recurrent hepatic failure | | Van Hove et al [2010] |
| *FBXL4* | <5% | Seizures | Facial dysmorphism, skeletal abnormalities, poor growth, GI dysmotility, renal tubular acidosis | Multiple RCE deficiencies | Shamseldin et al [2012] |
| **Leigh syndrome assoc w/defects of mitochondrial gene expression** | | | | | |
| *TRMU* | 1 person | LS reported in 1 person | Usually causes benign reversible liver failure w/o neurologic symptoms | Multiple RCE deficiencies | Taylor et al [2014] |
| *GTPBP3* | <1% | | HCM | | Kopajtich et al [2014] |
| *MTFMT* | <5% | Cystic leukoencephalopathy in some & typically shows a milder clinical course | May be slowly progressive in some, w/survival into 20s | | Tucker et al [2011], Hayhurst et al [2019] |
| *EARS2* | <5% | Leukoencephalopathy w/ thalamus & brain stem involvement & ↑ lactate (MRI); MRI changes may improve w/time. | Improvement can occur; liver failure in some cases. | | Martinelli et al [2012] |
| *FARS2* | <1% | Severe epilepsy; Alpers neuropathology in some cases | | Isolated complex IV defic in 1 person; enzymology not performed in any others | Shamseldin et al [2012] |
| *IARS2* | 1 person | LS → death at 18 mos in 1 child; SNHL; peripheral sensory neuropathy | Cataracts, growth hormone defic, & skeletal dysplasia in 3 adults | Enzymology not performed | Schwartzentruber et al [2014] |

*Table 1. continued from previous page.*

| Gene | Proportion of AR LSS Caused by Biallelic Variants in Gene | Distinguishing Clinical & Laboratory Features | | | Reference |
|---|---|---|---|---|---|
| | | Neurologic [1] | Other | Laboratory Findings | |
| *NARS2* [7] | <1% | SNHL | | Multiple RCE deficiencies | Simon et al [2015] |
| *PTCD3* | 1 person | | | | Borna et al [2019] |
| *MRPS34* | <1% | | Microcephaly | | Lake et al [2017] |
| *GFM1* | <1% | Axial hypotonia; spasticity; refractory seizures | Progressive hepato-encephalopathy in some cases | | Valente et al [2007] |
| *GFM2* | <1% | | | | Fukumura et al [2015] |
| *TSFM* | <1% | Juvenile onset; ataxia; neuropathy; optic atrophy | Growth retardation; HCM | | Ahola et al [2014] |
| *MTRFR* (*C12orf65*) | <1% | Ophthalmoplegia; optic atrophy; axonal neuropathy | Relatively slow disease progression | Multiple RCE deficiencies (fbs) | Antonicka et al [2010] |
| *PNPT1* | <1% | Choreoathetosis & dyskinesia; also isolated SNHL | Severe hypotonia | Complex III+IV defic in liver in 1 person (nml activ in mb & fbs) | Vedrenne et al [2012] |
| **Leigh syndrome assoc w/defects of mitochondrial cofactor biosynthesis** | | | | | |
| *PDSS2* [8] | <1% | Refractory seizures | Nephrotic syndrome | Complexes I+III, II+III, & coenzyme $Q_{10}$ defic (mb) | López et al [2006] |
| *COQ9* [8] | <1% | Refractory seizures | Antenatal onset; IUGR; HCM | | Smith et al [2018] |
| *LIAS* | <1% | Seizures w/burst suppression (EEG) | Mild HCM | Combined defic of PDH + glycine cleavage enzyme, ↑ urine & plasma glycine, deficient lipoylated proteins (western blot) | Baker et al [2014] |
| *LIPT1* | 1 person | 1 person w/LS; 2 w/FILA | Liver dysfunction | ↑ glutamine & proline, ↓ levels of lysine & BCAAs & *normal* glycine (unlike other lipoic acid synthesis defects); severe ↓ of PDH & α-KGDH activ & strongly ↓ BCKDH activ (fbs); nml RCE activ | Soreze et al [2013], Tort et al [2014] |
| **Leigh syndrome assoc w/defects of mitochondrial membrane lipids, dynamics, & quality control** | | | | | |

*Table 1. continued from previous page.*

| Gene | Proportion of AR LSS Caused by Biallelic Variants in Gene | Distinguishing Clinical & Laboratory Features | | | Reference |
|---|---|---|---|---|---|
| | | Neurologic [1] | Other | Laboratory Findings | |
| *SERAC1* | <5% | SNHL | MEG(H)DEL syndrome; may have liver involvement in infancy that later normalizes | 3-methylglutaconic aciduria, variable RCE deficiencies | Wortmann et al [2012], Maas et al [2017] |
| *MFF* | <1% | Seizures; optic atrophy; peripheral neuropathy | | Multiple RCE deficiencies; elongated mitochondria & peroxisomes (EM) | Koch et al [2016] |
| *SLC25A46* | 2 persons | Seizures; spastic diplegia; optic atrophy | | ↑ mt connectivity | Abrams et al [2015], Janer et al [2016] |
| *CLPB* | <1% | | Cataract, neutropenia, HCM | 3-methylglutaconic aciduria, multiple RCE deficiencies | Saunders et al [2015] |
| **Leigh syndrome assoc w/ primary pyruvate dehydrogenase complex deficiency** | | | | | |
| *PDHB* [8] | <1% | CC agenesis/hypoplasia | | PDH deficiency (fbs) | Quintana et al [2009] |
| *DLAT* [8] | <1% | Episodic dystonia | | | Head et al [2005] |
| *DLD* [8] | <1% | Episodic encephalopathy | Hypoglycemia, ketoacidosis, liver failure | ↑ plasma BCAAs, PDH deficiency (fbs) | Grafakou et al [2003], Quinonez et al [2013] |
| *PDHX* [8] | <1% | Thin CC/CC agenesis; status epilepticus late in disease (teens/20s) | | PDH deficiency (fbs) | Schiff et al [2006] |
| **Leigh syndrome assoc w/defects of B vitamin transport & metabolism** | | | | | |
| *SLC25A19* [9] | <1% | Bilateral striatal necrosis; episodic encephalopathy; chronic progressive polyneuropathy → distal weakness & contractures | | Enzymology not performed | Spiegel et al [2009] |
| *TPK1* | <1% | Episodic encephalopathy; ataxia; dystonia; spasticity | | 2-ketoglutaric aciduria | Mayr et al [2011] |
| *BTD* [8] | <1% | Deafness; optic atrophy; seizures; ataxia [8] | Alopecia, eczema | Characteristic organic aciduria | Mitchell et al [1986] |
| *SLC19A3* [8] | <5% | See footnote 8. | | RCE activity nml | Fassone et al [2013], Gerards et al [2013] |
| **Leigh syndrome assoc w/mitochondrial toxicity** | | | | | |
| *HIBCH* | <5% | Developmental regression; seizures; ataxia | | ↑ plasma 4-hydroxybutyrylcarnitine levels; variable deficiency of RCEs & PDH | Ferdinandusse et al [2013] |

*Table 1. continued from previous page.*

| Gene | Proportion of AR LSS Caused by Biallelic Variants in Gene | Distinguishing Clinical & Laboratory Features | | | Reference |
|---|---|---|---|---|---|
| | | Neurologic [1] | Other | Laboratory Findings | |
| *ECHS1* | <5% | Psychomotor delay; SNHL; nystagmus; hypotonia; spasticity; athetoid movements | HCM | ↑ urinary excretion of S-(2-carboxypropyl) cysteine; normal RCE activ in 1 person, multiple RCE deficiency in 1 other | Peters et al [2014], Sakai et al [2015] |
| *ETHE1* | <1% | Neurodevelopmental delay & regression; pyramidal & extrapyramidal signs | Acrocyanosis, petechiae, & diarrhea in infancy | Ethylmalonic aciduria | Mineri et al [2008] |
| *SQOR* | 2 families | Episodic encephalopathy following infections | Liver failure in 1 person | Complex IV deficiency in 1 person (mb & liver); RCE activ in fb nml in 1 person | Friederich et al [2020] |
| *SLC39A8* | 1 family | Dystonia; seizures; hypotonia; cerebellar atrophy | Strabismus; short stature; recurrent infections | ↓ blood & urine manganese, type II glycosylation defect | Riley et al [2017] |

α-KGDH = alpha-ketoglutarate dehydrogenase; AR = autosomal recessive; BCAA = branched-chain amino acid; BCKDH = branched-chain ketoacid dehydrogenase; CC = corpus callosum; EEG = electroencephalogram; EM = electron microscopy; fbs = cultured skin fibroblasts; FILA = fatal infantile lactic acidosis; GI = gastrointestinal; HCM = hypertrophic cardiomyopathy; IUGR = intrauterine growth restriction; LS = Leigh syndrome; LSS = Leigh syndrome spectrum; mb = muscle biopsy; MEGD(H)EL syndrome = 3-methylglutaconic aciduria with deafness-dystonia, encephalopathy, (hepatopathy) and Leigh-like syndrome; MMA = methylmalonic aciduria; MRS = magnetic resonance spectroscopy; mt = mitochondrial; PDH = pyruvate dehydrogenase; RCE = respiratory chain enzyme; SNHL = sensorineural hearing loss

*1.* Neurologic findings other than those of classic Leigh syndrome

*2.* Genes encoding subunits are listed first, followed by genes encoding assembly factors.

*3.* Founder pathogenic allelic variant in French-Canadian population from Saguenay-Lac St Jean

*4.* Founder pathogenic variant in Lebanese population

*5.* Ashkenazi Jewish founder variant

*6.* Founder variant in Faroe Islands

*7.* Isolated SNHL without Leigh syndrome in some individuals; Alpers syndrome in others

*8.* Potentially treatable; see Management.

*9.* Allelic with Amish lethal microcephaly, mitochondrial thiamine pyrophosphate carrier deficiency

## Autosomal Dominant Leigh Syndrome Spectrum

***DNM1L.*** To date, *DNM1L* is the only gene known to be associated with autosomal dominant LSS [Zaha et al 2016]; heterozygous *de novo* variants in this gene account for <1% of LSS. *DNM1L*-LSS is associated with infantile spasms with burst suppression on EEG; laboratory findings include multiple respiratory chain enzyme deficiencies and elongated mitochondria and peroxisomes on electron microscopy. Autosomal recessive *DNM1L*-related disease has been reported but – to date – not in association with LSS.

## X-Linked Leigh Syndrome Spectrum

Causes of X-linked nuclear gene-encoded LSS are summarized in Table 2.

**Table 2.** X-Linked Leigh Syndrome Spectrum

| Gene | Proportion of LSS Caused by a Hemizygous or Heterozygous Variant in Gene | Distinguishing Features | Laboratory Findings | Reference |
|---|---|---|---|---|
| *PDHA1* | ~10% | Psychomotor retardation; seizures; choreoathetosis; dystonia; episodic ataxia in some; microcephaly; cerebral atrophy; cystic lesions in basal ganglia, brain stem, & cerebral hemispheres; agenesis of CC; facial dysmorphism | ↓/↓-normal lactate/ pyruvate ratio in blood & CSF; PDH deficiency (fbs) | Rahman et al [1996] |
| *NDUFA1* | <1% | DD; axial hypotonia; nystagmus; choreoathetosis; myoclonic epilepsy; survival to 30s in 2 cases | Complex I deficiency (mb) | Fernandez-Moreira et al [2007] |
| *AIFM1* | <1% | Encephalomyopathy w/bilateral striatal lesions | Multiple RCE deficiencies (mb) | Ghezzi et al [2010] |

CC = corpus callosum; CSF = cerebrospinal fluid; DD = developmental delay; fbs = cultured skin fibroblasts; LSS = Leigh syndrome spectrum; mb = muscle biopsy; PDH = pyruvate dehydrogenase; RCE = respiratory chain enzyme

# 3. Evaluation Strategies to Identify the Genetic Cause of Nuclear Gene-Encoded Leigh Syndrome in a Proband

Once Leigh syndrome spectrum (LSS) is considered in an individual, determining the specific cause (see Table 1 and Table 2) aids in discussions of prognosis and treatment (see Management) and in genetic counseling.

The following information can be used to establish the specific cause of nuclear gene-encoded LSS for a given individual: clinical findings, family history, specialized testing, and molecular genetic/genomic testing.

## Clinical Findings

Clinical manifestations of LSS are described in Tables 1 and 2.

Retrospective review of the currently known genetic causes of nuclear gene-encoded Leigh syndrome (see Tables 1 and 2) suggests some differences in phenotype, but clinical findings in individuals with variants in different genes typically overlap [Rahman et al 2017]. Hence, it would now be unusual for specific clinical and/or imaging findings to guide testing of a subset of genes, but these differences may be useful in guiding variant curation. For example:

- More than 40 individuals with pathogenic variants in *SURF1* or *LRPPRC* have been reported [Debray et al 2011, Wedatilake et al 2013] (see Table 1). Mean survival is longer in those with SURF1 deficiency (5.4 years) than in those with LRPPRC deficiency (1.8 years), apparently due to the occurrence of more frequent and severe metabolic crises in the latter. SURF1 deficiency also appears to have a high incidence of hypertrichosis and peripheral neuropathy [Wedatilake et al 2013].
- Brain malformations are typically seen in males with a hemizygous variant in *PDHA1* and some females with a heterozygous variant [Patel et al 2012] (see Table 2). Specific brain tracts may be involved in some subgroups of complex I deficiency; for example, brain stem lesions are seen within the mamillothalamic tracts, substantia nigra, medial lemniscus, medial longitudinal fasciculus, and spinothalamic tracts on $T_2$-weighted MRI in individuals with mutation of *NDUFAF2* [Fassone & Rahman 2012].

## Family History

A three-generation family history should be obtained with attention to other relatives with neurologic manifestations, or other clinical features compatible with a mitochondrial disorder. Documentation of relevant findings in relatives can be accomplished either through direct examination of those individuals or by review of their medical records including the results of molecular genetic testing, neuroimaging studies, and autopsy examinations.

Specific findings such as a family history in which affected individuals are related to each other through females (i.e., no male-to-male transmission) may prompt initial investigation of X-linked genes, or consanguinity may prompt initial investigation of autosomal recessive genes. Of course, such features are sometimes a chance occurrence and the possibility of an underlying mitochondrial DNA (mtDNA) variant should be followed up with more comprehensive testing if no pathogenic variants are identified in nuclear genes [Alston et al 2011].

## Biochemical Testing

Elevated lactate levels in blood and/or cerebrospinal fluid can:

- Suggest LSS as opposed to other disorders with similar clinical findings;
- Implicate mutation of one of the genes causing PDH deficiency when the ratio of lactate to pyruvate is normal to low [Debray et al 2007].

**Measurement of enzyme activity.** Activity of enzymes, such as PDH, are typically measured in cultured skin fibroblasts (fbs; see Tables 1 and 2), and respiratory chain enzymes are typically measured in a skeletal muscle biopsy (mb; see Tables 1 and 2).

- Although identifying an enzyme defect can help prioritize molecular genetic testing, this approach can still leave a large number of genes to be tested (e.g., respiratory chain complex I-deficient Leigh syndrome has to date been shown to be caused by pathogenic variants in at least 15 autosomal genes (see Table 1), one X-linked gene (see Table 2), and six genes encoded by mtDNA.
- Moreover, although muscle biopsy was traditionally used as a first-line diagnostic test in the investigation of Leigh syndrome and other mitochondrial disorders, the widespread availability of multigene panels and comprehensive genomic testing has obviated the need for muscle biopsy in many instances. However, in a small minority of individuals enzymatic testing of a muscle or skin biopsy may be necessary to confirm pathogenicity of variants of uncertain significance identified by multigene panel, exome or genome sequencing.

## Molecular Genetic Testing

Testing approaches can include use of a **multigene panel**, or **more comprehensive genomic testing of an exome or genome**.

**A mitochondrial disorders multigene panel** that includes some or all of the genes listed in Tables 1 and 2 is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. Of note, given the rarity of some of the genes associated with nuclear gene-encoded LSS, some panels may not include all the genes mentioned in this overview. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. (5) While the vast majority of

individuals with classic Leigh syndrome have nuclear or mtDNA defects related to mitochondrial energy generation, this may not be true for individuals with Leigh-like syndrome; thus, use of a multigene panel with a more extensive gene list may be considered.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

**Comprehensive genomic testing** does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

If exome or genome sequencing is not diagnostic, analysis for copy number variants, typically by algorithmic analysis for read depth and other parameters, (often called **exome array**) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

### Testing for Treatable Disorders

Treatable disorders should be rapidly tested for biochemically or genetically as indicated; or if this is not possible, trials of the relevant vitamins/cofactors should be instituted as soon as the diagnosis is considered. Ideally, therapy should continue until these disorders have been excluded by biochemical and/or genetic testing, and continued for life if the diagnosis is confirmed.

Treatable causes of nuclear gene-encoded LSS (see Treatment of Manifestations):

- Biotin-thiamine-responsive basal ganglia disease, also known as thiamine transporter-2 deficiency (caused by mutation of *SLC19A3*)
- Biotinidase deficiency (*BTD*)
- Coenzyme $Q_{10}$ biosynthesis defect (*PDSS2*, *COQ9*)

## 4. Management of Nuclear Gene-Encoded Leigh Syndrome

### Treatment of Manifestations

**Specific treatment** is possible for the following three nuclear gene-encoded Leigh-like syndromes:

- **Biotin-thiamine-responsive basal ganglia disease** (also known as thiamine transporter-2 deficiency) (mutation of *SLC19A3*). Biotin (5-10 mg/kg/day) and thiamine (in doses ranging from 300-900 mg) should be given orally as early in the disease course as possible and continued lifelong. Symptoms typically resolve within days.
- **Biotinidase deficiency** (*BTD*). All symptomatic children with profound biotinidase deficiency improve when treated with 5-10 mg of oral biotin per day. Biotin treatment should be continued lifelong in all individuals with profound biotinidase deficiency.
- **Coenzyme $Q_{10}$ biosynthesis deficiency** (*PDSS2*, *COQ9*). Supplementation with oral coenzyme $Q_{10}$ (10-30 mg/kg/day in children and 1200-3000 mg/day in adults) should be commenced as early in the disease course as possible and continued lifelong [Rahman et al 2012].

**Supportive management** for any of the causes of nuclear gene-encoded LSS includes the following:

- **Acidosis.** Sodium bicarbonate or sodium citrate is appropriate for acute exacerbations of acidosis.
- **Seizures.** Appropriate anti-seizure medications tailored to the type of seizure should be administered under the supervision of a neurologist. Sodium valproate and barbiturates should be avoided because of

their inhibitory effects on the mitochondrial respiratory chain [Melegh & Trombitas 1997, Anderson et al 2002].

- **Dystonia**
  - Benzhexol, baclofen, tetrabenezine, and gabapentin may be useful, alone or in various combinations; an initial low dose should be started and gradually increased until symptom control is achieved or intolerable side effects occur.
  - Botulinum toxin injection has also been used in individuals with Leigh syndrome and severe intractable dystonia.
- **Cardiomyopathy.** Medical therapy may be required and should be supervised by a cardiologist.
- **Nutrition.** Regular assessment of daily caloric intake and adequacy of dietary structure including micronutrients and feeding management is indicated. While the ketogenic diet may be indicated for individuals with pyruvate dehydrogenase (PDH) deficiency or drug-resistant epilepsy, there is no evidence for efficacy of the ketogenic diet in other forms of LSS.
- **Psychological support** for the affected individual and family is essential.

### Prevention of Secondary Complications

**Anesthesia** can potentially aggravate respiratory symptoms and precipitate respiratory failure; thus, careful consideration should be given to its use and to monitoring the individual prior to, during, and after its use [Shear & Tobias 2004, Niezgoda & Morgan 2013].

### Surveillance

Affected individuals should be followed at regular intervals (typically every 6-12 months) to monitor progression and the appearance of new manifestations. Neurologic, ophthalmologic, audiologic, and cardiologic evaluations are recommended. Surveillance may be directed by knowledge of phenotypes known to be associated with specific gene defects [Rahman et al 2017].

### Agents/Circumstances to Avoid

A recent Delphi review has examined drug safety in mitochondrial disorders [De Vries et al 2020].

## 5. Genetic Counseling of Family Members of an Individual with Nuclear Gene-Encoded Leigh Syndrome

*Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional.* —ED.

### Mode of Inheritance

Nuclear gene-encoded Leigh syndrome spectrum (LSS) can be inherited in an autosomal recessive, X-linked, or autosomal dominant manner.

- Of the more than 80 nuclear gene-encoded LSS-related genes identified to date, pathogenic variants in all but four genes are associated with **autosomal recessive** inheritance.
- LSS caused by a heterozygous or hemizygous pathogenic variant in *AIFM1, NDUFA1,* or *PDHA1* is inherited in an **X-linked** manner. Note: Almost equal numbers of males and females affected with *PDHA1*-LSS have been reported [Lissens et al 2000, Imbard et al 2011]. Although relatively few affected

individuals with *NDUFA1*-LSS and *AIFM1*-LSS have been reported, it is expected that the same sex ratio would be seen in all three X-linked disorders.
- LSS caused by a heterozygous pathogenic variant in *DNM1L* is an **autosomal dominant** disorder; to date, all individuals with *DNM1L*-LSS have had the disorder as the result of a *de novo* pathogenic variant.

Genetic counseling regarding risk to family members depends on accurate diagnosis, determination of the mode of inheritance in each family, and results of molecular genetic testing.

## Autosomal Recessive LSS – Risk to Family Members

**Parents of a proband**

- The parents of an affected child are obligate heterozygotes (i.e., presumed to be carriers of one LSS-causing pathogenic variant based on family history).
- If the causative pathogenic variants have been identified in the proband, molecular genetic testing is recommended for the parents of a proband to confirm that both parents are carriers and to allow reliable recurrence risk assessment. (*De novo* variants are known to occur at a low but appreciable rate in autosomal recessive disorders [Jónsson et al 2017].)
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

**Sibs of a proband**

- If both parents are known to be heterozygous for an LSS-causing pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

**Offspring of a proband.** Individuals with autosomal recessive LSS are not known to reproduce.

**Other family members.** Each sib of the proband's parents is at a 50% risk of being a carrier of a pathogenic variant.

**Carrier detection.** Carrier testing for at-risk relatives requires prior identification of the pathogenic variants in the family.

## X-Linked LSS – Risk to Family Members

**Parents of a male proband**

- The father of an affected male will not have X-linked LSS nor will he be hemizygous for an *AIFM1, NDUFA1,* or *PDHA1* pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote. Note: The 11 heterozygous mothers reported by Imbard et al [2011] were said to be asymptomatic. In the authors' experience, however, some learning difficulties or other features are often present.
- If a woman has more than one affected child and no other affected relatives and if the pathogenic variant identified in the proband cannot be detected in her leukocyte DNA, she most likely has germline mosaicism. (Note: If the mother has both somatic and germline mosaicism for the variant, she may be mildly/minimally affected.)
- If a male is the only affected family member (i.e., a simplex case):
  - The mother may be a heterozygote (approximately 25% of mothers of children with *PDHA1* pathogenic variants were found to be heterozygous for the pathogenic variant [Lissens et al 2000, Imbard et al 2011]); or

- The proband may have a *de novo* pathogenic variant, in which case the mother is not a heterozygote. Data reported by Lissens et al [2000] and Imbard et al [2011] suggest that up to 75% of affected individuals have a *de novo* pathogenic variant. In at least seven affected individuals, somatic mosaicism has been demonstrated with the *de novo* variant presumably occurring in early or mid-embryogenesis [Imbard et al 2011].

**Parents of a female proband.** A female proband may have inherited the *AIFM1, NDUFA1,* or *PDHA1* pathogenic variant from either her mother or (theoretically) her father (if he has germline mosaicism for the pathogenic variant), or the pathogenic variant may be *de novo*.

**Sibs of a male proband.** The risk to sibs of a male proband depends on the genetic status of the mother:

- If the mother of the proband has an *AIFM1, NDUFA1,* or *PDHA1* pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant are likely to be affected with manifestations ranging from mild learning difficulty to LSS depending on the X-chromosome inactivation ratio.
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is greater than that of the general population because of the possibility of maternal germline mosaicism.

**Sibs of a female proband.** The risk to sibs of a female proband depends on the genetic status of the mother (see above) and the father. Theoretically, the father of an affected female may have germline mosaicism for a pathogenic variant, in which case all of his daughters (and none of his sons) would be at risk of inheriting a pathogenic variant.

**Offspring of a male proband.** Males with X-linked LSS are not known to reproduce.

**Offspring of a female proband.** Each child of a female with X-linked LSS has a 50% chance of inheriting the pathogenic variant; males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant are likely to be affected with manifestations ranging from mild learning difficulty to LSS depending on the X-chromosome inactivation ratio.

**Other family members.** The proband's maternal aunts may be at risk of being heterozygous and the aunts' offspring may be at risk of inheriting a pathogenic variant and being affected.

## Autosomal Dominant LSS – Risk to Family Members

**Parents of a proband**

- All probands reported to date with *DNM1L*-LSS whose parents have undergone molecular genetic testing have the disorder as the result of a *de novo* pathogenic variant.
- Molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the *DNM1L* pathogenic variant found in the proband cannot be detected in parental DNA, the pathogenic variant most likely occurred *de novo* in the proband. Another possible explanation is that the proband inherited a pathogenic variant from a parent with germline mosaicism. Although theoretically possible, no instances of parental germline mosaicism have been reported to date.

**Sibs of a proband.** The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband has the *DNM1L* pathogenic variant, the risk to the sibs of inheriting the variant is 50%.

- If the *DNM1L* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].

**Offspring of a proband.** Individuals with *DNM1L*-LSS are not known to reproduce.

**Other family members.** Given that all probands with autosomal dominant *DNM1L*-LSS reported to date have the disorder as a result of a *de novo* pathogenic variant, the risk to other family members is presumed to be low.

## Prenatal Testing and Preimplantation Genetic Testing

Once the pathogenic variant(s) have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Note: For families with X-linked LSS, molecular genetic prenatal test results cannot be used to predict the risk of an affected outcome for a female conceptus heterozygous for the familial pathogenic variant.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

# Resources

*GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.*

- **United Mitochondrial Disease Foundation**
  **Phone:** 888-317-UMDF (8633)
  **Email:** info@umdf.org
  www.umdf.org
- **Association Contre Les Maladies Mitochondriales**
  France
  **Phone:** 33 6 30 84 58 27
  **Email:** assoammi@gmail.com
  www.association-ammi.org
- **Deutsche Gesellschaft für Muskelkranke e.V.**
  Germany
  **Email:** info@dgm.org
  www.dgm.org
- **International Mito Patients**
  www.mitopatients.org
- **Mito Foundation**
  Australia
  **Phone:** 61-1-300-977-180

**Email:** info@mito.org.au

www.mito.org.au

- **MitoAction**

  **Phone:** 888-648-6228

  **Email:** support@mitoaction.org

  www.mitoaction.org

- **MitoCanada Foundation**

  Canada

  **Phone:** 289-807-2929; 877-708-6486 (MITO)

  **Email:** info@mitocanada.org

  www.mitocanada.org

- **Mitocon – Insieme per lo studio e la cura delle malattie mitocondriali Onlus**

  *Mitocon is the reference association in Italy for patients suffering from mitochondrial diseases and their families and is the main link between patients and the scientific community.*

  Italy

  **Phone:** 06 66991333/4

  **Email:** info@mitocon.it

  www.mitocon.it

- **People Against Leigh Syndrome (PALS)**

  **Phone:** 713-248-8782

  www.peopleagainstleighs.org

- **The Freya Foundation**

  *The aim of The Freya Foundation is to raise awareness for the condition called PDH, or pyruvate dehydrogenase deficiency complex.*

  United Kingdom

  www.thefreyafoundation.co.uk

- **The Lily Foundation**

  United Kingdom

  **Email:** liz@thelilyfoundation.org.uk

  www.thelilyfoundation.org.uk

- **RDCRN Patient Contact Registry: North American Mitochondrial Disease Consortium**

  Patient Contact Registry

# Chapter Notes

## Author Notes

Professor Rahman's web page

Professor Thorburn's web page

Professor Rahman's research interests include identification of novel nuclear genes causing mitochondrial disease using a combination of approaches including homozygosity mapping and exome and genome next-generation sequencing. Her group has identified a number of nuclear genes causing childhood-onset mitochondrial disorders, including genes involved in mitochondrial DNA maintenance and expression, complex I and complex IV function, and biosynthesis of coenzyme $Q_{10}$. Other research interests aim to identify biomarkers and novel therapies for childhood mitochondrial disorders.

David Thorburn's research focuses on improving diagnosis, prevention, and treatment of mitochondrial energy generation disorders. This has included translating knowledge of mitochondrial DNA genetics into reproductive options for families, defining diagnostic criteria and epidemiology, and discovery of new "disease" genes through next-generation DNA sequencing. His group also uses cellular and mouse models to understand pathogenic mechanisms and trial new treatment approaches.

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