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NLM Citation: Goldstein A, Falk MJ. Single Large-Scale Mitochondrial DNA Deletion Syndromes. 2003 Dec 17 [Updated 2023 Sep 28]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Single Large-Scale Mitochondrial DNA Deletion Syndromes

Synonyms: mtDNA Deletion Syndromes, SLSMDS

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Created: December 17, 2003; Updated: September 28, 2023.

Summary

Clinical characteristics

Single large-scale mitochondrial DNA deletion syndromes (SLSMDSs) comprise overlapping clinical phenotypes including Kearns-Sayre syndrome (KSS), KSS spectrum, Pearson syndrome (PS), chronic progressive external ophthalmoplegia (CPEO), and CPEO-plus.

KSS is a progressive multisystem disorder with onset before age 20 years characterized by pigmentary retinopathy, CPEO, and cardiac conduction abnormality. Additional features can include cerebellar ataxia, tremor, intellectual disability or cognitive decline, dementia, sensorineural hearing loss, oropharyngeal and esophageal dysfunction, exercise intolerance, muscle weakness, and endocrinopathies. Brain imaging typically shows bilateral lesions in the globus pallidus and white matter.

KSS spectrum includes individuals with KSS in addition to individuals with ptosis and/or ophthalmoparesis and at least one of the following: retinopathy, ataxia, cardiac conduction defects, hearing loss, growth deficiency, cognitive impairment, tremor, or cardiomyopathy. Compared to CPEO-plus, individuals with KSS spectrum have more severe muscle involvement (e.g., weakness, atrophy) and overall have a worse prognosis.

PS is characterized by pancytopenia (typically transfusion-dependent sideroblastic anemia with variable cell line involvement), exocrine pancreatic dysfunction, poor weight gain, and lactic acidosis. PS manifestations also include renal tubular acidosis, short stature, and elevated liver enzymes. PS may be fatal in infancy due to neutropenia-related infection or refractory metabolic acidosis.

CPEO is characterized by ptosis, ophthalmoplegia, oropharyngeal weakness, variable proximal limb weakness, and/or exercise intolerance.

CPEO-plus includes CPEO with additional multisystemic involvement including neuropathy, diabetes mellitus, migraines, hypothyroidism, neuropsychiatric manifestations, and optic neuropathy.

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Rarely, an SLSMDS can manifest as *Leigh syndrome*, which is characterized as developmental delays, neurodevelopmental regression, lactic acidosis, and bilateral symmetric basal ganglia, brain stem, and/or midbrain lesions on MRI.

Diagnosis/testing

The diagnosis of an SLSMDS is established in a proband with characteristic clinical features by identification of a mitochondrial DNA (mtDNA) deletion ranging in size from 1.1 to 10 kb on molecular genetic testing. SLSMDSs can be identified in DNA from blood, buccal cells, and urine in affected children; analysis of skeletal muscle tissue may be required to detect an SLSMDS in an affected adult.

Management

Targeted therapy: Folinic acid supplementation in individuals with KSS with low 5-methyltetrahydrofolate in CSF or white matter abnormalities on brain MRI.

Supportive care: Consider mitochondrial supplement therapies such as coenzyme Q_{10} and antioxidants; optimize nutrition and exercise regimen to prevent acute decompensation; physical and occupational therapy for myopathy and/or ataxia; standard treatment with anti-seizure medication; hearing aids or cochlear implants for sensorineural hearing loss; developmental and educational support; feeding therapy; consider gastrostomy tube placement if poor weight gain, choking, or aspiration risk is present; dilation of the upper esophageal sphincter to alleviate cricopharyngeal achalasia; prophylactic placement of cardiac pacemaker in individuals with cardiac conduction block, with consideration of an implantable cardioverter defibrillator; hormone replacement therapy per endocrinologist; electrolyte monitoring and replacement for renal tubular acidosis; eyelid slings and/or ptosis repair for severe ptosis; eye ointment for dry eyes; eyeglass prisms for diplopia; transfusion therapy for individuals with PS with sideroblastic anemia; replacement of pancreatic enzymes for exocrine pancreatic insufficiency; ventilatory support for respiratory abnormalities that may occur in individuals with Leigh syndrome; standard treatment of anxiety and/or depression; social work support and care coordination as needed.

Surveillance: Annual neurology assessment for ataxia, neuropathy, seizures, and myopathy; annual audiology evaluation; annual assessment of developmental progress, educational needs, and cognitive issues; annual evaluation by a neuro-ophthalmologist and/or retinal specialist and oculoplastics; measurement of growth parameters and evaluation of nutritional status and safety of oral intake at each visit; annual assessment of mobility and self-help skills with physical medicine, occupational therapy, and/or physical therapy; EKG and echocardiogram every six to 12 months; annual assessment with an endocrinologist; BUN and creatinine, with consideration of cystatin C in those with low muscle mass; complete blood count in those with PS to assess transfusion needs with additional labs per hematologist, and ferritin for those needing recurrent transfusions as needed; annual complete blood count in those with other SLSMDSs; fecal fat and fecal elastase as needed based on symptoms; monitor for evidence of aspiration and respiratory insufficiency at each visit; assess family needs at each visit.

Agents/circumstances to avoid: Volatile anesthetic hypersensitivity may occur. Avoid prolonged treatment with propofol (>30-60 minutes). Medications should be reviewed with a physician familiar with mitochondrial disorders including a thorough individualized assessment of risk vs benefit as several medications may be toxic to mitochondria.

Genetic counseling

SLSMDSs are almost never inherited, suggesting that these disorders are typically caused by a *de novo* single large-scale mitochondrial DNA deletion (SLSMD) that occurs in the mother's oocytes during germline development or in the embryo during embryogenesis. If the mother is clinically unaffected and the proband

represents a simplex case (i.e., a single affected family member), the empiric risk to the sibs of a proband is very low (at or below 1%). If the mother is affected, the recurrence risk to sibs is estimated to be approximately 4% (one in 24 births). Maternal transmission to more than one child has not been reported to date. Prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are scientifically possible but technically prohibitive as next-generation sequencing methodology does not accurately quantify heteroplasmy level of an SLSMD and droplet digital quantitative PCR cannot reliably detect less than 10% heteroplasmy levels of an SLSMD. Further, prenatal testing is not clinically available due to the inability to accurately interpret the clinical prognosis based on prenatal diagnostic results of an SLSMD.

GeneReview Scope

Single Large-Scale Mitochondrial DNA Deletion Syndromes: Phenotypic Spectrum

Frequency	Phenotype
Predominant phenotypes	• Kearns-Sayre syndrome (KSS) • KSS spectrum (includes KSS) • Pearson syndrome (also referred to as Pearson marrow-pancreas syndrome) • Chronic progressive external ophthalmoplegia (CPEO) [1] • CPEO-plus
Rare phenotype	Leigh syndrome

1. For other genetic causes of this phenotype, see Differential Diagnosis.

For discussion of terminology used to describe single large-scale mitochondrial DNA deletion syndromes, see Nomenclature.

Diagnosis

A diagnostic algorithm has been proposed for single large-scale mitochondrial DNA deletion syndromes (SLSMDSs) by Gorman et al [2016].

Suggestive Findings

SLSMDSs **should be suspected** in probands with clinical features present in any of the following overlapping phenotypes.

Kearns-Sayre Syndrome (KSS) / Kearns-Sayre Syndrome Spectrum (KSS Spectrum)

Clinical features. Onset before age 20 years with the classic clinical triad of:

- Pigmentary retinopathy (progressive vision impairment due to rod-cone dystrophy), the pivotal feature that distinguishes KSS from chronic progressive external ophthalmoplegia (CPEO)
- CPEO including ptosis
- Cardiac conduction abnormality including bundle branch block, which may progress to complete heart block

Note: Individuals with **KSS spectrum** have ptosis and/or ophthalmoparesis and at least one of the following: retinopathy, ataxia, cardiac conduction defects, hearing loss, growth deficiency, cognitive impairment, tremor, and/or cardiomyopathy.

Additional clinical features

- Endocrinopathies: diabetes mellitus, hypoparathyroidism, hypothyroidism, adrenal insufficiency, growth hormone deficiency
- Myopathy: muscle weakness, exercise intolerance, and/or fatigue
- Dementia (cognitive decline)
- Learning disability
- Cerebellar ataxia
- Tremor
- Sensorineural hearing loss
- Short stature
- Poor weight gain, feeding intolerance, and dysphagia or achalasia (bulbar weakness)
- Renal impairment including chronic kidney failure and/or renal tubular acidosis (elevated urine amino acids, hypokalemia, and metabolic acidosis)
- Exocrine pancreatic insufficiency (reduced fecal elastase and/or increased fecal fat)
- Seizures (may be provoked by electrolyte disturbance or unprovoked)

Biochemical laboratory features

- Cerebrospinal fluid (CSF) protein concentration exceeding 100 mg/dL (>1 g/L)
- Elevated lactate and pyruvate in blood and CSF; commonly elevated at rest and increased excessively in blood after moderate activity
- Muscle biopsy typically showing ragged red fibers (RRF) with modified Gomori trichrome stain and hyperactive fibers with succinate dehydrogenase (SDH) stain. Both RRF and some non-RRF fail to stain with histochemical reaction for cytochrome-*c* oxidase (COX) (e.g., combined COX−, SDH+ fibers). Excess lipid and abnormal mitochondria may be seen on electron microscopy.
- Biochemical studies of electron transport chain enzyme activity in muscle tissue usually shows decreased activity of complexes containing mitochondrial DNA (mtDNA)-encoded subunits (I, III, IV), especially when enzyme values are corrected for the activity of citrate synthase that is used as a marker of mitochondrial content. However, depending on the proportion of mtDNA with the deletion (heteroplasmy load), biochemical studies may be unrevealing.

Electrophysiologic and imaging features

- **Echocardiogram.** Cardiomyopathy
- **Electromyogram and nerve conduction studies.** Consistent with myopathy, but may also show evidence of neuropathy
- **Brain MRI** may show leukoencephalopathy, often associated with cerebral or cerebellar atrophy, bilateral basal ganglia lesions (typically involving the globus pallidus), and midbrain / brain stem lesions (Leigh syndrome pattern) [Broomfield et al 2015, Moscatelli et al 2022].
- Electroencephalogram (EEG) may show focal or generalized epileptiform features in those that have recurrent seizures (epilepsy).

Pearson Syndrome (PS)

Clinical features. Onset typically in first year of life:

- Pancytopenia, refractory anemia
- Sideroblastic anemia (ringed sideroblasts, detected by iron stains of the bone marrow), typically transfusion dependent until natural resolution that often occurs in early childhood
- Exocrine pancreatic dysfunction with increased fecal fat (identified qualitatively by Sudan staining of feces or quantitatively by measuring fecal fat) and reduced fecal elastase
- May be fatal in infancy due to neutropenia-related infections or refractory lactic acidosis
- Poor weight gain, short stature

Chronic Progressive External Ophthalmoplegia (CPEO) / CPEO-Plus

Clinical features

- Ptosis
- Extraocular muscle paralysis (ophthalmoplegia)
- Proximal limb weakness (myopathy)
- Dysphagia
- Exercise intolerance

CPEO-plus includes additional multisystemic features: neuropathy, diabetes mellitus, migraine, hypothyroidism, psychiatric symptoms, and/or optic neuropathy.

Note: (1) Individuals with features of CPEO-plus and pigmentary retinopathy are classified as KSS spectrum. (2) Young adults with clinical manifestations of CPEO-plus may be better classified as KSS spectrum; see Clinical Description and Nomenclature.

Leigh Syndrome

Clinical features. Psychomotor regression, especially with physiologic stressors or intercurrent illnesses

Biochemical laboratory features. Elevated lactate in blood and/or CSF

Imaging features. Brain MRI showing characteristic T_2-weighted hyperintense lesions in the basal ganglia and midbrain / brain stem that are often bilaterally symmetric but may fluctuate over time. Note: Individuals with SLSMDSs typically have globus pallidus involvement, whereas other genetic causes of Leigh syndrome result in lesions of the caudate/putamen (see Differential Diagnosis).

Establishing the Diagnosis

The diagnosis of an SLSMDS **is established** in a proband with suggestive findings and a single large-scale mitochondrial DNA deletion (SLSMD) ranging in size from 1.1 to 10 kb identified by molecular genetic testing (see Table 1).

Molecular genetic testing approaches can include **deletion/duplication analysis of the mitochondrial genome**, use of a **multigene panel**, and **comprehensive genomic testing**.

Deletion/Duplication Analysis of the Mitochondrial Genome

The occurrence of mtDNA heteroplasmy may result in variable tissue distribution of mtDNA with an SLSMD. An SLSMD can be identified in DNA from blood leukocytes and/or urine sediment in all reported affected children. A skeletal muscle biopsy may be necessary in adults to confirm the diagnosis [Broomfield et al 2015].

- **Sequencing of long-range PCR products** or **quantitative PCR analysis** identifies an SLSMD. The deletion breakpoints can then be mapped by mtDNA sequence analysis. **Quantitative PCR** methods, such as digital droplet PCR analysis, can quantify the mtDNA deletion heteroplasmy level.
- **Next-generation sequencing** can identify an SLSMD with exact breakpoints and quantify the heteroplasmy load of the SLSMD [Bosworth et al 2017].

Note: Southern blot analysis was historically used for identification of an SLSMD but is not as sensitive as next-generation sequencing in detecting low-level heteroplasmy for an SLSMD and may fail to distinguish an SLSMD from multiple mtDNA deletions in the same region.

KSS. An SLSMD is usually present in all tissues of individuals with KSS, and can be identified in **blood leukocytes**, **buccal cells**, and **urine sediment**. However, skeletal muscle biopsy may be necessary to establish the

diagnosis if testing in blood or urine is negative, especially in older individuals. Note: (1) Large-scale duplications of mtDNA may coexist with an SLSMD in some individuals with KSS. The incidence of mtDNA duplications also being present in an individual with KSS is not known.

PS. The SLSMD is usually more abundant and can be reliably identified in **blood leukocytes** than in other tissues in individuals with PS. On rare occasions, examination of the bone marrow may reveal the SLSMD if not present in leukocyte DNA.

CPEO. Analysis for an mtDNA deletion in **skeletal muscle tissue**, obtained by open muscle biopsy or by percutaneous needle muscle biopsy, should be performed, as SLSMDs are typically confined to skeletal muscle in individuals with CPEO.

CPEO-plus is multisystemic and the SLSMD may be present in other tissues, including **blood leukocytes**, **buccal cells**, and urine **sediment**. Molecular testing in skeletal muscle tissue may be necessary if the SLSMD is not identified.

Leigh syndrome. An SLSMD can be detected in **blood leukocytes**, **buccal cells**, and **urine sediment** in children with SLSMD-related Leigh syndrome.

Multigene Panel

A mitochondrial disease multigene panel that includes **deletion/duplication analysis of the mitochondrial genome** (see Differential Diagnosis) may be considered 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*. (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.

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

Comprehensive Genomic Testing

When the diagnosis of an SLSMDS has not been considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (e.g., exome sequencing, genome sequencing, mitochondrial genome sequencing) that includes deletion/duplication analysis of the mitochondrial genome may be considered.

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

Table 1. Molecular Genetic Testing Used in Single Large-Scale Mitochondrial DNA Deletion Syndromes

Deletion [1]	Method	Proportion of Probands with an SLSMD Based on Clinical Phenotype			
		KSS	PS	CPEO	Leigh syndrome
1.1- to 10-kb deletion of mitochondrial genome [2]	**Deletion/duplication analysis of the mitochondrial genome [3]**	100% [4]	100%	See footnote 5.	<5% [6]

KSS = Kearns-Sayre syndrome; CPEO = chronic progressive external ophthalmoplegia; PS = Pearson syndrome; SLSMD = single large-scale mitochondrial DNA deletion

1. See Molecular Genetics for information on deletions detected in mitochondrial DNA (mtDNA). Duplications rarely occur with an SLSMD.

2. More than 150 different SLSMDs have been associated with KSS [Damas et al 2014].

3. Testing that identifies deletions/duplications not readily detectable by standard sequence analysis. Methods used may include a range of techniques including long-range PCR, quantitative PCR, and next-generation sequence analysis. Note: The mitochondrial genome has homology with regions of the nuclear genome; therefore, assays that depend on hybridization must be used with caution.

4. The diagnosis of KSS requires identification of an SLSMD. A deletion of 4,977 bp known as m.8470_13446del4977 is the most common deletion [Schon 2003].

5. Numerous pathogenic variants in either mtDNA or nuclear genes also cause CPEO that is often associated with other clinical manifestations. Identification of multiple (small- or large-scale) mtDNA deletions suggests a pathogenic variant in a nuclear gene (see Differential Diagnosis).

6. An SLSMD can cause clinical and brain MRI findings consistent with Leigh syndrome. Leigh syndrome has more than 111 monogenic causes, including pathogenic variants in nuclear and mitochondrial genes (see ClinGen Expert Panel Curations).

Clinical Characteristics

Clinical Description

Single large-scale mitochondrial DNA deletion syndromes (SLSMDSs) predominantly comprise overlapping phenotypes including Kearns-Sayre syndrome (KSS), KSS spectrum, Pearson syndrome (PS), chronic progressive external ophthalmoplegia (CPEO), and CPEO-plus (see Table 2). Leigh syndrome is rarely a manifestation of a single large-scale mitochondrial DNA deletion (SLSMD).

Table 2. Single Large-Scale Mitochondrial DNA Deletion Syndromes: Frequency of Phenotypes

Phenotype	Cohort of 34 Children [1]	Cohort of 228 Adults & Children [2]
KSS	29%	7%
KSS spectrum	0%	25%
PS	32%	3%
CPEO	9%	57%-64% [3]
CPEO-plus	21%	
No phenotype assigned	9%	

CPEO = chronic progressive external ophthalmoplegia; KSS = Kearns-Sayre syndrome; PS = Pearson syndrome

1. Broomfield et al [2015]

2. Mancuso et al [2015]

3. Using classic criteria for CPEO (ptosis, ophthalmoplegia, dysphagia, proximal limb weakness, exercise intolerance), 57% met criteria for CPEO.

Onset. In a cohort of 34 children with an SLSMDS, the most common initial manifestation was isolated ptosis (47%); the second most common presenting feature was transfusion-dependent anemia (32%) [Broomfield et al 2015]. In children identified with an SLSMDS, the median age at presentation was age one week to three months for those with PS and age six years for the other phenotypes.

Although individuals with an SLSMDS may be assigned a clinical diagnosis based on features at the time of presentation, the phenotypes comprise a continuous spectrum of disease, and features evolve with time (see Table 3). In addition, several features strongly associated with the development of KSS are not included in the clinical criteria (e.g., sensorineural hearing loss, poor weight gain, short stature, cognitive impairment, tremor, cardiomyopathy) [Mancuso et al 2015].

Table 3. Single Large-Scale Mitochondrial DNA Deletion Syndromes: Frequency of Select Features

Feature		Two Cohorts of 34 [1] & 42 Children [2]	Cohort of 228 Children & Adults [3]	Comment
Neurologic	Dysautonomia	86%		69% of children w/SLSMDSs were reported to have ≥1 neurologic manifestation. [2]
	Exercise intolerance	77%	20%	
	Muscle weakness	26%-71%	47%	
	Sensorineural hearing loss	31%-67%	18%	
	Ataxia	6%-69%	12%	
	Migraine headaches	37%	4%	
	Dysarthria	34%		
	Gross motor delays	26%		
	Hypotonia	24%	8%	
	Cognitive impairment	23%	4%	
	Muscle wasting		18%	
	Dysphagia		15%	
	Increased CK		15%	
	Muscle pain		6%	
	Seizures	6%-9%		
	Neuropathy		4%	
	Tremor	3%	3%	
Ocular	Ptosis	54%-64%	92%	
	Retinopathy	34%-38%	11%	
	Ophthalmoparesis	26%	84%	
	Corneal thickening	9%		
	Recurrent uveitis	3%		
Cardiac	Conduction defects	45%-66%	5%	Right bundle branch block, arrhythmia, complete heart block
	Cardiomyopathy	~10%	3%	
Endocrine	Short stature	9%-76%	10%	92% of children w/SLSMDSs were reported to have ≥1 endocrine manifestation. [2]
	Diabetes mellitus	24%-26%	9%	
	Hypoparathyroidism	9%-57%		
	Adrenal insufficiency	9%	3%	
	Hypothyroidism	3%		

Table 3. continued from previous page.

Feature		Two Cohorts of 34 [1] & 42 Children [2]	Cohort of 228 Children & Adults [3]	Comment
Hematologic	Neutropenia	91%	2%	All children w/hematologic manifestations had PS.
	Thrombocytopenia	73%		
	Anemia	32%-77%	5%	
Other	Renal manifestations	80%-85%	2%	Tubular &/or glomerular dysfunction
	Psychiatric manifestations	69%	3%	
	Poor weight gain	63%-89%		
	Increased liver enzymes	31%	5%	
	Insomnia	29%		

CK = creatine kinase; SLSMDSs = single large-scale mitochondrial DNA deletion syndromes
1. Broomfield et al [2015]
2. Reynolds et al [2021]
3. Mancuso et al [2015]

Kearns-Sayre Syndrome (KSS) and KSS Spectrum

KSS is a multisystem disorder with onset before age 20 years, defined by a classic clinical triad of pigmentary retinopathy (sometimes referred to as retinitis pigmentosa), CPEO, and cardiac conduction defect. KSS predominantly affects the central nervous system, skeletal muscle, and heart. Onset is usually in childhood, with ptosis, ophthalmoplegia, or both. Exercise intolerance and impaired night vision (nyctalopia) may be early symptoms. Additional findings may include cerebellar ataxia, tremor, elevated cerebrospinal fluid protein, dysphagia, cricopharyngeal achalasia, sensorineural hearing loss, endocrinopathies (diabetes mellitus, growth hormone deficiency, hypoparathyroidism, adrenal insufficiency), renal involvement, learning disability, cognitive decline/dementia, abnormal brain MRI, poor weight gain, short stature, and cardiomyopathy. KSS may progress to death by young adulthood.

Note: Individuals with **KSS spectrum** have ptosis and/or ophthalmoparesis and at least one of the following: retinopathy, ataxia, cardiac conduction defects, hearing loss, growth deficiency, cognitive impairment, tremor, and/or cardiomyopathy.

Central nervous system involvement manifests as sensorineural hearing loss, cerebellar ataxia, impaired intellect (intellectual disability and/or dementia), and tremor.

Brain MRI may show leukoencephalopathy often associated with cerebral and cerebellar atrophy, basal ganglia lesions (typically involving the globus pallidus), and midbrain / brain stem lesions, similar to those seen in individuals with Leigh syndrome [Broomfield et al 2015, Moscatelli et al 2022]. A secondary cerebral folate deficiency has been reported in individuals with KSS; supplementation with folinic acid can be beneficial [Quijada-Fraile et al 2014] and may reverse white matter abnormalities seen on imaging with corresponding subjective improvement in coordination.

Compared to other mitochondrial encephalomyopathies (e.g., MELAS, MERRF, NARP), individuals with KSS only very rarely have metabolic strokes. In a recent retrospective analysis of metabolic stroke, one individual had an SLSMD and received intravenous arginine therapy for worsening ophthalmoplegia and ataxia together with new onset of atonic episodes. After intravenous arginine administration, partial improvement was seen in atonic episodes. MRI revealed bilateral symmetric basal ganglia and white matter lesions [Ganetzky & Falk 2018].

Ophthalmologic manifestations. Pigmentary retinopathy of KSS affects low-light vision more prominently than visual acuity, leading affected individuals to report impaired night vision (nyctalopia). Fundoscopy reveals an atypical "salt-and-pepper" retinopathy. Electroretinogram often reveals rod-cone retinal dystrophy. Visual field testing reveals normal visual fields. Peripheral vision may be compromised by ptosis. Vision generally deteriorates insidiously, making age at onset difficult to discern.

Skeletal muscle involvement is progressive and manifests as ptosis, extraocular muscle paralysis (ophthalmoplegia), oropharyngeal and esophageal dysfunction, exercise intolerance, fatigue, and limb muscle weakness (proximal > distal). The defect of extraocular movement is usually symmetric but may cause blurred or double vision. Ptosis is usually asymmetric and exacerbated by fatigue.

Heart involvement is most commonly characterized by conduction (bundle branch) block, which can be progressive and quickly lead to complete heart block. Complete heart block has been reported in children ages five to 13 years. [Broomfield et al 2015]. Cardiomyopathy has been reported in several individuals [Broomfield et al 2015]. Cardiac MRI is an emerging tool used to detect subclinical cardiac involvement [Kabunga et al 2015]. Prophylactic pacemaker is advised, as the conduction block may rapidly progress to complete heart block and asystole [Trivedi et al 2018].

Endocrinopathies are common in individuals with KSS and include mitochondrial diabetes mellitus, hypoparathyroidism, growth hormone deficiency, adrenal insufficiency, and irregular menses [Al-Gadi et al 2018]. Mitochondrial diabetes mellitus may be caused by both insulin deficiency and insulin resistance, and is associated with higher hemoglobin A1c, lower body mass index, lower rates of diabetic ketoacidosis, higher associated neuropathy and nephropathy rates, and less diabetic ophthalmologic involvement. Individuals may present with extreme hypocalcemia and tetany due to hypoparathyroidism [Katsanos et al 2001, Al-Gadi et al 2018]. Short stature may be the result of growth hormone deficiency, poor weight gain, and/or exocrine pancreatic enzyme deficiencies.

Kidney disease. Renal tubular acidosis occurs in individuals with KSS and may be the presenting feature [Eviatar et al 1990, Broomfield et al 2015]. The kidney is the most frequently affected organ over the course of disease, with tubular or glomerular dysfunction occurring in 85% (17/20) [Broomfield et al 2015]. Impaired kidney function can be determined by decreased glomerular filtration rate (GFR) or abnormal elevation of urinary tubulopathy markers such as retinol-binding protein (RBP) [Bernard et al 1987] or N-acetyl-3-glucosaminidase (NAG) [Vaidya et al 2008] – potentially useful screening biomarkers in presymptomatic individuals [Herget-Rosenthal et al 2004]. Electrolyte abnormalities such as hypokalemia, hypophosphatemia, hypochloremia, acidosis, hyponatremia, and/or hypomagnesemia may be present at baseline or occur during acute illness and require monitoring and replacement therapies.

Prognosis. One study investigated whether the presence of a specific clinical manifestation could predict other features, a common question from individuals with SLSMDSs. Those with retinopathy had statistically significant increased incidence of hearing loss, ataxia, and poor growth. Those with ataxia had statistically significant increased incidence of hearing loss, retinopathy, poor growth, cognitive involvement, and tremor. Those with cardiac conduction defects had statistically significant increased incidence of hearing loss and cardiomyopathy [Mancuso et al 2015].

Pearson Syndrome (PS)

PS manifests clinically with bone marrow failure resulting in pancytopenia, severe refractory, transfusion-dependent sideroblastic anemia, and variable exocrine pancreatic insufficiency. In one study, age of onset for PS was 0.3 ± 0.8 years [Mancuso et al 2015]. In addition, multisystem involvement results in poor weight gain, hypotonia, and metabolic derangements including lactic acidosis. PS features are variable and progressive.

Pancytopenia. PS is associated with variable neutropenia, thrombocytopenia, and transfusion-dependent macrocytic, sideroblastic anemia with normocellular or hypocellular bone marrow.

Sideroblastic anemia. Anemia typically appears in the first year of life and may be the initial manifestation of bone marrow failure or accompanied by pancytopenia. Sideroblastic anemia is defined by the presence of anemia and ringed sideroblasts in the bone marrow. Ringed sideroblasts are normoblasts (precursors to mature red blood cells) with excessive deposits of iron in the mitochondria and are detected by iron stains of bone marrow. In addition, there is striking vacuolization of the hematopoietic progenitor cells and hemosiderosis.

Exocrine pancreatic dysfunction due to pancreatic fibrosis is manifest clinically by poor weight gain, growth deficiency, malabsorption, chronic diarrhea, and excessive fat excretion in the stools (steatorrhea), which can be identified by Sudan staining of the feces or measurement of fecal fat and/or fecal elastase. The gold standard is the secretin stimulation test, which requires placing a catheter in the duodenum and is technically difficult to perform in infants. Exocrine pancreatic dysfunction is a variable feature that is not seen in up to 73% of individuals with PS [Farruggia et al 2016].

Renal tubular defects. Renal Fanconi syndrome with resultant electrolyte disturbances is seen in individuals with PS. Renal tubular acidosis results in elevation of several urinary amino acids, metabolic acidosis that may require bicarbonate replacement, and electrolyte disturbances (hypokalemia, hypomagnesemia) that may require replacement therapy.

Additional features may include hydrops fetalis, hepatic involvement with elevated transaminases and steatosis, microcephaly, endocrinopathies (growth hormone deficiency, hypothyroidism, hypoparathyroidism, diabetes mellitus, and adrenal insufficiency), skin findings (poikiloderma), splenic atrophy, impaired cardiac function, and acute metabolic decompensations during intercurrent illness. One study including six individuals with PS reported the following frequency of findings: elevated liver enzymes (67%), poor weight gain (50%), hypotonia (33%), CPEO (33%), diabetes mellitus (33%), renal manifestations (33%), and lactic acidosis (67%) [Mancuso et al 2015].

Prognosis. Death may occur in early infancy or childhood due to metabolic decompensation, liver failure, or sepsis due to neutropenia. Four of six individuals with PS had died at follow up (about four to six years later) in one study [Mancuso et al 2015]. Survival and spontaneous recovery from bone marrow dysfunction after several years is possible, with a transition to clinical manifestations of KSS. In an Italian cohort of 11 individuals with PS, 64% developed neurologic symptoms (weakness, exercise intolerance, ataxia) and clinical manifestations of KSS [Manea et al 2009, Morel et al 2009, Williams et al 2012, Crippa et al 2015, Farruggia et al 2016].

Chronic Progressive External Ophthalmoplegia (CPEO) and CPEO-Plus

CPEO is predominantly a myopathic disorder characterized by progressive ptosis and extraocular muscle paralysis (ophthalmoplegia) typically presenting in adulthood. The mean age of onset is 26 years. CPEO variably also includes severe oropharyngeal and proximal limb weakness. The disorder is compatible with a normal life span.

Individuals with CPEO-plus who do not meet clinical criteria for KSS or KSS spectrum can have the following additional multisystemic features: neuropathy, diabetes mellitus, migraine headaches, hypothyroidism, psychiatric involvement, and optic neuropathy. Brain MRI is typically normal. Note: (1) Those with cardiac conduction defect and/or pigmentary retinopathy are instead diagnosed with KSS or KSS spectrum. (2) Childhood onset of progressive ptosis and ophthalmoplegia is more typical of KSS spectrum.

Leigh Syndrome

Leigh syndrome typically begins in infancy or early childhood and is characterized by psychomotor regression or delay (especially with stressors such as infection) with disease manifestations involving the brain stem, basal

ganglia, or both. Leigh syndrome involves regression of developmental milestones and lactic acidosis, which are less common in other SLSMDSs. The brain MRI is typically abnormal in SLSMDSs, showing characteristic T_2-weighted hyperintense lesions in the basal ganglia and midbrain / brain stem that are often bilaterally symmetric but may fluctuate over time; the globus pallidus is predominantly affected in SLSMD-related Leigh syndrome, whereas other genetic causes of Leigh syndrome result in lesions of the caudate/putamen.

Genotype-Phenotype Correlations

For all mitochondrial DNA (mtDNA) pathogenic variants, including SLSMDs, clinical expressivity depends on three factors:

- Relative abundance of mtDNA with the deletion (**heteroplasmy load**)
- Tissue distribution of mtDNA with the deletion
- Tissue vulnerability to impaired oxidative metabolism (**threshold effect**)

Tissue vulnerability thresholds likely do not vary substantially among affected individuals, whereas variable proportions of the mtDNA deletion and their tissue distribution may account for the wide spectrum of clinical findings in individuals with KSS.

The SLSMD is present in all tissues in individuals with KSS, is predominantly present in hematopoietic cells of individuals with PS, and is confined to skeletal muscle in individuals with CPEO, explaining the variability in phenotype. Infants with PS may develop KSS later in life due to the gradual decrease in SLSMDs in rapidly dividing blood cells and the gradual increase in SLSMDs in postmitotic tissues.

In some reported cohorts, disease severity and progression correlate with mtDNA heteroplasmy levels as well as mtDNA deletion size and location [Grady et al 2014]. A meta-analysis of published cohorts [Grady et al 2014] compared the degree of cytochrome-*c* oxidase (COX)-negative fibers on muscle biopsy (as a marker of biochemical severity), age of onset of clinical manifestations, and disease burden (as measured by the Newcastle Mitochondrial Disease Adult Scale [NMDAS]) with the mtDNA deletion size, deletion location, and heteroplasmy level. Grady et al [2014] found that the age of onset of clinical manifestations directly correlated with deletion size, location (e.g., deletions including complex III and IV subunit genes *MT-CYB* and *MT-COX*), and heteroplasmy levels, factors that were significant predictors of disease progression as measured by NMDAS scores. A web tool is available for prognosis and predicted disease progression based on these factors: research.ncl.ac.uk/mitoresearch.

In a study of 228 individuals with SLSMDs, deletion length was greater in those with KSS spectrum compared to those with CPEO, and the percentage of heteroplasmy was inversely related to age of onset of manifestations [Mancuso et al 2015].

Thus, the genotype-phenotype correlations in SLSMDSs remains controversial, with some cohorts reporting a correlation between age of onset and deletion size or inclusion of *MT-CYB* within the deletion and others finding no correlation [Grady et al 2014, Broomfield et al 2015, Mancuso et al 2015].

Penetrance

Penetrance is a function of the proportion of mtDNA with the deletion. However, the authors are not aware of any non-penetrant individuals. To date, individuals with low-level heteroplasmy (e.g., 25%-33% in muscle) are symptomatic [Broomfield et al 2015, Mancuso et al 2015].

Nomenclature

The terms "KSS spectrum" and "CPEO-plus" were introduced by Mancuso et al [2015] in order to establish more inclusive designations for individuals with SLSMDs and phenotypes outside established clinical criteria for KSS or CPEO.

- **KSS spectrum** includes individuals with KSS and individuals with ptosis and/or ophthalmoparesis and at least one of the following: retinopathy, ataxia, cardiac conduction defects, hearing loss, growth deficiency, cognitive impairment, tremor, and/or cardiomyopathy.
- **CPEO-plus** includes individuals with myopathy and multisystemic findings who do not fulfill clinical criteria for KSS spectrum.

Pearson syndrome may also be referred to as "Pearson marrow-pancreas syndrome." (Of note, the term "sideroblastic anemia and exocrine pancreatic dysfunction" is not currently used.)

Leigh syndrome has also been described as "subacute necrotizing encephalomyelopathy."

Prevalence

An epidemiologic study of an adult population in northeast England estimated the prevalence of SLSMDs at 1.2 in 100,000 [Schaefer et al 2008, Gorman et al 2016]. The number of adults with an SLSMD was reported to be 1.5 in 100,000 individuals (95% confidence interval: 1-2.1) [Gorman et al 2016].

Genetically Related Disorders

No other phenotypes are known to be associated with single large-scale mitochondrial DNA deletions. See Primary Mitochondrial Disorders Overview.

Differential Diagnosis

Kearns-Sayre syndrome (KSS) and chronic progressive external ophthalmoplegia (CPEO) must be differentiated from other disorders associated with ophthalmoplegia. The ptosis in individuals with single large-scale mitochondrial DNA deletion syndromes (SLSMDSs) is typically asymmetric, compared to the other causes listed in Table 4, in which the ptosis is typically more symmetric as well as fluctuating.

Table 4. Disorders with Progressive External Ophthalmoplegia to Consider in the Differential Diagnosis of KSS and CPEO

Gene	Disorder	MOI	Features of This Disorder Not Typically Associated with KSS or CPEO
~35 genes incl: *CHAT* *CHRNE* *COLQ* *DOK7* *RAPSN*	Congenital myasthenic syndromes (See also **Myasthenia Gravis** after this table.)	AR AD [1]	• Primary muscle disorders • Do not involve cardiac muscle • Not multisystemic in nature
DMPK	Myotonic dystrophy type 1	AD	Myotonia
DNA2	*DNA2*-related mitochondrial DNA maintenance defects	AD	• PEO w/variable, slowly progressive features; onset: childhood to adulthood • Slender build • Facial muscle weakness; exertional dyspnea; obstructive sleep apnea; myopathy w/weakness, atrophy, exercise intolerance, myalgia, & cramps; gait disturbance • ↑ CK

Table 4. continued from previous page.

Gene	Disorder	MOI	Features of This Disorder Not Typically Associated with KSS or CPEO
LRP12	Oculopharyngodistal myopathy (OMIM 164310)	AD	• Onset in early adulthood • Distal limb weakness • Frequent respiratory muscle weakness
MT-TL1	*MT-TL1*-related PEO; selected example: m.3243A>G	Mat	• Stroke-like episodes • Typically large maternal family history of multiple persons w/deafness & diabetes
MYH2	*MYH2*-related myopathy (OMIM 605637)	AR AD	• Childhood-onset myopathy • Generalized & extraocular muscle weakness • Minor progression (i.e., slowly progressive or nonprogressive) • Not multisystemic
OPA1	Optic atrophy type 1 (OMIM 165500)	AD	Optic atrophy w/variable other neurologic signs
PABPN1	Oculopharyngeal muscular dystrophy (OPMD)	AD	• Late onset • Ptosis w/mild ophthalmoparesis • Severe dysphagia • Abnormal EMG/NCV
POLG	*POLG*-related PEO (See *POLG*-Related Disorders.)	AD AR	• Highly variable phenotypes • adPEO presentation: generalized myopathy, sensorineural hearing loss, axonal neuropathy, ataxia, depression, parkinsonism, hypogonadism, cataracts, premature ovarian/testicular failure • arPEO presentation: PEO may be initial feature; however, additional manifestations may appear years later (as for adPEO) • Mitochondrial DNA depletion • Typically adult onset
RRM2B	*RRM2B*-related PEO (See *RRM2B* Mitochondrial DNA Maintenance Defects.)	AD AR	• AR form may be multisystemic severe disorder w/ marked progressive weakness due to skeletal myopathy. • AD form incl CPEO & variable manifestations: hearing loss, dysphagia, dysmotility, myopathy (exercise intolerance, fatigue, weakness), COX-deficient fibers & RRF on muscle biopsy, dysarthria, ataxic gait, peripheral neuropathy, & mood disorders.
SLC25A4	*SLC25A4*-related PEO (See Mitochondrial DNA Maintenance Defects Overview.)	AD	Childhood- or adult-onset PEO w/variable myopathy, cardiomyopathy, & encephalopathy
TWNK	*TWNK*-related PEO	AD	• Adult onset (age 20-40 yrs) • Progressive hearing loss, cataracts, cardiomyopathy, dysphagia • Skeletal myopathy w/exercise intolerance, fatigue, progressive muscle weakness, myopathic EMG, & RRF & ↓ COX levels on muscle biopsy • DD, parkinsonism, gait difficulties, sensory ataxia • Cognitive decline, cerebral atrophy, peripheral neuropathy • Endocrinopathies (diabetes, infertility) • Mood disorders

Table 4. continued from previous page.

Gene	Disorder	MOI	Features of This Disorder Not Typically Associated with KSS or CPEO
TYMP	Mitochondrial neurogastrointestinal encephalopathy disease	AR	• Peripheral neuropathy & GI dysmotility • ↓ thymidine phosphorylase & ↑ thymidine in blood

AD = autosomal dominant; AR = autosomal recessive; adPEO = autosomal dominant PEO; arPEO = autosomal recessive PEO; CPEO = chronic progressive external ophthalmoplegia; DD = developmental delay; CK = creatine kinase; COX = cytochrome-*c* oxidase; EMG = electromyography; GI = gastrointestinal; KSS = Kearns-Sayre syndrome; Mat = maternal; MOI = mode of inheritance; NCV = nerve conduction velocity; PEO = progressive external ophthalmoplegia; RRF = ragged red fibers

1. Congenital myasthenic syndrome (CMS) is typically inherited in an autosomal recessive manner. Less commonly, CMS is inherited in an autosomal dominant manner.

Myasthenia gravis (OMIM 254200), also associated with progressive external ophthalmoplegia, can be distinguished from KSS and CPEO by fluctuating weakness and diplopia; response to Tensilon® & Mestinon® therapy; abnormal electromyography / nerve conduction velocity repetitive stimulation; and absence of anti-acetylcholine receptor (AChR) and anti-muscle-specific kinase (MuSK) antibodies in serum. Myasthenia gravis is a complex disorder and is thought to be associated with both genetic and non-genetic etiologies (see Melzer et al [2016]).

Pearson syndrome. See Table 5.

Table 5. Disorders in the Differential Diagnosis of Pearson Syndrome

Gene	Disorder	MOI	Comment
~22 genes incl: *RPL5* *RPL11* *RPS19* *RPS26*	Diamond-Blackfan anemia (DBA)	AD XL	• Inherited blood disorder assoc w/anemia & variable congenital abnormalities • In a cohort of 362 individuals clinically (but not genetically confirmed) diagnosed w/DBA, 2.2% had an SLSMD identified, consistent w/PS. [1]
ANAPC1 *RECQL4*	Rothmund-Thomson syndrome	AR	Skin rash (poikiloderma), small size, feeding difficulties, poor weight gain, chronic diarrhea, anemia, & neutropenia

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; mtDNA = mitochondrial DNA; PS = Pearson syndrome; SLSMD = single large-scale mitochondrial DNA deletion; XL = X-linked

1. Alter [2014]

Leigh syndrome has been associated with more than 111 monogenic causes [Lake et al 2016] (see also ClinGen Gene-Disease Validity: Leigh syndrome), including defects of the pyruvate dehydrogenase complex (see Primary Pyruvate Dehydrogenase Complex Deficiency Overview) and deficiencies of respiratory chain enzymes. Autosomal recessive, autosomal dominant, X-linked, and maternal (mitochondrial DNA) inherited forms have been reported (see Nuclear Gene-Encoded Leigh Syndrome Spectrum Overview and Mitochondrial DNA-Associated Leigh Syndrome and NARP). A child with a genetically confirmed SLSMD and a Pearson syndrome, KSS, and Leigh syndrome overlapping clinical presentation was reported with a novel *de novo* pathogenic variant in *SSBP1* in addition to the mitochondrial DNA deletion [Gustafson et al 2019].

For other causes of:

- **Ataxia**, see Hereditary Ataxia Overview;
- **Sensorineural hearing loss**, see Genetic Hearing Loss Overview;
- **Pigmentary retinopathy**, see Nonsyndromic Retinitis Pigmentosa Overview;
- **Sensorineural hearing loss and retinitis pigmentosa**, see Usher Syndrome Type I and Usher Syndrome Type II.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with a single large-scale mitochondrial DNA deletion syndrome (SLSMDS), the evaluations summarized in Table 6 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 6. Single Large-Scale Mitochondrial DNA Deletion Syndromes: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Neurologic	Neurologic eval	• To consider brain MRI (esp before cochlear implants or pacemaker are indicated) • Consider EEG if seizures are a concern in the setting of normal electrolytes (i.e., unprovoked seizures).
Hearing	Audiologic eval	Assess for hearing loss.
Development/ Cognition	Developmental &/or cognitive assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education in children
Feeding/ Nutrition	Nutrition / feeding team eval	• To incl assessment of weight, eval of nutritional status, & aspiration risk • Consider eval for gastrostomy tube placement in persons w/dysphagia, poor weight gain, &/or aspiration risk.
Eyes	• Ophthalmologic eval for retinal dystrophy • Consider oculoplastics for ptosis, neuro-ophthalmology for prisms.	To assess for reduced vision, abnormal ocular movement, best corrected visual acuity, refractive errors, strabismus, & more complex findings (e.g., retinal dystrophy) that may require referral for subspecialty care &/or low vision services
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Cardiology	• EKG • Echocardiogram	To assess for arrythmias & complete heart block
Endocrine	• Assessment of growth, thyroid, parathyroid, diabetes mellitus, adrenal insufficiency • TSH, free T_4, parathyroid hormone, calcium, magnesium, glucose, hemoglobin A1c, fructosamine, AM cortisol • Referral to endocrinologist	
Renal	• BUN:Cr ratio, GFR, NAG, cystatin C • Urine amino acids, urine electrolytes	Referral to nephrologist for those w/abnormal labs
Hematologic	CBC	In those w/KSS, PS, & CPEO
	Ferritin	

Table 6. continued from previous page.

System/Concern	Evaluation	Comment
Pancreatic	• Assessment for poor weight gain, poor growth, greasy stools • Fecal fat, fecal elastase	
Pulmonology	• Pulmonary eval for airway clearance & maintenance (e.g., assessment of need for drying agents for hypersalivation to prevent aspiration) • Pulmonary function studies	In infants w/Leigh syndrome & children & adults w/ dysphagia or neuromuscular weakness due to KSS spectrum or CPEO-plus
	Sleep study	To assess for insomnia, OSA, &/or sleep disturbance
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of SLSMDSs to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	• United Mitochondrial Disease Foundation • MitoAction • C.H.A.M.P. Foundation

ADL = activities of daily living; BUN = blood urea nitrogen; CBC = complete blood count; CPEO = chronic progressive external ophthalmoplegia; Cr = creatinine; EKG = electrocardiography; GFR = glomerular filtration rate; KSS = Kearns-Sayre syndrome; MOI = mode of inheritance; NAG = acetyl-3-glucosaminidase; OSA = obstructive sleep apnea; OT = occupational therapy; PS = Pearson syndrome; PT = physical therapy; SLSMDSs = single large-scale mitochondrial DNA deletion syndromes; T_4 = thyroxine; TSH = thyroid-stimulating hormone

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Targeted Therapy

In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure. —ED

Folinic acid supplementation in individuals with Kearns-Sayre syndrome (KSS) with low 5-methyltetrahydrofolate in cerebrospinal fluid or white matter abnormalities on brain MRI. Suggested dosing is 1.5-5 mg/kg/day with maximum of 100 mg/day. Further studies are needed to make definitive statements regarding the efficacy of this therapy, but it has been reported to improve neurologic symptoms in a few individuals and has been adopted as standard practice in mitochondrial medicine [Quijada-Fraile et al 2014, Barcelos et al 2020].

Supportive Care

Table 7. Single Large-Scale Mitochondrial DNA Deletion Syndromes: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
General mitochondrial dysfunction	• Consider mitochondrial supplement therapies such as coenzyme Q_{10} & antioxidants. • Optimize nutrition & exercise regimen to prevent acute decompensations.	Antioxidants may ameliorate damage from reactive oxygen species.
Myopathy &/or ataxia	PT & OT	Equipment to prevent falling, maintain independent mobility
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [1]
Hearing	Hearing aids or cochlear implants for SNHL	Consider obtaining brain MRI before cochlear implants are placed.
Developmental delay / Intellectual disability	Developmental & educational support	
Nutrition / Poor weight gain	• Feeding therapy • Gastrostomy tube placement may improve nutritional intake for those w/persistent feeding issues, choking, or aspiration risk due to dysphagia.	Low threshold for clinical feeding eval &/or radiographic swallowing study when showing clinical signs or symptoms of dysphagia; may be at risk of refeeding syndrome
Cricopharyngeal/esophageal achalasia	Dilation of upper esophageal sphincter	
Cardiac conduction block	• Mgmt per cardiologist & cardiac electrophysiologist • Prophylactic placement of cardiac pacemaker in persons w/cardiac conduction block, w/ consideration of implantable cardioverter defibrillator	
Endocrine disorders	Hormone replacement per endocrinologist	
Renal tubular acidosis / Chronic kidney failure	Electrolyte monitoring & replacement	• Acute changes may be provoked by stressors (fever, vomiting) & require sudden increase in dosing needs. • Renal dosing of medications • Dialysis may be necessary in those w/ end-stage kidney failure.
Eyes	• Placement of eyelid slings &/or ptosis repair for severe ptosis • Standard treatments incl eye ointment for dry eyes • Eyeglass prisms for diplopia • Lutein & NAC has been used for retinopathy. [2] • Mgmt of cataracts per ophthalmologist	Mgmt per ophthalmologist, neuro-ophthalmologist, oculoplastic surgeon, & retinal specialist as needed.
Pancytopenia / Sideroblastic anemia	Transfusion therapy for persons w/PS	Although chelation may be necessary to minimize iron overload in those treated w/RBC transfusions, sedated heart & liver MRI are not typically necessary, as the transfusion-dependent period is usually <2 yrs

Table 7. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Pancreatic insufficiency	Pancreatic enzyme replacement	In those w/PS & KSS
Respiratory compromise	Ventilatory support for persons w/Leigh syndrome & respiratory compromise	
Psychosocial	Standard treatments for anxiety &/or depression	
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; KSS = Kearns-Sayre syndrome; NAC = N-acetylcysteine; OT = occupational therapy; PS = Pearson syndrome; PT = physical therapy; RBC = red blood cell; SNHL = sensorineural hearing loss
1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.
2. Barcelos et al [2020]

Surveillance

The Mitochondrial Medicine Society (MMS) published surveillance standards (summarized in Table 8) for individuals with mitochondrial disease to monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations [Parikh et al 2017].

Table 8. Single Large-Scale Mitochondrial DNA Deletion Syndromes: Recommended Surveillance

System/Concern	Evaluation	Frequency
Neurologic	Neurology assessment for ataxia, neuropathy, seizures or changes in seizures, & myopathy	Annually
Hearing	Audiology eval	
Development/ Cognition	Monitor developmental progress, educational needs, & cognitive issues.	
Ophthalmology	Eval by neuro-ophthalmologist &/or retinal specialist & oculoplastic surgeon for CPEO, ptosis, pigmentary retinopathy, w/surveillance testing as indicated (e.g., electroretinography, optical coherence tomography, visual fields)	Annually, or more frequently as needed
Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake	At each visit
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	Annually
Cardiac	EKG & echocardiogram to monitor cardiac conduction & contractility	Every 6-12 mos after diagnosis per cardiologist
Endocrinology manifestations	• Assessment w/endocrinologist • Fructosamine may more accurately measure blood glucose.	Annually
Renal	• BUN:Cr ratio • Consider cystatin C in those w/low muscle mass	
Hematology	• In those w/PS, CBC to assess transfusion needs; additional labs per hematologist • In those w/PS needing recurrent transfusions, ferritin to assess need for chelation	Per hematologist
	In those w/other SLSMDSs: CBC	Annually

Table 8. continued from previous page.

System/Concern	Evaluation	Frequency
Exocrine pancreatic dysfunction	Fecal fat, fecal elastase	As needed based on symptoms
Respiratory	Monitor for evidence of aspiration, respiratory insufficiency.	At each visit
	Referral to pulmonologist	As needed
Family/Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	At each visit

BUN = blood urea nitrogen; CBC = complete blood count; CPEO = chronic progressive external ophthalmoplegia; Cr = creatinine; EKG = electrocardiography; OT = occupational therapy; PS = Pearson syndrome; PT = physical therapy; SLSMDSs = single large-scale mitochondrial DNA deletion syndromes

Agents/Circumstances to Avoid

Volatile anesthetic hypersensitivity may occur. Avoid prolonged treatment with propofol (>30-60 minutes) [Hsieh et al 2017, De Vries et al 2020]. Guidelines for anesthesia in individuals with mitochondrial disease are available [Hsieh et al 2017, De Vries et al 2020].

Note: Previously, avoidance of numerous medications was recommended in individuals with primary mitochondrial disorders including SLSMDSs. However, a recent expert review panel utilizing a Delphi consensus method updated the recommendations on medication safety and advised affected individuals to consult with the physician managing their mitochondrial disease.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

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

Single large-scale mitochondrial DNA deletion syndromes (SLSMDSs) are almost never inherited, suggesting that these disorders are typically caused by a *de novo* single large-scale mitochondrial DNA deletion (SLSMD) that occurs in the mother's oocytes during germline development or in the embryo during embryogenesis.

Risk to Family Members

Parents of a proband

- The father of a proband is not at risk of having the SLSMDS.
- The mother of a proband with an SLSMDS is usually unaffected. Typically, testing of maternal somatic tissues does not detect the SLSMD, although the mother of the proband may have the SLSMD in a population of her oocytes (i.e., maternal germline mosaicism).
- The SLSMD is almost always *de novo* in the proband, occurring either in the mother's oocyte or during embryogenesis.

Sibs of a proband

- If the mother is clinically unaffected and the proband represents a simplex case (i.e., a single affected family member), the empiric risk to the sibs of a proband is very low (at or below 1%).
- If the mother is affected, the recurrence risk to sibs is estimated to be approximately 4% (one in 24 births) [Chinnery et al 2004, Pitceathly et al 2012]. A "bottleneck" between oocyte and embryo allows for only a minority (perhaps hundreds to a few thousand) of maternal mitochondrial DNA (mtDNA) molecules to populate the fetus; it is extremely rare for a maternal mtDNA molecule with the SLSMD to slip through this bottleneck. Maternal transmission to more than one child has not been reported to date.

Offspring of a proband

- The likelihood that an affected woman will have an affected child is estimated to be approximately 4% (one in 24 births) [Chinnery et al 2004, Pitceathly et al 2012]. A "bottleneck" between oocyte and embryo allows for only a minority (perhaps hundreds to a few thousand) of maternal mtDNA molecules to populate the fetus; it is extremely rare for a maternal mtDNA molecule with the SLSMD to slip through this bottleneck.
- Offspring of a male proband with an SLSMD are not at risk.

Other family members. The risk to other family members of being affected or of having an SLSMD is extremely low.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected.

Prenatal Testing and Preimplantation Genetic Testing

Once the SLSMD has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are scientifically possible but technically prohibitive as next-generation sequencing methodology does not accurately quantify the heteroplasmy level of an SLSMD and droplet digital quantitative PCR cannot reliably detect less than 10% heteroplasmy levels of an SLSMD. Further, prenatal testing is not clinically available due to the inability to accurately interpret the clinical prognosis based on prenatal diagnostic results of an SLSMD. Due to mitotic segregation of mtDNA during cell division, the proportion of abnormal mtDNA in amniocytes and chorionic villi is unlikely to correspond to heteroplasmy levels in other fetal or adult tissues.

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.

- **The Champ Foundation**

  The Champ Foundation supports research toward better treatment and a cure for single large-scale mitochondrial deletion syndromes (SLSMDS), like Pearson syndrome.

  Email: contact@thechampfoundation.org

  www.thechampfoundation.org

- **Foundation Fighting Blindness**

  7168 Columbia Gateway Drive

  Suite 100

  Columbia MD 21046

  Phone: 800-683-5555 (toll-free); 800-683-5551 (toll-free TDD); 410-423-0600

  Email: info@fightblindness.org

  www.fightingblindness.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

  mitoaction.org

- **Muscular Dystrophy Association (MDA) - USA**

  Phone: 833-275-6321

  www.mda.org

- **The Charlie Gard Foundation**

  United Kingdom

  Email: hello@thecharliegardfoundation.org

  www.thecharliegardfoundation.org

- **The Lily Foundation**

  United Kingdom

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

- **United Mitochondrial Disease Foundation**
  Phone: 888-317-UMDF (8633)
  Email: info@umdf.org
  www.umdf.org
- **eyeGENE – National Ophthalmic Disease Genotyping Network Registry**
  Phone: 301-435-3032
  Email: eyeGENEinfo@nei.nih.gov
  https://eyegene.nih.gov/
- **Monogenic Diabetes at the University of Chicago**
  Registry includes individuals with mitochondrial diabetes mellitus which includes individuals with SLSMDs.
  www.monogenicdiabetes.uchicago.edu
- **RDCRN Patient Contact Registry: North American Mitochondrial Disease Consortium**
  Patient Contact Registry

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table B. OMIM Entries for Mitochondrial DNA Deletion Syndromes (View All in OMIM)

157640	PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA WITH MITOCHONDRIAL DNA DELETIONS, AUTOSOMAL DOMINANT 1; PEOA1
256000	LEIGH SYNDROME, NUCLEAR; NULS
530000	KEARNS-SAYRE SYNDROME; KSS
557000	PEARSON MARROW-PANCREAS SYNDROME

Molecular Pathogenesis

The origin of large-scale mitochondrial DNA (mtDNA) deletions is uncertain. However, it has been noted that deletions fall into two classes [Mita et al 1990]:

- Class I: Mitochondrial DNA deletion is flanked by perfect direct repeats that may be a result of homologous recombination or slipped mispairing.
- Class II: Mitochondrial DNA deletion is not flanked by any homologous sequences and the cause of the deletion is unknown.

Deletions vary in size, heteroplasmy load, and tissue distribution among affected individuals. However, the size of the mtDNA deletion is uniform in an affected individual, implying that the population of mtDNA molecules with the deletion is a result of clonal expansion of a single mtDNA molecule with the deletion early in oogenesis or in embryogenesis [Schon 2003]. From the blastocyst, the mtDNA molecule with the deletion can enter all three germ layers to cause Kearns-Sayre syndrome, segregate predominantly in the hematopoietic lineage to cause Pearson syndrome, or segregate in skeletal muscle to cause progressive external ophthalmoplegia [DiMauro & Schon 2003]. The hypothesis of clonality implies that a single rearranged molecule present in the

oocyte or the embryo multiplies excessively to form the trillions of deleted mtDNA molecules in the affected individual. How the selective amplification of deleted mtDNAs occurs is unknown, but the bottleneck concept described above may be part of the answer.

Single large-scale mtDNA deletions (SLSMDs) encompass several tRNA genes. Thus, mtDNA with an SLSMD are transcribed into RNA, but the processed transcript encoding polypeptides is not translated because the SLSMD removed the essential tRNAs needed for protein synthesis [Schon 2003]. Larger deletions may also remove mRNAs required for synthesizing the mtDNA-encoded subunits of respiratory chain complexes I, III, IV, or V, leading to impaired mitochondrial energy production.

The most common SLSMD, m.8470_13446del4977 (NC_012920.1) is present in about one third of individuals with an SLSMD syndrome.

Chapter Notes

Author Notes

Mitochondrial Medicine Society (MMS). The MMS is a group of clinicians dedicated to the evaluation, diagnosis, management, and education of mitochondrial disorders.

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Revision History

- 28 September 2023 (sw) Comprehensive update posted live
- 31 January 2019 (sw) Comprehensive update posted live
- 3 May 2011 (me) Comprehensive update posted live
- 8 February 2006 (me) Comprehensive update posted live
- 17 December 2003 (me) Review posted live
- 17 July 2003 (sdm) Original submission

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