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FBXL4-Related Encephalomyopathic Mitochondrial DNA Depletion Syndrome

Synonyms: FBXL4 Deficiency; *FBXL4*-Related Early-Onset Mitochondrial Encephalopathy; Mitochondrial DNA Depletion Syndrome 13 (MTDPS13), Encephalomyopathic Type

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Summary

Clinical characteristics

FBXL4-related encephalomyopathic mitochondrial DNA (mtDNA) depletion syndrome is a multi-system disorder characterized primarily by congenital or early-onset lactic acidosis and growth failure, feeding difficulty, hypotonia, and developmental delay. Other neurologic manifestations can include seizures, movement disorders, ataxia, autonomic dysfunction, and stroke-like episodes. All affected individuals alive at the time they were reported (median age: 3.5 years) demonstrated significant developmental delay. Other findings can involve the heart (hypertrophic cardiomyopathy, congenital heart malformations, arrhythmias), liver (mildly elevated transaminases), eyes (cataract, strabismus, nystagmus, optic atrophy), hearing (sensorineural hearing loss), and bone marrow (neutropenia, lymphopenia). Survival varies; the median age of reported deaths was two years (range 2 days – 75 months), although surviving individuals as old as 36 years have been reported. To date *FBXL4*-related mtDNA depletion syndrome has been reported in 50 individuals.

Diagnosis/testing

The diagnosis of *FBXL4*-related mtDNA depletion syndrome is established in a proband by identification of biallelic pathogenic variants in *FBXL4* on molecular genetic testing.

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Management

Treatment of manifestations: Management is best provided by a multidisciplinary team including neurology, nutrition, clinical genetics/metabolism, and developmental pediatrics. Other specialties may be involved as needed. To date no definite treatment is available; thus, treatment is mainly supportive: assuring adequate nutrition and standard treatment of neurologic complications including developmental delay / intellectual disability, seizures, cardiac complications, eye involvement, and hearing loss. Administration of cofactors and antioxidants, used in mitochondrial disorders with (generally) limited evidence of benefit, may be considered.

Surveillance: No surveillance guidelines have been published. The treating physician should decide about the frequency of follow up of eyes, hearing, heart, feeding difficulties, liver, neurologic complications, and neutropenia based on the patient's findings.

Genetic counseling

FBXL4-related mtDNA depletion syndrome is inherited in an autosomal recessive manner. When both parents are heterozygous carriers, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier (heterozygote), and a 25% chance of being unaffected and not a carrier. Once the *FBXL4* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

FBXL4-related encephalomyopathic mitochondrial DNA (mtDNA) depletion syndrome **should be suspected** in individuals with early-onset (often congenital) lactic acidosis along with a combination of the following clinical features, brain MRI findings, and supportive laboratory findings.

Clinical features

- Developmental delay. Often global with severe speech impairment and lack of ambulation
- Neurologic findings, Hypotonia, seizures, movement disorders, such as ataxia, autonomic dysfunction
- Feeding difficulty and failure to thrive
- Abnormal growth. Intrauterine growth restriction, short stature, microcephaly (congenital and acquired)
- Cardiovascular abnormalities. Hypertrophic cardiomyopathy, congenital heart malformations, arrhythmia, pulmonary hypertension

Brain MRI findings

- White matter abnormalities (19/32 individuals reported). T_2-weighted hyperintensities, delayed or poor myelination, and leukodystrophic changes
- Cerebral atrophy (14/32). Progressive; could be evident as early as age three months [Bonnen et al 2013, Huemer et al 2015]
- Basal ganglia abnormalities, including lesions and abnormal signal intensities (11/32)
- Pervientricular cysts (9/32)
- Thin corpus callosum (6/32)
- Cerebellar hypoplasia (6/32)
- Arachnoid cysts (4/32)
- Brain stem atrophy (4/32)
- Stroke-like episodes (1/32) [Ebrahimi-Fakhari et al 2015]

Only one child (who died at age 20 months) was reported to have a normal brain MRI [Bonnen et al 2013].

MR spectroscopy may show high lactate peak in the brain and cerebrospinal fluid [Bonnen et al 2013, Antoun et al 2016, Barøy et al 2016, Dai et al 2017].

Supportive laboratory findings

- Persistently elevated lactate levels (range: 3-21 mmol/L; median: 13 mmol/L) were observed in all individuals. When assayed, cerebrospinal fluid lactate levels were also elevated [Huemer et al 2015, Barøy et al 2016, Dai et al 2017].
- Hyperammonemia is seen in about 50% of individuals. Although ammonia levels close to 500 µmol/L have been reported [Dai et al 2017], the mean level was 141 µmol/L, median level 99 µmol/L, and range 30-485 µmol/L.
- Mild to moderate elevations in creatine kinase were reported in six of 13 individuals in one study [Huemer et al 2015].
- Muscle tissue and skin fibroblasts show [Bonnen et al 2013, Gai et al 2013, Huemer et al 2015, Antoun et al 2016, Barøy et al 2016, Pronicka et al 2016, Dai et al 2017, Morton et al 2017]:
  - Variably reduced mtDNA content (range: 10%-70%; mean: ~30% of tissue- and age-matched controls); and
  - Decreased activity of multiple complexes on electron transport chain activity assay in 80% of affected individuals. There is usually combined, though variable, deficiency of all complexes.
- Muscle histology can show fiber size variability, lipid and glycogen accumulation, and variable reduction in COX activity. Enlarged and structurally altered mitochondria can be seen on electron microscopy [Bonnen et al 2013, Gai et al 2013, Huemer et al 2015, Antoun et al 2016, Barøy et al 2016, Dai et al 2017].

Establishing the Diagnosis

The diagnosis of *FBXL4*-related mtDNA depletion syndrome **is established** in a proband by identification of biallelic pathogenic variants in *FBXL4* on molecular genetic testing (see Table 1).

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel or single-gene testing) and **genomic testing** (comprehensive genome sequencing) depending on the phenotype.

Gene-targeted testing requires the clinician to determine which gene(s) are likely involved, whereas genomic testing may not. Children with the suggestive clinical, laboratory, and neuroimaging findings could be diagnosed using gene-targeted testing (see Option 1), whereas those with clinical features indistinguishable from many other mitochondrial disorders are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the clinical, laboratory, and brain MRI findings suggest the diagnosis of *FBXL4*-related mtDNA depletion syndrome, molecular genetic testing approaches can include **single-gene testing** and use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *FBXL4* is performed first. If only one pathogenic variant is found, gene-targeted deletion/duplication analysis could be considered; however, to date no exon or whole-gene deletions have been reported.
- **A multigene panel** that includes *FBXL4* and other genes related to mtDNA depletion syndromes (see Differential Diagnosis) may also be considered. 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*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic

cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Of note, given the rarity of *FBXL4*-related mtDNA depletion syndrome some panels for mtDNA depletion syndromes may not include this gene. (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.

Option 2

When the phenotype is indistinguishable from many other mitochondrial disorders molecular genetic testing approaches can include a combination of **genomic testing** (comprehensive genome sequencing) or **gene-targeted testing** (multigene panel):

- **Comprehensive genomic testing** (when available) includes exome sequencing and genome sequencing [Wortmann et al 2015, Pronicka et al 2016].

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

- **A multigene panel** for inherited mitochondrial disorders may also be considered.

Table 1. Molecular Genetic Testing Used in *FBXL4*-Related mtDNA Depletion Syndrome

Gene [1]	Method	Proportion of Probands with Pathogenic Variants [2] Detectable by Method
FBXL4	Sequence analysis [3]	50/50 [4]
	Gene-targeted deletion/duplication analysis [5]	None reported to date

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Bonnen et al [2013], Gai et al [2013], Huemer et al [2015], Antoun et al [2016], Barøy et al [2016], Pronicka et al [2016], van Rij et al [2016], Dai et al [2017], Morton et al [2017]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Clinical Characteristics

Clinical Description

FBXL4-related mtDNA depletion syndrome has been reported in 50 individuals to date [Bonnen et al 2013, Gai et al 2013, Huemer et al 2015, Antoun et al 2016, Barøy et al 2016, Pronicka et al 2016, van Rij et al 2016, Dai et al 2017, Morton et al 2017]. It mainly presents as congenital lactic acidosis along with developmental delay, other neurologic manifestations, feeding difficulty, growth failure, and variable involvement of other organs.

Age of onset was soon after birth in the majority of reported individuals (median age of onset: one day; range 1 day – 13 years). Only five individuals presented after age six months, including a female presenting at age 13 years [Pronicka et al 2016].

In two children, the disease presented prenatally: one male was born at 26 weeks' gestation following preterm labor resulting from polyhydramnios that was believed to be due to hypotonia and decreased fetal movement [van Rij et al 2016]; another male was delivered at 34 weeks' gestation due to prenatally diagnosed supraventricular tachycardia [Dai et al 2017].

The common clinical manifestations summarized in Table 2 are discussed below the table.

Table 2. Clinical Manifestations of *FBXL4*-Related Mitochondrial DNA Depletion Syndrome

Clinical Manifestation	Frequency
Neurologic	**50/50 (100%)**
• Developmental delay • Hypotonia • Seizures • Movement disorders [1] • Ataxia • Autonomic dysfunction • Stroke-like episodes	• 45/45 (100%) • 39/42 (93%) • 14/42 (33%) • 5/17 (29%) • 4/15 (27%) • 3/12 (25%) • 1/32 (3%)
Growth	
• Failure to thrive • IUGR • Short stature • Microcephaly (congenital & acquired)	• 25/33 (76%) • 18/31 (58%) • 17/31 (55%) • 14/36 (39%)
Gastrointestinal	
• Feeding difficulties • Hepatopathy	• 27/31 (87%) • 8/24 (33%)
Cardiac	**20/37 (54%)**
• Cardiomyopathy • Congenital heart malformations • Arrhythmia • Pulmonary hypertension	• 10/37 (27%) • 7/37 (19%) • 6/41 (15%) • 4/37 (11%)
Ophthalmologic	**20/30 (67%)**
• Cataract • Strabismus • Nystagmus • Optic atrophy	• 5/30 (17%) • 5/31 (16%) • 6/30 (20%) • 3/30 (10%)
Other	
• Neutropenia • Hearing impairment	• 8/43 (19%) • 4/33 (12%)

IUGR = intrauterine growth restriction, defined as birth weight <10th centile

1. Movement disorders reported include dystonia, choreoathetosis, hyperkinetic movements, and tremors [Gai et al 2013, Barøy et al 2016, Pronicka et al 2016].

Neurologic. Developmental delay is usually global, associated with severe speech impairment and lack of ambulation in the majority of reported cases. All affected individuals alive at the time they were reported (age range: 1 month – 36 years; median age: 3.5 years) demonstrated significant developmental delay [Gai et al 2013, Huemer et al 2015, Antoun et al 2016, Barøy et al 2016, Pronicka et al 2016, Dai et al 2017].

Hypotonia is severe and early onset, often presenting in the neonatal period.

Seizures started at age four months in one infant [Dai et al 2017]. Seizure types reported include complex partial seizures [Barøy et al 2016] and absence and generalized seizures [Gai et al 2013].

Other less commonly reported neurologic manifestations for which clinical information is available include:

- Movement disorders including hyperkinetic movements [Barøy et al 2016], dystonia and choreoathetosis [Gai et al 2013], and tremors [Pronicka et al 2016];
- Recurrent stroke-like episodes starting at age ten years in a girl who was reported at age 13 years [Ebrahimi-Fakhari et al 2015, Huemer et al 2015].

Gastrointestinal manifestations. Feeding difficulties are a major problem for most individuals with *FBXL4*-related mtDNA depletion syndrome. Factors contributing to the feeding difficulties include hypotonia, gastroesophageal reflux disease, frequent vomiting, and swallowing dysfunction. Recurrent aspiration was reported in six individuals [Gai et al 2013]. Many require nasogastric tube feeding or gastrostomy.

Hepatopathy manifests as mildly elevated transaminases. Liver failure has not been reported to date. Of note, one individual with baseline mild increases in transaminases experienced further increase in liver enzymes following initiation of a ketogenic diet (initiated due to initial suspicion of pyruvate dehydrogenase deficiency) [Barøy et al 2016].

Cardiac. Cardiomyopathy, the most common cardiac manifestation, is typically hypertrophic. Left ventricular non-compaction was reported in one individual [Huemer et al 2015].

Congenital heart malformations include atrial septal defect, ventricular septal defect, patent foramen ovale, patent ductus arteriosus, tricuspid regurgitation, and tetralogy of Fallot (TOF). Other than TOF, the reported cardiac malformations are either relatively common or physiologic, bringing into question whether these are true associations or chance occurrences.

Arrhythmias include supraventricular tachycardia and Wolff-Parkinson-White syndrome [Antoun et al 2016, Barøy et al 2016, Dai et al 2017].

Ophthalmologic. Cataract was congenital in three individuals [Bonnen et al 2013, Gai et al 2013, Huemer et al 2015].

Other reported eye findings include nystagmus and optic atrophy [Huemer et al 2015, Morton et al 2017].

Immunologic. Neutropenia was either episodic or persistent. Neutropenia appeared to predispose to infections and poor wound healing [Huemer et al 2015].

One individual had lymphopenia and hypogammaglobulinemia in addition to neutropenia [Antoun et al 2016].

Even without neutropenia, some individuals were prone to recurrent infections which in some cases resulted in metabolic decompensation and death [Bonnen et al 2013, Gai et al 2013].

Distinctive facial features. About 70% of affected individuals have some variable distinctive facial features, including the following: thick eyebrows, short, upslanted palpebral fissures with epicanthus, broad nasal bridge, bulbous nasal tip, and smooth and long philtrum.

Less frequently reported manifestations

- Respiratory distress, likely due to hypotonia and weak muscles, was reported in six individuals [Gai et al 2013, Dai et al 2017].
- Sensorineural hearing impairment was reported in four individuals [Huemer et al 2015, Barøy et al 2016, Dai et al 2017, Morton et al 2017].
- Other uncommon features include renal tubular acidosis (5 individuals), progressive scoliosis (2 individuals), non-specified exercise intolerance (4 individuals), and sleep dysfunction.
- Several males had hypospadias and/or cryptorchidism. One male had hypoplastic scrotum [Huemer et al 2015].

- One individual developed exocrine pancreatic deficiency [Gai et al 2013].

Prognosis. *FBXL4*-related mtDNA depletion syndrome is associated with a high rate of death in childhood: 43% (20 of 47) of reported children are deceased; seven died early in infancy. The median age of death was two years (range 2 days – 75 months). The 27 individuals alive at the time that they were reported ranged in age from one month to 36 years (median age: 3.5 years). Because of the small number of reported individuals, it is possible (indeed, likely) that the published literature is biased towards more severe cases and, thus, the full clinical spectrum (and prognosis) is yet to be appreciated.

Genotype-Phenotype Correlations

No genotype-phenotype correlations are known.

Prevalence

FBXL4-related mtDNA depletion syndrome is rare; the exact prevalence is unknown.

To date, 50 affected individuals from different ethnic groups – including Arabs, persons of northern European heritage, and Latin Americans/Hispanics – have been reported [Bonnen et al 2013, Gai et al 2013, Huemer et al 2015, Antoun et al 2016, Barøy et al 2016, Pronicka et al 2016, van Rij et al 2016, Dai et al 2017, Morton et al 2017].

Consanguinity was reported in 64% of cases.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with biallelic pathogenic variants in *FBXL4*.

Differential Diagnosis

FBXL4-related mtDNA depletion syndrome needs to be differentiated from other mtDNA depletion syndromes, a genetically and clinically heterogeneous group of autosomal recessive disorders that are characterized by a severe reduction in mtDNA content leading to impaired energy production in affected tissues and organs.

Mitochondrial DNA depletion syndromes occur as a result of defects in mtDNA maintenance caused by pathogenic variants in nuclear genes that function in either mitochondrial nucleotide synthesis (e.g., *TK2*, *SUCLA2*, *SUCLG1*, *RRM2B*, *DGUOK*, and *TYMP*) or mtDNA replication (e.g., *POLG* and *TWNK*). The function of *FBXL4* is not yet known.

Mitochondrial DNA depletion syndromes are phenotypically classified into myopathic, encephalomyopathic, hepatocerebral, and neurogastrointestinal forms (Table 3) [El-Hattab & Scaglia 2013].

Myopathic forms present in infancy or early childhood with hypotonia, proximal muscle weakness, and feeding difficulty. Cognition is usually spared. Typically, there is rapid progression of muscle weakness with respiratory failure and death within a few years of onset.

Encephalomyopathic mtDNA depletion syndromes present in infancy with hypotonia and developmental delay. Depending on the underlying defect, other features, including deafness, movement disorders, Leigh like syndrome, and renal disease, can be observed.

Hepatocerebral forms present with early-onset liver dysfunction and neurologic involvement, including developmental delay, abnormal eye movements, and peripheral neuropathy.

Neurogastrointestinal forms, the prototype of which is mitochondrial neurogastrointestinal encephalopathy (MNGIE) disease, present in adolescence to early adulthood with progressive gastrointestinal dysmotility, cachexia, and peripheral neuropathy.

Table 3. Mitochondrial DNA Depletion Syndromes

Phenotype [1]	Gene	Mitochondrial DNA Depletion Syndrome #, Type	Reference [2]
Hepato-cerebral	*DGUOK*	3, hepatocerebral type	Deoxyguanosine Kinase Deficiency
	POLG	4A, Alpers type	*POLG*-Related Disorders
	MPV17	6, hepatocerebral type	*MPV17*-Related Hepatocerebral Mitochondrial DNA Depletion Syndrome
	TWNK (C10orf2)	7, hepatocerebral type	OMIM 271245
	TFAM	15, hepatocerebral type	OMIM 617156
Encephalo-myopathic	*SUCLA2*	5, encephalomyopathic type w/methylmalonic aciduria	*SUCLA2*-Related Mitochondrial DNA Depletion Syndrome, Encephalomyopathic Form with Methylmalonic Aciduria
	FBXL4	13, encephalomyopathic type	*FBXL4*-Related Encephalomyopathic Mitochondrial DNA Depletion Syndrome
	SUCLG1	9, encephalomyopathic type with methylmalonic aciduria	*SUCLG1*-Related mtDNA Depletion Syndrome, Encephalomyopathic Form with Methylmalonic Aciduria
	RRM2B	8A, encephalomyopathic type w/renal tubulopathy	*RRM2B*-Related Mitochondrial Disease
	OPA1	14, encephalocardiomyopathic type	OMIM 616896
	ABAT	Encephalomyopathic type	OMIM 613163
Neurogastro-intestinal	*TYMP*	1, MNGIE type	Mitochondrial Neurogastrointestinal Encephalopathy Disease
	POLG	4B, MNGIE type	*POLG*-Related Disorders
	RRM2B	8B, MNGIE type	*RRM2B*-Related Mitochondrial Disease
Myopathic	*TK2*	2, myopathic type	*TK2*-Related Mitochondrial DNA Depletion Syndrome, Myopathic Form
	AGK	10, cardiomyopathic type (Sengers syndrome)	OMIM 212350
	MGME1	11, myopathic type	OMIM 615084
	SLC25A4	12B, cardiomyopathic type	OMIM 615418

1. Within each phenotypic category, mtDNA depletion syndromes are ordered by relative prevalence.
2. See hyperlinked *GeneReview* or OMIM phenotype entry for more information.

Management

Evaluations Following Initial Diagnosis

To establish the extent of the disease and needs in an individual diagnosed with *FBXL4*-related mtDNA depletion syndrome, the evaluations following diagnosis (if not performed as part of the evaluation that led to diagnosis) listed in Table 4 are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Eyes	Ophthalmologic eval	

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
ENT	Hearing assessment	
Cardiovascular	Cardiac eval w/EKG & echocardiography	Consider referral to cardiologist if results are abnormal.
Gastrointestinal	Nutritional eval; swallowing assessment for feeding difficulties	
	Eval of liver function w/AST/ALT, bilirubin, total protein, albumin, & coagulation profile	
Neurologic	• Neurology consultation incl comprehensive neurologic exam • Brain MRI to evaluate extent of disease	
	Electroencephalogram	If history of seizures
Immunologic	Complete blood count to evaluate for neutropenia	Consider more detailed immunologic eval if history of recurrent infections.
Miscellaneous/ Other	Developmental eval to provide baseline level of functioning & recommendations for services (speech, occupational, & physical therapy)	
	Consultation w/clinical geneticist &/or genetic counselor	

Treatment of Manifestations

Management is best provided by a multidisciplinary team including neurology, nutrition, clinical genetics / metabolism, and developmental pediatrics. Other specialties including gastroenterology, cardiology, hematology, immunology, ophthalmology, and nephrology may be involved based on the associated complications.

No definite treatment is available to date; thus, treatment is mainly supportive (Table 5). Administration of cofactors and antioxidants, used in mitochondrial disorders with (generally) limited evidence of benefit, may be considered.

Table 5. Treatment of Manifestations in Individuals with *FBXL4*-related mtDNA depletion syndrome

Manifestation/Concern	Treatment	Considerations/Other
Inadequate nutrition	A nasogastric tube or gastrostomy tube are frequently needed due to feeding difficulties & failure to thrive.	In 1 affected child, improved nutrition resulted in improvement in hypogammaglobulinemia & neutropenia. [1]
Seizures	Standard treatment w/antiepileptic drugs	
Immobility/wheelchair dependence	Consultation w/physical medicine & rehab specialists to help w/mobility or assistive devices (e.g., wheelchair)	
Cardiomyopathy & arrhythmia	Standard treatment per cardiologist recommendations	
Neutropenia	Consider granulocyte colony stimulating factor. [2]	
Significant acidosis	Consider bicarbonate therapy.	
Cataract &/or strabismus	Surgical treatment if indicated	
Hearing loss	Hearing aids	

1. Antoun et al [2016]
2. Huemer et al [2015]

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy. In the United States, early intervention is a federally funded program available in all states.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed.

Ages 5-21 years

- In the US, an IEP based on the individual's level of function should be developed by the local public school district. Affected children are permitted to remain in the public school district until age 21.
- Discussion about transition plans including financial and medical arrangements should begin at age 12 years. Developmental pediatricians can provide assistance with transition to adulthood.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies and to support parents in maximizing quality of life.

Consideration of private supportive therapies based on the affected individual's needs is recommended. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.

In the US:

- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility.
- Consider use of durable medical equipment as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function (e.g., feeding, grooming, dressing, and writing).

Oral motor dysfunction. Assuming that the individual is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended for affected individuals who have difficulty feeding due to poor oral motor control.

Communication issues. Consider evaluation for alternative means of communication (e.g., Augmentative and Alternative Communication) for individuals who have expressive language difficulties.

Prevention of Secondary Complications

Regular immunization to prevent life-threatening infections is indicated.

Antibiotic prophylaxis may be indicated for those with immunodeficiency [Antoun et al 2016].

Surveillance

No surveillance guidelines have been published. The following evaluations should be performed on a regular basis, with the treating physician determining the frequency based on initial presentation and severity of the condition.

Table 6. Recommended Surveillance for Individuals with *FBXL4*-Related mtDNA Depletion Syndrome

System/Concern	Evaluation
Eyes	Ophthalmologic eval
ENT/Mouth	Hearing eval
Cardiovascular	Echocardiogram & electrocardiogram to monitor for development of cardiomyopathy &/or arrhythmia, respectively
Gastrointestinal	Continued assessment of nutrition & growth
	Measurement of serum lactate, electrolytes, & liver function tests w/AST/ALT, bilirubin, total protein, albumin, & coagulation profile
Neurologic	Regular neurologic evals & developmental assessments
Immunologic	Complete blood count

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 access to 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

FBXL4-related mtDNA depletion syndrome is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are typically heterozygotes (i.e., carriers of one *FBXL4* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- In the (usual) instance in which both parents are carriers: at conception, each sib of an affected individual has 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. *FBXL4*-related mtDNA depletion syndrome is typically lethal before reproductive age.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *FBXL4* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *FBXL4* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing 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 carriers or are at risk of being carriers.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the *FBXL4* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

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 Charlie Gard Foundation**
  United Kingdom
  Email: hello@thecharliegardfoundation.org
  www.thecharliegardfoundation.org
- **United Mitochondrial Disease Foundation**
  Phone: 888-317-UMDF (8633)
  Email: info@umdf.org
  www.umdf.org
- **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 A. FBXL4-Related Encephalomyopathic Mitochondrial DNA Depletion Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
FBXL4	6q16.1-q16.2	F-box/LRR-repeat protein 4	FBXL4	FBXL4

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for FBXL4-Related Encephalomyopathic Mitochondrial DNA Depletion Syndrome (View All in OMIM)

605654	F-BOX AND LEUCINE-RICH REPEAT PROTEIN 4; FBXL4
615471	MITOCHONDRIAL DNA DEPLETION SYNDROME 13 (ENCEPHALOMYOPATHIC TYPE); MTDPS13

Gene structure. *FBXL4* comprises nine exons and spans 79 kb. See Table A, **Gene** for a detailed summary of gene and protein information.

Pathogenic variants. About 50% of reported variants are missense; others include nonsense, splice site, and frameshift variants [Bonnen et al 2013, Gai et al 2013, Huemer et al 2015, Antoun et al 2016, Barøy et al 2016, Pronicka et al 2016, van Rij et al 2016, Dai et al 2017].

Normal gene product. *FBXL4* encodes the F-box and leucine-rich repeat protein 4 (FBXL4) which localizes to the mitochondria via a mitochondrial targeting sequence [Bonnen et al 2013, Gai et al 2013]. While the exact function of this protein is not known, it is believed to have an important role in mitochondrial maintenance. This is supported by findings in muscle tissue and/or skin fibroblasts from individuals with biallelic *FBXL4* pathogenic variants which showed decreased activity of multiple respiratory chain enzymes, disturbance of the mitochondrial network, loss of membrane potential, and variable depletion of mitochondrial DNA content [Bonnen et al 2013, Gai et al 2013, Antoun et al 2016]. Of note, these biochemical defects were rescued by introduction of wild type *FBXL4* [Bonnen et al 2013, Gai et al 2013].

Abnormal gene product. *FBXL4* pathogenic variants result in loss of FBXL4 protein function, which in turn results in impaired mtDNA maintenance manifesting as mtDNA depletion and impaired energy production [Bonnen et al 2013, Gai et al 2013].

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Chapter Notes

Revision History

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