Coffin-Lowry Syndrome

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Summary

Clinical characteristics.

Coffin-Lowry syndrome (CLS) is usually characterized by severe-to-profound intellectual disability in males; less severely impaired individuals have been reported. Neuropsychiatric concerns can include behavioral problems, loss of strength, progressive spasticity or paraplegia, sleep apnea, or stroke. Stimulus-induced drop attacks (SIDAs) in which unexpected tactile or auditory stimuli or excitement triggers a brief collapse but no loss of consciousness are present in approximately 20% of affected individuals. Typically SIDAs begin between mid-childhood and the teens. Characteristic facial features may be more apparent with age. Upper-extremity differences may be subtle and include short, soft, fleshy hands with tapered fingers as well as fleshy forearms. Progressive kyphoscoliosis is one of the most difficult aspects of long-term care. Affected females tend to have intellectual disability in the mild to moderate range and may also have the typical facial, hand, and skeletal findings noted in males.

Diagnosis/testing.

The diagnosis of CLS is established in males with the identification of a hemizygous pathogenic variant in *RPS6KA3*. The diagnosis of CLS is usually established in a female proband with identification of a heterozygous pathogenic variant in *RPS6KA3* by molecular genetic testing. Genetic mechanisms other than skewed X-chromosome inactivation in a heterozygous female (e.g., biallelic *RPS6KA3* pathogenic variants or whole or partial deletion of one X chromosome in a female with an *RPS6KA3* pathogenic variant on her other X chromosome) have been reported. Careful examination of an intellectually normal female relative of an affected individual may reveal mild facial and/or hand manifestations.

Management.

Treatment of manifestations: SIDAs are treated with medications such as clonazepam, valproate, selective serotonin reuptake inhibitors, or benzodiazepines; trials with different medications with efforts to optimize the dosage may be needed to improve outcome. Individuals who experience frequent SIDAs may require use of a protective helmet or a wheelchair and should be protected, if possible, from being startled. Risperidone may be of benefit to individuals who display destructive or self-injurious behavior. Feeding difficulties,

abnormal growth velocity, behavioral problems, kyphoscoliosis, and obesity (if present) are treated in a standard manner.

Prevention of secondary complications: Intervention to prevent progression of kyphoscoliosis to the point of cardiorespiratory compromise.

Surveillance: Periodic hearing, dental, and vision examinations; annual clinical cardiac examination, adding an echocardiogram every five to ten years; regular monitoring of the spine for progressive kyphoscoliosis.

Agents/circumstances to avoid: Individuals who experience SIDAs should be protected as much as possible from being startled and/or from falls.

Genetic counseling.

CLS is inherited in an X-linked manner. Approximately 70%-80% of probands have no family history of CLS, and 20%-30% have more than one additional affected family member. Children of a woman known to be heterozygous are at 50% risk of inheriting the pathogenic variant. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be heterozygous and at high risk for at least some developmental delay and mild physical signs of CLS. Molecular genetic testing for at-risk female relatives and prenatal testing for pregnancies at increased risk are possible in families in which the pathogenic variant has been identified in an affected family member.

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Diagnosis

Coffin-Lowry syndrome is an X-linked intellectual disability disorder. Individuals recognized to have this disorder are typically male, although affected females have also been reported. There are no formal diagnostic criteria.

Suggestive Findings

Coffin-Lowry syndrome (CLS) **should be suspected in a male** with the following findings:

- **Developmental delay / intellectual disability.** Affected males typically have moderate-to-severe intellectual disability; since the advent of molecular genetic testing, more mildly affected males are being identified [Field et al 2006].
- **Characteristic craniofacial features** (particularly in an affected older child or adult; see Figure 1, Figure 2, and Figure 3):
    - Usually prominent forehead and supraorbital ridges with thick eyebrows
    - Usually marked widely spaced eyes with downslanted palpebral fissures; occasionally, relatively normal periorbital region with mild telecanthus
    - Consistent, often striking, nasal findings including depressed bridge, blunt tip, and thick alae nasi and septum, resulting in small nares
    - Wide mouth, usually held open; thick vermilion of the upper and lower lips with everted vermilion of the lower lip

    - Coarse facial appearance in childhood with progression to a more "pugilistic" look with age
    - Prominent ears
- **Upper extremity differences**
    - Short, soft, fleshy hands, often with remarkably hyperextensible fingers, and a short horizontal palmar crease across the hypothenar area
    - Fingers that taper markedly from relatively wide proximally to narrow distally, with small terminal phalanges and nails (see Figure 4). The differences in the hands may sometimes be subtle (see Figure 5).
    - Soft, malleable hands with an almost "plush-cushion" feel to the palm, as may be seen in an obese individual
    - Full, fleshy forearms: a potentially useful sign in diagnosing a younger child
- **Musculoskeletal features**
    - Frequent pectus carinatum and/or excavatum
    - Childhood onset of kyphoscoliosis that is often progressive

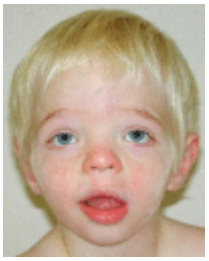

Figure 1.

AP view of a boy age two years with CLS showing relatively fine facial features but with widely spaced eyes, mildly downslanted palpebral fissures, short nose with broad columella, and thick, slightly everted vermilion of the lips (Affected individual (more...)

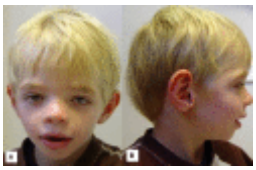

Figure 2.

AP and lateral view of the same boy in Figure 1 at age five years, showing a more triangular-shaped face, increasing coarseness, and expression of the typical facial signs of CLS (Affected individual has a known *RPS6KA3* pathogenic variant.)

Figure 3.

AP view of an adolescent showing relatively mild facial signs but with widely spaced eyes, mildly downslanted palpebral fissures, thick vermilion of the upper and lower lips, and small teeth. The columnella is broad but nares are a good size, perhaps (more...)

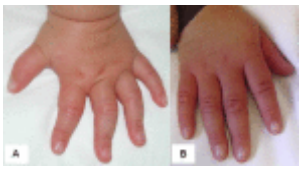

Figure 4.

Hand of the child illustrated in Figure 1 and Figure 2 A. At age two years

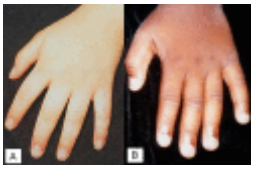

Figure 5

A. Hand of an older child showing classic tapering and soft appearance B. More subtle differences seen in the hand of the individual illustrated in Figure 3

Note: Several authors have stated that the diagnosis may be difficult in the young child. Indeed, more than in most syndromes, the facial characteristics of CLS become increasingly discernible with age. However, even in neonates, the diagnosis of CLS is most often apparent if considered.

Radiographic findings in CLS are nonspecific individually or as a pattern but may be helpful when the diagnosis is suspected [Hanauer & Young 2002]:

- Thickened skull with large frontal sinuses
- Anterior beaking of the vertebrae with narrow disc spaces and related degenerative vertebral changes
- Kyphoscoliosis
- Narrow pelvis
- Metacarpal pseudoepiphyses, poor modeling of the middle phalanges, and tufting of the distal phalanges (Metacarpophalangeal profiles do not appear to aid diagnosis.)
- In some individuals, mild cerebral atrophy, hypoplasia of corpus callosum, periventricular white matter changes in parietal and frontal lobes, and/or compression of the foramen magnum on cranial MRI [Tos et al 2015, Upadia et al 2017]

CLS **should be suspected in a female** with any of the characteristics listed as raising suspicion in males.

- Females with full manifestation (including mild-to-moderate intellectual disability with typical facial, hand, and skeletal findings) have been reported [Young 1988, Plomp et al 1995, Fryssira et al 2002, Hunter 2002, Jurkiewicz et al 2010].
- Careful examination of an intellectually normal female relative of an affected individual may reveal mild facial and/or hand manifestations.

Establishing the Diagnosis

Male proband. The diagnosis of CLS **is established in a male proband** by identification of a hemizygous pathogenic variant in *RPS6KA3* (also known as *RSK2*) on molecular genetic testing (see Table 1).

Female proband. The diagnosis of CLS **is usually established in a female proband** by identification of a heterozygous pathogenic variant in *RPS6KA3* on molecular genetic testing (see Table 1). Genetic mechanisms other than skewed X-chromosome inactivation in a heterozygous female (e.g., biallelic *RPS6KA3* pathogenic variants or whole or partial deletion of one X chromosome in a female with a *RPS6KA3* pathogenic variant on her other X chromosome) have been reported [Jacquot et al 2002].

Molecular testing approaches can include **single-gene testing**, use of a **multigene panel**, and **more comprehensive genomic testing**:

- **Single-gene testing.** Sequence analysis of *RPS6KA3* is performed first and followed by gene-targeted deletion/duplication analysis if no pathogenic variant is found.
- **A multigene panel** that includes *RPS6KA3* and other genes of interest (see Differential Diagnosis) may 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. (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.

- **More comprehensive genomic testing** (when available) including exome sequencing and genome sequencing may be considered. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene or genes that results in a similar clinical presentation).

  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 Coffin-Lowry Syndrome

Gene [1]	Test Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by This Method
RPS6KA3	Sequence analysis [3, 4, 5]	90%-95% [6]
	Gene-targeted deletion/duplication analysis [7]	5%-10% [6]
Unknown [8]	NA	

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. 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. Lack of amplification by PCR prior to sequence analysis can suggest a putative (multi)exon or whole-gene deletion on the X chromosome in affected males; confirmation requires additional testing by gene-targeted deletion/duplication analysis.

5. Note: Schneider et al [2013] identified a deep intronic pathogenic variant that results in an aberrant protein that would not be detected by routine sequencing of exon region.

6. Human Gene Mutation Database, Delaunoy et al [2001], Delaunoy et al [2006]

7. 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.

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Clinical Characteristics

Clinical Description

Individuals recognized to have this disorder are typically male, although affected females have also been reported. Such females have findings that range from severe (as seen in males) to very mild. As more individuals (both male and female) are identified through molecular testing prior to a suspected clinical diagnosis, milder manifestations are being recognized.

Manouvrier-Hanu et al [1999] reported two sibs with an unusually mild presentation associated with a missense variant. The authors are aware of an individual with a proven *RPS6KA3* pathogenic missense variant who is able to work in a fast-food restaurant [C Skinner, personal communication].

Age at diagnosis is variable based on the physical features and availability of testing.

Development

Coffin-Lowry syndrome (CLS) is typically characterized by severe-to-profound intellectual disability in males, although those with mild disability have been reported [Young 1988, Hanauer & Young 2002, Hunter 2002, Pereira et al 2010]. Affected females tend to have intellectual disability in the mild to moderate range.

- Early developmental assessments may overestimate the ultimate developmental prognosis [Hunter 2002]. Early milestones are variably delayed with speech typically more severely affected than motor development.
- Due to hypotonia, individuals may present early in life with feeding problems.

Neuropsychiatric

Individuals with CLS are often described as generally happy and easygoing, although self-injury and other behavioral problems have been reported.

Detailed neurologic assessment may be hampered by the severe intellectual disability. Findings reported include the following:

- Loss of strength and muscle mass
- Both decreased and increased deep tendon reflexes
- Sleep apnea
- Stroke
- Progressive spasticity
- Progressive paraplegia with loss of the ability to walk (ascribed to both calcification of the ligamenta flava and congenital stenosis of the spinal canal [Hunter 2002])
- Stimulus-induced drop attacks (SIDAs) that occur when unexpected tactile or auditory stimuli or excitement triggers a 60- to 80-millisecond electromyographic silence in the lower limbs, resulting in a brief collapse (though no loss of consciousness) [Crow et al 1998, Nakamura et al 1998, Hahn & Hanauer 2012]:
    - See Nelson & Hahn [2003] for a video illustration of SIDAs.
    - Onset occurs between ages four and 17 years and a mean age at onset of 8.6 years [Nakamura et al 2005].
    - SIDAs were reported in 20% (34/170) of individuals in the CLS Foundation database [Stephenson et al 2005].

Changes with age. Stephenson et al [2005] have also emphasized that the nature of the movement disorder may change with age and that a single individual may have more than one type of neurologic sign. The range of manifestations include cataplexy that varies with the stimulus, hyperekplexia, a prolonged tonic reaction, and true epileptic seizures. Epileptic seizures affect approximately 5% of individuals with CLS [Stephenson et al 2005].

Typical Physical Characteristics

See also Suggestive Findings.

Craniofacial. Characteristic craniofacial features (see Figure 1, Figure 2, and Figure 3) may be more apparent with age.

Upper-extremity differences may be subtle. These include short, soft, fleshy hands with tapered fingers as well as fleshy forearms.

Musculoskeletal. Progressive kyphoscoliosis is one of the most difficult aspects of the long-term care of individuals with CLS. The precise prevalence is not known, but at least 47% of affected males and 32% of females have been reported to have progressive kyphoscoliosis [Hunter 2002]. The rates were higher in a series reported from an orthopedic referral clinic [Herrera-Soto et al 2007]. Although no accepted definition of severity has been adopted in published reports, it is clear that the severity often progresses over time and that respiratory compromise caused by kyphoscoliosis may contribute to premature death.

Sternal deformation in the form of pectus carinatum and/or excavatum frequently occurs.

Other minor skeletal changes that may be seen on radiographs are of no clinical consequence.

Cardiovascular. Approximately 14% of affected males and 5% of affected females have cardiovascular disorders [Hunter 2002]. These percentages may be underestimates as many individuals with CLS have not had thorough initial or ongoing cardiac assessment. Reports have included: abnormalities of the mitral, tricuspid, and aortic valves; short chordae; cardiomyopathy (in one individual, with endocardial fibroelastosis); unexplained congestive heart failure; and dilatation of the aorta and of the pulmonary artery [reviewed in Hunter 2002]. An individual reported by Facher et al [2004] had a restrictive cardiomyopathy. Martinez et al [2011] reported an individual with CLS who had left ventricular non-compaction cardiomyopathy with a restrictive pattern. Cardiac anomalies may contribute to premature death. There has not been a systematic review of cardiovascular disorders in individuals with CLS.

Growth. Prenatal growth is normal; growth failure usually occurs early in the postnatal period. Males and severely affected females generally fall below the third centile in height but are expected to track a curve. The reduced height may reflect disproportionately short lower limbs [Hunter 2002, Touraine et al 2002]. While microcephaly is common, many individuals with CLS have a normal head circumference.

Dental. Dental anomalies are common and include small teeth, malpositioning, open bite, hypodontia of secondary teeth, advanced or delayed eruption of primary teeth, and premature loss that appears to have more than one cause. The palate is high. With age, the retrognathia in the younger child tends to be replaced by prognathism.

Hearing loss is reported in 30% [Pereira et al 2010]. Hunter reported hearing loss in 14/89 affected males and 1/22 affected females [Hunter 2002].

- An audiogram may reveal sensorineural hearing loss.
- Malformation of the labyrinth has been reported, as has late onset of hearing loss [Rosanowski et al 1998].
- Clustering of hearing loss within families may occur.

Vision problems. Significant visual problems appear to be uncommon, although cataract, retinal pigment atrophy, and optic atrophy have been reported and the incidence of chronic eyelid irritation (blepharitis) may be increased [reviewed in Hunter 2002].

Neuroimaging studies have not demonstrated a consistent pattern of brain abnormality, but the following findings have been reported [Tos et al 2015, Upadia et al 2017]:

- Abnormalities of the corpus callosum including thinning and agenesis, reported by several authors [Kondoh et al 1998, Wang et al 2006].
- Multiple focal frontal hypodensities visible on MRI [Kondoh et al 1998]. Hypodensities attributed to focal areas of CSF were reported in three affected sibs by Wang et al [2006]; they also showed thinning of the corpus callosum, vermian hypoplasia, and mild ventricular asymmetry. The authors concluded that the degree of intellectual disability correlated with the severity of the MRI findings.
- Periventricular white matter abnormalities
- Constricted foramen magnum (decreased diameter)
- Reduced gray- and white-matter volume without evidence of ventriculomegaly *ex vacuo* on quantitative MRI in affected males and females, suggesting an early neurodevelopmental abnormality such as reduced cellular proliferation [Kesler et al 2007]

Neuropathology. Abnormal gyration and lamination have been noted at autopsy [Coffin 2003].

Other. Findings reported in single individuals include rectal prolapse, uterine prolapse, jejunal diverticuli, colonic diverticuli with reduced ganglion cells, popliteal ganglion, pyloric stenosis, unilateral renal agenesis, anteriorly placed anus, increased facial pigment, and enlarged trachea [reviewed in Hunter 2002].

Mortality. Life span is reduced in some individuals with CLS. Of individuals reported in the literature, death occurred in 13.5% of males and 4.5% of females at a mean age of 20.5 (range: 13-34) years [Hunter 2002].

- Complicating factors have included cardiac anomalies, panacinar emphysema, respiratory complications, progressive kyphoscoliosis, and seizure-associated aspiration.
- Coffin [2003] reported that one of his original patients died at age 18.8 years of pneumonia superimposed on chronic lung and heart disease, and a second individual died at age 18 years of acute food aspiration.
- The authors are aware of an individual with CLS who had life-threatening central and obstructive sleep apnea, and of another male who had a history of chronic obstructive

and central sleep apnea who died from respiratory complications after surgery for jaw advancement.
- One affected male and one obligate heterozygote female died of Hodgkin disease [reviewed in Hunter 2002].

Heterozygous Females

Heterozygous females show markedly variable phenotypes with mild facial coarsening, tapering fingers, short stature, normal intelligence, or varied degrees of intellectual disability. Such individuals may have a higher rate of psychiatric illness than that found in the general population. Six (8.8%) of 68 women (22 females with CLS, 38 unaffected heterozygotes, and 8 "affected" sisters) have had psychiatric diagnoses, including schizophrenia, bipolar disease, and "psychosis" [reviewed in Hunter 2002]. One of two women studied by Micheli et al [2007] was described as having a "psychosis" and one of two affected sisters reported by Wang et al [2006] as having schizophrenia.

Genotype-Phenotype Correlations

Although no strong correlation exists between phenotype and location or type of *RPS6KA3* pathogenic variant, individuals with certain missense pathogenic variants may tend to have milder disease expression [Delaunoy et al 2001]. The family classified as having a form of nonsyndromic intellectual disability (MRX19; see Genetically Related Disorders) had a missense variant in *RPS6KA3*, which caused an 80% reduction in ribosomal S6 kinase enzyme activity, in contrast to most pathogenic variants in individuals with CLS, which cause a total loss of ribosomal S6 kinase enzyme activity [Merienne et al 1999]. This finding indicates that some *RPS6KA3* variants probably give rise to non-CLS phenotypes or nonsyndromic X-linked intellectual disability.

Nakamura et al [2005] suggested that truncating variants, either in or upstream from the N-terminal kinase domain, may cause a particular susceptibility to stimulus-induced drop attacks (SIDAs). However, the finding of an affected female with SIDAs who has a heterozygous pathogenic variant in the region encoding the C-terminal kinase domain of the protein would argue against this correlation [Rojnueangnit et al 2014].

Nomenclature

Early authors referred to Coffin syndrome until it was recognized that the individuals reported by Lowry et al [1971] had the same syndrome.

Some early texts and papers confused Coffin-Siris syndrome and CLS.

Prevalence

No estimate of the prevalence of CLS has been published. Based on the authors' experience, a rate of 1:40,000 to 1:50,000 may be reasonable – although it may underestimate the actual prevalence.

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Genetically Related (Allelic) Disorders

Nonsyndromic intellectual disability. Two families have now been reported by Field et al [2006] to have nonsyndromic intellectual disability associated with a pathogenic variant in *RPS6KA3*.

One form of nonsyndromic intellectual disability (MRX19) has been shown to be caused by an *RPS6KA3* pathogenic missense variant [Merienne et al 1999]; another individual with a pathogenic missense variant and only mild intellectual disability was reported by Delaunoy et al [2001].

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Differential Diagnosis

The diagnosis of Coffin-Lowry syndrome (CLS) in the older male child or adult is usually straightforward. The findings in a young child or more mildly affected female may overlap with other syndromes:

- **Borjeson-Forssman-Lehmann syndrome** (BFLS; OMIM 301900) is an X-linked disorder characterized by severe intellectual disability, hand findings similar to those of CLS, short nose with anteverted nares that may have a thick septum and small nares, and kyphoscoliosis. Additional findings are large, prominent ears and visual problems. Individuals with BFLS also have extreme hypogonadism and tend to have marked gynecomastia. Females may show partial expression of the syndrome. Absent findings are marked wide-spaced eyes, wide mouth, and thick vermilion of the lips. Pathogenic variants in *PHF6* are causative [Lower et al 2002].

While CLS shares some facial findings with Williams syndrome, the genetically heterogeneous FG syndrome, X-linked alpha-thalassemia intellectual disability (ATRX) syndrome, and Pitt-Hopkins syndrome, none of these disorders shows the hand changes seen in CLS, and each has additional distinguishing features:

- **Williams syndrome** also includes cardiovascular disease (elastin arteriopathy, peripheral pulmonary stenosis, supravalvular aortic stenosis, hypertension), connective tissue abnormalities, intellectual disability (usually mild), a specific cognitive profile, unique personality characteristics, growth abnormalities, and endocrine abnormalities (hypercalcemia, hypercalciuria, hypothyroidism, and early puberty). Feeding difficulties often lead to failure to thrive in infancy. More than 99% of affected individuals have a contiguous gene deletion of the Williams-Beuren syndrome critical region (WBSCR) that encompasses the elastin gene (*ELN*). Williams syndrome is transmitted in an autosomal dominant manner. Most cases are *de novo* occurrences.
- **FG syndrome type 1** (see *MED12*-Related Disorders) shares with CLS: X-linked inheritance, intellectual disability, a broad forehead, widely spaced eyes with downslanted palpebral fissures, a thick vermilion of the lower lip, kyphoscoliosis, pectus excavatum, and characteristic behaviors. It is distinguished by its disproportionate macrocephaly; constipation that may be associated with anal anomalies; broad thumbs and halluces; prominent fingertip pads; and small, rounded, cupped ears that often have an overfolded superior helix [Graham et al 1998].

Hypotonia often evolves into joint restriction. Partial absence of the corpus callosum and fused mammillary bodies are relatively common.

- **Alpha-thalassemia X-linked intellectual disability (ATRX) syndrome** is characterized by distinctive craniofacial features, genital anomalies and severe developmental delays with hypotonia, intellectual disability, and mild-to-moderate anemia secondary to alpha-thalassemia. Genital anomalies range from hypospadias and undescended testes to severe hypospadias and ambiguous genitalia, to normal-appearing female genitalia in individuals with a 46,XY karyotype. ATRX syndrome is caused by pathogenic variants in *ATRX*.
- **Pitt-Hopkins syndrome** is characterized by distinctive facial features that become more apparent with age, significant developmental delay / intellectual disability, and episodic hyperventilation and/or breath-holding while awake, which occurs in about half of affected individuals. Other common findings are behavioral issues, hand stereotypic movements, seizures, constipation, and severe myopia. Pitt-Hopkins syndrome is caused by haploinsufficiency of *TCF4* resulting from either a pathogenic variant in *TCF4* or a deletion of the chromosome region in which *TCF4* is located (18q21.2)

Chromosome disorder. Individuals with a variety of chromosome disorders may have features of Coffin-Lowry syndrome. Two examples:

- McCandless et al [2000] reported a family with del(10)(q25.1q25.3) in which affected members had findings suggestive of CLS.
- Concannon et al [2002] reported an individual with features of CLS and a complex chromosome rearrangement (involving chromosomes 2,3,7, and 11).

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Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Coffin-Lowry syndrome (CLS), the following evaluations are recommended:

- Measurement of height, weight, and head circumference
- History and neurologic examination to assess for changes in gait or in bowel or bladder function and for epilepsy or movement disorder
- Developmental assessment and formulation of an intervention plan
- Complete musculoskeletal examination with particular attention to the chest and spine; radiographic assessment if clinically indicated
- Developmental, age-appropriate hearing assessment
- Dental evaluation
- Physical examination of the heart and ECG, with baseline echocardiogram
- Polysomnographic study to rule out obstructive sleep apnea
- Ophthalmologic evaluation, including refraction and fundoscopy
- Evaluation of appropriate family members for signs of the condition
- Assessment of the family's capacity to care for the child, especially if mother is affected intellectually
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Individuals with CLS should be provided with every opportunity to develop communication skills and to participate in activities and self-care in order to develop a degree of independence.

Awareness of stimulus-induced drop attacks (SIDAs) should allow early intervention to minimize the occurrence of triggering stimuli and to provide protection from falls:

- Trials with different medications and efforts to optimize the dosage may improve outcome [O'Riordan et al 2006, Arslan et al 2014].
    - SIDAs were reduced in an affected person treated with clonazepam [Arslan et al 2014].
    - A trial of antiepileptic drugs (AEDs) (e.g., valproate), or selective serotonin reuptake inhibitors may be indicated [Fryssira et al 2002], although generally they are not effective.
    - Benzodiazepines, sometimes in increasing doses, have proved effective in some cases [Touraine et al 2002, Nakamura et al 2005].
    - In an individual who was not helped by a variety of medications, Havaligi et al [2007] reported a good response with sodium oxybate.
    - Improvement of events occurred in a male after treatment of obstructive sleep apnea with tracheostomy [Imataka et al 2016].
- If attacks occur with great frequency a protective helmet may be indicated and use of a wheelchair may be required to prevent falling and injury.

Risperidone may be of benefit to individuals who display destructive or self-injurious behavior [Valdovinos et al 2002].

Feeding difficulties, abnormal growth velocity, and obesity, if present, should be assessed and treated in a standard manner.

Treatment of behavioral problems is standard and requires periodic reassessment.

Treatment of kyphoscoliosis is standard but requires reassessment well into adulthood.

Prevention of Secondary Complications

Early recognition of spinal problems such as kyphoscoliosis and stenosis may allow prevention of progression and/or intervention to prevent long-term cardiovascular or neurologic complications that may be life threatening.

Similarly, early recognition of some cardiac anomalies may allow prevention of secondary complications or prolongation of adequate function. Some individuals with CLS may require subacute bacterial endocarditis (SBE) prophylaxis.

Attention to vision and hearing may prevent some secondary behavioral changes. Identification and treatment of blepharitis may prevent eye rubbing and potential corneal damage.

Attention to dental hygiene and gum disease may reduce the risk of premature tooth loss.

Surveillance

The following are appropriate:

- Periodic tests of hearing and vision
- Cardiac evaluation performed at diagnosis and annual physical cardiac examination thereafter. Even if initial echocardiogram is normal, it should be repeated every five to ten years in light of uncertainty as to the incidence and range in age of onset of cardiomyopathy [Massin et al 1999, Facher et al 2004].
- Monitoring of the spine for the development of progressive kyphoscoliosis. There should be a high index of suspicion for narrowing of the spinal canal with attention to change in gait and bowel/bladder habits, expression of pain, and focal neurologic changes such as clonus or abnormal tendon reflexes.
- Routine dental evaluation as in the general population but with particular attention to the risk of tooth loss

Note: A table containing suggested guidelines for follow up of individuals with CLS is provided in Hunter [2010].

Agents/Circumstances to Avoid

Individuals with CLS who experience SIDAs should be protected as much as possible from being startled and/or from falls.

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.

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Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Coffin-Lowry syndrome (CLS) is inherited in an X-linked manner.

Approximately 70%-80% of probands have no family history of CLS, and 20%-30% have more than one affected family member [Delaunoy et al 2001]. The high incidence of simplex cases (i.e., CLS in a single individual in a family) can be attributed to genetic selection that occurs against heterozygous females who are intellectually disabled [Jacquot et al 1998a].

Risk to Family Members

Parents of a proband

- Male:
  - If a male is the only affected family member (i.e., a simplex case), the mother may be a heterozygote or the affected male may have a *de novo* *RPS6KA3* pathogenic variant, in which case the mother is not a carrier. About 70%-80% of affected males represent simplex cases, roughly 2/3 of which occur *de novo* [Pereira et al 2010].
  - In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote. Note: If a woman has more than one affected child and no other affected relatives and if the *RPS6KA3* pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism [Jacquot et al 1998b, Horn et al 2001].
  - Recommendations for the mother of a proband include examination for signs of CLS (e.g., coarse facial features, full lips, and/or tapering fingers) and, if a pathogenic variant has been identified in the proband, molecular genetic testing.
  - The father of an affected male will not have the disorder nor will he be hemizygous for the *RPS6KA3* pathogenic variant; therefore, he does not require further evaluation/testing.
- Female:
  - A female proband may have inherited the *RPS6KA3* pathogenic variant from her mother or, in the theoretic case of paternal germline mosaicism, her father.
  - Recommendations for the mother of a proband include examination for signs of CLS and, if a pathogenic variant has been identified in the proband, molecular genetic testing.
- Detailed evaluation of the parents and review of the extended family history may help distinguish probands with a *de novo* pathogenic variant from those with an inherited pathogenic variant. Molecular genetic testing of the mother can typically determine if the pathogenic variant was inherited.

Sibs of a proband

- The risk to the sibs of a proband depends on the genetic status of the mother. Theoretically, the genetic status of the father (if the proband is female) could be a factor in risk to sibs in the event of paternal germline mosaicism for an *RPS6KA3* pathogenic variant.
- If the mother of the proband has a pathogenic variant, the chance of transmitting it in each pregnancy is 50%:
  - Male sibs who inherit the pathogenic variant will be affected; female sibs who inherit the pathogenic variant will be heterozygous and at high risk for at least some developmental delay and mild physical signs of CLS.

    - As expected with random X-chromosome inactivation, a mildly affected woman may have a severely affected daughter.
    - Heterozygous females may show mild-to-moderate skewing of X-chromosome inactivation that does not correlate with IQ [Simensen et al 2002].
- In the absence of any physical signs or intellectual impairment, the mother of a proband with no known family history of CLS is probably at low risk of being heterozygous.
- Germline mosaicism has been demonstrated in this condition. Thus, even if the pathogenic variant found in the proband has not been identified in the mother's DNA, sibs of the proband are still at increased risk of inheriting the pathogenic variant [Jacquot et al 1998b, Horn et al 2001].

Offspring of a proband

- Males and severely affected females with CLS typically do not reproduce.
- Women with CLS have a 50% chance of transmitting the pathogenic variant to each child; sons who inherit the pathogenic variant will be affected; daughters will be heterozygous and at high risk for at least some degree of developmental delay and mild physical signs of CLS.

Other family members. If the mother of the proband is found to have a pathogenic variant, her female family members may be at risk of being heterozygous (asymptomatic or symptomatic); and her male family members may be at risk of being affected depending on their genetic relationship to the proband.

Heterozygote (Carrier) Detection

Molecular genetic testing of at-risk female relatives to determine their genetic status is most informative if the pathogenic variant has been identified in the proband.

Note: (1) Females who are heterozygous for this X-linked disorder will have a range of clinical manifestations (see Clinical Description). (2) Identification of female heterozygotes requires either (a) prior identification of the *RPS6KA3* pathogenic variant in the family; or (b) if an affected male is not available for testing, molecular genetic testing first by sequence analysis, and if no pathogenic variant is identified, by gene-targeted deletion/duplication analysis.

Related Genetic Counseling Issues

Specific counseling issues

- Significant social resources may be required to support developmentally delayed women with CLS and their families with respect to reproductive choices and child care.
- Caution should be used in interpreting the results of molecular genetic testing of a mother of a proband with no known family history of CLS (i.e., a simplex case) in whom a *RPS6KA3* pathogenic variant has been identified. Germline mosaicism has been observed; thus, it is appropriate to offer prenatal testing even when the pathogenic variant identified in an affected offspring is not detected in maternal leukocyte DNA.

Family planning

- The optimal time for determination of genetic risk, clarification of genetic status, and discussion of the availability of prenatal testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young women who are affected, heterozygous, or at risk of being heterozygous.

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 Diagnosis

Once the *RPS6KA3* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis are possible.

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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.

- **Coffin-Lowry Syndrome Foundation**

  Phone: 425-427-0939

  Email: CoffinLowry@gmail.com

  CLSF

- **National Institute of Neurological Disorders and Stroke (NINDS)**

  PO Box 5801

  Bethesda MD 20824

  Phone: 800-352-9424 (toll-free); 301-496-5751; 301-468-5981 (TTY)

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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.

Coffin-Lowry Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
RPS6KA3	Xp22.12	Ribosomal protein S6 kinase alpha-3	RPS6KA3 @ LOVD	RPS6KA3	RPS6KA3

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 Coffin-Lowry Syndrome (View All in OMIM)

300075 RIBOSOMAL PROTEIN S6 KINASE, 90-KD, 3; RPS6KA3
303600 COFFIN-LOWRY SYNDROME; CLS

Molecular Pathogenesis

RPS6KA3 (RSK2), the gene associated with CLS, encodes a growth factor-regulated serine/threonine kinase that is a member of the Ras signaling cascade. Humans have four closely related RPS6KA (RSK) genes; each gene has two non-identical kinase catalytic domains, both of which are required for maximal activity [Yntema et al 1999, Yang et al 2004]. Members of the *RSK* family participate in cellular events such as proliferation and differentiation.

Gene structure. The *RPS6KA3* transcript NM_004586.2 comprises 22 exons; it is named for ribosomal S6 kinase (alternate name: *RSK2*). For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Pathogenic variants in *RPS6KA3* are distributed throughout the gene with no evidence of clustering associated with a specific phenotype.

In the largest study to date (250 individuals), 71 pathogenic variants were found in 86 unrelated families. Almost 60% caused or predicted protein truncation; 38% were missense variants, 20% nonsense variants, 18% errors of splicing, and 21% intragenic deletions or insertions [Delaunoy et al 2001].

A smaller study of 106 unrelated individuals with suspected CLS found 28 pathogenic variants (26%). Of the 28 pathogenic variants, 60% caused or predicted protein truncation; 36% were missense, 21% nonsense, 11% errors of splicing, and 32% intragenic deletions or insertions [Abidi & Schwartz, unpublished].

Splice site pathogenic variants and an intronic LINE-1 insertion that disrupts the normal function of the protein have been reported [Zeniou et al 2002, Martínez-Garay et al 2003, Zeniou et al 2004]. (For more information, see Table A.)

Recently, Schneider et al [2013] have identified a deep intronic pathogenic variant that results in an aberrant protein. This finding warrants analysis for pathogenic variants at the RNA level in all individuals with a highly suggestive clinical diagnosis of CLS and in whom exon screening has failed to detect a pathogenic variant.

Full- and partial-gene duplications have been reported. Matsumoto et al [2013] report a microduplication including the entire *RPS6KA3* in a family with mild ID, ADHD, localization-related epilepsy, and pervasive developmental disorder (PDD). Marques Pereira et al [2007] report an in-frame, tandem multiexon duplication in an individual with CLS. Given the high frequency of Alu sequences within the gene, they suggest that these may be a relatively common event; however, additional studies are needed.

Normal gene product. Ribosomal protein S6 kinase alpha-3 (RPS6KA3) is involved in kinase activation in a number of pathways including ras-MAPK, protein kinase C, and adenyl cyclase [Harum et al 2001, Pereira et al 2010]. RPS6KA3 regulates neurite formation [Ammar et al 2013], mediates activation of PLD1 to produce the lipids required for exocytosis [Zeniou-Meyer et al 2008, Zeniou-Meyer et al 2009], and regulates the release of neurotransmitters [Zeniou-Meyer et al 2010].

Association of *RPS6KA3* with nonsyndromic XLMR (MRX19; see Genetically Related Disorders) as well as CLS indicates that the gene is critical for cognitive function. *RPS6KA3* expression shows both temporal and spatial restriction in human embryogenesis, with homogeneous brain expression from the telencephalon to the rhombencephalon at nine weeks' gestation [Guimiot et al 2004]. *RPS6KA3* has also been shown to activate CREB (*c*AMP *r*esponse *e*lement *b*inding protein), which is involved in neuronal survival and conversion from short- to long-term memory [Harum et al 2001].

RPS6KA3 also plays an important role in maintaining genomic stability by mediating cell cycle progression and DNA repair [Lim et al 2013]. Through the MAPK/RSK pathway and the epidermal growth factor (EGF)-stimulated phosphorylation of histone H3, it appears to play a role in stimulation of the cell cycle between G0 and G1.

Abnormal gene product. Pathogenic variants in *RPS6KA3* give rise to both CLS and nonsyndromic XLMR. The pathogenic variants in individuals with CLS result in the loss of kinase activity of the gene product. However, the pathogenic variant associated with MRX19 occurs outside the kinase domains and results in reduction of RPS6KA3 activity, suggesting that the brain is more sensitive to levels of RPS6KA3 activity than are the other organ systems affected in CLS.

In a sample of seven individuals, Harum et al [2001] showed a correlation between IQ and the degree of attenuation of the RPS6KA3-mediated CREBtide phosphorylation response in lymphoblasts.

Yang et al [2004] proposed that lack of phosphorylation of ATF4 by RPS6KA3 may interrupt the normal regulatory role of ATF4 in osteoblast differentiation, accounting for some of the

bone anomalies seen in CLS, as well as possibly explaining the progressive nature of the kyphoscoliosis

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