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Coffin-Lowry Syndrome

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Summary

Disease characteristics. Coffin-Lowry syndrome (CLS) is characterized by severe to profound mental retardation in males. Intellect ranges from normal to profoundly retarded in heterozygous females. The facial appearance is characteristic in the affected, older male child or adult. The hands are short, soft, and fleshy, often with remarkably hyperextensible fingers that taper from wide (proximally) to narrow with small terminal phalanges and nails. Males are consistently below the third centile in height. Microcephaly is common. Cardiac abnormalities may be present and can contribute to premature death. Stimulus-induced drop episodes (SIDEs), with onset typically from mid-childhood to the teens, may be present in approximately 20% of affected individuals; unexpected tactile or auditory stimuli or excitement triggers a brief collapse but no loss of consciousness. Progressive kyphoscoliosis is one of the most difficult aspects of long-term care. Life span may be reduced.

Diagnosis/testing. The diagnosis of CLS is established in males with severe developmental delay, characteristic craniofacial and hand findings, and radiographic findings. Carrier females may be mildly affected. Molecular genetic testing of *RPS6KA3*, the only gene known to be associated with CLS, can be used to confirm but not to rule out the diagnosis of CLS. Sequence analysis identifies mutations in about 35%-40% of probands.

Management. Treatment for individuals with CLS who experience SIDEs includes medications such as valporate, clonazepam, or selective serotonin uptake inhibitors; individuals who experience frequent SIDEs may require use of 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. Surveillance includes periodic hearing, dental, and vision examinations; annual cardiac examination, including echocardiogram by age ten years and repeated every five to ten years; and regular monitoring of the spine for progressive kyphoscoliosis.

Genetic counseling. CLS is inherited in an X-linked dominant manner. About 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 a carrier are at 50% risk of inheriting the disease-causing mutation. Males who inherit the disease-causing mutation will be affected; females who inherit the disease-causing mutation will be carriers and at high risk for at least some developmental delay and mild physical signs of CLS. Prenatal diagnosis and carrier testing for at-risk pregnancies are available in families in which a disease-causing mutation has been identified in an affected family member or in which linkage studies can exclude the X-chromosome that carries (or potentially carries) the mutation.

Diagnosis

Clinical Diagnosis

Affected Males

Clinical findings. The most important clinical signs of Coffin-Lowry syndrome (CLS) in affected males are the following [Hanauer & Young 2002]:

- **Craniofacial.** In the affected older male child or adult, the facial appearance is characteristic:
  - Usually prominent forehead and eyebrows; full supraorbital ridges
  - Usually marked ocular hypertelorism with downslanting palpebrae; occasionally, relatively normal periorbital region with mild telecanthus
  - Consistent, often striking nasal findings including low bridge, blunt tip, and thick alae nasi and septum, resulting in small nares
  - Large mouth, usually held open; patulous lips with everted lower lip
  - Prominent ears
- **Extremities**
  - 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
  - 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**
  - Frequent *pectus carinatum* and/or *excavatum*
  - Childhood onset of kyphoscoliosis that is often progressive

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 in confirming the diagnosis [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.)

Affected Females

The degree of developmental delay and craniofacial and limb changes ranges from severe (as seen in males) to completely absent. Careful examination of an intellectually normal female relative of an affected individual may reveal mild facial and/or hand manifestations.

Testing

Ribosomal S6 kinase enzyme assay

- Ribosomal S6 kinase enzyme assay, performed on cultured fibroblasts or transformed lymphoblasts, may show reduced activity in males with an *RPS6KA3* mutation. Such testing is available on a research basis only.
- The assay is not useful in females because of the broad range of enzyme activity resulting from X-chromosome inactivation [Delaunoy et al 2001].

Molecular Genetic Testing—*GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory by at least one US CLIA-certified laboratory or a clinical laboratory outside the US. GeneTests does not independently verify information provided by laboratories and does not warrant any aspect of a laboratory's work. Listing in GeneTests does not imply that laboratories are in compliance with accreditation, licensure, or patent laws. Clinicians must communicate directly with the laboratories to verify information.* —ED.

Gene. *RPS6KA3(RSK2*) is the only gene known to be associated with CLS.

Other loci. It has been suggested that not all individuals with a clinical picture thought to be consistent with CLS have mutations in the *RPS6KA3* gene [Delaunoy et al 2001; Zeniou, Pannetier et al 2002]. However, whether this finding points to true genetic heterogeneity in CLS or to clinical lumping of disparate conditions remains to be determined.

Clinical uses

- Confirmatory diagnostic testing
- Carrier testing
- Prenatal diagnosis

Clinical testing

- **Sequence analysis.** Although sequence analysis is available on a clinical basis, no studies have reported the mutation detection rate using this method. The data available on mutation detection rate are from studies using mutation scanning (currently available on a research basis only); it is expected that complete bidirectional sequencing of all exons and the intron-exon boundaries of *RPS6KA3* would be at least as sensitive as the methods used in the following two mutation scanning studies:
  - In a study including more than 250 individuals with the clinical features of CLS, single-strand conformation polymorphism analysis (SSCP), combined in one study with cell function assays, identified mutations in about 37% of

individuals [Jacquot, et al 1998; Delaunoy et al 2001; Zeniou, Pannetier et al 2002].

- In 106 unrelated individuals with CLS, mutations were identified in 26% [Abidi & Schwartz, unpublished]. In this study, one splice site mutation was found by bidirectional sequencing that was initially missed by mutation scanning using SSCP. Of note, almost all of the mutations found in this group were found in the first half of the study, lending support to the view that the low overall detection rate may reflect a lowered clinical threshold for testing.

- **Deletion/duplication analysis** is available clinically to detect the less common large duplications/deletions in *RPS6KA3* in affected individuals.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Coffin-Lowry Syndrome

Test Method	Mutations Detected	Mutation Detection Frequency [1]	Test Availability
Sequence analysis	*RPS6KA3* mutations	~35%-40% [2]	Clinical Testing
Deletion/duplication analysis	*RPS6KA3* deletions/duplications	Unknown	

1. Proportion of affected individuals with a mutation(s) as classified by gene/locus, phenotype, population group, genetic mechanism, and/or test method

2. Mutation detection frequency from studies using mutation scanning (currently available on a research basis only). The sensitivity of complete bidirectional sequencing of all exons and the intron-exon boundaries of *RPS6KA3* is expected to be at least as great as that using mutation scanning.

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

- In an affected male, bidirectional sequencing of the 22 exons of *RPS6KA3* should detect any mutation present in the coding region or at the intron/exon boundaries.
- Deletion/duplication analysis can be considered in individuals in whom a mutation is not identified by sequence analysis.
- An assay of ribosomal S6 kinase enzyme activity can be performed on a research basis in males whose phenotype is consistent with CLS but in whom no *RPS6KA3* mutation is found by sequence analysis; this test is not useful in females.

Genetically Related (Allelic) Disorders

Mild mental retardation. Two sibs with mild expression of CLS were reported to have missense mutations in *RPS6KA3* [Manouvrier-Hanu et al 1999]. One form of nonsyndromic mental retardation (MRX19) has been shown to be caused by an *RPS6KA3* missense mutation [Merienne et al 1999]; another individual with a missense mutation and only mild mental retardation was reported by Delaunoy et al (2001). The advent of molecular genetic diagnosis may aid in confirming the diagnosis of additional mild cases similar to those reported by Manouvrier-Hanu et al (1999).

Clinical Description

Natural History

Development. Coffin-Lowry syndrome (CLS) is characterized by severe to profound mental retardation in males; intellect ranges from normal to profoundly retarded in heterozygous females. Early developmental assessments may overestimate the ultimate developmental prognosis [Hunter 2002].

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 mental retardation. Findings reported include loss of strength and muscle mass, both decreased and increased deep tendon reflexes, sleep apnea, stroke, progressive spasticity, and progressive paraplegia with loss of the ability to walk. The latter has been ascribed to both calcification of the ligamenta flava and congenital stenosis of the spinal canal [Hunter 2002].

Of particular note are stimulus-induced drop episodes (SIDEs), with onset typically from mid-childhood to the teens. Stephenson et al (2005) recorded a prevalence of 20% (34/170) from the CLS Foundation database. Females may also be affected [Fryssira et al 2002]; during a SIDE, unexpected tactile or auditory stimuli or excitement trigger a 60- to 80-millisecond electromyographic silence in the lower limbs that results in a brief collapse though no loss of consciousness [Crow et al 1998, Nakamura et al 1998]. In the second of two individuals reported by Nelson & Hahn (2003), typical SIDEs at age six years were later replaced by brief myoclonic jerks and tonic spasms, which were accompanied by increased tonic EMG activity.

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 manifestations range from cataplexy that varies with the stimulus, hyperekplexia, a prolonged tonic reaction, and true epileptic seizures. Nelson and Hahn (2003) provide a video illustration of SIDEs.

Epileptic seizures affect about 5% of individuals [Stephenson et al 2005].

Female carriers 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 heterozygotes, and eight 'affected' sisters) have had psychiatric diagnoses, including schizophrenia, bipolar disease, and 'psychosis' [reviewed in Hunter 2002].

Cardiovascular. About 14% of affected males and 5% of affected females have cardiovascular disease [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. Cardiac anomalies may contribute to premature death.

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]. 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. At least two deaths have occurred during surgery for kyphoscoliosis.

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

Growth. Prenatal growth is normal; growth failure often occurs early in the postnatal period. Males and severely affected females generally fall below the third centile in height but generally track a curve. While microcephaly is common, many individuals with CLS have a normal head circumference.

Dental. Dental anomalies are common and include small teeth, malpositioning, hypodontia, delayed eruption, and premature loss. The palate is high. With age, the retrognathia in the younger child tends to be replaced by prognathism.

Hearing loss. It is likely that only a minority of individuals with CLS have had formal assessments of vision and hearing. However, 14/89 affected males and 1/22 affected females have been reported to have hearing loss [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 seem 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 may show increased intraventricular, subarachnoid, and Virchow-Robin spaces [Patlas et al 2003]. Abnormalities of the corpus callosum have been reported [Kondoh et al 1998]. An individual was reported with 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 some mild ventricular asymmetry. The authors concluded that the degree of mental retardation correlated with the severity of the MRI findings.

Reiss, Schwartz et al (unpublished study) observed lower gray and white matter volume without evidence of ventriculomegaly *ex vacuo*, suggesting an early neurodevelopmental abnormality such as reduced cellular proliferation. However, the hippocampal volumes were enlarged, relative to total brain volume and compared to controls. Larger hippocampal volumes correlated with increasing age (rho=.986, $P<0.000$). The corpus callosum and cerebellar vermis were also relatively enlarged compared to total brain volume.

In a single MRS study, the basal ganglia and periventricular white matter were reported as normal [Patlas et al 2003].

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

Other. Findings reported in single individuals include rectal prolapse, uterine prolapse, jejunal diverticuli, colonic diverticuli, 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 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.

One affected male and one obligate carrier female died of Hodgkin disease [Gilgenkrantz et al 1988, Sivagamasundari et al 1994]. Another carrier mother had a Wilms tumor (see Wilms

Tumor Overview) [Hartsfield et al 1993] and a monozygotic twin of an affected individual died of a posterior fossa tumor [Manouvrier-Hanu et al 1999].

Genotype-Phenotype Correlations

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

In a sample of seven individuals, Harum et al (2001) showed a correlation between IQ and the degree of attenuation of the *RPS6KA3*-mediated *CREB*tide phosphorylation response in lymphoblasts.

Yang et al (2004) proposed that lack of phosphorylation of *ATF4* by *RSK2* may interrupt the normal regulatory role of *ATF4* in osteoblast differentiation, accounting for some of the bony anomalies seen in CLS, as well possibly explaining the progressive nature of the kyphoscoliosis.

Nakamura et al (2005) suggested that truncating mutations, either in or upstream from the N-terminal kinase domain, may cause a particular susceptibility to SIDEs.

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; this may, however, underestimate the actual prevalence.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

The diagnosis of CLS in the older male child or adult usually does not present a problem. The findings in a young child or more mildly affected female may overlap with other syndromes. Similarly, older female children and adults, even when they are the proband, can be diagnosed readily when they fully express the syndrome.

Borjeson-Forssman-Lehmann syndrome (BFLS) is an X-linked recessive disorder characterized by severe mental retardation, hand findings similar to those of CLS, short anteverted nose 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 hypertelorism, large mouth, and full lips. Mutations in the *PHF6* gene are causative [Lower et al 2002].

While CLS shares some facial findings with Williams syndrome, the genetically heterogeneous FG syndrome, and X-linked alpha-thalassemia mental retardation (ATRX) 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, mental retardation (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. Over 99% of affected individuals have a contiguous gene deletion at 7q11.2, detectable by fluorescent in situ hybridization (FISH) or targeted mutation analysis.
- FG syndrome shares with CLS: X-linked inheritance, mental retardation, a broad forehead, ocular hypertelorism with downslanting palpebral fissures, a prominent lower lip, kyphoscoliosis, *pectus excavatum*, and some 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 mamillary bodies are relatively common.
- Alpha-thalassemia X-linked mental retardation (ATRX) syndrome is characterized by genital anomalies and severe developmental delays with hypotonia and mental retardation. Genital anomalies range from hypospadias and undescended testicles to severe hypospadias and ambiguous genitalia, to normal-appearing female genitalia in 46,XY males. ATRX syndrome is caused by mutations in the *ATRX* gene.

McCandless et al (2000) reported a family with del(10)(q25.1q25.3) who had findings suggestive of CLS. Thus, it is reasonable to obtain chromosome studies in individuals with an atypical or doubtful diagnosis of CLS.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease 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 by age ten years
- Ophthalmologic evaluation including refraction and fundoscopy

- Evaluation of appropriate family members for signs of the condition

Treatment of Manifestations

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

Awareness of SIDEs 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]. A trial of antiepileptic medication (e.g., valproate, clonazepam, or selective serotonin uptake inhibitors) may be indicated [Nakamura et al 1998, Fryssira 2002].
- If attacks occur with great frequency, 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. Intervention should be directed at preventing progression of kyphoscoliosis to the point of cardio-respiratory compromise, which 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 SBE (subacute bacterial endocarditis) prophylaxis.

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

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

Surveillance

- Periodic tests of hearing and vision
- Annual physical cardiac examination, with echocardiogram by age ten years. Even if normal, the latter 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 (2005).

Agents/Circumstances to Avoid

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

Therapies Under Investigation

Search ClinicalTrials.gov 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.

Other

Significant social resources may be required to support families of women with CLS and developmental delay.

Genetics clinics, staffed by genetics professionals, provide information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section may include disease-specific and/or umbrella support organizations.

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. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory. —ED.

Mode of Inheritance

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

Risk to Family Members

Parents of a proband

- About 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 mentally retarded [Jacquot, Merienne, De Cesare et al 1998].
- The father of an affected male will not have the disease nor will he be a carrier of the mutation.

- In a family with more than one affected individual, the mother of an affected male is an obligate carrier.
- Mothers of a proband should be examined for signs of CLS such as coarse facial features, full lips, and/or taperingfingers.
- If a disease-causing gene mutation has been identified in the proband, it is reasonable to offer molecular genetic testing to the mother.

Sibs of a proband

- The risk to the sibs of a proband depends upon the carrier status of the mother.
- If the mother of the proband has a disease-causing mutation, the chance of transmitting it in each pregnancy is 50%.
  - Male sibs who inherit the mutation will be affected; female sibs who inherit the mutation will be carriers and at high risk for at least some developmental delay and mild physical signs of CLS..
  - As expected with random X-chromosome inactivation (lyonization), a mildly affected woman may have a severely affected daughter.
  - Female carriers 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 mental impairment, the mother of a proband with no known family history of CLS is probably at low risk of being a carrier.
- Germline mosaicism has been demonstrated in this condition. Thus, even if the disease-causing mutation 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 disease-causing mutation [Jacquot, Merienne, Pannetier et al 1998; 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 disease-causing mutation to each child; sons who inherit the mutation will be affected; daughters will be carriers 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 disease-causing mutation, her female family members may be at risk of being carriers (asymptomatic or symptomatic) and her male family members may be at risk of being affected depending upon their genetic relationship to the proband.

Carrier Detection

Carrier testing of at-risk female relatives is clinically available if the mutation has been identified in the proband.

Related Genetic Counseling Issues

Specific counseling issues

- Significant social resources may be required to support developmentally delayed women with CLS as well as 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 male with no known family history of CLS (i.e., a simplex case) in whom a disease-causing mutation has been identified. Germline mosaicism has been observed; thus, it is appropriate to offer prenatal testing to such women even when the mutation identified in an affected offspring is not detected in their DNA.

Family planning. The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.

DNA banking. 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, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables may differ from that in the text; tables may contain more recent information. —ED.

Table A. Molecular Genetics of Coffin-Lowry Syndrome

Gene Symbol	Chromosomal Locus	Protein Name
RPS6KA3	Xp22.2-p22.1	Ribosomal protein S6 kinase alpha-3

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Coffin-Lowry Syndrome

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

Table C. Genomic Databases for Coffin-Lowry Syndrome

Gene Symbol	Locus Specific	Entrez Gene	HGMD	GeneCards	GDB	GenAtlas
RPS6KA3	RPS6KA3	6197 (MIM No. 300075)	RPS6KA3	*RPS6KA3*	365648	RPS6KA3

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Molecular Genetic Pathogenesis

RPS6KA3(RSK2), the gene associated with Coffin-Lowry syndrome (CLS), encodes a growth factor-regulated serine/threonine kinase. Humans have four closely related *RSK* genes; each gene has two non-identical kinase catalytic domains, both of which are required for maximal activity [Trivier et al 1996, Yntema et al 1999, Yang et al 2004].

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, with higher levels in the ventricular zone than in the cortical plate [Guimiot et al 2004].

Ribosomal protein S6 kinase alpha-3 (RPS6KA3), the protein encoded by *RPS6KA3*, is involved in kinase activation in a number of pathways including ras-MAPK, protein kinase C, and adenyl cyclase [Harum et al 2001]. 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. *RPS6KA3* has also been shown to activate CREB (cAMP response element binding protein), which is involved in neuronal survival and conversion from short- to long-term memory [Harum et al 2001]. Cells from individuals with CLS have shown defective EGF-stimulated phosphorylation of S6 [Trivier et al 1996], H3 [Sassone-Corsi et al 1999], and CREB [Harum et al 2001], and one or more of these pathways may play a role in causing some of the manifestations of CLS.

Normal allelic variants: The gene, comprising 22 exons, is named *RPS6KA3* for ribosomal S6 kinase (alternate name: *RSK2*). Some polymorphisms in *RPS6KA3* that are not associated with a disease phenotype have been found [Delaunoy et al 2001; Abidi & Schwartz, unpublished].

Pathologic allelic variants: Mutations in *RPS6KA3* are spread throughout the gene with no evidence of clustering associated with a specific phenotype.

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

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

Disease-causing intronic point mutations resulting in aberrant splicing and intronic insertion of a truncated LINE-1 element have been reported [Zeniou, Ding et al 2002; Martinez-Garay et al 2003; Zeniou et al 2004]. (For more information, see Genomic Databases table above.)

Normal gene product: Ribosomal protein S6 kinase alpha-3 (RPS6KA3) is a serine/threonine kinase and a member of the Ras signaling cascade. The protein is phosphorylated by MARK kinases in response to growth factors, insulin, and oncogenic transformations. Members of the *RSK* family participate in cellular events such as proliferation and differentiation. The fact that a mutation in *RPS6KA3* results in nonsyndromic XLMR (MRX19) as well as CLS indicates that the gene is critical for some cognitive functions of the brain.

Abnormal gene product: Mutations in the *RPS6KA3* gene give rise to both CLS and nonsyndromic XLMR. The mutations in individuals with CLS result in the loss of kinase activity of the gene product. However, the mutation associated with MRX19 occurs outside the two kinase domains of the gene and results in a reduction to 80% RPS6KA3 activity. This

suggests that the brain is more sensitive to levels of RPS6KA3 activity than the other organ systems affected in CLS.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. -ED.

National Institute of Neurological Disorders and Stroke
Coffin Lowry Information Page

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

Revision History

- 6 August 2007 (cd) Revision: deletion/duplication analysis available clinically
- 31 August 2006 (me) Comprehensive update posted to live Web site
- 27 December 2004 (cd) Revision: change in molecular genetic testing availability
- 28 June 2004 (me) Comprehensive update posted to live Web site
- 16 July 2002 (me) Review posted to live Web site
- 24 January 2002 (ah) Original submission