Coffin-Lowry syndrome (CLS)

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Abstract
Coffin-Lowry syndrome (CLS) is an X-linked semi-dominant inherited disorder. Typically male patients exhibit growth retardation, psychomotor retardation, hypotonia, and progressive skeletal deformations. In addition, they present with characteristic facial dysmorphism and proximally puffy digits, which are diagnostic criteria. A majority of female carriers have only minimal manifestations. CLS has been described in various ethnic groups and does not appear to be particularly rare, as its incidence is estimated to be 1/50,000-100,000 males/year. Loss of function mutations in the gene located on chromosome Xp22.2 which encodes the growth-factor induced protein kinase RSK2 is responsible for the CLS. There is a high allelic heterogeneity with, to date, over 80 different mutations distributed throughout the gene, the vast majority being found only in individual families. No specific treatment is currently available.

Keywords
Coffin-Lowry syndrome; RSK2; *RPS6KA3*; kinase; Ras/MAPK pathway; diagnosis; X-linked mental retardation.

Definition

The Coffin-Lowry syndrome (CLS) is a syndromic form of X-linked mental retardation that was initially and independently described by Coffin *et al.* [1966] and Lowry *et al.* [1971] and definitively distinguished by Tentamy *et al.* (1975).

Diagnostic criteria

The diagnosis is based on clinical examination (see Gilgenkrantz *et al.*, 1988, Young, 1988). In adult male patients, the disease has a well-defined phenotype and in most cases it can be diagnosed by professionals trained in genetic disorders. Characteristic features are psychomotor retardation, typical facial dysmorphism and progressive skeletal deformations. Large, soft hands with lax skin and tapering fingers, is usually a strong diagnostic feature. However, the clinical presentation of CLS may vary markedly variable in both severity and the expression of uncommonly associated features, occasionally leading to diagnostic difficulties. In addition, the physical characteristics are usually very mild during infancy and CLS may be confused with other

syndromes. In most cases mutation analysis is essential to confirm the diagnosis.

Differential diagnosis
In young male patients in particular, the mild physical features of CLS may lead to the diagnosis of other syndromes, most notably alpha-thalassemia with mental retardation syndrome (ATR-X, MIM # 300032), but also to the diagnosis of fragile X syndrome (MIM 309550), Sotos syndrome (MIM # 117550), Williams syndrome (MIM # 194050) and lysosomal storage disease (Plomp *et al.*, 1995).

Prevalence
CLS has been reported in various ethnic groups (Young, 1988). Its incidence remains unknown. However, if we rely on the number of patients referred to our diagnostic laboratory for mutation screening, it can be estimated to be about 1 per 50-100 000 males.

Clinical description

Growth and development
Intrauterine growth is often slow but the birth weight is usually normal. Short stature is observed during the first months of life. Final adult height is usually below the third percentile. Microcephaly has been reported but only in a small proportion of patients.

Craniofacial features
In adult patients, the facial dysmorphism include prominent forehead and supraorbital ridges with hypertelorism and downward slanting of the palpebral fissures; the nose is bulbous with a thick septum and anteverted nares as well as thick alae and septum; the mouth is wide and open with protruding tongue, full everted lips, and small, irregular or missing teeth; the ears, although of normal length, are often prominent or low set.

Limb abnormalities
They are relatively minor but characteristic of CLS. The hands are large with thick lax skin, short tapered and puffy fingers. The fingers are frequently hyperextensible with short nails. Dermatoglyphic studies consistently reveal an unusual transversal hypothenar crease. Forearm fullness, due to the presence of excess subcutaneous fat, is frequent and may be useful for early diagnosis (Hersh *et al.*, 1984). Flat feet have been reported in a number of patients. Syndactyly has been documented in one patient at least (personal observation).

Skeletal abnormalities
Growth retardation and retarded bone age are common. The most frequent and salient skeletal anomalies are spinal kyphosis and scoliosis, with dysplasia of the vertebral bodies at the thoracolumbar junction. Kyphosis and scoliosis may be caused by the associated ligamentous laxity and modifications of the intervertebral disks. Less constant changes include pectus carinatum or excavatum and cervical ribs, narrow iliac wings and shortening of the long bones of the lower limbs. Skeletal abnormalities usually continue to deteriorate progressively, often requiring surgery in adulthood.

Radiological findings
They may include large frontal sinuses, calvarial hyperostosis, anterior wedging of the vertebral bodies, narrow intervertebral spaces, short sternum with unachieved longitudinal fusion of the paired sternal segments, ligamentum flava calcification, short metacarpals and phalanges, drumstick terminal phalanges with distal tufting and retarded bone age. These changes, which may continue to deteriorate progressively, are distinctive and contribute to the confirmation of the diagnosis. Brain anomalies, such as hydrocephalus or callosal dysgenesis, have occasionally been described (Ozden *et al.*, 1994).

Psychomotor development and behaviour
The cognitive deficit in CLS males is significant, with IQ scores ranging from very low to moderate (between 15 and 60), but clustering in the severely deficient range. Partington *et al.* (1988) found no evidence for intellectual deterioration with age, although it had been reported previously (Coffin *et al.*, 1966, Procopis *et al.*, 1972). Speech development is always affected but to variable degrees. Sitting, crawling and walking are delayed. Affected individuals tend to be loving, friendly and easy to get along with. Their temperament remains friendly throughout life and, despite their limited verbal abilities, their communication skills are good.

Other features
Microcephaly has been reported for a small number of cases. Ventricular dilatation with or without hydrocephalus has also been documented in some patients (Coffin *et al.*, 1966 Lowry *et al.*, 1971, Temtamy *et al.*, 1975, Hunter *et al.*, 1982).
Fryns *et al.* (1977) described frequent episodes of sudden, non-epileptic collapses with atonia in 2 CLS-affected brothers. These drop attacks were generally induced by a loud noise or excitement, and their severity worsened and

frequency increased with age. Subsequently, those authors observed the same sudden collapse phenomenon in one additional male out of 20 CLS patients examined (Fryns and Smeets, 1998). It is worth noting that these drop attacks symptoms increased in frequency and severity in the two brothers initially described, together with progression of torsion scoliosis and muscle wasting, while they completely disappeared in the latter-described male after surgical correction of scoliosis. Crow *et al.* (1998) reported the same non-epileptic collapses with atonia, which they described as a cataplexy-like phenomenon, in three male patients. Electroencephalogram (EEG), magnetic resonance imaging (MRI) brain and cerebral angiography were all normal in these patients. The authors also provided evidence of neuromuscular dysfunction as part of the phenotype by showing abnormalities on muscle ultrasound in four carriers of the gene *RPS6KA3*, responsible for CLS.
Seizures have been described in several patients with CLS (Lowry *et al.*, 1971, Fryns *et al.*, 1977, Partington *et al.*, 1988).
Sensorineural hearing deficit has been described in some patients (Wilson and Kelly, 1981, Hunter *et al.*, 1982, Collacott *et al.*, 1987, Hartsfield *et al.*, 1993). The deficit is bilateral and its severity may vary widely. In addition intrafamilial variability is possible (Hartsfield *et al.* 1993).
Congestive heart failure due to mitral valve regurgitation has been described in a few patients (Temtamy *et al.*1975, Hunter *et al.*, 1982, Machin *et al.*, 1987, Charles *et al.*, 1988). Autopsy revealed fibrosed and shortened chordae tendineae of the valve in one of these patients (Machin *et al.*, 1987) and cardiomyopathy with endomyocardial fibroelastosis in a second patient (Charles *et al.*, 1988). Massin *et al.*, (1999) reported a patient with recurrent episodes of congestive heart failure secondarily attributed to congenital mitral valve regurgitation and primary myocardial disease. These findings and the previous ones suggested that a myocardial disorder may be part of the CLS.

CLS in children
The clinical features of CLS are not evident at birth and even during infancy. Affected male newborns usually show only hypotonia and hyperlaxity of joints. Retarded growth and psychomotor development gradually appears during the first months of life. A persistent large anterior fontanel beyond the age of two years has been reported in several cases. Facial coarsening is mild and usually hard to detect during infancy. It progressively becomes pronounced and characteristic only in late childhood or adolescence. However, during infancy, prominent forehead, hypertelorism, anteverted nares, tented upper lip, fullness of the forearms and the transverse hypothenar crease may be evident. Tapered fingers are present at birth and seem to be the most reliable feature during infancy. Other possible early signs are sensorineural hearing deficit and premature tooth loss (Hartsfield *et al.*, 1993). Sternal malformations have been described in a few males at birth (Tentamy *et al.*, 1975). However, skeletal deformities usually become apparent only after the age of 2 years.

Clinical expression in female patients
The clinical features are much more variable but consistently less severe in female carriers than in affected males, sometimes overlapping with a nearly normal phenotype. Some of the physical features seen in males can also be found, but they are not as prominent and not present in all affected females. The most consistent features are a coarse face with prominent brow, hypertelorism, thick nasal tissues, soft fleshy hands with thick fingers tapering distally and variable radiographic findings similar to those of male patients. While no skeletal defect is usually observed in female patients, they tend to be of short stature. Cognitive function of female carriers may be mildly impaired or normal. They are frequently reported to have experienced learning difficulties at school. Psychiatric illness (psychotic behavior and schizophrenia) has been described in a few female patients (Haspeslagh *et al.*, 1984, Collacott *et al.*, 1987).

Treatment
No specific treatment for CLS is available. Current effective management of patients focuses on supportive and symptomatic therapy. In particular, sensorineural hearing deficit should be treated very early in order to improve the development and life quality of the patients. Progressive spine deformation (scoliosis and/or kyphosis) may require surgery in adulthood.

Etiology
Loss of function mutations in the gene *RPS6KA3* encoding the growth-factor induced protein ribosomal S6 kinase-2 RSK2 are responsible for the CLS.

The CLS gene and its protein product
RPS6KA3 was identified in 1996 by positional cloning of the chromosome Xp22.2 region (Trivier *et al.*, 1996). Its open reading frame is split into 22 exons and it encodes a protein of 740 amino acids, RSK2, which contains 2 non-

identical kinase catalytic domains (Bjorbaek *et al.* 1995, Jacquot *et al.*, 1998). In humans, the gene encoding RSK2 belongs to a family comprising four very closely related members (80-85 % amino-acid sequence identity), RSK1 to RSK4, and homologs have been identified in vertebrate and invertebrate (C *elegans*, Drosophila) genomes. RSKs are serine-threonine protein kinases, acting in the Ras-Mitogen-Activated Protein Kinase (MAPK) signaling pathway. They are directly phosphorylated and activated by ERK1/2 (extracellular signal-regulated kinases) in response to a broad range of cellular perturbations, including stimulation with insulin and growth factors, neurotransmiters, oncogenic transformation and UV irradiation. RSKs activation is accompanied by the phosphorylation of four residues, one in each kinase domain (Ser227 and Thr577) and two in the linker region (Ser369 and Ser386). The N-terminal kinase catalytic domain phosphorylates the substrates of RSK and its activity is regulated by the C-terminal kinase catalytic domain, the linker region and 3-phosphoinositide-dependent protein kinase-1 (PDK1). RSKs have been involved in several important cellular events, including proliferation and differentiation, cellular stress response and apoptosis. cAMP responsive element-binding protein (CREB), histone H3, and c-Fos have been demonstrated to be *in vivo* targets of RSK2. Its induction is therefore thought to influence gene expression (See review by Frodin *et al*., 1999) their name, Ribosomal S6 Kinase, was attributed because it is a good substrate *in vitro*, but it has recently been shown that it is not a substrate *in vivo*. The nature of the anatomical and physiological defects in CLS patients in relationship to RSK2 mutations is still poorly understood. A mouse model for CLS, obtained by homologous recombination and carrying targeted mutations at the *RPS6KA3* locus, was recently described (Dufresne *et al*., 2001). It provides a powerful tool to examine the role of RSK2 in brain development, cognitive function, and bone formation in more detail.

Spectrum of mutations

The screening of 250 unrelated patients with clinical features suggestive of CLS allowed the identification of more than 80 distinct disease-associated *RPS6KA3* mutations (Jacquot *et al.*, 1998a, Delaunoy *et al.*, 2001). Approximately 40% percent of these mutations are missense mutations, 20% are nonsense mutations, 20% are splicing errors and 20% are short deletion or insertion events. Only three large deletions, two involving two exons and the third one only one exon, have been found so far. Mutations occurred throughout all exons, except exons 1, 2 and most of them have been found in one family only. Nine mutations have been found in female probands identified through learning disabilities and mild but suggestive physical phenotypes, but who have no affected male relatives. The vast majority of mutations can be predicted to cause loss of function of the mutant allele. About 60% of the mutations result in premature translation termination. Most of the missense mutations affect residues conserved in all known RSK-family members from humans to C *elegans*, supporting their pathogenic significance. Functional studies have revealed diminished or absent kinase activity for some of these mutant proteins. There is no obvious correlation between the location of mutations and clinical phenotype. However, some missense mutations are associated with milder phenotypes. In one family (MRX19), a missense mutation was associated solely with mild mental retardation (Merienne *et al.*, 1999). These milder phenotypes correlated with residual activities of the mutant RSK2 proteins. In a total of 44 families, for which samples were available from the mothers of the probands, 25 (57%) mutations occurred *de novo* in the proband. It is a higher frequency than expected. Germ-line mosaicism has been reported in some families (Jacquot *et al.*, 1998b). Information about *RPS6KA3* and a continuously updated overview of all RSK2 mutations are available on the following web page (http://www-ulpmed.u-strasbg.fr/chimbio/diag/coffin).

Diagnostic methods

Mutation screening of the gene encoding RSK2 has been extensively performed by Single Strand Conformation Polymorphism (SSCP) analysis followed by sequencing of exons exhibiting variants. Primer sets for PCR amplification of the 22 exons and PCR conditions were reported in Jacquot *et al.* (1998a) and Delaunoy *et al.* (2001).

Immunoblotting and RSK2 assays can be used as rapid diagnostic tests for CLS (Merienne *et al.*, 1998). A Western blot can be performed on lymphocyte-protein extracts directly prepared from fresh (less than 24 hours) blood samples. Mutations leading to premature translation termination and some other changes result in the absence of detectable RSK2 with the anti-RSK2 antibodies commercially available. The kinase assay requires either a fibroblast or a lymphoblast cell line but remains the diagnostic method of choice as it detects all the classes of mutations and also provides information on possible residual enzyme activity. These assays

can be performed on cultured amniocytes for prenatal diagnosis. Unfortunately, female-carrier detection cannot be carried out by Western-blot analysis or by kinase assay.

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