European Journal of Human Genetics (2010) 18, 627–633

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PRACTICAL GENETICS

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# Coffin–Lowry syndrome

**Coffin–Lowry syndrome (CLS) is a syndromic form of X-linked mental retardation, which is characterized in male patients by psychomotor and growth retardation and various skeletal anomalies. Typical facial changes and specific clinical and radiological signs in the hand are useful aids in the diagnosis. CLS is caused by mutations in the *RPS6KA3* gene located at Xp22.2, which encodes RSK2, a growth-factor-regulated protein kinase. *RPS6KA3* mutations are extremely heterogeneous and lead to loss of phosphotransferase activity in the RSK2 kinase, most often because of premature termination of translation.**

In brief

- Coffin–Lowry syndrome is an X-linked semidominant syndrome characterized typically by severe psychomotor and growth retardation, facial dysmorphism, digit abnormalities, and progressive skeletal changes.
- The clinical presentation of CLS may, however, be markedly variable in severity and in the expression of clinical features.
- Female carriers show variable involvement, which can range from short stubby digits in a woman of normal facial appearance and intelligence to quite marked facial dysmorphism with moderate retardation.
- The estimated incidence is 1:50 000 to 1:100 000 and approximately 70–80% of patients are sporadic cases.
- Highly heterogeneous loss-of-function mutations in the *RPS6KA3* gene are responsible for CLS.
- Two-thirds of cases arise from new mutations.
- Mutation in *RPS6KA3* is detected in approximately 50% of patients referred to our laboratory for mutation screening.

## INTRODUCTION

Coffin–Lowry syndrome (CLS; OMIM 303600) is a rare syndromic form of mental retardation that shows X-linked inheritance. The condition was described for the first time, independently, by Coffin *et al*[1] and Lowry *et al*[2] and was definitively distinguished by Tentamy *et al*,[3] who proposed the eponym 'Coffin–Lowry syndrome'. Cardinal features of CLS are growth and psychomotor retardation, characteristic facial and digital abnormalities, and progressive skeletal alterations. Approximately 70–80% of probands have no family history of CLS, whereas 20–30% have more than one additional affected family member. This high incidence of sporadic cases may be attributed to genetic selection that occurs against hemizygous males and heterozygous females who are mentally retarded. CLS is caused by heterogeneous loss-of-function mutations in the *hRSK2* (90-kDa ribosomal S6 kinase) gene (*RPS6KA3*) that maps to Xp22.2. The diagnosis of CLS is established in males with moderate-to-severe developmental delay, characteristic craniofacial and hand findings, and radiographic findings. Carrier females are more often mildly affected. Molecular genetic testing of *RPS6KA3*, the only gene known to be associated with CLS, can be used to confirm the diagnosis of CLS. No estimate of the prevalence of CLS has been published. On the basis of the experience of the researchers, a rate of 1:50 000 to 1:100 000 may be reasonable; this may, however, underestimate the actual prevalence.

## CLINICAL OVERVIEW

The clinical features are summarized in Table 1. In very young children, physical characteristics are generally mild and not very specific. Affected newborn males often show hypotonia and hyperlaxity of joints, whereas growth parameters are often within the normal range. Broad, tapering fingers may be present at birth. Facial abnormalities, including hypertelorism, frontal bossing, and thick lips, become apparent in early childhood. However, the typical facial appearance is usually apparent only by the second year of life and shows progressive coarsening thereafter with increasing prominence of the glabella and protrusion of the lips. Retardation of growth and psychomotor development become apparent gradually in the first years of life. Other possible early signs are sensorineural hearing deficit and microcephaly.

The typical facial aspect in adult male patients includes a prominent forehead, orbital hypertelorism, downward-slanting palpebral fissures, epicanthic folds, large and prominent ears, thick everted lips, and a thick nasal septum with anteverted nares. Orodontal findings include typically a high narrow palate, a midline lingual furrow, hypondontia, and peg-shaped incisors. Patients show hyper-extensible, soft, and fleshy hands with lax skin and joints and tapering stubby fingers. These latter features are already present at birth, and are a strong diagnostic feature. Other reported findings include a short horizontal crease in the hypothenar region and fullness of the forearms owing to increased subcutaneous fat. Skeletal malformations appear progressively in most patients and may include delayed bone development, spinal kyphosis/scoliosis, and pectus carinatum or excavatum. Radiographic changes include cranial hyperostosis, abnormal shape and end plates of the vertebral bodies, delayed bone age, metacarpal pseudoepiphyses, and tufting of the distal phalanges[4] (Table 1 and Figure 1).

Cognitive deficiencies in CLS patients are prominent, but markedly variable in severity, including between siblings. However, the vast majority of patients are severely affected, with IQ scores ranging from

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*European Journal of Human Genetics* (2010) **18,** 627–633; doi:10.1038/ejhg.2009.189; published online 4 November 2009

Keywords: Coffin–Lowry syndrome; X-linked mental retardation; *RPS6KA3* gene; RSK2; Ras- ERK signaling pathway

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Received 28 August 2008; revised 23 September 2009; accepted 23 September 2009; published online 4 November 2009

**Table 1 Clinical features of Coffin–Lowry syndrome**

| |
|---|
| *Neurological manifestations* |
| Mental retardation |
| Developmental delay |
| Speech delay |
| Generalized congenital hypotonia |
| Seizures (5% of patients) |
| Drop attacks (20% of patients) |
| Sensorineural hearing defect (30% of patients) |
| Ventricular dilatation |
| *Growth* |
| Small stature |
| Stooped posture |
| *Facial features* |
| Macrocephaly |
| Broad nose |
| Anteverted nares |
| Large ears |
| Hypertelorism |
| Downslanted palpebral fissures |
| Thick/everted lips |
| Large mouth |
| Frontal bossing |
| Maxillary hypoplasia |
| High vaulted/narrow palate |
| *Limbs* |
| Large soft hands |
| Short puffy tapered fingers |
| Hyperextensible joints |
| Transverse hypothenar crease |
| Forearm fullness |
| Flat feet |
| *Thorax* |
| Pectus caritum/excavatum (80% of patients) |
| Kyphosis/scoliosis (80% of patients) |
| *Cardiac* |
| Mitral regurgitation (15% of patients) |
| *Teeth* |
| Anodontia/oligodontia |
| Abnormal dental position |
| *Radiology* |
| Drumstick terminal phalanges |
| Delayed bone development |
| Ligamenta flava calcification |
| Narrow intervertebral spaces |
| Anterior vertebral body defect |
| Thickened skull |
| *Other features* |
| Hernia |

moderate to profound (between 15 and 60). Very mild cases of the disease have been reported, with in particular in a few families only non-syndromic mental retardation.[5–7] Development of speech is always impaired in CLS patients. However, variable degrees of severity have been observed. For instance, some patients can acquire a substantial capability of oral communication when proper care is provided, whereas other patients, especially in combination with hearing impairment, never speak. Despite the limited verbal abilities, the communication skills are good. Motor development is also delayed, marked in infancy by generalized hypotonia. The age of walking is delayed, and difficulties in ambulating may persist with a clumsy gait. The affected individuals are usually cheerful, easy going, and friendly. Behavioral problems have been reported in few male patients.[8,9]

Other uncommonly associated manifestations include epileptic seizures that affect approximately 5% of individuals[9] and sensorineural hearing loss (approximately 30% of male patients in the series of patients analyzed in our laboratory), which can be profound. Stimulus-induced drop episodes, with onset typically from mid-childhood to the teens, is present in approximately 20% of affected individuals;[10] unexpected tactile or auditory stimuli or excitement triggers a brief collapse but no loss of consciousness. Cardiac involvement has been reported in approximately 15% of affected males, usually in the form of mitral valve dysfunction.[9] Cardiac anomalies may contribute to premature death. A morphometric study of the brains of the patients revealed a reduced total brain volume, with a particular effect on cerebellum and hippocampus.[11]

Female heterozygotes show variable involvement that can range from short stubby digits with normal appearance and intelligence to quite marked facial dysmorphism with moderate retardation.[4] Frequently, they are reported to have learning difficulties at school. X-inactivation studies have revealed either no[12] or mild–to-significant skewing.[13] In the latter study, the correlation coefficient between IQ and X-inactivation status was not significant in carrier females. Obesity and psychiatric illness (depression, psychotic behavior, and schizophrenia) have been described in few female carriers.[9] Epilepsy may occasionally develop.

Of the individuals reported in the literature, death occurred in 13.5% of males and in 4.5% of females at a mean age of 20.5 (range 13–34) years.[9]

## DIFFERENTIAL DIAGNOSIS

Coffin–Lowry syndrome in young male patients may be confused with other syndromes, most notably *á*-thalassemia with mental retardation syndrome (ATR-X; OMIM 300032), Borjeson-Forssman-Lehmann syndrome (BFLS; OMIM 301900), FG syndrome (OMIM 309550), Williams syndrome (OMIM 194050), and Pitt-Hopkins syndrome (OMIM 610954). On the basis of our experience, diagnostic confusion most often results with ATR-X syndrome. The almost constant presence of genital anomalies and absence of large fleshy hands and fingers as well as downslanding fissures in ATR-X serve as distinguishing features. Moreover, the vast majority of ATR-X-affected males show hemoglobin H (β4) inclusions in peripheral red blood cells. Finally, in ATR-X, carrier manifestations are very uncommon. Diagnostic testing or mutational analysis should allow these conditions to be excluded in most cases.

## MOLECULAR AND GENETIC BASIS OF CLS

By using a positional cloning approach, it was shown that loss-of-function mutations in the *RPS6KA3* gene are responsible for CLS.[14] The coding region of this gene is split into 22 exons and encodes a serine/threonine kinase, RSK2 (ribosomal S6 kinase 2).[15]

The *RPS6KA3* gene is subject to strong allelic heterogeneity with over 140 distinct inactivating mutations that have so far been

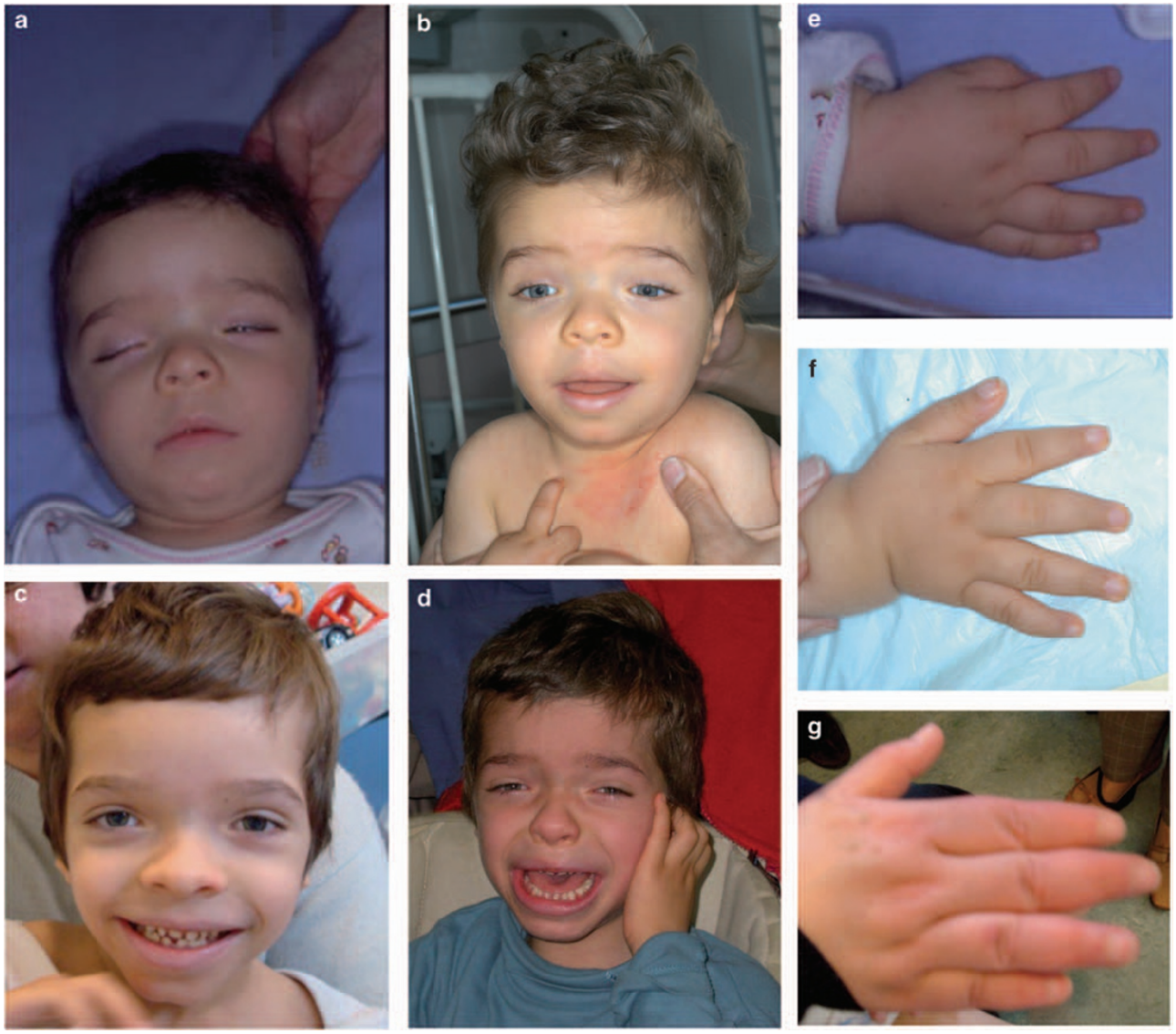


**Figure 1** (**a**–**d**) Facial views of a boy with CLS at different ages showing evolution during infancy of facial gestalt. (**a**) At 9 months, (**b**) at 18 months, (**c**) at 3 years, and (**d**) at 6 years. Note the large forehead, hypertelorism, downslanting palpebral fissures, long philtrum, anteverted nares, and thick lips. This boy carries an RPS6KA3 intragenic duplication previously reported.[16] (**e**–**g**) Views of the hands of the same patient. Note the typical broad tapering fingers (**e**) at 9 months, (**f**) at 18 months, and (**g**) at 5 years.

identified in CLS patients (Delaunoy *et al*[16] and unpublished from our group). Mutations are distributed throughout the gene with no clustering and the vast majority is unique to a single family. Approximately 30% of mutations are missense mutations, 15% nonsense mutations, 20% splicing errors, and 30% short deletion or insertion events. Only five large intragenic deletions and two large duplications have so far been reported.[16–18] In addition, a *de novo* insertion of a 5′-truncated LINE-1 element was documented in one family.[19] *RSK2* mutations invariably cause a reduction or loss of RSK2 kinase activity.

Two-thirds of *RSK2* mutations cause premature translation termination, out of which the vast majority results in complete loss of function of the mutant allele. One-third of *RSK2* mutations exert their effects by substituting one amino acid for another. A number of missense mutations alter known phosphorylation sites critical for RSK2 catalytic function, ATP-binding sites, or the extracellular regulated kinase (ERK) docking site, and their detrimental effect is obvious. The mechanism by which the remaining missense mutations exert their effects is less evident, but in most cases the secondary structure of the kinase domains is disrupted.[16]

In the series of patients analyzed in our laboratory, no consistent relationship has been observed between specific mutations and the severity of the disease or the expression of particular features. However, Nakamura *et al*[20] provided some evidence that truncating mutations resulting in a protein containing the RSK2 N-terminal kinase domain may not be associated with drop episodes, whereas truncating mutations resulting in smaller RSK2 proteins and disrupting this domain may induce drop episode events. In addition, a few missense mutations leading to partial abolition of RSK2 phosphotransferase activity of the mutant protein were associated with very mild phenotypes, suggesting a role of residual activity in determining the severity of the syndrome.[5–7]

## RSK2 PROTEIN FUNCTION

RSK2 is a growth factor-regulated serine-threonine protein kinase of 740 amino acids (90 kDa) that acts at the distal end of the ras-mitogen-activated protein kinase (MAPK) signaling pathway. In humans, RSK2 belongs to a family that includes four members, RSK1-4 (also known as $p90^{rsk}$ or MAPKAP-K1 family), which are encoded by different genes, and share a highly conserved structure. RSK orthologs have been identified in mouse, rat, chicken *Xenopus laevis,* and *Drosophila.*[21] The various RSK proteins are all widely expressed in mammals and many cell types express several members. In human and mouse embryonic brain, as well as in adult mouse brain, the highest levels of RSK2 expression are observed in regions with high synaptic activity, including the neocortex, the hippocampus, and Purkinje cells, which are essential components in cognitive function and learning.[22]

RSK proteins are composed of two functional kinase catalytic domains: the N-terminal kinase domain belongs to the AGC kinase family and the C-terminal kinase domain belongs to the CamK family. The two kinase domains are connected by a 100-amino-acid linker region containing a PDK docking site. RSK proteins are directly phosphorylated and activated by ERK1/2 in response to growth factors, many polypeptide hormones, and neurotransmitters. A docking site for ERK1/2 is located at the extreme C-terminus of RSK. The N-terminal kinase domain phosphorylates downstream targets and is activated through a sequential phosphorylation cascade involving PDK1, the C-terminal kinase domain of RSK, and ERK1/2.[21] In addition, it has recently been shown that FGFR3, by interacting with, and phosphorylating two tyrosine residues within the C-terminal region of RSK2, influences RSK2 activation.[23] Altogether, the data provide evidence that RSKs have an important role in cell-cycle progression, differentiation, and cell survival.[21]

In the cytosol, RSK proteins have been shown to phosphorylate many substrates, including GSK3, L1CAM, the Ras GEF-Sos, IkB, the p34cdc2-inhibitory kinase Myt1, the translation factors eEF2, eIF4B, and the pro-apoptotic protein BAD (Figure 2). Moreover, upon activation a fraction of the cytosolic RSK molecule translocates to the nucleus in which it is thought to regulate gene expression through phosphorylation of transcription factors, such as CREB 1, ERα, Nurr 77, and SRF, as well as histones.[21] The respective contributions of each RSK family member to the *in vivo* activation of most of these substrates are currently not well defined. However, it was shown that EGF-induced phosphorylation of CREB and histone H3 is altered in CLS patients, suggesting that these substrates are specifically activated through RSK2.[24] Furthermore, RSK2 was also shown to associate with the transcriptional coactivator protein CREB-binding proteins (CBP) and p300. RSK2 also contributes to transcriptional induction of cFos, probably through phosphorylation of SRF, and it phosphorylates the cFos protein.[24] Recent data have provided evidence that RSK2 is also a specific modulator of phospholipase D activity in calcium-regulated exocytosis.[25] Rsk2 has, in addition, a specific role in modulating the MAPK-pathway; it exerts a feedback inhibitory effect on the ERK pathway by phosphorylating SOS, which in turn leads to inhibition of Ras.[21] The transcription factor ATF4 (CREB2) was identified as a specific substrate of RSK2 in osteoblasts.[26] RSK2 was shown to directly phosphorylate the $5\text{-}HT_{2A}$ serotonin receptor, thereby modulating $5\text{-}HT_{2A}$ receptor signaling.[27] Finally, RSK2 contains a C-terminal sequences that binds PDZ (postsynaptic density fraction (PSD)95_discs large_ ZO-1) domains, protein–protein interaction domains found in many synaptic proteins. Binding of RSK2 to PDZ domain proteins and phosphorylation of these proteins or their binding partners may regulate excitatory synaptic transmission.[28]

A Rsk2-null mouse has been created in our laboratory, as a model for CLS. The mutant mice show a mild reduction of bone mass and some mild teeth anomalies but no other gross anomalies. In fact, the mutant mice develop a progressive osteopenia due to impaired osteoblast function. Lack of phosphorylation of the transcription factor ATF4 by RSK2 was found to be a cause of the skeletal abnormalities. ATF4 is required for the timely onset of osteoblast differentiation, for terminal differentiation of osteoblasts, and for osteoblast-specific gene expression. In addition, RSK2 was shown to participate in the regulation of type I collagen synthesis, the main constituent of the bone matrix.[26] Lack of ATF4 phosphorylation by RSK2 is very likely to contribute to the skeletal phenotype of CLS. Recent studies based on our RSK2 KO mice provide evidence that RSK2 also has a critical role in FGFR3-induced hematopoietic transformation[23] and is a pivotal factor linking the stress response to survival and proliferation.[29]

Our RSK2-KO mice show no obvious brain abnormalities at the anatomical and histological levels. Behavioral studies revealed normal motor coordination, but a profound retardation in spatial learning and a deficit in long-term spatial memory, providing evidence that RSK2 has similar roles in mental functioning in both mice and humans.[30] The cortical dopamine level was found increased in mrsk2_KO mice and was accompanied with an over-expression of dopamine receptor type 2 and the dopamine transporter.[31] Data strongly supported the notion that the dopaminergic dysregulation may be caused by a tyrosine hydroxylase hyperactivity. An increase in phosphorylated ERK, which may be responsible for the increased level of tyrosine hydroxylase (TH) activity, was also observed. This cortical hyperdopaminergia may explain not only some non-cognitive but also cognitive alterations showed by mrsk2_KO mice.

A second independent line of RSK2-deficient mice has been reported.[32] These latter mice show motor coordination deficits in addition to impaired spatial navigation. These mice, but not our RSK2-KO mice or CLS patients, also show an age-dependent 50–70% loss of white adipose tissue mass despite normal food intake.[32] Differences in phenotypic expression between the two lines remain unexplained.

In Drosophila, there is only one *rsk* gene (*S6KII*) that is most homologous to the human *RSK2* gene. Full deletion of this gene in Drosophila leads to short-term memory defects in a classical olfactory learning paradigm, but cause no visible external morphological defects.[33] RSK acts as a negative regulator of ERK-dependent bouton growth at the *Drosophila* neuromuscular junction.[34]

## DIAGNOSTIC

Patients with CLS can usually be diagnosed on the basis of clinical presentation and radiological findings. However, as the clinical presentation may be markedly variable both in severity and in the expression of uncommonly associated features, it may occasionally lead to diagnostic difficulties. Recognizing CLS in very young children or in females is also often difficult. In these cases, *RSK2* mutation analysis may be the only means by which a definitive and rapid early diagnosis is possible. Screening for *RSK2* mutations is also essential for genetic counseling and prenatal diagnosis. A systematic sequencing strategy of the PCR products from the 22 exons and intron–exon boundaries of the *hRSK2* gene is applied in our laboratory.[16] However, failure to detect a mutation in a patient does not rule out the diagnosis of CLS as duplications and some mutations affecting splicing (3–5% from the series of patients analyzed in our laboratory) may not be detectable by this strategy.

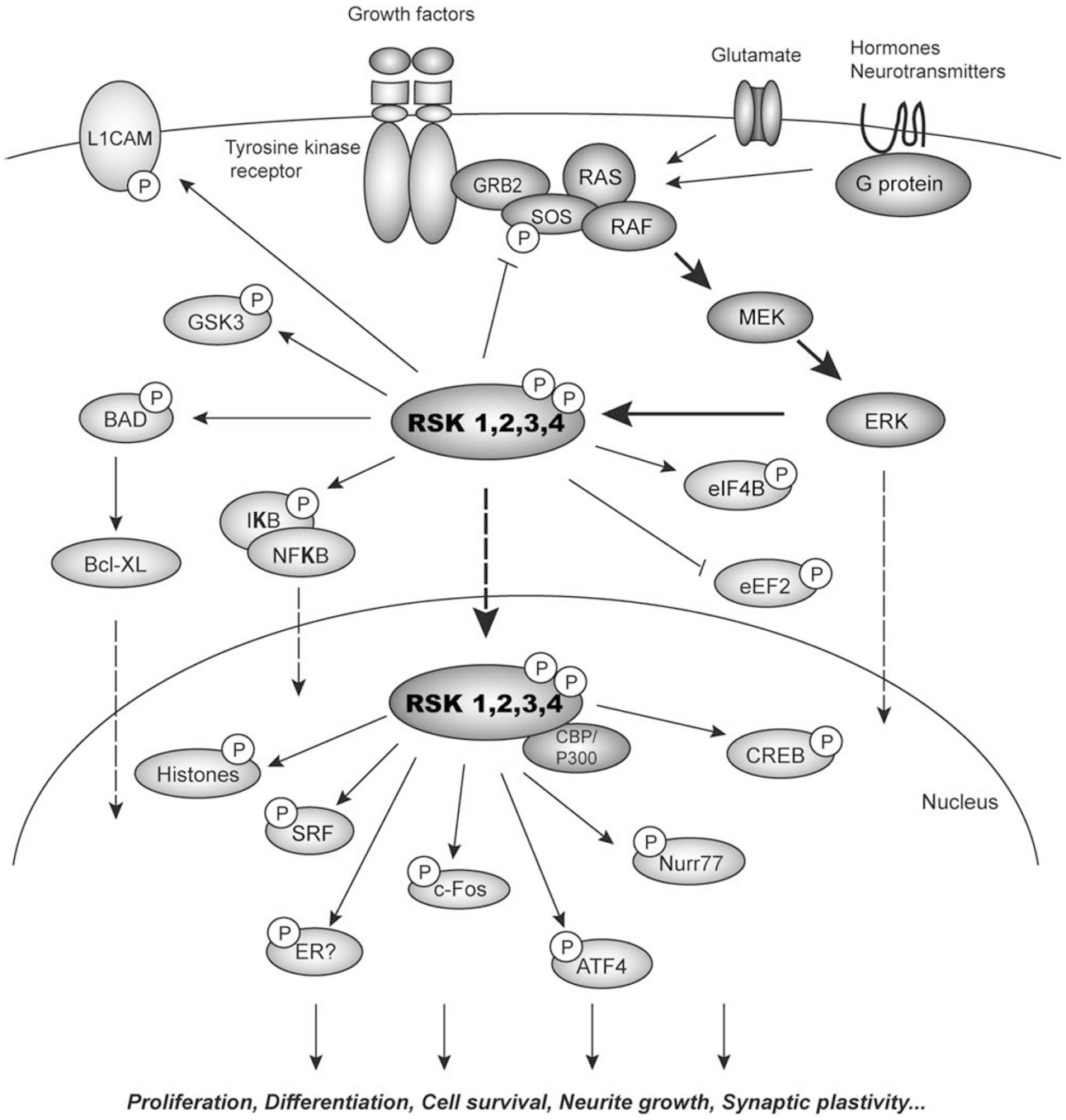


**Figure 2** The RSK signaling pathway.

Western blot analysis has proved to be an important adjunct in identifying patients lacking protein product despite no detectable mutations, in males whose phenotype is consistent with CLS. This may be the case in particular for some mutations affecting splicing or for some intragenic deletions or duplications. Western blot analysis can be performed on lymphocyte protein extracts prepared directly from fresh (<24 h) blood samples, or from a lymphoblast or a fibroblast cell line. An *in vitro* kinase assay has also been developed that would certainly be the diagnostic method of choice, as it can potentially detect all classes of mutations and also provide information on a possible residual enzymatic activity.[12] However, it can only be used on a fibroblast cell line established from the patient. Both western and kinase assays may be used for prenatal diagnosis as the RSK2 protein is readily detectable in cultured amniocytes. Unfortunately, female carrier detection is not feasible by either of these assays because of random X inactivation. Interestingly, an *in vitro* kinase assay that can be used to detect female carrier patients has recently been reported.[35] No mutation has been found in the *RPS6KA3* gene in approximately 50% of the patients referred to our laboratory for mutation screening, even after further analysis using western blot. It is

very likely that misdiagnosis has the most important role in the failure to detect mutations in such a high proportion of patients. However, some patients clearly have a disease that is phenotypically very similar to CLS, which is not caused by RSK2 defects, suggesting genetic heterogeneity.[12]

Finally, Field *et al*[7] have recently reported screening for RSK2 mutations in 300 families with undiagnosed suspected X-linked mental retardation. They identified pathogenic mutations in three families: in two families, the clinical diagnosis had been nonsyndromic mental retardation (isolated mild mental retardation) and in the third family, although CLS had been suspected, the clinical features were atypical and the intellectual disability was only mild to moderate. Two additional families with atypical cases of the disease have also been documented.[5,6] This suggests that *RSK2* mutations not producing the classical phenotype are a rare, but not insignificant, cause of nonsyndromic X-linked mental retardation, and that strict reliance on characteristic dysmorphic features may result in a missed diagnosis.

## GENETIC COUNSELING

Coffin–Lowry syndrome is inherited in an X-linked dominant manner. Approximately 70–80% of probands have no family history of CLS. Males who inherit the disease-causing mutation will be affected, whereas females who inherit such 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.

Approximately two-thirds of mutations arose *de novo* in the proband. Indeed, in our laboratory, out of a total of 95 families in which proband's mother could be analyzed, the mutation in the propositus has not been detected in the leukocytes of the mothers in 63 families (66.3%). The latter included 59 families with sporadic cases and four families with two or three affected siblings. Evidence for gonadal mosaicism was clearly shown in the latter four families (Jacquot *et al*,[36] Horn *et al*,[37] and A Hanauer unreported observations). This result suggests that germline mutation mosaicism is not uncommon and that the recurrence risk in families with a single affected child with CLS, even when the mother is negative for a mutation, may be significant. Most of the families in which the mother was negative for the mutation in the propositus included one to four healthy siblings. Haplotyping of these families is ongoing, using *RPS6KA3* flanking microsatellites. There was no obvious indication of somatic mosaicism in either the 63 mothers who were negative for mutation in the propositus or in the patients in peripheral blood lymphocytes. However, we have not yet excluded the possibility that any of these mothers is a somatic mosaic in additional areas, which are not reflected in lymphocyte-based PCR analysis. Thus, screening of DNA extracted from other cell sources is also ongoing. Altogether, the results are expected to help in determining precisely the recurrence risk after the birth of a single CLS-affected child in a family.

## TREATMENT AND CARE

Early diagnosis of CLS is essential for proper management of the patients, including surveillance of some specific complications. Surveillance includes periodic hearing, dental, and vision examinations; annual cardiac examination, including echocardiogram by the age of 10 years and repeated every 5 to 10 years; and regular monitoring of the spine for progressive kyphoscoliosis. There is no specific treatment. Sensorineural hearing deficit should be addressed very early to improve the development and quality of life of the patients. Treatment for individuals with CLS who experience drop attacks includes medications such as valporate and clonazepam or selective serotonin uptake inhibitors. If stimulus-induced drop episodes occur with great frequency, use of a wheelchair may be required to prevent falling and injury. Progressive worsening of kyphosis and/or scoliosis can cause severe cardiorespiratory compromise and often requires surgical correction.[38]

## CONCLUSIONS

Despite intensive research, the disease mechanism involved in CLS and the phenotype are unexplained. The relationship between genotype and phenotype is not well understood. The specific physiological roles of RSK2 are also unclear, although the identification of a growing number of substrates suggests some possibilities.

The cellular bases and physiopathological mechanisms underlying mental retardation in CLS patients have not yet been fully elucidated. Little is currently known about the cellular effects of RSK2 in neurons. However, there is growing evidence for implication in neuronal survival, neurite growth, functional maturation, and synaptic plasticity.

Nuclear targets for RSK2 include transcription factors and histones, in accordance with a major role in regulation of gene expression. Ongoing research is focused on the characterization of the molecular pathways that are controlled through RSK2, and in particular on the identification of target genes whose expression is directly influenced by RSK2 in hippocampus and cortex.

It is hoped that through these combined approaches, potential targets may be identified for therapeutic intervention in CLS patients.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## ACKNOWLEDGEMENTS

CLS studies in our team have been supported by the Agence Nationale pour la Recherche (ANR-05-NEUR-005-01), the Fondation Jérome Lejeune, the Institut National de la Santé et de la Recherche Médicale, the Centre National de la Recherche Scientifique, the Université Louis Pasteur and the Hôpital Universitaire de Strasbourg.

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