Short reports

Unreported *RSK2* missense mutation in two male sibs with an unusually mild form of Coffin-Lowry syndrome

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Abstract

An unreported missense mutation of the ribosomal S6 kinase 2 (*RSK2*) gene has been identified in two male sibs with a mild form of Coffin-Lowry syndrome (CLS) inherited from their healthy mother. They exhibit transient severe hypotonia, macrocephaly, delay in closure of the fontanelles, normal gait, and mild mental retardation, associated in the first sib with transient autistic behaviour. Some dysmorphic features of CLS (in particular forearm fullness and tapering fingers) and many atypical findings (some of which were reminiscent of FG syndrome) were observed as well. The moderate phenotypic expression of this mutation extends the CLS phenotype to include less severe mental retardation and minor, hitherto unreported signs. The missense mutation identified may be less deleterious than those previously described. As this mutation occurs in a protein domain with no predicted function, it could be responsible for a conformational change affecting the protein catalytic function, since a non-polar amino acid is replaced by a charged residue.

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Precise diagnosis of mental retardation (MR) syndromes is important for genetic counselling. As well as fragile X syndrome, many X linked MR conditions have been described, so that diagnostic difficulties may occur, especially in cases of mild MR and non-specific dysmorphic features (as seen with facial hypotonia and an everted lower lip). However, some genes responsible for these syndromes have been identified, allowing confirmation of the suspected clinical diagnosis by DNA analysis, even with atypical presentations, and extending the phenotypic spectrum of the disease. Here we report two cases with a mild form of Coffin-Lowry syndrome (CLS).

CLS (MIM 303600) is an X linked, semidominant, mental retardation syndrome, described by Coffin *et al*[1] and Lowry *et al*[2] as separate entities. A few years later, Temtamy *et al*[3] reported that these syndromes were one single condition called Coffin-Lowry syndrome. In male patients with CLS, severe mental retardation, abnormal gait, characteristic facial changes, and skeletal abnormalities are the rule. Less severe clinical manifestations are observed in most female heterozygotes. The gene for CLS has been localised to Xp22.3-p22.1,[4 5] and identified as ribosomal S6 kinase 2 (*RSK2*).[6] As expected for a severe X linked disease, considerable heterogeneity of mutations, widespread throughout the coding sequence, has been found in patients with typical CLS.[7 8] Here we describe two mildly retarded male sibs with some dysmorphic features of CLS. This diagnosis was confirmed by the identification of an *RSK2* mutation.

Case reports

These two male patients were the second and third children of healthy parents with very distant consanguinity. Their older sister was born by caesarian section and was healthy apart from an inguinal hernia surgically repaired at 8 years of age. After the first birth, the mother had three spontaneous first trimester miscarriages. Both parents were of above average intelligence and denied any family history of mental retardation. The mother had three healthy brothers and another brother who died at birth of umbilical cord strangulation. Both parents' chromosomes were normal (karyotyping was done because of the three miscarriages).

The first patient (fig 1) was born at term after an uneventful pregnancy apart from maternal hypertension. Fetal movements were normal. Caesarean section was performed because of breech presentation and the previous caesarean section. Neonatal measurements were within normal limits (length 50 cm, weight 3200 g, OFC 36 cm). At 3 months of age right inguinal and umbilical hernias were surgically repaired. At that time hypotonia was observed. Further developmental milestones were delayed and he did not sit until 9 months or walk until 22 months of age. Furthermore, regression of psychomotor development was

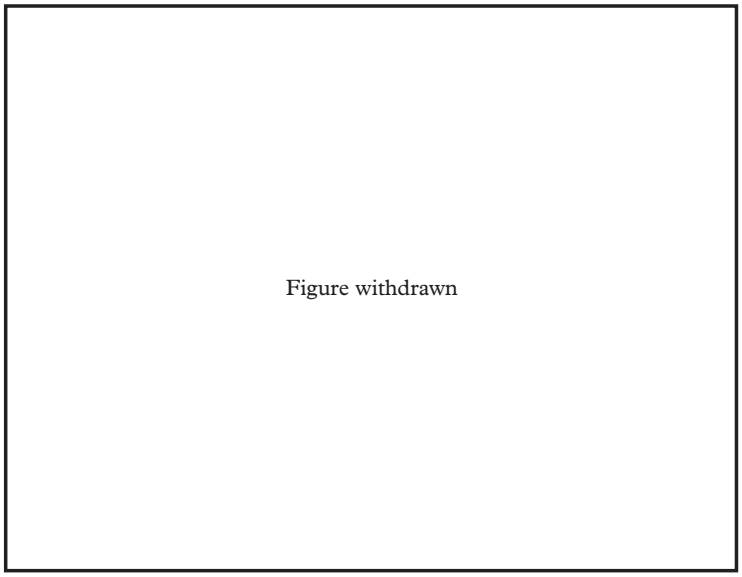

Figure 1 (A-E) Patient 1 aged 3 years, 4 years 9 months, 7 years 9 months, 9 years, and 9 years 9 months, respectively. Note the course of the dysmorphic features with age. Macrocephaly present in early childhood (A) resolved later (C, D, E). Note hypertelorism, full lateral upper eyelids, short nose with depressed bridge, anteverted nostrils with a thick columella, large mouth with full, everted lower lip, small, widely spaced teeth, and large ear lobes. (All photographs reproduced with permission.)

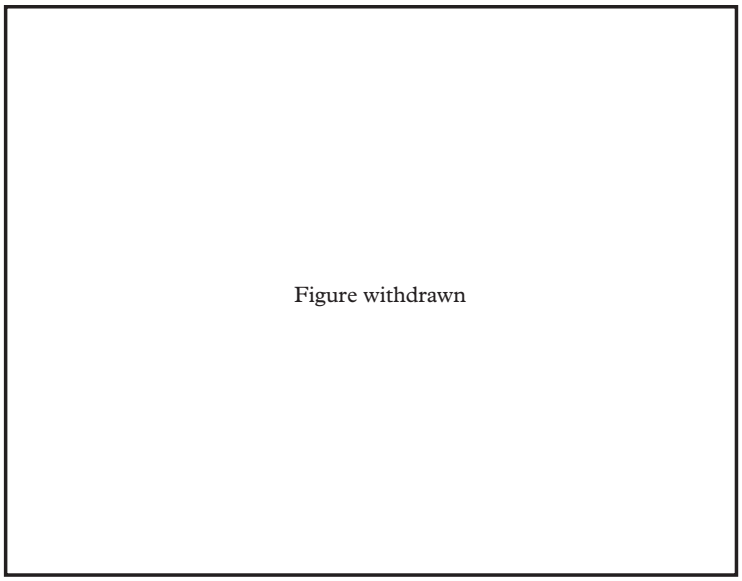

Figure 2 (A-E) Patient 2 aged 9 months, 2½ years, 5½ years, 6 years 11 months, and 7 years 9 months, respectively. Macrocephaly present in early childhood (A, B) resolved later (D, E). Note also frontal upsweep of the hair, epicanthic folds, telecanthus, downward slanting palpebral fissures, moderate fullness of the upper lateral eyelids, moderately anteverted nares, and a large mouth with a somewhat full lower lip.

observed at 18 months of age with decreased contact with his parents, rocking, and loss of the few words known. Autism was diagnosed and intensive psychotherapy was started from the age of 2 years with rapid recovery of normal contact. However, further psychomotor development was slightly retarded with speech delay and backwardness at school. He used nappies up to 3 years of age in the day time and 5 years at night. Moreover, the patient had frequent diarrhoea, moderate growth retardation (−1.5 SD) with bone age retarded 2 years, a large OFC in early childhood which later decreased (OFC 52.5 cm at 3 years of age (+2 SD), 53 cm at 4½ years (+1.5 SD), and 54 cm at 9 years of age (+1 SD)), very late closure of the fontanelles (3 years 3 months of age), and characteristic facies (fig 1). The teeth erupted at the right time but were irregular.

At the age of 10 years (fig 1E), height was 126 cm (−1.8 SD), weight 27 kg (−0.8 SD), and OFC 55 cm (+1.3 SD). He presented with hypertelorism (interpupillary distance 6.3 cm, >97th centile; intercanthal distance 3.7cm, >97th centile), full lateral upper eyelids, a short nose with a depressed bridge and a thick columella extending above the anteverted nostrils, a large mouth with a full, everted lower lip, a high palate with small, widely spaced teeth, and large ear lobes. Slight fullness of the forearms was noted. His hands were small and bulky with fullness of the proximal phalanges of the fingers and distal tapering, but no abnormal crease was present in the hypothenar area. His big toes were broad. Moreover, hypopigmented skin areas following the lines of Blaschko were observed on the right side of his body. He spoke well, attended a school for slightly retarded children, read and wrote simple words, counted up to 70, and had been able to dress without supervision since 6 years of age and to ride a bicycle since 7 years of age. He was an easy going, quiet, pleasant boy, who was particularly sensitive to frustrations, which resulted in occasional fits of anger. Hearing and eye examination and cerebral CT scan were normal. *X* rays showed no anomaly apart from a 2½ year delay in bone age and somewhat short metacarpals.

The second patient (fig 2) was born at term after an uneventful pregnancy apart from maternal hypertension. Fetal movements were normal. Caesarean section was performed because of the two previous ones; however, presentation was normal. Neonatal measurements were within normal limits (length 50 cm, weight 3800 g, OFC 36 cm). Hypotonia was noted during the neonatal period. At 2 months of age a right inguinal hernia was surgically repaired. Motor development was delayed; he did not sit until 12 months or walk until 32 months of age. Other developmental milestones were less delayed; the child used nappies up to age of 18 months in the day time and 2 years at night. Speech was only slightly delayed. Like his brother, he had frequent diarrhoea, moderate growth retardation (−1.5 SD) with bone age retarded 2 years, large OFC in early childhood which later decreased (OFC 49 cm at 1 year of age (+2 SD), 52 cm at 2½ years of age (+2 SD), and 53.5 at 5½ years of age (+1.5 SD)), late closure of the fontanelles (2½ years of age), and characteristic facies (fig 2). The teeth erupted at the right time but were irregular.

At the age of 7½ years (fig 2E) height was 116 cm (−1.2 SD), weight 21 kg (−0.8 SD), and OFC 54 cm (+1.5 SD). He had frontal upswept hair, epicanthic folds, telecanthus (interpupillary distance 5.5 cm, 75th centile; inner canthal distance 3.3 cm, 75-97th centile), downward slanting palpebral fissures, fullness of the upper lateral eyelids, a small, upturned nose with depressed bridge and anteverted nares, a large mouth with a full

lower lip, a high palate with small, widely spaced teeth, and normal ears. As in his brother, slight fullness of the forearms, small hands without an abnormal crease in the hypothenar area but fullness of the proximal phalanges of the fingers, and distal tapering were noted. No hypopigmented skin areas were observed. The anus was slightly displaced anteriorly. He spoke well, was one year behind at school, and had been able to dress without supervision since 5 years of age and to ride a bicycle since 6 years of age. He was a pleasant, hyperactive boy. Hearing and eye examination and cerebral MRI were normal. *X* rays showed no anomaly apart from a delay in bone age of 2¼ years, a right cervical rib, and somewhat short metacarpals.

The mother is an intelligent young woman. At the age of 2 years, she underwent radiotherapy and nephrectomy because of a right Wilms tumour. When examined at the age of 37 years, height was 163 cm and OFC 55 cm. She had no dysmorphic features, but photographs taken in her childhood showed anteverted nares, which were also present in one of her healthy brothers and, according to her, in other family members. Her hands and forearms showed some fullness as did those of her father. *X* rays showed some increased tufting in the distal phalanges of her fingers.

A chromosomal anomaly, as well as fragile X syndrome (MIM 309550) and ATRX syndrome (MIM 300032), were excluded. FG syndrome (MIM 305450) was considered because of the hypotonia, macrocephaly, and some of the dysmorphic features especially in the younger patient, pigmentation anomalies in the older, and anteriorly placed anus in the younger. However, despite the mild mental retardation, some of the characteristics of the face (short nose with anteverted nostrils, full, everted lower lip) associated with the fullness of the forearms and the tapering fingers led us to study the *RSK2* gene implicated in Coffin-Lowry syndrome (CLS). Mutational screening of the *RSK2* gene (performed as described in Jacquot *et al*[7]) showed a T to A transversion in exon 7, leading to the substitution of an isoleucine for a lysine (I189K) in both affected sibs and their mother. This substitution was shown to be a de novo event, since it was not found in either of the mother's parents. Haplotype analysis, using two tightly linked markers flanking CLS, showed that the X chromosome bearing the nucleotide change was of grandpaternal origin (not shown). The presence of this amino acid change was tested on 130 normal chromosomes under the same SSCP conditions and was not found (data not shown). In addition, protein database comparison showed that isoleucine 189 is a highly conserved residue present in all known *RSK*s (including the homologues identified in *Drosophila* and *Xenopus laevis*), suggesting a functional role. Together, these findings support the conclusion that this amino acid alteration is indeed responsible for the atypical phenotype observed in this family.

Discussion

Here we describe two mildly retarded male sibs with a mild form of CLS inherited from their healthy mother. CLS is an X linked mental retardation syndrome resulting from mutations of the ribosomal S6 kinase 2 gene (*RSK2*).[6] CLS is usually characterised in male patients by hypotonia, delayed closure of the anterior fontanelle, severe mental retardation (IQ<50[9]) with frequent microcephaly and abnormal posture, small stature with delayed bone age, fullness of the forearms, laxity of the joints, tapering fingers, transverse crease in the hypothenar area, and a "pugilistic" facies characterised by a prominent frontal region, hypertelorism, downward slanting palpebral fissures, a short nose with a thick septum and anteverted nares, a large mouth with full, everted lips, and small, widely spaced teeth with premature loss of primary dentition. The patients' skin is described as "soft" and "velvety".[9–17] Furthermore, hernias, hearing loss, visceral neuropathy, radiculomyelopathy, "cataplexy", cerebral white matter hypodense areas, premature cataract, cervical ribs, and hydrops fetalis have been described in some instances.[9 17–22] Most heterozygous females are mildly affected with mental retardation of various degree sometimes associated with psychosis or "drop episodes", small stature, microcephaly, characteristic facies (prominent brows, telecanthus, thick nasal septum, everted lower lip), and tapered fingers with typical radiographic tufting of the terminal phalanges.[10 13 17 24 25] Diarrhoea, anteriorly placed anus, and hypopigmented skin lines have not previously been described in CLS and could be coincidental. Hypotonia, developmental delay, delayed closure of the fontanelles, and hypotonic facial changes are non-specific findings observed in many MR syndromes.

We describe two brothers with mild MR and additional findings leading to diagnostic difficulties. In early childhood, severe hypotonia, macrocephaly, and delay in closure of the fontanelles were the most obvious features, associated in the first sib with transient autistic behaviour. A few years later, the hypotonia had completely resolved, the gait was normal, but mild MR persisted. The pleasant personality, macrocephaly with telecanthus, and broad big toes in both boys, as well as pigmentation anomalies in one sib and slightly anteriorly displaced anus and frontal upsweep of the hair in the other, were reminiscent of FG syndrome. As the children became older, the macrocephaly decreased, forearm fullness and tapering fingers were more obvious, and the facies coarsened (figs 1 and 2) with anteverted nares and fully everted lower lip, leading to the possible diagnosis of a mild form of CLS. DNA analysis identified a mutation of the *RSK2* gene and confirmed the diagnosis.

These observations are of interest because the moderate phenotypic expression of this mutation extends the CLS phenotype to include less severe mental retardation. As the missense mutation identified has never been found in typical CLS patients, it may be less deleterious than those previously described

(deletion, nonsense, and other missense mutations). However, the biochemical effect of this mutation is not clear since it occurs in a protein domain with no predicted function. However, it could be hypothesised that a conformational change affects the protein catalytic function, since a non-polar amino acid is replaced by a charged residue. Thus, it would be of interest to study the effect of this missense mutation on the biochemical activity of *RSK2*.

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