ELECTRONIC LETTER

Coffin-Lowry phenotype in a patient with a complex chromosome rearrangement

N Concannon, A-M Hegarty, R L Stallings, W Reardon

J Med Genet 2002;**39**:e41 (http://www.jmedgenet.com/cgi/content/full/39/8/e41)

The eponym Coffin-Lowry syndrome has been used by clinical geneticists for over a quarter of a century now, since first proposed by Temtamy *et al*[1] in 1975. The syndrome refers to a recognisable clinical condition, characterised by mental retardation, characteristic facial appearance, and skeletal abnormalities. Most geneticists would consider that the condition represents a fairly good example of "gestalt" diagnosis, the recognition of a familiar pattern on observing the face. Young[2] has tabulated the facial features in this condition, identifying coarseness, hypertelorism, antimongoloid slant, pouting, everted lower lips, and a broad nose as the most frequently observed features. In addition, affected subjects frequently have pectus excavatum/carinatum, kyphosis or scoliosis, and broad hands, often with tapering fingers and hypothenar crease.

Inherited as an X linked condition, the classical phenotype is described in affected males. However, carrier females frequently manifest clinical characteristics of the condition. Mapping of the locus indicated a location in Xp22.3-p22.1.[3] Subsequently, disease causing mutations have been described in the ribosomal protein S6 kinase (*RSK2*).[4–6] A wide range of different types of mutations have been described, distributed throughout the gene, many associated with premature translation termination, and most associated with predicted loss of function of the mutant allele.[6] The application of these findings in clinical practice has served not just to expand the understanding of the mutational basis of the classical syndrome, but has also shown that atypical, mild forms of Coffin-Lowry syndrome exist.[7] Despite these occasional clinical surprises, most patients harbouring pathogenic mutations of the *RSK2* locus have shown clinical characteristics consistent with those expected in Coffin-Lowry syndrome.[5] However, as established by a recent mutational screen in 250 patients clinically suggestive of Coffin-Lowry syndrome, mutations are found in by no means all such patients.[6] Indeed mutations were not identified in 66% of patients included in the mutation studies. While a proportion of these cases may represent failed detection owing to the procedures used for screening, it is also very likely that many patients with clinical features suggestive of Coffin-Lowry syndrome are caused by mutations at other loci.

A recent report by McCandless *et al*[8] records many clinical and radiological characteristics of Coffin-Lowry syndrome in a patient with a chromosome 10q25.1-25.3 deletion. The close resemblance between the patient described with the deletion and the classical Coffin-Lowry phenotype led the authors to speculate that other molecular elements of the RSK2 mediated pathway might be disrupted in their patient and that there might be a further locus, possibly autosomal, for Coffin-Lowry syndrome. Similarly, the observation recently reported by Kondoh *et al*[9] of a Coffin-Lowry syndrome phenotype in a Japanese patient with de novo 8p23 duplication raises a similar prospect, although it must be acknowledged that the dysmorphic features in the latter case were less convincing to a western eye. To this growing body of evidence, cumulatively suggestive of alternative loci for Coffin-Lowry syndrome, we now add a patient with several classical clinical features associated with a complex, apparently balanced, chromosomal rearrangement.

Figure 1 The facial features aged 18 years, showing hypertelorism, frontal prominence, everted, thickened lips, and large nose.

CASE REPORT

The patient is an 18 year old male. He is the oldest offspring of his non-consanguineous parents, there being three healthy younger sibs. Antenatal and perinatal history was normal. He came to attention because of epileptic seizures from the age of 9 months. All motor milestones were severely delayed. Examined at 18 years, he had no speech, continues on long term antiepileptic medication, and has contractures of the lower limbs secondary to confinement to a wheelchair in a residential facility. However, he does walk, despite the contractures and shows no evidence of ataxia.

The facial features are striking (fig 1) with a prominent brow, hypertelorism, a large nose with a thickened septum, and pouting, everted lower lip. The fingers are short, though not tapering. There is a deep pectus carinatum.

Apart from specific chromosomal investigation detailed below, HbH inclusion bodies have specifically been sought but are not present. Also SSCP screening of the *RSK2* locus has been normal.

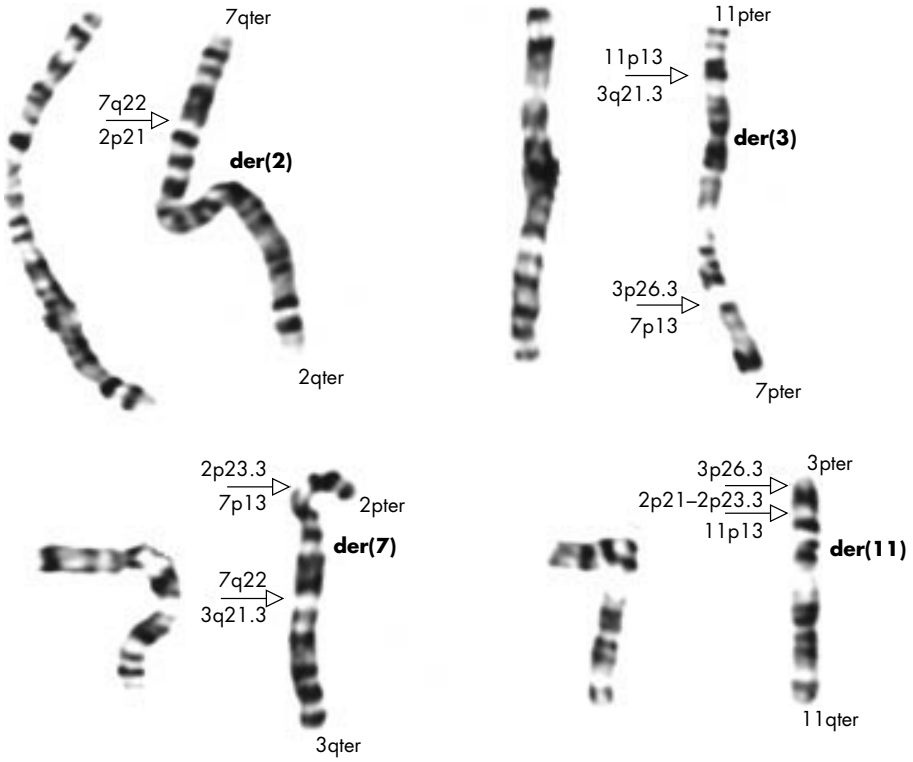

Figure 2 G banded derivative chromosomes 2, 3, 7, and 11 (right) with the respective normal chromosomes displayed on the left (650 band resolution). The telomeres found at the ends of each derivative chromosome are designated. Arrows indicate the breakpoint regions on each derivative chromosome. For example, the region 7q22 to 7qter is attached to band 2p21 on the derivative chromosome 2. The region 2p21 to 2p23.3 could be in either orientation and is sandwiched in between the telomere region of 3p and band 11p13 on the derivative chromosome 11.

METHODS

G banding was carried out on lymphocyte metaphases from the patient by standard treatment with trypsin and Leishman's stain. Fluorescence in situ hybridisation (FISH) analysis was carried out with subtelomeric probes for chromosomes 2p (Genbank U31389), 2q (D2S447), 3p (D3S4559), 3q (D3S4560), 7p (Genbank G31341), 7q (STS 2000H), 11p (D11S2071, 11q (VIJyRM2072), WCP2, WCP3, WCP7, and WCP11 from VYSIS under conditions recommended by the supplier.

RESULTS

Analysis of G banded metaphase spreads showed a complex karyotype with translocations involving chromosomes 2, 3, 7, and 11. Fig 2 displays each of the four derivative chromosomes with their respective breakpoints and identifies the subtelomeric regions that are present at the end of each chromosome arm. Seven breakpoints were required to generate the patient's karyotype.

The derivative chromosome 2 was broken at two locations, 2p21 and p23. 3. The region 2p23.3-pter was attached to the 7p13 region of the derivative chromosome 7, while the 2p21-p23.3 region was inserted between band 11p13 on the derivative 11 and the 3p26.3 subtelomeric region. The orientation of 2p21-p23.3 is unknown. The region 7q22-qter was attached to band 2p21 of the derivative chromosome 2. The derivative chromosome 3 has the region 11p13-pter attached to 3q21.3 and the region 7p13-pter attached to 3p26.3. Finally, the derivative chromosome 7 has 2p23.3-pter attached to 7p13 and 3q21.3-qter attached to 7q22. All of these observations were confirmed by FISH analysis with subtelomeric probes for the p and q arms of each chromosome (fig 3), and whole chromosome painting probes for each chromosome (data not shown).

At a gross cytogenetic level the karyotype appears to be balanced. This was confirmed by comparative genomic hybridisation (CGH) which indicated normal green to red fluorescence ratio profiles for chromosomes 2, 3 , 7, and 11. Cytogenetic analysis of both parents was normal.

DISCUSSION

Gestalt recognition of the facial phenotype continues to be important in recognising patients with Coffin-Lowry syndrome, although mistakes can and have occurred. A celebrated example relates to the photographs used in an earlier edition of a well known textbook of dysmorphology to illustrate Coffin-Lowry syndrome, the patient in question subsequently being shown to have ATRX. While some patients with clinical features of Coffin-Lowry syndrome will be shown to have *RSK2* gene mutations, many such patients will not.[6] Accordingly, investigators are seeking alternative loci, possibly involved in the same signalling pathway as *RSK2*, mutation of which might offer an explanation for the phenotype seen in patients such as ours. In this context the non-specific chromosomal localisation of the *RSK1* locus to chromosome 3,[10] disrupted in the patient we report, may possibly be significant, especially in view of the identification of the *RSK4* locus in a critical region for mental retardation t(Xq21).[11] The *RSK1* locus represents a gap in the recently published draft sequence of the human genome since our research of the database indicates that this region is apparently not covered by any of the large stretches of contiguous DNA sequence.[12]

While the karyotype of our patient appears to be balanced, the confirmation that it has occurred de novo, allied to the normal investigations for ATRX, strongly suggests that the clinical features are a direct consequence of the chromosomal disruption. This report adds to a growing body of data cumulatively suggesting that *RSK2* mutation alone does not account

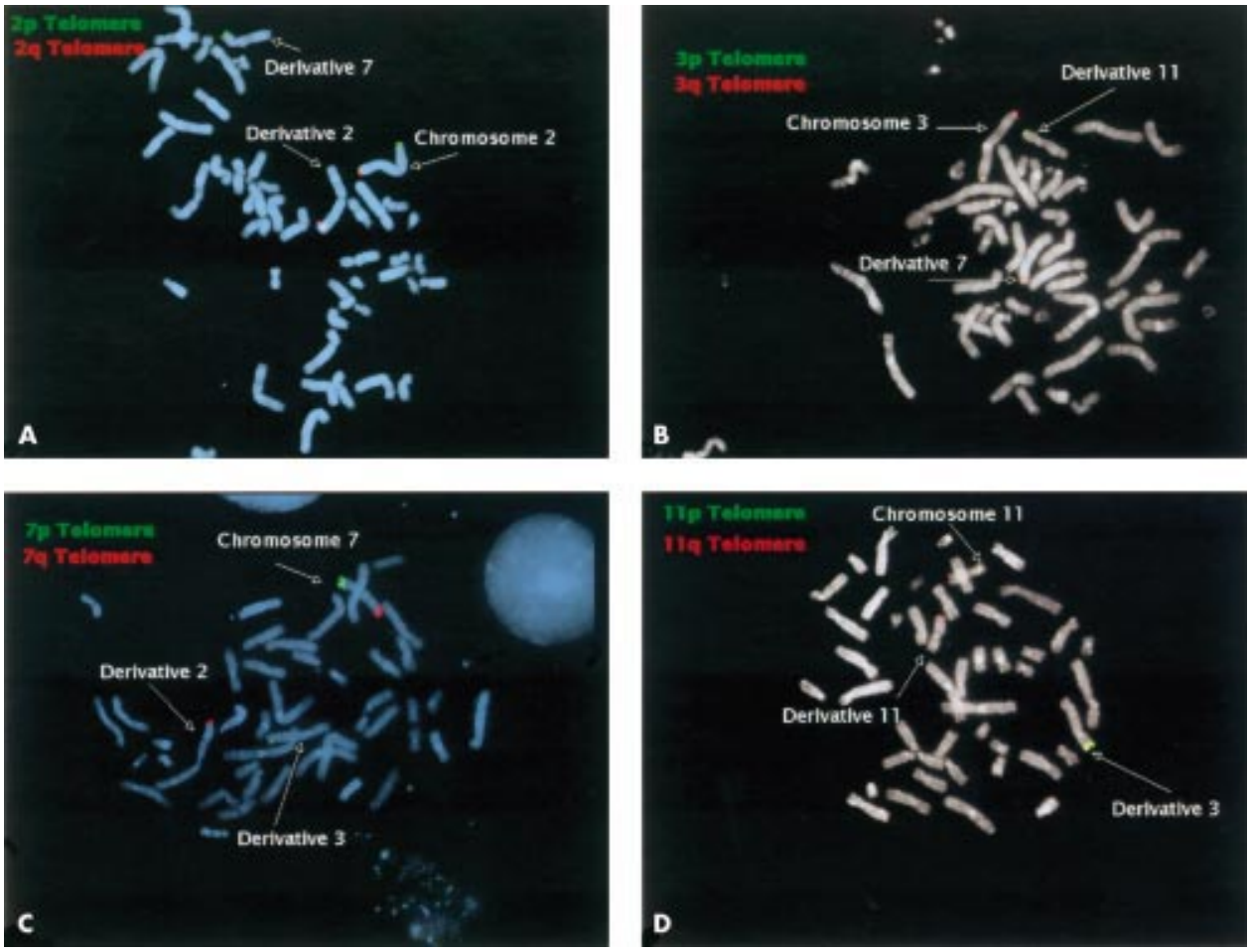

Figure 3 FISH analysis with p (spectrum green) and q (spectrum red) arm subtelomere probes from chromosomes 2 (A), 3 (B), 7 (C), and 11 (D). Each normal chromosome and derivative chromosome is labelled.

for all patients with Coffin-Lowry syndrome features and that additional, possibly autosomal, loci may be involved in generating the facial phenotype which we associate with this condition.

ACKNOWLEDGEMENTS

The authors wish to thank the patient's family for consent to publish his photograph and Dr A Hanauer for undertaking *RSK2* mutation analysis.

Authors' affiliations

N Concannon, A-M Hegarty, R L Stallings, W Reardon, National Centre for Medical Genetics, Our Lady's Hospital for Sick Children, Crumlin, Dublin 12, Ireland
R L Stallings, Conway Institute of Biomedical and Biomolecular Research, University College Dublin, Dublin, Ireland

Correspondence to: Dr W Reardon, National Centre for Medical Genetics, Our Lady's Hospital for Sick Children, Crumlin, Dublin 12, Ireland; willie.reardon@olhsc.ie

REFERENCES

1 **Temtamy SA**, Miller JD, Hussels-Maumenee I. The Coffin-Lowry syndrome: an inherited facio-digital mental retardation syndrome. *J Pediatr* 1975;**86**:724-31.
2 **Young ID**. The Coffin-Lowry syndrome. *J Med Genet* 1988;**25**:344-8.
3 **Hanauer A**, Alembik Y, Gilgenkrantz S, Mujica P, Nivelon-Chevallier A, Pembrey ME, Young ID, Mandel JL. Probable localisation of the Coffin-Lowry locus (CLS) in Xp22.2-p22.1 by multipoint linkage analysis. *Am J Med Genet* 1988;**30**:523-30.
4 **Trivier E**, De Cesare D, Jacquot S, Pannetier S, Zackai E, Young I, Mandel JL, Sassone-Corsi P, Hanauer A. Mutations in the kinase Rsk-2 associated with Coffin-Lowry syndrome. *Nature* 1996;**384**:567-70.
5 **Abidi F**, Jacquot S, Lassiter C, Trivier E, Hanauer A, Schwartz CE. Novel mutations in Rsk-2, the gene for Coffin-Lowry syndrome. *Eur J Hum Genet* 1999;**7**:20-6.
6 **Delaunoy JP**, Abibi F, Zeniou M, Jacquot S, Merienne K, Pannetier S, Schmitt M, Schwartz CE, Hanauer A. Mutations in the X-linked RSK2 gene (RPS6KA3) in patients with Coffin-Lowry syndrome. *Hum Mutat* 2001;**17**:103-16.
7 **Manouvrier-Hanu S**, Amiel J, Jacquot S, Merienne K, Moerman A, Coeslier A, Labarriere F, Vallee L, Croquette MF, Hanauer A. Unreported *RSK2* missense mutation in two male sibs with an unusually mild form of Coffin-Lowry syndrome. *J Med Genet* 1999;**36**:775-8.
8 **McCandless SE**, Schwartz S, Morrison S, Garlapati K, Robin NH. Adult with an interstitial deletion of chromosome 10 [del(10)(q25.1q25.3)]: overlap with Coffin-Lowry syndrome. *Am J Med Genet* 2000;**95**:93-8.
9 **Kondoh T**, Takano J, Sugawara H, Ida T, Harada N, Matsumoto T, Matsumoto N, Niikkwa N. Clinical manifestations of Coffin-Lowry syndrome associated with de novo 8p23 duplication. *Am J Hum Genet* 2001;**69**:293 (abstract 646).
10 **Moller DE**, Xia CH, Tang W, Zhu AX, Jakubowski M. Human rsk isoforms: cloning and characterization of tissue-specific expression. *Am J Physiol* 1994;**266**:C351-9.
11 **Yntema HG**, van den Helm B, Kissing J, van Duijnhoven G, Poppelaars F, Chelly J, Moraine C, Fryns JP, Hamel BCJ, Heilbronner H, Pander HJ, Brunner HG, Ropers HH, Cremers FPM, van Bokhoven, H. A novel ribosomal S6-kinase (RSK4; RPS6KA6) is commonly deleted in patients with complex X-linked mental retardation. *Genomics* 1999;**62**:332-43.
12 **International Human Genome Sequencing Consortium**. Initial sequencing and analysis of the human genome. *Nature* 2001;**409**:860-921.