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

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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 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 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. 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. 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. 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. 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. 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 records many clinical and radiological characteristics of Coffin-Lowry syndrome in a patient with a chromosome 10q23.1-25.3 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 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.

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 with hypertelorism, frontal prominence, everted, thickened lips, and large nose. The fingers are short, though not tapering. There is a deep pectus carinatum. The facial features aged 18 years, showing hypertelorism, frontal prominence, everted, thickened lips, and large nose.

Figure 1
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. 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, disrupted in the patient we report, may be significant, especially in view of the identification of the RSK4 locus in a critical region for mental retardation t(Xq21). 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.

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 direct consequence of the chromosomal disruption. This report adds to a growing body of data cumulatively suggesting that RSK2 mutation alone does not account for all cases of Coffin-Lowry syndrome.
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.

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REFERENCES


