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SHORT REPORT

Identification of an unbalanced cryptic translocation between the chromosomes 8 and 13 in two sisters with mild mental retardation accompanied by mild dysmorphic features

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Recently, much attention has been given to subtelomeric chromosomal rearrangements as important aetiological factors leading to idiopathic mental retardation. However, detection of these aberrations is difficult, mostly due to technical limitations and lack of genotype–phenotype relationships. We report on a family with a history suggestive of segregation of a chromosomal anomaly. In two mildly mentally retarded sisters with a similar phenotype consisting of obesitas, skin atrophy of the lower limbs and mild facial dysmorphisms, a subtle unbalanced cryptic translocation (46,XX,der(13)t(8;13)(q24.3;q34)) was detected on routine cytogenetic investigation followed by additional FISH studies. The translocation originated from the mother. *European Journal of Human Genetics* (2000) **8**, 637–640.

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Introduction

Mental retardation, defined as an intelligence quotient less than 70, is a common disorder affecting about 3% of the population. So far, aetiological factors have been found only in less than half of all retarded patients. Standard cytogenetic analysis has revealed that chromosomal anomalies are responsible for approximately 40% of severe (IQ < 55) and 10–20% of mild (IQ < 55–70) mental retardation.[1–3] However, preliminary findings indicate that terminal regions of chromosomes relatively often harbour cryptic chromosome abnormalities, which might be responsible for more than 7% of all cases of severe and 0.5% of mild mental retardation.[4,5] In this case report we present a family in which a subtelomeric chromosomal rearrangement segregates, which has caused mild mental retardation accompanied by mild dysmorphic features in two sisters and, in the past, probably in two of their grandmother's brothers.

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Case reports

A healthy 29-year-old male, the second child of a sibship of three children from non-consanguineous parents (Figure 1; IV-2), was referred to our clinical genetics department for genetic counselling. His mother (Figure 1; III-1) was the only live-born child of a family in which there had been several miscarriages. Two brothers of the grandmother (Figure 1; II-3 and II-4) were known to have been mentally retarded. During the Second World War they both died at approximately 40 years of age in an institution for the mentally handicapped.

The two sisters of the proband, 31 and 25 years of age, respectively (Figure 1; IV-1 and IV-3), were both also known to have mild mental retardation of unknown cause.

The oldest sister was born at term with no known birth data. Up to the age of 4 years no abnormalities were reported, except for some developmental delay. When the girl was 6 years old, she was under observation because of psychomotor retardation and speech problems. Features reported by that age were hypotonia and muscular atrophy, resulting in a myopathic appearance and hyperlaxity of the joints. At the age of 14 years, the retardation had become more evident and

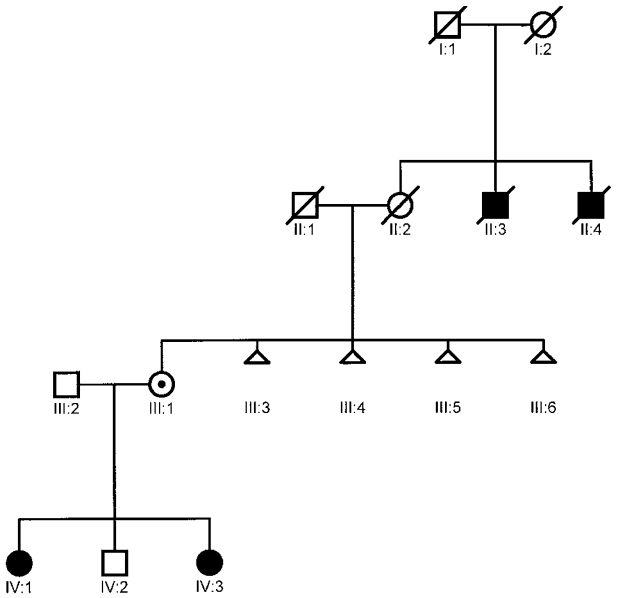

Figure 1 Pedigree of the family.

there were problems in her social behaviour. On physical examination the only feature reported was strabismus of the right eye. Menarche had just started.

At referral, she lived with her sister and they both worked in a sheltered environment. On examination we saw a friendly, mentally retarded obese woman with height of 171 cm, weight of 96.9 kg, and a skull circumference of 56 cm. Her face showed mild dysmorphic features with thin lips and a bulbous nose with large nares and a wide columella below the level of her nares. Her face was quite similar to that of her sister and, moreover, showed resemblance to the mentally retarded sibs of the grandmother. Other features were lordosis, valgus position of the knees and pes planes. The skin of the distal part of the lower extremities was pigmented and atrophic. The distal ends of all the digits showed broadening.

The third and youngest child of this family was born at term with a birth weight of 3380 g. In early childhood developmental milestones were delayed. She started walking at 2 years and talking at 4 years of age.

From 9 to 11 years of age she lived in a medical and developmental psychological child centre. Apart from psychomotor retardation and behaviour problems (negative and lacking concentration), no somatic features were reported and, like her sister, she did not attend a clinic until adulthood.

At referral, she was 25 years old, with a height of 177 cm, weight 90 kg and skull circumference 56 cm. Her facial appearance was quite similar to that of her sister and the sibs of the grandmother. She also showed some muscle weakness resulting in lumbar lordosis, valgus position of knees and pes planes.

Cytogenetic studies

Cytogenetic studies of the two sisters (IV-1 and IV-3) were performed according to routine GTG-banding techniques on cultured peripheral lymphocytes. Although hardly visible, in one of the probands (IV-1) some metaphases seemed to show a very slight difference between the distal long arms of both chromosomes 13 (band 13q34). Since it remained uncertain whether this was due to an aberration or just a reflection of natural differences in contraction of the DNA (Figure 2), we performed fluorescence *in situ* hybridisation (FISH) with a number of subtelomeric probes from the long arm of chromosome 13 (Figure 3).

Two cosmids – cos-2002el, supplied by Cytocell Ltd, Oxfordshire, UK, and cos-2053 from Dr Flint, MRC, Oxford, UK[6] – and one yeast artificial chromosome (YAC908C3, from Dr Haaff, Max Planck Institut, Berlin, Germany), were used. To our surprise the YAC probe gave a very clear signal at the telomeres of both chromosomes 13 in both sisters, whereas the cosmids showed a signal on only one chromosome 13 in both sisters. Since the YAC is known to be localised somewhat more proximally than both the cosmids, a deletion or subtle translocation should have occurred at the distal part of one chromosome 13, somewhere between the YAC sequences and both cosmids.

To examine the origin of this abnormality, both parents were studied. Whilst the father showed completely normal results after GTG-banding and FISH studies, in the mother only one chromosome 13 showed a signal with both cosmids, whereas a second signal was present on the telomere of the long arm of one chromosome 8. As expected the YAC revealed a signal on both chromosomes 13. These results were confirmed with a subtelomeric probe from 8q (cosmid

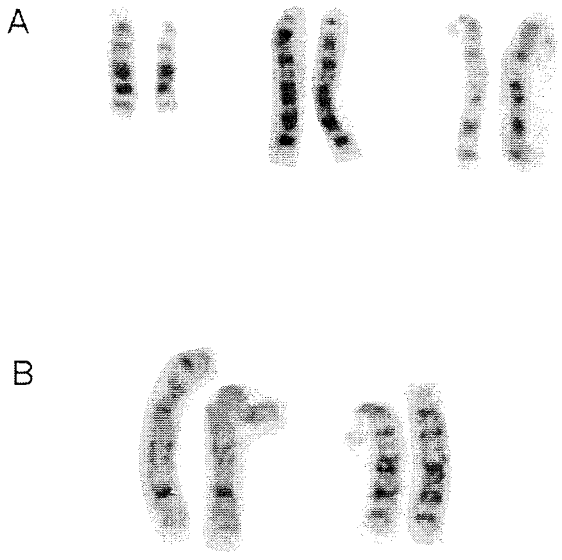

Figure 2 **A** GTG-banded chromosome 13 from three cells of one of the probands with different contraction of the chromosomes, and **B** chromosome 8 (on the left) and 13 (on the right) from the mother.

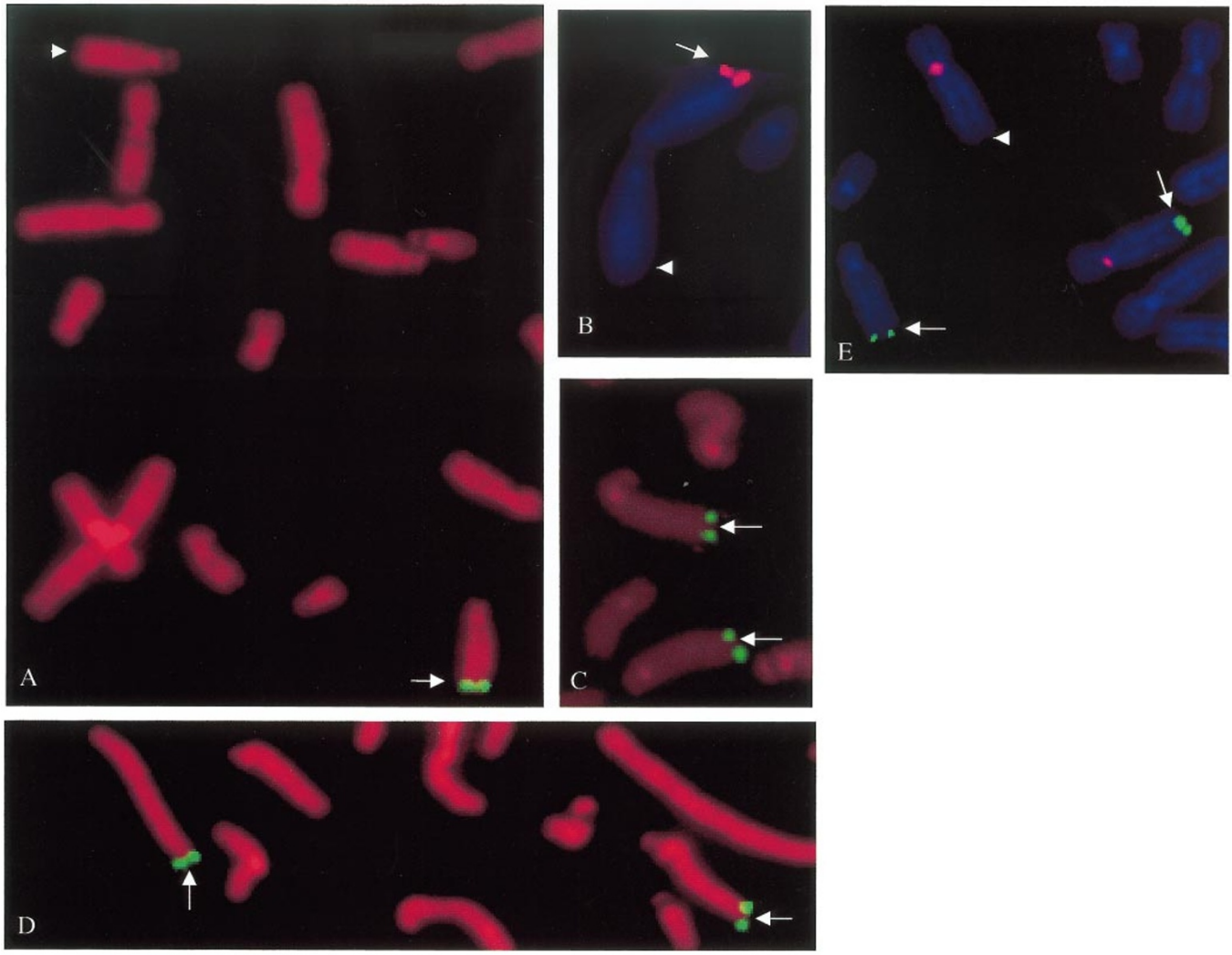

Figure 3 FISH results with subtelomeric probes from chromosome 13 on metaphases of one of the patients (**A**–**C**: cos-2053, cos-2002el, and YAC908C3). Arrows point to the non-deleted chromosomes 13 and arrowheads to chromosomes 13 lacking a signal; and of the mother (**D**, **E**), where **D** is the result with cos-2053 showing a signal on the normal chromosome 13 and the aberrant chromosome 8 (arrows) and **E** shows the signals of cos-192A5 (8q) on one chromosome 13 and the normal chromosome 8 (arrows). The centromeres of both chromosomes 8 are stained with a centromere-specific probe showing also the aberrant 8 (arrowhead).

192A5,[6]) which gave in the mother a signal on only one chromosome 8 and on the derivative chromosome 13 (Figure 3), whereas in both patients three signals were present on both chromosomes 8 and the derivative chromosome 13 (results not shown).

Thus a subtle balanced translocation between the ends of the long arm of chromosomes 8 and 13 is present in the mother, which has led to an unbalanced situation in the patients, with a very small terminal deletion (monosomy) of the long arm of chromosome 13 and a trisomy for 8qter. The initial proband (IV-2) showed normal results in regular GTG-banding and FISH studies.

Discussion

We have presented two sibs with mental retardation and dysmorphic features. Both patients have the same chromosomal abnormality, namely a monosomy for the most distal part of the long arm of chromosome 13 and a trisomy for the distal part of band 8q24.3.

The 13q syndrome had already been recognised as an entity in 1969[7] and since then a large number of patients has been described. However, specific diagnostic criteria are difficult to define because the manifestation of symptoms varies considerably between patients with a partial 13q deletion. The critical region for the severe 13q deletion

phenotype is probably at best in band 13q32. More distal deletions usually result in mental retardation accompanied by only minor anomalies.[8,9]

A partial trisomy of 8q has been described in at least 18 cases in the literature, all involving 8q23/24.1 8qter. Stengel-Rutkowski *et al*[10] established a spectrum of features from 15 cases of partial 8q trisomy in the literature. Comparing our patients to this spectrum, the most resemblant signs are limited to flared nasal wings and large nares only. Therefore, it is likely that they express only a (small) part of this spectrum. A trisomy 8q24.3 qter as present in our patients, has been observed in only one other family, where a 2qter deletion and 8qter duplication caused Albright hereditary osteodystrophy (AHO)-like phenotype.[11] As suggested in this paper, the 2qter deletion is most probably responsible for the AHO-like phenotype, which compromises the phenotypic effects, if any, of the 8qter duplication.

Our data confirm the need for additional studies when routine cytogenetic investigations are negative in a family suspect for the segregation of a chromosomal aberration. Currently, in patients suspected of having a chromosomal abnormality but lacking specific dysmorphic features, no (molecular) diagnostic routine screening of submicroscopic chromosomal aberrations is performed, although recently several new approaches have become available. Molecular cytogenetic (FISH) studies as well as DNA polymorphisms can be applied to find such chromosomal abnormalities. FISH with specific (sub)telomeric probes has the advantage that both balanced and unbalanced rearrangements can be recognised. The present family indicates the importance of subtelomeric probes (YAC was not deleted), otherwise one may misinterpret the results.

Recently, Knight *et al* described the screening of a large series of mentally retarded patients using telomeric probes.[4] Cryptic chromosomes rearrangements were found in 7.4% of moderately or severely handicapped and in 0.5% of mildly retarded individuals and were familial in almost half of the cases. These results emphasise the importance of extensive genetic studies in certain cohorts of the mentally handicapped, and subsequent adequate genetic counselling.

Acknowledgements

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