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Ring Chromosome 22 Resulting in Partial Monosomy in a Mentally Retarded Boy

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ABSTRACT

We describe a 7-year-old boy presenting with mental retardation and hyperactivity. Clinical features include microcephaly, hypertelorism, epicanthic eye folds and antimongoloid slant. He also has large ears, large hands and feet, and torticollis. The karyotype was 46, XY, r (22) (p13q13). In situ hybridisation studies with a subtelomeric probe for distal 22q confirmed that the ring was deleted causing partial monosomy of 22q.

Keywords: partial monosomy, mental retardation

INTRODUCTION

Ring chromosomes are a rare occurrence, and their abnormal morphology makes characterisation by conventional G-banding analysis difficult, resulting in few reports of well characterised rings. Most cases of ring chromosome 22 would be expected to show loss of part or all of the short arm in addition to loss of some long arm material. Loss of short arm material is unlikely to have any phenotypic effect. However, partial monosomy resulting from deletion of part of the long arm is known to be associated with a syndrome involving global developmental delay, mental retardation, severe delay in speech and language skills but only minor facial dysmorphology[1]. Patients with ring chromosome 22 may have clinically significant deletions of 22q and application of fluorescent in situ hybridisation (FISH) techniques to ring chromosomes in order to confirm that deletion has occurred, is a useful adjunct to conventional cytogenetic studies.

Case report

The patient is a 7-year-old Chinese boy referred to Hospital Sultanah Aminah by his general practitioner because of mental retardation and hyperactivity. He is the son of non-consanguineous parents, Chinese father aged 37 years and Thai mother aged 32 years. There is no history of mental retardation in either family. He has a 4-year-old sister who is well and phenotypically normal. He was delivered at term by breech extraction with a birthweight of 3.2 kg. The antenatal, intrapartum and postpartum periods were apparently uneventful. At age 8 months, delay in attaining milestones was noted and he was seen by several private practitioners. He has a history of 2 generalised afebrile seizures at age 9 months but was not hospitalised. He rolled over at 10 months, walked at 3 years and at present, aged 7 years, is able to speak only 2 – 3 words with poor receptive language. No formal psychological tests were done due to lack of personnel and facilities. At 7 years, his weight was 21 kg (50th percentile), height 121 cm (50th percentile) and head circumference 47 cm (< 3rd percentile). Abnormal features include microcephaly, hypertelorism, epicanthic eye folds and antimongoloid slant. He has large ears, large hands and feet, and has torticollis (Figs 1 & 2). His lungs were clear. There was no organomegaly and no heart murmur. His right testis was undescended. CNS examination showed normal tone with normal reflexes. Blood count and urine analysis were normal, as were CT scan of the brain and EEG.

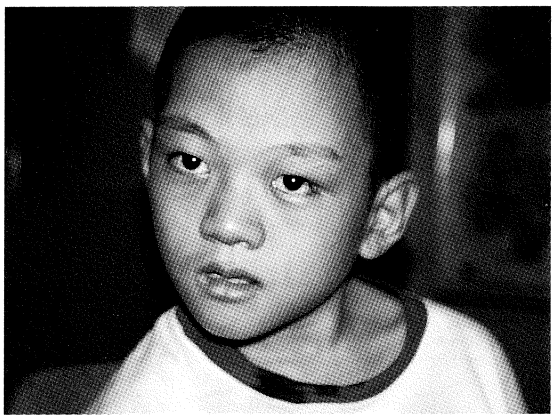

Fig 1 – Photograph of patient showing facial dysmorphology and torticollis.

Fig 2 – Photograph of patient's large hands.

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Cytogenetic findings

Karyotyping was performed on G-banded metaphase chromosomes after routine PHA stimulated peripheral blood culture. Synchronisation by thymidine block[2] was used to obtain high resolution chromosomes. Chromosome analysis showed 59 of 62 cells to have a ring chromosome 22 (Fig 3). The remaining three cells were missing the ring chromosome and were therefore monosomic for chromosome 22. However, these cells probably represent mitotic instability rather than true mosaicism. The morphology of the ring chromosome did not allow for determination of any deleted segments. However, it was thought likely that the ring chromosome would have lost the 22q telomeric segment. In order to test this hypothesis, in situ hybridisation with the cosmid probe N85A3 (Cytocell)[3] was performed. This probe is the last unique cosmid on 22q[4] lying approximately 70 – 110 kb from the telomere in band 22q13.3[3]. The TUPLE-1 probe mapping to 22q11 acted as a control and marker for chromosome 22. The procedure used was in accordance with the manufacturer's instructions. In all 25 cells analysed, the TUPLE-1 probe gave positive signal on both the normal chromosome 22 and the ring chromosome. The N85A3 probe gave positive signal only on the normal chromosome 22 in all cells examined. No signal was present on the ring chromosome, confirming deletion of the distal part of 22q13 (Fig 4). Parental karyotypes were normal, no evidence of mosaicism was detected in 30 cells from each parent.

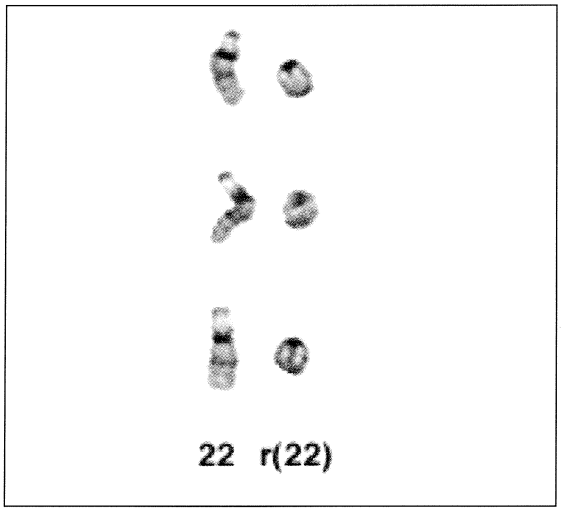

Fig 3 – Partial karyotypes showing normal chromosome 22 and ring chromosome 22.

DISCUSSION

Ring chromosome 22 is a rare occurrence. Early publications[5] dismissed the idea of a ring chromosome 22 syndrome. However, Hunter et al[6] suggested that the most commonly reported features of mental retardation with disproportionate verbal delay, reduced head circumference, hypotonia, unsteady gait, large ears with abnormal configuration and epicanthic eye folds did in fact suggest a r(22) syndrome. Teyssier and Moreau[7] reported familial transmission of a r(22) from a phenotypically normal woman to her daughter, a 27-year-old woman, without dysmorphic features or mental retardation,

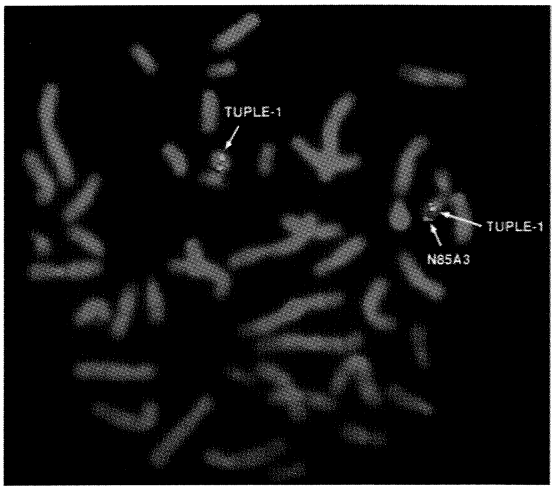

Fig 4 – In situ hybridisation with TUPLE-1 and N85A3. The normal chromosome 22 shows hybridisation with both TUPLE-1 and N85A3. The ring chromosome 22 shows hybridisation with only TUPLE-1.

indicating that significant deletion is not universal in the production of ring chromosomes. Gustavson et al[8] reported a ring chromosome 22 in a mentally retarded boy, and also produced evidence for a deleted ring 22 by way of gene dosage effect for arylsulphatase A activity.

It would be expected that the clinical features associated with ring chromosome 22 would be similar to those seen in association with pure deletion of the terminal region of chromosome 22. Deletions involving 22q13.3 are generally associated with a common phenotype which includes global developmental delay, hypotonia, severe delays in expressive speech and mild facial dysmorphic features. It would seem appropriate to consider r(22) as a special subset of deletion 22q with the proviso that rings, like deletions, can vary in the size of the deleted segment and thus can vary in their phenotypic effect. Small deletions are associated with minimal dysmorphology although mental impairment can be profound. The patient described here exhibits the microcephaly, global developmental delay, severe delay in expressive speech, mild facial dysmorphology and large ears seen in the del(22)(q13) and r(22) syndromes. However, hypotonia was not noted. Large hands and feet have been noted previously in only one patient with del(22)(q13.3)[1].

Small deletions may not be cytologically detectable in a ring chromosome, therefore additional techniques are required to demonstrate deletion in such patients. Recent studies of patients with deletions of chromosome 22 have utilised FISH[9,10] or molecular genetic techniques[1] to fully characterise the deletion. In this paper, we describe a similar FISH strategy to demonstrate deletion in a ring chromosome 22. The probe used, cosmid N85A3 is particularly valuable for identifying small terminal deletions due to its proximity to the telomere.

This case helps to further delineate the del(22)(q13) and r(22) syndromes. It illustrates that mental retardation and developmental delay should be investigated with chromosomal study, and that FISH can be a useful adjunct to conventional chromosome analysis.

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