A 3½ year old girl with distal trisomy 19q defined by FISH

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Abstract

A 3½ year old girl was evaluated because of developmental delay. Short stature was evident with height between the 3rd and 10th centiles, while weight and head circumference were on the 50th centile. Dysmorphic features consisted of a high bossed forehead, pointed short ear lobes, small nose, bilateral convergent strabismus, left simian crease, a gap between the first and second toes bilaterally, mild clinodactyly, and a broad, barrel shaped thorax. Cytogenetic investigations showed an unbalanced karyotype, 46,XX,10q+, which was de novo in origin. Fluorescence in situ hybridisation (FISH) using three library probes (from chromosomes 10, 19, and 19q) and a YAC probe (from 10q telomere) showed that the additional material on 10q was derived from chromosome 19q.

The patient had an unbalanced translocation, 46,XX,-10,+der(10)t(10;19)(q26.3;q13.3), which resulted in distal trisomy 19q. Few other cases of proven distal trisomy 19q are available for comparison of clinical features.

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De novo unbalanced karyotypes resulting from apparent duplications pose a problem of interpretation when the origin of the duplicated segment cannot be precisely defined and the mechanism not absolute.¹ The most common mechanism is an unbalanced translocation; only exceptionally will there be an interstitial duplication or duplication deficiency. In an unbalanced rearrangement with an additional segment on a chromosome, the monosomic segment will usually be the end of the chromosome while the trisomic segment stems from elsewhere. The clinical features can thus be the result of partial monosomy or partial trisomy or both.

In the investigation of apparent duplications, the first step is to test the parents. For de novo rearrangements, the use of FISH with a library probe from the putative chromosome is a simple procedure and will show if the additional material is derived from this chromosome. If not, subsequent evaluation may be difficult. Different strategies have been used to define the additional material, such as targeted

chromosome band painting after microdissection of the aberrant chromosomal region,¹ multicolour FISH,² and comparative genomic hybridisation (CGH).^{3,4} These specialised techniques may not be readily available and CGH is not an ideal technique to determine the origin of unbalanced structural abnormalities.

We evaluated a girl with intellectual handicap and an unbalanced 10q+ chromosome using FISH in conjunction with G banded chromosomes to identify the duplicated segment on 10q.

Case report

The proband was the first child of unrelated, healthy parents born when the mother was 27 and the father 31 years of age. There were no other sibs and no significant family history. The pregnancy was complicated by pre-eclampsia at 35 weeks necessitating induction of labour. She was born at 37 weeks' gestation by normal vaginal delivery with birth weight 2590 g, birth length 45 cm (both between the 3rd and 10th centiles), and birth head circumference 31.5 cm (3rd centile). Apgar scores were 5 at one minute and 8 at five minutes. She developed hypothermia with a low blood glucose level and was nursed in a humidicrib. She made a rapid recovery and was fully breast fed. She had bilateral dislocated hips which were treated by splinting. She was noted to have strabismus at 6 months of age and this was surgically corrected at 12 months. The parents stated that as an infant she was never demanding, rarely cried, and was happy to play alone.

The parents first sought help at 12 months because of delayed milestones. She crawled at 14 months, walked at 19 months, and single words developed at 2 years of age. When seen at 3½ years, she was an active, "busy" child, who communicated by pointing rather than with words. Eye contact and changes in facial expression were poor and her gait was immature and clumsy. Her height was 90 cm (3rd centile), weight was 15.8 kg, and head circumference 49.7cm (50th centile). Dysmorphic features noted were high bossed forehead, short thick neck, flat nasal bridge, downturned corners of the mouth, pointed short ear lobes bilaterally (fig 1), a gap between the first and second toes bilaterally, left simian crease, mild bilateral clinodactyly, and broad barrel shaped chest. There was a spider naevus on the left side of the face and a fading strawberry naevus (1.5 cm) on the right shoulder. She had not

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Figure 1 Anterior view of the proband, aged 3½ years. The facial features of high bossed forehead, slightly short nose, and short neck are subtle.

had seizures and there were no focal neurological signs.

At 3½ years, investigations of liver, renal, and thyroid function tests, urine metabolic screen, blood glucose, creatine kinase, and full blood count were all within the normal range. Bone age was consistent with chronological age. She was not toilet trained. Developmental assessment showed significant delay with overall skills at a 2 year level and language development at the 21 month level.

CYTOGENETICS

Peripheral blood was set up in 72 hour cultures and slides were GTG banded by standard techniques. Microscopic analysis showed an unbalanced karyotype with additional material on the terminal end of the long arm of chromosome 10, 46,XX,10q+ (fig 2). This had the appearance of a duplication of 10q25 to 10q26. No other cytogenetic abnormality was detected. The parents both had normal chromosomes.

FISH

Standard methods were used with fresh slides made from the suspension retained after the cytogenetic harvest.⁵ The chromosome 10 library probe (Cambio CHR10) showed that on one chromosome 10 the signal did not extend completely to the terminal end of 10q (fig 3, top). After a thorough perusal of the karyotype to match the terminal ends of each chromosome arm with the banding pattern and size of the unpainted region, the 19 library (Cambio CHR19B) was used. Three signals

Figure 2 Partial GTG banded karyotype of the two chromosomes 10, with the arrow indicating the 10q+. Below is a chromosome 19 pair, which supported the likely involvement of chromosome 19q.

were obtained; both chromosomes 19 were fully painted and a signal was present on the terminal der(10q) (not shown).

Further FISH studies used a telomere YAC from 10q (HTY3136) (biotinylated and detected with FITC conjugated avidin), hybridised simultaneously with the microdissection painting probe from the long arm of chromosome 19,⁶ (labelled with digoxigenin and detected with Cy3 conjugated anti-digoxigenin antibody). Only one signal was detected with the 10q probe, indicating deletion of the 10q telomere (fig 3, bottom) and this appeared to involve only the telomere associated region, with no loss of 10q euchromatin. The translocation of 19q material was seen on the der(10) with the 19 long arm probe (fig 3, bottom).

Discussion

In our case, the imbalance appeared cytogenetically to be a duplication 10q. FISH showed an unbalanced translocation with the additional material derived from chromosome 19q. Apparent duplications such as presented here provide an appropriate use of FISH in the clinical evaluation of a case and should be performed. We used three hybridisation procedures in a routine laboratory setting. When clinical information is not specific enough, as in our case, to point to a region of interest, investigation could be facilitated by use of the new Chromoprobe-M multiprobe system (Cytocell, Oxfordshire). This is a device which allows simultaneous detection of all 24 chromosomes on a single slide and could be performed in most routine FISH laboratories.

Our case is the first case of trisomy distal 19q proven with FISH. The reported phenotype comes from only eight to 10 cases.⁷⁻⁹ Clinically our patient had many of the features described, namely dysplastic ears, high bossed forehead, flat nasal bridge, short nose, short neck, barrel

Figure 3 Investigations with FISH. (Top) Metaphase spread with the 10 library probe. One chromosome 10 is completely painted, while in the other the paint falls short of the telomere (arrowhead). (Bottom) Digitised pseudocoloured image of a metaphase spread. The 19q microdissection probe is painted in red and the YAC clone for 10q telomere in yellow. There are two large red signals from the normal 19q chromosomes plus a smaller red signal on the terminal end of chromosome 10q (arrowhead). The der(10) chromosome does not give a yellow signal with the 10q telomere probe, present on the normal chromosome 10q.

shaped chest, clinodactyly, short stature, and moderate intellectual handicap. However, she

lacked other features, such as coarse hair, microcephaly, epilepsy, downward slanting palpebral fissures, hypertelorism, and loose nuchal skin. She had a normal mouth and dentition.

The variability in the clinical features may be the result of the size of the trisomy (in our case quite small) and some of the more severe features could be attributed to the concomitant monosomy. There was no cytogenetic evidence of monosomy 10q (fig 3) in our patient but she had two features found previously in monosomy 10qter and not described in trisomy 19q, namely fine hair and dislocated hips.⁷ Both are non-specific and common at birth and the finding that among only 10 cases this is the first of partial trisomy 19q with hip dislocation is not surprising. Our conclusion is that the patient has essentially "pure" trisomy 19(q13.3-qter).

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