A patient with Wolf-Hirschhorn syndrome originating from translocation t(4;8)(p16.3;q24.3)pat

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Abstract

We present here a 7 year old girl with the clinical signs of Wolf-Hirschhorn syndrome (WHS). Only on high resolution banding was a deletion of 4p16.3 suspected in both the proband and the father. Further studies using simultaneous R banding and FISH, with cosmid probe pc847.351 containing the mildly repetitive fragment 847-EC, confirmed the diagnosis and showed a paternal balanced translocation t(4;8)(p16.3;q24.3).

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Wolf-Hirschhorn syndrome (WHS) is a rare chromosomal deletion syndrome involving the distal short arm of chromosome 4 (4p), first described by Wolf *et al*¹ and Hirschhorn *et al*.² It is characterised by prenatal and postnatal growth retardation, developmental delay with microcephaly, and a characteristic facial appearance of hypertelorism, downward slanting palpebral fissures, prominent glabella giving the peculiar Greek helmet profile, high arched eyebrows, low set, abnormal ears, and a short prominent philtrum with downturned corners of the mouth. Other associated anomalies include seizures, congenital heart defects, scalp defects, and genital anomalies in the form of hypospadias or cryptorchidism or both.^{3,4}

In many cases WHS results from de novo terminal deletions of chromosome 4p ranging in size from approximately one half of the short arm down to submicroscopic deletions with a fairly constant phenotype.⁵⁻⁷

Transmission from balanced translocation carriers is now well documented by the improved techniques of high resolution banding and FISH studies suggesting that those carriers could have been missed in earlier studies.^{8,9}

We report here a 7 year old girl whose clinical features are suggestive of WHS with a subtle deletion 4p16.3 shown by high resolution banding. A paternal balanced translocation t(4;8)(p16.3;q24.3) was suspected. R banding-FISH technique confirmed the results obtained by clinical and cytogenetic studies.

Case report

The patient is a 7 year 11 month old girl born at 38 weeks' gestation to a 24 year old mother and a 24 year old father. The family history is negative for developmental abnormalities. Her birth weight was 2070 g, length 44 cm, and

head circumference 32.5 cm. She had Apgar scores of 8 and 9 at one and five minutes, respectively, and was neonatally followed up for muscular hypotonia.

The patient was first seen at the age of 10 months for retarded growth and motor development. Her extremities appeared then to be disproportionately short but x rays were not suggestive of bone dysplasia. The hands and feet were small. She had a triangular face with a relatively broad forehead, widely spaced eyes and inner canthi, and a small, narrow chin. The nose appeared short and had a wide tip, and the philtrum was short. The auricles were slightly posteriorly rotated and the right helix was dysmorphic. Her dysmorphic findings remained essentially unchanged during the follow up. She had been treated for strabismus and also for increased intraocular pressure. Eruption of the teeth has been delayed. She has remained short and slim with a height at -4 SD, weight at -15%, and a head circumference at -3 SD.

She had suffered from febrile convulsions at the age of 7 and 9 months, and from Lennox type epilepsy from the age of 1 year. She is on antiepileptic medication and has been free from seizures since the age of 6 years. She is severely retarded and cannot speak. She is clumsy but is able to walk and run. She has suffered from frequent otitis media infections (fig 1).

CYTOGENETICS AND FISH STUDIES

Chromosome preparations were made from cultures of blood lymphocytes and a lymphoblastoid cell line. High resolution G banding was obtained after synchronisation of the culture with bromodeoxyuridine (Sigma Chemical Co, St Louis, MO, USA).

R banding was accomplished by a method adapted from Larramendy *et al*¹⁰ to allow simultaneous detection of R bands and FISH.

DNA from cosmid probe pc847.351 (38 Kbp), which is part of the D4F26 locus at the 4p terminus and contains the mildly repetitive 847 EC fragment,¹¹ was labelled with biotin 14-dATP using a BRL-nick translation kit (Nick Translation Kit, Bethesda Research Laboratories, Gaithersburg, MD, USA). Denaturation, hybridisation, and detection were carried out as described elsewhere.^{8,12}

Results

Chromosomal analysis by G banding on prometaphases suggested the presence of a small

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Figure 1 (A,B) Facial appearance of the patient at the age of 6 years.

Figure 2 Cut out of chromosomes 4 and 8. (A) Patient, arrowhead indicates der(4). (B) Father, arrowheads indicate der(4) and der(8).

deletion in terminal 4p in the proband. Study of both parents showed that the mother had a normal karyotype (46,XX) while the father was suspected to have a balanced translocation t(4;8) (fig 2).

After FISH was applied to the proband, signals could be seen in only one 4p in all metaphases studied, confirming the cytogenetic diagnosis of del(4p16.3). In the father, signals were detected in one 4p and also on the ter-

минаl long arm of a C group chromosome. The simultaneous R banding-FISH technique was applied and by appropriate filter combinations (Zeiss 02, 09, 15) the chromosome was easily identified to show the characteristic R banding pattern of chromosome 8 (fig 3). Thus this father is a balanced translocation carrier of t(4;8)(p16.3;q24.3).

Discussion

Our case was suspected to have del(4p16.3) by high resolution G banding, which was confirmed by the application of FISH. The critical region of WHS has been defined to be less than 2 Mb in the terminal region of chromosome 4p16.3.^{6,13} Recently a case with de novo interstitial deletion of chromosome 4p(p15.31p16.3) without the classical WHS phenotype was reported.¹⁴ Our case confirms further that the critical region of WHS is in distal 4p16.3. Simultaneous R banding-FISH technique proved to be very useful in the iden-

Figure 3 (A) A metaphase from the patient's father studied by fluorescence in situ hybridisation with cosmid probe pc 847.351 shows avidin-FITC (fluorescein isothiocyanate) signals (Zeiss 09 filter). (B) The same metaphase through the Zeiss 15 filter shows propidium iodide R bands. Arrows indicate the 4;8 translocation: from the other homologue of chromosome 4 the terminal area of the p arm (4p16.3) is translocated to 8q24.3.

tification of the origin of the paternal balanced translocation t(4;8)(p16.3;q24.3).

About 13 to 15% of WHS 4p monosomies result from parental translocation carriers.¹⁵ In our case the deletion was inherited from the father. However, earlier reports have shown that mothers carry the translocation more frequently than fathers,^{8,9,16,17} whereas in de novo deletions the origin of the affected chromosome is more frequently paternal.^{13,18-22}

As subtle deletions may be overlooked by common banding techniques, we recommend performing FISH studies for patients who have features of WHS. Moreover, detection of translocation carriers calls for FISH studies of parents.

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