Interstitial deletion of the distal long arm of chromosome 4, del (4)(q33-q35), in association with paternal balanced translocation

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ABSTRACT

Interstitial deletions of the long arm of chromosome 4 are rare. The deletions may occur at the proximal or the distal portions of the chromosome and different breakpoints may be involved. We report an interstitial deletion of 4q: 46XY der 4 (q28;q35) in a six-year-old boy with dysmorphic features associated with moderate mental retardation. Parental chromosomal analysis showed a balanced paternal translocation.

Keywords: 4q interstitial deletion, chromosome abnormality, intersitial deletion, mental retardation, paternal dislocation, short stature

Singapore Med J 2008; 49(11): e336-e339

INTRODUCTION

Interstitial deletions of the long arm of chromosome 4 are rare.[1,2] Most of the cases that have been reported involve different breakpoints. The clinical presentation and features of the affected individuals are relatively similar and the parents' chromosomes are usually normal. In this report, we describe interstitial deletion of 4q33–q35 in a child whose father had reciprocal translocation of chromosomes 4 and 19. We also compared the clinical features of patients with other levels of breakpoints in previous reports with those identified in our index case.

CASE REPORT

The propositus is a six-year-old boy who was referred for short stature and eczema. He was born at term and was the third child of a non-consanguineous marriage. Both parents were 37 years of age, and the siblings of the patient were healthy. There was no prenatal history of medication, alcohol intake or smoking. His birth weight was 2.4 kg. He had delayed psychomotor development: he was only able to say a few meaningful words but could not recognise alphabets or colour. His pronunciation was not clear. At the current age of six years, his speech and language performance were comparable to a 30-month-old child. On physical examination, the boy weighed 15 kg, had a height of 103 cm and a head circumference of 51.8 cm. He had a midline frontal prominence, closely-placed eyebrows, bilateral epicanthic folds, long philtrum, and a small mouth (Fig. 1). The nipples were widely-spaced. There was only one interphalangeal joint in both right and left fifth fingers. He also had hypoplastic nails. The soles of his feet were eczematous. No hearing impairment or gross neurological abnormalities was identified. Cardiovascular examination was normal. Investigations for inborn error metabolism were negative.

Fig. 1 Photograph shows the propositus with dysmorphic features due to an interstitial deletion of the distal long arm of chromosome 4.

The patient's parents gave their informed consent prior to their blood being taken for analysis. Giemsa banded chromosome studies were performed on cultured peripheral blood lymphocytes of the patient and his parents using standard protocols. Comparative genomic hybridisation (CGH) analysis was performed as described previously.[3] Equal amounts of biotin-labelled DNA of the patient (test DNA) and digoxigenin-labelled DNA of a healthy proband (reference DNA) were hybridised in the presence of Cot-1 DNA to metaphase spreads from a healthy male donor. After three days of hybridisation, probe detection was carried out using FITC (spectrum green) for biotin- and Cy3 (spectrum red) for digoxigenin-labelled DNA probes. Image acquisition, processing and evaluation of 12 metaphase spreads were performed

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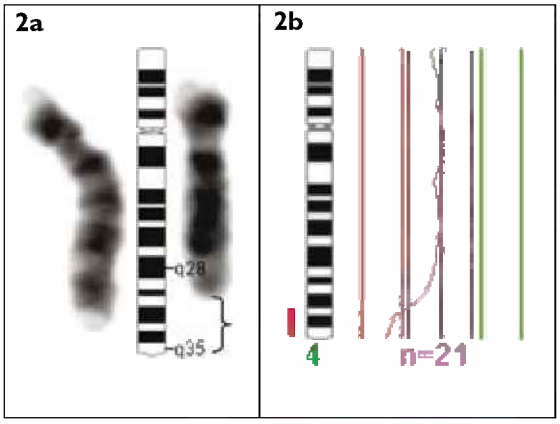

Fig. 2 Illustration shows (a) G band analysis of chromosome 4 of the patient. Brackets indicate the assumed deleted segment (4)(q28q35). (b) CGH analysis confirms the deleted segment between q33 and q35.

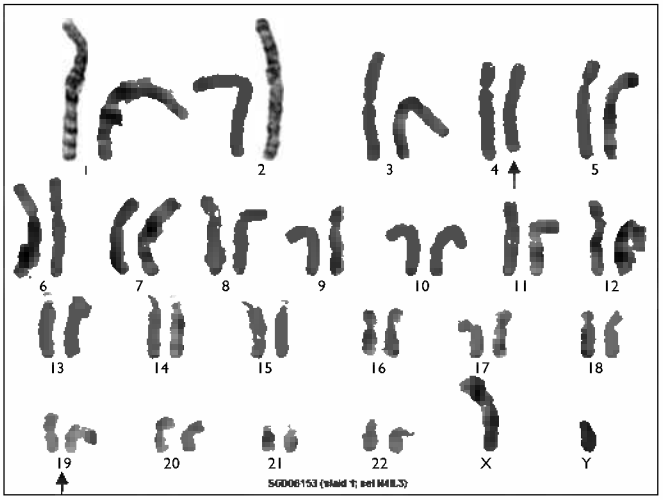

Fig. 3 Karyotype of the father shows a balanced translocation between chromosome 4 and 19 (arrows).

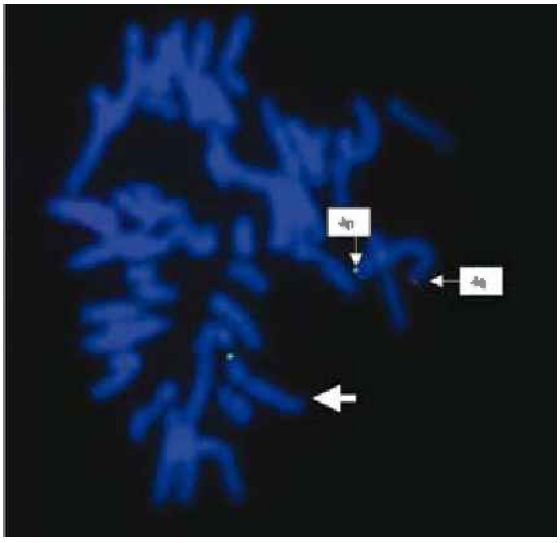

Fig. 4 FISH analyses of the propositus as chromosomes show an absence of an orange signal on chromosome 4 (thick arrow), confirming distal 4q deletion.

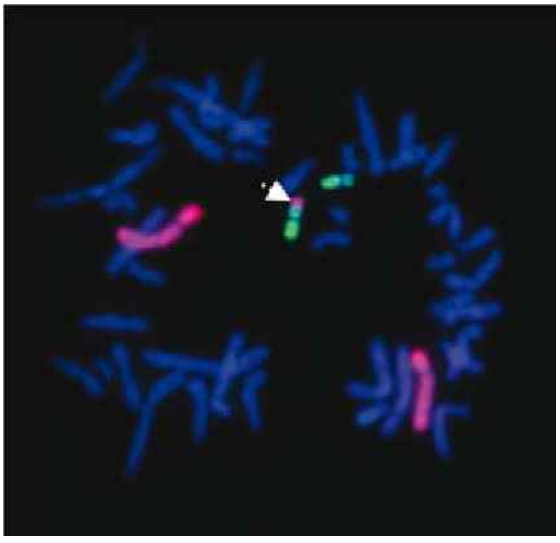

Fig. 5 Whole chromosome paint analysis on the father's blood shows translocation of chromosome 4 material (pink colour) onto chromosome 19 (green colour).

using Cytovision CGH software. The threshold values for detection of genomic imbalances were 0.8 for losses and 1.2 for gains.

Fluorescent in situ hybridisation (FISH) analysis was performed on the same peripheral blood samples harvested for cytogenetic analysis. 10 µL of dual-colour probe cocktail consisting of Telvysion 4p SpectrumGreen probe (SpectrumGreen-labelled, Vysis, Downers Grove, IL, USA) and Telvysion 4q SpectrumOrange probe (SpectrumOrange-labelled, Vysis, Downers Grove, IL, USA) was applied to the sample and contained with coverslips sealed with rubber cement. The samples and probes were code-natured and hybridised using the Vysis HYBrite Denaturation/Hybridisation System. The HYBrite unit was programmed to allow five minutes of denaturation at 73°C, followed by overnight hybridisation at 37°C. Post-hybridisation wash was performed in 0.4 × SSC / 0.1% NP-40 (72°C, two minutes) followed by wash-in 2 × SSC / 0.1% NP-40 (room temperature, one minute). The slides were air-dried in the dark, then counterstained with 10 µL of DAPI (4,6-diamidino-2-phenylindole). The FISH signals were visualised using Vysis filter sets and an Olympus BX51 epifluorescence microscope attached to a FISHView image acquisition and analysis system for FISH (Applied Spectral Imaging, Necharhausen, Germany).

G banding analyses (450–500 band level) performed on ten metaphase spreads from the patient revealed a structurally-abnormal chromosome 4q. The karyotype was assumed as 46 XY, del (4)(q28q35) (Fig. 2a). CGH analysis disclosed a deletion of bands 4q33–q35 in chromosome 4 (Fig. 2b). The mother showed normal chromosomes. However, the father showed a balanced translocation between chromosomes 4 and 19 by conventional cytogenetics (Fig. 3). The profile of the father's chromosomes by CGH analysis was in the

Table I. Distal deletions of the long arm of chromosome 4: a comparison of the breakpoints in previous reports with the present case.

Break points	q32–q34[2,10-12]	q33–q35 [13-15]	q33–q35*	q31–qter[4,5]	q32–qter[6]	q33–qter[7,8]	q34–qter[4,9]	q34.2–qter[18]
No. of cases	4	4	1	22	4	12	5	1
Mental retardation	*	*	*			*	*	
Moderate	*	*	*	*	*	*		
Mild	*	*				*	*	*
Growth retardation	*	*	*	*	*	*	*	*
Craniofacial								
Abnormal skull	*	*	*	*	*	*		
Hypertelorism		*		*	*	*		
Upslanting palpebral fissures		*		*		*	*	
Epicanthic folds	*		*	*		*	*	
Broad nasal bridge	*	*	*	*	*	*		*
Small nose				*	*	*	*	
External ear abnormality		*		*	*	*	*	
High arched palate				*		*	*	*
Cleft lip/palate	*	*		*	*	*		*
Micrognathia	*			*	*	*		
Skeletal								
Abnormal fifth finger	*	*	*	*	*	*	*	*
Abnormal palmar crease	*			*	*	*		
Abnormal toes	*	*		*	*	*	*	
Cardiac defect	*	*		*	*	*		*
Genitourinary	*	*		*	*	*		

* Present case

balanced state. There were no chromosomal losses or gains. FISH analysis on the patient's blood confirmed interstitial deletion of 4q (Fig. 4). FISH analysis on the father's blood showed terminal deletion of 4q with the deleted part of 4q being translocated onto the other autosome, believed to be chromosome 19. Further analysis of the father's blood with whole chromosome paint confirmed translocation of chromosome 4 material onto chromosome 19 (Fig. 5).

DISCUSSION

Chromosomal imbalances, such as deletions, may either involve terminal or interstitial segments of the chromosomes. The deletions may affect either the p arm or the q arm of the chromosome. Chromosomal imbalances affecting the long arm of chromosome 4 have been reported in a variety of clinical conditions. The chromosomal deletions are mainly terminal and mostly involved breakpoints at 4q31,[4,5] 4q32,[6] 4q33[7,8] and 4q34.[4,9] Interstitial deletions of 4q, however, were less frequently reported.[2,10-12] Most reported cases of terminal and interstitial deletion 4q arose *de novo* with cases of familial autosomal chromosomal deletions being rarely documented. The few reports which have been described had involved mothers, maternal grandmother and sons.[9,12-14] All of the previously-reported cases had the same interstitial deletions of the long arm of chromosome 4 in the affected members of the family.

In this current case report, the propositus had inherited from his father the abnormal chromosome 4q which demonstrated interstitial 4q deletions of regions q33–q35. The father of our propositus did not demonstrate any phenotypic abnormalities since there was no evidence of loss or gain of chromosomal material based on the findings of comparative genomic hybridisation. To date, there have only been four reported cases of interstitial 4q33–4q35 deletions.[13-15] In this report, we compared the phenotypic abnormalities of our patient with those of the previously-reported cases involving similar interstitial 4q33–4q35 deletions. We also compared the clinical features seen in interstitial 4q33–4q35 deletions with that of other cases demonstrating deletions in the adjacent regions (Table I). Our patient had similar clinical features with other previously-reported cases of 4q33–4q35 interstitial deletions. However, we note that three out of four previously-described cases had cardiac and genitourinary defects. Fortunately, our patient did not have any cardiac or genitourinary abnormality.

A review of the previous reports also indicate that there are more patients with large terminal deletions such as q31–qter, while there are less number of cases involving interstitial 4q deletions (Table I).[4,6,8,14,15] Although the breakpoints occurred at different levels of the chromosome, the clinical findings described for each

type of breakpoint deletions were rather similar in that they comprised variable mental and growth retardations with phenotypical characteristics involving craniofacial, digital, skeletal and cardiac anomalies. Therefore, it was difficult to clinically determine the level of breakpoints based on the clinical features. Mental and growth retardations were consistently seen in all cases involving both terminal and interstitial 4q deletions. However, moderate mental retardation was more common in patients with deletions involving breakpoint region q33, while patients with deletions distal to q34 had a milder degree of mental retardation.

Fagan and Morris postulated that the more distal the breakpoint deletion (q33 instead of q31), the more varied and milder the phenotype.[16] While it can be generally observed that a larger amount of missing chromosomal material constitute greater and major craniodysmorphic features, we can also conclude that milder phenotypes occur in patients with more distally-located deletions. From the observations of previous reports, we concur with Keeling et al, who suggested that the critical region for the 4q terminal deletion syndrome appears to be at breakpoint region q33.[11] Therefore, it can be postulated that the genes in the q33 region are critical for the development of craniofacial, skeletal, cardiac and genitourinary abnormalities. Chromosomal analysis has always been the gold standard in diagnosing patients with dysmorphic features and learning disabilities. Larger amounts of deletions can easily be identified with conventional cytogenetics using high resolution banding. However, high resolution banding may miss a more distally located interstitial and terminal 4q deletion.

Recent development of molecular cytogenetic techniques, such as FISH and CGH, has helped to identify more cases of interstitial deletions of 4q. This report demonstrates the advantages of performing these relatively new techniques, as the techniques are more specific and sensitive than conventional cytogenetics in the identification of small interstitial and terminal deletions. A study by Tiso et al used radiation hybrid mapping to localise the CPP32 gene to the 4q33-q35 region.[17] CPP32 is a human cell death gene and appears to be the key mammalian homologue acting early in the cell death pathway. In their research, Tiso et al observed that each of the four caspase family genes mapped colocalises with an autosomal dominant malformation syndrome and suggested that William syndrome (OMIM 194050) as a candidate genetic disease at 4q33–q35. All the four published cases with interstitial deletion of 4q33–q35 had variable and mild dysmorphic features. In most instances, a straightforward diagnosis could not have been made as there were many possibilities due to the mild and non-specific clinical features. Therefore, a database of cases with interstitial deletions 4q33-–q35 will be helpful.

ACKNOWLEDGEMENTS

We would like to thank Ms Ezanee Mohd Hanif and Mrs Nor Zarina Zainal Abidin for their excellent technical assistance.

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