Interstitial deletion of the distal long arm of chromosome 4

P Sarda, G Lefort, J P Fryns, C Humeau, D Rieu

Abstract

We report the first case of an interstitial deletion of the distal long arm of chromosome 4 (q31.22→q34.2). The major clinical features are described and compared to those of other published reports of del 4q, mainly those sharing a common deleted segment with the present case (both interstitial and terminal). This comparison suggests that the characteristic phenotype attributed to terminal deletions of 4q31→qter probably mainly results from loss of the segment q31→q33-34.

A review of published reports shows that interstitial deletions of the distal long arm of chromosome 4 are rare.^{1,2} We report a new case of an interstitial deletion in a female infant with physical characteristics resembling those encountered in terminal 4q31 deletions.^{3,4}

Case report

The proband was born to a gravida 8, para 8 mother. To our knowledge the other sibs are normal. At the end of a poorly monitored pregnancy marked by maternal alcohol abuse the child was born at term by spontaneous vaginal delivery. Birth weight was 2700 g, length 46 cm (< 3rd centile), and head circumference 32 cm (10th centile). The Apgar score was 0 necessitating tracheal intubation and transfer to the neonatal intensive care unit; assisted ventilation was necessary for 10 days owing to meconium aspiration.

The major physical finding needing urgent surgery was a cardiac defect, consisting of

coarctation of the aorta and an interventricular communication. In addition, ultrasound scan of the kidneys detected a duplication of the left collecting system and skeletal radiographs showed bilateral hypoplastic first ribs and fusion of the second and third lumbar vertebrae.

All other internal organs, particularly the brain, appeared normal. Cardiac surgery was immediately instigated and by the end of the first month the heart defect was completely corrected.

At the age of 18 months postnatal growth failure was evident: weight was 8.5 kg (< 2 SD), height 71 cm (< 3 SD), and OFC 43 cm (< 3 SD). The child had mild hypotonia and was unable to sit up unaided. Psychomotor development was delayed with speech impairment. The child functioned at a 10 month level at 18 months of age. No visual or auditory abnormality was observed. She had minor dysmorphic features (fig 1), including an asymmetrical face, a narrow and prominent forehead, hypertelorism, and epicanthic folds (inner canthal distance 32 mm (> 97 centile) and interpupillary distance 55 mm (> 97 centile)). The nose was short, with an abnormally broad nasal bridge and anteverted nares, the philtrum was long and flat, and the upper lip was prominent. The ears were posteriorly rotated but otherwise normal. Both hands showed tapering of the fingers and clinodactyly. As the parents were unwilling to take care of the child, she was admitted to a centre for mentally retarded children.

CYTOGENETIC ANALYSIS

Peripheral lymphocyte and fibroblast cultures were set up. Harvesting and metaphase

Department of Pediatrics and Medical Genetics, University of Montpellier, Hôpital Saint-Charles, Montpellier, France.
P Sarda
D Rieu

Cytogenetics Laboratory, University of Montpellier, Hôpital Saint-Charles, Montpellier, France.
G Lefort
C Humeau

Centre for Human Genetics, University Hospital, Leuven, Belgium.
J P Fryns

Correspondence to Dr Sarda, Service de Pédiatrie II, Hôpital Saint-Charles, 34059 Montpellier, France.

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Figure 1 Craniofacial dysmorphism of the proband at 18 months.

Figure 2 Partial karyotype of the patient (after high resolution G banding) showing the interstitial deletion with breakpoints assigned to 4q31.22 and 4q34.2.

spreads were prepared by standard procedures. RHG banding studies in both tissues showed an interstitial deletion of the long arm of chromosome 4.

Subsequent high resolution G banding on lymphocytes assigned breakpoints to 4q31.22 and 4q34.2 (fig 2). The proband's karyotype is 46,XX,del(4)(q31.22→q34.2). The parents were not available for study. A cell line is being established.

Discussion

To the best of our knowledge no interstitial deletion of chromosome 4 with breakpoints at q31.22→q34.2 has been reported before. Terminal deletions of the long arm of chromosome 4 have been described frequently and a relatively constant phenotype can be recognised in del(4)(q31→qter). The salient features are craniofacial dysmorphism including hypertelorism, a short, upturned nose, a depressed nasal bridge, cleft palate with or without Pierre-Robin sequence, micrognathia, and external ear abnormalities.^{3,4}

Other major physical findings include abnormalities of the fingers (absent digits, clinodactyly, camptodactyly, abnormal thumb or hallux implantation, tapering fingers, pointed or duplicated fifth nail), abnormal palmar creases, congenital heart defects, and genitourinary malformations. Progress is marked by postnatal growth failure and moderate or severe mental retardation. The loss of the terminal segment 4q34→qter seems to have little clinical impact. The unique report of del(4)(q34→qter) by Lin *et al*³ describes the case of a 23 year old male patient with only very little facial dysmorphism and mild mental retardation. The major physical features of terminal deletions are summarised in the table.

Most interstitial deletions of the long arm of chromosome 4 involve the q11→q31 region; few cases involving q31 or more distal segments have been reported. A review of published reports showed two cases of interstitial deletion involving a common segment with our case. The first report was a case of del(4)(q24→q32).¹ There were very few clinical features that were common to this case and the present case, only psychomotor retardation, slight dysmorphic features, and a urinary defect. The second report² concerned del(4)(q33→q35.1) in a mother and her two children, who had very mild craniofacial dysmorphism (long philtrum, thin upper lip, and

Distal deletion of the long arm of chromosome 4: comparison of the breakpoints in previous reports and in the present patient.

	Previous cases				Present case	
Breakpoints	q31→qter	q32→qter	q33→qter	q34→qter	q33→q35.1	q31.22→q34.2
No of cases	19	4	6	1	3	1
Clinical characteristics						
General						
IUGR	3	1	0	0	0	0
Postnatal growth retardation	15	2	5	0	0	1
Death before 2 years	9	1	0	0	0	0
Mental retardation (if survival > 3 months)	11	4	4	1	3	1
Seizures	4	0	1	0	0	0
Craniofacial						
Abnormal skull	12	3	4	0	0	1
Asymmetrical face	3	1	1	0	0	1
Hypertelorism	11	2	3	0	0	1
Epicanthic folds	7	0	3	0	0	1
Upward slanting palpebral fissures	4	0	3	0	1	0
Short nose	18	2	2	0	0	1
Anteverted nares	7	2	3	0	1	1
Depressed nasal bridge	18	3	2	0	0	1
Cleft palate/lip	17	4	2	0	0	0
Robin sequence	5	4	0	0	0	0
Low or posteriorly rotated ears	10	3	1	0	1	1
External ear abnormality	13	3	2	1	0	0
Limbs						
Hand malformations	17	4	4	0	0	1
Transverse palmar crease	13	1	2	0	0	0
Abnormal toes	13	3	4	0	1	0
Internal malformations						
Cardiac defect	11	3	2	0	0	1
Genitourinary defect	9	1	2	0	0	1
Gastrointestinal defect	4	0	0	0	0	0
Bone abnormalities	0	0	0	0	0	1

borderline low set, posteriorly rotated ears) and moderate mental retardation.

The comparison of the features of the different deletions (terminal and interstitial) in the table shows that the phenotype of our patient is more closely related to that of patients with terminal deletions of 4q31→qter (congenital heart defects, genitourinary defects, moderate mental retardation, postnatal growth failure, and craniofacial dysmorphism). Certain features noted in the proband, such as postnatal growth failure, psychomotor developmental retardation, and some dysmorphic traits (in particular the smooth philtrum and short nose) may be related to maternal alcohol abuse. These abnormalities are common in fetal alcohol syndrome and in chromosome 4 deletions including the segment q31.22→q34.2 and it is therefore impossible to attribute these features to one or the other of these aetiologies. It seems likely that both the chromosome abnormality and maternal alcohol abuse contributed to the clinical findings.

Monosomy of the segments q33→q35.1 and q34→qter seems to be characterised by only

mild to moderate mental retardation and minor dysmorphism, without visceral defects. It would thus appear, as supported by our observation, that the characteristic phenotype attributed to terminal deletion 4q31→qter probably mainly results from loss of the segment q31→q33–34.

Note added in proof

The gene involved in FSH muscular dystrophy has been assigned to the segment 4q31→qter. No clinical signs of this muscle disease were noted in our patient at the age of 18 months.

- 1 Serville F, Broustet A. Pericentric inversion and partial monosomy 4q associated with congenital anomalies. *Hum Genet* 1977;39:239–42.
- 2 Curtis MA, Smith RA, Sibert JO, *et al.* Interstitial deletion, del(4)(q33q35.1), in a mother and two children. *J Med Genet* 1989;26:652–4.
- 3 Lin AE, Garver KL, Diggans G, *et al.* Interstitial and terminal deletions of the long arm of chromosome 4: further delineation of phenotypes. *Am J Med Genet* 1988;31:533–48.
- 4 De Michelena MI, Campos PJ. Terminal deletion 4q in a severely retarded boy. *Am J Med Genet* 1989;33:228–30.