Interstitial deletion of bands 4q12→q13.1: case report and review of proximal 4q deletions

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Abstract

We report a 6 year old child with a small de novo interstitial deletion of proximal 4q, karyotype 46,XX,del(4)(pter→q12::q13.1→qter). She has made good developmental progress and attends normal school with minimal assistance. We review published reports and clinical findings in patients with proximal 4q deletions. (*J Med Genet* 1997;34:862-865)

Keywords: interstitial deletion; 4q deletion; piebaldism

Case report

The proband was the second child born to healthy, unrelated, white parents. The mother was 34 years old at the time of the birth, the father 45 years old. The father had a normal son from his first marriage. The second pregnancy with his first wife was terminated after the diagnosis of Klinefelter's syndrome.

The pregnancy with the proband was unremarkable and she was born by normal vaginal delivery at term with a weight of 2900 g (10th centile). She fed well from 2 days of age. There was no neonatal hypotonia. At 6 weeks of age, her development was assessed as normal. At 4 months of age poor head control was noted. The earliest recorded head circumference was 46 cm at 8 months of age (90-97th centile).

She was referred for investigation at 7 months of age because of generalised hypotonia with marked head lag, poor hand coordination, dysmorphism, and hypopigmented skin patches. Chromosome analysis showed a small deletion of band 4q12→4q13.1 (karyotype 46,XX,del(4)(pter→q12::q13.1→qter)) (fig 1). Both parents had normal karyotypes.

At the age of 20 months, height was 86.7 cm (50-75th centile), weight 14 kg (>75th centile), and head circumference 53 cm (>97th centile). She had red hair without pigmentary changes and blue eyes with marked central hypopigmentation. She had a broad, prominent forehead. There were epicanthic folds and a flat nasal bridge. There was no dystopia canthorum. She had a small chin and an unusual lower lateral incisor. There were well defined hypopigmented patches over each shin and a more diffuse hypopigmented patch over her abdomen. Her hands and feet were normal.

She was able to walk independently and spoke several single words with meaning at the age of 16 months. A Griffiths assessment at 22 months showed a developmental age of 18.3 months.

At 2 years 3 months of age, two single white hairs were noted in her forelock and a small

Figure 1 Enlargement of two copies of chromosome 4 from the proband with ideogram showing interstitial deletion of bands 4q12→q13.1.

area of depigmentation was seen in her left eyebrow. A CT scan of the brain showed normal ventricles with a narrow sagittal cleft in the inferior aspect of the cerebellar vermis. At 5 years 4 months, audiometry showed bilateral conductive deafness of 35 dB. The tympanic membranes were dull and retracted. Her hearing improved following bilateral grommet insertion and adenotonsillectomy.

She was last reviewed at 6 years 6 months (fig 2). She had started wearing glasses for a left convergent strabismus several months before review. Her weight was 32.9 kg (>97th centile), height 121 cm (75th-90th centile), and OFC 55.3 cm (>97th centile). She still had excessive drooling. Her irides were pale green with a blue rim, but the other pigmentary findings were unchanged. The philtrum was short and her chin small. Her tone was normal. There have been no seizures and no growth retardation.

She went to nursery school from the age of 3 years 8 months and her development was assessed as appropriate for normal school at 4 years. She has attended normal school from 4 years 8 months and currently receives extra help for 20 minutes each week. She is socially well integrated and there have been no reports of behavioural difficulties.

Discussion

We report a child with a small de novo interstitial deletion involving bands 4q12→q13.1. This child has made good developmental progress and shows no evidence of internal malformations.

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Figure 2 The proband (A) front view and (B) profile.

Proximal interstitial deletions of 4q are rarer than distal deletions.¹ We found 12 reported cases of deletions involving bands 4q11→q21 (table 1)²⁻¹⁴; the reports of Henningsen *et al*² and Mikkelsen *et al*¹⁴ describe the same patient. The majority (9/12 cases) were de novo deletions and two were the result of unbalanced segregation of a reciprocal translocation.^{2,3} One deletion was associated with a duplication of 4q12→q13 in mosaic form (karyotype published as 46,XX,del(4)(4pter→q12::q13qter/46,XX,ins(4,4)(q12)(q12/q13)).⁷

Most of the cases with proximal 4q deletions were born at term following a normal pregnancy (table 1). The commonest clinical findings were non-specific, including developmental delay (speech delay was usually more marked than motor delay), growth retardation, and hypotonia. Poor feeding was common.^{3,5,8,9} Although unilateral renal agenesis and haemodynamically insignificant cardiac murmurs^{6,10,11} were reported, major malformations were rare. Seizures have been described in several children.^{5,6,8}

The dysmorphic features noted with proximal deletions of 4q include a high "domed" forehead or a prominent forehead.^{2,6,8,9} A short skull with a flat occiput and a square head have also been described.^{2,13} Oblique palpebral fissures,^{6,7} epicanthic folds,^{2,4,6,7,9} dystopia canthorum,⁹ and a broad or flat nasal bridge^{2,4,6,9,10} were other reported features. Ears were frequently low set.^{2,4,6-8,13} The mouth was described as small, broad with a short upper lip, or as having downturned corners.^{2,3,9} Retromicrognathia, micrognathia, and a receding chin have also been noted.^{2,7,10} A small posterior cleft palate was reported in one case.²

In the limbs, small hands and feet,^{5,6,9} short fingers and toes or stubby digits,^{5,12,13} and minor digital anomalies such as fifth finger clinodactyly were common. Joint laxity involving all joints or only the small joints of the body has been described.^{3,8}

Regarding the trunk, nipples were noted to be widely spaced or hypoplastic.^{2,8,10,11} Bony abnormalities that have been published include asymmetry of the cranial bones and a small anterior cranial fossa,⁶ delayed bone age,^{3,6} short arms and legs and a short thoracic spine,⁵ kyphosis or scoliosis,^{7,11} and hypoplastic cervical ribs.⁸

Ocular anomalies included unilateral microphthalmia with bilateral colobomata,¹¹ blue sclerae with pigmented retinal clumps,⁸ hypermetropia,^{5,12} and a divergent squint.^{2,5} Dental abnormalities with delayed tooth eruption, enamel defects, or irregular teeth were relatively common.^{3,8,12,13} Two children had deafness.^{9,11} Physical differences that were reported in only one case were hypospadias and cryptorchidism,⁸ aplasia cutis of the vertex,¹⁰ and umbilical and abdominal herniae.^{5,13}

Despite an overlap in the clinical findings between some of the patients with proximal 4q deletions, a distinct phenotype remains difficult to define. Several patients shared similar breakpoints (for example, 4q12→4q21 or 4q21.1^{3,6,8-11}) and yet had phenotypes that varied significantly in severity. For example, one patient had a mild clinical course with normal growth and absence of seizures¹⁰ and another was more seriously affected with growth retardation, seizures, and marked developmental delay.⁶ In general, those with a more severe phenotype had more pronounced developmental and growth retardation and seizures.

The most likely reasons for the clinical heterogeneity are variations in the size of the chromosome deletions and differences in the remaining genetic background of patients. Significant phenotypic effects owing to imprinting of chromosome 4 are thought to be unlikely.¹⁵

Our proband has made good progress and attends normal school. The relatively small size of the chromosome deletion may explain her milder delay in comparison to the other

Table 1 Proximal 4q deletions

Reference	Our case									
	2	3	4	6	13	8	9	10	11	12
Chromosome deletion	4q11→13 translocation	4q11→21 de novo	4q12→21.1 translocation	4q12→21 de novo	4q12→21 de novo	4q12→21.1 de novo	4q12→21.1 de novo	4q12→21.1 de novo	4q12→21.1 de novo	4q13→21 de novo
Maternal age	30 y	23 y	17 y	32 y	18 y	41 wk	37 y	7 mth	22 y	34 y
Paternal age	37 y	22 y	36 wk	34 y	19 y	43 cm	Term	Normal	47 y	Term
Gestation		Term	1900 g	Term	Term	2400 g	3940 g	3240 g	3240 g	2720 g
Weight		3300 g		3400 g		43 cm				
Length		49.5 cm								
Hypotonia										
Weight	21 kg (10-25)	12.2 kg (<3)	9.0 kg (10-50)	14.2 kg (10-25)	19 kg (<5)	19 kg (<5)	4.31 kg (15)	Normal	+	32.9 kg (>97)
Centile	7.5 y	3.5 y	13 mth	4 y	4 y	6.5 y	2 mth	7 mth	3y 10 mth	11 mth
Age	117 cm	87 cm	72 cm	89.7 cm	101 cm	101 cm	52 cm	Normal	3y 10 mth	58.5 cm
Height	117 cm	87 cm	72 cm	89.7 cm	101 cm	101 cm	52 cm	Normal	3y 10 mth	121 cm
Centile	7.5 y	3.5 y	13 mth	4 y	4 y	6.5 y	2 mth	7 mth	3y 10 mth	11 mth
Age	51.5 cm	50 cm	45.3 cm	4 y	4 y	49 cm	41 cm	Normal	3y 10 mth	55.3 cm
OFC	51.5 cm	50 cm	45.3 cm	4 y	4 y	49 cm	41 cm	Normal	3y 10 mth	65 y
Centile	7.5 y	3.5 y	13 mth	4 y	4 y	6.5 y	2 mth	7 mth	3y 10 mth	65 y
Motor development		Walked with help 3.5 y	Sat alone 10 mth	Walked with help 4 y	Walked 4 y	Walked 6.5 y	Stood alone 1 y	7 mth	Sat supported 3 y 10 mth	Walked alone 16 mth
Speech development		No speech 3.5 y		Walked 4 y	Walked 4 y	No speech 6.5 y				Single words 16 mth
Development quotient		DQ 13 mth at 3.5 y					DQ 7-8 mth at 13.5 mth	DQ 65		DQ 12 wk at 11 mth
Piebaldism		+	+	+	+	+	+	+	+	+

reported children with proximal 4q deletions (table 1), but her level of achievement remains noteworthy. In particular, her development is much better than one other patient who had a deletion with similar breakpoints, although this patient also had extra 4q material in mosaic form.⁷

The proband has macrocephaly and is without growth retardation. Relative macrocephaly has also been described in two of the other patients with proximal 4q deletions.^{3,9}

Our case has depigmented skin on her abdomen and limbs. Piebaldism is an autosomal dominant trait comprising white hair or a white forelock with patches of white skin on the anterior trunk and limbs without extracutaneous manifestations.¹⁶ The pale skin patches are deficient in melanocytes and the piebald trait is thought to be caused by defective melanocyte proliferation or migration from the neural crest during early development or both.¹⁶

Hypopigmentation has been reported in several cases of 4q12 deletions^{3,4,8,10,13} and is thought to be pathognomonic of a deletion in this chromosome band. More recently, piebaldism has been shown to be the result of mutations in the c-kit proto-oncogene at 4q12.^{16,17} Hemizygosity for the c-kit gene is also known to cause piebaldism and the gene has been found to be deleted in at least one patient with a proximal 4q deletion and hypopigmentation.^{10,18} The piebaldism in patients with proximal 4q deletions is therefore likely to be the result of the deletion including the c-kit proto-oncogene at 4q12. However, cytogenetic nomenclature (and the current resolution of microscopic analysis) does not allow distinction between patients with deletions of 4q12 with different breakpoints in this chromosome band. It is therefore possible that the discrepancy in the finding of piebaldism in some patients with 4q12→21 deletions^{3,4,8,10,13} and not in others^{2,6,9,11} can be explained by the deletions in patients with normal pigmentation not including the c-kit proto-oncogene.

Neural crest cells are also involved in the formation of the irides and it might therefore be expected that some patients with piebaldism will have hypopigmentation of the irides similar to the proband.¹⁹ In practice, this finding is infrequently reported and was not described in three patients with piebaldism and mutations of the c-kit proto-oncogene¹⁷ or in one patient with an interstitial 4q deletion who was hemizygous for the c-kit gene.¹⁸ This variability in iris pigmentation is likely to result from the uneven expression of the decreased pigmentation in the piebald trait.

Finally, the father of our case had previously had a child with Klinefelter's syndrome by a different partner. Klinefelter's syndrome has been reported in another pregnancy to a different couple who also had a child with a 4q deletion.⁹ The connection between the chromosomal aneuploidy and the interstitial deletion in these families is unknown.

Conclusion

We have reported a girl with a proximal 4q deletion (karyotype 46,XX,del(4)(pter→q12::

q13.1→qter). Our patient has a broad forehead, epicanthic folds, and a broad nasal bridge with a small chin. She has hypopigmented skin patches over her trunk and limbs and two white hairs in her forelock. She shows no evidence of growth retardation and has macrocephaly. Developmental assessment showed mild delay and she is making satisfactory progress in mainstream school.

We have reviewed the previously reported findings associated with proximal 4q deletions. Although skin hypopigmentation can be considered to be pathognomonic for a chromosome deletion in this region, a distinct phenotype is hard to define and clinical severity is very variable.

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