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A terminal deletion of the long arm of chromosome 4 [46,XX,del(4)(q33)] in an infant with phenotypic features of Williams syndrome

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SUMMARY A female infant with peripheral pulmonary artery stenosis, growth retardation, and developmental delay was noticed to have facial features consistent with a diagnosis of Williams syndrome. Chromosome analysis revealed a deletion of the terminal portion of the long arm of chromosome 4 (4q33→qter). This is the seventh reported case of this chromosome disorder. It is possible that this chromosome region is specific for the Williams syndrome phenotype but it is more likely that the syndrome is heterogeneous. Chromosome analysis should be performed in all suspected cases with particular attention to the long arm of chromosome 4.

Attempts to associate specific malformation syndromes with chromosome defects have, on occasion, met with success. There have been no convincing reports of an association between Williams syndrome and chromosomal anomaly, however, with the exception of one child with a de novo 12;15 translocation,¹ though it is likely that Williams syndrome is of genetic origin. There are suggestions of an overlap with the autosomal dominant supra-valvular aortic stenosis syndrome and it is possible that those cases with heart defects and major developmental delay have an unrecognised chromosome deletion as their basis.² We report a child with features of the syndrome and a terminal deletion of

4q. There have been several reports of isolated terminal deletions of the long arm of chromosome 4, the majority of which have involved deletion of the distal two-thirds of the long arm from band 4q31.³⁻¹⁸ Two reports have described cases of deletion from 4q32,^{19,20} while a further six cases in five reports^{13,21-24} have involved the terminal portion from 4q33. The present case is the seventh report of this rare terminal deletion. The child was diagnosed initially as suffering from Williams syndrome. The clinical features are assessed together with other published reports in order to expand knowledge of this particular chromosome disorder and also to evaluate whether this portion of the genome is specific for Williams syndrome.

Case report

The proband was a female infant born on 2.4.85, weighing 3200 g, after an uneventful term pregnancy. Her mother, aged 37 years, had two children by a previous marriage, a boy of 17 years and a girl of 13 years, both healthy. The father, aged 28 years, had a sister who died at the age of 5 years with what was probably an atrioventricular septal defect. The father himself had no evidence of cardiac abnormality and was otherwise healthy.

Failure to thrive and slow feeding led to regular hospital review of the proband in the first three months and recognition of a heart murmur led to referral for further investigation. A degree of cardiac decompensation had responded to 50 µg digoxin daily prescribed before referral. An electrocardiogram revealed right ventricular hypertrophy and an echocardiogram showed narrowing of the right and left pulmonary arteries, but a normal main pulmonary artery and normal intracardiac structures. These findings, together with the presence of systolic

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murmurs over the lung fields, indicated the presence of peripheral pulmonary artery stenosis.

This cardiac defect together with her failure to thrive, giving a body weight and head circumference below the 3rd centile, and unusual facies led to a diagnosis being made of Williams syndrome. Analysis of banded chromosomes revealed a deletion of the terminal portion of chromosome 4 (4q33→qter) (fig 1.) The karyotype of both parents was normal. Serum calcium levels at 3 months were normal and remained so on subsequent analysis.

Clinical review at 7 months showed a weight of 4.75 kg and a head circumference of 40 cm, both significantly below the 3rd centile. The facial features were still very suggestive of Williams syndrome with stellate iris pattern, malar flattening, fullness of the cheeks, short nose, long philtrum, and a tendency to hold the mouth open (figs 2 and 3). There was valgus deformity of both big toes and the second, third, and fourth toes were longer than average, the fourth being folded beneath the second and third. There were single creases on both palms.

The physical features at this stage were noted to be compatible with the other reported cases of 4q33→qter deletion and also compatible with the Williams syndrome. The only features in the proband and somewhat out of keeping with the latter diagnosis were the absence of an obvious medial eyebrow flare and lips which were not particularly full.

At 11 months, feeding and weight gain had improved but developmental delay was still apparent with inability to sit or stand unaided and absence of meaningful words. She was beginning to roll from her back to her front, bring her hands together in the midline, and could clap. Her cardiac

FIG 2 Facial appearance of proband at 7 months.

FIG 3 Lateral view of face at 7 months.

FIG 1 Chromosome defect in proband: 46,XX,del(4)(q33).

status remained unchanged and she was asymptomatic. Additional features in keeping with the label of Williams syndrome were delayed eruption of deciduous dentition and a cheerful outgoing nature.

Discussion

The table contains a summary of the physical features of the other six reported cases of 4q deletion distal to band q33. Half had heart defects, though in only one of these was the defect specified. The case described by Tompkins *et al*²² had "aortic stenosis, pulmonary stenosis, and right bundle branch block". None of the reported cases of 4q—manifested the classic features of Williams syndrome, including infantile hypercalcaemia, but on the other hand none of the published photographs is entirely out of keeping with the diagnosis. It is suggested in the review in this issue² that the classic Williams syndrome with either supravalvular aortic stenosis or peripheral pulmonary artery stenosis may be related to the autosomal dominant form of these cardiac disorders with the more extensive malformation syndrome resulting from a small deletion rather than a single gene defect. If this were the case, the present report would suggest that the terminal portion of chromosome 4 is a likely location. The report of a child with Williams syndrome featuring a de novo 12;15 translocation¹ suggests that these may be alternative locations.

Another, perhaps more plausible, explanation is that the Williams phenotype is not homogeneous. If

this is the case, it is possible that among children labelled as having Williams syndrome there are other examples of deletion of the terminal portion of the long arm of chromosome 4. It is important that cases investigated before the availability of chromosome banding are reviewed.

When large families with supravalvular aortic stenosis are investigated using DNA linkage techniques to localise the gene, probes from the chromosome 4 library localised to the distal long arm should be regarded as candidates for linkage analysis.

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TABLE Clinical features of cases of 4q deletion.

	Reported cases (6)	Present case
<i>Developmental</i>		
Preterm delivery	3/4	—
Small for dates	5/6	—
Growth retardation	6/6	+
Developmental delay	4/5	+
Oropharyngeal incoordination	2/6	—
<i>Craniofacial</i>		
Microcephaly	4/6	—
External ear abnormality	2/6	—
Hypertelorism	1/6	—
Epicanthic folds	2/6	+
Upward slanting palpebral fissures	4/6	—
Short nose and flat nasal bridge	3/6	+
Cleft lip	1/6	—
Cleft palate	2/6	—
Mild micrognathia	6/6	+
Anteverted nostrils	3/6	—
<i>Musculoskeletal</i>		
Hand anomalies	4/6	+
Altered palmar flexion creases	3/6	+
Malpositioned toes	4/6	+
Bone age delayed	2/5	?
<i>Organ systems</i>		
Heart defects	3/6	+
Hypospadias/cryptorchidism	1/2	—

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A de novo X;13 translocation with abnormal phenotype

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SUMMARY We describe a female infant who presented with hypotonia and developmental delay. Her karyotype showed a de novo balanced translocation between the X chromosome and chromosome 13, with breakpoints at Xq13 and 13p11. The normal X was late replicating in all cells examined. The cause of this patient's abnormal phenotype is discussed.

Case report

The proband, a female, was born at term by normal delivery (birth weight 2.9 kg) to a 37 year old mother and 31 year old father. The parents were non-consanguineous, of normal intelligence, and had a normal son.

Neonatal examination revealed ligamentous laxity and marked hypotonia. She had hypertelorism, bilateral epicanthic folds, and a retroussé nose.

At 10 months of age, she was sitting with support (from 7 months) and reaching out for objects with an immature grasp. Her head control was poor and she had persistent hypotonia. She had smiled at 3 months and rolled over at 7 months. Investigations showed a normal CK level (163 IU/ml), a normal

EMG, and normal motor nerve conduction velocity (40 m/s).

Review at 18 months of age showed a height below the 3rd centile and head circumference on the 3rd centile. She could sit alone but fell forwards frequently and would not support her weight when held standing. Her speech was delayed, with vocalisations only, and one word ("Dad"). Examination of the eye for retinoblastoma was negative.

CYTOGENETIC FINDINGS

Peripheral blood lymphocytes from the proband and both parents were cultured for chromosome studies

FIGURE Basic fuchsin stained partial metaphase¹ showing the two derived chromosomes and their normal counterparts. From left to right: the normal chromosome 13; der(13) (13qter→cen→13p11::Xq13→Xqter); the normal late replicating X with its characteristic shadowed appearance; and der(X) (Xpter→cen→Xq13::13p11→13pter).

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