Interstitial deletion of the long arm of chromosome 18, del(18)(q12.2q21.1): a report of three cases of an autosomal deletion with a mild phenotype

Albert Schinzel, Franz Binkert, Debra M Lillington, Margaret Sands, Richard J Stocks, Richard H Lindenbaum, Helen Matthews, Hilary Sheridan

Abstract

We describe three unrelated patients with apparently identical interstitial deletions of the segment (18)(q12.2q21.1). They were a short and markedly mentally retarded 5 year old girl, a macrocephalic and obese 2½ year old boy with moderate mental retardation, and a macrocephalic, severely mentally retarded 5 year old boy. Findings common to all five liveborn patients so far identified as carrying this deletion include a pattern of minor dysmorphic features (prominent forehead, ptosis of the upper eyelids, full periorbital tissue, epicanthic folds, strabismus), muscular hypotonia, seizures, behavioural disorders, and lack of major malformations.

Terminal deletion of the long arm of chromosome 18, del(18)(q21qter) is frequently found, and is associated with a characteristic phenotype.¹ Interstitial deletions in the long arm of chromosome 18, by contrast, are rare. Only three patients with deletions of chromosome 18 (q12.2q21.1), including one mosaic in a prenatally detected fetus, have been reported so far.²⁻⁴ We present three further patients with deletion of this segment.

Institute of Medical Genetics, University of Zürich, Raemistrasse 74, 8001 Zürich, Switzerland.
A Schinzel, F Binkert

Department of Cytogenetics, Norfolk and Norwich Hospital, Brunswick Road, Norwich NR1 3SR.
D M Lillington, M Sands

James Paget Hospital, Gorleston, Yarmouth NR31 6LA.
R J Stocks

Department of Medical Genetics, Churchill Hospital, Headington, Oxford OX3 7LJ.
R H Lindenbaum, H Matthews, H Sheridan
Correspondence to Professor Schinzel.

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Case reports

The main findings in the three patients are listed in the table and this information is not necessarily duplicated in the text. In patients 1 and 2, birth measurements were not recorded.

CASE 1

Patient 1 was from Zürich, Switzerland. This girl was the second of five children of unrelated and healthy parents of Albanian origin. At birth, her father was 26 and her mother 24 years old. Delivery took place at home. Psychomotor development was delayed from birth. Free sitting was achieved at 12 months and walking at 4 years 9 months. Tonic-clonic seizures began at 2 years of age and thereafter occurred at regular intervals.

At the age of 4 years 11 months (figs 1 and 2), her height was 100 cm, weight was 16.5 kg, and head circumference was 50 cm. In addition to the findings listed in the table, she showed the following abnormalities: brachycephaly, short and slightly prominent forehead, a hypotonic facies, flaring of the medial eyebrows, curved eyelashes, no strabismus, short palpebral fissures (2.3 cm, mean for age 2.45 cm), and a short nose with a moderately prominent bridge and sharp tip, a hypoplastic philtrum, no marked maxillary hypoplasia, no mandibular overbite, downturned corners of the mouth, small and carious teeth, prominent lateral palatine ridges, large ears with large lobules (ear length 6.5 cm=75th to 97th centile), no prominence of the antihelices, and normal auditory canals. She also had a broad neck, normal chest and protuberant abdomen, hypoplastic labia majora and minora, perianal and perigenital eczema, small hands (hand length 12 cm=25th centile) with tapering fingers, no transverse palmar creases, no clinodactyly of the fifth fingers, small feet (length 15.5 cm=3rd to 25th centile) with normal toes, and a naevus measuring 3×4 cm over the lateral left hip. She spoke two or three words, but was completely incontinent. Cardiac examination and abdominal palpation was normal. Psychomotor development was judged to be at a level of about 1 to 1½ years with more marked deficit in

Main features of the present three patients compared to the patients of Wilson et al² and Wilson et al.⁴

Finding	Patients in this report			Reference No	
	1	2	3	2	4
Sex	F	M	M	M	M
Age at last examination (y)	4 11/12	2 5/12	4 10/12	7	1
Height/length centile	<3	?	50	>97	10
Weight centile at last examination	10-25	>90	25	>97	<5
Head circumference centile at last examination	10-25	>90	>97	>97	25
High/prominent forehead	+	—	+	?	+
Upward slanting palpebral fissures	+	—	—	—	—
Ptosis of upper eyelids	+	—	+	?	+
Full periorbital tissue	+	+	?	+	+
Epicanthic folds	—	+	+	?	+
Strabismus	—	+	+	—	+
Muscular hypotonia	+	+	—	+	+
Mental retardation	+	+	+	+	+
Behaviour abnormalities	+	—	+	+	?
Seizures/abnormal EEG	+	+	+	—	+

Figure 1 Patient 1 aged 4 years 10 months.

Figure 2 Genitalia of patient 1, showing hypoplasia of labia majora and minora.

language and fine motor skills as compared to gross motor and social skills. There was muscular hypotonia, but tendon reflexes were normal. Formal testing was impossible because of non-cooperation and anxiousness.

CASE 2
Patient 2 was from Norwich, England. This male patient was the product of a normal, term pregnancy and was the first child of healthy, unrelated parents. Delivery was normal, and the birth weight was 3010 g. Mental development was moderately delayed, and by 13 months there was significant delay in language and motor skills with associated poor cognitive processes. He suffered febrile convulsions at 13 months, 15 months, and 20 months and was placed on anticonvulsant therapy. Clinical examination at the age of 1 year 8 months showed a weight of 14.6 kg (90th to 97th centile) and a head circumference of 54 cm (above the 97th centile). At 2 years 5 months (fig 3) his weight was 18.65 kg (above the 97th centile) and head circumference was 56 cm (above the 97th centile). He had minor facial anomalies (table)

(hypotonic facies with short palpebral fissures, synophrys, left intermittent convergent squint, flaring of the medial eyebrows, long philtrum, prominent antihelices, narrow auditory canals) and pes planus, but no apparent internal malformations. At 2 years 1 month, his mental development was assessed to correspond to 16 months, but there were no behavioural problems. When fully assessed at 3 years 2 months, he was not able to give his name, but used symbolic gestures and could follow simple directions only. He was unable to copy a cross or understand size or colour, and he was only able to scribble with a pencil. He was not able to post or place basic shapes. He now wears spectacles for astigmatism

and hyperopia. There was no bowel or bladder control.

CASE 3

Patient 3 was from Oxford, England. This boy, the second child of healthy, unrelated parents, was born after a normal pregnancy; delivery was at 37 weeks and birth weight was 2600 g. A wide nasal bridge was noted, but there were no major problems in the newborn period or in early infancy. However, motor development and speech were greatly delayed; he sat unsupported at about 1 year and walked at 18 to 21 months. He developed temper tantrums and autistic behaviour. A moderate hearing loss was diagnosed at 12 months. There were recurrent bowel problems, which were helped by the introduction of a milk free, disaccharide free, and gluten free diet.

Psychomotor assessment at 15 months suggested a

Figure 3 Patient 2 at 2 years 1 month.

Figure 4 Patient 3 at 3 years 11 months.

Figure 5 Chromosomes 18 from a GTG banded metaphase of patient 1. The deleted homologue is on the right. Arrows on the normal homologue (left) point to the breakpoints.

developmental age of 10 months, that is, a developmental quotient of 67, but later assessments indicated more severe retardation, to between 40% and 50% of normal. At 4 years there was very little useful speech, and he was not yet toilet trained.

At 2 years his head circumference was 52 cm (90th to 97th centile). At 4 years 10 months (fig 4) his height was 108 cm and weight 20 kg (25th and 75th centile, respectively). He had high arched eyebrows with lateral flaring, a wide nasal bridge, and unusually shaped ear pinnae. The cranial vault was large, but the face was long and narrow. He had convergent strabismus, but otherwise the examination was normal.

CYTOGENETIC INVESTIGATIONS

GTG banded chromosomes from the three probands disclosed an interstitial deletion within the long arm of chromosome 18; band 18q12.3 and possibly parts of the adjacent interbands 18q12.2 and 18q21.1 were missing (fig 5). The karyotypes were 46,XX,del(18)(q12.2q21.1) (patient 1) and 46,XY,del(18)(q12.2q21.1) (patients 2 and 3). The karyotypes of the parents of the three probands were normal.

Discussion

Terminal deletion of 18q, with a breakpoint in 18q21.1, causes a distinct and easily recognisable malformation syndrome with the cardinal features of growth retardation, mental retardation, midface

hypoplasia, narrow auditory canals and prominent antihelices, and proximally placed thumbs. Coloboma of the iris, cleft palate, and cardiac malformations are frequently observed.¹ Patients with more terminal deletions have so far not been reported, with the exception of ring chromosomes where it is often difficult to define the breakpoints properly.

Of the three previously reported cases with interstitial deletion of chromosome 18 (q12.2q21.1), one was a 24 week old fetus whose dysmorphic pattern could not be properly evaluated³; in addition, the deletion was only present in about 30% of metaphases. A 7 year old boy had almost no abnormal findings; he was tall, obese, and mentally retarded and showed autistic and aggressive behaviour.⁴ The third case, a boy who died at 2½ years of age,² and our three patients have many features in common: absence of major, life threatening malformations, a high and narrow forehead, ptosis of the upper eyelids, a short nose, hypotonia, and severe mental retardation.

Thus, it currently seems that patients with interstitial deletion of chromosome 18 (q12.2q21.1) lack major malformations and their survival is not grossly limited. They show a pattern of mostly ill defined dysmorphic facial features and usually rather severe mental retardation in association with seizures. Other features which are probably associated include obesity, a large head, and a tendency to develop behavioural disorders. Not unexpectedly, their clinical picture does not resemble that of terminal deletion of 18q, del(18)(q21.3qter), which causes a distinct and easily recognisable malformation syndrome.¹

Mr Eddy Maher performed the photography of case 3.

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4 Wilson GN, Al Saadi AA. Obesity and abnormal behaviour associated with interstitial deletion of chromosome 18(q12.2q21.1). *J Med Genet* 1989;26:62-3.