

Smith-Magenis syndrome: a new contiguous gene syndrome. Report of three new cases

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Abstract

Interstitial deletion of the short arm of chromosome 17 was detected in three patients. They all had a similar phenotype with mental retardation, behavioural problems, facial dysmorphism, brachycephaly, a broad face with a flat midface, and short and broad hands. All three cases were ascertained over a six month period by two neuropaediatricians aware of this specific anomaly, which suggests that this microdeletion is not particularly rare. Comparison of the clinical and cytogenetic findings in a total of 24 patients allows a new contiguous gene syndrome to be defined that only high resolution analysis can detect. In two cases, molecular analysis confirmed the cytogenetic results. The Charcot-Marie-Tooth type Ia gene has recently been localised to the 17p11.2 sub-band.

The introduction in the early 1980s of prometaphase analysis led to the identification of submicroscopic chromosomal anomalies. Small deletions or duplications have been detected in some well delineated syndromes, such as Prader-Willi syndrome, Angelman syndrome, Miller-Diecker syndrome, and Beckwith-Wiedemann syndrome, and have also been found to be at the origin of new clinical syndromes.

Smith *et al.*,¹ in 1982, first described an interstitial deletion in the proximal short arm of chromosome 17: del(17)(p11.2). The 17p11.2 band was deleted in two unrelated patients presenting with cleft palate and cardiac malformation. In 1984, Patil and Bartley² reported a smaller deletion in the 17p11.2 sub-band, del(17)(p11.2-p11.2), in a single patient with mental and growth retardation, hypotonia, hearing

loss, and facial dysmorphism. This microdeletion has now been reported in 21 patients²⁻⁷ and a new clinical syndrome has emerged. Thus it can be assumed that deletion 17p11.2 is not such a rare constitutional structural chromosomal aberration.

We present three new patients with partial 17p11.2 deletion and review previously published cases. The three new cases confirm that the clinical spectrum of the syndrome is specific enough to lead to clinical diagnosis at about 3 years of age.

Case reports

CASE 1

The patient, a boy, was born at term after an uncomplicated pregnancy. The parents, a 24 year old mother and a 25 year old father, were both healthy. He was the second child of this couple, the first was stillborn at 7 months of gestation. The couple had two other normal children, a boy and a girl.

At birth his weight was 2800 g, length 47 cm, and head circumference 31.5 cm. The Apgar score was normal. The neonatal period was unremarkable, but the parents described him as being "too calm a baby". Slight motor delay was observed during this period; he sat at 10 months and walked at 16 months. He spoke single words at 2 years. Delayed development became increasingly obvious with age.

At 3 years, he was referred to a neuropaediatric clinic for evaluation of his speech delay and behavioural disturbance. He spoke only about 20 isolated words. He was hyperactive with a very short attention span and frequent temper tantrums. He showed psychotic behaviour with repetitive activity, making abnormal noises with his nose and tongue, bruxism, and insomnia.

On physical examination, his height was 88 cm (-2 SD), weight 13 kg, and head circumference 48 cm (-2 SD). He was brachycephalic with frontal bossing, mild facial hypoplasia, mild epicanthus, a short philtrum, broad nasal bridge, downturned mouth, and small, turned under ears. His voice was hoarse and low pitched. The hands were short and broad with bilateral clinodactyly of the fifth fingers. Bilateral testicular ectopia was present. Audiogram was normal and the EEG subnormal with slow

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rhythms. Psychomotor testing using the Terman Merrill scale at 6.5 years gave a score of 65.

CASE 2

The patient, a girl, was the second child of healthy parents; the mother was 35 and the father 31 years old. The first child was normal. The patient was born at term after an uncomplicated pregnancy. Her birth weight was 3200 g, height 47 cm, and head circumference 35 cm. She developed respiratory distress owing to a pneumothorax but recovered quickly.

When she was 8 days old she was referred to the Medical Genetics Centre because of facial dysmorphism. She was brachycephalic with a broad, flat face, epicanthus, strabismus, a broad nasal bridge, small nose, small philtrum, carp shaped mouth, micrognathia, and low set ears with hypoplastic helices. Karyotyping with R banding was performed and found to be normal. During her first year she was very quiet and she walked at 19 months.

When she was 3 years old, she was examined in a neuropaediatric department for speech delay and behavioural problems. She was overactive and anxious with poor language development; she used only single words. Physical examination showed normal growth: weight 15 kg (+1 SD), height 90 cm (-1 SD), and head circumference 49 cm. Facial dysmorphism was increasingly obvious with age (fig 1). The hands were short, she had genu valgum, and her feet were flat and short with partial syndactyly of toes 2/3. Her voice was hoarse. Audiogram showed a moderate conductive hearing loss. Serous otitis media was treated with myringotomy tubes. EEG was

subnormal with slow rhythms. Psychomotor testing was possible at 4.5 years and the Terman Merrill scale showed moderate mental retardation with full scale IQ of 65.

CASE 3

The patient, a girl, was born at term after a normal pregnancy. The mother was 23 years old and the father 24. Birth weight was 3300 g, height 49 cm, and head circumference 35 cm. The family history was unremarkable. She sat at 8 months and walked at 19 months.

When she was 30 months old, she was evaluated in a neuropaediatric department because of marked speech delay: she was only able to say "mam". She was hyperactive, irritable, and autoaggressive, with no concentration span. She made frequent guttural noises.

Physical examination showed a height of 88 cm (-1 SD), weight of 13 kg, and head circumference of 49.5 cm. The facial dysmorphism (fig 2) comprised brachycephaly with malar hypoplasia, strabismus, mild epicanthus, broad nasal bridge, small nose with anteverted nostrils, prominent upper lip, small philtrum, macrostomia with carp shaped mouth, highly arched palate, micrognathia, and small ears with abnormally attached superior helices. Frequent otitis media was treated with myringotomy tubes. The hands and feet were broad and short with partial syndactyly of toes 3/4 and she had genu valgum. Hyperkeratosis was present with mild hirsutism. Neurological examination showed hypertonic Achilles tendons and brisk reflexes. CT scan

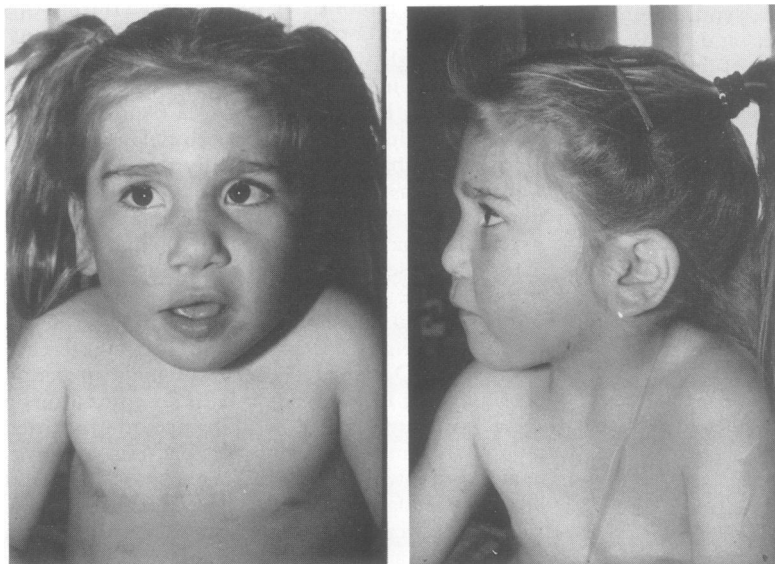


Figure 1 Front and lateral view of case 2 aged 5 years.



Figure 2 Front and lateral view of case 3 aged 8 years.

was normal. Routine cytogenetic analysis with R banding failed to show any anomaly.

At the age of 8 years, she was examined by the neuropaediatricians. Because of the clinical similarities with recently diagnosed cases 1 and 2, we decided to re-evaluate her karyotype with high resolution banding.

CYTOGENETIC STUDIES

In these three cases, chromosomal studies were performed on phytohaemagglutinin stimulated lymphocytes, with both standard and high resolution techniques. In the standard technique the lymphocytes were cultured for 72 hours and harvested by

standard methods. R banding was performed by heat controlled denaturation and Giemsa staining. No precise chromosomal rearrangement could be detected in any of the three cases but in cases 1 and 3 there was a query concerning the short arm of one chromosome 17, which looked slightly shorter than the other.

High resolution banding was performed according to Camargo and Cervenka.⁸ Lymphocytes were synchronised with methotrexate and released by BrdU. RBB banded chromosomes were obtained by the fluorochrome-photolysis-Giemsa technique⁸ and an interstitial deletion in the proximal part of chromosome 17 short arm involving band p11.2 was seen in each case (fig 3).

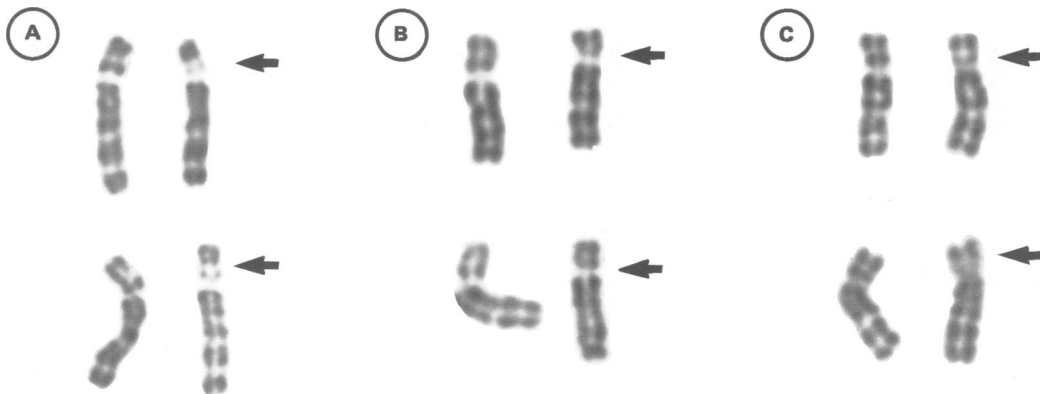


Figure 3 R banded chromosomes 17 of case 1 (A), case 2 (B), and case 3 (C). The normal 17 is on the left and the deleted 17 on the right in each case.

In case 1, about 50% of the 17p11.2 band seemed to be deleted. The size of the deletion in cases 2 and 3 was difficult to determine accurately but seemed to be slightly smaller than in case 1.

Discussion

High resolution cytogenetics have led to the definition of a new recognisable syndrome comprising a distinct clinical phenotype and microdeletion (17p11.2). We have described three children evaluated in the Department of Neuropaediatrics at about 3 years of age because of speech delay associated with behavioural disturbances. Case 1 was also referred to the medical genetics department because of his facial dysmorphism. Standard karyotyping showed an anomaly of 17p which was confirmed and refined by high resolution banding techniques. Because of their clinical similarities with case 1, and despite a normal karyotype using standard techniques, both cases 2 and 3 were reassessed cytogenetically using high resolution banding. A 17p11.2 microdeletion was detected in the two cases, confirming the clinical diagnosis.

The considerable clinical similarity between the three patients was remarkable. Comparison of our cases with 21 previously published cases¹⁻⁷ makes it possible to delineate the clinical features which suggest this diagnosis (table). All patients have moderate to severe mental retardation with marked speech delay. Speech is more affected than motor ability as walking usually starts between 18 and 24 months. Behavioural disturbances are always found including hyperactivity with short attention span, irritability, and aggressiveness. Some autistic features are frequent with self-mutilation and self-stimulation activity.

All patients have a strikingly similar facial appearance. A combination of brachycephaly, mild facial hypoplasia, and broad nasal bridge is always observed. Frequent features are apparent telecanthus, short philtrum with carp shaped mouth, low set and malformed ears, and mandibular prognathism. The degree of prognathism, however, is age dependent and is present in the older patients. The youngest patients have micrognathia rather than prognathism.³ The voice is hoarse with a deep, rasping quality, as pointed out by Smith *et al*,³ and

Smith-Magenis syndrome: clinical findings in 21 patients with deletion 17p11.2.

	Previous cases	Present report			Total
		Case 1	Case 2	Case 3	
Sex (ratio F/M)	≈ 1 (9 F/12 M)	M	F	F	≈ 1
Age examined	3 mth–62 y	3 y	3 y	8 y	3 mth–62 y
Mental retardation					
Speech delay	18/18	+	+	+	21/21
Hyperactivity	17/17	+	+	+	21/21
Behavioural problems	14/17	+	+	+	17/20
Craniofacial					
Brachycephaly	20/21	+	+	+	23/24
Mild facial hypoplasia	19/21	+	+	+	22/24
Broad face	17/19	–	+	+	19/21
Prominent forehead	14/21	+	–	–	15/22
Broad nasal bridge	19/21	+	+	+	22/24
Carp shaped mouth	16/18	+	+	+	19/21
Micrognathia	5/20	+	+	–	7/23
Prognathism	12/20	–	–	+	13/23
Malformed ears	13/19	+	+	+	16/23
Strabismus	6/16	–	+	+	8/19
Epicanthus	5/20	+	+	–	7/23
Telecanthus	12/20	–	–	+	13/23
Limbs					
Short/broad hands	14/15	+	+	+	17/18
Digital anomalies (clinodactyly/syndactyly)	13/18	+	+	+	16/21
Growth/development	14/21	+	–	–	15/24
Central nervous system					
Hypotonia	6/14	–	–	–	6/17
Seizures	6/9	–	–	+	7/12
Other					
Hearing loss	10/20	–	+	+	12/22
Coarse voice	9/14	+	+	+	12/17
Heart murmur	7/20	–	–	–	7/23
Genital anomalies	7/20	–	–	–	7/23
Cleft palate	2/21	–	–	–	2/24

may be a good diagnostic clue. Otitis media is frequent with conductive hearing loss. The hands are short and broad with brachydactyly, clinodactyly of the fifth fingers, and syndactyly of the toes.

Other clinical signs have been reported. Growth retardation is present in about 50% of patients. Ophthalmological anomalies have also been described,⁷ as have dermatological signs like hyperkeratosis and hirsutism.⁶ Visceral malformations, facial clefts, congenital heart defects, cardiac murmur, and renal and genital anomalies are rare.

The sex ratio is equal: among the 24 reported cases, 13 were females and 14 were males, as reported by Lockwood *et al.*⁶ The ages at which the patients have been described range from the neonatal period to 62 years. This explains the phenotypic variability, particularly for facial dysmorphism. In our case 2, the typical facial features were present at birth but the diagnosis was difficult without the other specific signs. A review of published reports indicates that diagnosis is clinically possible at 3 years when phenotypic expression of the three major signs is complete: speech delay, facial dysmorphism, and short hands. This syndrome should be considered when evaluating children with speech delay and behavioural disturbances and knowledge of these characteristic signs allows high resolution analysis to be focused on a specific chromosome. The frequency of this microdeletion is difficult to establish but appears to be high. Our three patients were identified over a 6 month period in a single centre and Lockwood *et al.*⁶ reported a similar frequency.

High resolution analysis is necessary to reveal this microdeletion because of its small size. The deletion involved at least 50% of band 17p11.2 both in our cases and the other previously published cases. In two cases reported by Smith *et al.*¹ the 17p11.2 band was completely missing but the phenotype included cardiac defect and cleft palate.

These microdeletions always appear *de novo* and no parental chromosomal rearrangements have been found. In contrast with the deletion in Miller-Dieker syndrome, which has been localised to the distal short arm of chromosome 17 (17p13) through an inherited translocation,^{9,10} the Smith-Magenis syndrome was discovered only through the improvement in cytogenetic techniques. Four translocations involving a breakpoint in 17p11.2 have been reported.¹¹ In all the cases, the unbalanced rearrangement led to a trisomy 17p by adjacent 1 segregation. No monosomy 17p11.2-pter has been observed, probably because this type of rearrangement is lethal. The short arm of chromosome 17 seems to be a hot spot for rearrangement in two specific regions, 17p11.2 and 17p13. This non-random distribution of breakpoints may be explained

by repetitive sequences in these regions of chromosome 17. The sequences may be of Alu type found in R+ bands, which are frequently associated with rearrangements, as described by Lehrman *et al.*¹² Deletion might be the consequence of asymmetrical pairing and unequal exchange arising within repeated sequences during meiosis.¹³

Several genes, such as the ubiquitin gene,¹⁴ the genes for the cytokeratin family,¹⁵ and the gene for Charcot-Marie-Tooth disease type Ia, have already been located in the 17p11.2 region. The mapping of the Charcot-Marie-Tooth disease gene was obtained by linkage analysis.¹⁶⁻¹⁸ Using three probes linked to the Charcot-Marie-Tooth disease gene (pEW 301, pUC 10-41, and pYNM 67, supplied by ATCC), we have shown that probes pU 10-41 and pYNM 67 are deleted in our cases 2 and 3, but neither the previously published patients, nor our three patients show any neuromuscular anomaly (Moncla *et al.*, submitted). It is likely that the gene for Charcot-Marie-Tooth disease is located outside the observed deletions. Construction of a somatic cell line is in progress for our patients.

A more sophisticated molecular approach to this new 'contiguous gene syndrome'¹⁹ is now necessary to characterise the genes involved in the deletion better.

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