Chromosome subband 17p11·2 deletion: a minute deletion syndrome

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SUMMARY Interstitial deletion of the short arm of chromosome 17 was detected in three unrelated patients with mental retardation and multiple congenital malformations. These patients were identified at a single centre over a six month period suggesting that del(17)(p11·2p11·2) is not a rare constitutional chromosome rearrangement. Comparison of the phenotypic features in a total of 19 patients with del(17)(p11·2p11·2) shows a consistent clinical phenotype with moderate to severe mental retardation, microbrachycephaly, prominent forehead, broad face, flat midface, prognathism, short, broad hands, and behavioural anomalies such as self-mutilation. The sex ratio is unremarkable, parental ages are normal, and survival is usually unimpaired. Chromosome resolution of at least 500 bands appears necessary to detect this deletion.

Each new chromosome abnormality in clinical cytogenetics tends to be claimed to be associated with a recognisable syndrome. If the chromosome abnormality is a structural one, the breakpoints are often noted to be near fragile sites and oncogenes.

This report comprises three new cases and a review of published reports of a deletion syndrome that does appear to be emerging: the del(17)(p11·2p11·2) syndrome. No fragile site or oncogene is known to be in chromosome subband 17p11·2.¹

The first full description of a patient with this syndrome was by Patil and Bartley² who reported an 'interstitial deletion of the short arm of chromosome 17' in a patient with mental and growth retardation, congenital hypotonia, conductive hearing loss, esotropia, prominent premaxilla, and short philtrum. Smith *et al*³ described nine patients with del(17)(p11·2p11·2) and Stratton *et al*⁴ reported another six patients with this deletion.

We report three patients with del(17)(p11·2p11·2) who were identified at our centre over a six month period and review the other published reports of this chromosome deletion. We comment upon the phenotypic findings and emphasise characteristic features.

Case reports

CASE 1

This 29 year old Vietnamese female was born near Saigon when her father was 41 and her mother 35 years old. She is the seventh of 10 children. One of the 10 children died at the age of three of an infectious illness. The others are living and, apart from the patient, are reportedly normal. No information is available on the pregnancy. Labour was short and the delivery was cephalic. There were clearly neonatal problems since the patient was transferred after birth to a large hospital in Saigon, but the exact nature of these problems is unknown. The mother had not smoked tobacco or consumed alcohol during pregnancy.

The patient had feeding difficulties during infancy and recurrently vomited breast milk. She sat at 12 months and walked at about 18 months. She has temper tantrums and has inexplicably assaulted other family members at times. She is moderately to severely mentally retarded. She has not had seizures.

The patient was evaluated for urinary incontinence after immigration to the USA at the age of 29. She was found to have a vesicovaginal fistula and a urachal diverticulum. The fistula was presumed to be congenital as she was a nulligravida and had never been continent of urine. In addition, the patient was found to have a markedly raised level of

parathyroid hormone (C-terminal PTH 1008 pg/ml, N-terminal PTH 184 pg/ml) and calcifications in the basal ganglia in the presence of chronic renal failure. Testing is not yet complete to determine whether the raised PTH is the result of pseudohypoparathyroidism or renal failure alone.

We evaluated the patient at the age of 29. Height, weight, and head circumference were below the 3rd centile. There was brachycephaly, but the forehead was not prominent (fig 1). The midface was flat. The eyes appeared normal and the inner canthal, interpupillary, outer canthal, and palpebral fissure measurements were within normal limits. The ears were normal in position but were dysplastic with a peaked upper helix. There was partial bilateral hearing loss. The mouth was turned down at the corners. Dentition was abnormal with multiple caries. The tongue was large and prominent and there was striking prognathism. The hands and feet

were below the 3rd centile in length. The fingers were short (<3rd centile) with prominent proximal interphalangeal joints on fingers 2 to 5 bilaterally and broad distal phalanges with wide, rounded nails. The hands and knuckles had chew marks indicative of mild self-mutilation and there was marked hyperkeratosis of the palmar surface of the hands and fingers not resulting from manual activity. Mild cutaneous webbing was present between toes 1 and 2.

CASE 2

This 17 year old Caucasian female was born when her father was 26 and her mother 25 years old. She is in foster care. She has one older sister, aged 24, reportedly in good health. She also had three younger sibs, a male and female who died in infancy from complications of prematurity, and a sister who died at four years of tuberculous meningitis. No pregnancy history is available. Spontaneous vaginal delivery occurred without complications.

No developmental milestones are known. She has poor socialisation skills as well as symptoms of bed wetting, hyperactivity, insomnia, and aggressive behaviour, particularly toward males. She has some autistic behaviour including self-stimulation by rocking. However, she does maintain eye contact. She has 'absences' which are thought to be seizure activity. She has never been known to self-mutilate. IQ has been estimated at 40.

We evaluated the patient at the age of 17. Height, weight, and head circumference were below the 3rd centile. There was no brachycephaly or prominence of the forehead (fig 2). The face was broad with malar flattening. The eyes were widely spaced and upward slanting. There was no evidence of strabismus. The ears were mildly low set with posterior rotation and attached lobules. Hearing was grossly normal. The nose had a depressed root and small upturned tip with anteverted nares. The philtrum and mouth were normal. The palate was high. There was no evidence of abnormal dentition. Examination of the hands showed marked brachydactyly (fig 3), prominent proximal interphalangeal joints, clinodactyly of the fifth digits bilaterally, a single palmar crease on the left, and unremarkable dermatoglyphics. There was mild cutaneous syndactyly between toes 2, 3, and 4 with nail dysplasia. There was restriction of movement at the radioulnar joints bilaterally, more marked on the left than the right, with associated cubitus valgus on the left. The scalp hair pattern was unremarkable. There was marked hirsutism and synophrys. A full neurological evaluation was unremarkable with the exception of slightly decreased muscle tone. The patient had normal secondary sex characteristics and regular menstruation.

FIG 1 Frontal and lateral facial views of patient 1 aged 29 years.

CASE 3

This 10 year old Caucasian male was born when his mother and father were both 26 years old. He is the third of four children. He was born at term by vaginal delivery after an uncomplicated pregnancy. The mother is a non-smoker and non-drinker, and took only prenatal vitamins.

The patient sat at over a year of age. He was walking by two years, spoke by three years, and was using sentences by four years. He has been conti-

nent by day since the age of four, but is still enuretic. He is noted to have sudden temper tantrums, particularly against his sibs. He has a very short attention span. He exhibited some wrist biting as a child and now continues to display head banging and occasionally will rip off his fingernails and toenails.

We evaluated the patient at the age of 10 years. Height was at the 25th centile while weight and head circumference were at the 95th and 90th centiles respectively. Hair pattern was normal except for a

FIG 2 Frontal and lateral facial views of patient 2 aged 17 years.

FIG 3 The hands of patient 2: note brachydactyly and prominent interphalangeal joints.

centrally placed posterior whorl. The patient had brachycephaly with a prominent forehead, bitemporal narrowing, a broad face, broad nasal bridge, and flat midface (fig 4). The eyebrows were flared medially. There were deep creases under the eyes. The right pupil was consistently larger than the left. There was heterochromia iridis. The ears were low set with an overfolded, tethered, superior helix. The nose had a slightly depressed root, wide base, and ski-tip bridge. There was a normal philtrum, a normal palate with wide alveolar ridges, and exces-

sive serration of his central and lateral incisors. The phallus was small with retractile testes. Examination of the hands showed markedly short, wide fingers, with mild fifth finger clinodactyly and single palmar flexion creases. There were extra creases in the hypothenar area. There was hyperextensibility of the wrist, hand, and finger joints. Finger and toenails were short and wide. There was an increased space between toes 1 and 2 and mild cutaneous syndactyly of toes 2 to 4. Toes 2 to 5, bilaterally, were short (fig 5).

FIG 4 Frontal and lateral facial views of patient 3 aged 10 years.

FIG 5 The feet of patient 3: note brachydactyly of toes 2 to 5.

CYTOGENETIC STUDIES

Chromosome studies on our three cases were performed on blood lymphocytes stimulated with phytohaemagglutinin. The cells were cultured for 72 hours at 37°C in 5% CO₂ in air. The medium (RPMI 1640) was supplemented with 25% fetal calf serum and 1% glutamine.

Low resolution metaphase chromosomes were prepared at the 375 to 500 band stage by routine methods. High resolution chromosomes at the 700 to 850 band stage in prophase and prometaphase were prepared by methotrexate block followed by bromodeoxyuridine release and exposure to acti-

nomycin D.⁵ Cells were harvested by standard methods and trypsin G (GTG) banded.

CYTOGENETIC RESULTS

Patients 1, 2, and 3 had a deletion of the proximal region of the short arm of chromosome 17 (fig 6). The deletion involved most of band 17p11·2. High resolution studies indicated that most, but not all, of band 17p11·2 was absent in these three patients. Studies of 100 cells per patient failed to show evidence of mosaicism. The patients therefore had 46,XX or XY,del(17)(p11·2p11·2).

Chromosome studies on the parents of patients

FIG 6 850 band stage idiogram of chromosome 17⁶ with presumed breakpoints in band p11·2. G banded chromosome 17 homologues of patients 1, 2, and 3 with normal 17 on the right and deleted 17 on the left in each case.

TABLE Clinical findings in 19 patients with del(17)(p11·2p11·2).

Area	Feature	Published reports	Patient 1	2	3	Total
Craniofacial	Brachycephaly	15/15	+	-	+	17/18
	Prominent forehead	11/15	-	-	+	12/18
	Broad face	14/15	-	+	+	16/18
	Broad nasal bridge	13/16	-	+	+	15/19
	Flat midface	16/16	+	+	+	19/19
	Upper lip turned down at corners	8/14	+	-	-	9/17
	Prominent jaw	10/16	+	-	-	11/19
	Abnormal dentition	6/13	+	-	+	8/16
	Malpositioned ears	8/16	-	+	+	10/19
	Malformed ears	10/15	+	-	+	12/18
Limbs	Strabismus	6/12	-	-	-	6/15
	Short broad hands	10/11	+	+	+	13/14
	Other digital anomalies	9/14	+	+	+	12/17
	Abnormal palmar creases	6/15	+	+	+	9/18
Visceral/CNS	Heart malformations	7/16	-	-	-	7/19
	Genital anomaly	6/15	NR	-	-	7/17
	Hypotonia in infancy	5/8	NR	NR	NR	5/8
	Seizures	5/10	-	-	-	6/13
Growth/development	Growth failure	12/16	+	+	-	14/19
	Microcephaly	6/16	+	+	+	9/19
	Mental retardation	16/16	+	+	+	19/19
	Hyperactivity	12/12	-	+	+	14/15
	Self mutilation	9/12	+	+	+	11/15
Speech/hearing	Speech delay	14/15	+	-	+	16/17
	Hearing loss	9/16	+	NR	-	10/19
	Hoarse/deep voice	5/10	+	+	+	8/13

and 3 were normal. The mother of patient 2 was normal and the father was unavailable. Patients 2 and 3 had been studied on previous occasions in 1980 and 1982 and low resolution chromosome studies had failed to show a deletion.

Discussion

With the addition of the three cases reported here, interstitial deletion of band 17p11.2 has been described in 19 unrelated patients. From these patients a clinically recognisable phenotype is emerging. The clinical features found in 40% or more of the cases with del(17)(p11.2p11.2) are listed in the table.

All patients have moderate to severe mental retardation with speech acquisition more severely affected than motor abilities. Behavioural anomalies, including hyperactivity, aggression, and self-stimulatory and self-mutilating actions, appear very common.

The patients often exhibit growth failure. The most consistent dysmorphic features are brachycephaly with a broad face and nasal bridge, a flat midface, and short, broad hands. Common features include prominent forehead, prognathism, abnormal dentition, malpositioned ears, microcephaly, and hearing loss. Seizure activity, heart malformations, genital and digital anomalies, and abnormal palmar creases can also be present. Less frequent clinical findings which have been observed include dry, hyperkeratotic skin over the surface of the hands in cases 6 and 7 of Smith *et al.*,³ in case 4 of Stratton *et al.*,⁴ and in case 1 reported here. In addition, generalised hirsutism, synophrys, upward slanting palpebral fissures, Brushfield spots, iris colobomata, scoliosis, hemivertebrae, sacral lipomata, and renal anomalies are occasionally seen.

Of 19 reported cases, 11 are males and eight are females. There is thus no significant deviation from the normal sex ratio.

Parental ages at birth are known for 14 mothers and nine fathers of the patients reviewed here. The mean maternal age at birth is 26.8 years with a range of 15 to 41. The mean paternal age at birth is 30.7 years with a range of 25 to 41. There appears to be no evidence for an obvious parental age contribution to this deletion.

At last physical evaluation, patient age ranged from birth to 65 in women and from birth to 16 in males. One male died at five months from post-operative cardiogenic shock. To the best of our knowledge all other patients are alive. The mean age at last evaluation was 15.5 years. There appears to be no evidence of reduced life span.

No familial chromosome rearrangements predisposing to this deletion have yet been reported. However, familial rearrangements including inver-

sions and translocations have been reported in other similar deletion syndromes (Prader-Willi, Miller-Dieker, aniridia, retinoblastoma).⁷⁻¹⁰

Two of the patients here had been previously studied with low resolution chromosome analysis which had failed to show a detectable deletion. This suggests a need for band resolution of at least 500 bands. There is a wide variation in the size and quantity of deleted material, as one would suspect. Patients who present with this clinical picture and have had normal chromosome studies may need to be re-evaluated with higher resolution banding.

The mechanisms by which del(17)(p11.2p11.2) arise are not fully established. Clearly, there must be two breaks in 17p11.2 with excision and loss of the intervening segment. These two breaks could arise by chance alone or could result from breaks occurring at as yet undescribed fragile sites. Un-even crossing over within 17p11.2 could be responsible. Finally, crossing over might occur within a parental 17p11.2 inversion loop. Such an inversion involving only one band would be undetectable cytogenetically.

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