Translocations involving 4p16.3 in three families: deletion causing the Pitt-Rogers-Danks syndrome and duplication resulting in a new overgrowth syndrome

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Abstract
Three families are reported who have a translocation involving 4p16.3. Nine subjects are described with the clinical features of the Pitt-Rogers-Danks (PRD) syndrome confirming pre- and postnatal growth failure, microcephaly, severe mental retardation, seizures, and a distinctive facial appearance; a deletion of 4p16.3 was seen in all eight patients studied with fluorescence in situ hybridisation (FISH). Eleven subjects had a new syndrome with physical overgrowth, heavy facial features, and mild to moderate mental handicap; a duplication of the chromosome region 4p16.3 was found in the four subjects studied. It is suggested that the growth abnormalities in these two families may be explained by a dosage effect of the fibroblast growth factor receptor gene 3 (FGFR3), which is located at 4p16.3, that is, a single dose leads to growth failure and a triple dose to physical overgrowth. We describe the molecular mapping of the translocation breakpoint and define it to within locus D4S43.

In 1984 Pitt, Rogers, and Danks¹ described four patients, two of them sisters, with a similar clinical picture of severe mental retardation, pre- and postnatal growth failure, and an unusual facial appearance which they suggested was a new autosomal recessive syndrome. Except for some single case reports,²⁻⁴ little interest has been shown in the Pitt-Rogers-Danks (PRD) syndrome until Clemens *et al*⁵ found a microdeletion of 4p16.3 in a girl with the syndrome using the probe commercially available for the detection of the Wolf-Hirschhorn (WH) syndrome (Oncor Inc). This finding has been confirmed in five other patients⁶⁻⁹ including the two sisters in the original paper.¹ Clinical details of three unrelated cases have been published⁸⁻⁹ and the patient reported by Donnai² was shown not to have the 4p16.3 deletion.¹⁰ Here we present nine patients with the PRD syndrome and a 4p16.3 deletion, seven from one family, allowing some enlargement of the clinical picture.

In two of the translocation families there were 11 subjects with a new overgrowth syndrome; four of these were shown to have the alternate segregation product leading to duplication of 4p16.3. The short stature and severe mental retardation of those with the PRD syndrome contrasted sharply with the mild to moderate mental retardation and physical overgrowth of those with the 4p16.3 duplica-

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Figure 1 Pedigrees of families 1 and 2 indicating those with the PRD and overgrowth syndromes.

Table 1 Height, weight, and head circumference (HC) of subjects with the PRD syndrome

Subject	Sex	Gestation (wk)	Age (y-mth)	Height (cm)	Weight (kg)	HC (cm)
Family 1 III.7	M	40	0-0	—	2.0	—
			14-0	—	23.0	49.5
			29-0	149	—	51.0
III.5	M	43	0-0	—	2.15	—
			2-5	75	6.7	44.5
			5-4	92	—	48.0
			19-0	137	26.5	51.0
			29-0	149	34.5	51.0
III.15	F	40	0-0	—	2.15	—
III.18	F	40	31-0	132	—	47.0
			0-0	—	2.45	—
			1-2	71	7.49	39.5
IV.6	F	36	27-0	140	—	46.5
			0-0	—	1.98	—
			0-9	60	5.20	41.0
			2-2	78	7.50	—
			4-11	96	12.0	46.0
IV.7	F	36	9-4	126	—	48.0
			0-0	—	1.10	—
			6-6	108	—	47.0
II.9	M	—	25-0	153	—	49.5
			55-0	153	—	50.0
Family 2	M	40	0-0	—	2.40	—
			1-3	67	6.80	44.5
			2-0	74	7.20	46.0
			7-0	103	14.0	50.5
			13-9	142	—	52.0
Family 3	M	42	0-0	—	2.52	—
			0-7	61	5.80	40.0
			6-7	100.5	13.00	47.0

All measurements at or below the 3rd centile

tion. These two different groups of patients are described and the relationship between the PRD and WH syndromes is discussed. We also describe the molecular cytogenetic characterisation of the 4p16.3 breakpoints in the three translocation families using FISH. In one family, the breakpoint has been defined to within D4S43.

Case reports

The three families were all from New South Wales, Australia. Family 1 was first reported by Dey¹¹ in 1971 under the title “Familial mental

retardation associated with low birthweight dwarfism”. Dey’s focus was on those with severe mental retardation and growth failure, but she recognised that two members of the family had milder mental retardation and normal or tall stature. An updated pedigree is shown (fig 1) which indicates the subjects with these two contrasting syndromes. Family 2 had one boy with the PRD syndrome and three subjects with the overgrowth phenotype (fig 1) and family 3 had a boy with the PRD syndrome. Those with the same syndrome will be grouped together for description.

SUBJECTS WITH THE PRD SYNDROME

Of the nine patients, five were male and four female with ages ranging at last assessment from 6 to 55 years.

Family 1

III.7 (born in 1963) and III.5 (1960). The early years of III.7, the proband in family 1, and his brother III.5 have been described by Dey.¹¹ In brief both boys had pre- and postnatal growth failure (table 1) with feeding problems and slow development. Both learned to walk but not to speak. Both became epileptic following a bout of status epilepticus at the age of 8 months in III.7 and 10 years in III.5 with occasional grand mal seizures thereafter. Both were institutionalised before the age of 5 years. Dey¹¹ described III.7 at 3½ years of age as “a very thin, elfin-like infant, very hypotonic.... with a triangular face and widely spaced prominent slate-grey eyes” (fig 2). In hospital case records of III.5 at 5 years of age, he was said to be “deep in his own world, watching his fingers, mannerisms, smiling to himself, notices but not interested in (his) surroundings”. The brothers were cared for in the same institution into adult life. Both passed through puberty, had small testes but mature genitalia and normal body hair, and both had proportional short stature and microcephaly (table 1).

At 29 years III.7 had a shield shaped rather than triangular face (fig 2). His eyes were prominent with the sclera visible below the iris; there was keratoconus and a mild left external strabismus. The lips were full with a short philtrum. He had a scar over a pilonidal sinus, 10° limitation of extension of the right elbow, small hands and feet, and normal palmar creases. There was little eye contact and he appeared preoccupied. He had numerous stereotyped hand movements and usually rolled a small stick or piece of cloth against his lower lip (fig 2). There was a bald patch of thickened, rugose skin on the top of his head from rubbing it from side to side on the floor (fig 3).

At the age of 32 III.5 had thick, curly hair, prominent, “cauliflower” ears, and deep set eyes with small bilateral pterygia. The nose was prominent and the philtrum short (fig 2). The skin was dry and rough. The hands were small and stubby with spindling of the fingers, deep palmar creases with bilateral Sydney lines, and extra flexion creases over some of the fingers (fig 4). He had an extensive repertoire of complex mannerisms including a peculiar high

Figure 2 Family 1: subjects III.5 and III.7 with the PRD syndrome. Top row, III.7 at 3 years, 9 months, and 29 years. Bottom row, III.5 at 5 years and 28 years.

Figure 3 Odd mannerisms and gestures in the PRD syndrome. From above left, clockwise: the boy from family 3 (two pictures), the boy from family 2, III.7 and III.5 (two pictures) from family 1.

Figure 4 Extra flexion creases in the fingers in the PRD syndrome. Top row: outer two pictures from IV.6, middle from III.5, and bottom right III.18 from family 1; bottom left, the boy from family 2.

stepping gait, squatting, grimacing, and stereotyped hand movements (fig 3). He preferred to be alone and had little communication with others.

III.18 (1965), III.15 (1959), IV.6 (1980), and IV.7(1981). Very similar early histories were reported for these members of family 1 and the two boys with the PRD syndrome from families 2 and 3. Most had been hospitalised for failure to thrive. Epilepsy starting with status epilepticus persisted throughout childhood in III.18 and IV.6. III.18 was seen at the age of 27 when she had short stature, microcephaly, and dark, curly hair. Her face was shield shaped with a thin upper lip, a large mouth, and a short philtrum. The eyes were prominent with severe keratoconus and astigmatism (fig 5). She had extra flexion creases over the proximal phalanx of the second fingers of both hands (fig 4). She

Figure 5 Four subjects with the PRD syndrome. Top: the boy from family 3 aged 6½ years. All others from family 1: from above down, IV.7 at 4 years and 9 years, IV.6 at 8 years, and III.18 at 31 years. Note slightly prominent eyes, short philtrum, prominent, slightly upturned nose, and wistful expression in the three children. III.18 has obvious keratoconus probably unrelated to the PRD syndrome; it was segregating as an independent autosomal dominant trait in the family.

lived at home, attended a sheltered workshop, and could describe by mime and a few words something of what she did there. She displayed several hand mannerisms. III.15 was seen briefly at the age of 31; she had microcephaly with thick brown hair. She was short and obese with a double chin and large breasts. She appeared to have a happy temperament but was severely intellectually handicapped.

IV.6 was placed in foster care at the age of 2 years. Bilateral inguinal hernias were repaired at 5 years. On examination at 8 years, her

Figure 6 Normal facial appearance in the PRD syndrome. Top: III.4 aged 7 from family 2. Bottom: II.9 aged 55 from family 1.

height was average (table 1) but she had microcephaly. She had slightly prominent eyes, a mild left external strabismus, thick lips with a short philtrum, and a prominent nose (fig 5). The hands were small with extra flexion creases on the 2nd to 4th fingers (fig 4). She had a wistful, preoccupied expression showing only slight interest in what was going on; she had few words and carried out only the simplest instructions. She made repeated small stereotyped movements of the hands. Later she went

Table 2 Height, weight, and head circumference (HC) of subjects with the overgrowth syndrome

Subject	Sex	Age y-mth	Height cm (~ centile)	Weight kg (~ centile)	HC cm (~ centile)
Family 1					
II.11	M	15-0	159 (10)	51.0 (25)	—
		18-0	173 (25)	—	—
		19-8	178 (70)	82.5 (80)	—
		28-5	188 (90)	—	56 (50)
II.12	M	13-0	140 (3)	33.5 (7)	50 (<3)
		17-5	150 (<3)	35.0 (<3)	—
		21-0	162 (<3)	—	52 (<3)
		22-0	170 (15)	55.8 (10)	—
II.13	M	28-0	176 (45)	65.0 (30)	—
III.2	M	45-0	185 (90)	—	62 (>97)
III.8	M	33-0	197 (>97)	—	59 (>97)
III.8	F	21-0	178 (>97)	80 (97)	59 (>97)
III.9	F	41-0	169 (80)	—	56 (60)
II.11	F	28-0	167 (75)	—	55 (50)
II.12	F	28-0	166 (75)	—	55 (50)
Family 2					
III.1	M	Birth	54 (97)	3.95 (90)	—
		0-5	69 (75)	9.6 (>97)	43 (50)
		2-0	89 (75)	17.2 (>97)	49.5 (70)
		6-3	121 (75)	25 (90)	52.5 (60)
		18-5	181 (75)	78 (75)	59 (>97)
III.2	F	Birth	48 (20)	3.03 (30)	34.5 (45)
		0-6	69 (90)	8.35 (90)	44 (90)
		1-4	82 (75)	12.1 (90)	—
		9-10	131 (25)	31.5 (50)	54.5 (60)
		16-8	168 (80)	66 (80)	56 (75)
III.3	F	Birth	53 (97)	2.8 (10)	—
		0-3	60.5 (60)	6.6 (90)	41 (60)
		0-6	67.5 (75)	9 (97)	44.5 (97)
		0-9	74 (95)	10.6 (97)	45.6 (97)
		1-0	79 (97)	12.9 (>97)	48 (>97)
		15-9	179 (>97)	88 (>97)	59 (>97)

Figure 7 Members of family 2 in relation to one another as shown in the pedigree in fig 1. Seated from left to right: three subjects with the overgrowth syndrome contrasting with the fourth boy with the undergrowth of the PRD syndrome.

through a normal puberty but there was little change in her behaviour by the age of 16.

IV.7 grew and developed slowly but faster and further than her sister and was able to profit by special schooling. At 6 years of age she was short with microcephaly. She had a rather mournful expression (fig 5) with the sclera visible below the iris. The nose was prominent, the philtrum short, and the lips full.

II.9 (1946). Almost nothing is known about his early life except he did not speak appreciably until adolescence and was admitted to an institution at the age of 21. When seen by Dey¹¹ at the age of 25 he had short stature with microcephaly and a receding hairline. When seen by us aged 55 there had been little change except for increasing baldness (fig 6). Facial features were unremarkable but there was a rather prominent glabella and straight nose with slight upturning at the tip. He was able to carry on a reasonable conversation and was living in a hostel with some degree of supervision.

Family 2

III.4 (1982). Coronal hypospadias was noted at birth. Diagnoses entertained in early life were the Russell-Silver syndrome, renal tubular acidosis, the Johanson-Blizzard and Zellweger syndromes. At 5 years he had a bout of haematuria ascribed to a urinary infection but proteinuria persisted with normal renal function. A year later a renal biopsy showed focal, segmental glomerulosclerosis. On examination at the age of 7 years he was a small child with moderate to severe intellectual handicap. He related well socially except for episodes of staring into space. He had some odd posturing of his hands (fig 3). The face was triangular with a small chin, pointed nose, flared alae nasi, short philtrum, thin lips, and a wide mouth (figs 3 and 6). There was a mild alternating strabismus. The teeth were crowded in the upper jaw, the ears soft and outfolded. The hands were small with hyperextensible fingers and extra flexion creases (fig 4). At the age of

Figure 8 Members of family 1 with the overgrowth syndrome; places in pedigree and ages indicated. Note large heads (except for II.12), bushy eyebrows with synophrys, prominent supraorbital ridges, short nose, and short philtrum.

13 (fig 7) he remained in good health but mild proteinuria persisted.

Family 3

The proband (1984). He was the only child of unrelated parents. Coronal hypospadias was seen at birth. Between 8 months and 2 years he

had a few grand mal seizures. Bilateral radioulnar synostosis was shown on x rays. When examined at 6 years he had only 10 words and limited feeding and dressing skills. The eyes were prominent with sclerae often visible below the iris. The nose was broad and flat, the philtrum short but well demarcated (figs 3 and 5). There was an extra flexion crease over the proximal phalanx of the 5th finger. He had a pleasant personality but related only intermittently to others, often staring into space and making rather bizarre gestures with his hands (fig 3). There was little change in his condition by the age of 11 years.

SUBJECTS WITH OVERGROWTH

Of the 11 subjects five were male and six female ranging in age from 15 to 45 years when last seen.

Family 1

II.11 (born 1942, died 1984). This was the first person with overgrowth in family 1 (fig 1). He had been admitted to a long stay institution for the mentally retarded at the age of 13 years. He and his brother (II.12) was seen by one of us (GT) in 1971.¹² He had an IQ of 44 and was described in the language of the times as “dull and biddable”. At the age of 25 he was a tall, well proportioned, well muscled man with broad shoulders, big hands and feet, normal genitalia, abundant pubic hair, and deeply pigmented nipples. He had heavy facial features with a square jaw, big lips, and prominent supraorbital ridges accentuated by bushy eyebrows that met across the midline (fig 8). Sequential measurements from the institution (table 2) show remarkable increases in height continuing well into adult life. He died from rheumatic heart disease aged 42.

II.12 (1945-1980). He was admitted to the same institution at the age of 13 years. In childhood he had had a left sided empyema and a left diaphragmatic hernia which, years later at necropsy, was found to contain stomach, bowel, and transverse colon. His IQ was 45. He had occasional grand mal seizures and an episode of status epilepticus aged 23. A photograph at the age of 21 (fig 8) taken alongside his brother (II.11) showed a shorter, less well built man with normal body proportions, slight gynecomastia, normal genitalia, and normal body hair. He had a small head but bushy eyebrows and facial features similar to II.11. At the time of admission to the institution, he had short stature probably because of his chronic respiratory disease, but he showed remarkable catch up growth in adolescence with increases in height continuing into adult life (table 2). He died from a perforated gastric ulcer at the age of 34.

II.13 (1947) and III.2 (1956). All the other members of family 1 with the overgrowth syndrome were seen personally but not in circumstances where detailed examination was possible. Only sparse historical information was obtained. II.13 had had a difficult childhood and little schooling and lived in the community on a pension. He was tall with big hands and feet, a big head with prominent supraorbital

Figure 9 Partial G banded karyotypes of each translocation (and FISH results) using probe D4S96. (A) Family 1: *ish t(1;4)(q44;p16.3)* (D4S96+;D4S96-,D4S174+). (B) Family 2: *t(4;8)(p16.2;p23.1)*. (C) Family 3: *isht(4;21)(p16.3;q22.3)* (D4S96-,D4S174+;D4S96+).

ridges, and bushy eyebrows that just met across the midline (fig 8). III.2 grew rapidly in childhood and at 10 years was said to be the size of a 12 year old. He was in a special class at school and later had occasional employment; he married and had a daughter. He was described by others in the family as a "gentle giant". He was a tall, strong man with a big frame, big hands, a big head with bushy eyebrows (fig 8), and prominent supraorbital ridges.

II.8 (1948) and III.9 (1948). II.8 fed poorly in infancy but then grew rapidly. She was slow at school but held a job as a stablehand for a year before she married and had a large, robust son. She was a big woman, somewhat obese, with big hands and a large head (table 2). III.9 had been married and had a daughter but the child was taken into care. She was labelled as having schizophrenia but, at 48, she lived in her own house in the community with minimal supervision. She was a big woman of above average height with a heavy frame and obesity. She had thick hair, bushy eyebrows, and synophrys (fig 8). Her twin sisters (III.11 and III.12, 1951, probably monozygotic) had similar heavy builds which contrasted sharply with that of their mother and of their younger sister, III.15, with the PRD syndrome. After their mother died these twins lived independently caring for their young sister. The obligate carriers (II.1, II.3, II.8, and III.3) were of normal intelligence with average height and body size.

Family 2

III.1 (1982). This boy grew steadily throughout childhood with a height between the 75th and 90th centiles (table 2). At the age of 18 he

had a large head and measurements of his right hand, palm, and foot were above the 90th centile. He had a high arched palate, full lips, a short philtrum, and prominent supraorbital ridges (fig 7). He had an orchidopexy at the age of 13. He had been slow to pass his developmental milestones, had poor coordination of his movements, and some echolalia as a young child. His IQ was 50. In his early teenage years he was diagnosed as having the Asperger syndrome with obsessional behaviour over dressing routines and repeatedly writing out the same local railway timetable year after year.

III.2 (1979). His sister grew at a slower pace. She had only minimal breast development and no menstruation by the age of 16 years. The hands and feet were large with all measurements at the 75th centile or above. Overgrowth of soft tissues was evident in her face (fig 7) and the possibility of a storage disorder had been raised on several occasions. She had strabismus. Her IQ was 54. She had similar obsessional behaviour to her brother though this was less pronounced.

III.3 (1980). She was born after a normal pregnancy. She had hyperextended legs which were treated with casts and operative release of the left rectus femoris muscle. She grew rapidly and reached the 97th centile for height before the age of 1 year. She was slow to pass her developmental milestones, attended a special class at school, and had an IQ of 65. She was good tempered, rather shy, and had learned to cook meals and do housework. On examination at the age of 15 (fig 7), she was tall (table 2) with a large head, large hands and feet, and a deep voice.

Investigations

Most of the subjects with the PRD syndrome had been investigated for failure to thrive, short stature, or seizures. A variety of tests had been carried out including blood counts, serum and sweat electrolytes, urinary amino acids and mucopolysaccharides, small bowel biopsies, a fecal fat balance, an insulin tolerance test, liver and thyroid function tests, TORCH screens, muscles biopsies, a lumbar puncture, EEGs and skull x rays, a CT scan of the head, lysosomal enzymes in white cells, and serum long chain fatty acids and chromosome studies; all were normal or showed only non-specific changes. Bone ages were reported as 3-4 years behind chronological ages in III.5 and III.7 from family 1 at ages 5-6 years. Those subjects with overgrowth had far fewer investigations, mainly chromosome studies and screening tests for storage disorders.

CYTOGENETIC STUDIES

Leucocyte cultures were initiated from peripheral blood samples and harvested by standard cytogenetic procedures. High resolution GTG chromosome analysis was performed on all family members as indicated in fig 1. In family 3, one PRD patient, one translocation carrier, and one unaffected subject were studied.

Figure 10 Partial karyotypes for (A) PRD patient, displaying hemizygosity of probe D4S96, and (B) an overgrowth syndrome patient, showing three signals with the same cosmid probe D4S96.

FLUORESCENCE IN SITU HYBRIDISATION (FISH)
The cosmid probe for locus D4S96 (4p16.3) was obtained from Oncor Inc (Gaithersburg, MD, USA) and probes pC847.351 (locus D4F26), 33c6 (locus D4S43), and 21f12 (locus D4S180) from D Callen. Probes pC385.12 (locus FGFR3), 184d6, 19h1, 27h9, 58b6, 141a8, 108f12, and 10d12 were provided by T Wright. Cosmids were extracted with the Wizard Miniprep system (Promega) and labelled with digoxigenin 11-dUTP (Boehringer

Table 3 Clinical data on the present series and other published cases of the PRD syndrome

	Other published cases ¹⁻⁹	Present series	Total
Number	10	9	19
Sex ratio (M:F)	3:7	5:4	8:11
Age at last assessment	3y 4mth - 41y 9mth	11y - 55y	3y 4mth - 55y
Growth			
Gestation (weeks)			
Number	10	8	18
Mean	39.2	39.4	39.4
Range	37-42	36-43	36.43
Birth weight (g)			
Number	10	8	18
Mean	2.06	2.06	2.06
Range	1.13-2.60	1.10-2.52	1.10-2.60
"Failure to thrive"	4/8	7/8	11/16
Short stature*	10/10	7/9	17/19
Microcephaly*	10/10	8/9	18/19
Level of mental handicap			
Moderate	4	2	6
Severe	6	4	10
Profound	0	3	3
Mannerisms	—	6/9	6/9
Seizures	9/9	5/8	14/17
Facial appearance			
Prominent eyes	10/10	5/9	15/19
Telecanthus	7/10	0/9	7/19
Beaked or flared nose	8/10	4/9	12/19
Extra digital or palmar flexion creases	2/4	4/7	6/11

Other findings were: limited elbow movement 5, hypospadias 2, eye abnormalities 7 (strabismus 3, glaucoma, optic atrophy, myopia 1 each), ureteric reflux 1, inguinal hernia 1, self-correcting PDA 1, good response to growth hormone 1.
*Defined as 2 SD or more below their appropriate means.

Mannheim) by nick translation. In situ hybridisation was performed according to the Oncor protocol. The label was visualised with FITC and the chromosomes counterstained with propidium iodide or DAPI (4,6 diamidino-2-phenylindole). Images were enhanced by the Powergene Digital Imaging system (Perceptive Scientific Instruments Inc, UK).

Results
MOLECULAR CYTOGENETIC ANALYSIS
Members of family 1 showed normal karyotypes on high resolution GTG banding and FISH using chromosome paints for each autosome, even though a translocation had been suspected as the basis for the contrasting phenotypes found in the family. However, with the probe specific for locus D4S96, a cryptic translocation was shown (fig 9A), that is, one probe signal from locus D4S96 was seen at 4p16.3 and one signal at chromosome 1q44. All six subjects with the PRD syndrome studied showed hemizygosity for this locus. In the two subjects with the overgrowth syndrome, three hybridisation signals were seen, thus indicating three copies of locus D4S96 (not shown).

In family 2, a normal karyotype had been reported some 15 years previously. Further analysis by high resolution GTG banding showed an abnormal karyotype in the PRD subject: 46,XY,add(4)(p16). A reciprocal translocation was then identified in the patient's mother, aunt, and grandmother (fig 9B). The proband showed the unbalanced segregation product of this translocation which resulted in a deletion of chromosome 4p16.3 and duplication of chromosome 8p23.1. Two patients in this family with the overgrowth syndrome showed the other unbalanced derivative form of this translocation: 46,XX,der(8)t(4;8)(p16.2;p23.1)mat, that is, duplication of 4p16.3 and monosomy 8p23.1. Using the probe D4S96, the deletion in the PRD patient (fig 10A) and duplication of this locus in the overgrowth patients were confirmed (fig 10B).

In family 3, the PRD patient and his parents showed normal karyotypes on routine GTG banded analysis. The probe D4S96 showed a cryptic translocation (fig 9C) in the father: 46,XY,ish t(4;21)(p16.3;q22.3)(D4S96-, D4S174+,D4S96+). The mother's karyotype showed no abnormalities. The PRD patient was deleted for one copy of locus D4S96 (fig 10A).

DELETION MAPPING
Cosmid probes for loci D4S90, D4S96, FGFR3, D4S43, and D4S180 were applied to a translocation carrier from each family to locate the breakpoints¹³ (fig 11). Although the breakpoints of the three translocations were different, all shared a common deleted region that included the locus FGFR3 and the Wolf-Hirschhorn critical region (WHCR), as recently defined by Reid *et al.*¹⁴

To characterise the breakpoint on 4p16.3 further, FISH techniques were used with the cosmid contig on the smallest of our 4p translocated segments (family 1). Overlapping cosmids, spanning 390 kb, between loci

Figure 11 Location of 4p breakpoints in the three translocations and Wolf-Hirschhorn critical region (WHCR) on the current map of 4p16.3.¹³ Partial contig of cosmid probes used in the study are in bold. Solid patterns indicate the regions involved in each translocation and the broken lines show undefined regions. To the left of the map, the region between FGFR3 and D4S43 has been expanded to show the additional cosmid probes we used to define the breakpoint to be within locus D4S43 in family 1.

Table 4 Differences in clinical features between the Wolf-Hirschhorn and Pitt-Rogers-Danks syndrome

Clinical feature	Wolf-Hirschhorn syndrome	Pitt-Rogers-Danks syndrome
Major congenital malformations	Common	Not reported
Early mortality	High	Low
Walking unassisted	Uncommon	Late but usual
Survival to adult life	Unusual	Common
Facial appearance	Conspicuously abnormal, prominent glabella, straight nose, hypertelorism	Usually abnormal, prominent eyes, small nose, short philtrum, wistful expression
Distal 4p trisomy/4p16.3 duplication in other family members	Profound mental retardation, microcephaly, short stature, skeletal anomalies	Moderate physical overgrowth, coarse facial features, mild to moderate intellectual handicap

FGFR3 and D4S43 (fig 11) were applied on an obligate carrier of family 1. Probes for each of the loci studied between 4pter and D4S43 were found in the translocated segment. This narrows the breakpoint to a 40 kb region, between cosmids 108f12 and 10d12 which are within locus D4S43.

Discussion

THE PRD SYNDROME

The present series confirms that the PRD syndrome is marked by pre- and postnatal growth retardation, microcephaly, severe intellectual handicap, seizures, a distinctive facial appearance, and deletion of 4p16.3. It is clear that survival into adult life is the rule and that in a small proportion of patients height may reach the lower end of the normal range and intellectual handicap may be moderate rather than severe. The PRD syndrome is a seizure disorder sometimes starting with status epilepticus followed by recurrent seizures which pose significant problems during childhood but lessen thereafter. The facial appearance is distinctive in childhood but less so in adult life; it is hard to delineate. Those features contributing to the facial gestalt seem to be prominent eyes with the sclera visible below the iris, a small nose, short philtrum, a wistful expression, and detached demeanour. However, in some the facial appearance may be normal. Curious, rather bizarre, but often graceful stereotyped hand movements and mannerisms are common as are extra flexion creases on the fingers.

The main clinical features in this series and those of the other published cases of the PRD syndrome are shown in table 3.

THE OVERGROWTH SYNDROME

This syndrome comprises generalised overgrowth, mild to moderate mental handicap, and duplication of 4p16.3. The soft tissues are involved with thickening and coarsening of the face and abundant head hair with bushy eyebrows and synophrys. Bony overgrowth leads primarily to a heavy body frame with a large head circumference, prominent supra-orbital ridges, a square jaw, but a rather small, upturned nose. Hands and feet are big with stature well above average. The degree of mental handicap varies from moderate to mild with no specific behavioural characteristics. Considerable variation is seen in the manifestations of this syndrome between various members of the same family.

The finding of a 4p16.3 deletion by Clemens *et al*⁷ in the PRD syndrome was amply confirmed in all the eight PRD patients who were tested. The regions involved in the translocations in each family overlapped the WH syndrome critical region.^{15 16} This raises the question as to whether these two syndromes are separate conditions or aspects of the same genetic entity. On the clinical level, although both syndromes are marked by growth failure, severe mental retardation, and seizures there are considerable differences (table 4). The major congenital malformations and early mortality of the WH syndrome¹⁷ contrast strongly with the minor congenital malformations and survival into adult life seen in the PRD syndrome. The facial appearance in the two syndromes differs. The WH syndrome can be recognised in the newborn period by hypertelorism and a straight nose with a wide and prominent glabella, likened to the Greek warrior helmet.^{17 18} In the PRD syndrome

prominent eyes, a small nose, and a wistful expression are characteristic. We suggest that some of the older children described as having the WH syndrome may well be examples of the PRD syndrome (for example, the probands of the two familial cases described by Wilson *et al.*,¹⁹ the patients of Stengel-Rutkowski *et al.*²⁰ and El-Rifai *et al.*,²¹ and patient 3 of Estabrooks *et al.*²²). We believe that the two syndromes are different entities.

Cytogenetic reports of 22 families with translocations involving specifically chromosome 4p16 have been reported.^{14 18 23} All describe patients with the WH syndrome who have the unbalanced (deletion) segregants of a translocation. Five reports describe family members with the alternate segregation product, that is, duplication of 4p16; however, no clinical features were given for these. One patient with the karyotype 46,XX, der(8)t(4;8)(p15.32;p22), that is with a duplication of 4p15.32 and deletion of 8p22, was reported at 3 months of age to be developmentally and physically normal.²³

The WH syndrome can also result from deletion of a larger segment of 4p. The alternate segregation product then is the trisomy 4p syndrome which has been well described. Although clinical manifestations may vary from one person to another, the commonest features are short stature, profound mental retardation, and various skeletal anomalies.^{17 24 25} This contrasts sharply with the physical overgrowth and only mild to moderate intellectual handicap seen in our two families where the deleted 4p16.3 had caused the PRD syndrome.

The partial monosomy or trisomy of the other chromosomes involved in each of the translocations we describe did not appear to alter either of the two contrasting phenotypes. Affected subjects were readily identifiable in each of the three families.

The phenotype of this new overgrowth syndrome is comparatively mild and would not have been recognised if affected subjects had been met individually. It was the co-occurrence of the overgrowth in this syndrome with the undergrowth of the PRD syndrome in the same families which brought it to light. Although physical overgrowth was detectable in childhood it became most obvious in late adolescence and early adult life. The growth pattern and physical appearance differed from that seen in the Beckwith-Wiedemann and Simpson-Golabi-Behmel syndromes and there were no accompanying major organ malformations. There are some similarities between the facial features found in this syndrome and the autosomal dominant acromegaloid syndrome described by Hughes *et al.*²⁶ but intellectual handicap is not part of that disorder. The Sotos syndrome should be distinguishable clinically. Using the strict criteria suggested by Cole and Hughes,²⁷ we have now tested six patients with this syndrome and have not found a 4p16.3 duplication. In practice there are difficulties in diagnosing²⁷ and differentiating^{28 29} these and other overgrowth syndromes. We believe that a search for a cryptic 4p16.3 duplication is warranted in patients with atypical features of

the Sotos syndrome and in those with overgrowth and intellectual handicap where a storage disorder is suspected but not found biochemically.

In families 1 and 2, subjects with the PRD and overgrowth syndromes were found in the same sibship. Transmission of both syndromes was through males and females. It should be stressed that whereas subjects with the PRD syndrome are unlikely to reproduce, those with overgrowth can (for example, III.2, 8, and 9 in family 1). The expectation is that their offspring will be either unaffected or have the overgrowth syndrome, thus mimicking autosomal dominant inheritance.

While different breakpoints of 4p were found in each of our three translocation families, the region deleted or duplicated included the locus for the fibroblast growth factor receptor gene 3 (FGFR3) in all of them. The functions of FGFR3 are not yet clear but in the mouse it is expressed in embryogenesis both in brain and prebone cartilage.^{30 31} It has been found that mutations in FGFR3 cause achondroplasia and thanatophoric dysplasia^{32 33} and two point mutations involving the codon of amino acid residue 540 of FGFR3 cause hypochondroplasia,³⁴ all of which are marked by growth failure. We suggest that FGFR3 could be a candidate gene for the growth abnormalities in the PRD and overgrowth syndromes in our two families: a single dose or haploinsufficiency leading to growth failure and three doses to overgrowth.

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Addendum

Since submitting this paper, Wright *et al.* (*Hum Mol Genet* 1997;6:317-24) have narrowed the WHSCR to 260 kb. A new locus, D2S132, defined by the cosmids 108f12 and 10d12 is the new proximal breakpoint. This is identical to the translocation breakpoint in our family 1.

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