Paternally inherited duplications of 11p15.5 and Beckwith-Wiedemann syndrome

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Abstract

We present a three generation family in which a father and son have a balanced chromosome translocation between the short arms of chromosomes 5 and 11 (karyotype 46,XY,t(5;11)(p15.3;p15.3)). Two family members have inherited the unbalanced products of this translocation and are trisomic for chromosome 11p15.3→pter and monosomic for chromosome 5p15.3→pter (karyotype 46,XY,der(5)t(5;11)(p15.3;p15.3)pat). Paternally derived duplications of 11p15.5 are associated with Beckwith-Wiedemann syndrome (BWS) and both family members trisomic for 11p15.5 had prenatal overgrowth (birth weights >97th centile), macroglossia, coarse facial features, and broad hands. We review the clinical features of BWS patients who have a paternally derived duplication of 11p15.5 and provide evidence for a distinct pattern of dysmorphic features in those with this chromosome duplication. Interestingly, our family is the fifth unrelated family to be reported with a balanced reciprocal translocation between the short arms of chromosomes 5 and 11. The apparently non-random nature of this particular chromosome translocation is suggestive of sequence homology between the two chromosome regions involved in the translocation.

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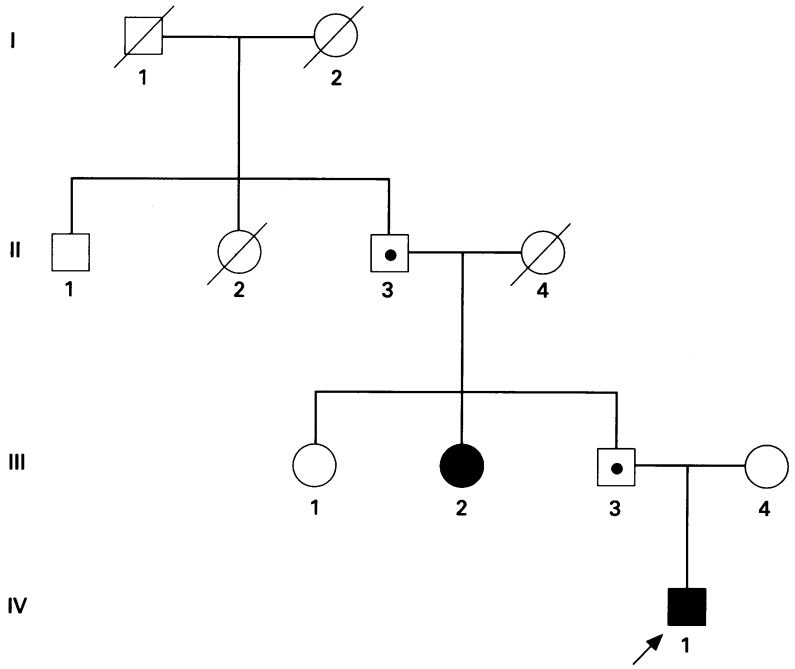

Figure 1 The family pedigree. Subjects II.3 and III.3 carry a balanced translocation (46,XY,t(5;11)(p15.3;p15.3)) and III.2 and IV.1 have inherited the unbalanced products with karyotypes (46,XX,der(5)t(5;11)(p15.3;p15.3)pat) and (46,XY,der(5)t(5;11)(p15.3;p15.3)pat) respectively.

Case report

The family pedigree is shown in fig 1. The proband (IV.1) was the first child born to unrelated white parents. The mother was 32 years old and the father 33 years old at the time of his birth. The father had had an inguinal hernia repair at 6 weeks of age but was otherwise well.

During the pregnancy polyhydramnios and a thick umbilical cord were detected by ultrasound scanning. The proband was born by normal delivery at 37 weeks of gestation with a weight of 4100 g (>97th centile) and head circumference of 32.5 cm (10th-50th centile). At birth he was noted to be oedematous and dysmorphic with hypertelorism, small eyes, and epicanthic folds. The ears were dysplastic with incisura intertragica. He had a large, protuberant tongue. There was mild neck webbing and his body skin was lax and redundant. The nipples were widely spaced and there was a small umbilical hernia. He was hypotonic with marked head lag and a poor grip. Tube feeding was required for the first 12 days of life. A diagnosis of BWS was considered but there was no asymmetry or palpable abdominal organomegaly and there were no recorded episodes of hypoglycaemia. Chromosome analysis in the neonatal period showed apparently normal male chromosomes.

He had one febrile convulsion at the age of 18 months which was complicated by a transient paresis. No further seizures were reported. His motor development was normal and he sat independently at 8 months and walked at 13 months of age. His speech development was delayed and he could only manage single words at the age of 3 years.

At the age of 4 years (fig 2), height was 102.5 cm (50th-75th centile), weight 18.5 kg (75th-90th centile), and head circumference 51.5 cm (50th-75th centile). His fringe had a marked upsweep with a double cowlick. He had thick facial skin with coarse features and a persistently large tongue. The ears were fleshy with thick helices and lobes. His hands were broad with tapering fingers.

At the age of 15, he was a quiet, shy boy who attended normal school in a special unit with "one to one" assistance full time. His head circumference was 55 cm (50th centile) and height was 162.5 cm (3rd centile). His tongue was less prominent and fifth finger clinodactyly

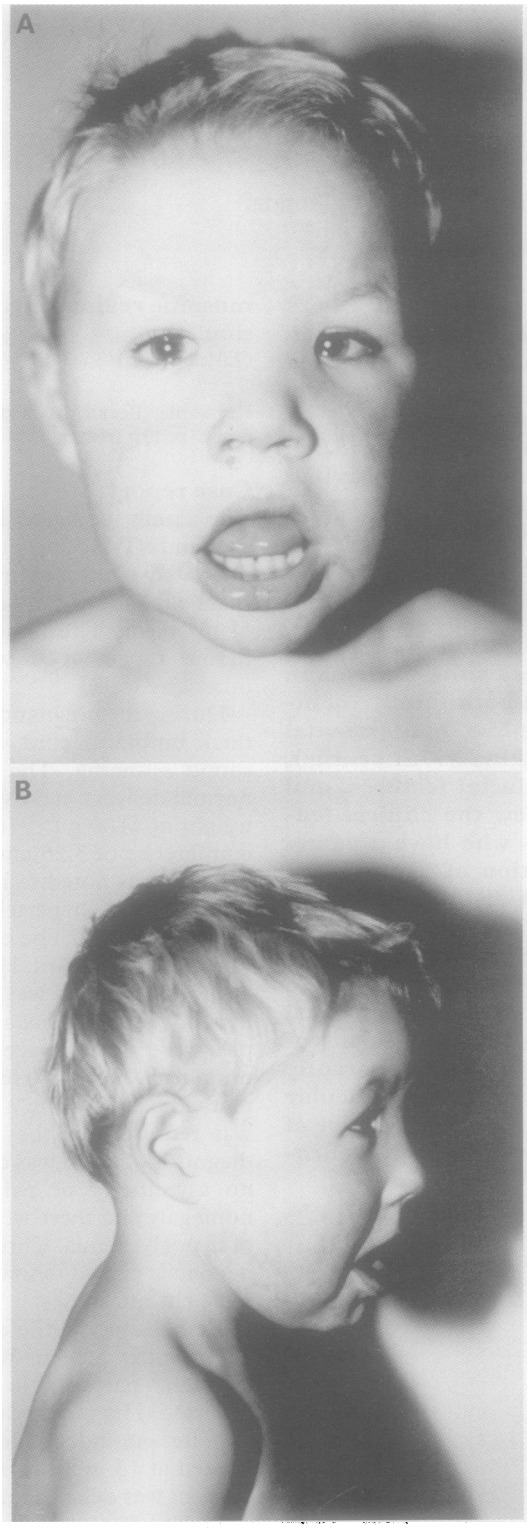

Figure 2 The proband aged 4 years, (A) front view and (B) profile. (All photographs reproduced with permission.)

was noted. The remainder of the physical examination was unchanged.

A paternal aunt of the proband (III.2, fig 1) had a similar pattern of dysmorphic features with prenatal overgrowth (birth weight 4830 g (>97th centile) at term), epicanthic folds, hypertelorism, a broad, coarse face, large tongue, and a thick neck (fig 3). She had prominent ears, strabismus, and large teeth with irregular lower incisors and premolars. The hands were broad with single palmar creases and fifth finger clinodactyly. She had febrile convulsions at the age of 2 years and subsequently developed grand mal epilepsy which was controlled by anticonvulsant medication. She had severe learning difficulties (her IQ was assessed as 30) and required care in an institution from the age of 4 years.

Cytogenetic analysis

Chromosome analysis was repeated on the proband and his parents when the proband was 15 years of age. High resolution G banding showed that the proband had inherited the unbalanced products of an apparently balanced translocation carried by his father (karyotype of proband 46,XY,der(5)t(5;11)(p15.3;p15.3)pat (fig 4A); karyotype of proband's father: 46,XY,t(5;11)(p15.3;p15.3) (fig 4B)). Karyotyping in other family members showed that the proband's paternal aunt had inherited the same unbalanced products as the proband from her father (karyotype of proband's paternal aunt 46,XX,der(5)t(5;11)(p15.3;p15.3)pat, not shown; karyotype of aunt's father 46,XY,t(5;11)(p15.3;p15.3), not shown). Both the proband and his aunt were therefore trisomic for chromosome bands 11p15.3→pter and monosomic for chromosome bands 5p15.3→pter.

Discussion

In this family, the father and paternal grandfather of the proband carry a balanced translocation between chromosomes 5 and 11 (karyotype 46,XY,t(5;11)(p15.3;p15.3)). The proband and his aunt have inherited an unbalanced form of the translocation and are trisomic for the distal part of chromosome 11 (11p15.3→pter) and monosomic for the tip of chromosome 5 (5p15.3→pter). Paternally derived duplications of 11p15.5 are associated with BWS and both family members had prenatal overgrowth, macroglossia, and dysmorphic features in keeping with this syndrome.[1-6]

The majority of cases of BWS are sporadic.[2 5] However, around 15% of BWS patients have a positive family history and autosomal dominant families with incomplete penetrance and variable expression of the clinical features have been described.[7 8] In sporadic cases, 20-28% of BWS patients have been found to have uniparental disomy (UPD) for the paternal allele of chromosome 11.[9 10] A comparison of patients with BWS and UPD for chromosome 11 with BWS patients without UPD showed an increased incidence of hemihypertrophy (6/9 *v* 1/23) and a decreased incidence of exomphalos (0/9 *v* 13/23) in the cases with UPD.[10] Other studies have reported an increased incidence of tumours in BWS patients with UPD.[9 11]

The BWS gene(s) has been mapped to 11p15.5 by linkage studies.[12 13] A sex bias in the transmission of BWS in families (the clinical features are passed on from mother to offspring two to three times more frequently than from father to offspring), the finding of UPD in BWS patients, and the sex bias in the chromosome anomalies associated with BWS (the duplications of 11p are always paternal and the balanced translocations and inversions are

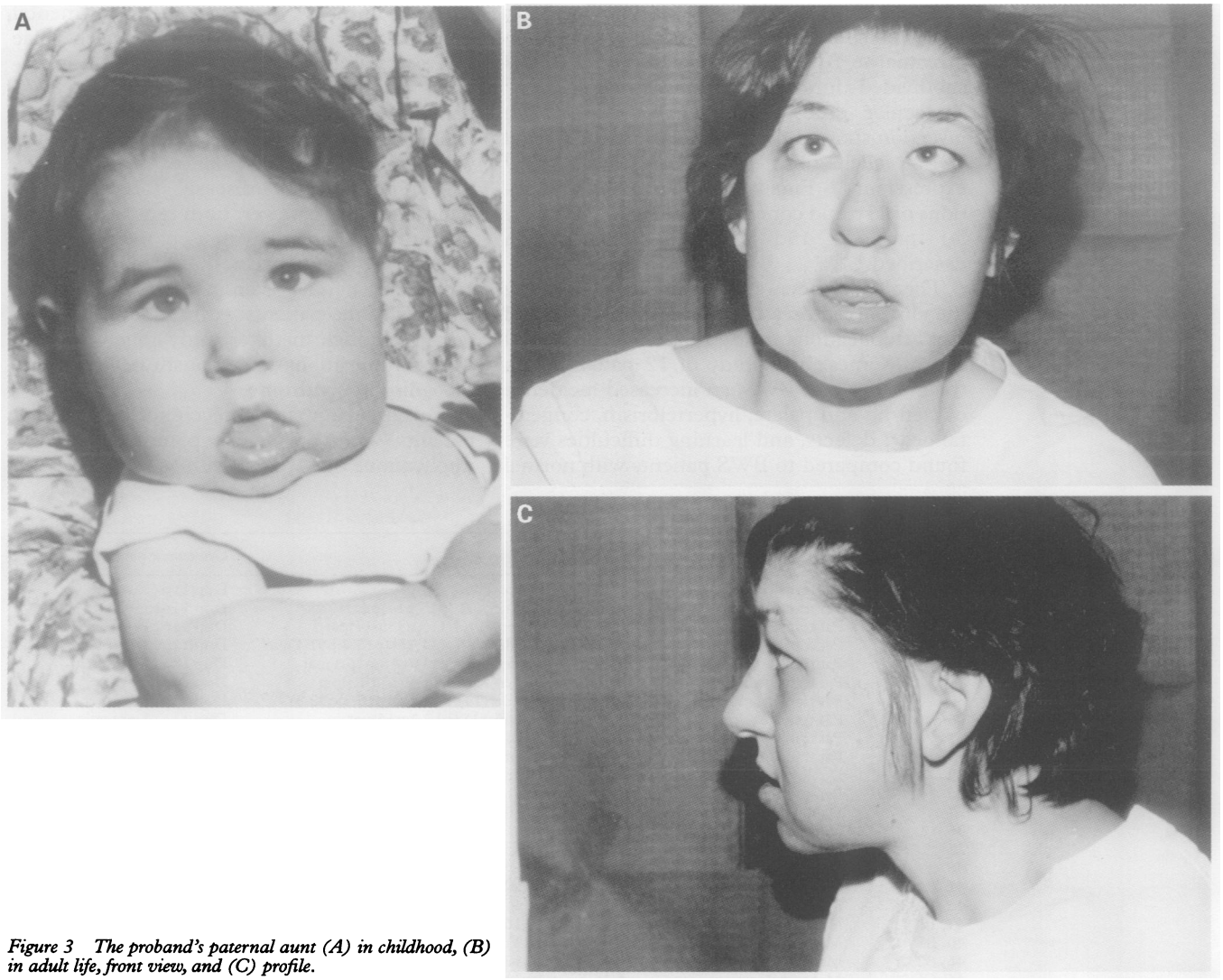

Figure 3 The proband's paternal aunt (A) in childhood, (B) in adult life, front view, and (C) profile.

maternal) have led to the hypothesis that the responsible gene(s) is imprinted.[6 7 14] Candidate gene(s) for BWS localised to 11p15.5 have included insulin-like growth factor 2 (IGF2), a maternally imprinted growth promoter thought to cause overgrowth and the development of embryonal tumours,[15-18] and H19, a paternally imprinted gene that produces a product with growth inhibitory and antitumourigenic effects.[19-21] The "opposite" imprinting of IGF2 and H19 is likely to be regionally controlled.[22] At least some of the clinical features of BWS (for example, somatic overgrowth) could result from increased IGF2 expression, either as a result of paternal UPD for chromosome 11, imprinting mutations of the maternal allele that repress the H19 gene and release the maternal copy of the IGF2 gene from transcriptional repression,[21 22] or from maternal mutations causing biallelic expression of IGF2 without altering H19 expression.[23]

Recently, mutations in the imprinted $p57^{KIP2}$ gene at 11p15.5 disrupting the normal $p57^{KIP2}$ protein were found in 2/9 patients with BWS.[24] Disruption of the KVLQT1 gene by maternal balanced translocations has been reported in five families with BWS.[25] The KVLQT1 gene lies between $p57^{KIP2}$ and IGF2 on 11p15.5 and is expressed from the maternal allele only in most fetal tissues.[25] The involvement of the $p57^{KIP2}$ and KVQLT1 genes in BWS suggests that there are several imprinted genes at 11p15 important in this syndrome and that the abnormal expression of any one gene might lead to BWS.[25]

Cytogenetic abnormalities have been found in 2-3% of persons with BWS.[5] The commonest anomaly is a duplication of chromosome bands 11p13→15 resulting from the unbalanced segregation of a paternal translocation (table 1[26-35]) or a paternal inversion.[36] De novo duplications of paternal origin involving 11p15.5 have also been described in patients with BWS.[28 36-38] One de novo translocation resulting in duplication of 11p13→pter has been reported in a girl with BWS.[39]

The clinical features of BWS are thought to be caused by increased IGF2 expression from the extra paternal copy of this gene in those with the duplication.[40]

The other main type of cytogenetic abnormality found in patients with BWS is less common (table 1). Balanced chromosome translocations or inversions with a breakpoint on 11p can be passed from phenotypically normal mothers to their offspring who may then show the clinical effects of BWS (table 1[40-46]). The breakpoints of these translocations and inversions have been found to cluster in two distinct regions, BWSCR1, a 450 kb region

200-400 kb centromeric to the IGF2 gene at 11p15.5 and BWSCR2, a 2000 kb region proximal to BWSCR1 at 11p15.3-15.4 that is subdivided into at least two regions.[25 40 43] Molecular study of one family with an inversion showed derepression of the maternal IGF2 allele but no change in H19 expression.[23 45] Finally, two patients with deletions of 11p and concordant twins with trisomy for part of 15q and BWS have been described.[47-49]

There have been several studies comparing the clinical features of patients with BWS and 11p duplications and those with normal chromosomes. In a study of 12 patients with trisomy 11p and BWS, an increased incidence of cleft lip and palate, hypertelorism, congenital heart defects, and learning difficulties were found compared to BWS patients with normal chromosomes.[50] A higher frequency of mental retardation, early death, and inguinal herniae was also found in BWS patients with duplications of 11p.[31] These studies suggest BWS patients with a duplication have a higher incidence of the physical differences associated with chromosome imbalance (for example, congenital heart disease and mental retardation[51]). However, both reports included one or more patients with a complex chromosome rearrangement in the 11p duplication group and neither examined the dysmorphic features of the patients with trisomy 11p15 in detail, although the later study concluded that 11p15 duplications could constitute a clinically recognisable syndrome.[31]

We have compared the clinical features of patients with BWS and paternally derived duplications of 11p15.5 with those from BWS

Table 1 Chromosome rearrangements and BWS

Reference	*Chromosome rearrangement*	*Karyotype of proband*	*Cytogenetic anomaly*
26	Pat translocation	46,XY,t(2q +pat)	Dup 11p
27	Pat translocation	46,XY,der(5),t(5;11) (p15;p14)pat	Dup 11p15→pter
28	Pat translocation	46,XY,−4,+der(4) t(4;11)(q33;p14)pat	Dup 11p14→pter
29	Pat translocation	46,XY,−18,+der(18), t(11;18)(p15.4;p11.1)pat	Dup 11p15.4→pter
30	Pat translocation	46,XY,−5, +der(5), t(5;11)(p15;p15.1)pat	Dup 11p15.1 →pter
31	Pat translocation	46,XX,−4,+der(4), t(4;11)(q35;p13)pat	Dup 11p13→pter
32	Pat translocation	46,XX,−14,+der(14) t(11;14)(p15.3;q32.3)	Dup 11p15.3→pter
33	Pat translocation	46,XY,der(5)t(5;11) (p15.2;p14)pat	Dup 11p14→pter
34	Pat translocation	46,XY,−10,+der(10) t(10;11)(q26;p15)	Dup 11p15→pter
35	Pat translocation	46,XY,−21,+der(21) t(11;21)(p15.2;q22.3)pat	Dup 11p15.2 →pter
39	De novo translocation	46,X,−X,+der(X) t(X;11)(p22.1;p13)	Dup 11p13→pter
36	Pat inversion	46,XY,rec(11), dup(p13→p15),del(q23→q25)	Dup 11p13→p15
37	De novo duplication	Trisomy 11p (excluding 11p13)	Dup 11p (excluding 11p13)
36	De novo duplication		Dup 11p15
28	De novo duplication		Dup 11p15
38	De novo duplication		Dup 11p15
41	Mat translocation	46,XX,t(11p;22q)	Breakpoint 11p
42, 1632[46]	Mat translocation	46,XX,t(9;11) (p11.2;p15.5)	Breakpoint 11p15.5
43, 1217[46]	Mat translocation	46,XX,t(11;16)(p15.5;q12)	Breakpoint 11p15.5
40, B10.1[46]	Mat translocation	46,XX,t(4;11)(p15.2;p15.4)	Breakpoint 11p15.4
46, B23.1[46]	Mat translocation	46,XX,t(11;12) (p15.5;q13.1)	Breakpoint 11p15.5
46, CD2[46]	Mat translocation	46,XX,t(10;11)(p13;p15.5)	Breakpoint 11p15.5
44	Mat translocation	46,XX,t(11;16)(p15;q13)	Breakpoint 11p15
45	Mat inversion	46,XX,inv(11)(p11.2p15.5)	Breakpoint 11p15.5
40, WH5.3[46]	Mat inversion	46,XX,inv(11)(p15.4;q22.3)	Breakpoint 11p15.4
47	De novo deletion	46,XY,del(11)(p11.1p11.2)	Del 11p11.1→11.2
48	De novo deletion	46,XX,del(11)(p11p13)	Del 11p11→13
49	Mat duplication	46,XX,dup(15)(q11.2-q13)mat	Dup 15q11.2→13

Table 2 Clinical features of patients with duplication of 11p and BWS

	Reference																
Clinical feature	*26*	*27*	*28(2)*	*29(1)*	*29(2)*	*31*	*32*	*33*	*34(3)*	*35*	*39*	*36(1)*	*37*	*36(2)*	*28(1)*	*38*	*Our case*
Sex	M	F	M	M	M	F	F	M	F	M	F	M	M	F	F	M	M
Gestation	Term	Term	32+ w	38 w	Term	39 w		34 w	35 w	38 w		31.5 w	30+ w	39 w	36 w	Term	40 w
Birth weight (g)	5075	2700	2200	4500	4450	3100	5200	90%	3150	3700	Normal	3600	4160	4100	3400	>98%	4100
Polyhydramnios								+				+	+	+			+
Macroglossia	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Overgrowth	+	+	+	+	+		+	+	+	+		+	+	+		+	+
Abdo wall defect				+		+	+		+	+	+	+	+	+	+		+
Hypoglycaemia				+	+										+		
Ear anomalies				+	+		+	+		+	+	+	+	+			
Facial naevus												+					
Visceromegaly				+	+	+		+		+	+			+	+	+	
Renal anomalies		+				+			+						+	+	
Hemihypertrophy									+								
Cleft palate			+										+				
Inguinal hernia	+		+	+		+							+				
Cardiac malform		+		+	+									+	+		
Seizures		+							+				+	+			
Develop delay	+	+				+		+	+	+	−	+	+	+	+		+
Neoplasia					+												
Survival	10 y	10 y	† 1 d	† 16 w	† 13 w	† 108 d	1 y	6 y	1 y	3.5 y	4 y	6 m	15 y	3.5 y	2 y	Infancy	16 y

Overgrowth was defined as weight or length above 90th centile. Abdo wall defect = anterior abdominal wall defect, defined as omphalocele, umbilical hernia or diastasis recti. Ear anomalies were defined as ear lobe creases, grooves, or pits. Cardiac malform = cardiac malformations. Develop delay = developmental delay. d = days; w = weeks; m = months; y = years; % = centile; † = died.

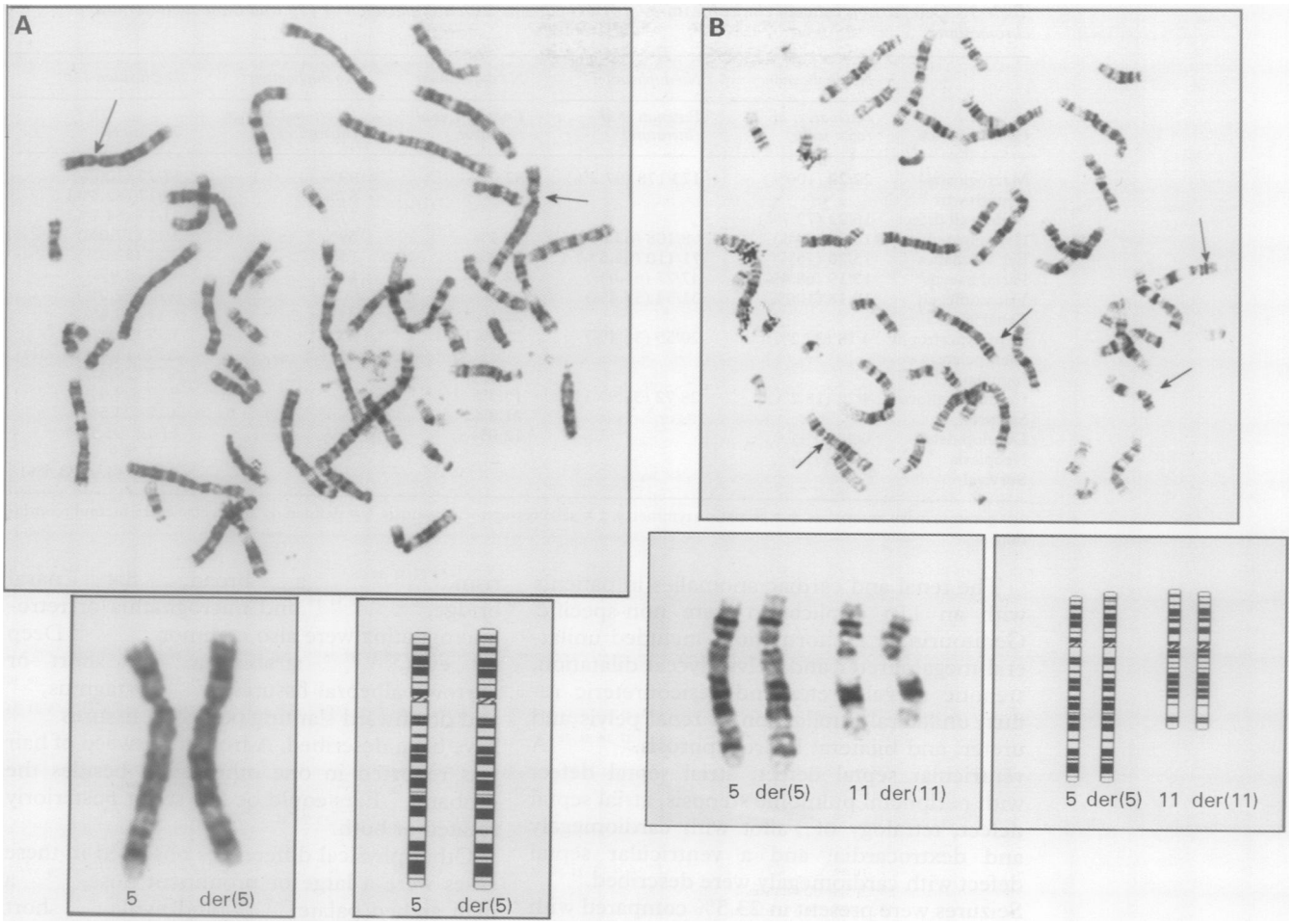

Figure 4 (A) Partial karyotype of the proband (46,XY,der(5)t(5;11)(p15.3;p15.3)pat). (B) Partial karyotype of the proband's father (46,XY,t(5;11)(p15.3;p15.3)).

patients and normal chromosomes (tables 2 and 3). We selected previously reported cases with a duplication of 11p and BWS, defined by the presence of two out of the three accepted major clinical criteria (macroglossia, anterior abdominal wall defect, and pre- or postnatal overgrowth >90th centile).[5] The cases of 11p duplications described by Wales *et al*[52] and Anderson *et al*[53] did not fulfil these criteria and were excluded. We chose to include reports of BWS patients with 11p duplications where only a short clinical description was provided.[32 33 39] We have included the proband but not his paternal aunt as she was not examined in our clinic.

The incidence of clinical features in subjects with BWS and normal chromosomes has been the subject of several reviews.[1-6] It is likely that the variation in the frequency of features is influenced by factors such as the mean age of the patients at diagnosis/examination, ethnic and environmental differences, and the number of researchers involved.[54] We have therefore compared the results from our 17 patients with one patient study and three published reviews (table 3).

Our study included 17 patients (table 2). The incidences of macroglossia, overgrowth, and congenital cardiac disease were comparable in BWS patients with a duplication of 11p and those with normal chromosomes, although there was considerable variation in the estimated frequencies of congenital cardiac disease (table 3). The incidence of visceromegaly in the patients with an 11p duplication was comparable with the incidence reported in the published reviews but lower than in one patient series (table 3^2). Hypoglycaemia was less common in those with an 11p duplication (17.6% compared with published frequencies of 30.4-63%, table 3). In one patient with an 11p duplication, the hypoglycaemia was detected after the neonatal period and was difficult to control by diet.[29] The incidence of facial naevus flammeus was markedly lower in those with an 11p duplication (5.9% compared with published frequencies of 32.1-68.4%, table 3). However, facial naevi in BWS become less obvious after 1 year of age[5] and some of the patients with 11p duplications were not examined until later in childhood. Only one patient with trisomy 11p15 (5.9%) was described as having hemihypertrophy.[34]

Developmental delay was markedly more common in those with a chromosome duplication and was a feature in all but one of the patients who survived infancy (tables 2 and 3). However, delay was not mentioned in the reports of Tonoki *et al*[32] or Chernos *et al.*[38] In the majority of cases, the delay was moderate to severe[26-28 36 37] compared to the mild delay that is found in a minority of BWS patients with normal chromosomes.[5] Hypotonia was also reported in several patients.[28 29 31 35]

Table 3 Comparison between clinical features of BWS patients with a duplication of 11p and those with normal chromosomes

Clinical feature	No duplication Pettenati et al[2] (own series)	No duplication Pettenati et al[2] (literature)	No duplication Engström, et al[3] (literature)	No duplication Elliott and Maher[5] (literature)	Duplication 11p This study
Macroglossia	22/22 (100%)	173/178 (97.2%)	82.0%	99%	17/17 (100%)
Overgrowth				87%	14/17 (82.4%)
Abdo wall defect	16/22 (72.7%)			77%	11/17 (64.7%)
Hypoglycaemia	10/20 (50%)	68/108 (63.0%)	30.4%	59%	3/17 (17.6%)
Ear anomalies	15/20 (75%)	71/110 (64.5%)	38.0%	75%	9/17 (52.9%)
Facial naevus	13/19 (68.4%)	47/77 (61.0%)	32.1%	62%	1/17 (5.9%)
Visceromegaly	18/18 (100%)	31/54 (57.4%)			9/17 (52.9%)
Renal anomalies			24.1%*	62%	5/17 (29.4%)
Hemihypertrophy	4/18 (22.2%)	20/55 (36.4%)	12.6%†	23%	1/17 (5.9%)
Cleft palate				3%	2/17 (11.8%)
Inguinal hernia			5.7%		5/17 (29.4%)
Cardiac malform	4/22 (18.2%)	28/72 (38.9%)	15.5%	9%	5/17 (29.4%)
Seizures			21.8%‡		4/17 (23.5%)
Develop delay	0/22 (0%)		12.0%	4%§	11/12 (91.7%)
Neoplasia	1/20 (5%)			4%	1/17 (5.9%)
Survival					4 died <1 y (23.5%)

* = genitourinary anomalies. † = somatic asymmetry. ‡ = seizures-apnoea-cyanosis. § = defined as moderate/severe mental retardation.

The renal and cardiac anomalies in patients with an 11p duplication were non-specific. Genitourinary malformations included unilateral megaloureter and pelvicalyceal dilatation, stenotic megaloureter and vesicoureteric reflux, unilateral duplication of renal pelvis and ureter, and bilateral hydronephrosis.[27 28 31 38] A ventricular septal defect, atrial septal defect with peripheral pulmonic stenosis, atrial septal defect, tetralogy of Fallot with cardiomegaly and dextrocardia, and a ventricular septal defect with cardiomegaly were described.[27-29 36] Seizures were present in 23.5% compared with an incidence of 21.8% in BWS patients with normal chromosomes (table 3).

Four patients (23.5%) died in their first year of life[28 29 31] compared with an estimated mortality rate of 20-21% for BWS patients with normal chromosomes.[2 55] One case was found to have an adrenocortical carcinoma on post mortem examination, the only patient in our study known to have developed a malignancy.[29 56]

In our opinion, the patients with trisomy 11p15 had a distinct and recognisable phenotype. Craniofacial features included a prominent occiput,[29 31 35 36] a prominent or flat forehead with frontal bossing,[26 31 34 35 38] and a round face with full or puffy cheeks.[26 28 29 35 36] Epicanthic folds,[26 28 31 33 34 38] hypertelorism,[27 28 31 34-38] a broad, flat nasal bridge,[26 28 29 31 34 35] and micrognathia or retromicrognathia were also common.[28 29 31 35] Deep set eyes,[26 27 37 38] strabismus,[26 34 37] short or narrow palpebral fissures,[27 35 37] nystagmus,[26 36] and downward slanting palpebral fissures[26 31 34] have been described. A frontal upsweep of hair was reported in one other child besides the proband.[35] Ears could be low set or posteriorly rotated or both.[27-29 35]

Other physical differences observed in these cases were a large or prominent nose,[27-29 37] a high arched palate,[26 31 35] bifid uvula,[26 37] short neck,[27 29 31 35 37] scoliosis,[35-37] and widely spaced nipples.[28 34 35] Hands and feet were broad with broad/short digits.[26 27 29 35] Skin was described as soft, fine, or wrinkled.[26 31 35] Four boys had cryptorchidism.[26 28 36 37]

The phenotype of those with the duplication was distinguished by a persistent pattern of dysmorphism. The facial dysmorphism remained despite increasing age (see photographs published by Falk *et al*[26] (patient aged 9 years), Rethoré *et al*[37] (patient aged 15 years), and the paternal aunt of the proband, fig 3), a finding in marked contrast to patients with BWS and normal chromosomes in whom the BWS phenotype becomes harder to recognise with time.[5 6]

In 11 of the patients in our study, the duplication of 11p was the result of a paternal translocation and accompanied by monosomy for a different chromosome region (table 1). The contribution of the chromosome deletions to the pattern of craniofacial dysmorphism is difficult to estimate.

The proband is also monosomic for the distal short arm of chromosome 5 from 5p15.3→pter, the chromosome region associated with the cri du chat syndrome.[57 58] Molecular studies of this region suggest a contiguous gene syndrome in which the most telomeric locus is concerned with speech development.[59] The proband's marked speech delay in comparison to his normal early motor milestones could be explained by the finding that he is monosomic for this chromosome region.[59]

Table 4 Translocations between chromosomes 11p, 5p, 4q and 16q

Reference	Chromosome rearrangement	Karyotype of proband	Breakpoints
27	Pat translocation	46,XY,der(5)t(5;11)(p15;p14)pat	11p14 5p15
64	Pat translocation	46,XX,der(5),t(5;11)(p15;p12)pat	11p12 5p15
30	Pat translocation	46,XY,−5,+der(5),t(5;11)(p15;p15.1)pat	11p15.1 5p15
33	Pat translocation	46,XY,der(5)t(5;11)(p15.2;p14)pat	11p14 5p15.2
Our patient	Pat translocation	46,XY,der(5)t(5;11)(p15.3;p15.3)pat	11p15.3 5p15.3
28 (case 2)	Pat translocation	46,XY,−4,+der(4)t(4;11)(q33;p14)pat	11p14 4q33
31	Pat translocation	46,XX,−4,+der(4),t(4;11)(q35;p13)pat	11p13 4q35
43	Mat translocation	46,XX,t(11;16)(p15.5;q12)	11p15.5 16q12
44	Mat translocation	46,XX,t(11;16)(p15;q13)	11p15 16q13

Duplications of chromosome 11p have been described independently of the BWS phenotype in several unrelated patients.[60-64] A consistent pattern of dysmorphism was suggested in an early review, comprising a high, prominent forehead with frontal upsweep of hair, flat supraorbital ridges, hypertelorism or telecanthus, downward slanting palpebral fissures, a broad, flat nasal bridge with a broad, short nose, full, round cheeks, a cleft palate/lip, and a bifid uvula.[65] In our judgement, only one of these patients had a similar pattern of dysmorphism to the patients with BWS and an 11p duplication.[64]

This report is the fifth to describe a chromosome translocation between the short arms of chromosomes 5 and 11 (table 4). Interestingly, translocations with similar breakpoints between chromosomes 11p and 4q and 11p and 16q have also been published (table 4). Non-random chromosome anomalies are well recognised in tumour cytogenetics and a strong correlation between a specific, "primary" chromosome rearrangement in tumour tissue and the type of malignancy has been documented.[66] In somatic cells, the evidence for non-random chromosome rearrangements is as yet less clear. However, the occurrence of translocations with similar breakpoints may be suggestive of homologous sequences at the chromosome breakpoints involved in the translocations. Alternatively, the translocations may result in the production of a fusion gene conferring an advantage in terms of cell growth and causing the BWS phenotype.

Conclusion

We report a family in which two members with a paternally derived duplication of chromosome 11p15.3→pter have BWS. We have compared the clinical features in patients with BWS and a paternally inherited duplication of 11p with those from BWS patients who have normal chromosomes.

Those with the chromosome duplication had a decreased incidence of hypoglycaemia, facial naevus flammeus, and hemihypertrophy, but an increased incidence of moderate to severe learning difficulties. There was a distinct and persistent pattern of physical differences in those with the chromosome duplication, including features of a prominent occiput, a prominent/flat forehead, a round face with full cheeks, deep set eyes with epicanthic folds, hypertelorism, a broad, flat nasal bridge, and micrognathia.

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