The phenotypic effects of chromosome rearrangement involving bands 7q21.3 and 22q13.3

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Abstract

We report a family in which the proband has a direct insertion of band 7q21.3 into chromosome 22 at 22q13.3, karyotype 46,XX,dir ins(22;7)(q13.3;q21.2q22.1). Two of her children have unbalanced chromosome rearrangements involving 7q21.3, with one girl monosomic for the region and a boy trisomic for the region. The child monosomic for band 7q21.3 has a split hand/split foot (SHSF) anomaly and her clinical features are consistent with the 7q21-q22 contiguous gene deletion syndrome. In situ hybridisation studies have shown that the proband and her son have a submicroscopic deletion of chromosome band 22q13.3. Interstitial deletions of this chromosome band have rarely been reported.

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Figure 1 The family pedigree. See text for details.

which two or more members have had cytogenetic rearrangements involving the ectrodactyly critical region are rare. We report such a family, in which one member who is monosomic for the chromosome band 7q21.3 has a left split hand anomaly. In addition, two other family members have a rarely described submicroscopic deletion of chromosome band 22q13.3.

Case reports

The pedigree of the family is shown in fig 1. The proband (II.1) was initially referred for genetic counselling after the birth of her son,

There is compelling evidence for an autosomal dominant gene for SHSF anomalies, or ectrodactyly, in the cytogenetic region 7q21-q22¹ (the ectrodactyly critical region). Families in

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Figure 2 The proband aged 22 years (A) front view and (B) side view. (All photographs reproduced with permission.)

Figure 3 (A) The proband's daughter aged 4 months. (B) The proband's daughter's left hand showing split hand anomaly.

III.3. Although aware of the risks of chromosome abnormalities in further children, she chose not to have prenatal diagnosis in any of her pregnancies and was re-referred after the birth of her daughter, III.5.

THE PROBAND

The proband was the only child of healthy, non-consanguineous, white parents who subsequently divorced. Details of her early medical history are sparse owing to emigration of the proband's mother with whom she spent most of her childhood before returning to the UK. She was born by normal vaginal delivery with a weight of 3680 g (10th–50th centile). She sat at 1 year and walked at 15 months of age. Paediatric assessment at 2 years reported that she had only four clear words and her play was recorded to be at the 14 month level. She required special school education and her learning problems were attributed to an episode of *Haemophilus influenzae* meningitis at the age of 6 weeks.

At the age of 18 she was reassessed medically when a mitral valve prolapse (haemodynamically insignificant) was discovered. A number of dysmorphic features were noted and chromosome analysis showed an abnormal karyo-

type (see below). The karyotypes of both parents were normal and there was no other significant family history.

On examination at the age of 26 years (fig 2), her height was 168 cm (75th–90th centile) and her head circumference 59.5 cm (>97th centile). Her intellectual ability was not formally assessed but was clearly limited. She could read and write and lived independently with support but has not been able to care for any of her children long term. She had a wide, broad forehead. Her nose had a bulbous tip with a prominent columella. There was retro-micrognathia and jaw malocclusion with over-biting of the top jaw. The palate was high and arched. Her speech was nasal and indistinct. Her hair growth was luxuriant and the hair was of a slightly unusual texture. She had long, thin fingers with soft and flat fingernails. Her toes were of relatively normal length apart from the second toes which were short bilaterally and she had a high instep.

Her first pregnancy resulted in a stillborn female child delivered at 28 weeks (III.1, fig 1). She reported that the child looked normal and there are no records of cytogenetic analysis being performed. She then had a number of first trimester miscarriages (only one is included in fig 1; the exact numbers and details were difficult to establish but none was karyotyped). Her last three pregnancies all resulted in liveborn children, two with unbalanced karyotypes (III.3 and III.5) and one daughter with a normal karyotype who has had no medical problems (III.4).

CASE III.3

The proband's son was born after an uneventful pregnancy by spontaneous vaginal delivery at 42 weeks of gestation. Birth weight was 3470 g (10th centile). A small chin and high arched palate were noted at birth. Chromosome analysis showed an abnormal karyotype (see below). He was hypotonic during the first year of life and has shown global developmental delay. He achieved independent walking at 2 years of age. On formal assessment at 3 years 8 months he had a developmental quotient of 51, functioning at an average developmental age of 23 months. A renal ultrasound scan at 22 months showed mild dilatation of the right renal pelvis but he has had no subsequent renal problems.

At the age of 3 years 8 months, his height was 105 cm (90th centile) and head circumference 57 cm (>97th centile). He had a prominent, long forehead with sparse temporal hair. The nasal bridge was wide and the nose was anteverted with a bulbous tip and a prominent columella. The philtrum was short and he had a prominent Cupid's bow. He had a high arched palate and micrognathia. His ears were simple and low set. There was cutaneous syndactyly of both second and third toes. He had mild pectus excavatum. Cardiovascular examination including echocardiography was normal. Neither of his testes was fully descended. Permission was not given for publication of his pictures.

CASE III.5

The proband's daughter (fig 3A) was noted to have intrauterine growth retardation from 31

Figure 4 Partial karyotypes of the proband, her son, and daughter with ideogram of rearrangement.

weeks of gestation. She was delivered by elective caesarean section for this and maternal hypertension at 38 weeks of gestation. Birth weight was 2080 g (<3rd centile). Dysmorphic features and a split hand anomaly were noted at birth. Subsequent cytogenetic analysis was abnormal (see below). She was treated on special care for three weeks because of feeding difficulties which have gradually resolved during the first year of life. She has shown moderate developmental delay and when last reviewed (but not examined) at the age of 18 months she was crawling, pulling to stand, and saying one word.

Her measurements at the age of 10 months were weight 5580 g (well below the 3rd centile), length 66.5 cm (<3rd centile), and head circumference 39.5 cm (well below the 3rd centile). On examination there was positional plagiocephaly in addition to her microcephaly. She had prominent eyes and the nose had a wide bridge and bulbous tip. The ears were low set with overfolded helices. She had a small jaw. The digits were relatively long apart from the left hand which had a split hand deformity with absence of the second finger (fig 3B).

Cytogenetic analysis

The proband's karyotype at the age of 18 years was reported as 46,XX,22q+. Reinvestigation after the birth of her son led to reinterpretation of the karyotype as a direct insertion of band 7q21.3 into chromosome 22 at 22q13.3, karyotype 46,XX, dir ins(22;7)(q13.3;q21.2q22.1) (fig 4). The insertion was confirmed using a chromosome 7 painting probe by in situ hybridisation studies with standard techniques² (fig 5A).

Her son inherited the derived maternal chromosome 22 and the normal chromosome 7 and was therefore trisomic for band 7q21.3, karyotype 46,XY,-22,+der(22) dir ins(22;7)(q13.3;q21.2q22.1)mat (fig 4). The proband's daughter

received the derived maternal chromosome 7 and the normal chromosome 22 and was monosomic for band 7q21.3, karyotype 46,XX,-7,+der(7) dir ins(22;7)(q13.3;q21.2q22.1)mat (fig 4).

Studies on lymphoblastoid cell lines established from the proband (data not shown) and her son (fig 5B, C) showed that probe D22S75 (mapped to the DiGeorge critical region at 22q11.2³) and probe D22S169 (mapped to chromosome 22q13.3, Dr J Flint, personal communication) had two hybridisation signals. However, probe D22S39 (mapped to chromosome 22q13.3 proximal to probe D22S169⁴) was deleted on one chromosome, showing a submicroscopic deletion of chromosome 22q at 22q13.3 (fig 5B).

Discussion

SHSF anomalies have been strongly associated with chromosomal rearrangements involving a critical region at 7q21.3-q22.1,^{1 6-21} although there is evidence for locus heterogeneity.⁵ Families in which two or more members have had cytogenetic rearrangements of the SHSF critical region have rarely been described. A four generation pedigree with a balanced translocation involving 7q22.1 and SHSF in two family members has been documented.¹⁶ A two generation family with ectrodactyly, ectodermal dysplasia, and clefting (EEC syndrome) and a paracentric inversion with a breakpoint at 7q22.1 has also been reported.¹⁷ Finally, a family with EEC syndrome has been published with a more proximal breakpoint at 7q11.21.^{22 23}

The location at 7q21-q22 of a contiguous gene deletion syndrome comprising ectrodactyly, growth retardation, developmental delay, hypertelorism, ear malformations, components of the Robin sequence, and genitourinary abnormalities has been proposed.¹² Our patient, monosomic for band 7q21.3, has similar clinical findings with SHSF, growth retardation

Figure 5 (A) FISH study of the proband's lymphocytes using chromosome 7 paint showing insertion of chromosome 7 material into chromosome 22. (B) FISH study of lymphoblastoid cells from the proband's son showing normal hybridisation signals for the probe D22S75 (mapped to 22q11.2), but absent signals for the probe D22S39 (mapped to 22q13.3 proximal to the probe D22S169) on the derived chromosome 22. (C) FISH study of lymphoblastoid cells from the proband's son using probe D22S169 (mapped to 22q13.3). Normal hybridisation signals can be seen on both the normal and the derived chromosome 22.

tion, microcephaly, developmental delay, ear malformations, and micrognathia.

The absence of SHSF in the proband could be explained by the cytogenetic breakpoints on band 7q21.3 lying proximal or distal to a gene for SHSF that has been shifted intact to chromosome 22. However, reduced penetrance of

the ectrodactyly gene^{16 17} and genomic imprinting¹⁷ could also explain the absence of ectrodactyly in the proband.

In previously described patients, the SHSF anomalies have involved either the lower limbs or the right hand or both.^{16 18 21} Interestingly, the proband's daughter has an SHSF anomaly affecting only the left hand. A cytogenetic deletion removing an entire critical gene might be expected to result in a larger or more symmetrical defect. However, SHSF anomalies are well known to be very variable, even within a family, and local factors acting at the time of limb pattern formation are thought to be important in the heterogeneous expression of SHSF.^{16 17}

The proband and her son have a small submicroscopic deletion of chromosome 22 at 22q13.3. The majority of reported cases of distal 22q deletions involving 22q13 have been de novo terminal deletions.²⁴⁻³⁰ A common phenotype found in seven patients comprised generalised developmental delay with severe delay in expressive speech, normal or accelerated growth, hypotonia, and dysmorphic features including macrocephaly, dolichocephaly, dysplastic ears, epicanthic folds, and ptosis.³⁰ An interstitial deletion of 22q13.1→22q13.33 was described in an 18 month old girl with global delay, hypotonia, full cheeks, epicanthic folds, a wide nasal bridge, long philtrum, and thick lower lip.³¹ A 6 month old boy with a submicroscopic deletion of 22q13.3 detected by in situ hybridisation had premature closure of the metopic suture, midfacial hypoplasia, low set and posteriorly rotated ears, a prominent nose, a small mouth with a high arched palate, micrognathia, and digital anomalies including syndactyly between the third and fourth left fingers.³² Neonatal hypotonia, tricuspid insufficiency, severe anaemia, and cranial malformations with agenesis of the corpus callosum, unusual Sylvian fissures, and probable polymicrogyria were also noted.³²

A 12 year old boy with mild mental retardation, delayed expressive speech, bilateral accessory nipples, and normal facies was found to have a de novo deletion of 22q13.3 with microsatellite markers.³³ Further molecular studies showed a microdeletion of the terminal 130 kb of 22q and healing of the broken telomere end by the addition of telomere repeats.³⁴ A 22 year old girl with severe mental retardation (IQ<20) and facial dysmorphism (micrognathia, a prominent nose, a gap between the upper two incisors, simple ears, long and thin fingers, bilateral 2/3 syndactyly of the toes, right talipes equinovarus, pes cavus, and left calcaneovarus deformity) was also reported with a de novo subtelomeric deletion of 22q.³³

The clinical findings in the proband's son (generalised developmental delay with severe delay in expressive speech, normal growth with macrocephaly, hypotonia, dolichocephaly, low set ears, and micrognathia) are similar to the patients described above although the findings are non-specific and it is difficult to assess the contribution from the chromosome 7 band. The proband shares the same deletion as her son and yet her physical findings are very

different with a much milder degree of developmental delay. The difference in phenotype is likely to result from the extra chromosomal material at 7q21.3 in the proband's son.

Duplications of 7q21.3 have been infrequently reported and previously described patients have generally had larger duplicated segments than the son in this family.³⁵⁻³⁶ A comparison of physical findings between our patient and reported cases is therefore difficult. Our patient did not have growth retardation³⁷ or a low birth weight.³⁸ However, macrocephaly, frontal bossing, low set, dysplastic ears, microretrognathia, and genital anomalies have previously been described in patients with duplications of 7q21→qter.³⁶⁻³⁷

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