

Case report: Y;6 translocation with deletion of 6p

Ophir D. Klein^a, Kendall Backstrand^a, Philip D. Cotter^{a,b,c}, Elysa Marco^d, Elliott Sherr^d and Anne Slavotinek^a

Translocations between the Y chromosome and an autosome are rare. We report a phenotypic male with a translocation between the Y chromosome and chromosome 6p, leading to partial 6p monosomy and XX male syndrome. He is the second child to be reported with this karyotype. Phenotypic findings included growth retardation, severe developmental delay, a Dandy-Walker malformation, cardiac and urogenital abnormalities, bilateral hearing loss, cleft palate, severe kyphoscoliosis, minor digital anomalies, and a hypoplastic phallus. Craniofacial dysmorphism consisted of dolichocephaly, hypertelorism, down-slanting palpebral fissures, depressed nasal bridge and a tented upper lip. Cytogenetic analysis showed the karyotype 46,XX,der(6)t(Y;6)(p11.2;p23).ish der(6)(SRY+,6pTEL48-). The effects of partial monosomy 6p are discussed and compared to other

patients with interstitial and terminal 6p deletions. *Clin Dysmorphol* 14:93-96 © 2005 Lippincott Williams & Wilkins.

Clinical Dysmorphology 2005, 14:93-96

Keywords: Y;6 translocation, 6p deletion, XX male

^aDivision of Medical Genetics, Department of Pediatrics, University of California San Francisco, San Francisco, CA, ^bDivision of Medical Genetics, Children's Hospital and Research Center, Oakland, CA, ^cUS Labs, Inc., Irvine, CA and ^dDivision of Child Neurology, Department of Pediatrics, University of California San Francisco, San Francisco, CA.

Correspondence and requests for reprints to Anne Slavotinek, Department of Pediatrics, University of California, San Francisco, Room U585P, 533 Parnassus St., San Francisco, CA 94143-0748.

Tel: +1 415 514 1783; fax: +1 415 476 9976; e-mail: slavotia@peds.ucsf.edu

Received 19 August 2004 Accepted 24 December 2004

Introduction

The XX male syndrome is usually associated with a translocation of the sex-determining region Y (*SRY*) gene onto the X chromosome, and Y;autosome translocations are rare (Zenteno-Ruiz *et al.*, 2001). *SRY* encodes a sequence-specific DNA binding protein that leads the bipotential gonad to form testes, and thus the presence of *SRY* on an autosome directs testis formation in an XX individual lacking other Y-chromosome regions (Vilain and McCabe, 1998). Subsequent hormonal secretions from the testes lead to development of the male phenotype. XX males often have a Klinefelter phenotype because of the presence of two X chromosomes (Zenteno-Ruiz *et al.*, 2001). To date, there has been only one previous report of a Y;6 translocation with a partial 6p monosomy (Kelly *et al.*, 1989). This patient's phenotype was remarkably similar to the one reported here.

Deletions of the short arm of chromosome 6 have primarily been reported in the distal-most regions, from 6p22 to the telomere. With the exception of ring chromosome 6 anomalies, there are fewer than 50 cases of 6p deletions reported. Two 6p deletion syndromes consisting of varying combinations of malformations have been proposed (Davies *et al.*, 1999; Mirza *et al.*, 2004). The first of these is caused by interstitial deletions of 6p and includes orofacial clefts, short neck, clinodactyly or syndactyly, and central nervous system, cardiac, and kidney malformations. Terminal deletions of 6p, in contrast, have been associated with ocular anomalies, hypertelorism, and deafness.

In this communication, we report a patient with partial monosomy for the short arm of chromosome 6 and XX male syndrome due to the presence of the *SRY* gene. His phenotype consists of features from both the interstitial and terminal 6p deletion syndromes, including growth and developmental delay, craniofacial dysmorphism, bilateral hearing loss, cleft palate, and cardiac, skeletal, central nervous system and urogenital abnormalities. He also had a mildly hypoplastic phallus, presumably due to the XX male syndrome.

Case report

Clinical description

The proband was the second child born to healthy, non-consanguineous parents. The mother was a 27-year-old G3P1 and had one spontaneous abortion prior to this pregnancy. The father was 38 years old. The family history was unremarkable. A prenatal ultrasound showed a Dandy-Walker cyst and unilateral right hydronephrosis. No information regarding the patient's genitalia was recorded. A female karyotype, 46,XX, was noted on amniocentesis. A male infant was born by spontaneous vaginal delivery at 35 weeks of gestation. Birth weight was 2.3 kg (5th percentile), length was 45.7 cm (5th percentile), and head circumference was 33.5 cm (25th percentile). His Apgar scores were 4, 6 and 7 after 1, 5 and 10 minutes, respectively, and he required temporary intubation for respiratory distress. The neonatal examination showed hypertelorism, low-set ears, micrognathia, and feet that were described as inverted. He had a grade III/VI systolic ejection murmur and his neurological

examination noted diffuse hypotonia and diminished deep tendon reflexes. He had normal male genitalia.

His initial evaluation included a brain MRI that confirmed the Dandy–Walker abnormality with a posterior fossa cyst and showed partial agenesis of the corpus callosum, ventriculomegaly, and cerebellar vermis hypoplasia. An echocardiogram revealed a small atrial septal defect and branch pulmonary stenosis, both considered to be hemodynamically insignificant. A renal ultrasound scan confirmed right-sided hydronephrosis and a pelvic ultrasound scan found no evidence of female reproductive organs. The infant also had an abnormal newborn hearing screen, and he has since been diagnosed with severe bilateral sensorineural hearing loss.

A repeat karyotype was performed on peripheral blood lymphocytes, and was also reported as 46,XX. Fluorescence *in situ* hybridization (FISH) studies were positive for the *SRY* gene, although the location of this gene was not identified.

The patient was seen at our hospital at 6 years of age for a spinal fusion to correct a severe kyphoscoliosis. History revealed that his developmental progress had been markedly delayed. He rolled over at 15 months, sat without support at 22 months and walked without assistance at 4 years and 6 months. He began babbling at 15 months and spoke his first word at 5 years of age. By 6 years and 10 months of age, he spoke few words but was able to run and jump. The patient's surgical history was significant for placement and revisions of a gastrostomy tube, a cystoperitoneal shunt and a ventriculoperitoneal shunt for hydrocephalus.

His growth parameters fell below the 3rd percentile within the first few months of life and at age 6 years and 10 months, his weight was 15 kg (< 3rd percentile; 50th percentile for 3.5 years), length was 96 cm (< 3rd percentile; 50th percentile for 3.2 years) and head circumference was 46.5 cm (< 3rd percentile; 50th percentile for 13 months). On examination at 6 years and 10 months of age, he had striking craniofacial dysmorphism including dolichocephaly with a high forehead, hypertelorism, down-slanting palpebral fissures, a depressed nasal bridge and a tented upper lip with downturned corners of the mouth (Figure 1). Other physical findings included a high arched palate with a small posterior cleft, inverted and hypoplastic nipples, a minor pectus excavatum, slightly broad and hypoplastic thumbs, camptodactyly and clinodactyly of the fifth fingers, and a hypoplastic phallus. On neurological examination, he was alert, interactive and followed simple commands. There was no evidence of cataracts, retinal dysplasia or optic nerve abnormalities. He had sensorineural hearing loss bilaterally and facial diplegia. Motor exam showed full upper extremity strength with normal tone. Since the spinal fusion, he has developed decreased bulk in both calves as well as spastic

Fig. 1



(A) The proband's facial features at age 4 years. (B) The proband's facial features at age 6 years. Please see text for clinical details.

diplegia. Radiographs of the spine showed thoracic kyphosis and thoracolumbar scoliosis. Posterior scalloping and increased craniocaudal dimension of the vertebral bodies was noted, which was attributed to non-weight bearing status.

Cytogenetic and fluorescence *in situ* hybridization analyses

Cytogenetic analysis of peripheral blood lymphocytes using GTG-banding was performed using standard protocols. A female karyotype containing a terminal deletion of the distal short arm of one chromosome 6 was observed (Figure 2).

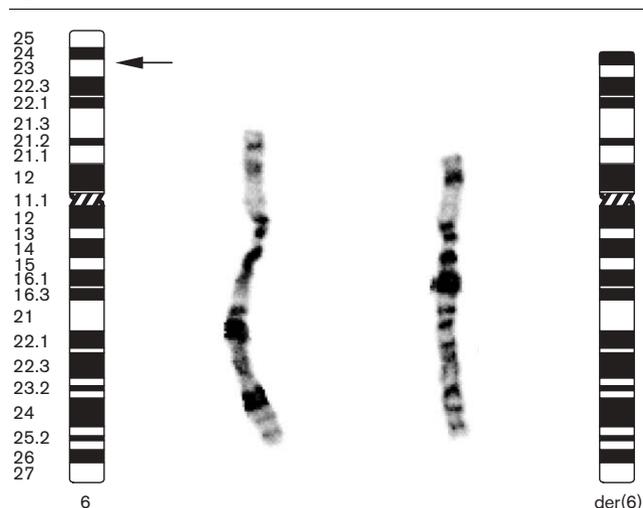
Dual color FISH analysis was performed with SpectrumGreen-labeled 6pter (6pTEL48) and SpectrumOrange-labeled 6qter (RM2158) probes (Vysis, Downer's Grove, IL) kit, according to the manufacturer's instructions. The 6qter probe was present on both the normal and der(6) chromosomes, and the 6pter probe was deleted from the der(6) chromosome (Figure 3A). Additional FISH analysis with SpectrumGreen-labeled DXZ1 and SpectrumOrange-labeled *SRY* (Yp11.3) probes (Vysis) was performed according to the manufacturer's instructions, and showed a positive signal for the *SRY* locus on the distal short arm of the der(6) chromosome (Figure 3B).

Based on the GTG-banding and FISH analyses the proband's karyotype was interpreted as 46,XX,der(6)-t(Y;6)(p11.2;p23).ish der(6)(*SRY* + ,6pTEL48-). The paternal karyotype was 46,XY with the *SRY* locus present at Yp11.3 (data not shown).

Discussion

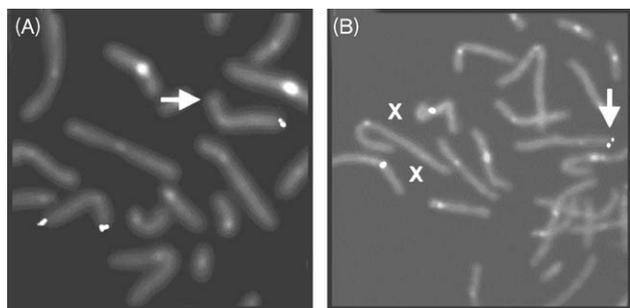
We report a 6 year old phenotypic male with a Y;6 translocation who has monosomy for the short arm of chromosome 6 from 6p23 → 6pter and a 46,XX karyotype. The paternal karyotype was normal, and thus it is likely that the unbalanced translocation in the proband

Fig. 2



Partial ideogram and karyotype showing the normal and derivative chromosomes 6 from the proband. The 6p breakpoint is indicated with an arrow.

Fig. 3



(A) FISH analysis with 6p and 6q subtelomeric probes, showing loss of signal for the 6p subtelomeric probe on the der(6) chromosome (arrowed). (B) FISH analysis with DXZ1 and SRY probes showing signal for SRY on the der(6) chromosome (arrowed).

occurred *de novo* during gametogenesis in the father. To date, there has been only one previous report of a Y;6 translocation associated with a partial 6p deletion (Kelly *et al.*, 1989). That patient, who had a similar 6p breakpoint at 6p23, had microcephaly, Dandy–Walker cyst, hypertelorism and downslanting palpebral fissures, corneal eye opacification consistent with Rieger eye anomaly, profound hearing loss, atrial septal defect, and equinovarus. These features, with the exception of the ocular anomaly, were all seen in our patient, who had additional skeletal anomalies.

Deletions of the short arm of chromosome 6 have most commonly been reported in the distal chromosome

regions, from 6p22 to the telomere. Two distinct 6p deletion syndromes consisting of varying combinations of malformations have been proposed (Davies *et al.*, 1999; Mirza *et al.*, 2004). Interstitial deletions within 6p22→p24 were correlated with short neck, clinodactyly or syndactyly, and brain, heart, palate and kidney defects. More distal deletions in 6p25 were correlated with ocular anomalies, hypertelorism and deafness. Our patient's deletion included both part of the 6p22→p24 region and the telomeric 6p25 region, and thus he had features from both of these syndromes.

A recent report suggests the presence of loci for Dandy–Walker malformation in the 6p22→p24 region and for hearing development in the 6p24→p25 region, although no candidate genes have been identified (Mirza *et al.*, 2004). The deletion present in our patient is consistent with these proposals. Haploinsufficiency for several genes on distal 6p could account for the developmental delay, including neuritin, a gene of unknown function expressed in the nervous system, at 6p25.1, and either of the two spinocerebellar ataxia loci at 6p23, *SCA1* and *SCABD*. The severe spinal abnormalities are not typical of distal 6p deletions, but a patient with translocation 6;10 leading to deletion of 6p25 had severe Larsen-like syndrome (James *et al.*, 2003). This patient had severe kyphoscoliosis. Orofacial clefting, as seen in our patient, is also common in 6p deletion syndrome. Ten out of 16 reports of 6p deletions examined by one author had orofacial clefting (Topping *et al.*, 2002), and a locus for orofacial clefting, *OFC1*, has been described at 6p24.3 (Schultz *et al.*, 2004). Interestingly, many patients with 6p terminal deletions have eye anomalies, presumably due to haploinsufficiency for the forkhead transcription factor *FOXC1* (Mirza *et al.*, 2004; Mirzayans *et al.*, 2000; Zhang *et al.*, 2004). The absence of eye defects in our case is further indication that eye development can occur relatively normally in the absence of one copy of *FOXC1* (Davies *et al.*, 1999). *FOXC1* haploinsufficiency may also contribute to the cardiac defects in 6p deletion patients (Mirza *et al.*, 2004), as this gene is involved in cardiac development (Winnier *et al.*, 1999). Patients such as ours with distal 6p deletions are hemizygous for *BMP6* and endothelin-1. The absence of these genes has not been correlated with human developmental defects, but as they are important in murine embryonic development (Gajavelli *et al.*, 2004; Kim *et al.*, 2001; Naeve GS *et al.*, 1997), their absence may contribute to some of the features in our patient.

The phenotypic similarity to the previously reported case of Y;6 translocation (Kelly *et al.*, 1989) – in particular, the microcephaly, severe growth retardation, Dandy–Walker cyst, atrial septal defect, hearing loss, hypertelorism and downslanting palpebral fissures – parallels the similar deletions of 6p23→pter. The first case had some different features from ours, however, including prenatal growth retardation with all growth parameters below the

3rd percentile at 38 weeks of age, an atretic ear canal and cerebral atrophy. Additionally, the hypogonadism in the earlier case manifested as cryptorchidism, but a normal penis was reportedly present at 3 months. The differences between the two cases may be due to small differences in the size or location of the deletions or to the effects of modifier genes. These patients represent a distinctive combination of XX male with interstitial and terminal 6p deletions. The occurrence of such similar translocations in these two patients may be coincidental, or it may represent the presence of homologous recombination sites near the translocation breakpoints.

In summary, we report a patient with deletion of 6p23→pter and XX male syndrome due to the presence of the *SRY* gene. Y;autosome translocations associated with the XX male syndrome, such as this one, are extremely rare (Nataf *et al.*, 2002; Zenteno-Ruiz *et al.*, 2001). The XX male syndrome is often characterized by normal male genitalia at birth and later development of hypoplastic external male genitalia (Zenteno-Ruiz *et al.*, 2001), as was observed in our patient. The features in this case – developmental delay, structural defects in the palate, brain, skeleton, heart and kidneys, hypertelorism, and deafness – encompass those reported in cases with interstitial and terminal 6p deletions, and the patient has additional features including severe scoliosis. This case provides further evidence for the existence of 6p deletion syndromes, and perhaps for a ‘6p deletion/XX male syndrome’. Future genetic studies of human deletion cases and of mouse models with syntenic deletions will help to clarify the functions of genes in the 6p chromosomal region.

References

- Davies AF, Mirza G, Sekhon G, Turnpenny P, Leroy F, Speleman F, *et al.* (1999). Delineation of two distinct 6p deletion syndromes. *Hum Genet* **104**:64–72.
- Gajavelli S, Wood PM, Pennica D, Whittmore SR, Tsoulfas P (2004). BMP signaling initiates a neural crest differentiation program in embryonic rat CNS stem cells. *Exp Neurol* **188**:205–223.
- James PA, Aftimos S, Oei P (2003). Severe musculoskeletal phenotype associated with an unbalanced t(6;10) translocation: clarification of the locus for this phenotype on distal 6p. *Am J Med Genet* **119A**:288–292.
- Kelly PC, Blake WW, Davis JR (1989). Tandem Y/6 translocation with partial deletion 6 (p23→pter). *Clin Genet* **36**:204–207.
- Kim RY, Robertson EJ, Solloway MJ (2001). Bmp6 and Bmp7 are required for cushion formation and septation in the developing mouse heart. *Dev Biol* **235**:449–466.
- Mirza G, Williams RR, Mohammed S, Clark R, Newbury-Ecob R, Baldinger S, *et al.* (2004). Refined genotype-phenotype correlations in cases of chromosome 6p deletion syndromes. *Eur J Hum Genet* **12**:718–28.
- Mirzayans F, Gould DB, Heon E, Billingsley GD, Cheung JC, Mears AJ, *et al.* (2000). Axenfeld-Rieger syndrome resulting from mutation of the FKHL7 gene on chromosome 6p25. *Eur J Hum Genet* **8**:71–74.
- Naeve GS, Ramakrishnan M, Kramer R, Hevroni D, Citri Y, Theill LE (1997). Neurtin: a gene induced by neural activity and neurotrophins that promotes neuritogenesis. *Proc Natl Acad Sci U S A* **94**:2648–2653.
- Nataf V, Senat MV, Albert M, Bidat L, de Mazancourt P, Roume J, *et al.* (2002). Prenatal diagnosis of a 45,X male with a SRY-bearing chromosome 21. *Prenat Diagn* **22**:675–680.
- Schultz RE, Cooper ME, Daack-Hirsch S, Shi M, Nepomucena B, Graf KA, *et al.* (2004). Targeted scan of fifteen regions for nonsyndromic cleft lip and palate in Filipino families. *Am J Med Genet* **125A**:17–22.
- Topping A, Harris P, Moss AL (2002). The 6p deletion syndrome: a new orofacial clefting syndrome and its implications for antenatal screening. *Br J Plast Surg* **55**:68–72.
- Vilain E, McCabe ER (1998). Mammalian sex determination: from gonads to brain. *Mol Genet Metab* **65**:74–84.
- Winnier GE, Kume T, Deng K, Rogers R, Bundy J, Raines C, *et al.* (1999). Roles for the winged helix transcription factors MF1 and MFH1 in cardiovascular development revealed by nonallelic noncomplementation of null alleles. *Dev Biol* **213**:418–431.
- Zenteno-Ruiz JC, Kofman-Alfaro S, Mendez JP (2001). 46,XX sex reversal. *Arch Med Res* **32**:559–566.
- Zhang HZ, Li P, Wang D, Huff S, Nimmakayalu M, Qumsiyeh M, *et al.* (2004). FOXC1 gene deletion is associated with eye anomalies in ring chromosome 6. *Am J Med Genet* **124A**: 280–287.