Two 46,XX,t(X;Y) females with linear skin defects and congenital microphthalmia: a new syndrome at Xp22.3

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Abstract

We describe two females with *de novo* X;Y translocations, who presented at birth with irregular linear areas of erythematous skin hypoplasia involving the head and neck, along with eye findings that included microphthalmia, corneal opacities, and orbital cysts. The features in these children are similar to but distinct from those seen in females with Goltz syndrome and incontinentia pigmenti. Cytogenetic analysis has shown the X chromosome breakpoint in both females to be at Xp22.3. We suggest that this syndrome is the result of a deletion or disruption of DNA sequences in the region of Xp22.3.

Case reports

CASE 1

This female, the second child of healthy, unrelated parents, the father aged 23 and the mother aged 26, was born after an uneventful pregnancy at 41 weeks by normal delivery, birth weight 2640 g.

At birth she was noted to have hypoplastic, irregular, linear skin defects with a 'scalded' appearance involving her face and upper neck, marked bilateral

microphthalmia, and a corneal opacity of the left eye (fig 1). Minor cutaneous syndactyly was present on the second/third toe of the right foot.

Examination under anaesthesia at 4 months of age showed a perforation of the right cornea with a prolapsed iris. The corneal opacity in the left eye was at the level of the posterior stroma. In addition, there were peripheral synechiae and collarette adhesions, retinoscopy showed 10 dioptres of myopia, and examination of the fundus showed a myopic disc. The lens was clear and intraocular pressures were normal.

At 8 months of age her height and weight were below the 3rd centile and her early developmental milestones were within normal limits allowing for the degree of visual handicap. In addition, her skin lesions were much less obvious.

Cranial CT scan was normal apart from some enlargement of the third ventricle. Steroid sulphatase activity was present at a normal female level.

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Figure 1 Clinical appearance of case 1.

Cytogenetics

Routine peripheral blood chromosome analysis showed additional material on the short arm of one X chromosome. The extra material was identified by G, C, and Q banding as being from the long arm of the Y chromosome. The breakpoints appeared to be at Xp22.3 and Yq11.2 (fig 2).

Studies after BrdU labelling in late S phase showed that the X;Y translocation chromosome was late replicating in all 50 cells examined. Both parents had normal karyotypes.

CASE 2

This child was born by forceps delivery, weighing 3900 g, after 42 weeks' gestation. She was the first child of healthy, unrelated parents, the father aged 29 and the mother 28. The mother complained of two brief episodes of abdominal pain at six and 20 weeks of pregnancy.

At birth the baby was noted to have bilateral microphthalmia with a left orbital cyst, linear skin defects in a reticular pattern on the face, neck, shoulders, and upper chest (fig 3), an anteriorly displaced anus, and a midline sacral dimple surrounded by a flat erythematous area about 1 cm in diameter, resembling a capillary naevus.

At the age of 3 days the left eye and its cyst were

Figure 3 Clinical appearance of case 2.

removed. The baby fed well and thrived. At 3 months she was found to perceive light and to have visual evoked cortical and electroretinographical responses to a flash stimulus. The skin defects had healed leaving linear atrophic scars.

At the age of 7 months she developed meningitis which settled with antibiotics but recurred twice over the next month. Myelography was normal, but surgical exploration showed a dermoid cyst of the spinal theca, which communicated with the sacral skin dimple and which was removed.

At the age of 2 years 10 months her height and weight were well below the 3rd centile and her vision, which had previously been good enough for navigation, had deteriorated to colour perception. She had difficulty in walking long distances and there was a lack of sphincter control in bowel and bladder. Developmental milestones were otherwise normal.

Eye pathology

The enucleated eye showed highly disorganised anterior chamber structures, including sclerocornea with a thickened epithelium above dense collagen with a disorganised, whorled, unlamellated appearance, a focal attempt at Descemet's formation, and adherent vascular iris or ciliary body stroma bordered by a disorganised double layer of pigment epithelium; in some areas a small cyst was formed. Mast cells were plentiful in this abortive iris tissue and there was an admixture of active chronic inflammatory cells. No

Figure 2 Case 1: normal X and t(X;Y) showing G banding (top), and t(X;Y) showing C banding (bottom).

Figure 4 Case 2: normal X and t(X;Y) showing G banding (left), and t(X;Y) showing C banding (right).

migration of neural crest melanocytes had occurred. No development of lens or posterior segment structures was seen.

Cytogenetics

Routine peripheral blood chromosome analysis showed additional material on the short arm of one X chromosome. The extra material was identified by G and C banding as being from the long arm of the Y chromosome (fig 4). The breakpoints appeared to be at Xp22.3 and Yq11.2. No studies of X chromosome replication were done. Both parents had normal karyotypes.

Discussion

Bernstein,¹ in a recent review of X;Y translocations, quoted data on 13 46,Y,t(X;Y) males, 19 46,X,t(X;Y) females, and four 46,X,t(X;Y) males. Of the 19 46,X,t(X;Y) females, 14 were ascertained as relatives of 46,Y,t(X;Y) males. Short stature, with or without disproportionate limb shortening, was their only consistent abnormality. Among their 46,Y,t(X;Y) male relatives, additional findings were variable mental retardation, ichthyosis, hypogonadism, and dysmorphic facies. The breakpoints in these families were at Xp22 (localised in some to Xp22.3) and Yq11. The t(X;Y) did not contain male determining factors, and clinical features were assumed to result mainly from hemizygosity in the females and nullisomy in the males for the region Xp22→pter. Of the five sporadic 46,X,t(X;Y) females reviewed, three were essentially similar to the familial cases with an Xp22 breakpoint, and two, with a more proximal Xp breakpoint, had streak gonads.

The syndrome described here has not previously been reported in t(X;Y) females, suggesting that a specific Xp breakpoint is required for its expression. Molecular mapping of the breakpoints in our cases and in cytogenetically similar cases without the syndrome will test this hypothesis.

Johnston *et al*² have reported a sporadic 46,X,t(X;Y) female with imperforate anus, rectovaginal fistula, retinal pigmentation, hydronephrosis, and a pre-auricular pit, as well as the expected short stature and short limbs. This combination of abnormalities could be consistent with the syndrome described here in milder form. Two further cases of what is almost certainly the same syndrome are known to us. The first is a 46,XX male reported by Hultén and colleagues as part of the abstract by Al-Gazali *et al*³ (this also includes the two cases described in detail in this paper). The case of Hultén, to be reported in detail elsewhere, was shown by in situ hybridisation to have Y material translocated to the short arm of one X (M Hultén, 1989, personal communication). The clinical features included congenital skin defects of the face and neck, bilateral microphthalmia with corneal opacities, hypospadias, and short stature. The second case⁴ is a female with a de novo deletion of Xp22.2→pter and very similar clinical features. These cases confirm our suggestion that the syndrome is caused by the loss or alteration of a specific region of Xp.

It is interesting to compare these phenotypes with those described by Curry *et al*⁵ in two families, where small deletions of the Xp22.3 region were associated with chondrodysplasia punctata, steroid sulphatase deficiency, short stature, mental retardation, and a lack of Xg blood group expression in affected males. Females heterozygous for the deletion showed only short stature. Similar features were reported by Ballabio *et al*⁶ in two male cousins who had inherited an X;Y translocation.

Investigations of steroid sulphatase and Xg blood groups are still incomplete in our families, but case 1 had levels of steroid sulphatase consistent with the presence of two doses of the gene. Radiologically, neither of our patients showed signs of chondrodysplasia punctata. This suggests that the critical sequences for the present syndrome are distal to the steroid sulphatase locus, in which case it is difficult to explain why the patients referred to in the last paragraph did not show the syndrome.

Deletion or disruption of coding sequences on Xp is the most obvious explanation for our findings, but it raises two further questions: (1) why has the same syndrome not been described as an X linked gene mutation, and (2) is expression of the condition related to X inactivation?

Among known X linked mutations, the diagnoses of incontinentia pigmenti and Goltz syndrome were considered in our cases but were rejected on clinical

Phenotypic features of the two cases reported and the case of Hultén³ compared with the features of Goltz syndrome and incontinentia pigmenti.

	Goltz syndrome	IP	Present cases
<i>General</i>			
Growth retardation	+	+	3/3
Developmental delay	+	+	?
<i>Skin and appendages</i>			
Hypoplasia and scarring	+	+	3/3
Blistering	+/-	+	-
Pigmentary abnormalities	+	+	-
Fat herniation	+	-	-
Papilloma	+	-	-
Capillary naevus	-	-	2/3
Hypodontia/microdontia	+	+	-
Hair changes	+	+	-
Nail changes	+	+	-
<i>Ocular</i>			
Strabismus	+	+	-
Anophthalmia	+	-	-
Microphthalmia	+	+	3/3
Coloboma of iris/choroid/retina	+	+	-
Retinal detachment	-	+	-
Corneal clouding/opacity	+/-	-	2/3
<i>Skeletal</i>			
Syndactyly	+	+	(1)/3
Hypo/aplasia of fingers and toes	+	-	-
Vertebral	+	+	?
Clavicle and ribs	+	+	?
Osteopathia striata	+	-	?

grounds. The clinical features of these two syndromes and of our patients, plus the patient of Hultén,³ are compared in the table. Goltz syndrome⁷ is thought to be caused by an X linked mutation lethal in males, but the position of the gene on the X chromosome is unknown. Incontinentia pigmenti was thought, on the basis of affected females with X;autosome translocations, to be caused by a mutation at Xp11,^{8,9} but family linkage studies have failed to confirm this.¹⁰ The oculocerebrocutaneous syndrome¹¹ was also considered but our patients did not show the central nervous system defects and periorbital appendages found in that condition.

Preferential inactivation of the normal X, which allows expression of recessive gene disruptions in X;autosome translocations, does not seem to be the rule in X;Y translocations. The limited observations reviewed by Bernstein¹ suggest that the t(X;Y) chromosome is more likely than the normal X to be inactivated, as it was in our case 1. Most of the observations were made on lymphocytes, however, which may be misleading in relation to the tissues mainly affected. The patchy, streaky nature of the clinical features could directly reflect X inactivation patterns. In that case, variable expression of the syndrome would be related to variations in X inactivation pattern. On the other hand, a breakpoint

location distal to steroid sulphatase, as suggested above, would imply that X inactivation was irrelevant to expression, as this part of Xp is thought to escape inactivation.¹²

Whether or not X inactivation is involved, it is necessary to explain why a site specific break should be expressed with clinical features that are not seen with larger Xp deletions. This could occur if our cases were producing a gene product with an inhibitory effect rather than inactivity.

The syndrome's predilection for the head and neck suggests involvement of neural crest derived tissues and might have interesting implications for developmental biology when its molecular basis is known. The fact that the syndrome has not been reported with X;autosome translocations or as an X linked gene defect in males suggests that, like Goltz syndrome and incontinentia pigmenti, it may be lethal in hemizygotes (although, as noted above, males lacking that part of the X expected to include this syndrome have survived).

Fertility of t(X;Y) females has repeatedly been observed. Half of their sons are expected to inherit the translocated X and to be nullisomic for X linked loci distal to the Xp breakpoint. This has resulted in steroid sulphatase deficiency, hypogonadism, short stature, minor dysmorphic features, and, in some cases, mental retardation.¹ Affected sons of our t(X;Y) females are expected to show the syndrome described here unless, as suggested above, it is lethal in males, in which case there will be a deficiency of males among their children.

Molecular analysis should allow the relative positions of the genes on Xp22→pter to be determined and the relevant coding sequences for this new syndrome to be identified.

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