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BRIEF REPORT — CASE REPORT

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Another observation of microphthalmia in an XX male: microphthalmia with linear skin defects syndrome without linear skin lesions

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Abstract A case of microphthalmia with Xp microdeletion is reported. The patient was a boy who showed bilateral microphthalmia with corneal opacities, hypospadias without evidence of hypogonadism, and a conduction disturbance of the heart (Wenckebach conduction). No skin lesion was discerned. High-resolution chromosome analysis revealed the karyotype of 46,X,del(X)(p22). The phenotype was considered to be microphthalmia with linear skin defects (MLS) syndrome without skin lesions. Polymerase chain reaction and fluorescence in-situ hybridization analyses revealed that the chromosome aberration resulted from an X;Y translocation: the presence of pseudoautosomal boundary Y and the sex-determining region of Y was confirmed, while Xp deletion involving the region distal to DXS1129 was ascertained. Thus the chromosome designation using the ISCN 1995 nomenclature is 46,X,der(X),t(X;Y)(p22.13;q11.2). Despite the absence of skin lesions, the Xp deletion of our patient corresponded to those of previously reported typical cases of MLS syndrome. Our observation further supports the current hypothesis that the phenotypic variation of MLS syndrome represents tissue-different X inactivation rather than different genetic effects of two contiguous genes.

Key words Microphthalmia with linear skin defects syndrome (MLS) · X inactivation · Xp microdeletion · XX male · Atrioventricular block

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Introduction

Microphthalmia with linear skin defects (MLS) syndrome (MIN 309801; McKusick et al. 1994) is a rare congenital malformation syndrome that results from microdeletions of Xp22.3. Most affected individuals are females and affected males are XX males with a karyotype of 46,X,der(X)t(X;Y) (Al-Gazali et al. 1990; Stratton et al. 1998). The clinical manifestations include microphthalmia and hypoplastic skin lesions on the head, face, and neck. Heart defects, short stature, anal anomalies, and mental retardation are occasional features. The phenotypic variations are significant and some patients possess only one of the two major anomalies. To date, 22 affected individuals have been reported (Ropers et al. 1982; Al-Gazali et al. 1988; 1990; Donnenfeld et al. 1990; Temple et al. 1990; Allanson and Richter 1991; Gericke et al. 1991; Thies et al. 1991; Lindor et al. 1992; Naritomi et al. 1992; Happle et al. 1993; Schaefer et al. 1993; 1996; Bird et al. 1994; Eng et al. 1994; Lindsay et al. 1994; Mucke et al. 1995; Stratton et al. 1998).

Cytogenetic studies of MLS syndrome have revealed a variety of sexchromosome aberrations, including del Xp22 (-pter) in 11 female patients, translocation between the X and an autosomal chromosome in five female patients, X;Y translocation in four female patients, 46,XX in two female patients, of whom one did not undergo high-resolution analysis (Happle et al. 1993) and the other with a normal karyotype who did (Bird et al. 1994), as well as two XX male patients. Recent molecular investigations of Xp microdeletions in MLS syndrome have detailed the critical region of the genetic map (Schaefer et al. 1993; 1996).

Here, we report a boy who had the karyotype of 46, X,der(X)t(X;Y) and microphthalmia, but not skin lesions. The Xp microdeletion was clarified with polymerase chain reaction (PCR) and fluorescence in-situ hybridization (FISH) techniques. The relation of the extension of the Xp microdeletion in MLS syndrome with its phenotypic variations is discussed.

Case report

A newborn infant was referred because of microphthalmia and hypospadias. The patient was the second child of healthy unrelated parents, a 31-year-old father and a 31-year old mother, and was born at full term after an unremarkable pregnancy and delivery. Birth weight was 3056 g, length 50 cm, and head circumference 33 cm. The family history was not noteworthy, other than the fact that the mother previously experienced a spontaneous abortion. The older brother of the patient was healthy. On physical examination, the gender phenotype of the patient was male with hypospadias. Both testes were found in the scrotum and measured 12 mm (right) and 6 mm (left) in maximum length. The penis measured 3 cm (−0.7 SD) in stretched length. No skin abnormalities were evident. Neurologic assessment yielded normal findings. Cardiac evaluation revealed second-degree atrioventricular block (Wenckebach conduction) without cardiac anomalies. Ophthalmologic examination showed bilateral microphthalmia and corneal opacities (Fig. 1a). No evidence of coloboma or retinal lacuna was noted. Routine hematological and biochemical tests were normal. Endocrinological examinations did not show evidence of hypogonadism. Abdominal ultrasound, magnetic resonance imaging (MRI), intravenous

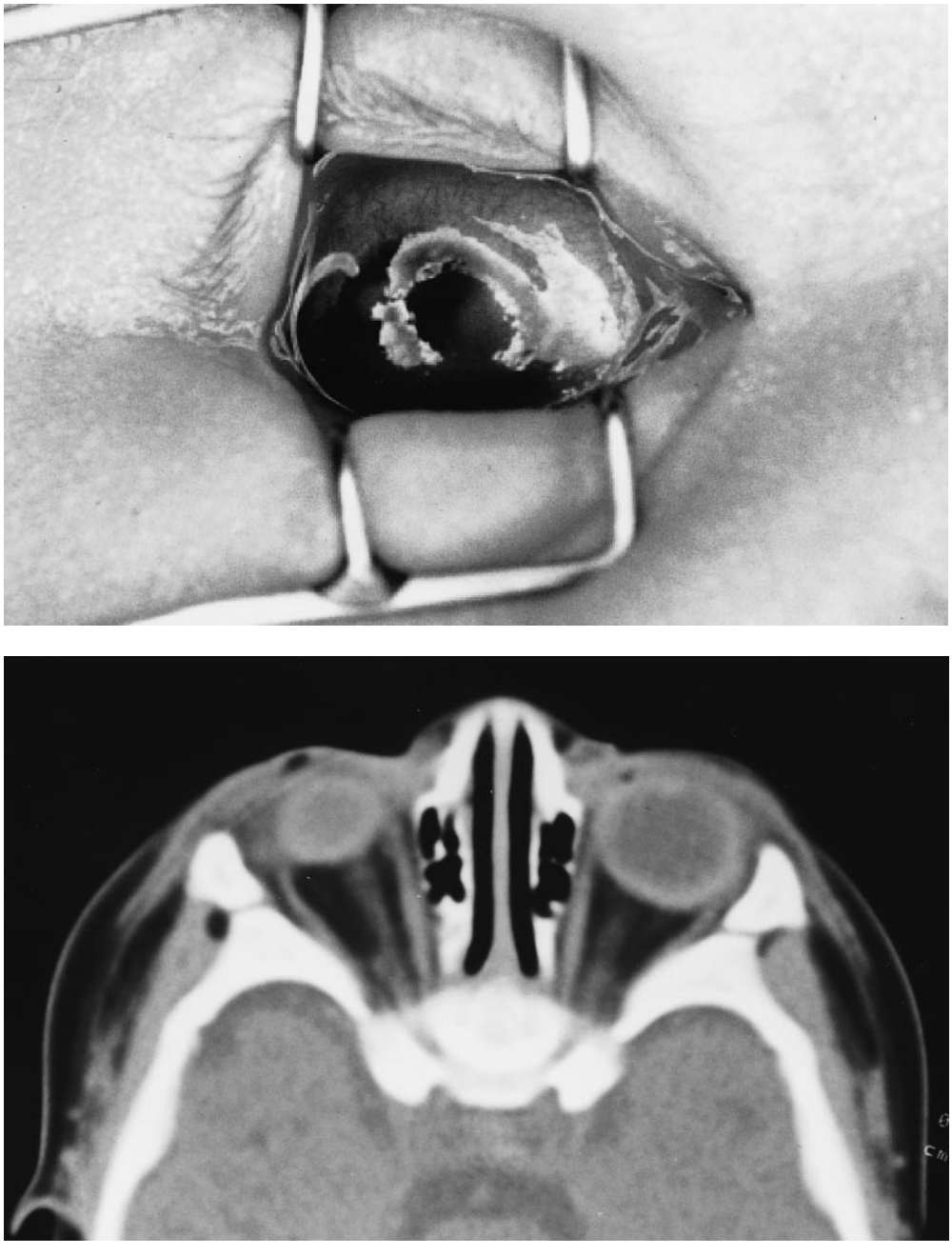

Fig. 1 **a** Microphthalmia and corneal opacity (right eye). **b** Computed tomography of the orbit

urography, and retrograde urography demonstrated a normal male genitourinary system. Computed tomography (CT) of the brain and a skeletal survey showed normal findings. CT of the orbit revealed bilateral microphthalmia with an intact optic nerve sheath and retrobulbar space (Fig. 1b). The right bulbar diameter was 11 mm and the left was 15 mm. The ophthalmologic examination of the mother was essentially normal except for myopia. Chromosomes were analyzed by G banding, Q banding, and high-resolution techniques, and the karyotype was designated as 46,X,del(X)(p22) (Fig. 2). The results of Y-specific boundary sequences assayed by PCR and Xp sequences assayed by FISH are summarized in Table 1. DNA was obtained from the patient's venous blood samples. DNA probes of known regional location were provided by other investigators. Band intensity was measured and compared with the intensity control. Pseudoautosomal boundary Y (PABY) and the sex-determining region of Y (SRY) were detected, while AMGL (a centromere region) and the Yq loci were not. FISH analysis revealed deletions distal to DXS1129. Thus the chromosome designation using the ISCN 1995 nomenclature is 46,X,der(X),t(X;Y)(p22.13;q11.2). Chromosomal analyses of the parents and older brother revealed normal karyotypes.

Discussion

The gender manifestations of the present patient corresponded to those of previously reported XX males with SRY (Magenis et al. 1982; 1987; Mittwoch 1992), whereas the combination of Xp microdeletion with ophthalmologic manifestations in our patient attracted a diagnosis of MLS syndrome despite the absence of linear skin defects. Until now, two XX males with MLS syndrome have been reported (Al-Gazali et al. 1990; Stratton et al. 1998), and, unlike our patient, both patients exhibited ocular and skin abnormalities characteristic of MLS syndrome. Consequently, the presence of SRY does not modify the phenotype of MLS syndrome.

Table 1 Summary of the genetic analysis of DNA markers

Xp sequences					
Locus	DXS410	AMG	DXS1129	DXF22S4	DXS16
Result	−	−	+	+	+
Yp sequences					
Locus	PABY	SRY	AMGL	DYZ3	DYS139
Result	+	+	−	−	−

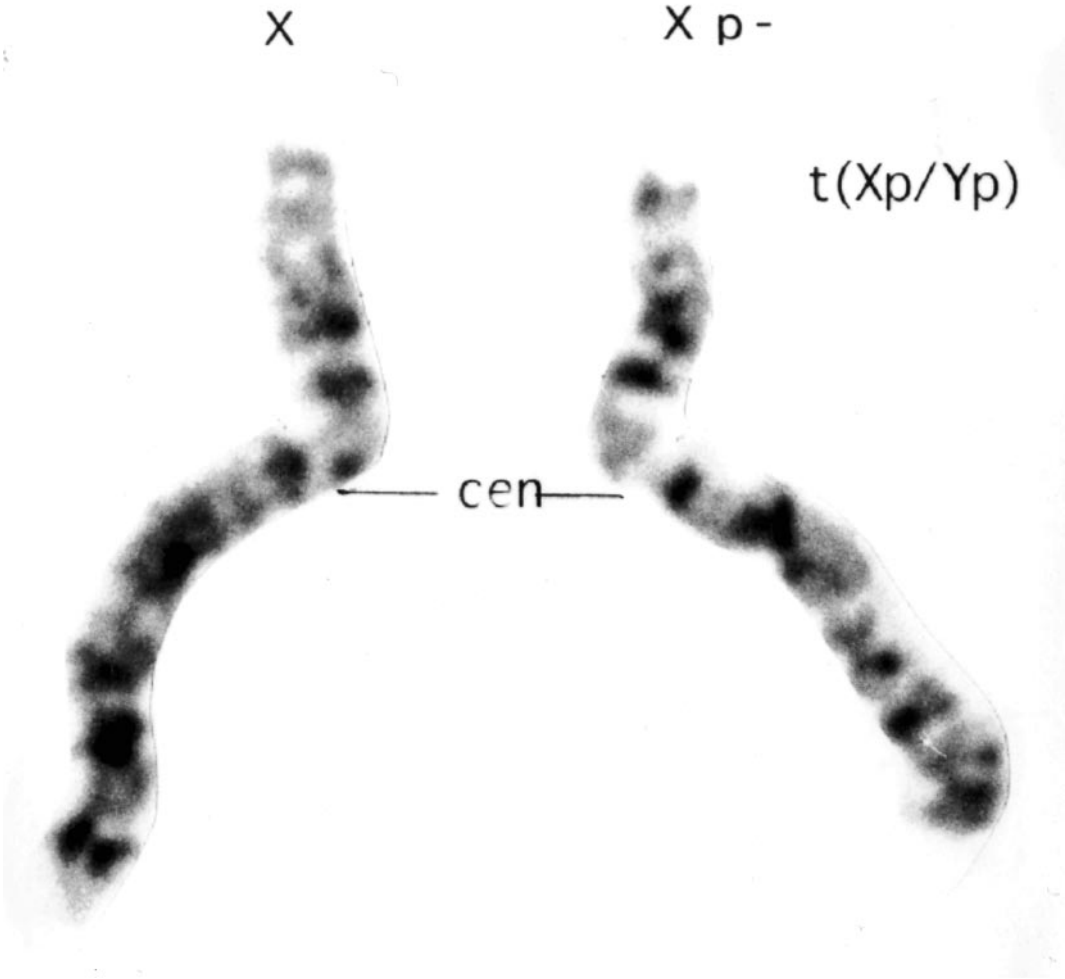

Fig. 2 Xp microdeletion was detected using high-resolution techniques and the karyotype was designated as 46,X,del(X)(p22)

Table 2 MLS syndrome

	Karyotype	Sex	Ocular findings	Dermatologic findings	Heart findings	Reference
(A) Reported cases with both microphthalmia and skin defect						
1	46,X,der(X) t(X;Y)	M	microphthalmia (L,R)	linear hypoplasia over neck and face	ND	Al-Gazali et al. (1988, 1990) Lindsay et al. (1994)
2	46,X,der(X) t(X;Y) (p22.3;q11.2)	F	microphthalmia (L,R) corneal opacity (L) corneal perforation (R)	linear defect	ND	Al-Gazali et al. (1988)
3	46,X,der(X) t(X;Y) (p22.3;q11.2)	F	microphthalmia orbital cyst	linear defects one face, neck, shoulders, and chest	ND	Al-Gazali et al. (1988)
4	46,X,del(X) (p22.31)	F	microphthalmia (L,R)	patchy cutis aplasia on face, neck, and extremities	ND	Friedman et al. (1988)
5	46,X,del(X) (p22.2)	F	microphthalmia (L) sclerocornea (L,R)	raw linear lesions on face and neck	ND	Temple et al. (1990)
6	46,X,del(X) (p22.2)	F	microphthalmia (L,R) corneal opacities	hypoplastic erythematous areas on head and neck	ND	Allanson and Richter (1991)
7	46,X,del(X) t(2;X) (p25.1;p22.1)	F	microphthalmia sclerocornea (L,R)	linear skin lesions on face and neck	ND	Gericke et al. (1991)
8	46,X,der(X) t(2;X) (p25.1;p22.1)	F	microphthalmia sclerocornea (L,R)	linear skin lesions on face and neck	ND	Gericke et al. (1991)
9	46,X,del(X) (p22.3)	F	microphthalmia (R) corneal clouding (L,R) iris coloboma (R) embryotoxon (L) chorioretinopathy	linear desquamative eruption on face and neck depigmentated lesions on trunk	ND	Naritomi et al. (1992)
10	46,X,del(X) (p22.1p22.31)	F	microphthalmia (L,R) corneal clouding (L,R)	linear hypoplasia with telangiectasia on face and neck hypopigmented patches on trunk	AV block (Mobitz II)	Naritomi et al. (1992)
11	46,X,der(X) t(X;?) (p22.3;?)	F	microphthalmia (L,R) sclerocornea dense cataract	reticulolinear nonvesicular lesions on face and neck	VSD, ASD overriding aorta azygos continuation junctional rhythm wandering pacemaker	Lindor et al. (1992)
12	46,X,del(X) (p22.1)	F	microphthalmia (L,R) corneal opacity (L,R) glaucoma (L,R) retinal detachment (L,R)	linear lesions on face	patent foramen ovale	Lebel et al. (1992) Eng et al. (1994)
13	46,XX (not high resolution)	F	microphthalmia (L,R) blepharophimosis	linear erythematous lesion on right cheek and neck	cardiomyopathy ventricular fibrillation	Happle et al. (1993)
14	46,X,del(X) (p22.2)	F	microphthalmia (L,R) cloudy cornea (L,R)	reticulolinear scar-like lesions on face	ND	Lindsay et al. (1994)
15	46,X,del(X) (p22.2)	F	(+)	(+)	?	Magenis (Schaefer's pers. commun.)
16	46,X,der(X) t(X;Y)	M	microphthalmia	linear skin streaks	secundum ASD	Stratton et al. (1998)
(B) Reported cases with only microphthalmia (no skin defect)						
1	46,X,der(X) t(X;3) (p22.2;q12)	F	microphthalmia	No skin lesion	ND	Ropers et al. (1982)
2	46,X,der(X) t(X;3) (p22.2;p22.2)	F	microphthalmia (R) sclerocornea (R) defects in retinal pigment epithelium	No skin lesion	normal	Donnenfeld et al. (1990)
3	46,X,del(X) (p22.3)	F	microphthalmia iridoschisis	No skin lesion	ND	Thies et al. (1991)
4	46,X,der(X) t(X;Y) (p22.13;p11.2)	M	microphthalmia	No skin lesion	AV block (Wenckebach)	Koyama et al. (1993) Present case (1998)
(C) Reported cases with only skin defect (no microphthalmia)						
1	46,X,del(X) (p22.2)	F	ND (fetus)	wide skin defect	ND	Lindsay et al. (1994)
2	46,XX	F	No microphthalmia	erythematous depressed lesions on face and neck	ASD WPW syndrome oncotic cardiomyopathy	Bird et al. (1994)
3	46,X,del(X) (p22.2)	F	No microphthalmia	(+)	?	Beaudet (Schaefer's pers. commun.)

ND, not documented; AV block, atrioventricular block; VSD, ventricular septal defect; ASD, atrial septal defect; WPW, Wolf–Parkinson–White

Table 3 Breakpoints of reported cases

	Case	DXS410	AMG	DXS1135	DXS1129	DXS1144	DXS22S4	PRPS2	DXS16
Reported cases									
M + S	3		−	−	−	−	+	+	+
M + S	5	−	−	+	+	+	+	+	+
M + S	9		−	−	−	−	+	+	+
M + S	15	−	−	+	+	+	+	+	+
S	1		−			−	−	−	+
S	2	−	−	−	−	−	+	+	+
S	3		−			−	−	−	+
Present case									
M	4	−	−		+		+		+

M + S, microphthalmia and skin lesions; M, only microphthalmia; S, only skin lesions. Case numbers correspond to those in Table 2

The relationship between the clinical features and the karyotypes of previously reported cases with MLS are summarized in Table 2(A–C). These cases were divided into three categories, comprising the first group with both microphthalmia and skin lesions (Table 2A), the second group with only microphthalmia (Table 2B), and the third group with only skin lesions (Table 2C). Although there has been debate on whether or not only microphthalmia or skin lesions warrant a diagnosis of MLS syndrome, recent investigations of deletion maps of these three groups have elucidated that the extension of the Xp deletion significantly overlaps among the three groups (Table 3); thus either ocular or skin lesions, along with microdeletion of the Xp critical region, are regarded as sufficient for a diagnosis of MLS syndrome (Wapenaar et al. 1993; Schnur and Wick 1995; Temple and Al-Gazali 1995).

Moreover, it is intriguing that Xp microdeletion is generally larger in the third group than in the first and second groups: the regions distal to DXS1135 are invariably deleted in the first and second groups, whereas more proximal regions are included in the deletion of the third group. This fact imposes some difficulty in accounting for the phenotypic variations among the three groups based on the contiguous gene theory. The hypothesis of tissue-specific X chromosome inactivation with a deletion of a single gene or very closely located genes is more acceptable.

The differential diagnosis of MLS syndrome includes Lenz microphthalmia syndrome (LM), Aicardi syndrome (AS), and focal dermal hypoplasia (FDH) or Goltz syndrome (Wettke-Schafer and Kanther, 1983; Rodini et al. 1992; Shastry, 1993; Paulger et al. 1997). In particular, there has been much debate on whether or not MLS syndrome, AS, and FDH represent variable phenotypes of the same contiguous gene syndrome or the variable consequences of defects of the same gene (Lindsay et al. 1994; Ballabio et al. 1995). Schaefer et al. (1996) showed that the highly conserved human holocytochrome *c*-type synthetase gene is located in the MLS critical region and that the gene is deleted in all cases with MLS, but not in patients with FDH or AS; thus the authors tentatively concluded that AS and FDH are distinctive from MLS syndrome. Further molecular investigations are required to resolve this issue.

It should be emphasized that our patient had Wenckebach conduction. To date, five cases of MLS syndrome with heart diseases (e.g. congenital heart defects, cardiomyopathy, and conduction disturbances) have been reported. These have included intermittent junctional rhythm and wandering atrial pacemaker with congenital heart defects (Lindor et al. 1992), ventricular fibrillation with hypertrophic cardiomyopathy (Happel et al. 1992), Morbitz II atrioventricular block (Naritomi et al. 1992), oncocytic cardiomyopathy with congenital heart defect and Wolf–Parkinson–White syndrome (Bird et al. 1994), and secundum atrial septal defect (Stratton et al. 1998). Schaefer et al. (1996) speculated that the deficiency of human holocytochrome *c*-type synthetase may be related to conduction disturbances in MLS syndrome. Accordingly, patients with MLS syndrome should be scrutinized for potentially hazardous heart problems.

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