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ARTICLE

Functional disomy of the Xq28 chromosome region

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We report on two patients, a boy and a girl, with an additional Xq28 chromosome segment translocated onto the long arm of an autosome. The karyotypes were 46,XY,der(10)t(X;10)(q28;qter) and 46,XX,der(4)t(X;4)(q28;q34), respectively. In both cases, the *de novo* cryptic unbalanced X-autosome translocation resulted in a Xq28 chromosome functional disomy. To our knowledge, at least 17 patients with a distal Xq chromosome functional disomy have been described in the literature. This is the third report of a girl with an unbalanced translocation yielding such a disomy. When the clinical features of both patients are compared to those observed in patients reported in the literature, a distinct phenotype emerges including severe mental retardation, facial dysmorphic features with a wide face, a small mouth and a thin pointed nose, major axial hypotonia, severe feeding problems and proneness to infections. A clinically oriented FISH study using subtelomeric probes is necessary to detect such a cryptic rearrangement.
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Introduction

Small imbalances of chromosome subtelomeric regions such as 1pter or 22qter deletions are associated with a recognizable clinical phenotype. Clinical recognition of these specific phenotypes allows targeted FISH studies using specific subtelomeric probes to confirm the diagnosis, instead of testing all chromosome subtelomeric regions, which is cumbersome and expensive.

For the X chromosome, clinical manifestations depend on both functional and structural imbalances. Indeed, inactivation of one X chromosome in cells of female mammals ensures that both sexes have a single active X chromosome and, therefore, the same level of X-linked genes expression.[1] In males, duplication of any part of the X chromosome leads to structural and functional disomy of the corresponding genes. It may result from an intrachromosomal duplication, an unbalanced translocation or an 'aneusomie de recombinaison' following an uneven number of crossing overs within a pericentric inversion. In females, failure of X chromosome dosage compensation could result from a great variety of mechanisms.[2]

Here, we report on two patients, a boy and a girl, with a *de novo* unbalanced cryptic X-autosome translocation producing a Xq28 chromosome functional disomy.

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Clinical reports

Patient 1

This boy was the first child of young and unrelated parents. He was born at term by normal delivery after an uneventful pregnancy. At birth, his weight was 2940 g (−1 SD), size

48 cm (−1 SD) and head circumference 34 cm (−0.75 SD). Severe feeding difficulties with gastroesophageal reflux, persistent vomiting and constipation required gastrostomy at 18 months of age, followed by plasty for reflux at 2 years 5 months of age. Growth parameters normalized after gastrostomy. Tracheomalacia and laryngomalacia were corrected at 3 months of age. He had frequent respiratory infections. Examination including brain magnetic resonance imaging (MRI), muscular biopsy and electromyogram of the pharynx were normal. At 30 months of age, the patient had a significant psychomotor delay. Major axial hypotonia contrasted with conserved peripheral tonus. He had no head control and could not sit without support. Visual attention was poor. Speech was absent. He had a peculiar face with bitemporal narrowing, prominent metopic suture, bilateral epicanthus, broad nasal bridge, a thin and short pointed nose, short philtrum, small mouth, round cheeks and a pointed chin (Figure 1a). He had soft palate clefting. Ears were abnormally shaped. There were minor anomalies of hands and feet (tapering fingers, clinodactyly and overlapping IV/III toes) and abnormal genitalia (hypoplastic scrotum with small testes). His weight was 14 kg (within average), size 86 cm (−1 SD) and head circumference 48 cm (−2 SD). Skin was thin with apparent venous network. Bone age was delayed with hypomineralization. Metabolic screening of plasma and urine was normal. When seen at 5 years 3 months of age, he was able to sit, clap his hands and obeyed simple orders. Gastrostomy was still required. The patient deceased at 6 years 10 months of respiratory infection. Two sibs, a boy and a girl, are healthy.

Patient 2

This girl was the third-born child from a 34-year-old G3-P3 mother and a 37-year-old unrelated father. She was born via Caesarean section for breech presentation. Her birth weight was 3070 g, length 49 cm and OFC 35 cm. Clinical examination showed a Pierre Robin sequence with glossoptosis, microretrognathia and posterior palatal cleft, poor sucking, major axial hypotonia with normal peripheral tonus, a peculiar face with hypotelorism, small mouth, dysplastic ears and long fingers (Figure 1b). Feeding difficulties with bilious vomiting and persistent slow intestinal transit required parenteral nutrition for 2 months. Rectal biopsy was normal. Laryngomalacia was noted. Brain MRI showed discrete delay of myelinization. Ultrasound of the abdomen and the urogenital tract was normal. There were only 11 ribs. From 2 months, oral feeding was undertaken with orogastric tube feeding during night. Palatal cleft was corrected surgically at 9 months of age. Severe respiratory complications followed. At 11 months, her weight was 8.4 kg (−0.7 SD), size 69.5 cm (−0.7 SD) and head circumference 43 cm (−3 SD). Severe delayed milestones were noted. She was unable to sit without support. She grasped toys and transferred them from one hand to another. Clinical examination noted a flat forehead, thin and arched eyebrows with sparse internal part, a small thin and pointed nose, a small mouth with downturned corners and asymmetric ears with abnormal helix folding. Neck was short, and fingers and toes were long and overlapping. Skin was thin with apparent venous network. At 3 years of age, she was able to sit alone and to stand briefly with support. Gastrostomy was still necessary since she was unable to drink. She had numerous respiratory and urinary tract infections. Eczema was noted.

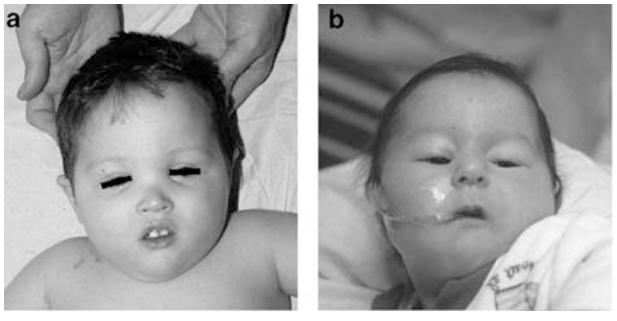

Figure 1 Characteristic facial features in (**a**) patient 1 and (**b**) patient 2.

Material and methods

Standard karyotyping using RHG and/or GTG banding and high-resolution banding studies after synchronization and BrdU incorporation (RBG) were performed on patients and parents peripheral blood lymphocytes (ISCN 1995).[3] For the first patient, standard karyotype was also performed on fibroblasts obtained after skin biopsy.

Probes used for FISH studies included chromosome X and chromosome 10 specific painting probes obtained from monochromosomal hybrid cell lines, as well as 4pter and 4qter, 10pter and 10qter and Xpter and Xqter subtelomeric probes (Cytocell® Ltd), and the Chromoprobe Multiprobe-T System (Cytocell® Ltd). Hybridizations were performed following the manufacturer's instructions. Two other clones were used: YAC 878A7(DXS8091), which maps between FRAXA and FRAXE, and BAC 258L6(D10S212) located on 10qter. They were selected from CEPH and RPCI11 libraries. YAC and BAC DNAs were labeled by nick translation according to a standard protocol. Comparative genomic hybridization (CGH) was carried out as described previously.[4,5]

Results

Patient 1

Standard GTG and RHG as well as high-resolution RBG karyotypes obtained from lymphocytes were interpreted as

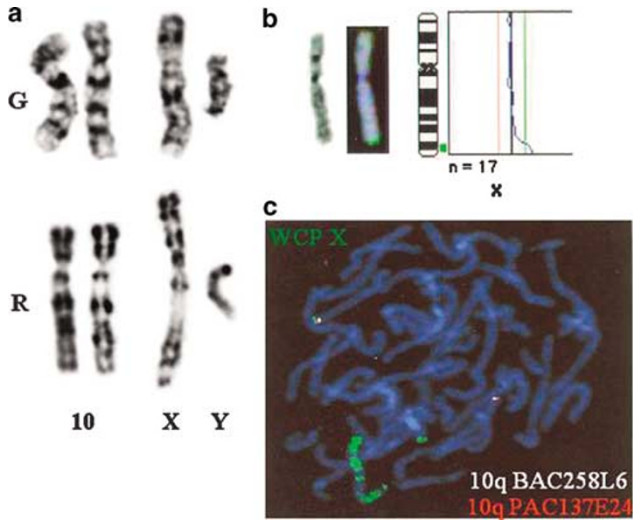

Figure 2 Patient 1. (**a**) GTG and RGB-banded chr 10 and XY. (**b**) Gain of band Xq28 shown by CGH. (**c**) FISH study shows that the translocation breakpoint is distal to the 10q subtelomeric probe. PAC 137 E24 in red and BAC 258L6 in white are still present on the der(10). A short segment distal to PAC 137 E24 is painted with WCPX.

normal at an ISCN 500–850 band resolution (Figure 2a). Chromosomal study from cutaneous fibroblasts was normal. Prader–Willi syndrome (PWS) was excluded by cytogenetic and molecular studies. A CGH study showed a Xq28 gain (Figure 2b). FISH study using subtelomeric X probes showed two signals for Xqter, one on Xqter and another one on the tip of chromosome 10qter. FISH with chromosome X and chromosome 10 painting probes confirmed the presence of an additional Xq segment onto 10qter. No material from chromosome 10 could be detected on Xqter. Both the BAC 258L6 (D10S212) probe and the 10qter subtelomeric probe (Cytocell® Ltd) hybridized on 10qter (Figure 2c). This showed that the breakpoint on the long arm of chromosome 10 was distal to the subtelomeric probe. The YAC 878A7 (DXS8091) probe was not translocated. This indicated that disomy was limited to the Xq28 band. Karyotypes of both parents were normal. Therefore, patient's karyotype was interpreted as 46,XY.ish,der(10)t(X;10)(q28;qter)
(wcpX+,DXS8091−,DXS7059+,D10S2490+) *de novo*. In summary, in this boy, there were two functional copies of Xq28, one on the normal X chromosome and another one on the tip of 10qter. In addition, the 10qter monosomy was limited to a very small segment distal to the Cytocell subtelomeric probe. Consequently, the phenotype derives completely or almost completely from the Xq28 disomy.

Patient 2

GTG and RHG karyotypes were normal. High-resolution RBG banding karyotype pointed towards a 4qter anomaly (Figure 3a). FISH study using subtelomeric probes confirmed a 4qter monosomy (Figure 3b). FISH study using all

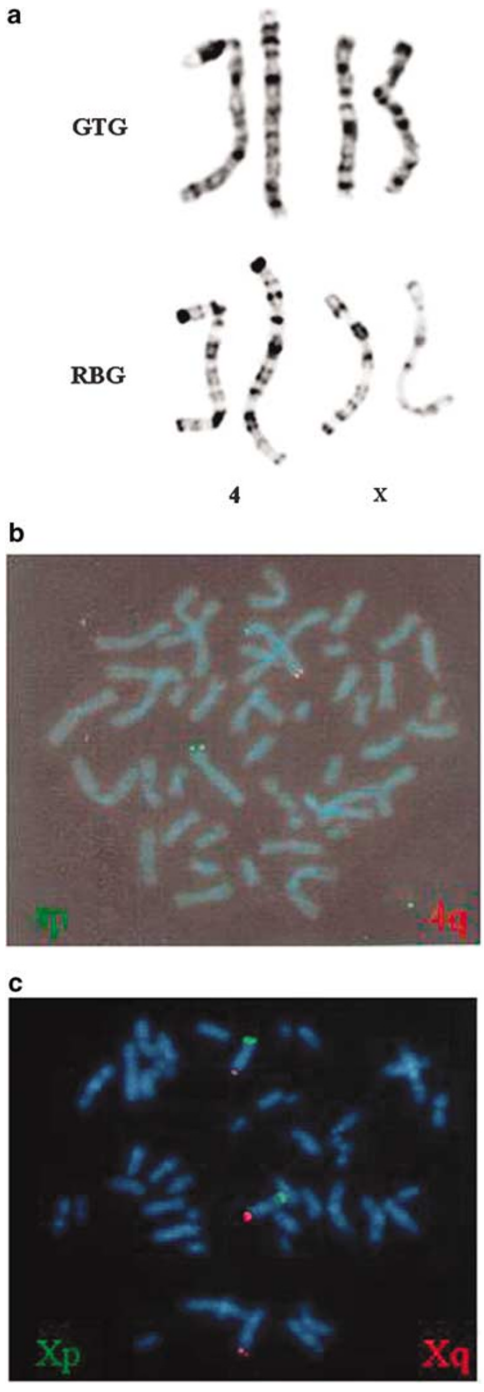

Figure 3 (**a**) GTG- and RBG-banded chr 4 and X. (**b**) The 4q subtelomeric probe (Cytocell®) shows only one signal. (**c**) The Xq subtelomeric probe (Cytocell®) shows three signals, one on a B-group chromosome.

chromosome subtelomeric probes (Cytocell® Ltd) showed three signals for the Xqter probe. One signal was present on each chromosome Xqter and the third signal was on the tip of the long arm of a B group chromosome (Figure 3c). The YAC 878A7 (DXS8091) probe was not translocated to 4qter.

Karyotypes of both parents were normal. Therefore, the patient's karyotype was interpreted as 46,XX,add(4)(q34).ish, der(4)t(X;4)(q28;q34)(DXS8091−, DXS7059+, 4qtel11−) *de novo*. In summary, in this girl, there were three copies of band Xq28: one on each X chromosome and another one translocated to 4qter. As one copy on the X chromosome was inactivated, it remained two functional copies of chromosome Xq28, yielding a Xq28 functional disomy associated with a short monosomy of band 4q35.

Discussion

In all, 17 patients carrying a Xq28 disomy could be selected from the literature[6–15] (Table 1). Eight out of these 17 cases, observed in seven independent families, were due to the same intrachromosomal rearrangement, that is, a duplicated Xq26.3 or Xq27-qter segment attached to the Xp22.3 band. Five cases were due to Xq–Yq translocations and four cases, two in a girl, to X-autosome translocations.

In addition, we report on a boy and a girl with a chromosome Xq28 functional disomy. The boy (patient 1) had two functional copies of the Xq28 chromosome segment, one on the X chromosome and another one on the der(10) chromosome, whereas the girl had two functional copies of Xq28, one on her active X chromosome and another one on the der(4) chromosome. Although the pseudoautosomal region 2 at the tip of Xqter escapes the process of X-inactivation, this region is only 0.4 Mb in size. In both patients, cytogenetic studies localized the breakpoint in Xq28 distal to YAC 878A7 (DXS8091). Therefore, both patients have a functional disomy for a Xq28 chromosome segment smaller than 7.5 Mb in size. This region is particularly rich in genes.

Xq–Yq translocations

The phenotype associated with a Xq28 functional disomy was first reported by Lahn *et al*.[6] They described three unrelated boys with severe mental retardation, generalized hypotonia, dysmorphic features and a Xqter functional disomy due to a translocation onto the long arm of a nonfluorescent Y chromosome. The translocated segment was estimated to be 5–10 Mb in size. The breakpoint on the X chromosome was distal to the FRAXA locus. The duplicated segment included factor VIII, G6PD and GABRA3 genes. Two other cases of Xq–Yq translocation with functional disomy of Xqter were described recently by Teek *et al*, who reported a boy with severe hypotonia, hypogenitalism and chronic interstitial pneumonia, and by Novelli *et al*, who reported a 8-year-old male with similar clinical features.[14,15] Both patients had a der(Y)t(X;Y)(q28;q11.2).

Xq–Xp rearrangements

Vasquez *et al*[7] describe a family where a maternally transmitted Xq27-qter duplication was associated with an abnormal phenotype in two male cousins and their aunt. The mothers were not mentally impaired, but had a short stature. The abnormal X chromosome was late replicating in mothers, but early replicating in the mentally impaired aunt. Clinical manifestations observed in both cousins included low birth weight, failure to thrive, hypotonia, developmental delay and respiratory infections. They also had inguinal hernias and hypoplastic genitalia with undescended testicles. Inheritance of a Xq27-qter duplication was also described by Goodman *et al*[8] in four severely affected males born from three unrelated, phenotypically normal carrier women. Mensurations at birth were below the 3rd centile and neonatal course included feeding difficulties. Here again, the abnormal X chromosome was late replicating in carrier mothers. Lammer *et al*[10] reported on a boy with a maternally derived Xq27.2-qter duplication. His phenotype included hypotonia, a small penis with hypoplastic scrotum and undescended testes, short feet, failure to thrive and resemblance to neonatal PWS was noted. Lastly, Kokalj-Vokac *et al*[12] reported a boy with a recombinant X chromosome from a maternal inversion, yielding a Xq27.3-qter duplication.

X-autosome translocations

Akiyama *et al*[9] reported a severely retarded boy carrying a Xq26-qter disomy due to a *de novo* unbalanced t(Xp;21p) translocation. Bialer *et al*[11] reported a girl with unbalanced translocation of Xq28 to 13p who had prenatal onset growth retardation, hypotonia, microcephaly and trigonocephaly and died at 24 months of pneumonia. Recently, Lachlan *et al* reported four unrelated patients with functional Xq disomy, two of which corresponding to interstitial duplications in boys and two others, one boy and one girl, to unbalanced X-autosome translocation.

The clinical features observed in 17 patients with terminal Xq functional disomy are summarized in Table 1. They were compared to those observed in our patients. Common craniofacial findings include microcephaly, premature closure of the fontanels or ridged metopic suture, a large face with full cheeks, a small mouth with downturned corners and palate anomalies. Most patients have prenatal onset growth retardation. Postnatal growth retardation was present in all cases, but it was not observed in our patients, presumably because they had early parenteral nutrition. Major axial hypotonia is constant and usually present at birth. In most cases, major feeding difficulties with gastroesophageal reflux are noted. Severe constipation is frequently reported. Severe developmental delay is observed in most patients. Some of the patients are unable to walk and speak at 7–8 years of age. Seizures are noted in some children. Hypoplastic genitalia with scrotal hypoplasia with or without cryptorchidism are noted in boys. Hypoplasia of labia minora and majora was noted in our female patient. At birth, the association of severe hypoto-

Table 1 Clinical findings on 19 patients with a Xq terminal functional disomy

	Novelli[14]	*Lahn 1*[6]	*Lahn 2*[6]	*Lahn 3*[6]	*Teek*[15]	*t(Xq;Yq)*	*Vasquez 1*[7]	*Vasquez 2*[7]	*Koklalj-Vokac*[12]	*Goodman 1*[8]	*Goodman 2*[8]	*Goodman 3*[8]
Mechanism	der(X)t (Xq;Yq)	der(X)t (Xq;Yq)	der(X)t (Xq;Yq)	der(X)t (Xq;Yq)	der(X)t (Xq;Yq)	5	dup(X) mat	dup(X) mat	rec(X) inv(X)	dup(X) mat	dup(X) mat	dup(X) mat
Origin	*De novo*	*De novo*	*De novo*	*De novo*	*De novo*		Inherited	Inherited	Mat	Inherited	Inherited	Inherited
Disomic segment	Xq27.3-qter	Xq28	Xq28	Xq28	Xq28		Xq26.3-qter	Xq26.3-qter	Xq26.3-qter	Xq27.2-qter	Xq27.2-qter	Xq27.2-qter
Sex	M	M	M	M	M	5 M	M	M	M	M	M	M
Age	8 yr	8 yr	8 yr	5.5 yr	13 mo		5 mo	7 mo	13 mo	12 mo	5 mo	7 yr
Cesarean section	–	?	?	?	?	0/1	+	–	?	+	+	+
Growth retardation	< 3rd	5–10	2	5	+	4/5	< 3rd	< 3rd	3rd	< 3rd	< 3rd	< 3rd
Microcephaly	+	+	+	+	+	5/5	+	+	+	+	+	+
Major hypotonia	+	+	+	+	?	4/4	+	+	+	+	+	+
Developmental delay	+	+	+	+	+/–	5/5	Severe	Severe	Severe	Severe	Severe	Severe
Seizures	–	+	+	+	?	3/4	?	?	?	–	–	–
Prominent metopic suture	–	?	?	?	–	0/2	–	–	?	–	–	–
Small mouth	+	?	?	+	?	2/2	?	?	+	?	?	?
Abnormal palate/ maxillar alveolus	+	+	+	?	?	3/3	?	?	+	+	?	+
Small feet	+	+	?	+	?	3/3	?	?	?	?	?	+
Hypoplastic genitalia/ cryptorchidism	+	+	+	?	+	4/4	+	+	+	+	–	+
Inguinal hernias	–	?	?	?	?	0/1	+	+	?	+	?	?
Severe feeding problems	?	+	+	+	?	3/3	?	?	?	+	+	+
Constipation	?	?	?	?	?	?	?	?	+	?	?	+
Respiratory infections	+	?	?	?	+	2/2	+	+	+	?	+	+
Urinary tract infections	?	?	?	?	?	?	?	?	?	?	+	?

	Goodman 4[8]	*Lammer*[10]	*reaXqXp*	*Akiyama*[9]	*Lachlan 4*[13]	*Lachlan 3*[13]	*Bialer*[11]	*Case 1*	*Case 2*	*t(X;A)*	*Total*
Mechanism	dup(X) mat	dup(X) mat	8	der(21)t (Xq;21p)	der(20)t (Xq;20q)mat	der(10)t (Xq;10p)	der(13)t (Xq;13p)	der(10)t (Xq;10q)	der(4)t (Xq;4q)	6	19
Origin	Inherited	Inherited		*De novo*	Mat	*De novo*	*De novo*	*De novo*	*De novo*		
Disomic segment	Xq27.2-qter	Xq27.2-qter		Xq26.3-qter	Xq27.1-qter	Xq27.2-qter	Xq28	Xq28-qter	Xq28-qter		
Sex	M	M	8M	M	F	M	F	M	F	3M 3F	16M 3F
Age	7 yr	5 mo		9 mo	8 mo	3 yr	18 mo	3 yr	Birth/3 yr		
Cesarean section	–	–	4/7	+	+	?	–	–	+	3/5	7/13
Growth retardation	< 3rd	+	8/8	< 3rd	< 3rd	< 3rd	5	–	–	4/6	16/19
Microcephaly	+	+	8/8	+	+	+	+	+	+	6/6	19/19
Major hypotonia	+	+	8/8	+	+	+	+	+	+	6/6	18/18
Developmental delay	Severe	Severe	8/8	Severe	Severe	Severe	Moderate	Severe	Severe	6/6	19/19
Seizures	+	?	1/4	+	–	–	?	–	–	1/5	5/13
Prominent metopic suture	–	+	1/7	+	–	+	Trigonocephaly	+	–	4/6	5/15
Small mouth	?	?	1/1	?	+	?	+	+	–	3/4	6/7
Abnormal palate/ maxillar alveolus	+	+	5/5	+	+	+	–	+	+	5/6	13/14
Small feet	+	+	3/3	?	?	?	?	+	+	2/2	8/8
Hypoplastic genitalia/ cryptorchidism	+	+	7/8	+	?	+	–	+	+	4/5	15/17
Inguinal hernias	?	?	3/3	?	–	+	?	–	–	1/4	4/8

Table 1 (*Continued*)

	Goodman 4[8]	*Lammer*[10]	*reaXqXp*	*Akiyama*[9]	*Lachlan 4*[13]	*Lachlan 3*[13]	*Bialer*[11]	*Case 1*	*Case 2*	*t(X;A)*	*Total*
Severe feeding problems	+	+	5/5	+	+	+	+	+	+	6/6	14/14
Constipation	+	?	3/3	?	?	?	?	+	+	2/2	5/5
Respiratory infections	+	+	7/7	+	–	+	+	+	+	5/6	14/15
Urinary tract infections	?	+	2/2	–*	?	?	?	+	+	2/3	4/5

*Disturbed renal function.

nia, feeding difficulties and hypogenitalism may be suggestive of neonatal PWS.

It is worth noting the location of the breakpoints in X-autosome translocations implicating Xq28. In five out of six cases, including our case 1, the Xq28 segment is translocated to regions rich in repeated sequences, the short arm of an acrocentric in two cases[9,11] and the region distal to the unique subtelomeric probe in three cases including our case 1.[13] The euchromatic part of the Y long arm that is implicated in the five cases of Xq–Yq translocation is rich in repeat units, yielding massive palindromes.[16] Band Xq28 is gene rich and has a complex genome architecture. At least five of the Xq28 genes are implicated in genomic disorders manifesting as Mendelian traits due to nonallelic homologous recombination between low-copy repeats.[17] During the course of higher primates evolution, a duplicative transposition from Xq28 to pericentromeric 2p11 occurred once and dispersed among pericentromeric regions as part of a larger duplicon cassette. All these observations suggest that higher-order genomic architecture might play a role in rearrangements implicating Xq28.

Conclusion

Functional disomy of part of the X chromosome is a rare event. It is usually lethal except in a mosaic state resulting from X-inactivation in girls or when the segment involved is very small. Functional disomy for the Xq28 chromosome region yields a recognizable phenotype including distinctive facial features, major axial hypotonia, severe feeding difficulties, abnormal genitalia and proneness to infections. Severe developmental delay is almost constant. A new subtelomeric phenotype is emerging. In patients presenting with these clinical features, a Xqter subtelomeric probe should be used to exclude the presence of a Xq28 chromosome functional disomy.

Acknowledgements

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