

## TWO PATIENTS WITH X CHROMOSOME DUPLICATION: dupXp AND dupXq

Ozer O<sup>1</sup>, Yilmaz Z<sup>1</sup>, Simsek E<sup>2</sup>, Derbent M<sup>3</sup>, Guner S<sup>3</sup>, Sahin FI<sup>1\*</sup>

**\*Corresponding Author:** Feride I. Sahin, Department of Medical Genetics, Faculty of Medicine, Baskent University, Kubilay sok. No: 36, 06570 Maltepe, Ankara, Turkey; Tel.: +90-312-232-44-00/302; Fax: +90-312-231-91-34; E-mail: feridesahin@hotmail.com

### ABSTRACT

Structural abnormalities of the X chromosome may lead to different phenotypes, depending on the chromosome region affected. We report phenotypic findings of two patients who had X chromosome duplications. One had a menstrual irregularity, a low hairline, cubitus valgus and suffered from dyslexia. The other had multiple congenital anomalies, severe mental-motor retardation and intractable epilepsy. The karyotypes were 46,X,dup(X) (p11.3p21) and 46,X,dup(X)(q13q25) respectively.

**Key Words:** Duplication, X Chromosome

### INTRODUCTION

Rare duplications can occur on the short or on the long arm of the X chromosome and may be familial or of *de novo* origins [1-4]. Most X chromosome duplications are thought to have a prezygotic origin, as suggested by the absence of a normal cell line and lack of mosaicism [1]. A 1:1 segregation in a female heterozygote is expected to result in male hemizygotes and female heterozygotes who inher-

it the dup(X) duplication [2]. A familial inverted duplication of an X chromosome was traced to a grand-parental mitotic error [3]. The importance of pedigree analyses and family studies in determining the origin of such duplications needs no emphasis.

Patients who carry a dup(X) chromosome provide opportunities to evaluate genotype/phenotype correlation in relation to X chromosome gene content and inactivation. Such abnormalities are generally well tolerated in female carriers because of preferential inactivation of the abnormal X, which can restore, at least in part, a balanced genetic makeup [4]. In contrast, males with dup(X) which is genetically active, have a functional partial X disomy and are of abnormal phenotype [5]. Here we report on two female patients with 46,X,dup(X)(q13q25) and 46,X, dup(X)(p11.3p21) karyotypes, respectively.

### CASE REPORT

Patient 1 is an 18-year-old female who was referred to the Obstetrics and Gynecology Department at Baskent University, Ankara, Turkey, because of a menstrual irregularity. She reached menarche at 12 years of age. She had regular menstrual periods while on low-dose estrogen-progesterone therapy. Her height was 182 cm and weight was 69 kg. She had a low hairline, cubitus valgus and dyslexia. The follicle stimulating hormone level was 16 mIU/ml (normal range: 12-14 mIU/ml) and magnetic resonance imaging (MRI) showed normal uterus and ovaries (Table 1). Chromosome analysis in our cy-

<sup>1</sup> Department of Medical Genetics, Faculty of Medicine, Baskent University, Ankara, Turkey

<sup>2</sup> Department of Obstetrics and Gynecology, Faculty of Medicine, Baskent University, Ankara, Turkey

<sup>3</sup> Department of Pediatrics, Faculty of Medicine, Baskent University, Ankara, Turkey

**Table 1.** Summary of findings in two patients with X chromosome duplications

Finding	Patient 1	Patient 2
Karyotype	46,X,dup(X)(p11.3p21)	46,X,dup(X)(q13q25)
Age at diagnosis	18 years	9 months
Inherited from	Mother	<i>de novo</i>
Dysmorphic features	low hairline, cubitus valgus	Brachycephaly, mental motor retardation, hypoplastic ears, Simian'line, camptodactyly, flexion contractures of the thumbs, overlapping of toes
Endocrine problems	high FSH level	not detected
Genital tract	normal	normal
Additional problems	menstrual irregularity, dyslexia	feeding problems and vomiting, recurrent urinary tract infections, growth failure

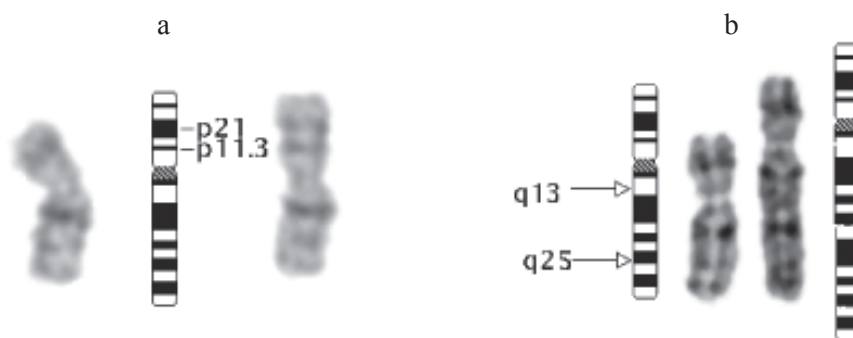
togenetic laboratory of a standard peripheral blood culture with chromosome harvesting revealed a karyotype of 46,X,dup(X)(p11.3p21) (Figure 1a). Since her mother had experienced menopause at the age of 34, she was also karyotyped and also showed 46,X,dup(X) (p11.3p21). The family was informed of the condition during genetic counseling sessions. The patient is being treated for menstrual problems.

Patient 2 is a 9-month-old girl who was referred to our hospital for multiple congenital anomalies and intractable epilepsy. She was the first child of non consanguineous parents. She was born at term following a microinjection pregnancy achieved by intracytoplasmic sperm injection because of oligospermia, her birth weight being 1740 g. Length and head circumference at birth were not recorded. The pregnancy was uncomplicated and there was no history of maternal exposure to teratogen. Prenatal ultrasonographic examinations and maternal serum

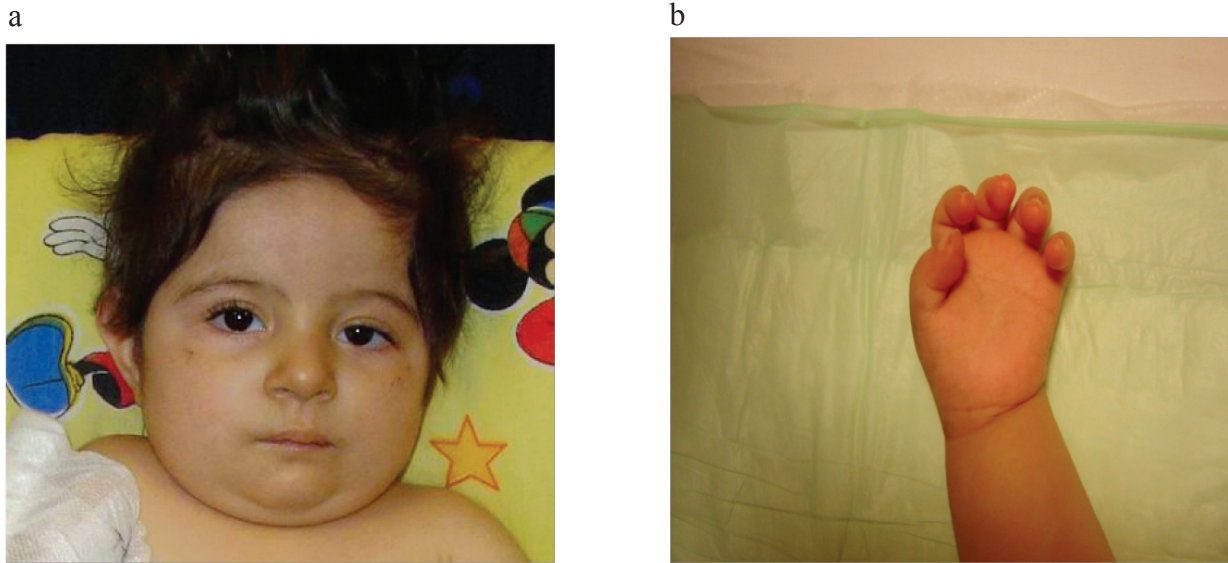
screening test results were normal. The family history was unremarkable.

At 9 months her weight was 5.2 kg (<3rd centile for age), length 58.2 cm (<3 centile for age), and head circumference 39.2 cm (<3rd centile for age). She had mental and motor retardation. Head control was gained at 4 months. She was unable to sit unassisted and had brachycephaly. Her ear lobules were hypoplastic, the right helix being straight and prominent (Figure 2a). Simian line and camptodactyly of the left hand (Figure 2b), flexion contractures of the thumbs, and overlapping of the toes were noted on the extremities. Breast feeding could not be provided. Feeding problems and vomiting, recurrent urinary tract infections, and growth failure were among the problems encountered during follow-up examinations (Table 1).

Complete blood count, routine biochemical testing of liver and kidney functions, serum levels of electrolytes, creatine phosphokinase, ammonia,



**Figure 1.** Partial karyotypes of case 1 (a) and case 2 (b).



**Figure 2.** Facial appearance (a), camptodactyly and Simian sign of left hand (b) of case2.

lactate and pyruvate, amino acid analysis of the urine and blood, and screening for prenatal infection gave normal results. Chromosome analysis revealed a karyotype of 46,X,dupX(q13q25) (Figure 1b). The parents had normal karyotypes. Cranial MRI, abdominal ultrasonographic examination and echocardiography findings were normal. Ophthalmologic examination was unremarkable. The patient remained under clinical monitoring about her neurological problems. The parents were informed at the clinical follow-up, and probable future problems were explained.

## DISCUSSION

Abnormal X chromosomes that contain duplicated material can arise *de novo* or be of familial origin [2,6-8]. Most reported cases of X chromosome duplications that are phenotypically normal are familial, whereas those with abnormal phenotypes arise as *de novo* mutations [9]. This is consistent with the findings in our patients. Patient 1 is regarded as familial with the duplicated X being inherited from the mother. In a familial case with dicentric inverted Xp duplication also inherited from the mother, the phenotype of the daughter was abnormal [10]. This is similar to our patient 1 who had phenotypic characteristics of the karyotype different from the mother. We suggest that submicroscopic rearrangements can be responsible for the phenotypic differences between the two generations.

The similarity between mother and patient was menstrual irregularity. She was informed about the low possibility of becoming pregnant. If she should have a baby with an Xp duplication karyotype, he could be mentally retarded and may have an abnormal phenotype. Should she have a daughter with a similar karyotype, she may not necessarily be protected by selective X chromosome inactivation, and may therefore have phenotypic abnormalities.

Most dup(Xq) females appear phenotypically normal, or may manifest with short stature, dysmorphic facial appearance and gonadal dysgenesis [11,12]. Patient 2 had growth retardation, feeding problems and vomiting but external genitalia were normal as reported in similar cases [9,11].

Recurrent infections in the respiratory or urinary tracts have been reported in male dup(Xq) cases [13-15]. A female patient with duplication from Xq12 to qter had otitis media during infancy [11]. Patient 2 had recurrent urinary tract infections. As the patient did not have any other bacterial or fungal infections such as pyoderma or suppurative otitis, we concluded that recurrent urinary tract infections are coincidental and did not plan detailed immunologic test and quantitative immunoglobulin levels were not evaluated.

The proximal region of Xq contains genes that normally escape X chromosome inactivation [6]. A two-fold increased expression of X-linked genes in Xq duplication patients has been reported [3,16,17]. Patient 2 with one breakpoint on Xq13, may have

active genes in the duplicated region which lead to the phenotypic findings.

Different inactivation patterns have also been reported in dup(X) patients [6,10,18]. In some cases there was full inactivation in all cells, in others a mosaic pattern of inactivation was observed [8,18,19]. Although selective X inactivation relatively diminishes phenotypic reflections, abnormal phenotypes could be observed in cases with pure dup(X) inactivation [9,19]. Epigenetic regulation of gene expression differs in the two arms of the X chromosome [19]. About 35% of genes on Xp were expressed, whereas only 5% were expressed on Xq [9,20]. The genes that escape inactivation have clinical significance as phenotype candidates in patients with X chromosome abnormalities [20]. While we observed a gonadal dysgenesis phenotype in our patient with the Xp duplication, our case with Xq duplication had a more severe phenotype which included mental retardation and multiple dysmorphic features. We think the clinical reflections will be illuminated, with more detailed studies of the genes located on the X chromosome.

**REFERENCES**

1. Narahara K, Kodama Y, Kimura S, Kimoto H. Probable inverted tandem duplication of XP in a 46,XY,Xp+ boy. *Jinrui Idengaku Zasshi* 1979; 24(2): 105-110.
2. Gardner RJM, Sutherland GR, Eds. *Chromosome Abnormalities and Genetic Counseling, 3rd ed.* Oxford: Oxford University Press, 2004.
3. Schwartz S, Schwartz MF, Panny SR, Peterson CJ, Waters E, Cohen MM. Inherited X-chromosome inverted tandem duplication in a male traced to a grandparental mitotic error. *Am J Hum Genet* 1986; 38(5): 741-750.
4. Leppig KA, Disteche CM. Ring X and other structural X chromosome abnormalities: X inactivation and phenotype. *Semin Reprod Med* 2001; 19(2): 147-157.
5. Cheng SF, Rauen KA, Pinkel D, Albertson DG, Cotter PD. Xq chromosome duplication in males: clinical, cytogenetic and array CH characterization of new case and review. *Am J Med Genet A* 2005; 135(3): 308-313.
6. Zhang A, Weaver DD, Palmer CG. Molecular cytogenetic identification of four X chromosome

7. Stankiewicz P, Thiele H, Schlicker M, Cseke-Friedrich A, Bartel-Friedrich S, Yatsenko SA, Lupski JR, Hansmann I. Duplication of Xq26.2-q27.1, including SOX3, in a mother and daughter with short stature and dyslalia. *Am J Med Genet A* 2005; 138(1): 11-17.
8. Portnoi MF, Bouayed-Abdelmoula N, Mirc M, Zemni R, Castaing H, Stephann J, Ardalan A, Vialard F, Nouchy M, Daoud P, Chelly J, Taillemite JL. Molecular cytogenetic analysis of duplication Xp in a female with an abnormal phenotype and random X inactivation. *Clin Genet* 2000; 58(2): 116-122.
9. Tihy F, Lemyre E, Lemieux N, Dallaire L. De novo dup(X)(q22.1q25) in a girl with an abnormal phenotype. *Am J Med Genet* 1999; 87(4): 302-305.
10. Tuck-Miller CM, Martinez JE, Batista DAS, Kearns WG, Wertelecki W. Duplication of the short arm of the X chromosome in mother and daughter. *Hum Genet* 1993; 91(4): 395-400.
11. Armstrong L, McGowan-Jordan J, Brierley K, Allanson JE. De novo dup(X)(q22.3q26) in a girl with evidence that functional disomy of X material is the cause of abnormal phenotype. *Am J Med Genet A* 2003; 116(1): 71-76.
12. Van Dyke DL, Miller MJ, Weiss L. The origin of inverted tandem duplications and phenotypic effects of tandem duplication of the X chromosome long arm. *Am J Med Genet* 1983; 15(3): 441-450.
13. Apacik C, Cohen M, Jakobeit M, Schmucker B, Schuffenhauer S, Thurn und Taxis E, Genzel-Boroviczeny O, Stengel-Rutkowski S. Two brothers with multiple congenital anomalies and mental retardation due to disomy (X)(q12→q13.3) inherited from the mother. *Clin Genet* 1996; 50(2): 63-73.
14. Goodman BK, Shaffer LG, Rutberg J, Lepert M, Harum K, Gagos S, Ray JH, Bialer MG, Zhou X, Pletcher BA, Shapira SK, Geraghty MT. Inherited duplication Xq27-qter at Xp22.3 in severely affected males: molecular cytogenetic evaluation and clinical description in three unrelated families. *Am J Med Genet* 1998; 80(4): 377-384.
15. Lammer EJ, Punglia DR, Fuchs AE, Rowe AG, Cotter PD. Inherited duplication of Xq27.2→qter: phenocopy of infantile Prader-Willi syndrome. *Clin Dysmorphol* 2001; 10(2): 141-144.
16. Thode A, Partington MW, Yip MY, Chap-

man C, Richardson VF, Turner G. A new syndrome with mental retardation, short stature and an Xq duplication. *Am J Med Genet* 1988; 30(1-2): 239-250.

17. Yokoyama Y, Narahara K, Tsuji K, Moriwake T, Kanzaki S, Murakami M, Namba H, Ni-nomiya S, Highuchi J, Seino Y. Growth hormone deficiency and empty sella syndrome in a boy with dup(X) (q13.3→q21.2). *Am J Med Genet* 1992; 42(5): 660-664.

18. Aughton DJ, Al Saadi AA, Jhonson JA, Transue DJ, Trock GL. dup(X)(q13-qter) in a girl

with growth retardation, microcephaly, develop-mental delay, seizures, and minor anomalies. *Am J Med Genet* 1993; 46(2): 395-400.

19. Vokac NK, Ciglenecki PS, Erjavec A, Za-gradisnik B, Zagorac A. Partial Xp duplication in a girl with dysmorphic features: the change in replica-tion pattern of late- replicating dupX chromosome. *Clin Genet* 2002; 61(1): 54-61.

20. Carrel L, Cottle AA, Goglin KC, Willard HF. A first-generation X-inactivation profile of the human X chromosome. *Proc Natl Acad Sci USA* 1999; 96(25): 14440-14444.

