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ORIGINAL ARTICLE

TWO PATIENTS WITH X CHROMOSOME DUPLICATION: dupXp AND dupXq

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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 inherit 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-

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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	*de novo*
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,

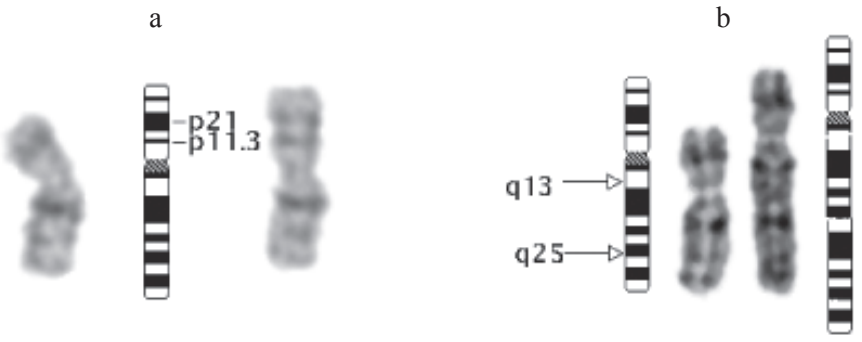

Figure 1. Partial karyotypes of case 1 (a) and case 2 (b).

a b

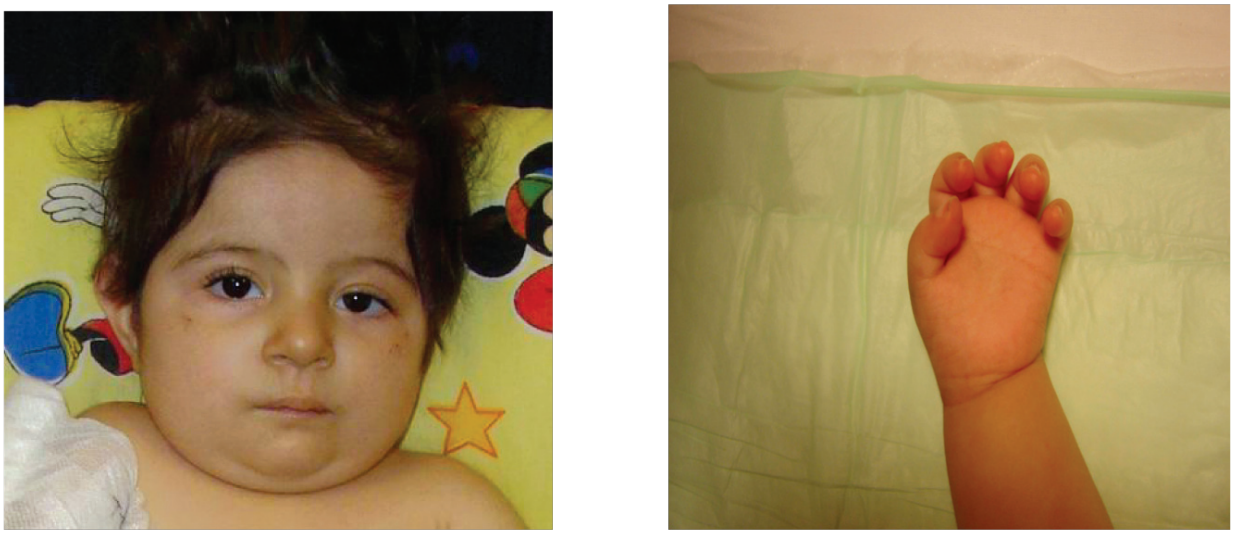

Figure 2. Facial appearance (a), camptodactyly and Simian sign of left hand (b) of case2.

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 bowith 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 pyodemia or supurative 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.

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