A report of a patient with duplication of 7p13→pter and deletion of 2p23→pter due to a maternal 2p;7p translocation

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SUMMARY: Türköver BB, Sayar C, Toksoy G, Elçioğlu N. A report of a patient with duplication of 7p13→pter and deletion of 2p23→pter due to a maternal 2p;7p translocation. Turk J Pediatr 2009; 51: 174-179.

We report a patient with severe developmental delay, failure to thrive, microbrachycephaly, large anterior fontanel, ocular hypertelorism, broad nasal bridge, low-set ears, long philtrum, micrognathia, partial cleft palate, broad distal digits, abnormal palmar creases, joint contractures, and cardiovascular anomaly. Cytogenetic analysis with high resolution chromosome banding showed an unbalanced karyotype of 46,XX, der(2)t(2;7)(p23;p13) originating from a maternal balanced translocation. Our patient showed a duplication of 7p13→pter and a deletion of 2p23→pter. Our analysis suggests that duplication 7p is associated with a recognizable characteristic phenotype.

Key words: 7p duplication, 2 p deletion, multiple congenital anomaly syndrome.

Duplication 7p results in a syndrome of developmental, craniofacial, limb, and cardiovascular anomalies. The extent of the duplicated segment and additional chromosomal aberrations has varied among reported cases, which makes the delineation of a well-defined 7p trisomy syndrome difficult. Common findings in duplication 7p include psychomotor retardation; large anterior fontanel; hypertelorism; dolichocephaly or microbrachycephaly; large, apparent low-set angulated ears; micrognathia and high-arched palate; joint dislocations/contractures; abnormal palmar creases; and cardiac septal defects[1-4].

In order to better understand the relationship between duplication of 7p material and its resulting phenotypic manifestations, we describe here an additional case of duplication 7p13→pter originating from a maternal balanced carrier.

Case Report

The female proband (Fig. 1) was delivered after 41 weeks of gestation by cesarean section. The mother and father were both 28 years old, originated from the same small village in Turkey and had two healthy sons. At birth, the child weighed 2800 g (<3rd percentile), was 47 cm in length (<3rd percentile) and had an occipitofrontal circumference of 33 cm (<3rd percentile). She had meconium aspiration and was hospitalized because of respiratory distress. She appeared as a microbrachycephalic infant. Her anterior fontanel and cranial sutures were open. She had thin hair, eyelashes and eyebrows. Her nasal bridge was broad, high and short, and the nasal tip was rounded with anteverted nares. The palpebral fissures were aligned horizontally. There was ocular hypertelorism, strabismus and nystagmus. She had malformed low-set ears with heavy

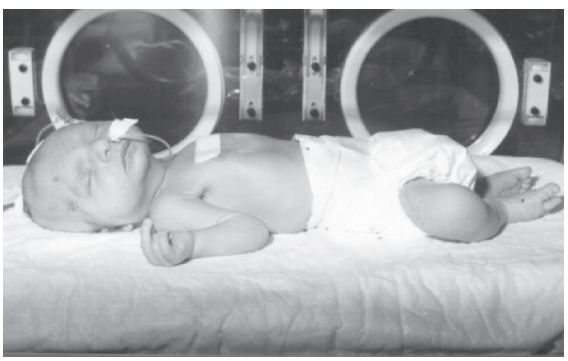

Fig. 1. The newborn patient. Note hypertelorism, micrognathia, low-set, malformed ears, flexion contractures and distal widening of the digits.

helices. There was partial cleft palate with micrognathia, and the philtrum was long. Her neck was short and webbed. All digits showed distal widening, especially of the thumbs and halluces. The fingers had flexion contractures. Both hands had single flexion creases. She had normal female external genitalia. She had a slight pectus excavatum and auscultation of the heart revealed a III/VI systolic murmur. Babygram showed cardiomegaly, and echocardiography demonstrated patent ductus arteriosus. Cranial ultrasound and cranial computerized tomography (CT) were normal. Abdominal ultrasonography revealed stasis in the right renal pelvis. Until 14 months of age, she had been frequently hospitalized because of respiratory infections and severe developmental delay, with protein and energy malnutrition. She died at 14 months with severe neurodevelopmental delay, protein and energy malnutrition, flexion contractions of the joints, clenched hands, micrognathia and a large anterior fontanel (Figs. 2, 3). Her echocardiography at that time showed patent foramen ovale and mild tricuspid regurgitation, and her abdominal ultrasonography was normal.

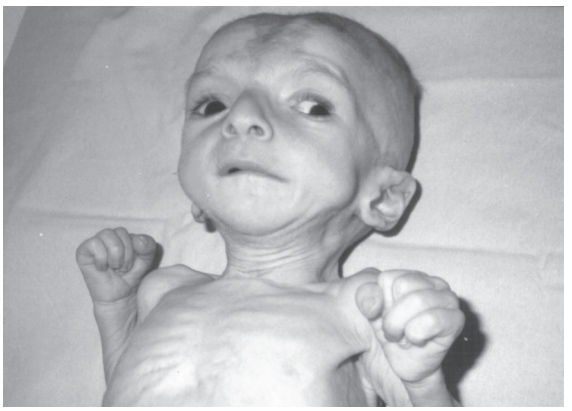

Fig. 2. The patient at age 14 months. Note large anterior fontanel and severe neurodevelopmental delay with contractions.

Fig. 3. The patient at 14 months of age with severe neurodevelopmental delay.

Cytogenetic Studies

High resolution G-banded lymphocyte chromosomal studies showed one normal chromosome 2 and one abnormal chromosome 2 with extra material on the p arm. The mother had a balanced translocation between 2p23 and 7p13. Her karyotype was 46,XX,t(2;7)(p23;p13) (Fig. 4). The karyotype of the propositus was interpreted as 46,XX,der(2)t(2;7)(p23;p13)mat (Fig. 5). Thus, the propositus had a

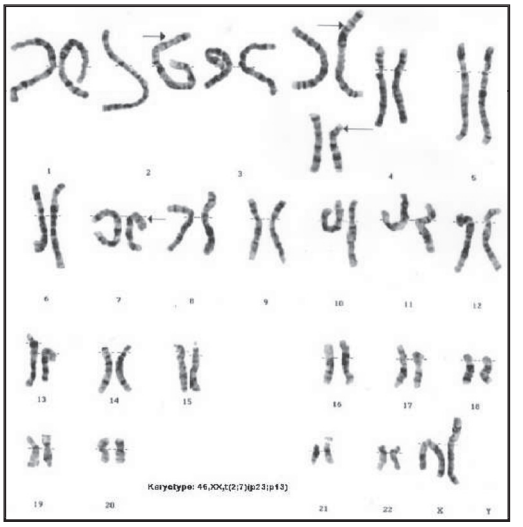

Fig. 4. The karyotype of the mother with a balanced translocation between 2p23 and 7p13.

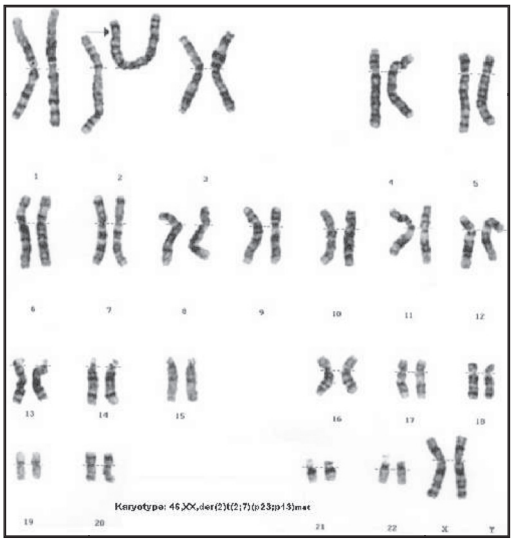

Fig. 5. The karyotype of the patient with a duplication of 7p13→pter and a deletion of 2p23→pter.

duplication of 7p13→pter and a deletion of 2p23→pter. The chromosomes of the father were normal. As the mother is a balanced translocation carrier, prenatal diagnosis for subsequent pregnancies was offered to the family with genetic counselling in view of the increased recurrence risk of a liveborn aneuploid child[5].

Discussion

The present case had a duplication of 7p13→pter and a deletion of the region 2p23→pter. The clinical findings of the patient may have been caused by the duplication of chromosome 7p and a deletion of 2p.

When we review the literature regarding duplication 7p, a characteristic pattern of malformations was recognized with developmental, craniofacial, limb and cardiovascular manifestations. The main phenotypic features in association with psychomotor retardation include micro- and/or brachycephaly; large anterior fontanel; hypertelorism; large, apparent low-set angulated ears; micrognathia and high-arched palate; joint dislocation, contractures or hyperextensibility; abnormal palmar creases; and cardiac septal defects[1-4]. Kozma et al.[6] reviewed 37 published cases and concluded that the most common medical complications were those of the musculoskeletal system, as a third of the affected individuals displayed hypotonia. Cai et al.[7] described 47 cases of 7p duplication, of which 24 were transmitted by balanced reciprocal translocations. Table I shows the spectrum of the clinical findings of trisomy 7p based on 59 reported cases, as reviewed by Cai et al.[7] and Kozma et al.[6], and updated with 12 new cases[8].

The patient presented herein had findings common to other cases of duplication 7, such as severe neurodevelopmental delay, microbrachycephaly, large anterior fontanel, hypertelorism, low-set ears, micrognathia, partial cleft palate, broad nasal bridge, joint contractures, broad digits, abnormal palmar creases, and cardiovascular anomaly.

The previously reported four cases trisomic for 7p13→pter all had mental retardation, microbrachycephaly, large anterior fontanel, ocular hypertelorism, low nasal bridge, low-set ears, abnormal palate, broad digits, abnormal palmar creases, joint contractions, hypotonia, and cardiovascular system malformations. One had a high large forehead and two had abnormal eye slants[9-12] (Table II). Table III shows the other involved chromosomes in these patients. A mild phenotypic variability was recognized from patient to patient in trisomy 7p patients, which may reflect the influence of additional monosomies.

Deletions of the distal portion of 2p are rare and no specific phenotype exists for the distal interstitial deletions. To our knowledge, there are only five cases reported of deletions involving regions from 2p23 to 2pter[13-15], whereas one case involved a terminal deletion of chromosome

Table I. Comparison of the Spectrum of the Clinical Findings of this Case with Previously Reported Patients with Trisomy 7p Syndrome

Clinical features	Number of patients in whom this feature has been described[a] (n=59)	This case
Mental retardation	49	+
Microbrachycephaly	27	+
High large forehead	27	–
Large anterior fontanel	38	+
Ocular hypertelorism	37	+
Abnormal slant	26	–
Low nasal bridge	27	+
Low–set ears	38	+
Abnormal palate[b]	35	+
Skeletal anomalies[c]	33	+
Abnormal palmar creases	19	+
Cardiovascular abnormalities	24	+
Hypotonia	25	–

[a]In the remaining cases, the feature was either described as being absent, or was not commented on.
[b]High-arched and/or cleft palate.
[c]Broad halluces/thumbs/digits, foot and thorax malformations, joint contractures, or dislocations.

Table II. Clinical Findings in Duplication of 7p13→pter

Clinical features	7p13→pter (n=4)	Our case
Mental retardation	3/3	+
Micro-and/or brachycephaly	3/3	+
High large forehead	1/3	–
Large anterior fontanel	3/3	+
Ocular hypertelorism	3/3	+
Abnormal slant	2/3	–
Low nasal bridge	3/3	+
Low-set ears	4/4	+
Abnormal palate[a]	3/3	+
Skeletal anomalies[b]	4/4	+
Abnormal palmar creases	3/3	+
Cardiovascular abnormalities	4/4	+
Hypotonia	2/2	–
Psychomotor retardation	2/2	+
Case Reference No. in Table III	1-4	5

[a] High-arched and/or cleft palate.
[b] Broad halluces/thumbs/digits, foot and thorax malformations, joint contractures, or dislocations.

Table III. Other Involved Chromosomes in Patients Cited in Table II

Case Reference No.	Source	Other involved chromosome	Authors
1	de novo	2	Subrt et al., 1973
2	Pat; BRT	8p	Moore et al., 1982
3	Mat; BRT	6q	Krüger et al., 1989
4	Mat; BRT	3q	Roman Ortiz et al., 1992
5	Mat; BRT	2p	This case

Pat: Paternal source. Mat: Maternal source. BRT: Balanced reciprocal translocation.

2p24[16] and one case a distal interstitial deletion of 2p24.2-p25.1[17]. Previously reported patients have microcephaly, rectangular face, apparent low-set ears, fifth finger clinodactyly, hypotonia, and developmental delay. Three cases had a high forehead, high-arched palate, and micrognathia; two cases had prominent metopic suture, down-slanting palpebral fissures, congenital heart defects, and hearing loss; and one case had hypertelorism (Table IV).

Our case did not have a rectangular face, fifth finger clinodactyly, bow-shaped mouth, prominent occiput, arched eyebrows or prominent metopic suture as seen in these five

Table IV. Clinical Findings in del (2) (p23)

Clinical findings	del(2)(p23)	del(2)(p23p25)	del(2)(p23.1p25.1)	Del(2)(p24)	del(2)(p24.2p25.1)	This case
Microbrachycephaly	+	+	+	+	+	+
Prominent occiput	–	+	+	–	–	–
Prominent metopic suture	–	+	+	–	–	–
Rectangular face	+	+	+	+	+	–
Ptosis	–	–	+	–	–	–
High forehead	+	+	+	–	–	–
Arched eyebrows	–	–	+	–	+	+
Hypertelorism	NA	–	–	NA	+	+
Strabismus	+	+	–	–	–	–
Down-slanting palpebral sutures	+	–	+	–	–	–
Low-set ears	+	–	+	–	+	+
Bow-shaped mouth	+	+	+	+	–	–
Palatal anomalies	–	+	+	+	–	+
Micrognathia	+	+	–	+	–	+
Fifth finger clinodactyly	+	+	+	+	+	–
Cardiac anomalies	–	+	–	+	–	+
Hearing loss	–	–	–	+	+	–
Hypotonia	+	+	–	+	+	–
Failure to thrive	+	+	+	–	–	+
Developmental delay/mental retardation	+	+	+	+	+	+

cases, but did have the characteristic phenotype seen in trisomy 7p patients. Strabismus and severe neurodevelopmental delay seen in our patient may also be an effect of 2p deletion.

The cytogenetic data on duplication 7p suggest that 7p15→pter is a critical region for abnormal phenotypes during mental and physical development[4]. In these reported cases, bands 7p15 and 7p21 are most frequently involved. Cai et al.[7] reported a patient with duplication of 7p21.2→pter who was similar to reported cases with a 7p15→pter or larger duplications of 7p, suggesting that the critical segment causing the characteristic phenotype of 7p duplication syndrome, including the large anterior fontanel, exists at 7p21.2 or 7p21.2→pter. In comparing the extent of duplication in other cases, anomalies such as mental retardation, microcephaly, and congenital heart disease do not appear to be specific for assignment of specific gene(s) to 7p21. Brachycephaly may or may not be a specific phenotype in 7p21 duplication[18]. Ahlbom et al.[19] reported that there is a region around the distal part of band 7p21 that in three copies might contribute to many of the facial features common to patients with partial trisomy 7p. Phenotypic variations may be found even for those patients with apparently the same duplication segment, which can be related to the inter-syndromic variability as a result of the different locations of the breakpoints within the same band, or the presence of different deleted regions derived from the translocation.

A number of diseases and candidate genes of significance to development have been mapped to the distal short arm of chromosome 7. These genes are CRS1 (OMIM no.123100; 7p21.2-7p21.3), ACS3 (OMIM no. 101400; 7p21.2.), TWIST (OMIM no. 601622; 7p21), HOXA13 (OMIM no.142959; 7p14.2-15), GLI3 (OMIM no. 165240; 7p13) and MEOX2 (OMIM no. 600535; 7p22.1-p21.3). The PREB gene involved in skeletal, facial and genital defects has been mapped to chromosome 2p23[20]. Gdf7 gene of interest in the context of neural tube development has been mapped to 2p23-24. SOX11, MYT1L and SNTG2 genes, thought to play an important role in the developing central nervous system, are mapped to 2p25.3[21].

We have reported herein a patient with duplication of 7p13→pter and a deletion of 2p23→pter to reinforce the characteristic patterns of malformations of 7p duplication, which include severe neuromotor retardation, microbrachycephaly, joint contractions and a large anterior fontanel not compatible with life.

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