

## The clinical phenotype of the derivative (8)t(7;8)(q22;p23.3) in two siblings

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### = Abstract =

We report on 2 siblings with a partial trisomy of 7q (7q22→qter) and concomitant partial monosomy of 8p (8p23.3→pter), which were shown by FISH using probes located at the telomere region of each chromosome. All the balanced translocation carriers (father and a sister) in this family had a normal phenotype. The 2 siblings with the same abnormal karyotype had similar multiple congenital anomalies and dysmorphic features. During the follow-up, the first male patient died in the neonatal period, but the female sibling is still alive at 2 years and 6 months of age. (*Korean J Pediatr* 2008 51:1241-1244)

**Key Words :** Partial trisomy 7q, Partial monosomy 8p

### Introduction

Trisomy 7q or 7q duplication has been described with specific craniofacial dysmorphic features and clinical manifestations, since the chromosomal abnormality was first described by Vogel et al. in 1973<sup>1,2)</sup>. But, trisomy 7p syndrome rarely originates de novo; it usually results from a parental balanced translocation, which alters the phenotype attributable to trisomy 7q.

Here we report on two siblings with partial trisomy 7q (7q22→qter) and monosomy 8p (8p23.3→pter) resulting from a paternal balanced translocation t(7;8)(q22;p23.3). Fluorescent in situ hybridization (FISH) analysis performed in two siblings after birth showed that distal 8p material (8p23.3→pter) was translocated to 7q (7q22→qter). The translocation carriers (the father and a sister) had a normal phenotype. However, the siblings with the same abnormal karyotype had multiple congenital anomalies.

There are few previous reports on a translocation between

chromosome 7q and 8p. Partial trisomy of 7q (7q22→qter) with concomitant partial monosomy of 8p (8p23.3→pter) we describe here seems a very rare cases with a translocation between chromosome 7q and 8p.

### Case Report

The maternal pregnancy history was significant for three spontaneous abortions during the first trimester even though the parents are non-consanguineous and healthy. And the first pregnancy ended in the delivery of a baby (patient 1) with multiple anomalies; that baby died during the neonatal period. But, the second baby, their first daughter, was phenotypically normal. The third baby, their second daughter (patient 2), however, had similar dysmorphic craniofacial features and congenital anomalies to the first baby (patient 1).

#### Patient 1

The baby, a male, was the product of a first pregnancy and delivered by emergency Cesarean section due to fetal decelerations at 37 weeks and 5 days of gestation. Prenatal ultrasound, two weeks before delivery, revealed polyhydramnios and intrauterine growth retardation. Respiratory distress, a weak cry with hoarseness and hypotonic posture were noted soon after birth. The growth profiles of birth weight and height were 2,190 g and 40.2 cm respectively,

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both of which were below the 10th centile. The head circumference was 35 cm in the 50–75<sup>th</sup> centile.

At birth, the patient had dysmorphic features, including a prominent forehead, protruded occiput, large open fontanelle, triangular face, micophthalmia, hypertelorism, broad nasal ridge, low-set and malformed ears, bifid uvula, cleft palate, micrognathia, prognathia, short neck, single umbilical artery, micropenis, bilateral simian creases, camptodactyly, clinodactyly, second toes overlapping great toes, rocker-bottom feet, hypertrichosis, and hyperlaxity in multiple joints. The postnatal imaging studies showed: spinal dysraphism involving the cervical, thoracic and lumbar spines, multiple hemivertebrae involving the lumbar spines, mild scoliotic deformity of the thoracolumbar spines; midsagittal subependymal cysts; and a patent ductus arteriosus. The baby died on the 18<sup>th</sup> postnatal day due to aspiration pneumonia, congestive heart failure and renal failure.

#### Patient 2

The baby, a female, was the product of a third pregnancy and delivered by Cesarean section at 37 weeks and 6 days of gestation. The mother was transferred to the obstetric department at Chonnam National University Hospital due to polyhydramnios and fetal intrauterine growth retardation detected 2 months prior to delivery. At birth, her weight, height and head circumference were 2,030 g (<10<sup>th</sup> centile), 44 cm (<10<sup>th</sup> centile) and 34.5 cm (75–90<sup>th</sup> centile), respectively.

At birth, the patient had dysmorphic features that included frontal and parietal bossing, protrusion of the occiput, slightly dehiscent suture lines, micophthalmia, narrow palpebral fissures, hypertelorism, epicanthus, a small nose, a slightly short nasal ridge, low-set and malformed ears, a small and triangular mouth, a high arched palate, microretrognathia, a short and wide neck, a wide thorax, wide-spaced nipples, a short sternum, a single umbilical artery, bilateral simian palmar creases, fifth finger clinodactyly, broad thumbs, broad great toes, second toes overlapping great and third toes, and rocker-bottom feet. However, additional abnormalities were detected at 15 months: bushy eyebrow, long eyelash, poor implanted teeth, hypertrichosis on the forehead and back, and excess of subcutaneous tissue on the back of the feet and hands. In addition, premature breast buds were noted at 21 months.

The echocardiography at birth showed a large patent ductus arteriosus (PDA) and a secundum atrial septal defect.

The large PDA was ligated surgically on the 10th day after delivery. The echocardiography followed up at six months of age, revealed left ventricular concentric hypertrophy additionally.

At five months, the infant was admitted to the hospital due to suspicion of seizures. The electroencephalography showed very low amplitude theta activity without normal sleep spindles. Brain magnetic resonance imaging revealed hydrocephalus and delayed myelination.

At 2 years and 4 months of age, the patient weighed 10.2 kg (3<sup>rd</sup> centile), measured 76 cm (<3<sup>rd</sup> centile), and had a head circumference of 49 cm (75–90<sup>th</sup> centile). She had cervico-axial hypotonia and developmental delay. In addition, she had recurrent subluxation of the shoulders, bilateral dislocation of the hips and hyperlaxity of the joints. She had poor tolerance of food through the mouth, and good tolerance through a nasogastric tube. Although alive at 2 years 6 months of age, she was hospitalized frequently due to aspiration pneumonia, respiratory distress and poor oral feeding.

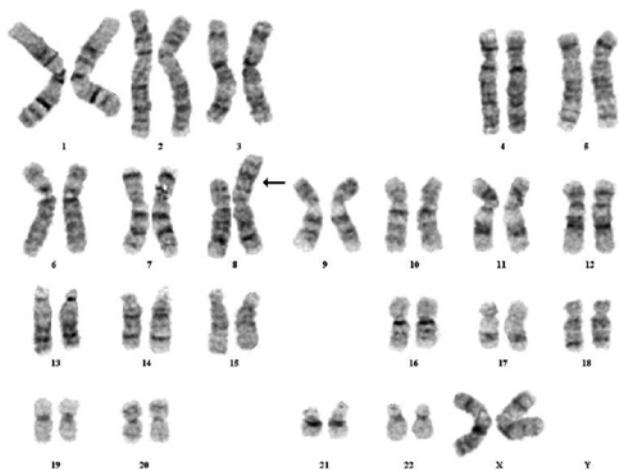
#### Cytogenetic and FISH Studies

The karyotype was performed on peripheral blood from the two patients, their phenotypically normal sister and their parents. The high-resolution G-banded metaphase chromosomes in 20 cells showed an apparently balanced translocation between chromosomes 7 and 8 in the father [46,XY, t(7;8)(q22;p23.3)] and the phenotypically normal sister [46,XX, t(7;8)(q22;p23.3)]. In addition, the abnormal derivative chromosome in patient 1 [46,XY, der(8)t(7;8)(q22;p23.3)pat] and in patient 2 [(46,XX, der(8)t(7;8)(q22;p23.3)pat] (Fig. 1, 2). The mother had a normal 46,XX karyotype.

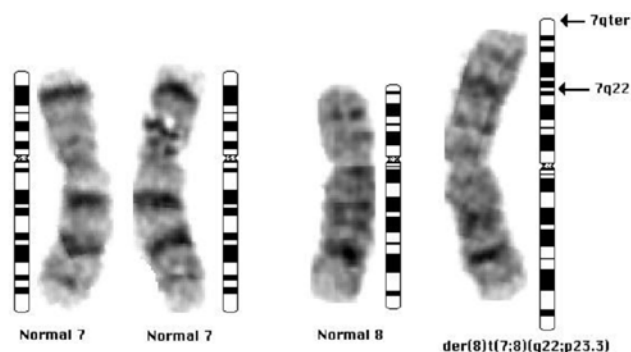
The abnormal karyotype [der(8)t(7;8)(q22;p23.3)] of the patients was confirmed by FISH studies on lymphocytes from patient 2 using 7q and 8p telomere probes. FISH with the 7q telomere probe showed three fluorescent signals: two from the normal chromosome 7 and one from the derivative chromosome. However, the FISH with an 8p telomere probe demonstrated only one fluorescent signal from the normal chromosome 8.

#### Discussion

The craniofacial abnormalities reported in trisomy 7q include: macrocrania or macrocephaly, wide large open fontanelles, frontal bossing, hypertelorism, epicanthal folds, strabismus, small and down slanting palpebral fissures, long



**Fig. 1.** High resolution G-banded karyotype from peripheral blood lymphocytes of patient 2 - a female karyotype with an abnormal derivative chromosome 8 with a larger than normal short arm [(46, XX, der(8)t(7;8)(q22;p23:3)pat].



**Fig. 2.** Ideogram of a normal chromosome 8 and the extra portion of the chromosome from patient 2 - this shows chromosomal translocation [der(8)t(7;8)(q22;p23:3)].

eyelashes, low nasal bridge, small nose, large and low-set ears, abnormal pinnae, high arched palate, cleft palate, macroglossia and microretrognathia<sup>2,3</sup>. Abnormal brain imaging such as ventriculomegaly<sup>2,3</sup> has also been reported. Other dysmorphic features include short neck, wide spaced nipples, anomalies of the hands and feet, single palmar creases, abnormal genitals such as micropenis, low birth weight, axial hypotonia, skeletal anomalies such as kyphoscoliosis, anterior dislocation of the shoulders, and congenital hip dislocation<sup>2,3</sup>. The clinical manifestations associated with trisomy 7q by organ systems are laryngomalacia, lung hypoplasia, and pulmonary hypertension, congenital heart defects (e.g. a ventricular septal defect and hypertrophic cardiomyopathy) and kidney malformations<sup>2,3</sup>. The follow-up studies have shown neonatal or early death, failure to thrive during infancy, developmental retardation, and glaucoma<sup>2,3</sup>. In the

current cases, most of the above specific craniofacial dysmorphic features were observed at birth. Even though there was no kidney malformation, other organ anomalies were present.

The above-mentioned clinical manifestations have been outlined into three distinct clinical entities depending on the duplicated regions of 7q (the 7q31-qter, 7q32-qter and 7q22-q31 regions) since 1977<sup>3</sup>. But, some have suggested that the clinical features of trisomy 7q depend on the size of the duplicated 7q<sup>3-5</sup>, not the different duplicated region. Among the three 7q regions, patients with the interstitial duplication of the 7q22-q31 region have been suggested as having more severe clinical manifestations with more frequent early death than those with the other two 7q partial trisomy regions<sup>3</sup>. In the current case, although the two patients had identical abnormal karyotypes, the first patient, a male, died on the 18th postnatal day. The female patient is still alive at 2 years and 6 months of age, even though she has growth retardation, psychomotor developmental delay, recurrent subluxation of the shoulders and hips, poor tolerance to food, and recurrent respiratory infections.

Monosomy 8p or 8p deletion also shows specific dysmorphic phenotypes and congenital anomalies; especially in the heart, even though the malformations are variable depending on the size and location of the deletion on chromosome 8p<sup>6</sup>. For example, a patient with a proximal 8p23.1 deletion, the WI-8327 to D8S1825 region likely includes more than one gene critical for heart differentiation, and is frequently associated with many different congenital heart defects<sup>7,8</sup>. However, more distal deletions spanning from D8S1819 to the telomere are not as frequently associated with congenital heart defects<sup>8</sup>. In the current study, the deleted part of 8p was the terminal 8p23.2 distal to DS1819; FISH analysis and short tandem repeat analysis at the molecular level to define the 8p breakpoint could not be performed in this case. The other congenital anomalies reported with monosomy 8p in addition to the heart include agenesis or hypoplasia of the corpus callosum, pyloric stenosis, gut malrotation, hepatosplenomegaly, diaphragmatic hernia, genito-urinary anomalies (e.g. hypospadias and cryptorchidism) and intrauterine growth retardation<sup>7-10</sup>. The phenotype associated with monosomy 8p syndrome includes hypotonia; microcephaly, a prominent metopic suture; coarse face or facial dysmorphism such as a high and narrow forehead, small, deep set and almond shaped eyes, abnormal slanting of the palpebral fissures, ptosis, strabismus, a flat nasal bridge, broad cheeks,

retrognathia, a small jaw, hypertelorism, a high arched palate, low-set malformed ears, a short inner canthal distance; broad chest and widely spaced nipples, pectus excavatum; and foot deformities<sup>7-9</sup>. On follow up, other problems are observed such as developmental delay, mental retardation, cerebral palsy, seizures, and hyperactive or impulsive behavior<sup>7-9</sup>.

The current cases of two siblings with partial trisomy 7q (7q22→qter) and monosomy 8p (8p23.3→pter) showed specific dysmorphic features that have been reported in patients with trisomy 7q but not monosomy 8p. The siblings had some features not yet reported in prior cases of trisomy 7q or monosomy 8p: second toes overlapping the adjacent toes, excess of subcutaneous tissue on the back of the feet and hands and early breast buds. The patients had anomalies more frequently observed in trisomy 7q. This might have been because the deleted region on 8p was too small (near to telomere) to detect the findings related to monosomy 8p.

### 한 글 요약

#### 오누이에서 발생한 derivative (8)t(7;8)(q22;p23.3) 염색체 이상 증후군의 임상 증상

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7번과 8번 염색체의 전위에 의한 염색체 이상 증후군은 드물게 보고되고 있어 그 임상적 특징에 대한 정보가 적다. 저자들은 비슷한 특이한 외형과 다발성 기형을 보인 오누이에서 동일하게 derivative (8)t(7;8)(q22;p23.3) 염색체 이상 증후군을 관찰하여 그 임상적 특징과 추적 관찰한 경과를 보고하는 바이다.

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