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Different Segregation of Chromosomes 5 and 7 in Two Generations and Related Phenotypic Findings

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Aim: In this study, we aimed to put forth the clinical consequences of rearrangement between chromosomes 5 and 7 observed in one fetus, one newborn infant (siblings) and their parents.

Materials and Methods: We performed chromosomal analysis in one fetus, one newborn (siblings) and their parents, applying standard protocols to fetal blood, amniotic fluid and peripheral blood samples. We performed both prenatal and postnatal karyotyping in the newborn infant.

Results: We described rearrangements related to chromosomes 5 and 7 in these individuals. We found that the curetted fetus and newborn infant were carriers of unbalanced and balanced rearrangements, respectively. We also found that the mother was a carrier of derivative chromosome 5 with [46,XX,der(5)t(5:7)(p15p11)] karyotype. The prenatal and postnatal karyotypes of the newborn infant confirmed an apparently identical nonreciprocal translocation between chromosomes 5 and 7, the same rearrangement as we found in the mother. We also found that the curetted fetus was carrier of derivative chromosome 5, [46,XY,der(5)t(5:7)(p15p11)mat]. The der(5) contained a complete short arm of chromosome 7. Otherwise both chromosomes 7 appeared normal. The fetus had malformations consistent with trisomy 7p as a result of familial derivative 5. However, the lung findings have not been reported before.

Conclusions: Karyotype analysis should be routinely performed in parents of partial trisomy patients and would be beneficial in identifying parents who clearly have a significant recurrence risk for abnormal offspring.

Key Words: Fetus, karyotyping, translocation, derivative chromosome 5

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İki Kuşakta 5 ve 7. Kromozomların Farklı Ayrılma Biçimleri ve Bunlarla İlişkili Fenotipik Bulgular

Amaç: Bu çalışma ile kürete edilmiş bir fetüste, bir yenidoğanda ve bunların ebeveynlerinde 5 ve 7. kromozomlar arasında görülen yeniden düzenlenmenin klinik sonuçları değerlendirildi.

Yöntem ve Gereç: Bu çalışmada kürete edilmiş bir fetüs, bir yeni doğan ve bunların ebeveynlerinden fetal kan, amnion sıvısı ve periferik kan materyallerine standart protokoller uygulanarak karyotip analizi yapıldı.. Yeni doğana, prenatal ve postnatal olarak karyotipleme işlemi uygulandı.

Bulgular: Analizler sonucunda; 5. ve 7. kromozomlar arasında translokasyon saptandı.. Kürete edilmiş fetüste dengesiz ve yeni doğanda dengeli translokasyon bulundu. Fenotipik olarak normal annede, türemiş bir 5. kromozom gözlemlendi. Annenin karyotipi, 46,XX,der(5)t(5:7)(p15p11) şeklinde idi. Annedeki bu dengeli translokasyon kürete edilmiş fetüste 46,XY,der(5)t(5:7)(p15p11)mat dengesiz karyotip şeklinde idi. Türemiş 5. kromozom, 7. kromozomun kısa kolunun tamamını taşıyordu. Bunun dışındaki 7. kromozomlar normal görünüyordular. Fetüs, 7p trizomisi (türemiş 5. kromozomdan kaynaklı 7p trizomisi) ile uyumlu çeşitli yapısal bozukluklar gösteriyordu. Bununla birlikte fetüste, bu olgu ile ilişkili olarak literatürde rastlanmayan akciğer bulguları olduğu kaydedildi.

Sonuç: Elde edilen bulgulara göre; parsiyel trizomili hastaların ebeveynlerinin rutin karyotip analizleri yapılmalıdır. Bu analizler,riskli ailelerin sonraki gebeliklerinde anormal çocuk doğurma riskini azaltmada fayda sağlayacaktır.

Anahtar Sözcükler: fetüs, karyotipleme, translokasyon, türemiş 5. kromozom

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Introduction

Trisomy for the short arm of chromosome 7 is rare and usually associated with a familial balanced translocation (1). Furthermore, there are some cases resulting from a partial *de novo* 7p duplication. These cases are of great interest in phenotype-genotype correlation studies. The majority of children with unbalanced karyotypes from such families had small duplications of distal 7p. The most common mechanism leading to 7p duplication is unbalanced segregation of a parental nonreciprocal translocation at meiosis. There is also one report of familial transmission of inverted duplication of 7p (2). *De novo* 7p duplications appear to be even rarer than the familial cases, with only three cases having been reported so far (3-5). A characteristic phenotype associated with trisomy 7p has been defined (6). Large fontanelles and sutures, hypertelorism, large and apparently low-set ears, high-arched palate, hip joint dislocation or contractures, a high frequency of cardiac septal defect, and mental retardation have been reported as the most common features of this phenotype.

Here, we present clinical and cytogenetic examination results of two cases of trisomy 7p and derivative 5 due to a derivative chromosome inherited from the mother, who has a nonreciprocal 5;7 translocation.

Materials and Methods

Subjects

A 27-year-old woman was referred for cytogenetic investigation to our amniocentesis laboratory at 18 weeks of gestation in April 2004 because of a history of a curettage in the Faculty of Medicine Hospital, Çukurova University, Adana, Turkey, in October 2001. Her husband was 30 years old. They were phenotypically normal and healthy, and there was no family history of congenital anomalies. The mother's first pregnancy loss occurred 3 years ago, prior to 23 weeks of gestation. This aborted fetus had been found abnormal according to second-trimester ultrasound examination. In this ultrasound examination, growth retardation, oligohydramnios and hygroma were observed.

Cytogenetic Analysis

In the case of the curetted fetus, the blood cells obtained from the term placenta were grown in culture for chromosomal analysis. The preparations were

obtained from 72-hour culture of fetal blood lymphocytes, using standard protocol. The G-banding was performed on metaphase chromosomes.

In the case of the newborn infant, the mother was first referred to our amniocentesis laboratory for karyotyping. At that time, a level III ultrasound revealed an active and normal-appearing fetus. Amniotic fluid (20 ml) was obtained transabdominally and amniocentesis was performed, using flask cell culture. Standard protocol was used for obtaining chromosome and G-banding technique was used for staining. Secondly, after normal delivery, the newborn infant was subjected to chromosomal analysis, based on blood lymphocyte culture. Consequently, the results obtained from amniocentesis were compared with results obtained from the lymphocyte culture.

Both parents were also subjected to chromosomal analysis, based on standard blood lymphocyte culture and G-banding technique. Twenty metaphases were microscopically analyzed for each case.

Results

Clinical Findings

Autopsy was performed on the curetted fetus, and findings were as follows: the 72 g fetus had a head circumference of 22.5 cm, crown-rump length of 21 cm, crown-heel of 31 cm and toe-heel of 4.2 cm, which were appropriate for gestational age. The external examination showed pes equinovarus, mild nuchal edema, long filtrum, hypertelorism, large forehead, wide fontanelles, short toe, medial deviation of the index finger, large and low-set ears, a preauricular ear pit on the left, micrognathia, and short neck. The lungs were hypoplastic and the right lung had two lobes. During the dissection of the heart and the vascular system, hypoplasia of the right ventricle and dilatation of the right atrium and left ventricle were detected. The atresia of the pulmonary valve, large secundum type atrial septal defect (ASD), ventricular septal defect (VSD), stenosis of tricuspid valve and overriding aorta were also noticed (Figure 1). There were no gross abnormalities in the gastrointestinal system or central nervous system. The kidneys showed normal fetal lobulation. There was no remarkable clinical finding in the newborn infant or parents.



Figure 1. General, facial, foot and heart appearances of the newborn infant.

Cytogenetic Findings

After cytogenetic analysis, the curetted fetus's karyotype confirmed the presence of the derivative chromosome 5 in all of the cells analyzed. All cells were found to have trisomy of 7p, [46,XY,der(5)t(5:7)(p15p11)mat] (Figure 2a). Analysis revealed a structural chromosomal abnormality, arising from a large amount of chromosomal material on the short arm of one chromosome 5. The meaning of this was derivative chromosome 5, containing materials from chromosome 7. Otherwise, both chromosomes 7 were shown as normal. These results demonstrated the presence of an unbalanced translocation resulting in trisomy 7p.

The father showed normal chromosome complements. However, karyotype of the mother showed a rearrangement involving chromosomes 5 and 7. The karyotype of mother was designated as 46,XX,der(5)t(5:7)(p15p11) (Figure 2b). The breakpoint was on the centromere of a chromosome 7 and the complete short arm of this chromosome was transported

onto band 5p15 of a chromosome 5 (Figure 2b). This showed that the complete trisomy of the fetus was derived from chromosome 7 of the mother.

In the case of the newborn infant, amniocentesis showed an abnormal karyotype; 46,XY,der(5)t(5:7)(p15p11) (Figure 2c). This karyotype was apparently concordant with the mother's karyotype. This type of derivation is not known to be associated with any clinical effect. Therefore, the pregnancy was continued to term without complications. After birth, the result of the newborn infant's karyotyping also confirmed an apparently identical derivative of chromosome 5. Otherwise, the physical examination of the offspring was normal and the baby was healthy.

The mother was counseled regarding prenatal diagnosis in the next pregnancy. Thereafter, the following pregnancy of the mother was terminated because of the karyotyping result, based on second-trimester amniocentesis, which showed that the fetus was carrier of trisomy 7p.

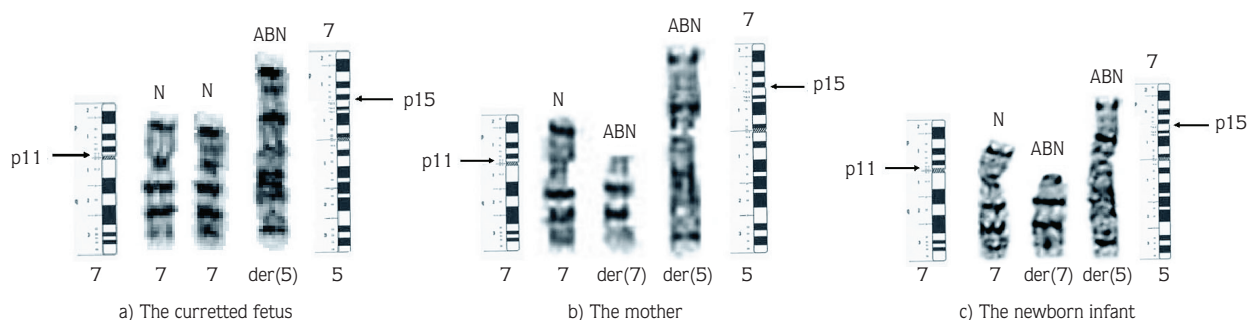


Figure 2. G-banding partial karyotype and schematic drawing of chromosomes 5 and 7 showing balanced and unbalanced chromosomal rearrangement.

Discussion

Chromosomal rearrangements occur at a low frequency in the general population (7). Thus, reporting of any rearrangement, specifically in relation with some clinical findings, is important. With this in mind, we conducted and presented this study describing one unbalanced and two balanced rearrangements of chromosomes 5 and 7 in one curretted fetus, one newborn infant and their mother, respectively. Theoretically, prevalence of this translocation is less than 1% in the population. Thus, an aneuploid conceptus with either a duplication or deletion is likely to be viable unless duplicated or deleted segments involve essential genes. Consistently, in a previously reported study, a phenotypically normal mother and her two daughters with different phenotypes were shown to have a derivative chromosome 5.

In the family presented, a phenotypically normal newborn infant had one balanced translocation involving chromosomes 5 and 7. This rearrangement was in the heterozygous state and the same rearrangement was also found in the mother. Transmissible duplications and deletions usually occur in the heterozygous state because they are transmitted through the parent (8). This type of derivation is not known to be associated with any clinical effect because there is no genetic material loss. As is known, in the heterozygous state, a carrier of balanced rearrangements also has normal complementary chromosomes, which usually leads to a normal phenotype (9). The presence of the der (5) in a normal mother suggested that the translocation itself may be harmless or asymptomatic. The newborn infant's karyotype had the same rearrangement as the mother's and the newborn was healthy as well. If the chromosome behaves normally during the meiotic divisions, half of the gametes receive a normal chromosome, and the other half a chromosome with the duplication or deletion (8). This shows that the offspring carrying the rearranged chromosome has received a gamete involving the derivative chromosome.

Malformations observed in the current fetus with trisomy 7p are tabulated alongside malformations found previously in other cases in Table 1. There is concordance between the findings of the current fetus and of all the

Table 1. Phenotypic manifestations in patients with trisomy 7p11-pter.

Present Case	In Previous Series ^a
Physical Features	
Broad nasal bridge	+
Hypertelorism	+
Micrognathia	+
Large and low-set ears	+
Long philtrum	+
Prominent forehead	+
Large fontanelles	+
Limb deformities	+
Nuchal edema	-
Short toes	-
Short neck	+
Pre-auricular ear pit	-
Cardiovascular abnormalities	
Ventricular septal defect	+
Ostium secundum type atrial septal defect	+
Hypoplasia of right heart	-
Hypoplasia of right ventricle	+
Dilatation of right atrium	+
Dilatation of left ventricle	-
Overriding aorta	-
Atresia of pulmonary valve	-
Stenotic tricuspid valve	-
Lung	
Hypoplastic lungs	-
Two lobes at right lung	-
Other abnormality -not available	

^a The series was composed of 37 live births and 3 fetuses.

described cases of trisomy 7p, excluding the lung findings. It seems that, despite the varying extent of the trisomic segment, most cases described with trisomy of regions from 7p11, p12, p13, p14 or p15 to pter share common features. However, it is said that the severity of effect for duplication type aberrations depends on their size, gene content, heterozygosity or homozygosity and the organisms in which they occur (8). Our case had three

copies of complete short arm of chromosome 7. These duplications usually result from a chromosomal imbalance in one parent of a translocation carrier (10-12). There is also a report of familial transmission of inverted duplications of 7p (2).

In our case, observed predominant facial changes were consistent with trisomy 7p-originated malformations, specifically, the large fontanelle in early childhood, prominent forehead, and hypertelorism. Mutations in the TWIST gene located at 7p21 have been found in Saethre-Chotzen syndrome and craniosynostosis cases (13,14). It is conceivable that three copies of the TWIST locus contribute to a reverse phenotype with delayed closure of fontanelles and sutures (15). Our case also had striking large fontanelles (Figure 1).

Striking observations of our case were cardiovascular abnormalities with the most common malformations being hypoplasia of the right heart, hypoplasia of right ventricle, dilatation of right atrium, dilatation of left ventricle, overriding aorta, atresia of the pulmonary valve and stenotic tricuspid valve (Figure 1). It has been proposed that the MEOX2 gene, mapped to 7p22.1-21.3 (16), could be responsible for heart defects associated with trisomy 7p (6). It has been hypothesized that more than one segment on 7p may be involved in normal cardiac development (12).

Since this is the first reported case of the association of trisomy 7p with lung abnormalities, one can argue that oligohydramnios can also cause pulmonary hypoplasia. Our case also had oligohydramnios. Thus, trisomy 7p triggering oligohydramnios-pulmonary hypoplasia cascade can be another probable explanation. This data warrants further investigation of the chromosome 7p arm, in an effort to identify genetic risk factors for lung development and oligohydramnios.

In conclusion, it is possible in the present case to identify the clinical features most likely to be caused by trisomy 7p. Three copies of the short arm of chromosome 7 may be the cause of many of the facial features common in patients with trisomy 7p. In addition to known abnormalities, the new findings in our case are lung abnormalities. This suggests that chromosome 7p may contain gene(s) playing a role in lung development. However, for couples with a known chromosomal rearrangement, prenatal diagnosis is essential if a viable offspring with an abnormal clinical outcome is likely. It is also recommended that cases of clinically normal subjects with unbalanced karyotypes be published so that informed and correct decisions can be made by parents prenatally when a similar rearrangement is identified.

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