A Case with Mosaic Ring Chromosome 18

Mozaik Ring Kromozom 18 Olan Bir Olgu

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ABSTRACT

The classical mode of ring chromosome formation is by break forming in both arms of the affected chromosome, fusion of the breaking points and loss of the distal fragments. Ring chromosome of the chromosome 18 is relatively common among ring chromosomes and the rate of having typical clinical sings of 18p and 18q sydromes vary related to the length of the deletion in 18p and 18q. Ring 18 phenotype is characterised by growth retardation, mental retardation and nonspecific abnormalities, also facial dysmorphism and malformations may be observed. Our case referred with congenital malformation, motor mental retardation (MMR), short stature, high palate, pectus excavatus was evaluated genetically. GTL banding and FISH methods were performed for the metaphase plaques obtained from peripheral lymphocytes cultered for 72 hours. The karyotype of the case was detected to be 46,XX,r(18)[25]/46,XX[75] and confirmed by FISH analysis.

Key Words: Ring chromosome 18, chromosome analysis, abnormality

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ÖZET

Ring kromozom oluşumunun klasik modu, etkilenen kromozomun her iki kolunda kırık oluşması, kırılma noktalarının füzyonu ve distal fragmanların kaybıdır. 18. kromozomun ring kromozomu, ring kromozomlar içinde nadirdir ve 18p ve 18q'daki delesyon büyüklüğüne bağlı olarak 18p ve 18q sendromlarının tipik klinik işaretlerine sahip olma oranı değişir. Ring 18 fenotipi, gelişme geriliği, mental retardasyon ve başlıca spesifik olmayan anomalilerle karakterize olup, fasiyal dismorfizm ve malformasyonlar gözlenebilir. Konjenital malformasyon, motor mental retardasyon (MMR), kısa boy, yüksek damak, pektus ekskavatus ön tanılarıyla refere edilen olgumuz genetik açıdan değerlendirilmiştir. Olguya ait periferik kan lenfositlerinden 72 saatlik kültür sonucu elde edilen metafaz plaklarına GTL bantlama ve FISH metodları uygulanmıştır. Yapılan kromozom analizi sonucu olgunun karyotipi 46,XX,r(18)[25]/46,XX[75] olarak belirlenmiş, FISH analizi sonucunda bu karyotip doğrulanmıştır.

Anahtar Sözcükler: Ring kromozom 18, kromozom analizi, anomali

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INTRODUCTION

Ring chromosomes are rare chromosomal disorders that usually occur *de novo*. The classic shape of ring reveals itself through the formation of fracture in both arms of the affected chromosome, fusion of the broken points and loss of the distal fragments (1). Amongst the other ring chromosomes, ring chromosome 18 is relatively common and clinical manifestations, depending on the size of deletions on 18p and 18q, corresponds to the typical symptoms of 18q and 18p deletion syndromes. The severity of the clinical characteristics of the ring chromosome carriers is largely dependent on the size of deletion of the chromosomal segments (1, 2). Ring 18 phenotype is characterized by growth retardation, severe mental retardation and other non-specific abnormalities. Dysmorphism and facial malformations can be seen (1). In this study, using conventional techniques and FISH analyses we report a chromosomal karyotype of 46,XX,r(18)[25]/46,XX[75] in a 11 year old female patient.

CASE REPORT

The patient with preliminary findings of congenital malformations, motor mental retardation (MMR), short stature, high-arched palate and pectus excavatum was evaluated cytogenetically. At the time of birth the parents were both aged 24; this was their 2nd child and the 2nd full term pregnancy. The case had one older and one younger healthy sisters (Figure 1). The birth weight of the baby was 3100 g, and growth retardation was noticed when the child was 1.5 years old. When the patient was 2 years old, she presented with congenital malformations, motor mental retardation (MMR), short stature, high arched palate, pectus excavatum, large-and down-set ears, bilateral strabismus, ptosis, prominent front incisor teeth, hypertelorism, depressed nasal bridge, broad nose wings, lower corners of the mouth, long frenulum, pes planus in both feet, frequent infections, slurred speech and patent ductus arteriosus (PDA).

This study has been presented as a poster at European Human Genetics Conference in Vienna, Austria between May 23-26 2009, and in VII. National Medical Genetics Congress in Çanakkale between May 6-9 2008.

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Metaphase plaques of the patient's peripheral blood lymphocytes, obtained from a 72h culture, were evaluated using GTL-banding and FISH. Twenty five of 100 metaphase plaques were determined to be 46,XX,r(18) (Figure 2) and it is verified by FISH method performed with the probes cep 18 (Aqua) and telomere 18q (Red). As a result of the chromosome and FISH analysis, the karyotype of the patient was determined to be 46,XX,r(18)[25]/46,XX[75].

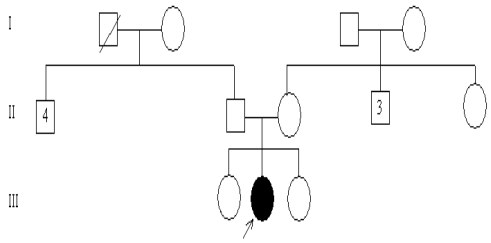

Figure 1. Pedigree analysis

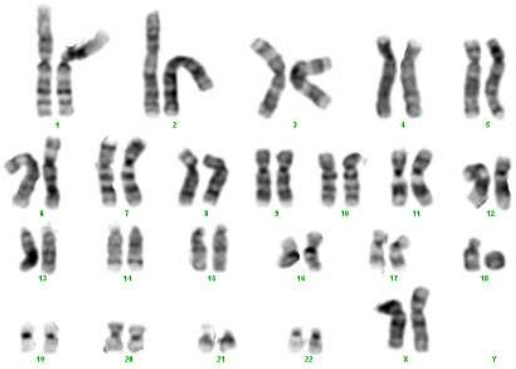

Figure 2. Karyotype of the case, 46,XX,r(18)

DISCUSSION

Ring chromosome results from a ring shape when the two ends of a chromosome fuse. There are several ways by which a ring chromosome may form. Chromosome arm fracture and fusion of the ends of the proximal fractures along with the loss of distal chromosome material can lead to the formation of the ring. The reason for this process of DNA strand breaks and fusion is not yet known. Alternatively, the rings can result from telomere dysfunction. This is a fusion of terminal ends of a chromosome, without a significant loss of genetic material. Animal models and *in vitro* studies have shown that the mechanism of the formation of telomeric ring may be activated after the removal of protective proteins at the ends of chromosomes during the shortening of telomeric DNA (3, 4). Rings that produce amplified sequences may also occur, although not necessarily from the two processes described above. This event may result from "break-fusion-bridge" that frequently occur during recombination events (3).

Additional chromosomal abnormalities usually occur in patients with ring chromosome because of sister chromatid exchange occurring over the course of mitosis and that result in the formation of dicentric rings, interlocked rings and other structural conformations. These unstable chromosomes that may accompany loss of ring chromosomes can lead to the production of monosomic cells that may be compatible or incompatible with life (5). Thus, the ring chromosomes in somatic cells of an individual may vary in number and structure and may lead to a mosaic karyotype through a process called "dynamic tissue-specific mosaicism" (6). This cytogenetic variation seems to be often dependent on the size of the ring, the rate of sister chromatid exchange in the ring chromosome, and viability of cell lines with monosomic or abnormal ring chromosomes (7).

Ring 18 syndrome is characterized by severe mental retardation (91%), growth retardation (85%), microcephaly (86%), brain and ocular malformations, hypotonia (85%), macrodactyly (80%) and other skeletal abnormalities. Facial dysmorphisms can be listed as moderate facial dysplasia, epicanthal folds, hypertelorism, low corners of the mouth, micrognathia, low-set dysplastic ears and webbed neck (1). Other findings include ptosis (73%), strabismus (58%), bulb anomalies, cleft lip/palate, depressed nasal bridge, short neck, vertebral and rib anomalies, clear distance between nipples, abnormalities of the external genitalia, atresia of the external auditory canal, cardiac defects (53%), renal abnormalities, hearing impairment and reduction in serum IgA. Several ring 18 syndrome phenotypes including mental retardation (91%), growth retardation (85%), hypertelorism (76%), epicanthal folds (73%), ptosis (73%), strabismus (58%), heart defects (53%), low localized dysplastic ears (68%), lower corners of the mouth (88%), depressed nasal bridge, high-arched palate (43%) were also observed in our case(1).

Ring 18 syndrome patients show clinical features that are reminiscent of 18q-syndrome (1, 2) and can also show clinical symptoms of 18p-syndrome due to deletion of the p arm terminal (1). In some cases the clinical features of both syndromes may be present (8). The parents of the patient in the current study were with normal chromosome organization that supports the *de novo* development of ring chromosome 18 in our patient. Clinical findings of the patient are in general in agreement with ring 18 syndrome as a result of the peripheral lymphocyte culture and FISH analysis that revealed a karyotype 46,XX,r(18)[25]/46,XX[75].

Conflict of Interest

No conflict of interest was declared by the authors.

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