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Case Report Open Access

A Mosaic Ring Chromosome 21 in a Patient with Mild Intellectual Disability not Evidenced by Array-Cgh

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Abstract

We report a case of a two year-old girl with persistent thrombocytopenia, syndactyly, and mild psychomotor delay with speech delay. Proband chromosomal analysis from peripheral blood detected a mosaicism with two cell lines: the first with a ring chromosome 21 46,XX,r (21) (88%), and the second 45,XX,-21 (12%). In uncultured cells the level of mosaicism was 15% for the 46,XX,r(21) cell line and 85% for the 45,XX,-21 cell line. A different level of mosaicism was detected on buccal smear cells with a r(21) in 94%, and monosomy 21 in 6% of cells. The findings in the different cell lines are consistent with loss of the ring chromosome in the blood line.

Keywords: Chromosome 21; Ring; Mosaic; Array-CGH

Introduction

Ring chromosome 21 is a rare genetic condition originally identified in patients with dysmorphic features and congenital malformations [1]. Similar aberrations have also been reported in phenotypically normal individuals [2,3]. There are three different types of r(21) recognized. Types 1 and 2 are associated with a loss of material from chr. 21. Type 3 is associated with extra material from chr. 21. Patients with type 1 have generally a normal phenotype, with only occasional reports of short stature. The type 2 ring is associated with a wide variety of phenotypes, with varying severity. They commonly are associated with short stature, microcephaly, seizures, learning disabilities, heart defects, cleft lip and palate, and thrombocytopenia. Patients with type 3 ring 21 have features similar to Down syndrome [4-6].

We report on a patient with mild intellectual disability and dysmorphic features with a 46,XX,r(21)(p13q22.3)/45,XX,-21 karyotype showing a different level of mosaicism in cultured and non-cultured cells. Such mosaicism was tissue dependent.

Case Report

This report concerns a 2-years-old girl with a r(21) born at term after an uneventful pregnancy and delivery, the second child of healthy non consanguineous parents. Birth weight was 3000 g (10^{th} -25^{th} percentile), length 48 cm (25^{th}-50^{th} percentile), and head circumference was 35 cm (50^{th}-75^{th} percentile). Family history was unremarkable. She had slight delay in psychomotor development, including speech delay. She could sit at the age of 9 months, and walk unsupported at the age of 12 months. The patient was referred to our Unit because of persistent thrombocytopenia and syndactyly, pes planus and a bilateral Babinski sign. The remainder of physical examination revealed curly hair, thin upper lip, broad nasal bridge and tip. She had normal stature, head circumference, and deep tendon reflexes (Figure 1). Hearing screen, electrocardiography, echocardiography, abdominal ultrasound and ophthalmologic examination were normal.

Cytogenetic analysis was performed using standard techniques, on Giemsa banded chromosomes from peripheral blood lymphocytes, showing a karyotype: 46,XX,r(21)(p11q22.2)(88%)/45,XX,-21(12%) (100 metaphases investigated). Parental karyotypes were normal, as well as that of the healthy brother (100 metaphases investigated).

Array-Comparative Genomic Hybridization (a-CGH) using the CytoChip 575-Kb resolution bacterial artificial chromosome (BAC) array (BlueGnome, Cambridge, United Kingdom) was performed according to the recommendations of the manufacturer. Data were analyzed using the BlueFuse for microarray software package (BlueGnome). A-CGH analysis showed monosomy 21 (Figure 2).

Fluorescence In Situ Hybridization (FISH) experiments were performed on the same cytogenetic specimen using the following commercial DNA probes: alpha-sat 13/21, tel 21q, AML1 on 21q22

Figure 1: The proband showing curly hair, thin upper lip, broad nasal bridge and tip.

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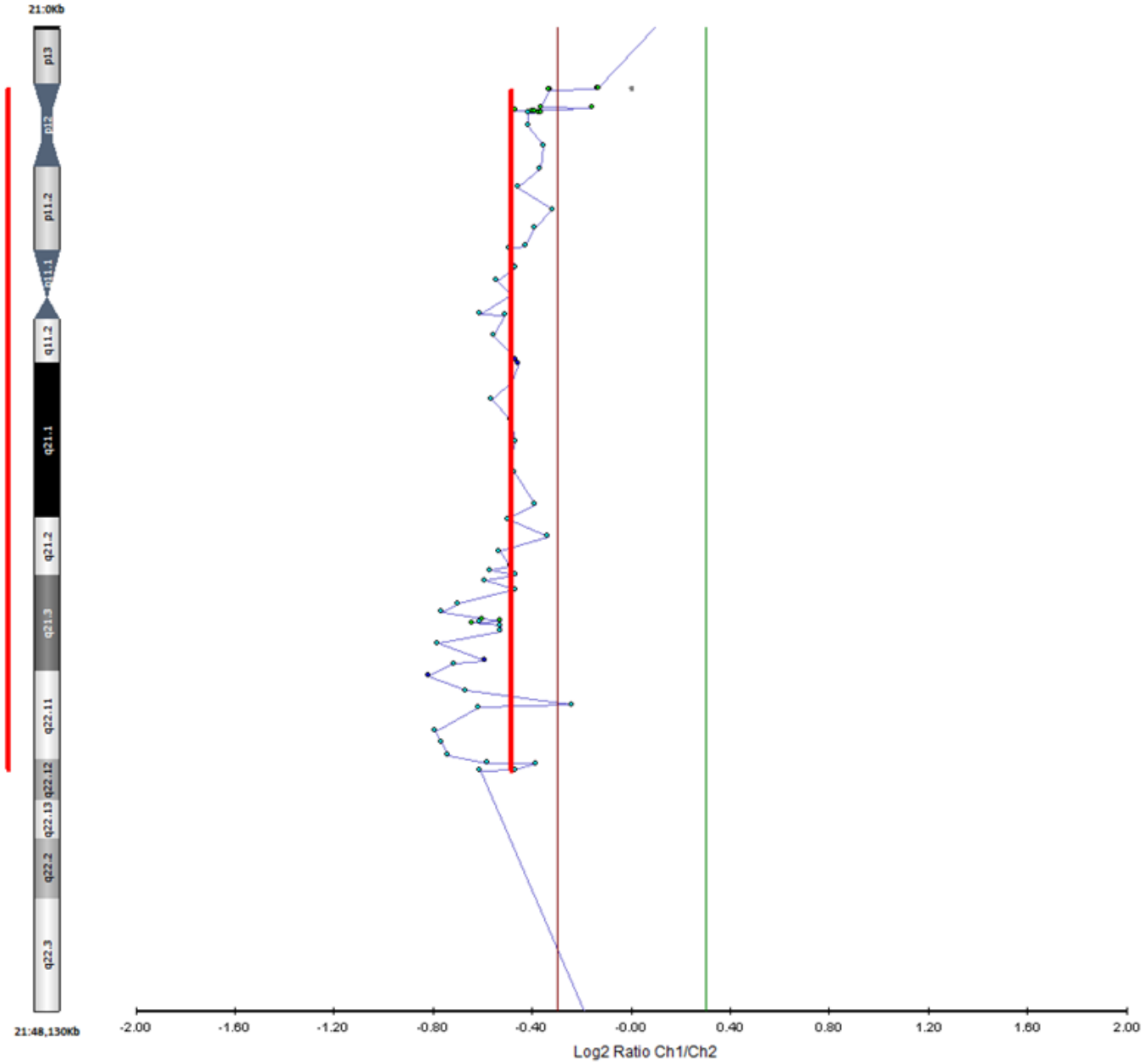

Figure 2: Array-CGH analysis showing the complete monosomy of chromosome 21.

and whole 21 chromosome painting (Cytocell, Italy; Kreatech, Italy). The probes were applied following standard procedures outlined by the manufacturers. Dual-color FISH images were digitally generated using the Isis FISH imaging software (MetaSystems). 300 cells were scored for each sample. FISH analysis showed a r(21) in 77% of examined cells and a monosomy 21 in 23% (300 cells investigated). FISH studies showed that the breakage and reunion have occurred at bands 21p11 and 21q22.2 (Figures 3a and 3b).

A further FISH analysis performed on uncultured lymphocytes from peripheral blood using the same DNA probes showed a r(21) in 14% of examined cells and a monosomy 21 in 86% (300 cells investigated). The same probes on buccal smear cells showed a different level of mosaicism with a r(21) in 94% and a monosomy 21 in 6% of cells (300 cells investigated) (Figures 3c and 3d).

Discussion

Different mechanisms have been proposed for r(21) formation [6,7]. In our patient, the deletion of terminal regions of chromosome 21 revealed that the ring was generated by the most common mechanism of ring formation, consisting of breakage and reunion of the short and long arms. The high degree of phenotypic variability in patients with r(21) could be explained by two mechanisms: the molecular structure of the ring, and its instability, that leads to different degrees of mosaicism.

The size of the deleted or duplicated region in patients carrying

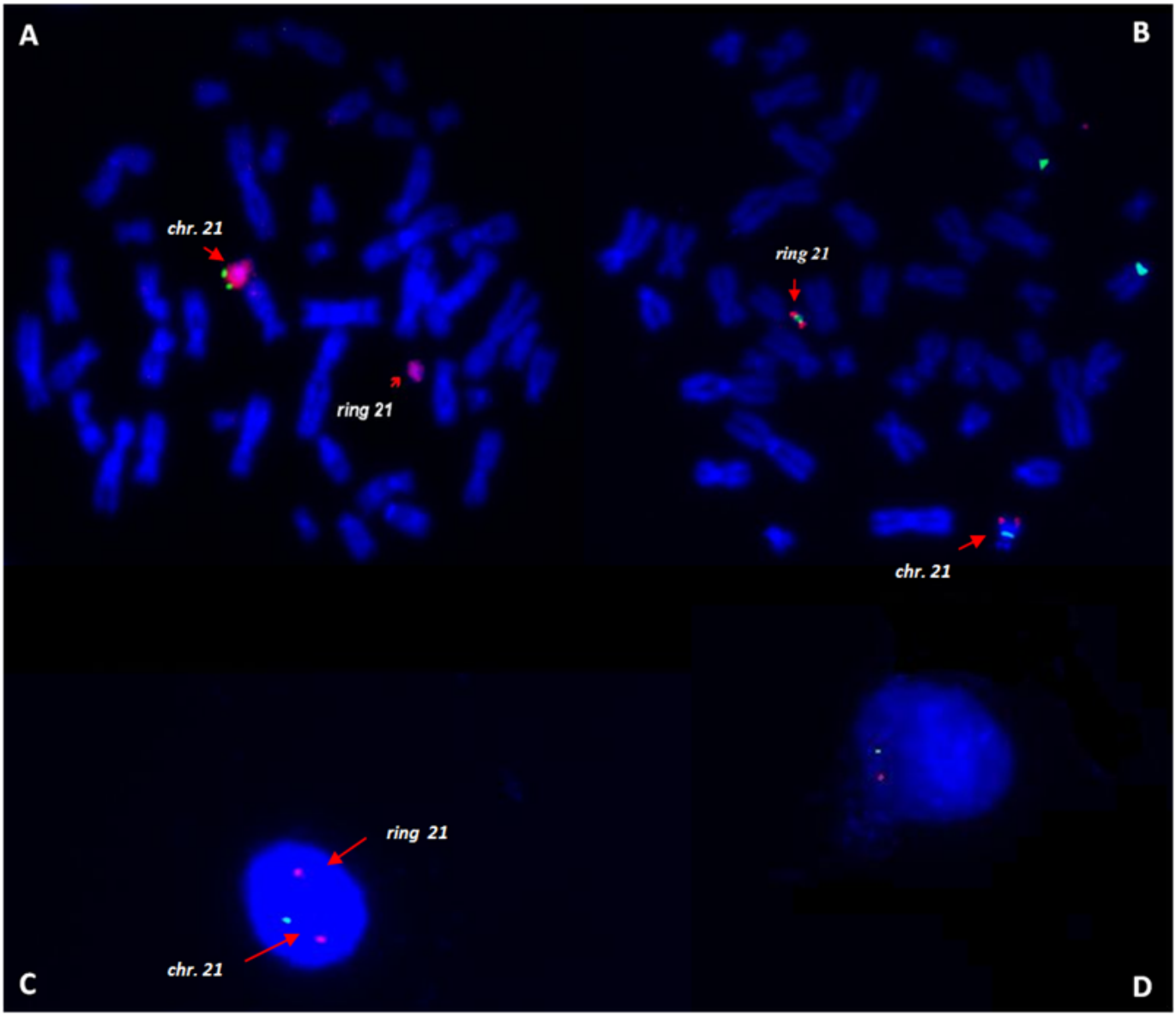

Figure 3: FISH analysis on peripheral blood (A-B) and buccal smears cells (C-D): A) probes whole chromosome painting (red) and tel21q (green) showing a normal chromosome 21 and a r(21); B) probes alpha-sat 13/21 (green) and locus specific 21q22 (red) showing breakpoints at 21p11 and 21q22.2; C) probes locus specific 21q22 (red) and tel21q (green) showing a normal chromosome 21 and a r(21); D) probes locus specific 21q22 (red) and tel21q (green) showing a monosomic cell.

a r(21) is closely associated with the phenotypic variability [5,8]. A wide range of phenotypes have been reported, apparently dependent on the size and position of the deleted region [9-11]. The hemizygosity for a proposed critical region between 21q22.1 and 21q22.2 may be responsible for the "21q-syndrome", with a well-characterized phenotype [9,10]. However, terminal deletions of both arms of chromosome 21 have also been reported in healthy people, suggesting that the critical region is not at the telomeres [5,8].

The postzygotic instability of ring chromosomes can generate different degrees of mosaicism, resulting in monosomic subclones lacking the ring chromosome, and cell lines where the normal chromosome is replaced by the ring [8,12]. The variable amount of such mosaicism in different tissues could further influence the phenotype [8].

Our patient has only some of the symptoms reported in literature namely mild speech and motor delay, thrombocytopenia, and some dysmorphic features.

In this case cytogenetic analysis showed a mosaic karyotype 46,XX,r(21)(p11q22.2)(88%)/45,XX,-21(12%), with a low level of monosomic cells. FISH analysis on cultured cell from peripheral blood substantially confirmed the karyotype results. Surprisingly, array CGH performed on uncultured peripheral blood cells demonstrated a complete monosomy of chromosome 21. A new FISH analysis carried out on uncultured peripheral blood cells showed a different percentage of monosomic cells (86%), versus 12% reported by karyotype. Moreover, a further FISH analysis on buccal smear cells demonstrated a 6% of monosomic cells, while the rest were 46,XX,r.

In the present case FISH analysis was able to identify the variable

mosaicism in cultured and uncultured cells. An array-CGH test performed without a previous cytogenetic analysis would have failed to identify the ring. Balanced chromosome rearrangements are not identified by array-CGH, but another limitation of CGH is its reduced ability in identifying a low-level mosaicism [13]. A-CGH is used to detect copy number variations but not mosaicism and in cases where a terminal deletion is seen a ring would be considered in the differential diagnosis. Ring chromosomes are unstable structures during mitosis due to the instability and dysfunction of the centromere and/or instability of the ring chromosome. Cases with small ring chromosomes frequently show monosomic subclones lacking the ring chromosome and cell lines where the ring replaces one of the normal chromosomes [3,9,12]. Moreover, the amount of mosaicism may be variable in different tissues, further influencing the phenotypic variability [8]. Preferential growth of the different cell lines under culture contribute to the variability seen. In this case a screening test for chromosomal aberrations performed only with array-CGH would have missed the aberration in mosaic form. Such mosaicism was only identified after culturing that gave the line with the r(21) an advantage.

Mosaicism level and mosaic cell line rate variation among different cultured and uncultured tissues observed in our case support mosaicism in critical tissues as of relevance for r(21) phenotype-genotype correlations.

To the best of our knowledge, the present patient represents a new case of intellectual disability and minor dysmorphic features associated with r(21) and the first case of mosaicism studied in different tissues.

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