

PARTIAL TRISOMY OF CHROMOSOME 9 INHERITED BY ADJACENT SEGREGATION 2 OF A BALANCED RECIPROCAL TRANSLOCATION IN THE MOTHER: RARE MECHANISM IN CHROMOSOMAL ABNORMALITIES

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ABSTRACT

Background: Reciprocal translocations are one of the most common structural chromosomal rearrangements in humans, they are due to the exchange of chromosome material between two nonhomologous chromosomes.

If a person carries a balanced reciprocal translocation, meiosis may produce normal gametes, as well as gametes with either balanced or unbalanced abnormalities, depending on the segregation pattern during gametogenesis. All types of segregations can occur, although with different percentages. The adjacent-2 segregation is the less common one and it often leads to non-viable products in many species.

Case presentation: We report a case of an 18 months-old female patient, who was referred to the medical genetics' consultation for psychomotor retardation and facial dysmorphism. A postnatal constitutional karyotype was performed in our laboratory on a peripheral blood sample followed by a parental karyotype. The results revealed an additional derivative chromosome 9 in the patient resulting from an adjacent-2 segregation in the mother.

Conclusion: This observation highlights the possible occurrence of rare mechanisms of segregation during meiosis in families with a reciprocal translocation. Investigating these events is crucial for both diagnosis and genetic counseling.

Keywords:

Reciprocal translocations, segregation mechanisms, adjacent-2 segregation, congenital malformations.

INTRODUCTION

Reciprocal translocations are an exchange of chromosomal segments between two non-homologous chromosomes. They are commonly balanced without pathological consequences in their carrier [1]. However, during meiotic chromosomes segregation, they can cause the production of unbalanced gametes leading to recurrent miscarriage, infertility or congenital malformations in the offspring [2]. The alternate type is most frequently observed with transmission of non-rearranged chromosomes or balanced translocation in nearly 90% of cases; adjacent-1 segregation is the most frequent form of imbalance, although adjacent-2 and 3:1 segregation event can also occur. However, segregation 4:0 has never been observed. Adjacent-2 segregation is rare, and it often leads to non-viable products in many species. It is observed in about 3–4% of unbalanced human progeny resulting from parents with translocations [1]. This proportion varies based on several factors according to published studies. We report a family where the mother carries a reciprocal translocation causing a rare unbalanced chromosomal condition in the daughter because of a rare type of chromosomal segregation (adjacent-2).

MATERIALS AND METHODS

Clinical summary

An 18 months-old female patient, the third of their siblings, non-consanguineous, was referred to the medical genetics' consultation for significant psychomotor retardation, hypotonia and facial dysmorphism. The maternal age at birth was 33 years, and the paternal age was 38 years. The clinical examination of the patient showed a short stature with a height less than -3 SD and a weight less than -4 SD, the head circumference was at -2 SD. The patient had significant facial dysmorphism with a narrow forehead, low anterior hairline, palpebral slits oriented down and out, hypotelorism, canthal dystopia, enophthalmos,

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bulky nasal bridge, hanging columella, downturned corners of mouth, thin lips and macrognathism, low-set ears. The neck was short and the nipples were widely spaced. Extremities examination showed slender fingers and a rocker bottom left foot. The patient had a brother who died at the age of 2 years. The mother reports that the child has Down syndrome (Figure 1). The child's photo indeed shows a phenotype consistent with Trisomy 21, although the karyotype has not been performed.

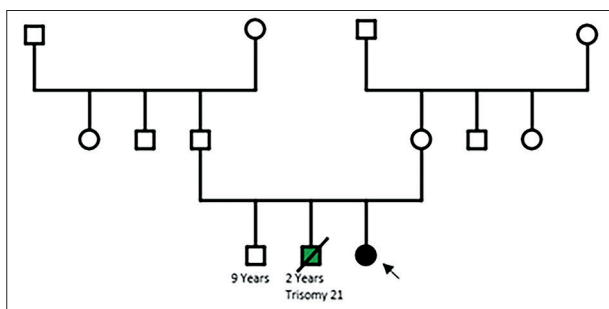


Figure 1. Family pedigree.

Investigations

We performed in our laboratory a postnatal constitutional karyotype on a peripheral blood sample, with a lymphocyte culture, using conventional RHG banding. 25 cells were analysed.

Metaphase analysis in our patient identified the following abnormalities:

- The presence of three chromosomes 9: two chromosomes had a normal structure, the third is a derivative chromosome (der(9)) (Figure 2, see the red arrow)
- The presence of one normal chromosome 21.

Therefore, the chromosomal formula of this karyotype is **46,XX,+der(9),-21. (Figure 2, c)**

Parental karyotypes were also performed and we analysed 25 cells for each karyotype. The father's karyotype was normal (46, XY) (Figure 2, a), while the mother's showed a reciprocal translocation between the long arm of chromosome 9 and the long arm of chromosome 21: **46,XX,t(9;21)(q22;q21) (Figure 2, b).**

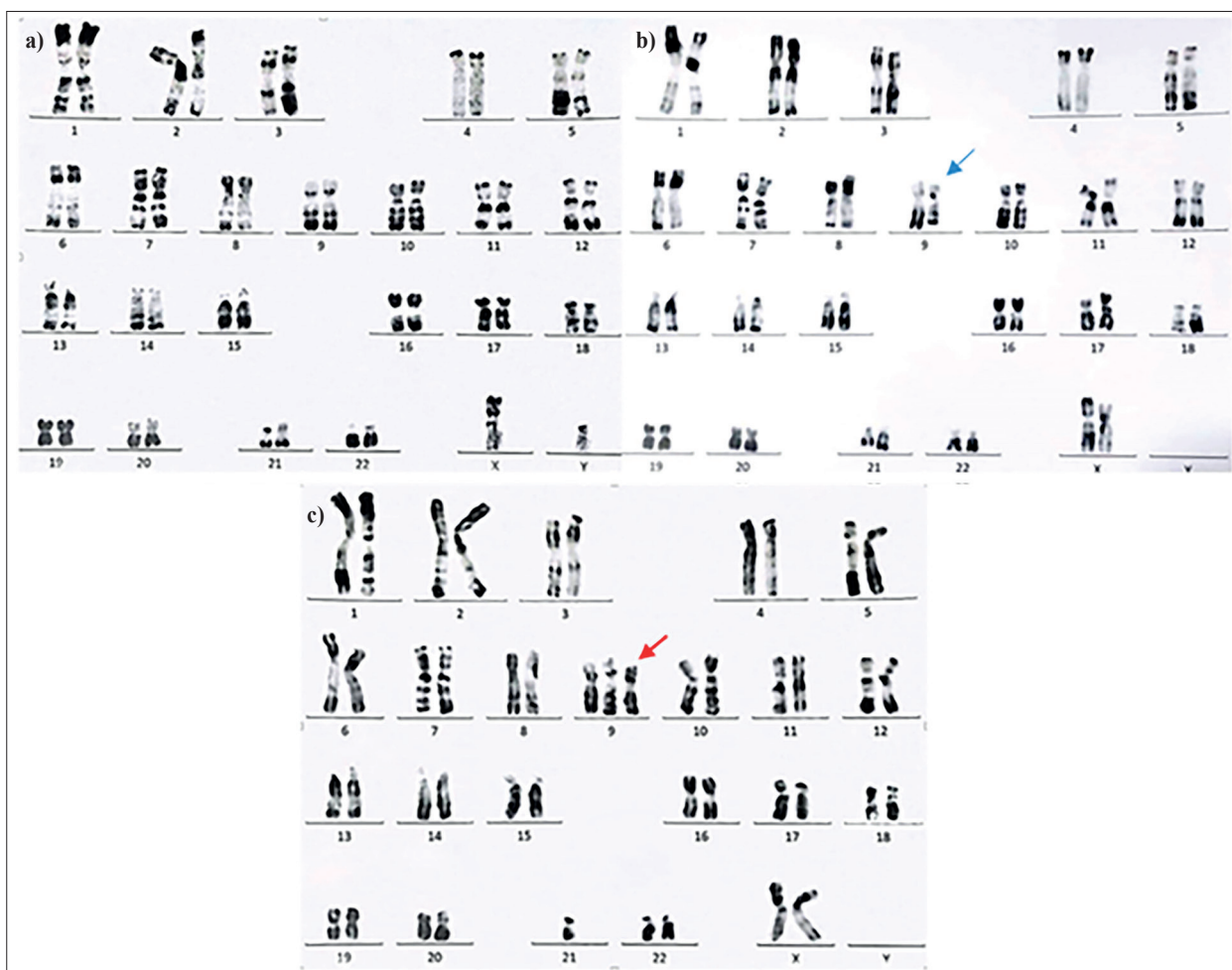


Figure 2. The results of karyotypes, a: The father's karyotype. b: The mother's karyotype. c: The proband's karyotype.

It is then a derivative chromosome 9 resulting from an adjacent-2 translocation between chromosomes 9 and 21 in the mother. The karyotype formula according to The International System for Human Cytogenetic Nomenclature (ISCN) is therefore: **46,XX,+der(9)t(9;21)(q22;q21) dmat,-21.**

DISCUSSION

Theoretical background of adjacent-2 segregation:

Reciprocal translocations are one of the most common structural chromosome rearrangements in humans, with an incidence of approximately 0.14% in newborns [3]. If a person carries a balanced reciprocal translocation, meiosis can either produce normal gametes, or gametes with balanced or unbalanced abnormalities, depending on the segregation mechanisms [3].

In our case, the segregation was done according to the adjacent-2 type. This is a very rare case where the normal chromosome 9 has matched with its homologous chromosome 9 structurally rearranged (with a part of chromosome 21), (Figure 3.) This type of segregation produces 2 types of gametes, which leads to an unbalanced egg after the fertilization, therefore, a partial trisomy of the chromosome 9 and a partial monosomy of the chromosome 21 were produced in our case.

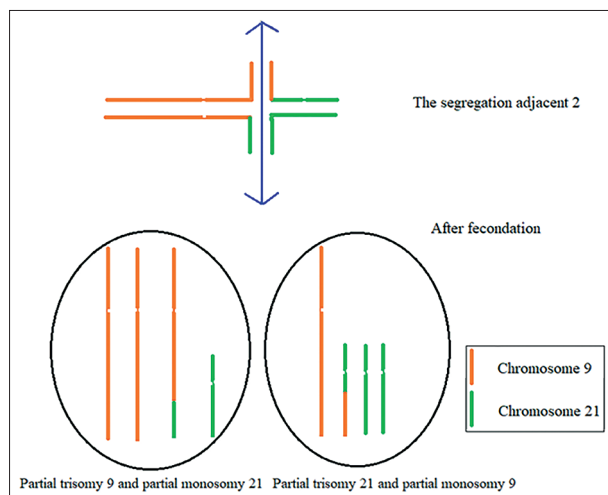


Figure 3. The segregation pattern of adjacent-2 segregation.

Literature overview:

The incidence of the adjacent-2 segregations depends on many factors and it led to many studies with conflicting data. Some studies say that the recombination depends on the carrier's gender like Ogilvie et al. who suggests that adjacent-2 segregation probability was higher in the male

carriers while Ko et al. reported that there is no implication of the carrier's age or chromosomal breakpoints [4,5]. Nevertheless, others authors concluded to the potential involvement of the carrier's age, chromosomal breakpoints, or the nature of the translocated segment (patients with shorter translocated segments produced more adjacent-1 products, whereas those with shorter centric segments had a tendency to produce higher numbers of adjacent-2 products [3,6].

Two recent studies were interested in analyzing the meiotic behavior of translocation; including Zhang et al. who suggests that meiotic segregation modes can be affected by the gender, the location of translocation breakpoints, the age of the carrier and the chromosome type. While Wang et al. reported an implication of the terminal breakpoints and the acrocentric chromosomes, with no involvement of the carrier's gender [7,8]. Adjacent-2 Segregation has a repetitive nature [9]. That may explain the origin of trisomy 21 in the brother, by fertilization of the other gamete resulting in a partial trisomy of the chromosome 21 and a partial monosomy of the chromosome 9. Although the karyotype was not performed, a free Trisomy 21 cannot be ruled out.

Genotype–phenotype correlation:

The chromosomal abnormality is responsible for a trisomy of the region 9pter to 9q22 and a monosomy of the region 21pter to 21q1 (more precise localization of breakpoints requires the use of complementary molecular cytogenetic techniques). The majority of the features in our patient were described in trisomy 9p [10,11] including enophthalmia, palpebral slits oriented down and out, nose dysmorphism, spaced nipples, short neck and psychomotor retardation. A lot of cases that reported having partial trisomy 9 have the 9p syndrome criteria [12]. The region 9q1 has no phenotypic consequences because it's a heterochromatin. The 9q2 region is responsible for micrognathia, abnormalities of the cranial sutures involving widely patent fontanelles, malformations of the urogenital and cardiovascular systems; these are not present in our patient [11]. For the monosomy 21q1, one case was reported in the literature and he had rocker bottom feet and slender fingers which were also present in our patient [11].

Implications for counseling:

The patient is regularly followed in multidisciplinary medical consultation. We explained to the parents in a genetic counseling consultation the risk of recurrence of partial trisomy 21 or partial trisomy 9 in subsequent pregnancies. The possibilities of prenatal or preimplantation diagnosis for future procreations have been discussed.

CONCLUSION

We report through this observation the possibility of the onset of rare mechanisms of segregation during meiosis in case of reciprocal translocations. The awareness of recurrence risk and the mechanism of chromosomal segregation is important in genetic counseling. Despite their disparity, the data on these rare abnormalities in the literature available to date, contribute to the evolution of their comprehension.

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Not applicable.

DECLARATION OF INTEREST

The authors report no conflicts of interest.

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