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Duplication 2p and Monosomy 8p in mosaicism: clinical, molecular cytogenetic and molecular markers of a unique case

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ABSTRACT

We report on a female patient, with a de novo mosaicism for a structural rearrangement producing trisomy 2p21→pter and monosomy 8p21→pter. GTG bands and fluorescence in situ hybridization (FISH) in lymphocytes identified: mos 46,XX,der(8)(8qter→8p21::2p21→pter),9qh$^+$[52]/ 46,XX,9qh$^+$[82]. Fibroblasts showed the same cell lines in 15 and 12 cells respectively. DNA profiling with fourteen autosomal STR markers, did not reveal a chimerism status in our patient. She did not present the classical phenotype described for trisomy 2p and for monosomy 8p probably due to approximately 60% of the patient's cells being normal. The abnormality probably arose in a very early stage of development during the first post-fertilization divisions with a non-sister chromatid exchange event between chromosomes 2 and 8 producing three cellular clones: a normal clone, one with trisomy 2p and monosomy 8p and a third with monosomy 2p and trisomy 8p. Only the first two cell lines were found in both lymphocytes and fibroblasts of hypopigmented skin; the third may have been lost or limited to other tissues.

Key words. Mosaicism 8p. Duplication 2p. FISH. Monosomy 8p. Mosaicism 2p

Duplicación 2p y monosomía 8p en mosaicismo: clínica, citogenética molecular y marcadores moleculares de un caso único

RESUMEN

En este trabajo se describe a una paciente que presenta mosaicismo para un rearreglo cromosómico que produjo trisomía 2p21→pter y monosomía 8p21→pter. El cariotipo con bandas G y la hibridación in situ *con fluorescencia (FISH) en cultivo de linfocitos mostraron la fórmula cromosómica: mos46,XX,der(8)(8qter→8p21::2p21→pter),9qh$^+$[52]/ 46,XX,9qh$^+$[82] y en fibroblastos se encontró el mismo mosaicismo en 15 y 12 células respectivamente. El perfil de DNA con catorce marcadores STR, descartó quimerismo en la paciente. El cuadro clínico no fue el clásico descrito para la trisomía 2p y para la monosomía 8p, por la presencia del mosaicismo con 60% de células normales. El rearreglo probablemente se originó en una etapa muy temprana del desarrollo, durante las primeras divisiones después de la fecundación con un intercambio de cromátides no-hermanas entre los cromosomas 2 y 8 que produjo tres clonas celulares: una normal, una con trisomía 2p y monosomía 8p y una tercera con monosomía 2p y trisomía 8p. Sólo encontramos las dos primeras líneas celulares tanto en linfocitos como en fibroblastos de piel obtenidos de una zona hipopigmentada; la tercera línea posiblemente se perdió o se limita a otros tejidos.*

Palabras clave. *Mosaicismo 8p. Duplicación 2p. FISH. Monosomía 8p. Mosaicismo 2p.*

INTRODUCTION

Fewer than 28 reports of mosaicism involving an unbalanced structural rearrangement with a normal cell line have been published. It has been proposed that these mosaics are produced by a post-fertilization event with non-sister chromatid exchange.[1] These events are rare, and no reports have been published involving mosaicism of a similar structural alteration involving chromosomes 2 and 8.

In this study, we present the first report of a patient with a mosaicism for a structural alteration producing trisomy 2p21→pter and monosomy 8p21→pter. This mosaicism was identified by fluo-

rescence *in situ* hybrization (FISH), and the chimerism was ruled out by short tandom repeat (STR) analysis.

CLINICAL REPORT

The patient, a 3-year-old girl, was the fourth child of young, healthy, non-consanguineous parents. The pregnancy was complicated by threatened abortions at 3 and 7 months and reduced fetal movement was reported. Labor and delivery were normal: birth weight was 2300g, length 41 cm and cyanosis was reported.

Psychomotor development was delayed and her global coefficient of development at the age of three years was 55%. Physical examination showed head circumference of 44cm ($<3^{rd}$ percentile), height and weight ($<3^{rd}$ percentile), prominent forehead, depressed nasal bridge, downturned nose, upturned palpebral fissures, downturned corners of the mouth, and low-set ears (Figure 1).

Diastasis recti, aberrant palmar creases, hypotonia of inferior limbs, and linear hypopigmentation in back and thorax were noted. Renal ultrasonography was normal, EKG showed slight pulmonary insufficiency and cystourethrography appeared normal. A brain CT scan showed hypoplasia of corpus callosum.

CYTOGENETIC AND MOLECULAR STUDIES

Chromosome analysis of the patient and both parents was carried out using conventional techniques for GTG banding in peripheral blood lymphocytes. Karyotype on fibroblasts from the patient's hypopigmented skin was also done.

Fluorescence *in situ* hybridization (FISH) was done using the protocols established by Oncor® Inc. and Vysis Inc. (Downers Grove, IL, USA). A whole chromosome paint for chromosome 8 (WCP, Oncor, USA), Chromoprobe Multiprobe (Cytocell), TelVysion (Vysis) and a probe for a unique sequence in region 2p23 (LSI ALK, Vysis) were used.

To detect a possible chimerism in our patient we performed DNA profiling by PCR analysis of fourteen STR loci[2] as previously described.[3] As template for the PCR, genomic DNA was isolated from leukocytes from patient and her parents and from the patient's buccal cells.

RESULTS

GTG banding analysis of the patient's lymphocytes, with a resolution of 500 bands, showed a normal cell line and another with extra chromosomal material on the short arm of one chromosome 8. The karyotype in lymphocytes was reported mos 46,XX,add(8p),9qh$^+$[52]/46,XX,9qh$^+$[82], while fibroblasts showed the same cell lines in 15 and 12 cells respectively. Chromosome analysis of the parents was normal.

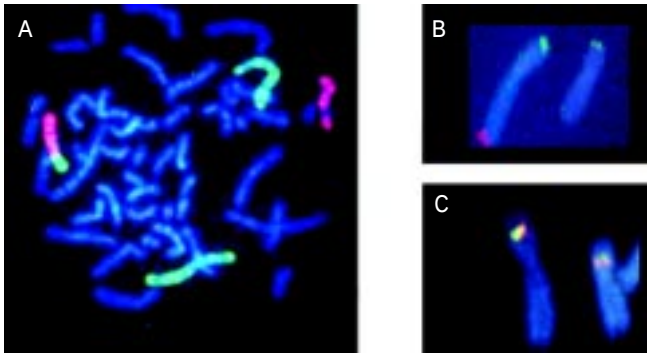
FISH was performed using the whole chromosome paint probe for chromosome 8 revealing that the additional material was not derived from the same chromosome; the multiprobe and telVysion probes showed that the material was coming from the short arm of chromosome 2.

– COLOR –

Figure 1. Patient facies showing prominent forehead and a depressed nasal bridge.

– COLOR –

Figure 2. Partial karyotype with GTG-banding showing the normal chromosomes 8 and 2 and the derivative chromosome 8.



– COLOR –

Figure 3. Fluorescece in situ *hybridization. A. Metaphase with the whole chromosome paint probe for chromosome 2 (green) and 8 (red) showing the partial trisomy of chromosome 2. B. Telomeric probes for 2p (green) and 2q (red) on chromosomes 2 (left), and the chromosome 8der showing hybridization with 2p telomere (right). C. The fluorescent probe of unique sequence for the region 2p23 LSI ALK shows normal hybridization on one chromosome 2 (left) and hybridization on 8der (right).*

The breakpoints were determined using GTG banding analysis with fluorescent probes of unique sequences in metaphase chromosomes (Figures 2 and 3).

These cytogenetic and FISH results indicated that the patient's karyotype was a mosaicism for a cell line with a partial trisomy 2p and a partial monosomy 8p and a normal cell line: mos 46,XX,der(8)(8qter→8p21::2p21→pter),9qh$^+$[52]/46,XX,9qh$^+$[82].

The DNA profiling with fourteen autosomal STR markers did not reveal a second genotype in any of the genomic DNA samples analyzed (leukocytes and buccal cells) (data not shown). This result rules out chimerism in our patient.

DISCUSSION

We report a patient whose karyotype showed a normal cell line and another with trisomy 2p21→pter and monosomy 8p21→pter *de novo*. Although more than 60 cases with partial trisomy 2p and more than 40 cases with monosomy 8p, have been reported, the karyotype of this girl is unique.

The most common clinical characteristics of patients with trisomy 2p, with breakpoints between bands 2p12 and 2p25, include: mental retardation, pre and postnatal growth retardation, hypotonia, microcephaly, broad forehead, hypertelorism, ptosis, strabismus, myopia, short palpebral fissures, depressed nasal bridge, low set ears with microtia, micrognathia, and cardiac and urogenital defects. Neural tube defects, bronchopulmonar hypoplasia, diaphragmatic hernia, gastrointestinal anomalies, and neuroblastoma have also been reported[4,5]. The clinical characteristics of patients with alterations in 2p have helped to localize candidate genes involved in the development of the neural tube (2p24), in bronchopulmonar hypoplasia (2p21-25), in diaphragmatic hernia (2p23-25), in heart development (2p22.3-25), and neuroblastoma (2p23-24).6,7 Our patient only showed a few of these characteristics as shown in table 1.

Additionally, more than 30 cases of terminal or interstitial deletions of the short arm of chromosome 8 have been reported. The most common regions involved are 8p21 and 8p22.[8] These deletions may be *de novo* or produced by the segregation of an abnormal derivative chromosome when one of the parents carries a balanced translocation.[9] The most common clinical characteristics are: pre and postnatal growth retardation, microcephaly, dysmorphic facial features (depressed nasal bridge, bilateral internal epicanthal folds, malformed ears, micrognathia, short neck, prominent alveolar ridges) congenital cardiac defects, behavior and language problems, and in males, hypospadias and hypogonadism. Some patients also present a single palmar crease, brachymesophalangy, clinodactyly, and overlapping toes.[10-14]

The behavioral problems such as aggressiveness, hyperactivity and low tolerance have been partially

Table 1. Clinical characteristics of patients with trisomy 2p and monosomy 8p.

Clinical manifestations	Trisomy 2p	Monosomy 8p	Present case
Mental retardation	+	+	+
Behavior problems and seizures	-	+	?
Growth retardation	+	+	+
Language impairment	-	+	+
Hypotonia	+	-	+
Microcephaly	+	+	-
Broad and prominent forehead	+	-	+
Hypertelorism	+	+	-
Internal epicanthal folds	-	+	-
Depressed nasal bridge	+	+	+
Low set, posteriorly rotated ears	+	+	+
Microstomia	-	+	-
Ocular alterations	+	-	-
Cardiopulmonary malformations	-	+	+
Diaphragmatic hernia	+	-	-
Hypospadias and/or cryptorchidism	+	+	-
Neuroblastoma	+	-	-
Linear hypopigmentation	-	-	+
Hypoplasia of corpus callosum	-	-	+

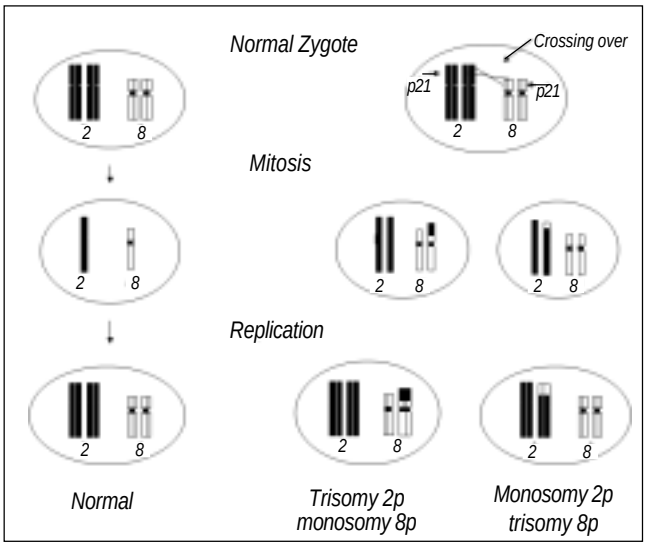


Figure 4. Ideograma describing a possible mechanism for formation of a mosaic.

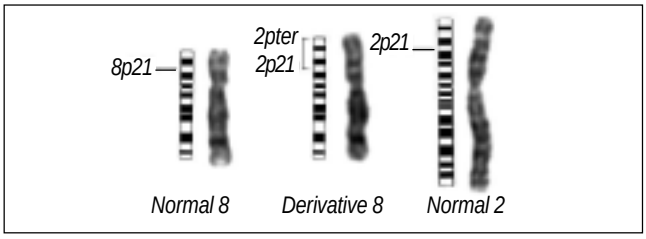


Figure 5. Partial kariotipe with GTG bands showing the rearrangement.

attributed to a gene localized in 8p23.1.[10] As for partial trisomy 2p, our patient did not present the classical phenotype of monosomy 8p (Table 1). The linear areas of hypopigmentation on back and thorax have not been described as part of the clinical manifestations of trisomy 2p or deletion 8p, and may be explained by the presence of cellular mosaicism.

Cellular mosaicism involving a normal cell line and an unbalanced autosomal structural rearrangement that does not involve a ring chromosome or an extra marker chromosome is very rare. These alterations may arise by post-fertilization mitotic errors involving non-sister chromatid exchange as proposed by Zaslav[1] (Figure 4). In our case, this may have been the mechanism occurring in a very early developmental stage since the percentage of each cell population is approximately 50%. These type of events usually produce three cell populations, one normal and two abnormal. In both fibroblasts and lymphocytes of our patient we only found two cellular populations, one normal and the other with partial trisomy 2p21→pter and partial monosomy 8p21→pter. The daughter cell with the partial monosomy 2p21→pter and partial trisomy 8p21→8pter could have been non viable and lost or may be present in another tissue not analyzed (Figure 5).

In summary, our patient has a partial trisomy 2p21→pter and partial monosomy 8p21→pter in both lymphocytes and fibroblasts; however, the normal cell line accounting for approximate 60% of the cell population, may be the reason for not presenting the classical clinical characteristics described for these alterations.[15] The psychomotor and developmental retardation, as well as cardiopulmonary malformations have been described for both trisomy 2p and monosomy 8p and are features which our patient shares with other reported cases (Table 1). Follow up is recommended due to other clinical manifestations described for these alterations, including behaviors problems or neuroblastoma which may appear in later years.

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Recibido el 26 de febrero de 2007.
Aceptado el 11 de septiembre de 2007.