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Down´s syndrome with "Mirror image" duplication. Report of a case

(Síndrome de Down con duplicación "Imagen en espejo". Reporte de un caso)

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SUMMARY

A rare variant of trisomy 21 is the "mirror image" duplication of chromosome 21. The possible mechanism for the formation of this chromosomal rearrangement is not known yet.
The clinical diagnosis of these patients usually presents no special difficulty. Nevertheless, the karyotyping, and the determination of the origin of this duplication can provide the basics for genetic counseling.
Clinical case. A baby with stigmata of Down syndrome was found to be a "mirror image" (reverse tandem) duplication of chromosome 21: 46, XX, der (21;21) (21pter→21q22: :2lq22→21pter) This chromosome rearrangement apparently appeared de novo.
Discussion. Four mechanisms are discussed for the origin of the abnormal chromosome: (a) exchange inter-intrachromosomal, (b) parapericentric inversion, (c) telomeric fusion between two chromosomes 21 and (d) translocation between two chromosomes in a trisomy 21 zygote.
The present report supports the association between trisomy of band 2lq22 and the Down phenotype.

Key words: Down's syndrome, Down's syndrome and reverse tandem duplication, "mirror image" and 21 trisomy.

RESUMEN

Una variante rara de la trisomía 21 es la duplicación "imagen en espejo" del cromosoma 21. El posible mecanismo de formación de este rearreglo cromosómico aún no se conoce.
El diagnóstico clínico de estos pacientes no presenta dificultad. Sin embargo, el análisis cromosómico y la determinación del origen de esta duplicación provee las bases para el consejo genético.
***Caso clínico.** Una niña con fenotipo de síndrome de Down mostró una duplicación en tándem reversa "imagen en espejo" del cromosoma 21: 46, XX, der (2 1; 21) (2 l pter→21q22: :21q22→2l pter). El rearreglo cromosómico detectado en esta paciente aparentemente surgió de novo.*
***Discusión.** Cuatro mecanismos son propuestos para explicar el origen del cromosoma anormal: (a) intercambio interintracromosomal, (b) inversión parapericéntrica, (c) fusión telomérica entre dos cromosomas 21, y (d) translocación entre dos cromosomas 21 en un cigoto con trisomía 21.*
El presente estudio apoya la asociación entre la trisomía de la región cromosómica 21q22 y el fenotipo de síndrome de Down.

***Palabras clave:** Síndrome de Down, Síndrome de Down y duplicación en tándem reversa, "'imagen en espejo" y trisomía 21.*

Down´s syndrome or trisomy 21 occurs in approximately 1 in 750 live births in all ethnic groups, thus constituting the most common single genetic cause of moderate mental retardation.

Down's syndrome has been associated with a variety of karyotypes: whole trisomy, unbalanced Robertsonian translocation, isochromosome of the long arm of chromosome 21, partial trisomy, double trisomies, and mosaicism.

A rare variant of trisomy 21 is the "mirror image" duplication of chromosome 21. Examples of patients with this alteration were 4 published as early as 1963.[2,3] In 1965, Lejeune et al suggested a tandem inverse duplication (repeated DNA sequences joined tail to tail) in these patients. Later, few cases have been described in the literature.[5-15] The possible mechanism for the formation of this chromosomal rearrangement is not known yet.

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The clinical diagnosis of these patients usually presents no special difficulty. Nevertheless, the karyotyping, and the determination of the origin of this duplication can provide the basics for genetic counseling. This report describes a girl with a tandem reverse duplication of a chromosome 21: 46,XX, der (21;21) (21pter→21q22::21q22→21pter). The possible origins of this duplication are discussed.

CLINICAL CASE

The propositus was born at term weighing 2,250 g after an apparently normal gestation and delivery. She was the first child of healthy parents. At the time of birth of the child, the mother was 16-years-old, and the father was 19-years-o1d. The nonconsanguineous parents are phenotypically normal and healthy. They give no family history of abortions, or congenital abnormalities.

Most of the clinical features corresponding to Down's syndrome were noted in the infant soon after birth: slant to the eyes, low set ears, the nose was short with a flat nasal bridge, short neck, forehead wide and flat, broad hands with stubby fingers, partial clinodactyly of the 5th digit, and a single palmar crease on the right hand were also noted. Congenital heart disease (systolic murmur), micrognathia and jaundice were observed. The rest of the physical examination was normal.

Cytogenetic studies. Peripheral blood lymphocytes were cultured and harvested by standard methods. Usual banding techniques GTG, CBG, and NORs were performed.[16] The karyotypic analysis of 100 metaphases revealed a chromosomal complement of: 46,XX, der (21;21) (21pter→21q22::21q22→21pter).

The G banding showed a reverse tandem duplication of two chromosomes 21 joined together near the telomeres of their long arms *(Figure 1A)*. The C-banding *(Figure 1B)* revealed two centromeres at both ends of the rearranged chromosome. The duplicated chromosome had similar stalks in both arms and satellites visualized by NOR technique *(Figure 1C)*.

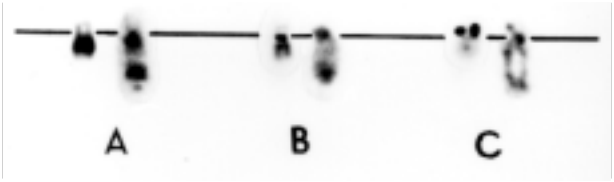

Figure 1. *The "tandem inverse" duplication of chromosome 21 demonstrated by: (A)GTG, (B)CBG, and (C)Ag-NORs. The duplicated chromosome is on the right of each pair, and at the left of the normal chromosome 21.*

Chromosome analysis from cultured blood lymphocytes of both parents revealed normal karyotypes.

DISCUSSION

Down´s syndrome involving reverse tandem duplication of a chromosome 21 is rare.[2-15] The possible mechanism of formation of this chromosomal rearrangement is not known.[14]

Our patient presented a karyotype: 46, XX,-21, + psu dic (21) t(21;21) (q22;q22). The cytogenetic findings indicate that the breakpoint of the two chromosomes 21 involved in the tandem reverse occurred at the most distal end of the long arms (2lq22).

The C pattern showed a dicentric chromosome. However, inactivation of one of the two centromeres is necessary for the stability of the derived chromosome. The factors controlling activation (dominance) and inactivation (suppression) are still unknown.[17]

The presence of similar satellites at both ends provides evidence that the duplicated chromosome derived from a single paternal chromosome 21.

The origin of this duplication is difficult to determine with certainty. However, the following hypotheses are proposed:

In the first hypothesis, an exchange is assumed between sister chromatids of the same chromosome 21 (intrachromosomal), or between the long arms of two chromosomes 21 (interchromosomal). If the breakpoints were at the same sites of each chromosome or chromatid (homotopic), the derived chromosome would be symmetrical. If the breakpoints were at different (heterotopic) sites the resulting chromosome would be asymmetrical.

An analysis of similar published cases suggests that this mechanism may prevail.[14]

A second possibility assumes a para-pericentric inversion. The paracentric inversion with crossover with the loop, needs two breaks. This mechanism would lead to a symmetrical appearance of the duplication (mirror image), and it would not be distinguishable from interchromosomal interchange.

On the other hand, the pericentric inversion with crossover with the loop, needs only one break, but the resulting chromosome would be asymmetrical.

A third explanation suggests the telomeric fusion of the long arms of two chromosomes 21 after opening of telomeric palindromes, without loss of chromosomal material. However, recent molecular studies revealed a partial deletion of distal 21q in the tandem reverse duplication.[15]

A fourth hypothesis, the less likely, involves a translocation between two chromosomes 21 in a trisomy 21 zygote at very early stage of postzygotic development.

For this hypothesis we would expect a 47, XX +21 cell line, and this was not the case.

Although the four explanations are theoretically possible, we support the hypothesis of "intrachromosomal interchange" with homotopic breakpoints because:

1. Presence of a symmetric derived chromosome.
2. This mechanism would need only one abnormal event.
3. The presence of similar satellites at both ends indicate that the duplication in tandem derived from a single paternal chromosome 21.
4. The intrachromosomal interchange can also explain duplications of variable length with reference to the breakpoint.

The phenotype of our patient was not significantly different from that of patients with trisomy for the whole chromosome 21, hence the band 2lq22 (critical region responsible for Down's phenotype) is triplicated. The present report supports the association between trisomy of band 2lq22 and the Down phenotype.

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