

Mosaicism for trisomy 3q arising from an unbalanced, de novo t(3;15)

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Abstract

We report on a 2½ year old girl who is dysmorphic, developmentally delayed, and mosaic for an unbalanced, de novo translocation between chromosomes 3 and 15. The karyotype from peripheral blood lymphocytes is 46,XX (50) and the karyotype from skin fibroblasts is 46,XX (28)/46,XX,der(15)t(3;15)(q11;p11) (23). The mechanism for the generation of this unbalanced, de novo translocation is discussed.

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Duplication of part of the long arm of human chromosome 3q causes a distinct and severe syndrome that leads to multiple congenital abnormalities.¹ Some of the malformations include hypertrichosis, hypertelorism, seizures and brain malformations, ocular anomalies, anteverted nostrils, long philtrum, maxillary prognathism, downturned corners of the mouth, cleft palate, micrognathia, malformed auricles, short/webbed neck, clinodactyly, congenital heart malformations, and chest deformities.¹ The majority of the cases have involved duplication of the segment 3q21-qter. Cases of mosaicism for dup(3q) are very rare. We report on a case with mosaicism for trisomy 3q that involves a very large region of the long arm (3q11-qter).

The proband was a normal term delivery, birth weight 3290 g. The pregnancy had been normal. Dysmorphic features were noted shortly after birth in that she had entropion with narrow fissures and bilateral enophthalmos. On examination at 14 months she was noted to have a prominent forehead with flat supra-orbital ridges (fig 1). Palpebral fissures were upward slanting and the nasal root was broad. Her ears were simple and low set. The outer canthal, interpupillary, and inner canthal distances were 8, 4.5, and 2.5 cm respectively. The head circumference was 45 cm. Subsequently she exhibited significant developmental delay. Many investigations on this child were normal including chromosome analyses of blood, metabolic workup, and CT scan of the brain. The parents were non-consanguineous with a previous history of one miscarriage. All parental karyotypes from lymphocytes were normal.

In view of the dysmorphic features of the proband, chromosome analyses were performed on two independently derived fibroblast cell lines from a skin biopsy and short term lymphocyte cultures. The fibroblast cell



Figure 1 Photograph of the proband (reproduced with permission).

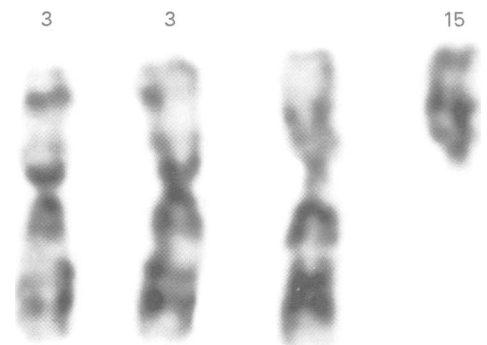


Figure 2 G banded chromosomes 3, 15, and t(3;15) from the proband's skin fibroblasts.

lines are available upon request. Skin fibroblast and short term lymphocyte cultures were initiated and harvested by standard protocols.^{2,3} G band analyses were carried out using trypsin digestion followed by Giemsa staining. Fifty out of 50 metaphases from the short term lymphocyte cultures had a normal 46,XX karyotype. Twenty-eight out of 51 G banded metaphases had an apparently normal 46,XX karyotype, while 23 out of 51 metaphases had the karyotype 46,XX,der(15)t(3;15)(q11;p11) (fig 2). We conclude that ~45% of skin fibroblast cells were essentially trisomic for chromosome 3q. FISH analyses with a TRITC labelled chromosome 15 painting probe and a FITC labelled chromosome 3 painting probe confirmed the origin of the translocated chromosomes and confirmed that chromosome 3 and 15 material was not inserted anywhere else in the genome of the fibroblast cells (fig 3). FISH protocols for chromosome painting were carried out by methods provided by the supplier of the probes (Cytocell Ltd, Banbury, UK).

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The simplest explanation for the origin of the t(3;15) fibroblast cells is that the translocation occurred during embryogenesis. A single

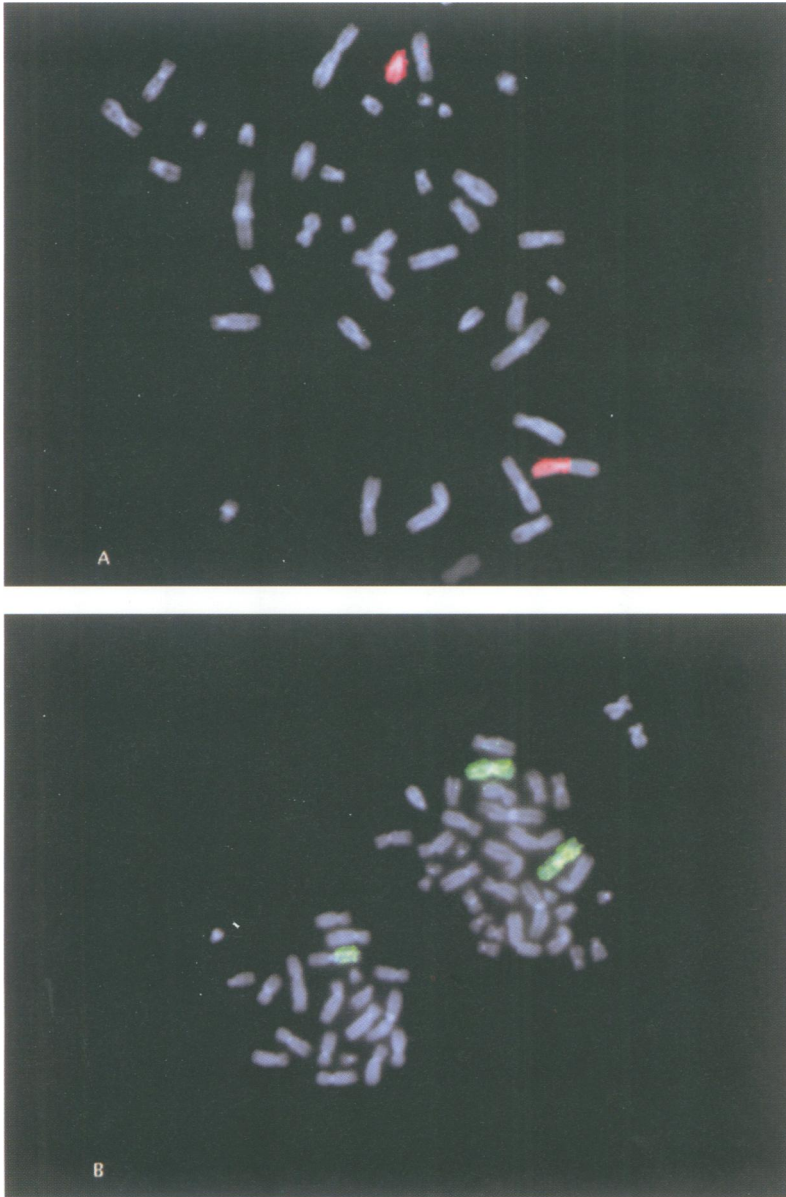


Figure 3 (A) FISH of trisomic metaphases with TRITC labelled chromosome 15 painting probe. (B) FISH with FITC labelled chromosome 3 painting probe.

step mechanism involving a translocation between a chromatid of chromosome 3 and a chromatid of chromosome 15 following DNA replication could explain the origin of the unbalanced karyotype (fig 4). Theoretically, four different cell types could occur following a translocation between the chromatids of two different chromosomes, depending upon how the chromatids segregate. One might obtain a normal cell and a cell containing a balanced reciprocal translocation (fig 4). Alternatively, one might expect two cell types that are unbalanced, one essentially trisomic for 3q (that is, 46,XX,der(15)t(3;15)(q11;p11)), the other monosomic for 3q (that is, 46,XX,der(3)t(3;15)(q11;p11)). The latter cell type was not observed, possibly because it was not viable.

FITC labelled primers for chromosome 3p microsatellite loci D3S1764, D3S1744, and D3S2418 were used to PCR amplify genomic DNA from the proband's fibroblasts. No loss of heterozygosity on chromosome 3p was detected following genotyping of PCR products with a Pharmacia automated DNA sequencer (that is, both alleles were present in equal doses, data not shown). Thus, a more complicated hypothesis involving loss of the der(3)t(3;15)(q11;p11) and reduplication of a normal chromosome 3 in order to explain the unbalanced karyotype seems unlikely.

Among the approximately 40 reported cases of partial trisomy 3q syndrome, the vast majority of cases involve duplicated regions smaller than 3q21-3qter.¹ It is difficult to compare the proband of this study with other cases of partial trisomy 3q because the proband in our case is mosaic and is trisomic for a much larger portion of 3q than that reported in the majority of trisomy 3q cases. In addition, many cases of partial trisomy 3q syndrome also have regions on other chromosomes that are deleted. In this regard, it should be noted in our case that cells possessing the t(3;15) are apparently missing a very small segment of distal 15p. This is not generally thought to be clinically significant.

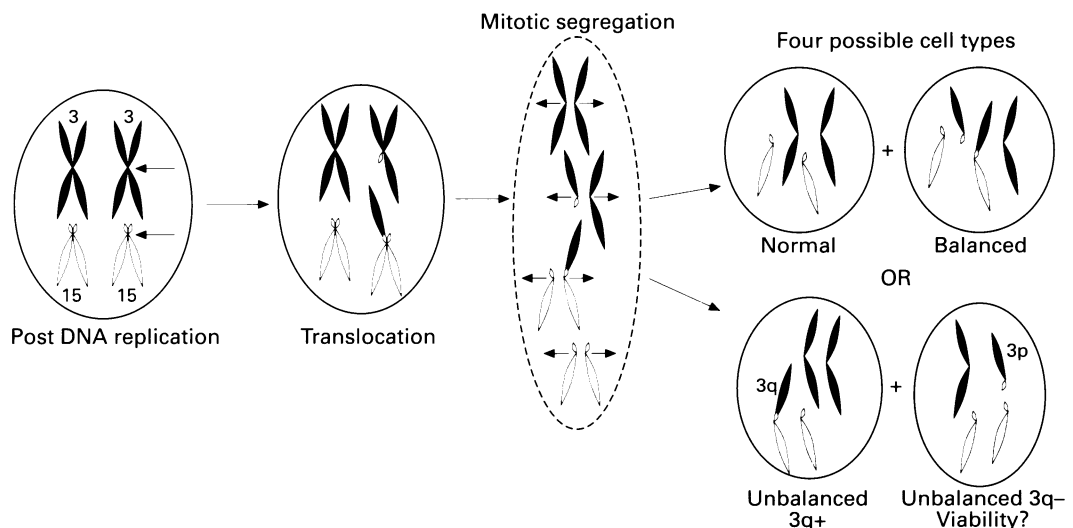


Figure 4 Illustration showing the origin of the unbalanced karyotype found in some of the proband's skin fibroblast cells.

One previously reported case of trisomy 3q syndrome had duplication of the entire long arm of chromosome 3 owing to inheritance of a maternal reciprocal translocation between chromosomes 3 and 15.⁴ Although the chromosome breakpoints in the case described by Wilson *et al*⁴ on both chromosomes 3 and 15 (3q11 and 15p11) were very similar to the case reported here, the earlier case had more severe abnormalities and survived for only 14 hours. The proband in this study has apparently survived because of the mosaicism for cells with normal and unbalanced karyotypes.

In terms of the practice of clinical cytogenetics, it is difficult to answer the question of whether cases of mosaicism are under-represented because a single tissue type (that is, blood) is used for chromosome analyses in the vast majority of cases. Clearly, chromosome

analysis on fibroblast cells is too costly to perform in every case where analysis of lymphocytes yields normal karyotypes. Nevertheless, this case further underlines the value of cytogenetic analyses from more than one tissue type in cases where the phenotype is suggestive of a chromosomal abnormality.

- 1 Steinbach P, Adkins WN, Caspar H, *et al*. The dup (3q) syndrome: report of eight cases and review of the literature. *Am J Med Genet* 1981;10:159-77.
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- 4 Wilson GN, Dasouki M, Barr M. Further delineation of the dup (3q) syndrome. *Am J Med Genet* 1985;22:117-23.