Intrachromosomal insertions: a case report and a review

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Summary. We describe the phenotype of a child having a recombinant chromosome 3 with a duplication 3q13.2 →q25 derived from a paternal inv ins(3)(p25.3q25q13.2). A review of 27 reported cases of intrachromosomal insertions has revealed that for a carrier of intrachromosomal insertion the risk of a child with an unbalanced karyotype is 15%. This risk may be higher for particular insertions. The recombinant chromosome can have a duplication or a deletion of different segments depending on whether the insertion is direct or inverted, paracentric or pericentric, and whether there is meiotic crossing over in the inserted or the interstitial non-inserted segment. Several of the insertions have been difficult to interpret and some of them have been mistaken for paracentric inversions. Caution is therefore indicated in interpreting parental karyotypes of a child with a deletion or a duplication, particularly if it is interstitial. This is because, whereas a risk of recurrence of a child with an unbalanced karyotype is low in de novo cases and for carriers of paracentric inversions, it is high for carriers of insertions.

Introduction

Chromosomal rearrangements involving three breaks, such as an insertion, have been estimated to be relatively rare: 1 in 5000 live births (Chudley et al. 1974) as compared with 1 in 500 for two-break rearrangements (Jacobs et al. 1974). Insertions may be inter- or intrachromosomal. In an interchromosomal insertion or an insertional translocation, an interstitial segment from one chromosome is inserted into one of the arms of another chromosome. Unbalanced products in this case are mostly caused by segregation resulting in a duplication or a deletion of the inserted segment. If the inserted segment is long enough for homologous pairing, recombinant chromosomes may be formed on rare occasions as a result of crossing over in the inserted segment (Jalbert et al. 1975). An intrachromosomal insertion, on the other hand, is one in which there is a "shift" of a chromosome segment within a chromosome. If the shift is from one arm into the other, it is an extraradial or a pericentric insertion. Similarly, if the shift is within the same arm, it is an intraradial or a paracentric insertion. An insertion is direct or inverted depending on whether its polarity with respect to the centromere remains the same or is inverted. Unbalanced products in the case of intrachromosomal insertions are always recombinants.

Chromosomal insertions or shifts, both spontaneous and induced, have been described in Drosophila (Muller 1940). Indeed, the first translocation found by Bridges in 1923 was an interchromosomal shift. Two interchromosomal insertions have been described in experimental mice (Searle et al. 1983; Cattanach 1974). One of these, Is(7;1)40H (Searle et al. 1983), is associated with sterility in the male and reduced fertility in the female. Multivalent structures with chiasmata in the inserted segment have been observed at meiosis I in oogenesis and spermatogenesis. In man, before the advent of the banding techniques, paracentric insertions and paracentric inversions remained undetected, whereas pericentric insertions could be deduced by the identification of the recombinants (Therkelsen et al. 1973; Webb et al. 1988).

We present a child with a recombinant derived from a paracentric inverted insertion, and review the published reports of intrachromosomal insertions.

Case report

The patient is a male child, born after an uneventful pregnancy as the first child of healthy non-consanguineous parents. Delivery at 41 weeks of gestation was uncomplicated. Birth weight was 2650 g (< P10), length 48 cm (P3), and head circumference 34.5 cm (P25). Multiple congenital abnormalities were noted, including hypotonia, relative macrocephaly with wide sutures, bilateral cleft lip and palate, broad nasal bridge, buphthalmos of the right eye with opalescent enlarged cornea, glaucoma and divergent strabismus, bilateral optic disc coloboma, low set ears and a small man-
Fig. 1a, b. The patient showing relative macrocephaly, bilateral cleft lip and palate, buphthalmos and divergent strabismus of the right eye, low-set ears and a small mandible.

dible. The dysmorphic features are depicted in Fig. 1a, b. The clinical course was complicated by severe feeding problems, partly on account of the cleft lip and palate and partly on account of reflux of unknown cause. Pyloric hypertrophy as a cause for recurrent vomiting was excluded. Growth hormone levels were normal. Growth and psychomotor development are severely delayed. An MRI scan of the brain revealed underdevelopment of the corpus callosum.

Results

Chromosome investigation revealed an abnormal chromosome 3 with a long short arm. Chromosomes of the parents showed that the mother had a normal female karyotype. The father had an abnormal 3 in which the short arm was identical to that of the child, but the long arm was shorter. Figure 2 shows chromosome pairs 3 from three cells of the father and from three cells of the child. Figure 3 is a diagrammatic representation of the normal 3, the abnormal 3 of the father and the abnormal 3 of the child. In the abnormal chromosome of the father, a segment from the long arm of 3 (q13.2→q25) has been inserted into the short arm in band 3p25.3. This chromosome was interpreted as an inv(3)(p25.3q25q13.2). The child’s chromosome 3 had a normal long arm but the short arm was identical to that of the abnormal 3 of the father. This chromosome was therefore interpreted as having a duplication of the segment q13.2→q25.

Investigation of the family revealed that two brothers of the father were also carriers of the inv(3). The paternal grandfather had a normal male karyotype. The paternal grandmother was dead. Three sisters of the grandmother were tested and were all found to have a normal female karyotype.

Fig. 2. Chromosome pairs 3 from a three cells of the father and b three cells of the child.

Fig. 3. Diagrammatic representation of a the normal 3, b the abnormal 3 of the father, inv(3)(p25.3q25q13.2), and c the abnormal 3 of the child, rec(3), dup q13.2→q25, inv(3)(p25.3q25q13.2)pat