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Review article

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 were indistinguishable from pericentric inversions. 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 pericentric 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 (< *P*10), length 48 cm (*P*3), and head circumference 34.5 cm (*P*25). 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-

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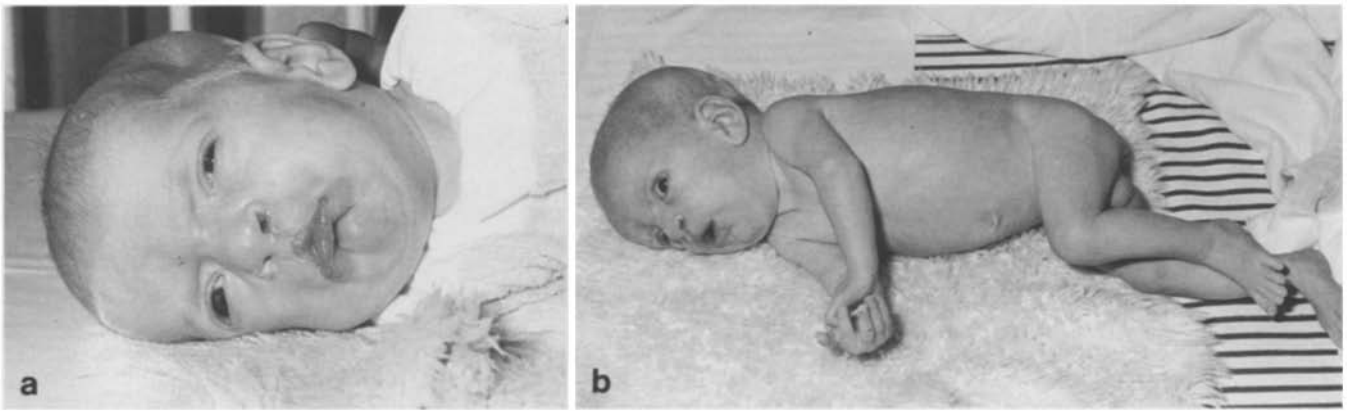

Fig. 1a, b. The patient showing relative macrocephaly, bilateral cleft lip and palate, buphthalmos and divergent strabismus of the right eye, low-set ears and a small mandible

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 ins(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 ins(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.

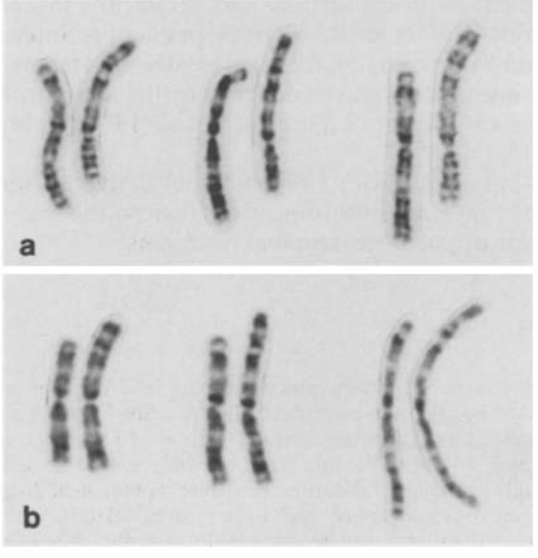

Fig. 2. Chromosome pairs 3 from **a** three cells of the father and **b** three cells of the child

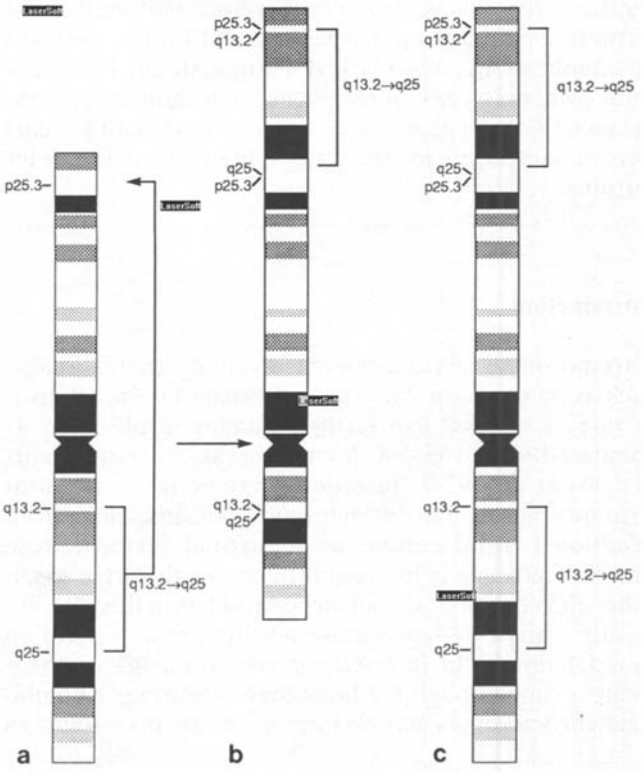

Fig. 3. Diagrammatic representation of **a** the normal 3, **b** the abnormal 3 of the father, inv ins(3)(p25.3q25q13.2), and **c** the abnormal 3 of the child, rec(3).dup q13.2→q25.inv ins(3)(p25.3q25q13.2)pat

Discussion

Phenotype of the child

The abnormalities described in our patient are most probably a consequence of the chromosome abnormality. There have been numerous reports describing the phenotype of patients with dup(3q). Steinbach et al. (1981) have reviewed 31 cases, including 8 of their own, and Wilson et al. (1985) have reported 3 cases and have reviewed the phenotype of a total of 40 patients. Additional cases have been reported by Preus et al. (1986), Montero et al. (1988) and Kleczkowska et al. (1988).

Phenotype-karyotype correlations are usually complicated by the fact that most cases of a chromosome duplication are associated with a deletion of another chromosome segment. After updating Table 1 of Steinbach et al. (1981) by including details from other reports (see above) and our own case, we notice that, in 11 out of 40 cases of dup(3q), there is a deletion of 3p25→pter. This deletion is associated with an abnormal phenotype and severe mental retardation (Ramer et al. 1989; Meinecke 1990). In 18 cases, a deletion of another chromosome was involved. In 3 of these, a substantial deletion was present, wereas in 15 cases, the deletion involved a minimal terminal segment. In the remaining 11 cases, there was either a deletion of the short arm of an acrocentric chromosome (5 cases) or no deletion at all (6 cases, including ours). The dup(3q) in these two groups may be considered to be a "pure" duplication.

A characteristic phenotype for dup(3q) has emerged. Features noted in 75% of the reported cases (Steinbach et al. 1981; Wilson et al. 1985) include hypertrichosis, an abnormal head shape, a broad nasal root, anteverted nares, a long upper lip, maxillary prognathia, downturned corners of the mouth, highly arched palate, cleft palate, malformed auricles, short or webbed neck, abnormal chest, cardiac defects, clinodactyly and brain abnormalities and/or seizures.

The facial features of these patients resemble those of patients with Cornelia de Lange syndrome. No chromosome abnormality has been found in the latter syndrome (Breslau et al. 1981).

There appears to be no clear relationship between the phenotype and the length of the duplicated segment. Wilson et al. (1985) have stated that duplication 3q25→qter is sufficient to generate the characteristic face and that the duplication of the whole of 3q leads to a slightly more severe phenotype. Montero et al. (1988) have noted that practically all patients with a duplication of 3q21→qter have cardiac malformations, whereas those with duplications of segments distal to 3q25 have none. However, patients having a duplication of long (Fryns et al. 1978) and short (Williamson et al. 1981) segments and exhibiting only minor phenotypic abnormalities have been described.

Our patient is unusual. He has only some of the dup(3q) features described above and does not resemble patients with Cornelia de Lange syndrome. He does not have cardiac defects. He has a characteristic phenotype that can be directly correlated to dup(3)(q13.2→q25), as there is no concurrent deletion of any other chromosome segment. To our knowledge dup(3)(q13.2→q25) has not previously been reported.

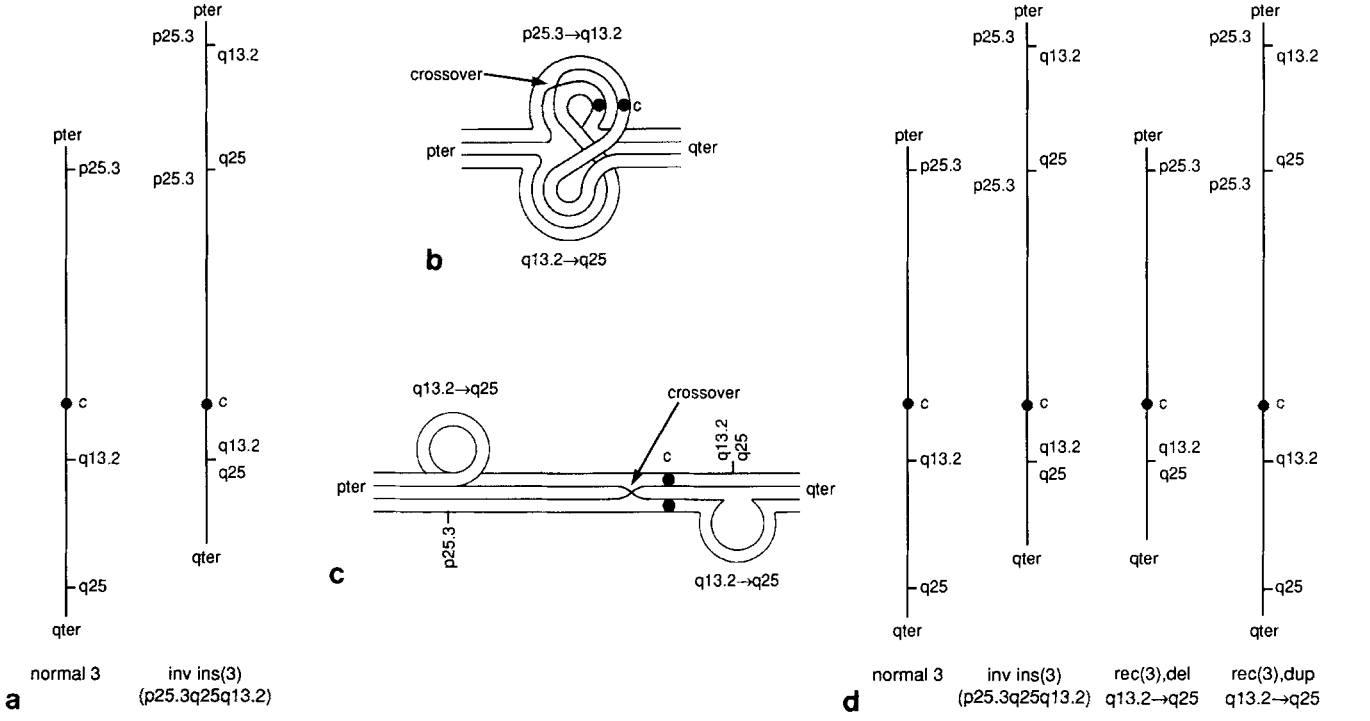

Fig. 4. Diagram showing the mechanism of origin of the recombinant chromosome in the child: **a** the normal and the inv ins(3) of the father; **b**, **c** alternative pachytene diagrams depending on whether pairing takes place along the whole length of the chromosome (**b**) or whether pairing fails in the inserted segment (**c**); **d** meiotic products following a single crossover in the non-inserted segment (p25.3→q13.2). The last of these was found in the child

Origin of the abnormal chromosome in the child

During meiosis, pairing of homologous segments can take place by forming two loops (Fig. 4b). Alternatively, pairing may fail in the inserted segment q13.2→q25 (Fig. 4c). In either case, a single crossover at pachytene between two of the four chromatids in the centromeric segment between the breakpoints p25.3 and q13.2 would result in four types of chromatids (Fig. 4d): 1) normal 3, 2) inv ins(3)(p25.3q25q13.2) as in the father, 3) rec(3), del q13.2→q25, inv ins(3)(p25.3q25q13.2)pat, and 4) rec(3), dup q13.2→q25,inv ins(3)(p25.3q25q13.2)pat as in the child.

Review

In Table 1, we have listed 27 cases of intrachromosomal insertions that have been reported. This list includes two cases (Sparkes et al. 1979; Valcárcel et al. 1983) that were reported as paracentric inversions and that were later re-interpreted as insertions (Hoegerman 1979; Callen et al. 1985).

The chromosomes involved are 1, 2, 3, 4, 5, 7, 9, 11, 13, 16, 18 and the X. The most frequently involved chromosomes are 1 (4 cases), 3 (3 cases), 5 (4 cases), 9 (3 cases) and 13 (3 cases).

Reason for referral

Out of 27 families, 25 were referred following the birth of an abnormal child with a recombinant chromosome (Table 1). One family (Roberts et al. 1986) was referred for psychotic behaviour that appeared to be segregating independently from the chromosome insertion. Another case was that of an ins(X) (Grass et al. 1981) in a girl with primary amenorrhea. One of the breakpoints of the insertion was in the critical region (Sarto et al. 1973), thus explaining the phenotype of the patient.

Table 1. Reported cases of intrachromosomal insertions

First author and year	Insertion	Recombinants (no. of individuals)
Pericentric		
1. Garver (1976)	ins (1)(p32q25q32)	del 1q25–q32 (3) dup 1q25–q32 (2)
2. Palmer (1977)	inv ins(1)(p22q32q31)	dup 1q31–q32
3. Pan (1977)/ Garver (1978)	ins (1)(p32q25q31)	dup 1q25–q31 (5) del 1q25–q31 (2)
4. Pfeiffer (1987)	dir ins (1)(p31.3q31q41)	dup 1q31–q41 (2)
5. Therkelsen (1973)	dir ins (2)(p34p13p24)	dup 2p13–p24 (2)
6. Pai (1983)	ins (2)(p13q31q33)	del 2q31–q33 (2)
7. Present case	inv ins (3)(p25.3q25q13.2)	dup 3q13.2–q25
8. Hastings (1990)	ins (4)(q31.3p14p16)	dup 4p14–p16
9. Martin (1985)	inv ins (5)(p13q33q22)	dup 5q22–q33
10. Miller (1979)	ins (7)(q22p15p21)	del 7p15–p21 dup 7p15–p21
11. Strobel (1980)	inv ins (11)(q14.5p14.1p11.3)	dup 11p11.3–p14.1 del 11p11.3–p14.1
12. Forsythe (1988)	ins (11)(p14.2q23.3q24.2)	dup 11q23.3–q24.2
13. Vekemans (1990)	dir ins (13)(p13q12q14)	dup 13q14–qter/del p13–pter
14. Cohen (1983)	ins (16)(q13p11p13)	dup 16p11–p13
15. Daniel (1988)	ins (16)(q13p11.2p13.3)	dup 16p11.2–p13.3
16. Daniel (1988)	inv ins (18)(p11.2q23.1q12.3)	del 18q12.3–q23.1
17. Grass (1981)	ins (X)(p11q22q24)	–
Paracentric		
18. Wyandt (1980)	inv ins (3)(p25.5p21.1p13.5)	del 3p21.1–p13.5
19. Watson (1990)	dir ins (3)(p26.2p11.1p14.2)	dup 3p11.1–p14.2
20. Webb (1988)	dir ins (5)(p15.2p14.2p14.1)	dup 5p15.1–p14.3
21. Valcárcel (1983)/ Callen (1985)	ins (5)(p13.1p15.1p15.3)	del 5p15.1–p15.3 dup 5p15.1–p15.3 (2)
22. Cross (1991)	dir ins (5)(q31.3q22q23.2)	del 5q22–q23.2 (2)
23. Allderdice (1983)	inv ins (9)(q22.1q34.3q34.1)	dup 9q34.1–q34.3 (11)
24. Narahara (1986)	dir ins (9)(q34.3q22.1q31.3)	dup 9q22.1–q31.3 (2)
25. Kajii (1987)	inv ins (9)(q34.3q22.3q21.2)	dup 9q21.2–q22.3 (2)
26. Sparkes (1979) / Hoegerman (1979)	inv ins (13)(q12q22q14)	del 13q14–q22
27. Roberts (1986)	inv ins (13)(q21.3q32q31)	–

Table 2. Reproductive outcome of 9 families studied for three or more generations. N, Normal karyotype; C, tested or obligate carriers of insertion; MCA, multiple congenital abnormalities

First author and year	No. of carriers (generations)	No. of pregnancies of carrier or partner	No. of spontaneous abortions	Live births	Karyotyped				Not karyotyped	
					N	C	dupl	del	Normal	MCA
Pan (1977) / Garver (1978)	8 (3)	28	2	26	3	15	4	1	1	2[a]
Miller (1979)	2 (2)	16	5	11	–	2	1	1	5	2
Cohen (1983)	14 (3)	45	4	41	13	19	2	–	5	2 (1[b])
Allderdice (1983)										
Kindred 1	5 (3)	21	3	18	4	5	3	–	6	–
Kindred 2	3 (2)	10	2	8	1	2	1	–	4	–
Kindred 3	2 (2)	5	–	5	2	1	1	–	–	1[b]
Kindred 4	6 (2)	21	–	21	5	6	2	–	5	3[b]
Valcárcel (1983)	4 (2)	13	4	9	1	5	2	1	–	–
Narahara (1986)	3 (2)	9	3	6	1	1	1	–	2	1[b]
Kajii (1987)	5 (2)	18	1 (+ 6 induced)	11	1	5	2	–	3	–
Roberts (1986)	3 (3)	7	–	7	2	4	–	–	1	–
Garver (1976)	2 (2)	6	–	6	–	1	1	2	–	2[b]
Total	57	199	24 (+ 6 induced)	169	33	66	20	5	32	13

[a] Perinatal death
[b] Individuals with phenotype resembling that of a child with a duplication or a deletion

Risk of abortion and recurrence risk

Although the number of insertions reported is small, we have attempted to obtain risk estimates for spontaneous abortions and of the recurrence of a live born child with a recombinant chromosome. The reproductive outcome for carriers of intrachromosomal insertions in 9 families studied for three or more generations is shown in Table 2. Four separate kindreds that most probably exhibit the same ins(9) that has been reported by Allderdice et al. (1983) are included separately in the Table 2. There were 199 pregnancies in 57 carriers or their partners, of which 24 ended in spontaneous abortion. This figure of 12% is no higher than that in the general population. There was no difference between male and female heterozygotes.

Data from these 9 families (Table 2) show that, out of 169 live births, 25 children had either a deletion or a duplication of a chromosome segment. Excluding 11 probands to allow for ascertainment bias and including 11 children with the same phenotype as the proband or with multiple congenital abnormalities, a figure of 25 out of 169 (15%) unbalanced progeny is obtained. Separation of these data for the sexes shows no significant difference between the risk of recurrence for male heterozygotes (9 out of 54) and that for female heterozygotes (16 out of 98).

However, these figures are small and the risk is probably considerably higher. This is because nearly all the families (25 out of 27) were referred after the birth of a child with a recombinant, and nearly half (12 out of 25) of these had two or more unbalanced children (in 7 of these families, within a single sibship). For particular insertions, the risk may be close to the maximum theoretical risk of 50%. Allderdice et al. (1983) have found a risk of 31% for female carriers of inv ins(9) (q22q34.3q34.1). The recurrence risk for heterozygotes of intra- and interchromosomal insertions is higher than for carriers of any other autosomal rearrangement (Daniel et al. 1988).

Ratio of carriers to non-carriers

Most of the data cannot be used to estimate the ratio of carriers to non-carriers among the normal progeny of the heterozygotes. Pooled data from two sufficiently large families (Pan et al. 1977; Cohen et al. 1983) show that there are 34 carriers, 16 non-carriers and 6 untested individuals. After excluding proband sibships and carrier individuals in direct ascent (to remove the ascertainment bias), there are still significantly more carriers (29) than non-carriers (15) of the insertion. Even if all 6 untested individuals were to have a normal karyotype, a trend towards more carriers remains. Similar excess of transmission has been found for translocations (Ford and Clegg 1969; Hamerton 1971) and is attributed mainly to ascertainment bias. However, in some reports, there appears to be an excess of transmission of the translocations, even after correcting for ascertainment bias (Petrosky and Borgaonkar 1984; Stene and Stengel-Rutkowski 1988). There is as yet no explanation for this selective transmission.

Type of recombinants

In 23 out of the 25 families, the proband had either a deletion or a duplication of the inserted segment. In one case, the non-inserted segment, i.e. the segment that lies between the point of excision and the point of insertion, was duplicated (Webb et al. 1988), and in another, a long terminal segment was duplicated, whereas the short terminal segment was deleted (Vekemans and Morichon-

Table 3. Recombinants resulting from a single crossover at meiosis of different types of intrachromosomal insertions

Type of insertion	Segment with the crossover	Possible recombinants	Examples from the reported cases in Table 1
Pericentric, direct	Non-inserted	del inserted	1, 3, 10[a]
		dup inserted	1, 3, 5, 8, 10, 12, 14, 15[a]
Pericentric, direct	Inserted	dup terminal p + del terminal q del terminal p + dup terminal q	13
Pericentric, inverted	Non-inserted	del inserted	11, 16
		dup inserted	2, 7, 9, 11
Pericentric, inverted	Inserted	del non-inserted (acentric) dup non-inserted (dicentric)	
Paracentric, direct	Non-inserted	del inserted	21
		dup inserted	19, 21, 23
Paracentric, direct	Inserted	del non-inserted	
		dup non-inserted	20
Paracentric, inverted	Non-inserted	del inserted	18
		dup inserted	22, 24, 25
Paracentric, inverted	Inserted	dup terminal p + del terminal q (dicentric) del terminal p + dup terminal q (acentric)	

[a] For these examples, it is not specified whether the insertion is direct or inverted. Some of them may belong to the third group above, i.e. inverted pericentric insertions with a crossover in the non-inserted segment

Delvallez 1990). Of the 25 families, 5 had children with a deletion, 15 had children with a duplication, and 5 had some children with a duplication and some with a deletion of the same chromosome segment. There were four times as many children with a duplication of a chromosomal segment than with a deletion (Table 3). Moreover, in those families where both types of recombinants were found, patients with a deletion of a chromosome segment were more severely affected than those with a duplication of the same segment (Garver et al. 1976; Pan et al. 1977; Miller et al. 1979). Indeed, in the family reported by Miller et al. (1979), whereas the presence of del(7)(p15p21) was associated with multiple congenital abnormalities and early infant death, a mentally retarded male with dup(7)(p15p21) was still alive at the age of 32. This is in agreement with the generally accepted notion that excess chromosomal material (trisomy) is less harmful than a deficiency (monosomy).

The type of recombinant chromosome depends on the size of the inserted and the non-inserted segment. For cases of paracentric shifts, the distinction between the inserted segment and the non-inserted segment is arbitrary. If one of these segments is inverted, then it may be presumed to be the inserted segment. In most cases, the inserted segment is short and the non-inserted segment is long. During meiosis, therefore, homologous pairing is likely to take place in the non-inserted segment. If the inserted segment is also long enough to give homologous pairing, a double loop will be formed during meiosis (Fig. 5). A single crossover in the non-inserted segment would produce two unbalanced recombinants, one with a duplication and one with a deletion of the inserted segment. This is true for both para- and pericentric insertions regardless of whether they are inverted or direct (Table 3, Fig. 5). This type of recombinant is the most common. A single crossover in the other loop, i.e. in the inserted segment, would in the case of pericentric inverted and paracentric direct insertions, give recombinants with either a duplication or a deletion of the non-inserted segment. Recombinants with a duplication of one terminal segment and a deletion of the other terminal segment would be formed in the case of pericentric direct and paracentric inverted insertions (Table 3, Fig. 5). If the centromere lies in the duplicated or the deleted segment, then the recombinant would be a dicentric or an acentric, respectively. The latter would most certainly and the former would most probably be incompatible with life, unless a sex chromosome was involved. No recombinants with dicentric or pseudodicentric chromosomes, as have been reported for recombinants from a paracentric inversion (Mules and Stamberg 1984; Worsham et al. 1989), have as yet been demonstrated in cases of intrachromosomal insertion. Apart from these, examples of all possible types of recombinations have been found (Table 3). More than one crossover involving different strands or both loops would give recombinants with duplications or deletions of different segments.

Difficulty in identification and interpretation

Identification of the insertion was difficult in at least eight of the reported cases (Therkelsen et al. 1973; Garver et al. 1976; Sparkes et al. 1979; Allderdice et al. 1983; Wyandt et al. 1980; Strobel et al. 1980; Valcárcel et al. 1983; Vekemans and Morichon-Delvallez 1990). Four of these were originally interpreted as paracentric inversions with unbalanced meiotic products, and only later were re-interpreted as paracentric insertions by either the same authors (Kelly et al. 1979; Wyandt et al. 1980; Allderdice et al. 1980, 1983) or different authors (Sparkes et al. 1979; Hoegerman 1979; Valcárcel et al. 1983; Callen et al. 1985). Indeed, as Callen et al. (1985) have pointed out, of all the cases of paracentric inversions with unbalanced progeny (reviewed by Madan 1988), it is only in those cases where the recombinant

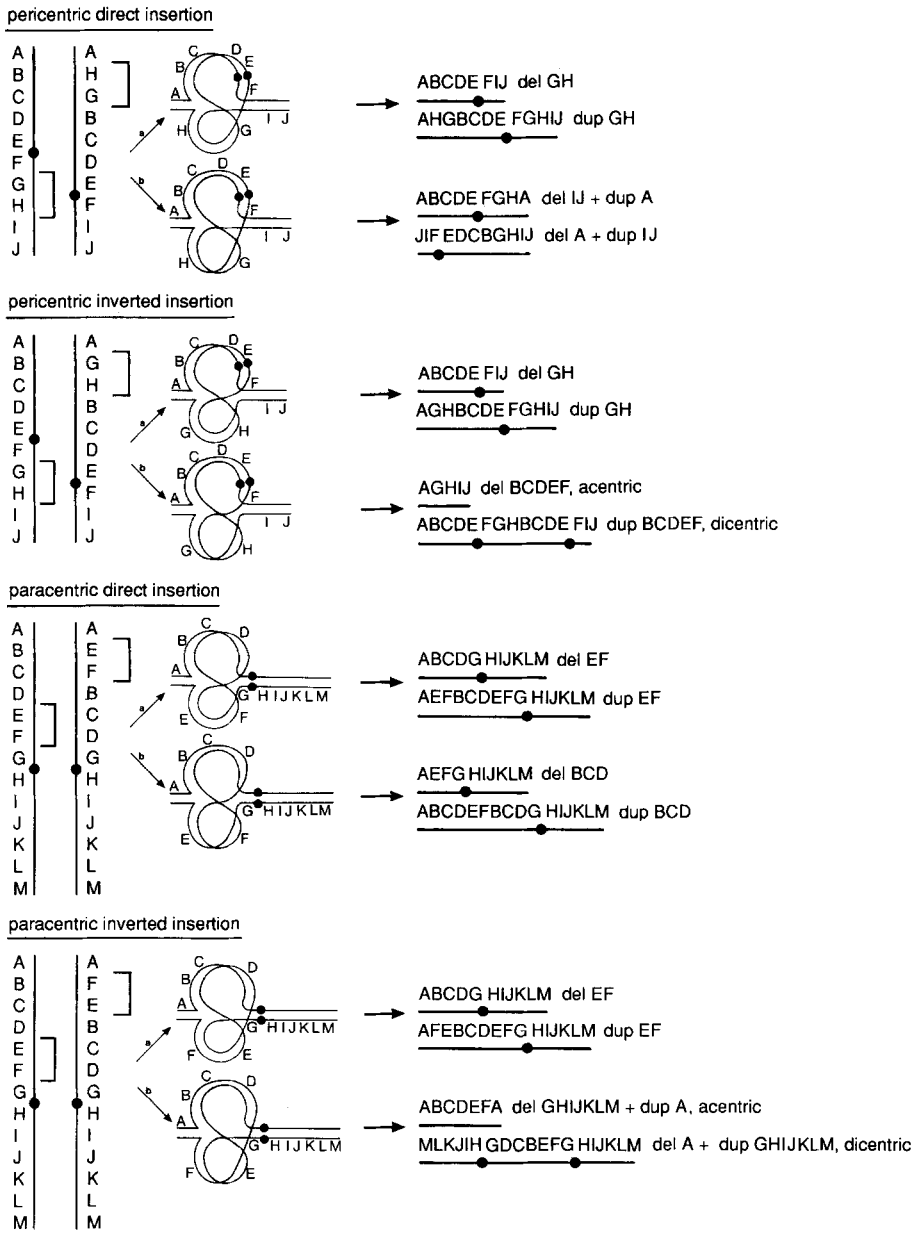

Fig. 5. Diagram showing the recombinants resulting from a single crossover in a non-inserted segment *(arrow a)* and an inserted segment *(arrow b)* during meiosis in carriers of different types of intrachromosomal insertions. Only the two crossover chromatids are shown

chromosome is a pseudodicentric (Mules and Stamberg 1984; Worsham et al. 1989) that there is convincing evidence that it is a direct consequence of a paracentric inversion. All other cases of a small deletion or a duplication, particularly of an interstitial segment in an abnormal child, may well be open to re-interpretation as an intrachromosomal insertion. Although chromosomal insertions are rare, the frequency of insertions may turn out to be higher than hitherto suspected, following the introduction of high-resolution banding techniques in recent years.

Caution is required in interpreting parental karyotypes of an abnormal child with a small deletion or a duplication. Whereas the risk of recurrence is low for carriers of paracentric inversions or following de novo deletions or duplications, this risk is high for insertion heterozygotes. Prenatal diagnosis is strongly indicated in the latter case.

Conclusions

The phenotype of the child can be directly correlated with the duplication of segment 3q13.2→q25, as there is no concurrent deletion of any other chromosome segment. A review of 27 cases of intrachromosomal insertions shows that, whereas for insertion heterozygotes there is no increase in the rate of spontaneous abortion, the risk of a liveborn child with a recombinant chromosome is 15%. This risk may be higher for particular insertions. Interpretation in cases of chromosomal insertions is difficult; nevertheless, correct identification is important because of the high risk associated with insertions.

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