Clin Genet 2009: 75: 505–513
Printed in Singapore. All rights reserved

CLINICAL GENETICS
doi: 10.1111/j.1399-0004.2009.01187.x

Review

Inverted duplications deletions: underdiagnosed rearrangements??

Zuffardi O, Bonaglia M, Ciccone R, Giorda R. Inverted duplications deletions: underdiagnosed rearrangements??
Clin Genet 2009: 75: 505–513. © John Wiley & Sons A/S,2009

Molecular techniques led to the discovery that several chromosome rearrangements interpreted as terminal duplications were in fact inverted duplications contiguous to terminal deletions. Inv dup del rearrangements originate through a symmetric dicentric chromosome that, after asymmetric breakage, generates an inv dup del and a deleted chromosome. In recurrent inverted duplications the dicentric chromosome is formed at meiosis through non-allelic homologous recombination. In non-recurrent inv dup del cases, dicentric intermediates are formed by non-homologous end joining or intrastrand annealing. Some authors hypothesized that in these cases the dicentric may have been formed directly in the zygote. Healing of the broken dicentric chromosomes can occur not only in a telomerase-dependent way but also through telomere capture and circularization thus creating translocated or ring inv dup del chromosomes. In all the cases reported up to now, the duplicated region was always longer than the deleted one, but we can safely assume that there is another group of rearrangements where the deleted region is longer than the duplicated portion. In general, in these cases, the cytogeneticist will suspect the presence of a deletion and confirm it by FISH with a subtelomeric probe, but he/she will almost certainly miss the duplication. It is likely that the conventional analysis techniques used until now have led to a substantial underestimate of the frequency of inv dup del rearrangements and that the widespread use of array-CGH in routine analysis will allow a more realistic estimate. Obviously, the concomitant presence of deletion and duplication has important consequences in genotype/phenotype correlations.

O Zuffardi[a,b,c], M Bonaglia[d], R Ciccone[a], and R Giorda[d]

[a]Biologia Generale e Genetica Medica, Università di Pavia, Pavia, Italy, [b]Fondazione IRCCS C Mondino, Pavia, Italy, [c]Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, [d]Eugenio Medea Scientific Institute, Bosisio Parini, Lecco, Italy

Corresponding author: Orsetta Zuffardi, Genetica Medica, Università di Pavia, Via Forlanini, 14 27100 Pavia, Italy.
Tel.: +39 382 987733;
fax: +39 382 525030;
e-mail: zuffardi@unipv.it

Received 12 December 2008, revised and accepted for publication 9 March 2009

Recurrent inv dup del(8p)

History of a recurrent rearrangement

The paradigmatic example of a rearrangement with an inverted duplication contiguous to a distal deletion is the inv dup del(8p). This is a recurrent rearrangement (about 1:20,000 newborns) reported in the literature since 1976 (1) associated with severe mental retardation, corpus callosum agenesis, important scoliosis in adulthood. The presence of an inverted duplication ("mirror duplication" (2)) had been hypothesized based on the banding pattern, whereas the demonstration that a concurrent deletion was also present in all inv dup(8p) cases had to wait for the availability of molecular techniques (3,4). Further molecular studies (5,6) on several cases demonstrated that the rearrangement had always the same breakpoints, with a single copy region of about 4–5 Mb interposed between the deletion and the duplication region. The deleted region has a size of 8 Mb whereas the duplication region varies in size from about 12 Mb to the entire short arm including the centromere. The findings that some inv dup del(8p) ended with an apparently inactive centromere (a second alphoid signal at distal 8p without any chromatids' constriction) and that three alleles were present in the duplication region (5) reinforced the hypothesis of Weleber (1) that the rearrangement originated through end-to-end fusion between

the short arms of chromosome 8 homologues. This would result in the formation of a symmetric dicentric chromosome. Since a dicentric chromosome is by definition unstable, it would subsequently undergo asymmetric breakage generating a duplicated-deleted chromosome with an inverted duplication and a simply deleted chromosome. The size of the duplication would vary according to where the breakage occurred between the two centromeres of the dicentric chromosome. The largest duplications reported up to now are those in which the dicentric ends with a second alphoid signal. This recurrent breakpoint (6 out 16 cases in ref. 5) indicates that, at anaphase, the dicentric is particularly fragile at the level of the second centromere. All published inv dup del (8p) cases have been ascertained by karyotype analysis that revealed an abnormal chromosome 8 with additional material on its short arm. Successive FISH analysis with chromosome 8 painting and subtelomeric 8p probes led to the identification of the chromosome 8 origin of the extra material on the short arm and of a distal deletion, respectively. Further dual-color FISH experiments with probes located in the duplicated segment demonstrated the inverted orientation of the duplicated segment (5,6). The introduction of whole genome array-CGH analysis allowed a rapid definition of the size of the deleted and duplicated segments (7,8) and led to the discovery of cases with a more complex situation with the inv dup del(8p) capped with a portion of 8q24.13-qter (7).

The rearrangement is mediated by homologous segmental duplications

As hypothesized (3), the dicentric was found to be the result of unequal recombination between homologous low copy repeats (LCRs, REPD and REPP, Fig. 1A), constituted by complex repeats containing olfactory receptor gene clusters lying at 8 and 12 Mb on the short arm of chromosome 8 and flanking a single copy region (6,9). The rearrangement was the result of non-allelic homologous recombination (NAHR) leading to the formation of a dicentric (qter->p23.1::p23.1->qter) and a reciprocal acentric chromosome (pter->p23.1::p23.1->pter) (Fig. 1B). As expected from classical cytogenetics, the dicentric and acentric chromosomes are the two products of a

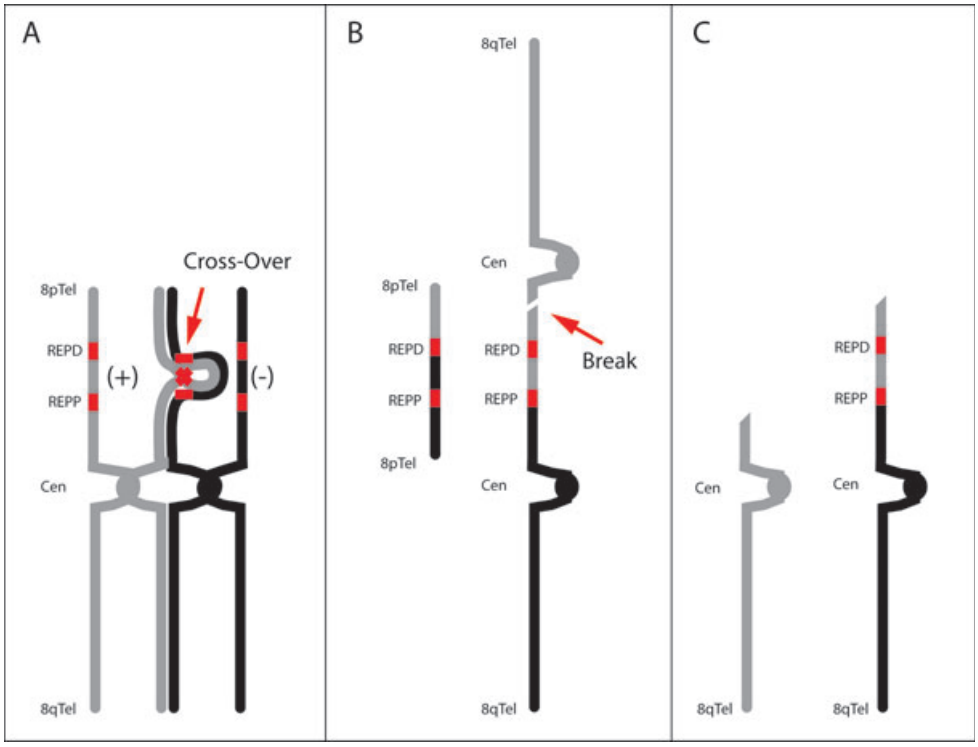

Fig. 1. Mechanism of recurrent inv dup del(8p) formation. (A) Abnormal meiotic pairing between chromosomes 8 in a subject heterozygous (+/-) for the REPD/REPP inversion and non-allelic homologous recombination between the LCRs leads to the formation (B) of an acentric der(8p) and a dicentric 8qter-8p23.1::8p23.1-8qter chromosome. Breakage of the dicentric chromosome leads to the creation (C) of 8p- and inv dup del(8p) chromosomes. The REPD and REPP LCRs are indicated by red boxes. Recombination and breakpoint locations are shown by arrows.

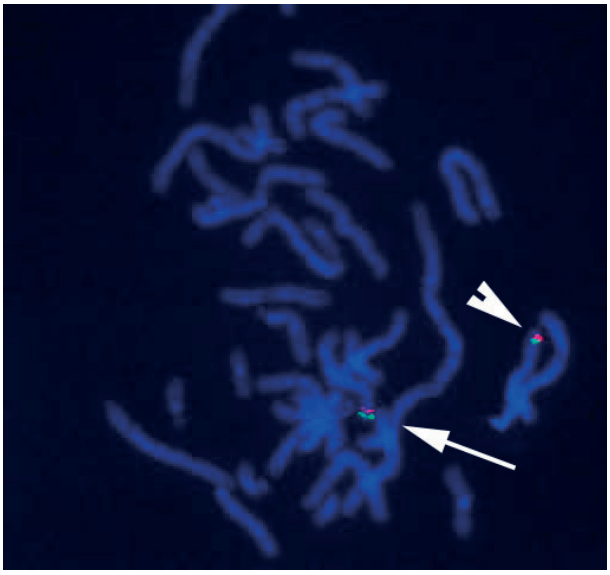

Fig. 2. Metaphase from a mother transmitting the inv dup del(8p). FISH with BACs RP11-399J23 (green) and RP11-589N15 (red) shows that the green signal is located at pter in one chromosome 8 (arrow) and proximal to the red signal in the other one (arrowhead) indicating the presence of a cryptic paracentric inversion in the latter.

crossing-over within a cryptic paracentric inversion at 8p23.1 between the deletion and duplication regions (Fig. 1A). We have demonstrated that all these rearrangements originate at the meiosis of a parent who is heterozygous for the cryptic paracentric inversion (Fig. 2). The inversion is a polymorphism present in heterozygous state in about a quarter of the population (6,9). Among the twenty-seven inv dup del(8p) cases we studied for parental origin, only one originated at the paternal meiosis from a father heterozygous for the inversion, while all the others originated from a heterozygous inverted mother (Table 1). The derivative acentric chromosome is either lost or it acquires a neocentromere and gets rescued (6,10). The dicentric chromosome, in theory, can undergo breakage during meiosis or it can be inherited as such in the zygote. A few cases of mosaicism with different derivatives of the dicentric indeed suggest that the dicentric is usually present in the zygote: both Soler et al (11) and Pramparo et al (12) found in chorionic villi samples two cell lines, one with a del(8)(p11), the other one with an inv dup del(8p). In the case analyzed by Pramparo et al, a third cell line was also present with an inv dup del(8p) ending with the satellites of a D or a G short arm, suggesting that here the inv dup del(8p) had been stabilized through telomere capture leading to a translocated inv dup del chromosome. Although the mosaicism was not confirmed in the product of conception because it was not available, these findings indeed suggest that in the zygote the dicentric chromosome undergoes differential breakage in different cells leading to different cell lines. The most viable one(s) will be detected at birth.

Other recurrent inv dup del chromosomes

Apart from supernumerary marker chromosomes (SMCs), the inv dup del(8p) is by far the most frequent among the rearrangements of this type. Among the others, very few cases are formed through NAHR. We are aware of only one other case of inv dup del clearly mediated by NAHR. It is an inv dup del(Xp) with breakpoints at the VCX gene family at Xp22.31 (Iascone et al, in preparation). On hindsight, it is clear that many SMCs belong to this category of rearrangements: apart from the acentric inv dup del(8)(pter->p23.1::p23.1->pter), the well-known inv dup(15) and inv dup(22) seem to follow the same scheme.

The inv dup(15)

The inv dup(15) is the most common SMC in humans, accounting for as much as 60% of all those observed (13). It is generally asymmetric, with a single copy region between the two duplication regions. Similarly to inv dup del(8p), they originate at the maternal meiosis through either interchromosomal or intrachromosomal abnormal recombination. The 15q11-q13 region contains several blocks of homologous LCRs which may give rise to a variety of rearrangements. Depending on the LCRs involved in their formations, these SMCs may have variable size and structure. They can be divided in two main categories: small SMC(15)s and large SMC(15)s. Small SMC(15)s, whose frequency is 0.14–0.72 per 1000 newborns (14), do not contain the Prader-Willi/Angelman syndrome (PWS/AS) region, and their formation occurs proximally to this region which contains two blocks of LCRs known as BP1 and BP2. These marker chromosomes can be *de novo* or inherited and are not usually associated with a pathological phenotype, although male carriers may be infertile. Uniparental disomy associated with small SMC(15)s has been reported, responsible for either PWS or AS (15). These small SMCs have also been reported in association with the PWS/AS 15q11-q13 deletion (16). Large SMC(15)s are usually *de novo* and maternally derived. The presence of this marker chromosome is mostly associated with mental retardation, seizures, autistic behavior and/or other psychiatric problems (17,18).

Table 1. Microsatellites analyses in 27 cases of inv dup del(8p) and their parents

		Deletion region			Duplication region			
Cases	Microsatelites	M	F	P	M	F	P	Parental origin
1	D8S518;D8S552	242/248	ND	226	173/175	ND	171/173/175	mat
2	D8S262;D8S552	114	112/114	112	175/181	165/171	165/175/181	mat
3	D8S262;D8S261	114	110/116	110	121/133	123/129	121/123/133	mat
4	D8S262;D8S258	112/114	108/116	116	144/146	142/146	142/144/146	mat
5	D8S518;D8S1809	226	240/246	240	166/170	158/166	158/166/170	mat
6	D8S262;D8S552	115/117	ND	113	166/174	ND	166/172/174	mat
7	D8S262;D8S261	109/111	ND	113	125/129	ND	123/125/129	mat
8	D8S1819;D8S261	217	203/211	203	123/129	135/137	123/129/137	mat
9	D8S1819;D8S261	203/213	203/219	213	123/135	125/129	125/127/135	pat
10	D8S1824;D8S258	230/244	228/238	238	142/146	146/150	142/146/150	mat
11	D8S1819;D8S549	203/216	216/218	218	162/164	166	162/164/166	mat
12	D8S518;D8S258	226/248	226/240	240	142/144	146	142/144/146	mat
13	D8S1824;D8S1809	230/244	230/238	238	152/158	170/172	152/158/170	mat
14	D8S1824;D8S511	232/252	240/246	240	130/132	128/130	128/132*	mat
15	D8S1819;D8S511	217/219	203/217	203	128/132	128/130	128/130/132	mat
16	D8S262;D8S258	108	112/114	114	142/144	138/144	138/142/144	mat
17	D8S518;D8S511	226	ND	242	130	ND	128/130*	mat
18	D8S518;D8S511	226/242	226/248	248	128/130	130/132	128/130/132	mat
19	D8S262;D8S552	115	ND	123	172/178	ND	172/176/178	mat
20	D8S1819;D8S258	211	203/217	203	144/146	144/148	144/146/148	mat
21	D8S1824;D8S511	245	229/245	229	129	127/131	129*/131	mat
22	D8S262;D8S511	116	116/118	118	127/129	127/131	127/129*	mat
23	D8S262;D8S511	110/114	116	116	125/127	127/129	125/127/129	mat
24	D8S518;D8S511	226	ND	242	129	ND	127/129*	mat
25	D8S518;D8S552	226/244	226/242	242	176/178	168/172	172/174/178	mat
26	D8S518;D8S261	242/250	226/242	226	123/127	129	123/127/129	mat
27	D8S262;D8S552	108	112/114	114	174/176	166/176	174/176*	mat

For each case, two microsatellites (the first deleted and the second duplicated) have been reported. None of these cases has been investigated by array-CGH analysis.
M: mother; F: father; P: proband. ND: not determined.

Because of the presence of several blocks of LCRs, large SMC(15)s may have more than one recurrent breakpoint but in all cases they fall distally to the PWS/AS region. As a consequence, these markers contain two copies of the PWS/AS region which seems to be at least partially the cause of the pathological phenotype. Paternally derived large SMC(15)s have never been reported. One explanation is that such paternally derived marker chromosomes may be lethal; however, paternally derived interstitial triplications of the PWS/AS region have been described (19,20). Another explanation is that spermatozoa carrying large SMC(15)s are selected against, as suggested by some studies (14,21). Two possible mechanisms have been proposed to explain the formation of SMC(15)s: a mechanism is based on NAHR between LCRs leading to the formation of a small dicentric and a large acentric chromosome which is subsequently lost. This recombination may occur either between homologues or between sister chromatids (18). Alternatively, a normal chromosome may undergo a premeiotic breakage losing a large segment of its long arm. After replication, the sticky ends of the two broken chromatids join to form the dicentric.

The inv dup(22)

Another common SMC is the inv dup(22). Although the most common genomic disorder occurring at 22q11 is the interstitial deletion causative of DiGeorge/Velocardiofacial syndrome (DGS/VCFS), the richness of segmental duplication of this region catalyzes, through NAHR, the formation of other types of rearrangements, including inv dup(22). Depending on which segmental duplication(s) trigger(s) the formation of the rearrangement, inv dup(22) can be symmetric or asymmetric and can have variable size: these markers can contain zero, one or two copies of the DGS/VCFS region (22). These supernumerary markers are usually associated with the cat-eye syndrome (CES), characterized by ocular coloboma, anal atresia, congenital heart defects, renal malformations, male genital anomalies, skeletal defects, and

borderline-to-moderate mental retardation. However, the phenotypic spectrum of this genomic disorder is extremely variable also because most of them are in mosaicism with a normal cell line. In contrast with SMC(15), inv dup(22) can originate both at maternal and paternal meiosis and non-allelic recombination may occur either between homologues or between sister chromatids (22). Here, again, no reciprocal acentric product has ever been reported, seemingly reflecting its lethality.

Non-recurrent inv dup del chromosomes

Inverted duplications/deletions have been identified at least at the following chromosome ends: 1p (23), 1q (24,25), 2p (26), 2q (27), 3p (28, 29), 4p (30,31), 4q (32), 5p (33,34), 7q (35,36), 9p (37), 9q (38), 10p (35), 10q (35), 11p (39), 14q (40,41), 15q (42), 18q (43), 21q (44) and Xp (45,46). In the majority of the above-mentioned cases, identification of the rearrangement occurred after a chromosome with an abnormally long arm had been detected by conventional cytogenetic techniques, then FISH analysis with a subtelomeric probe had shown a terminal deletion. Additional FISH with more proximal probes would then reveal the associated duplication and two color FISH would demonstrate its inversion. It is important to note that FISH analysis with commercial subtelomeric probes, that can be located even 300–400 Kb proximal to the telomeric end, may not be able to detect the distal deletion concurrent to the contiguous inverted duplication. We recently published the case of an inv dup del(2p) (26) in which the subtelomeric FISH marker was preserved and the deletion could only be demonstrated by high resolution array-CGH. In all these cases the duplicated region was always longer than the deleted one, but we can safely assume that there is another group of rearrangements where the deleted region is longer than the duplicated portion. In general, in the latter inv dup del cases, the cytogeneticist will suspect the presence of a deletion and confirm it by FISH with a subtelomeric probe, but he/she will almost certainly miss the duplication. It is likely that until now conventional analysis techniques have led to a substantial underestimate of the frequency of inv dup del rearrangements and that the widespread use of array-CGH in routine analysis will allow to reach a more realistic estimate.

Unlike the recurrent inv dup del rearrangements, in most cases occurring by NAHR, the non-recurrent inv dup dels are generated by alternative mechanisms (Fig. 3). In fact, illegitimate repair of a double-strand break (DSB) by non-homologous end joining (NHEJ) (47) or intrastrand annealing (48) can also form dicentrics. Breakpoint junction analysis at the DNA sequence level revealed that none of the inv dup del rearrangements studied were mediated by segmental duplications or facilitated by the presence of short inverted repeats (IR). Homology between the two breakpoint regions was limited to a dinucleotide (26) or trinucleotide (23) (Case 40), suggesting microhomology-mediated intra-strand repair of ds-breaks, which favours intrachromatid misalignment and recombination. The presence of a single copy sequence between deleted and duplicated regions was demonstrated in this type of rearrangements (23,26) (Cases 30 and 40 in ref 23). The size of the single-copy region ranges between 1.7 Kb (Case 30) (23) and 4.5 Kb (26). In 2 out of 3 cases (Case 30 in ref. 23 and ref. 26), the breakpoint between normal and deleted sequence is in a region without any apparent structural features, while the breakpoint between normal and duplicated sequence lies within a G/C-rich region or a low complexity repeat, seemingly able to assume a non-B DNA structure (49). This secondary structure can probably protect the chromosome end from further degradation and facilitate repair. Repair could be effected through a breakage-fusion-bridge (BFB) cycle, as stated by Ballif and colleagues (23), or by another process involving non-homologous end joining (NHEJ) or microhomology-mediated intrastrand repair (50). It is likely that the same general structure, and consequently the same process, may underlie all non-recurrent inverted duplications associated to terminal deletions. In all these cases we have no clear demonstration that the original dicentric chromosome originated at the parental gametogenesis. In fact, some authors hypothesized that the dicentric had been formed directly in the zygote after subtelomeric breakage and sister chromatid reunion (51).

Inverted duplications/ triplications and interstitial triplications

A new type of rearrangement consisting of the duplication of 8p23.1 and the triplication of 8p23.2 [dup trp(8p)], mediated by the combined effects of two unrelated low copy repeats (LCRs), was found in two patients affected by mental retardation and minor facial dysmorphisms (52). The first set of LCRs consisted of the two OR-REPs involved in the recurrent inv dup del (8p). The second type of LCRs consisted of short (15 kb) repeats lying

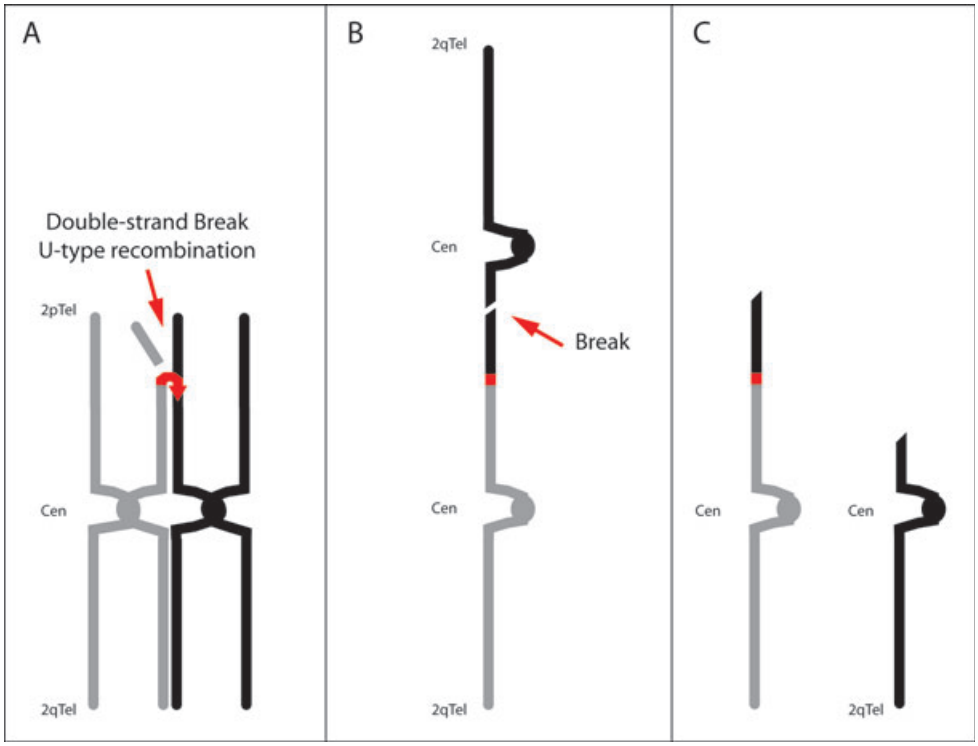

Fig. 3. Mechanism of non-recurrent inv dup del(2p) formation. (A) Double-strand break followed by U-type exchange or micro-homology-mediated intrastrand pairing leads to the formation (B) of a dicentric 2qter-2p25.3::2p25.3-2qter chromosome. Breakage of the dicentric chromosome leads to the creation (C) of 2p- and inv dup del(2p) chromosomes. The U-type exchange is shown in red. Recombination and break locations are shown by arrows.

in inverted orientation at 8p23.2 and enclosing a non-repeated sequence of approximately 130 kb. The molecular characterization of a third case with a dicentric chromosome 8, deleted in its distal 8p portion, demonstrated that the rearrangement had been generated by NAHR between the short IRs. Based on our findings, we proposed a model showing that a second recombination event at the level of the OR-REPs leads to the formation of the dup trp(8p) chromosome. This rearrangement can only arise during meiosis in heterozygous carriers of the polymorphic 8p23.1 inversion, whereas in subjects with non-inverted chromosomes 8 or homozygous for the inversion only the classic dicentric chromosome can be formed.

Inv dup del and ring chromosomes

Recently two papers (41,53) have been published describing ring chromosomes in which array-CGH analysis showed not only the expected deletion at one or both chromosome ends but also a contiguous duplication (Fig. 4). In three of these cases FISH analysis demonstrated that the duplication was inverted (Fig. 1 in ref. 41 and Fig. 2 in ref 53). Rossi et al (53) found that 7 out 33 ring chromosomes were in fact not only deleted but also duplicated indicating that a precise mechanism is operating. Here, again, the presence of an inv dup del chromosome, although in a circular form, led us to hypothesize that the starting point was a symmetric dicentric chromosome present in the zygote or in early embryogenesis. Its breakage would have led to an inv dup del that in the absence of telomerase would stabilize itself through circularization. If we consider that an asymmetric breakage of such a dicentric chromosome results in the formation of an inv dup del and a simply deleted chromosome and that both need to be healed, we might hypothesize that also some "regular" ring chromosome having only the expected deletion can originate through an original dicentric chromosome.

Inv dup del and de novo unbalanced translocations

On 2002, Kostiner et al, (54) described an inv dup del(8p) case having a cytogenetically detectable piece of chromosome 18q on the distal end of its short arm, suggesting that the chromosome was stabilized by telomere capture. We found

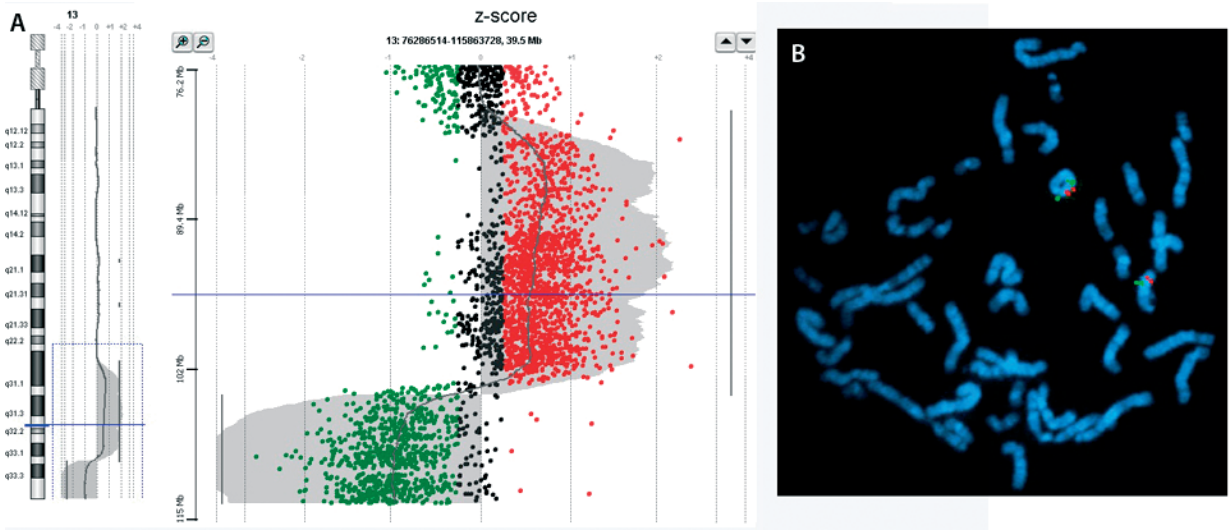

Fig. 4. A: array-CGH (244A, AGILENT) of a r(13) (Case 7 in Rossi et al, 2008) showing a 20 Mb duplication concomitant to a distal 10 Mb deletion. B: dual colour fluorescence *in situ* hybridisation (FISH) of the same r(13) with BAC RP11-164b1, green, and RP11-122a8, red showing that the duplication is inverted.

two similar cases that, on the basis of subtelomeric FISH on a p+ chromosome, were originally interpreted as unbalanced translocations. Both were *de novo* and only array-CGH analysis to size the unbalanced regions led to the discovery that they were inv dup del stabilized through telomere capture. These findings indeed suggest that also some *de novo* unbalanced translocations may derive from the same mechanisms of classical inv dup del rearrangements, once again demonstrating that in the absence of telomerase different mechanisms operate to heal broken chromosomes.

Recurrence risk

There is no recurrence risk for any of the *de novo* imbalances we discussed. Thus, no invasive prenatal investigations are indicated after the birth of a child with a *de novo* inv dup del chromosome. Even the inv dup del(8p)s, that are the recombinant products of a parental 8p23.1 heterozygous inversion, are always single events reflecting either the rarity of the abnormal recombination or the early lethality of zygotes with an almost complete trisomy 8 due to the presence of the dicentric chromosome. In fact, dicentric 8p with an inactive centromere has been reported only in mosaic with an 8p deletion cell line (55) or in uniparental disomy (52,56). It has been estimated that the frequency of the inv dup del(8p) is of about 1:20.000 newborns (5). However, we do not know the frequency of NAHR leading to this rearrangement or to its reciprocal acentric chromosome. This information can only be gained through sperm-based assays to measure the de novo rate of these rearrangements (57).

Final conclusions

We showed that several rearrangements in humans are secondary to the formation of a symmetric dicentric chromosome. In some cases this dicentric is formed at meiosis, whereas in other cases it is not definitely clear whether it is formed during parental gametogenesis or in early embryogenesis. The instability of the dicentric and the low or absent telomerase activity in cleavage stage embryos (58) lead the chromosome derived from breakage of the dicentric to form different types of rearrangements including classical inv dup del, ring and unbalanced translocation chromosomes. In several of them a single copy region interposed between the deleted and the duplicated regions has been demonstrated whenever high resolution genome-wide arrays and/or breakpoint cloning has been performed (26).

These new technological approaches are only now allowing investigators to bring to light the complexity and frequency of these types of rearrangements.

Acknowledgements

This work was supported by CARIPLO 2007 (5197) to OZ, by Telethon Grant GGP06208 to MCB and RG and by Telethon Grant GGP08226 to RC.

References

1. Weleber RG, Verma RS, Kimberling WJ et al. Duplication-deficiency of the short arm of chromosome 8 following artificial insemination. Ann Genet 1976: 19: 241–247.
2. Taylor KM, Francke U, Brown MG et al. Inverted tandem ('mirror') duplications in human chromosomes:inv dup 8p, 4q, 22q. Am J Med Genet 1977: 1: 3–19.
3. Dill FJ, Schertzer M, Sandercock J et al. Inverted tandem duplication generates a duplication deficiency of chromosome 8p. Clin Genet 1987: 32: 109–113.
4. Minelli A, Floridia G, Rossi E et al. D8S7 is consistently deleted in inverted duplications of the short arm of chromosome 8 (inv dup 8p). Hum Genet. 1993: 92: 391–396.
5. Floridia G, Piantanida M, Minelli et al: The same molecular mechanism at the maternal meiosis I produces mono and dicentric 8p duplications. Am J Hum Genet 1996: 58: 785–796.
6. Giglio S, Broman KW, Matsumoto N et al. Olfactory receptor-gene clusters, genomic-inversion polymorphisms, and common chromosome rearrangements. Am J Hum Genet 2001: 68: 874–83.
7. Buysse K, Antonacci F, Callewaert B et al. Unusual 8p inverted duplication deletion with telomere capture from 8q. Eur J Med Genet 2009: 52: 31–36.
8. Sherr EH, Owen R, Albertson DG et al. Genomic microarray analysis identifies candidate loci in patients with corpus callosum anomalies. Neurology 2005: 65: 1496–1498.
9. Sugawara H, Harada N, Ida T et al. Complex low-copy repeats associated with a common polymorphic inversion at human chromosome 8p23. Genomics 2003: 82: 238–244.
10. Velinov M, Gu H, Genovese M et al. Characterization of an analphoid, neocentromere-positive inv dup 8p marker chromosome using multiplex whole chromosome and subtelomere FISH analyses. Ann Genet 2004: 47: 199–205.
11. Soler A, Sánchez A, Carrió A et al. Fetoplacental discrepancy involving structural abnormalities of chromosome 8 detected by prenatal diagnosis Prenat Diagn 2003: 23: 319–322.
12. Pramparo T, Giglio S, Gregato G et al. Inverted duplications: how many of them are mosaic? Eur J Hum Genet 2004: 12: 713–717.
13. Roberts SE, Maggouta F, Thomas NS et al. Molecular and fluorescence in situ hybridization characterization of the breakpoints in 46 large supernumerary marker 15 chromosomes reveals an unexpected level of complexity. Am J Hum Genet 2003: 73: 1061–1072.
14. Eggermann K, Mau UA, Bujdosó G et al. Supernumerary marker chromosomes derived from chromosome 15: analysis of 32 new cases. Clin Genet 2002: 62: 89–93.
15. Wendy P Robinson, Joseph Wagstaff, Fabiana Bernasconi, et al. Uniparental disomy explains the occurrence of the Angelman or Prader-Willi syndrome in patients with an additional small inv dup(15) chromosome. J Med Genet 1993: 30: 756–760.
16. Liehr T, Brude E, Gillessen-Kaesbach G et al. Prader-Willi syndrome with a karyotype 47,XY,+min(15)(pter->q11.1:) and maternal UPD 15–case report plus review of similar cases. Eur J Med Genet 2005: 48: 175–181.
17. Leana-Cox J, Jenkins L, Palmer CG et al. Molecular cytogenetic analysis of inv dup(15) chromosomes, using probes specific for the Prader-Willi/Angelman syndrome region: clinical implications. Am J Hum Genet 1994: 54: 748–756.
18. Crolla JA, Harvey JF, Sitch FL et al. Supernumerary marker 15 chromosomes: a clinical, molecular and FISH approach to diagnosis and prognosis. Hum Genet 1995: 95: 161–170.
19. Cassidy S, Conroy J, Becker L, Schwartz S. Paternal triplication of 15q11-q13 in a hypotonic, developmentally delayed child without Prader-Willi or Angelman syndrome. Am J Med Genet 1996: 62: 205–212.
20. Ungaro P, Christian SL, Fantes JA et al. Molecular characterisation of four cases of intrachromosomal triplication of chromosome 15q11-q14. J Med Genet 2001: 38((1)): 26–34.
21. Cotter PD, Ko E, Larabell SK et al. Segregation of a supernumerary del(15) marker chromosome in sperm. Clin Genet 2000: 58: 488–492.
22. McDermid HE and Morrow BE. Genomic Disorders on 22q11. Am J Hum Genet 2002: 70: 1077–1088.
23. Ballif BC, Yu W, Shaw CA et al. Monosomy 1p36 breakpoint junctions suggest pre-meiotic breakage-fusion-bridge cycles are involved in generating terminal deletions. Hum Mol Genet 2003: 12: 2153–2165.
24. Mewar R, Harrison W, Weaver DD et al. Molecular cytogenetic determination of a deletion/ duplication of 1q that results in a trisomy 18 syndrome-like phenotype. Am J Med Genet 1994: 52: 178–183.
25. De Brasi D, Rossi E, Giglio S et al. Inv dup del (1)(pter->q44::q44->q42:) with the classical phenotype of trisomy 1q42-qter. Am J Med Genet 2001: 104: 127–130.
26. Bonaglia MC, Giorda R, Massagli A et al. A familial inverted duplication/deletion of 2p25.1–25.3 provides new clues on the genesis of inverted duplications. Eur J Hum Genet 2008:: Sep 24.
27. Bonaglia MC, Giorda R, Poggi G et al. Inverted duplications are recurrent rearrangements always associated with a distal deletion: description of a new case involving 2q. Eur J Hum Genet 2000: 8: 597–603.
28. Jenderny J, Poetsch M, Hoeltzenbein M et al. Detection of a concomitant distal deletion in an inverted duplication of chromosome 3. Is there an overall mechanism for the origin of such duplications/deficiencies? Eur J Hum Genet 1998: 6: 439–444.
29. Kennedy D, Silver MM, Winsor EJ et al. Inverted duplication of the distal short arm of chromosome 3 associated with lobar holoprosencephaly and lumbosacral meningomyelocele. Am J Med Genet 2000: 91: 167–170.
30. Kondoh Y, Toma T, Ohashi H et al. Inv dup del(4)(:p14–(> p16.3::p16.3–> qter) with manifestations of partial duplication 4p and Wolf-Hirschhorn syndrome. Am J Med Genet A 2003: 120A: 123–126.
31. Beaujard MP, Jouannic JM, Bessières B, Borie C, Martin-Luis I, Fallet-Bianco C, Portnoï MF. Prenatal detection of a de novo terminal inverted duplication 4p in a fetus with the Wolf-Hirschhorn syndrome phenotype. Prenat Diagn 2005: 25: 451–455.
32. Van Buggenhout G, Maas NM, Fryns JP, Vermeesch JR. A dysmorphic boy with 4qter deletion and 4q32.3–34.3 duplication: clinical, cytogenetic, and molecular findings. Am J Med Genet A: 2004: 131: 186–189.
33. Sreekantaiah C, Kronn D, Marinescu RC et al. Characterisation of a complex chromosomal rearrangement in a patient with a typical catlike cry and no other clinical findings of cri-du-chat syndrome. Am J Med Genet 1999: 86: 264–268.
34. Wang JC, Coe BP, Lomax B, MacLeod PM, Parslow MI, Schein JE, Lam WL, Eydoux P. Inverted duplication with

terminal deletion of 5p and no cat-like cry. Am J Med Genet A 2008: 146A: 1173–1179.
35. Hoo JJ, Chao M, Szego K et al. Four new cases of inverted terminal duplication: a modified hypothesis of mechanism of origin. Am J Med Genet 1995: 58: 299–304.
36. Stetten G, Charity LL, Kasch LM et al. A paternally derived inverted duplication of 7q with evidence of a telomeric deletion. Am J Med Genet 1997: 68: 76–81.
37. Teebi AS, Gibson L, McGrath J et al. Molecular and cytogenetic characterisation of 9p- abnormalities. Am J Med Genet 1993: 46: 288–292.
38. Wyandt HE. Reported tandem duplication/deletion of 9q is actually an inverted duplication. Am J Med Genet 2001: 100: 82–83.
39. Fisher AM, Thomas NS, Cockwell A et al. Duplications of chromosome 11p15 of maternal origin result in a phenotype that includes growth retardation. Hum Genet 2002: 111: 290–296.
40. Chen CP, Chern SR, Lin Sp et al. A paternally derived inverted duplication of distal 14q with a terminal 14q deletion. Am J Med Genet A 2005: 139A: 146–150.
41. Knijnenburg J, van Haeringen A, Hansson KB et al. Ring chromosome formation as a novel escape mechanism in patients with inverted duplication and terminal deletion. Eur J Hum Genet 2007: 15: 548–555.
42. Genesio R, De Brasi D, Conti A et al. Inverted duplication of 15q with terminal deletion in a multiple malformed newborn with intrauterine growth failure and lethal phenotype. Am J Med Genet A 2004: 128A: 422–428.
43. Courtens W, Grossman D, Van Roy N et al. Noonan-like phenotype in monozygotic twins with a duplication-deficiency of the long arm of chromosome 18 resulting from a maternal paracentric inversion. Hum Genet 1998: 103: 497–505.
44. Pangalos C, Théophile D, Sinet PM et al. No significant effect of monosomy for distal 21q22.3 on the Down syndrome phenotype in "mirror" duplications of chromosome 21. Am J Hum Genet 1992: 51: 1240–1250.
45. Milunsky J, Huang XL, Wyandt HE et al. Schizophrenia susceptibility gene locus at Xp22.3. Clin Genet 1999: 55: 455–460.
46. Dupont C, Lebbar A, Teinturier C et al. First reported case of intrachromosomal cryptic inv dup del Xp in a boy with developmental retardation. Am J Med Genet A 2007: 143A: 1236–1243.
47. Okuno Y, Hahn PJ, Gilbert DM. Structure of a palindromic amplicon junction implicates microhomology-mediated end joining as a mechanism of sister chromatid fusion during gene amplification. Nucleic Acids Res 2004: 32: 749–756.
48. Tanaka H, Cao Y, Bergstrom DA et al. Intrastrand annealing leads to the formation of a large DNA palindrome and determines the boundaries of genomic amplification in human cancer. Mol Cell Biol 2007: 27: 1993–2002.
49. Bacolla A, Wells RD. Non-B DNA conformations, genomic rearrangements, and human disease. J Biol Chem 2004: 279: 47411–47414. Review.
50. Shaw CJ, Lupski JR. Implications of human genome architecture for rearrangement-based disorders: the genomic basis of disease. Hum Mol Genet 2004: 13: R57–R64.
51. Daniel A, St Heaps L, Sylvester D et al. Two mosaic terminal inverted duplications arising post-zygotically: Evidence for possible formation of neo-telomeres. Cell Chromosome 2008: 10: 7–1.
52. Giorda R, Ciccone R, Gimelli G et al. Two classes of low-copy repeats comediate a new recurrent rearrangement consisting of duplication at 8p23.1 and triplication at 8p23.2. Hum Mutat 2007: 28: 459–468.
53. Rossi E, Riegel M, Messa J et al. Duplications in addition to terminal deletions are present in a proportion of ring chromosomes: clues to the mechanisms of formation. J Med Genet 2008: 45: 147–154.
54. Kostiner DR, Nguyen H, Cox VA et al. Stabilization of a terminal inversion duplication of 8p by telomere capture from 18q. Cytogenet Genome Res 2002: 98: 9–12.
55. Ciccone R, Mattina T, Giorda R et al. Inversion polymorphisms and non-contiguous terminal deletions: the cause and the (unpredicted) effect of our genome architecture. J Med Genet 2006: 43: e19.
56. Piantanida M, Dellavecchia C, Floridia G et al. Ataxic gait and mental retardation with absence of the paternal chromosome 8 and an idic(8)(p23.3): imprinting effect or nullisomy for distal 8p genes? Hum Genet 1997: 99: 766–771.
57. Turner DJ, Miretti M, Rajan D, et al. Germline rates of de novo meiotic deletions and duplications causing several genomic disorders. Nat Genet. 2008: 40: 90–95.
58. Liu L, Bailey SM, Okuka M et al. Telomere lengthening early in development. Nat Cell Biol 2007: 9: 1436–1441.