



Review

The embryo battle against adverse genomes: Are de novo terminal deletions the rescue of unfavorable zygotic imbalances?

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ABSTRACT

De novo distal deletions are structural variants considered to be already present in the zygote. However, investigations especially in the prenatal setting have documented that they are often in mosaic with cell lines in which the same deleted chromosome shows different types of aberrations such as: 1) neutral copy variants with loss of heterozygosity that replace the deleted region with equivalent portions of the homologous chromosome and create distal uniparental disomy (UPD); 2) derivative chromosomes where the deleted one ends with the distal region of another chromosome or has the shape of a ring; 3) U-type mirror dicentric or inv-dup del rearrangements. Unstable dicentrics had already been entailed as causative of terminal deletions even when no trace of the reciprocal inv-dup del had been detected. To clarify the mechanism of origin of distal deletions, we examined PubMed using as keywords: complex/mosaic chromosomal deletions, distal UPD, U-type dicentrics, inv-dup del chromosomes, excluding the recurrent inv-dup del(8p)s which are known to originate by NAHR at the maternal meiosis. The literature has shown that U-type dicentrics leading to nearly complete trisomy and therefore incompatible with zygotic survival underlie many types of de novo unbalanced rearrangements, including terminal deletions. In the early embryo, the position of the postzygotic breaks of the dicentric, the different ways of acquiring telomeres by the broken portions and the selection of the most favorable cell lines in the different tissues determine the prevalence of one or the other rearrangement. Multiple lines with simple terminal deletions, inv-dup dels, unbalanced translocations and segmental UPDs can coexist in various mosaic combinations although it is rare to identify them all in the blood.

Regarding the origin of the dicentric, among the 30 cases of non-recurrent inv-dup del with sufficient genotyping information, paternal origin was markedly prevalent with consistently identical polymorphisms within the duplication region, regardless of parental origin. The non-random parental origin made any postzygotic origin unlikely and suggested the occurrence of these dicentrics mainly in spermatogenesis.

This study strengthens the evidence that non-recurrent de novo structural rearrangements are often secondary to the rescue of a zygotic genome incompatible with embryo survival.

1. Introduction

Highlighting of the distal ends of chromosomes by fluorescent *in situ* hybridization (FISH) assays showed that rearrangements of these regions were present in approximately 5% of individuals with intellectual disabilities (ID) (Flint et al., 1995). In about half of the cases, de novo deletions were documented and a few years later some of them were

associated with specific malformation syndromes (De Vries et al., 2003). In the remaining half, the deletion resulted from an unbalanced translocation, of which one parent carried the balanced form in 60% of cases (Flint and Knight 2003). Replacement of FISH subtelomeres with array comparative genomic hybridization (array-CGH) confirmed the burden of de novo telomeric deletions among ID individuals and showed that telomere imbalances were significantly of greater size than previously

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estimated, albeit cryptic to conventional cytogenetics (Ledbetter and Martin 2007). Regarding the origin of the de novo subtelomeric deletions, the absence of mosaic conditions, at least as emerged from the FISH analysis in a large cohort of individuals with developmental disabilities (Ravnan et al., 2006), suggests that these events occur during gametogenesis rather than being postzygotic. The concept of the prezygotic origin of the rearrangement is reinforced by the paternal bias reported for copy number variant (CNV) deletions in general (Hehir-Kwa et al., 2011; Ma et al., 2017; Belyeu et al., 2021) and some terminal deletions involving specific chromosome ends such as 5p, 18q, 22q, with those of paternal origin more frequent than those of maternal one (J Overhauser et al., 1990; Cody et al., 1997; Sarasua et al., 2014). On the contrary, in some cases of subtelomeric deletions that have been more recently analyzed through broad cytogenomic approaches, complex mosaics have been detected (see as examples: Shimada et al., 2015; Dos Santos et al., 2018; Shiohama et al., 2020), indicating postzygotic mechanisms as crucial if not in the origin, at least in the formation of the final rearrangement. To reinforce this hypothesis, those cases in which next to the cell line with the deleted chromosome a second one was identified in the same or in other tissues, where the abnormal chromosome had an inverted duplication of a portion that preceded the terminal deletion (inv-dup del) or was a pseudodicentric chromosome (Soler et al., 2003; Pramparo et al., 2004; Chabchoub et al., 2007; Schlade-Bartusiak et al., 2013; Rittinger et al., 2015; Chen et al., 2019; Huynh et al., 2021, Bonaglia et al. 2022_Clinical Report). These results clearly indicated that the original rearrangement was not the deleted chromosome but rather a dicentric whose asymmetric break would precisely lead to the formation of an inverted duplication with a terminal deletion (inv-dup del) chromosome and its reciprocal with a simple distal deletion (Florida et al., 1996; Giglio et al., 2001; Pramparo et al., 2004; Ciccone et al., 2006; Zuffardi et al., 2009). Possible explanations for the many instances in which the deleted chromosome was of different size in respect to the hypothetical reciprocal inv-dup del chromosome (Pramparo et al., 2004; Voet et al., 2011) are (1) the dicentric was present in more than one cell of the early embryo and underwent different ruptures in the different cells, thus creating different derivative products of which only some survive the selection constraint, or (2) the dicentric chromosome, originally present in a single cell, underwent multiple break-fusion-bridge (BFB) cycles whenever the products derived from its break were not stabilized by telomeric sequences. Indeed, it is precisely the ways in which these sequences are acquired from the two derivatives of the dicentric that determine the final type of the rearrangement. While the failure to acquire telomeric sequences leads to the formation of a chromosomal ring, with or without inverted duplication (Rossi et al., 2008), the capture of the distal portion of another chromosome by the deleted or inv-dup del chromosomes, forms a de novo unbalanced translocation, respectively simple or complex, as shown (Bonaglia et al., 2018). Of note, more and more publications are showing that the missing telomere of deleted chromosomes is frequently acquired from the normal homolog by somatic recombination. This event can lead to a mosaic condition with a cell line still having the deleted chromosome presumably stabilized by the telomeric repeated sequences of an unknown donor chromosome and a second cell line or even more cell lines in which the originally deleted chromosome is now in UPD for regions of different size coming from the intact homolog (Kotzot, 2008; Milosevic et al., 2014; Knijnenburg et al., 2017; Van Opstal et al., 2019). All of these data indicate that terminal deletions are highly unstable rearrangements and a detailed genomic investigation in different tissues often reveals unexpected variability in deletion size, segmental UPD size, and abnormal chromosome conformation (Van Opstal et al., 2019; Kato et al., 2020; Bonaglia et al. 2022_Clinical Report). In this study we discuss the results of the literature trying to highlight (i) why if distal deletions are always the byproduct of a dicentric chromosome, the presence of mosaicism is only rarely evidenced in postnatal studies and (ii) if and how mosaicism can affect genotype-phenotype correlations.

2. Methods

2.1. Research of the literature

Starting from the consideration that the de novo non-recurring CNVs, especially the loss ones, have preferential paternal origin (Hehir-Kwa et al., 2011; Ma et al., 2017; Belyeu et al., 2021), we thought that if indeed distal deletions derive from a mirror-dicentric chromosome, the other derivatives of the dicentric break, ie inv-dup del chromosomes, should also be mainly of paternal origin. Furthermore, every possible clue for an association between this type of chromosomal rearrangements and the rise in paternal age was also examined, although among the de novo DNA modifications only the single nucleotide and insertion-deletion variants but not the structural ones correlate to such an increase (Belyeu et al., 2021). To this end, we searched PubMed using as keywords: inv-dup del chromosomes, U-type dicentric chromosomes, complex chromosomal deletions, mosaic chromosomal deletions, and distal UPD, excluding the recurrent inv-dup del (8p)s which are known to originate in maternal meiosis I through non-allelic homologous recombination (NAHR).

3. Results

3.1. Research of the literature

As shown in Table 1, we were able to collect 29 cases where the origin of the parents was investigated.

Paternal origin was largely prevalent with only 7 of them (75%, 22/29; Binomial exact test, $P = 0.008$) showing the maternal origin of the rearrangement. Unfortunately, the age of the parents at birth was not reported in any of the cases. Informative microsatellites/SNPs within the duplication region were consistently homozygous. In four of these articles the inv-dup del is indicated as present in mosaic with a second cell line showing terminal deletion (Lin et al., 2007; Rittinger et al., 2015; Bonaglia et al., 2018 and Bonaglia et al. 2022_Clinical Report).

4. Discussion

4.1. De novo unbalanced structural rearrangements may not be representative of what was the genomic situation of the zygote

For years, the identification of a de novo structural chromosomal anomaly in a subject affected by a constitutive pathological condition was considered representative of what had been the situation of the zygote and still that of the whole organism. In fact, the prevailing idea until at least the first decade of this century was that any de novo derivative chromosome was already present as such in the zygote, having formed in the parental germline. This last point was reinforced by two observations: (1) in recurrent rearrangements the endpoints are characterized by large sequences of homology (low copy repeats: LCR) that allow NAHR to occur during parental meiosis; (2) almost 73% of de novo structural mutations have a paternal origin (Belyeu et al., 2021) making it unlikely a postzygotic origin for which a random parental origin would be expected.

However, early suspicions that the structural anomalies identified either before or after birth might not represent the zygote genome came from the discovery that mosaicism is a very common condition, perhaps the rule rather than the exception: “genome mosaicism—one human, multiple genomes” (Lupski, 2013). Indeed, the current idea was that of a zygote with a normal genome that during embryogenesis would acquire variants presumably lethal if germline, as exemplified by the gain-of-function variants in the PI3K-AKT-mTOR signaling pathway. Although the constitutive ones are the basis of many oncogenic processes, in mosaic conditions these variants are responsible for hemimegalencephaly and different types of cortical dysplasia, depending on the gene, mutation, level of mosaicism, and tissue distribution (Dobyns

Table 1

Inv-dup del cases reported in the literature with known parental origin; inv-dup del(8p) cases were excluded.

Inv-dup del cases	[Reference]	Parental origin(*)	Pre-/Postnatal ascertainment	Homogeneous/mosaic
Inv-dup del(2q)	Bonaglia et al. (2009)	Mat	Postnatal	Homogeneous
Inv-dup del(2q)	Vera-Carbonell et al. (2010)	Mat	Postnatal	Homogeneous
Inv-dup del(2q)	Bonaglia et al., (2018) (case 39)	Pat	Postnatal	Homogenous
Inv-dup del(2q)	Hermetz et al., (2014) (case EGL044)	Pat	Postnatal	Homogenous
Inv-dup del(2q)	Hermetz et al., (2014) (case EGL398)	Pat	Postnatal	Homogenous
Inv-dup del(4p)	Paskulin et al. (2009)	Pat	Postnatal	Homogeneous
Inv-dup del(4p)	Bonaglia et al., (2018) (case 52)	Pat	Postnatal	Homogenous
Inv-dup del(5p)	Hermetz et al., (2014) (case EGL106)	Pat	Postnatal	Homogenous
Inv-dup del(5p)	Bonaglia et al., (2018) (case 45)	Pat	Prenatal	Mosaic
Inv-dup del(7q)	Stetten et al. (1997)	Pat	Postnatal	Homogeneous
Inv-dup del(7q)	Bonaglia et al., (2018) (case 41)	Pat	Postnatal	Homogeneous
Inv-dup del(8q)	Rodríguez et al. (2011)	Pat	Postnatal	Homogeneous
Inv-dup del(9p)	Chabchoub et al. (2007)	Pat	Postnatal	Mosaic
Inv-dup del(9p)	Chen et al. (2011)	Mat	Prenatal	Homogeneous
Inv-dup del(10p)	Chen et al. (2019)	Mat	Prenatal	Homogeneous
Inv-dup del(10q)	Kibe et al., 2011	Pat	Postnatal	Homogeneous
Inv-dup del(10q)	Chen et al. (2012)	Pat	Postnatal	Homogeneous
Inv-dup del(13q)	Rossi et al., (2008) (case 7)	Pat	Postnatal	Homogeneous
Inv-dup del(14q)	Chen et al. (2005)	Pat	Postnatal	Homogeneous
Inv-dup del(15q)	Rossi et al., (2008) (case 13)	Pat	Postnatal	Homogeneous
Inv-dup del(16p)	Bonaglia et al., (2018) (case 40)	Pat	Postnatal	Homogeneous
Inv-dup del(18q)	Hermetz et al., (2014) (case 18q-34c)	Pat	Postnatal	Homogenous
Inv-dup del(18q)	Hermetz et al., (2014) (case 18q-207c)	Pat	Postnatal	Homogenous
Inv-dup del(18q)	Hermetz et al., (2014) (case 18q-223c)	Pat	Postnatal	Homogenous
Inv-dup del(18q)	Hermetz et al., (2014) (case 18q-62c)	Pat	Postnatal	Homogenous
Inv-dup del(18q)	Hermetz et al., (2014) (case 18q-119c)	Pat	Postnatal	Homogenous
Inv-dup del(18q)	Hermetz et al., (2014) (case 18q-207c)	Pat	Postnatal	Homogenous
Inv-dup del(18q)	Rittinger et al., 2015	Mat	Postnatal	Mosaic
Inv-dup del(18q)	Lin et al. (2007)	Mat	Prenatal	Mosaic
Inv-dup del(18q)	Bonaglia et al. ClinicalReport_2022	Mat	Postnatal	Mosaic
TOT number	30 cases	7 Mat 23 Pat	4 prenatal 26 postnatal	5 Mosaic; 25 Homogeneous

LEGEND: * homozygosity for all the informative microsatellites/SNPs was systematically detected in the duplicated segment; Mat: Maternal; Pat: Paternal.

and Mirzaa, 2019). Also the unexpected high rate of structural chromosomal abnormalities identified by microarray in blastomeres of embryos obtained from in vitro fertilization (see Vanneste et al., 2009 and related comment in Ledbetter, 2009) has been interpreted as the acquisition of a new genetic structure that has nothing to do with the original zygotic genome: “many, but often not all, blastomeres of an embryo acquire a genetic makeup during cleavage that is not representative of the original zygotic genome” (Voet et al., 2011). In contrast, the hypothesis that the zygote had an anomalous genome and subsequent variations, even different in the different cells, could correct any potential inconsistency with embryonic development was largely underestimated, despite the correction of the trisomy or, more rarely, of the monosomy by means of trisomy or monosomy rescue were for all to see. Furthermore, there are increasing reports of spontaneous remission of monogenic diseases and genomic imbalances through so-called revertant mosaicism elicited by mitotic recombination (Glembotsky et al., 2020; Nomura, 2020; Garelli et al., 2019; Twaroski et al., 2019; Dos Santos et al., 2018; Papenhausen et al., 2021), further demonstrating that a genetically abnormal zygote can modify its genome during embryogenesis or even later, sometimes even reversing its life prospects (Revy et al., 2019). Several evidences suggest that the original conformation of the de novo structural chromosomal anomalies was not the current one. Among them, those unbalanced translocations in which the derivative chromosome is of biparental origin (Giorda et al., 2008; Robberecht and Voet, 2013; Bonaglia et al., 2018), and the jumping translocations in which the same segment of a donor chromosome is transferred to two or more receptor chromosomes (Lejeune et al., 1979; Rivera et al., 1990; Jewett et al., 1998; Devriendt et al., 1997; Lefort et al., 2001; Hemmat et al., 2013; Zhang et al., 2013). The contribution to the derivative chromosome of the two parental genomes in the first case and the high promiscuity of specific chromosomal portions that attach to different chromosomal ends in the second one, indicated an intense postzygotic remodeling which however was triggered by an

original trisomy, either still residing in part of the cells (Devriendt et al., 1997; Bonaglia et al., 2018) or evidenced by the presence of three alleles in the duplicated region of the derivative chromosome, two of which coming from the mother (Bonaglia et al., 2018). In some of these cases, the duplicated region represents the portion left after a chromothripsis event on the supernumerary chromosome derived from maternal nondisjunction (Bonaglia et al., 2018). In fact, the distal end of the chromothrised chromosome is donated to the terminal of a receiving chromosome, which becomes the derivative one (Weckselblatt et al., 2015). Some de novo small supernumerary marker chromosomes (sSMC) originate with the same mechanism of chromothripsis provided that the centromeric region of the supernumerary chromosome present in the trisomic zygote is also recovered after the pulverization event (Kurtas et al., 2019). The presence or absence of telomeric regions will determine the shape of the sSMCs as a ring or a linear chromosome. Postzygotic modification similar to the partial rescue of full trisomies have been reported in association with the rare mirror dicentric chromosomes where two almost complete identical chromosomes joined by their short or long arms form a specular structure in a context of 46 chromosomes. Taking as an example the recurrent inv-dup del (8p), which is the best known among the inv-dup del rearrangements, several evidences indicate that NAHR at maternal meiosis I (Florida et al., 1996) gives rise to a mirror dicentric chromosome 8qter- > p23.3::p23.3- > qter that passes intact into the zygote. In fact, in rare cases a pseudodicentric chromosome, psu dic(8)(p23.3), originating precisely at maternal meiosis, has been identified in patients with 45 chromosomes missing the normal chromosome 8 or having a second cell line with the normal chromosome 8 and the psu dic(8)(p23.3), a condition that underlines the inability to survive a non-mosaic trisomy 8 (Piantanida et al., 1997; Giorda et al., 2007; Li et al., 2015). Moreover, although the inv-dup del (8p) syndrome is not reported as a mosaic condition (ORPHAcode: 96092; Unique, 2019), some patients are described with a cell line deleted for part or even nearly the entire short

arm of the chromosome 8 (Vermeesch et al., 2003; Hand et al., 2010). In contrast, complex mosaics are the rule in chorionic villi with clones that still have the dicentric 8qter->8p23::>8p23->qter, 8p deletions of different lengths, 8p translocated derivatives, or even inv-dup del (8p) ending with a portion of another chromosome (Soler et al., 2003; Pramparo et al., 2004; Huynh et al., 2021), leading to a final product that, at least in blood, is characterized by the same deletion in all the cases whereas the concomitant duplication can extend from 8p23.1 up to the second centromere of the original dicentric (Florida et al., 1996). Ways to stabilize the broken products can even lead to paternal UPD segments in the maternal derivative chromosome 8 (Buysse et al., 2009; Knijnenburg et al., 2017), sometimes driving to wrong interpretations (Oren et al., 2019).

Overlapping mosaic patterns have been reported in the numerous non-recurring inv-dup del rearrangements, again indicating that, regardless of whether they are recurrent or non-recurrent, they are the end products of an intermediate dicentric chromosome.

4.2. Mechanisms of formation of non-recurrent mirror dicentric chromosomes and their postzygotic derivatives

Disentangling of breakpoints and trios' genotyping in non-recurrent inv-dup dels revealed that the meiotic NAHR was incompatible with the origin of the original mirror dicentric, rather showing a replication-based mechanism that repaired an initial double-strand break followed by 3'-5' exonuclease erosion of a single filament and its template switch (Hermetz et al., 2014; Kato et al., 2020). In contrast to the recurrent inv-dup del(8p), the neutral-copy region interposed within the inverted and non-inverted segment has a size of few kb or even less, presumably corresponding to that of the single-stranded region created by exonuclease resection and the eventual nucleotides insertion at the junction of the two filaments. Accordingly, dicentrics leading to non-recurrent inv-dup dels and reciprocal distal deletions occur outside meiosis and are therefore either of premeiotic or postzygotic origin also in agreement with the presence of identical polymorphisms within the duplication regions. Again, this is in contrast with the presence of both the maternal alleles within the duplicated region of the inv-dup del(8p)s. Furthermore, most of the non-recurrent inv-dup dels are of paternal origin (see Table 1), which indicates that the original mirror dicentrics from which they derive are paternal germline aberrations. The rare cases of maternal origin, even with identical duplication polymorphisms, suggest their origin in the limited number of mitotic divisions of the oogonia preceding the prophase of meiosis I before birth or in the early postzygotic divisions. Interestingly, 3 of the 7 maternal cases reported in Table 1 are inv-dup del (18q) although it is unclear whether they share breakpoints. If so, the rearrangements could be mediated by small, unnoticed low copy repeats acting as substrate for NAHR variants. Some relationship could also be considered with nondisjunction at meiosis II, as suggested by the homozygosity of the markers in the duplicated region and the fact that chromosome 18 is one of the few in which nondisjunction events occur mainly at meiosis II (Hassold and Hunt, 2001). The preferential paternal origin of de novo structural variants was recently confirmed through genome sequencing of 2396 families by Belyeu et al. (2021). It's interesting that both in the numerous de novo structural variations they considered and in our few inv-dup del rearrangements, the percentage of cases of paternal origin amounted to just over 70%. Belyeu et al. also showed that no effect of parental age appears to emerge on the occurrence of structural de novo variants, despite the known link between single nucleotide de novo variants and paternal age and trisomies and maternal age. Regarding the inv-dup del cases, systematic data on the age of the parents is lacking both for the recurrent and non-recurrent ones.

4.3. Recurrent and non-recurrent mirror dicentric chromosomes: are they the basis for apparently non-mosaic distal deletions?

Numerous apparently "pure" deletions have been documented in mosaic with an inv-dup del rearrangement of the same chromosome (Pramparo et al., 2004; Ciccone et al., 2006; Schlade-Bartusiak et al., 2013; Chabchoub et al., 2007; Manolagos et al., 2008; Sheth et al., 2020) and in some cases mosaics have been documented, mainly in placental samples, where the deletion is of different sizes in the different clones (Van Opstal et al., 2019; Bonaglia et al., 2011; Bonaglia et al. ClinicalReport_2022). Not infrequently in these cases one or more cell lines without any deletion but with segmental isodisomy of different length for the otherwise deleted regions has been documented, either in the same or other tissues (Langemeijer et al., 2020; Van Opstal et al., 2019; Caldwell et al., 2020; Dos Santos et al., 2018). The case reported by Bonaglia et al. ClinicalReport_2022 is paradigmatic: after the diagnosis of 18q homogeneous deletion, the other cell lines, however not so secondary, were highlighted only after the application of molecular technologies which made it impossible to ignore some log2 ratio values that indicated a few mosaic copy number variants and the need for further investigations. The intense post-zygotic remodeling can occur for a series of BFB cycles or for different breaks in different cells of the dicentric chromosome, provided that it does not undergo breakage at the first zygotic mitosis. The fate of the different degradation products and their conservation in the different tissues during embryogenesis and later on depends on a series of hitherto unpredictable factors. The position of the postzygotic breaks of the dicentric, when it goes through mitosis with the two centromeres attached to opposite spindle pole bodies, is probably not random. Florida et al. (1996) showed that 6 of the 16 cases of inv-dup del (8p) ended at the level of the second centromere, pointing to the preferential break of dicentric chromosomes at centromeric/pericentromeric regions as also demonstrated in budding yeast (Lopez et al., 2015). It is not known whether this break definitively eliminates the activity of the second centromere or if the broken dicentric can be immediately stabilized by the hypothetical formation of a neo-telomere or it undergoes subsequent BFB cycles or even if these cycles occur only in dicentrics with breaks between the two centromeres. We do not even know what determines the telomere stabilization modality of any broken portion, that is what determines the acquisition of the telomere from another chromosome instead of the homologous one, or finally how in the absence of one telomere a ring chromosome can be formed (Fig. 1). The selection modalities of the most suitable lines for cell survival in the different tissues is also unknown, that is what regulates the prevalence of one or the other rearrangement and of the various combinations of mosaics. A very similar situation of ignorance applies to those trisomies that end as de novo unbalanced translocations rather than small supernumerary chromosomes, conditions which in any case represent the partial rescue of an unviable situation (Bonaglia et al., 2018; Kurtas et al., 2019).

In summary, (i) advanced genomic analyses show that in many cases de novo distal deletions are of different sizes in different cells and sometimes in mosaic with inv-dup del rearrangements of the same chromosome; mosaics with unbalanced translocations in which the deleted chromosome acquires the telomere from another chromosome are frequent and, they can easily go unnoticed if the size of the donor chromosome is small. Moreover, mosaics where the deleted chromosome is in the shape of a ring chromosomes are not unusual; (ii) segmental UPD regions of different sizes, in which in part of the cells the deleted regions are replaced with their homologous (allelic) counterpart, have been reported multiple times. It should be noted that this condition, not devoid of possible pathogenetic effects related to the loss of heterozygosity, could have been mistaken for a postzygotic mosaic with a normal and a deleted cell line as reported for example by Galvin et al. (Galvin et al. 2015) and Oneda et al., (2017).

It follows that terminal deletions mainly derive from a prezygotic unstable rearrangement such as a dicentric chromosome which

preferentially originates at spermatogonial stage as a consequence of replication fork stalling and template switching (Kato et al., 2020).

4.4. Copy neutral-LOH (CN-LOH) and the inheritance of mosaic conditions

According to our data and partly in contrast with the current idea of the postzygotic origin of some structural de novo rearrangements, we hypothesize that many distal deletions derive from a structural chromosomal anomaly -mainly a dicentric chromosomes-, which was formed during the gametogenesis. The unexpected finding is undoubtedly the presence of clones in which the chromosomal arm affected by the deletion is present as UPD region from somatic recombination with the

normal homolog. This phenomenon, so far documented mainly as an acquired second hit in tumors and as a segmental mosaic 11p15 paternal UPD in a quarter of patients with Beckwith-Wiedemann syndrome (Duffy et al., 2019; Coorens et al., 2021), reveals a common rescue mechanism not only in placental and fetal cells (Van Opstal et al., 2019; Caldwell et al., 2020; Dos Santos et al., 2018) but also in postnatal tissues, probably being the main mechanism for the spontaneous remission of autosomal dominant diseases in the course of life. Indeed, the finding that CN-LOHs are by far the most frequent autosomal mosaic chromosomal alterations in hematopoietic genome of the almost 500.000 40 to 70-year-old persons of the UK Biobank (Loh et al., 2020) suggests that this type of variant has been so far largely underestimated in mosaic conditions associated with germline structural rearrangements.

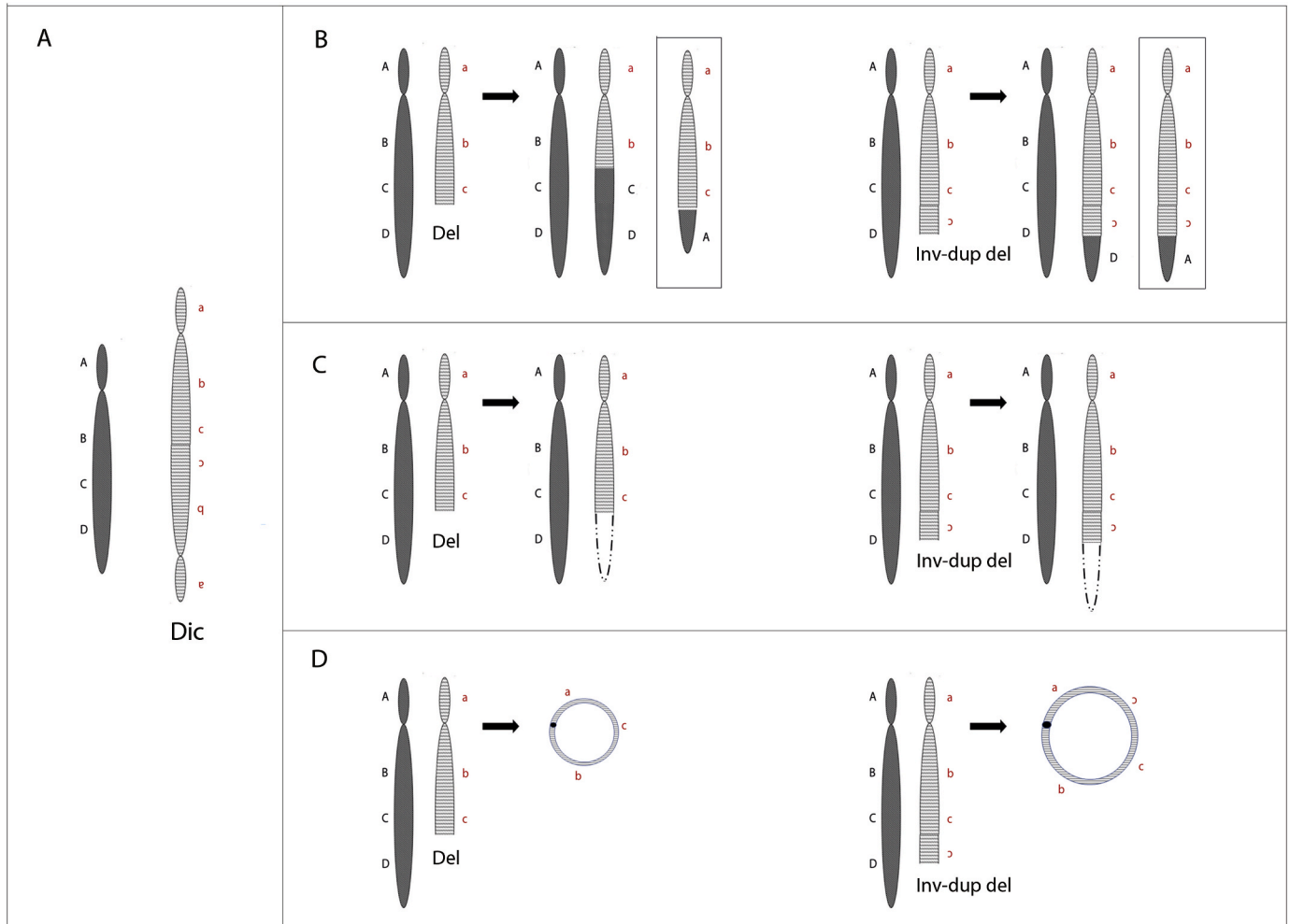


Fig. 1. Schematic representation of postzygotic rearrangements derived from asymmetric breaks of mirror dicentric chromosomes*
 A: normal chromosome (homogeneously gray) and homologous mirror dicentric chromosome (gray and white lines) whose asymmetrical break leads to a distally deleted chromosome (a, b, c) and an inv-dup del chromosome (a, b, c, c with the “c” portions arranged in opposite directions). The stabilization of the two derivatives can take place in different ways that are not mutually exclusive. B: somatic recombination leading to segmental uniparental disomy. In most cases, the deleted part is replaced by a much larger region of the homologous chromosome in respect to the originally deleted one, shown here as the neutral copy number “C-D” replacing the lost “c”; in cases of simple deletion, mosaicism has also been reported with different cell lines characterized by segmental UPDs of different size, suggesting that multiple recombination events may occur (Dos Santos et al., 2018). B, squares: in rare cases, recombination has also been reported that occurs with the portion of the arm opposite to the deleted one, with consequent duplication of the “A” recombined region (Fan and Siu, 2001; Ballif et al., 2004; Buysse et al., 2009; Knijnenburg et al., 2017). C) transposition of the distal region of another chromosome to the deleted (left) or the inv-dup del (right) chromosome leading to a simple or inv-dup del unbalanced translocation (“telomere capture”). D) the deleted (left) or the inv-dup del (right) chromosome folds back on itself and, recombining with the distal region of the opposite arm, forms a simple ring chromosome or an inv-dup del ring. The molecular details of this type of rearrangement have not yet been elucidated.
 * The presence of the two reciprocal derivatives, i.e. deleted and inv-dup del, has never been documented in the mosaic cell lines of the same patient, suggesting that the disruption of mirror dicentric chromosomes from different BFB cycles may generate different derivatives.
 Note that (i) stabilization of broken chromosomes through neo-telomere formation was not considered in this scheme. Indeed, the difficulty of sequencing the complex telomeric and subtelomeric regions has so far limited investigations to a few tumors (Hartlieb et al., 2021); (ii) stabilization of the two derivatives can take place in different ways not mutually exclusive as shown by the numerous mosaics reported mainly in prenatal diagnosis of the recurrent inv-dup del(8p).

Interestingly, the “deletion - neutral LOH copy” sequence can unexpectedly become a transgenerational trait. In fact, at least three papers have been published that demonstrate that de novo deletions of 11q, present in siblings with Jacobsen syndrome (Afifi et al., 2008; Johnson et al., 2014; Kawai et al., 2019) were inherited from healthy mothers with isodisomy for the erased region. In one of the families, one of the affected siblings was himself a mosaic with 11q deletion in one cell line and isodisomy in the other. These data show that not only was the healthy mother a mosaic for a cryptic deletion, but the mosaic condition may become a dominant hereditary trait in appropriate genomic contexts which in this case were probably present in one of the two siblings, but not in the other. The concept of a genomic context shaping post-zygotic remodeling is emerging from the analysis of those variants instrumental for clonal selection. According to Thompson et al. (Thompson et al., 2019) and Loh et al., (2020), this genomic context is based on the balance between the immediate elimination of cells with imbalances harmful to cell reproduction and instead the clonal expansion of cells with favorable imbalances, all in a polygenic context.

4.5. *Partial trisomy rescue reinforces the evidence that chromosomal number abnormalities can undergo changes during embryogenesis and become de novo unbalanced structural abnormalities*

It should be kept in mind that also trisomies, the most frequent chromosomal abnormalities in humans, mainly resulting from maternal meiotic nondisjunction, can trigger intense modifications during early embryogenesis in order to limit their intrinsic lethality, and again create a state of mosaicism with one or a few cell lines predominating in the different tissues. The lethality of trisomic embryos can be modified by a chromothripsis event which removes the supernumerary chromosome either totally or partially. In the latter case, three types of structural anomalies can be formed: (i) unbalanced translocations where at least the telomeric region of the supernumerary chromosome stick to the distal portion of another chromosome (Bonaglia et al., 2018), (ii) insertional translocations where non-telomeric and sometimes non-contiguous portions of the supernumerary chromosome are inserted inside another chromosome (Kato et al., 2017), and (iii) small supernumerary marker chromosomes which are most frequently derived by interstitial non-contiguous portions of the supernumerary chromothrised chromosome (Kurtas et al., 2019). In all conditions the phenotypic consequences are linked to the alteration of the gene dosage and the three-dimensional architecture but also to the eventual UPD consequent to the chromothripsis of the paternal chromosome that forms the sSMC.

4.6. *Genotype-phenotype relationship may not be limited to the actual imbalance of the deletion*

A crucial question is whether and to what extent mosaic cell lines influence the final phenotype of those carriers of terminal deletions. In most cases, patients have characteristics largely overlapping those associated with almost all chromosomal imbalances (psychomotor retardation/intellectual disability, growth retardation, non-specific dysmorphic facial features). This makes it difficult to discriminate how these features are affected by the additional imbalances of other cell lines. In the case presented by Bonaglia et al. ClinicalReport_2022 the patient's clinical condition was fairly in agreement with those of the distal 18q deletions although the presence of asymmetrical malformations, such as unilateral coloboma of the iris, stress on underlying mosaicism. It is curious that the same asymmetric malformation was reported in a mosaic case of 18q- (Galvin et al., 2015).

The fact remains that genotype-phenotype associations are in general far from satisfactory also because the classic clinical characteristics of mosaicism (ie segmental abnormalities of skin pigmentation or asymmetrical growth of bilateral body parts), can easily escape in prenatal diagnosis.

5. Conclusions

Collectively, our observations support the hypothesis that most de novo chromosome anomalies are not primary rearrangements but rather the result of many different genomic modifications induced by the presence of a supernumerary chromosome or a dicentric mirror chromosome. The selection of the clone(s) that will be identified in blood or other accessible tissues will depend not only on the size and gene content of the aneuploidy/UPD regions but also on the set of variants present in genes instrumental for clonal expansion (Loh et al., 2020). It follows that given the complexity of the clone selection event, even the phenotypic effects of mosaicism are not so far predictable. However, it is important to emphasize that clones not present in the blood can remain in inaccessible tissues and be inherited in the offspring causing pathogenetic conditions that are not present in the parent. Undoubtedly, reports regarding 11q deletions and unbalanced translocations (Johnson et al., 2014; Kawai et al., 2019; Blanluet et al., 2021) teach that the risk of recurrence of apparently de novo deletions must be assessed in the parent of origin also excluding UPD in the regions corresponding to the proband's aneuploidy and not only by investigating the parent for the presence of mosaics.

Emerging evidence from the distal deletions of 11q is that the correction of the deletion through somatic recombination appears to be independent of the extent of the imbalance. In the case of siblings with the same der (11) t (2q; 11q) (Blanluet et al., 2021), the distal deletion of 11q is 1.6 Mb and none of the genes within the region are likely to be loss-of-function intolerant. Yet it is evidently sufficient to favor the clonal expansion of the cells in which segmental UPD

has formed for a region far greater (56 Mb) than the region of deletion. It therefore seems that in the presence of an average unfavorable first hit such as the distal 11q deletion, the acquisition of a CN-LOH that contains genes favorable to the survival of the cell, promotes its clonal expansion regardless of the age of the subject and the size of the deletion. Indeed, vulnerability to clonal hematopoiesis with specific acquired CN-LOH mutations, including that of 11q, has been well documented in the aging population (Loh et al., 2020). In conclusion, the clonality of CN-LOH that corrects the initial deletion depends on the gene content and probably on the genomic context rather than on the size of the deletion itself. Similarly, in the light of the data documenting the coexistence of clones with deletions of different sizes in the same individual (Bonaglia et al., 2011, case 20; Dos Santos et al., 2018; Van Opstal et al., 2019), some baffling reports on the expansion of the size of a terminal deletion from parent to proband (Faravelli et al., 2007; South et al., 2008) could be explained assuming that the smaller deletion of the parent represents only one of the two deleted clones rather than an amplification of the deletion at parental meiosis.

A final but crucial answer is why if distal deletions are always the secondary product of a dicentric chromosome, the presence of mosaicism is only rarely highlighted in postnatal studies. Certainly, it cannot be excluded that the early embryonic bottlenecks that modulate the original aneuploidy and allow the survival of the zygote select a single cell line within the inner cell mass thus determining the confined placental mosaicism. Overall, the analyses of plasma cell-free DNA are expected to overcome the difficulties of DNA analysis also in inaccessible tissues and not only in blood.

Ethical approval and consent to participate

This study was approved by ethical review boards at Scientific Institute, IRCCS Eugenio Medea, Bosisio Parini (Approval number: Prot. N. 07/19 – CE)

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Authors' contributions

Introduction and discussion were written by OZ and shared by all authors. All authors contributed equally to all aspects of the manuscript.

Declaration of competing interest

The authors declare no conflict of interest.

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