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ORIGINAL ARTICLE

Insight into the mechanisms and consequences of recurrent telomere capture associated with a sub-telomeric deletion

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Abstract A complex mosaicism of the short arm of chromosome 1 detected by SNP microarray analysis is described in a patient presenting a 4-Mb 1p36 terminal deletion and associated phenotypic features. The array pattern of chromosome 1p displayed an intriguing increase in divergence of the SNP heterozygote frequency from the expected 50% from the centromere towards the 1p36 breakpoint. This suggests that various overlapping segments of UPD were derived by somatic recombination between the 1p homologues. The most likely explanation was the occurrence of a series of events initiated in either a gamete or an early embryonic cell division involving a 1pter deletion rapidly followed by multiple telomere captures, resulting in additive, stepped increases in frequency of homozygosity towards the telomere. The largest segment involved the entire 1p, and at least four other capture events were observed, indicating that at least five independent telomere captures occurred in separate cell lineages. The determination of breakpoint position by detection of abrupt changes in B-allele frequency using a moving window analysis demonstrated that they were identical in blood and saliva, the tissues available for analysis. We developed a model to explain the interaction of parameters determining the mosaic clones and concluded that, while number, size, and position of telomere captures were important initiating determinants, variation in individual clone frequencies was the main contributor to mosaic differences between tissues. All previous reports of telomere capture have been restricted to single events. Other cases involving multiple telomere capture probably exist but require investigation by SNP microarrays for their detection.

Keywords telomere capture · UPD · mosaicism · SNP microarray

Abbreviations

SNP	Single nucleotide polymorphism
FISH	Fluorescence in situ hybridization
Mb	Megabase
OMIM	Online Mendelian Inheritance in Men
CNV	Copy number variation
UPD	Uniparental disomy
sUPD	Segmental uniparental disomy

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Introduction

Monosomy 1p36 syndrome (OMIM #607872) is caused by variably sized sub-telomeric deletions of the short arm of chromosome 1 (Shapira et al. 1997). Deletions of 1p36 are one of the commonest in humans and have an estimated incidence of 1:5000–1:10,000 (Heilstedt et al. 2003). Patients carrying the 1p36 deletion manifest cognitive impairment and characteristic facial features. They may also present other clinical features including seizures, growth and hearing impairment, hypotonia, and heart defects (Gajecka et al. 2007). Although the deletion size and breakpoint positions are variable between patients, the core clinical manifestations are fairly consistent (Shimada et al. 2014).

Four classes of chromosome rearrangements in individuals with monosomy 1p36 have been identified: derivatives of unbalanced translocations, interstitial deletions, apparently simple terminal truncations, and complex rearrangements. Simple terminal truncations, in which a sub-telomeric portion of 1p36 is lost along with the telomere, are the most common, and 67% of de novo rearrangements appear as simple terminal truncations at the sequence level (Gajecka et al. 2007; Heilstedt et al. 2003).

Eukaryotic chromosome stability relies on the presence of intact telomeres (Lustig 2003), and unless adequately repaired, telomere loss generates senescence and/or apoptotic cell death (Blasco 2005). Terminal deletions can be stabilized by "telomere healing," in which telomerase adds telomere sequences to the ends of the broken chromosomes, denominated "neo-telomeres" (Chabchoub et al. 2007; Flint et al. 1994). Less frequently, terminal deletions can be stabilized by "telomere capture"(Bonaglia et al. 2011), with a terminally deleted chromosome acquiring a new telomere sequence usually from a chromatid of a normal homologue, and much less frequently from a heterologous chromosome. A common feature of telomere capture is that not only the telomere region itself is captured, but also variable lengths of the donor chromosome arm, effectively creating either segmental uniparental disomy (sUPD) of the chromosome arm, when captured from a homologue segment, or partial trisomy, when captured from a non-homologous segment. In such cases, the gain of a functional telomere presumably outweighs the disadvantages of creating allelic or genomic imbalances (Yu and Graf 2010). Additionally, but much less frequently, terminal deletions can also be stabilized by ring chromosome formation (Knijnenburg et al. 2007) or entering a breakage-fusion-bridge cycle (Ballif et al. 2003).

Here, we describe a terminal 1p36 deletion associated with mosaic segmental uniparental disomy of the non-deleted part of 1p. This was detected by SNP microarray analysis in a patient with clinical features of 1p36 deletion syndrome. The heterozygosity frequency shows that the contribution of the two-parental chromosome 1 homologues increasingly deviates from 50%, from the pericentromeric 1p12 region towards the 1p36 deletion breakpoint, compatible with mosaicism involving increasing levels of sUPD of different sized segments of 1p.

Patients and methods

Patient

The patient is a 26-year-old male born to healthy and non-consanguineous parents. The pregnancy was uncomplicated and delivered by cesarean section. At his birth, the father and mother were 21 and 20 years old, respectively. His older brother is healthy, and his mother had a spontaneous abortion at approximately 4 weeks' gestational age. His parents report a first-degree cousin presenting severe intellectual disability. The patient presented a combination of developmental delay, intellectual disability, seizures, and delayed speech, compatible with features of the 1p36 deletion syndrome. His G-banded karyotype was normal.

Written informed consent for publication was obtained from the parents of the Patient. This research was approved by the Ethics Committee of the Biosciences Institute, University of São Paulo.

Saliva and peripheral blood samples from the patient and peripheral blood samples from both parents were obtained for molecular and cytogenetic studies.

We are willing to make DNA samples available from both blood and saliva from our patient to other groups wishing to collaborate on the molecular analysis of repetitive telomere capture phenomena. In this endeavor, the presence of four breakpoints associated with telomere capture within a single chromosome arm, combined with knowledge of their approximate location, should greatly assist in defining which types of DNA signature are most likely to be involved in telomere capture.

SNP microarray

DNA was isolated using a standard phenol-chloroform protocol. Patient's genomic DNA both from saliva and blood were hybridized, according to the supplier's instructions, to a CytoSNP 850 K BeadChip (Illumina, USA), containing 850,000 SNP probes covering the whole-genome. Data were analyzed using BlueFuse Multi 4.1 Software (BlueGnome Ltd., Cambridge, UK), and log R ratio and B-allele frequency (BAF) values were plotted along the chromosomal coordinates.

For the statistical analysis (Conover 1999), we used all microarray data points exported by the Bluefuse software. Only data for heterozygote genotypes were used, resulting in an average of $\sim 18 \times 10^3$ SNPS along the entire chromosome 1 or an average density of ~ 73 SNPs per Mb. We developed a model predicting that B-allele variation along the short arm of chromosome 1 of this patient must occur in steps, in which the position of more abrupt and larger changes along the chromosome indicated the putative positions of capture events. Detection of breakpoint positions along 1p was performed using a moving window analysis in which statistically significant changes in B-allele frequency were detected by comparing the averages of the allele frequencies between consecutive 2 Mb windows moved in 0.5 Mb steps. The breakpoint positions were most easily recognized in saliva because of the generally higher amplitude of B-allele changes compared to blood. However, the breakpoint positions established in blood closely matched those found in saliva to within several megabases but required a larger number of window movements to do so. The breakpoint locations were used in all further comparisons between tissues and segments; we applied Kruskal-Wallis non-parametric statistical analyses to evaluate changes in B-allele frequencies along the chromosome to determine UPD segment lengths and confirm breakpoint positions (Supplementary Material).

FISH

Metaphase chromosome spread preparations were obtained from lymphocyte cultures of peripheral blood, according to standard protocols. Fluorescence in situ hybridization (FISH) was performed on chromosome preparations from the patient and both parents. BAC probe RP11-465B22, which maps within the 1p36 segment deleted in the Patient, was labeled with biotin (FITC; green), and a chromosome 1q44 probe (CTB-160H23), used as a control, was labeled with digoxigenin (Rodamine; red).

Results

The SNP array analysis in both blood and saliva of the Patient revealed a constitutive ~ 4 Mb terminal deletion of the short arm of chromosome 1 (arr[GRCh37] 1p36.33p36.32 (82,154_4,111,187)×1) (Fig. 1). The B-allele frequency (BAF) plot indicated complete absence of heterozygosity within the deleted segment, as expected. However, the frequency of heterozygous genotypes in the non-deleted 1p portion increasingly diverged from the expected 50% proportion from the centromere towards the deletion breakpoint; this could be explained by stepped reduction of heterozygosity matched by increases in mosaic uniparental disomy of 1p segments. This mosaic pattern was observed in both saliva and blood (Fig. 2a, b), the only tissues available for investigation. Despite the higher frequency of sUPD in saliva, the two tissue profiles were qualitatively very similar, with increasing levels of sUPD distributed in at least five segments along the whole 1p. These patterns are consistent with the presence of the same five cell lines in both saliva and blood, but with different levels of mosaicism.

Although we were unable to directly visualize a consistent difference between segments A and B in blood, statistical testing of all possible segment differences for B-allele frequencies resulted in detection of a small but highly significant difference; this established that the telomere capture, comprising the full short arm of chromosome 1 (segment B) initially only detected in saliva, was also present in blood. Figure 2c displays the quantitative estimates of average B-allele frequencies calculated for each segment in blood, saliva and five controls; the minor differences between control segments were largely non-significant (see Supplementary Material) and most likely caused by variation between samples and array experiments.

Visual inspection of Figs. 2a, b shows that the position of four of the five observed breakpoints fall into the distal half of 1p, a region long known to contain G/C enriched stretches (Costantini et al. 2006) and a lower frequency of SNPs than in proximal 1p (Hinds et al. 2006). Significantly, the most proximal breakpoint directly adjacent to the heterochromatic block associated

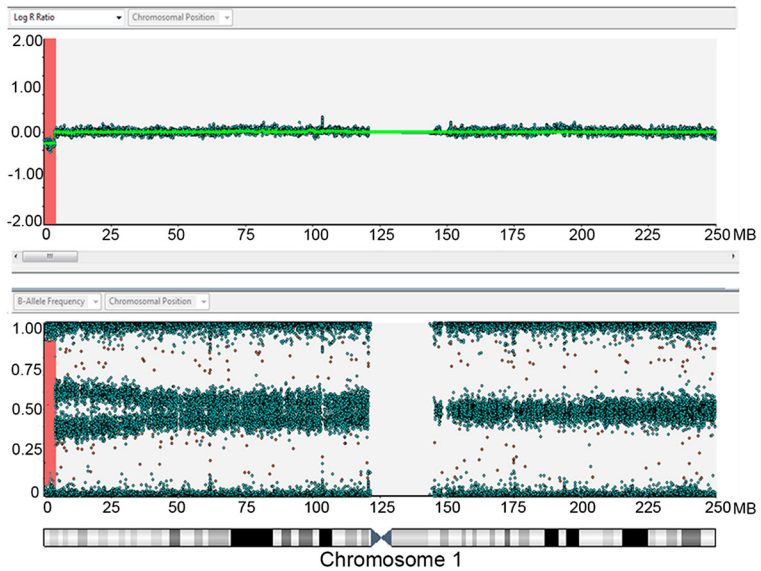

Fig. 1 SNP array analysis of chromosome 1 (saliva). Copy number profile (LogR ratio) is shown in the top panel and genotype (B-allele frequency) in the bottom panel. The copy number profile shows the ~4 Mb deletion (red bar) at 1p36.33p36.32 (chr1:82,154_4,111,187;hg 19); as expected, the corresponding SNP pattern shows absence of heterozygosity in the deleted segment, but an unique pattern of stepped increases in allele frequency was observed in the non-deleted portion of 1p. The heterozygosity increasingly positively diverged from the expected 50%, from the centromere towards the 1p36 breakpoint

with the centromere of chromosome 1 is also located in a region with localized G/C enrichment. Figure 2c displays the quantitative estimates of average B-allele frequencies calculated for each segment in blood, saliva, and five controls. When examined at a higher resolution on the microarray intensity measurements, the five breakpoints were all located either within or directly adjacent to regions of a lower density SNP probe, which are indicated by the indentations on the outer edges of the SNP distribution in Figs. 2a and b at some of the breakpoint locations (the average SNP frequency of the 2–3 Mb surrounding and immediately adjacent to the five breakpoint locations averaged 39 per Mb, in contrast to 96 per Mb in other regions of chromosome 1p, a 2.5-fold difference).

FISH on lymphocyte metaphases revealed the 1p36 deletion in most of the cells (94/100) (Fig. 3a). Although SNP microarray profiles did not show detectable heterozygosity in the 1p36 deletion region, signals of 1pter on both chromosomes 1 were observed in 6/100 metaphases (Fig. 3b). Retrospective evaluation of the 1p36 deletion profile (Fig. 1) showed that the −0.25 logR ratio was compatible with mosaicism, since the non-mosaic deletion logR ratios in our cohort are approximately −0.35.

Metaphases from both parents had normal hybridization patterns, pointing to the patient's deletion having arisen as either a de novo 1p36 deletion in a parental gamete or an early embryonic cell division.

Discussion

Although terminal deletions have been described for every human chromosome, the molecular mechanisms that generate and stabilize such deletions remain incompletely understood.

Here, we describe a de novo terminal deletion of the short arm of chromosome 1 combined with a complex sUPD, present in both blood and saliva, the only tissues available for investigation. Earlier studies suggested that telomere capture was the most probable mechanism for stabilizing terminal deletions (Slijepcevic and Bryant 1998). However, more recent papers propose that stabilization of terminal deletions most frequently occurs by addition of telomere sequences directly onto the broken ends, i.e., addition of telomere sequences by telomerase, referred to as chromosome healing (Bonaglia et al. 2011; Fortin et al. 2009).

The most striking feature of the present case was the laddered divergence of a split pattern of B-allele frequency from the centromere towards the deletion breakpoint in the heterozygosity data of the SNP arrays, without copy number changes (Fig. 1). Our statistical

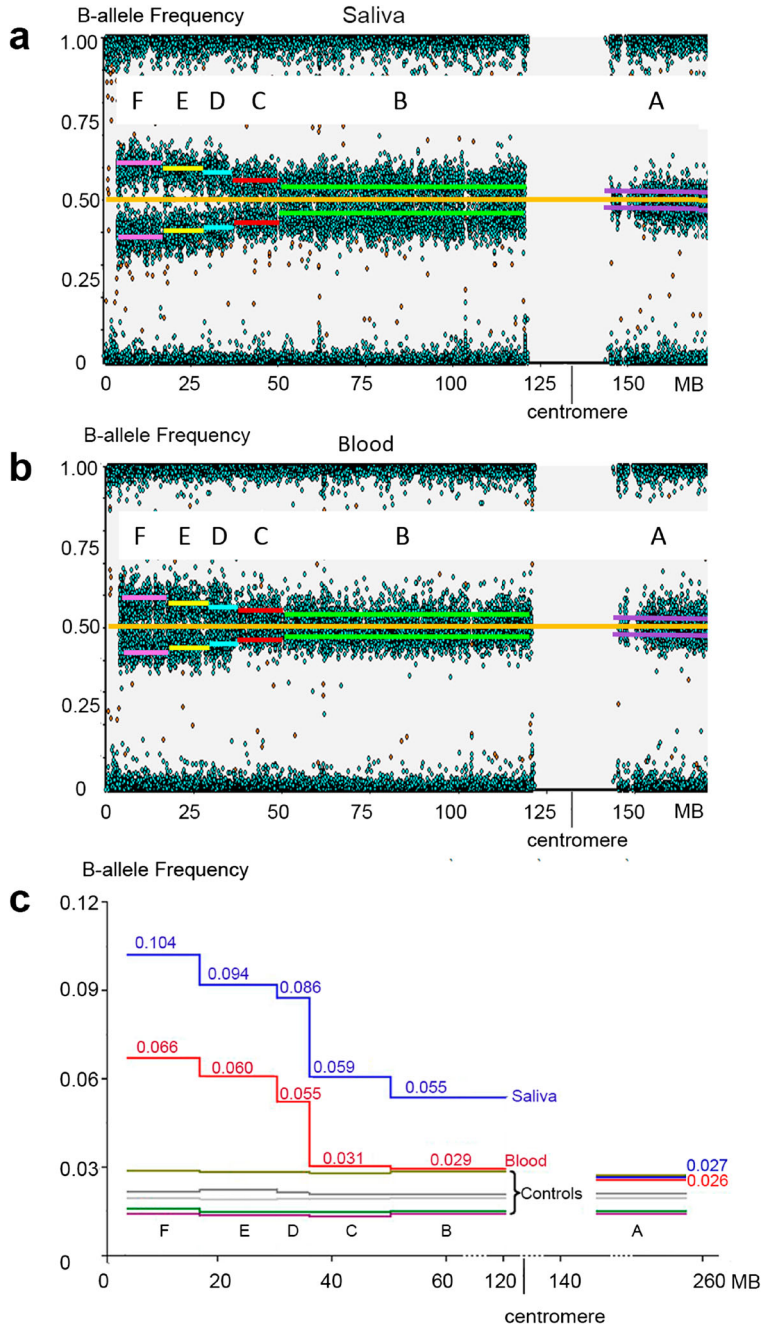

Fig. 2 Data from the SNP arrays show variable B-allele frequencies on the short arm and proximal long arm of chromosome 1, in saliva (**a**) and blood (**b**). The orange line represents the expected average 50% B-allele frequency for heterozygosity. The profiles exhibit five levels of UPD mosaicism (B–F), with no detectable UPD on segment A. Note that, despite the higher frequency of cells with segmental UPD in saliva than blood, the tissue profiles are very similar. **c** The calculated average B-allele frequencies in heterozygosity for segments A to F in blood and saliva, and five controls are shown

analyses show that this intriguing pattern can be explained by the additive overlap of B-allele frequencies within chromosome 1p of five mosaic cell lines independently derived from the short arm of the normal chromosome 1 by somatic recombination through telomere capture, matched by a corresponding decrease in the proportion of the remaining 1p segments of the deleted chromosome 1. The presence of five similar mosaic cell lines in both tissues implies that the independent telomere capture events must have all occurred in a precursor of both tissues, presumably at an extremely early stage of embryogenesis. A schematic representation of the events giving rise to this complex UPD mosaicism is given in Fig. 4. According to this model, the deletion detected by microarray analyses would be mosaic, with each type of mosaic cell line

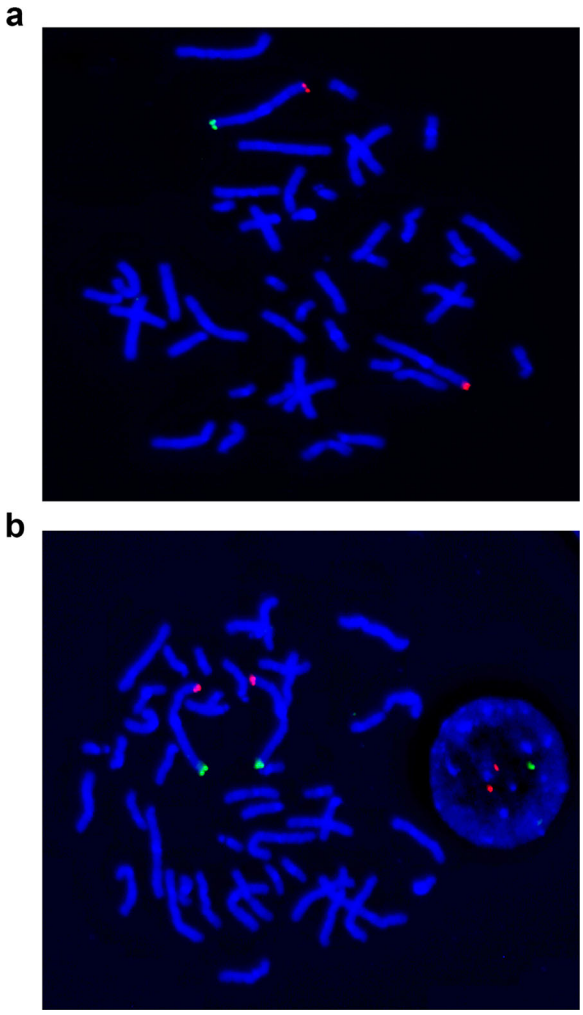

Fig. 3 FISH using a probe that maps to the 1p36 segment deleted in the patient (green signal), and of a control probe located at the sub-telomeric region of the long arm of chromosome 1 (red signal), on cultured lymphocyte metaphases from the proband. **a** The green signal is observed on the short arm of only one chromosome 1, consistent with the 1p36 deletion detected by SNP array analyses, while the control red signal is observed on both chromosomes. **b** The green signal is observed on the short arm of both chromosomes 1, showing the presence of a minor cell line without the 1p36 deletion. The pictures were taken in a Photomicroscope Zeiss with a × 10 ocular and × 100 objective

containing different but partially overlapping stretches of 1p UPD segments. Indeed, the FISH analysis showed that two patterns of hybridization were present: one without a sub-telomeric signal in one 1p homologue, confirming the original 1p36 deletion, and the other with 1p36 signals present on both homologues denoting occurrence of telomere capture (Fig. 3a, b). Regarding cells that had retained the 1p36 deletion, we assume that the deleted chromosome had become stabilized through creation of a neo-telomere by telomerase activity (telomere healing), although this was difficult to confirm in all metaphases due to the presumptive small size of the neo-telomere repeat regions (Sprung et al. 1999) and the impossibility of morphologically distinguishing the normal and deleted chromosome 1 homologues.

Although we have no independent method to infer how variations in B-allele frequency in our patient directly relate to the frequency of mosaicism of each cell line, the classic study of Conlin et al. (2010) on variations in B-allele frequency between independent patients, exhibiting various levels of mosaicism (Conlin et al. 2010), suggests that the F segment in saliva from our patient is present in ~ 20% of the cells, decreasing to ~ 5% in segment B; the corresponding values in blood vary between ~ 15 and ~ 2%, all significantly lower than those observed in saliva. The main differences in allele profiles between blood and saliva are largely attributable to the higher frequency of cells with deletion of the entire 1p (segment B) in saliva than in blood, resulting in a larger addition to the B-allele frequencies of the downstream segments C to F. However, although the ratio of mosaicism between adjacent captured segments in both tissues remains approximately the same, it is not identical, probably due to genetic drift arising from differences in cell line proliferation during the differentiation process.

The breakpoints appear to have arisen in regions with a localized lower frequency of SNPs and a more broadly dispersed increase in G/C content. Several studies claim that such regions have an enhanced likelihood of repeat sequence mediated somatic recombination (Costantini and Bernardi 2009) similar to that more recently postulated for CNV initiation (Bose et al. 2014).

We have no firm idea which of the putative repetitive sequences are likely to be involved, and further molecular analyses comparing the DNA structure of the five breakpoints within the same chromosome arm will be required: this endeavor should be greatly assisted by the a priori information on the approximate breakpoint locations.

Although there are multiple descriptions of segmental UPD arising in cancer cells leading to mosaicism between different cell lines (Rumi et al. 2011; Makishima and Maciejewski 2011), there are, as yet, no documented instances of this occurring in cancer by telomere loss followed by subsequent telomere capture and its sequelae (for review, see Maciejowski and de

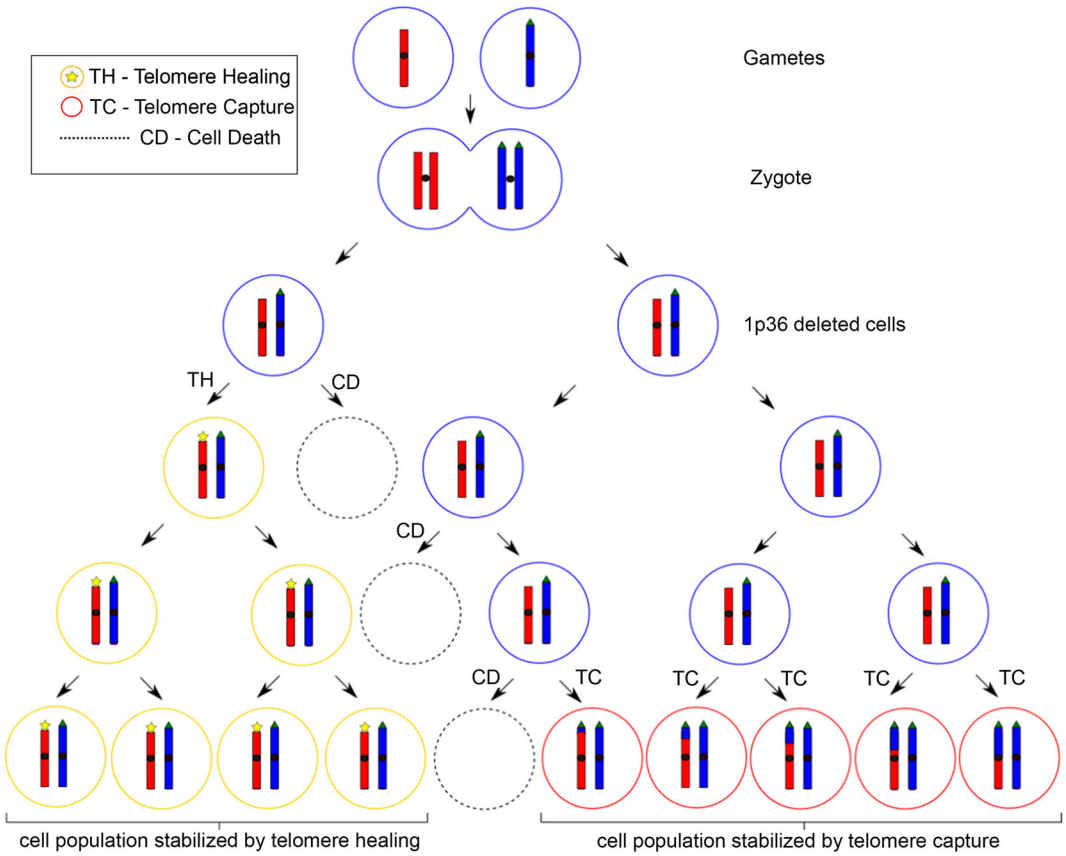

Fig. 4 A model for the origin of the complex mosaic 1p segmental uniparental disomy. A heterozygous 1p36 terminal deletion originated either in a gamete or early in the embryo. Unless the missing telomere is reinstated, cell death occurs. In an early division, telomere healing gave rise to a preponderant cell population with the original 1p36 deleted chromosome, but with addition of neotelomeres (telomere healing). In cells with an unrepaired 1p36 deletion, recurrent telomere capture by mitotic homologous recombination produces various populations of cells with homozygosity of the 1p homologous telomere as well as variable lengths of the normal homologous short arm, dependent upon the position of recombination. The overlap of different lengths of segmental UPD in these cells explains the unusual SNP pattern observed by array analysis (Figs. 1 and 2)

Lange 2017). This may be because, even if telomere loss and recapture does occur in cancer cells, it may be extremely difficult to distinguish from UPD arising through conventional chromatid recombination mechanisms, unless the original deleted chromosome remains as evidence in at least one of the derived cancer cell lines.

Martin et al. (2016) investigated a mosaic 20p13 → pter deletion by SNP array analysis and proposed rescue by mitotic recombination as the mechanism leading to one population of cells with a 20p deletion and another with normal copy number, but exhibiting segments of UPD (homozygosity) in 20p13 → pter. However, multiple telomere captures arising from one particular rearrangement have never been documented previously, either because recurrent telomere capture is an extremely rare event or because, in the absence of genotype profiling derived from SNP arrays, it cannot be distinguished from a single telomere capture.

In conclusion, although in the present case telomere capture appears to be the primary mechanism responsible for stabilization of the deleted chromosome, the independent and repetitive nature of the captures resulted in transfer of multiple segments of various lengths from the normal 1p to the deleted 1p. This, in combination with a cell population stabilized by telomere healing, gave rise to an extremely complex admixture of 1p UPD in the two tissues studied.

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Compliance with ethical standards Written informed consent for publication was obtained from the parents of the Patient. This research was approved by the Ethics Committee of the Biosciences Institute, University of São Paulo.

Competing interests The authors declare that they have no competing interests.

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