RESEARCH NOTE

Concurrent psu dic(21)(q22.3) and t(13;17)(q14.1;p12) in a mosaic Down's syndrome patient: review of thirty-one similar dicentrics

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Introduction

Pseudodicentric 'mirror-image' chromosomes 21 with breakage and reunion at 21q22 and satellites on both ends have been ascertained in 46 chromosome Down's syndrome (DS) patients since the prebanding era (e.g., Richards *et al*. 1965). A distal deletion was first suspected on banded chromosomes (Cantú *et al*. 1980) and then confirmed by molecular methods in several cases (Pangalos *et al*. 1992; Wandall *et al*. 2002; Sheth *et al*. 2007; Egashira *et al*. 2008). Here we report on the concurrence in a DS infant of a psu dic(21)(q22) with a balanced t(13;17)(q14.1;p12) and summarize 30 unequivocally identified psu dic(21)(q22) chromosomes found in sporadic DS patients (Jernigan *et al*. 1974; López-Pajares *et al*. 1976; Kosztolanyi 1988; Pangalos *et al*. 1992; Sánchez *et al*. 2001; Sheth *et al*. 2007; Sato *et al*. 2008; Thi *et al*. 2010, and references therein); further three instances alluded only in abstracts were disregarded because no parental data were given.

Patient, methods and results

The 18-month-old propositus was karyotyped because of a classical DS phenotype; at his birth, paternal age was 35 and maternal age was 31 years. The analysis of G-banded metaphases (figure 1a) from a lymphocyte culture revealed a mosaicism with two 46-chromosome cell lines in sizeable proportions; the first one (n = 40) had a normal chromosome 21 pair without heteromorphisms while the second one (n = 30) had a normal 21 and a psu dic(21)(q22.3) with a single primary constriction and similar stalks and satellites at both ends which tested positive with Ag staining; incidentally, this technique also disclosed that the inactivated centromere was Cd-negative (figure 1b). In addition, there was a balanced (13;17)(q14.1;p12) translocation in all cells. A FISH assay (>10 metaphases analysed) with a mix of a dual 17p RAI1/LIS1 (Cytocell, Cambridge, UK) and a 170-kb subtelomere-terminal 21q (Vysis, Downers Grove, USA) probes gave the following results: in the clone without the psu dic(21), both normal 21 homologues exhibited the expected 21q subtelomeric signal (images not shown) whereas in the other clone (figure 2), the dicentric chromosome exhibited the subtelomeric 21q signal which sometimes appeared duplicated (insets in figure 2); in all cells, the der(17) displayed the *RAI1* locus while the der(13) showed the *LIS1* signal. Thus, the patient's karyotype was 46,XY,t(13;17)-(q14.1;p12) [40]/46,XY,t(13;17)(q14.1;p12),psu dic(21)-(q22.3) [30]. ish der(13)(LIS1+),der(17)(RAI1+, LSI1–),psu dic(21)(q22.3)(subtel+ or ++). Parents have not yet been karyotyped.

To assess a possible parental age effect on the origin of these seemingly *de novo* pseudodicentrics (all 44 tested parents from 22 couples, including a mother with a 13;14 Robertsonian translocation, have had normal chromosomes 21), we excluded where appropriate three cases of paternal and two cases of maternal descent (Pfeiffer and Loidl 1982; Pangalos *et al*. 1992; Sheth *et al*. 2007). Because parental ages were unknown for five other patients, the calculation considered 24 cases of proven or possible paternal origin and 23 cases of proven or possible maternal origin. Mean/median paternal and maternal ages derived from this series were 31.25/30 (range 19–48; 95% CI 28.53–34.09) and 28.09/27 (range 16–44; 95% CI 25.37–31.53) years, respectively.

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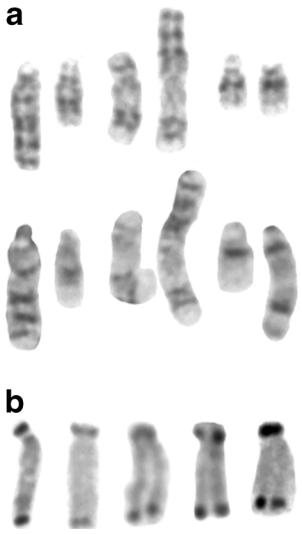

Figure 1. (a) Patient's G-banded chromosomes illustrating the t(13;17)(q14.1;p12) and the psu dic(21)(q22.3); the former was found in all cells but the latter (second row) only in ~43% of them. (b) Five psu dic(21) chromosomes after NOR and Cd staining; each pseudodicentric exhibits a diminished or absent constriction at the inactivated Cd-negative centromere and has similar NORs at both ends.

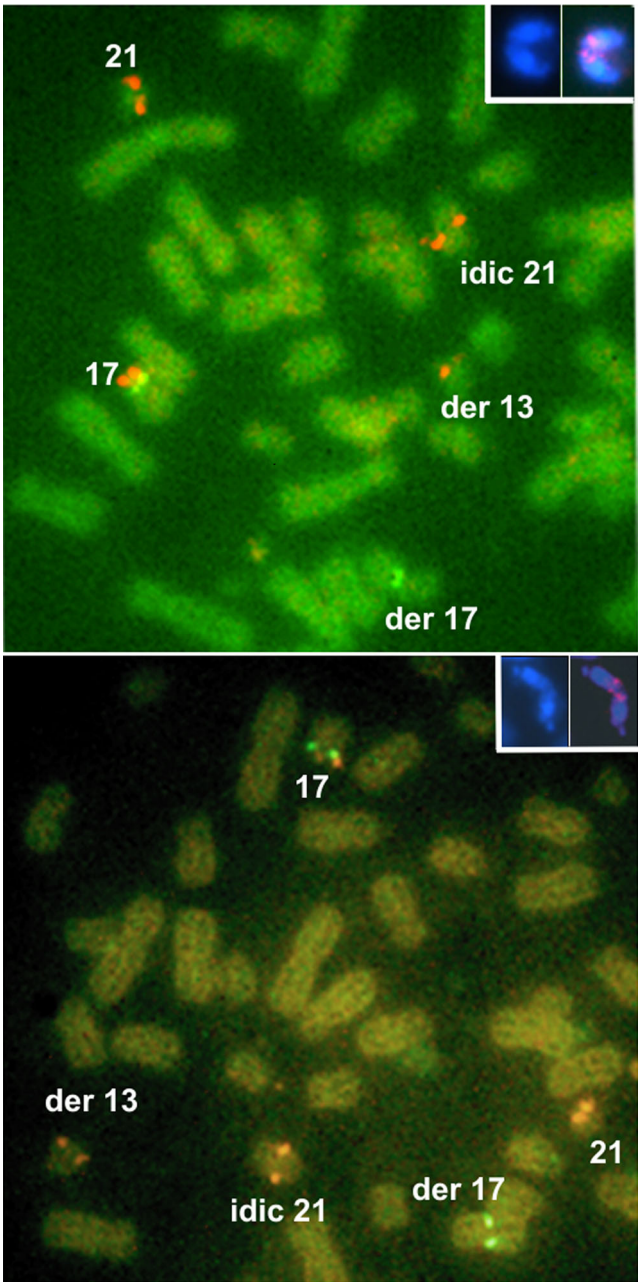

Figure 2. Two partial metaphases with both the t(13;17) and the psu dic(21) after FISH with a mix of the subtelomeric 21q (red) and 17p RAI1/LIS1 (green/red) probes. Except for the normal homolog 13, all other relevant chromosomes are indicated. Two further psu dic(21) with a double 21q subtelomeric signal along with DAPI counterstaining are also shown (see insets).

Discussion

Analogously to isodicentric sex chromosomes resulting from homology-mediated recombination between opposing palindrome arms on sister chromatids with occasional crossover resolution (Lange *et al*. 2009; Koumbaris *et al*. 2011) and to bisatellited dicentric extra markers derived from chromosomes 15 and 22 (Emanuel and Saitta 2007), psu dic(21)(q22) chromosomes also appeared to result from a sister-chromatid recombination (Pfeiffer and Loidl 1982; Pangalos *et al*. 1992; Sheth *et al*. 2007) presumably mediated by segmental duplications or other repeats mapped at 21q distal. Although this anomalous recombination usually occurs at meiosis I, the observation of two mosaic patients carrying a psu dic(21) plus a free 21 in a 46-chromosome cell line and two normal chromosomes 21 in the second clone (Karukaya and Yokoyama 1980; this report) is consistent with the crucial event occurring in an early mitosis of a normal zygote with loss of the counterpart monosomy 21 clone. The alternative of a trisomic zygote with the psu dic(21) to explain such mosaicisms seems less likely because it requires dissociation of the pseudodicentric coupled with loss of one 21; yet, the finding of two subtelomeric signals in the present mirror-image chromosome points to a telomeric fusion or association as the underlying mechanism (see also Thi *et al*. 2010). This apparent heterogeneity is further expanded by the mosaic 45,XX,psu dic(21)/46,XX,psu dic(21) DS patient first reported by Richards *et al*. (1965) and then restudied by G-bands (Jernigan *et al*. 1974). Anyhow, the similar appearance of both satellited ends in each psu dic(21) described so far further supports its origin from a single chromosome. In fact, this conclusion is well illustrated by the psu dic(21) with 'bright satellites' of paternal origin observed in one patient (Pfeiffer and Loidl 1982) and the unique patient having a 46,XX,psu dic(21)(q22.13), ins(13;21)(q12.1;q22.13q22.3)dn karyotype where the segment distal to the recombination 21q22.13 breakpoint was inserted into chromosome 13 (Sato *et al*. 2008); incidentally,

the fate of 21q telomere in the latter rearrangement was not ascertained.

The concomitant 21q22.3 terminal deletions documented by molecular methods in six patients (Pangalos *et al*. 1992; Wandall *et al*. 2002; Sheth *et al*. 2007; Egashira *et al*. 2008) and ranging from telomeric repeats (Wandall *et al*. 2002) to 2.1 Mb (Egashira *et al*. 2008) or even ~2.4 Mb (patient TY in Pangalos *et al*. 1992) of the ~5.5 Mb 21q22.3 subband (2009 GRCh37/hg19 Assembly) are consistent with the rather typical DS phenotype of the 31 subjects here compiled; indeed, a compound clinical picture with signs of monosomy 21q22.3 such as large ears with unfolded helices, high nasal bridge, and retromicrognathia has seldom been observed (Cantú *et al*. 1980; patient TY in Pangalos *et al*. 1992). In comparison, terminal and interstitial 'pure' deletions involving 21q22.1q22.2 have been associated with variable and severe phenotypes (e.g., Matsumoto *et al*. 1997; Carrascosa-Romero *et al*. 2013). Although both psu dic(21) chromosomes tested by FISH with a 21q subtelomere probe had no detectable deletions (Thi *et al*. 2010; present patient), they may also have lost the telomeric repeats. Such a breakage heterogeneity in eight molecularly assessed psu dic(21) composites is comparable to that observed in idic(Y) (Lange *et al*. 2009; Beaulieu-Bergeron *et al*. 2011) and idic(X) (Koumbaris *et al*. 2011) chromosomes.

Of note, only one bona fide bisatellited psu dic(21) with the band 21q22 'clearly not duplicated' (i.e. with an ostensibly larger deletion) in a 46 chromosome patient without DS is on record (Hagemeijer and Smith 1977). In contrast, a similar or smaller psu dic(21) occurring as an extra chromosome has been found in several clinically heterogeneous patients lacking the DS phenotype (Rost *et al*. 2004). These observations indicate that 21q22 deletions can partially account for the lack of healthy 45 chromosome subjects with a psu dic(21) who analogously to i(21q) carriers may be expected to occur.

The remarkable mitotic stability common to all 31 psu dic(21)(q22) chromosomes has been related to centromere inactivation inferred from the usual lack of the primary constriction at the suppressed centromere; in fact, this epigenetic phenomenon has been proved either by Cd-bands (Matsubara *et al*. 1981; Sato *et al*. 2008; this report) or antibody staining for centromeric proteins (Wandall *et al*. 2002). Whether the inactivation always affects the same centromere or there is alternation (e.g., Rivera *et al*. 1989) remains unclear. Such a seemingly complete inactivation of one of two centromeres located some 65 Mb apart in these stable dicentric autosomes compares with the full centromere silencing (lack of the CENP-E protein) observed in idic(Yp) chromosomes whenever the intercentromeric distance was ≥12.3 Mb (Lange *et al*. 2009) but contrasts with the pronounced mitotic instability documented in another sample of idic(Y) chromosomes exhibiting an intercentromeric distance of ≥20 Mb (Beaulieu Bergeron *et al*. 2011) and with the fact that both centromeres of experimentally induced human autosomal dicentrics were still functional even with an intercentromeric distance of 50 Mb (Stimpson *et al*. 2010). Then, it seems that centromere inactivation in dicentric chromosomes depends on several factors and may be a highly individualized phenomenon.

The mean and median parental ages in this series are consistent with the lack of a parental age effect documented in other *de novo* unbalanced rearrangements (Sibbons *et al*. 2012; Rivera *et al*. 2013, and references therein) but diverge from the increased paternal age observed in a sample of 26 *de novo* balanced reciprocal translocations of paternal origin (Thomas *et al*. 2010). The seemingly random parental origin ascertained in five cases (Pfeiffer and Loidl 1982; Pangalos *et al*. 1992; Sheth *et al*. 2007) compares with a similarly unbiased parentage found in a series of 23 diverse duplications (Sibbons *et al*. 2012).

Finally, the present concurrence of a seemingly *de novo* mosaic psu dic(21) arisen postzygotically with a nonmosaic t(13;17) appears to be a fortuitous event that further illustrates the difficulty to—rather than being trapped in Kouska's fallacy (Lubinsky 1986)—properly assess the coexistence of two findings in a single patient.

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