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Atypical 22q11.2 deletion in a patient with DGS/VCFS spectrum

Sintia Iole Nogueira[a,*], **April M. Hacker**[b,c], **Fernanda T.S. Bellucco**[a], **Denise M. Christofolini**[a], **Leslie Domenici Kulikowski**[a], **Mirlene C.S.P. Cernach**[d], **Beverly S. Emanuel**[b,c], and **Maria Isabel Melaragno**[a]

[a] Disciplina de Genética, Departamento de Morfologia e Genética, Universidade Federal de São Paulo, Rua Botucatu 740, São Paulo, SP 04023-900, Brazil

[b] Division of Human Genetics, Department of Pediatrics, The Children's Hospital of Philadelphia, Philadelphia, PA, USA

[c] The University of Pennsylvania School of Medicine, Philadelphia, PA, USA

[d] Centro de Genética Médica, Universidade Federal de São Paulo, São Paulo, SP, Brazil

Abstract

Deletions in region 22q11.2 usually occur between two low copy repeat regions (LCRs), which are preferred chromosome sites for rearrangements. Most of the deletions encompass the same ~3 or ~1.5 Mb region, with breakpoints at LCR A and D or at LCR A and B, respectively. We report on a patient with clinical features of the 22q deletion syndrome who presents a novel, atypical deletion, smaller than 1.5 Mb, with distal breakpoint in LCR B and proximal breakpoint within no known LCR site.

Keywords

22q11.2 Deletion; Atypical deletion; FISH

1. Introduction

Deletions of chromosome region 22q11.2 are associated with a broad spectrum of clinical phenotypes, including the DiGeorge (DGS) and velocardiofacial (VCFS) syndromes. The most frequent feature is a conotruncal heart defect, often associated with facial dysmorphisms, cleft palate, thymus hypoplasia, and learning disability [9]. Most deletions (84–90%) encompass ~3 Mb, known as the typically deleted region. Smaller deletions, spanning 1.5 Mb, are found in about 7–14% of the cases [2,15]. In addition, atypical deletions have also been described in a few patients [2,4,6,8,10–14,16,20]. We report here on a patient with 22q11.2 deletion syndrome with a unique deletion 22q11.2 with distal breakpoint in LCR B and proximal breakpoint mapped within no known low copy repeat (LCR) site.

2. Clinical report

The proband, a female infant, was delivered at term by cesarean section after an uneventful pregnancy. Birth weight was 3750 g (75–90th centile) and length 51 cm (50–75th centile). No problem was apparent at birth. Further on, the mother noticed that the child choked after feeding. On physical examination, at 9 years and 7 months of age, the patient's weight was 45 kg (95th centile), length 145 cm (90–95th centile), and head circumference 54 cm (<2 SD).

*Corresponding author. Tel./fax: +55 11 5576 4260., sintia.morf@epm.br (S.I. Nogueira).

The mother's height was 169 cm (75–90th centile) and father's 182 cm (75–90th centile). She had a long, hypotonic and flaccid face, malar hypoplasia, ocular hypertelorism, prominent nasal bridge, a bulbous nasal tip, protuberant cup-shaped ears with overfolded helices, preauricular pits, downturned oral commissures, micrognathia and generalized hypotonia (Fig. 1). During infancy, she had had airway obstruction and presented with tapered digits, feeding difficulty, failure-to-thrive, nasal regurgitation, severe hypernasality, velopharyngeal insufficiency, language impairment and mild conductive hearing loss. The echocardiogram showed no structural heart abnormality.

The motor development was at lower limit of normality. Concerning cognitive development, she presented learning disability, extreme socialization difficulty and mild mental retardation.

3. Cytogenetic analysis with fluorescence in situ hybridization (FISH)

A 22q11.2 deletion was detected by FISH in the patient's metaphase spreads from peripheral blood lymphocyte cultures, using the Tuple1 probe (Cytocell®). It is a *de novo* deletion, since the parents' karyotypes were found to be normal. In order to determine the size of the deletion, FISH analyses were performed with a commercial probe for the DiGeorge chromosome region, *N25* (D22S75) (Vysis®), and different cosmid probes along the typical deleted region: c103a2 (PH11), c46a9, c87h3 (a cosmid containing the promoter of the *UFD1L/CDC45L* genes), c68a1 (N41, D22S788), c87f9 (*ZNF74*), c2c9 (HCF2), and c45c9 (LN80). FISH analyses with cosmid probes were performed as previously reported [15]. FISH signals for probes c87h3, N25 and c68a1 were present on only one of the patient's two chromosomes 22. For all other probes, signals were present on both chromosomes 22. Thus, we concluded that the proximal breakpoint is located between cosmids c46a9 and c87h3, and the distal breakpoint in LCR B, between cosmids c68a1 and c87f9. This atypical deletion is smaller than the common 1.5 Mb deletion and has a somewhat more distal proximal breakpoint, never described before (Fig. 2).

4. Discussion

The 22q11.2 region is highly susceptible to rearrangements, especially deletions [16]. The high frequency (1/4000 live births) of the 22q11.2 deletion [18] can be explained by the presence of chromosome-specific low copy repeats flanking (LCR A and D) or within the typically deleted region (LCR A′, B and C) [3,16]. Since LCRs present chromosome-specific repeated DNA sequences, they can be prone to misalignment during meiosis and unequal recombination exchanges, resulting in chromosome rearrangements in the 22q11.2 region [16]. In a cohort of 277 patients, Saitta et al. [15] found that 241 deletions spanned the same ~3 Mb region between LCR A and D, 20 involved a nested ~1.5 Mb deletion between LCR A and B, five had a deletion between LCR A and C, another five between LCR A′ and D, and six were atypical deletions. Shaikh et al. [16] stated that 22q11.2 LCRs share 97–98% nucleotide sequence identity. The size and the homology among them seem to be related to the frequency of each type of deletion. The 3 Mb deletion is the most frequent one, since it is mediated by the largest LCRs, A and D, which share 250 kb of duplicated sequence in a complex arrangement. On the other hand, the 1.5 Mb deletion is flanked by LCRs A and B, which share a common block of 135 kb [16]. Atypical deletions have been reported, either nested within the typical 3 Mb deleted region or having no overlap with it. Some of them have breakpoints in two different LCRs [2,4–6, 12–14,16], others have only one breakpoint in a known LCR [1,2,8,10,11], and others still have breakpoints outside the known LCRs [20,21]. Our patient has a deletion that differs from the recurrent or atypical deletions known so far. One breakpoint is located within LCR B (distal) and the other between cosmids c46a9 and c87h3 (proximal), which are not part of LCR A′. Our proximal breakpoint differs from the ADU breakpoint (LCR A′) of the deletion reported by Carlson et al. [2]. Deletions occurring in no known LCR could be mediated by smaller duplicated blocks or by another mechanism yet to be discovered through a more detailed

molecular analysis of atypical deletions [16]. Recently, Uddin et al. [19] achieved the molecular characterization of the deletion breakpoint sequences in a 2.3 Mb deletion and found a shared sequence common to both breakpoints that share >90% sequence similarity to each other and also to Alu elements. They concluded that, since LCRs contain highly repetitive elements such as Alu elements, these may also be implicated in chromosome rearrangements. Concerning the clinical phenotype of the 22q11.2 deletion syndrome, literature shows a great variability and an unclear correlation between deletion size and phenotype [2,13,17]. An interesting fact is that some patients with atypical deletions not involving the typically deleted region present a typical 22q11.2 deletion phenotype with conotruncal heart defect [4,7,12–14]. The patient described in the present paper has the 22q11.2 deletion phenotype, lacking only congenital heart defect, which is known not to be an obligate trait of the syndrome. Further molecular analysis needs to be performed in atypical deletions, mainly those with breakpoints located in no known LCR, as in the present case. Such studies may contribute to the discovery of other mechanisms of deletion origin, different from LCR misalignment.

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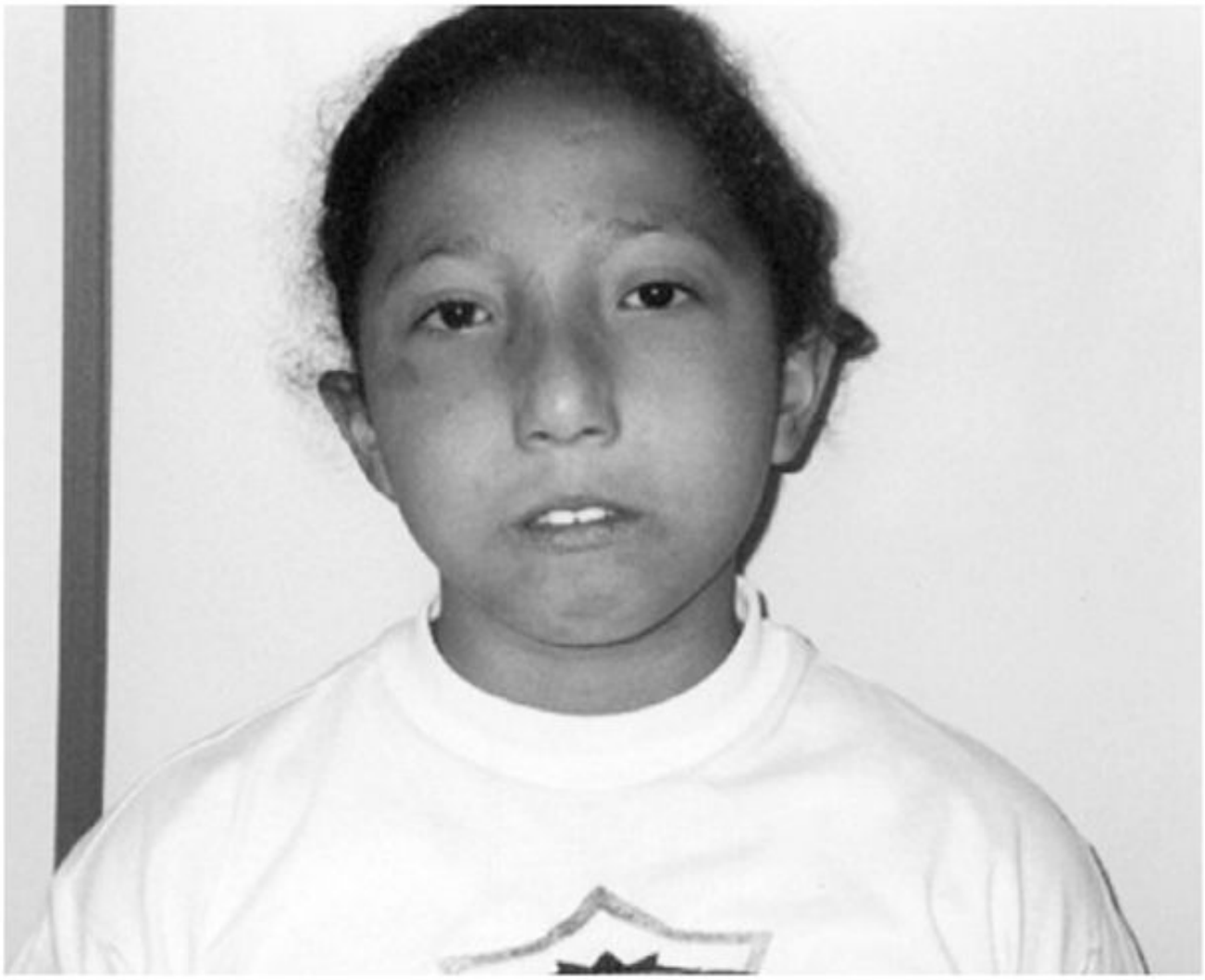

Fig. 1.
Patient at age 9 showing long and asymmetric face, malar hypoplasia, downturned oral commissures, ocular hypertelorism, bulbous nasal tip and micrognathia.

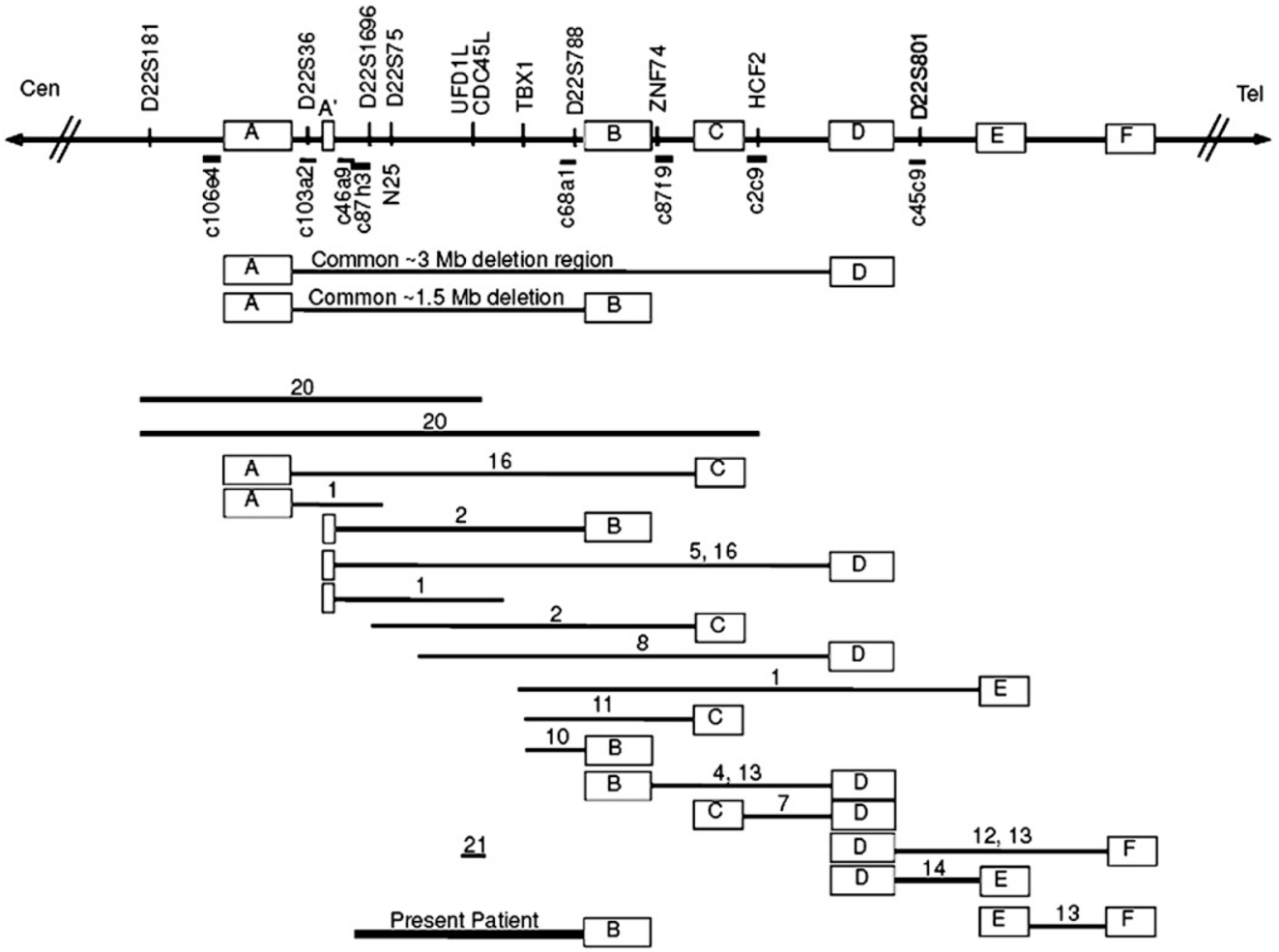

Fig. 2.

Region 22q11.2 showing the locations of LCR A to LCR F (in the boxes), STS markers and genes (above the line) and FISH cosmid probes (below the line). The lines and reference numbers represent the atypical deletions described previously. Our patient (V.A.O.) presented an atypical deletion with proximal breakpoint between cosmids c46a9 and c87h3 and distal breakpoint in LCR B.