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Short report

Atypical deletion of 22q11.2: Detection using the FISH *TBX1* probe and molecular characterization with high-density SNP arrays

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ABSTRACT

Despite the heterogeneous clinical presentations, the majority of patients with 22q11.2 deletion syndrome (22q11.2 DS) have either a common recurrent 3 Mb deletion or a less common, 1.5 Mb nested deletion, with breakpoint sites in flanking low-copy repeats (LCR) sequences. Only a small number of atypical deletions have been reported and precisely defined. Haploinsufficiency of the *TBX1* gene was determined to be the likely cause of 22q11.2 DS. The diagnostic procedure usually used is FISH using commercially probes (N25 or TUPLE1). However, this test does not contain *TBX1*, and fails to detect deletions that are either proximal or distal to the FISH probes. Here, we report on two patients with clinical features suggestive of 22q11.2 DS, a male infant with facial dysmorphia, pulmonary atresia, ventricular septal defect, neonatal hypocalcemia, and his affected mother, with facial dysmorphia, learning disabilities, and hypernasal speech. They were tested negative for 22q11.2 DS using N25 or TUPLE1 probes, but were shown deleted for a probe containing *TBX1*. Delineation of the deletion was performed using high-density SNP arrays (Illumina, 370K). This atypical deletion was spanning 1.89 Mb. The distal breakpoint resided in LCR-D, sharing the same distal breakpoint with the 3 Mb common deletion. The proximal breakpoint was located 105 kb telomeric to TUPLE1, representing a new breakpoint variant that does not correspond to known LCRs of 22q11.2. We conclude that FISH with the *TBX1* probe is an accurate diagnostic tool for 22q11.2 DS, with a higher sensitivity than FISH using standard probes, detecting all but the rarest deletions, greatly reducing the false negative rate.

1. Introduction

The 22q11.2 deletion syndrome (22q11.2 DS) is the most common microdeletion syndrome in humans, occurring with an incidence of 1 in 4000 [28]. The phenotype is highly variable, including DiGeorge and velocardiofacial syndromes (DGS/VCFS). DGS/VCFS are characterized by multiple developmental anomalies occurring with varying severity, including craniofacial, thymic, parathyroid defects, cardiovascular malformations, neurological and behavioral manifestations [24]. Most 22q11.2 microdeletions are sporadic in origin, but approximately 10% of deletions are inherited [17]. About 97% of patients have either a common recurrent approximately 3 Mb deletion or a smaller, less common, approximately 1.5 Mb nested deletion. The deletions apparently occur as a result of homologous recombination between nonallelic flanking low-copy repeat (LCR) sequences located in 22q11.2 [8]. A minority of patients have smaller overlapping and non-overlapping 22q11.2 deletions [3,5,23,26,33]. Most studies have reported no correlation between deletion size and phenotype in 22q11.2 DS [5,15,26]. However, there are several studies suggesting that deletions of the proximal part of the common 3 Mb deletion are not associated with learning difficulties [23]. Haploinsufficiency of *TBX1*, mapped to the 1.5 Mb region associated with DGS/VCFS, is thought to be responsible for many of the phenotypic traits of the 22q11.2 DS [16,21,34,35]. The majority of the 22q11.2 microdeletions can be ascertained using a standard fluorescence in situ hybridization (FISH) assay with diagnostic probes from the proximal commonly deleted region on 22q11.2, TUPLE1 or N25. However, this test fails to detect deletions that are either proximal or distal to these FISH probes.

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Here, we report on two patients with clinical features suggestive of 22q11.2 DS, a male infant and his affected mother, who tested negative for 22q11.2 DS using currently available commercial FISH probes, but were shown deleted for a probe containing the *TBX1* gene. The extent and breakpoints of this atypical 22q11.2 deletion were precisely characterized using high-density SNP arrays.

2. Clinical report

The proband, the first child of unrelated parents, was a male infant born prematurely to a 36-year-old mother at 31 weeks' gestation after premature rupture of membranes. Birth weight was 1550 g (10–50th centile), length 42 cm (50th centile), and head circumference 29 cm (10–50th centile). Soon after birth, he was admitted to the neonatal intensive care unit with respiratory distress due to hyaline membrane disease. Physical examination revealed dysmorphic facial features, including hypertelorism, narrow and downwards slanting palpebral fissures, a prominent nose, retromicrognathia, prominent and dysmorphic ears, and long fingers (Fig. 1). The palate and uvula were normal. Echocardiography revealed the presence of pulmonary atresia plus major pulmonary collateral arteries and a ventricular septal defect. Renal and cranial ultrasounds were normal. Neonatal hypocalcemia was noted in the first week of life. The complex heart defect required surgical repair on the first month of life. The possibility of 22q11 deletion syndrome was raised based on the heart defect, hypocalcemia, and his facial appearance. His 35-year-old father was healthy. His mother was considered to show findings suggestive of being a carrier for the same deletion. She had a history of learning disabilities, and hypernasal speech. She presented with microcephaly, dysplastic ears, mild hypertelorism, asymmetric long face, and long fingers (Fig. 1).

3. Cytogenetic and molecular analysis

Chromosome preparations were made from peripheral blood cultures using standard protocols. GTG-banded chromosomes showed normal karyotypes in the patient and in both parents. The patient and his parents were initially evaluated by fluorescence in situ hybridization (FISH) analyses on metaphase spreads using commercial diagnostic probes for DGS/VCFS, TUPLE1 and N25 (D22S75) probes (Cytocell, Cambridge, UK), according to the protocol supplied by the manufacturer. Because of the clinical findings in the patient, additional analysis was undertaken, and he was further evaluated by FISH using a *TBX1* specific probe (Kreatech, Amsterdam NL). FISH was negative for a deletion when the N25 and TUPLE1 probes were used. However, the patient was deleted for the *TBX1* probe, confirming a diagnosis of 22q11.2 DS. His mother was found to have a similar deletion (Fig. 2). Thus, both patients had an atypical deletion involving *TBX1*. The father's FISH analysis was found to be normal. In order to determine the extent of the deletion and the breakpoints location, we performed higher-resolution genomic analysis in the patient by using single nucleotide polymorphism (SNP) arrays, (platform Illumina's HumanCNV370-Quad

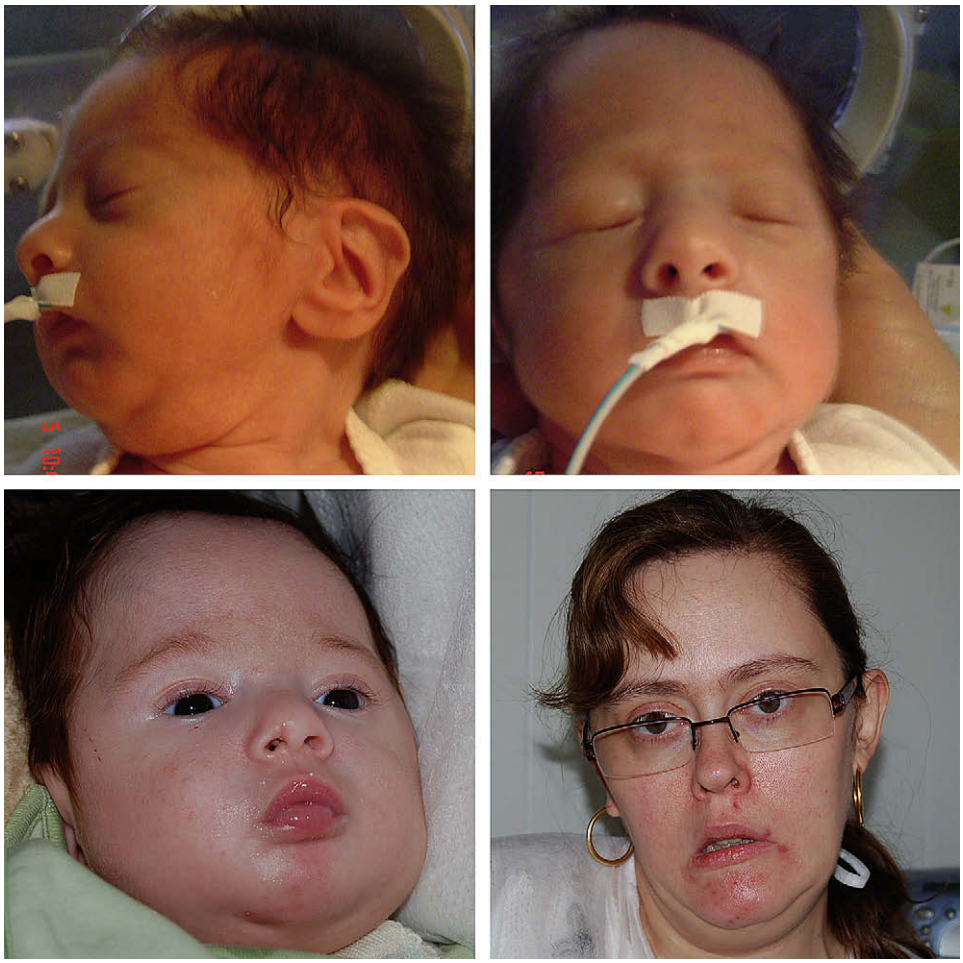

Fig. 1. Photographs of the patient at age 10 days, 2 months, and of his mother.

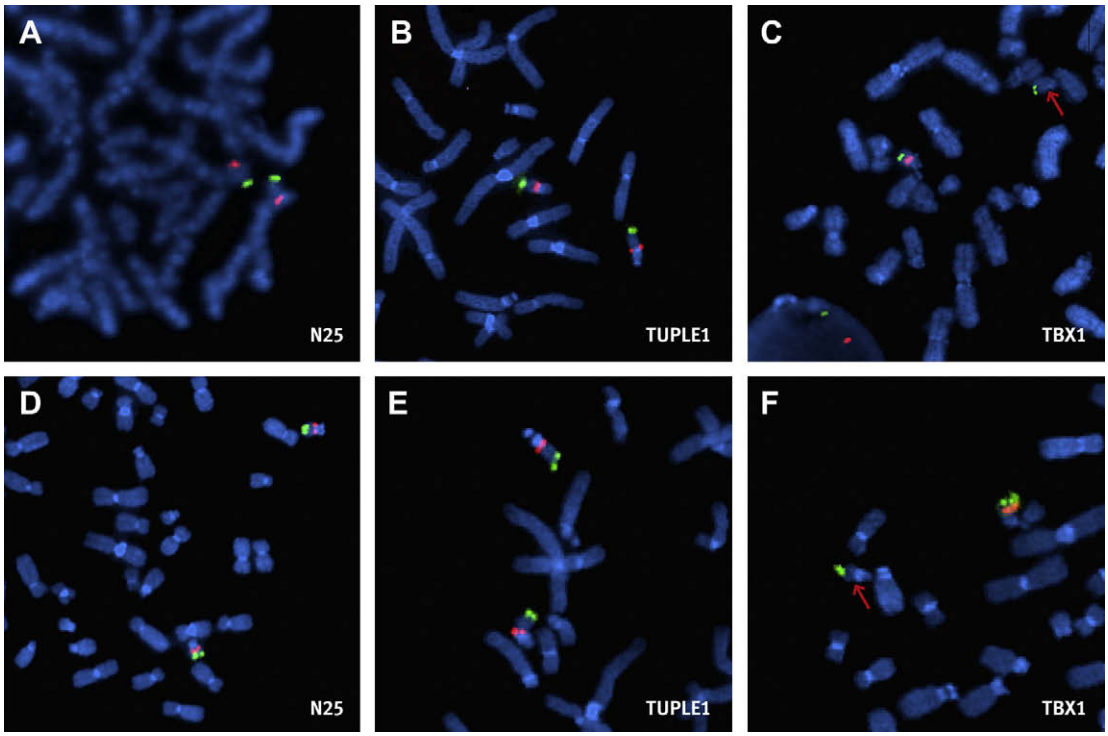

Fig. 2. FISH analysis using an N25 (®Cytocell), TUPLE1 (®Cytocell), and the *TBX1* (®Kreatech) probes, showing the atypical 22q11.2 deletion. The newborn boy (A–C) and his mother (D–F) are negative by FISH analysis for the N25/TUPLE1 probes but are positive for the deletion using the *TBX1* probe.

genotyping BeadChip arrays 370 K). This array contains 317 000 TagSNPs and 52 000 non-polymorphic markers with a mean spatial resolution of approximately 7.7 kb. A total of 250 ng DNA from the patient was processed according to the manufacturer's instruction (http://www.illumina.com). Data analysis was done by examination of signal intensity (log R ratio) and allelic composition (allelic frequency) with BeadStudio Version 3.2 software (Illumina, Inc.). Breakpoints of the deletion were defined as the first and last SNP comprised in the region of the deletion, which were homozygous and presented a decreased log ratio (in the order of −0.5). Mapping of the deleted and non-deleted markers on the chromosomal sequence placed the proximal breakpoint site between markers rs 2871029 (normal proximal SNP at 17 893 930 bp), and rs 13056098 (aberrant proximal SNP at 17 904 402 bp) and the distal site between markers rs 11703181 (normal distal SNP at 19 795 780 bp) and rs 140392 (aberrant distal SNP at 19 792 353 bp) on 22q11.2 (distance from 22p telomere according to NCBI genome build 36-March 2006). Thus, SNP analysis indicated that the hemizygous deletion in this patient was 1.89 Mb, overlapping the 3 Mb common deletion (Fig. 3). The distal breakpoint resides in LCR-D, sharing the same distal breakpoint with the 3 Mb common deletion. The proximal breakpoint was located 105 kb telomeric to *HIRA* (TUPLE1), representing a new breakpoint site that does not correspond to known LCRs of 22q11.2 (Fig. 4).

4. Discussion

The 22q11.2 DS is usually associated with the common 3 Mb or the 1.5 Mb proximally nested deletions, both encompassing the *TBX1* gene [9]. Both, haploinsufficiency and gain of function of *TBX1*, due to deletions or rare mutations, were determined to be the likely cause of DGS/VCFS [16,21,31,34,35]. So far, currently diagnostic FISH probes commercially available contain the TUPLE1 gene (*HIRA*) or the N25 marker sited in the *CLTCL1* gene, and are, approximately 465 kb and 325 kb respectively, centromeric to *TBX1*. Our patients, a newborn boy with facial dysmorphia, neonatal hypocalcemia, a congenital heart defect, and his affected mother with a milder phenotype, presented with characteristic features associated with 22q11.2 DS. Both patients were tested negative for 22q11.2 DS using currently available commercial FISH probes, but were shown deleted for a probe containing the *TBX1* gene, indicating an atypical 22q11.2 deletion. To date, only a limited number of atypical deletions in 22q11.2 have been reported (Fig. 4). These deletions, nested within the large typically deleted region vary both in size and breakpoints position, most encompassing the *TBX1* gene [3,5,14,18,19,23,29,32,33]. Only rare patients showed atypical deletions outside the *TBX1* region, in the distal half of the 3 Mb region [6,11,13,20,23]. Many of these deletions, including our case, are missed by using only the standard FISH probes (Fig. 4). In addition, deletions distally adjacent to the 3 Mb region have also been reported, and have been found in patients with specific characteristics only weakly suggestive of 22q11.2 DS [4,22,23,25] (Fig. 4). They represent a novel genomic disorder distinct genomically and clinically from the DG/VCF deletion syndromes. The two distinctive syndromes share an overlapping cardiac phenotype [4,23,25]. With the clinical implementation of newer higher-resolution techniques, such as the 22q11.2 multiplex ligation-dependent probe amplification (MLPA), with high numbers of markers across the 22q11.2 region, or genomic microarrays, which are now capable of providing sensitive methods effective for not only detecting, but also sizing the deletions, the number of patients detected with 22q11.2 deletion variants is almost certainly going to increase [9,12,30]. However, for laboratories doing MLPA analysis, the high-definition MLPA 22q11 kit is a more sensitive method for the detection of copy number changes on the long arm of chromosome 22, offering an efficient alternative to the currently available detection methods [9,12,30].

Most DGS/VCFS patients exhibit significant clinical variability [24]. Our report of variant 22q11.2 deletion, in a family with DGS/VCFS characteristic features, is consistent with most studies indicating that expression of 22q11.2 DS does not appear to be related

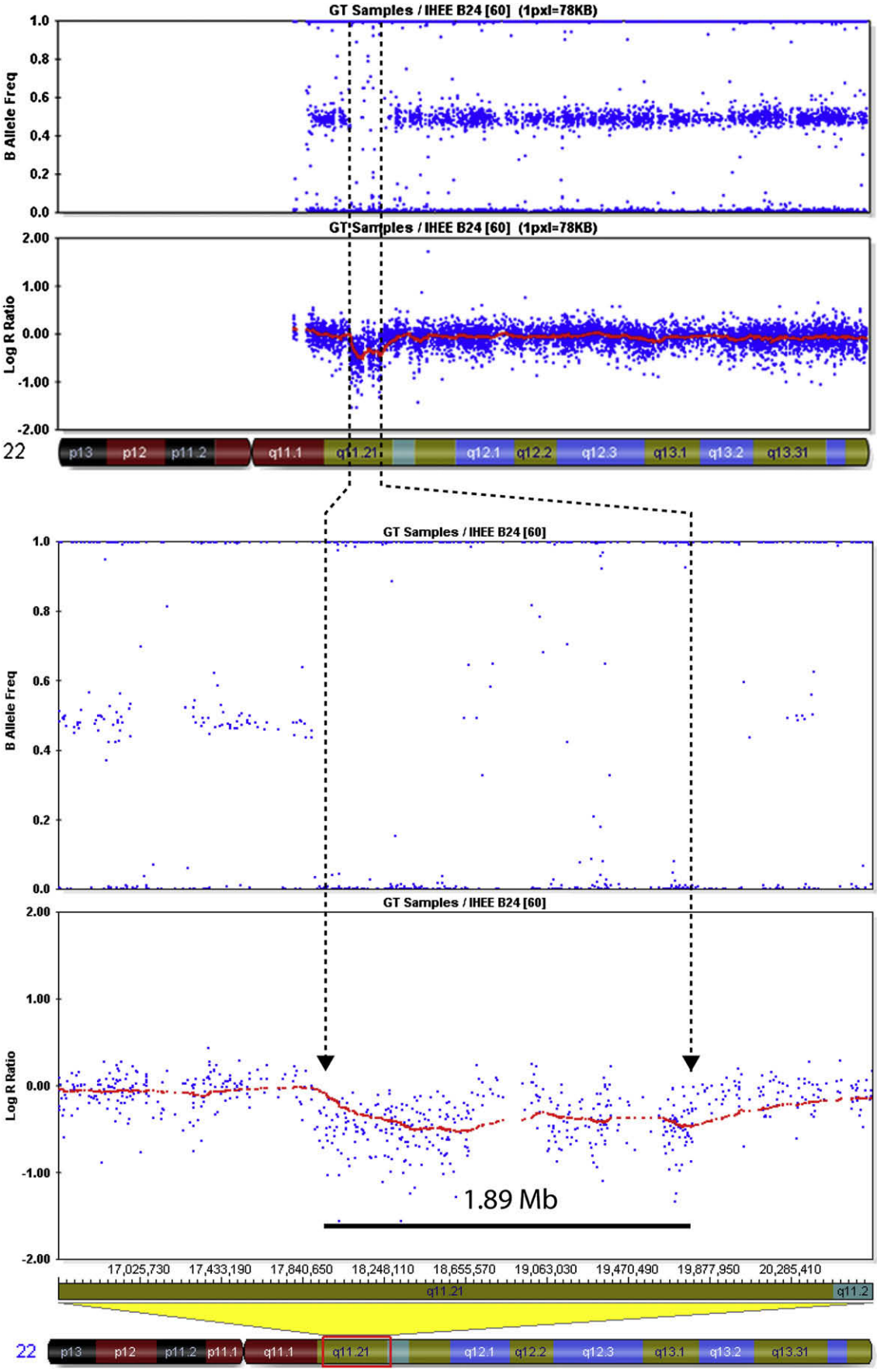

Fig. 3. Analysis of genotype and copy number data for the 22q deletion based on SNP genotyping using BeadStudio software (Illumina). Results are shown for log R ratio (a measure of copy number; *y*-axis) versus genomic position on chromosome 22. The B allele frequency panel indicates the presence of BB genotype calls (B allele frequency of 1.0), AB calls (frequency of 0.5) and AA calls (frequency of 0.0). Arrows point at the deletion in the 22q11.2 region.

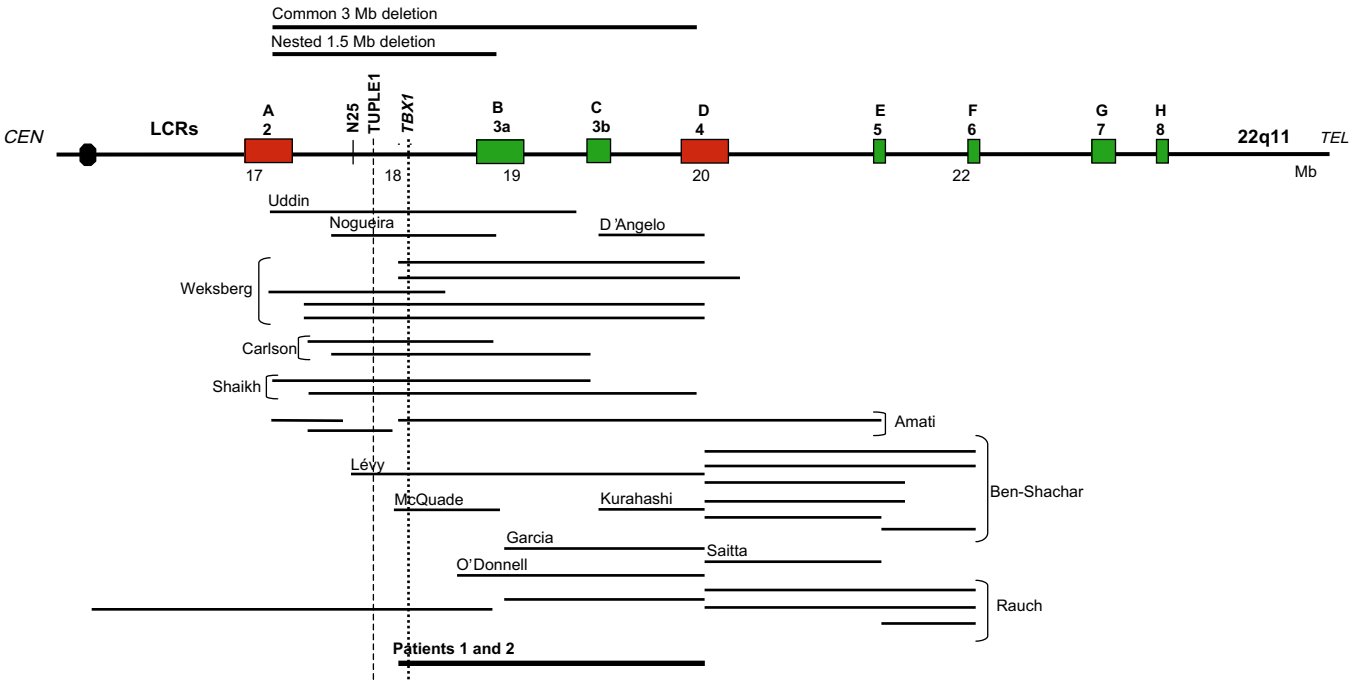

Fig. 4. Scheme of the 22q11.2 region, showing FISH probes used, LCRs 22, and 22q11.2 deletions. The 3 Mb and 1.5 Mb typical deletions are marked above the chromosome. Below it are the approximate positions of published cases and our case with atypical deletion.

to length of the deletion [5,15]. However, a recent study reported possible genotype–phenotype correlation, showing association of significant developmental delay with the distal part of the common deletion region [23]. There is limited information on the endpoints of the breakpoint regions in affected patients [9,15,26]. The endpoints of the recurrent 22q11.2 deletions appear to localize to blocks of duplicated LCR sequences found at several locations on chromosome 22 [8,29]. The typically deleted 3 Mb region in 22q11 DS is flanked by the largest LCR-A and LCR-D, while the 1.5–2 Mb deletions are flanked by LCR-A and LCR-B or LCR-A and LCR-C [29]. The high-resolution array (Illumina, 370 K) used to delineate the deletion detected in our patients, revealed that the proximal breakpoint site was narrowed down to a 11 kb region between markers rs 2871029 and rs 13056098, and the distal breakpoint was located to a 3.4 kb region between markers rs 11703181 and rs 140392 on 22q11.2. This represents a variant deletion of 1.89 Mb length, contained within the common 3 Mb deletion region, including *TBX1*. This variation in deletion endpoint has been previously reported in other atypical deletions (Fig. 4). The distal breakpoint matches with other reported deletions in the LCR–D region, but the proximal breakpoint represents a breakpoint site that does not correspond to known LCRs of 22q11.2 (Fig. 4). Three

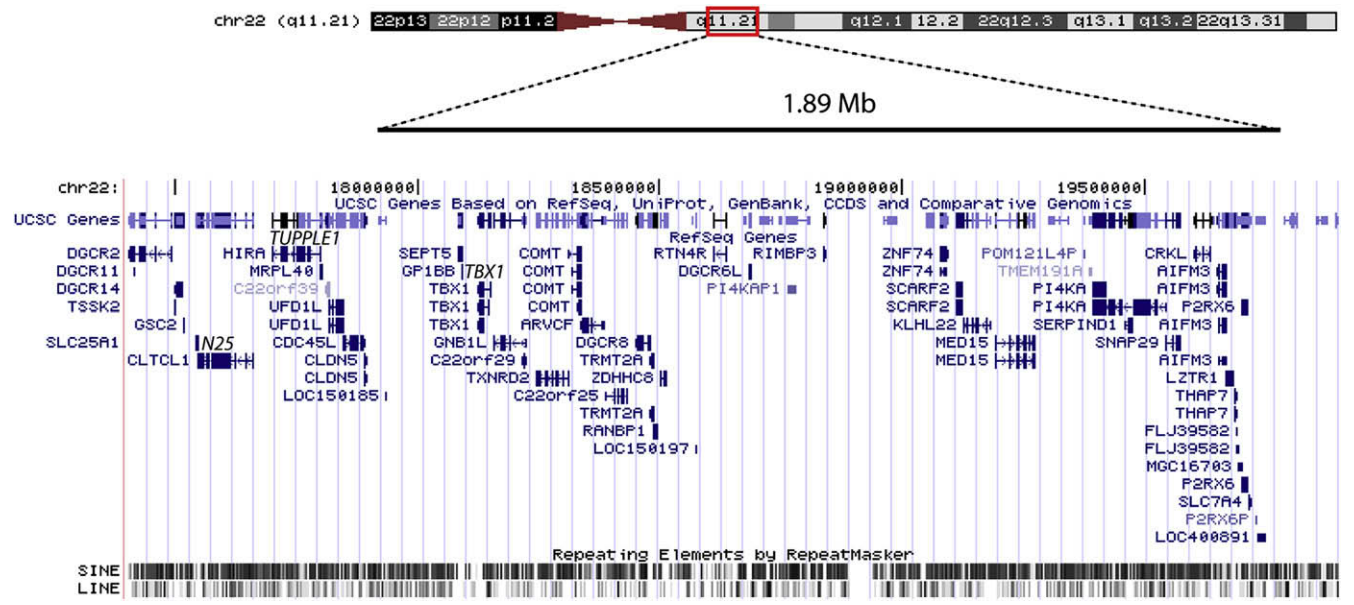

Fig. 5. Genomic map of the 22q11.2 region, integrated in a custom track of the UCSC browser, showing our 1.89 Mb deletion, genes, FISH probes (in italic), and the repeat masker track (SINE/Alu elements).

atypical deletions previously reported share probably similar proximal breakpoints, one having also a similar distal breakpoint, supporting the recurrence of breakpoints in specific region of 22q11.2, but not necessarily in specific sites containing LCRs in 22q11.2 [3,33]. Breakpoints outside of LCRs may be mediated by other repeat elements present in the 22q11.2 region, likely including SINE/Alu elements [12,19,32,33]. According to the UCSC genome database (http://genome.ucsc.edu/), SINE/Alu elements might be also located in our proximal breakpoint area (Fig. 5). Using high-resolution techniques, it has been demonstrated that the typical 3 Mb deletion regularly also differs in its extent between patients. This might eventually be of utility in explaining differences in the mechanism of the rearrangement, as well in findings explanations for the extreme variability in the spectrum of the phenotype [9,12,33].

Phenotypic variability has also been observed in familial cases of 22q11.2 DS sharing identical deletions [7,27]. The milder phenotypic expression of deleted parents in comparison with their children is also corroborated by our familial case, similar to previous reported studies. None of the parents had a congenital heart defect, whereas velopharyngeal insufficiency or cleft palate, and various degrees of mental retardation have been documented in some of them [7,17]. Milder affected parents could also have undetected low-level mosaic, which would explain their milder phenotype. Stochastic, environmental and genetic factors likely modify the phenotype of patients with the disorder [2]. Other studies of familial deletions concluded that smaller 1.5 Mb deletions were more prevalent in 16 families studied (67%), suggesting that smaller size was more favorable and likely to be transmitted [1,10]. However, in a study of 30 families, Saitta et al. (2008) [27] showed that most families had the typical 3 Mb deletion, with a size distribution similar to de novo cases, suggesting that familial deletions reflect a similar underlying mechanism to those occurring de novo.

In conclusion, our case illustrates the need to investigate further those patients with a suggestive phenotype but a normal FISH result with classical commercial probes. FISH with a *TBX1* probe is an accurate diagnostic tool for 22q11.2 DS, with a higher sensitivity than FISH using standard probes, and would detect all but the rarest deletions, greatly reducing the false negative rate. However, higher-resolution techniques such as MLPA and array-CGH, are now capable of providing more sensitive methods for the detection of copy number changes on the long arm of chromosome 22 [9,12,30]. Thus, the ultimate choice for diagnostic purposes will depend upon the level of suspicion of a 22q11.2 anomaly.

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