RAPID COMMUNICATION

Novel Rearrangement of Chromosome Band 22q11.2 Causing 22q11 Microdeletion Syndrome-Like Phenotype and Rhabdoid Tumor of the Kidney

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The 22q11.2 microdeletion syndrome is the most frequent microdeletion syndrome in humans, yet its genetic basis is complex and is still not fully understood. Most patients harbor a 3-Mb deletion (typically deleted region [TDR]), but occasionally patients with atypical deletions, some of which do not overlap with each other and/or the TDR, have been described. Microduplication of the TDR leads to a phenotype similar, albeit not identical, to the deletion of this region. Here we present a child initially suspected of having 22q11 microdeletion syndrome, who in addition developed a fatal malignant rhabdoid tumor of the kidney. Detailed cytogenetic and molecular analyses revealed a complex de novo rearrangement of band q11 of the paternally derived chromosome 22. This aberration exhibited two novel features. First, a microduplication of the 22q11 TDR was associated with an atypical 22q11 microdeletion immediately telomeric of the duplicated region. Second, this deletion was considerably larger than previously reported atypical 22q11 deletions, spanning 2.8 Mb and extending beyond the *SMARCB1/SNF5/INI1* tumor suppressor gene, whose second allele harbored a somatic frameshift-causing sequence alteration in the patient's tumor. Two nonallelic homologous recombination events between low-copy repeats (LCRs) could explain the emergence of this novel and complex mutation associated with the phenotype of 22q11 microdeletion syndrome. Hum Mutat 26:1–6, 2005. © **2005 Wiley-Liss, Inc.**

KEY WORDS: 22q11 microdeletion syndrome; microduplication; nonallelic homologous recombination; rhabdoid tumor; *SMARCB1*; *SNF5*; *INI1*

INTRODUCTION

Microdeletions in chromosome band 22q11.2 are present in 1/3,000–1/5,000 newborns, occurring de novo in the majority (75–90%) of cases [Perez and Sullivan, 2002; Yamagishi, 2002]. They are associated with heart defects, mainly of the conotruncus and the aortic arch, abnormal facies with characteristic ear anomalies, hypoplasia or absence of the thymus and the parathyroid, cleft palate or velopharyngeal dysfunction, learning disabilities or borderline mental retardation, and neuropsychiatric disorders [Perez and Sullivan, 2002; Yamagishi, 2002]. The phenotype of the 22q11.2 deletion syndrome (22q11DS) is highly variable, even though almost 90% of patients exhibit a deletion of the same ~3-Mb region, termed the "typically deleted region" (TDR) [Lindsay, 2001; Shaikh et al., 2000; Yamagishi, 2002]. Another 7 to 10% harbor a 1.5-Mb deletion that is contained entirely within the TDR [Bartsch et al., 2003; Shaikh et al., 2000]. In a minority of cases, smaller, but not always overlapping, deletions within the TDR have been observed [Amati et al., 1999; Lindsay, 2001; O'Donnell et al., 1997]. Further complicating the search for (a) gene(s) whose haploinsufficiency is critically responsible for the 22q11DS phenotype, patients from two different families were found to have deletions immediately telomeric, but entirely outside, of the TDR [Rauch et al., 1999; Saitta et al., 1999]. Nonallelic homologous recombination (NAHR) between low-copy repeats (LCRs)—stretches of highly similar sequence present in several positions of a chromosome—has been proposed to underlie the de novo emergence of several recurrent microdeletions and microduplications, including 22q11 deletions [Bailey et al., 2001; Collins et al., 1997; Dunham et al., 1999; Edelmann et al., 1999a,b; Shaw and Lupski, 2004]. Recently, complementary

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duplications of the 22q11 TDR have also been reported. They were associated with a phenotype that largely resembled that of the 22q11 microdeletion syndrome [Ensenauer et al., 2003; Hassed et al., 2004].

The *SMARCB1/SNF5/INI1* tumor suppressor gene (MIM# 601607), whose product forms part of the SWI/SNF chromatin remodeling complex, is located approximately 2.5 Mb telomeric of the 22q11 TDR. *SMARCB1* mutations have been found in a large proportion of human rhabdoid tumors, a difficult to classify but particularly aggressive tumor type of infancy and early childhood that most often affects the kidney or the central nervous system. Both somatically acquired and germ line mutations in *SMARCB1* have been described. The latter are usually point mutations, with deletion of the wild-type allele in the tumor [Biegel et al., 2002; Sevenet et al., 1999a,b; Versteege et al., 1998].

Here, we describe a patient who initially presented with features suggestive of the 22q11 microdeletion syndrome, but in infancy developed a fatal malignant rhabdoid tumor of the kidney. He had a complex, hitherto undescribed de novo rearrangement of chromosome band 22q11.2 that involved both the TDR and the *SMARCB1* gene.

MATERIALS AND METHODS

The *TUPLE1/ARSA* probe for the 22q11 TDR, the TelVysion multiprobe fluorescence in situ hybridization (FISH) system for the detection of subtelomeric abnormalities, as well as the *BCR/ABL* probe were purchased from Vysis (Downers Grove, IL), and used according to the manufacturer's instructions. DNA from 22q11 BAC clones identified from public databases was labeled with Spectrum Green or Spectrum Orange by nick translation (Vysis), and hybridized to NaOH-denatured metaphase spreads. To screen for duplication of *TUPLE1*, 200 interphase cells were analyzed per sample. A cutoff value for false positivity (average +3 standard deviations of aberrant hybridization patterns) was determined using samples from five unaffected individuals, and was 4.4%.

Array CGH was done on a 14182 BAC clone array comprising the linker adapter PCR products of the 1-Mb Sanger set [Fiegler et al., 2003], the COSTB19 subtelomeric array (www.costb19.net) and the tiling path for chromosomes 4, 9, 10, 11, 16, 17, 22, and X [Krzywinski et al., 2004; Osoegawa et al., 2001] (BACPAC Resources, Children's Hospital Oakland Research Institute; http://bacpac.chori.org/home.htm). A detailed description of all protocols can be found at www.molgen.mpg.de/~abt_rop/molecular_cytogenetics/ProtocolsEntry.html. In brief, DNA labeled by random priming (Bioprime labeling kit; Invitrogen, CA) was hybridized to slides for 24 hr at 42°C on a slide booster (IMPLEN, Germany; www.implen.de). After stringent washes, slides were scanned using an Axon 4000B (Axon Instruments, CA; www.moleculardevices.com/transition), and images were analyzed with GenePix 5.0 software (Axon Instruments). Normalization based on the median subgrid, visualization of the results, and analysis of LCR content of each clone were performed using CGHPro (comparative genomic hybridization) (Chen et al., unpublished results; freely available for noncommercial users from Wei@molgen.mpg.de).

To search for sequence alterations in the *SMARCB1* gene, published primers [Grand et al., 1999] were employed to amplify *SMARCB1* exons 2, 4, 5, 6, and 7. PCR products were cloned into pCR4-TOPO (Invitrogen, Groningen, The Netherlands; www.invitrogen.com), and sequenced using the Thermo-Sequenase sequencing system (Amersham Pharmacia, Uppsala, Sweden) and a LiCOR sequencer (MWG Biotech, Ebersberg, Germany).

RESULTS

The patient was the second child of a healthy 28-year-old gravida III, para II and her 30-year-old husband. After birth, a right preauricular tag was removed. A hearing test disclosed hypacusis (60–80 decibel), necessitating a hearing aid. At the age of 6 months, the patient was referred to the hospital because of recurrent respiratory tract infections, and later on with chronic otitis media. At that time, the size of the thymus and number of T-lymphocytes were shown to be within normal ranges, but developmental retardation, a ventricular septal defect and dextroposition of the heart were recognized, as well as dysmorphic features suggestive of a syndromic disorder. The latter included: brachycephaly with prominent occipital bone; squared face with bitemporal narrowing and full cheeks; almond shaped palpebral fissures; long eyelashes; lachrymal duct stenosis; short nose; long philtrum; thin upper lip; down-turned corners of the mouth; retrognathia; low-set, dysplastic, over-folded ears; broad short neck with loose skin; sacral and cubital dimples; right Simian crease; clinodactyly; and sandal furrow of the toes (Fig. 1A and B). The kidneys, which had been normal at a first ultrasound examination, were controlled repeatedly. At 9 months of age, the patient had developed a rapidly growing tumor of his right kidney. After cytostatic therapy, resection of the renal tumor and of colorectal and local lymph node metastases was performed and showed that the right kidney was almost completely infiltrated by

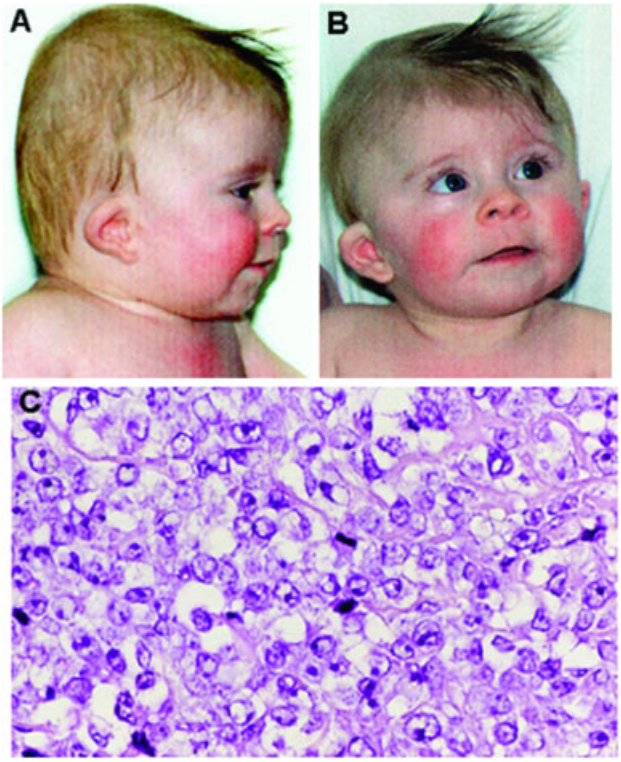

FIGURE 1. **Clinical presentation of the patient. A,B: The patient at the age of 6 months, displaying brachycephaly with prominent occiput, narrow temples, full cheeks, almond-shaped eyes with long eyelashes, short nose, long philtrum, thin upper lip, retrognathia, and low set, small, and over-folded ears, with a scar from removal of a right preauricular tag. C: Histology (hematoxylin and eosin [H & E] staining) of the highly malignant rhabdoid tumor of the kidney shows characteristic cytology with vesicular nuclei, prominent nucleoli, distinct nuclear membranes, and numerous atypical mitoses.**

necrotic tumor masses 7.5 × 6.5 × 6 cm in diameter. Because of the characteristic cytology displaying vesicular nuclei, prominent nucleoli and distinct nuclear membranes, and despite the lack of rhabdoid tumor patterns and of cytokeratin expression, the genetically suspected diagnosis of a highly malignant rhabdoid tumor of the kidney was confirmed (Fig. 1C). The patient died at the age of 19 months, after extensive cytostatic therapy, from multiple metastases of his tumor. Autopsy was not performed.

Cytogenetic examination of the patient's peripheral blood (PB) lymphocytes revealed a normal male karyotype, 46,XY. A polymorphic decrease in the length of the satellite stalks and the satellites of the short arm of one chromosome 22 was inherited from the father (data not shown). Because of the initial clinical findings and phenotypic features, FISH with the *TUPLE1/ARSA* probe (MIM# 188400, MIM# 607574), designed to detect deletions of the 22q11 TDR, was performed, but yielded a normal signal pattern (data not shown). A multiprobe FISH screen for subtelomeric abnormalities failed to detect any subtelomeric alterations. However, the chromosome 22 control probe was absent from the paternal chromosome 22, as identified by the 22p polymorphism (data not shown). This control probe corresponds to the *BCR* locus (MIM# 608232), which maps approximately 1.9 Mb telomeric of the TDR and 500–600 kb centromeric of the *SMARCB1* tumor suppressor gene. To precisely map this unusual deletion, FISH experiments with a panel of 22q11 BAC clones were performed, and revealed that the deletion spanned approximately 2.8 Mb and included the *SMARCB1* gene (Fig. 2). Its proximal breakpoint coincided with the distal breakpoint of the 22q11 TDR. Array CGH at tiling path resolution for chromosome 22 confirmed the size and position

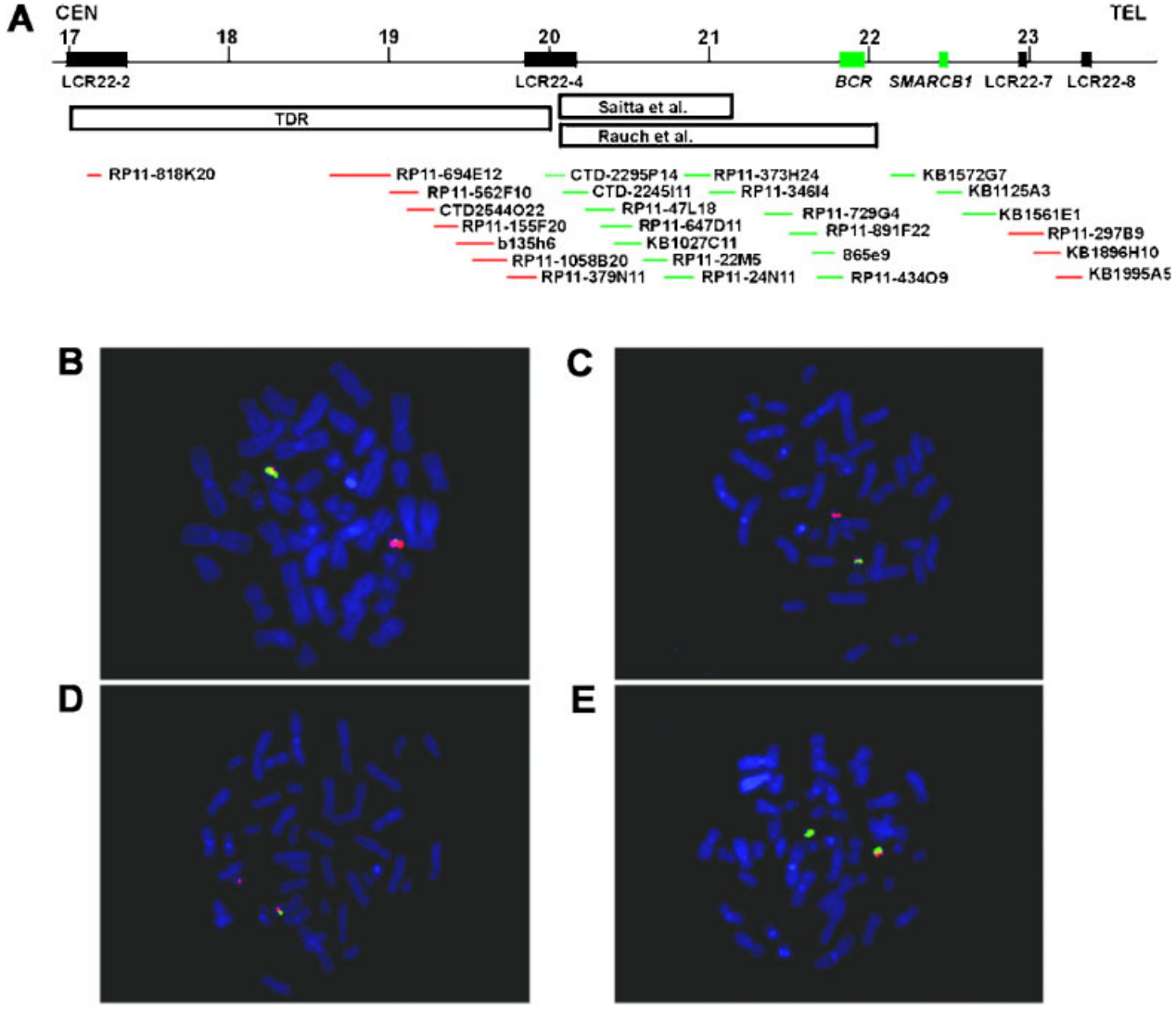

FIGURE 2. **FISH analysis. A: Schematic of the 22q11 region and of the BAC clones employed for FISH. Genomic distance from the telomere of the p-arm is indicated in megabases (Mb). Relevant low-copy repeat regions (LCR22) [Dunham et al., 1999; Edelmann et al., 1999b] are indicated by black boxes, and the *BCR* and *SMARCB1* genes by green boxes. The TDR and the atypical deletions described by Saitta et al. [1999] and Rauch et al. [1999] are represented by open boxes. Clones symbolized by red lines hybridized to both chromosomes 22 in the patient's metaphase cells; clones symbolized by green lines were deleted from one homolog. Clone CTD-2295P14 is represented by a dotted line because it yielded much weaker signals on one chromosome 22 than on the other, suggesting that it was partially deleted. B: Cohybridization of clones CTD-2295P14 (green) and RP11-1058B20 (red). C: Cohybridization of clones KB1125A3 (green), containing the *SMARCB1* gene, and KB1896H10 (red). D: Cohybridization of clones CTD-2245I11 (green) and RP11-297B9 (red). E: Cohybridization of clones RP11-379N11 (green) and KB1561E1 (red).**

of the patient's deletion. Furthermore, it revealed a duplication of a 2.8-Mb region, which is located immediately centromeric of the deletion and corresponds to the 22q11 TDR (Fig. 3). Corroborating the latter result, several clones from the duplicated region displayed stronger FISH signals on one chromosome 22 than on the other. Moreover, in the majority of metaphases, a more intense signal from the duplicated BAC RP11-1058B20 was present on the deletion chromosome 22, identified by the lack or reduced intensity of a signal from the cohybridized clones RP11-24N11 and RP11-373H24, or CTD-2295P14 (Fig. 2B; and data not shown). Thus, the duplication and the deletion were present on the same, i.e., the paternally-derived, chromosome 22. Inspection of interphase nuclei hybridized with the *TUPLE1/ARSA* probe further confirmed the microduplication: three *TUPLE1* and two *ARSA* signals were found in 123 out of 200 (62%; cutoff value for false positivity, 4.4%) interphase nuclei. A normal signal constellation (two *TUPLE1* and two *ARSA* signals) was present in 66 out of 200 (33%) nuclei, and could indicate the presence of a mosaic. However, this ratio of aberrant to normal signal patterns is within the range observed for other 22q11 microduplication patients [Ensenauer et al., 2003], and no evidence for a mosaicism of the adjacent microdeletion was found in a total of over 600 analyzed metaphases.

FISH with the *BCR/ABL* probe (MIM# 608232, MIM# 189980) and with BAC clones KB1027C11, bK865E9, and KB1125A3 on metaphase spreads from the patient's parents showed that neither of them carried the deletion present in the patient. Also, analysis of interphase nuclei hybridized with the *TUPLE1/ARSA* probe revealed a normal signal pattern in 188 out of 200 interphase nuclei of the paternal sample, excluding the presence of a microduplication. Finally, the absence of any 22q11 copy number aberrations from the paternal DNA was confirmed by array CGH. Thus, the complex rearrangement present in the patient's paternally-derived chromosome 22 occurred de novo during gametogenesis.

To determine whether the second *SMARCB1* allele was somatically inactivated in the patient's tumor, the most frequently mutated *SMARCB1* exons 2, 4, 5, 6, and 7 [Biegel et al., 2002; Sevenet et al., 1999a], were amplified, cloned, and subjected to sequence analysis. A 2-bp deletion, c.666_667delCT (relative to the first in-frame ATG codon in the cDNA sequence deposited under GenBank Accession# NM_003073.3), was found in *SMARCB1* exon 6 in eight out of eight clones derived from two independent PCR amplifications (four each). This sequence alteration leads to a frameshift and the introduction of a stop codon immediately downstream from it, after amino acid position L222. It truncates the SMARCB1 protein in the middle of the highly conserved repeat domain 1, which is necessary and sufficient to mediate important interactions with other proteins [Cheng et al., 1999; Morozov et al., 1998]. This sequence alteration was not found in DNA from the patient's peripheral blood (four clones), nor in the DNA from either of his parents (two clones each), indicating that it was somatically acquired.

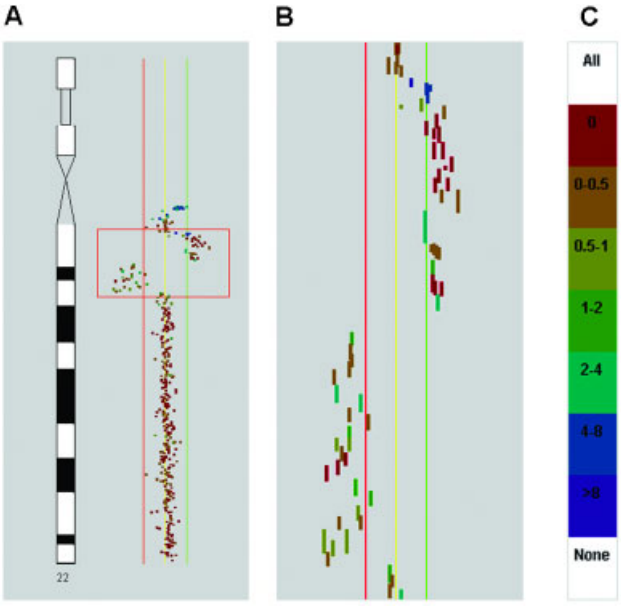

FIGURE 3. **Array-CGH result for chromosome 22 as displayed by CGHPro. DNA from an LCL cell line derived from the patient's peripheral blood lymphocytes was hybridized to a 14182 BAC clone array. Results were comparable to those obtained with DNA extracted directly from the patient's peripheral blood leukocytes. A: The ratios of each chromosome 22 clone are plotted in a size dependent manner along the chromosome ideogram. The green and red lines represent $\log_2$ ratios of 0.3 (gains) and −0.3 (losses), respectively. B: Zoom in of the aberrant region in 22q11. The first duplicated clone is CTD-2280L11, starting at position 17048519; the last duplicated clone is RP11-294A09, ending at position 19849078. The first deleted clone is CTD-2245I11, starting at position 20114134; the last deleted clone is RP11-619K17, ending at position 22944693. The clones at the breakpoints are characterized by an increased content of low-copy repeats as indicated by their coloring according to the code shown in (C). LCR content: 0=low; 8=high.**

DISCUSSION

We describe herein a child with mild phenotypic features suggestive of 22q11 microdeletion syndrome and a fatal malignant rhabdoid tumor of the kidney. The patient had a congenital rearrangement of chromosome band 22q11 of previously unreported extent and complexity: a microduplication of the ~2.8-Mb region deleted in the majority of patients with 22q11DS was combined with a ~2.8-Mb deletion immediately telomeric of the TDR. Both aberrations arose de novo on the paternally-derived chromosome. FISH and CGH results suggested that both the duplication and the deletion endpoints were located within LCR regions (Figs. 2 and 3). Therefore, two meiotic nonallelic homologous recombination events could explain the formation of this novel complex rearrangement.

The question arises as to which of these aberrations is responsible for which aspect of the patient's clinical phenotype. Unlike in other published cases with atypical 22q11 microdeletions [Rauch et al., 1999; Saitta et al., 1999], the deletion in our patient included the *SMARCB1* tumor suppressor gene. Even though at least 50 known or predicted genes are reduced to a haploid state by this deletion, a crucial role of *SMARCB1* in the emergence of the tumor is supported by the fact that a truncating somatic sequence alteration of the second allele was present in the tumor tissue. While we cannot formally exclude the possibility that this sequence change arose in the course of preoperative chemotherapy, the well-established role of *SMARCB1* as a tumor suppressor in rhabdoid tumors [Biegel et al., 2002; Sevenet et al., 1999a, b; Versteege et al., 1998] makes it plausible that the sequence alteration occurred in the process of malignant transformation and contributed to tumor formation. It is noteworthy, though not unprecedented, that in contrast to the classical order of mutations in tumor suppressor genes—point

mutation followed by deletion of the second allele—the opposite order was observed in our case [Biegel et al., 2002; Sawada et al., 1996; Sevenet et al., 1999b].

The genetic basis for the 22q11DS-like phenotype of our patient is more difficult to assign: apart from microdeletions of the 22q11 TDR, microduplications of this region, as well as atypical microdeletions adjacent to and telomeric of it, have been reported in association with 22q11DS-like features [Ensenauer et al., 2003; Hassed et al., 2004; Rauch et al., 1999; Saitta et al., 1999]. Clinical overlaps between the 22q11 microduplication and microdeletion syndromes may include cardiac, aortic, and urogenital anomalies, developmental retardation, hearing loss, cleft palate and velopharyngeal insufficiency, absent thymus and T cell deficiency, and many craniofacial dysmorphic features including those of our patient [Ensenauer et al., 2003]. Overlaps of features between and phenotypic variability within the different conditions hamper a correct diagnosis by clinical criteria alone. Therefore, the duplication or the deletion or both could have played a role in the congenital phenotype of our patient. On the other hand, our observations raise the intriguing possibility that microduplications of the TDR may have been associated with previously described atypical microdeletions, and have caused the 22q11DS-like phenotype of these patients, a scenario not excluded by the experiments presented in these reports [Rauch et al., 1999; Saitta et al., 1999]. The converse proposition—that atypical microdeletions were associated with the 22q11 microduplications, and responsible for their phenotype—is rendered unlikely by the microsatellite analyses of Ensenauer et al. [2003]. Our data therefore suggest that it may be worthwhile to investigate patients with atypical 22q11 deletions for the presence of other 22q11 aberrations, and add an important novel facet to the search for genes causally involved in the phenotype of disorders caused by genomic rearrangements of chromosome band 22q11.

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