An Inherited Atypical 1 Mb 22q11.2 Deletion Within the DGS/VCFS 3 Mb Region in a Child With Obesity and Aggressive Behavior

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To the Editor:

The DiGeorge, Velocardiofacial, and Conotruncal Anomaly Face syndromes (DGS/VCFS/CTAF) are known collectively as the 22q11.2 deletion syndrome (22q11 DS) [Shaikh et al., 2000; Swillen et al., 2000]. Although most individuals have the same large 3 Mb 22q11.2 de novo deletion, a recurrent 1.5–2 Mb proximally nested deletion is more common in familial cases of 22q11.2 DS [Iascone et al., 2002; Adeyinka et al., 2004; Fernandez et al., 2005]. Atypical smaller or uniquely placed deletions have been described in only a few patients [Kurahashi et al., 1996, 1997; Amati et al., 1999; Shaikh et al., 2000; Garcia-Minaur et al., 2002; Rauch et al., 2005]. We report on a rare 1 Mb 22q11.2 deletion in a female patient with obesity, hyperphagia, and aggressive behavior, and in her mother who had a major depressive disorder. The deletion was identified serendipitously in the proband during a microdeletion screening for syndromic obesity and was limited to the most telomeric region of the 3 Mb typically deleted region.

The patient (Fig. 1) was the first child of non-consanguinous parents with an unremarkable family history. Decreased fetal movement was reported. She was delivered at term by caesarean. Apgar scores were 8 and 9 at 1 and 5 min, respectively. The birth weight was 2.9 kg (~25th centile), length 48 cm (~10th centile), and the OFC 34 cm (~25th centile). Neonatal jaundice was treated with phototherapy. The sucking reflex was present, but she fed with difficulty until 1 year of age when gastroesophageal reflux was diagnosed. Delayed closure of anterior fontanel was reported. She walked independently at 1 year and 4 months. On examination at 4 years of age, the OFC was 52 cm (50–98th centile), height was 101 cm (25–50th centile), and weight was 27 kg (>97th centile). She had a narrow forehead, synophrys, upslanted palpebral fissures, deep-set eyes, divergent strabismus of the right eye, small mouth and thin lips, high-arched palate, short philtrum, retrognathia, small hands, and pes planus. Her problems included speech articulation, sleep difficulties, hyperphagia, decreased sensitivity to pain, hyperactivity, and aggressive behavior, such as beating strangers, and self-injurious behaviors including head banging, biting, hair pulling, and skin picking. When re-evaluated at age 8 years, there were no significant changes. Compulsive food eating and behavioral problems had worsened. She weighed 67 kg (>97th centile) with truncal obesity, and height was 130 cm (50–75th centile). She took antipsychotic medication to control aggressiveness and attended a special education school.

The patient’s mother has had a major depressive disorder and anxiety for 10 years, for which she has taken several psychiatric medications. She had similar facial features to her daughter including divergent strabismus on the right eye, and a hypernasal speech. She weighed 71 kg and was 160 cm tall (BMI 27.7, overweight). She was otherwise...
healthy and had successfully obtained a higher education degree.

The patient’s routine laboratory exams, including thyroid function, glucose, cholesterol, triglycerides, calcium, and phosphate were normal. Newborn screening for sickle cell disease, galactosemia, and congenital adrenal hyperplasia was also normal, as well as hearing evaluation, abdominal ultrasonography, echocardiography, and electrocardiography. Brain MRI disclosed abnormal signal in the posterior periventricular white matter, possibly secondary to gliosis, or incomplete myelination. The 400–550-band resolution karyotype was normal and the suspected diagnosis of Prader–Willi syndrome (PWS) was ruled out by methylation analysis of the SNURF-SNRPN exon 1 [Zeschnigk et al., 1997].

Informed consent was obtained from both parents to include the patient in an ongoing research of syndromic obesity [Delrué and Michaud, 2004]. Multiplex ligation probe-dependent amplification (MLPA) with the SALSA kits P023, P064, and P204 (MRC-Holland, Amsterdam, The Netherlands) was carried out according to the manufacturer’s instructions [Schouten et al., 2002]. Electrophoresis and fragment analysis were performed using the MegaBACE™ 1000 DNA analysis system and Fragment Profiler software version 1.2 (GE Healthcare). Statistical analyses of the results for kits P064 and P023 were carried out using an excel spreadsheet developed by National Genetics Reference Laboratories (NGRL, Manchester, UK). For a comprehensive explanation of the analysis see www.ngrl.org.uk/Manchester. The analysis for kit P204 was performed visually, because no spreadsheet is currently available.

The first MLPA screening with kit P064, that detects deletions and duplications of chromosomal regions frequently involved in mental retardation syndromes, disclosed a deletion of probe SNAP29 in the patient and her mother (data not shown). Kit P023, specific for 22q11 DS, confirmed the deletion in both mother and daughter and revealed an additional deletion of probe LZTR1 (data not shown). Kit P204, especially designed to map 22q11 deletion breakpoints, was used to characterize our patient’s deletion extension. The P204 probemix provides 37 probes in 22q11.2 and a few probes in the low-copy repeats (LCR) regions -A and -D (see the online Table II at http://www.interscience.wiley.com/jpages/1552-4825/suppmat/index.html). Both mother and daughter showed deletions of three probes mapped to genes SNAP29, LZTR1, and P2RXL1, and of a probe in the distal LCR-D (Fig. 2). Probe LCRD-b has shown to give false positive and false negative results and is currently being redesigned (MRC-Holland, personal communication). Therefore, no results for probes within LCR-D were used to define our deletion’s breakpoints. The proximal deletion breakpoint was mapped between probes PCQAP and SNAP29, a region of 305 Kb containing LCR-C, and the distal deletion breakpoint was located within a 420 Kb region between probes P2RXL1 and HIC2, comprising LCR-D (Fig. 3). Considering the recombination mechanisms mediated through LCR22 repeats, it is likely that both mother and patient have a 1 Mb C–D deletion in the distal region of the 3 Mb region. Microsatellite analysis of five markers (D22S1638, D22S1648, D22S944, D22S1623, D22S1709) spanning the 3 Mb region showed no maternal contribution of D22S1709 and normal segregation for the other markers (data not shown).

The typically deleted 3 Mb region in 22q11 DS is mediated by the largest LCR-A and LCR-D (A–D deletion), while the 1.5–2 Mb deletion is mediated by LCR-A and LCR-B (A–B deletion) or LCR-A and LCR-B.
FIG. 2. Characterization of 22q11.2 deletion in the mother and daughter by MLPA with kit P204. A. Results obtained on a DNA control sample. Relative copy number of a genomic target sequence is detected as fluorescent signals (Y-axis) of the amplification product generated by each probe (X-axis). MLPA probes are shown above the corresponding peaks (c = control probes) and do not correspond to the physical 22q11 map. B. Electropherogram of the patient and her parents. Dotted arrows indicate the position of the aberrant MLPA probe compared to peak signal intensity of the control sample. Black arrows show corresponding probes with peak intensity similar to the control peak profile.

FIG. 3. Schematic overview of the DGS/VCFS 22q11.2 typically deleted region. LCR22 -A, -B, -C, and -D are indicated as filled boxes. The sizes of the boxes are proportional to the estimated size of each LCR22 (<350 kb, 135 kb, 75 kb, and 250 kb, respectively [Shaikh et al., 2000]). Microsatellite markers used in the study are shown above the line. The genes detected by MLPA probes within the TDR in kit P204 are labeled with italic. Asterisks indicate the maximum deleted region. The probes/markers that disclosed deletions are underlined. Bars below the map depict the common ~3 Mb deletion (A–D) and the ~1.5–2 Mb nested deletion (A–B or A–C) as mentioned in Shaikh et al. [2000]. The gray bar represents the deletion interval (C–D) described in our patient.
LCR-C (A–C deletion) [Shaikh et al., 2000] (see Fig. 3). Only three patients have shown deletions in the distal half of the 3 Mb region, two of them delineated as having a B–C deletion [Garcia-Minaur et al., 2002; Rauch et al., 2005], and a single patient with a C–D deletion [Kurahashi et al., 1996, 1997]. This report describes the second report of an atypical 1 Mb C–D deletion, the first one transmitted from mother to daughter. Despite the fact that most of DGS/VCFS patients have the same 3 Mb deletion, the 22q11 DS is among the most clinically variable syndromes. While the majority of studies have shown that this variability has no correlation with the size of the deletion [Goldmuntz, 2005; McDonald-McGinn et al., 2005], a recent study reported possible genotype–phenotype correlations [Rauch et al., 2005]. In 350 DGS/VCFS patients, atypical distal deletions were only weakly suggestive of 22q11.2 DS, whereas patients with conotruncal congenital heart defects or with typical DGS/VCFS phenotype had the common 1.5–3 Mb deletion.

In addition to obesity and hyperphagia, our patient has aggressive and self-injurious behavior, learning disabilities, delayed emergence of speech, and articulation problems. Her dysmorphic facial features were subtle and not typical for this syndrome. Her mother had an even milder phenotype, accompanied by a major depressive disorder and hypernasal voice. In contrast, the previously described patient with a C–D deletion had a congenital heart defect and typical facial features. The lack of resemblance between our patient and that described by Kurahashi et al. [1996, 1997] (Table I) suggests that for smaller atypical deletions, there seems to be no clear genotype–phenotype correlation, although additional patients should be studied.

Although the observation of these atypical deletions may appear to be inconsistent with the presence of a unique major gene causing the 22q11 DS, a TBX1 mutation has recently been identified in patients with no detectable 22q11.2 deletions [Yagi et al., 2003]. CRKL has also been implicated in the underlying molecular mechanism of 22q11 DS [Guris et al., 2001] and would explain those cases with more distal deletions given that it is mapped to the C–D interval. Recent studies pointed to an important role of COMT and DGCR2 genes, both mapped within the A–B interval, in the pathology of the psychiatric and behavioral disorders of 22q11 DS [Shifman et al., 2006; Weksberg et al., 2007]. However, a B–C deletion was reported in a patient with early signs of psychiatric illness, whose schizophrenic father was not available for analysis [Rauch et al., 2005]. Our C–D deleted patient started showing severe behavioral problems before the age of 4 years, and her carrier mother had suffered from major depressive disorder since age 26. These findings suggest that another gene, within the C–D interval, could also be responsible for the onset of neuropsychiatric disorders in 22q11 DS.

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**TABLE I. Common Clinical Findings in the 22q11.2 Deletion Syndrome [Bassett et al., 2005; Goldmuntz, 2005; McDonald-McGinn et al., 2005] Compared to Those Presented in Our Case and in One Previously Described Patient With a Similar 1 Mb C–D Deletion [Kurahashi et al., 1996, 1997]**

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<tr>
<td>Congenital heart disease (7%) (Particularly conotruncal malformations)</td>
<td>Pulmonary atresia and tetralogy of fallot</td>
<td>Absent</td>
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<tr>
<td>Palatal abnormalities (69%) (especially velopharyngeal insufficiency)</td>
<td>No cleft palate</td>
<td>High arched palate</td>
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<td>Hypocalcemia (50%) (other endocrinologic disorders&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>No hypocalcemia</td>
<td>No hypocalcemia</td>
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<tr>
<td>Immune deficiency (77%)</td>
<td>No thymic hypoplasia</td>
<td>Absent</td>
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<tr>
<td>Speech and language disabilities&lt;sup&gt;b&lt;/sup&gt;</td>
<td>No nasal voice &lt;sup&gt;c&lt;/sup&gt;</td>
<td>Speech delay and articulation problems</td>
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<tr>
<td>Feeding disorders&lt;sup&gt;d&lt;/sup&gt; (30%)</td>
<td>Typical facial features</td>
<td>Mild facial features</td>
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<tr>
<td>Otolaryngologic problems&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td>Learning disability</td>
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<tr>
<td>Characteristic facial features</td>
<td></td>
<td>Hyperphagia, aggressiveness, hyperactivity, sleep problems</td>
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<td>Cognitive or learning disabilities (70–90%)</td>
<td></td>
<td>Obesity cerebral white matter alterations</td>
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<td>Behavioral problems and/or psychiatric disorders&lt;sup&gt;f&lt;/sup&gt;</td>
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<sup>a</sup>Growth hormone deficiency and thyroid disease.

<sup>b</sup>Speech delay, hypernasality (64–84%), articulation problems (62–77%).

<sup>c</sup>Nasopharyngeal (70%) or gastroesophageal reflux, esophageal dysmotility, constipation.

<sup>d</sup>Chronic otitis media, sinusitis, hearing deficits (28% of adults).

<sup>e</sup>Autistic spectrum, attention deficit and hyperactivity, anxiety, depression, social withdrawal, obsessive-compulsive disorder, schizophrenia.

<sup>f</sup>Renal (31%) and skeletal abnormalities, CNS alterations, obesity (35% of adults), etc.
REFERENCES


