Letter to the Editor

A further Angelman syndrome patient with UPD15 due to paternal meiosis II nondisjunction

To the Editor:

Uniparental disomy (UPD) is a rare genetic mechanism found in about 1–5% of Angelman syndrome (AS) cases (1–4).

Recently, Gyftodimou et al. (5) described the first case of AS with UPD15 due to paternal meiosis II (MII) nondisjunction, and it prompted us to describe the second similar case, detected among 4 AS patients with UPD ascertained when we were investigating the pattern of recombination associated with nondisjunction of chromosome 15 (data not shown). Our patient is a 10-year-old girl born to a 40-year-old mother and 47-year-old father. Her birth weight and height were 2400 g and 46 cm, respectively. At the time of examination, her weight and length were above the 75th percentile and outer frontal circumference (OFC) was 51 cm (2 < p < 50). She also presented with neuropsychomotor delay, macrostomia with spaced teeth, absence of speech, ataxic gait, frequent laughter with a happy disposition, seizures with onset at 8 years of age, sleep disturbance, and fascination with water (Fig. 1).

Methylation analysis was performed using the probe containing exon 1 of SNRPN gene, and the characteristic AS pattern was obtained. The karyotype was normal. Microsatellite analyses were performed according to Mutirangura et al. (6) and disclosed paternal UPD, since all markers tested showed inheritance only of paternal alleles within and outside the AS critical region. The most proximal marker (D15S542) and the markers located in 15q11–q13 region (D15S11, GABRB3, and D15S113) showed reduction to homozygosity of paternal alleles. Markers outside the PWS/AS region (CYP19, D15S117, D15S131, and D15S115) showed expected patterns consequent to inheritance from both paternal chromosomes. These results can be seen in Table 1 and suggest a MI nondisjunction event in the father with, at least, one crossover. The marker D15S984 located between the loci D15S131 and D15S115 was noninformative.

Two different mechanisms can lead to UPD15 in an AS patient due to an MII error: 1. A paternal MII nondisjunction and fertilization of this disomic sperm with a normal egg, resulting in a trisomic fetus with subsequent loss of maternal chromosome 15 (review in (7)); 2. fertilization of a disomic sperm with a nullisomic egg involving both maternal and paternal nondisjunction errors.

It is well known that MI errors are associated with the majority of maternal UPD15 cases in Praeder–Willi syndrome (PWS), whereas the chromosomes in paternal UPD15 are usually consistent with a postzygotic nondisjunction or duplication origin (7, 8). Paternal MII nondisjunction mecha-

Fig. 1. The patient at the age of 8\(\frac{11}{12}\) years.
isms can also be responsible for UPD15 in AS patients as is evident by these two described cases. It has been suggested that AS patients with UPD15 present with a milder phenotype compared with patients with deletions (9–11). Our patient developed seizures at 8 years of age, which usually appear earlier in patients with deletions. Her weight and height were above the 75th percentile, features also predominant among UPD15 AS patients (4).

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Acknowledgements
We thank Dr Robert D Nicholls for kindly provided the SNRPN probe for methylation assay. This work is supported by FAPESP.

References

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