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Letter to the Editor

Maternal uniparental disomy of chromosome 16 in a patient with adenine phosphoribosyltransferase deficiency

To the Editor:

Adenine phosphoribosyltransferase (APRT) deficiency (OMIM ID +102600) is an autosomal recessive disorder (1) that results in the accumulation of adenine. Adenine is oxidized by xanthine dehydrogenase in 2,8-dihydroxyadenine (2,8-DHA) that is excreted in the urine, is insoluble and crystallizes, leading to stone formation and tubulointerstitial nephropathy (2). The *APRT* gene maps to 16q24 and contains five exons (3).

The proband was the second child born to healthy non-consanguineous parents of European origin. Prenatal ultrasounds showed moderate intrauterine growth retardation and hyperechogenic bowel associated with CMV primoinfection and small ventricular septal defect. Magnetic resonance imaging at 36 weeks showed no cerebral abnormalities. Caryotype after amniocyte culture was normal (46, XX). Birth weight, height and OFC were 2850 g [−1 standard deviation (SD)], 47 cm (−2 SD) and 34 cm (−0.5 SD), respectively, at gestational age of 40 weeks and the girl showed catch-up growth after birth, being at the 50th percentile for height and weight at 3 years. Echocardiography confirmed small ventricular septal defect. At the age of 13 months she had acute pyelonephritis and developed persistent hematuria. Renal ultrasound showed a kidney stone in the right pelvis that was treated with extracorporeal lithotripsy. Stone analysis showed 2,8-DHA lithiasis and 2,8-DHA crystals were found in the urine. APRT activity in erythrocytes was null. She was treated with hydration and allopurinol. Three years later she had no symptoms, renal ultrasound was normal and search for crystals in the urine was negative.

Sequencing of the *APRT* gene (after written informed consent from parents) showed the c.400+2insT mutation in the homozygous state in the proband (Fig. 1a). Reverse transcriptase polymerase chain reaction (RT-PCR) using RNAs from proband's lymphocytes showed a single amplification product lacking exon 4 (Fig. 1b). As expected, the mutation was present in the heterozygous state in her mother (Fig. 1a). Unexpectedly, it was not found in her father (Fig. 1a). RT-PCR from parents' lymphocyte RNA showed two amplification products (with and without exon 4) in the mother, but a single product (with exon 4) in the father (Fig. 1b). APRT enzyme activity was intermediate in the mother (0.21 for a normal from 0.40 to 0.60 nmol/min/mg) but was normal (0.43) in the father, ruling out an heterozygous deletion in the father. We tested three microsatellite markers surrounding the *APRT* gene (D16S520, D16S3023 and D16S3121) in the proband, her unaffected brother and both parents. No paternal markers were detected in the patient around the *APRT* locus (Fig. 1a). Non-paternity was excluded by using microsatellites markers from different chromosomes. Genotyping of 15 additional markers spanning the entire chromosome 16 in the family showed a complete absence of paternal contribution (Fig. 1a). The microsatellite analyses indicated that this girl had maternal uniparental disomy (UPD) with proximal heterodisomy and distal isodisomy. Thus UPD16 very probably arose from postzygotic correction of a trisomic 16 embryo because of maternal nondisjunction event in the first meotic segregation. To date, several maternal UPD16 fetuses and liveborns have been reported. Many showed clinical abnormalities such as fetal demise or neonatal death (4), severe intrauterine growth retardation, body stalk anomaly, imperforate anus, congenital heart disease, central nervous system anomalies (5, 6) and were frequently associated with trisomy16-confined placental mosaicism (7). These clinical findings may be because of imprinting effect, high level of trisomic cells in placenta, undetected mosaicism for trisomy 16 in the individuals and/or recessive diseases as a result of isodisomy. Other maternal UPD16 carriers without severe postnatal phenotype have been reported (8). Our patient showed moderate intrauterine growth retardation as well as a small interventricular septal

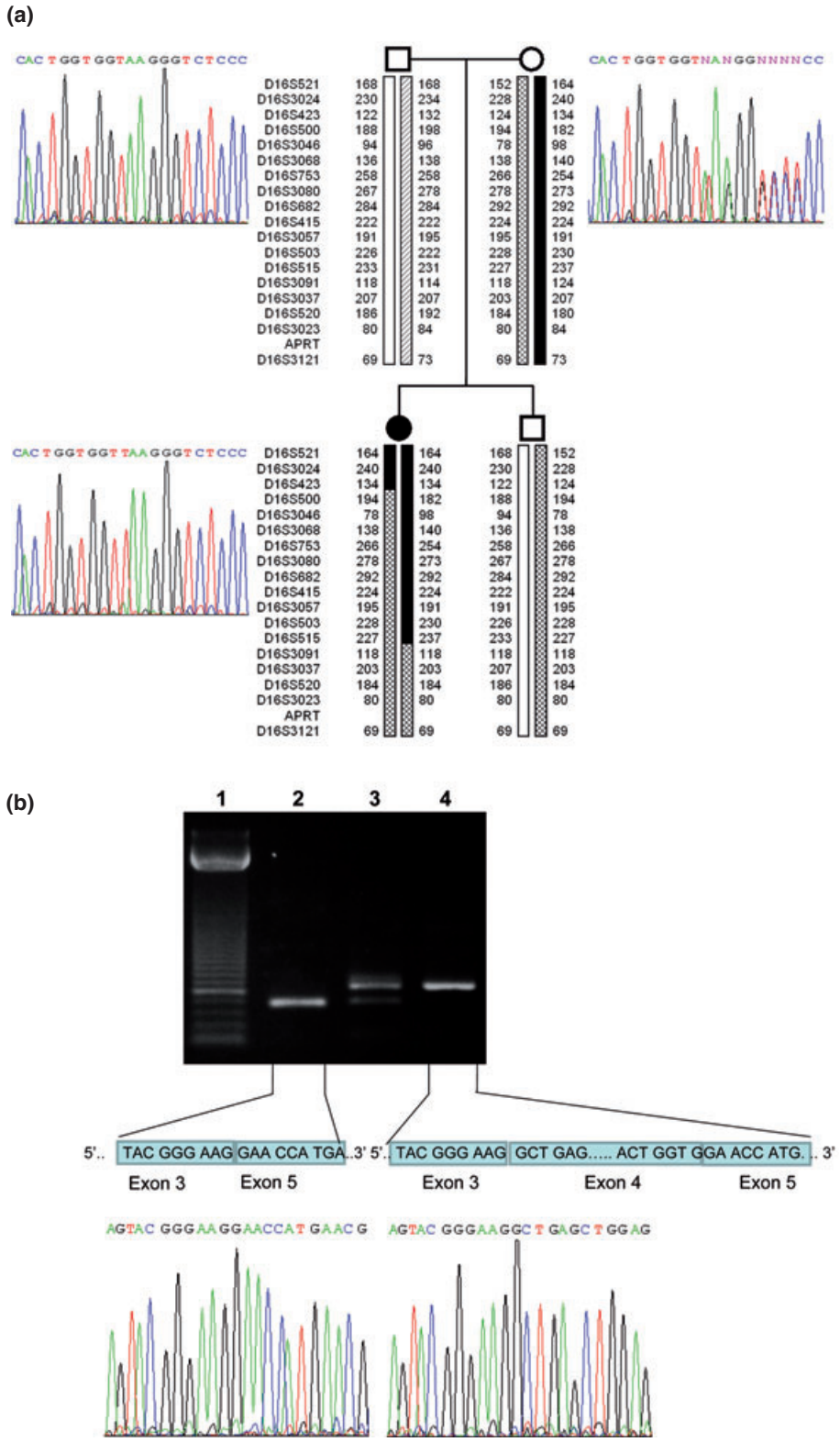

Fig. 1. (**a**) Pedigree of the family with partial nucleotide sequence of the *APRT* gene showing the c.400+2insT mutation in the homozygous state in the affected daughter, the same mutation in the heterozygous state in her mother, and a normal sequence in her father, as well as patterns of microsatellites of chromosome 16 seen in the four family members. (**b**) Polymerase chain reaction (PCR) amplification products from *APRT* cDNAs. Line 1: size marker (50 bp ladder Invitrogen, Carlsbad, CA); line 2: the affected daughter has a single shorter amplification product of 193 bp; line 3: the mother shows normal (272 bp) and abnormal (193 bp) products; line 4: the father has a single, normal sized (272 bp) product. The sequence of the two amplification products and corresponding chromatograms are shown.

defect but no other congenital abnormalities, and her disease was clearly related to APRT deficiency. Maternal UPD and/or trisomy 16-confined placental mosaicism may have contributed to fetal growth restriction and to the cardiac defect. In conclusion, the absence of other severe associated phenotype in our patient indicates the lack of imprinted gene on chromosome 16. In addition, our observation, which is the first evidence of UPD in APRT deficiency, illustrates the need to consider UPD in cases of homozygosity of a rare mutation in non-consanguineous families.

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