Rett syndrome (RTT) is a neurodevelopmental disorder affecting females in a sporadic manner. In a high proportion of patients the disease is caused by de novo dominant mutations at MECP2 gene (Xq28). The existence of RTT males has been discussed extensively, and less restrictive diagnostic criteria have been proposed to include this variant, which should be considered when evaluating boys with idiopathic developmental regression, autistic features, and loss of hand function. Nevertheless, no MECP2 analysis has been reported from Rett-like males to date. Analysis of 2 familial cases showed that boys carrying the same MECP2 mutation that caused RTT in their sisters suffered from severe–fatal neonatal encephalopathy. Recent data, however, demonstrate that the clinical spectrum of MECP2 mutations is wider than previously expected. With a frequency comparable to that of fragile X syndrome, recessive nonspecific X-linked mental retardation can be caused by missense mutations at MECP2, different than those causing RTT. Mutations have also been described in patients with congenital nonprogressive encephalopathy and in some cases of Angelman syndrome (AS), the only reported AS boy being a somatic mosaic for a MECP2 truncating mutation.5

We document the first MECP2 analysis of a boy with classic RTT and a normal 46,XY karyotype. The patient is 14 years of age and fulfills eight of nine necessary criteria, seven of eight supportive criteria, and no exclusion criteria, according to the Rett Syndrome Diagnostic Criteria Work Group. Genetic informed consent was obtained and the study was approved by the Ethical and Investigation Commissions of our hospital.

MECP2 sequencing of two independent patients' DNA samples from peripheral lymphocytes revealed the presence of a heterozygous change 398G→A, causing an R133H substitution. The mutation had been previously described in 2 RTT female patients. As the boy had a normal karyotype, heterozygosity could be explained by (1) a low frequency mosaicism for a Klinefelter syndrome, discarded by FISH on prophase nuclei; (2) a mosaicism for a Klinefelter syndrome, discarded by FISH on high-resolution karyotype and observation of hemizygosity for X-linked markers and two intragenic MECP2 polymorphisms; or (3) somatic mosaicism for the mutation. To test this last hypothesis, DNA was prepared from the patient’s oral mucosa and sequenced. The normal sequence, with only a small amount of the mutated allele, was observed. These results demonstrated that the RTT boy is a somatic mosaic for the R133H mutation and seemed to indicate that the mutation is present in a high proportion of lymphocytes but at a lower frequency in oral mucosa. To specifically test and semiquantify the heterozygous status of the mutation, an amplification refractory mutation system (ARMS) experiment was designed. Both the normal and mutated alleles were amplified in the patient’s lymphocytes and oral mucosa.

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