Letter to the Editor

A patient with classic Rett syndrome with a novel mutation in MECP2 exon 1

To the editor:

Rett syndrome (RTT) is known to be caused by mutations in the MECP2 gene that encodes methyl-CpG-binding protein 2. However, these mutations are only detected in ~85% of individuals with classic RTT, and thus the genetic cause is still unknown in the remaining patients (1). A new MeCP2 transcript, termed MeCP2_e1 (GenBank accession number AY541280), has recently been identified, which encodes a distinct N-terminus (newly annotated exon 1 containing 21 amino acids) (2, 3). The new transcript is predominantly expressed in the brain and may be more directly associated with RTT phenotype than the previously known MeCP2_e2 transcript (2, 3). However, to our knowledge, only four mutations, which are all frame-shift mutations, have been reported in the new exon 1 (3–5), and mutations in exon 1 in the patients with RTT are believed to be rare (1, 6). Here, we report another patient with RTT with a novel frame-shift mutation in exon 1.

The patient is a 5-year-old girl born to healthy and non-consanguineous parents. The patient was delivered spontaneously at the 41 weeks of gestation. The weight, length and occipito-frontal circumference of the patient at birth were 3380 g [−0.5 standard deviation (SD)], 50 cm (−0.4 SD) and 32.5 cm (−0.5 SD, no microcephaly), respectively. There were no eventful episodes in the pre- and perinatal period. She was noted to have a mild developmental delay during the first year of life. She had acquired several words by the age of 1 year but had lost them by the age of 1.5 years. She started walking at the age of 19 months. At the age of 21 months, she developed brief seizures with abnormal spike discharges on electroencephalogram, and valproic acid was administrated. At the age of 4 years, stereotypic ‘hand wringing’ movements, gait ataxia, periodic apnoea and intermittent hyperventilation appeared, and she lost acquired purposeful hand skills. Her development quotient (DQ = developmental age/observed age) at the age of 5 years was estimated to be 29/100, with especially low points in upper limb function. She met all necessary established RTT diagnostic criteria (European Pediatric Neurology Society Meeting 2001).

A mutation in MECP2 exon 1 was found in the patient by direct sequencing [c.59_60delGA (p.Arg20ThrfsX40)] (Fig. 1a). This mutation was not observed in the parents. The X-chromosome inactivation (XCI) pattern obtained by a methylation-specific polymerase chain reaction assay (7) was found to be of a random pattern (48 : 52) in the patient’s lymphocytes (Fig. 1b). The random XCI pattern was consistent with those observed in many brains of the patient with RTT in a previous study (8).

To our knowledge, this is the first RTT case with an exon 1 mutation reported from Asia. We found this patient among the four Japanese patients with RTT who were analysed (detection rate 25%), two of whom showed mutations in a transcriptional-repression domain (TRD) region of MECP2, suggesting that patients with exon 1 mutations may be more common than those previously reported. Out of the seven reported patients with RTT with mutations within the exon 1 [reviewed by Bartholdi et al. (5)] and one patient described here, six patients (75%) show a relatively more severe, classic RTT phenotype. This is probably because the mutations cause disruption of the N-terminus, resulting in early truncation of the brain-dominant type transcript (MeCP2_e1), and because the disruption ablates not only MeCP2_e1 translation but also MeCP2_e2 translation (9). Angelman syndrome (AS) is an epigenetic disease that is molecularly overlapped with RTT (10), and a subset of patients with AS has shown mutations in the exons 3 and 4 (11), suggesting that some other patients with AS possibly have mutations in the exon 1. These data indicate that the analysis of mutations in the newly annotated exon 1 represents a new opportunity to improve our clinical understanding of the RTT phenotype.
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References


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