Letter to the Editor

Mutations found within exon 1 of MECP2 in Danish patients with Rett syndrome

To the Editor:

Rett syndrome (RTT; MIM 312750) is a neuro-developmental disorder almost exclusively diagnosed in females. From the age of 6–18 months, affected persons suffer a gradual reduction of acquired purposeful hand use and speech, accompanied by delay in head growth and temporary loss of contact, manual and gait dyspraxia, seizures and respiratory dysfunction. Repetitive, stereotyped hand movements appear and are a hallmark of the disease (1).

In 1999, mutations in the X-linked gene methyl-CpG-binding protein 2 (MECP2; MIM 300005) were first reported in RTT patients (2). MECP2 consists of four exons (3). Originally, MECP2 was thought to produce only one transcript including all four exons with a translation start site in exon 2 (MeCP2_e2). Two recent studies have identified an alternatively spliced transcript consisting of exons 1, 3 and 4 leading to the new MeCP2_e1 isoform (4, 5). A classic RTT patient with a mutation within exon 1 was also described (4). The MeCP2_e1 protein appears to be the predominant isoform in the human brain (4, 5).

About 85% of the classic RTT patients harbor a de novo mutation in the coding region of exon 3 or 4 of MECP2 or large genomic rearrangements (6). In contrast, no mutations specific to exon 2 have been identified. Since exon 1 has been considered to be a non-coding exon, it has not been incorporated in the normal DNA screening for RTT.

Evans et al. (7) sequenced exon 1 from 97 RTT patients, who had previously been tested for MECP2 mutations in exons 2–4. Their results were negative and they concluded that mutations in this exon are not common.

The findings of the new MECP2 transcript led us to look for mutations in exon 1 in the Danish patient group.

We identified two mutations in a group of 10 Danish RTT patients by direct sequencing of exon 1 and the promoter region of MECP2. The 10 patients had previously been tested negative for mutations, first by direct sequencing of MECP2 exons 2, 3 and 4 and second by multiplex ligation-dependent probe amplification technique of all four exons.

Patient 1 was a female, born in 1977, diagnosed with classic RTT in 1987 and died in 2002. We identified a novel duplication of 5 bp (CGCCG) in the open-reading frame of exon 1. The mutation, c.23_27dupCGCCG, causes a frameshift, introducing a stop codon downstream after 44 missense amino acids (p.Ser10ArgfsX45) (Fig. 1b). The mutation was not detected in DNA from the parents.

Patient 2 is a female, born in 1968 and diagnosed with classic RTT in 1987. Sequencing analysis showed an 11 bp deletion, c.47_57del. The mutation creates a frameshift and a premature stop codon (p.Gly16GlufsX22) (Fig. 1c). Neither of the parents harbor the mutation.

Thus far, only one mutation within exon 1 has been reported (4). It is noteworthy that this mutation is identical with the mutation we found in patient 2. Two additional classic RTT patients have been reported with deletions of exon 1, or involving both exons 1 and 2, respectively (4, 8). Recently, we have found a deletion covering exons 1 and 2 in a third classic RTT patient (9). As exon 2 mutations have never been reported to solely cause RTT, this strengthens the hypothesis that loss of MeCP2_e1 is sufficient to cause classic RTT and an intact MeCP2_e2 is not capable of compensating for this loss.

Of 69 patients with classic RTT in Denmark, 60 harbor mutations in exon 3 or 4, and an additional four patients have been identified with large deletions that cover both exons 3 and 4. With our new findings of two exon 1 mutations, the overall mutation detection rate in this group is 96% (66/69). 9% of the mutations in our subgroup of classic patients would not have been found by conventional sequencing of exons 2, 3 and 4.

Mutations in exon 1 may be more common than previously reported, but may be restricted
to the classic RTT phenotype. Our findings emphasize the importance of mutation screening of exon 1 in classic RTT patients who do not have mutations in exons 2–4.

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References


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