Clinical Variability in Rett Syndrome

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ABSTRACT

The clinical variability of Rett syndrome, associated with mutations in the MECP2 gene, varies from classically symptomatic female patients to asymptomatic female patients, and male patients who have none of the diagnostic features considered pathognomonic of this disease. Multiple factors contribute to this variability. In our studies, mutations closer to the amino-terminus, prior to amino acid 255, led to severe clinical manifestations, such as inability to walk, severe dysphagia, and urinary organic acid abnormalities, compared with mutations toward the carboxyl-terminus. However, we found no correlation between severity and mutation type (missense versus nonsense). Despite the importance of mutation location to clinical severity, the widely varying severity within the same mutation suggests that in females, X-chromosome inactivation or other epigenetic phenomena also have roles in determining severity. We propose that stages 1 and 2 of the disease are a consequence of failed, time-linked, postnatal expression of MeCP2 in cerebellar neurons. This, in association with glutamate N-methyl-D-aspartate receptor-mediated neuroexcitotoxic injury to the differentiating neurons, results in the transient age-specific autistic-like behavior, motor, and cognitive dysfunction associated with these stages. (J Child Neurol 2003;18:662–668).

The neurologic manifestations of microcephaly, seizures, severe mental retardation, respiratory irregularities, stereotyped behaviors, and the four clinical stages of Rett syndrome are now well known. In 70 to 80% of patients, these clinical signs are found to be associated with mutations in the MECP2 gene located in the chromosome Xq28 region. As shown in Figure 1, Rett syndrome differs from other neurodegenerative disorders in not having a progressive, downhill course leading to death but instead having a single period of regression in infancy and early childhood. This regression is characterized by developmental arrest, loss of language skills, and transient autistic-like behaviors such as poor eye contact, reduced sleep, and irritability. Subsequently, there is recovery of social interaction, with amelioration of these symptoms and stabilization of the clinical

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Figure 1. Schematic representation of the natural history Rett syndrome compared with other neurologic disorders.
progression (Figure 2). The four stages of the disease are not easily explained, nor is the function of MeCP2 understood, apart from its role as a transcription repressor. Also, the timing of MeCP2 expression in neuronal development is not clear, nor is it clear which genes are subject to repression by MeCP2.

Despite the growing knowledge of Rett syndrome genotypes, fundamental issues about the fluctuating clinical course and phenotypic variability remain unclear, the most salient of which is the limited correlation between MeCP2 mutations and clinical features such as preserved speech variant or unaffected carriers. In addition, 20 to 30% of patients with the phenotype of Rett syndrome fail to demonstrate mutations in MECP2. This would indicate that mutations can be present in regions of the gene that are not usually surveyed, such as regulatory elements and non-coding regions, there is genetic heterogeneity, or there is somatic mosaicism. Surprisingly, the male patients reported with mutations in MECP2 do not match the clinical features commonly seen in their female counterparts.

Recent studies demonstrate that there is increasing expression of MeCP2 in neurons as they become more differentiated, suggesting that MeCP2 functions in launching or maintaining neuronal maturation. This notion is well supported, especially by the recently reported studies in wild-type rodent olfactory receptor neurons, in which MeCP2 expression correlates with neuronal maturation immediately preceding synaptogenesis. The clinical stages and variability in Rett syndrome are the outcome of diverse factors, most importantly the spatiotemporal expression of MeCP2 in brain, type of MECP2 mutation, X-chromosome inactivation status, and the genetic background of the individual. Environmental influences on normal and abnormal MeCP2 function are unknown. Skewed X-chromosome inactivation is a factor in many asymptomatic to mildly affected carrier females, who are invariably the source of familial cases of Rett syndrome and give birth to both affected male and female children. The most striking example of skewed X-chromosome inactivation is in the discordant monozygotic twins reported by Hoffbauer et al., both of whom carried a heterozygous 1160(del26) deletion not detected in the parents. Quantitative X-chromosome inactivation studies showed an X-chromosome inactivation ratio in the peripheral blood of 98:1 in the unaffected twin but 40:60 in the affected twin. Recognizing that various known and unknown factors alter the phenotype, we have devised a clinical severity scale that in part correlates with the genotype. Similar correlations have been described previously.

Our recent observations are shown below in Tables 1, 2, and 3. We also present a theory for the biologic basis of stages 1 and 2 of the disease.

**EXPLAINING STAGES 1 AND 2 OF RETT SYNDROME**

The significant change in behavior, designated as stage 2 in the natural history of the disease, occurs in the previously apathetic, developmentally marginal, hypotonic infant (stage 1), swiftly prompting medical attention between the ages of 10 months and 2 years. Although numerous studies have pointed to striking developmental irregularities in early infancy, most importantly in the deceleration of head circumference beginning at 2 to 4 months of life, many of the subtle signs of developmental lag or abnormal posturing are underplayed or unrecognized until stage 2. The child with Rett syndrome is symptomatic at birth, but, because there are no overt signs such as seizures or irritability, there is little concern. Because stage 2 of the disease brings about noticeable behavioral and clinical changes, including onset of seizures, autistic-like features,
Table 1. MECP2 Mutations in 20 Patients With Rett Syndrome and Urine Organic Acids

<table>
<thead>
<tr>
<th>MECP2 Mutations</th>
<th>Increased Levels (n = 8/20)</th>
<th>Organic Acids</th>
<th>Normal Levels (n = 12/20)</th>
<th>Medications</th>
<th>N</th>
<th>Age (yr)</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>R106W</td>
<td>1</td>
<td>5</td>
<td>2KG; Fum; 2EHA</td>
<td>Valproate</td>
<td>1</td>
<td>6</td>
<td>Lam/Valproate</td>
</tr>
<tr>
<td>T158M</td>
<td>3</td>
<td>3</td>
<td>2KG; 3MGc</td>
<td>Topiramide</td>
<td>1</td>
<td>3</td>
<td>Lam/Valproate</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td></td>
<td>Fum; Glut; 4-hydroxyphenylactic acid</td>
<td></td>
<td>1</td>
<td>5</td>
<td>Lam/Valproate</td>
</tr>
<tr>
<td>R168X</td>
<td>1</td>
<td>1</td>
<td>Lactate; 3MGc; Fum</td>
<td></td>
<td></td>
<td></td>
<td>Topiramide</td>
</tr>
<tr>
<td>R255X</td>
<td>1</td>
<td>3</td>
<td>2KG; glycerophosphate; lactate</td>
<td></td>
<td>1</td>
<td>3</td>
<td>Topiramide</td>
</tr>
<tr>
<td>796del(1)</td>
<td>1</td>
<td>2</td>
<td>2KG</td>
<td></td>
<td>1</td>
<td>3</td>
<td>Topiramide</td>
</tr>
<tr>
<td>806del(6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>3</td>
<td>Lam/Valproate</td>
</tr>
<tr>
<td>R270X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>3</td>
<td>Lam/Valproate</td>
</tr>
<tr>
<td>R294X</td>
<td>1</td>
<td>3</td>
<td>3HB; 3HV; Fum; Glut</td>
<td></td>
<td>1</td>
<td>3</td>
<td>Lam/Valproate</td>
</tr>
<tr>
<td>R306C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>3</td>
<td>Lam/Valproate</td>
</tr>
<tr>
<td>1010del(191)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>3</td>
<td>Lam/Valproate</td>
</tr>
<tr>
<td>1161del(6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>3</td>
<td>Lam/Valproate</td>
</tr>
<tr>
<td>1163del(26)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>3</td>
<td>Lam/Valproate</td>
</tr>
</tbody>
</table>

CBZ = carbamazepine; 2EHA = 2-ethylhexadecylate; Fum = fumarate; Glut = glutarate; 3HB = 3-hydroxyisobutyrate; 3HV = 3-hydroxyisovalerate; 2KG = 2-ketoglutarate; Lam = lamotrigine; 3MGc = 3-methylglutacoxylate; Topir = Topiramate; Valp = Valproate.

failed language, tremulousness, sleep disturbance, and irritability, this stage often leads to consideration of autism or a neurodegenerative process, resulting in multiple biochemical and neuroimaging tests.

Bauman and Kemper demonstrated diffuse alterations in neuronal morphology, suggesting that the changes caused by MeCP2 abnormalities were not cell autonomous. They also noted a simplified inferior olive nucleus in the post-mortem brain stem of female patients with Rett syndrome, indicating prenatal onset of modified and disrupted neuronal architecture. The inferior olivary nucleus is intimately connected to deep cerebellar nuclei and Purkinje cells, which, in turn, directly or indirectly influence medullary, pontine, midbrain, and cortical activity. These prenatal deficits in the brain stem and deeper layers of cortex likely contribute to the behavioral changes seen in stage 1. Of interest is the finding that the head circumference is normal at birth. However, because of the demand for postnatal dendritic arborization and activity-dependent synaptic proliferation and pruning, early deceleration of head growth ensues when MeCP2-deficient cortical neurons fail to mature.

The temporal differences in the onset of MeCP2 expression in rodent cerebellum for Purkinje cells (first postnatal week) and in granule cells (fourth postnatal week), reported in this issue by Johnston et al., suggest a link between the developmental time course of MeCP2 expression in the cerebellum and the onset of neuromotor and behavioral changes manifested in stages 1 and 2 of the disease. MeCP2 expression occurs during a critical period when synaptic connections are being established among cerebellar neurons, then from cerebellar neurons to brainstem structures, and, ultimately, to cerebral cortical regions. The cerebellum plays a critical role in language, motor, and cognitive development and also exhibits pathologic involvement in autism. Subjects with autism demonstrate visuospatial attention deficits, multisensory modulation defects, arrested language development, and stereotyped behaviors much like subjects with Rett syndrome, particularly in stage 2. Cerebellar pathologic is described in patients. Therefore, the apathy, hypotonia, and autistic phase of stages 1 and 2 could reflect an age-sensitive epoch of MeCP2 malfunction in cerebellar Purkinje and granule cells within the complex cerebellar circuitry, affecting cortical and brainstem motor and cognitive activities during this period. The subsequent failure of MeCP2 expression in granule cells to the existing Purkinje, brain stem, and cortical neuronal abnormalities would initiate the changes from stage 1 to stage 2 with the precipitous shift in clinical manifestations.

The aberrant overexpression of glutamate N-methyl-D-aspartate (NMDA) receptors noted in frontal cortex in this younger age group could augment the encephalopathic clinical state in stage 2. The excitotoxicity caused by an upsurge of NMDA receptors in the developing brain could indeed be a trigger for abnormal electroencephalograms and ictal

Table 2. MECP2 Mutations in 80 Patients With Rett Syndrome and Clinical Correlates

<table>
<thead>
<tr>
<th>Mutation (n)</th>
<th>Microcephaly (%)</th>
<th>Not Walking (%)</th>
<th>Seizures (%)</th>
<th>Scoliosis (%)</th>
<th>Hyperventilation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R106W (10)</td>
<td>100</td>
<td>50</td>
<td>30</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>R133C (3)</td>
<td>67</td>
<td>1</td>
<td>100</td>
<td>22</td>
<td>100</td>
</tr>
<tr>
<td>T158M (17)</td>
<td>94</td>
<td>53</td>
<td>41</td>
<td>53</td>
<td>76</td>
</tr>
<tr>
<td>R168X (14)</td>
<td>100</td>
<td>71</td>
<td>50</td>
<td>21</td>
<td>79</td>
</tr>
<tr>
<td>R255X (7)</td>
<td>86</td>
<td>57</td>
<td>29</td>
<td>29</td>
<td>43</td>
</tr>
<tr>
<td>R294X (9)</td>
<td>100</td>
<td>44</td>
<td>44</td>
<td>22</td>
<td>67</td>
</tr>
<tr>
<td>R306X (11)</td>
<td>82</td>
<td>18</td>
<td>27</td>
<td>18</td>
<td>36</td>
</tr>
</tbody>
</table>

100% = maximum severity; 0% = absence of finding.
Table 3. MECP2 Mutations in 37 Patients With Rett Syndrome and Gastrointestinal Dysfunction

<table>
<thead>
<tr>
<th>MeCP2 Mutations</th>
<th>n (N = 37)</th>
<th>Age/Age Range</th>
<th>Reflux</th>
<th>Constipation</th>
<th>Failure to Thrive</th>
<th>Dysphagia</th>
</tr>
</thead>
<tbody>
<tr>
<td>R106Q</td>
<td>1</td>
<td>8 yr</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>R106W</td>
<td>1</td>
<td>4 yr</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>T168M</td>
<td>3</td>
<td>4–7 yr</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>R168X</td>
<td>6</td>
<td>2–16 yr</td>
<td>2</td>
<td>5</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>R255X</td>
<td>4</td>
<td>3.5–11 yr</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>796del(1)</td>
<td>1</td>
<td>4 yr</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>807delC</td>
<td>1</td>
<td>3.5 yr</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>R270X</td>
<td>5</td>
<td>3.5–10 yr</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>R294X</td>
<td>2</td>
<td>4–13 yr</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>R306C</td>
<td>2</td>
<td>4–5 yr</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1161del(6)</td>
<td>1</td>
<td>4 yr</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Negative</td>
<td>10</td>
<td>3–15 yr</td>
<td>1</td>
<td>4</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

activity in stage 2, which later subsides with age when the NMDA receptor expression is reduced. Such neuronal hyperexcitability affecting cerebellar granule cell, mossy fiber, and Purkinje cell synapses could account for the tremulousness and gait disturbance that become obvious in stage 2.

**BIOCHEMICAL DEFECTS IN RETT SYNDROME**

A wide variety of tests to demonstrate a single consistent biochemical abnormality in Rett syndrome have not been informative. There have been, however, frequent reports of biochemical or histologic evidence of mitochondrial involvement in this disorder, and attempts to identify an abnormality in the mitochondrial genome were not fruitful. We examined urine organic acids by quantitative gas chromatographic mass spectrometry for evidence of mitochondrial involvement. Of the 20 patients we tested with known mutations in the MECP2 gene (see Table 1), 8 had increased levels of urine organic acids in patterns characteristic of mitochondrial disease. Although blood lactate was not elevated, sampling was random and not optimized for detecting the milder degrees of lactic acidosis. The urinary organic acid patterns found were nonspecific with regard to the type of mitochondrial abnormality but were general markers for either primarily or secondarily (e.g., redox abnormality) disturbed mitochondrial substrate transport.

In this cohort, we noted that patients with lesions at or preceding amino acid 255 were more likely to have urine organic acid abnormalities (\( P < .005 \)) than those with mutations after this region. Although older subjects were not tested, we noted that among patients less than 10 years of age, neither age nor anticonvulsant medications correlated with the urinary organic acid abnormalities. The physiologic basis for these changes remains speculative, and the occurrence of patients with similar mutations with and without urine organic acid abnormalities could reflect the effects of skewed X-chromosome inactivation. Nevertheless, understanding these biochemical phenomena awaits clarification of as yet poorly understood epigenetic influences, the specific genes that MeCP2 affects, and the timing of its influence. Until then, the presence of urinary organic acid abnormalities that suggest mitochondrial dysfunction should not misdirect the diagnostic search or treatment for a primary mitochondrial disorder in patients with a phenotype of Rett syndrome.

**MOLECULAR CORRELATES OF CLINICAL FEATURES**

We evaluated the correlation of clinical features to eight common types of molecular defects in the MECP2 gene among 80 female subjects with Rett syndrome aged 1 to 32 years (mean age 13 years). We noted more severe clinical deficits in walking (\( P = .05 \)) in patients with mutations proximal to and including amino acid 255, as shown in Table 2. However, all three patients with the R133C mutation did not have gait difficulty, although the number of subjects was small. Those subjects with mutations in amino acid 255 and beyond the transcription repressor domain had a similar degree of microcephaly, but other parameters showed lesser involvement, especially mutations toward the distal end (e.g., R306C).

We analyzed the relative frequency of five specific phenotypic features of Rett syndrome (see Table 2), for which we have established severity scales—namely, microcephaly, inability to walk, seizures, scoliosis, and hyperventilation—in different types of MECP2 mutations. Inability to walk was the most discriminating clinical feature with regard to mutation location. Contingency table analyses demonstrate that a higher proportion of individuals with mutations proximal to amino acid 255 in the transcription repressor domain are unable to walk (\( P = .068 \)) compared with individuals with more distal mutations. If subjects with the milder R133C missense mutation are removed from the analyses, however, this difference becomes significant (\( P = .049 \)). Similar results are obtained when subjects with transcription repressor domain-located nonsense mutations (R255X, R270X, R294X = 11/14) are contrasted with the more distally located missense mutation (R306 = 2/11; \( P = .059 \)). Among our patients, deletions in MECP2 were all located in the distal portion, and such lesions were noted as single occurrences; therefore, they were not included in the analysis. However, a higher number of patients with deletions manifest milder signs and present more often as atypical cases. More significant differences between the eight mutation types might be
detected if clinical severity is correlated with the levels of normal MeCP2 protein rather than DNA mutation patterns—emphasizing the need for such analyses.

Patients with Rett syndrome have significant autonomic involvement resulting in gastrointestinal abnormalities and peripheral vasomotor instability.69-71 The gastrointestinal manifestations include (1) constipation, (2) reflux, (3) dysphagia, and (4) failure to thrive. To determine if these gastrointestinal features could be genotype dependent, we evaluated 37 girls with the phenotype of Rett syndrome (ages 3–15 years; mean age 7.4 years), of whom 27 had identifiable mutations in MeCP2 and 10 were negative, as shown in Table 3. Mutation-positive patients had a wide distribution of mutations throughout exons 3 and 4 of the MECP2 gene. All except one of these mutation-positive patients manifested varying degrees of gastrointestinal dysphagia requiring medical intervention. Interestingly, the one patient without gastrointestinal symptoms had a deletion (1161del(6)) involving the most distal part of the coding region. Patients with more proximal mutations had a greater number of gastrointestinal problems. The more severe oropharyngeal dysphagia correlated well (P < .05) with mutations (R106Q, T158M, and R168X) affecting the proximal portion of the protein, suggesting that girls with mutations in that portion of the gene could be predisposed to considerable neuroenteric dysfunction.72 Hoffbuhr et al noted a similar association between proximal MECP2 mutations and severity of neurologic symptoms in Rett syndrome, in particular, the velocity of head growth.73,74 Severe gastrointestinal manifestations, such as dysphagia requiring early gastrostomies, occur in patients with mutations affecting the proximal portions of the gene. Such mutations must cause more severe brainstem neuronal involvement, in addition to the generalized autonomic dysfunction that contributes to reflux and constipation.

**DISCUSSION**

The clinical course of the Rett syndrome phenotype is marked by a bewildering deterioration in infancy, termed stage 2, that resembles autism. The underpinnings of this phase of the disease are poorly understood because it differs from other degenerative processes of the nervous system, a schematic representation of which is shown in Figures 1 and 2. Interestingly, Bauman et al reported that the inferior olivary nucleus in the postmortem brainstem of girls with Rett syndrome was simplified. These results indicate early changes in a brainstem structure that has important links between cerebellum and cortical thalamic pathways.75 Because the normal undulations of the inferior olivary nucleus develop between 28 and 32 weeks, the morphologic changes in the inferior olivary nucleus likely occur prior to 32 weeks' gestation.76 Such prenatal involvement of neurons could account for stage 1 of early infancy in Rett syndrome.

The collective changes observed in stage 2, namely, the pathognomonic clinical features, autoradiographic evidence of transient increased glutamate/NMDA receptors in the postmortem brain of young patients with Rett syndrome (see Figure 2), mitochondrial abnormalities, and period of postnatal MeCP2 expression in wild-type murine cerebellar granule cells, suggest a time-sensitive impact of MeCP2 dysfunction on cortical and cerebellar neurons resulting in stage-specific postnatal clinical signs and symptoms. NMDA receptor-dependent activation of cyclic adenosine monophosphate-responsive element binding protein, an important transcription factor for cell differentiation, is required for survival of cerebellar granule cells.77-79 The overexpression of NMDA glutamate receptors found in the cortical regions might be an attempt to increase neuronal viability. Such compensatory increases in NMDA receptors could cause excitotoxic injury and have an adverse effect on differentiating neurons in the postnatal cerebellum. In addition, NMDA receptor activation increases intracellular free calcium, resulting in calcium loading of mitochondria that would increase oxidative damage to these vulnerable cells.80 Such effects on other organs could account for the abnormal urinary organic acids. Alternatively, and perhaps more likely in view of the systemic nature of the mitochondrial abnormalities, down-regulation of mitochondrial function could be a specific effect of MeCP2 dysfunction. According to the Henneberry hypothesis, such impairment of mitochondrial function would increase the likelihood of NMDA-mediated neuronal injury.81 Whether mitochondrial dysfunction is a primary or secondary consequence of impaired MeCP2 activity, the presence of mitochondrial abnormalities in the more severely affected patients with Rett syndrome has important implications for therapy in patients identified in the early stages. Conversely, it is important to recognize that some patients between the ages of 1 and 2 years with primary mitochondrial disease (and normal MeCP2) regress in a manner that closely parallels stage 2 of Rett syndrome. This seems to be especially common in children with the mild form of mitochondrial complex I deficiency. However, such children with primary mitochondrial defects usually do not lose purposeful hand use (R. Kelley, unpublished observations).

Understanding the time course and biologic basis of these age-specific effects, shown in Figure 2, is essential for distinguishing the ontogenetic expression of MeCP2 and appropriate medical management of patients with Rett syndrome. Recent reports of cyclooxygenase-2 inhibition in the rescue of cerebellar granule cells from glutamate-mediated cell death and contributions of transplanted bone marrow and embryonic cerebellar cells in regeneration of cerebellar cells and their connections are provocative.82-84

Mutations in MECP2 manifest substantial clinical variability. Since the announcement of an association of MECP2 mutations with Rett syndrome, there has been a spate of information, with some opposing views regarding genotype–phenotype correlations.85-88 Our analysis of the clinical features in female patients with Rett syndrome suggests a gradation of clinical severity, with more severe signs when mutations precede the proximal part of the transcription repressor domain—up to amino acid 255 compared with lesions distal to this region—regardless of
whether they result in truncations, missense mutations, or deletions. The milder cases have been termed "atypical" because of absence of deceleration of brain growth, preservation of speech, purposeful use of hands, or ability to walk. Most of these subjects have also been shown to have mutations in the distal portions of the gene. Similar correlations are found in our study of urine organic acids (see Table 1) and gastrointestinal disturbances (see Table 3). Mutations in the amino-terminal correlate significantly with a more severe clinical presentation compared with those closer to the carboxyl-terminal of MeCP2.

The affinity with which MeCP2 binds methylated DNA has been measured.23 Relative to wild-type MeCP2, proteins with missense mutations causing substitutions in the methyl-binding domain—R106W, R133C, and F155S—have a 100-fold or more reduction in binding affinity to methylated DNA. However, T158M, a mutant also in the methyl-binding domain region, showed only 2-fold impairment. In a separate study, functional analyses of MeCP2 mutations in transient expression systems24 showed responses similar to those above. An exception was R133C, which retained the same function as normal MeCP2; thus, this result contrasts with the binding affinity studies. The complexity of correlating clinical severity and genotype is further highlighted by considering these in vitro observations to the patients with T158M mutations, who were as severely affected as those with the R106W mutation (see Table 2). We conclude that more complex mechanisms affecting not just individual neurons but cell-cell interaction, the number of normal cells within a functional unit, genetic background, and the type of MECP2 mutation must influence the phenotype.

A significant degree of clinical variability could result from nonrandom X-chromosome inactivation patterns, where favoring the normal X chromosome would result in unaffected or minimally affected carrier female subjects. Some of these individuals were identified because of a recurrence of Rett syndrome in their offspring.13,14,17,24 Individuals with germline mosaicism would be asymptomatic but capable of transmitting the disease and, unfortunately, would be difficult to identify because other tissues might not reflect the mutation.14,60 Therefore, when a child with a mutation in MECP2 has been identified, it is important to consider prenatal testing for subsequent pregnancies in the mother, even when a mutation in MECP2 is not identified in her DNA.55,56

References


