Will my Rett syndrome patient walk, talk, and use her hands?

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First recognized by Andreas Rett in 1966 and rediscovered in 1983,[1] Rett syndrome (RS) is among the most common causes of mental retardation, affecting upwards of 1 in 10,000 girls. Extensive clinical characterization has revealed a distinctive clinical entity. Stereotypic almost constant hand-rubbing in wakefulness is its most recognizable symptom. Social anxiety akin to autism is another. The latter increases the former, and the girls appear as though they are, and perhaps they truly are, wringing their hands in anxiety, hence the use of the term hand-wringing. The disease begins in mid-infancy with decelerating head growth after a period of normal development. The neurologic regression starts between 6 and 36 months with developmental arrest, and loss of or reduction in hand use, speech, and communication skills, and social interest. Additional features include a typical pattern of disease progression with the regression reaching a plateau and not progressing further, in contradistinction to other neurodegenerative diseases, and autonomic abnormalities including irregular breathing and cold blue extremities.[2]

RS is caused by mutations in the X-linked *MECP2* gene, which encodes the methyl-CpG binding protein 2 transcription repressor.[3,4] More than 200 different mutations have been reported but over 70% of cases are due to four missense mutations (R106W, R133C, T158M, R306C), four nonsense protein-truncating mutations (R168X, R255X, R270X, R294X), large deletions destroying most of the gene, and a cluster of mutations near the end of the gene that abrogate only the very end of the protein (c-terminal truncations). The MECP2 protein has three major functional regions, a methylated DNA binding domain (MBD), a transcription repression domain (TRD), and a nuclear localization signal (NLS). The c-truncation mutations are distal to all three of these domains and produce a protein still possessing these important active sites (figure). More than 10 RS genotype-phenotype correlation studies have been published. Some found no significant phenotypic differences. Others reported group differences: girls with missense mutations and c-terminal truncations were milder than those with early truncations.[5,6] One study was sufficiently powered, 100 cases, to allow comparisons of the phenotypes associated with individual common mutations with the rest of the cohort.[7]

In the current issue of *Neurology*®, Neul et al.[8] rigorously phenotype 200 cases using an elaborate quantitative rating system covering 13 separate RS features. This allows them to directly compare the phenotypes associated with each individual common mutation. This impressive body of work is designed to maximally tease out phenotypic variance specific to each of the common mutations, and it does. In their tables one can see trends toward greater likelihood of ambulation, hand use, and speech with some of the mutations compared to others. However, strikingly, the major conclusion one draws from the work is that there is in fact very little difference in the phenotypes associated with the common RS genotypes, and that RS due to common mutations is a highly unvarying disorder. What statistically significant differences Neul et al. do find had been noted in previous studies,[5-7] but now become firmly established. They find that patients with missense mutation R133C, truncating mutation R294X (which spares the MBD, NLS, and most of the TRD), or c-terminal truncation mutations are statistically significantly more likely to walk and have purposeful hand use and some speech (usually no more than short phrases) than patients with R168X (which spares the MBD but deletes the NLS and TRD) or with large deletion mutations (figure). Patients with other common mutations, i.e., the majority of patients, are not

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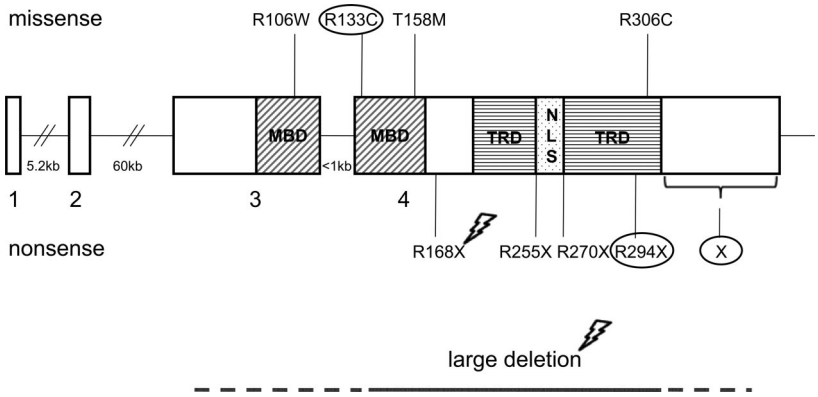
Figure Structure and common Rett syndrome mutations of the *MECP2* gene



The gene's four exons are numbered. MBD = methylated DNA binding domain; TRD = transcription repression domain; NLS = nuclear localization signal; X = location of the group of c-terminal truncation mutations; bar with dashed ends = group of large-deletion mutations that delete at least the fourth exon; circled mutations = associated with mild phenotype; flash symbol = mutations associated with severe phenotype.

significantly different from either the mild or the severe groups.

The authors of the present study conclude that we are now better able to counsel families of patients with RS. Indeed through their study we now have much improved prognostic knowledge. We know what to expect with each mutation, on average. But we still cannot predict whether a particular child with a severe mutation, e.g., R168X, will turn out to be among the 80% in that group who cannot walk, or the 20% who can, or whether a girl with a mild mutation, e.g., R133C, will be in the 50% of her group who can speak or the 50% who cannot. The intragroup differences may be due to genetic factors, e.g., the degree of X-inactivation skewing in the CNS and modifier genes, which cannot be altered, or they may be mainly due to behavioral interventions such as physiotherapy and speech therapy, which can. The Neul et al. study was not designed to measure the kind and amount of therapies each patient received and therefore cannot tell us whether, e.g., walkers in the severe group walk because they received intensive physiotherapy. Ultimately, families want to know what they can do for their children. The Neul et al. study is the end of the beginning of our ability to tell them.

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