Mutations in the C-terminus of CDKL5: proceed with caution. European Journal of Human Genetics 2013.

This study from France looks at mutations affecting the last 3 exons (19 - 21) of the CDKL5 gene. The authors investigated 30 female patients with a clinically heterogeneous phenotype, ranging from nonspecific mental retardation to a severe neonatal encephalopathy. They were all screened for CDKL5 mutations which 2 were found to have. The first was a 2 year old girl who had severe encephalopathy with severe developmental delay, and seizures with apneas that started at the age of 3 months. She had a previously unreported mutation affecting exon 20. The second was an 11 year old female who presented with moderate developmental delay, intellectual disability, speech delay and a number of other features. She was found to have a mutation in exon 21 that had previously been reported.

In each case parental screening identified that the asymptomatic father of each female also carried the same mutation. The 11 year old was subsequently found to have a deletion involving the SOX5 gene on chromosome 12. The authors also review the literature where mutations affecting exons 19 - 21 have been reported. Their interpretation of these cases lead them to discuss the possibility that mutations in this region of the CDKL5 gene may not be pathogenic. The authors therefore suggest that screening for mutations in exons 19 - 21, and specifically after codon 938, may not be useful in establishing a diagnosis of atypical Rett syndrome.

Note - a nice little study validating the previous paper from Williamson (below) suggesting that the main CDKL5 protein in the human brain is translated from exons 2 - 18 and part of intron 18. I just wish they had said a CDKL5 disorder instead of atypical Rett syndrome!