CDKL5 in different atypical Rett syndrome variants:
Description of the first eight cases from Spain.
Journal of Pediatric Epilepsy 2012.

This study is from the Saint Joan de Deu Children's Hospital in Barcelona. Over a 26 year period, 408 patients were diagnosed with classical or variant Retts. There were 258 children identified who had mutations of the MECP2 gene. Of the remaining 150 without a genetic diagnosis, testing for CDKL5 mutations was offered to 53 girls and 9 boys who had either early epilepsy, polymorphic seizures or drug-resistant seizures. They found 8 (15%) of the girls, but none of the boys, had novel pathogenic mutations of the CDKL5 gene. There were variations in the phenotypes of the 8 children, compared to those described in other studies and which have been taken to be characteristic of CDKL5. For instance, the 3 stages of epilepsy as described by Bahi-Buisson were not observed, with only 4 children developing seizures within the first few months of life. There were 3 who developed their seizures at 11 months, 2 and 3 years of age and 1 who did not appear to have developed seizures at all. There were 2 children who regained some speech having previously lost it. The authors report some association between the severity of the phenotype and the location of the mutation with the more severely affected having a mutation at the proximal region of the gene. The authors conclude that testing for CDKL5 must be mandatory in patients with Rett syndrome and early epilepsy, in those with epileptic encephalopathy with onset in the first year of life as well as in those with classical or variant Retts without an identifiable MECP2 gene mutation.

Note - This article clearly throws a slight spanner in the works in that some variation is introduced into what, up to now, have been considered fairy constant characteristics of children with CDKL5, particularly in relation to the presence of early seizures. It therefore at least raises the possibility that the spectrum of CDKL5 phenotypes may be broader than first thought. This issue of the Journal also has an editorial by Jeffrey Neul from the Texas Children's Hospital, which includes a short review of this article. He concludes that perhaps CDKL5 should now be recognised as a distinct clinical disorder with specific unique characteristics rather than as a variant of Rett syndrome, and that not to do so might be a disservice to both clinical medicine and to those with the condition. Bravo!

Further Note - A subsequent Letter to the Editor regarding this article has pointed out that one of the described mutations, which affects almost the very end of the C-terminal domain, may only have "minimal" clinical effect. This is because a mutation at this site (which is in exon 20) affects that part of the CDKL5 gene which is not used to make the particular form of the protein that may be relevant in CDKL5 disorders (see last paper above). This may explain some of the variation in presentation described in the paper, in that the individual with this mutation may not in fact have a CDKL5 related disorder. The plot thickens!!!