Genes of Early-Onset Epileptic Encephalopathies: From Genotype to Phenotype. Paediatric Neurology 2012.

This is a review of genetic disorders associated with early-onset epileptic encephalopathies and the associated phenotypes, including CDKL5. The authors report that to-date 53 pathologic mutations of CDKL5 have been reported consisting of 12 missense, 4 nonsense, 8 splice-site, 22 deletions and 7 frameshift mutations. They state that no correlation has been established between the site of mutation and clinical severity and then go on to discuss a more severe epileptic encephalopathy as described by Bahi-Buisson et al. They review the 3 stages of epilepsy in CDKL5as described by Bahi-Buisson et al and the EEG findings as described in studies by Pintaudi et al and Melani et al.

Note - A good review article although a lot of information to digest. There also seems to be some ambiguity here about what is known so far about the site of mutation and the severity of the phenotype. This paper states that there is no correlation between severity and site of mutation (giving references), but then refers to the study by Bahi-Buisson which suggests that there may be. This is the ambiguity I can't quite sort out - the CDKL5 gene has been designated Online Mendelian Inheritance in Man OMIM® no. *300203 (the * indicates that this designation applies to the gene and its mutations) and it is to this designation that there is said to be no relation between site and severity.

However, there is also another designation, OMIM® #300672 which is a descriptive designation for a phenotype (indicated by the #) and refers to a more severe form of epileptic encephalopathy also associated with CDKL5 -and which according to the study by Bahi-Busson has a phenotype that may well be related to the site of mutation. If the genetic basis for both designations lies within the CDKL5 gene, why have 2 designations or are they being considered as distinct entities? There must be a straight-forward answer here but for now this remains slightly confusing (to me at least) and although I contacted OMIM® to clarify this, I am not sure that I am any the wiser for the response (I would be grateful for clarification from anybody!!) Clearly, the bottom line is that more children with CDKL5 mutations need to be studied to understand the relationship between site of mutation and severity of phenotype, and ultimately, severity will probably depend on several factors, and not just the site of mutation.