Recurrent mutations in the CDKL5 gene: Genotype-phenotype relationship. American Journal of Medical Genetics 2012.

This study from France looks at whether there is a relationship between mutation and severity of phenotype. A total of 26 CDKL5 mutations were identified in 358 unrelated females who had been referred with encephalopathy and early seizures. Most of these mutations were unique but 8 were recurrent mutations that had previously been described in other studies (including studies published by this group). By studying females with recurrent mutations in both this study and those from previous studies, the authors have drawn some conclusions about the relationship between site of mutation and severity of phenotype. They looked at mutations occurring in 3 particular areas of the CDKL5 protein, the ATP binding site and the ST kinase active site, both of which lie in the catalytic or kinase domain, and the large C-terminal domain of the protein. They found that mutations affecting the ST kinase site and the C-terminal domain produced more severe phenotypes (refractory epilepsy, limited hand skills, non-walkers) than mutations affecting the ATP binding site. The mutations identified were missense and truncating mutations in the ST kinase segment and frameshift mutations in the C-terminal domain. In the ATP binding site, the recurrent mutations were all missense mutations at amino acid position 40, and when compared to girls with other CDKL5 mutations (presumably in this same area), those with this particular mutation (which is termed p.Ala40Val) tended to present with better hand use and better ability to walk. They also looked at whether X-inactivation (see The story of CDKL5) might also have an effect on phenotype but were unable to draw any useful conclusion.

Note - Overall I found this quite compelling reading really and it certainly builds on previous studies that have suggested links between position of mutation and phenotype. I was a little unsure about the exact number of girls in this study who actually had CDKL5, but overall I think it is a good and useful study. The fact that certain mutations at the C-terminal of the protein (which is well away from the kinase domain) are also associated with more severe phenotypes presumably suggests something about the 3-D structure of the CDKL5 protein in terms of how the C-terminal interacts with the kinase domain. There is a suggestion that part of the C-terminal might stabilise the protein against degradation and mutations here might therefore accelerate degradation -a view perhaps supported by the study below regarding a novel transcript. Who knows!