Loss of CDKL5 disrupts kinome profile and event-related potentials leading to autistic-type phenotypes in mice.
PNAS 2012.

This is the first CDKL5 study to be published based on research using knockout mice and was supported by charitable funds from the IFCR. The authors describe the generation of mice with a deletion of exon 6, which causes the production of a shortened protein truncated within the kinase domain. In order to remove the potential effects of X-inactivation, male mice were studied and compared to those with a normal Cdkl5 gene, termed wild-type (WT) mice. The results of the study were broadly presented in 3 domains, clinical, EEG analysis, and molecular biology.

Clinical - using standard tests of locomotion, sociability, and fear conditioning, Cdkl5 mice demonstrated hyperactivity, impaired motor control and decreased anxiety compared to WT mice. They also demonstrated impaired social behaviour, such as social interaction and nesting, and impairment of learning and memory. Many of these features are comparable to those observed in individuals with autism spectrum disorders and in those with atypical Rett syndrome.

EEG analysis - despite the prevalence of seizures in children with a CDKL5 disorder, no spontaneous epileptic activity was recorded in Cdkl5 mice compared to the WT controls. There were 2 theories put forward for this. Firstly, although there are huge similarities between the CDKL5protein in humans and that in mice, CDKL5 in humans may have an additional distinct function that is absent in mice and therefore renders humans more susceptible to epilepsy. Secondly, the particular strain of mice used in this study, are known to be more resistant to seizure activity...oh ! However, there was a positive side to this... yes read on. When studying the function of neurons and neural circuits, if a deficit or malfunction is found, it can be difficult to determine whether this is primarily due to the genetic defect or secondary to the effects of any associated seizure activity. The authors of this study did observe disruption in neural circuit communication and in a particular activity of neurons, known as low-frequency event-related oscillations. The fact that seizure activity was absent in these mice suggests that these abnormalities are directly due to the Cdkl5 mutation.

Molecular biology - (the complicated bit) the molecules on which an enzyme acts are known as its substrates. The substrates of CDKL5 are not known. CDKL5 is a kinase and the set of all kinases in the body is known as the kinome. The authors were able to look at a range of potentialCDKL5 substrates by studying changes in the kinome profile of the mice. A number of potential substrates were identified, including the kinases AMPK, PKA and AKT. The eventual conclusion of the authors is that loss of CDKL5 function causes disruption of multiple signal transduction pathways - which are effectively the controlling networks of cell function.

Note - this is clearly an important study in the evolution of our knowledge of CDKL5 disorders. Although the absence of seizures is a little disconcerting, we see such variation in the phenotypes of our own children that we shouldn't be too surprised if mice themselves turn out to be different in the way they are affected. I think the most exciting part of this study is in relation to the studies on the molecular biology, where our current knowledge is so sparse. Now, direct effects of mutations can be studied in more detail. Ultimately, this may be of far more value, in terms of relating to humans that the clinical studies, and the results of this study should establish starting points for further research to give us a better understanding of the exact role of CDKL5 in brain physiology.