Mapping pathological phenotypes in a mouse model of CDKL5 Disorder.
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This is a paper from Italy on a Cdkl5 knockout mouse model. The authors present a number of studies on the cellular and behavioural aspects of Cdkl5 deficient mice. Absence of the Cdkl5 protein in the mice was confirmed using 2 standard techniques - western blotting and immunofluorescence.

Cell biology
Localisation of the Cdkl5 protein - further immunofluorescent studies also showed a number of features. In normal (wild-type) mice, the Cdkl5 protein is found both in the nucleus of neurons and in their cytoplasm. Furthermore, there is a specific type of neuron - called a pyramidal neuron - and although the Cdkl5 protein is present in the cytoplasm of pyramidal neurons of the cortex, it seems to be more prominent in the cytoplasm of pyramidal neurons in a specific area of the brain called the hippocampus -which is located under the cerebral cortex.
Dendrites - which are the branched projections of neurons, are particularly important as Cdkl5 activity seems to focus within these structures. Dendritic arborisation (the complexity of their appearance and therefore function) was found to be significantly reduced in knockout mice, and this was associated with a reduction in the thickness of the cortex and of the hippocampus.
Signalling - cell signalling (also known as signalling pathways) are the many complex processes that control and co-ordinate the different activities of cells. Some signalling factors known to be affected in Rett syndrome were examined in Cdkl5 knockout mice. One such factor, called BDNF, was found to be normal, as were levels of the Mecp2 protein itself. However, another signalling factor, known as "Akt" was found to be reduced along with levels of phosphorylated "ribosomal protein S6" - also called "rpS6" - a protein that is a component of ribosomes, the protein factories that convert RNA into proteins - see The Genetics of CDKL5.
Cdkl5 and Mecp2 - Previous studies have shown a link between Cdkl5 and Mecp2 (Rett) function in the brain. The authors of this study were able to show that they probably also have distinct functions in the brain as well.

Clinical
Behaviour - a number of behavioural tests were performed on the knockout mice and their responses compared to normal (wild-type) mice. Abnormal clasping was seen in a significant number of the knockout mice whereas no or very low levels were seen in the wild-type mice. Knockout mice showed significantly decreased locomotion in a familiar home-cage environment but normal locomotion in a new unfamiliar environment, suggesting that the capacity for locomotion itself may not be the source of their deficit. Knockout mice also showed a reduction in head tracking (their responses to visual stimuli) which appeared to be due to deficient visual processing in their visual cortex that is, their eyes are working but their brains can't fully organise the visual signals - presumably representing cortical visual blindness.
Seizures - None of the knockout mice showed evidence of spontaneous seizures - as with other knockout mice. However, when epileptic producing drugs were given they did show abnormal EEG responses compared to wild-type mice.

Mapping phenotypes - we know that different parts of the brain are involved in different functions (speech, hearing, vision, movement, etc). Different parts of the brain are also characterised by different types of neurons. In the final part of their paper, the authors describe the development of so called “conditional” knockout mice, in which the Cdkl5 gene has been selectively removed from specific types of neurons found in different areas of the brain. The idea here was to see whether some of the characteristics we see in the CDKL5 disorder could individually be mapped to different types of neurons. The researchers found that deficits in behaviour were associated with absent Cdkl5 in one type of neuron in the forebrain, while limb control and eye tracking changes occurred with Cdkl5 deficiency in a different type of neuron of the motor and visual cortical pathways. The authors suggest that therapies aimed at re-expressing CDKL5 in cortical pyramidal neurons may be successful in reversing the most debilitating behavioural phenotypes of the disorder - possibly a plug for PRT !

Overall, the authors concluded that their knockout mouse models exhibits several core features of the CDKL5 disorder and therefore serve as useful animal models of the disorder. The authors go on to discuss the signalling pathways that may be involved and suggest that the down regulation of the “rpS6” pathway may be a common signalling deficit in both the CDKL5 disorder and Rett syndrome, indicating that defective translational regulation, in other words - a problem with the control of protein production - is a potential core mechanisms for the common pathological features of both disorders. However, their studies also suggest that Cdkl5 and Mecp2 may, in addition, act through different signaling mechanisms to affect common targets.

Note - this is great stuff and covers various aspects which is a little difficult to do justice to. Large parts of the paper are fairly technical as the authors are obliged to describe the techniques involved in developing their mouse model and their subsequent cellular studies. Some of their results corroborate the results of previous studies and there are also some new findings presented. The work they present on signalling is particularly technical but extremely important. What they are saying here is - right, we know where the Cdkl5 protein is in the brain, now let's see what other pathways are missing as a result of its deficit. I imagine that studying related signalling pathways will be the way a lot of future research into CDKL5 will go. We may also see more mouse models of specific mutations being produced soon - let's hope!! Finally, the study represents the combined efforts of various individuals from a number of centres in Italy and Switzerland. I think it is to their credit that this work has been published as an open-access article.