GluD1 is a common altered player in neuronal differentiation from both MECP2-mutated and CDKL5-mutated iPS cells.
European Journal of Human Genetics 2014.

This is a joint paper from Italy and the US about research into the molecular targets of CDKL5 and MeCP2. The study arises from the observation that children with a CDKL5 disorder share some characteristics with those who have Rett syndrome. A previous study has shown that CDKL5 and MeCP2 belong to the same molecular pathway. The authors of this study further hypothesise that amongst the genes that both CDKL5 and MeCP2 each influence, some may be common to both, and this might therefore explain some of the similarities in phenotype between the two conditions. The aim of their study therefore, was to identify whether there were any common genes.

The authors studied gene expression in iPS cells derived from 2 patients (1 male and 1 female) who had CDKL5 mutations and 1 patient with a MeCP2 mutation. They identified one particular gene - the GRID1 gene - that was downregulated in both CDKL5 and MeCP2 mutated cells. Following this, the iPS cells with CDKL5 (the female) and MeCP2 mutations were then differentiated through Neuronal Precursor Cells (NPC's) into mature neurons. When the authors then analysed the expression of the GRID1 gene in both the NPC's and the mature neurons for both mutations, they found (apparently to their surprise) that the GRID1 gene was now upregulated or overexpressed in all cells. Their data therefore suggests that the GRID1 gene is dysregulated in some way by both CDKL5 and MeCP2. They go on to suggest a mechanism through which MeCP2 might cause this change in regulation but do not appear to offer a mechanism for CDKL5.

Note - So .... "what does this all mean??" I hear you cry.....! Well, this study provides further evidence that at the molecular level CDKL5 and MeCP2 share some common pathways, and in particular, that they both regulate expression of the GRID1 gene - although we know from the mouse model study below that CDKL5 and MeCP2 have distinct pathways as well. A nice study but a little disappointing that the authors still tended to describe CDKL5 as a variant of Rett syndrome and they didn't really suggest a mechanism by which CDKL5 also regulates the GRID1 gene. I think this work was presented in Bologna and had I understood it then I might have asked the odd question or two ... missed opportunities .. oh well, at least another small piece of the jigsaw. Also, for your information - the GRID1 gene codes for something called a Glutamate delta-1 (GluD1) receptor. GluD1 receptors are expressed throughout the forebrain during development with high levels in the hippocampus in adulthood. A recent article from the US proposed that GluD1 receptors were crucial for normal functioning of synapses and that the absence of GluD1 might lead to specific abnormalities in learning and memory - so there are some correlates here with what we see in the CDKL5 disorder. Oh, and if you don't quite understand what iPS cells are, then have a look at the "Future Research" section at the bottom of The CDKL5 Protein .