**Gene therapy with AAV-CDKL5 vectors in models of CDKL5 disorder**

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CDKL5 disorder is a severe neurodevelopmental disorder caused by mutations in the X-linked cyclin-dependent kinase-like 5 (CDKL5) gene. It predominantly affects females that typically present with severe epileptic encephalopathy, intellectual disability, microcephaly, autistic features, sleep disturbances and motor dysfunction. Currently, there is no therapy apart from antiepileptic drugs for seizure management. We set out to develop a gene replacement therapy, by first characterising the CDKL5 transcript and protein isoforms expressed in human brain, human neuronal cell lines and hESC-derived cortical interneurons. We found that the hCDKL5\_1 and to a lesser extent the hCDKL5\_2 isoforms were expressed in these and cloned their coding region downstream of the CBh promoter in ssAAV2 transfer plasmids. High titre rAAV vectors pseudotyped with either AAV9, the variant capsid PHP.B or the hybrid capsid DJ were produced. We found that AAV-DJ-CDKL5 vectors were the most efficient in transducing CDKL5-mutant iPSC-derived neural progenitors and their isogenic controls, which were subsequently differentiated into mature neurons. Intrajugular delivery of 1x1012 vg of AAV-PHP.B-GFP vectors in wild-type mice transduced neurons and glia in brain, spinal cord, DRGs and retina more efficiently than AAV9. CDKL5 KO mice were treated with 1x1012 vg of AAV-PHP.B-CDKL5 vectors via the intrajugular route at 28-30 days of age. Behavioural testing was conducted at 1-2 months after vector delivery and brains were taken for analysis after 3 months. CDKL5-treated KO mice exhibited significant motor improvements compared to GFP-treated controls. We are conducting further analysis to ascertain if this gene therapy could be translated to CDKL5 patients.