Gene therapy rescues pathological deficits, improves behavioral aspects, and prolongs survival in CLN3-, CLN6-, and CLN8-Batten Disease

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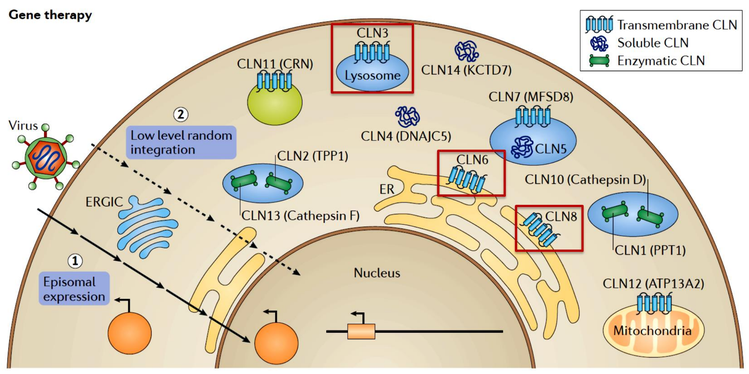
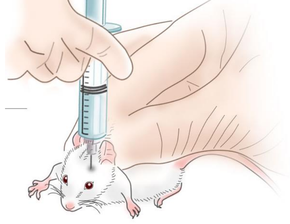
AAV9-Mediated Gene Therapy to Treat Batten Disease

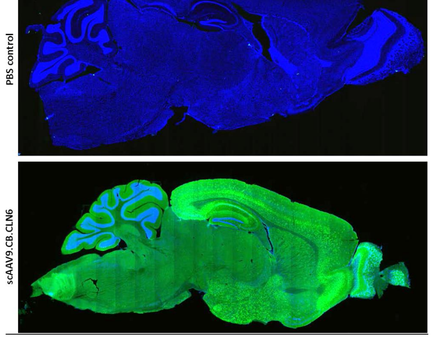


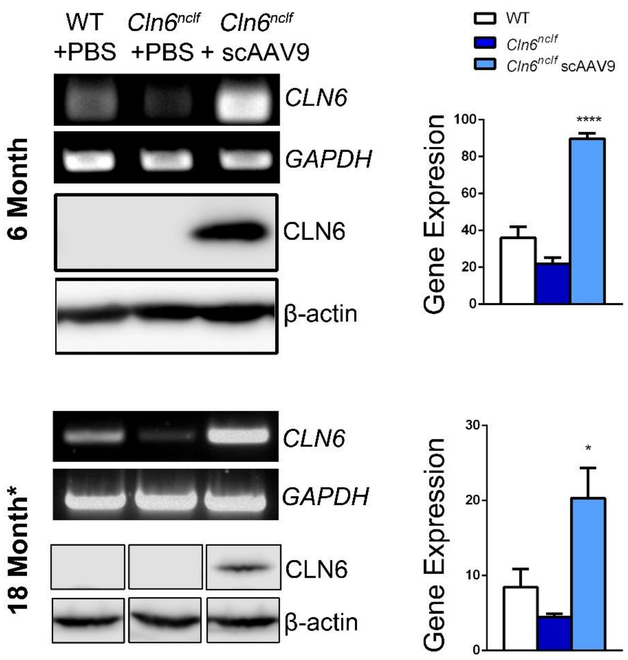
Mutation	Selective CNS Pathology	Visual Phenotype	Behavioral Phenotype
Cln3$^{\Delta ex7-8}$	Purkinje cell loss; GABAergic neuron loss	Retinal atrophy and altered pupillary light reflex	Motor coordination deficits
Cln6^{nclf}	Decreased cortical and cerebellar glutamine, glutamate, and GABA;	Retinal atrophy	Hind limb paresis at 8 months; memory and learning deficits; death at 12-15 months
Cln8^{mnd}	Neuronal death in hippocampus and spinal cord; GABAergic neuron loss;	Retinal atrophy (photoreceptor cells)	Seizures; limb paresis at 6 months; hyperactivity; aggression; memory loss; death at ~12 months

A single administration of AAV9 results in widespread and sustained CNS expression



Widespread sustained expression with Single ICV injection of virus





Acknowledgements

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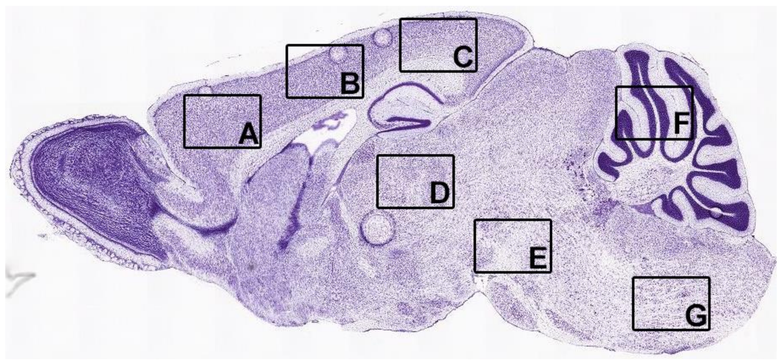
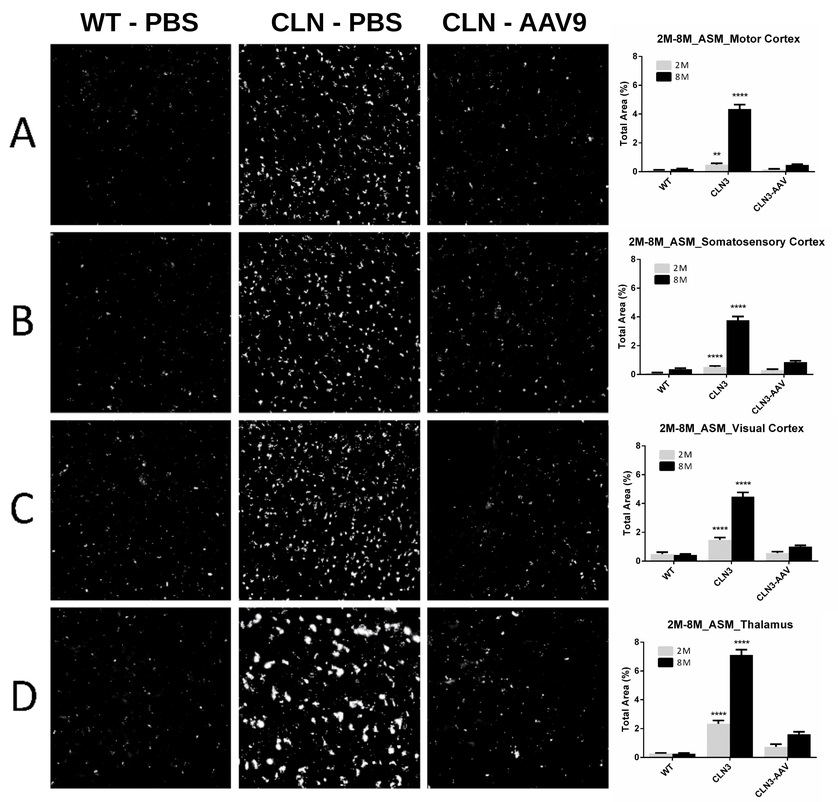
Gene Therapy Prevents Pathological Hallmarks of Batten Disease

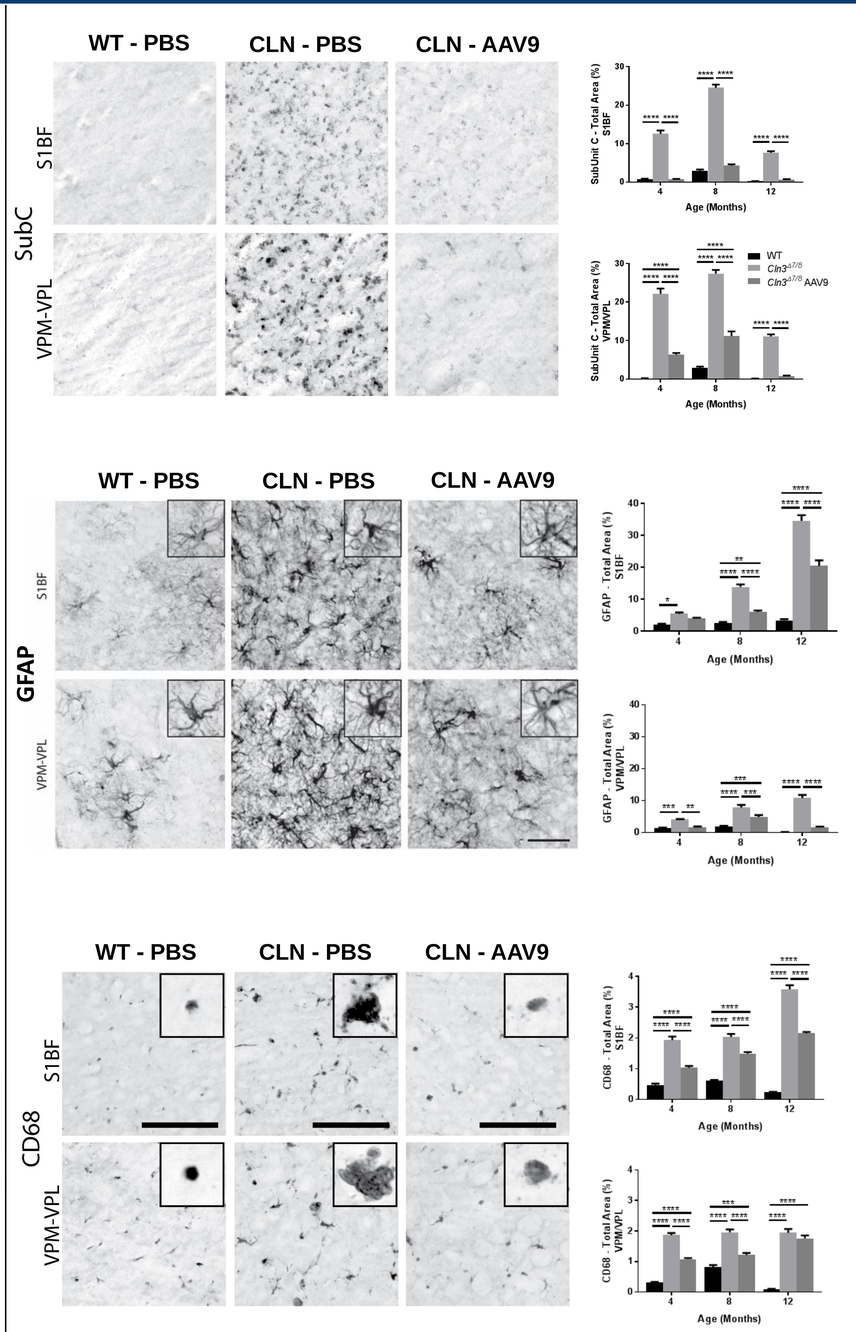
Mutation	ASM Accumulation	Subunit C Accumulation	Astrocyte Activation (GFAP)	Microglia (CD68)
Cln6^{nclf}	1M	1M	1M	2M
Cln3$^{\Delta ex7-8}$	2M	2M	4M	4M
Cln8^{mnd}	1M	1M	2M	2M

Age at which pathology is first detected in different mouse models of Batten Disease

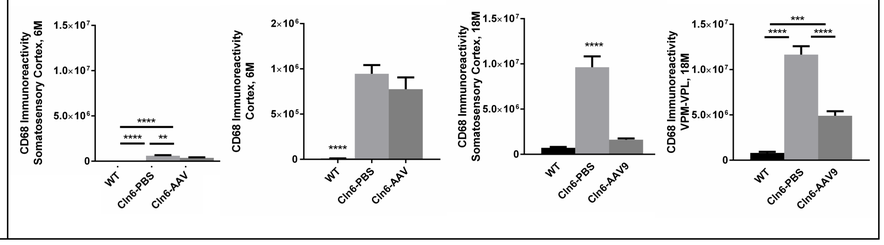




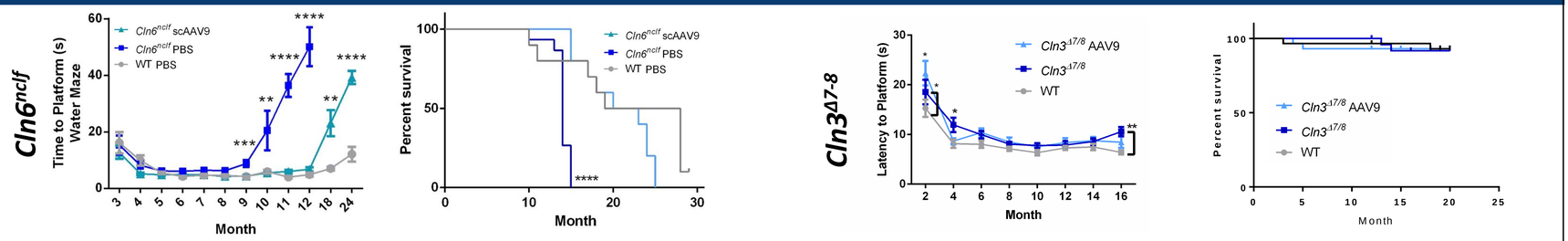
Representative images of Autofluorescent Storage Material Accumulation (ASM) in the motor cortex (A), somatosensory cortex (B), visual cortex (C), and thalamus (D). Quantification of ASM accumulation at 2M and 8M for Cln3



Representative images of ATP synthase Subunit C, GFAP, and CD68. Quantification for Cln3 is included at 2, 8, and 12 months (Right). Cln6 CD68 data included at 6 months and 18 months (Below)



Gene Therapy Delays Behavioral Hallmarks of Batten Disease and Prolongs Lifespan



Delays in *Cln8^{mnd}* phenotype:

ASM Accumulation	Subunit C Accumulation	Astrocyte Activation (GFAP)	Microglia (CD68)	MWM	Lifespan
8M and counting	8M and counting	8M and counting	8M and counting	Phenotype delayed 2M	Increased 3M and counting