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Therapeutic approaches for ARSACS: preclinical studies

Autosomal recessive spastic ataxia of Charlevoix–Saguenay (ARSACS) is a neurodegenerative disorder caused by mutations in the SACS gene, leading to loss of the large multidomain protein sacsin and resulting in progressive ataxia, peripheral neuropathy, and spasticity. To develop a therapeutic strategy capable of preventing early disease manifestations, we evaluated an adeno-associated virus–based minisacsin gene replacement approach in presymptomatic mice. We first administered a single intravenous dose in newborn control mice to test the safety and expression. The gene therapy product was robustly expressed in the soma and dendrites of cerebellar Purkinje neurons as well as spinal motor neurons, confirming efficient neonatal CNS delivery. We next assessed therapeutic potential in ARSACS mice to determine whether early gene supplementation could alter disease onset or progression. Motor coordination abnormalities were significantly attenuated following the gene therapy administration. Longitudinal behavioral analysis an improvement of ataxia, reflected by fewer foot slips on a narrow beam, suggesting that the administered dose may be insufficient for long-term rescue or that repeated dosing could enhance the therapeutic effect. The gene therapy product prevented the early onset of abnormal motor coordination and delayed the development of peripheral neuropathy, although maximal muscle strength remained unchanged. We next administered the gene therapy product to symptomatic mice and the experiments are still in progress. In parallel, mechanistic studies have focused on understanding neurofilament bundling, a hallmark of sacsin deficiency. We identified dysregulation of CK1α signaling and its adaptor proteins FAM83H and FAM83B in ARSACS patient fibroblasts and in ARSACS Sacs-/- cerebellum. These proteins were upregulated and localized to sites of intermediate filament aggregation, and functional studies revealed that CK1α inhibition or knockdown of its adaptor proteins induced neurofilament bundling. Partial rescue with a CK1α activator suggests that a defective priming phosphorylation step may underlie the pathological accumulation of neurofilaments in ARSACS. This mechanistic insight provides additional therapeutic angles that may complement minisacsin gene replacement. Taken together, our findings demonstrate that neonatal delivery of gene therapy improves early neurological function, protects cerebellar structure, reduces retinal pathology, and opens a path toward the development of non-invasive biomarkers. These advances in preclinical studies are promising for the development of a gene therapy for ARSACS and efficacy in symptomatic mice are in progress. All together our work provide a foundation for advancing therapeutic strategies into future preclinical and clinical development.