Public Abstract
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Title:EXPLORING MODIFIERS IN SPINAL MUSCULAR ATROPHY: THE POWER OF AAV9

Spinal Muscular Atrophy (SMA) is the second most common autosomal recessive disorder. The rate of new occurring cases is 1 in 6,000, with a carrier frequency of 1 in 35. SMA is characterized by the loss of Survival Motor Neuron 1 (SMN1) gene, resulting in the degeneration of motor neurons located in the spinal cord, atrophy of muscles, paralysis, and eventually death. We utilize scAAV9, a viral vector, as a tool for introducing heterogeneous genes as a method for delivery. We and others have shown that delivery of full length SMN1 to the “delta 7” SMA mouse model fully rescues the disease. Therefore, we employ scAAV9 to introduce genes that are designed to modify the disease phenotype. Furthermore, we will investigate which domains of SMN are important for its function with scAAV9. SMNrp1 is a putative paralogue to SMN; the Tudor domain of SMNrp1 is highly similar to the Tudor domain of SMN. Both SMNrp1 and SMN are involved in spliceosome formation, therefore we hypothesized that SMNrp1 may be able to restore the function of SMN, making it a potential candidate as a modifier for SMA. Another example of a potential modifier of SMA is alpha-synuclein, which functions with synaptic vesicle recycling at the pre-synaptic membrane. Reduced alpha-synuclein protein and mRNA levels have been shown to correlate with reduced levels of SMN protein. Therefore, we hypothesized that alpha-synuclein may work with SMN to stabilize and protect motor neurons from SMA. Our results showed that SMNrp1 was unable to modify the SMA phenotype, while alpha-synuclein partially rescued the phenotype. In order to determine which functional domains within the SMN protein are particularly relevant for the development of SMA, we interrogated the ability of phylogentically diverse SMN proteins to ameliorate the SMA phenotype in mice. Phylogentically more distant species, such as Drosophila or S. pombe were hypothesized to be unable to restore SMN function, because of the reduced conservation of SMN protein domains. For this study, the severe SMN?7 mouse model was utilized. We found that Smn from C. elegans, Drosophila, and S. pombe were not able to rescue the phenotype of SMA mice. However zebrafish was able to rescue the phenotype and Xenopus partially rescued the phenotype of SMA mice. These studies will provide insight into the function of SMN as well as provide evidence for potential therapeutics for SMA.