

UTILIZING GENE THERAPY METHODS TO PROBE THE GENETIC REQUIREMENTS TO
PREVENT SPINAL MUSCULAR ATROPHY.

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ABSTRACT

Spinal Muscular Atrophy (SMA) is a neurodegenerative disease characterized by loss of motor neurons, progressive muscle atrophy, and ultimately death. The SMN gene is known to cause SMA, however the role of SMN in SMA pathology is disputed.

To this end, we aimed to establish a minimal functional domain of SMN. Using viral-based gene therapy methods, we delivered variants of SMN into the SMN Δ 7 mouse model of SMA. We monitored phenotypic improvement to determine which variants of SMN were able to benefit the SMA condition. In our initial screen, homologs of SMN from several different model organisms were chosen to represent a "evolutionary-guided" minimal domain. Accordingly, we found that SMN homologs from *D. rerio* and *X. laevis* provided significant benefit, while those from *C. elegans*, *D. melanogaster* and *S. pombe* did not. In comparing the sequential differences between those homologs that rescue with those that do not, we identified the profilin-interacting domain as a candidate region responsible for these differences. By creating chimeric proteins and mutated versions of SMN, we determined that the profilin-interacting domain is required for SMN function, but insufficient to restore function to extremely minimal SMN domain constructs such as *C. elegans Smn*.