Journal of Genetic Syndromes & Gene Therapy

OPEN ACCESS Freely available online

Perspective

Splicing Defects and Therapeutic Restoration in Spinal Muscular Atrophy

Daniel Kovalenko*

Department of Neurogenetics and Neuromuscular Research, University of Toronto, Toronto, Canada

DESCRIPTION

Spinal Muscular Atrophy (SMA) is an autosomal recessive neuromuscular disorder characterized by progressive degeneration of alpha motor neurons in the anterior horn of the spinal cord. The condition results in muscle weakness, atrophy, and impaired motor function. SMA is primarily caused by loss-of-function mutations or deletions in the *SMN1* gene, which encodes survival motor neuron protein, essential for motor neuron maintenance and axonal transport.

The *SMN1* gene produces full-length survival motor neuron protein that participates in the assembly of small nuclear ribonucleoproteins, which are critical for pre-mRNA splicing. In SMA, absence of functional SMN protein disrupts RNA processing in motor neurons, leading to cellular stress, impaired axonal integrity, and eventual neuronal death. This selective vulnerability of motor neurons remains an area of active investigation, as SMN protein is ubiquitously expressed in all tissues.

Humans possess a paralogous gene, *SMN2*, which is nearly identical to *SMN1* but differs by a single nucleotide change in exon 7. This subtle difference causes most *SMN2* transcripts to exclude exon 7 during splicing, resulting in a truncated and unstable protein. However, a small proportion of full-length protein is still produced, and the number of *SMN2* gene copies significantly influences disease severity. Individuals with higher *SMN2* copy numbers tend to exhibit milder phenotypes due to increased residual SMN protein production.

Clinically, SMA is classified into several types based on age of onset and motor function. Type I is the most severe form, presenting in infancy with profound hypotonia, respiratory insufficiency, and inability to achieve motor milestones such as sitting independently. Type II and III forms present later in childhood with varying degrees of motor impairment, while Type IV manifests in adulthood with relatively mild symptoms. Despite this classification, there is a broad clinical spectrum influenced by genetic and molecular modifiers.

The primary pathological feature of SMA is degeneration of motor neurons, leading to progressive muscle atrophy. Muscle weakness typically affects proximal muscles more than distal muscles. Respiratory muscles are also involved in severe cases, leading to ventilatory failure. Histological examination reveals loss of motor neurons, muscle fiber atrophy, and evidence of denervation. Diagnosis of SMA is confirmed through genetic testing that identifies deletions or mutations in the *SMN1* gene. Molecular diagnostic techniques such as multiplex ligation-dependent probe amplification are commonly used to detect exon deletions. Assessment of *SMN2* copy number provides additional prognostic information. Early diagnosis through newborn screening programs has become increasingly important, enabling intervention before irreversible motor neuron loss occurs.

Therapeutic development in SMA represents one of the most significant advances in gene-targeted medicine. One of the first approved treatments is nusinersen, an antisense oligonucleotide that modifies splicing of *SMN2* pre-mRNA. By promoting inclusion of exon 7, nusinersen increases production of functional SMN protein. This intrathecally administered therapy has shown significant improvement in motor function and survival in treated patients. Another major therapeutic approach is gene replacement therapy using adeno-associated viral vectors. Onasemnogene abeparvovec delivers a functional copy of the *SMN1* gene to motor neurons, enabling sustained expression of SMN protein. This one-time intravenous treatment has demonstrated substantial improvements in motor milestones, particularly when administered early in life. However, long-term efficacy and safety continue to be monitored.

A third pharmacological option is risdiplam, an orally administered small molecule that also modifies *SMN2* splicing. Unlike antisense therapies, risdiplam distributes systemically and increases SMN protein levels across multiple tissues. Clinical studies have shown improved motor function and stabilization of disease progression in a wide range of SMA patients. Research continues to explore additional therapeutic targets beyond SMN restoration. Neuroprotective strategies aim to support motor neuron survival even in the presence of low SMN levels. These include modulation of apoptotic pathways, enhancement of axonal transport, and reduction of cellular stress responses. Combination therapies are being investigated to maximize functional outcomes.

Correspondence to: Daniel Kovalenko, Department of Neurogenetics and Neuromuscular Research, University of Toronto, Toronto, Canada, E-mail: daniel.kovalenko.sma@utoronto.ca

Received: 01-Dec-2025, Manuscript No. JGSGT-25-41633; **Editor assigned:** 03-Dec-2025, PreQC No. JGSGT-25-41633 (PQ); **Reviewed:** 17-Dec-2025, QC No. JGSGT-25-41633; **Revised:** 24-Dec-2025, Manuscript No. JGSGT-25-41633 (R); **Published:** 31-Dec-2025, DOI: 10.35248/2157-7412.25.16.474

Citation: Kovalenko D (2025). Splicing Defects and Therapeutic Restoration in Spinal Muscular Atrophy. J Genet Syndr Gene Ther. 14:474.

Muscle-directed therapies are also under evaluation. Since SMA affects both motor neurons and muscle tissue, interventions targeting muscle function may complement SMN-based treatments. Agents that enhance muscle growth and regeneration are being studied to improve strength and mobility. The introduction of disease-modifying therapies has dramatically changed the natural history of SMA. Early-treated infants can now achieve motor milestones that were previously unattainable. However, variability in response remains, particularly in individuals treated later in disease progression. This highlights the importance of early detection and intervention. Rehabilitation and supportive care remain essential components of management.

CONCLUSION

Spinal muscular atrophy is a genetic neuromuscular disorder caused by loss of function in the *SMN1* gene and modulated by *SMN2* copy number variation. Advances in antisense therapy, gene replacement, and small molecule splicing modulation have transformed treatment outcomes. Continued research into complementary pathways and early intervention strategies is essential for further improving long-term motor function and quality of life in affected individuals. Physical therapy helps maintain joint mobility and muscle function, while respiratory support is critical in severe cases. Nutritional management is also important due to feeding difficulties and increased metabolic demands.