Medora

La community dei professionisti della salute By Roche

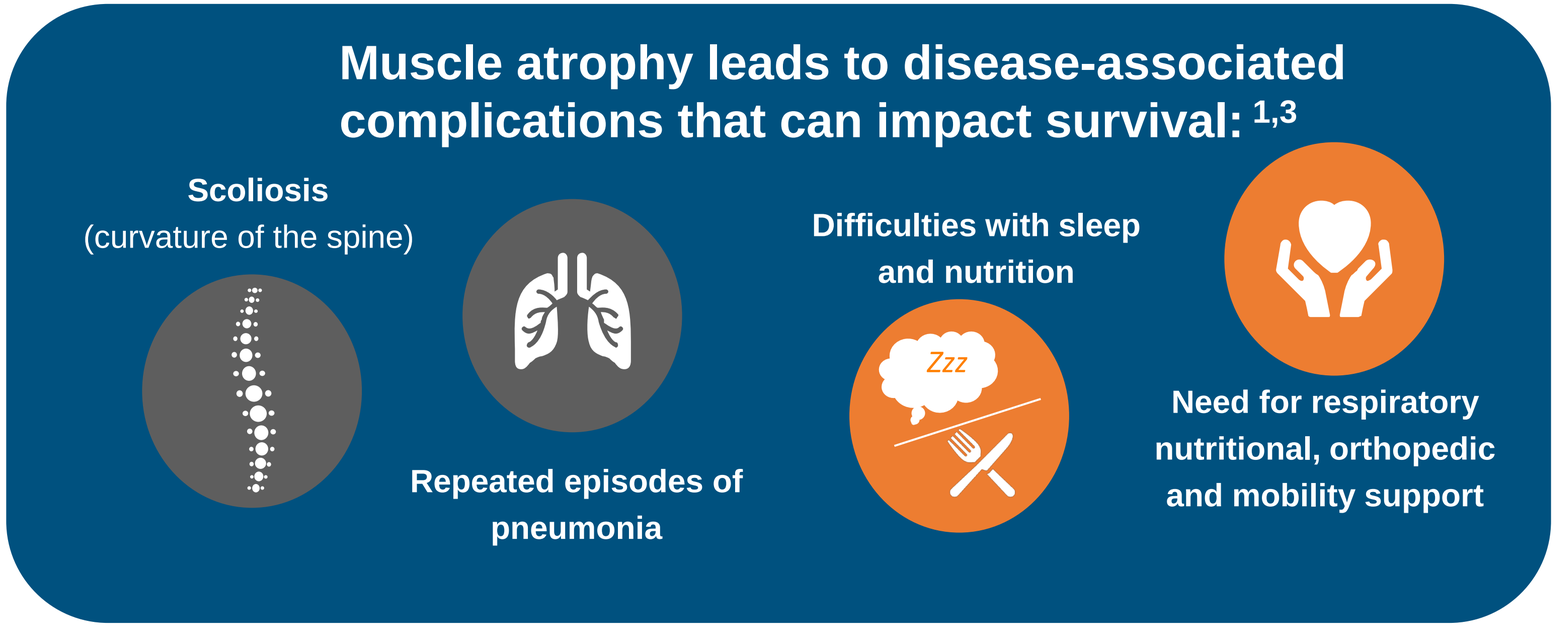
SMA
Spinal Muscular Atrophy

SMA
Spinal Muscular Atrophy

1. Spinal Muscolar Atrophy

SMA is a progressive, debilitating neuromuscular disease

- SMA is characterized by:
  - Progressive muscle denervation
  - Skeletal muscular atrophy
  - Overall weakness
  - Loss of motor function and ambulation[1–3]



SMA, spinal muscular atrophy.

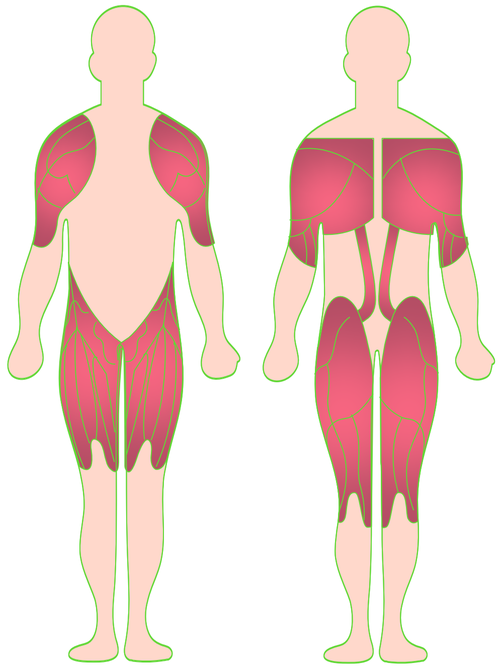
1. D'Amico A, et al. Orphanet J Rare Dis. 2011; 6:71; 2. Prior TW. Genet Med. 2010; 12:145–152; 3. Crawford TO and Pardo CA. Neurobiol Dis. 1996; 3:97–110.

Symmetrical muscle weakness affects proximal muscle groups more than distal muscles

Legs more affected than arms. Motor milestones are frequently delayed[1]

Severity of muscle weakness dependent on age of onset1

Proximal muscles[2]



Front **Back**

Feeding and breathing difficulties. Severely affected patients have shallow, diaphragm reliant breathing[1]

Impaired head control1

SMA, spinal muscular atrophy.

1. D'Amico A, et al. Orphanet J Rare Dis. 2011; 6:71; 2. Graphical elaboration from https://www.mda.org/disease/spinal-muscular-atrophy (Accessed October 2019).

SMA is a rare autosomal recessive genetic disease

In the US, a rare disease is defined as one that affects fewer than 200,000 individuals, and in Europe, fewer than 1 in 2,0001

Estimated incidence of SMA:

1 in 6,000

to

1 in 11,000

live births2,4

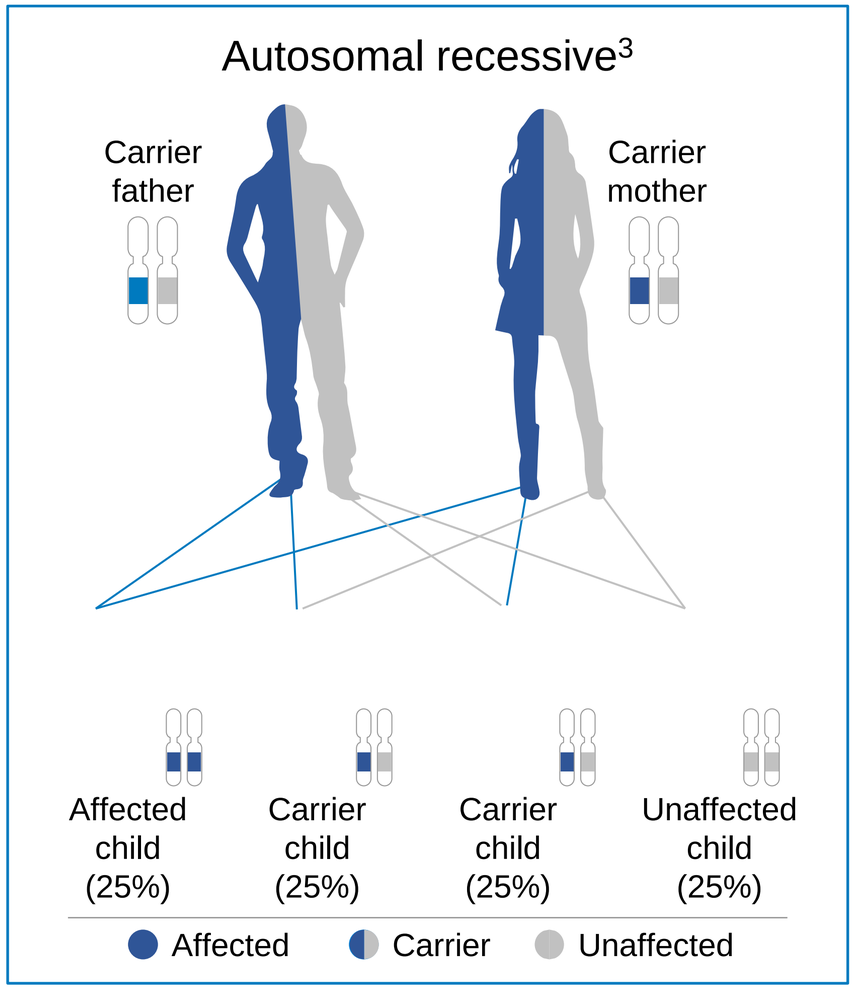
SMA, spinal muscular atrophy.

1. Aronson JK, et al. Br J Clin Pharmacol. 2006; 61:243–245; 2. Sugarman EA, et al. Eur J Hum Genet. 2012; 20:27–32; 3. D'Amico A, et al. Orphanet J Rare Dis. 2011; 6:71; 4. Markowitz JA, et al. Pediatr Neurol. 2012; 46:1–12

SMA is caused by a deficiency in SMN protein

Mutations and/or deletions in the *SMN1* gene → Insufficient levels of the SMN protein, critical for motor neurons[1]

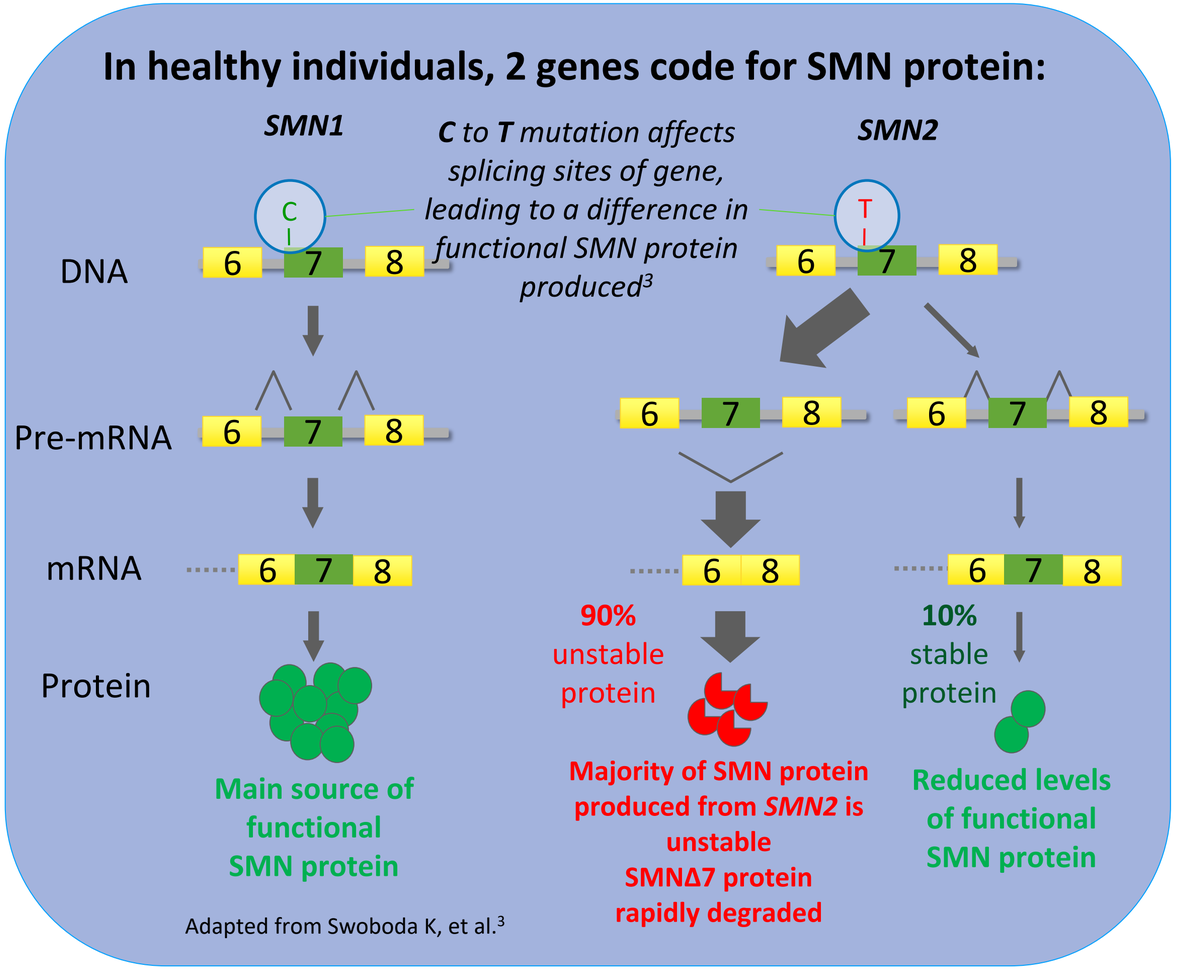
- SMA is an autosomal recessive genetic disorder: both copies of the *SMN1* gene need to have the mutations for the phenotype to be expressed[1]
- Carriers of a single copy of the mutated gene show no signs or symptoms[1]
  - Carrier prevalence is reported to be 1 in 45 for most populations[2]
- Two carriers have a 25% chance of having a child with an autosomal recessive condition[3]



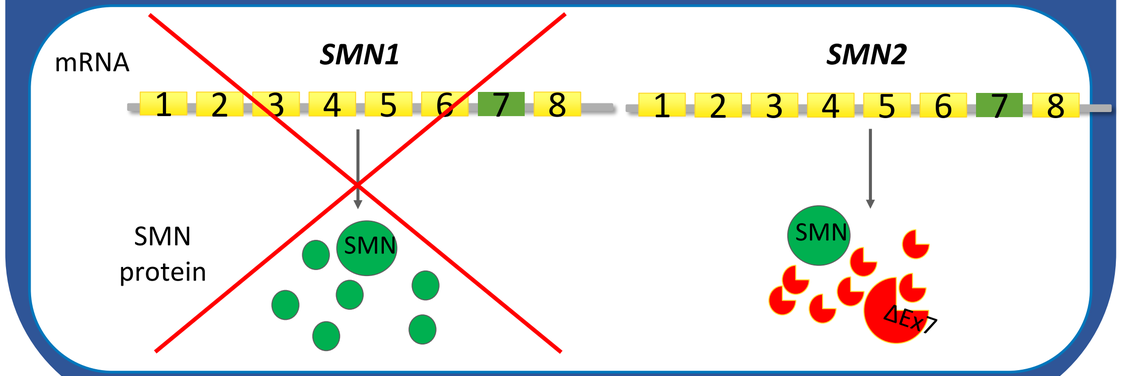
SMA, spinal muscular atrophy; SMN, survival of motor neuron.

1. Genetics Home Reference. https://ghr.nlm.nih.gov/condition/spinal-muscular-atrophy. Accessed October 2019;
2. Verhaart I, et al. Orphanet J Rare Dis. 2017; 12:124;
3. Graphical elaboration from U.S. National Library of Medicine http://rosalind.info/glossary/recessive-allele/ (Accessed October 2019).

The SMN1 gene is the main source of functional SMN protein



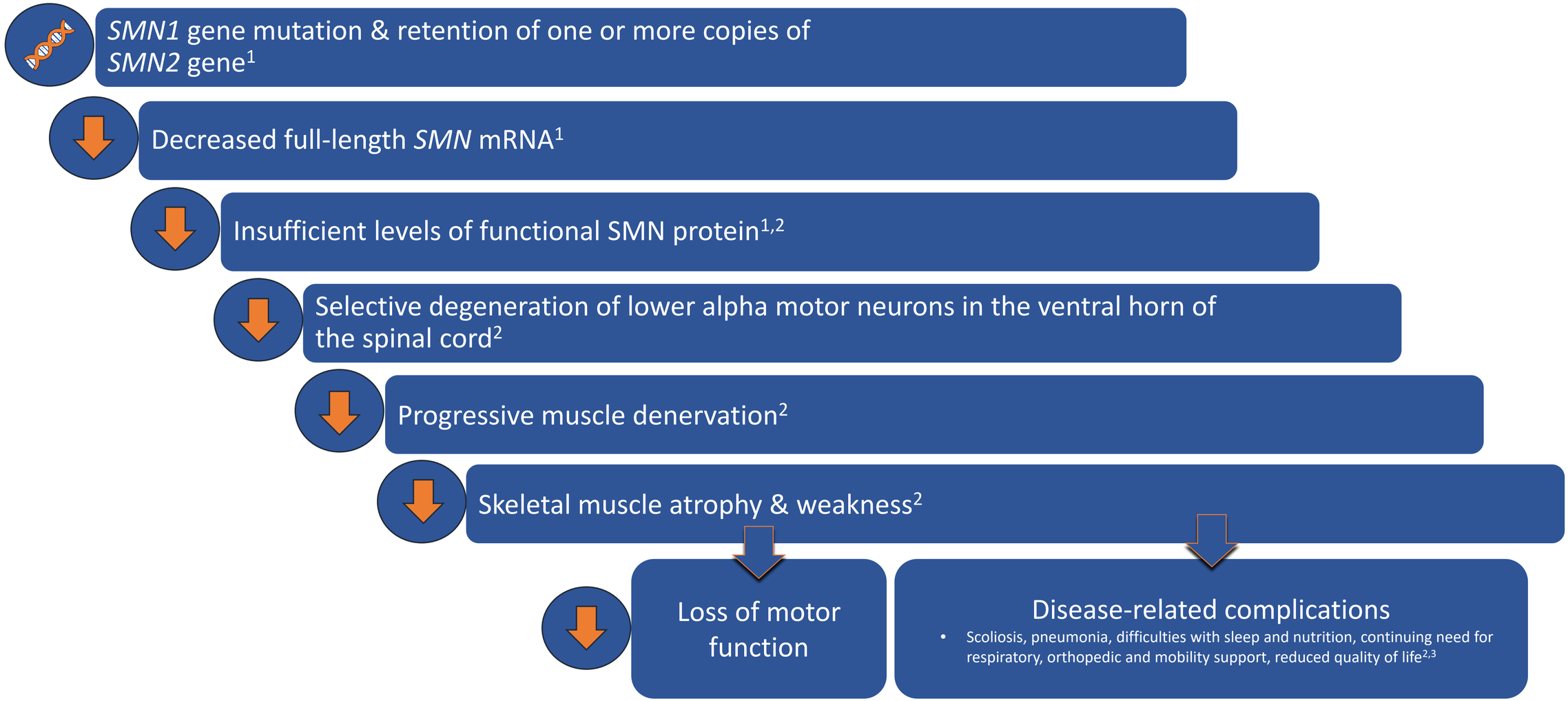
- In SMA :
- Mutations in the *SMN1* gene result in insufficient levels of the SMN protein1
- *SMN2* produces only low levels of functional SMN protein that are not sufficient to fully compensate for mutations/deletions in the *SMN1* gene2,3



C, cytosine; ΔEx7, exclusion of exon 7; SMA, spinal muscular atrophy; SMNΔ7, non-functional version of the SMN protein; SMN, survival of motor neuron; T, thymine.

1. Genetics Home Reference. https://ghr.nlm.nih.gov/condition/spinal-muscular-atrophy. Accessed October 2019); 2. Lorson CL, et al. PNAS. 1999; 96:6307–6311;
3. Prior TW. Genet Med. 2010; 12: 145–152; 4. Adapted from Swoboda K, et al. J Clin Invest. 2011; 121:2978–2981.

Reduced SMN protein leads to motor neuron loss and muscle atrophy[1]



SMN, survival of motor neuron.

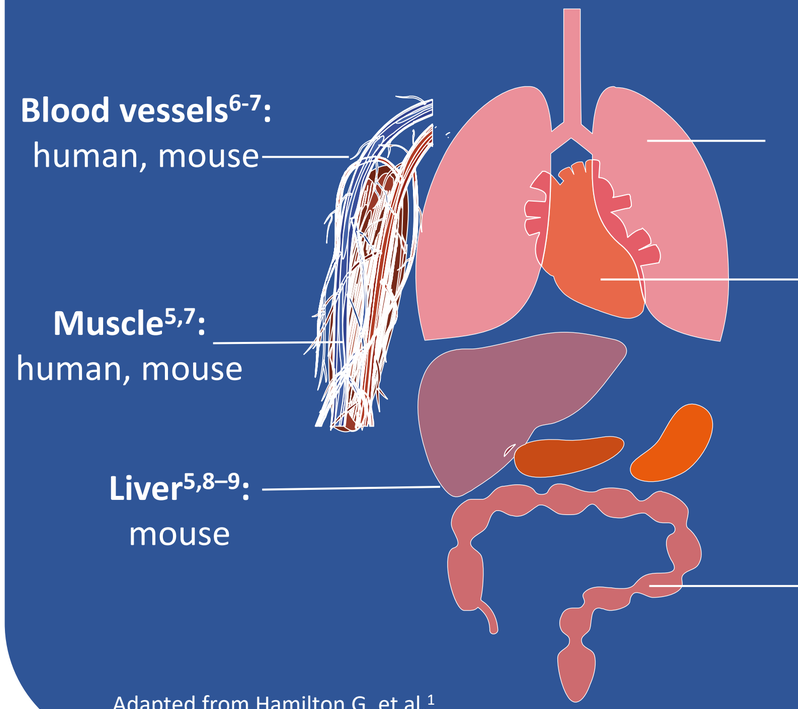
1. Prior TW, Genet Med. 2010; 12:145–152; 2. D'Amico A, et al. Orphanet J Rare Dis. 2011; 6:71; 3. Crawford T, et al. Neurobiol Dis. 1996; 3:97–110.

Increasing evidence suggests SMN depletion directly affects cells and tissues in both the CNS and periphery*

- Increasing evidence suggests SMN depletion directly affects cells and tissues in both the CNS and periphery[1]
- NMJ dysfunction has been observed in mouse models of SMA[2]
- SMN protein is required for skeletal muscle differentiation *in vivo*[3]
- Vascular and cardiac abnormalities reported in patients with severe SMA[1,4]
- Long-term data from investigational therapies may help to identify the role of peripheral SMN protein

Restoration of SMN in both the CNS and periphery was required for long-term rescue of a severe SMA mouse model[5]

Overview of non-neuromuscular systemic pathology in SMA1



Adapted from Hamilton G, et al.[1]

*Evidence from preclinical animal models.CNS, central nervous system; NMJ, neuromuscular junction; SMA, spinal muscular atrophy; SMN, survival of motor neuron.

1. Hamilton G, et al. Trends Mol Med. 2013; 19:40–50; 2. Martínez-Hernández R, et al. J Pathol. 2013; 229:49–61; 3. Bricceno KV, et al. Hum Mol Genet. 2014; 23:4745–4757; 4. Wijngaarde CA, et al. Orph J Rare Dis. 2017; 12:67; 5. Hua Y, et al. Nature. 2011; 478:123–126; 6. Heier CR, et al. Hum Mol Genet. 2010; 19:3906–3918; 7. Schreml J, et al. Eur J Hum Genet. 2013; 21:643–652; 8. Vitte JM, et al. Am J Pathol. 2004; 165:1731–1741; 9. Szunyogova E, et al. Sci Rep. 2016; 6:34635; 10. Gombash SE, et al. Hum Mol Genet. 2015; 24:3847–3860; 11. Sintusek P, et al. PLoS One. 2016; 11:e0155032.

SMA type is determined by age of onset and maximum motor function achieved[1]

- Presently there are five clinical classifications of SMA, however, the phenotypes of SMA may change since the discovery of disease modifying therapies
- SMA is not associated with cognitive impairment, and intellectual development is normal for SMA patients[1]

Type	Severity	Age of onset	Motor function achieved			Typical symptoms	Typical *SMN2* copy no.*	Lifespan
			Able to sit	Able to stand	Able to walk			
0[2,3]	Severe	Prenatal	✗	✗	✗	• Severe hypotonia	1	<6 months
1[4–8]	Severe	0–6 months	✗	✗	✗	• Respiratory failure	2	<2 years
2[4–8]	Intermediate	<18 months	✓	✗	✗	• Respiratory complications • Wheelchair-bound	3	>2 years
3[4–8]	Mild	>18 months	✓	✓	Assisted or unassisted	• Muscle weakness	3–4	Normal
4[3,9]	Mild	>5 years	✓	✓	✓	• Very slow progressive muscle weakness	>4	Normal

*Copy number of SMN2 varies from 1 to 6 copies in SMA patients, with an inverse relationship observed between SMA type and SMN2 copy number5.
SMA, spinal muscular atrophy; SMN, survival of motor neuron.

1. Viollet L and Melki J. Handbook of Clin Neuro: Ped Neuro Part III. 2013; 113:8; 2. Dubowitz V. Eur J Ped Neuro. 1999; 3:49–51; 3. Butchbach M. Front Mol Biosci. 2016; 3:7; 4. Prior TW. Genet Med. 2010; 12:145–152; 5. Crawford TO, et al. PLOS. 2012; 7:4; 6. Munsat T. Neuromuscul Disord. 1991; 1:81; 7. Munsat T and Davies K. Neuromuscul Disord. 1992; 2:423–428; 8. Bladen CL, et al. J Neurol. 2014; 261:152–163; 9. D'Amico A, et al. Orphanet J Rare Dis. 2011; 6:71.

Clinical classification of SMA[1]

Type 0/Type 1a
Most severe weakness
Contractures; cardiomyopathy
Death in weeks

Type 1b
Most typical Type 1 form
Feeding and respiratory problems
Death by second year of life

Type 1c
Feeding and respiratory problems
Plateau in first 2 years

SMA, spinal muscular atrophy.
Adapted from Talbot K and Tizzano EF. Gene Ther. 2017; 24:529-533.

Clinical classification of SMA [2, 3 and 4]

Type 2
Survival to adolescence/adulthood
Weaker cases may lose sitting ability (2a)
Stronger cases may stand with support (2b)

Type 3a
Early loss of ambulation
Normal lifespan

Type 3b
Later loss of ambulation
Normal lifespan

Type 4
Ambulant until later in life
Normal lifespan

SMA, spinal muscular atrophy.
Adapted from Talbot K and Tizzano EF. Gene Ther. 2017; 24:529-533.

Medora

Il futuro della medicina, l’avanguardia di noi medici.

La community dei professionisti della salute
By Roche