Spinal Muscular Atrophy: Genetic Etiology

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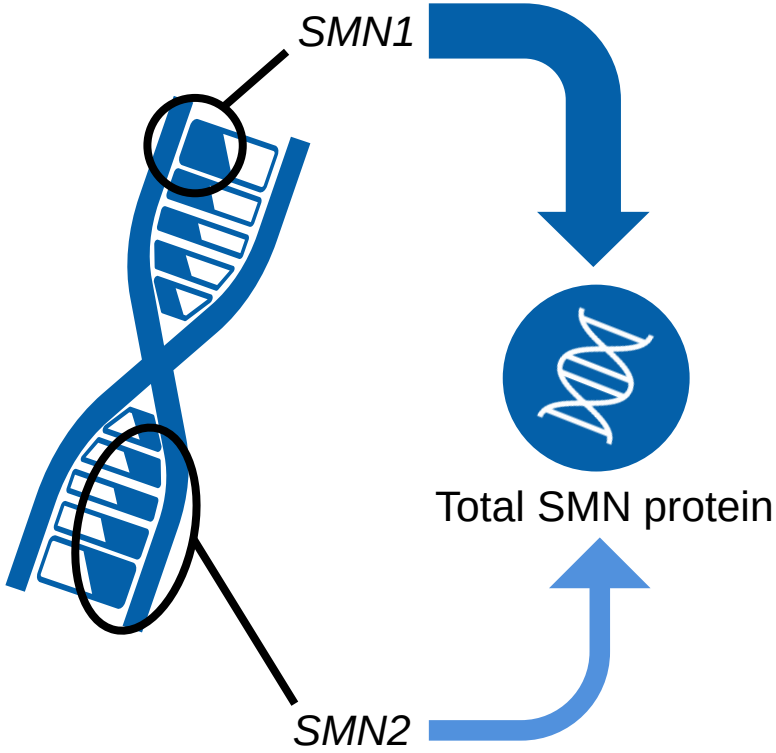
Genetic Etiology of SMA

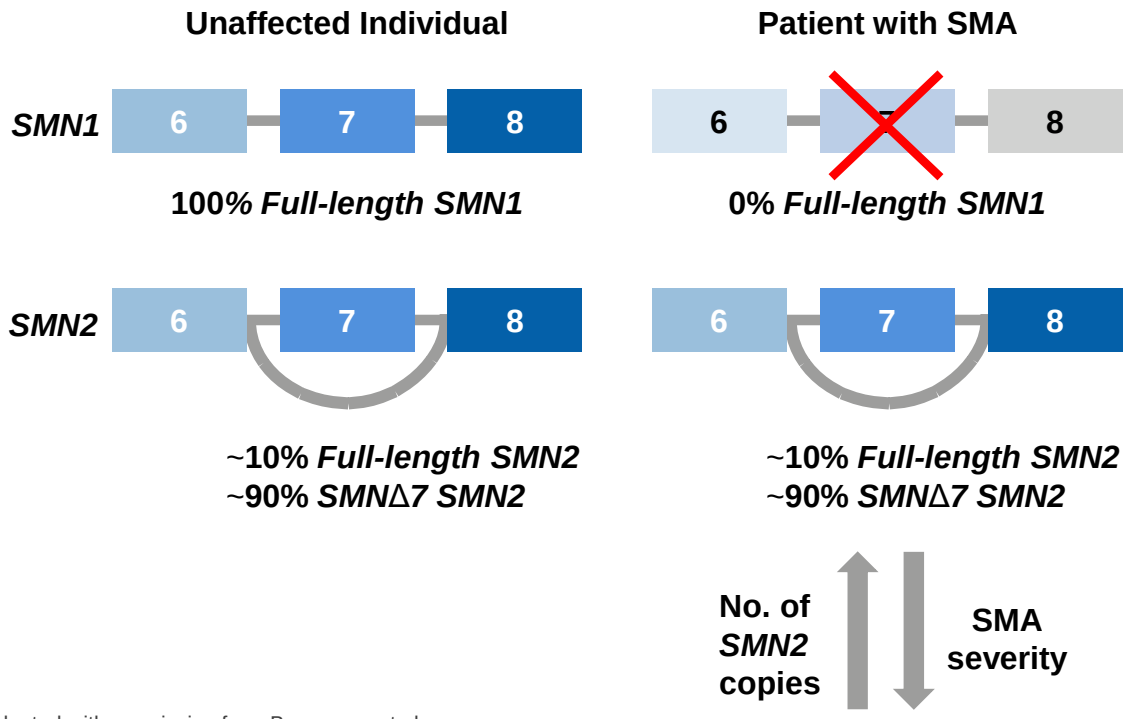
- SMA is an autosomal recessive genetic motor neuron disease caused by loss-of-function mutations or deletions of *SMN1*[1]
- *SMN1* and *SMN2* encode the SMN protein, which is essential for normal cellular and neuronal development[2]
- The severity of SMA is moderated by the number of copies of the nearly identical *SMN2* gene, which makes a minor contribution to the total SMN production[2]



SMA, spinal muscular atrophy; SMN1, survival motor neuron 1 gene; SMN2, survival motor neuron 2 gene.

1. Bowerman M et al. *Dis Model Mech.* 2017;10(8):943-954. **2.** Chaytow H et al. *Cell Mol Life Sci.* 2018;75(21):3877-3894.

SMN Production via *SMN1* and *SMN2*



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SMN1, which is missing or nonfunctional in patients with SMA, produces the majority of functional SMN protein

~90% of SMN protein from *SMN2* is nonfunctional owing to a cytosine-to-thymine substitution in *SMN2* that promotes alternative splicing of exon 7 (*SMNΔ7*)

Multiple copies of *SMN2* can partially compensate for loss of *SMN1*

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SMN2 and Severity of SMA

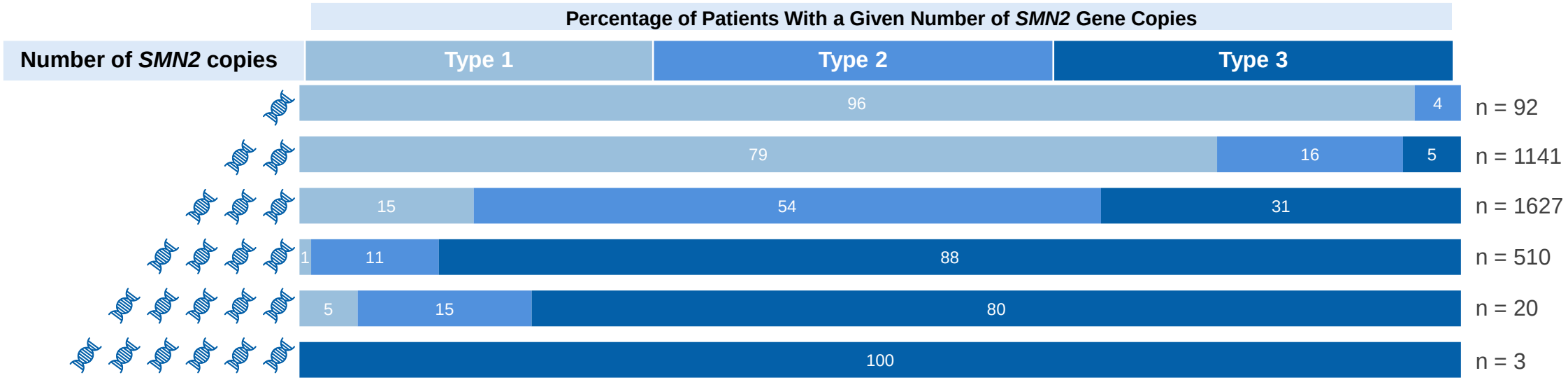
- *SMN2* copy number inversely correlates with SMA severity[1]
- SMA is classified into 3 main types by the age at which symptoms first occur[2]
  - Newer classifications by motor milestones of nonsitter, sitter, and walker are increasingly used to better inform disease management in light of emerging therapeutic options[1]

SMA type	**Type 0**	**Type 1**	**Type 2**	**Type 3**	**Type 4**
Age at symptom onset[2]	Prenatal	Up to 6 months	6 to 18 months	>18 months to ≥3 years	Adult
Typical *SMN2* copy number[1]	1	2	3	3 to 4	≥4
Motor milestones[1]		**Nonsitter**	**Sitter**	**Walker**	

SMA, spinal muscular atrophy; SMN, survival motor neuron.
1. Wirth B et al. *Annu Rev Genomics Hum Genet.* 2020;21:231-261. **2.** Wijngaarde CA et al. *Neurology.* 2020;94(15):e1634-e1644.

Effect of *SMN2* Gene Copy Number on SMA Severity

- The number of *SMN2* gene copies increases with milder phenotypes
- Understanding correlations between *SMN2* copy number and disease severity could be valuable for predicting the likely evolution of patients with SMA



Adapted with permission from Calucho et al.

SMA, spinal muscular atrophy; SMN, survival motor neuron.
Data represent 3459 individuals from a Spanish cohort and global literature review.
Calucho M et al. *Neuromuscul Disord.* 2018;28(3):208-215.