Spinal Muscular Atrophy

Introduction for SMA Families

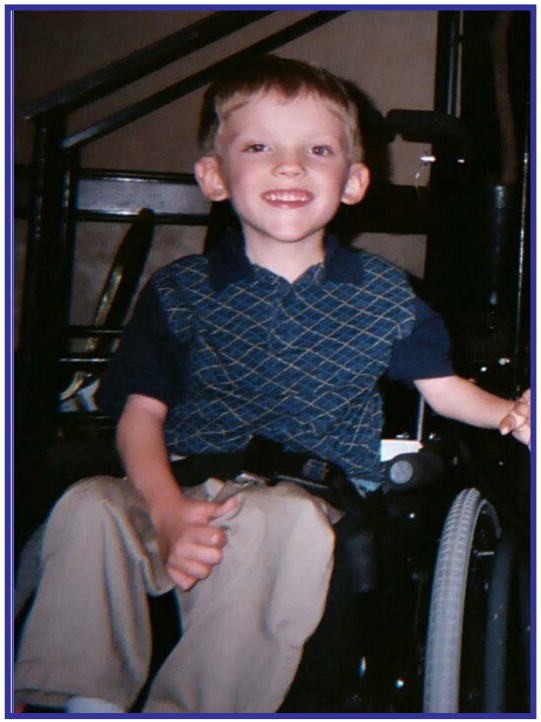
SMA Foundation
New York

SMA Is a Severe Neurological Disorder [1]

- Autosomal recessive genetic inheritance
- 1 in 50 people (approximately 6 million Americans) are carriers [2]
- 1 in 10,000 children born with SMA (incidence rate)
- Well-defined patient population
  - Estimated number of patients in the United States ~9,000
- Common rare disease: incidence comparable to cystic fibrosis, Duchenne muscular dystrophy, ALS
- Affects all racial and ethnic groups

SMA Is a Neuromuscular Disease

- Characterized by muscle atrophy and loss/lack of motor function
  - Proximal (closest to the spine) muscles most severely affected
  - Muscle weakness is the most common symptom
  - Surgery is commonplace: tracheotomy, feeding tube placement and/or spinal stabilization
  - Cognition/intellect, emotional development and sensory nerves unaffected



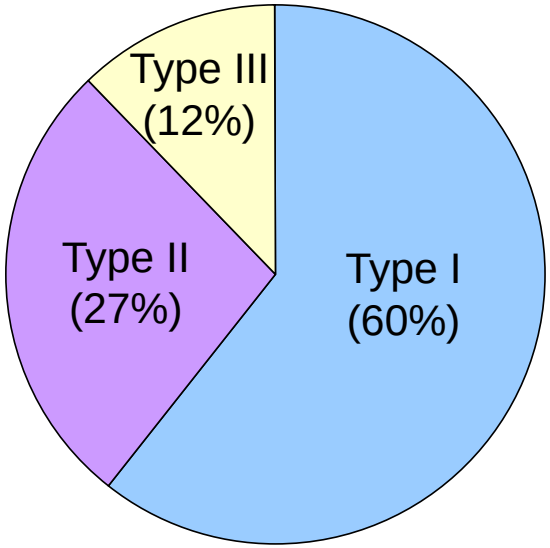
SMA Varies in Severity [3]

SMA Type	Severity	Age of onset	Highest function	Life expectancy
I (Werdnig-Hoffmann disease)	Severe	0-6 months	Never sits	<2 years
II	Intermediate	7-18 months	Sits but never stands	>2 years
III (Kugelberg-Welander disease)	Mild	>18 months	Stands and walks	Adult
IV (adult form)	Mildest	Second and third decade	Walks	Adult

- SMA has a continuous spectrum of symptoms that ranges from very severe to mild across the four classifications of SMA types
- SMA experts recommend that medical care for patients should be tailored to their current level of function. Please see for more information the Consensus Statement for Standard of Care [3] or the Family Guide to the Consensus Statement [4]

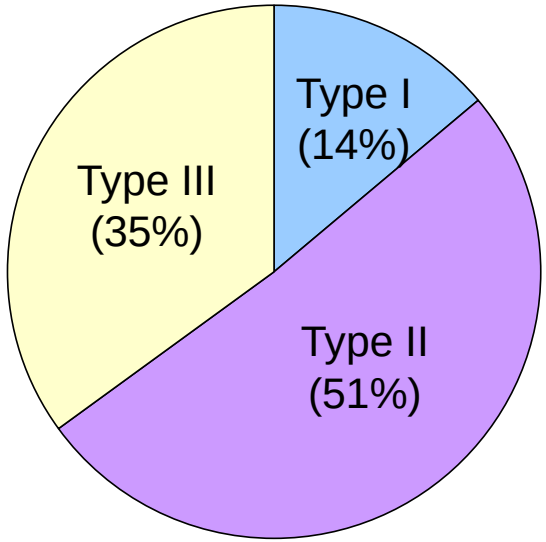
SMA Incidence and Prevalence Rates Are Different

SMA incidence:
estimated incidence per live birth



[5]

SMA prevalence:
estimated number of all SMA patients living in the population

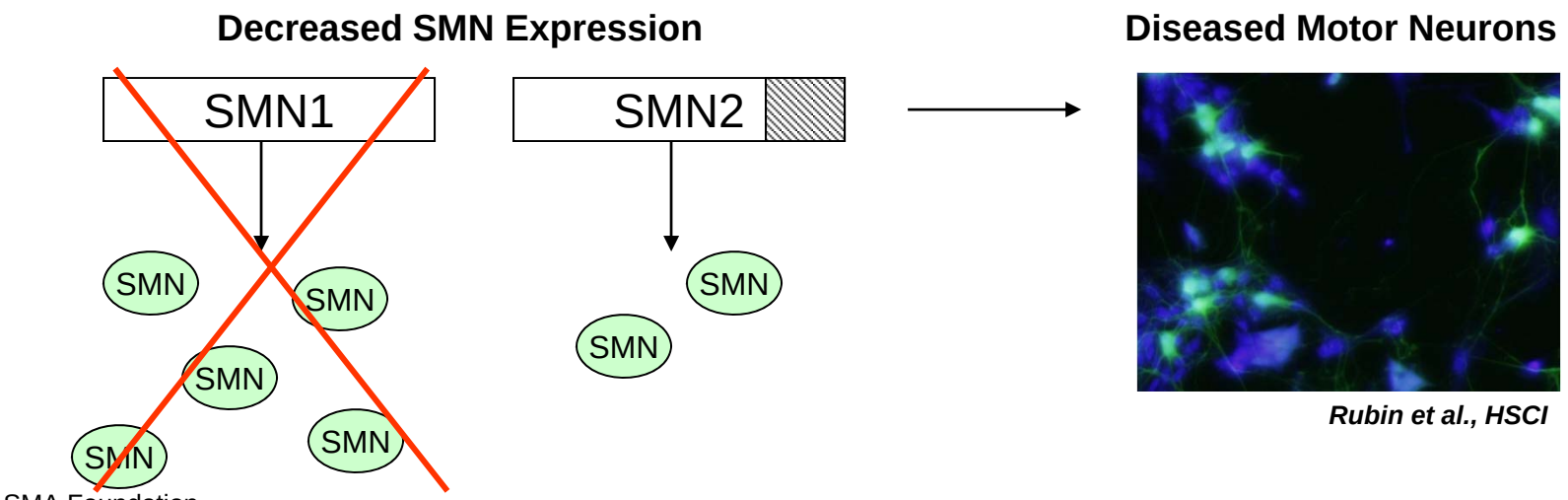


[6]

Type IV is not common; limited information available

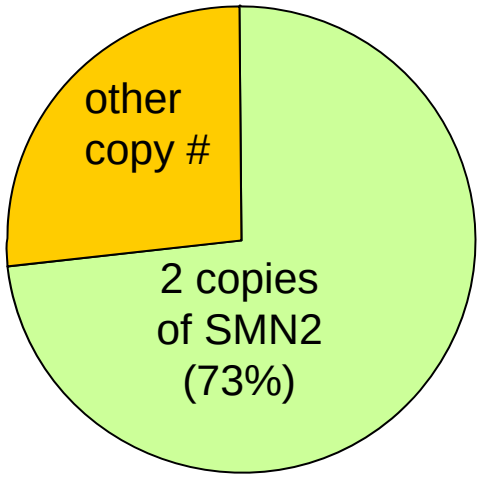
Spinal Muscular Atrophy Is Caused by Defects in the SMN1 Gene

- Mutations or deletions in SMN1 gene cause SMA: unlike most neurologic diseases, there is a single known cause [7]
- SMN1 gene encodes SMN protein
- SMA is a result of decreased levels of SMN protein
- There is an additional ("backup") copy of the SMN1 gene which is called SMN2
  - SMN1 and SMN2 genes are >99% identical, however SMN2 produces low levels of SMN protein

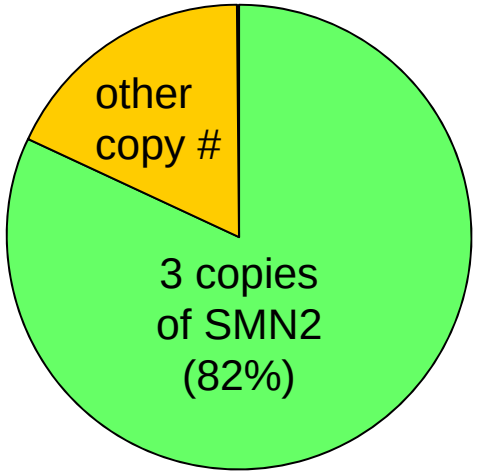


In SMA, when SMN1 Gene Is Defective, the Amount of SMN2 Is Important

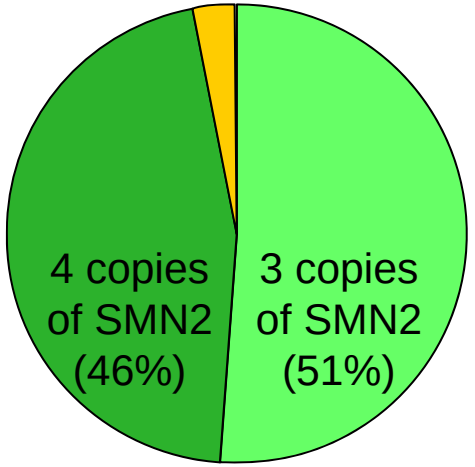
- In humans, the number of SMN2 genes varies from person to person [8]
- Generally, patients with less severe forms of SMA have more SMN2 copies
- There are exceptions; therefore SMN2 copy number does not predict what will happen with an individual patient



Type I



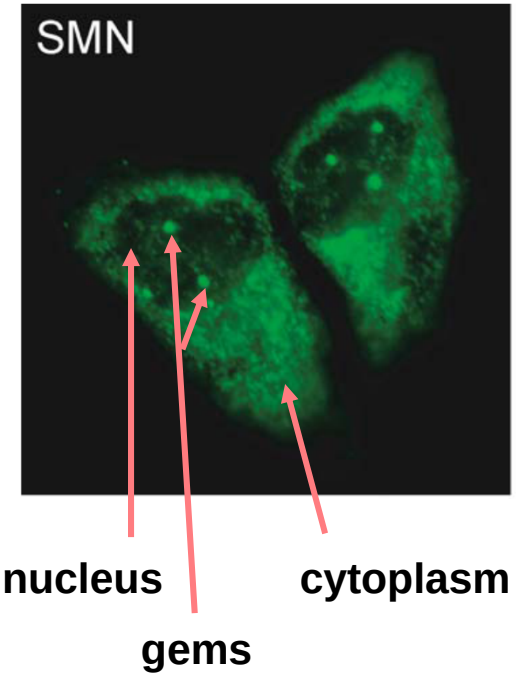
Type II



Type III

Functions of SMN Protein Are Increasingly Understood

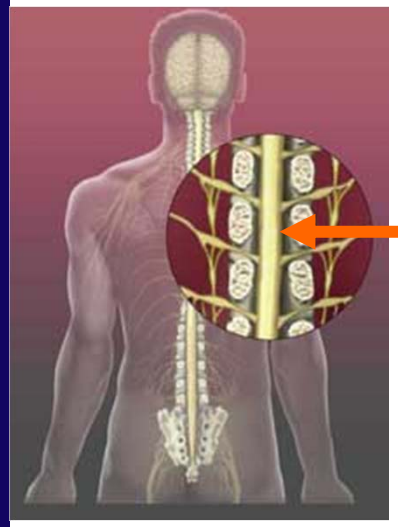
- SMN: Survival Motor Neuron
  - Essential in all species
  - Different levels are required in different cells
  - Present in both nucleus and cytoplasm
- SMN protein has multiple functions[10,11,12,13]
  - Biogenesis and metabolism of various ribonucleoprotein (RNP) complexes
    - Cytoplasmic assembly of spliceosome
    - Nuclear pre-mRNA splicing
  - Implicated in mRNA transport and regulation
  - Reduced SMN level leads to dysfunction/loss of α-motor neurons of the spinal cord



[9]

Two human cells stained with antibody to SMN protein (shown in green). SMN is highly enriched within discrete bodies called gems

α-Motor Neurons of the Spinal Cord Innervate Skeletal Muscles and Are Responsible for Muscle Contraction



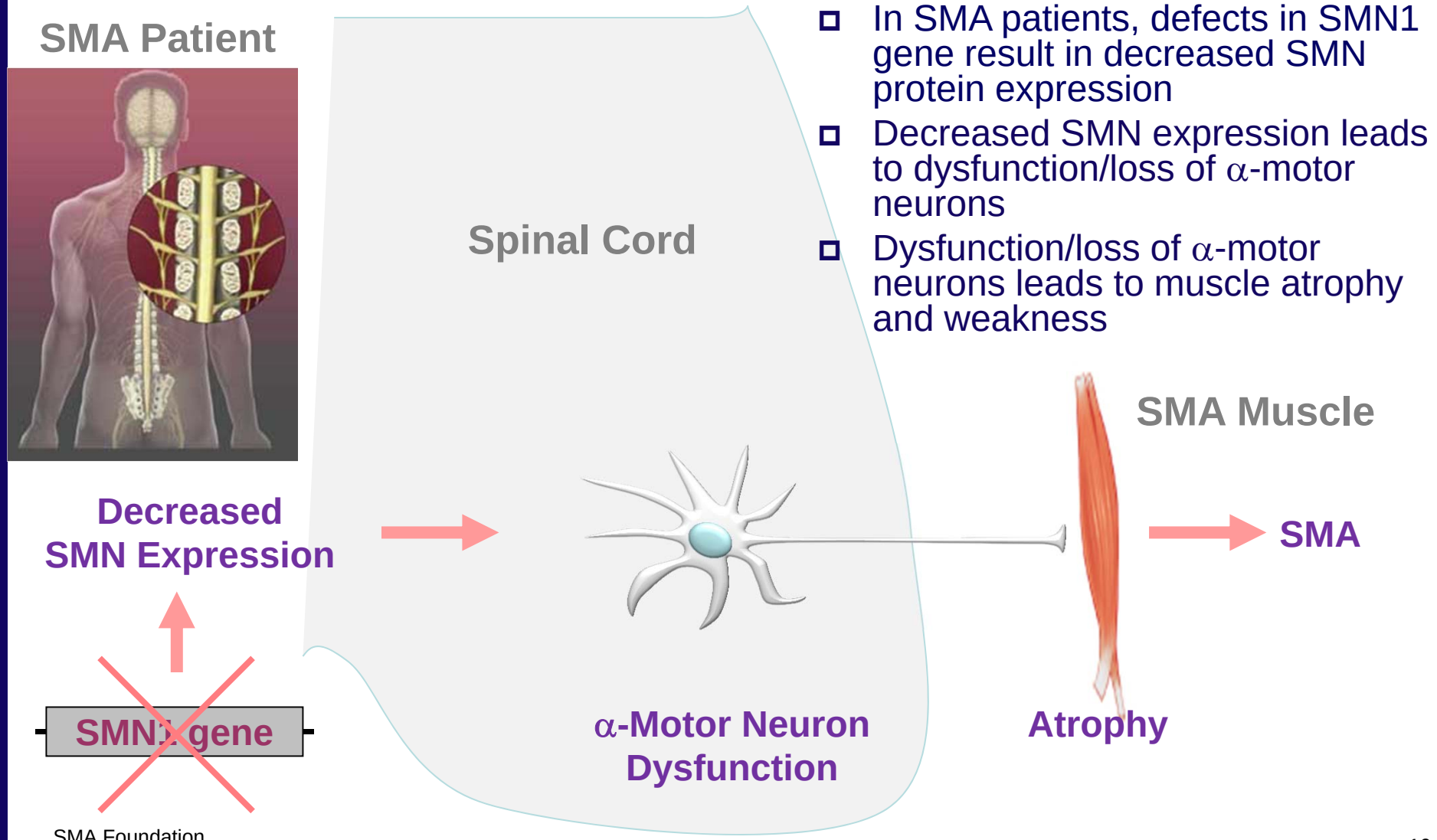
Spinal Cord

Normal Muscle

Normal α-Motor Neuron

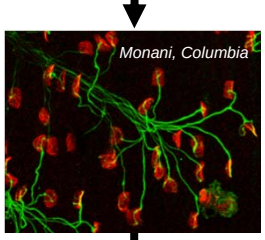
SMA Is Characterized by Dysfunction/Loss of α-Motor Neurons

- In SMA patients, defects in SMN1 gene result in decreased SMN protein expression
- Decreased SMN expression leads to dysfunction/loss of α-motor neurons
- Dysfunction/loss of α-motor neurons leads to muscle atrophy and weakness



Treatment Strategies for SMA Are Focused on Increasing SMN

Targets in Patients	Treatment Strategy [14]
GENE	SMN Gene Replacement
mRNA	Increase SMN Transcription
	Correct Splicing
	Stabilize Transcript
PROTEIN	Increase Translation of SMN
	Stabilize Protein



Preliminary Evidence Suggests that Increasing SMN May Be Beneficial for Patients

- SMN upregulation is achievable in mouse SMA models and provides functional and survival benefit
  - SMN upregulating therapies include: small molecules, antisense oligonucleotides, gene therapy [15]
  - Presymptomatic treatment in SMA mice prevents disease [16, 17]
  - Treatment at onset in SMA mice results in partial or complete reversal of SMA phenotype [15,17]
  - Treatment at progression in SMA mice is beneficial [17, 18]
- Treatment early in disease may provide greatest patient benefit
  - Infants born with even the most severe form of SMA have functional motor neurons
  - Newborn screening is an important tool to help to achieve early treatment

References

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