SMA FOUNDATION

SMA OVERVIEW



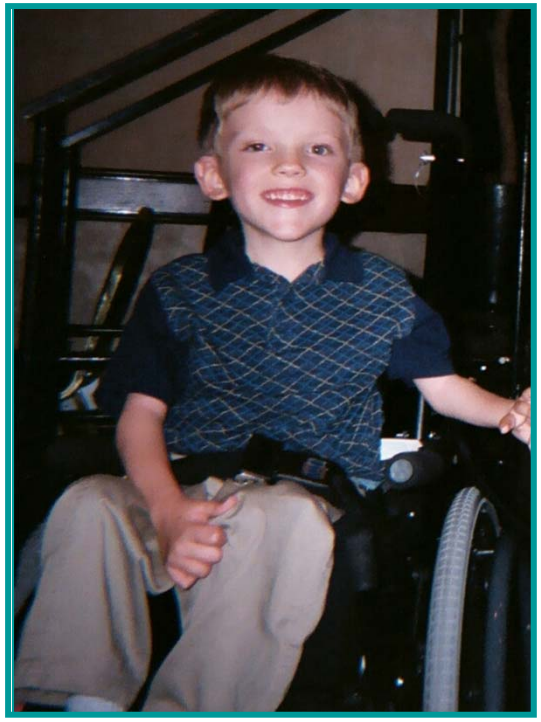


SMA IS A SEVERE NEUROLOGICAL DISORDER[1]

- Autosomal recessive genetic inheritance
- 1 in 50 people (approximately 6 million Americans) are carriers[2]
- 1 in 6,000 to 1 in 10,000 children born with SMA (incidence)[3]
- Well-defined patient population
- One of the most common rare diseases
  - According to a variety of sources, estimated number of patients in the United States is between 10,000 – 25,000 (prevalence)
  - Incidence comparable to cystic fibrosis, Duchenne muscular dystrophy and 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



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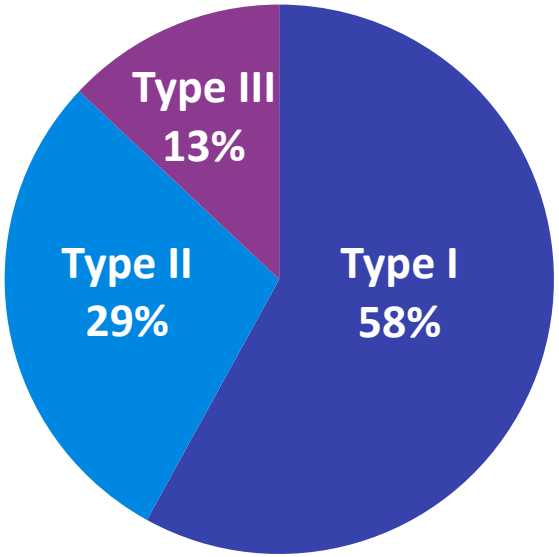
SMA VARIES IN SEVERITY [4]

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[4] or the Family Guide to the Consensus Statement[5]

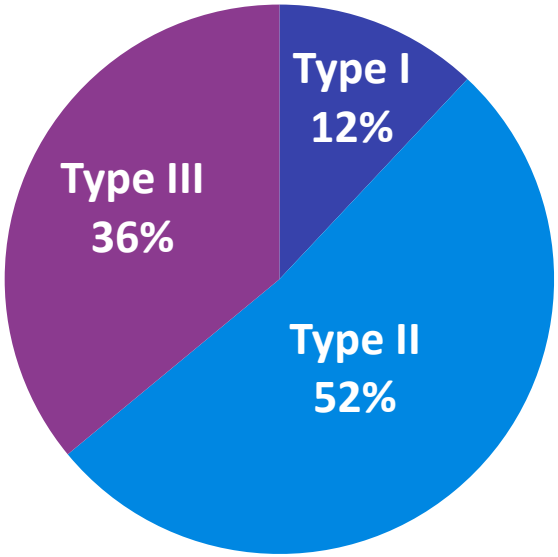
SMA INCIDENCE AND PREVALENCE ARE DIFFERENT

SMA incidence:
estimated incidence
per live birth



[6]

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



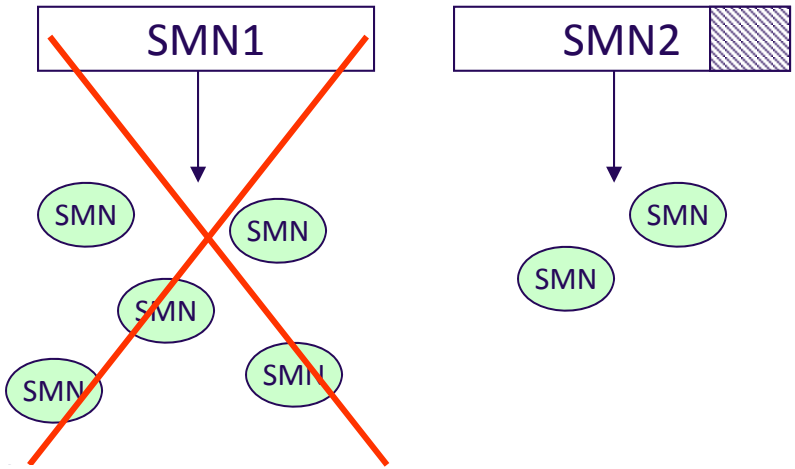
[7]

Type IV is not common; limited information available

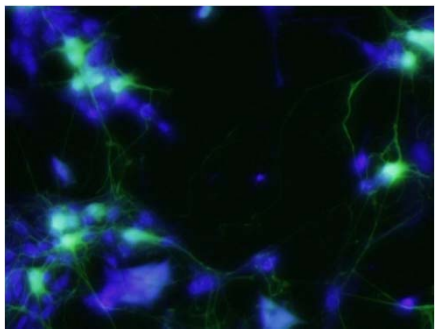
SPINAL MUSCULAR ATROPHY IS CAUSED BY DEFECTS IN THE SMN1 GENE

- Mutations or deletions in SMN1 gene cause SMA: unlike most neurologic diseases, there is a single known cause[8]
- 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

Decreased SMN Expression



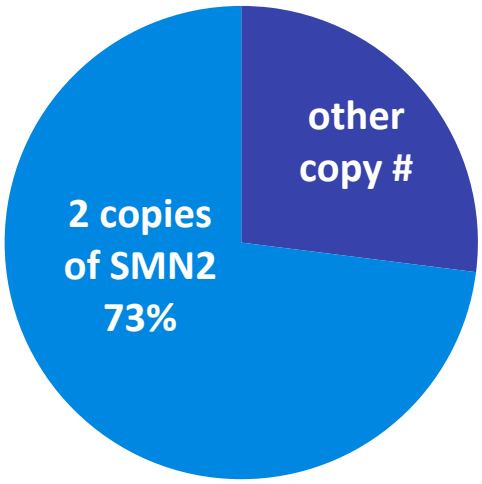
Diseased Motor Neurons



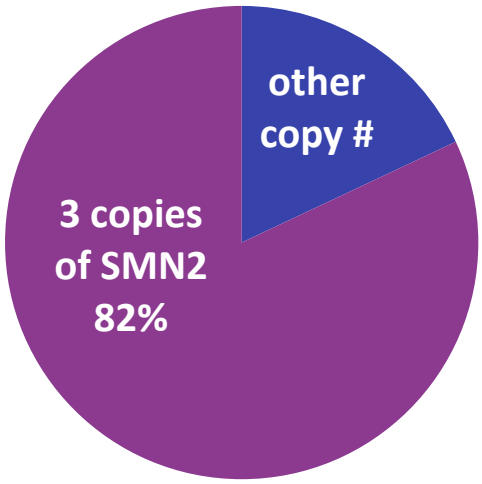
Rubin et al., HSCI

IN SMA, WHEN SMN1 GENE IS DEFECTIVE, THE AMOUNT OF SMN2 IS IMPORTANT

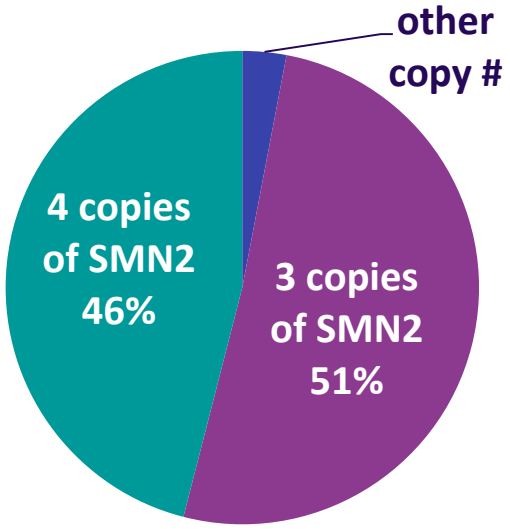
- In humans, the number of SMN2 genes varies from person to person[9]
- Generally, patients with less severe forms of SMA have more SMN2 copies
- There are exceptions; therefore SMN2 copy number does not predict what will happen with an individual patient



Type I



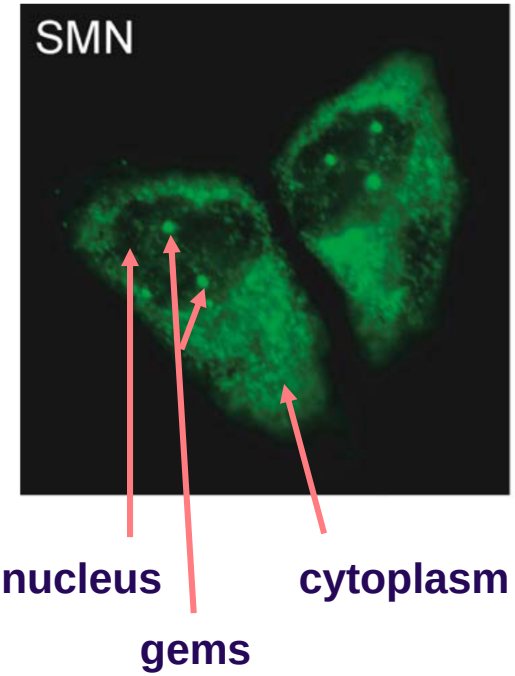
Type II



Type III

FUNCTIONS OF SMN PROTEIN ARE INCREASINGLY UNDERSTOOD

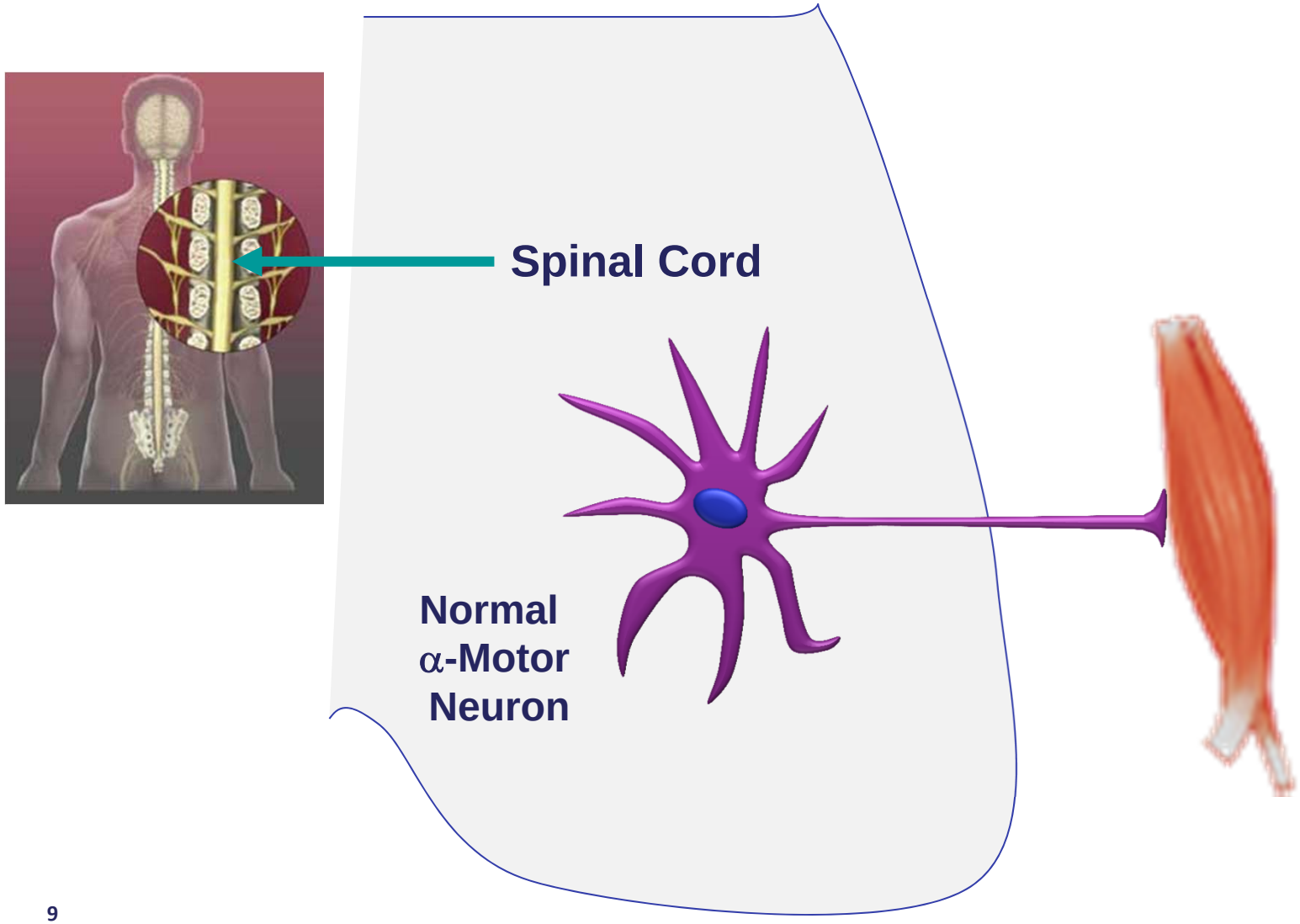
- SMN: Survival Motor Neuron
  - Essential in all species
  - Different levels are required in different cells
  - Present in both nucleus and cytoplasm
- SMN protein has multiple functions[11, 12, 13, 14]
  - Biogenesis and metabolism of various ribonucleoprotein (RNP) complexes
    - Cytoplasmic assembly 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



[10]

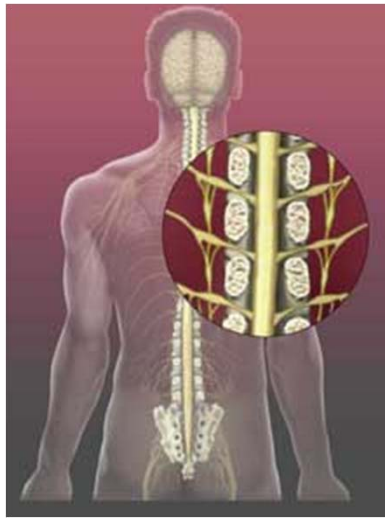
Two human cells stained with antibody to SMN protein (shown in green). SMN is highly enriched within discrete bodies called gems

α-MOTOR NEURONS OF THE SPINAL CORD INNERVATE SKELETAL MUSCLES AND ARE RESPONSIBLE FOR MUSCLE CONTRACTION



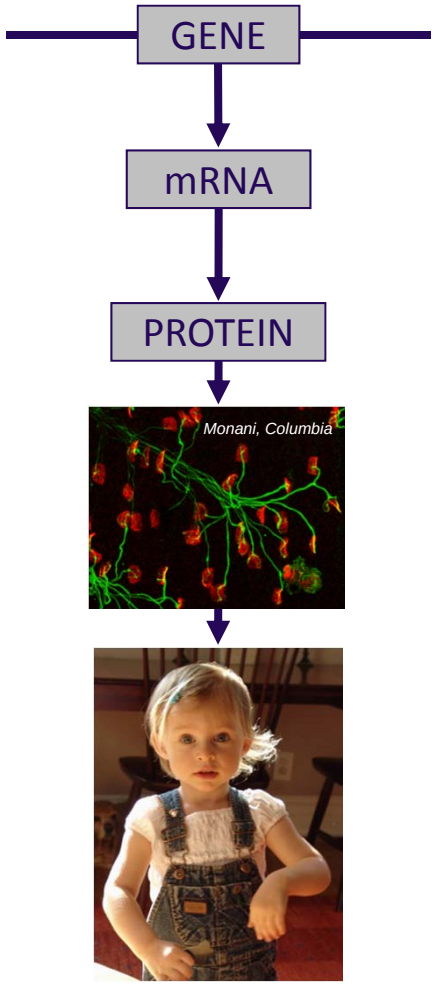
SMA IS CHARACTERIZED BY DYSFUNCTION/LOSS OF α-MOTOR NEURONS

- 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 [15]

SMN Gene Replacement

Increase SMN Transcription

Correct Splicing

Stabilize Transcript

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
  - Presymptomatic treatment in SMA mice prevents disease [16, 17]
  - Treatment at onset in SMA mice results in partial or complete reversal of SMA phenotype [16,18]
  - Treatment at progression in SMA mice is beneficial [17, 18, 19]
- 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

1. Crawford and Pardo, Neurobiol Dis 1996
2. Sugarman et al., European J of Hum Genet 2011
3. National Human Genome Research Institute http://www.genome.gov/20519681
4. Wang et al., J Child Neurol 2007
5. Patient Advisory Group of the International Coordinating Committee for SMA Clinical Trials http://www.smafoundation.org/pdf/A-Guide-to-SMA-Standard-of-Care-(English).pdf
6. Ogino et al., Eur J Hum Genet 2004
7. SMA Foundation estimation
8. Lefebre et al., Cell 1995
9. Feldkotter et al., Am J Hum Genet 2002
10. Gubitz et al., Exp Cell Res 2004
11. Paushkin et al., Curr Opin Cell Biol 2002
12. Pellizzoni, EMBO Rep 2007
13. Monani, Neuron 2005
14. Burghes and Beattie, Nat Rev Neurosci 2009
15. Burnett et al., Curr Treat Options Neurol 2009
16. Meyer et al., Human Mol Gen 2009
17. Lutz et al., J. Clin Invest 2011
18. Avila et al., J. Clin Invest 2007
19. Presentation at 15th Annual SMA Research Group meeting (Naryshkin)

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