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]

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

- 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

- Type I (60%)
- Type II (27%)
- Type III (12%)

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

- Type I (14%)
- Type II (51%)
- Type III (35%)

Type IV is not common; limited information available

[5]

[6]
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

Decreased SMN Expression → Diseased Motor Neurons

Rubin et al., HSCI
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.
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 \(\alpha\)-motor neurons of the spinal cord

*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 α-Motor Neuron
- Normal Muscle
SMA Is Characterized by Dysfunction/Loss of \( \alpha \)-Motor Neurons

- In SMA patients, defects in SMN1 gene result in decreased SMN protein expression.
- Decreased SMN expression leads to dysfunction/loss of \( \alpha \)-motor neurons.
- Dysfunction/loss of \( \alpha \)-motor neurons leads to muscle atrophy and weakness.
### Treatment Strategies for SMA Are Focused on Increasing SMN

<table>
<thead>
<tr>
<th>Targets in Patients</th>
<th>Treatment Strategy [14]</th>
</tr>
</thead>
<tbody>
<tr>
<td>GENE</td>
<td>SMN Gene Replacement</td>
</tr>
<tr>
<td>mRNA</td>
<td>Increase SMN Transcription</td>
</tr>
<tr>
<td>PROTEIN</td>
<td>Correct Splicing</td>
</tr>
<tr>
<td></td>
<td>Stabilize Transcript</td>
</tr>
<tr>
<td></td>
<td>Increase Translation of SMN</td>
</tr>
<tr>
<td></td>
<td>Stabilize Protein</td>
</tr>
</tbody>
</table>

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[Image: Monani, Columbia]
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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6. SMA Foundation estimation
7. Lefebre et al., Cell 1995
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12. Monani, Neuron 2005
13. Burghes and Beattie, Nat Rev Neurosci 2009
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15. Presentations at 13th Annual SMA Research Group meeting (Kaspar, Passini, Aebischer, Krainer)
17. Presentations at 13th Annual SMA Research Group meeting (Lutz/SMA Foundation, Burghes, Krainer)