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Spinal Muscular Atrophy (SMA)

SMA is a rare and devastating genetic disease caused by a lack of a functional survival motor neuron 1 (*SMN1*) gene, resulting in the rapid and irreversible loss of motor neurons, affecting muscle functions, including breathing, swallowing and basic movement.

SMA is a rare condition yet it is a leading genetic cause of infant death. Globally, about 1 in 54 people carry the genetic defect that leads to SMA. When both parents are carriers, their baby has a 25% chance of being diagnosed with the condition. It is imperative to diagnose SMA and begin treatment, including proactive supportive care, as early as possible to halt irreversible motor neuron loss and disease progression.

Four primary types of SMA

There are four primary types of SMA. The severity of SMA varies across a spectrum of types that each correspond to the copy number of the SMN2 gene, the “backup gene” that produces a small fraction (~10%) of functional SMN protein compared with *SMN1*.

Type 1: SMA patients typically have 1-2 copies of *SMN2*

- About 60% of all SMA cases are Type 1
- Early onset with diagnosis usually in an infant’s first six months
- Leads to death or the need for permanent ventilation and feeding support by the age of two in more than 90% of cases if untreated
- The symptoms are difficulty breathing and swallowing, poor head control, weak cry, and worsening muscle weakness and poor muscle tone (hypotonia), leading to “floppy” or “frog-leg” posture

Type 2: SMA patients typically have 2-3 copies of *SMN2*

- Onset between 6-18 months of age
- Reduced life expectancy; more than 30% will die by age 25 if untreated
- Most affected individuals will not be able to stand without support
- They may be able to sit independently early in development, but often lose this ability by their mid-teens
- They may experience trembling in their fingers and skeletal abnormalities, such as scoliosis and hip dislocation
- Difficulty with feeding and breathing often develop

Type 3: SMA patients typically have 3-4 copies of *SMN2*

- Symptoms typically appear in early childhood to early adulthood
- Individuals affected have difficulty walking, running and going up and down stairs
- They may lose their ability to stand or walk without support over time
- Their legs are more severely affected than their arms

Type 4: Adult onset

- Very rare
- Symptoms can start as early as 18 years but usually begin after age 30
- Mobility characteristics are similar to Type 3

The genetics behind SMA

Human DNA has many genes. Two genes that are involved in SMA are *SMN1* and *SMN2*.

SMN1 Gene: Inheritable Odds

Inheriting a mutated (changed) or missing *SMN1* gene prevents the body from producing adequate SMN (survival motor neuron) protein, which is critical to the survival of neurons that control our muscles.

People typically receive one copy of the *SMN1* gene from each parent. Only one functioning *SMN1* gene is needed to produce adequate levels of the SMN protein. Since SMA is a recessive trait, even though both parents may be healthy, each can carry and hand down a mutated (changed) or missing *SMN1* gene. If the child inherits both of these recessive *SMN1* genes, he or she will develop SMA.

Approximately 1 in 54 people carry the genetic defect for SMA, and two carriers have a 25% chance of having a child with SMA.

SMN2 Gene: A Secondary Source of SMN Protein

To make protein, the *SMN2* gene is read into an RNA sequence called pre-messenger RNA, or pre-mRNA. mRNA is the “recipe” for a protein, and is read (translated) by the cell to make a specific protein, in this case SMN. Small pieces of the pre-mRNA sequence called introns are often clipped out before mature mRNA is translated to make the protein.

Unfortunately, a piece that is supposed to remain, EXON 7, is inadvertently cut out of most of the mRNA strands coming from *SMN2*, resulting in ~90% of the protein product being an unstable, dysfunctional form of SMN protein that is degraded and only ~10% of the protein product being the full-length and functional SMN protein.

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