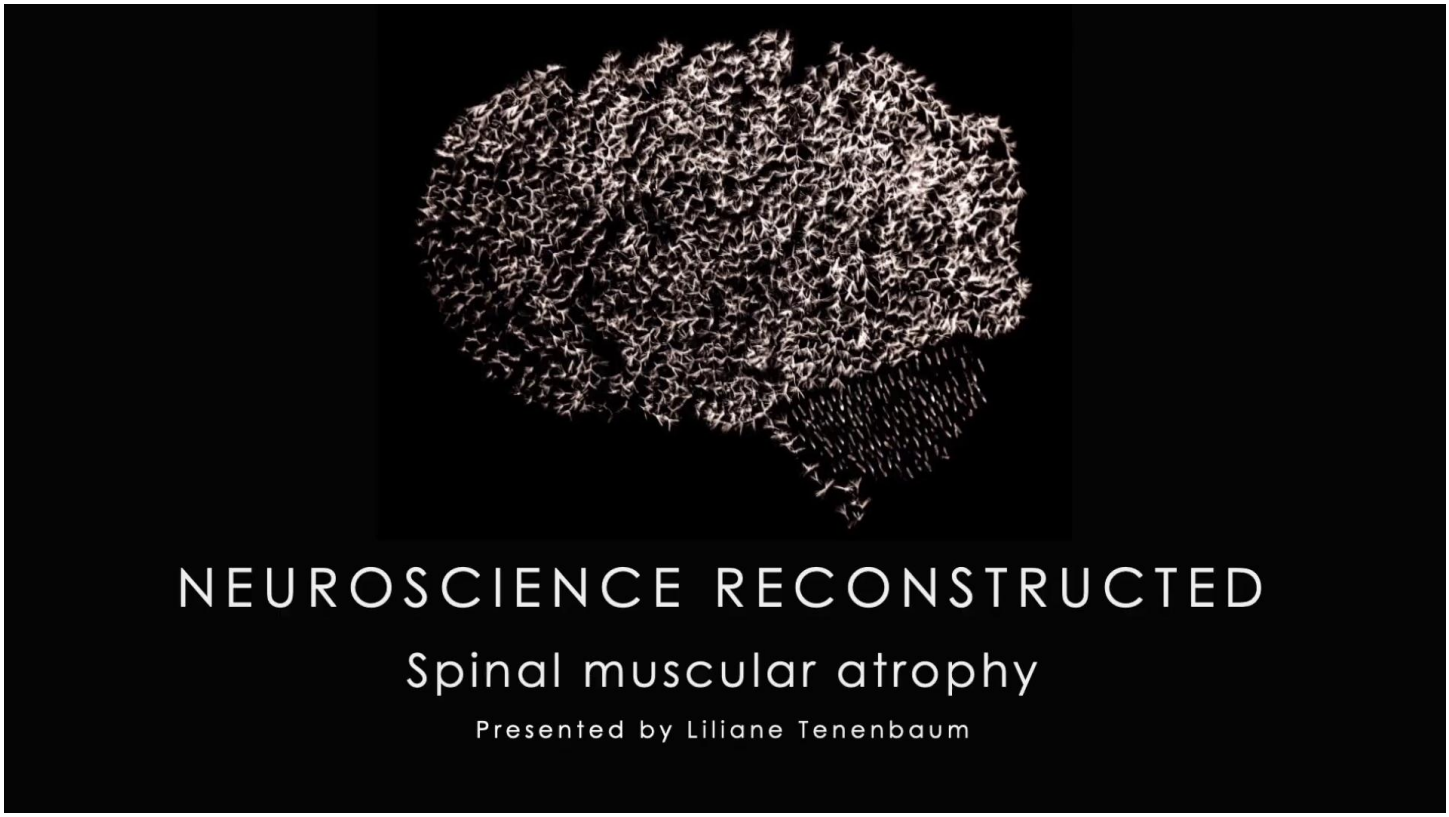


Search MOOC

Video

EPFL

Example: SMA

- Autosomal recessive disease due to mutation of the SMN1 gene; 1 in 6,000-10,000 births
- Early-onset neurodegenerative disease; loss of motor neurons
  - Muscle weakness and atrophy
  - Decline in respiratory and swallowing function
  - No treatment

Butchbach ME. Copy Number Variations in the Survival Motor Neuron Genes: Implications for Spinal Muscular Atrophy and Other Neurodegenerative Diseases. Front Mol Biosci. 2016 Mar 10;3:7. doi: 10.3389/fmolb.2016.00007.

Back to spinal muscular atrophy. It is a very rare disease. Only one child out of 6 to 10,000 are born with SMA. It's due to a mutation in the SMN1 gene. SMN1 is a protein that has multiple functions. No one until now understands exactly why it is actually giving rise to a motor neurone defect. It affects mainly motor neurons. It's known to be involved in splicing and RNA metabolism, but the specificity for motor neurone is not understood. It has been shown in knockout mice that SMN deficiency affects the development of axons. Therefore, you can understand that during development, the neurons will not make the right connections. The reason abut why it's specific to motor neurons, we don't know. I gave you here the incidents. One out of 10,000 babies are born with this mutation. But if you look at the overall population, we have only less than 10 cases per million inhabitants. This is very challenging to have enough patient to test a new therapy. What are the symptoms? It's a severe muscle weakness in atrophy. Due to that, there is a rapid decline in respiratory and swallowing function. This baby has to get respiratory support and they can never sit and even less walk.

Notes

Summary

0m 05s

Example: SMA

- Autosomal recessive disease due to mutation of the SMN1 gene; 1 in 6,000-10,000 births
- Early-onset neurodegenerative disease; loss of motor neurons
  - Muscle weakness and atrophy
  - Decline in respiratory and swallowing function
  - No treatment
- Different classes with different severities:

Type	Age of onset	Requires respiratory support at birth	Able to sit	Able to stand	Able to walk	Life expectancy
0	Prenatal	Yes	No	No	No	<6 months
1	<6 months	No	No	No	No	<2 years
2	6–18 months	No	Yes	No	No	10–40 years
3	>18 months	No	Yes	Yes	Assisted	Adult
4	>5 years	No	Yes	Yes	Yes	Adult

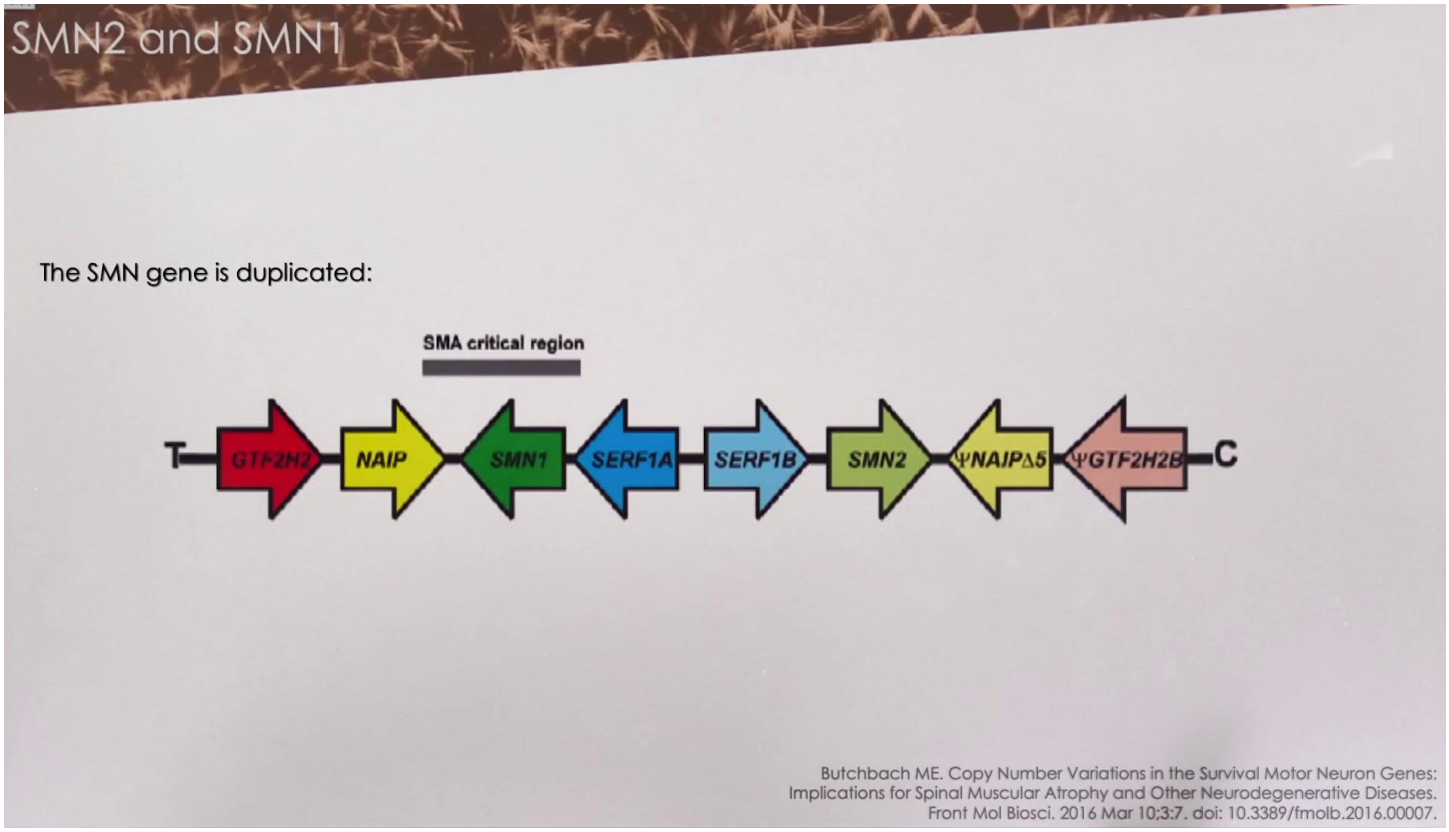
Butchbach ME. Copy Number Variations in the Survival Motor Neuron Genes: Implications for Spinal Muscular Atrophy and Other Neurodegenerative Diseases. Front Mol Biosci. 2016 Mar 10;3:7. doi: 10.3389/fmolb.2016.00007.

There is no other treatment. It's a very good case for risky but promising new treatment such as gene therapy. It's a recessive disease. The onset occurs very early in life. But interestingly, there are different types of SMA with very different severity. For example, type 0, the age of onset is before birth, and these babies immediately require respiratory support, and their life expectancy, will die before six months old. The different types have less and less severe symptoms. And for type 4, you see the age of onset is more than five years old, and these people can sit, stand, and walk, and they reach adult age.

Notes

Summary

2m 44s

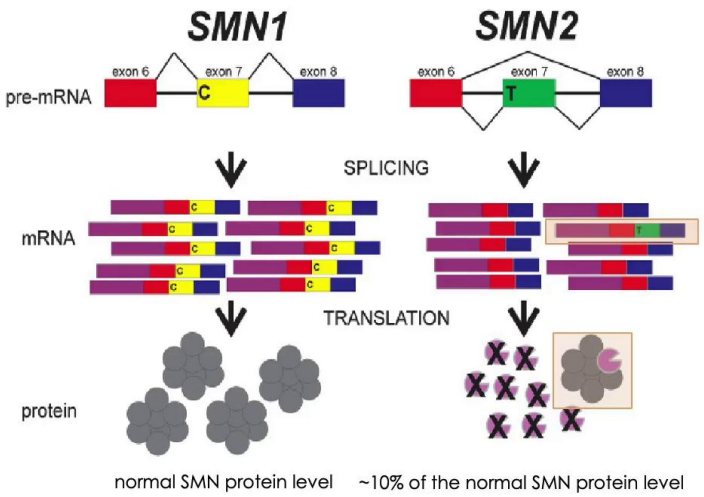


What is the genetic basis of the disease and how can we explain the different types? The region where all the mutation are found is the SMN1 gene, but this gene has a particularity. It has been duplicated. There is a SMN2 gene which is duplicated and inverted in everybody's genome.

Notes

Summary

4m 06s



A C>T **point mutation** in SMN2 affects an exon splicing enhancer sequence which enhances the inclusion of exon 7, leading to shorter SMN2 transcripts lacking exon 7.

Butchbach ME. Copy Number Variations in the Survival Motor Neuron Genes: Implications for Spinal Muscular Atrophy and Other Neurodegenerative Diseases. Front Mol Biosci. 2016 Mar 10;3:7. doi: 10.3389/fmolb.2016.00007.

Interestingly, here you have a part of the SMN gene and you see that exons six, seven, and eight are included in the messenger RNA, which is then translated into a normal SMN protein. SMN2 is actually a variant of SMN1 that has mutation in a site that affects exon splicing. You see here, instead of a C, it has a T in the beginning of exon 7. This mutation is located in a sequence which enhance the inclusion of exon 7. Most of the messenger RNA don't have exon 7, and the resulting protein is deficient. But in 10% of the case, nevertheless, the normal splicing occurs and exon 7 is included, you see here. This protein will be functional. It means that SMN2 is providing 10% of the normal SMN protein level. What happens in the disease?

Notes

Summary

4m 43s

Gene therapy for SMA

The severity of the disease is inversely proportional to the number of SMN2 copies:

Number of SMN2 copies	Type	Age of onset	Requires respiratory support at birth	Able to sit	Able to stand	Able to walk	Life expectancy
1	0	Pronatal	Yes	No	No	No	<6 months
2	1	<6 months	No	No	No	No	<2 years
3	2	0–18 months	No	Yes	No	No	10–40 years
4	3	>18 months	No	Yes	Yes	Assisted	Adult
5	4	>5 years	No	Yes	Yes	Yes	Adult

SMA is a simple case for gene therapy:

- The SMN1 deficiency can be **transcomplemented**
- One additional copy of SMN2 providing only 10% increased SMN protein level is theoretically enough to obtain clinical benefits

Butchbach ME. Copy Number Variations in the Survival Motor Neuron Genes: Implications for Spinal Muscular Atrophy and Other Neurodegenerative Diseases. Front Mol Biosci. 2016 Mar 10;3:7. doi: 10.3389/fmolb.2016.00007.

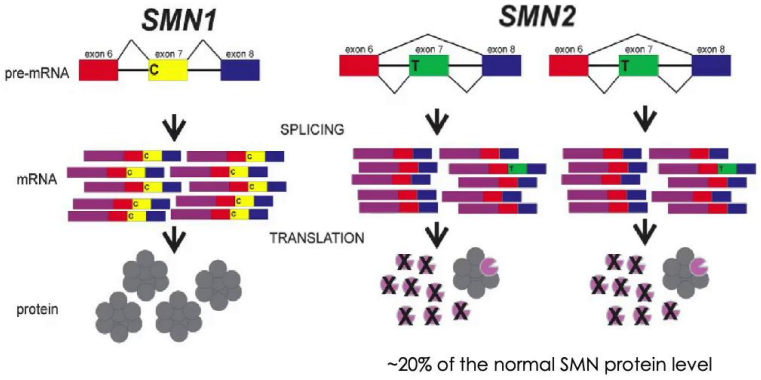
Actually, now we have an explanation for the different types of spinal muscular atrophy. What happens is that the SMN2 is always duplicated, but some people have more than one copy of SMN2. You can see here that the number of SMN copy is increasing with the classification from zero to four of the spinal muscular atrophy patients. In a way, the severity of the disease is inversely proportional to the number of SMN2 copies. Now, since we understood SMN2 is expressing the SMN protein, we understand that the more copies of SMN2 you have, the more functional SMN protein you will have. With five copies, you have 50% functional protein deriving from SMN2 in addition to SMN1. This is very interesting for gene therapy. First of all, it shows that the SMN1 deficiency can be transcomplemented. When you add a functional protein, it reverses, at least it reduces the symptom. That means that in theory, with only a 10% increase of SMN protein, you can get clinical benefit.

Notes

Summary

6m 27s

Gene therapy for SMA1: strategy 1



First strategy: deliver **SMN1 cDNA** to patients' neurons.

How?

Butchbach ME. Copy Number Variations in the Survival Motor Neuron Genes: Implications for Spinal Muscular Atrophy and Other Neurodegenerative Diseases. Front Mol Biosci. 2016 Mar 10;3:7. doi: 10.3389/fmolb.2016.00007.

The first patients that were targeted by this gene therapy strategy were type 1 SMA. In type 1 SMA, the SMN1 gene is inactivated, but you have two copies of SMN2. This 20% of the normal SMN proteins. The first strategy that was set up was to deliver the SMN1 cDNA to the patient neurons.

Notes

Summary

8m 30s