SCN2A INFORMATION SHEET #6

Gene Therapy

What is gene therapy?

- **Gene therapy** is a type of **precision medicine** that aims to treat health conditions by targeting the **gene** that is causing the condition (see Information Sheet #3 "Genetics 101") to learn about genes and how changes in genes cause health conditions)
- Gene therapy is a relatively new treatment. So far it is only being used in a small number of health conditions.
- There are several different types of gene therapy. The figure below shows how different gene therapies might target a gene that is causing a health condition like *SCN2A*.

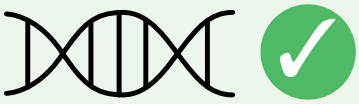
In short...

- There are many different types of **gene therapy.**
- All gene therapy has a common goal – to treat health conditions by **targeting the gene** that is causing the health condition.
- Gene therapies being investigated for the treatment of *SCN2A* include antisense oligonucleotides (ASOs), CRISPR activation, and tRNA-based gene therapy

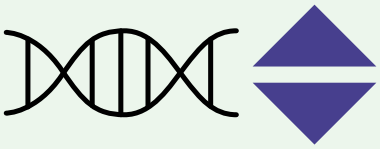
How the different types of gene therapy work

Turn the gene on or off

Add an unchanged (working) copy of the gene causing the condition

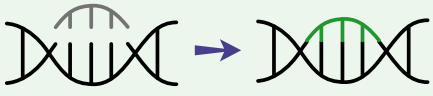


Turn the gene up or down



Remove the gene that is not working

Replace the part of the gene that is stopping it from working properly



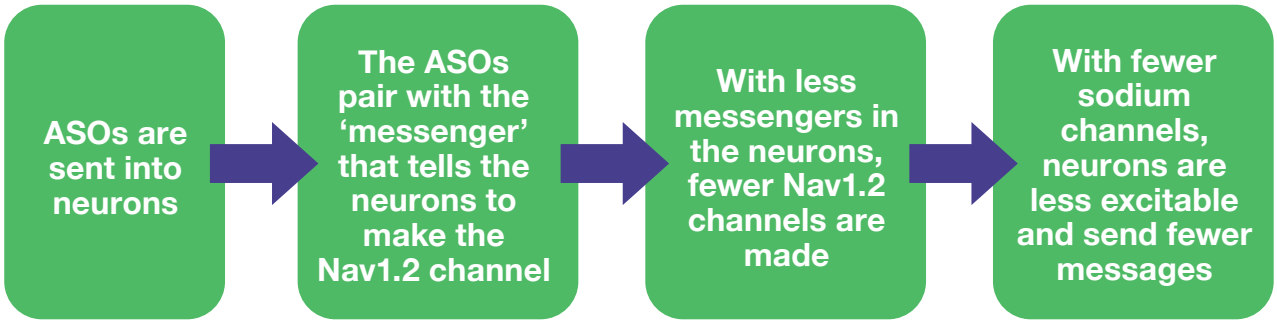
Advanced therapies for SCN2A

- Three types of treatment currently being investigated as potential treatments for SCN2A:
  - Antisense oligonucleotides (ASO)
  - CRISPR-activation (CRISPRa)
  - tRNA-based gene therapy.

Antisense oligonucleotides (ASOs)[1]

- An ASO is a type of chemical known as a nucleotide. DNA is also a nucleotide. (For more information about DNA, see Information Sheet #3 “Genetics 101”)
- In SCN2A, ASOs are being investigated to treat gain of function and loss of function changes in the SCN2A gene (for more information about gain of function and loss of function, see Information Sheet #2 “What does gain of function and loss of function mean?”).
- When there is a **gain of function** in the *SCN2A* gene, the Nav1.2 sodium channel in nerve cells (neurons) is overactive (see Information Sheet #1 “What is SCN2A”? for more information about the Nav1.2 sodium channel). The neurons send more messages than usual, which can cause seizures.

How ASOs work in SN2A

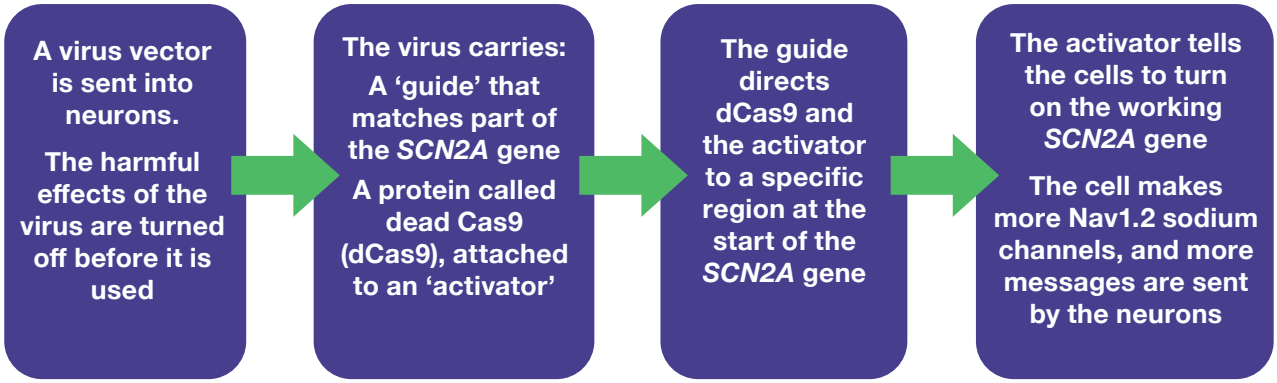


- ASOs have been tested in mice with gain of function changes in the *SCN2A* gene. In this mouse model the mice have seizures and shorter lives than mice without changes in *SCN2A.*
- When the *SCN2A* mice were given the ASO, they had less seizures and lived longer than the *SCN2A* mice that did not receive the ASO.
- An ASO to treat loss of function *SCN2A* is in the very early stages of clinical development.

CRISPR activation[2]

- CRISPR-Cas9 is a new genetic technology that can be used to edit (change) the genetic code. It can also be used to turn genes up or down.
- When there is a **loss of function** in the *SCN2A* gene, the Nav1.2 sodium channel may be underactive or there may be fewer Nav1.2 sodium channels. As a result, the neurons send fewer messages than usual.
- Individuals with loss of function changes usually have one working copy of the *SCN2A* gene and one that does not work properly. Overall this means that the neurons to not have enough working copies of the Nav 1.2 sodium channels.
- CRISPR activation (CRISPRa) is being investigated as a way of 'turning up' the working *SCN2A* gene in individuals with loss of function changes in *SCN2A*. This tells the neurons to make more Nav1.2 channels . Unlike regular CRISPR-Cas9, CRISPRa does not edit (change) the genetic code.

How CRISPRa works in SCN2A



tRNA-based gene therapy[3]

- A third type of gene therapy being investigated for **loss of function** *SCN2A* involves a special nucleotide called **transfer RNA** (tRNA).
- In many individuals with loss of function ***SCN2A***, a change in the *SCN2A* gene tells the cell to make shorter versions of the Nav1.2 sodium channel, which do not work properly.
- Researchers are investigating whether delivering a specially designed tRNA inside a virus vector can stop neurons from making the shorter Nav1.2 channels. Instead, they would make the full-size – working – version of Nav1.2.

More information

- MedlinePlus: What is gene therapy?
- MedlinePlus: What are genome editing and CRISPR-Cas9

References

1. Li M, et al. Antisense oligonucleotide therapy reduces seizures and extends life span in an SCN2A gain-of-function epilepsy model. J Clin Invest 2021;131:e152079. [PubMed].
2. Tamura S, et al. CRISPR activation rescues abnormalities in SCN2A haploinsufficiency-associated autism spectrum disorder. bioRxiv. 01 April, 2022. Available at https://www.biorxiv.org/content/10.1101/2022.03.30.486483v1. Accessed 17 July 2022.
3. Ahern C. A tRNA-based gene therapy approach for high-fidelity repair of SCN2A premature termination codons. Available at https://www.sfari.org/funded-project/a-trna-based-gene-therapy-approach-for-high-fidelity-repair-of-scn2a-premature-termination-codons/. Accessed 17 July