

What does gain of function and loss of function mean?

In short...

Changes (variants) in the *SCN2A* gene affect the way the Nav1.2 sodium channel works in brain cells (neurons)

- Gain of function (GOF) variants in the *SCN2A* gene make Nav1.2 **more** active than usual. This means **more** messages are sent between neurons
- Individuals with seizures that start soon after birth often have GOF variants
- Loss of function (LOF) variants make Nav1.2 **less** active than usual. This means **fewer** messages are sent between neurons
- Individuals with intellectual disability and/or autism spectrum disorders without epilepsy often have LOF variants

About *SCN2A* and Nav1.2 ¹

- *SCN2A* is a **gene** that tells the body to produce the protein called **Nav1.2**.
- Nav1.2 is an important **sodium channel** in the brain. It lets a chemical called **sodium** into and out of brain cells (**neurons**).
- The movement of sodium tells the neurons to 'fire', which sends messages between neurons and to the rest of the body.

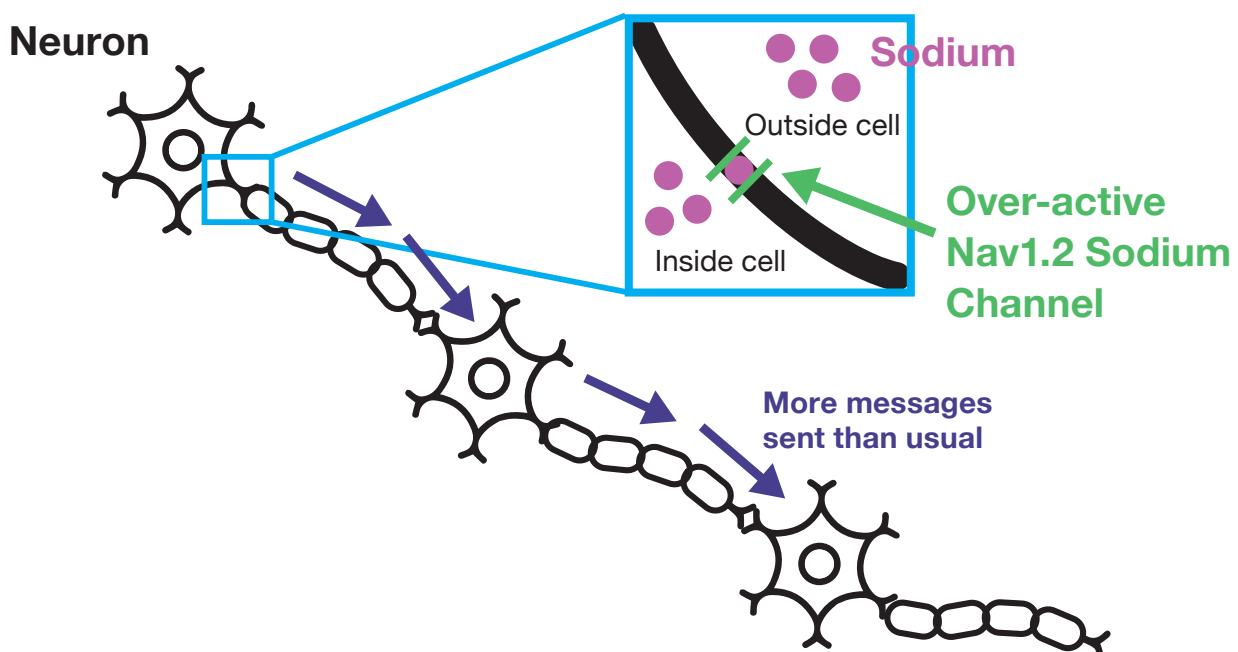
The impact of changes in the *SCN2A* gene ²⁻⁶

- Changes (variants) in the genetic code of the *SCN2A* gene affect the way the Nav1.2 channel works.
- A wide range of changes in the *SCN2A* gene have been seen. These have been broadly grouped into two different types: **gain of function** and **loss of function** variants.

Gain of function variants ⁷⁻¹¹

- **Gain of function** (GOF) variants result in a Nav1.2 channel that lets in **more** sodium than usual. The **overactive** channel can cause brain cells to fire **more frequently** than usual. This sends more messages between neurons.
- Often, individuals with GOF variants develop epilepsy. The more overactive the channel, the more severe the epilepsy.
- Intellectual disability is generally more severe in individuals with very overactive Nav1.2 channels compared to those with GOF variants leading to less active Nav1.2 channels.
- Individuals with GOF variants usually have a relatively good response to the antiseizure medicines known as sodium channel blockers.

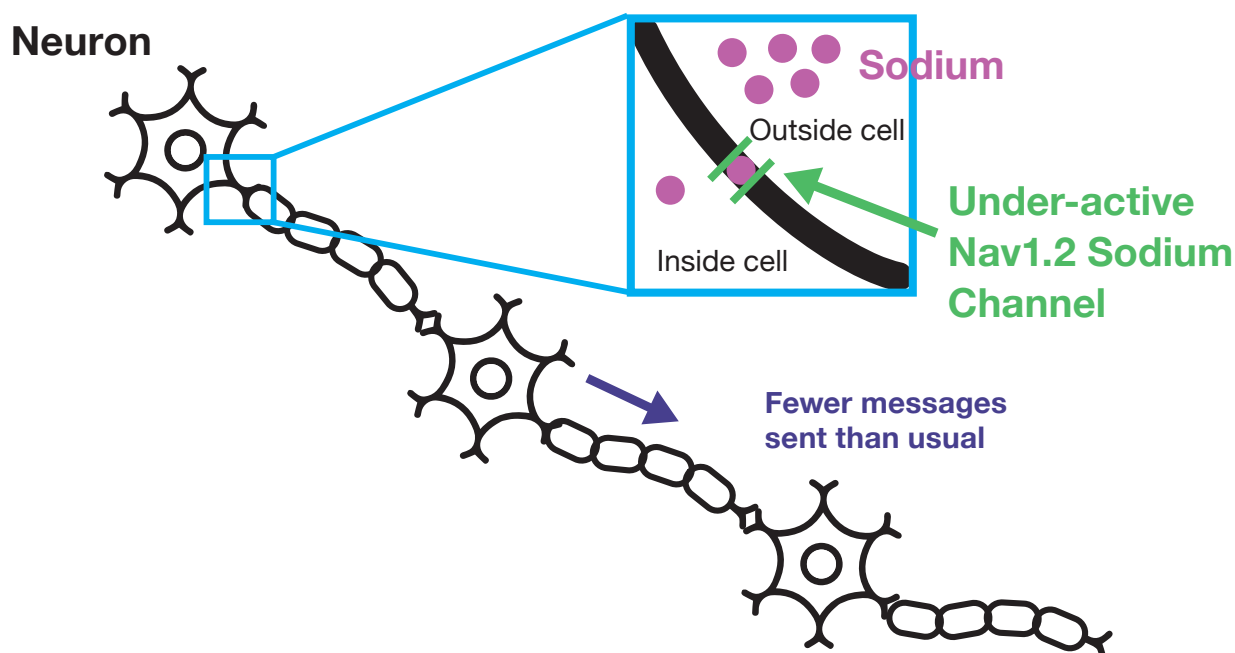
Gain of function



Loss of function variants ^{7,9,10}

- **Loss of function** (LOF) variants lead to a sodium channel that lets in **less** sodium than usual. The **underactive** channel can cause brain cells to fire **less frequently** than usual. Fewer messages are then sent between neurons.
- LOF variants have been seen in individuals with epilepsy, most often in those with seizures that develop after 3 months of age. Sodium channel blockers do not seem to be effective in these individuals.
- Individuals with intellectual disability and/or autism spectrum disorder without epilepsy most often have LOF variants.

Loss of function



Mixed or unclear variants ^{9,11}

- A small number of variants have been found that show mixed GOF and LOF effects.
- Others cannot be placed into either category.

How can I tell which variant I have?

- Your neurologist or clinical geneticist is the best person to discuss this with. They will be aware of the testing options available and/or will be able to interpret the results that have already been reported.
- However, this information is generally not routinely reported, and may only be available in research or clinical trial settings.

References

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