HOW DOES A VARIANT IN *CACNA1D* CAUSE HYPERINSULINISM?

HYPERINSULINISM GENES

This summarises our information sheet on what we know about **hyperinsulinism** (shortened to HI) caused by a **variant in *CACNA1D*** (known as ***CACNA1D*-HI**). For more on congenital HI, check out our information sheets available from the link here!

KEY MESSAGES:

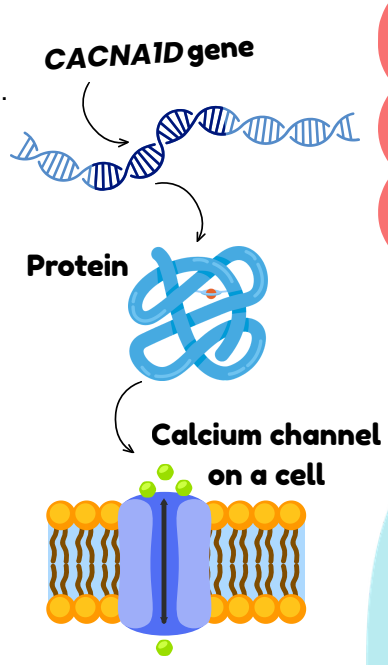
- ***CACNA1D*-HI** is caused by a **rare dominant *de novo* variant** in the *CACNA1D* gene
- The *CACNA1D* gene has the instructions to make a **protein** needed for a type of **calcium channel**
- Variants in *CACNA1D* make the **calcium channel overactive**, causing beta cells to release **too much insulin**, causing HI
- Because the *CACNA1D* calcium channel is **found around the body**, individuals can develop **other features** that **overlap with PASNA syndrome**
- The drug **diazoxide** was used to **manage the HI** in all the children, but it has been suggested that *CACNA1D*-HI could be treated with **calcium channel blockers** although **more research is needed**

WHAT IS *CACNA1D*-HI?

CACNA1D*-HI** is a genetic disorder caused by a **change (or variant)** within a **gene called *CACNA1D. Because this genetic variant is **present from birth**, *CACNA1D*-HI is considered a **congenital** condition.

HOW DO VARIANTS IN *CACNA1D* CAUSE HI?

The ***CACNA1D* gene** contains the instructions for a **protein** that makes a **calcium channel**.



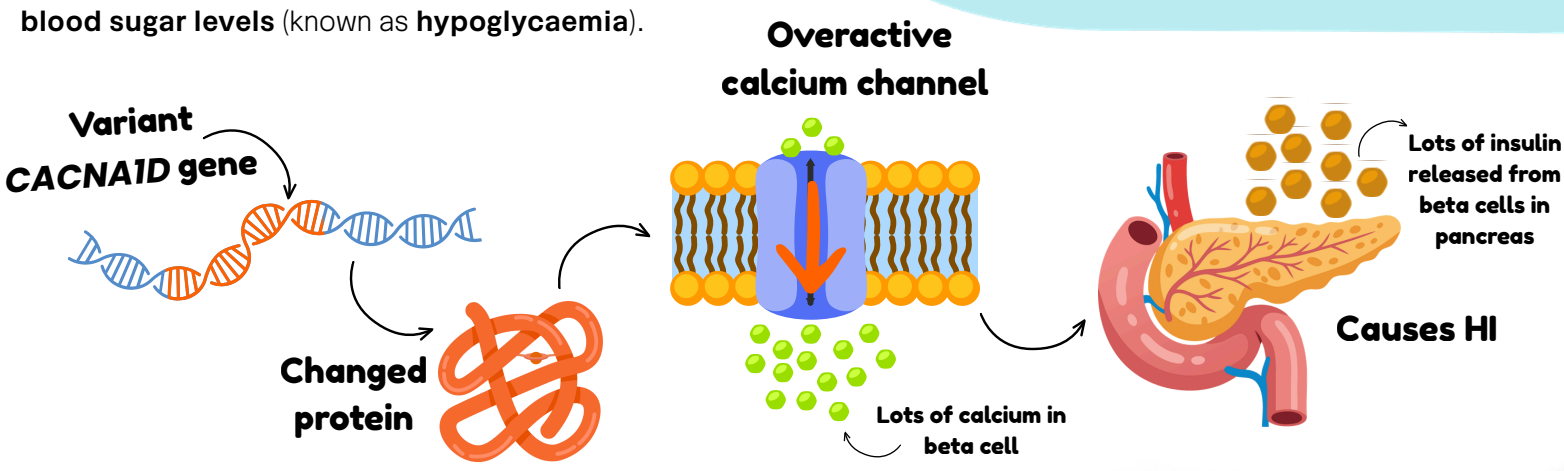
A calcium channel controls how much **calcium goes in and out of cells**. The amount of calcium released or taken into a cell can **change what a cell does**.

The calcium channel that *CACNA1D* helps to make is found in **lots of places** in the body, including in the **pancreas and the brain**.

In the pancreas, the calcium channel controls **how much calcium** is taken into the **beta cells,** which acts as a **signal** to **release insulin** into the blood.

In people with *CACNA1D*-HI, the **variant in *CACNA1D* changes the protein**. Because of this, the protein (and the calcium channel) **doesn't work properly.**

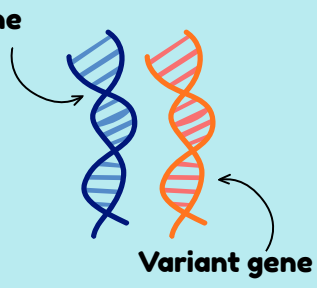
The calcium channel becomes **overactive** and lets **too much calcium** into the beta cells. This causes **more insulin** to be released into the blood, causing **low blood sugar levels** (known as **hypoglycaemia**).



IS IT RARE? HOW IS IT INHERITED?

CACNA1D-HI is a **very rare** form of HI. As of Spring 2025, we know of **8 children** diagnosed with this condition across the whole world.

CACNA1D variants that cause HI are **dominant variants.** To find out more about dominant variants, please look at our information sheet on the topic linked here.



In all 8 of the children, this variant was a ***de novo*** variant, meaning it happened for the **first time in the child.**

HOW DO YOU DIAGNOSE AND MANAGE IT?

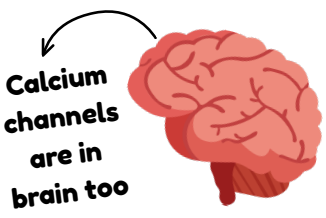
All of the reported children with *CACNA1D*-HI had an **increased weight at birth** and were diagnosed with **hypoglycaemia**.

At least 3 of the children were given the drug **diazoxide**, which was able to **treat the hypoglycaemia.**

The **HI lasted for different amounts of time** in each of the children, with one child having 'transient' hypoglycaemia for an unknown duration.

ARE THERE ANY OTHER ASSOCIATED FEATURES?

All 8 of the children with *CACNA1D*-HI have **additional features** that overlap with **PASNA syndrome.** These include:

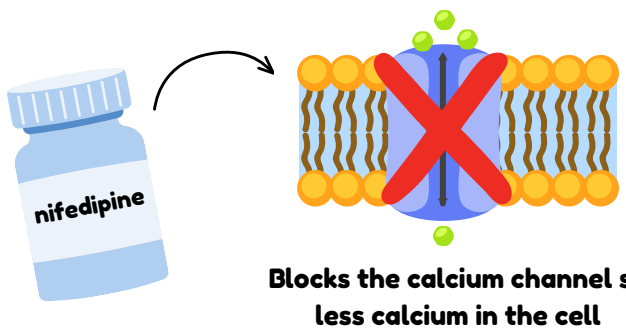


- Congenital primary aldosteronism (this can cause **high blood pressure** and **low potassium levels** in the blood known as hypokalaemia)
- Neurological abnormalities like **seizures, muscle weakness, developmental delay**, and **autism spectrum disorder**
- **Subtle changes** to the appearance of the **face** (called facial dysmorphisms)
- **Changes** to the **heart and blood vessels** (called cardiovascular abnormalities)
- **Hearing loss**
- **Cortical blindness**
- **Ambiguous genitalia**

The **number and severity** of these features are **very different** between these children. This suggests that *CACNA1D* variants cause a **broad range of symptoms** that can **vary between individuals.**

ARE THERE ANY OTHER POSSIBLE THERAPIES?

Because there is a genetic variant that **affects a calcium channel,** it has been suggested that **nifedipine,** a **calcium channel blocker**, could improve not only the **hypoglycaemia** but also the **neuromuscular symptoms.**



There is a **small amount of data** published on individuals with a *CACNA1D* variant who were treated with calcium channel blockers that **have varying results.**

There first needs to be **more studies** to check if this drug is right for people with *CACNA1D*-HI **before it can be offered as a treatment.**