HOW IS CONGENITAL HYPERINSULINISM INHERITED?

HYPERINSULINISM GENES

KEY MESSAGES:

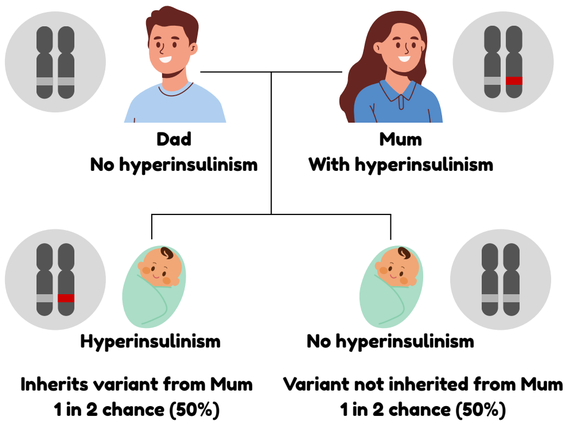
- **Congenital HI** is inherited in 2 main ways: **dominant** and **recessive**
- **Dominant** inheritance is where only **one copy of a variant** is needed. This variant is inherited from **one parent or is (or occurs) *de novo***
- **Recessive** inheritance is where **both copies of a gene** have a **variant**, one inherited from Mum and one from Dad
- **Focal congenital HI** is caused by a **variant inherited from an unaffected Dad** AND a **second random genetic event** that happens in the womb
- **Variable penetrance** is where **not everyone** who has the **same genetic variant** will **develop the condition**

This page summarises our information sheets on how **congenital hyperinsulinism** (shortened to HI) **is inherited**. Before reading this page, **check out our Introduction to Genetic Variation and Inheritance in Congenital HI quick-read explainer,** other information sheets, and glossary linked here!

DOMINANT INHERITANCE

To be affected with a dominant condition, **only one variant on one copy of the gene** is needed.

Dominant conditions can be **passed down through generations of a family** or appear for the **first time** in an individual (a ***de novo* variant**). These *de novo* variants usually happen in a **parent's egg or sperm cell** or happen in the **womb when the baby is growing**.



If someone has dominant congenital HI, **each of their children has a 1 in 2 (50%) chance of inheriting the variant**. The child is then predicted to develop congenital HI. Likewise, **each child has a 1 in 2 (50%) chance of not inheriting the variant** and being unaffected.

Changes in genes, such as ***ABCC8, GCK, GLUD1, HK1, SLC16A1, KMT2D, CACNA1D* or *HNF4A*** can cause dominantly inherited congenital HI. Dominant variants cause **diffuse pancreatic disease**.

Dominant variants can also lead to **variable penetrance**, explained more here.

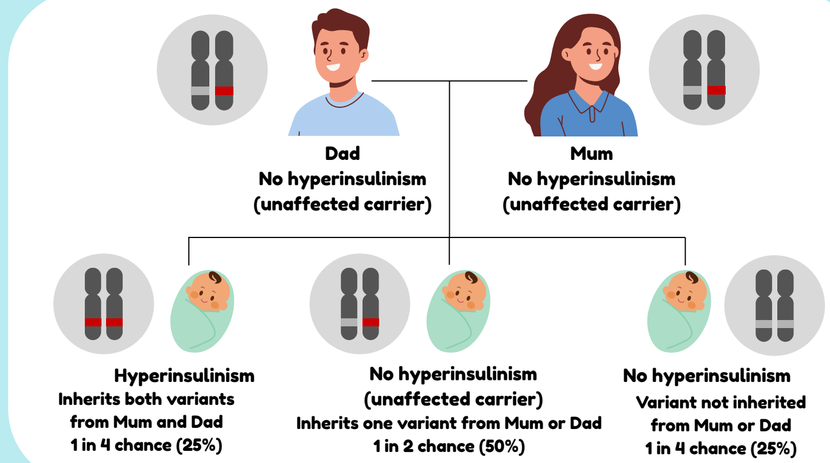
RECESSIVE INHERITANCE

To be affected with a recessive condition, **both copies of the gene must have a variant that causes congenital HI**. One copy would be inherited from Mum and one copy from Dad.

Recessive variants have been seen in the ***ABCC8, KCNJ11, HADH*, and *PMM2*** genes. These cause **diffuse pancreatic disease**.

Parents who have **one copy of a recessive variant** in their gene are referred to as a **carrier**. Carriers are **not expected to have congenital HI**, as **one recessive variant is not enough** to cause the disease.

When **both parents are both carriers** (each have one recessive variant in the same gene), **each of their children** has the following **chance of inheriting the variant**:



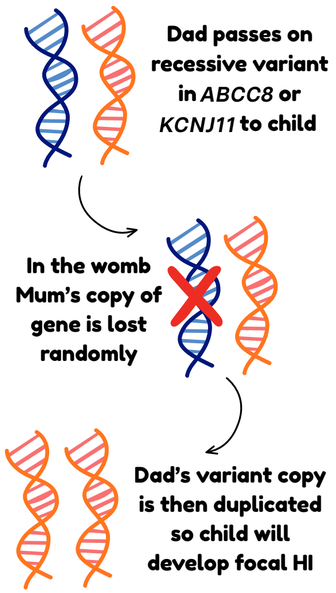
Each **child of a person with congenital HI caused by recessive variants** usually has a **low risk** of developing the condition because they **will only pass on one variant** to their child which is **not enough to cause HI**. **BUT** there are **2 situations** where there is an **increased likelihood** of a child being affected:

- The partner and the person with congenital HI are **related by blood**
- The genetic condition is particularly **common in the population** that the two parents are from

INHERITANCE OF FOCAL DISEASE

Focal congenital HI happens when **2 separate genetic events** come together.

First, a child **inherits a recessive variant** in one copy of the ***ABCC8* or *KCNJ11*** gene from their **unaffected Dad**.



The **second event happens** as the baby is growing **in the womb**. A cell in the pancreas **loses Mum's copy** of the same gene and **Dad's copy** of the gene is **duplicated**. The cell then has **2 identical copies of Dad's variant**.

This is a **random (sporadic) event** that happens **by chance** and **only within a cell in the pancreas**.

This has **2 consequences** within the **pancreas**:

- The cell starts to **multiply more than normal**, producing lots of cells to **form a focal lesion**
- All these cells within the lesion **have 2 copies of the recessive variant** causing them to **release too much insulin**

If a **Dad** carries a **variant in one copy of the *ABCC8* or *KCNJ11*** gene, there is a **1 in 2 (50%) chance** he will pass this **variant to his child**. Most of the time, the **child will be an unaffected carrier**, because the **second genetic event** that happens in the pancreas is **extremely rare**, occurring in about **1 in 270 pregnancies**.

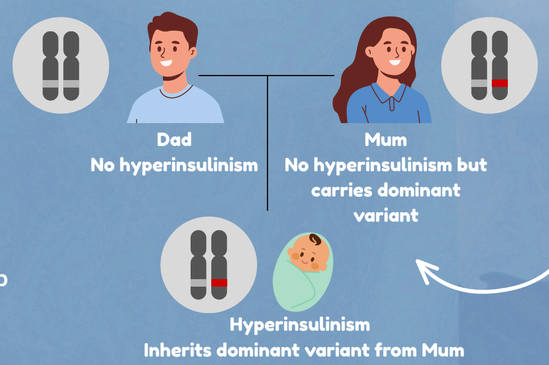
This means the chance of a **Dad with a recessive *ABCC8* or *KCNJ11* variant** having a **child with focal congenital HI** is about 1 in 540 (or **less than 1%**).

LESS THAN 1% CHANCE

VARIABLE PENETRANCE

Variable penetrance means that **not everyone who carries the same genetic variant** will **develop the condition**.

In people with **recessive congenital HI**, individuals who share the **exact same 2 recessive variants** may **not both develop the condition**.



Variable penetrance is observed in some **dominant forms** of congenital HI. For example, some people with a dominant variant in the ***ABCC8, GCK, HK1, GLUD1, SLC16A1*, or *HNF4A* gene** may have **mild symptoms or none**, yet they **can still pass the variant** to their children, who may develop congenital HI.

The same can happen the other way around, where the **parent** could have a **severe form** of congenital HI **caused by a dominant variant** and **passes the variant to their child**, but the child may have **mild or no symptoms**.