First version: Maya Ballantine, Pamela Bowman, Indi Banerjee, Sarah Dearman, Sarah Flanagan
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Mosaic Variants in Congenital Hyperinsulinism

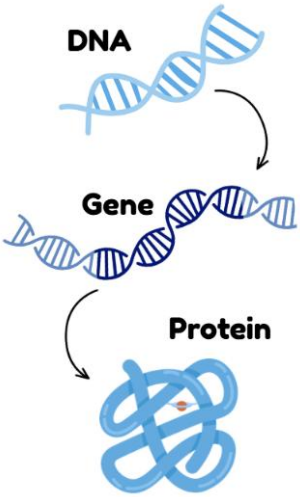
This information sheet summarises what **mosaic variants are in congenital hyperinsulinism (shortened to HI)**. This sheet is intended for information only and should not replace personalised advice or genetic counselling for you or your family. For more information on congenital hyperinsulinism, check out our other information sheets here.

All terms highlighted in **blue** can be found in our glossary, linked here.

Key Points

- A **mosaic variant** is where the genetic change is in **only some of the cells in your body**
- Having a **mosaic variant** in the **beta cells** of your **pancreas** can **cause congenital HI**
- Mosaic variants are ***de novo*** (which means they happen for the first time in that individual) and are **usually dominant variants**, although **some mosaic recessive variants** have been seen before
- People can have **different levels of mosaicism**, some people will have **high-level mosaic variants,** where a **larger proportion of cells have the genetic change,** and some will have **low-level mosaic variants,** where a **smaller proportion of cells have the genetic change**

What are Genes and Genetic Variation?



We are all **made up of trillions of cells**, and in each cell, there is a very important molecule called **DNA**. DNA is the body's **instructional manual** that tells the cell what it needs to do to function properly. These instructions are contained in **sections of DNA** called **genes**.

Each person has **2 copies of a gene**, one **inherited** from **Mum**, and one inherited from **Dad**. These genes each provide a **unique code** that makes **different proteins**, and these proteins **help the body grow, function and stay healthy**.

It is **normal to have some variation** in this **genetic** code between individuals because that is what makes us all different and unique. Sometimes though a **change (or variant) in a gene** can cause a **protein to not function properly**, leading to **health problems**. These are often called **genetic**, **congenital**, or **inherited conditions**.

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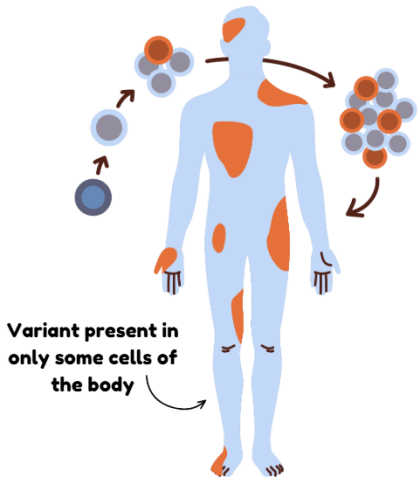
What is a Mosaic Variant?



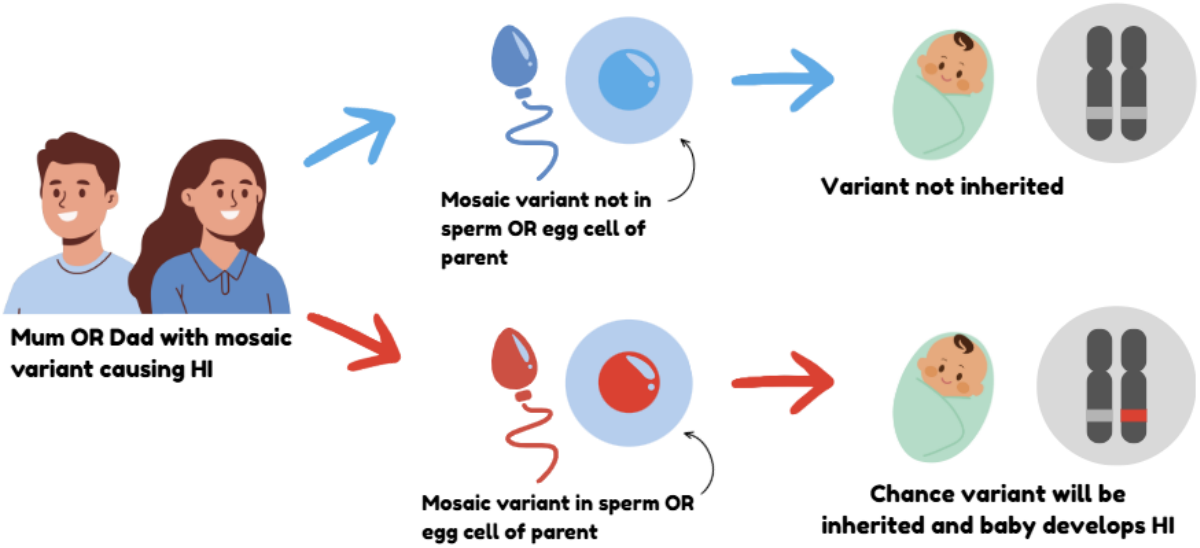
In most people with a **genetic change**, we know that the genetic change is **present in all cells** in their body. BUT if a **genetic change is present in the DNA of only some cells in the body**, it is called a **mosaic variant** (or **mosaicism**). If there is a mosaic variant present in the **beta cells** in the **pancreas**, it can **cause congenital HI**. We have seen mosaic variants in genes like ***GCK***, ***HK1***, ***GLUD1, KMT2D, KDM6A,*** and ***ABCC8***.

Mosaic variants that **cause congenital HI** are usually **dominant variants**, although some mosaic **recessive variants** **have been found before**. To learn more about dominant and recessive variants, check out our other information sheets linked here.

These mosaic variants are also ***de novo* variants**. This means the **mosaic variant appeared for the first time in the egg or sperm cells of the parents or in the baby as it was growing in the womb.**

Can Mosaic Variants Be Passed on to Other Family Members?

A person with HI caused by a mosaic variant **would not be expected to have a sibling with HI.** It is possible, though, that they could **have a child with HI** if the mosaic variant is **in their egg or sperm cells**. If the mosaic variant is passed on to their child, it is **no longer mosaic** because it will be **in every cell of the body** of the child. Knowing if the mosaic variant is in the egg or sperm cells is **not something that is easily measured** so it is **hard to know how likely it is for this to happen**. This should be **talked through with a genetic counsellor** or a **clinical geneticist**.



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How Do You Find a Mosaic Variant?

Mosaic variants are often found during genetic tests of blood samples. Laboratories can then **estimate the level of the mosaicism**, which shows **how many molecules of DNA carry the mosaic variant** in the body. This **can change around the body.** For example, the level of mosaicism in the blood could be different than in the pancreas, which could be different in the eggs or sperm cells.

Does Having a Mosaic Variant Change Your Symptoms?

We are looking to see if having a mosaic variant **changes how severe your symptoms are compared to someone who has a non-mosaic genetic change in the same gene which affects all their cells**. We want to understand if someone with a mosaic variant will have **milder symptoms** or may not get additional features.

For example, in congenital HI caused by a genetic change in the ***GLUD1*** gene, a common feature is **hyperammonaemia** because the **genetic change is also in the kidneys**. As ***GLUD1*** **mosaic variants** can be in the **pancreas** but **not in the kidneys,** some people may **develop HI** but **not develop hyperammonaemia**.

Getting Individualised Information and Accessing Genetic Counselling Services

Meeting with a **genetic counsellor** or **clinical geneticist** can be very helpful if you have **a family history of HI**. They can explain how HI might **affect you or your children** and **answer any questions**. Because everyone's family genetics are unique, the guidance you receive will be **personalised to your situation**. This can help you make **informed decisions** and **plan the future**. To book an appointment you usually need a **referral from your family doctor** (GP in the UK) or a **specialist doctor**.

Additional Resources

- **Mosaic Variants explained:** https://www.genomicseducation.hee.nhs.uk/genotes/knowledge-hub/mosaicism/
- **The role of the Genetic Counsellor:** https://www.genomicseducation.hee.nhs.uk/genotes/knowledge-hub/roles-in-clinical-genetics/#genetic-counsellors

This leaflet was developed by the Exeter Hyperinsulinism Genes team (www.hyperinsulinismgenes.org) in collaboration with The Children's Hyperinsulinism Charity UK (https://hyperinsulinism.co.uk/). Registered Charity: 1165562, Company Number: CE005407