First version: Maya Ballantine, Jacob Roberts, Indi Banerjee, Sarah Dearman, Pamela Bowman, Sarah Flanagan
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Variants of Uncertain Significance

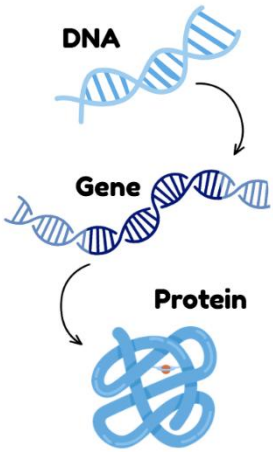
This information sheet summarises what **Variants of Uncertain Significance (or VUS)** are **in the context of congenital hyperinsulinism** (shortened to HI). This sheet is intended for information only and should not replace personalised advice or genetic counselling for you or your family. Check out our other information sheets here to find out more about other types of variants and their role in congenital HI.

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

Key Points

- Sometimes, a **change in your genes** can cause **congenital HI**
- These changes (or **variants**) are **investigated** and **put into categories** based on **how likely they are to cause congenital HI**
- When we **don't know** if the **genetic change is causing congenital HI** or if it's part of our **normal genetic variation**, it is called a **Variant of Uncertain Significance** or VUS
- A VUS **should not be used to make medical decisions** so your doctor will decide what is best for you **based on your symptoms**
- Some laboratories may **continue to research** the VUS and give an **updated report** once they **find enough information**
- This means the VUS could **eventually be reclassified** to **confirm** if it **is or is not the cause of the congenital HI**

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. These instructions are contained in **small sections of DNA** called **genes**.

Each person will have **2 copies of a gene**, one **inherited** from **Mum**, and one from **Dad**. These genes each provide a **unique code** that makes **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, 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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How Do We Know Which Genetic Changes Cause a Condition?

It is important to understand **if a change that is found in your genes causes congenital HI** or is just part of **normal genetic variation**. When a genetic change is found, the laboratory will **review all the evidence** (explained in the picture below) and **decide how likely it is to be the cause of congenital HI**.

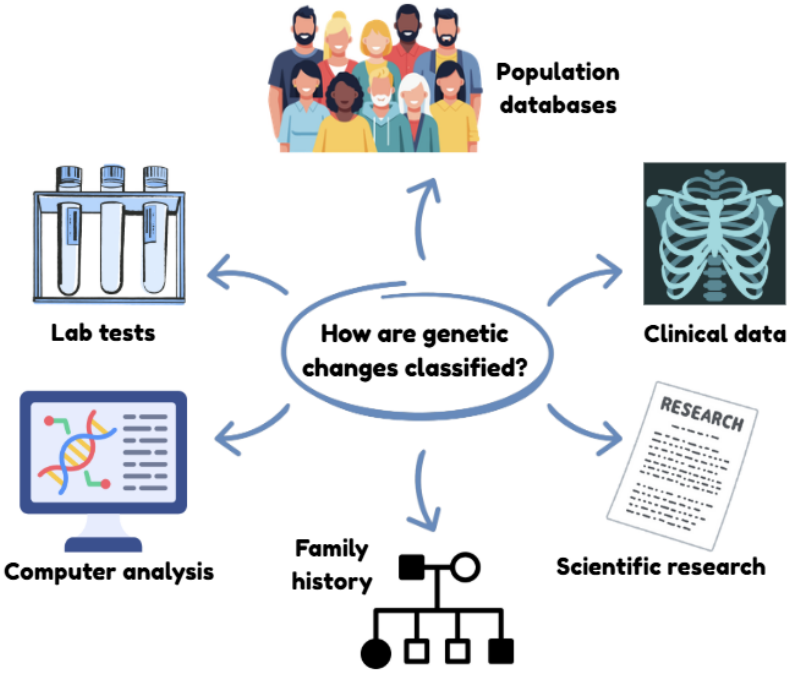
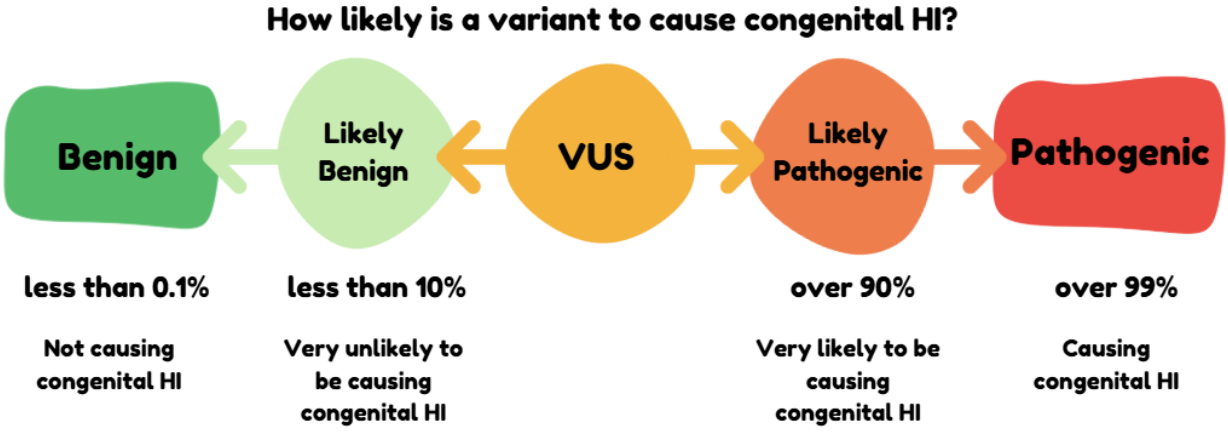


Image adapted from: Visual communication aids for genomics conversations — Knowledge Hub

- If there is lots of evidence that the genetic change **causes congenital HI**, it will be classified as a **pathogenic** or **likely pathogenic variant.**
- If there is evidence that a genetic change is **not a cause of congenital HI** and it is **part of our normal genetic variation** it will be classified as a **benign** or **likely benign variant.** Most laboratories do not include these types of genetic changes on genetic reports.

But sometimes, there is **not enough evidence** to be confident if the **genetic change causes congenital HI or is part of our normal variation**. These are called **Variants of Uncertain Significance (or VUS)**.



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What Happens If I Get A VUS Result?

As a VUS is **uncertain**, it **should not be used to make decisions** about treatment or management because it might be part of normal genetic variation. Instead, your **doctor will decide what the best options** are for your care **based on your symptoms**.

Some laboratories **may continue to research the VUS** and issue an updated report if new information becomes available. This may lead to the VUS being **reclassified,** which could **confirm or rule out the VUS as the cause of the congenital HI**. The **time it takes** for this to happen is **different for each VUS** and could take up to months or years.

How Often Should I Ask About My Genetic Diagnosis?

It is good to keep **asking your doctor** if there is **any new information available** that could change your genetic diagnosis. They could **talk to the scientists at the laboratory** and ask if there are **any updates for you**. Your doctor may also suggest **testing other family members** which could help them to **better understand the VUS.**

It is important to remember that it isn't unusual to have a VUS on a genetic report. As our understanding of genetics continues to improve, we expect that there will be **fewer test reports which include a VUS in the future**.

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** you have. Because everyone's genetics are unique, the guidance you receive will be **personalised**.

This support can help you make **informed decisions** and **plan the future**. To book any appointment you will usually need a **referral from your family doctor** (GP in the UK) or a **specialist doctor**.

Additional Resources

- **VUS explained:** https://www.genomicseducation.hee.nhs.uk/genotes/knowledge-hub/variant-of-uncertain-significance-vus/
- **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