UNDERSTANDING HOMOCYSTINURIA

Getting to know your diagnosis

HCU Network Australia
HCUNetworkAustralia.org.au

ABOUT THIS BOOKLET

This booklet provides educational information on a group of rare inherited metabolic disorders called the homocystinurias. The goal of this booklet is to help the reader understand and become more familiar with homocystinuria and deals specifically with the three most common forms – those due to cystathionine beta-synthase (CBS) deficiency (classical homocystinuria or HCU), a problem in cobalamin metabolism (cobalamin C disease or cblC) and methylenetetrahydro-folate reductase (MTHFR) deficiency. There are other forms of homocystinuria, not discussed here, that have their own specific genetic causes, clinical symptoms and treatment needs.

DISCLAIMER

This guide is for information only and should not be relied upon in place of medical advice. Any medical information is not intended as a substitute for informed medical advice. Consult a doctor or other health care professional for diagnosis and treatment of HCU. While all reasonable care in compiling the information has been made we make no warranty as to its accuracy.

SUPPORTERS

The production of this document was supported by the World Homocystinuria Awareness Day 2022 sponsors Aeglea BioTherapeutics, Travere, Codexis and Synlogic. HCU Network Australia independently developed the content herein and our supporters did not participate in the development of the document and are not responsible for the content and/or recommendations contained herein.

ACKNOWLEDGEMENTS

HCU Network Australia would like to acknowledge the assistance of the following people for their insight and expertise in preparing and reviewing this document:

Professor Martina Huemer: University Children's Hospital Zürich, Switzerland & Landeskrankenhaus Bregenz, Austria

Dr Andrew Morris: Central Manchester University Hospital, Manchester, United Kingdom

Pip Stosic: Medical writer, Sydney, Australia

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CONTENTS

GETTING TO KNOW YOUR DIAGNOSIS 3

WHAT IS HOMOCYSTINURIA? 3

WHY DO YOU HAVE HOMOCYSTEINE IN YOUR BODY? 4

WHAT CAUSES HOMOCYSTINURIA? 5

HOW IS HOMOCYSTINURIA DIAGNOSED? 5

WHAT ARE THE DIFFERENT TYPES OF HOMOCYSTINURIA? 6

CYSTATHIONINE BETA-SYNTHASE (CBS) DEFICIENCY 7

SEVERE METHYLENETETRAHYDRO-FOLATE REDUCTASE (MTHFR) DEFICIENCY 8

COBALAMIN C (CBLC) 9

GETTING TO KNOW YOUR DIAGNOSIS

The information provided in this booklet aims to help you understand your diagnosis so you can feel more in control and confident when talking to your healthcare team, family and friends about homocystinuria.

Knowing more about your condition is one of the best ways to understand what's going on in your body, what you can expect, and how treatment will help. It can also help you be more actively involved in managing your condition so that the risk of further health problems in the future are reduced.

There are different forms of homocystinuria – each having its own causes, health issues and treatments. This first part of this booklet talks generally about homocystinuria with the following sections giving more details on the three most common forms.

Don't worry if you are unsure about which homocystinuria applies to you – you can check with your doctor or other healthcare provider and they can confirm your diagnosis for you. Don't be afraid to ask them to repeat or write the information down.

It is important to remember that the diagnosis is only the first step on your journey and, although there is no cure for homocystinuria, it is a treatable condition.

WHAT IS HOMOCYSTINURIA?

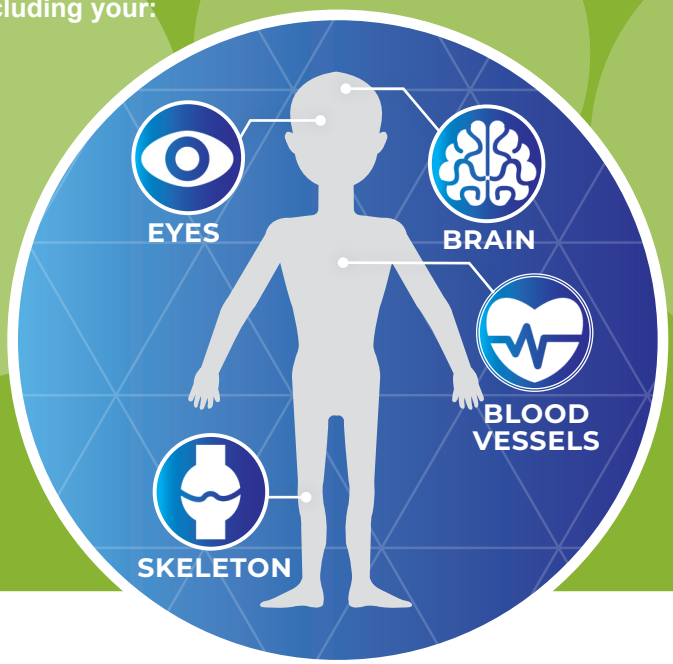
Homocystinuria is a rare, inherited, metabolic disorder that occurs when the body is unable to use (metabolise) certain amino acids properly. This results in a build-up of an amino acid called homocysteine in your blood.

Amino acids are the 'building blocks' of proteins and our body combines them in different ways to make all the proteins we need to grow and function correctly. Although hundreds of amino acids exist in nature, the human body only needs about 20 different amino acids – some of which we can only get from our food.

Sometimes, for example, when you have a **metabolic disorder,** chemical reactions in your body can be disrupted and your body may have trouble breaking down certain amino acids. These problems can then cause a build-up of harmful substances in your body.

Homocysteine is an amino acid that the body produces from another amino acid called **methionine.**

When high levels of homocysteine build-up in your blood it can be harmful and can affect different parts of your body, including your:



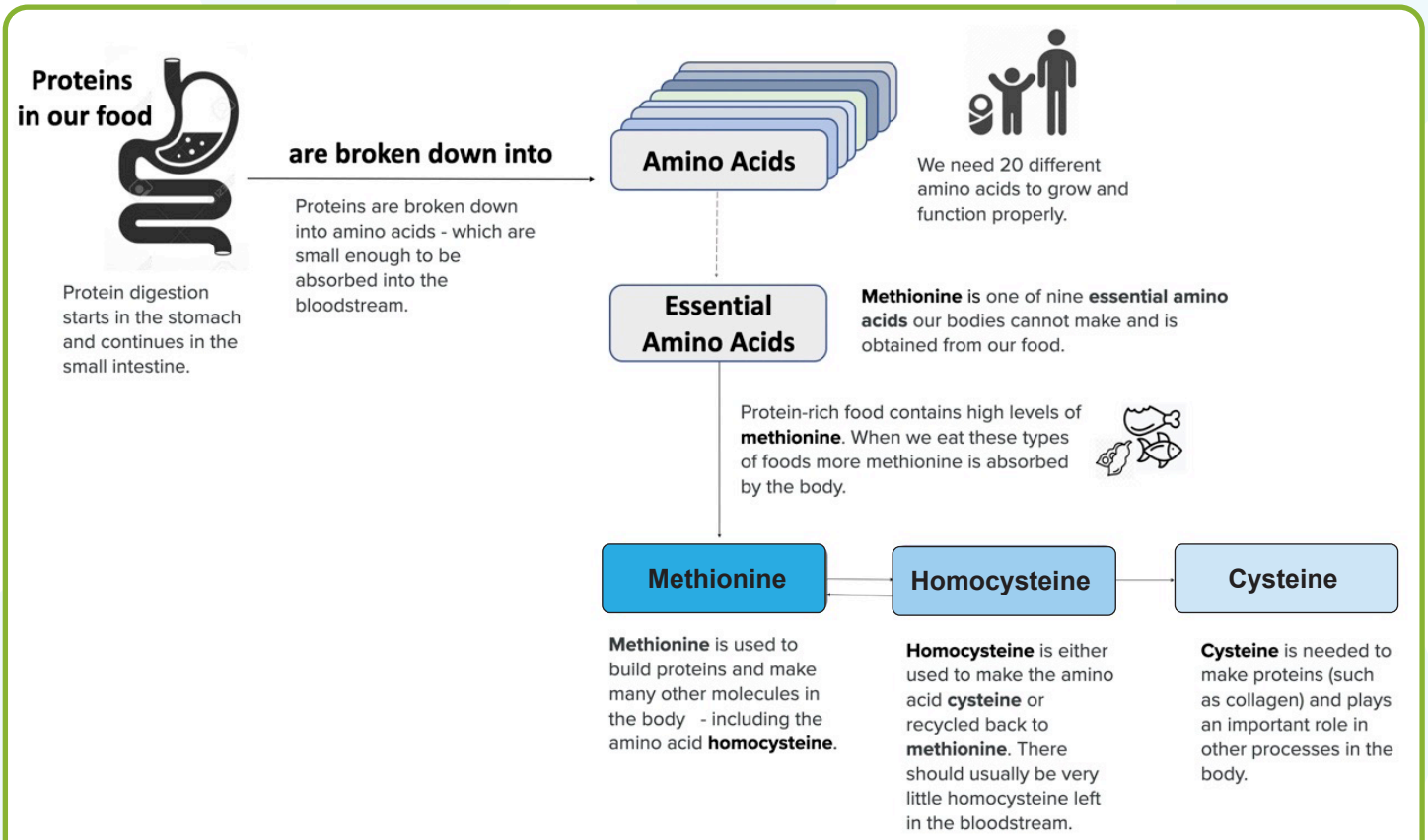
WHY DO YOU HAVE HOMOCYSTEINE IN YOUR BODY?

We all need homocysteine to make energy for our cells and to produce other chemicals important for growth and development.

Everyone produces homocysteine. Normally, there is very little homocysteine circulating in our body as it is quickly converted into another amino acid called cysteine or recycled back into methionine ready to be reused to build other proteins.

If homocysteine cannot be processed to either cysteine or back into methionine then harmful high levels of homocysteine start to build-up.

Methionine is one of the nine essential amino acids the body cannot make and we need to get it from the food we eat – it is the body's only source of homocysteine.



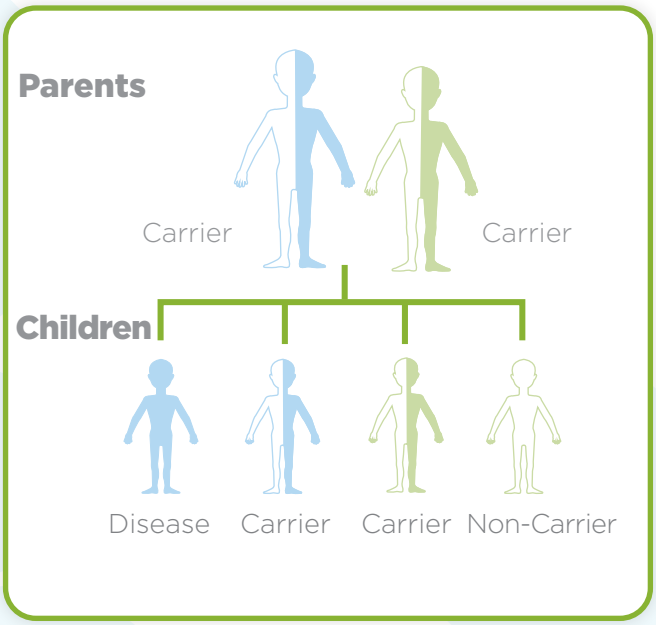
Proteins are broken down into smaller molecules called amino acids that are absorbed by the body and used to help us grow and function properly. Methionine is an important amino acid that we can only get from our food and is used to form homocysteine and cysteine.

WHAT CAUSES HOMOCYSTINURIA?

Our body needs a range of enzymes to help it process homocysteine. When you have homocystinuria you don't make these enzymes or you don't make enough of them, or they don't work properly.

An **enzyme** is a form of protein that helps speed up (catalyse) chemical reactions in your body. They attach themselves to certain molecules (such as homocysteine) and alter them in very specific ways allowing them to be quickly converted into other chemicals (such as cysteine).

The body knows how to make these enzymes because the 'recipe' is held in your genes – more specifically a pair of genes – one passed on (inherited) from your mother and the other from your father. Homocystinuria occurs when both copies of the gene don't work correctly – this is called autosomal recessive inheritance.



Homocystinuria is an autosomal recessively inherited disorder.
This means that you inherit faulty copies of the gene from both parents.

Some enzymes need helper molecules (called coenzymes or cofactors) to work properly, and many vitamins act as helper molecules in our bodies.

The enzymes involved in homocysteine metabolism need three vitamins (vitamins B6, B12 and folate) to work correctly – if any of these are not available (or not enough is available) then your body can also have problems either converting homocysteine to cysteine or back to methionine.

Although you can't change the faulty genes that cause homocystinuria by taking simple steps with your nutrition, supplements or medications, and lifestyle you can change the way the condition affects your health.

HOW IS HOMOCYSTINURIA DIAGNOSED?

In Australia, babies are tested at birth for homocystinuria. But these newborn screening tests do not currently detect all forms of homocystinuria and not all countries have newborn screening programmes.

If homocystinuria is not identified during this screening then it can be diagnosed later on through a combination of symptoms, biochemical tests and genetic testing.

High levels of homocysteine in your blood and urine along with certain symptoms are often the first indications you may have homocystinuria. The severity of symptoms will vary and depends on whether the faulty enzymes can still convert some homocysteine.

Symptoms also depend on the type of homocystinuria you have, which can often be vague or difficult to detect or overlap with other conditions – which may mean your road to a homocystinuria diagnosis has been a long and frustrating one.

WHAT ARE THE DIFFERENT TYPES OF HOMOCYSTINURIA?

There are many different forms of homocystinuria each with their own specific causes, symptoms and treatment needs. The three most common forms of homocystinuria are those due to:

Problems with how enzymes work

1. **Cystathionine beta-synthase (CBS) deficiency**
2. **Severe methylenetetrahydro-folate reductase (MTHFR) deficiency**

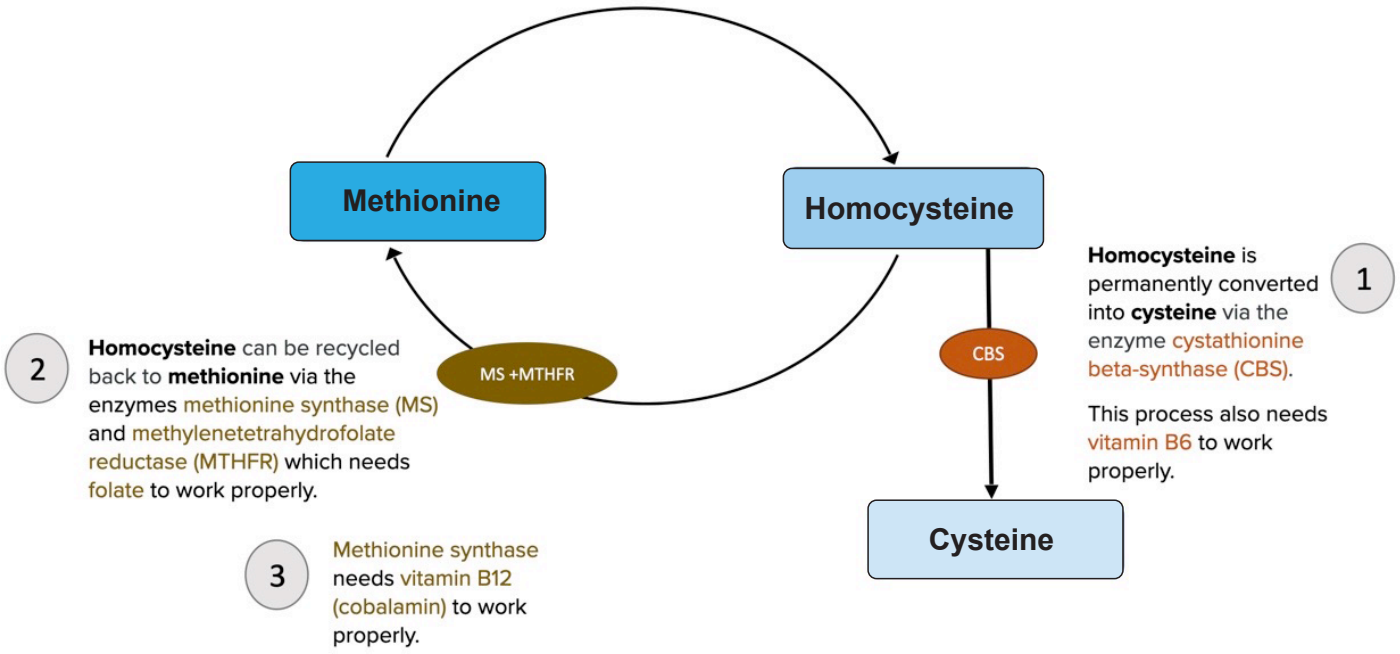
Problems with cofactors or coenzymes that help enzymes work

3. **Cobalamin C (cblC) disease**

Don't worry if you are unsure of your diagnosis or don't recognise any of the names above – you can check with your doctor or other healthcare provider to confirm your diagnosis.

More details on each these three common forms are given in the following sections and includes some of the other commonly used names for each condition.

A simplified version of the homocysteine conversion processes (or pathway) along with the problem points for each of the common forms of homocystinuria are shown in the following diagram.



Summary of the homocysteine conversion processes showing the problem points for the most common forms of homocystinuria due to:

1. Cystathionine beta-synthase (CBS) deficiency.
2. Methylenetetrahydro-folate reductase (MTHFR) deficiency.
3. Defects in cobalamin C (clbC) metabolism.

CYSTATHIONINE BETA-SYNTHASE (CBS) DEFICIENCY

Other names for this form of homocystinuria include:

- **Homocystinuria due to cystathionine beta-synthase deficiency**
- **Cystathionine β-synthase deficiency**
- **CBS deficiency**
- **Classic homocystinuria**
- **Classical homocystinuria**
- **Homocystinuria (HCU)**

This is the most common form of homocystinuria and is often referred to as classical homocystinuria or just 'homocystinuria'.

Here, homocystinuria is caused by a fault (mutation) in the CBS gene – there are more than 160 different mutations of the gene identified so far, but some only affect a very small number of people.

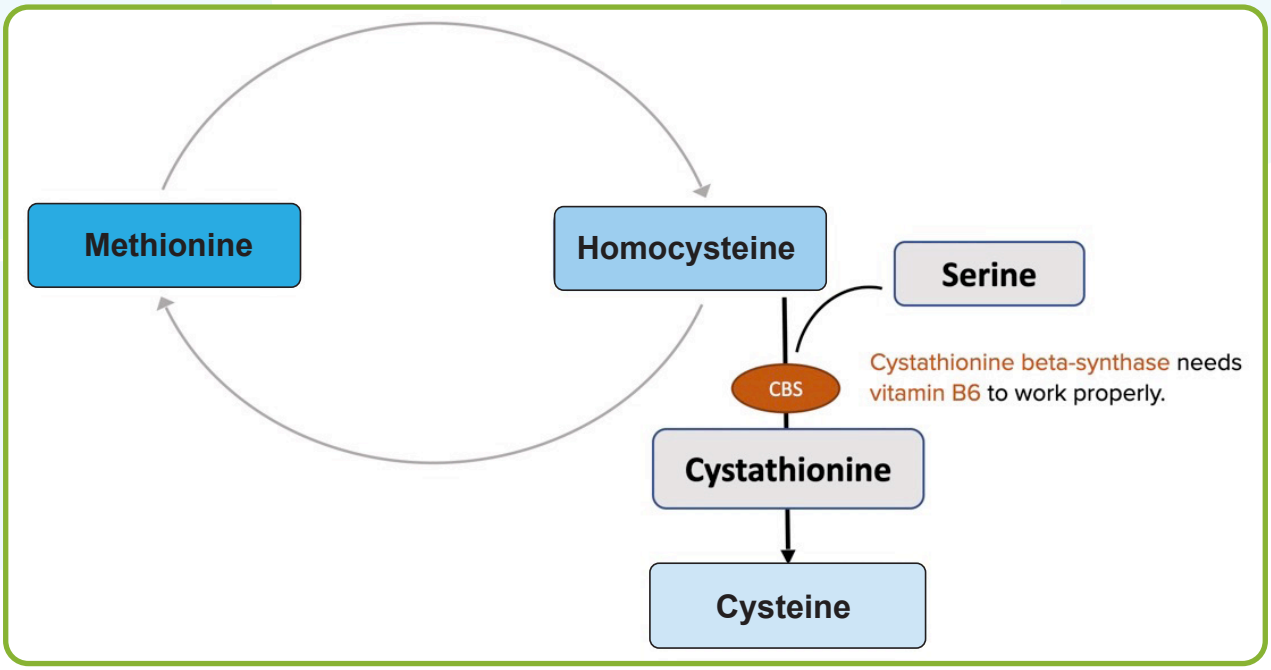
The CBS gene holds the instructions needed to make the enzyme called cystathionine beta-synthase (CBS). If the gene is faulty then either none or only small amounts of the CBS enzyme is produced – and the body is said to have a 'CBS deficiency'.

The CBS enzyme:

- Is needed to convert the aminoacids homocysteine and serine to cystathionine before it can then be converted to cysteine.
- Needs the help of vitamin B6 (pyridoxine) to work properly.

When the CBS enzyme is not produced or is not working properly it can lead to:

- High levels of homocysteine in your blood and urine – because homocysteine can't make cystathionine and starts to build-up
- Low levels of cystathionine and cysteine in the blood – because homocysteine can't be processed to make these two amino acids
- High levels of methionine in blood – because unused homocysteine is converted back to methionine and starts to build-up.



The parts of the body most commonly affected are the eyes, skeleton, brain and the blood vessels – health problems characteristic for this form of homocystinuria typically includes:

- Lens dislocation (this is often the first symptom noticed)
- Unusually tall stature with long, slender fingers and toes, along arms and legs
- Development problems
- Seizures
- Blood clots (thrombosis)

There are two types of homocystinuria caused by CBS deficiency:

- A 'milder' form where the levels of homocysteine can be controlled with vitamin B6 supplements (called vitamin B6-responsive)
- A more 'severe' form that does not respond to vitamin B6 supplements (called vitamin B6-non-responsive).

SEVERE METHYLENETETRAHYDRO-FOLATE REDUCTASE (MTHFR) DEFICIENCY

Other names for this form of homocystinuria include:

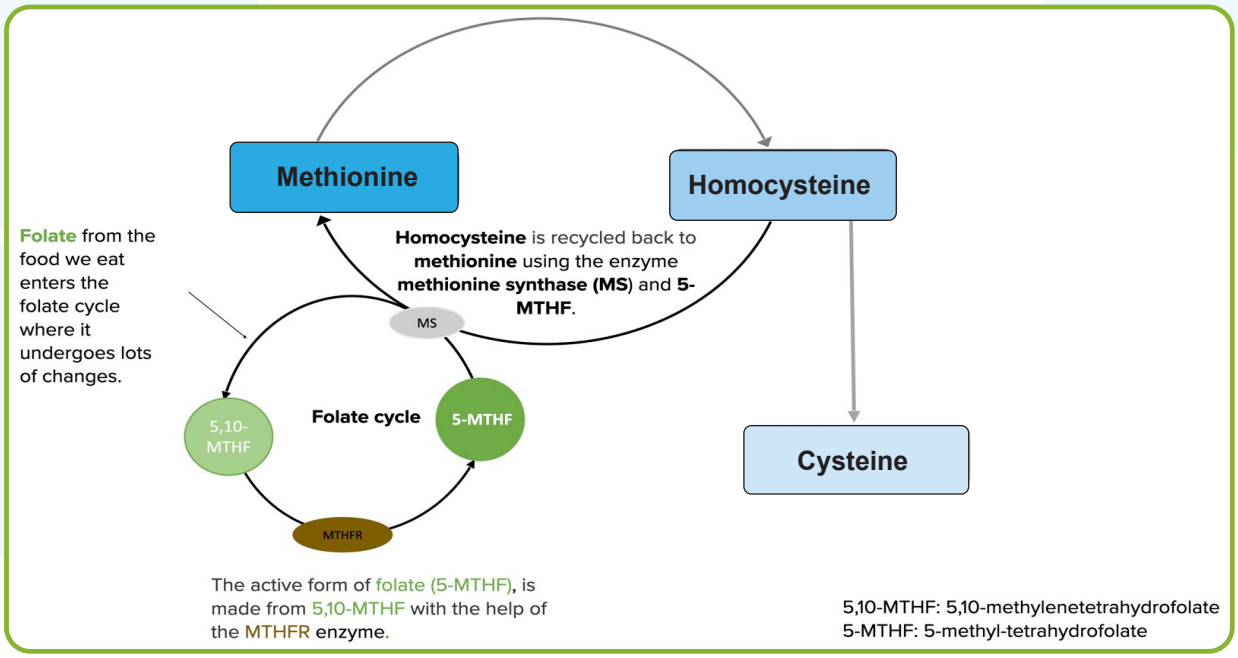
- **Homocystinuria due to methylenetetrahydro-folate reductase deficiency**
- **5,10 alpha methylenetetrahydro-folate reductase deficiency**
- **MTHFR deficiency**

Homocystinuria due to MTHFR deficiency is a condition where the processes that help your body produce the active form of folate, called 5-methyltetrahydrofolate (shortened to 5-MTHF or 5-methyl-THF), are affected.

This form of homocystinuria is caused by faulty **MTHFR genes** – over 40 different variations of this gene have been found so far. The MTHFR gene holds the instructions needed to make the enzyme called **methylenetetrahydro-folate reductase** (MTHFR). This enzyme helps regulate the levels of homocysteine in your body.

Your body uses **folate** (the natural form of vitamin B9) in lots of ways including making DNA, forming red blood cells and is vital for healthy growth and development. Folate is also needed to help recycle homocysteine back to methionine.

- When the MTHFR gene is working properly, the MTHFR enzyme helps your body convert folate to the active form 5-MTHF (needed to make methionine) through a process called methylation.
- When the MTHFR gene is faulty the body can't convert folate properly and this prevents methionine from being produced from homocysteine – and the levels of homocysteine start to increase.

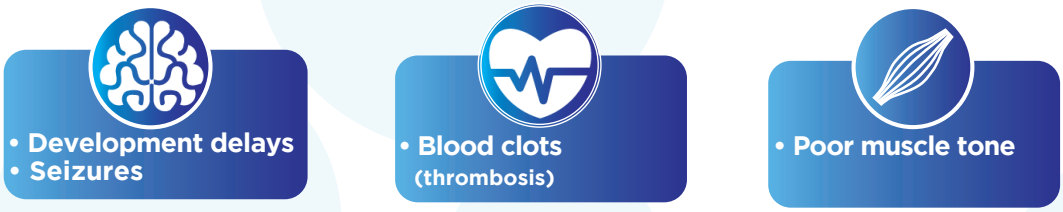


When the MTHFR enzyme is not produced or is not working properly it can lead to:

- High levels of homocysteine in blood and urine – because homocysteine is not being recycled back to methionine
- Low or low-normal levels of methionine in the blood – because homocysteine can't be recycled and no (or little) methionine is being made.

Symptoms vary depending on the type and number of gene mutations (or variants) you have. The parts of the body most commonly affected by MTHFR deficiency are the brain and central nervous system, and the blood vessels.

Health problems characteristic for this form of homocystinuria typically includes:



COBALAMIN C DISEASE (CBLC)

Other names for this form of homocystinuria include:

- **Methylmalonic acidemia with homocystinuria (MMA+HCU) cblC**
- **Methylmalonic aciduria and/with homocystinuria cblC**
- **Cobalamin C disease**
- **cblC**

This genetic disorder is a combination of two separate conditions:

- Methylmalonic acidemia (MAA) – where the body can't use a substance called methymalonyl-coenzyme A and methylmalonic acid builds up in the body.
- Homocystinuria (HCU) – where high levels of homocysteine build-up in the body.

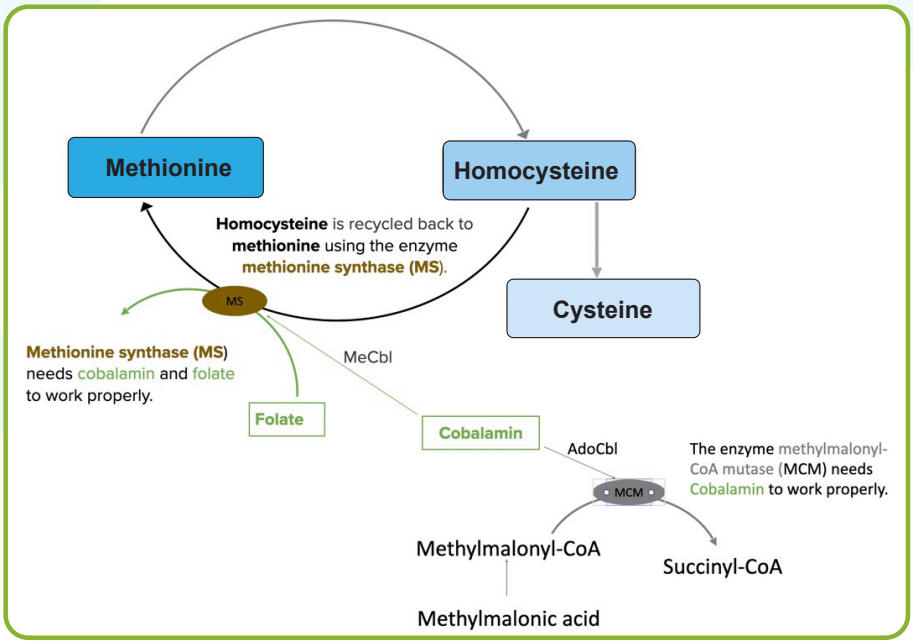
There are different forms of methylmalonic acidemia with homocystinuria which are caused by mutations in different genes – one of the more common forms is cobalamin C (cblC) which is caused by faults in the MMACHC gene.

Cobalamin (vitamin B12) is an important chemical involved in many different processes in the body.

In cobalamin C disease there is a problem with how cobalamin from food is converted into its two active forms – methylcobalamin (MeCbl) and adenosylcobalamin (AdoCbl) – by your body. These active forms of cobalamin act as helper molecules (cofactors) for two enzymes:

- Methionine synthase – MeCBl helps this enzyme convert homocysteine into methionine
- Methylmalonyl-CoA mutase – AdoCbl helps this enzyme convert methylmalonyl-CoA into succinyl-CoA.

If these enzymes don't function properly homocysteine and methylmalonic acid levels build-up in the body and can cause problems.



When there is a defect in cobalamin metabolism it can lead to:

- High levels of homocysteine in blood and urine – because homocysteine is not being recycled back to methionine
- High levels of methylmalonic acid in blood – because methymalonyl-coenzyme A is not being converted
- Low or low-normal levels of methionine in the blood – because homocysteine can't be recycled and no (or little) methionine is being made.

The symptoms can vary considerably and diagnosis is often delayed. The parts of the body most commonly affected by cobalamin C (cblC) are the brain, central nervous system, eyes and the blood vessels.

Health problems characteristic for this form of homocystinuria typically includes:

- **Involuntary eye movements**
- **Changes in the retina**
- **Poor eyesight**

- **Development delays**
- **Seizures**
- **Mental deterioration**

- **Blood clots (thrombosis)**
- **Low platelets and white blood cells**
- **Anaemia with large red cells**

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