Homocystinuria due to CBS deficiency

Introductory information

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Reviewed & Revised for North America
by: S. van Calcar

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as a service to metabolic medicine

TEMPLE
Tools Enabling Metabolic Parents LEarning

HCU

Homocystinuria

Homocystine in urine

Hyperhomocysteinemia

Too much homocysteine in blood

Enzymes

Enzymes are proteins that facilitate various chemical reactions in the body. They are involved in the biosynthesis (anabolism) and the degradation (catabolism) of all the substances in the body. This is called metabolism.

Cystathionine **b**eta-**S**ynthase (CBS) is an enzyme that is necessary for the metabolism of the amino acid methionine.

In homocystinuria, the activity of the CBS enzyme is decreased.

Enzymes

Another enzyme important for the metabolism of methionine and homocysteine is

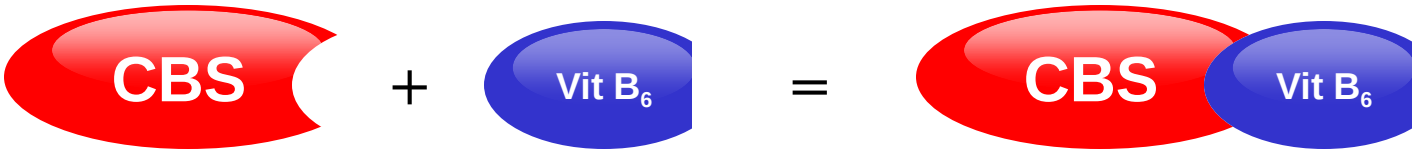
Betaine-**H**omocysteine **M**ethyl**t**ransferase (BHMT).

The BHMT enzyme works properly in a person with homocystinuria and it plays an important role in the treatment of homocystinuria.

Enzymes

Some enzymes cannot work without the help of vitamins – these are called cofactors.

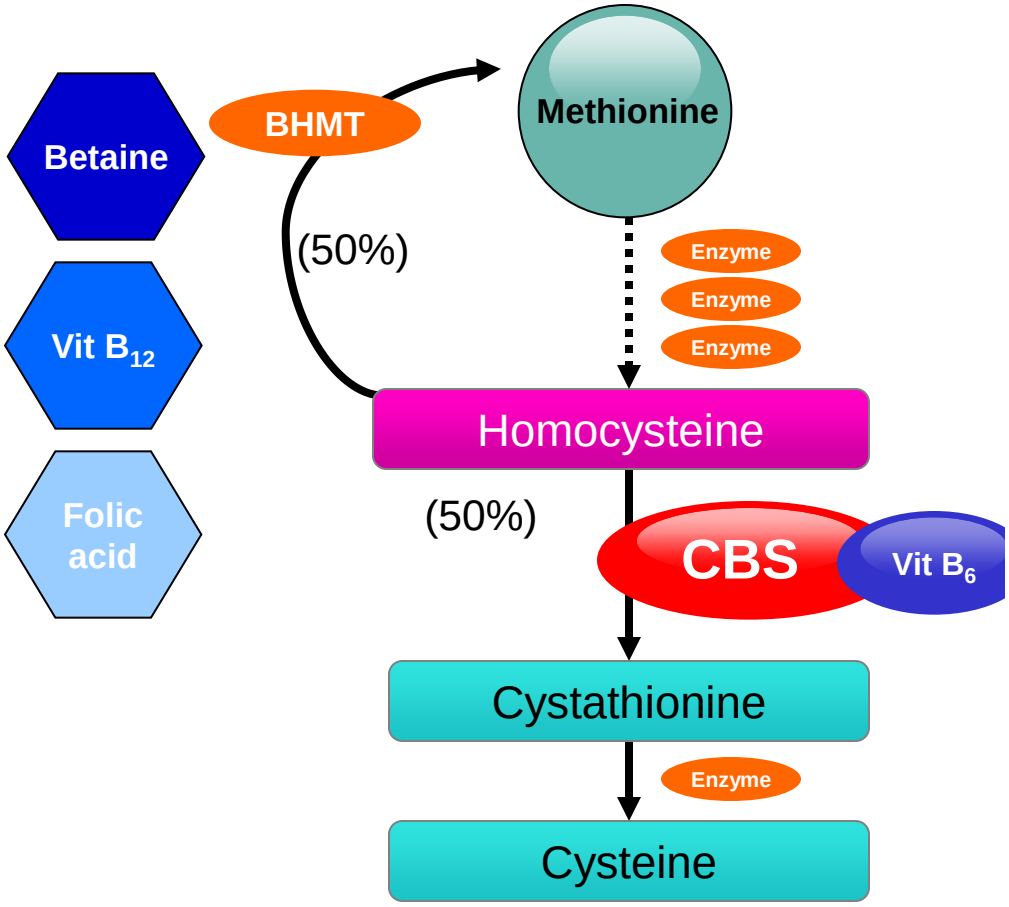
Cystathionine beta-Synthase (CBS) is such an enzyme and vitamin B_6 is its cofactor.



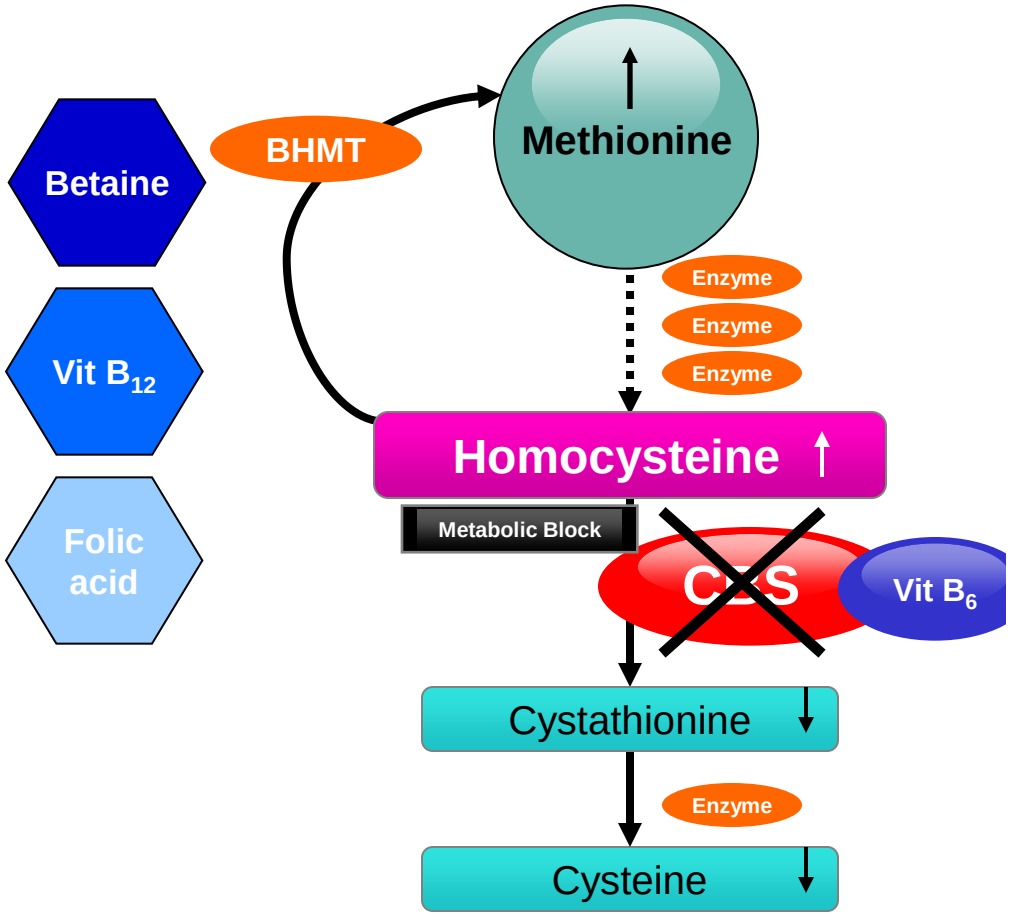
CBS inactive

CBS active

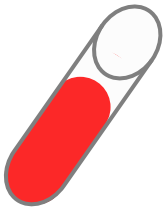
In a person without HCU: CBS works



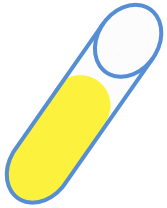
Metabolism in a person with homocystinuria: CBS is deficient



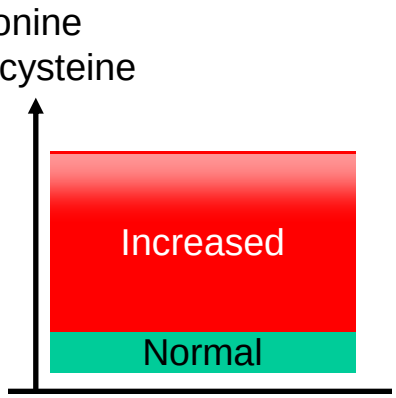
Diagnostic investigations

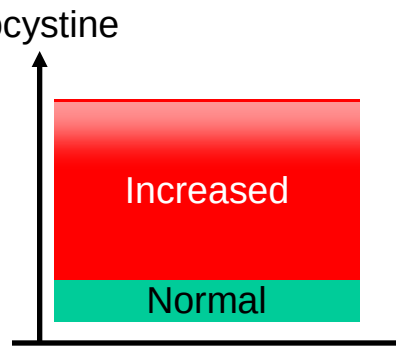


Venous blood



Urine sample





Plasma reference ranges:

Homocysteine: < 15 µmol/L

Methionine: 15-30 µmol/L

At time of diagnosis: plasma homocysteine is usually > 200µmol/L

Pathogenesis of HCU

Newborns do not have any symptoms. The symptoms develop in following years.

Eyes
Myopia, dislocation of the lenses, “dancing or shimmering” iris, glaucoma, retinal abnormalities

Vascular System
Thrombosis, thromboembolism, vascular occlusion, thrombophlebitis, pulmonary embolism, ischemic heart disease

↑ Homocysteine

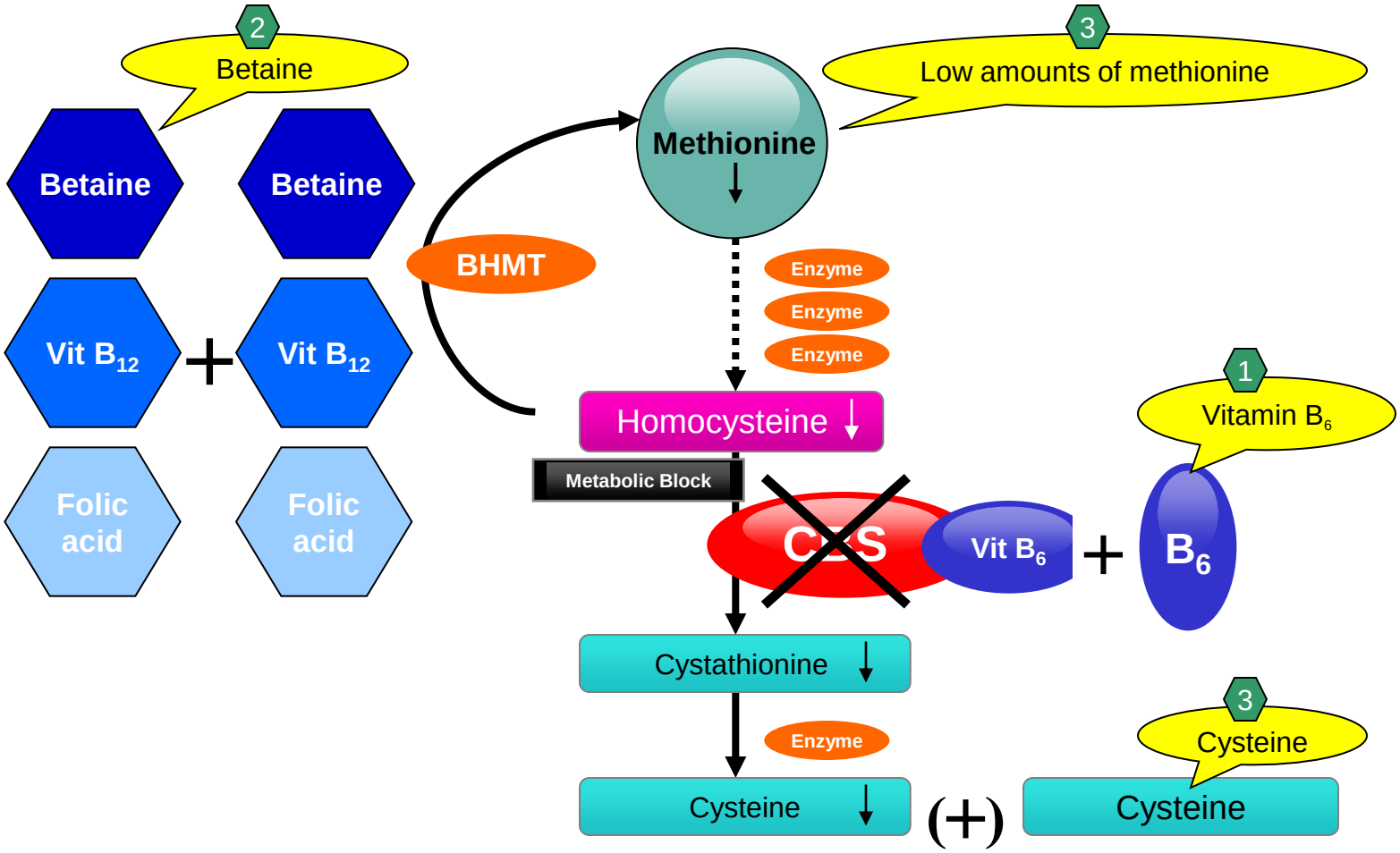
Skeleton
Tall and thin individuals, long extremities, arachnodactyly (“spider fingers”), knock-knees, scoliosis, chest deformities, osteoporosis

Central Nervous System
Developmental delay, intellectual impairment, epilepsy, focal neurological signs, psychiatric disorders

Management for HCU

The goal of management for HCU is to decrease the amount of homocysteine in the blood to a safe level so that it is not as harmful.

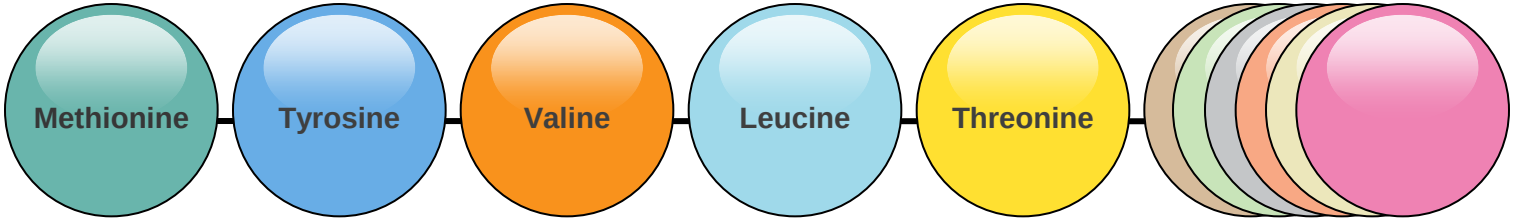
Elements of Management for HCU



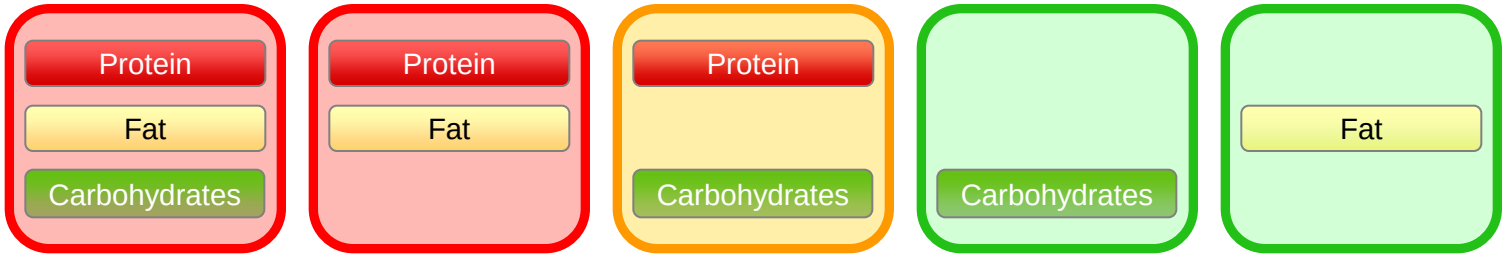
Food – Components of a normal diet

Protein | Fat | Carbohydrates

Protein consists of chains of amino acids



Natural Food



eg. milk, yogurt, nuts

eg. meat, poultry, fish, eggs, cheese

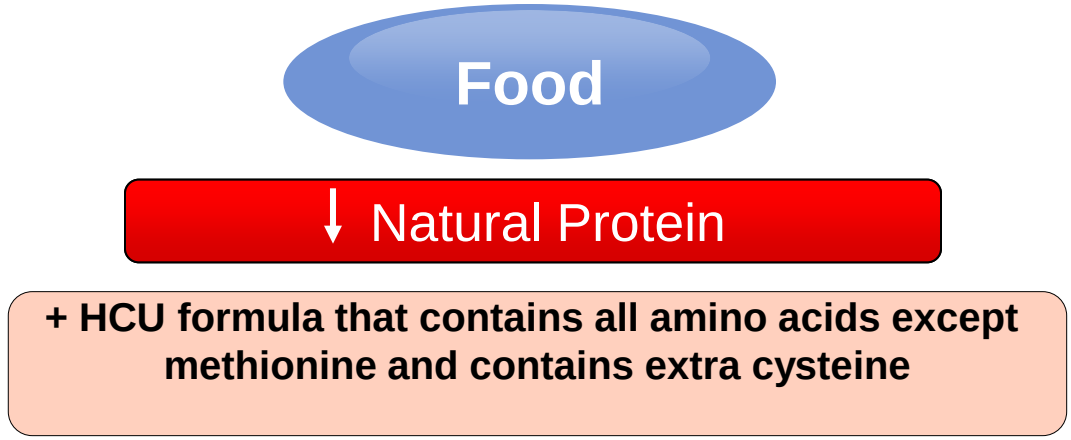
eg. fruit, vegetables, potatoes, cereal, pasta, rice

eg. sugar, juice

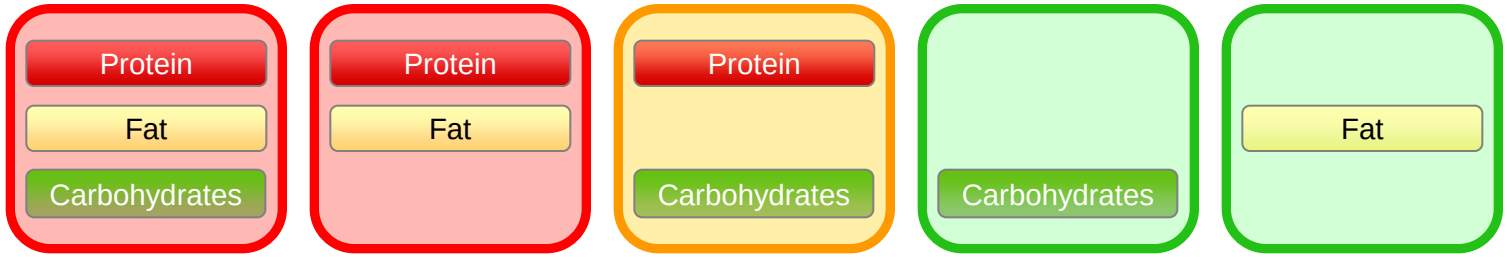
eg. oil, margarine, butter

Dietary Management

Low natural protein diet + formula that does not contain the amino acid methionine



Natural Food



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eg. sugar, juice

eg. oil, margarine, butter

Follow-up in homocystinuria

Systematic follow-up is necessary during management.

Goal: blood homocysteine < 50 µmol/L

Chromosomes, Genes, Mutations

A **chromosome** is like a cookbook.

A **gene** is like a recipe in the cookbook.

A **mutation** is like an error in the recipe or even a complete lack of a recipe.

The **enzyme** Cystathionine Beta Synthase (CBS) is produced constantly in the body following a specific recipe (**gene**). If the gene contains abnormal **mutations,** the **enzyme** cannot function correctly or be properly produced.

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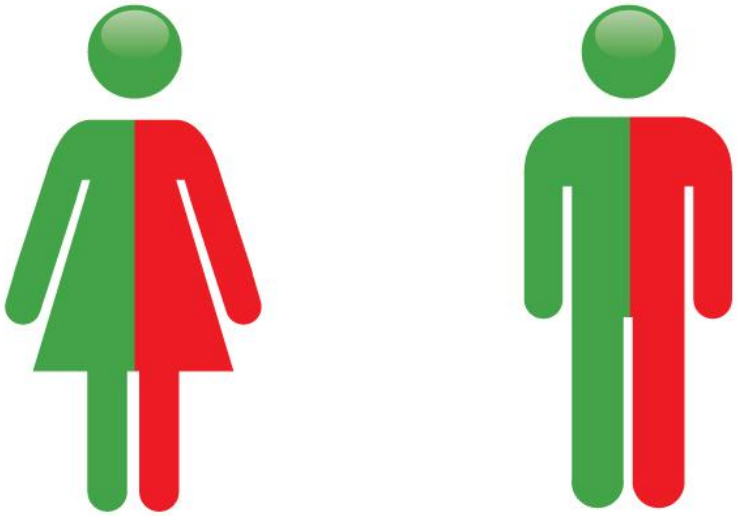
Inheritance

Both parents are carriers in autosomal-recessive inheritance

Mother is a carrier of
HCU



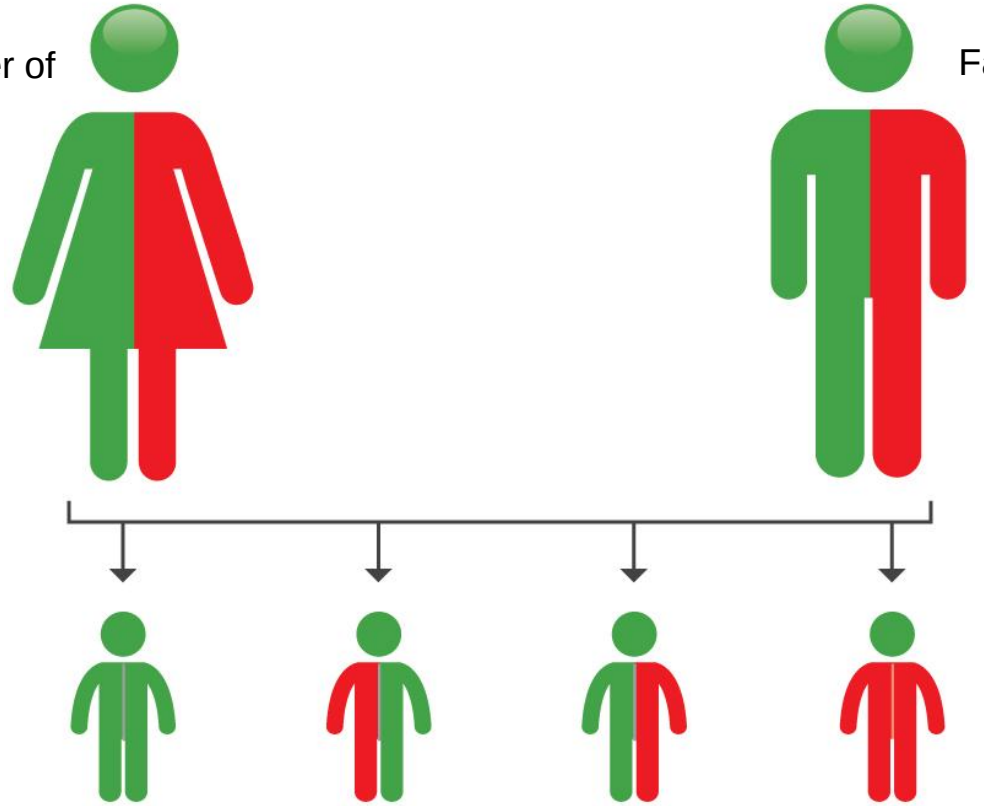
Father is a carrier of
HCU

Inheritance

There are 4 combinations for any child born to parents who are carriers

Mother is a carrier of **HCU**

Father is a carrier of **HCU**



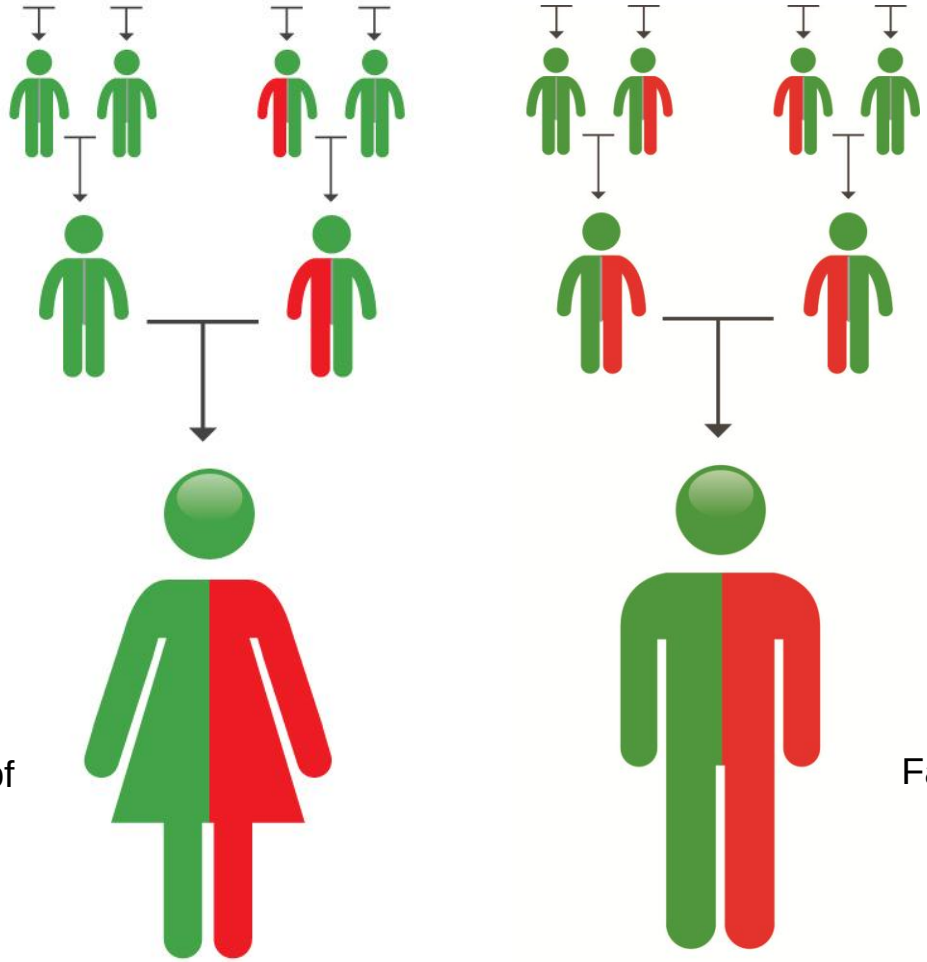
Child **is not** a carrier of **HCU**

Child **is** a carrier of **HCU**

Child **has HCU**

Inheritance

How HCU is inherited in families



Mother is a carrier of **HCU**

Father is a carrier of **HCU**

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Prognosis of HCU

Goal of Management: decrease homocysteine in the blood as soon as possible and keep it low

Effective management started in a newborn

- Normal intelligence
- Delay development of lens dislocation
- Prevent epilepsy
- Prevent osteoporosis
- Age-appropriate school education
- **No thromboembolism**

Effective management started later

- Any organ damage that is already present is not reversible
- **However:**

  dangerous and life-threatening thromboembolism can be avoided

In about 10% of patients, it is possible to normalize the homocysteine concentration in blood by only taking high doses of vitamin B_6

For some, it is not possible to normalize homocysteine even with complex management