Homocystinuria due to CBS deficiency

First information

Written by
Wendel, Burgard & Konstantopoulou

Supported by NUTRICIA as a service to metabolic medicine

TEMPLE
Tools Enabling Metabolic Parents LEarning

HCU

Homocystinuria

Homocystine in urine

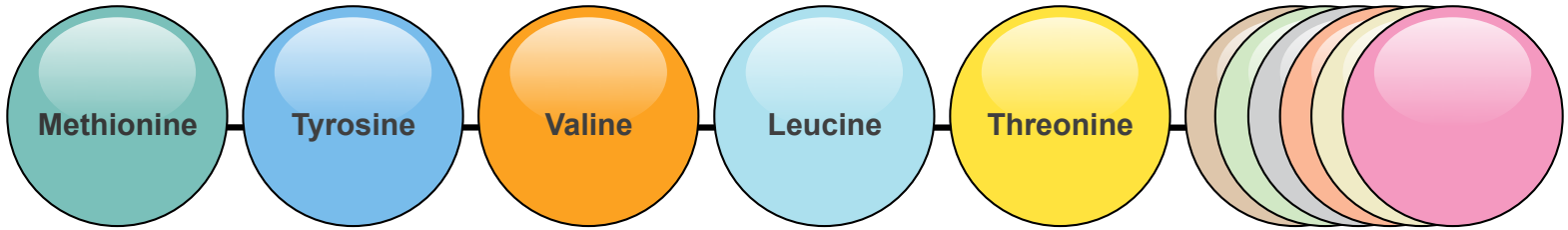
Hyperhomocysteinemia

Too much homocysteine in blood

Food – Components of a normal diet

Protein | Fat | Carbohydrates

Protein consists of chains of amino acids



Natural Food

Protein	Fat	Carbohydrates
✓	✓	✓
✓	✓	
✓		✓
		✓
	✓	

eg. milk, yoghurt, cereals

eg. meat, poultry, fish, eggs, cheese

eg. fruit, vegetables, potatoes

eg. sugar, lemonade

eg. oil, lard

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 (= metabolism).

Cystathionine **b**eta-**S**ynthase (CBS) is the enzyme which converts the protein component (= amino acid) methionine.

In homocystinuria the activity of the CBS enzyme is deficient.

Enzymes

Another enzyme important for the metabolism of methionine and homocysteine is

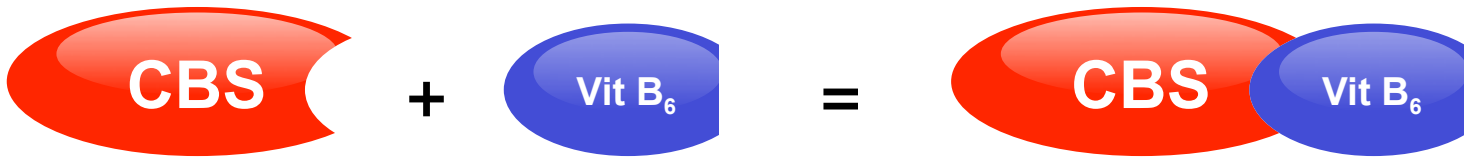
Betaine-**H**omocysteine **M**ethyl**t**ransferase (BHMT).

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

Enzymes

Some enzymes cannot work without the help of vitamins in the form of so called cofactors.

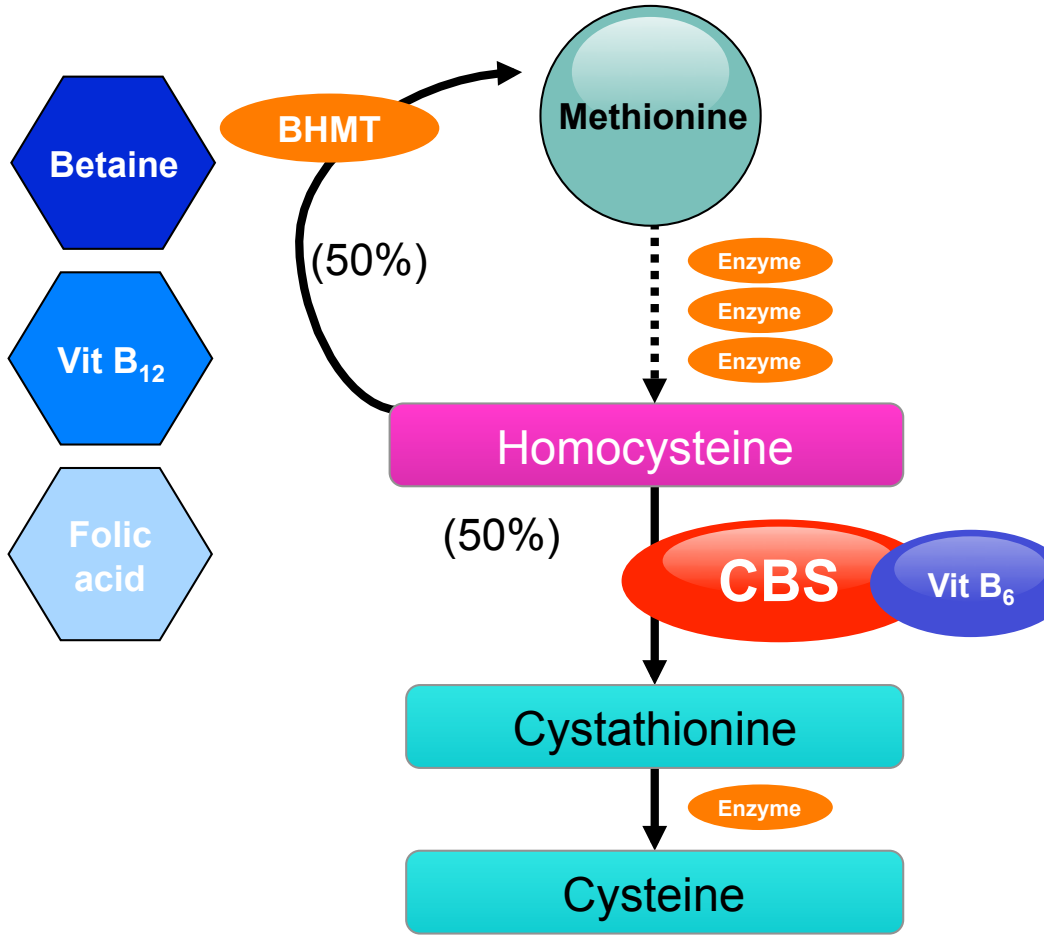
Cystathionine beta-Synthase (CBS) is such an enzyme and vitamin B_6 is its cofactor.



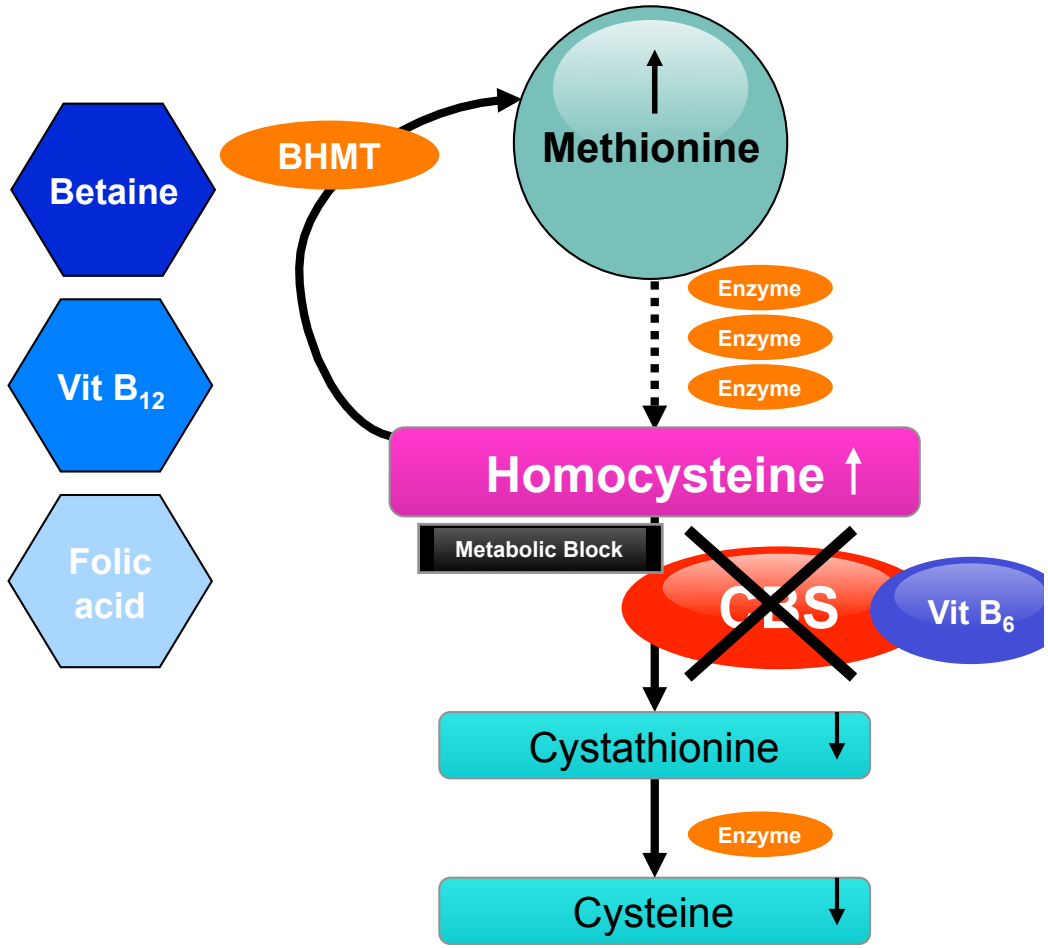
CBS inactive

CBS active

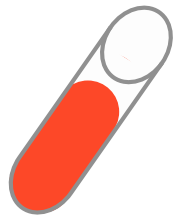
Healthy person: CBS works



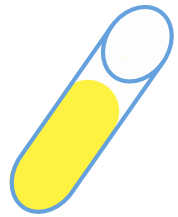
Metabolism in a patient with homocystinuria: CBS deficiency



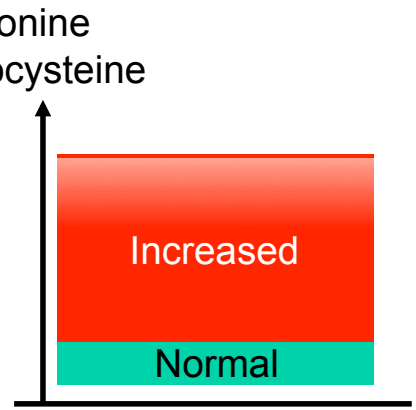
Diagnostic investigations

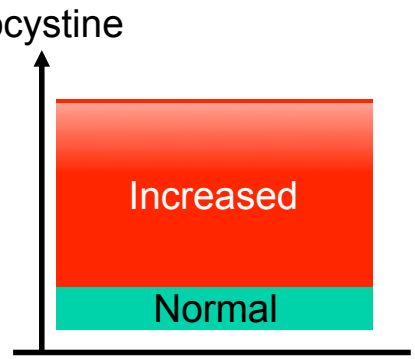


Venous blood



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

Newborns have no 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

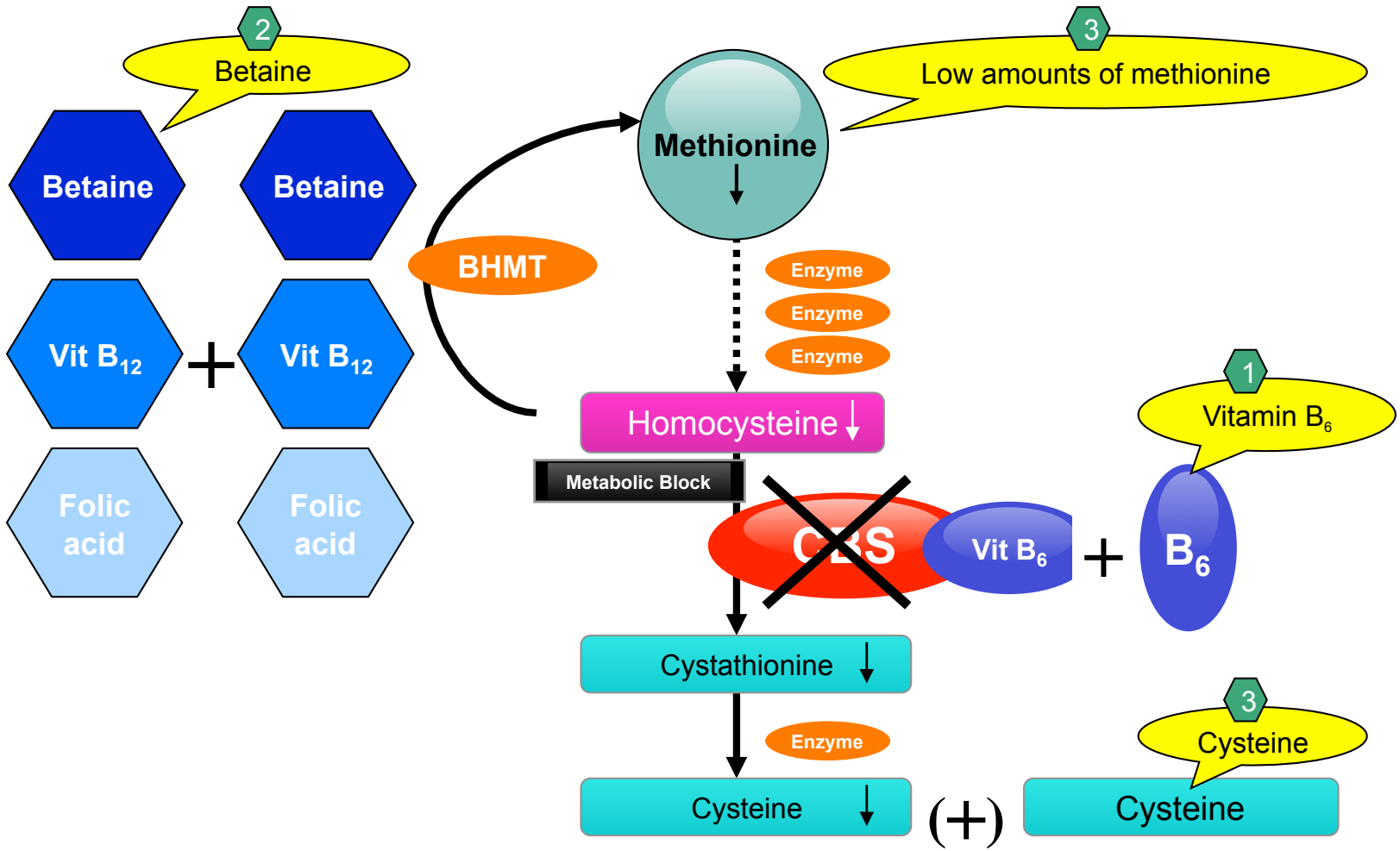
Central Nervous System

Developmental delay, intellectual impairment, epilepsy, focal neurological signs, psychiatric disorders

Treatment

The goal of homocystinuria treatment is to decrease the homocysteine concentration in the blood until it reaches a safe level, at which homocysteine is no longer harmful

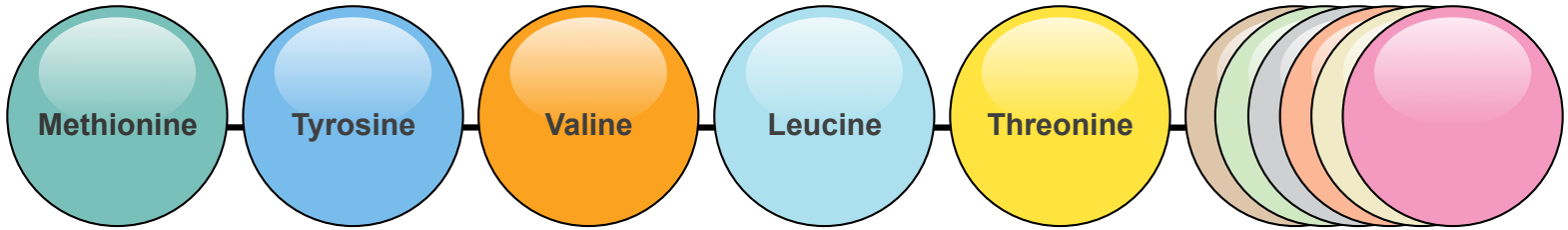
Treatment elements



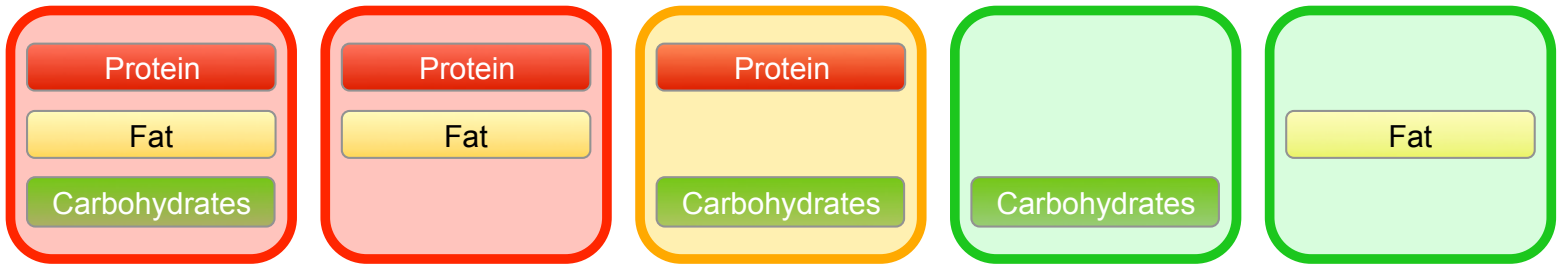
Food – Components of a normal diet

Protein | Fat | Carbohydrates

Protein consists of chains of amino acids



Natural Food



eg. milk, yoghurt

eg. meat, poultry, fish, eggs, cheese

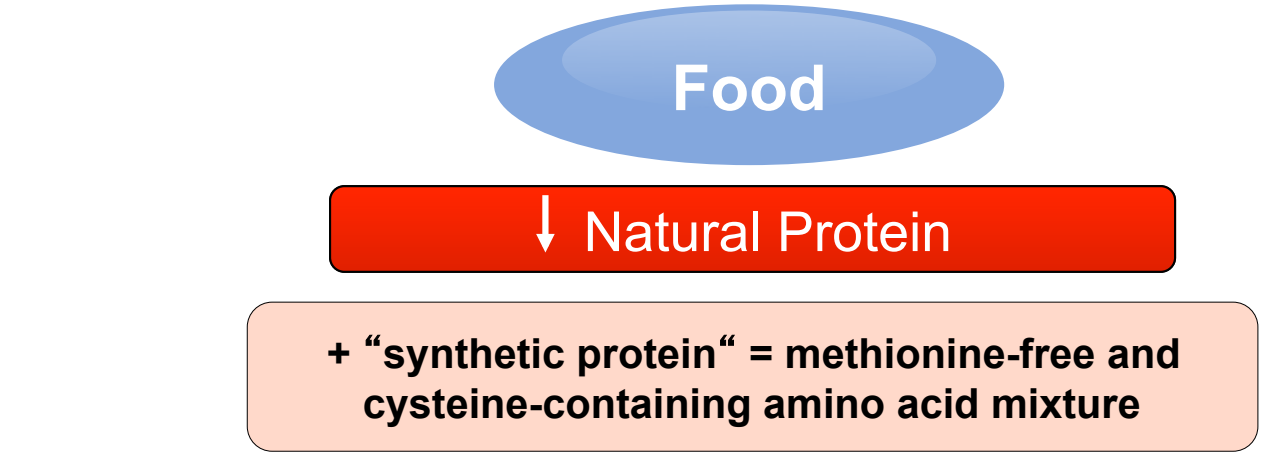
eg. fruit, vegetables, cereals

eg. sugar, lemonade

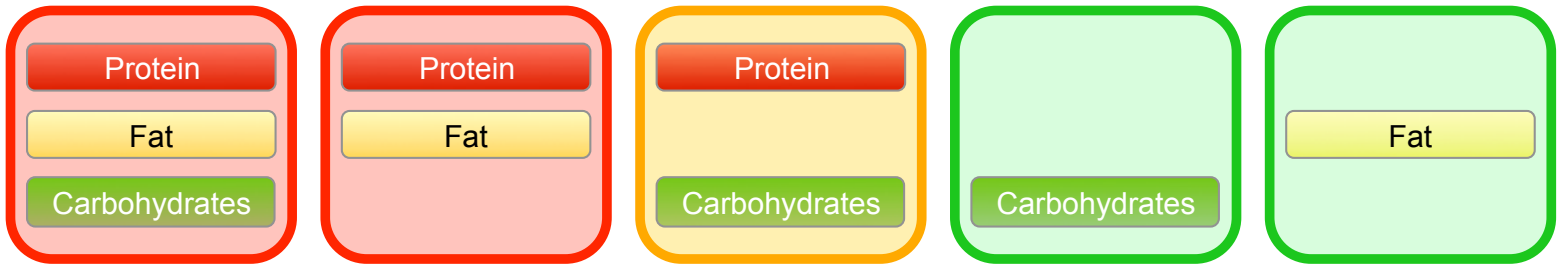
eg. oil, lard

Treatment

Low protein diet + methionine-free amino acid mixture



Natural Food



eg. milk, yoghurt

eg. meat, poultry, fish, eggs, cheese

eg. fruit, vegetables, cereals

eg. sugar, lemonade

eg. oil, lard

Follow-up in homocystinuria

Systematic follow-up is necessary during treatment.

Goal: blood homocysteine < 50 µmol/L

Chromosomes, Genes, Mutations

A **chromosome** is comparable to a cookbook.

A **gene** is comparable to a recipe for cooking.

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

The **enzyme** Cystathionine beta Synthase (CBS) has to be produced constantly in the body according to a specific recipe (**gene**). If the gene contains pathogenic **mutations** the **enzyme** cannot be properly produced.

Inheritance

Autosomal-recessive (carriers of HCU)

Mother is a carrier of **HCU**

Father is a carrier of **HCU**

Female egg cells

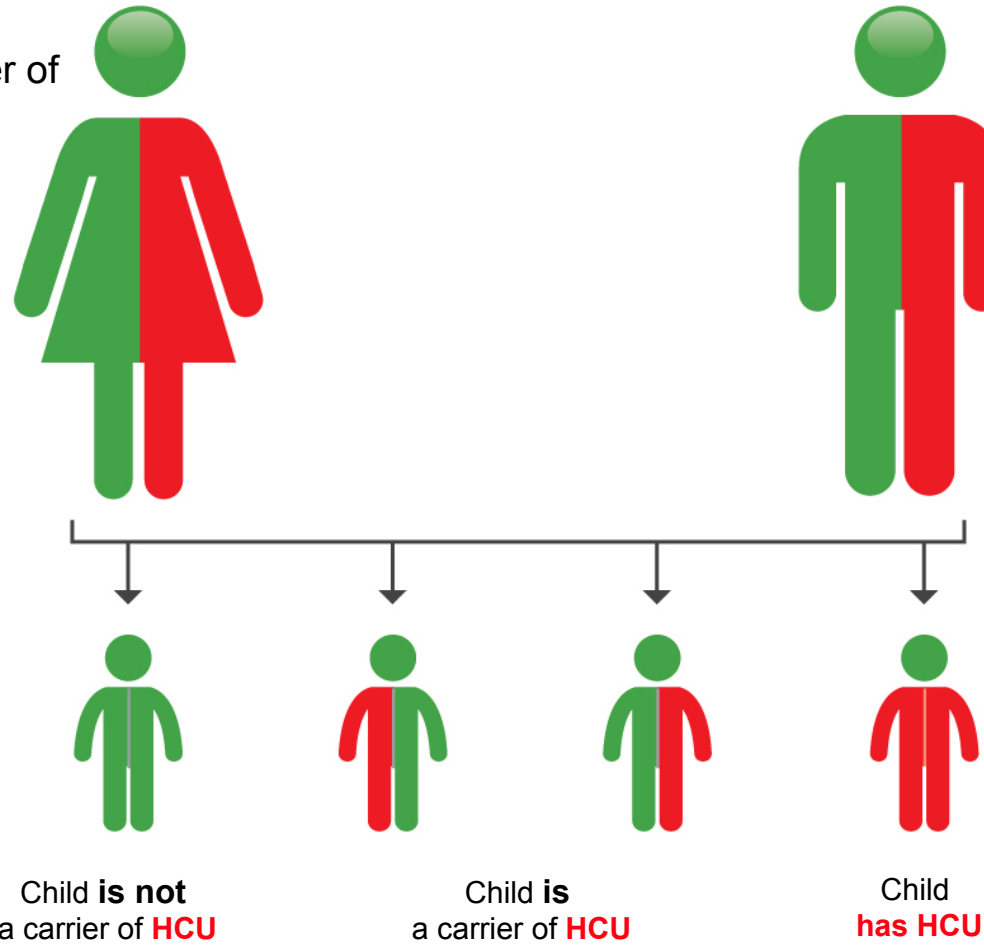
Male sperm cells

Inheritance

Possible combinations

Mother is a carrier of **HCU**

Father is a carrier of **HCU**



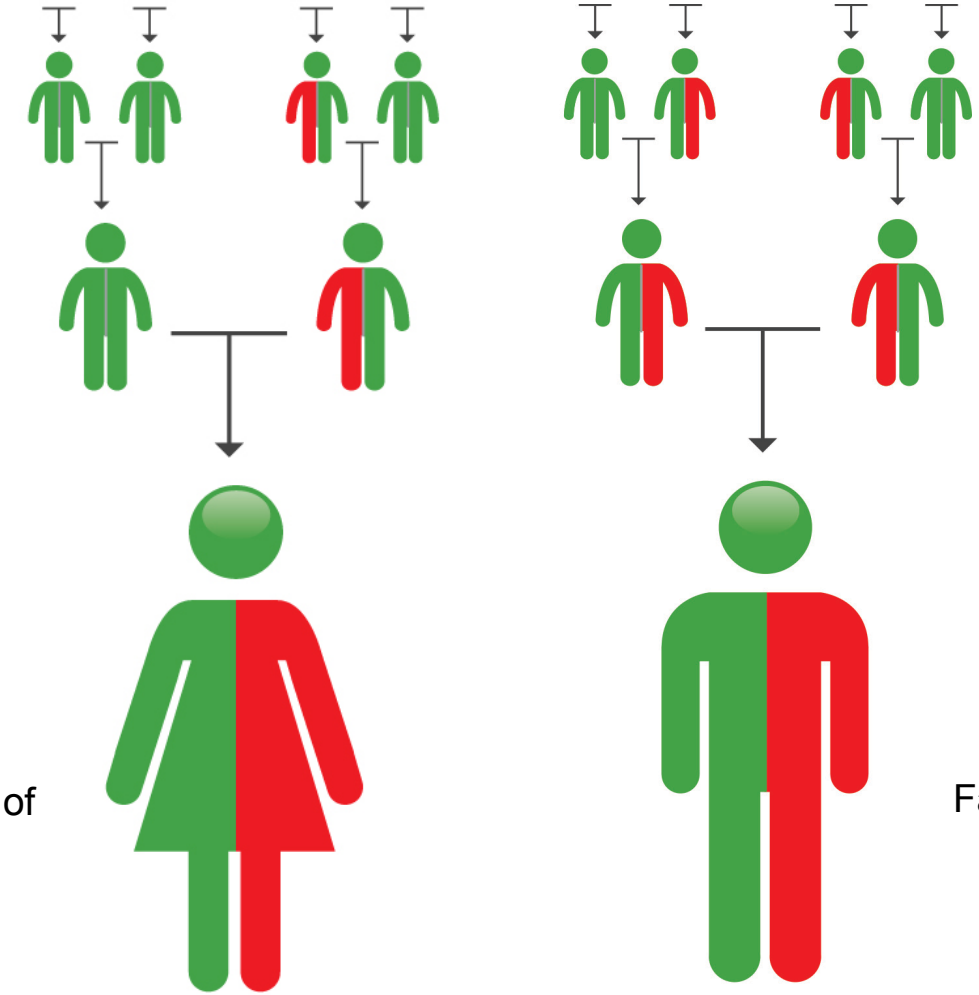
Child **is not** a carrier of **HCU**

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

Child **has HCU**

Inheritance

Where HCU derives from?



Mother is a carrier of **HCU**

Father is a carrier of **HCU**

Prognosis

Treatment start – decrease of the homocysteine concentration; the sooner, the better.

Effective treatment started in a newborn

- Normal intelligence
- Lens dislocation delay
- Avoidance of epilepsy
- Avoidance of osteoporosis
- Age-appropriate school education
- **No thromboembolism**

Effective treatment started later

- Organ damage already present is not reversible
- **However:**

  dangerous and life-threatening thromboembolism can be avoided

Only in approximately 10% of patients is it possible to normalise the homocysteine concentration in blood with the use of vitamin B_6

In the remaining patients it is not possible despite complex treatment