Hereditary tyrosinemia type I

Introductory information

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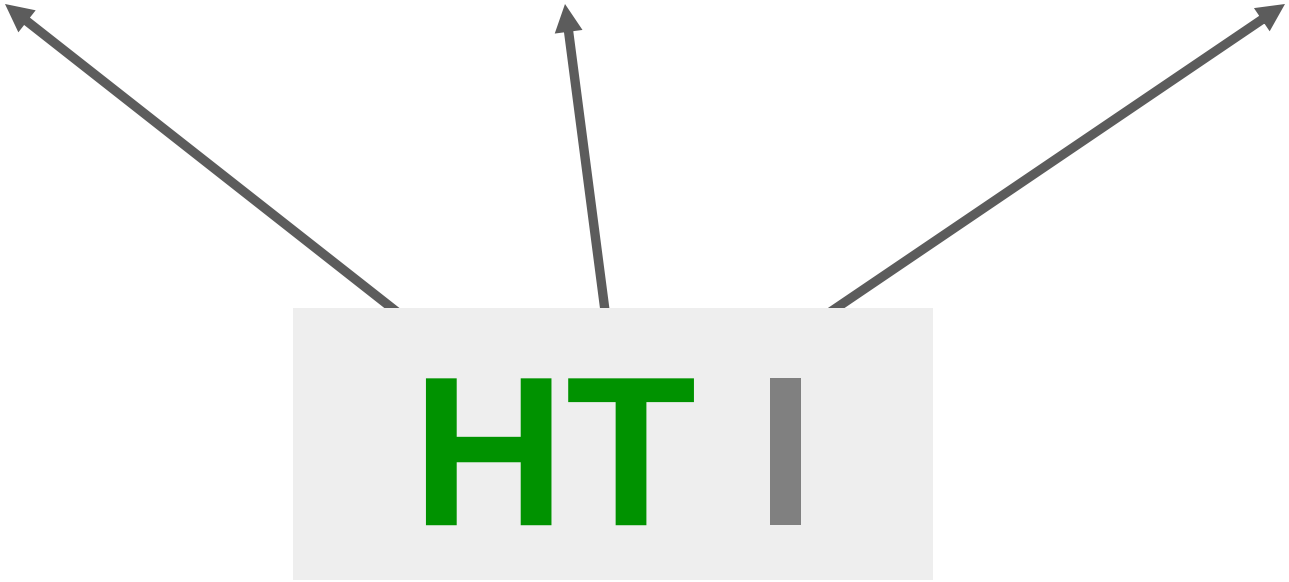
Hereditary tyrosinemia type I



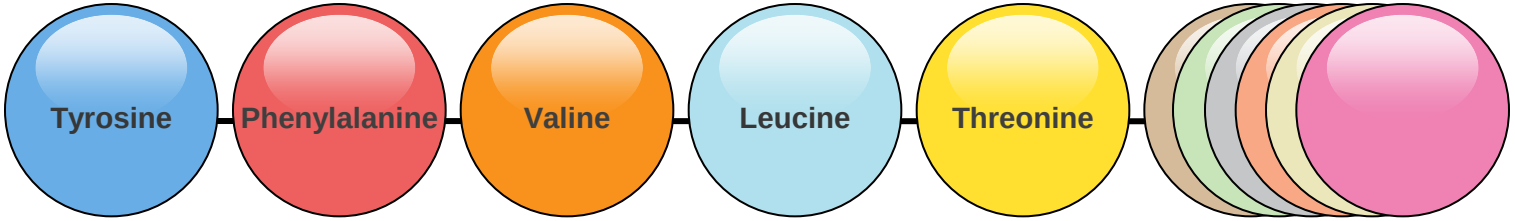
Tyrosinemia type I

(too much) tyrosine in the blood

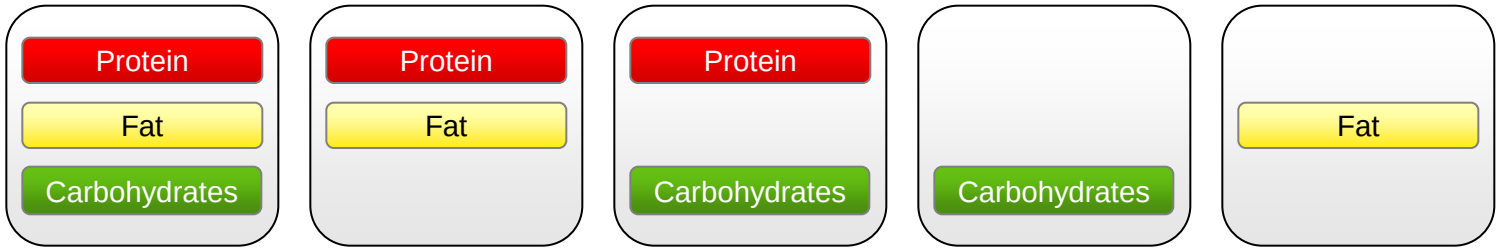
Food – Components of a normal diet

Protein | Fat | Carbohydrates

Protein consists of chains of amino acids



Natural Food



eg. milk, yogurt

eg. meat, poultry, fish, cheese, eggs

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

eg. sugar, lemonade

eg. oil, margarine

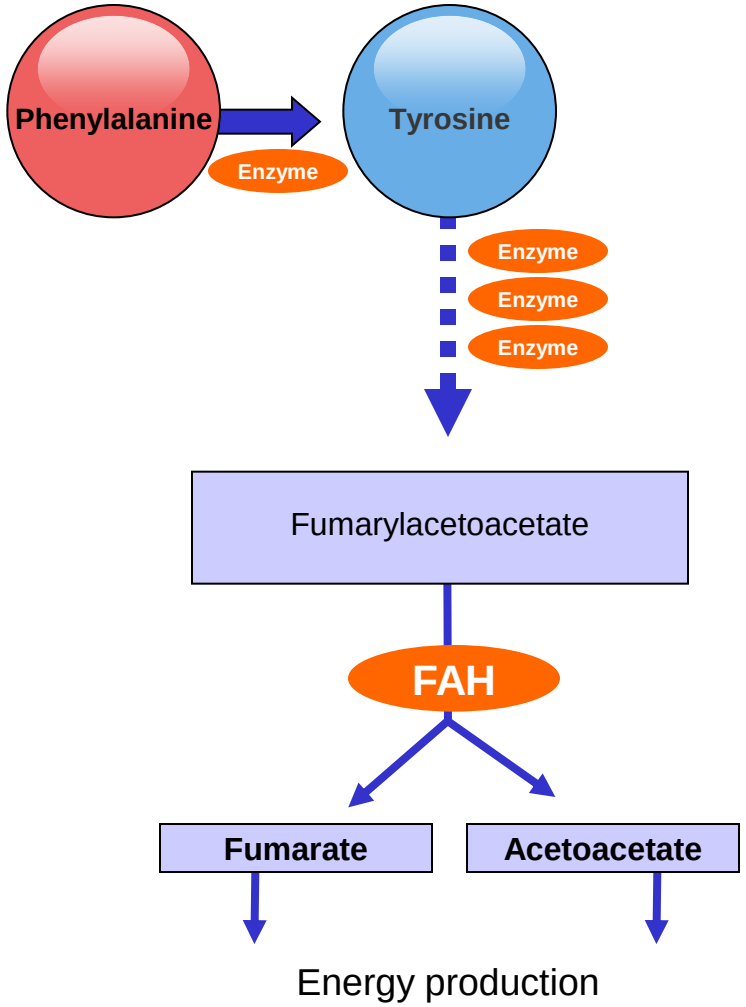
Enzymes

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

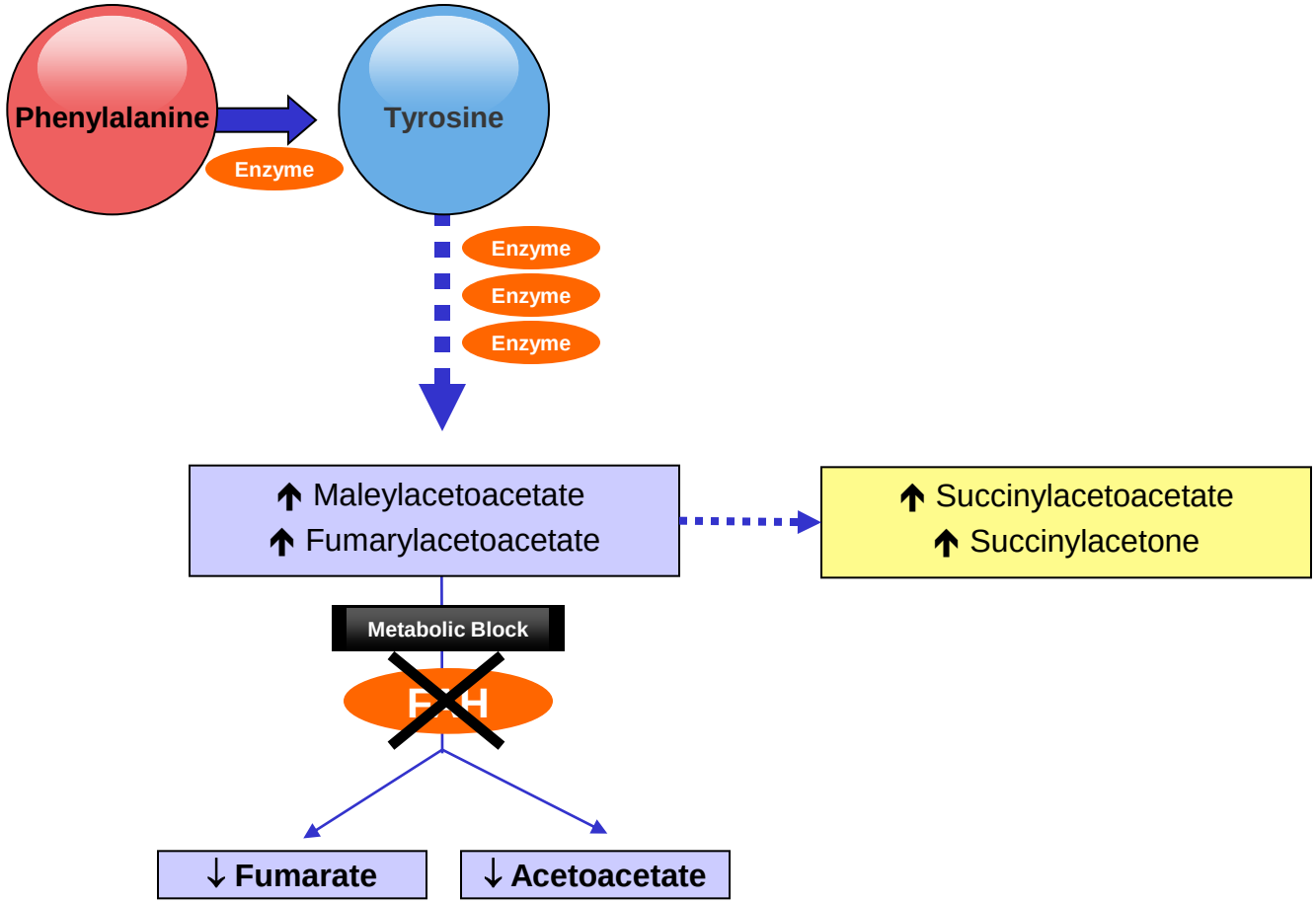
Fumaryl**a**cetoacetate **h**ydrolase (FAH) is the enzyme that participates in the metabolism of the amino acid tyrosine.

In type 1 tyrosinemia the activity of the FAH enzyme is decreased.

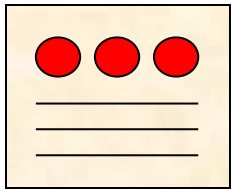
In normal metabolism: FAH works



In Hereditary Tyrosinemia Type I: FAH deficiency

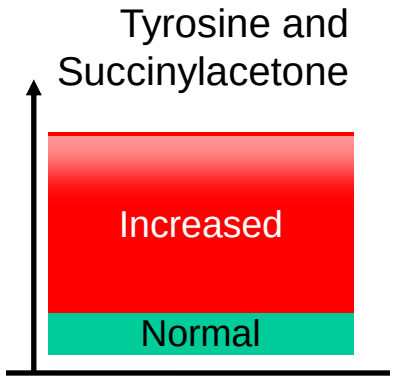


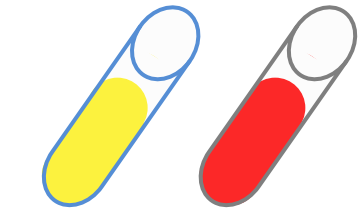
Diagnosis of HT-1



Dried blood spots

Metabolic/Newborn screening

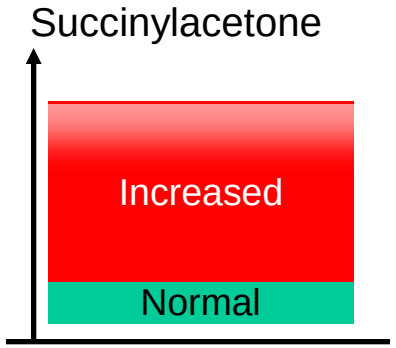




Urine sample

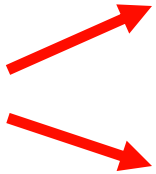
Venous blood

Confirmation of diagnosis



Pathogenesis of HT-1

High concentrations of



Maleylacetoacetate
Fumarylacetoacetate

Succinylacetoacetate
Succinylacetone

damage the liver, kidneys and the brain,
and cause neurological symptoms.

The disease course is variable:

from acute liver failure in the first weeks of life to the development of symptoms in adulthood.

Pathogenesis if HT-1

Maleylacetoacetate
Fumarylacetoacetate

→

The liver is the organ that is most affected

Symptoms in the first weeks of life: signs of acute liver failure

Vomiting, diarrhea, liver enlargement, bleeding tendency, jaundice, edemas

Liver diseases

Acute liver failure

Cirrhosis (early)

Hepatocellular carcinoma (early)

Pathogenesis of HT-1

Maleylacetoacetate
Fumarylacetoacetate

Succinylacetoacetate
Succinylacetone

Renal (Kidney) damage

Renal tubular dysfunction (can cause rickets = abnormal bone development)

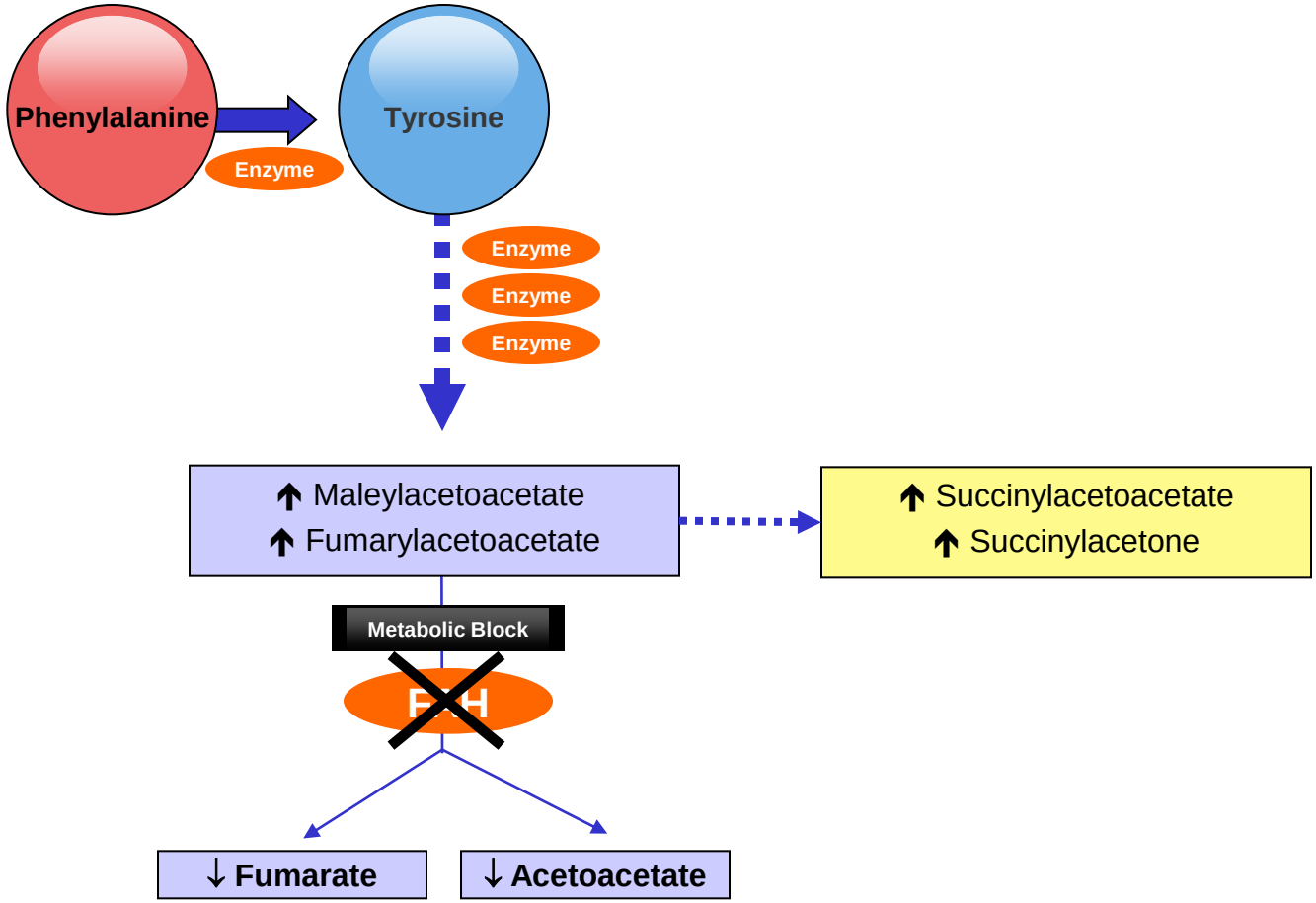
Renal failure

Neurological symptoms

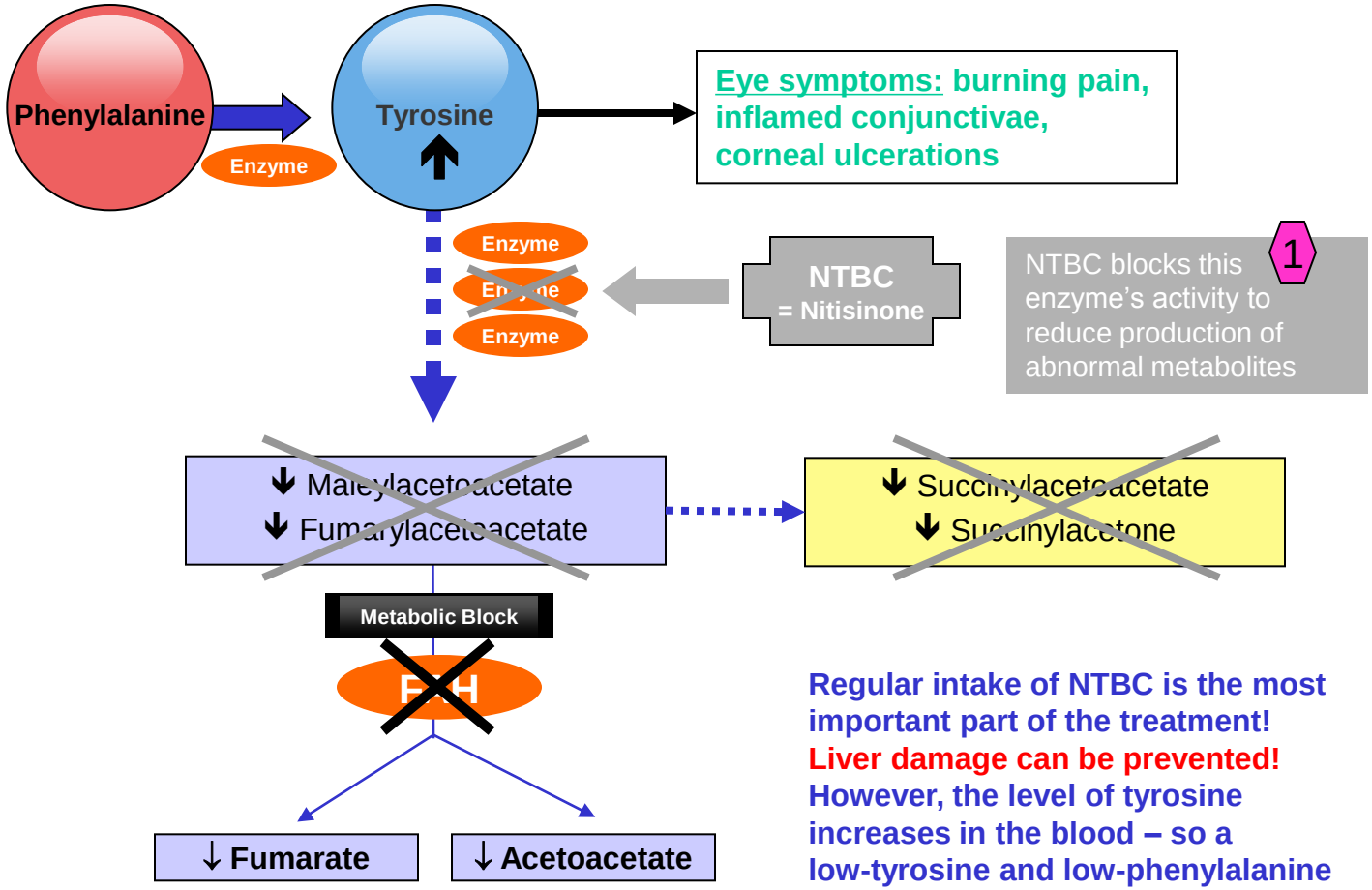
Acute neurological crises with painful paresthesia (sensation of pins & needles), paralyses

Learning difficulties

Metabolism in HT-1: Before management

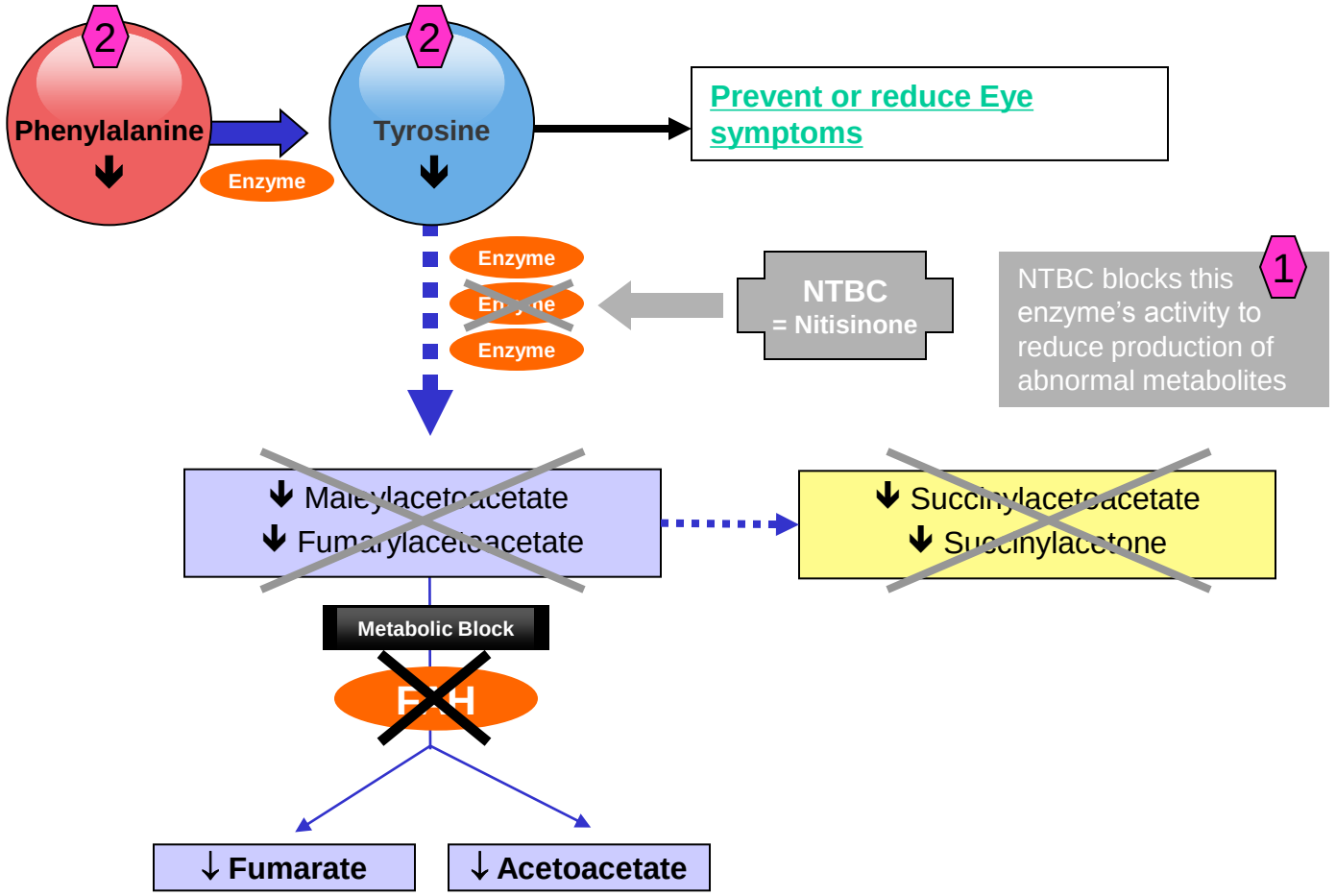


Treatment with NTBC [1] (Nitisinone)



Regular intake of NTBC is the most important part of the treatment!
Liver damage can be prevented!
However, the level of tyrosine increases in the blood – so a low-tyrosine and low-phenylalanine diet is required!

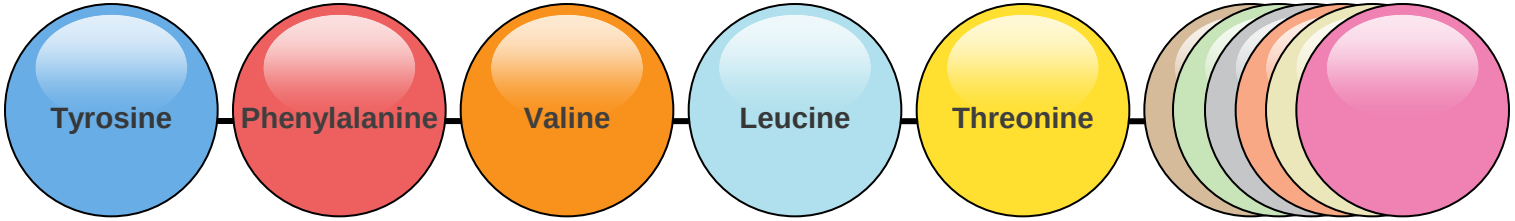
Low-tyrosine and low-phenylalanine diet 2



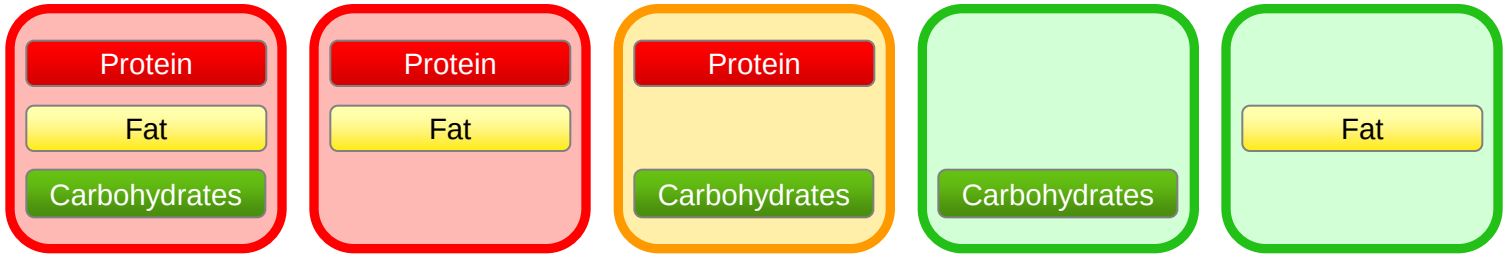
Food – Components of a typical diet

Protein | Fat | Carbohydrates

Protein consists of chains of amino acids



Natural Food



eg. milk, yogurt

eg. meat, poultry, fish, cheese, eggs

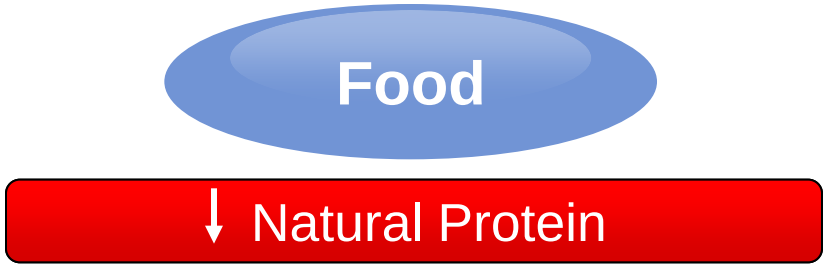
eg. fruit, vegetables, potatoes, cereals, pasta, rice

eg. sugar, lemonade

eg. oil, margarine

Diet Management of HT-1

A diet low in natural protein decreases the amount of tyrosine and phenylalanine intake



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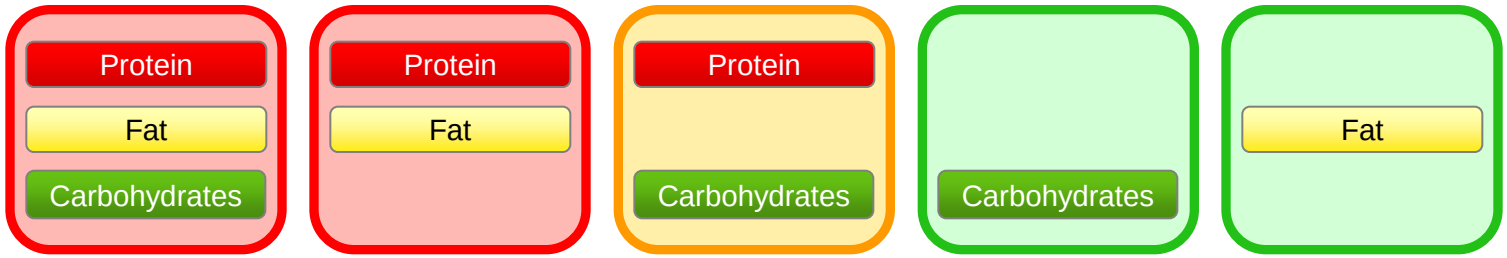

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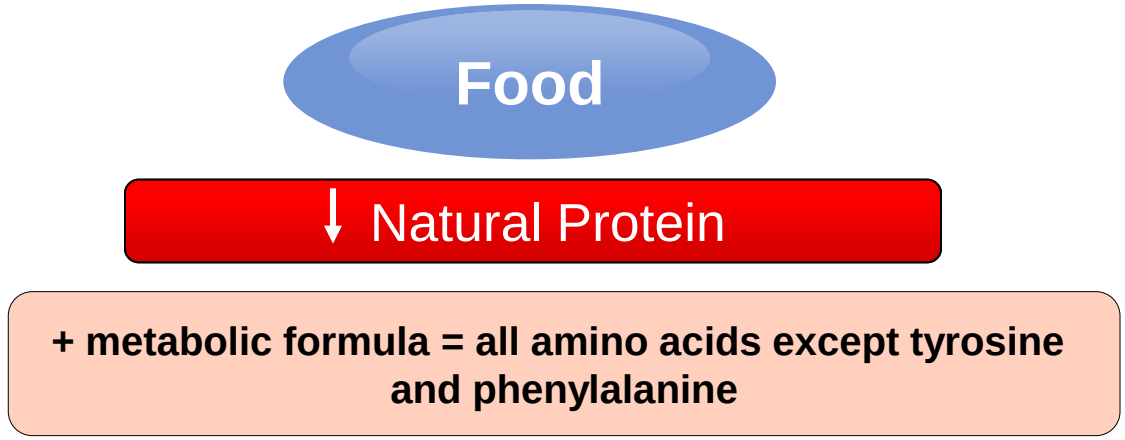
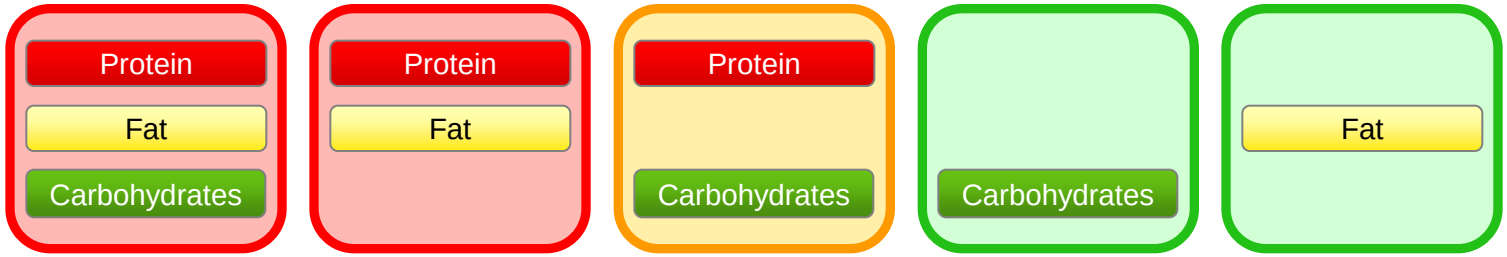
eg. oil, margarine

Diet Management of HF-1

Low natural protein diet + tyrosine-free and phenylalanine-free metabolic formula



Natural Food



eg. milk, yogurt

eg. meat, poultry, fish, cheese, eggs

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

eg. sugar, lemonade

eg. oil, lard

Follow-up in HT-1

Frequent follow-up is necessary with NTBC (Nitisinone) treatment and a low-tyrosine and low-phenylalanine diet. This includes the following tests:

1. Succinylacetone: as low as possible in blood and in urine
2. Plasma tyrosine: goal < 500 µmol/L
3. Plasma phenylalanine: prevent levels that are too low
3. Liver tests, coagulation tests

Chromosomes, Genes, Mutations

A **chromosome** is like a cookbook.

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

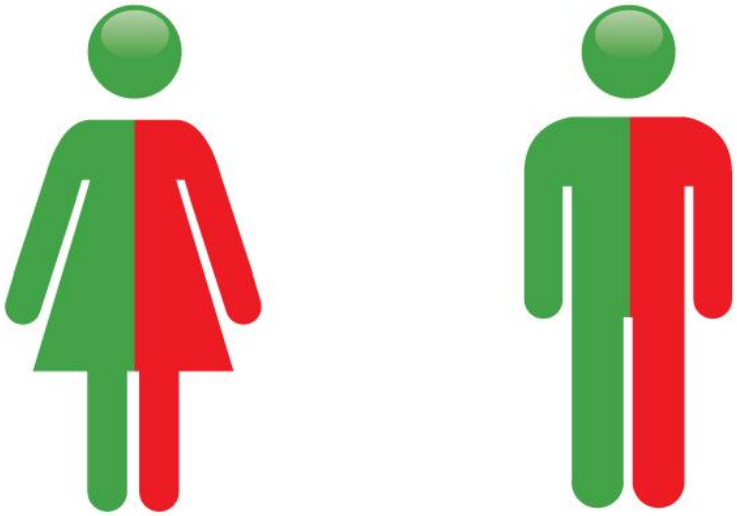
A **mutation** is like an error in the recipe or even a complete lack of the recipe.

The fumarylacetoacetate hydrolase (FAH) 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.

Inheritance of HT-1

Parents are carriers of HT-1 in autosomal-recessive

Mother is a carrier of
HT-I



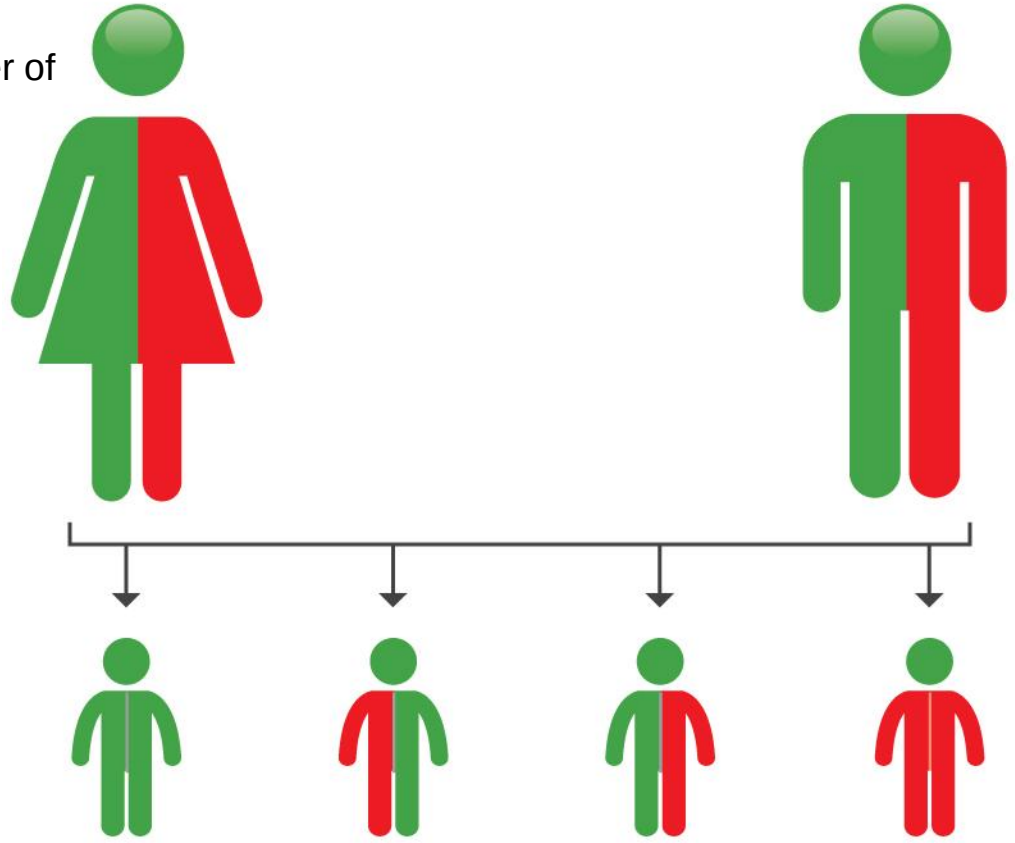
Father is a carrier of
HT-I

Inheritance of HT-1

Possible combinations

Mother is a carrier of **HT I**

Father is a carrier of **HT I**



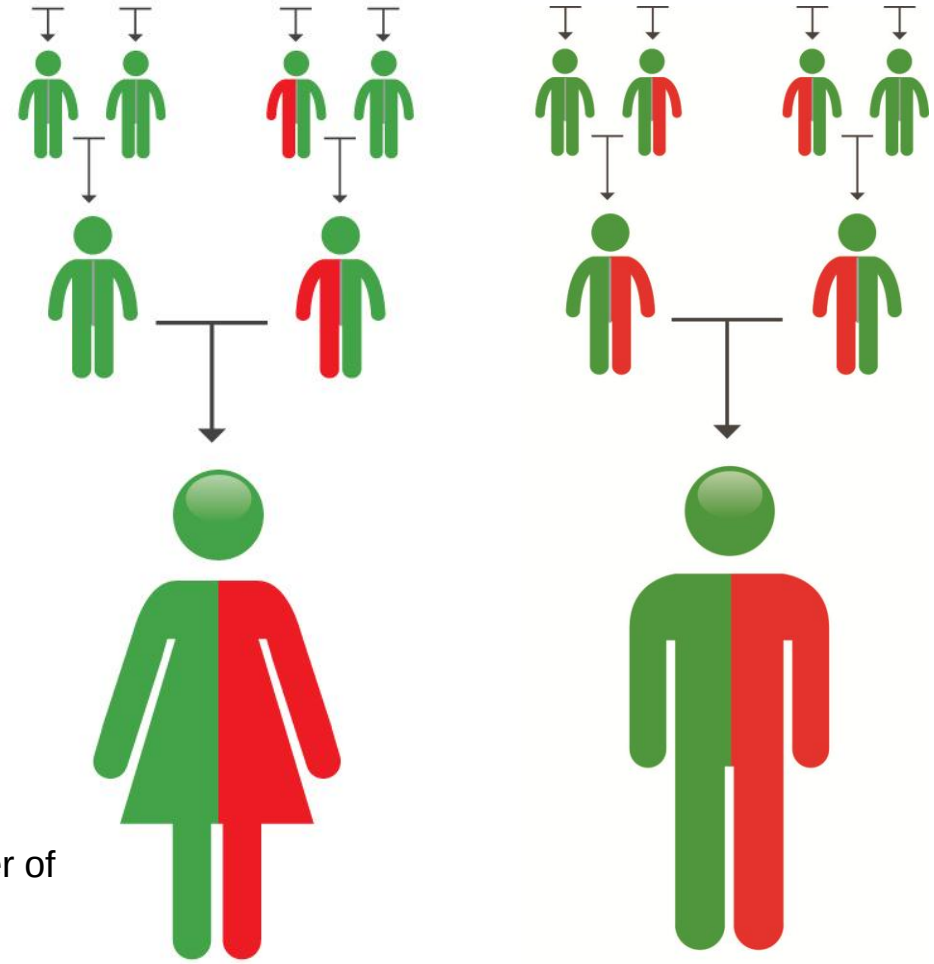
Child will not be a carrier of **HT I**

Child will be a carrier of **HT I**

Child **will have HT I**

Inheritance of HT-1

Where does HT-I come from?



Mother is a carrier of **HT-I**

Father is a carrier of **HT-I**

Summary

What is HT-I?	Defect in tyrosine metabolism
	⬆ Fumarylacetoacetate, ⬆ Succinylacetone, ⬆ Tyrosine

Optimal Management

1. **Intensive care**
2. **NTBC (Nitisinone)**
3. **Low-protein diet**

Result

- **Quick reversal of symptoms of acute liver damage**
- **Significantly lower risk of liver cirrhosis, hepatocellular carcinoma, kidney disease**
- **No neurological crises**

Follow-up

Laboratory tests
- Succinylacetone
- Liver function tests
- Kidney function tests
-Tyrosine and phenylalanine

Physical development
- Height and weight
- Head circumference

Imaging of the liver
- Ultrasound, CT/MRT

Development
- Intelligence (IQ)
- Neuropsychology

Insufficient Management

Result

Chronic disease course

- **Hepatocellular carcinoma**
- **Neurological crises**
- **Kidney damage**
- **Liver cirrhosis**

Acute liver failure
Death