

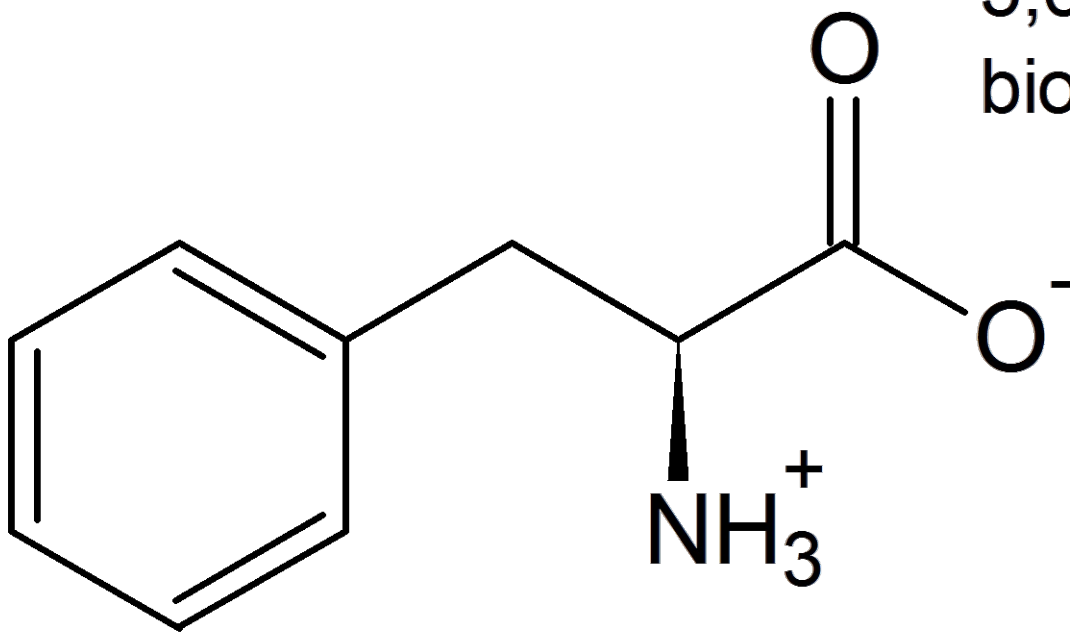
## Hereditary disorders of amino acid metabolism

Hereditary disorders of amino acid metabolism are AR inherited diseases. Phenylketonuria and hyperphenylalaninemia (PKU / HPA) are among the most common in the Czech Republic

Neonatal screening in the Czech Republic includes: hyperphenylalaninemia and disorders of sulfur amino acid metabolism (homocystinuria due to cystathionine beta-synthase deficiency - CBS and homocystinuria due to methylenetetrahydrofolate reductase deficiency - MTHFR), as well as some organic aciduria - maple acid syrup disease and isomeric acid syrup since 2016 also some disorders of the urea cycle (argininemia and citrulinemia type I).

Phenylketonuria  
(new variant)

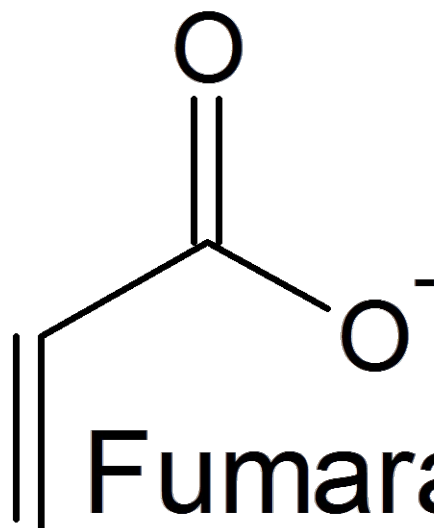
5,6,7,8-Tetrahydrobiopterin + O<sub>2</sub>



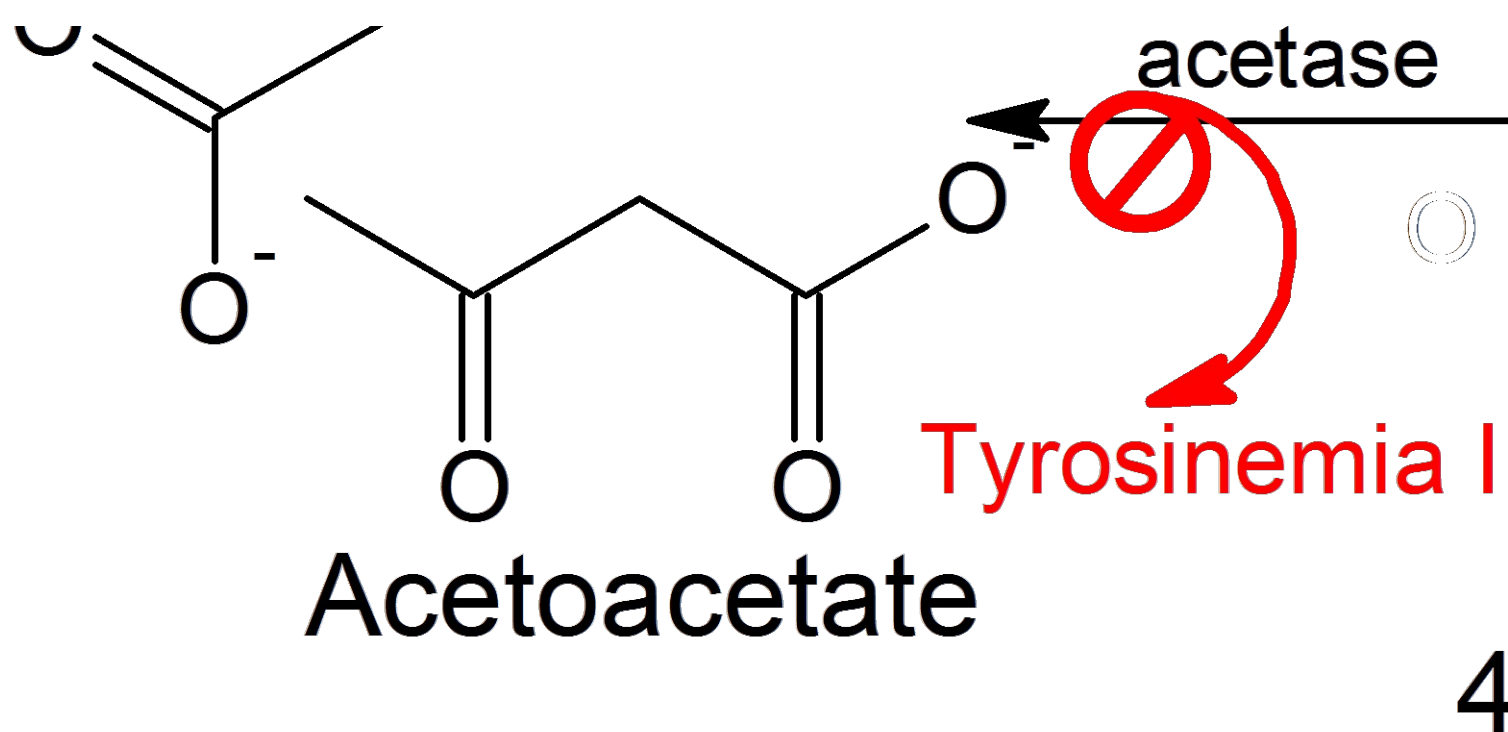
Phenylalanine

Phenylhydrazine

Phenylketonuria



Fumarate 4-Fumarylacetoacetic acid



Phenylalanine and tyrosine metabolism and its disorders

	incidence	affected enzyme	OMIM	links
hyperphenylalaninemia	1: 6500 (CZ), 1:13 000 (world)	phenylalanine hydroxylase (98%), tetrahydrobiopterin (2%)	# 261600	[1]
tyrosinemia I	1: 100,000 (world)	fumarylacetoacetate hydrolase and maleyl acetoacetate cis / trans isomerase (it is a dibasic enzyme)	# 276700	[2]
tyrosinemia II	rare	tyrosine aminotransferase	# 276600	[3]
tyrosinemia III	rare	4-hydroxyphenylpyruvate dioxygenase	# 276710	[4]
alkaptonuria	1: 100,000 - 1: 1,000,000 (world), 1:19,000 (Slovakia)	homogentate-1,2-dioxygenase	# 203500	[5]
homocystinuria	1-9: 1,000,000 (world)	cystathionine β-synthase	# 236200	[6]
cystinuria	1: 7000 (USA)	renal transport defect of some amino acids	# 220100	[7]
maple syrup disease	1: 185,000	branched alpha-acid dehydrogenase	# 248600 ; # 248611; # 248610; # 246900	[8]
isovaleric acidemia	1: 230 000 (world)	isovaleryl-CoA dehydrogenase	# 243500	[9]
glutaric aciduria	1:40 000 (whites)	glutaryl-CoA dehydrogenase	# 231670	[10]
methylmalonic aciduria	rare	methylmalonyl-CoA mutase	# 251000	[11]
propionic acidemia	rare	propionyl-CoA carboxylase	# 606054	[12]
urea cycle disorders	1:30 000 (world)			

### Congenital disorders of phenylalanine metabolism

- a group of diseases in which hyperphenylalaninemia occurs in the body
- AR hereditary , the gene is on chromosome 12 , the incidence is 1: 10,000
- types :**
- phenylalanine hydroxylase defect* - classic phenylketonuria (PKU)
  - dihydrobiopterin reductase defect* - atypical phenylketonuria
  - dihydrobiopterin biosynthesis defect* (cofactor) - atypical phenylketonuria
- pathogenesis** - phenylalanine and its alternative metabolites (phenylpyruvic acid, phenyllactic acid, phenylacetic acid and o-hydroxyphenylacetic acid) accumulate in the organism , which are excreted in the urine
  - Imbalance of plasma AMK impairs brain development
  - after the 6th year, it no longer damages the brain
  - phenylalanine inhibits enteral resorption of tyrosine (competes with the transporter) → disorder of melanin synthesis (skin and hair pigmentation is reduced), as tyrosine is the starting AMK for melanin production
- screening** - we use capillary blood from the heel on the 2nd - 3rd day after birth
  - the newborn should be on dairy at the time of collection
  - when the child is released from the maternity hospital on the 2nd or 3rd day - we will take the screening, but after the release the practitioner will ensure the collection of capillary blood for a control examination
  - Since 1 October 2009, nationwide neonatal screening has been performed using tandem mass spectrometry
  - formerly: Guthrie's method - we have *Bacillus subtilis* and its growth inhibitor on agar, we add blood, in the presence of Phe there is competition with the inhibitor and the bacteria start to multiply
- the diagnosis** can be made from the blood at the metabolic and molecular level, enzymatic examination from liver biopsy is not needed for diagnosis or treatment, but in all children with PKU it is necessary to examine pterin metabolism to differentiate forms
- clinical picture without treatment** : after birth the baby is without clinical symptoms, it gradually delays in psychomotor development
  - vomiting , hyperactivity and aimless movements of athetosis , frequent epileptiform convulsions and changes in EEG
  - microcephaly , blond hair, blue eyes and pale skin changes in the nature of seborrheic dermatitis or eczema
  - sweat smells strongly of the mouse
- treatment** : low-phenylalanine diet - a diet with reduced phenylalanine intake through the selection of low-food foods and phenylalanine-free supplements, daily requirement of AMK must be supplemented with a mixture of essential AMK without Phe, enriched with ions, trace elements and vitamins and especially tyrosine that the body is not able to create it in an endogenous way, or only in a minimal insufficient amount, so it is basically essential for phenylketonurics) - always depending on the age of the child
  - we have to reduce the Phe level to 100–300 μmol / l
  - the need for dietary treatment is lifelong, it is important later especially in pregnancy (psychomotor fetal retardation, microcephaly or VSV )
  - enzyme therapy - the enzyme pegvaliase is administered subcutaneously, which then converts Phe in the bloodstream into ammonia and trans-cinnamic acid. The disadvantage of this therapy is its financial complexity and immune response to enzyme molecules. The main advantage is that patients tolerate higher levels of Phe better and can relax the diet.

### Congenital disorders of tyrosine metabolism

- importance of tyrosine: protein synthesis ( proteosynthesis ), dopamine, adrenaline, noradrenaline, melanin and thyroxine;
- tyrosine is obtained partly from the diet and partly synthesized in the liver from phenylalanine;
- metabolic diseases with hyperthyrosinemia (hereditary AR, incidence 1: 50-100,000):
  - tyrosinemia I: fumarylacetoacetate hydroxylase (FAH) disorder,
  - tyrosinemia II: tyrosine aminotransferase disorder,
  - tyrosinemia III: 4-hydroxyphenylpyruvate dehydrogenase disorder (4-HPPD);

- secondary hyperthyrosinemia: manifestation of hepatopathy in neonates with congenital CMV infection ;
- transient hyperthyrosinemia: in the first 2 weeks of life with a high protein content in the newborn's diet; benign; rapidly decreases after administration of vit. C and reduction of protein intake.

#### Tyrosinemia type I

- **cause** : fumarylacetoacetate hydroxylase (FAH) disorder;
- **pathogenesis** : tyrosine is metabolized in the liver and kidneys by an alternative route to succinylacetone - tissue toxin → progressive impairment of liver and kidney function;
- clinical picture : failure, anorexia, vomiting, hepatomegaly, changes in muscle tone → liver and kidney failure.
  - in someone, a "porphyric crisis" with manifestations of peripheral neuropathy or paralytic ileus;
- **diagnosis** : acute disruption of the internal environment, hepatopathy, coagulopathy, high alpha-fetoprotein, increased tyrosine and methionine, increased serum succinylacetone concentration;
  - urine: increased succinylacetone concentration;
  - molecular genetic diagnostics;
- **therapy** : comprehensive treatment of acute crisis including hemodialysis;
  - long-term low-protein diet + supplementation of essential amino acids without phenylalanine and tyrosine + pharmacological treatment (NTBC, 2- (2-nitro-4-trifluoromethylbenzoyl) -1,3-cyclohexanedione) - inhibition of tyrosine degradation at the 4-HPPD enzyme level → inhibition of succinylacetone formation;
  - event. liver transplantation;
- **prognosis**: good with early diagnosis and treatment.

*More detailed information can be found on the Tyrosinemia page .*

### Disorders of sulfur amino acid metabolism

#### Homocystinuria

Cystine metabolism. The upper reaction is catalyzed by cystathionine β-synthetase (CBS), the lower is catalyzed by cystathionine γ-lyase

- homocysteine is a metabolite of methionine
- AR hereditary disease, incidence about 1: 10-20,000;
- **cause** : impaired cystathionine β-synthetase (CBS) activity, which is involved in the transulfuration of homocysteine to cystathionine; the activity of the enzyme depends on the presence of pyridoxine;
- **pathogenesis** : homocysteine, methionine and other metabolites accumulate above the enzyme block; there is a lack of cystathionine, cystine and other metabolites under the block;
- clinical manifestations : depends on the type of mutation and the response to pyridoxine treatment;
- 2 main types of homocystinuria:
  - pyridoxine-resistant → severe involvement of the CNS, connective tissue and vascular system as early as infancy or preschool;
    - mental development disorder, senior, marfanoid phenotype with arachnodactyly, chest deformities, generalized osteoporosis, lenticular myopia with subsequent lens ectopy, secondary glaucoma, thromboembolic events (life-threatening), hypopigmentation of the skin and skin adnexa
  - pyridoxine-sensitive → milder course, mostly only vascular system involvement (risk of thromboembolic complications);
- **diagnosis** : markedly elevated serum homocysteine levels, enzymatic and molecular examination;
- **treatment** : pyridoxine-sensitive → high doses of pyridoxine to stimulate residual CBS activity;
  - pyridoxine-resistant → lifelong low-protein diet with low methionine content, supplementation of essential amino acids without methionine, supplementation of ions, calcium, trace elements, vitamins and cysteine to correct cysteine deficiency; betaine administration (remethylation of homocysteine back to methionine);
- **prognosis**: unfavorable in case of late detection and late treatment.

#### Cystinuria

- AR hereditary disease; occurrence about 1: 6500;
- **cause**: dysfunction of the tubular transport system for cystine and dibasic amino acids (lysine, arginine, ornithine);
- **pathogenesis**: significantly reduced tubular reabsorption of cystine from primary urine back into the blood → cystinuria → formation of cystine stones;
- **clinical picture**: urolithiasis ;
- **therapy**: significantly increased fluid intake + pharmacotherapy: penicillamine (forms a disulfide with cysteine, which is more soluble).

*For more information, see Sulfur Amino Acid Metabolism Disorders .*

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### Congenital disorders of tryptophan metabolism

- essential AMK , ia for the production of nicotinic acid and serotonin .

#### Hartnup's disease

- AR hereditary .
- the basis is abnormal resorption of neutral AMK in the intestine and kidneys.
- usually does not cause any clinical signs.
- possibly skin photosensitivity is at the forefront.

### Organic aciduria

*See the Organic Aciduria page for more information .*

### Congenital disorders of the urea cycle

Urea cycle disorders are a group of enzymatic disorders that result in the accumulation of nitrogen in the form of ammonia , which is very toxic to the body and causes irreversible brain damage. The clinical manifestation of these diseases is usually the first days of life. Hyperammonaemia causes disorders of consciousness, convulsions, vomiting, cerebral edema. In older children, these disorders are most often manifested by psychomotor retardation, failure to thrive, vomiting, behavioral disorders, recurrent cerebral attachments , and headaches . The frequency of urea cycle disorders is approximately 1:30,000.

They include 5 inherited disorders:

	damaged enzyme	location	type of inheritance
<b>Hyperammonemia I</b>	carbamoyl phosphate synthetase (CPS1)	mitochondria	AR hereditary
<b>Hyperammonemia II</b>	ornithine carbamoyltransferase (OTC)	mitochondria	X bound , manifestations also in heterozygous girls
<b>Citrullinemia</b>	arginine succinate synthetase (ASS)	cytosol	AR hereditary
<b>Arginine succinaturia</b>	arginine succinase (ASL)	cytosol	AR hereditary
<b>Argininemia</b>	arginase (ARG1)	cytosol	AR hereditary

#### Clinical picture

Citrulinaemia is manifested in neonatal disorders by impaired consciousness, convulsions, liver failure and brain edema. Argininemia usually manifests itself in infancy or preschool with psychomotor development disorders, progressing with spastic quadriplegia.

#### Diagnostics

- neonatal laboratory screening (since 2016);
- hyperammonaemia, coagulopathy, respiratory alkalosis → metabolic acidosis;
- blood and urine amino acid tests; enzymatic and molecular examination;
- a milder form of hyperammonaemia is common in beta-oxidation disorders of fatty acids, in some types of organic acidurias;

#### Therapy

- ammonia elimination - hemodialysis;
- parenteral administration of glucose event. with insulin (to prevent further deepening of catabolism);
- low-protein diet, essential amino acid supplementation;
- sodium phenylbutyrate or sodium benzoate (ammonia reduction);
- in case of a febrile illness, further reduce protein intake, ensure sufficient energy with sweet drinks; in case of behavior change, apathy or vomiting iv glucose + sodium benzoate, event. elimination methods; with a rapid rise in ammonia levels, there is a risk of developing Reye's syndrome with cerebral edema;
- OTC disorder and citrulinaemia → fetal liver cell transplantation;

#### Prognosis

- according to the type of disorder, early diagnosis and treatment.

*See the Urea Cycle Disorders page for more information .*

## Links

### Related articles

- Hereditary disorders of sugar metabolism
- Hereditary disorders of fat metabolism
- Disorders of aromatic and branched chain amino acid metabolism

### Reference

- ws:Dědičné poruchy metabolismu aminokyselin

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