

Hereditary metabolic disorders / Pathogenetic mechanisms

Hereditary metabolic disorders (DMPs) are diseases caused by a genetic mutation . DMPs are most often monogenically inherited by Mendelian. Autosomal recessive inheritance and gonosomal recessive inheritance have the largest representation . Rarely, these disorders are manifested by autosomal dominant inheritance and gonosomal dominant inheritance. .

Heterozygotes tend to have a normal phenotype .

Enzymes are made in the body in larger amounts than needed, and half the amount is enough for metabolic processes.

DNA mutations → mRNA change → defective protein (enzyme)

Types of abnormalities by which mutations disrupt protein production

Abnormalities can be divided into **primary** and **secondary** . **Primary abnormalities** include transcriptional and translational disorders or protein folding disorders with changes in normal spatial conformation. Furthermore, we can include disorders of cofactor-enzyme binding.

Secondary abnormalities involve non-regulatory interactions. These are disorders of transcriptional and translational regulation.

Pathogenetic effects of mutations and their consequences

- loss of function
- enhancement of function - mutations enhance any of the normal functions of the protein or enhance the intensity of protein production
- gain new function
- incorrect protein expression (at place and time)

Consequences of pathogenetic mechanisms

1. substrate accumulation
2. product missing
3. accumulation of defective enzyme
4. the formation of the wrong product without the possibility of continuing the metabolic pathway
5. loss of multiple enzyme activities
 - if 2 or more enzymes share a common subunit
 - if they use a common cofactor

When accumulating a substrate, it is necessary to consider whether the substrate molecule is small or large. Small molecules (eg phenylalanine) are diffusely dispersed in body fluids, easily passing into the urine across the filtration barrier. Large molecules such as glycosaminoglycans (formerly mucopolysaccharides) accumulate at the site of formation.

Enzyme Defects - An example of phenylketonuria (PKU)

Phenylketonuria (PKU) is a mutation in the gene for PAH (phenylalanine hydroxylase), where the activity of the enzyme is less than 1%. More than 400 alleles are known for PAH , patients tend to be heterozygous, ie they have 2 different causal mutations. PKU can arise other than by mutations for PAH. The low percentage of all PKU is caused by a mutation in the gene for the cofactor PAH - tetrahydrobiopterin.

Hyperphenylalaninemia is a milder form of PKU . In this form, mutations in one or both alleles retain partial (residual) PAH enzyme activity, so they do not show as severe clinical symptoms as PKU.

Links

Related articles

- Hereditary metabolic disorders

References

THOMPSON, James Scott – THOMPSON, Margaret Wilson – NUSSBAUM, Robert L., et al. *Clinical Genetics: Thompson & Thompson*. 6. edition. Praha : Triton, 2004. pp. 426. ISBN 80-7254-475-6.

- ws:Dědičné metabolické poruchy/Léčba onemocnění způsobených poruchami metabolismu aminokyselin a sacharidů