Pharmacogenetics

Pharmacogenetics is a field that is based on both pharmacology and genetics. Pharmacogenetics monitors the hereditary variability of the organism's response dependent on the use of clinically significant drugs. A similar field is pharmacogenomics, which deals with investigating the effect of a drug on the entire genome.

Pharmacogenetic interactions

Most of the original observations were related to signs for which it was possible to **observe radical differences *(eg drug concentration in blood or metabolite waste in urine). Such differences could be observed by*** *changes in pharmacokinetics* (the effect of the organism on the given drug).

Differences in the response of organisms to drugs were caused, for example, by a ``defect in the molecule *of the transporter metabolizing enzyme u or one of the other factors involved in the ``absorption and breakdown of drugs . With different genetic make-up, there is an excessive or insufficient concentration of the drug in the body in different people.*

If the genetic polymorphism interferes with **pharmacodynamic** processes or is dependent on the interaction of several genes, the situation is more difficult. It depends on the **degree of gene expression'**, which is different for each individual and at the same time it is also very different within different **ethnic groups** or among people of **different ages**.

For example, the drug BiDil can be prescribed for cardiac problems only to African-Americans, it does not work for whites. Another example is antidepressant paroxetine, which can only be prescribed to people over the age of 18; it can cause self-harming or even suicidal behavior in younger people.

Classic cases of pharmacological interactions

The establishment of pharmacogenetics as an independent field occurred in the 1950s, when three *classic pharmacological interactions* were described.

Hemolytic anemia after administration of the antimalarial drug **primaquine'**. During World War II, this phenomenon was observed primarily among African-American soldiers fighting in Southeast Asia. The basis was glucose-6-phosphate-dehydrogenase deficiency (XR inheritance). **Prolonged respiratory arrest during anesthesia** caused by slow degradation of myorelaxans **succinylcholine** (suxamethonium) by butyrylcholinesterase. **Peripheral neuropathy** due to slow acetylation of the antituberculosis drug **isoniazid'** (INH) by recessive homozygotes in the N-acetyltransferase gene. It was not until the 1990s that causal mutations of the N-acetyltransferase 2 (*NAT2*) gene were elucidated. Recessive homozygotes (50% of the population) are slow inactivators of INH.

Pharmacogenomics methods

The goal of pharmagenomics is the development of individualized treatment procedures and the identification of the **most suitable type and dosage of drugs** for a specific patient.

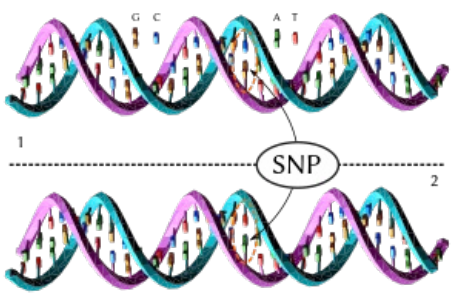
Association study

A relatively suitable method is the use of association studies. These deal with the '*phenotype-genotype* association*. E.g. the ``case-control* method, which compares the frequency of polymorphisms between the group ``in which the side effect appeared *and the ``control* group (in which it did not appear) after administration of the same drug. The disadvantages of this method are mainly the need for the investigated groups to be as similar as possible, except for the observed characteristic (representation of men and women, ethnic group, age, etc.).

🔎 *For more information see Association Study.*

SNP Polymorphism

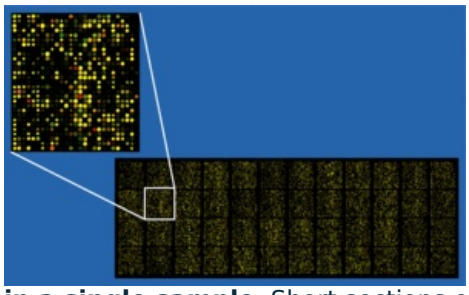
About 90% of all polymorphisms in humans[1]. of them they form the **SNP''*. These are most often clustered into* haplotype s *. Chromosomes are composed of short segments that have undergone a minimum number of [Crossing-over, its mechanism and significance|recombination changes]] within evolution. For that reason, haplotype mapping of the human genome began (the* HapMap project**



https://www.ncbi.nlm.nih.gov/variation/news/NCBI_retiring_HapMap/). If all haplotypes can be mapped, it will be possible to find out those at risk for a specific drug. Today, SNP mapping can be done using *SNP chips*.

🔎 *For more information see Nucleic Acid Polymorphism.*

Amplichip


A tool enabling the **simultaneous testing of tens of thousands of genes in a single sample**. Short sections of single-stranded DNA with a known nucleotide sequence are placed on the 1.5 x 1.5 cm chip. On the basis of complementarity, fluorescently labeled DNA from the analyzed sample binds to them. The results are evaluated by computer. The disadvantage of this method is its high cost.

🔎 *For more information see DNA Chips.*

Complicating factor

When investigating the genetic component, the *environmental factor* also plays a significant role, which complicates pharmacogenetic examinations. Other factors are of genetic origin, among which we include, for example, **incomplete penetrance'**, **phenocopy** and **genetic heterogeneity**.

Examples of drug metabolism polymorphisms

Metabolism of drugs

- application – absorption – tissue distribution – elimination
- there will be either a **degradation of the liver** or a transfer to the **target cells**
- in the target cells, the drug has a **therapeutic effect**, followed by degradation and elimination

``Metabolic speed *is influenced by enzymes - genetic makeup.*

As a sign, we monitor the *drug level* in the blood after administration of a standard dose. **The distribution of concentration values is:**

- **continuous**

unimodal (Gaussian) curve

polygenic inheritance

- **discontinuous**

bi or trimodal curve

monogenic inheritance

Furthermore, we monitor the **decrease in the level over time - *showing the*** *individual differences* in response to the drugs, including side effects. The dose is calculated on **body surface**.

Acatalasia

- lack of catalase enzyme activity (recessive dominant inheritance)

Fast/Slow Inactivators of Isoniazid

- cure for TB, in the population 50/50
- **recessive homozygotes** for the N-acetyltransferase enzyme with lower activity have frequent side effects during treatment (polyneuritis, skin rashes)
- Isoniazid (INH) is absorbed from the ``gastrointestinal tract
- in fast inactivators the level of INH in the blood drops quickly, in slow inactivators the concentration of INH remains high for a '*longer time*

Hereditary diseases with different drug response

Glucose-6-phosphate dehydrogenase (G6PD) deficiency

- inherited X-linked recessively
- pronounced neonatal jaundice + hemolytic crisis after administration of drugs - antimalarials, sulfonamides, acylpyrine

gout (arthritis uratica)

- disorder of purine metabolism
- uric acid crystals are deposited in the joints
- joint swelling
- **dominantly hereditary disease'** whose manifestation is influenced by diet
- '*heterogenously* conditioned disease
- after the administration of diuretics - chlorothiazide - the level of uric acid will increase and the problems will worsen

Alcohol = socially tolerated drug

- **ADH'** (alcohol dehydrogenase) - conversion to acetaldehyde
- **AcAIDH'** (acetaldehyde dehydrogenase) – breaking down acetaldehyde
- **disposition to alcoholism** is also genetically conditioned
- **human ADH'** = dimer from different combinations of 3 different polypeptides encoded by 3 loci
  - **ADH1**: expressed from the fetal period
  - **ADH2**: in adulthood
  - **ADH3'**

Nutrigenetics

In a certain parallel to pharmacogenomics, nutrigenomics examines how chemical substances contained in ordinary food influence the balance between health and disease through interaction with the individual's genome.

It is based on several basic assumptions:

1. Substances contained in food (micro- and macronutrients) act directly or indirectly on the human genome and thus change its structure or gene expression.
2. Under certain circumstances, diet can be a significant risk factor for a number of diseases in some individuals.
3. Some of the target genes of substances contained in food probably play a role in the onset, incidence, course and severity of some chronic diseases.
4. **The degree of influence of diet on the balance between health and disease may depend on the individual's particular genetic makeup.**
5. Nutritional intervention based on knowledge of both specific nutritional status and needs and genotype (individualized nutrition) can be used to prevent, alleviate or treat chronic diseases.

NUTRITION GENOMICS TOOLS

One of the important tools of nutritional genomics is **gene expression profiling** - **transcriptome'**, e.g. using cRNA or cDNA chips, analogous procedures have been developed for monitoring expression at the protein level (*proteome* ' – mainly two-dimensional electrophoresis and various forms of mass spectrophotometry) and metabolites (*metabolome*).

Specific expression profiles of genes, proteins and metabolites in response to a given food component or nutritional regimen form so-called "dietary signatures" , which are further investigated at the level of specific cells, tissues and whole organisms in order to understand the influence of nutrition on the balance between health and disease.

A classic example of a nutrigenetic interaction is persistent *lactose tolerance* in adulthood. In young mammals, including humans, a functional ``lactase *is an essential* enzyme *for the splitting of lactose present in milk into monosaccharides - glucose and galactose. The expression of lactase in the enterocytes of the small intestine is under strict control during development – it is suppressed during the fetal period, increases around birth and decreases again after weaning.*

Most adults are naturally lactose intolerant - consuming large amounts of milk (which contains 4-8% lactose) reacts with abdominal pain, flatulence, or diarrhea, because undigested lactose causes the osmotic transport of water into the lumen of the small intestine and is fermented by intestinal microflora bacteria.

Cultural adaptation to lactose intolerance is represented by fermented milk products, which, thanks to their significantly lower lactose content and sometimes the presence of lactase-secreting bacteria (Lactobacillus acidophilus), do not cause digestive problems in intolerant people. On the other hand, there are many adults, especially in the European population, who do not show signs of lactose intolerance and we speak of the so-called '*lactase persistence* '.< noinclude>

Links

External links

- Pharmacogenetics (Current genetics) (http://biol.lf1.cuni.cz/ucebnice/farmakogenetika.htm)
- Pharmacogenetics (Czech Wikipedia)

- Pharmacogenetics (English Wikipedia)
- E-Learning – lecture: pharmacogenetics, nutrigenetics (https://el.lf1.cuni.cz/admin/content/sco/info?sco-id=1926549&tab-id=9)

References

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Reference

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