THE IMPORTANCE OF TOXICOGENETICS IN EXPOSURE TO CHEMICAL CARCINOGENS AND MUTAGENS

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GENOTOXICITY

The fact that a chemical substance is genotoxic means that it can bind to nucleophilic regions of macro molecules such as DNA and RNA in cells due to its electrophilic property.

GENOTOXICITY

Since DNA is a molecule that carries hereditary information; genotoxicity can be defined as a toxic effect that occurs in the genetic material of cells.

GENOTOXICITY

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If a more detailed definition is made considering the direct and indirect effects that may occur in DNA:

- Mutation induction
- Observed events related with mutagenesis (unplanned DNA synthesis, etc.)
- DNA damage by forming DNA adducts (adduct=formation of addition product) can be defined as a series of events that can cause mutation.

MUTATION

Mutation is permanent hereditary changes in somatic or germinal (sex) cells.

Thus, the mutation can cause body cells to change and / or be transported to other generations by germinal cells.

MUTATION

Genotoxic effect	Mutation	-
Genotoxic effect	Mutation	+

MUTATION

Scientific researchs support a significant relationship between genotoxicity and cancer.

This relationship is the basis for the use of genotoxicity biomarkers as an indicator in human monitoring studies against the risk of cancer formation.

International Agency for Research on Cancer (IARC) classified the chemicals according to their carcinogenic effects due to the data obtained from the scientific studies.

TOXICOGENOMICS

Toxicogneomics

The response of the organism to environmental chemicals and drugs may vary depending on the genotype. Some patients respond well to medications, while others do not even benefit, and sometimes even side effects.

Toxicogneomics

Individuals can react differently to environmental chemicals (such as allergic reactions).

The identification of the human genome and the detection of polymorphisms on a large scale provided an understanding of the genetic basis and reasons for the response to chemical substances to differ from individuals. This scientific field of study is defined as "Toxicogenomics".

Only 0.1% of DNA, which constitutes the human genome and consists of about 3 billion base pairs, has a different sequence among individuals.

However, the information encoded by these regions, which correspond to a very small part of the genome, can cause very important biological differences. The most important examples are hereditary damage and diseases such as cardiovascular diseases and obesity.

PHARMACOGENETICS

Different drug activity

Individuals react differently to drugs

Pharmacognetics

It is extremely important to be able to determine whether an individual will benefit from a drug, or if it will encounter advers effects.

For this purpose, it is of great importance to investigate the relationship between Genotype and drug activities. These studies can be called as "Pharmacogenetics".

TOXICOGENETICS

Toxicogenetics

The purpose of pharmacogenetics; It is the illumination of the individual sensitivity difference observed in the emergence of a drug's side effect or benefit at the molecular genetic level.

These investigations can also be used to examine the toxic effects of chemicals exposed. In this case, these studies are examined under the title of "Toxicogenetics".

The main purpose of Pharmacogenetics or Toxicogenetics is to detect and protect sensitive individuals who may have toxic effects as a result of exposure to chemicals or drugs.

Normal Distribution

How the response to the drug changes?

How the response to drugs changes?

- **Genetic variations**

In particular, two types of genetic mutation events reveal all variations:

- Single base mutations where one nucleotide replaces another nucleotide
  -- Single nucleotide polymorphisms (SNPs)
- Addition or deletion of one or more nucleotides
- -- Tandem Repeat Polymorphisms
  -- Addition/Deletion Polymorphisms

- Polymorphism:
  It is a genetic variation that occurs at least 1% in a population
  Single nuceotide polymorphisms (SNPs)

- Only a single nucleotide changes

- SNP, can alter DNA sequence

  AAGCTTAC
  ATGCTTAC

- The most occurred genetic variations
  (%90-95)
  Single nucleotide polymorphisms (SNPs)

- Very common in human population

- A SNP is observed approximately every 1250 basis between two people.

- Most of them do not have a phenotypic effect

Tandem Repeat Polymorphisms

- Depends on the number of repeating units :

➢ "Microsatellit"s or Short Tandem Repeats (STR)

  - Repeating units: 1-6 basis (dinucleotide repeat: CACACACACACA)

➢ "Minisatellit"s

  - Repeating units: 14-100 basis

Addition/Deletion Polymorphisms

- Addition/Deletion (INDEL) polymorphisms are common variations that can be found scattered throughout the human genome

Related with individual differences;

➢ Only 20-40% of patients benefit from medication effectively.

➢ 70-80% of drug candidates failed in clinical trials

➢ Many drugs on the market have been withdrawed for their adverse effects.

- Using DNA sequence information to estimate and measure the responses of individuals to drugs;

➢ Personalized drugs

➢ Faster clinical trials

➢ Less side effects of drugs

- Different responses to drugs or chemicals result from protein-encoding gene polymorphisms. This difference may affect the pharmacokinetic parameters of a foreign chemical.

- Example: Polymorphisms that cause changes in xenobiotic metabolizing enzymes can affect the individual response to many drugs, such as diazepam, omeprazole and carbemazepine.

Metabolism Pharmacogenetic

The metabolism of drugs and other chemicals is carried out mainly through the Cytochrome P450 (CYP) family, which is one of the most important Phase I metabolism enzyme family.

Studies shows that many of the CYP genes are polymorphic. These findings alone provide a logical explanation of why individuals respond differently to xenobiotics.

Genetic polymorphisms in metabolism enzymes

Polymorphism in the CYP2D6 gene is one of the most studied topics, its effects on drug metabolism. The enzyme encoded by this gene is needed in the metabolism of 25% of drugs. Based on this estimate, it can be thought that 25% of the environmental chemical substances we are exposed to are responsible for the metabolism. CYP2D6 polymorphism can cause changes in many enzyme levels or activities.

6% of the white race has 2 invalid alleles for the CYP2D6 gene. As a result, these people cannot metabolize certain drugs and as a result, adverse effects occur due to drug use. In these "slow metabolizers" phenotype, an inactive protein is produced. The deletion (invalidation) of the gene or a base pair mutation that occurs in the gene can cause this negativity.

- Due to increased plasma concentrations in slow metabolizers:

- Deaths in children due to Fluoxetine (Prozac®)
  - Side effects of antipsychotic drugs were seen
  - Individuals with severe mental illnesses are more at risk of side effects, so their hospital stay can be prolonged

CYP2C9 can be given as another example. Polymorphism in the CYP2C9 enzyme especially affects individuals' response to warfarine, an anticoagulant. The fact that the answer is very different makes it difficult to determine the safe and effective dose of warfarin.

CYP2C9 metabolizes Warfarin. With the polymorphism in this enzyme, amino acids are added to the structure and the ability to metabolize Warfarin is significantly reduced. Therefore, higher levels of Warfarin are seen in the serum of such individuals.

It is extremely important to give a lower dose of warfarin to these individuals because the treatment dose in individuals with the normal CYP2C9 allele creates side effects in individuals with the polymorphic allele.

The other examples

- Succinylcholine Hydolysis
- G6P DEHYDROGENASE
- ISONIAZİD
- N-ACETYLTRANSFERASE
- Paraoxonase
- Glucuronyl transferase
- Gluthatione S-transferases (GSTs)

IN THE FUTURE
PERSONALIZED DRUGS