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PHARMACOGENETICS: INTERINDIVIDUAL DIFFERENCES IN RESPONSE TO DRUG- AN OVERVIEW

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INTRODUCTION

Vogel in 1959 first proposed the term "*Pharmacogenetics*" and in 1962, Kalow wrote the first monograph for the same. The field of pharmacogenetics was stimulated in 1970s when Vesell and Colleagues demonstrated that plasma half-lives of many drugs are less divergent among monozygotic twin pairs than among dizygotic twin pairs. Over 50 years down the lane examples of exaggerated responses to drugs, novel drug effects, or lack of effectiveness of drugs as a manifestation of inherited individual traits have been observed.

"*Pharmacogenetics is the study of genetically determined variations in drug response*".

Principle

The basic principles of genetic influences on drug action can be summarized as follows;

- Genetic factors influence a drug's action by affecting pharmacokinetic and pharmacodynamic properties. In clinical practice, this may result in an alteration of the intensity and the duration of the expected "normal" or "usual" effect of a drug or the occurrence of adverse drug reactions.
- Unexpected, uncommon, or "abnormal" effects of drugs may be associated with certain genetically transmitted disorders. Under these circumstances, the modified drug response may have both diagnostic and therapeutic implications.

Objectives of Research

1. Understanding how genetic factors influence a person's response to a drug could make new and existing treatments safer and more effective.
2. Identification of genetically controlled variations in responses to drugs.
3. Study of the molecular mechanisms causing these variations.
4. Evaluation of their clinical significance.
5. Development of simple method to identify individuals who may be susceptible to variable responses before drugs are administered.

Factors Responsible

These interindividual differences in response to drug are determined by combination of different factors;

1) Physiological factors (sex, age)
2) Pathological factors (liver disease, renal disease)
3) Environmental factors (other drugs, diet, smoking)
4) Genetic factors.

How important each of these factors is, varies from drug to drug and individual to individual. So, pharmacogenetics explores the genetically determined alterations in the drugs usual metabolic pathways and these alterations are associated with the accumulations and toxicity of a drug and shifts to different pathways that have toxic intermediates.

Goal of Pharmacogenetics

1. To understand how someone's genetic make up determines how well a medicine works in body.
2. What side effect are likely to occur, thus making it a field of growing interest in medicine and pharmaceutical industry.

The method of "genomics" have been increasingly applied to pharmacogenetics research as it emphasis on molecular structure and functions of genes. A relatively recent addition to the discipline is the field of "ecogenetics", which concerned with dynamic interaction between an individual genotype and environmental agents.

Cause of Variations

Genetically transmitted variations arise from mutation of DNA through which structural alterations occurs in a protein that affects that directly affects; drug absorption, distribution, metabolism and excretion or drug receptor interactions. Such polymorphisms, therefore, may give rise to variations in a drug's pharmacokinetic and pharmacodynamic characteristics.

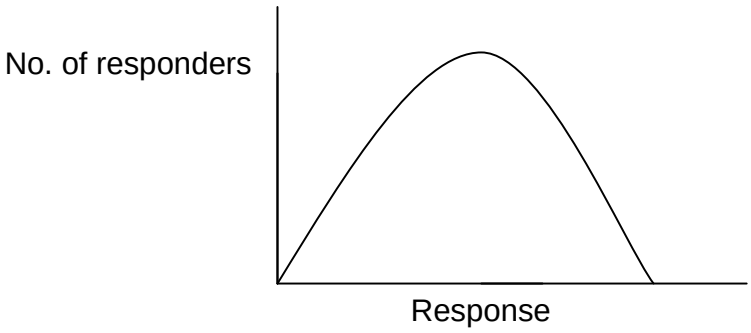
Study Methods

The extent to which genetic factor determine drug responsiveness is investigated by the means of population, family and twin studies.

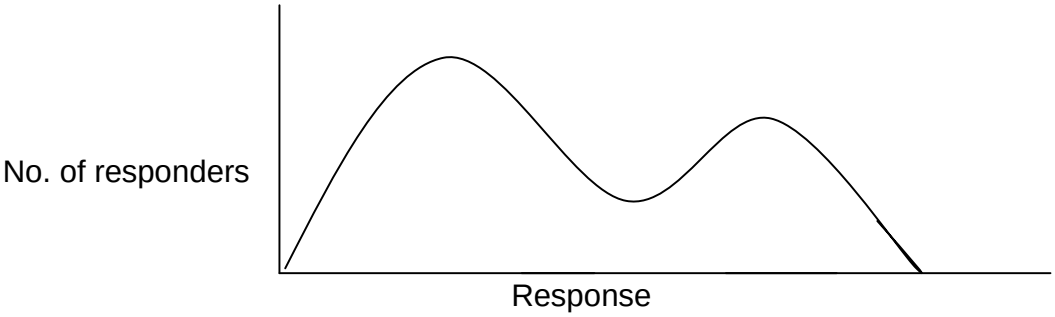
Population Studies: It involves administering usually a fixed dose of a drug to a large number of individuals and then measuring either the response to the drug or some pharmacokinetic characteristics (plasma half-life or plasma concentration at fix time after drug administration). From this data a frequency distribution curve is constructed.

The most common patterns of frequency distribution are;

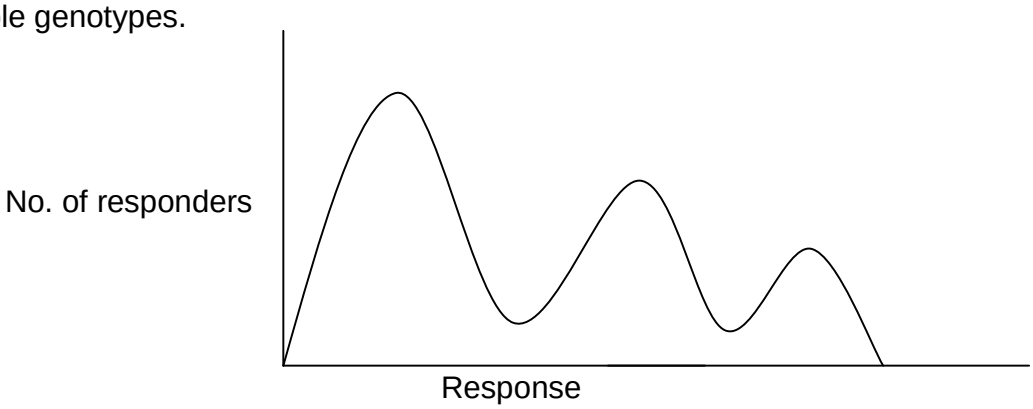
A) Unimodal Response: A Unimodal response shows single hump with Gaussian or continuous distribution. It is the most common pattern of the three and indicates that the response is under the control of a number of genes or polygenetic control.



B) Bimodal Response: A bimodal response shows two humps (discontinuous variations). This implies that the response is controlled by a single gene that is present in population in two forms (genetic polymorphism).



C) Trimodal Response: Trimodal response shows three humps. It is the rarest pattern of the three and indicates genetic polymorphism in which there is a phenotype for each of the three possible genotypes.



Family Studies: Family study established whether inheritance of a drug response follows a Mendelian dominant, recessive or sex-linked pattern. When variation in response does not adhere to a classical pattern of inheritance, insight into the genetic component determining the response can be obtained by studying drug response in parents and children. The heritability of drug response is obtained from the regression coefficient of the graph of the mid parent response plotted against the mean offering response. Higher value signifies greater genetic components.

Twin Studies: In such studies, a particular variable (drug plasma half-life) is compared in a pair of uniovular (identical twins) with that of a pair of a biovular (fraternal twins), the assumption being that environmental factor will be similar for each pair of twins.

Formula to estimate genetic component:

$$\frac{\text{(Variance within pair of fraternal twins - variance within pair of identical twins)}}{\text{Variance within pair of fraternal twins}}$$

Values near to 1 indicate a high degree of genetic control and those with values near to zero a negligible genetic component.

Benefits

Pharmacogenetics studies have a vital role to play in every step involved in;

Drug Discovery

1) Pathway Identification.
2) Target Identification.
3) Selection.
4) Screening.
5) Characterization.
6) Validations.

Drug Development

1) Preclinical studies.
2) Clinical studies.
3) Safety of the product launched in a population can be predicted with the availability of pharmacogenetic profile of drug.
4) Marketing aspect of the drug.

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