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Review Article

PHARMACOGENETICS: GENETICALLY DETERMINED VARIATIONS IN DRUG RESPONSE

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ABSTRACT

The appeal of pharmacogenetics lies in the possibility of personalized medicine. This sort of care has always been the goal of the doctor-patient relationship, with physicians considering a patient's family history and lifestyle when prescribing treatment. Access to information about an individual's genetic makeup would provide yet another source of personalized data and would therefore enable doctors to better define the nature of a disease and find the most effective treatment for a particular patient. With the help of pharmacogenetic studies, physicians will be able to administer treatment regimens that are personalized and adapted to each person's genetic makeup. Accordingly, two people with the same diagnosis might receive different therapies or drug dosages. This might in turn reduce health care costs, because physicians would be able to prescribe more targeted drugs and pharmaceutical companies would be able to develop and market drugs to specific groups of patients.

Keywords: Pharmacogenetic, genomics, pharmacokinetics, ecogenetics, variations.

INTRODUCTION

Origin of the term "*Pharmacogenetics*" was when Vogel in 1959 first proposed and in 1962, Kalow wrote the first monograph for the same and many more worked on 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 dizygotic twin pairs[(1-5)]. 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*". These inter-individual differences in response to drug are determined by combination of different factors; physiological factors (sex, age), pathological factors (liver disease, renal disease), environmental factors (other drugs, diet, smoking) and genetic factors. How important each of these factors is, varies from drug to drug and individual to individual[6]. 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. This review shows how different individuals differ in their response towards same drug[7,9]. 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",defined by Brewer in 1971, which concerned with dynamic interaction between an individual genotype and environmental agents (air,water, food, soil). More recent developments have broadened pharmacogenetic approaches to include novel genomic techniques with introduction of the term pharmacogenomics in the 1990's[10,11] .

Principle

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

- 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[6].

Definition

"*Pharmacogenetics is the study of genetically determined variations in drug response*"[(7).] "Study of interindividual variation in DNA sequence related to drug absorption and disposition (Pharmacokinetics) and/or drug action (Pharmacodynamics) including polymorphic variation in genes that encode the functions of transporters, metabolizing enzymes, receptors and other proteins". The term has been pieced together from the words pharmacology (the study of how drugs work in the body) and genetics (the study of how traits are inherited)[12, 13].

Objectives of research[6, 19]

1. Research focuses on genes, cells, and the overall physiology of the person to gain an understanding of the mechanism necessary for this technology to be applicable.
2. Research at the genetic level is attempting to identify those genes that predispose a person to a particular illness and reactions or allergies to specific medications. At the cellular level, scientists are using animal cells (i.e. mice) to understand how "spelling changes" in a person's genes effects drug responses.
3. Understanding how genetic factors influence a person's response to a drug and could make new/existing treatments safer and more effective.
4. Identification of genetically controlled variations in responses to drugs.
5. Study of the molecular mechanisms causing these variations.
6. Evaluation of their clinical significance.
7. Development of simple method to identify individuals who may be susceptible to variable responses before drugs are administered.
8. Correlating heritable genetic variation to drug response.
9. Determining "Right medicine for the right patient".

Goal

1. An ultimate goal of pharmacogenetics is to understand how someone's genetic make up determines how well a medicine works in body; as well as what side effect are likely to occur, thus making it a field of growing interest in medicine and pharmaceutical industry.
2. The identification of gene variants (alleles) that influence drug metabolism is one of the goals of pharmacogenetics[12,13].

Cause of variations

Genetically transmitted variations arise from mutation of DNA through which structural alterations occurs in a protein 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[6,14,15,18].

Study methods

The extent to which genetic factor determine drug responsiveness is investigated by the means of population, family and twin studies[6,15].

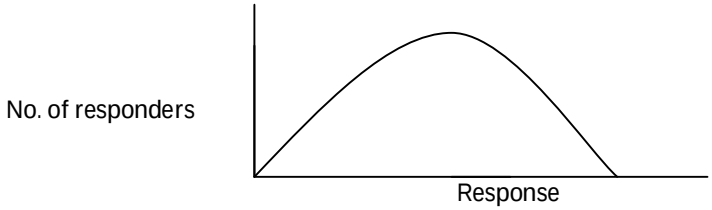
1) Population studies

It involves administering usually a fixed dose of a drug to a large number of individuals and then measuring either the response of 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;

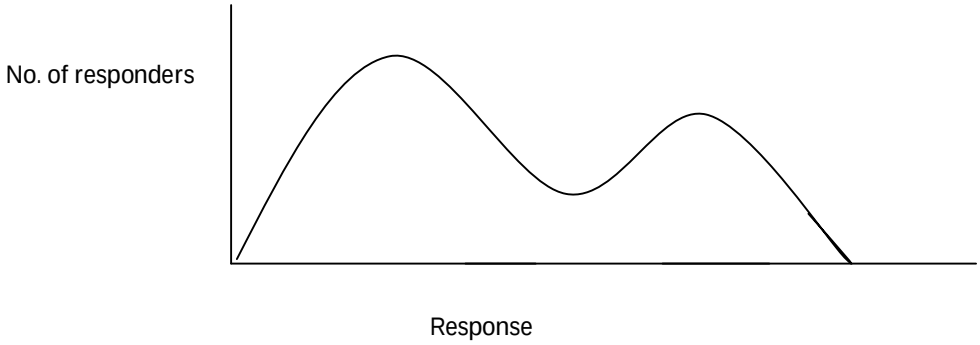
b) Uni-modal response

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.



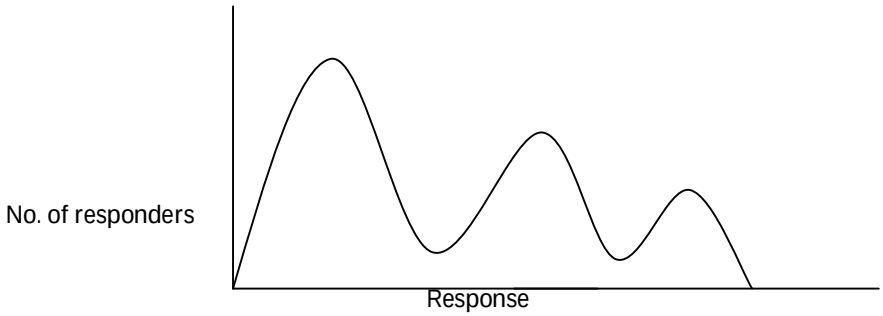
c) Bi-modal response

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).



d) Tri-modal 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.



1) Case studies

1. Codeine is an example of a drug whose metabolism is greatly influenced by genetics. For codeine to exert its effect, it first has to be converted into morphine by the body's enzymes. This chemical reaction occurs in the liver and is catalyzed by the cytochrome P450 enzyme, CYP2D6.
   However, up to 10% of individuals have a mutation in the *CYP2D6* gene that abolishes enzyme activity. Thus, codeine may have very little or no impact on these patients. People with this mutation cannot convert codeine to morphine and thereby cannot benefit from the analgesic effects of the drug. Identification of the *CYP2D6* mutation before therapy would allow physicians to prescribe a different pain control regimen, instead of resorting to trial and error[16,17].
2. In 2001, Wilson *et al*. tried to address the intersection of genetic variation, drug response, and race by assigning people to different groups depending on shared genetic regions — leaving race and ethnicity out of the equation entirely. In this study, researchers looked at variations in microsatellites, or sequences of two, three, or four nucleotides repeated 10 to 100 times along the DNA that show great variation in repeat length among individuals. Specifically, the researchers examined 16 microsatellites on chromosome 1 and 23 on the X chromosome in a heterogeneous group of individuals. Study participants were then assigned to four subclusters according to their microsatellite alleles, which roughly corresponded to four geographic areas: Western Eurasia, Sub-Saharan Africa, China, and New Guinea[16].

Wilson *et al*. next examined variations in genes encoding these enzymes, including CYP2D6, across the clusters they identified with their microsatellite analysis. They found that the genetic groupings (based on the microsatellite analysis) appeared to be more informative regarding differences in drug metabolism than

the groupings based on skin color or self-defined ethnic groups[16].

2) 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.

3) Twin studies

In such studies, a particular variable (drug plasma half-life) is compared in a pair of uni-ovular (identical twins) with that of a pair of a bi-ovular (fraternal twins), the assumption being that environmental factor will be similar for each pair of twins[18].

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.

Opposing opinions

1. Implication regarding genetic profiling of patients, which raises issues about confidentiality, privacy, and ownership that must be considered from a public health and a patient's right perspective.
2. The danger to patients is that this information could be a useful tool to insurance companies and employers who could utilize it for moral hazard considerations.
3. For example if a patient is told that they are susceptible for cancer later in life, is that helpful information for them to know, should they be treated for that condition earlier in hopes of preventing its manifestation?
4. Most of the pharmacogenomic research is currently at the preclinical stage.Both at this stage and the later clinical research stage, an important, but generally unexplored, issue is whether the target population is supportive of the research. In particular, it is important to consider-
   a) whether individuals are willing to participate in research by donating biological samples and sharing medical records with investigators,
   b) whether individuals are willing to undergo genetic testing as part of the research process,
   c) whether individuals have suspicions about the medical research establishment,
   d) whether concerns about privacy and confidentiality will cause individuals to decline to participate in research, and
   e) whether individuals are concerned about the morality of research into human genetic variation. Although these concerns are certainly common to all clinical trials, they warrant mention here because of the unique concerns centering around genetics in general [11,20].

Benefits

1. More Powerful Medicines

Pharmaceutical companies will be able to create drugs based on the proteins, enzymes and RNA molecules associated with genes and diseases. This will facilitate drug discovery and allow drug makers to produce a therapy more targeted to specific diseases. This accuracy not only will maximize therapeutic effects but also decrease damage to nearby healthy cells.

2. Better, Safer Drugs the First Time

Instead of the standard trial-and-error method of matching patients with the right drugs, doctors will be able to analyze a patient's genetic profile and prescribe the best available drug therapy from the beginning. Not only will this take the guesswork out of finding the right drug, it will speed recovery time and increase safety as the likelihood of adverse reactions is eliminated. Pharmacogenomics has the potential to dramatically reduce the estimated 100,000 deaths and 2 million hospitalizations that occur each year in the United States as the result of adverse drug response.

3. More Accurate Methods of Determining Appropriate Drug Dosages

Current methods of basing dosages on weight and age will be replaced with dosages based on a person's genetics --how well the body processes the medicine and the time it takes to metabolize it. This will maximize the therapy's value and decrease the likelihood of overdose.

4. Advanced Screening for Disease

Knowing one's genetic code will allow a person to make adequate lifestyle and environmental changes at an early age so as to avoid or lessen the severity of a genetic disease. Likewise, advance knowledge of a particular disease susceptibility will allow careful monitoring, and treatments can be introduced at the most appropriate stage to maximize their therapy.

5. Better Vaccines

Vaccines made of genetic material, either DNA or RNA, promise all the benefits of existing vaccines without all the risks. They will activate the immune system but will be unable to cause infections. They will be inexpensive, stable, easy to store, and capable of being engineered to carry several strains of a pathogen at once.

6. Improvements in the Drug Discovery and Approval Process

Pharmaceutical companies will be able to discover potential therapies more easily using genome targets. Previously failed drug candidates may be revived as they are matched with the niche population they serve. The drug approval process should be facilitated as trials are targeted for specific genetic population groups --providing greater degrees of success. The cost and risk of clinical trials will be reduced by targeting only those persons capable of responding to a drug.

7. Decrease in the Overall Cost of Health Care

Decreases in the number of adverse drug reactions, the number of failed drug trials, the time it takes to get a drug approved, the length of time patients are on medication, the number of medications patients must take to find an effective therapy, the effects of a disease on the body (through early detection), and an increase in the range of possible drug targets will promote a net decrease in the cost of health care[21-26].

Future prospective

In the future, advances gleaned from pharmacogenetics research will provide information to guide doctors in getting just enough of the right medicine to a person--the practice of "personalized medicine." The future of pharmacogenetics is unclear since it is a relatively new area of research. However, it is possible with the increasingly rapid progress of the biotechnology industry that this technology may come to fruition within the next 10-20 years. To utilize this technology, the process would include genetic profiling of each patient by their physician, who could thereby "personalize" their medicine to treat medical problems that may affect them in the future. The potential benefits of this are decreased adverse reaction to particular drugs.

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