Pharmacogenomics

Introduction

Pharmacogenomics is defined as "drug–genome interactions" -

Pharmacogenomics is the study of how genes affect a person's response to drugs. Among the most commonly studied are genetic sequence variants, structural changes in chromosomes, epigenetic variants (eg, changes in gene methylation), and variation in the expression profile of genes (changes in mRNA levels) or noncoding RNA (eg, changes in microRNA). The availability of high-throughput techniques to interrogate the entire genome has facilitated many pharmacogenomics studies (Next-generation DNA sequencing (NGS). By mapping an individual's genome to identify gene variants (polymorphisms), the likelihood of a positive response to drug therapy (drug response), the pharmacokinetics of the drug (drug metabolism), and the potential adverse event liabilities can be predicted.

This relatively new field combines pharmacology (the science of drugs) and genomics (the study of genes and their functions) to develop effective, safe medications and doses that will be tailored to a person's genetic makeup.

Pharmacogenomics has the potential to influence clinically relevant outcomes in drug dosing, efficacy, and toxicity that can result in subsequent recommendations for testing. It deals with the influence of acquired and inherited genetic variation on drug response in patients by correlating gene expression or single-nucleotide polymorphisms with pharmacokinetics (drug absorption, distribution, metabolism and elimination) and pharmacodynamics (effects mediated through a drug's biological targets).

Many drugs that are currently available are "one size fits all," but they don't work the same way for everyone. It can be difficult to predict who will benefit from a medication, who will not respond at all, and who will experience negative side effects (called adverse drug reactions). Adverse drug reactions are a significant cause of hospitalizations and deaths in the United States. With the knowledge gained from the Human Genome Project, researchers are learning how inherited differences in genes affect the body's response to medications. These genetic differences will be used to predict whether a medication will be effective for a particular person and to help prevent adverse drug reactions.

Each person's drug response is holistic -

A drug must differ individually as it depends on five factors: *genotype*, *epigenetic effects*, *endogenous influences*, *environmental factors*, and *microbiome differences*. Variability in inter-individual drug response can be classified as**: *monogenic* (Mendelian) *traits*** typically influenced by one or a few rare coding variants; *predominantly* ***oligogenic traits*** that usually represent variability largely elicited by a small number of major pharmacogenes; and *complex PGx traits*.

Advantages of Pharmacogenomics

1. Minimizes adverse drug reactions (ADRs) sue to mismatch of combination
2. Personalized medicine i.e., drug at par with persons genetic makeup (Ethnicity, gender etc)
3. Tailor treatments to meet patients' unique genetic pre-disposition, identifying optimal dosing.
4. Greater efficacy of drug and better pharmacokinetics
5. Improve drug safety.
6. Pharmacogenomics can be used to determine the cause of death in drug-related deaths
7. Facilitates effective drug development

Patient genotypes are usually categorized into the following predicted phenotypes in relation to drug metabolism:

- **Ultra-rapid metabolizer:** patients with substantially increased metabolic activity
- **Extensive metabolizer:** normal metabolic activity
- **Intermediate metabolizer:** patients with reduced metabolic activity; and
- **Poor metabolizer:** patients with little to no functional metabolic activity.

Efficacy of a medication is not only based on the above metabolic statuses, but also the type of drug consumed. Drugs can be classified into two main groups: **active drugs** and **prodrugs**.

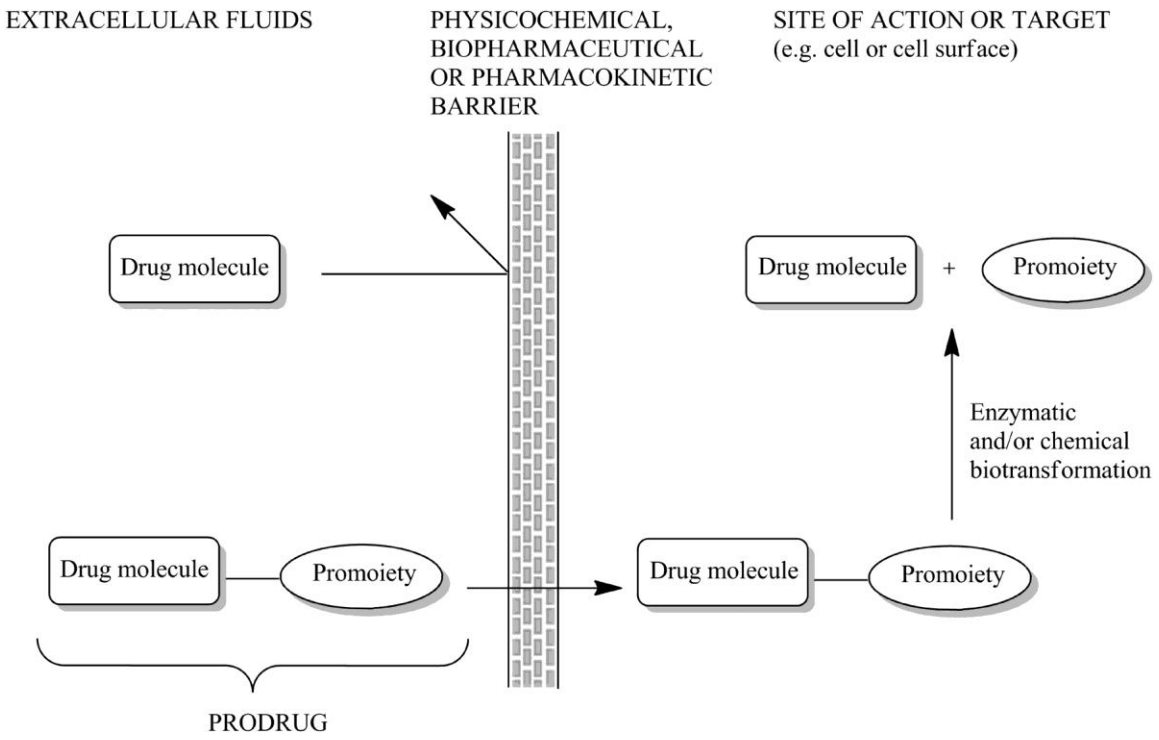
Active drugs refer to drugs that are inactivated during metabolism, and prodrugs are inactive until they are metabolized.

Active drugs

Explanation: An active drug results when a drug is metabolized by the body into a modified form which continues to produce effects in the body. Usually these effects are similar to those of the parent drug but weaker, although they can still be significant. (Example: 11-hydroxy-THC, morphine-6-glucuronide).

Prodrugs

Explanation: For example, we have two patients who are taking codeine for pain relief. Codeine is a prodrug, so it requires conversion from its inactive form to its active form. The active form of codeine is morphine, which provides the therapeutic effect of pain relief. (Example: Arbutin, Glucosinolate).



Prodrug	Active Substances
Glucosinolates	Isothiocyanates
Alliin	Allicin, ajoenes
Cumaroylglucoside	Coumarin
Arbutin	Hydroquinone
Salicin	Saligenin, salicylic acid
Bi-desmosidic saponin	Mono-desmosidic saponins
Ranunculin	Protoanemonin
THC-A	THC
Proto-vitamin B12	Vitamin B12
Cyanogenic glucoside	HCN
Rhein, sennosides	Antraquinonic aglucone
Hennosides	Lawsone
Vanilloside	Vanillin
Gein	Eugenol
Methylazoxymethanol	Cycasin

Polymorphism of Drug-metabolizing enzymes

Drug metabolism is dependent on enzymes produced by the vertebrates. **Cytochrome P450 (CYP family)** is the most prevalent drug-metabolizing enzymes (DME). The human CYP family consists of 57 genes. From a clinical perspective, the most commonly tested CYPs include: CYP2D6, CYP2C19, CYP2C9, CYP3A4 and CYP3A5. These genes account for the metabolism of approximately 70-90% of currently available prescription drugs.

Various combinations of DME alleles produce different genotypes along with different phenotypic expression.

Why drug metabolic ability varies individually?

Let's consider, person A receives one ***1 allele each** from mother and father to code for the **CYP2D6 gene**, then that person is considered to have an **extensive metabolizer (EM)** phenotype, as allele *1 is considered to have a normal-function **(this would be represented as CYP2D6 *1/*1).**

Whereas, person B on the other hand had received **one *1** allele from the mother and a ***4** allele from the father, that individual would be an Intermediate Metabolizer (IM) **(the genotype would be CYP2D6 *1/*4).**

Although both individuals are taking the same dose of codeine, person B could potentially lack the therapeutic benefits of codeine due to the decreased conversion rate of codeine to its active counterpart morphine.

Polymorphism of Drug transporters

Genetic variability in drug transporters plays a role in the resistance of malignant cells to anticancer agents. For instance, polymorphism in the ABC-binding cassette (ABC) gene may affect the function and expression of proteins. This may cause certain drug induced side effects and uncertainty in treatment efficacy.

One notable example is that in certain patients the reduced rate of methotrexate metabolism produced a severe methotrexate overdosing and nephrotoxicity. This defect is attributed to the heterozygous mutation (R412G) in the highly conserved amino acid arginine of the ABCC2 gene, which encodes the human multidrug resistant protein-2 (MRP2).

Interestingly, this mutated region is associated with substrate affinity and hence the mutant protein has a reduced rate of methotrexate elimination. In some other cases, a long-term use of methotrexate induces pancytopenia (which is determined by white blood cells and platelet counts.)

However, it is also known that polymorphisms always need not have to produce functionally defective proteins. For example, in the multidrug resistant gene (MDR1), certain polymorphisms may not have any effect on the drug response.

Thus, pharmacological studies on drug transporters are beneficial for predicting patients who are at risk in some cases at least.

How ethnicity and their genomic knowledge plays role in drug response in populations?

In order to use genomic knowledge to develop drugs and to improve health, we need to consider ethnical differences in different populations. There exists inter-ethnical differences in polymorphisms of genes encoding drug-metabolizing enzymes, transporters and disease associated proteins. A population genetics-based method to calculate the probability value for a variation in the gene is recently developed.

Genetic differences are greater within socially defined racial groups than between groups. Additionally, it has been found that genetic diversity decreases in noncoding regions whereas diversity of coding nonsynonymous SNPs is lower in regions containing a known protein sequence motif in individuals of European origin. Drug treatment may be tailored for greater effect if important genetic variation exists between racial and ethnic groups. By knowing these variants, patients can be classified into low, intermediate and high dose groups.

Warfarin therapy

For instance, warfarin therapy shows a wide variation among patients of different ancestries. This variation could be due to polymorphisms in the gene encoding vitamin K epoxide reductase complex 1. Accordingly, Chinese patients require lower dosages of heparin and warfarin than those usually recommended for white patients.

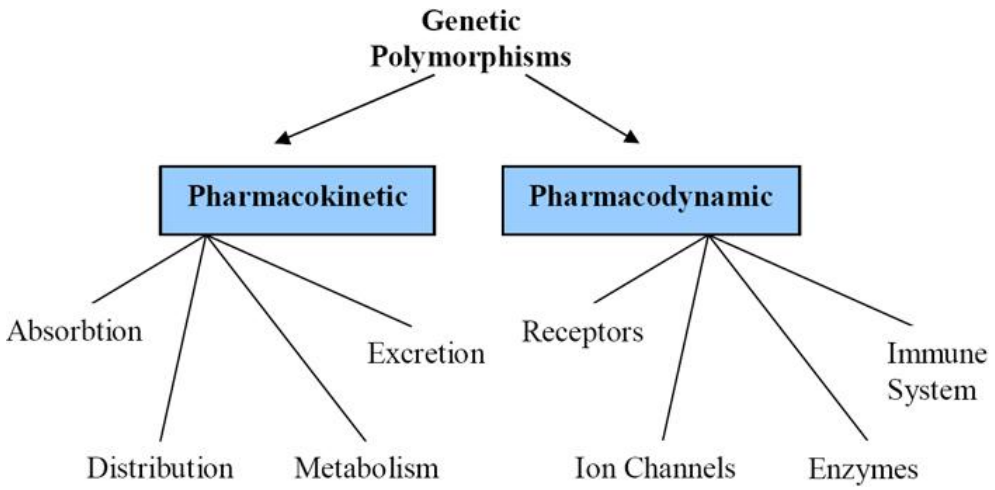
Treatment of heart failure

Additionally, BiDil (combination of two generic drugs, isosorbide dinitrate and hydralazine) treatment of heart failure in African-Americans heart patients reduced mortality by 43 %, claiming that African Americans and white Americans differentially respond to the treatment. This is claimed to be due to genetic differences in the pathophysiology of heart failure between the two groups.

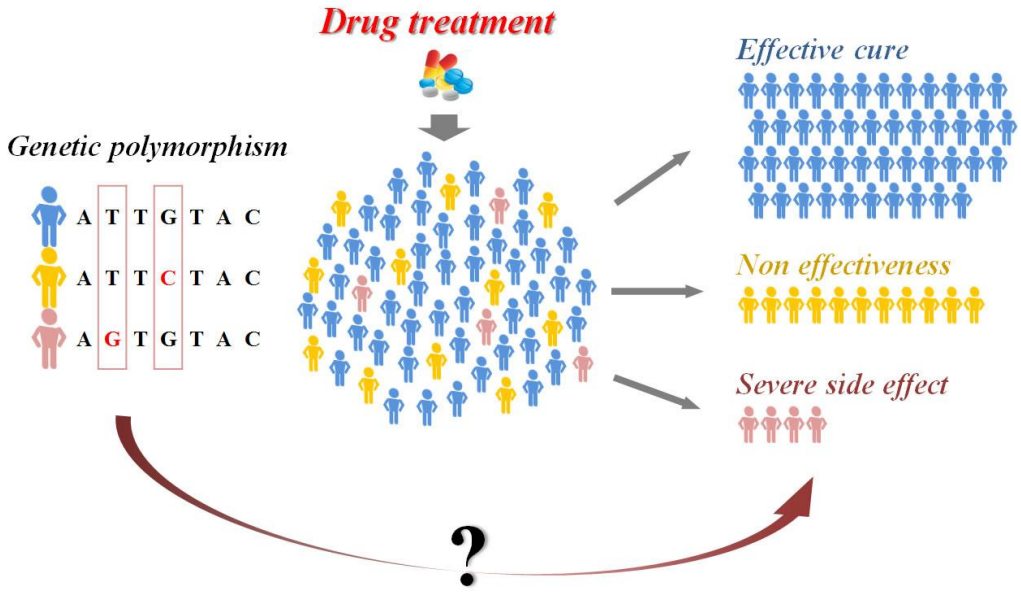
These findings have opened the debate on the biological basis of race and ethnicity and pharmacogenetics may provide a useful understanding of ethnic and racial differences. Even in this case, however, we are still ignoring several important parameters such as diet, economic, environmental and psychosocial factors. Pharmacogenetics study on race and ethnicity is worthwhile because these are useful indicators of genetic variation. However, this kind of race and ethnicity classification for medical treatment leads to discrimination.

Following Slides explains Pharmacogenomics better – have a see

What are the target areas where genetic polymorphism of human population affects drug metabolism thus pharmacogenomics becomes essential?



How genetic polymorphism determines drug's effectively?



How drug related toxicity varies within and between populations?

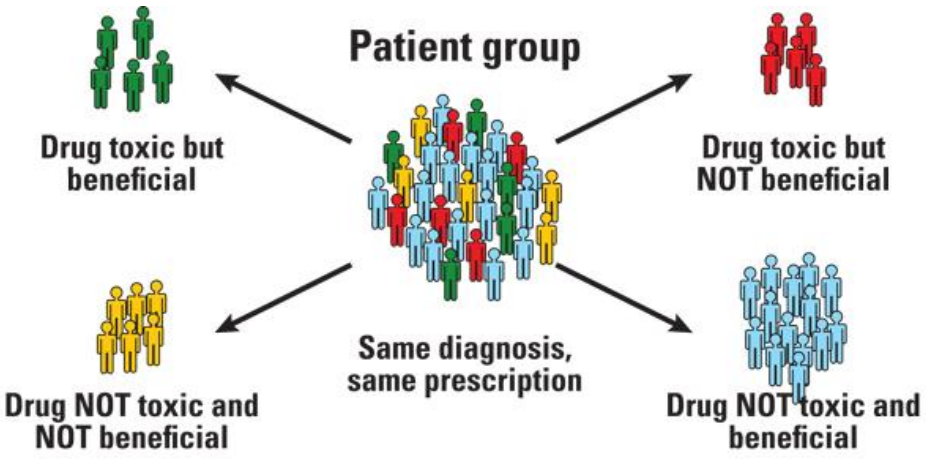
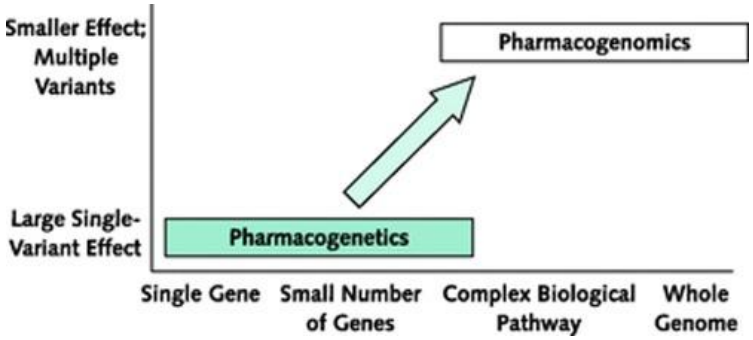


Figure explains the relationship between pharmacogenetics and pharmacogenomics approach



Pharmacogenetics: The study of the genetic basis for variations in drug response. Typical used to define the study of how variation in single gene influences the response to a single drug.
Single genes can have profound effects on response to drugs -> large effects from some polymorphisms
Pharmacogenomics: The study of how all of the genes (the genome) can influence responses to drugs.