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Pharmacogenomics: Advent of personalized medicine

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Abstract

Pharmacogenomics is the technology that analyses how genetic makeup affects an individual's response to drugs. Pharmacogenomics helps to predict response to a medication and negative side effects. It aims to develop effective, safe drug and optimize drug therapy with respect to the patients' genotype which leads to maximum efficacy and minimal adverse effect. Pharmacogenomics combines knowledge of genes, proteins and single nucleotide polymorphisms (SNPs) to speed the discovery of drug response markers. It has implications in diseases like heart diseases, cancer, asthma, HIV, depression and many other common diseases.

Key words: Pharmacogenomics, personalized medicine, drug response, single nucleotide polymorphisms, drug response markers, Pharmacokinetic, Pharmacodynamic.

Introduction

Pharmacogenomics combines pharmacology and genomics. It is the technology that analyses how genetic makeup affects an individual's response to drugs (1). It deals with the influence of genetic variation on drug response in patients by analysing the gene expression or single-nucleotide polymorphisms. Many drugs that are currently available in market are "one size fits all," and they work differently for different people. Pharmacogenomics helps to predict who will respond to a medication, who will not respond at all, and who will have negative side effects. Pharmacogenomics aims to develop effective, safe drug and optimize drug therapy customized with respect to the patients' genotype leading to maximum efficacy and minimal adverse effects (2). Such approaches promise the beginning of "personalized medicine".

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Pharmacogenomics combines knowledge of genes, proteins and single nucleotide polymorphisms (SNPs) to speed the discovery of drug response markers. It helps in identifying drug target, drug metabolism or disease pathways. Pharmacogenetic studies have established the importance of polymorphic drug metabolizing enzymes such as CYP2D6, a member of cytochrome P450 family; in the differential response to drugs (3). Recently, the genetic factors at the level of drug target or the disease pathway have been identified. For example, ApoE4, an allele at the apolipoprotien E locus, not only correlates with risk of developing Alzheimer's disease but also predicts poor response to cholinesterase treatment (4, 5). Polymorphism within a disease related gene is predictive of drug response. Each different disease like cancer, atherosclerosis Alzheimer disease, HIV/AIDS, asthma and neurodegenerative disorders have distinct etiologies and therefore, distinct responses to therapy. That is the basic principle of pharmacogenomics.

Determinants of drug response

The efficacy of drug response depends on genetic differences (polymorphism) in drug metabolism, pharmacokinetic variations and genetic differences in mechanism of drugs on its target, pharmacodynamic variations.

Pharmacokinetic variations

Isolation and sequencing of DNA clones of drug metabolizing enzymes allow the study of catalytic specificity and activity of many individual drug-metabolizing enzymes. Some of the widely studied enzymes are cytochrome P450 isoenzymes (CYP 450), N-acetyl transferase (NAT) isoenzymes, the UDP glucuronoyl transferase and the methyl transferases. CYP450 genes is the best studied one, which encode enzymes that influence the metabolism of more than 80 percent of current prescription drugs like, Codeine, clopidogrel, tamoxifen and warfarin (6,7). For most of the drugs, activity of CYP 450 determines how much and how long a drug remains in the body. In humans, six forms of CYP 450 viz; CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 are largely responsible for eliminating drugs (8). Individuals who are poor or slow metabolisers have enzyme deficiency related polymorphisms and are at an increased risk of concentration related toxicity. While others have polymorphism (e.g., gene amplification) that enhance enzyme activity/ levels; they are characterized as extensive or ultra rapid metabolisers and can be resistant to therapy. Poor metabolism of antidepressants, anti psychotics, b-blockers, antiarrhythmics, and others that leads to systemic accumulation and toxicity are linked with polymorphisms in CYP2C19 and glucuronosyl transferase locus UGT2B7; poor metabolisers of psychotropic drugs such as S-mephenytoin suffer from drowsiness or more serious side effects which are associated with CYP2D6 and CYP3A4 polymorphisms. In patients polymorphic for poor metabolisers forms of CYP2D6, terfenadine competes with erythromycin for CYP3A4, which slows the breakdown, leading to concentration-related toxicity (4, 9)

Pharmacodynamic variations

Genetic variations in receptor function have been relatively rare in healthy individuals. Metabolizing enzymes are low affinity systems and receptors are high affinity systems with specific structural requirements. Mutations in receptors result in individual differences in behaviour and drug responses. For example, large variations in efficacy of the psychotropic drug Sumitriptan have been attributed to single amino acid substitutions in 5-hydroxy tryptamine (5HT) receptors (4, 10). Thus genetic variation in both pharmacokinetic and pharmacodynamic factors attributes to variable drug response.

Pharmacogenetic markers

DNA genotyping studies evolved from linkage and association of complex disease. Linkage studies involve genotyping families with micro satellite-markers and the goal is to correlate inheritance of a particular chromosomal region with inheritance of disease. Association studies correlate the presence of chromosomal region and a trait (disease or drug response) in unrelated individuals of a population. Now, the rapid pace of DNA marker discovery together with novel genotyping techniques permit genome-wide association studies.

These technical considerations favour the use of SNP's that are simple base substitutions, occuring within and outside genes. SNP's are used as a diagnostic tool to predict drug response (11, 12, 13). DNA micro arrays (or DNA chips) are an evolving technology make it easy for doctors to examine their patients for the presence of specific SNP's quickly and affordably. A single micro array can now be used to screen 1,00,000 SNP's found in patient's genome in a matter of hours (4).

Application and uses

Doctors are starting to use pharmacogenomic information to prescribe drugs, but such tests are routine for only a few diseases like heart disease, cancer, asthma, HIV, depression and many other common diseases. In HIV disease, before prescribing the antiviral drug abacavir (Ziagen), doctors routinely check the genetic variant of the patient that makes them more likely to have a bad reaction to the drug. Another example is the breast cancer drug trastuzumab (Herceptin). Herceptin therapy works only for women having overproduction of a protein called HER2. US FDA also recommends genetic testing before giving the chemotherapy drug mercaptopurine (Purinethol) and irinotecan (Camptosar) to reduce side effects and increase risk of infection.

Apart from improving use and efficacy of existing drugs, pharmacogenomics research also leads to the development of better drugs. Scientists are using genomic information to identify and design drugs aimed at subgroups of patients with specific genetic profiles. Pharmacogenomic tools also aid in search for drugs that target specific molecular and cellular pathways involved in a disease. Pharmacogenomics research can be used to develop more personalized and cost-effective strategies for using drugs to improve human health.

Pharmacogenomics may help in reviving abandoned drugs. For example, development of the beta-blocker drugwon FDA approval to treat heart failure. But interest in Gencaro revived after tests showed that the drug worked well in patients with

two genetic variants that regulate heart function (14). Incancer, chemotherapy drugs, gefitinib (Iressa) and erlotinib (Tarceva), work much better in lung cancer patients whose tumors have a certain genetic change. On the other hand, research has shown that the chemotherapy drugs cetuximab (Erbitux) and panitumumab (Vecitibix) do not work very well in the 40 percent of colon cancer patients whose tumors have a particular genetic change (4).

Conclusion

Some gene alleles vary in frequency between specific populations. These alleles have differential responses to specific drugs. For example, The beta blocker Atenolol is an anti-hypertensive medication that is shown to be more effective for Caucasian patients than African American patients in US. Similarly, antiretroviral drug abcavir hypersensitivity is strongly associated with SNPs that varies in frequency between populations. The FDA approval of specific drugs affecting particular population has produced a storm of controversy over race-based medicine and genetic stereotyping. It is certain that pharmacogenomics has profound effect on drug usage and development process. It is now very important to have a clear focus on technologies and a synchronized multidisciplinary effort. At the same time, it is also necessary to frame detailed regulatory policies at an international level and national level. In developing countries, pharmacogenomics is still at nascent stage. Though the benefits are tremendous, the cost factor to develop pharmacogenomics based therapy is the major deterrent. Concerted efforts are necessary from international bodies, governments, and pharma majors to ensure that high efficacy drugs reach the common man at a feasible price.

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