Kathmandu University Medical Journal (2005), Vol. 3, No. 4, Issue 12, 428-430

Review Article

Pharmacogenomics – Therapeutic and ethical issues

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Abstract
Pharmacogenomics deals with the genetic basis underlying variable drug response in individual patients. It encompasses sum of all genes. Numerous genes may play a role in drug response and toxicity. The newly emerging genomic technologies enable the search for relevant genes and their variants to include the entire genome and help in the search for candidate genes. Moreover pharmacogenomic analysis can identify the disease susceptibility genes representing potential new drug targets. The current concept of drug therapy is to apply treatment for a large population group whereas application of pharmacogenomic will help individual application of drug therapy or on smaller patient sub population but whether this individualized medicine will lead to improved and economically feasible therapy is yet to be seen. This is again complicated by various ethical and legal issues. In this article some of the issues are highlighted.

Key words: Pharmacogenomics, SNPs.

Pharmacogenomics is an emerging branch in pharmacology and deals with the genetic basis of drug response and toxicity in patients. The terms come from the word pharmacology and genomics whereas pharmacogenetics incorporates the discipline of biochemistry and pharmacology and refers to the study of inherited variation in drug metabolism and response and correlates with phenotypic biomarkers.

Pharmacogenomics deals with the information about the genomic techniques such as DNA sequencing, gene mapping and bioinformatics to allow the researcher to identify the actual genetic basis of inter individual and inter racial variation in drug efficacy, metabolism and transport.

When a drug enters the body it reacts with numerous proteins, enzymes and receptors. These proteins determine all pharmacological response. Multiple polymorphisms in many genes may affect drug response, requiring a genome wide search for the responsible genes. Currently emphasis has been given to design drugs which will act against a particular disease at genomic level of the individual so that a positive desired outcome can be achieved with minimum adverse effects. So far the pharmaceutical companies design drugs which is like a free size garment i.e. ***"one size fits all"*** system but in reality it does not work. Sometimes it produces various disastrous effects that are responsible for 1(one) lakh death in United States and cost the country an estimated $100 billion per year.[1] Adverse Drug Reactions (ADR's) rank as the fifth cause of death in United States.[2]

This technique will introduce a dimension to individualize medicine and enable to develop personalize therapy – "a therapy with the right drug at the right dose in the right patient".
Now with the help of technical innovation such as DNA micro array and micro fluidic analytical devices have enabled the process of DNA sequencing and gene mapping required for genomic research. This procedure will allow the patients to be prescreened for specific relevant polymorphism before drug therapy is initiated.[3]

Polymorphism is generally defined as variation in DNA sequence that occurs in at least 1% of the population. The vast majority of polymorphism is single nucleotide polymorphism or SNP's (pronounced "snips") [4]. There are millions of one letter variation known as SNP (Single nucleotide polymorphisms). A subset of these variations provide crucial link to disease producing genes which also pinpoint the location of such a disease related gene and thus it can be used as a diagnostic tool. What makes SNPs helpful is that certain SNPs are found sprinkled throughout the population, so that by looking at the DNA of individuals who share

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a certain inherited conditions like drug reaction, or susceptibility, researchers sometimes identify a shared SNP.[5] For use of SNP of a person, DNA must be sequenced. But the gene sequencing technology is a very complicated and an expensive process, which will impede use of SNP for diagnostic purpose. However, the recent advancement in single DNA micro arrays or (DNA chips) showed that it can be used to screen 10,000.00 SNPs found in a patient's genome in a matter of hours. Attempts have been made to develop this micro array technology, which will probably soon bring about revolution in diagnosis and drug therapy.

***Ongoing Pharmacogenomic programme*:**

Various pharmacogenomic projects are going on in both developed and developing countries all over the world to find out the genetic basis of diseases and to develop diagnostic tools for various genetic disorders.

Asthma and allergy – attempts have been made to develop biosensors as diagnostic tool for allergy. Various new allergens have been identified and it is observed that SNP involving candidate genes, IL13 and IL12 has co relation with asthma and IGE levels and attempt has been made to develop DNA vaccine.

1. Research on neurodegeneration – such as calcium hypothesis on aging and dementia.
2. Study on Neuropsychopharmacology – the pharmacology of drugs that exert neural, psychological and behavioral changes in animal and human being.
3. Studies are going on to see the action of oxidant and anti – oxidant in molecular and cellular biology and their role in human disease and nutrition.
4. Various are studies are going on in tumor biology and proteomics to find out the genetic basis of diseases such as hepatocellular carcinoma, hepatitis B and C virus and Epstein – Barr virus etc. and in musculoskeletal tissue regeneration and repair.
5. Besides various pharmacogenomic research are going on to develop diagnostic facilities in cardiovascular, endocrine, hematology, renal disorders.

***Ethical Issues of Pharmacogenomics*:**

Although pharmacogenomics promises customized drug therapy specific to an individual's illness it will raise important ethical issues as well as challenges. They are broadly speaking: unequal distribution of benefits, discrimination involving individual benefits, conflicts in business and research interest and invasion into privacy.

1. ***Unequal distribution of benefits*** – The question of resource allocation comes when public money is spent on R. &D (research and development). Many believe that pharmacogenomics, like that of Human Genome project, represent a mal -allocation of resources when majority of the people are suffering from lack of food, safe drinking water, housing and disposal of wastes and other basic amenities of life. It appears to be a luxury to invest on pharmacogenomics which will benefit mostly rich and urbanized people. Contrary to this it is observed that hundreds of people die due to adverse reactions of ready made drugs because of their genetic variations which can be avoided by testing the genetic variation and prescribe the best available drug therapy which will decrease the recovery time and there by decrease the cost of hospitalization and personal miseries.

2. Discrimination ***involving the individual benefits*** – The new technology may be costly initially and thus will be accessible only to those who are rich enough to pay for the genetic tests as well as for the designer drug best suited for them. But it will take time. Often after the great achievement having a safe and effective drug experimenting on numerous sufferers, the sufferers will not get the benefit because they will be unable to pay the high cost of treatment. The glaring examples of numerous such sufferers are the sufferers of Gauchier's disease who helped companies to develop effective treatment were denied excess to the remedy by insurance companies due to high cost.[6]

3. ***Conflicts in business and research interest*** - The researchers who have invested the time, knowledge and expertise may be in a conflict of interest if they are conducting research for a company who is more interested in commercialization of their product.[7] They will ignore the interest of researchers after they have achieved their goal. Bringing a new drug into the market drug companies have to invest millions of rupees and they would definitely like to realize the cost from the consumers. Will these companies be ready to develop alternative drugs for individuals or for small patient population? On the other hand targeting well defined patient population will sharpen the analysis of risk benefit ratio and the clinical trials will be substantially reduced in size. So the approach

will help to know whether targeting small patient population with select drug is superior to treat many patients with the best drug available for a disease.[8] Besides development of multiple pharmacogenomic products to treat the same condition for different subset of population will complicate the process of prescribing and dispensing drugs and the physician will need a better understanding of genetics and an extra diagnostic procedure will be required to determine the suitable drug for each patient. Will they be ready to do so? One wonders!

4. ***Invasion into privacy*** - Genetic diseases often run in families. To study genetic sequences and the genomes it may require studying the family history of disease and health. Genetic information of an individual can stigmatize an individual as it predicts the person's future health and the individual may not like that these information be known to others especially in context of marriage and child bearing. This may also be a ground for job discrimination by employers and in insurance claim. The genetic information may be misused or abused in countries where there is strong social and cultural tradition for individual's reproductive freedom. Women in the developing countries are more vulnerable to such coercion in their reproductive choice especially in countries where there is deep rooted bias and discriminations against women. The genomic information in such countries will make many women to suffer from serious social injustice. So, therefore, it is very important to give serious thoughts by all concerned before genomic studies started and develop a regulatory structure to address these ethical issues. No doubt, if the policy makers can re-address these issues, pharmacogeneomics will play an integral role in disease assessment, drug development and selection of the right type of drug and there by reducing ADR's and saving millions of life.

What are the anticipated benefits of pharmacogenomics?

1. Decrease in overall cost of health care – Targeting a well defined population will sharpen analysis of risk benefit ratio and clinical trials will be substantially reduced in size.[8] It will decrease the length of time of hospitalization of patients as well as the number of medication. Thereby it will promote a net decrease in health care cost.
2. Decrease in number of adverse drug reactions. Phrmacogenomics has the potential to dramatically reduce the estimated 100,000 deaths and 2 million hospitalizations that occur each year in the United States as a result of ADR's.9
3. Advance screening for disease – Knowing ones genetic code will allow a person to make an adequate change in his lifestyle and environment at an early age so to avoid or lessen the severity of genetic disease and also to enable for careful monitoring and treatment.
4. Better vaccines – Better, inexpensive and stable vaccines can be developed using genetic material.
5. More powerful medicines - Can be developed which will have maximum therapeutic effects and less damage to nearby healthy cells.
6. Right drug in right dose in the right patient.

Reference

1. Ingelman – Sundberg M. Pharmacogenetics: an opportunity for a safer and more efficient pharmacotherapy. J Intern Med. 2001; 250:186.
2. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients. JAMA. 1998; 279:1200
3. Blanchard AP, Friend SH. Cheap DNA arrays-; it's not all smoke and mirrors. Nature Biotech. 1999; 17:953.
4. Russo E. Big pharma hedges its bets. The Scientist. 1999; 13:1.
5. Shi, Michael. Pharmacogenetic technologies. Pharmacogenetics in Patient Care Conference by American Association Clinical Chemistry, Nov. 6, 1998.
6. Marshall E. "Genetic Testing: Families Sue Hospital, Scientist for Control of Canavan Gene". Science, 2000; 290: 1062
7. B. Agnew. "Studies trace patchwork of conflict policies" Science Magazine, 2000; 290 : 1873
8. Mancinelli L, Cronin M, Sadee W. Pharmacogenomics: The Promise of Personalized Medicine. AAPS Pharm Sci. 2000; 2: 4.
9. J. Lazarou, B.H. Pomeranz, and P.N.Corey. Incidence of adverse drug reactions in hospitalized patients: a meta analysis of prospective studies. JAMA.1998; 279: 1200 – 1205.