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PHARMACOGENOMICS AND CANCER: THE SCIENCE TOWARDS THE DEVELOPMENT OF PERSONALIZED MEDICINE

Kaiser Jamil[1,2]*

[1]Bhagwan Mahavir Medical Research Center (BMMRC), 10-1-1, Mahavir Marg, Hyderabad 500004, Telangana,India.

[2]School of Life Sciences, Centre for Biotechnology and Bioinformatics, Jawaharlal Nehru Institute of Advanced Studies (JNIAS), Budha Bhawan, Secunderabad- 500003 Telangana, India.

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***Correspondence for Author**
Dr. Kaiser Jamil
Bhagwan Mahavir Medical Research Center (BMMRC), 10-1-1, Mahavir Marg, Hyderabad 500004, Telangana,India.

ABSTRACT

This article on Pharmacogenomics influencing cancer therapeutics summarizes the work leading to the development of personalized medicine. We present here the evidence of several genes responsible for interacting with various neoplastic drugs and their role in influencing the drug resistance or susceptibility. This research article deals with a wide spectrum of cancer patient's biopsy samples- from solid tumors and such as breast cancer and cervical cancer, and liquid tumors like Leukemias and correlated their SNP changes with respect to various chemo-treatments. We describe here the genomic instability in cancer genomes which occurs due to SNP changes affecting the drug response to chemotherapeutic agents. This leads to poor quality of life (QOL) of the patients, and increases their burden of suffering due to metastasis. Hence knowing the SNP changes or genotyping the tumor samples is of great advantage for better diagnosis and for selecting the right therapeutic agent depending on the patient's tumor profile. It is an attempt to bring out these aspects in this presentation by refereeing to the research conducted by us on discovering Biomarkers for drug toxicities. SNPs in the following genes, CYP1A1, GST-T1 & M1, MTHFR, and MDR1 were found to interfere in chemotherapeutic responses in these cancer patients. Hence knowing the SNP changes or genotyping the tumor samples will be a great advantage for

better diagnosis and for selecting the right therapeutic agent depending on the patient's tumor profile.

KEYWORDS: Cancer, chemotherapy; adverse drug reactions; drug metabolizing genes; SNPs; Biomarkers; Allelic imbalance; polymorphisms; target genes; molecular therapeutics; personalized medicine.

INTRODUCTION

Pharmacogenetics is becoming an increasingly important field in the study of cancer chemotherapy. Genetic factors could alter drug metabolism and activity and could predict drug toxicity and efficiency. As early as 1892, Sir William Osler made an observation that "If it were not for the great variability among individuals, medicine might as well be a science and not an art." The revolution in cancer research can be summed up in a single sentence: cancer is, in essence, a genetic disease involving more than 350 genes distributed over several chromosomes. In the last decade, many important genes responsible for the genesis of various cancers have been discovered, their mutations precisely identified, and the pathways through which they act characterized. There is now evidence that alterations in three types of genes are responsible for tumorigenesis: oncogenes, (dominant acting Ras, Raf, Myc, EGFR, Abl, PDGFR etc), tumor-suppressor genes [loss-of-function, require loss of both alleles (p53, Rb, BRCA, PTEN, NF1, Tsc2)] and stability genes like house keeping genes [1].

Advances in genetic technologies improve our understanding of disease etiology and those factors influencing response to treatment. Although there has been relatively little progress to date in using genetics to improve the treatment of common diseases, nevertheless there are some encouraging signs of progress in basic research. Our aim, via various studies, was to understand genes involved in pharmacogenomics, which seeks to identify the factors that influence responses to therapeutic agents, in cancer patients compared to healthy age matched volunteers using PCR, RFLP/SSCP, Sequencing and SNP analysis. Statistical analysis determines the significance of the results. The role of genes like CYPs, GSTs, MDR1, TS, MTHFR, SULT1A1, and DPD in cancers represents a test for ADR when the drug is administered. These were the first reports from India analyzing the association of polymorphisms in several drug metabolizing genes, showing the drug-gene interactions which are associated with various cancers, as listed in the references [2-37].

Unlike diseases like cystic fibrosis or muscular dystrophy, wherein mutations in one gene can cause the disease, no single gene defect 'causes' cancer. Human cells have multiple safeguards to protect them against the potentially lethal effects of cancer gene mutations [1], and only when several genes become defective then an invasive cancer develops, this phenomenon explains the functional network of cancer metasignature genes. Thus, it would be more relevant to consider mutated genes as contributors, rather than causative agents, of cancer.

As the scientific and medical communities begin to decipher the secrets locked in the human genome code, the way we approach the diagnosis, treatment and prevention of disease will change dramatically. With the detection of human genome, scientists have already created large databases filled with thousands of single nucleotide sequence changes. Some of these single nucleotide polymorphisms (SNPs) could define the genetic basis of what keeps healthy or makes us sick. Currently the most common applications for SNP related research tools are gene disease association studies, drug-gene interactions and drug target validation. Other popular applications are disease susceptibility studies or diagnostics, pharmacogenomic studies for clinical trials, drug target screening, and new technology development.

Epigenetic changes also contribute to speeding up the tumorigenesis process [38], and there is very little information in this area. Environment and environmental agents play a critical role in promoting carcinogenesis [39] and influencing drug response. It is an attempt to bring out these aspects in this presentation by refereeing to the research conducted by us on discovering Biomarkers for drug toxicities.

Genetic differences affecting patient's treatment response

Pharmacogenetics is the study of how genetic differences influence the variability in patients' responses to drugs [40]. In understanding this, advances may be made in two problem areas. Firstly, patients may experience life-threatening drug induced side effects. Secondly, a large number of patients do not respond to standard treatment. It is well recognized that different patients respond in different ways to the same medication. It is estimated that genetics can account for 20 to 95 percent of variability in drug disposition and effects [41]. Although many non-genetic factors influence the effects of medications, including age, environmental factors, habits, organ function, concomitant therapy, drug interactions and the nature of the disease, there are now numerous examples of cases in which inter-individual differences in drug response are due to sequence variants in genes encoding drug-metabolizing enzymes, drug

transporters, or drug targets [42-45]. Unlike other factors influencing drug response, inherited determinants generally remain stable throughout a person's lifetime.

Our work involves an ongoing quest to identify genomic factors that control drug response in individuals and populations. Clinical observations of inherited differences in drug effects were first documented in the 1950s [46], giving rise to the field of pharmacogenetics, and later known as Pharmacogenomics. It is a rapidly growing field that aims to define the genetic basis for inter-individual differences in drug response and to utilize this genetic information to predict the safety, toxicity and/or efficacy of drugs in individual patients or groups of patients. While drug-drug interactions and environmental factors significantly contribute to inter-individual variability in drug response, genetic factors (e.g., inherited variations in drug targets, drug metabolizing enzymes and/or drug transporters) also appear to have a critical impact on drug response and disposition (Figure 1). The significant heterogeneity associated with patient responses to chemotherapeutic agents and their narrow therapeutic indices, suggests that pharmacogenomics has the potential to provide individualized cancer treatment regimens [47, 48]. Therefore, there is a need for better understanding of the genetic determinants of chemotherapeutic response, which will in turn enable prospective identification of patients at risk for severe toxicity or those most likely to benefit from a particular treatment regimen (Figure 2). These findings could be translated to clinical practice through molecular diagnostics techniques such as genotyping, in order to guide and define the selection of optimal drug combinations and to determine dosage for the individual patient [48].

Role of Single Nucleotide Polymorphisms (SNPs)

Pharmacogenomic approaches have been applied to numerous existing chemotherapeutic agents to identify pertinent inherited variations that may predict patient response to chemotherapy better. Genetic variations may include nucleotide repeats, insertions, deletions and single nucleotide polymorphisms (SNPs), that may alter the amino acid sequence of the encoded proteins, RNA splicing, and gene transcription. Genetic polymorphisms in drug-metabolizing enzymes, transporters, and molecular targets have been actively explored with regard to functional changes in phenotype (with altered expression levels and/or change in activity of the encoded proteins) and their contribution to variable drug response [48].

We hope that by understanding the ways in which genes and SNPs mediate drug response we will come to understand the molecular basis of disease. The reasoning is that if one knows which biochemical pathways drugs act upon (as demonstrated by variations in genes coding

for proteins in those pathways), it should be possible to target those pathways for further research and intervention. Pharmacogenomics promises to allow us to use existing drugs in a more rational way, and to develop new drugs that are safer and more effective.

Clinically important polymorphisms

Our research studies also support the Drug-Gene Interaction principle, wherein patients experience adverse drug reactions (ADRs) due to genetic predisposition or due to single nucleotide polymorphisms (SNPs) in drug metabolizing genes. We determined the frequencies of polymorphisms and mutations in drug metabolizing enzymes like MTHFR [2, 25], TS [16], DPD [7] and CYP2D6 [17] & SULT1A1 [33] and correlated drug response in breast cancer patients compared to controls. The UTR region 6bp/0bp of TS polymorphism was statistically significant, the promoter region 2R/3R heterozygote genotypes were found to be protective for breast cancer risk, whereas combined genotypes showed 2 folds increased risk of breast cancer. A variation, A to G change was identified in few cases in CYP2D6; deletion of A was also identified in some cases in SULT1A1 gene. The heterozygous genotypes of MTHFR C677T polymorphism showed an association with response of the breast cancer, but the UT region of TS was important in drug response, whereas promoter region polymorphism showed that the non-responders showed an association with hetero and homozygous genotypes indicating that this gene may be important in drug response. Correlation analysis of CYP2D6 G1934A [17] and SULT1A1 G638A [33] polymorphisms with respect to tamoxifen showed that homozygous genotypes were significant in response rates.

Polymorphisms in the *MTHFR* gene with C677T and A1298C variation leads to reduced folate levels in patients treated with 5-FU and Methotrexate [2]. Polymorphisms like invariant (G>A, 630) splice site position in exon 14 of DPD gene also interrupts the functionality and increases the toxic levels in IDC of breast cancer patients under 5-FU treatment [2]. Pharmacogenomic studies can potentially be predictive of an individual's drug-response or adverse reactions or susceptibility to malignant disorders and may reveal new targets that can help in the design of new drugs. Based on our findings it is suggested that Genetic screening of the drug metabolizing enzymes for the presence of these polymorphisms in breast cancer patients will become increasingly useful in individualizing drug therapy, especially for drugs with a narrow therapeutic index (published work included here [2-37].

Recent studies also indicate that genetic variations vary substantially among different ethnic groups and that the evaluation of the haplotypes (combination of polymorphisms that are

inherited together) can often result in better correlation with phenotypes than with individual polymorphisms. The following examples describe some clinically relevant examples of genetic polymorphisms to illustrate the relevance of cancer Pharmacogenomics in optimizing chemotherapy as a way to enhance efficacy and safety.

Lima et al.'s [49] report on Arg16 and Gly16 polymorphism in β2-adrenergic receptor leading to responsiveness and non-responsiveness, respectively, to albuterol, a commonly used drug for Asthma, is a well-known example of differential response to a drug. Ile359Leu polymorphism in *CYP2C9* gene resulting in reduced drug clearance of warfarin (an anticoagulant used in patients with heart disease) and consequent death due to brain hemorrhage arising from overdose [50]; *CYP2D6*4* polymorphism resulting in impaired metabolism of debrisoquin, a commonly used drug for hypertension, and a lethal lowering of blood pressure (BP) [51]; low activity allele(s) of thiopurine methyltransferase (*TPMT*) gene in lymphoblastic leukemia patients and transplant recipients under treatment with azathiopurine leading to life threatening myelosuppression and hepatic toxicity [52, 53] are other common examples of varied drug response as well as adverse drug reactions.

Chemotherapy, although effective, is relatively nonspecific. It has long been hoped that an understanding of the molecular basis of cancer would lead to more specific or targeted therapies. The aim of the new targeted therapies is to better define the patients who will benefit from specific therapies, thereby allowing individualized therapy with improved clinical outcomes and less toxicity. Specific molecules like antigens and growth factor receptors of cancer cells are targeted in these strategies. Biologic therapy, adjuvant therapy, combinatorial therapy and the recent gene therapy followed the chemotherapeutic onslaught on cancer. Even genetic makeup of the patient is considered before devising treatment. For example, the SNPs are known to modulate the drug response as seen in case of MTHFR variant alleles. The picture of cancer has been further complicated by the fact that proteins like ubiquitin and associated enzymes, which highly expressed in some cancers, are responsible for triggering several pathways crucial to cell growth and survival in normal cells. In order to devise better treatment strategies, it has become indispensable to comprehend the genomic activity of a cancer cell.

It is imperative that a study undertaken in India should have national relevance. For example, response to pravastatin, a commonly used cholesterol-lowering drug among cardiovascular disease (CVD) patients is a good example for such a study. Response to this drug is linked to

polymorphism in cholesterol ester transferring protein (CETP) gene, patients with B1B1 and B1B2 genotypes responding better than those with B2B2 genotype [54]. Percentage of patients not responding to the drug (NR) or developing an adverse drug reaction (ADR) of clinical significance was reported. The statistical analysis of a pharmacogenomic study design critically depends on the definition of the disease because it is possible that different genes may have impact on the different subtypes of the same disease. Therefore, it is extremely important to carefully consider whether there is any underlying clinical heterogeneity in the manifestation of the disease. For this purpose, it may be useful to consider multiple clinical parameters and to assess these parameters quantitatively (even if on an ordinal scale).

Drug metabolizing Enzymes

Drugs usually interfere with metabolic processes (usually DNA synthesis) of lymphocytes and results in the blockage of cell division or interruption of vital cell functions such as RNA or protein synthesis. However, there are differences in the mechanism of action based on differences in the chemistry of the drugs; for example, the action of platinum based drugs is different from the alkylating agents. Hence, an investigation to determine the relative “risks” or “toxic” factors of these drugs could be very useful. Since it has been recognized for many decades that individual differences in response to chemotherapy exhibited either drug toxicity or a lack of therapeutic effect, we now know that these differences result in altered rates of biotransformation (metabolism).

Genetic polymorphisms of Cytochrome P450 result in the expression of Cytochrome P450 that are nonfunctional or exhibit lower enzymatic activities. This may result in unwanted side effects because of the inability to eliminate the active form of the drug causing elevated concentrations in the body. It may also result in the absence of a therapeutic effect because the active form of a drug is not formed.

Genetic heterogeneity and Drug Resistance

We know that it is characterized by genomic instability—tumor cells divide like mad and in that process their genomes are rarely transmitted faithfully. Breast cancer is no exception: any ten women with the disease will have ten different tumors—their cancers will be of different sizes, some will be more aggressive than others, and those tumors will each express their own peculiar set of genes (albeit with some overlap). Scientists and clinicians [55-58] have begun to make use of breast cancer’s heterogeneity to make predictions and guide treatment decisions. By examining the expression patterns of collections of genes that tend to be turned off or on

together in an array of tumor samples and the clinical outcomes of patients who developed those tumors, researchers are now able to predict who is most likely to experience recurrent breast cancer and who is likely to remain cancer-free. This information has practical implications. If her risk is low, a patient may not want to endure the hardships of chemotherapy; if her risk is high, she may choose a more aggressive course of treatment. For example, the variant that influences response to a drug in one racial or ethnic group might not have the same effect, on average, in another group because of different gene-gene or gene-environment interactions. For example, the 3435C→T polymorphism in *ABCB1* has been variably associated with altered drug response, pharmacokinetics and P-glycoprotein expression, but the correlation between the polymorphism and P-glycoprotein levels is not consistent across ethnic groups. If 3435C→T is the causal polymorphism (and this has not been proven), then this could be an example of physiological differences across ethnic groups.

Statistical analysis

All genotyping experiments in our studies were presented as allelic frequencies and Genotype distribution with those expected from Hardy-Weinberg Equilibrium (HWE) were made using chi square test, and Values of P (two –tailed) less than 0.05 were considered statistically significant. Odds ratio, were calculated using MedCalc for Windows, version 7.4.1.0 (*MedCalc Software, Mariakerke, Belgium*).

Genetic polymorphisms have influence on variability in human pharmacokinetics including differences in drug toxicity, drug interactions and response to chemotherapy. This genetic predisposition could be a reason for patients who experience drug-induced side effects and those who do not respond to standard drug treatment. In our study [3], we reported, for the first time, four novel SNPs in *CYP3A4* gene in the FNAC (fine needle aspiration cytology) and post chemotherapy blood samples. Significant association of the novel *CYP3A4* SNPs with the risk of adverse drug reactions was seen in breast cancer patients. The post chemotherapy status of breast cancer patients could be predicted using *CYP3A4* polymorphisms as prognostic markers even before the initiation of the treatment. These early detectable markers could assist the clinicians in planning patient specific chemotherapy. These biomarkers could be incorporated in the list of prognostic markers to allow accurate prediction of patient survival.

How many cancer genes are druggable targets?

Pharmacogenomics recognizes drug metabolizing genes and some cell surface markers like kinases, (for example- tyrosine kinase) and epidermal growth factors (EGFR), and apoptotic genes as druggable targets (Table 1). For the pharmaceutical companies this is a hot topic.

As more is learned about the genetic bases of common diseases, such diseases may be divided into distinct subclasses with similar phenotypes but different underlying genetic bases. In many cases, specific drugs are indicated for specific subtypes of a disease: for example, Herceptin is indicated for the subpopulation of individuals with breast cancer who express *ERBB2*, and Gleevec is indicated for individuals with chronic myeloid leukemia resulting from the *BCR-ABL1* gene fusion (Table 2). Similarly, two recent studies identified mutations in *EGFR* in lung cancers, which predict response to the tyrosine kinase inhibitor gefitinib (also known by the trade name Iressa) [59, 60]. The next "druggable targets" are the monoclonal antibodies and signal transduction inhibitors some are listed below:

Multiplicity of Genes Produces Many Forms of Cytochrome P450

Many Cytochrome P450 forms have emerged due to gene duplication events occurring in the last 5-50 million years [61]. The different forms of cytochromes P450 among various animal species have likely arisen from the selective pressure of environmental influences, such as dietary habits or exposure to environmental agents. It is logical that the primordial genes gave rise to Cytochrome P450 that metabolized endogenous substrates. Examination of the phylogenetic tree generated by comparing amino acid sequences and assuming a constant evolutionary change rate, leads to the conclusion that the earliest Cytochrome P450 evolved to metabolize cholesterol and fatty acids. Therefore they may have played a role in the maintenance of membrane integrity in early eukaryotes.

Oncologists and researchers are struggling to find out what is the magic mechanism by which they can increase the disease free survival. Answers to such questions may come from unconventional centers [62]. They could be from geneticists, molecular biologists or epidemiological findings, which relate to gene environment and gene drug interactions. Several studies have shown that CYP and GST genes, which carry polymorphisms, have been recognized as prognostic markers for acute myeloid leukemia (AML) [63, 64]. It has been demonstrated that these drug-metabolizing genes play a critical role in overall survival (OS). These polymorphisms modify the enzyme activity which results not only in inter individual differences, but also influences drug response and survival.

Drug companies and pharmacogenomics

In some ways the use of pharmacogenetics during the development of potential new therapies generates the most serious concerns because of its potential to influence the medicines that are brought to market. In the past, the basic model in drug development was to find drugs that are as widely applicable as possible, hence the effort to prove efficacy in large, expensive phase 3 trials. Now there is interest in carrying out smaller, less expensive trials using genetics. Although the idea of focusing clinical trials on subgroups of individuals is not new, as stratification by disease subtype has always been a goal of medical research, the use of genetics in this context is new. Pharmaceutical companies have long tended, when possible, not to pursue compounds known to be metabolized largely by highly polymorphic systems, such as *CYP2D6*, but pharmacogenetics has otherwise had a small role in drug development. Increasingly, however, there is interest in the use of systematic genetic analyses to identify the genetic causes of variable responses during the evaluation of new chemical entities. Some of the strategies applied by the drug companies include general targets in the cell cycle as illustrated in Figure 3.

However the recent trends in the widespread use of reverse genetic strategies could result in important changes in drug development, including reliance on more focused clinical trials. We anticipate that drug target validation and disease association studies will continue to be the most common SNP-related tasks in drug discovery and development. It is expected that very soon, the application of SNP studies in pharmacogenomics will begin to increase steadily and could quickly become a multibillion-dollar market itself.

Table 1: Showing the "Druggable Targets" Inhibitors Targetting Protein Kinases

Drug	Target	Cancer type
Trastuzumab inhibitor	HER2	Breast cancer
Imatinib inhibitor	BCR-Abl	Chronic Myeloid Leukemia
Gefitinib inhibitor	EGFR	Non-Small Cell Lung
Cetuximab inhibitor	EGFR	Colorectal Carcinoma
Bevacizumab inhibitor	VEGF	Colorectal Carcinoma
Erlotinib inhibitor	EGFR	Non-Small Cell Lung
Sorafenib multi-kinase inhibitor	Raf, VEGFR, PDGFR	Renal cell cancer
Sunitinib multi-kinase inhibitor	FLT3, VEGFR, PDGFR	gastrointestinal and kidney cancer, CML
Dasatinib multi-kinase inhibitor	(BCR-Abl, Src, Lck, Yes, Fyn, Kit, EphA2 and PDGFR) OF EGFR	Colon Cancer
Panitumumab inhibitor	EGFR / HER2	advanced or metastatic

Sources: compiled from internet.

Table 2: Signal Transduction Inhibitors; Monoclonal antibodies and small molecules

Drug	Target
Trastuzumab (Herceptin)	inhibition of HER2
Cetuximab (Erbitux)	inhibitor of EGFR
Bevacizumab (Avastin)	inhibition of VEGF
Panitumumab	inhibitor of EGFR Small molecule
Imatinib (Gleevec)	inhibition of BCR-Abl, Kit, and PDGF
Gefitinib (Iressa)	inhibition of EGFR
Cetuximab (Erbitux)	inhibitor of EGFR
Erlotinib (Tarceva)	inhibition of EGFR
Sorafenib	inhibition of c-Raf-1, B-Raf, VEGFR,
Sunitinib (Vectibix)	inhibition of FLT3, VEGFR, PDGFR, Kit
Dasatinib (Sprycell)	inhibitor of BCR-Abl, Src, Lck, Yes, Fyn,
Lapatinib	inhibition of EGFR, HER2

Sources: downloadable internet sources

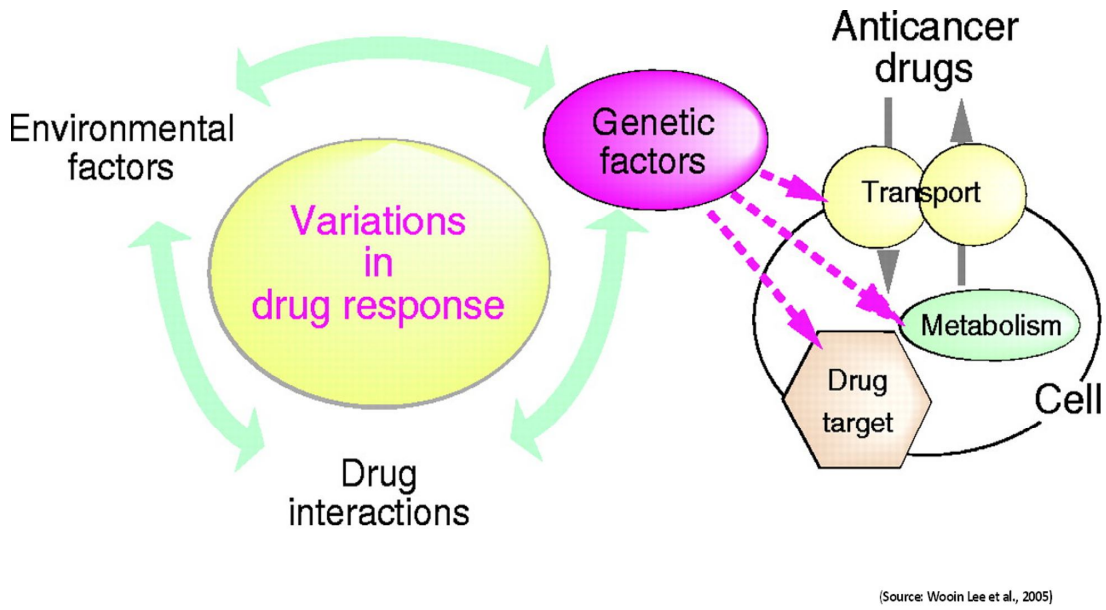

Figure 1: Multiple factors contributing to variations in drug responses (Source: Lee et al.[48]).

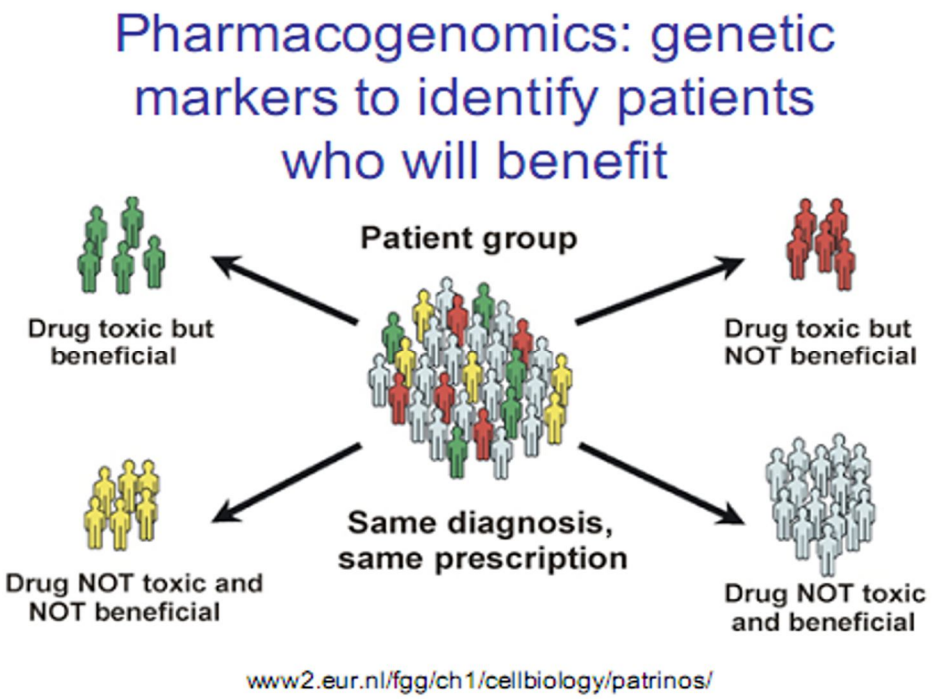

Figure 2: Pharmacogenomics for individualized treatment (Source: www2.eur.nl/fgg/ch1/cellbiology/patrinos/).

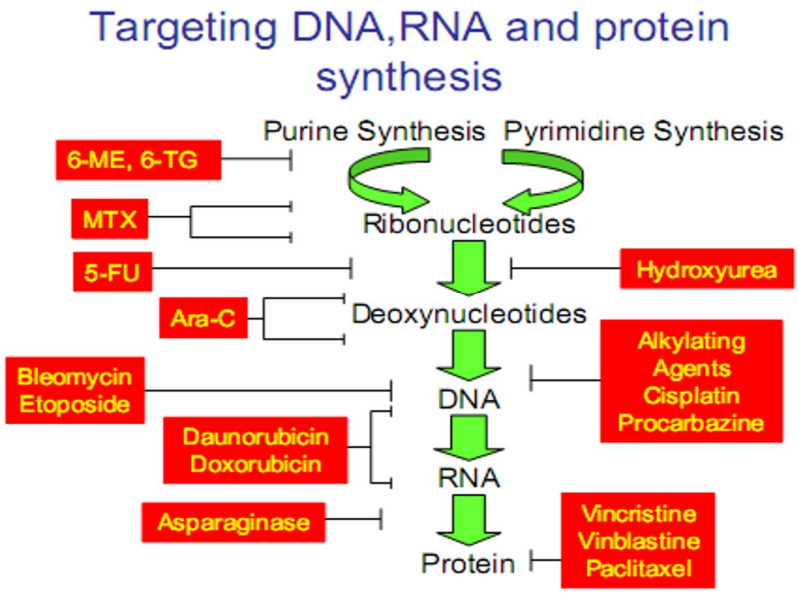

Figure 3: Common chemotherapeutic drug targets.

CONCLUSIONS

The important role of genetics in determining the effect (response and toxicity) to cancer chemotherapy is where the alteration of a gene coding for an important drug metabolizing enzyme results in increased toxicity (and occasionally altered efficacy). The knowledge of the expression of genes is critical to the action of the cancer chemotherapy drug that can be used to individualize therapy.

The aim of this article was to outline how advances in genetics could contribute, even if modestly, to disparities in the quality of health care among different individuals or groups. We now have the information and access to several databases to look at the pattern of genetic variations across the whole genome and its relationship to the history of human origins and the differential distribution of diseases across populations and geography. We can begin to dissect common the diversities and devise new therapeutic strategies to reduce adverse drug reactions, a key public health problem ranking between the fourth and sixth leading cause of death across the globe. Depending on how we use this information, the potential exists to describe simultaneously our similarities and differences without reaffirming old prejudices. Every year as many as 100,000 patients in hospitals die as the result of adverse drug reactions. How many of those deaths could be avoided if we knew in advance which drugs were safe and which weren't for those particular patients? And beyond those dire cases, how much more effectively could we treat sick people if we knew what variants in their genomes made certain drugs more effective than others for them? Welcome to the rapidly developing field of pharmacogenetics (or, as it is increasingly known, pharmacogenomics) its mission is to examine the genomes of patients and use that information to prescribe the right drugs at the right dose.

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REFERENCES

1. Vogelstein B, Kinzler KW (2004) Cancer genes and the pathways they control. Nat Med 10:789-799. http://www.ncbi.nlm.nih.gov/pubmed/15286780

2. Kumar K, Jamil, K (2006) Methylenetetrahydrofolate reductase (MTHFR) C677T and A1298C polymorphisms and breast cancer in South Indian population. Int J Cancer Res 2: 143 -151. www.dx.doi.org/10.3923/ijcr.2006.143.151
3. Suman G, Jamil K (2006) Novel CYP3A4 gene polymorphisms in post chemo breast cancer patients. Int J Cancer Res 2: 358-366. www.dx.doi.org/10.3923/ijcr.2006.358.366
4. Shanker S, Reddy SC, Jamil K, Vamsy MCh (2007) Genomic analysis of SNPs in Breast Cancer by using Bioinformatics databases. Ind J Biotech 6: 456-462. http://nopr.niscair.res.in/bitstream/123456789/3088/1/IJBT%206%284%29%20456-462.pdf
5. Khan S, Jamil K, Das P, Vamsy M, Sudha M (2007) Polymorphic sites (1236 and 3435) in mdr1 gene influencing drug response in breast cancer patients. Int J Pharmacol, 3: 453-460. www.dx.doi.org/10.3923/ijp.2007.453.460
6. Jamil K, Reddy H (2007) Can Polymorphisms in genes relate to overall survival in leukemias? Leuk Lymphoma, 48: 1070 – 1071. http://www.ncbi.nlm.nih.gov/pubmed/17577768
7. Kumar K, Murthy S, Jamil K (2007) Possible Associations of Splice Site Mutation of Dihydropyrimidine Dehydrogenase (IVS14+ 1G> A) in Adverse Drug Reactions in Some Invasive Ductal Carcinoma Patients. Int J Pharmacol, 3:130-136. www.dx.doi.org/10.3923/ijp.2007.130.136
8. Sabitha K, Reddy MVV, Jamil K (2008) GST genotypes in head and neck cancer patients and its clinical implications. African J Biotech, 7: 3853-3859. www.dx.doi.org/10.5897/AJB08.650
9. Khan M, Jamil K (2008) Study on the conserved and polymorphic sites of MTHFR using bioinformatic approaches. Trends in Bioinformatics, 1: 7-17. www.dx.doi.org/10.3923/tb.2008.7.17
10. Khan M, Jamil K (2008) Clustering cancer metasignature genes: Identification of cellular profiles of neoplastic and undifferentiated stages of cancer. Research Journal of BioTechnology, 3: 11 –17
11. Khan M, Jamil K (2008) Genomic distribution, expression and pathways of cancer metasignature genes through knowledge based data mining. Int J Cancer Res., 1: 1-9. www.dx.doi.org/10.3923/ijcr.2008.137.145

12. Suman G, Jamil K, Suseela K, Vamsy MCh (2009) Novel mutations of CYP3A4 in fine needle aspiration cytology samples of breast cancer patients and its clinical correlations. Cancer Biomark, 5: 33-40. http://www.ncbi.nlm.nih.gov/pubmed/19242060
13. Shaik AP, Jamil K, Das P (2009) CYP1A1 polymorphisms and risk of prostate cancer: a meta-analysis. Urol J., 6: 78-86. http://www.ncbi.nlm.nih.gov/pubmed/19472123
14. Shaik AP, Jamil K (2009) Polymorphisms in MGP gene and their association with lead toxicity. Toxicol Mech Methods, 19: 209-213. http://www.ncbi.nlm.nih.gov/pubmed/19730704
15. Shaik AP, Jamil K (2009) Individual susceptibility and genotoxicity in workers exposed to hazardous materials like lead. J Hazard Mater, 168: 918-924. http://www.ncbi.nlm.nih.gov/pubmed/19327888
16. Kumar K, Vamsy M, Jamil K (2010) Thymidylate synthase gene polymorphisms effecting 5-FU response in breast cancer patients. Cancer Biomark, 6: 83-93. http://www.ncbi.nlm.nih.gov/pubmed/20571234
17. Kumar CK, Reddy M, Jamil K, Vamsy M (2010) Genotyping of tamoxifen metabolizing enzyme (CYP2D6*4) and its clinical impact in breast cancer patients. Int J Gen Mol Bio., 2: 006–013. http://www.academicjournals.org/article/article1379589230_Kumur%20et%20al.pdf
18. Balaji AB, Jamil K, Maruthiram G, Habibulla CM (2010) Isolation of a novel population of multipotent stem cells from epidermal layer of human skin. Biology and Medicine, 2: 57-67. http://www.biolmedonline.com/Articles/Vol2_2_57-67.pdf
19. Khan M, Jamil K (2010) Phylogeny reconstruction of ubiquitin conjugating (E2) enzymes. Biology and Medicine, 2: 10-19. http://omicsonline.com/open-access/phylogeny-reconstruction-of-ubiquitin-conjugating-e-enzymes-0974-8369-2-055.pdf
20. Sabitha K, Reddy MV, Jamil K (2010) Smoking related risk involved in individuals carrying genetic variants of CYP1A1 gene in head and neck cancer. Cancer Epidemiol, 34: 587-92. http://www.ncbi.nlm.nih.gov/pubmed/20887941
21. Sultana SA, Kiranmaee S, Bammidi VK, Shaik AP, Jamil K (2011. Int J Cancer Res., 7: 99-113. www.dx.doi.org/10.3923/ijcr.2011.99.113
22. Shaik AP, Sultana A, Bammidi VK, Sampathirao K, Jamil K (2011) A meta-analysis of eNOS and ACE gene polymorphisms and risk of pre-eclampsia in women. J Obstet Gynaecol. 31: 603-607. http://www.ncbi.nlm.nih.gov/pubmed/21973132

23. Jamil K, Sabeena M (2011) Identification of Functional Diversity in the Enolase Superfamily Proteins, in Computational Biology and Applied Bioinformatics ed. H. S. Lopes (InTech), 311-328.
24. Lakshmi A, Muralidhar S, Kalyan Kumar C, Pavan Kumar A, Kalyana Chakravarthy P, Anjaneyulu V, Kaiser J (2012) COX-2 −765 G > C functional promoter polymorphism and its association with Oral Squamous cell Carcinoma. J Investig Clin Dent., 3: 182-188. http://www.ncbi.nlm.nih.gov/pubmed/22887904
25. Kalyan ChK, Jamil K, Raju GS (2011) Predicting drug-target interaction in cancers using homology modeled structures of MTHFR gene. Biology and Medicine, 3: 70-81. http://www.biolmedonline.com/Articles/Vol3_3_2011/Vol3_3_70-81.pdf
26. Jayaraman A, Jamil K (2011) The interaction of p53 and MDM2 genes in cancers, in silico studies and phylogenetic analysis. Biology and Medicine, 3: 01-12. http://www.biolmedonline.com/Articles/Vol3_3_2011/Vol3_3_1-12.pdf
27. Asimuddin M, Jamil K (2012) Insight into the DNA repair mechanism operating during cell cycle checkpoints in eukaryotic cells. Biology and Medicine, 4: 147-166. http://www.biolmedonline.com/Articles/Vol4_4_2012/Vol4_4_147-166_BM-4.pdf
28. Ahmed M, Jamil K (2012) BCL-2 as Target for Molecular Docking of Some Neoplastic Drugs. Cancer Sci. Ther.- Open Access Scientific Reports, 1: 458. www.dx.doi.org/10.4172/scientificreports.458
29. Ahmed M, Rayalu DJ, Jamil K (2012) Molecular docking studies targeting cyclooxygenase-2 (COX2) involved in cancer. International journal of Pharmaceutical Sciences and Healthcare, 4: 76-85. http://rspublication.com/ijphc/aug%2012/7.pdf
30. Jamil K, Jayaraman A, Rao R, Raju S (2012) In silico evidence of signaling pathways of notch mediated networks in leukemia. Comput Struct Biotechnol J. 1: e201207005. http://www.ncbi.nlm.nih.gov/pubmed/24688641
31. Jayaraman A, Jamil K (2012) Clusters of CDK2, CCND1, and CMYC genes involved in cancers: Acute Lymphocytic Leukemia (ALL) as a model. Biology and Medicine 4: 37-50. http://www.biolmedonline.com/Articles/Vol4_1_2012/Vol4_1_37-50.pdf
32. Jamil K, Mustafa SM (2012) Thioredoxin System: A Model for Determining Novel Lead Molecules for Breast Cancer Chemotherapy. Avicenna J Med Biotechnol 4: 1-10. http://www.ncbi.nlm.nih.gov/pubmed/23407461
33. Kumar ChK, Kandula M, Bhavani V, Laxmi A, Reddy NM, Jamil K (2013) Sulfotransferase 1A1 (SULT1A1) Polymorphism and Breast Cancer Risk: a Case-control

Study in South India. American Journals of Cancer Science, 2: 2-8. http://www.ivyunion.org/index.php/ajcs/article/download/201300125/pdf_9

34. Natukula K, Jamil K, Pingali UR, Attili VS, Madireddy UR (2013a) The codon 399 Arg/Gln XRCC1 polymorphism is associated with lung cancer in Indians. Asian Pac J Cancer Prev, 14: 5275-5279. http://www.ncbi.nlm.nih.gov/pubmed/24175813
35. Ahmed M, Jamil K (2013) Induction of Apoptosis through Cox-2 and Bcl-2 activation by Gefitinib, Cisplatin and 5-FU in HeLa cells. Int J Biotech Bioeng Res 4: 47-62. http://www.i-scholar.in/index.php/ijbbr/article/view/39141
36. Jamil K (2014) Clinical Implications of MTHFR Gene Polymorphism in Various Diseases. Biology and Medicine 6, e107. www.dx.doi.org/10.4172/0974-8369.1000e107
37. Jayaraman A, Jamil K (2014) Drug Targets for Cell Cycle Dysregulators in Leukemogenesis: In Silico Docking Studies. PLoS ONE, 9: e86310. http://www.ncbi.nlm.nih.gov/pubmed/24454966
38. Dolinoy DC, Weidman JR, Jirtle RL (2007) Epigenetic gene regulation: linking early developmental environment to adult disease. Reprod Toxicol, 23: 297-307. http://www.ncbi.nlm.nih.gov/pubmed/17046196
39. Soffritti M, Belpoggi F, Esposti DD, Falcioni L, Bua L (2008) Consequences of exposure to carcinogens beginning during developmental life. Basic Clin Pharmacol Toxicol, 102:118-124. http://www.ncbi.nlm.nih.gov/pubmed/18226064
40. Brazell C, Freeman A, Mosteller M (2002) Maximizing the value of medicines by including pharmacogenetic research in drug development and surveillance. Br J Clin Pharmacol, 53:224-331. http://www.ncbi.nlm.nih.gov/pubmed/11874384
41. Kalow W, Tang BK, Endrenyi L (1998) Hypothesis: comparisons of inter- and intra-individual variations can substitute for twin studies in drug research. Pharmacogenetics, 8:283-289. http://www.ncbi.nlm.nih.gov/pubmed/9731714
42. Evans WE, Relling MV (1999) Pharmacogenomics: translating functional genomics into rational therapeutics. Science, 286:487–491. http://www.ncbi.nlm.nih.gov/pubmed/10521338
43. Evans WE, Johnson JA (2001) Pharmacogenomics: the inherited basis for interindividual differences in drug response. Annu Rev Genomics Hum Genet, 2:9–39. http://www.ncbi.nlm.nih.gov/pubmed/11701642
44. Evans WE, McLeod HL (2003) Pharmacogenomics—drug disposition, drug targets, and side effects. N Engl J Med, 348:538–549. http://www.ncbi.nlm.nih.gov/pubmed/12571262

45. Lanfear DE, McLeod HL (2007) Pharmacogenetics: using DNA to optimize drug therapy. Am Fam Physician. 6: 1179-1182. http://www.ncbi.nlm.nih.gov/pubmed/17990842
46. Kalow W (1956) Familial incidence of low pseudocholinesterase level. Lancet, 268: 576-577. www.dx.doi.org/10.1016/S0140-6736(56)92065-7
47. Watters JW, McLeod HL (2003) Cancer pharmacogenomics: current and future applications. Biochim Biophys Acta, 1603:99-111. http://www.ncbi.nlm.nih.gov/pubmed/12618310
48. Lee W, Lockhart AC, Kim RB, Rothenberg ML (2005) Cancer pharmacogenomics: powerful tools in cancer chemotherapy and drug development. Oncologist, 10:104-111. http://www.ncbi.nlm.nih.gov/pubmed/15709212
49. Lima JJ, Thomason DB, Mohamed MH, Eberle LV, Self TH, Johnson JA (1999) Impact of genetic polymorphisms of the beta2-adrenergic receptor on albuterol bronchodilator pharmacodynamics. Clin Pharmacol Ther, 65: 519-525. http://www.ncbi.nlm.nih.gov/pubmed/10340917
50. Aithal GP, Day CP, Kesteven PJ, Daly AK (1999) Association of polymorphisms in the cytochrome P450 CYP2C9 with warfarin dose requirement and risk of bleeding complications. Lancet 353: 717-719. http://www.ncbi.nlm.nih.gov/pubmed/10073515
51. Weinshilboum R (2003) Inheritance and drug response. N Engl J Med, 348: 529-537. http://www.ncbi.nlm.nih.gov/pubmed/12571261
52. Heckmann JM, Lambson EM, Little F, Owen EP (2005) Thiopurine methyltransferase (TPMT) heterozygosity and enzyme activity as predictive tests for the development of azathioprine-related adverse events. J Neurol Sci., 231: 71-80. http://www.ncbi.nlm.nih.gov/pubmed/15792824
53. Chrzanowska M, Kuehn M, Januszkiewicz-Lewandowska D, Kurzawski M, Droździk M (2012) Thiopurine S-methyltransferase phenotype-genotype correlation in children with acute lymphoblastic leukemia. Acta Pol Pharm., 69: 405-410. http://www.ncbi.nlm.nih.gov/pubmed/22594254
54. Tantray JA, Kumar YS, Jamil K (2013) Pharmacogenomic studies of Cholesteryl Ester Transfer Protein (CETP) Genotypes in suspected CAD patients. Int J Pharm Sci Res 4: 3910-3916. http://dx.doi.org/10.13040/IJPSR.0975-8232.4(10).3910-16
55. Perou CM, Sørlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, et al. (2000) Molecular portraits of human breast tumours. Nature. 406: 747-752. http://www.ncbi.nlm.nih.gov/pubmed/10963602

56. Sørlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, et al. (2001). Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci USA. 98: 10869-10874. http://www.ncbi.nlm.nih.gov/pubmed/11553815
57. Gort M, Broekhuis M, Otter R, Klazinga NS (2007) Improvement of best practice in early breast cancer: actionable surgeon and hospital factors. Breast Cancer Res Treat. 102: 219-226. http://www.ncbi.nlm.nih.gov/pubmed/17028985
58. Ellsworth RE, Decewicz DJ, Shriver CD, Ellsworth DL (2010) Breast cancer in the personal genomics era. Curr Genomics. 11: 146-161. www.ncbi.nlm.nih.gov/pubmed/21037853
59. Natukula K, Jamil K, Pingali UR, Attili VSS, Madireddy URN (2013) Survival Analysis in Advanced Non Small Cell Lung Cancer Treated with Platinum Based Chemotherapy in Combination with Paclitaxel, Gemcitabine and Etoposide. Asian Pac J Cancer Prev. 14: 4661-4666. http://www.ncbi.nlm.nih.gov/pubmed/24083721
60. Nagalakshmi K, Jamil K, Pingali U, Reddy MV, Attili SS (2014) Epidermal growth factor receptor (EGFR) mutations as biomarker for head and neck squamous cell carcinomas (HNSCC). Biomarkers. 19: 198-206. http://www.ncbi.nlm.nih.gov/pubmed/24712396
61. Okita RT, Masters BSS (1997) Biotransformations: The cytochrome P450. In: Devlin, T.M. (ed.); Textbook of Biochemistry with Clinical Correlations; Wiley-Liss, New York, 981-999.
62. Kakarala, KK, Jamil K (2014) Sequence-structure based phylogeny of GPCR Class A Rhodopsin receptors. Mol Phylogen Evol.74: 66-96. http://www.ncbi.nlm.nih.gov/pubmed/24503482
63. Pelloso LA, Da Silva ID, De Souza NC, Yamamoto M, Botelho CA, Chauffaille Mde L (2007) CYP1A1 polymorphisms modify overall survival in acute myeloid leukemia patients. Leuk Lymphoma. 48:1211-1215. http://www.ncbi.nlm.nih.gov/pubmed/17577786
64. Davies SM, Robison LL, Buckley JD, Tjoa T, Woods WG, Radloff GA, Ross JA, Perentesis JP (2001) Glutathione S-transferase polymorphisms and outcome of chemotherapy in childhood acute myeloid leukemia. J Clin Oncol, 19:1279-1287. http://www.ncbi.nlm.nih.gov/pubmed/11230469