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A REVIEW ON THE ROLE OF PHARMACOGENOMICS IN DRUG DISCOVERY AND DEVELOPMENT

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ABSTRACT: Pharmacogenomics (constitute both branch i.e pharmacology and genetic) is the study of the role of genetics in drug response. It deals with the effect of genetic variation on drug response in patient by correlating the gene expression with the pharmacokinetic parameter i.e absorption, distribution metabolism and excretion. The Pharmacogenomics is used in the research to increase the safety and efficacy of the drug by targeting the drug at the particular site of genes. Pharmacogenetic also play important role in the study of effect of multiple genes in the pharmacological action of drugs. In Pharmacogenomics we identify and study about various component of the genes that affect the therapeutic of the drug. Most of the drugs fail to show therapeutic effect at the latter stages it may be due to unexpected adverse effect of drug that may be due to the effect of various component of genes. Pharmacogenetic studies can be used at various stages of drug development. In clinical studies, pharmacogenetic can be used in stratification of patient based on their genotype, which correspond to their metabolizing capacity. This helps in prevention of various adverse drug reaction and better outcomes of clinical trial.

INTRODUCTION: Pharmacogenomics and pharmacogenetic are two inter-related term that are widely used for the drug development and therapy. Pharmacogenomics is the broad term in which we study about all the component of genes to find out various determinant of drug response¹. The various treatment therapy like cancer chemotherapy and oral-anticoagulant are now carried out with the help of pharmacogenetic status of patient, to minimize the toxicity and failure of the drug therapy^{2,3}. At present the traditional method of selection of drug and dosage form is replaced by the pharmacogenetic method.

Definitions:

The study of variation in the drug response due to heredity character is called pharmacogenetic. The term pharmacogenetic was coined by Vogel in 1957⁴. And the term Pharmacogenomics was introduced recently. The term pharmacogenetic and Pharmacogenomics are used interchangeable as there is no standard definition of the Pharmacogenomics. Lindpainter stated that Pharmacogenetic is a term used to differentiate between the compound but Pharmacogenomics is a term used to differentiate between the patient⁵.

Sources of Variability:

Both the pharmacodynamic and pharmacokinetic factor is responsible for variation in drug response. Variability in the expression of the cytochrome P450 enzyme, which is responsible for phase I drug metabolism, has been focus of most of the work in pharmacokinetic. Cytochrome P450 2D6 (CYP4502D6), for example, in 8% of the U.K

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population the major CYP450D6 enzyme is absent which is responsible for the metabolism of 25% of drugs, including CNS (antidepressant and antipsychotic) and cardiovascular (β -blocker and anti-arrhythmic) drugs. Much less work has been done in pharmacodynamic factor causing variation in drug response, but as drug can affect almost any protein in the body, almost every gene may have an effect on how drugs vary in their response⁶.

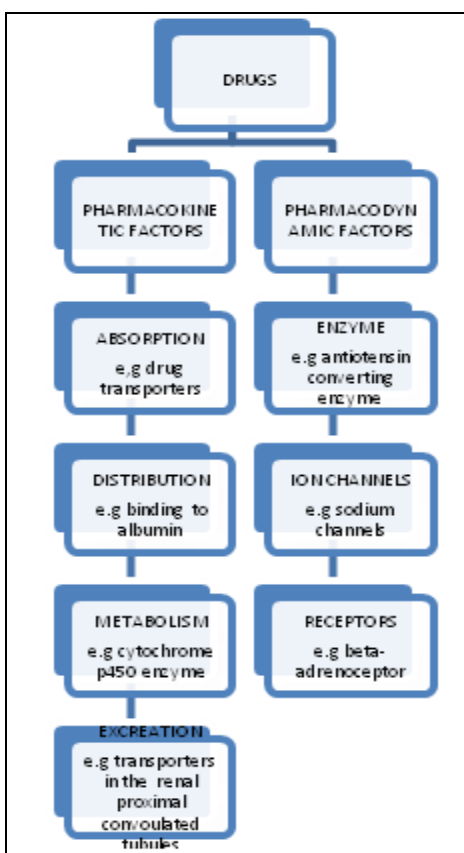


FIG.1: VARIATION IN THE DRUG RESPONSE CAN BE DUE TO GENETICALLY DETERMINED FACTOR IN PHARMACOKINETIC AND PHARMACODYNAMIC.

Difference from pharmacogenetics and pharmacogenomics:

The term pharmacogenetic and Pharmacogenomics are interchangeable, however in this paper the definition provided by the "Position paper on terminology in pharmacogenetics", issued by the European Agency for the Evaluation of Medicinal Products (EMA) and very recently adopted by the Committee for Proprietary Medicinal Products (CPMP) is used⁷. According to this paper, "pharmacogenetics is the study of inter individual variations in DNA sequence related to drug response", while "Pharmacogenomics is the study of the variability of the expression of individual

genes relevant to disease susceptibility as well as drug response at cellular, tissue, individual or population level. The terms are widely used in the various fields such as clinical development, drug designing and drug discovery.

Possible implication of pharmacogenetic/ Pharmacogenomics for drug development:

The use of pharmacogenetic and Pharmacogenomics principle in the drug development process has reduced the drug dose, increase the rate of absorption and drug targeting is increased remarkably. These are considered as below and in **Table 1**.

1. Target identification:

At present, the drugs that are present in the market act at less than 450 out of 1000 target in the human proteome⁸. By using the technique of Pharmacogenomics and pharmacogenetic the number of target for the drug therapy have been increased remarkably through:

- Detection of new protein that is involved in disease process.
- Targeting the disease causing process.

2. Pre-clinical drug development:

There is great impact of Pharmacogenomics in this phase of drug development. The in-vitro screening is only possible due to the identification of molecule defect, which is different in different people. For example: An advancement has been made by using the drug metabolizing enzyme i.e cytochrome P450 enzyme. These are the most important biological catalyst that are responsible for the metabolism of different types of drugs. This lead to the assessment of interaction of the drug with the enzyme such P450 enzyme.

3. Phase I-III studies:

These phases of clinical trial provide regulatory approval to launch medicine in the market. The phase I clinical trial typically cost is nearly about \$7 million, but it reaches upto \$43 million for phase III clinical trial. The refinement of the phase I study is carried out by using pharmacogenomics principle, which focus on individual genotype through pre-clinical testing⁹. The early identification of the

defect in the drug during phase I may lead to droop the compound in early stage, which help in saving the development cost and time.

In phase II, there may be further refinement of the pharmacogenetic determinants of drug response, which may provide information necessary for design of the phase III studies. The net effect may be a reduction in sample size for phase III studies, which may in turn result in more efficient and quicker drug development, and a net reduction in cost⁹.

4. Phase IV studies:

This phase refers to period when the licences is granted to launch medicine in market, so this phase is also known as the as postmarketing surveillance or pharmacovigilance. In this phase various study ranging from hypothesis- generation, reporting to hypothesis- testing, pharmacoepidemiological studies are carried out throughout the whole period

of the phase. With the help of Pharmacogenomics less effort is to be required to improve the marketing surveillance than harmonization of marketing authorization procedure and creation of single market¹⁰.

In the phase large no of patient are exposed to the drugs, so even detection of rare adverse effect is carried out. Different sample of DNA from patient treated with drug were stored, which allow pharmacogenetic testing and identification of genetic predisposing factor, which lead to improvement of the risk-benefit ratio. This is best explained by abacavir hypersensitivity study, which lead to identification of major genetic predisposing factor in the MHC locus¹¹. Any reduction in the total number of patient in the phase III study lead to need of large number of patient , more structured phase IV study in order to identify rare and long term toxicity. Prospective collection of DNA sample is possible in phase IV¹² but expensive.

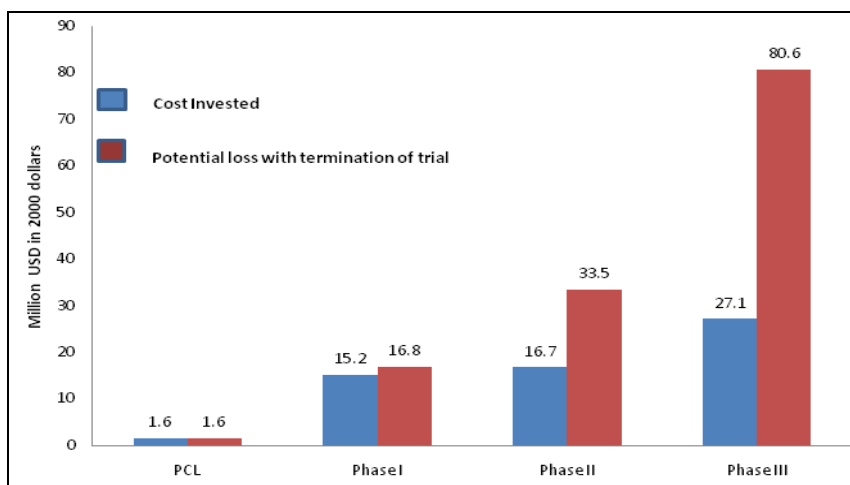


FIG.2: POTENTIAL FINANCIAL LOSS WITH PREMATURE TERMINATION OF A CLINICAL TRIAL¹³

PCL (Preclinical study):

TABLE 1: APPLICATION OF PHARMACOGENOMIC/PHARMACOGENETIC METHOD IN VARIOUS STAGE OF DRUG DEVELOPMENT¹³

Stage	Application of Pharmacogenomic/pharmacogenetics
Drug target identification	Identification and characterization of the gene coding for the drug targeting and to assess the variability, Patient selection- inclusion/exclusion criteria
Phase I clinical trial	
Phase II clinical trial	
Phase III clinical trial	Dose range selection
Phase IV clinical trial	Dose modification
Regulatory issues	Interpretation of trial results based on pharmacogenetics test results
Patient therapeutics	Analysis of report adverse event with pharmacogenomics data during development by FDA.
	Requirement for submission of pharmacogenetic data during development by FDA,
	Personalization of drug therapy.
	Pharmacogenetic data in drug labelling.
	Identification of responders and non responders.
	Identification of high risk group of adverse event.

History of Pharmacogenomic:

If we talk about the history of pharmacogenomics it takes us about 510 B.C back. in 510 b.c, Pythagoras investigated the potentially fatal reaction in some individual but not all individual on

ingestion of fava beans¹⁴. Since from this investigation there are numerous landmark (Table 2) that have suggested this field as research. Every 500-1000 bases of human genome varies is observed¹⁵

TABLE 2: HISTORICAL OVERVIEW OF PHARMACOGENETIC AND PHARMACOGENOMIC.

Year	Individual(s)	Landmark
510 B.C	Pythagoras	Recognition of the adverse event of ingestion of fava beans, later characterized to be due to deficiency of G6PD (Glucose-6-phosphate dehydrogenase. ¹⁴
1866	Mendel	Establishment of the rules of heredity ¹⁶
1906	Garrod	Publication of 'inborn error of metabolism' ¹⁷
1932	Snyder	Characterization of ' phenylthiourea nontaster' as an autosomal recessive trait ¹⁸
1956	Carson et al.	Discovery of glucose-6-phosphate dehydrogenase deficiency ¹⁹
1957	Motulsky	Further refined the concept that inherited defects of metabolism may explain individual differences in drug response ²⁰
1957	Kalow & Genest	Characterization of serum cholinesterase deficiency ²¹
1957	Vogel	Coined the term pharmacogenetics ²²
1960	Price Evans	Characterization of acetylator polymorphism ²³
1962	Kalow	Publication of 'pharmacogenetics – heredity and the response to drugs' ²⁴
1977/79	Mahgoub et al. and Eichelbaum et al.	Discovery of the polymorphism in dibrisoquine hydroxylase sparteine oxidase ^{25, 26}
1988	Gonzalez et al.	Characterization of the genetic defect debrisoquine hydroxylase , later termed CYP2D6 ²⁷
1988-2000	Various	Identification of specific polymorphisms in various phase I and phase II drug metabolizing enzymes, and latterly in drug transporters.
2000	Public- private partnership	Completion of the first draft of the human genome ^{28, 29}
2000	The international SNP (single nucleotide polymorphism) Map Working Group	Completion of Map of human genome sequence variation containing 1.42 million SNPs ³⁰

Current Success in Pharmacogenomic:**Codeine:**

In children and adult, codeine (3-methyl morphine) is one of the most widely used drug for the treatment of mild to moderate pain. Codeine itself does not have its analgesic effect, it get converted to its pharmacologically active metabolite, morphine in liver which is responsible for analgesic activity and have approximately 600 times more analgesic effect than that of codeine³¹. Recently the use of codeine has been decreased due to codeine related toxicity. The serious or fatal adverse reaction have been observed in the neonate after receiving the breast milk of the mother receiving standard dose of codeine for post-partum pain^{32, 33}.

Tonsillectomies and adenoidectomies adverse effect have been reported in the children taking codeine for relieving pain^{34, 35}. The cytochrome P450 2D6 (CYP450 2D6) is the enzyme which is

responsible for the biotransformation of the codeine to morphine, is highly polymorphic with over 100 genetic variants described in the CYP450 2D6 gene³⁶. The patient with more than three or more functional copies of CYP450 2D6 are classified as ultra rapidly metabolizers, which rapidly convert codeine to morphine and produces morphine toxicity even at very low dose. The morphin toxicity observed are respiratory depression and in rare case the death have been reported due to presence of these highly active alleles (CYP4502D6* 1xN/*2xN/*17Xn/*35Xn; where N represent number of copies)^{34, 37}. In some patient the codeine does not get converted into morphine due to the presence of poor metabolizing enzyme CYP4502D6 , hence minimal analgesic effect and pain relief³⁸.

The amount of morphine produced form the codeine varies from individual ranging from 0% to 75%³⁷. Clinical practice guideline have recently

been developed to inform physician on the use of genetic testing for safe and more effective dosing of codeine by identification of individuals^{36, 39}.

Warfarin:

Warfarin is an anticoagulant used for prevention and treatment of venous thromboembolism by inhibiting the enzyme vitamin K epoxide reductase, encoded in VKORC1, due to which the amount of vitamin K available for synthesis of coagulation factor get decreased. The dose of warfarin required to produce anticoagulant effect varies about 20 fold from individual to individual patient. In case of warfarin several adverse effect can be observed such as bleeding or thrombosis due to narrow therapeutic window and inappropriate dosing in individual⁴⁰. The dose of the warfarin depend upon both the genetic and clinical factor. For example genetic variant in VKORC1 as well as the cytochrome P450 2C9 (CYP2C9) gene, which is primarily responsible for metabolizing the pharmacologically active S-warfarin isomer, confer an increased variant [VKORC1rs9923231, CYP2C9 rs1799853(*2),rs1057910] requires lower warfarin doses to achieves equivalent therapeutic effects^{41, 42}.

The several other gene that influences the warfarin dose are cytochrome P450 4F2 (CYP4F2) and gamma glutamyl carboxylase (GGCX)^{43, 44}. The impact of the genes on the variation of warfarin dose is very minor after the accounting for VKORC1 and CYP2C9 variant. The recent study shows a significant association between warfarin and VKORC/CYP2C9 genome in pediatric patient, which shows that same genetic variants are important for warfarin dosing in children^{45, 46, 47}. For the predication of the accurate dose of warfarin several pharmacogenetic based dosing algorithms have been developed^{48, 49}.

Carbamazepine:

Carbamazepine is one of frequently used anticonvulsant drug used for treatment of the epilepsy, trigeminal neuralgia, bipolar disorder and seizure disorder in both children and adult^{50, 51}. The several sever side effect have been observed in patient taking carbamazepine such as life-threatening cutaneous adverse reaction, Hypersensitivity reaction, Stevens-Johnsonsyndrome(SJS) and toxic epidermal necrolysis(TEN)⁵². Hypersensitivity reaction is generally characterized by high fever, skin eruption and involvement of at least one internal internal organ with approximately mortality of 10%. SJS and TEN are serious bilistering reaction of skin and mucous membrane which mortality rate range from 10% to 50%⁵³. The genetic variants in human leukocyte antigen (HLA) region lead to carbamazepine induced hypersensitivity reaction in both child and adult.

The higher risk of SJS/TEN have been reported in patient carrying the HLA-B*1502 variant^{54, 55}. While HLA-A*31:01 allele is primarily predictive for HSS. The carbamazepine- induced SLS/TEN largely depend on the genetic of the patient ancestry. The number of the HLA-B*1502 variant is high (10-15%) in the Asia including china, Malaysia, Thailand, Indonesia, Tawani and Vietnam but rare (<1%) in Japan, Korea, Africa, America, European, and Hispanic population^{56, 57}.

Recently it have been reported that in European population the carbamazepine-induced adverse reaction including SJS/TEN and HSS is due to HLA-A*31:01 Haplotype. Pharmacogenomic testing for HLA-B*15:02 is in standard practice in at least 50 hospital in Taiwan and is currently recommended by the FDA for patient with ancestry in at risk-populations. For clinicians, clinical practice guidelines are available to make genotype-based decision for patient with an indication with carbamazepine therapy^{58, 59}.

TABLE 3:

Drugs	Associated gene(s)	Associated variants	Associated variant effect	Clinical practice recommendation	Reference
Codeine	CYP2D6	*1xN/*2xN/*35xN	Increased activity; Life-threatening CNS depressive effect	Avoid codeine use because of potential for toxicity. consider alternative analgesic.	36, 39
		*4xN/*3-*8 /*12/*15/*19/*20/*40/*42	No active; impaired/greatly reduced	Avoid codeine use because of lack of	36, 39

		/*44/*56	analgesia	efficacy. Consider alternative analgesic.	36, 39
		*9/*10/*11*17/*29/*41/*29/*50/*43/*55/*59	Reduced activity; reduced analgesia	Codeine used as per standard care. If no response, consider using alternative analgesic	
Warfarin	CYP2C9	rs1799853(*2)	Decreased activity; reduced dose requirement	Use of pharmacogenetic algorithm-based dosing is recommended when possible. Initial dosing ranges for patients with different combination of CYP2C9 and VKORC1 genotype provided on drug label.	60, 61
		Rs1057910(*3)	Decreased activity; reduced dose requirement		
	VKORC1	rs9923231	Reduced expression; reduced dose requirement		
Carbamazepine	HLA	B*1502	Increase risk of carbamazepine-associated Stevens-Johnson syndrome and toxicity epidermal necrolysis(SJS/TEN)	Do not use carbamazepine in native people that are positive for HLA-B*1502. If patient used carbamazepine for longer than 3 months with out	58, 59
		A*31:01	Increased risk of carbamazepine-associated hypersensitivity syndrome(HSS)		

Method of Studying Genetic Bases of Drug Response Variation:

1. Candidate gene approach:

In this method, the identification of genetic determinants of drug response variability involves identification of association between various allelic variants or SNPs within the candidate gene and the drugs response⁶². This method starts with the identification of the candidate genes. The drug response may be due to candidate genes, which code for the drug metabolizing enzyme, the drug transporting protein, protein involved in cellular mechanism and the receptor protein. The study that is carried with the help of candidate gene is generally for allelic variants. More than allelic variant or SNPs are found in candidate gene. This method of study is generally carried in people with altered drug response (case) and people with normal drug response (control). This method of the study of genetic base of drug response variation is less expensive than linkage disequilibrium studies and genome wide study⁶².

2. Genome wide scan:

This method of study is very extensive and elaborate form for the study of effect of various allelic variants occurring throughout the genome and the study of the drug response in diseased condition. In this the identification of all allelic variants are carried out in the entire human genome and SNP map is created. This method is carried for testing the drug response variation⁶³. The advantage of this method in comparison to the other method is that, it can identify the polygenic determinants of drug response. The human genome has approximately three million SNPs and it is very expensive to screen all the SNPs. As a result, only representative SNPs that are distributed in the human genome are selected for screening. This may range from 200000 to 300000⁶⁴.

3. Haplotype analysis:

This method of analysis is used for the study of the cluster of the SNPs occurring linkage disequilibrium in a chromosome and their

association with the drug response. This method of analysis is different from the genome wide scan. In that we only study about the selected Haplotype not the entire genome. Haplotype blocks are created by clustering selective SNPs and their linkage disequilibrium is tested for association with clinical outcomes. More information can be obtained from the Haplotype analysis than that of the pharmacogenetic study of the single nucleotide polymorphism and is cost effective. From above study we can identify the various genetic determinant for drug response and development of drug can be customized accordingly. The same method can be used in the clinical trial for determination of adverse effect.

Pharmacogenomics and Drugs Development:

Initially the drug discovery in psychiatric was based on the serendipity. After the identification of the lithium in 1949 and chlorpromazine in 1950s, the purgative mechanism of action were elucidated after drug were shown to be efficacious. The newer drug discover paradigms depends on the synthesis and identification of novel compound through combinatorial chemistry and screening for biological screening for biological activity against known receptor or other biological targets with established endogenous ligands or substance^{49, 60}.

The experimental paradigms used in the pharmacogenomics was borrowed from the field of the population genetics and methodology used in earlier genetic study of common complex disease^{60, 61}. According to the human genome project all the human genes available act as the potential drug target. Then the main challenge of the drug discovery is the functional and therapeutic utilization of these genes and their expressed product. The pharmacogenomics brought the Experimental paradigms from the field of population genetics and the methodology used in earlier genetic studies of common diseases^{60, 61}.

DNA microarray is an emerging powerful technological breakthrough that enables the study of global gene expression pattern and sequence variation at genome level⁶². DNA micro assay is the extended form of the southern bolt procedure in which the stretching of different cDNAs or oligonucleotide are carried on a solid surface such

as silica or glass plate. In microarray each DNA species represent specific gene or expressed sequence tag, which is used to identify different SNPs or transcripts by hybridization and fluorescence detection.

CONCLUSION: Pharmacogenomics is one of the most important tool used worldwide to find the adverse drug reaction as well as for the development of new drug. The cost and time for the development of new drugs can be minimized with the help of this tool. The personalization of the treatment can be carried out with the help of Pharmacogenomic/ pharmacogenetic study. So, the Pharmacogenomics is the future of the drug discovery and development. At present, however, it is not clear whether and what extent the genomic hypothesis can be tested within the framework of available clinical trial methodology. For example, the sample size for phase clinical trial is not more than 3000 to 4000 patient. But the genomic studies reduces the sample size than that of the current resource of any single pharmaceutical company or an academic laboratory.

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