Review Article

Drugs impact on CYP-450 enzyme family: A pharmacogenetical study of response variation

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Pharmacogenetics is the study of genetic basis in the individual response to drugs. A thorough knowledge of this will lead to a future where tailor-made drugs, suiting an individual, can be used. Scandinavian countries have been known for wide usage of pharmacogenetics and the most widely used application is for genotyping CYP2D6 in treating psychiatric illness. The CYP-450 enzyme, a super family of microsomal drug-metabolizing enzymes, is the most important of enzymes that catalyzes phase-I drug metabolism reaction. CYP2D6 is a member of this family and it has been most intensively studied and the best example of pharmacogenetics variation in drug metabolism. Neuro-transmitter and drug acting CNS viz. codeine, dextromethorphan, metoprolol and tryptyline etc. are well metabolized by this enzyme. Thus, CYP2D6 is one of the most important and responsible enzymes which regulates bioavailability and metabolism of drug. Presently 75 alleles of CYP2D6 have been described which are responsible for variance of metabolism and toxicity of drugs. Thus, by determining variance of CYP2D6 using molecular approaches viz., PCR, real-time PCR, DNA micro-array and molecular docking can determine the adverse effects, drug toxicity, bioavailability and therapeutic potential of new drug.

Key words: CYP2D6, pharmacogenetics, single neucleotide polymorphismneucleotide polymorphism

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Introduction

A person's environment, diet and overall health can influence how s/he responds to medicines. Genes are another factor which determining a person's response to drugs. Pharmacogenetics aims to understand the role of a person's genetic make-up play in the good effects and side-effects of a medicine in a person's body. A thorough knowledge of this will lead to a future where tailor-made drugs, suited for an individual, can be used.

Concurrently, wide usage of Pharmacogentics is seen in the Scandinavians Countries and the most widely used application is for genotyping CYP2D6 when treating psychiatric illness.

Genetic variation contributes to inter-patient differences in drug response. Such variations may occur for drug metabolism, drug transporter and drug target proteins. Most of the variations occurring in the human genome are single nucleotide polymorphism (SNPs) with an occurrence rate of at least one every 1000 base pairs. Genetic Polymorphism may cause an alteration in the efficacy of a drug or its toxicity.

Genes contain instructions for making proteins, including proteins which interact with drugs. Any change in a gene can result in changes in the associated protein involved i.e, an enzyme of dug metabolism. Individuals get one copy of a gene from each parent, but each of those copies may have a change or mutation. Mutation can result in production of an enzyme with reduced function or no enzyme may be produced at all. Depending on whether a Person has 0, 1 or 2 normal copies of genes, he or she may be grouped as poor, intermediate or rapid metabolizer. The less normal copies a person has, the poorer the metabolism, and hence, higher blood levels of the drug. This may result in greater effectiveness or more likely greater side effects.

History

Looking back, the first pharmacogentics trait to be observed was — "taste blindness" to a chemical called Phenylthiourea (PTU). Individuals with a certain gene

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profile were unable to taste PTU, while others could. This hereditary chemical insensitivity led researchers to understand the genetic differences between races. Mankind has known genetic sensitivity to various substances since time immemorial which can be corroborated by the fact that susceptibility to alcohol by certain ethnic groups was well known 100 years ago. The concept Pharmacogentics began in the 1950s, nearly by chance, as a result of isolating genetic differences in metabolizing rugs. Numerous findings provided an early stimulus for the development of Pharmacogentics For example, the inheritance of phase I reaction impairment studied on Succinylcholine (Muscle Relaxant). Since the 1950s, novel technologies have been combined with a new genetic approach to decipher variation at person to person level.

Pharmacogentics has been broadly applied in the study and treatment of cancers. A classical case of Pharamacogentics in oncology happened way back in

1988, when the Journal on Clinical Investigation reported the case of a 40-year-old woman being treated for breast cancer. The woman almost died from a standard done of chemothera [autic agent] since she possessed a genetic defect due to which she was unable to metabolize the drug. Pharmacogentics played a major role in understanding the cause and led to an entirely new approach to treatment. Till date, it is widely known that reaction to cancer treatment can very widely from patient from patient to patient.[1]

Pharmacokinetic Variations

Drug metabolism

Metabolism usually converts drug to metabolites which are more water soluble and thus more easily excreted. It can also convert products into therapeutically active compounds and may even result in the formation of toxic metabolites.

Pathway of drug metabolism is classified as:

(a) phase I reaction (Oxidation, Reduction, hydrolyis)

(b) phase II reaction (Acetylation, glucuronidation, Methylation etc).

The above said nomenclature is histamical which means that phase II reaction can precede phase I reaction and often can occur without oxidation,reduction, hydrolysis.

However, both the reactions often convert lipid soluble drugs into relatively more water- soluble metabolites. These fundamental reactions of drug metabolism are impacted by the individual's genetic Information. Approximately 1 in 3500 white people code for an atypical form of enzyme butyl cholinesterase which is relatively unable to hydrolyze succinylcholine (muscle relaxant) thereby prolonging drug induced muscle paralysis and resultant apnoea. Similarly it has been observed that common genetic variations in phase II reactions e.g. Acetylation can result in objectionable differences in the half life and plasma Concentration of drugs metabolized by N-acetyltransferase e.g. Isoniazid, Hydralazine and Procainamide. These variations in Acetylation has clinical consequences. The Cytochrome P-450 enzyme, a super family of microsomal drug metabolizing enzymes, is the most important of enzymes which catalyze phase I drug metabolism reactions.

One member of this family, CYP2D6 (cytochrome P-450 2D6), has been the most intensively studied and is the best example of Pharmacogenetic variation in drug metabolism. The CYP2D6 genetic polymorphism was originally discovered as a result of striking difference in the pharmacokinetics and therapeutic effects of drugs metabolized by this enzyme. Drugs as diverse as codeine, dextromethophan, metaprolol and tryptyline are all metabolized by this enzyme. CYP2D6 is needed to break down the drug and eliminate it. People who have low levels of enzymes metabolize drugs slowly and the drug will remain in the body for a longer period of time than it was metabolized quickly. Slow metabolizers are more likely to hace side effects. Moreover, people who produce low levels of CYP2D6 in liver will need smaller doses of drug hat are eliminated by this enzymes, while fast metabolizers i.e. people who have high levels of enzyme will need larger drug dose to get the same effect, by applying molecular genetic technique, 75

CYP2D6 alleles have been described. This CYP2D6 polymorphism is an excellent example of potential clinical implications of pharmacogentics. In some cases, the differences in drug responses can be correlated to ethnic background Noteworthy is the variation in Drug Metabolism enyzme in various ethnic groups [Table 1].[2]

Table 1: Classification of various families of CYP ISO-enzyme

Isoenzymes	Substrates	Inducers	Inhibitors	Effects
CYP2A6	Nicotines, 5-hydroxy coumarins	Not inducible	?	Inactive (1-3% of Caucasians) inactive (deletions common in Asians)
CYP2B6	Artemisinin, S-mephobarbital, S-ifosfamide, cyclophosphamide coumarin activation	Phenobarbital, cyclophosphamide	Not inducible	{Used in retroviral vector gene Rx of cancer!} expression in early childhood is poor
CYP2C8	TCA, diazepam (found in kidney, adrenal, brain, uterus, breast, ovary and duodenum), verapamil	Rifampicin, phenobarbitone	Cimetidine	Expression in early childhood is poor
CYP2C9	S-warfarin, phenytoin, diclofenac and other NSAIDS, tolbutamide, fluoxetine, torsemide, verapamil, dextromethorphan	Rifampicin, carbamazepine, ethanol	Fluconazole, ketoconazole, sulphonamides (sulfaphenazole), sulphinpyrazone, amiodarone, ritonavir, metronidazole minimal effect	Less active. phenytoin toxicity
CYP2C18	(Found in brain, uterus, breast, kidney and duodenum; liver levels ~10% of those of 2C8 and 2C9)	Phenobarbitone, artemisinin (?)	Sulfaphenazole, fluoxetine, omeprazole, ritonavir, fluvoxamine, oral contraceptives ticlopidine	Similar to 2C19; metabolizes cyclophosphamide, ifosfamide, verapamil, lansoprazole
CYP2C19	(Found in duodenum but few other extrahepatic tissues; lower hepatic expression than 2C9) (S) mephenytoin, phenytoin, diazepam, TCA (clomipramine, imipramine..), dextromethorphan, propranolol, omeprazole, progesterone, sertraline, aminopyrine	Phenobarbitone, artemisinin.	Sulfaphenazole, fluoxetine, omeprazole, ritonavir, fluvoxamine, oral contraceptives ticlopidine	Inactive (in up to 20% of Asians,3% of Caucasians, 19% of African Americans, 8% of Africans, up to 71% of Pacific islanders, Low activity allows dual Rx of *H pylori* with good success! Low B12 with long term omeprazole Rx! risk of phenytoin toxicity
CYP2D6 "debrisoquine hydroxylase" (about 2% of liver CYP, the only active 2D in man {rats have ~six!}) found mainly in the liver, with LITTLE intestinal activity	Debrisoquine, dextromethorphan, beta blockers, haloperidol, chlorpromazine, thioridazine dexfenfluramine, flecainide, propafenone, mexiletine, procainamide fentanyl, pethidine {=meperidine}, SSRIs (fluoxetine), TCAs, trazadone, zuclopenthixol, S-mianserin, tolterodine; azelastine	Not inducible	cimetidine { >>> ranitidine }, quini[di]ne, methadone, SSRIs Some TCAs (paroxetine fluoxetine norfluoxetine sertraline desmethylsertraline fluvoxamine, nefazodone, venlafaxine clomipramine amitriptyline), Antipsychotics (perphenazine thioridazine chlorpromazine haloperidol fluphenazine risperidone clozapine cis-thiothixine)	Common in Chinese, common in Black Africans, 10% of Caucasians are poor metabolisers;
CYP2E1 (about 7% of liver CYP)	Paracetamol {=acetaminophen}, ethanol pentobarbitone, tolbutamide, propranolol, rifampicin, Coumarin activation, Many volatile anesthetics: Isoflurane, sevoflurane, enflurane	Chronic ethanol intake, isoniazid, benzene	Disulfiram, (cimetidine) (acute ethanol intake!)	Association with alcoholic liver disease, liver cancer, lung and nasopharyngeal cancer (cigarettes) (Chinese polymorphism)

Pharmacodynamic Variations

Drug response

Genetic variations in drug target, e.g., receptors have a profound effect on drug efficacy.

The response to 12- agonists is affected by genetic polymorphism of 12-adrenoceptor (coded by ADRB2 gene). Three single nucleotide polymorphism in ADBR2 have been associated with altered expression, down regulates or Coupling of the receptor in response to 12-receptor agonists. In some individuals it has been noticed that a dose up to 20 times greater than normal may be required to produce the desired anticoagulant effect by Warfarin. The reduced activity of Warfarin is attributed to a genetically controlled reduction in binding affinity of Warfarin receptor.[3]

A life threatening malignant hyper thermis affects about one in 20,000 patients. This disorder causes a fatal elevation in body temp and is consequent to a hyper- metabolic response to a combination of a depolarizing muscle relaxant (SuccinylCholine) and a Potent Volatile inhalational General Anaesthetic (Halothane). The susceptibilty to the disorder (inherited in an autosomal dominant pattern) is due to mutation in the gene that encodes the ryanodine receptor (Calcium release channel).

ACE-inhibitor improves symptoms of survival in case of heart failure in Caucasians as compared to African-Americans. This implies that a genetic screening of individuals might be allowed to apply this knowledge in clinical practice. Certain drugs act by binding to specific chemicals called receptors sites on the surface of our body within body cells. Variation in those genes that code for receptors means that same people may produce receptors that do not interact well with the drug, for example. Some people do not respond to the bronchodilator Salbutamol as they show genetic variation in the gene those codes for a receptor on surface of S.M cellular lining the bronchial airways.

Drug Development

A sound knowledge of the genetic make-up of an individual can be of importance in drug treatments trials. In Alzheimer disease which affects 25% of people in older age group of over 85, the gene associated is called APOE. This gene occurs in three forms known as E2, E3 and E4. All three have the same primary function to produce an essential protein called apoliprotein E is split of contain slightly different information this protein modifies the development of Alzheimer disease by interfering with the production of a brain cortex and the ceels deteriorate. The most common form of gene is E3. The E4 from gene is Supposed be associated with Alzheimer disease and the same is also distinctly involved in drug treatment for Alzheimer diseases. Individuals with Alzheimer disease who have E2 and E3 from of APOE gene respond well to the drug Tacrine (r), while those with E4 do not.[4]

Ethical issues

The idea of targeting certain groups within population can be a touching subject, no matter how well intentioned, as in the case of targeting sickle cell anaemia screening in early 1970's to the American black population without appropriate knowledge. Such programs, if conceptualized, have to be carefully implemented to avoid a perception of stigma based or ethnicity. Moreover, questions might be raised on the assumptions that a person's race can indicate their genetic profile for drug response since all the people belonging to a particular ethnic group will not have the same genetic variations. Consequently, genetic profiling may culminate into denial of treatment to a certain ethnic group race if a Pharmacogenetic test that could determine more precisely how a person's reaction, was not available.

Merits

- Drugs may be developed targeting specific health problems that will maximize therapeutic effects but not decrease healthy cells.
- The likely hard of adverse effects might be reduced by having an idea of the drug to be used based on genetic profiling.
- Better vaccines made of genetic material having all the benefits of existing vaccines but with reduced risk of infections.
- The likelihood of over-dosage may be less if dosage

were based on a persons genetic makeup rather than a body weight or age

- Pharmacogenetics can be used in testing for reaction to is environmental toxins. This finds reference in today's times. Since many areas have high carcinogenic agents individuals susceptible to safe place for them to live a normal, healthy life.
- Revival of older drugs e.g. Clozapine where agranulocytes in 0.5 to 2% of patients limits the use of this agent as first therapy for Schizophrenia despite its proven efficacy.

Results and Discussion

In some cases, the differences in drug responses can be correlated to ethnic background Noteworthy is the variation in drug metabolism enzyme in various ethnic groups [Table 2].[5]

Conclusion

The ramification of Pharmacogentics is the ability to screen potential adverse reactions.

Table 2: The Variation in drug metabolism enzyme in various ethnic groups

Drug	Enzyme	Population	Effect
Sulfonamide, Chloramphenicol	Glucose-6-Phospate Dehydrogenase	Black males	Acute Haemolysis in different people
Nitrofurantoin			
Nalixidic acid			
Perhexiline (Antianginal)	CYP2D6	Asian, African	Neuropathy in poor metabolizers
TCA (Desipramine and nortryptyline)	CYP2D6		Inadequate anti-depressant response in ultra rapid metabolisers
Antipsychotic (Haloperidol)	CYP2D6	East Asians	Increase in plasma conc. and exagg. Response in intermediate metabolizers
Codeine, Tramadol (prodrugs)	CYP2D6	6-8% Swedens	Decrease in analgesic effect in poor metabolizers
		1% Chinese(PM's)	
Enalapril	CYP2D6	Blacks	
Prozac(Flouxitine)	CYP2D6	Black(PM's)	Likely to have more side effects
			(nausea,insomnia,terry headache)
Antiviral drug (ter.hep.C)		African-American	Do not respond well
(Alpha interferon and ribavarin)			
Narcotics		Asians more sensitive	Apnea
Debrisoquin	CYP2D6	10% of whites in N. America and Europe	Orthostatic hypotension
5-FU	Dihyropyrimide		Fatal increase drug effect, N.S. toxicity
	Dehydrogenase		
Isoniazid	Rapid Acetylation	East Asian	
	Slow Acetylation	Asian and Eskimos	
Warfarin	CYP2C9	Caucasian	Anti-coagulation (due to inactive variant if gene)
Omeprazole	CYP2C19	14.6% Chinese	Improved cureratis for *H. Pylori* in poor metabolizers
		18% Japanese	
Ethanol	Aldehyde Dehydrogenase	50% Japanese Chinese Asian	Facial Fluhing increased heart rate diaphoresis due to lack of enzyme

Biological anomalies in different population groups

Factor	Population	Effect
Heavy salivation	Blacks	Intubations difficult, drying agents given
Low K + Levels	Asian Males	Temporary paralysis
Sickle cell anaemia	Africans and Medite	
Likely multiple	Caucasian	
Cystic Fibrosis	Caucasian	
More likely to have nitric oxide in sufficiency	Black	
Lack Aldehyde	50% Japanese, Chinese and other Asian	Facial flushing, increase heart rate and diaphoresis
G-6PD deficiency	10% Black males	Hemolytic anemia
CYP2D6	7% Caucasian	Poor Metabolism
Decrease HDL and Increase TG	Indians	

Technological advances in the way of human genome project (completed in April 2003) will finally allow us to tailor drug therapies to each patient and move beyond 'race' as a crude indicator or genetic variations.

Genetic finger printing of an individual is already practical. This can determine the presence of polymorphism in genes and an individualized care can be given in future. Studies to correlate DNA finger prints with data present in medical records about medical history and drug response can be undertaken. These studies will have a deep impact on the ways in which new drugs are developed and used. Such programs, if conceptualized, have to be carefully implemented to avoid a perception of stigma based or ethnicity. Moreover, questions might be raised on the assumptions that a person/race can indicate their genetic profile for drug response since all the people belonging to a particular ethnic group will not have the same genetic variations. Consequently, genetic profiling may culminate into denial of treatment to a certain ethnic group/race if a Pharmacogenetic test that could determine more precisely how a person reacts was not available.

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