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Pharmacogenetics: The Scientific Basis

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1. Introduction

The history of genetic variations in drug responses can be traced to the 1950s with the observations that muscle relaxant suxamethonium chloride and drugs metabolized by N-acetyl transferase exhibit differences in response in patients. One in 3500 caucasians was found to possess the less efficient variant of the enzyme, butyryl cholinesterase that metabolizes suxamethonium chloride; an anaesthetic agent. As a consequence, the drug's effect is prolonged with slower recovery from surgical paralysis.

The term pharmacogenetics evolved from the combination of two areas of study namely pharmacology and genetics. Pharmacology is the study of how drugs work in the body and genetics is the study of how characteristics that result from the action of genes acting together are inherited and how they function in the cells of the body. Therefore, pharmacogenetics refers to genetic differences in metabolic pathways which can affect individual responses to drugs both in terms of therapy and adverse effects. Pharmacogenetics helps our understanding of why some individuals respond to drugs and others do not and why some require higher or lower doses to achieve optimal therapeutic responses.

In addition, pharmacogenetic information helps the physician to identify those patients who will respond favourably to therapy or develop side effects.

A recent offshoot of pharmacogenetics, termed pharmacogenomics is the study of drug response in the context of the entire genome. Pharmacogenomics facilitates information on variations in all the genes in a group of individuals simultaneously to determine the basis of variants in drug response. It is therefore not uncommon to find the two being used interchangeably. However for the purpose of this chapter, pharmacogenetics will be the focus.

Individual variation in response to drug ranges from failure to respond to drug therapy to drug to drug interactions when several drugs are taken simultaneously. The clinical consequences range from patients' discomfort through serious clinical illness to the occasional fatality. Approximately 7% of patients are affected by adverse drug reactions, increasing the overall hospital costs by 19% and drug costs by 15%. Some 0.3% of adverse drug reactions have fatal outcome (Topic 2010).

1.1 Individual variation in drug effects

Variation in drug metabolism and drug response among individuals of the same body weight and on the same drug dose can be due to temporary causes such as transient enzyme

inhibition, induction or permanent causes such as genetic mutation, gene deletion or amplification. (Shenfield 2004).

Genetic variability is known to affect drug absorption, drug metabolism and drug interactions with receptors. These therefore form the basis for slow or rapid drug absorption, poor, efficient or ultrarapid drug metabolism and poor or efficient receptor interactions.

A genetic mutation frequency exceeding 10% of a population is considered a genetic polymorphism (Meyer 2000). Genetic polymorphism based on drug metabolizing ability is related to four phenotypic classes. The phenotype of extensive or normal drug metabolizers (EM) is characteristic of the normal population. Individuals are either homozygous or heterozygous for wild type allele. Those individuals who are heterozygous for the wild type allele may have intermediate metabolizer phenotype (IM) and may require lower than average drug dose for optimal therapeutic response. Those individuals with mutation or deletion of both alleles for the determinant of phenotypic response can be classified as poor metabolizers (PM) and therefore prone to accumulation of drug substrates in their systems with attendant effects. The fourth class, termed the ultrarapid metabolizers (UM) possess enhanced drug metabolism capabilities due to gene amplification and are prone to drug failure because drug concentrations at normal doses are expected to be too low for therapeutic effects (Meyer 2000, Davies 2006).

There are ethnical and racial differences in the frequency of variant alleles and up to 10 – 20% of patients belong to the risk groups. (Evans 1986, Banjoko & Akinlade 2010).

1.2 Mechanism of genetic polymorphism

Pharmacogenetic polymorphism can manifest at the pharmacokinetic and pharmacodynamics levels. The pharmacokinetic level deals with gene polymorphism that modify concentrations of drugs and its metabolites at the site of their molecular action (polymorphism of drug metabolizing enzymes, drug transporters) whereas the pharmacodynamics level deal with polymorphism of action not related to its concentration (receptors, ion channels). Genetic variations are the result of multiple mechanism such as insertion, deletion, variable tandem repeats and microsatellites but the most frequent polymorphism are point mutation or single nucleotide polymorphism (SNPS). Some of the polymorphism are without consequences but others cause synthesis of altered proteins, truncated proteins, unstable proteins or proteins at the level of expression.

Genotype is the detailed gene structure of an individual whereas the more commonly measured phenotype is the outcome of metabolism of a drug in an individual. Since genotype is the result of interactions between genetic make up and the environment, it is not always concordant with phenotype.

1.3 Consequences of pharmacogenetics

The underpinning factors for the growing importance of pharmacogenetics are the necessity to prevent adverse drug reaction, obtain maximum benefits from drug therapy and reduce therapeutic failure.

Adverse drug reactions are thought to kill many hospitalized patients worldwide. In the US alone, the estimate of deaths attributable to drug reactions is about 100,000 annually and it is believed that many of these reactions are due to genetic variations. Thus many deaths are avoidable if genetic testing or genomic information of patients are available and utilized prior to therapy.

Pharmacogenetics will therefore permit gene profiling to answer questions about drug responses and promote the design of better and safer drugs. In addition, individualized dosing has the potential of better therapeutic outcome. Therefore pharmacogenetics is expected to revolutionise drug dosing and therapy. However, there are still many challenges to overcome. These include cost implications, standardization, quality control of testing, and relevance of biomarkers and tests. Nevertheless, the advent of pharmacogenetics and establishment of guidelines by regulatory bodies like Food and Drugs Administration (FDA) European Medicines Agency (EMA) and American Association of Clinical Chemists (AACC) are expected to impact individualized dosing of many drugs.

1.4 Confounding issues in pharmacogenetics

The understanding that drug response may be multifactorial helps us to recognize the importance of examining more than the classical "single gene-single protein concept which gave birth to pharmacogenomics. In addition, there are more evidences that modifications besides outright mutation of genes, for example, methylation of promoter region by epigenetic factor impact gene expression and drug responses. Moreover, genotype is not the only determinant of phenotype. For example, individuals whose genotypes falls extensive metabolizers via CYP2D6 can display a phenotype that would characterize them as poor metabolizers if they are co-administered low doses of quinidine which is a potent inhibitor of CYP2D6. Therefore, differences in phenotype does not necessarily translate into difference in pharmacologic response between subjects. In the same fashion, mutation of the genes may not necessarily translate into effect on drug metabolism (Henningson et al 2005).

Because of significant racial differences in genetic composition, it is important that caution is exercised in the interpretation of genetic testing. For example different genotypes may give rise to the same phenotype. In addition, there are varieties of mutations in NAT2 that give rise to slow acetylator status.

Furthermore the historical use of wild-type alleles and mutant alleles may not necessarily hold true for all the races hence the migration to the term reference and mutant alleles.

2. Basic genetics

Genetics is the study concerned with hereditary and variation. One of the most fundamental properties of all living organisms is the ability to reproduce. All organisms therefore inherit the genetic information specifying their structure and function from their parents. In the same manner, all cells arise from pre-existing cells, so the genetic material must be replicated and passed from a parent to progeny cell at each cell division. The hereditary molecules that are transmitted from one generation to the next i.e. inherited are called genes. These molecules (genes) reside in the deoxyribonucleic acid (DNA) that exist within all cells. The DNA in conjunction with a protein matrix forms nucleoprotein and become

organized into structures called chromosomes located in the nucleus or nuclear region of cells. The genes contains coded information for the synthesis of proteins and some ribonucleic acids (RNA). Occasionally, a change may occur spontaneously in some part of the DNA. This change is called mutation and may result in an alteration of the code designated for a particular function resulting in production of a defective protein.

A mutation may lead to a change in the physical appearance of an individual or change in some other measurable attributes of the organism called a character or trait. Through the process of mutation, a gene may be changed into two or more alternative forms called alleles. Each gene occupies a specific position on the chromosomes called the gene locus. All allelic forms of a gene therefore are found at corresponding positions on genetically similar (homologous) chromosomes.

All the genes on a chromosomes are said to be linked to one another and to belong to the same linkage group. Since a gene can be changed to alternative forms by the process of mutation, a large number of alleles are theoretically possible in a population of individuals. Whenever more than two alleles are identified at a gene locus in a population, such is described as multiple allele series.

Genetic information is stored and transmitted in the four letter alphabet and language of DNA (A,C,G,T) and ultimately expressed in the twenty letter alphabet of proteins. Protein biosynthesis is called translation because it involves the biochemical translation of information between languages.

A capital letter is commonly used to designate the allele that is dominant to other alleles in the series. For example letter "R" for a character is dominant over 'r' which is an allele that is recessive to all others in the series. Intermediate in their degree of dominance between the two extremes are usually assigned the lower case letter with superscript which in this example is r^* . Many genes may contribute to a single character or trait (polygenic traits) or traits exhibiting continuous variation. In addition, each gene may have multiple phenotypic effects (pleiotropy).

Each character is controlled by a pair of genes. The progeny or offspring are therefore hybrids of the parents, inheriting a pair of gene, one each from each parent. For example for trait for tallness being represented by letter T, possible genetic composition are TT, Tt, and tt whereby T allele is dominant over t. It is expected that an offspring with tt genetic composition will be short while those with TT or Tt will be tall.

The genetic composition of a trait is referred to as the genotype and the physical appearance corresponding to the genotype, in this example tallness is called the phenotype. With different generations of offsprings i.e. the filial generations, different genotypes and corresponding phenotypes are obtainable.

The originator of the classical principles of genetics is Macgregor Mendel who made public the result of his study of peas breeding in 1865. Mendel studied the inheritance of a number of well defined traits in the pea such as seed colour and was able to deduce general rules for their transmission. He was the first to observe that each trait was determined by a pair of inherited factors later termed the genes. Mendel's findings provided the template for determination of genotypes and phenotypes of different genetic diseases of humans, animals and plants and notable examples include: sickle cell disease, albinism and thalassaemias.

By 1900, Mendel's laws of inheritance were well established and are thus stated:

Law of segregation: Each parent possesses 2 copies of a unit of inheritance (now called the gene) for each trait. However, only one of these two genes (an allele) is transmitted through a gamete to the offspring.

Law of independent assortment: says segregation of one gene pair occurs independently of any other gene pair.

2.1 Chromosomes, genes and inheritance

Chromosomes are known to be carrier of genes. Most cells of higher plants and animals are diploid. i.e. they contain two copies of each chromosome. Formation of the germ cells; the sperm and egg involves a unique type of cell division termed meiosis. In this process, only one member of each chromosome pair is transmitted to each progeny cell. Therefore, the sperm and egg are haploid containing only one copy of each chromosome. The fusion of these two haploid cells at fertilization result in a new diploid organism; the offspring which consists of one member of each chromosome pair. Behaviour of chromosome pairs is directly related to their genes indicating a strong relationship between genes and chromosomes.

Genetic alterations i.e. mutation which is the basis of genetic diseases was first identified in the experiment with *Drosophila melanogaster* (the fruit fly) in the early 1900. Mutations in drosophila was observed to involve such phenotypes like eye colour and wing shape. Experimented evidences revealed that the genes governing these traits are inherited independently of each other, suggesting that these genes are located on different chromosomes that segregate independently during meiosis. Other genes are inheritable as paired characteristics and such are said to be linked to each other by virtue of being located on the same chromosome. The frequency of recombination between two linked genes depends on distance between them on the chromosomes. In addition, genes that are close to each other recombine less frequently than do genes further apart. Thus the differences with which the different genes recombine can be used to determine their relative position on the chromosome allowing the construction of a genetic map.

2.2 Genes, proteins and enzymes

Genes act by determining the structure of proteins which are responsible for directing cell metabolism through the activities of enzymes. Many genes encode enzymes that are important for catalysing biological synthesis (anabolic) and degradation (catabolic reactions) within a cell. These reactions grouped together into a series of reactions are called biochemical pathways and commence with the enzymes acting on their corresponding substrate.

The first indication linking genes and enzymes can be traced to 1909 when it was observed that patients suffering from phenylketonuria were suspected to have a genetic defect in the metabolism of the amino acid for phenylalanine. This line of thought was supported by the experiment of George Beadle and Edward Tatum in 1941 with the fungus; *Neurospora crassa*. Using mutant strains of the organism, they observed that each mutant required specific nutritional supplement such as a particular amino acid for growth. Furthermore, the

requirement for a specific nutritional supplement correlates with the failure of the mutant to synthesize that particular compound. Thus each mutant resulted in a deficiency in a specific metabolic pathway. Since metabolic pathways are known to be controlled by enzymes, these findings gave rise to the one - gene - one enzyme hypothesis which by implication means that each gene specified the structure of a single enzyme. However, the revelation that genes not only codes for proteins and enzymes but tRNAs resulted in this hypothesis being modified to one - gene - one - polypeptide concept.

Transfer RNA's (tRNAs) serve as adaptations between aminoacids and messenger RNA (mRNA) during translation. Prior to its use in protein synthesis, each aminoacid is attached by a specific enzyme to its appropriate tRNA. Base pairing between a recognition sequence in each tRNA and a complimentary sequence on the mRNA then directs the attached aminoacid to its correct position on the mRNA template.

2.3 Genetic polymorphism

Genetic polymorphism can be defined as differences in DNA sequence among individuals, groups or population. Genetic mutation can create genetic variance in a population and this can manifest in different ways. Somatic cell mutation can create a genetic variation in a cell population which may induce cancer and tumour when such mutation takes place in repressor genes controlling cell cycles such as p53 gene. On the other hand, germ line cell mutation can cause genetic diseases such as sickle cell disease, thalassemia, Parkinson's disease as well as defect of biochemical pathway that influence drug - receptor interaction with attendant deleterious effects on patients. Point mutation such as a single base nucleotide substitution (SNP) are common particularly with adverse drug reactions. Mutation that occurs in germ line cell would be inherited by the progeny and these mutated genes can spread in a population through the fertilization process. Mutations that occur in coding frame of DNA region that are responsible for synthesis of specific products could give rise to genetic disease. Similarly, mutation that affects enzymes responsible for biotransformation of drugs particularly C450 gene family and pharmacokinetic and pharmacodynamic gene functions can result in adverse drug reactions or drug inefficacy. These reasons make phamacogenetics an important area of study.

3. Basic pharmacology

Pharmacology is the study that deals with interaction of endogenously administered chemical molecules termed drugs with living systems. It involves such studies like (i) Pharmacokinetics (ii) Pharmacodynamics (iii) Toxicology

- i. **Pharmacokinetics** : Pharmacokinetics is the quantitative study of drug movement from administration throughout out the body till excretion. All pharmacokinetic processes involve transport of the drug across cell membrane, absorption, distribution and excretion
- ii. **Pharmacodynamics**: Pharmacodynamics coined from two Greek words pharmacon; drugs and dynamis: power, involves the physiological and biochemical effect of drugs and their mechanism of action at organ, systemic, subcellular and macromolecular levels. The pharmacodynamic process describes all those matters concerned with the pharmacological action of a drug, whether they be determinants of the therapeutic effect or of the toxic effect.

- iii. **Toxicology:** This is the study of poisonous effects of drugs and other chemicals. Although a speciality on its own, it is nevertheless still considered under pharmacology with regards to adverse drug effects.

3.1 Principles of drug actions

There are eight main drug actions and these are:

Stimulation: Through direct receptor agonism and downstream effect e.g. adrenaline stimulates heart, pilocarpine stimulates salivary glands. However, excessive stimulation is often followed by depression of that function e.g. high dose of picrotoxin, a CNS stimulant, produces convulsions followed by coma and respiratory depression.

Depression: Through direct receptor agonism and down stream effect e.g. barbiturates depress CNS while quinines depresses the heart. The action of this mechanism is selective.

Blocking/Antagonizing action: The drug binds the receptor but does not activate it.

Stabilizing action: In this case, the drug seems to act neither as a stimulant nor as a depressant but to stabilize general receptor activation like buprenorphine in opioid dependence or aripiprazole in schizophrenia.

Replacement: Refers to the use of natural metabolites including hormones and vitamins in deficiency stages e.g. levodopa in Parkinsonism, insulin in diabetes mellitus, iron in anemia and oestrogen replacement in women of menopausal age.

Direct beneficial chemical reaction: As in use of antioxidants like Vitamins C, E and B-carotene for free radical scavenging

Cytotoxic action: Selective cytotoxic action for parasite, bacterial or cancer cells, attenuating them without significantly affecting the host cells e.g. use of antibiotics like penicillin, zidovudine and cyclophosphamide

Irritation: A non-selective often noxious effect applicable to less specialized cells, for example the epithelial, connective tissue cells). Mild irritation may stimulate associated function e.g. bitters increase salivary and gastric secretions which results in increased blood flow to the site. However, strong irritation may result in inflammation, corrosion, necrosis and morphological damage with resultant diminution or loss of function. Therefore caution should be exercised in the administration because of tendency of excessive ingestion.

4. Metabolism of drug and other xenobiotics

Metabolism of drugs and other xenobiotics involves activities that modify the chemical structure of the substances which are foreign to the body's internal milieu. These reactions often act to detoxify poisonous compounds; however in some cases, the intermediate metabolite can themselves be toxic

The purpose of biotransformation is to convert lipophilic compounds to hydrophilic ones which will facilitate their excretion. The consequences of biotransformation is changes in pharmacokinetic characteristics.

Xenobiotics metabolism can be divided into three phases. In phase 1, enzymes such as cytochrome p450 oxidases introduce an active or polar group into the xenobiotics. These modified compounds are then conjugated to polar compounds in phase II reactions. The main enzyme that catalyses the reactions in phase II is glutathione S-transferase since it acts on a wide range of substrates.

The final phase; phase III may involve further metabolism of conjugates of phase II reactions like the processing of glutathione conjugates to acetylcysteine (mercapturic acid) conjugates before being recognized by efflux transporters and pumped out of the cells (Boylan & Chassaud 1969, Thormalley 1990)

Peculiar to all organisms is the possession of cell membranes which serve as hydrophobic permeability barriers to control access to their internal environment. Polar compounds cannot diffuse across these cell membranes, and the uptake of useful molecules is mediated through transport proteins that specifically select substrates from the extracellular mixture. The implication of this structure is that most hydrophilic molecules cannot enter the cells since they need to be recognized by specific transporters (Mizuno et al 2003).

The detoxification of reactive by-products is via a different mechanism. Because these species are derived from normal cellular constituents, they usually share the same polar characteristics therefore, specific designated enzymes can metabolize them. A notable example of these specific detoxification system is the glyoxalase system which catalyses the removal of the reactive aldehyde, methylglyoxal (Thormalley 1990) and the various antioxidant systems that eliminate reactive oxygen species (Sies 1997).

4.1 Phase I reactions

In Phase I reactions, a variety of enzymes act to introduce reactive and polar groups into their substrates. This is basically a functionalization reaction. One of the most common modifications in this phase is hydroxylation, a reaction catalysed by the cytochrome P-450 dependent mixed function oxidase system. These enzymes complexes act to incorporate an atom of oxygen into nonactivated hydrocarbons, which can result in either the introduction of hydroxyl groups, or Nitrogen, Oxygen and Sulphate- dealkylation of substrates (Schlichting et al 2000). Of all the enzymes involved in drug metabolism, the cytochrome P450 (CYP450) is regarded as the most important because many drugs are substrates for the enzymes of the group. In all, CYP3A4, CYP2D6, CYP2C9, CYP219, CYP2B6 and CYP1A2 subtypes play the most critical role and account for more than 90% of drugs metabolized by CYP 450 enzymes (Evans & Relling 1999). These enzymes have proven genetic polymorphism with associated drug responses (Hiratsuka et al 2002, Wong et al 2005, McAlpine et al 2011) and racial variations (Meyer 2004 & Suarez - Kurtz 2005).

Phenotypes of P450 are divided into four groups and these are; the extensive metabolizers (EM) who show low metabolic activities, the poor metabolizers (PM) who carry gene alterations on both alleles which are inherited in an autosomal manner, the intermediate metabolizers (IM) with metabolic capacity in between those of PM and EM and finally the ultra rapid metabolizers (UM) who show higher metabolic capacity than the EM. (Murphy 2001, Hiratsuka et al 2005). Genetic variations have been observed particularly with CYP 2D6, CYP2C9 and CYP2C19 genotypes (Ingelman - Sundberg 1999, Hiratsuka 2006). With regards to CYP2D6, five to ten percent of caucasians are poor metabolizers and have little

enzyme activities. In addition, there is a distinct racial diversity in the frequency of the classes. Examples of CYP450 catalyzed drug metabolic reactions include

- i. **Hydroxylation:** S-mephenytoin $\xrightarrow{\text{CYP3A4}}$ 4-OH-S-mephenytoin
- ii. **Epoxidation:** Carbamazepine $\xrightarrow{\text{CYP3A4/5}}$ 10,11 Epoxide
- iii. **Oxygenation:** Amines $\xrightarrow{\text{CYP 2D6}}$ Hydroxylamines
- iv. **O-dealkylation:** Dextromethorphan $\xrightarrow{\text{CYP2D6}}$ Dextrophan
- v. **N-demethylation:** Caffeine $\xrightarrow{\text{CYP2E1}}$ Theobromine
- vi. **N-demethylation:** Caffeine $\xrightarrow{\text{CYP1A2}}$ Paraxanthine
- vii. **N-demethylation:** Caffeine $\xrightarrow{\text{CYP2E1}}$ Theophylline
- viii. **Oxidative Group Transfer:** Parathion $\xrightarrow{\text{CYP2B6}}$ Paraoxon
- ix. **Dehydrogenation:** Acetaminophen $\xrightarrow{\text{CYP2E1}}$ N-Acetyl benzoquinoneimine
- x. **Ester Cleavage:** Loratidine $\xrightarrow{\text{CYP3A4, CYP2D6}}$ Desacetylated Loratidine
- xi. **Reduction:** Paraquat $\xrightarrow{\text{FLAVOPROTEIN REDUCTASE}}$ paraquat radicals

4.1.1 Non P450 enzyme catalysis

Besides the CYP 450 enzymes, other enzymes that participate in drug biotransformations include; monoamineoxidases, peroxidases, lactoperoxidases myeloperoxidases, prostaglandin-H-synthetase and flavin-containing monooxygenases.(FMO).Examples of the reactions they catalyse include:

- i. **Hydrolysis:** hydrolysis of peptide bond of Insulin
- ii. **Reduction:** Chloral Hydrate $\xrightarrow{\text{ALC. DEHYDROGENASE}}$ Trichloroethanol
- iii. **Oxidoreduction:** Alcohol $\xrightarrow{\text{ALC.DEHYDROGENASE}}$ Aldehyde

4.2 Phase II reactions

In phase II reactions, the activated xenobiotic metabolites are conjugated with charged species such as glutathione (GSH), sulfate, glycine or glycuronic acid and increased risk of early renal complications in type 2 diabetes mellitus (Banjoko & Akinlade 2010). These reactions are catalysed by substrate specific transferases which in total can metabolize almost any hydrophobic compound that contains nucleophilic or electrophilic group.

One of the most important of this group is the glutathione S-transferase (GSTs). The addition of large anionic groups such as glutathione detoxifies reactive electrophiles and produces more polar metabolites that cannot diffuse across membranes and may therefore be actively transported.

4.2.1 Glutathione conjugation

Glutathione is a tripeptide of glycine, cysteine and glutamic acid formed by the action of glutamylcysteine synthetase (glutathione synthetase).The enzyme glutathione transferase catalyses the conjugation of modified xenobiotic with glutathione. A large number of drugs are conjugated by glutathione during metabolism. Inhibitors of the enzyme include Buthione - S - Sulfoxine. Two types of reactions are common with glutathione. The first is displacement of halogen, sulfate, sulfonate or phosphonitro group. The second is the addition of glutathione to activated double bond or strained ring system. Some of the conjugation reactions include:

- i. N - acetylbenzoquinoneimine, an activated metabolic of acetaminophen.
- ii. O - demethylation of organophosphates
- iii. Activation of trinitroglycine to oxidized glutathione (GSSG) dinitrolycerine and Nitric oxide (NO) a vasodilator.

Distinct cytosolic and microsomal glutathione -S transferases have been identified. In all, four classes of soluble glutathione S transferase are known to exist. The enzyme also exhibit genetic polymorphism and overexpression of the enzyme leads to e.g. resistance of insects to DDT, corn to atrazine and cancer cells to chemotherapy. The enzyme also participates in reduction of hydroperoxides and prostaglandin metabolism. Inducers of the enzyme include 3-methylcholanthrene, phenobarbital, corticosteroids and antioxidants. GST exhibit specie specificity; for example, aflatoxin B₁ is not carcinogenic in mice because it conjugates with glutathione very rapidly in them. Conjugates are excreted intact in bile or converted to mercapturic acid in kidney and excreted in urine in a reaction catalysed by glutamyl transpeptidase an aminopeptidase

4.2.2 Uridyl Diphosphate Glucuronyl transferase (UDPG transferase)

The reaction of UDP Glucuronyl transferase results in the formation of O-, N-, S and C- glucuronides. Six forms of this enzyme have been identified in the liver. The cofactor for its reaction is UDP - glucuronic acid. Inducers include phenobarbital, indoles, 3 methyl cholanthrene and cigarette smoke. Some of its substrate are dextrophan, methalidone, morphine, p-nitrophenol, valproic acid, non steroidal anti-inflammatory drugs, bilirubin and steroid hormones. In Crigglar Najjar syndrome; a severe form of bilirubinaemia, the enzyme is inactive hence inducers have no effect. However, in Gilbert's syndrome; a mild form of hyperbilirubinaemia, phenobarbital can increase the rate of bilirubin glucuronidation to normal functions . Other substrates of the enzymes include, morphine and chloramphenicol. Conjugates of UDPG transferase are excreted in bile and urine. An S-glucuronidase from the gut microflora cleaves the glucuronic acid, the glycone formed can be reabsorbed to undergo enterohepatic cycling. Other associated reactions include metabolic activation of 2, 6 dinitrotoluene by S-glucuronidase; whereby the latter removes glucuronic acid from N-glucuronide. The nitrogroup is then reduced by microbial N-reductase and the resultant hepatocarcinogen may be reabsorbed.

4.2.3 Sulfation

The sulfation process is catalysed by sulfotransferases which are widely distributed in the body. The co-factor for their reaction is 3¹ phosphoadenosine 5 phosphosulfate (PAPS). Their conjugation result in highly water soluble sulfate esters which are eliminated in urine and bile. Examples of substances for sulfation include phenols, catecholamines and hydroxylamines. Sulfation is a high affinity, low capacity pathway which is limited by low PAPS level. Acetaminophen is a drug that undergoes both sulfation and glucuronidation. At low doses, sulfation predominates but at high doses glucuronidation predominates. Four sulfotransferases in human liver cytosol have been identified to date. Aryl sulfatases in gut microflora remove sulfate groups in a sort of enterohepatic recycling. Sulfation decreases pharmacologic and toxic activities but can also cause activation of chemically unstable groups to carcinogens, for example hydroxylamine.

4.2.4 Methylation

This is a common minor pathway of xenobiotic biotransformation which generally decreases water solubility. Enzymes that catalyse the reactions are called methyltransferases and the co-factor is S-adenosylmethionine (SAM). In methylation, a methyl group (CH₃) is transferred to O, N, S or C molecule on the substrates which include phenols, catecholamines and heavy metals like Hg, As and Se. There are several methyltransferases in human tissues examples of which are phenol - O - methyltransferases, catechol - O - methyltransferase, O-methyl transferase and S-methyl transferase. Genetic polymorphism has been observed in thiopurine metabolism in a reaction catalysed by a member of this group of enzymes. High activity allele causes increased toxicity and low activity allele causes decreased efficacy.

4.2.5 Acetylation

This is the major route of biotransformation of aromatic amines and hydrazines. The reaction is catalysed by N - acetyl transferases (NAT) enzyme and the co factor acetyl-coenzyme-A. The process generally causes a decrease in water solubility. Substrates of the enzyme include sulfanilamide, isoniazid, dapsone and caffeine. In humans three phenotypic forms have been identified and these are slow, intermediate and rapid acetylators (Evans 1999, Murphy 2001). Various mutations of the enzyme result in decreased enzyme activity or stability. Like every other entity exhibiting genetic polymorphism, there are various ethnic and tribal variations. For example, 70% of slow acetylator status was observed in Middle Eastern population, 50% in Caucasians and 25% in Asians (Hiratsuka 2006, Evans and Relling 1989). Drug toxicities in slow acetylators include nerve damage from dapsone and bladder cancer in cigarette smokers due to increased levels of hydroxylamines (Ohno and Yamaguchi 2000, Evans 1999, Hiratsuka et al 2006).

4.2.6 Amino acid conjugation

This is an alternative pathway to glucuronidation. Amino acid conjugation operate with two principles. The first is that carboxylic group (COOH) group of a substrate is conjugated with an amino (NH₂) group of glycine, serine, glutamine requiring co enzyme-A activation. Notable example is the conjugation of benzoic acid with glycine to form hippuric acid. Benzoic acid is commonly used as a preservative in carbonated drinks. Alternatively aromatic NH₂ or NHOH conjugate with COOH of serine proteins requiring ATP activation. This metabolic pathway demonstrate specie specificity in accepting amino acid. For example, in mammals, benzoic acid is conjugated by glycine whereas for the same substrate in birds, ornithine acts. Dogs and cats utilize taurine to conjugate bile acids while other non human primates utilize glutamine for conjugation. Metabolic activation of serine or proline results in N-esters of hydroxylamine which are unstable and may degrade to reactive electrophile.

4.2.7 Ribonucleoside/nucleoside synthesis

This pathway is important for the activation of many purine and pyrimidine antimetabolites used in cancer chemotherapy

4.3 Phase III reactions

Phase III reactions can be described as a stage of further modification and excretion. Although many authors do not regard this phase as a distinct phase, current knowledge of efflux transporters tend to support the categorization. A common example is the processing of glutathione conjugates to acetylcysteine (mercapturic acid) conjugates (Boyland and Chassaud 1969). In this scenario, glutamate and glycine residing in the glutathione molecule are removed by gamma-glutamyltranspeptidase and dipeptidases. Finally, the cysteine residue in the conjugate is acetylated. The conjugates and their metabolites can then be excreted from cells in phase III of their metabolism with anionic groups acting as affinity taps for a variety of membrane transporters of the multidrug resistance protein (MRP) family (Homolya et al 2003). These proteins are members of the family of ATP-binding cassette transporters and can facilitate the ATP dependent transport of a large varieties of hydrophobic ions (Konig et al 1999) and thus act to remove phase II products to the extracellular medium, where they may be further metabolized and excreted (Commandeur et al 1995).

Since the discovery of permeability glycoprotein (P - glycoprotein) complex; an initial member of the ATP binding cassette (ABC) family of drug transporters by Juliano and Ling in 1976, (Juliano and Ling 1976) research into this group of proteins has been gaining wide interests. Some of the membrane transporters confer on the cells the ability to be resistant not only to the selective agent but also to a broad spectrum of structurally and functionally distinct antibiotics and alkaloids. This phenotypic character is referred to as multiple drug resistance (MDR). The MDR genotype/phenotype relationship is complex with over 18 ABC genes associated with human disease (Dean and Annilo 2005).

In addition to the ABC transporters, other important drug/xenobiotic transporters include the organic cation transporters of the SLC 22A super family and the organic anion transporting peptides of the SLC21 superfamily (Hagenbuch 2010). It is expected that with the growing interests in this phase of drug metabolism, investigations on the transcriptional regulatory control of this important transport system in target organs such as the liver, kidney and central nervous system will become intense in the next few decades (Omiecinski 2011).

5. Target genes of pharmacogenetics

About 20 kinds of enzymes are involved in metabolism of drugs. The cytochrome enzyme (CYP450) is regarded as the most important enzyme in drug metabolism. About 15 types of this group have been identified in human beings where they catalyse the biotransformation of many xenobiotics. Other enzymes include thiopurine methyl transferase (TMPT) which metabolizes 6- mercaptopurine and azathioprine, uridyl diphosphate glucuronyl transferase (UDGT) responsible for the conjugation of bilirubin, N - acetyltransferase (NAT2) responsible for metabolism of sulpha containing drugs and caffeine, catachol - o - methyl transferase (COMT) responsible for the metabolism of levodopa and dihydropyrimidine dehydrogenase (DPD) a rate limiting enzyme for the metabolism of 5 - fluorouracil (5 FU). Genetic polymorphism has been identified in many of these enzymes with varying degrees of drug response (Evans & Relling 1999, Furuta et al 2001, McAlpine et al 2001, Suzuki et al 2011) Of all the enzymes involved in drug metabolism, the cytochrome P450.(CYP450) is regarded as the most important because many drugs are substrates for the enzyme of the

group. CYP3A4, CYP2D6, CYP2C9, CYP219, CYP2B6 and CYP1A2 play the most critical role and account for more than 90% of drugs metabolized by P450 (Evans & Relling 1999). These enzymes have proven genetic polymorphism with associated drug responses (Hiratsuka et al 2002, Wong et al 2005, McAlpine et al 2011) and racial variations (Meyer 2004 & Suarez - Kurtz 2005). As discussed earlier, genetic polymorphism can manifest at both pharmacokinetic and pharmacodynamic levels whereby many genetic variants of respective enzymes, membrane transporters, receptors and ion channels have been detected (Wiesler et al 2008, Phipps - Green et al 2010 & Bouamar et al 2011)

5.1 Pharmacokinetic related genes

5.1.1 Genes of phase I reaction enzymes

Genetic variations have been observed particularly with CYP2D6, CYP2C9 and CYP2C19 genotypes (Ingelman - Sundberg 1999, Hiratsuka 2006) and therefore will be further elucidated.

- i. **CYP2D6:** With regards to this CYP subtype, 5 - 10% of Caucasians are poor metabolizers and have little enzyme activity and there is a distinct racial diversity in the frequency of the classes. About 50 genetic polymorphisms of CYP2D6 have been reported. The popular ones are CYP2D6*3, CYP2D6*4 and CYP2D6*5. More than 90% of PMs in Caucasians are ascribable to these three genetic polymorphisms (Daly et al 1996, & Suzuki et al 2011). In blacks, the common variant is CYP2D6*17 (Evans 1989)
- ii. **CYP2C9:** is involved in the metabolism of an epileptic agent; phenytoin and an anticoagulant; warfarin. To date, 12 CYP2C9 variants have been reported. For example in cases with phenytoin, oral clearance decreased to one quarter in subjects with homozygous polymorphism for CYP2C9*3 (Kidd et al 1999, Scodo et al 2002, Linder et al 2009). Many studies focused on CYP2C9 polymorphism to link variability with warfarin therapy. However only about 10% of dosage variation can be attributed to CYP2C9 polymorphism. It is thought that environmental and genetic factors can influence warfarin response therefore dosage is individualized based on sex, age, vitamin K intake, and disease states. Warfarin dosing can be challenging because of its narrow therapeutic index and the serious risk of bleeding in overdose. Warfarin exerts its anticoagulant effects by inhibiting hepatic vitamin K epoxide reductase; an enzyme involved in the vitamin K epoxide reductase complex sub unit 1 (VKORC1). The gene that encodes this enzyme has been identified and is believed to contribute to the variability in warfarin response (Scodo et al 2002, Aquilante et al 2006, Linder et al 2009, Guengerich 2001).
- iii. **The CYP2C19:** enzyme metabolizes many drugs including the proton pump inhibitor; citalopram (lelexa) diazepam (valium) and imipramine (toranil). More than 16 variants of CYP2C19 associated with deficient, reduced, normal or increased activity have been identified. The most common genotypic variants for poor metabolizers are CYP2C19*2 and CYP2C19*3. The CYP2C19*17 variant is associated with ultrarapid metabolizers and seems to be common in Swedes (18%), Ethiopians (18%) and Chinese (4%). (Sum et al 2006). The proton pump inhibitor omeprazole (prilosec) is primarily metabolized by CYP2C19 to its inactive metabolite 5 - hydroxyl-omeprazole. Individuals who are CYP2C19 poor metabolizers can have five fold higher blood concentrations of omeprazole and experience superior acid suppression and higher cure rate than the rest

of the population. Conversely, blood concentrations of omeprazole are predicted to be 40% lower in ultrarapid metabolizers than the rest of the population and are therefore at risk of therapeutic failure. (Sum et al 2006)

5.1.2 Genes of phase II reaction enzymes

N - Acetyl Transferase: Activities of human hepatic drug metabolizing enzymes was earlier been recognized as a cause of inter - individual variation in the metabolism of drugs. Therefore acetylation of many drugs like isoniazid caffeine, nitrozepam and sulphonamide exhibit genetic polymorphism. The N - acetyl transferase (NAT) enzyme is controlled by two genes, (NAT 1) and (NAT 2) of which NAT2 A and B are responsible for clinically significant metabolic polymorphism. (Heiss 1988, Grant et al 1990). Three phenotypes have been recognized with activities of NAT2 and these are rapid acetylator (RA), intermediate acetylator (IA) and slow acetylator (SA) status (Cranswick 2005). The frequency of slow acetylator in Caucasians and Negro populations is 50% and 10% in Oriental groups. (.Evans D.A 1989) Slow acetylator phenotype is preponderant among different Arab populations irrespective of geographical location of the country. (Woolhouse et al 1997, At- Moussa et al 2002 & Desoky et al 2005). Three genetic polymorphisms NAT2*5, NAT2*6, NAT2*7 but not NAT2*4 (wild type allele) are responsible for almost all SAs in the Japanese (Huang et al 2002) Drug induced hepatitis caused by isoniazid occurs often in SA than RA (Ohno et al 2000) and Type II diabetes SA may be predisposed to progression to renal complications than their RA counterparts (Banjoko & Akinlade 2010).

Thiopurine - S -Methyl Transferase (TPMT): Catalyses the S - Methylation of the thiopurine agents, azathioprine, mercaptopurine and thioguanine. These agents are commonly used for a diverse range of medical indications including leukaemia, rheumatic diseases and organ transplant. The principal cytotoxic mechanism of these agents is mediated via incorporation of thioguanine nucleotides (TGN) into DNA. Thiopurines are inactive prodrugs that require metabolism to thioguanine nucleotides to exert cytotoxicity. This activation is catalyzed by a multienzyme pathway which include hypoxanthine phosphoribosyl transeferase (HPRT), oxidation by xanthine oxidase (XO) or methylation by TPMT. During metabolism, hypoxanthine-guanine phosphoribosyl transferase (HPGRT) converts 6-mercaptopurine to cytotoxic6-thioguanine nucleotide analogues, while thiopurine methyl transferase (TPMT) inactivates 6-mercaptopurine through methylation to form 6 -methylmercaptopurine. However, TMPT is the major pathway and it is highly variable and polymorphic. More than 12 TPMT alleles have been identified. The most common ones are TPMT*2, TPMT*3A, TPMT*3C, with all three associated with lower enzyme activity attributable to enhanced rates of proteolysis of the variant proteins (Donnan et al 2011, Haghuid et al 2011, Guengerich 2001). Caucasian infant patients with acute myeloid leukaemia carrying TPMT*2, TPMT*3A, TPMT*3B, TPMT*3C showed significantly higher concentrations of the thiopurine intermediate metabolite 6-mercaptopurine in their red cells that requires dose reduction or termination of thiopurine administration due to adverse effects such as myelosuppression (Relling et al 1999, Tavadia et al 2001).

Dihydro Pyrimidine Dehydrogenase (DPD): Dihydro pyrimidine dehydrogenase (DPD) is a rate limiting enzyme for the metabolism of the anti cancer drug; 5 fluorouracil (5FU). With DPD being responsible for over 50% of its biotransformation. Other substrates for DPD are carmofur, tegafur and doxifluridine. The gene encoding for DPD is DPDY and about 13

genetic variants have been reported (McLeod et al 1998, Collie - Duguid et al 2000). The genetic variant that is responsible for decreased DPD activity has been reported to be DPYD*2 with a polymorphism at the splicing recognition site. (Wei et al 1996) Administration of 5 - FU to the patients with decreased enzyme activity results in adverse effects such as leukocytopenia, stomatitis, diarrhea, nausea and vomiting (Etienne et al 1994)

Glutathione - S - Transferase (GST): GSTs and the human genes encoding these enzymes are highly polymorphic with about 50% and 25% of most populations having a mutation or complete deletion of these gene respectively rendering them deficient or lacking the enzyme. Major racial and ethnic differences exist and GST M and GST T1 are the major genes. Other GSTs include GST P1 and GST*A which are also subject to genetic polymorphism and have been implicated in resistance to anti cancer drugs. High GST activity has been associated with decreased risk of haematologic relapse, central nervous system response and improved prednisolone response. (Commandeur et.al 1995) Inherited GST - P1 allele encoding for the 11e 105 Val. amino acid substitution, has been associated with improved overall breast cancer survival compared with patients who have at least one wild type GST P1 allele. Conversely in patients with acute myeloid leukaemia treated with high doses of combination therapy, the homozygous GST - T1 deletion is associated with a higher risk of toxic death during remission. (Arruda et. al 2001)

Uridyl Diphosphate Glucuronyl Transferase (UGT): The UDP - glucuronyl transferase (UGT) belongs to a super family of membrane bound proteins localized in the endoplasmic reticulum and are responsible for glucuronidation of many xenobiotics and endobiotics. The UGT genes have been classified into families and sub families based on evolutionary divergence with all known human UGT's being in the UGT1A 2A and 2B sub families. (Mackenzie et al 1997, Randominska - Pandya et al 1999, Tukey & Strassburg 2000). To date, polymorphism in UGT1A1 have been more studied extensively and seem to have clinical significance. The anticancer drug irinotecan is metabolized by the enzyme and polymorphism resembling condition seen in Gilbert's syndrome characterised by total lack of UGT enzyme due to deletion of the gene which leads to fifty fold reduction in irinotecan metabolism and such patients can be at risk of toxicity (Huang et al 2002 Desai et al 2003).

5.1.3 Phase III reactions: Transporter genes

Membrane transporters as mentioned earlier are heavily involved in drug clearance and alter drug disposition by actively transporting drugs between organs and tissues. Therefore polymorphisms in the genes encoding these proteins may have significant effects on the absorption, distribution, metabolism and excretion of xenobiotics and may alter the pharmacodynamics of these agents. Uptake transporters are required for the uptake of some drugs into the cell whereas efflux transporters are responsible for pumping some drugs out of cells or preventing them from ever getting in. Transporters are also thought to be involved in drug - drug reactions.

The most important families of the transporters include (i) ATP binding cassette (ABC) family whose genes include important members like the multi drug resistance gene also classified as ABCB 1 i.e. (ABCB1/MDR1), ABCC1, ABCC2, uric acid transporter (ABCG2), breast cancer resistance protein BCRP also classified ABCG2 i.e. (BCRP/ABCG2).(ii) The solute transporter superfamily (SLC) which include the organic anion transport polypeptide

(SLC 21/OATP), organic cation transporter SLC 22 OCT), zwitterion/cation transporter (OCTNs), folate transporter (SLC19A1), neurotransmitter transporter (SLC6, SLC17, & SLC18) and serotonin transporter (5HTT). Genetic polymorphism in drug transporter genes have increasingly been recognized as a possible mechanism accounting for variation in drug response because these transporters play important roles in the gastrointestinal absorption, biliary and renal elimination and distribution to target sites of their substrates. (Meier et al 2007, Shu et al 2007, Choi & Song 2008)

5.1.3.1 The ABC family genes

ABCB1: Refers to ATP binding cassette (ABC) sub family B member 1, or MDR 1 also designated cluster of differentiation (CD243) is the permeability glycoprotein (P - glycoprotein). ABC genes are divided into seven distinct sub families (ABC1, MDR/TAP, MRP, ALD, OABP, CaCW 20 and White). Members of the MDR/TAP sub-family are involved in multi drug resistance. The protein encoded by this gene is an ATP dependent drug efflux pump of xenobiotics with broad substrate specificity. It is responsible for decreased drug accumulation in multi drug resistant cells and often mediates the development of resistance to cancer cells (Viguie 1998). This protein also function as a transporter in the blood brain barrier (Viguie 1998, Phipps - Green et al 2010). It likely evolved as a defense mechanism against harmful substances. Some of the functions of protein encoded by ABCB 1 gene include regulation of distribution and bioavailability of drugs, removal of metabolites and xenobiotics from cells into urine, bile and intestinal lumen, transport of compounds out of the brain across the blood - brain barrier, digoxin uptake, prevention of ivermectin entry into the central nervous system and protection of hematopoietic cells from toxins (Dean 2002.) Mutation of ABCB1 gene will therefore result in disruption of these functions. The activity of the transporter can be determined by both membrane ATPase and cellular calcein assays. Drug resistance had been observed in M89T, L662R, R669 and S1141T variants of the gene and decreased drug efficacy in W1108R variant. In addition, genetic variation in ABCB1 has been associated with both toxicity and drug response in 5-Fluoro-uracil (Gonzalez - Haba et al 2011) and paclitaxel therapy (Henningson et al 2011).

ABCC 1 genes: Multidrug resistant protein 1 (MRP1) an ATP bounding cassette transporter encoded by ABCC 1 gene is expressed in many tissues and function as an efflux transporter for glutathione, glycine and sulphate conjugates as well as unconjugated substrates. An evaluation of single nucleotide polymorphism (SNP) revealed 7 mutations in the gene (Colombo et al 2005) while in a Japanese study, 86 genetic variants were identified (Fukushina - Uesaka et al 2007). Mutations in ABC transporters cause or contribute to many different Mendelian and complex disorders including adrenoleukodystrophy, cystic fibrosis and retinal degeneration (Dean & Annilo 2005). There has been no evidence of clinical significance in studies of the variants. (Colombo et al 2005, Pauli Magrus & Kroetz 2005 & Fukushina - Uesaka 2007).

ABCC2 gene: ABCC2 genes codes for the ABCC2 or MRP2 protein. (MRP2) is an export pump expressed at tissue barriers. Genetic variants 24 e>T, 1249Ca>A and 3972 > T had been observed and are thought to cause inter individual differences of bioavailability of various endogenous and exogenous compounds (Colombo et al 2005, Laechelt et al 2011). About 27

other variants have also been detected (Colombo et al 2005). A haplotype dependent influence on transport capacity of ABCC2 had been observed but seems to be mainly based on post transcriptional modifications rather than transport rates (Laechelt et al 2011).

The ABCG2 gene encodes an inhibitor of breast cancer resistance protein (BCRP) (ABCG2) protein, another member of the ABC transporter. The protein confers protection against the development of breast cancers. Evaluation of single nucleotide polymorphism identified 16 variants (Morisaki et al 2005, Colombo et al 2005). Genetic polymorphism in ABCG2 might alter the transport activity of some drugs causing therapy in drugs like irinotecan, to cause severe myelosuppression (Choi et al 2009, Hampras et al 2010). A polymorphism, C421A observed in human placenta is not a genetic variant acting in cis but is considered to influence the translational efficiency (Kobayeshi et al 2005). Another genetic variant (ABCG2) (rs 2231142, Q141K) encoding a uric acid transporter is associated with gout in diverse populations (Phipps - Green et al 2010)

5.1.3.2 Solute Carrier Superfamily: (SLC) Genes

The solute carrier (SLC) superfamily of transporters consists of more than 300 members subdivided into 47 families. They are expressed in most tissues but primarily in liver, lungs, kidney and intestine.

- i. **OATP/SLC21:** Organic anion transporter facilitates movement of anion across the cell membrane. OATP1B and OATP1B3 are human hepatocyte transporters that mediate the uptake of various endogenous and exogenous substrates. Genetic variation was observed in the SLCO1B1 and SLCO1B3 genes which encode OATP1B1 and OATP1B3 proteins. Forty nine (49) and 41 nucleotide sequence variants leading to 10 and 9 in SLCO1B1 and SLCO1B3 genes respectively were identified (Bowin et al 2010). Furthermore, in OATPC (SLC21A6) and OATP3 (SLC22A8) genes, polymorphism did not appear to be associated with changes in renal and tubular secretory clearance in the latter but the former was associated with differences in the disposition kinetics of pravastin. Individuals with the OATP - C*15 allele (ASP 130 Ala 174) had a reduced total and non renal clearance compared with those of OATPC*15 allele (ASP130Val 174) (Nishizato Y et al 2003).
- ii. **SLC 19A1 (Folate Transporter) member 1:** The SLC19A1 are the proteins responsible for the transport of folate. Transport of folate into the mammalian cells can occur via receptor mediated (folate receptor 1) or carrier mediated (SLC19A1) mechanism. Methotrexate is an antifolate chemotherapeutic agent that is actively transported by the carrier mediated uptake system. Individuals carrying a specific polymorphism of SLC19A1 gene i.e (C80GG) have lower levels of folate. (Whetsine 2003, Matherly et al 2007) and those carrying the C80AA genotype treated with methotrexate have higher levels of this antifolate chemotherapeutic agent. This underpins requirements for personalized dosing with the drug based on patients genotype
- iii. **OCT/SLC22:** Most solute carrier transporters are localized at either the basolateral or apical plasma membrane of polarized cells but some are also expressed in mitochondria and other organelles (Wojtal et al 2009). The genes encoding the three organic cation transporter isoforms OCT1, OCT2 and OCT 3 are clustered together on the long arm of chromosome 8 in humans and carry out functions of transport of small organic cations with different molecular structures independent of sodium gradient. These organic

cation substrate include drugs like metformin, procainamide and cimetidine as well as endogenous compounds like dopamine and norepinephrine and toxic substances like tetraethylammonium bromide (TEA) (Kang et al 2007).

5.2 Pharmacodynamic related genes

- i. **Receptors:** Many receptors are involved with several signaling pathways. Example of which is epidermal growth factor receptor(EGFR). This receptor has been implicated in the oncogenesis and progression of several solid tumours thereby being identified as a suitable target for anticancer treatment. Polymorphism has been observed in the development of cancer on dinucleotide repeats in intron 1 of the EGFR gene and this has correlated with EGFR expression with therapeutic implication for treatment with tyrosinase kinase inhibitor. A higher proportion of Asians do overexpress EGFR that may influence their responses to tyrosine kinase inhibitor (Tan et al 2004).
G-protein Coupled Receptors (GPCR):Over 50% of all drug targets have G-protein coupled receptors (GPCR). Genes of GPR has more coding regions than non - GPCR genes making them more important for pharmacological investigations.
GABAA Receptor Mutation in GABAA receptor ion channel may be a reason for the diminished protection of anti epileptic drugs.
Insulin Receptor(INSR): The receptor is important in the management of diabetes mellitus patients and mutation of the gene encoding the receptor will result in poor response particularly in type 2 diabetes.Mutation of the gene has also been suspected to contribute to genetic susceptibility to the polycystic ovarian syndrome(Siega et al2002)
B2 Receptor: B2 agonist; albuterol (Proventil) is used to control acute attacks of asthma and are prescribed as needed .Patients with β_2 receptor arginine genotype experience poor asthma control with frequent symptoms and a decreasing scores of poor exploratory volume compared with those with glycine genotype (Cowburn et al 1998, de Maat et al 1999). Seventeen (17%) of whites and 20% of blacks carry the arginine genotype (Wechsler et al 2005)
- ii. **Ion Channels:** Many genes encode for different ion channels including those of the central nervous system which include KCNJ10, KCNJ3, CLCN2, GABRA1, SCN1B and SCN1A. Some polymorphism of this channel has been linked to idiopathic generalized epilepsy (Lucarini et al 2007)
 The 5-HT₃ receptor is a ligand-gated ion channel composed of five subunits. To date, five different human subunits are known; 5-HT_{3A-E}, which are encoded by the serotonin receptor genes HTR3A, HTR3B, HTR3C, HTR3D and HTR3E, respectively. Functional receptors are pentameric complexes of diverse composition. Different receptor subtypes seem to be involved in chemotherapy-induced nausea and vomiting (CINV), irritable bowel syndrome and psychiatric disorders. 5-HTR3A and HTR3B polymorphisms may also contribute to the etiology of psychiatric disorders and serve as predictors in CINV and in the medical treatment of psychiatric patients. (Niesler et al 2008).
- iii. **Enzymes:** Polymorphism of pharmacokinetic enzymes no doubt influence the pharmacodynamics of drugs. However there are few enzymes that influence drugs at the point of actions one of these enzymes is the tyrosine kinase which modulate receptor activities. Therefore polymorphism in tyrosine kinase gene will affect drugs at the target point.

Another important enzyme of drug target is vitamin K epoxide reductase complex subunit 1 (VKORC1). This enzyme is the drug target for warfarin an anticoagulant with a narrow therapeutic window and with serious consequences of bleeding in the event of an overdose. Variation in maintenance dose of warfarin is largely attributable to genetic variants in the genes that encode the drug target VKORC1 the major metabolizing enzyme. The two genetic polymorphisms explain 30 - 40% of the total variation in those on therapy.

Angiotensin converting enzyme (ACE) genes encode for ACE, a target for ACE inhibitors which improves symptom and survival in cases of heart failure. Genetic polymorphism is suspected to be causing greater effects of the drug in Europeans than Afro-Americans. Pre-treatment genetic screening is therefore apt to improve therapy

- iv. **Neurotransmitter Transporters:** Neurotransmitter transporters namely SLC6, SLC17 and SLC18 families are primarily expressed in the neurons of the central and peripheral nervous system. These transporters are the sites of action of various drugs of abuse e.g cocaine, amphetamine and other clinically approved drugs like desipramine, reserpine, benztropine and tiagabine. Genetic variation in the SLC6, SLC17 and SLC18 encoding genes may result in altered expression and function of these proteins. In particular, antidepressants and antiepileptic drugs target these neurotransmitters as part of their primary mechanism of action. Therefore genetic variations may affect the efficacy of such drugs.

6. Pharmacogenetic testing

A genetic test is the analysis of human DNA, RNA chromosomes, proteins or certain metabolites in order to detect alterations related to a heritable disorder. This can be accomplished by directly examining the DNA or RNA that makes up a gene (Direct testing), looking at markers co-inherited with a disease causing gene (linkage testing), assaying certain metabolites (biochemical testing), or examining the chromosomes (cytogenetic testing). Although genetic testing shares some features common with other kinds of laboratory testing, it is however unique in many ways and therefore requires special consideration. Pharmacogenetic testing can therefore be defined as utilization of aforementioned genetic biomarkers related to drug metabolism and effects. A biomarker can be described as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes to a therapeutic intervention (EMEA 2006)

Methods of Pharmacogenetic testing depends on the biomarker to be assessed. These vary from simple spectrophotometric estimation of metabolites to DNA sequences, use of PCR and DNA probes, enzymes linked immunosorbent assay, cell culture, gel electrophoresis high performance liquid chromatography and DNA hybridization techniques. It is not uncommon to use combined techniques to study clinical relevance of pharmacogenetic testing.

Because information on pharmacogenetics is still evolving, there is a necessity for guidelines to be adopted for ethical reasons, economic considerations and patient benefit. Overall, the quest for pharmacogenetic information is likely to grow. As a matter of fact some drugs already carry labels addressing such.

6.1 European medicines agency guideline for pharmacogenetic testing

The guidelines for European Medicines Agency (EMA) was designed by the Agency's committee for Human Medicinal Products (CHMP). The rationale for this guidelines include standardization, data analysis, interpretation, evaluation of clinical relevance, ethical consideration and setting the stage for technical, scientific and regulatory issues. The guidelines addresses the following among other issues.

- i. Chosen design and rationale
- ii. the population selected for pharmacogenetic studies (i.e. species, age, gender and other variable related to the phenotype e.g. for human exposure ethnic group)
 - *In the target population or relevant animal model
 - *In the study population e.g. matched groups (responders/non responders, presence/absence of adverse events)
- iii. The population size selected for PG studies and a discussion on the power to detect an association in appropriate
- iv. Predictive values (positive and negative) of the PG biomarkers as per clinical trials experience
- v. Assumptions on clinical utility e.g. benefit In using predictive pharmacogenetics testing versus other predictive biomarkers, use of a pharmacogenetic biomarker as a segregation marker or as a stratification tool for a subpopulation in a general matching population.

6.2 Pharmacogenetic testing and clinical benefits

The overall purpose of PG testing is clinical benefits. Pharmacogenetic testing have resulted in some clinical benefit so far, some of which can be life saving. It was observed that roughly about 106,000 deaths and 2.2 million serious events caused by adverse drug reactions were reported yearly (Lazarom 1998) and 5 - 7% of hospital admissions in US and Europe lead to the withdrawal of 4% of new medicines with attendant financial loss. Since such drugs were linked to metabolizing enzymes with known polymorphism, prudence dictates suggestion of pharmacogenetic testing in indicated instances Pharmacogenetics testing is expectedly becoming commonly required particularly with drugs with low therapeutic window (Phillips et al 2001). However, the decision to use pharmacogenetic testing will be influenced by the relative costs of genotyping technologies and the cost of providing a treatment to a patient with an incompatible genotype.

Notable clinical benefits of pharmacogenetic testing have been observed in NAT2 genotyping for isoniazid treatment (Hiratsuka et al 2002, Weishilbom et al 2003, Gardiner and Begg 2006) and CYP2C19 genotyping for omeprazole treatment (Desta et al 2002).

Others are TPMT genotyping for 6-mercaptopurine and azathioprine treatment (Relling et al 1999, Gardener and Begg 2006) mtDNA A155G genotyping for aminoglycoside treatment (Cortopassi and Hatchin 1994, Usami et al 1999) CYP 2D6 genotyping for codeine treatment (Bradford 2002) Hepatitis C genotype for pegylated interferon - alpha - 2a or pegylated - interferon - alpha - 2b treatment. (Ingelman - Sundberg et al 2009, Thomas et al 2009) and Dihydropyrimidine dehydrogenase (DPI) testing for 5-fluoro-Uracil (5FU) treatment (Gionzalez and Fernandez -Salguero, 1995, McMurrough et al 1996, Wei et al 1996, Van Kuilenburg et al 1998).

There are currently requirements of pharmacogenetic testing of specific drugs before they can be prescribed and these include cetuximab, trastuzumab, maraviroc and dasatinib. In December 2007, the FDA recommended testing for HLA-B* 1502 allele in patients with Asian ancestry before initiating carbamazepine therapy because of high risk of developing carbamazepine induced Steven's Johnson syndrome (SSS) or toxic epidermal necrolysis.

Pharmacogenetic testing is also recommended for patients treated with warfarin, thiopurine, valproic acid, irinotecan, abacavir or rasburicase.

Currently, drug labels contain information on pharmacogenetic tests which are classified as test required, test recommended and for information only.

7. Conclusion

With the application of molecular biology methods and completion of the human genome projects and establishment of guidelines for pharmacogenetics practices and applications, it is expected that the interwoven field of pharmacogenetics and pharmacogenomics will revolutionise personalized medicine. Furthermore the field of predictive medicine is expected to receive a boost from pharmacogenetic information with attendant reduction in morbidity and mortality particularly from adverse drug reactions and therapeutic failure. With more intense researches and genotyping profiling, the challenges of standardization and interpretation of pharmacogenetic testing are apt to be overcome. It is worthy of note that currently some drug labels carry information on pharmacogenetic testing and requirements for therapeutic use. The promise of pharmacogenetics is therefore improvement of the overall health being of the patients.

8. References

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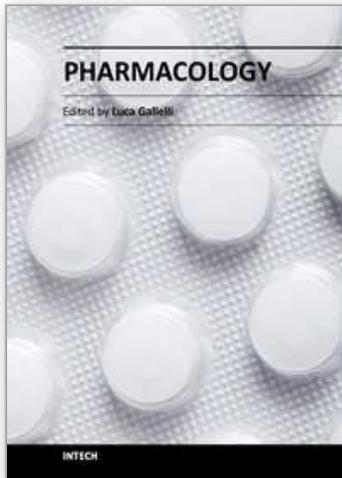
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