SPECIAL ARTICLE

PHARMACOGENETICS IN GHANA: REVIEWING THE EVIDENCE

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SUMMARY

Different clinical response of different patients to the same medicine has been recognised and documented since the 1950's. Variability in response of individuals to standard doses of drug therapy is important in clinical practice and can lead to therapeutic failures or adverse drug reactions. Pharmacogenetics seeks to identify individual genetic differences (polymorphisms) in drug absorption, metabolism, distribution and excretion that can affect the activity of a particular drug with the view of improving efficacy and reducing toxicity. Although knowledge of pharmacogenetics is being translated into clinical practice in the developed world, its applicability in the developing countries is low. Several factors account for this including the fact that there is very little pharmacogenetic information available in many indigenous African populations including Ghanaians. A number of genes including Cytochrome P450 (CYP) 2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, MDR1 and TPMT have been genotyped in the Ghanaian population since the completion of the Human genome project. There is however, an urgent need to increase pharmacogenetic research in Ghana to increase availability of data. Introducing Pharmacogenetics into the curriculum of Medical and Pharmacy training institutions will influence translating knowledge of pharmacogenetics into clinical practice. This will also equip health professionals with the skill to integrate genetic information into public health decision making.

Keywords: Pharmacogenetics, Polymorphisms, Cytochrome P450, Ghanaian, Population

INTRODUCTION

Different clinical response of different people to the same medicine has been recognised and documented since the 1950's with the observation of variable inherited clinical responses to drugs such as primaquine and isoniazid.[1] A drug may not be effective in some patients but may be more pharmacologically active or even toxic in other patients. This wide variability in the response of individuals to standard doses of drug therapy is an important problem in clinical practice where it can lead to therapeutic failures or adverse drug reactions (ADRs). In addition to non-genetic factors such as age, organ function, associated therapy and the nature of the disease causing variability in the effects of the medications, in many patients, genetic factors have been established to influence the use of medicines between individuals and remain stable throughout the life time of the patient. Recent research on drug metabolising enzymes (DMEs), drug transporters and drug receptors in relation to individual clinical response to the same drug dosage gave rise to the field of pharmacogenetics. Pharmacogenetics aims to identify polymorphisms in the genes that can affect the usefulness or efficacy of a particular drug, thereby increasing the number of patients responding to the drug and decreasing the number of individuals affected by ADRs. The ultimate aim of pharmacogenetics is to achieve individualised or tailored therapy. In addition to established medical practice of individualising medication doses based on renal or liver function, individualised or personalised medicine involves the use of both patient's genetic data and phenotypic information to choose therapy that will best maximise the efficacy of the drug and minimise adverse events.[2] Traditionally, two main methods have been used to determine the appropriate drug therapy for patients. The initial method is based on trial and error, where different first-line drugs are given until the most effective treatment is found. The second method is based on diagnoses; patients with the same disease receive the same treatment in a sort of "one size fits all" approach.[3] Despite improvements of this second approach over the trial and error, it is still fraught with challenges. Individualised therapy therefore seeks to minimise the problems associated with the "one size fits all" approach to drug therapy and to reduce cost for health care systems.

Although pharmacogenetics emerged several decades ago, only recently have the tools been in place for the field to flourish, partly led by the decoding of the human genome sequence and improving genotyping technologies.

The most common genetic variations within the human genome are single nucleotide polymorphisms (SNPs) accounting for nearly 90% of all these variations. SNPs play clinically important roles in enzyme activity and have been shown to either increase or decrease metabolism of many drugs. Variation in genes occurring in at least 1% of the population is termed as polymorphism.[4] Relevant polymorphisms associated with drug effects occur in genes encoding enzymes and transporters responsible for absorption, distribution, metabolism and excretion (ADME).[5]

DRUG DISPOSITION AND PHARMACOGENETICS

Drug Metabolism

Drug metabolism takes place in two phases classified as either phase I or phase II. Majority of enzymes involved in phase I metabolism belong to a large cytochrome P450 (CYP) family of drug metabolising enzymes that catalyse hydrolysis, reduction and oxidation reactions.[6] CYP is made up of 18 families which are divided into 44 subfamilies consisting of 57 genes.[2] CYP1, CYP2 and CYP3 families control the metabolism of most drugs. At least 75% of prescribed drugs on the market are metabolised by CYP3A, CYP2D6 and CYP2C.[7] Phase II enzymes are involved in reactions such as sulfation, acetylation conjugation and glucuronidation which may lead to the excretion of drugs by increasing the hydrophilicity of the substrate or deactivation of highly reactive substrates.[6] N-acetayltransferases 1 and 2 (NAT1 and NAT2), thiopurine S-methyltranferases (TPMT) and Uridine disphospahate glucoronosyltransferases (UGT) are the main phase II enzymes.

Drug Transporters

Drug transporters do play an important role in drug uptake, bioavailability, efficacy, toxicity and clearance.[8] Many drugs can be passively diffused across membranes, however, some have to be actively transported either by efflux and/or influx mechanism or through facilitated diffusion. There are two main types of transporters that affect ADME of drugs. These are the ATP-binding cassette (ABC) proteins and solute-linked carrier (SLC) proteins. Whereas the ABC transporters are efflux proteins,[8] the SLC proteins are influx transporters.[9] These drug transporters generally a have broad range of substrates and understanding genetic variations within the transporter genes is important for individualising therapy.

Drug Targets

Polymorphisms sometimes occur in drug targets and nuclear receptors which may not be directly involved in drug metabolism or transport but may be of equal pharmacogenomic importance because they may affect the patient's response to treatment. For example, SNPs found in epidermal growth factor receptor (EGFR) has been associated with better survival rates in patients with colorectal cancer and treated with irinotecan and cetuximab; which are anti epidermal growth factor receptor antibodies.[10] It is also known that pregnane X receptor (PXR), which is a nuclear receptor regulates the expression of many ADME genes, and therefore plays an important role in drug response.[11] The list of SNPs found in gene encoding drug metabolising enzymes, drug transporters and targets are growing. And these polymorphisms have been associated with drug effects in humans.[5]

Interethnic variations

Many clinically relevant polymorphisms have been demonstrated to vary between different populations.[12-14] For example, significant differences have been reported for *CYP2C9*2* and *CYP2C9*3* variant alleles at 3.3% and 2.3% respectively in African American populations.[15] In contrast, the *CYP2C9*2* variant allele was reported at 8-19% and the *CYP2C9*3* variant allele at 3.3-17% for populations defined as Caucasian.[13] *CYP2C9*2* variant allele was rarely seen in Asian populations while the *CYP2C9*3* variant allele was prevalent at 1.1-6.8% within the Asian populations.[13] Available data also suggests differences within defined ethnic groups.[16] For example, glutathione S-transferases (GST) which have been implicated in resistance of many anticancer agents have significantly lower frequencies for Tanzanian (0.16), South African (0.14), and Zimbabwean (0.24) as compared with Ghanaian populations (0.50).[17]

APPLICATIONS OF PHARMACOGENETICS DATA

Prescribing

There are many actual and potentially useful applications of pharmacogenetic. In the US, the Food and Drug Administration (FDA) has started adding pharmacogenetics information into prescribing information for a number of drugs including warfarin, carbamazepine and codeine, to assist prescribers achieve safe and rapid therapeutic doses.[18]

Pharmacogenetics testing

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is one of the pharmacogenetic tests that have been accepted as routine tests for a long time.

Patients with G6PD deficiency are at risk of haemolysis following the intake of certain medicines. Traditional laboratory tests and therapeutic drug monitoring assess the effects of these medicines.

Over the last 15 years, there has been an increase in the use of predictive genetic testing before prescribing some medicines. This testing has been recommended by the United States FDA, although this is not mandatory. These tests can help Clinicians and Pharmacists identify potential responders and/or non responders before treatment is started. The testing of SNPs of CYP2C9 and vitamin K epoxide reductase complex subunit 1 (VKORC1) is recommended before prescribing warfarin, a blood thinning agent. CYP2C9*2 which is a C to T mutation at position 430 results in 30% to 40% reduction in enzymatic activity of warfarin while VKORC1 is the site of action for warfarin and a G to A mutation at position -1639 within the promoter region of this gene has been associated with reduced enzyme activity. Patients with a combination of these variants may lead to a 'low dose' phenotype. Patients carrying the 'A' allele will require lower doses of warfarin to achieve therapeutic anti coagulation and avoid severe adverse reactions.[19]

Recent evaluation of a cohort of approximately 1500 Swedish patients confirmed that SNPs in VKORC1 and CYP2C9 can predict approximately 40% of dose variance, while non-genetic factors (age, sex, body mass index etc) jointly account for nearly 15%.[20] The use of this genetic information together with other clinical information is useful in determining the correct start dose of warfarin in patients.

Also in the US, prescribing guidance for drugs such as imatinib (Gleevec®) and trastuzumab (Herceptin®) now includes information on the use of predictive genetic tests that can assist prescribers to identify potential responders or those who are likely to develop ADRs. Trastuzumab is a drug designed to target an abnormal protein, HER2, which makes tumors grow. A third of breast cancers have a mutation in the gene that causes high HER2 levels. Patients with breast cancer that test positive for this mutation are likely to respond well to trastuzumab, shrinking the tumors, slowing down the disease progression and increasing survival.

Pharmacogenetics testing has increased over the years in UK. There is a routine testing for TPMT before prescribing thiopurine drugs such as Mercaptopurine and Azathiopurine in leukemia treatment. Patients with weakened version of TMPT cannot receive the regular dosage of the thiopurine drugs which interfere with DNA replication in rapidly dividing cells. TPMT deficiency patients need to be identified to prevent severe to fatal homological toxicity.

HLA-B*5701 genotyping is also recommended before the use of Abacavir to prevent drug related hypersensitivity. HLA-B*5701 testing before Abacavir use has been shown to be feasible, cost effective and saves lives.[21] Pharmacogenetics tests are now being used to supplement traditionally established diagnostic measurement of biomarkers in the blood to assist with dose determination and choice of medication. Clinical benefits of pharmacogenetics testing depend on the illness, treatment goals, cost and benefits.

Pharmacogenetics has the potential of facilitating drug discovery and allowing drug manufacturers to produce a therapy targeted at specific diseases using genome targets. Previously failed drugs can also be revived as they are matched with subgroup of patients with specific polymorphisms.

Whereas pharmacogenetics is being used in the developed world, the same cannot be said of Africa including Ghana. There is a fair amount of genotype data from published literature on the Ghanaian population compared to other African countries (Tables 1). This review seeks to examine these studies and their potential implications for drug therapy in Ghana.

PHARMACOGENETICS IN GHANA

Over the past decade, a significant amount of pharmacogenetic research has been carried out on the Ghanaian population by various research groups. The genes of interest for these researchers were based on their involvement in ADME of essential drugs. These genes have been listed in Table 1 and Table 2.

Interest in the area of pharmacogenetics in Ghana started with a study on the metabolism of pro- drugs Sparteine and Debrisoquine. The authors observed pronounced differences in the metabolism of these drugs between African and Caucasian populations.[22, 23] This observation of higher metabolic ratio values among Africans was attributed to mutations within the CYP2D6 gene. CYP2D6*17 allele which encodes the enzyme with lower catalytic function.[24] was found at a frequency of 26% among Ghanaian population.[25] The authors also observed the existence of other variants of CYP2D6*1 allele among Ghanaians which also encodes CYP2D6 enzymes with reduced catalytic capacity compared to Caucasian.[25] CYP2D6 enzymes are involved in the metabolism of several drugs and decrease expression of this enzyme may have implications for use of drugs such as chlorpromazine, codeine, fluoxetine, imipramine morphine, propranolol and ta-

moxifen found in Standard treatment guidelines (STG) and the essential medicines list (EML) of Ghana.

Other enzymes of pharmacogenetic importance have also been studied among Ghanaians. These include CYP3A4/5, CYP2C8, CYP2A6, CYP2B6, CYP2C9 CYP2C19 and CYP2D6. CYP3A4/5 enzymes have been reported to be expressed with high inter individual variability.[26] *CYP3A4*1B* variant, associated with a decrease in enzymatic activity of CYP3A4 gene, has been reported between 69% and 82% among Ghanaians (Table 1). *CYP3A4*1B* variant has also been associated with various diseases such as breast and prostate cancer.[27], treatment related leukaemia.[28] Men who are homozygote carriers of the *CYP3A4*1B* variant are at more significant risk of prostate cancer at a higher stage and grade.[27, 28]

Table 1: Allele frequencies of Phase I genes in Ghanaian population

Gene	Allele	No	Variant	Reference
Phase I enzymes				
CYP2A6	*1A *1B *4A *9 *9B *17	105 65 	0.81 0.12 0.019 0.057 0.05 0.12	29 30
CYP2B6	*6 516T 983C	 65 	 0.45 0.04	31 30
CYP2C8	*2	103 - 203	0.17 - 0.179	32-34
CYP2C9	*11 *11	195 195	0.02 0.02	32 32
CYP2C19	*2 *2	828 169	0.17 0.06	16 32
CYP2D6	*4 *5 *10 *17 *2 *2xN *4 *5 *10 *17 *2B	20 201 	0.10 0.05 0.125 0.15 0.11 0.16 0.7 0.6 0.31 0.28 0.03	35 25
CYP3A4	*1B *1B *1B *1B *1B	203 100 118 95 787	0.72 0.69 0.81 0.82 0.78	36 37 38 39 16
CYP3A5	*3C *5C	864 95	0.14 0.12	16 39
	*6	95	0.16	

*CYP2C8*2* and *CYP2C8*3* variants have been associated with reduced enzymatic activity. However, only the *CYP2C8*2* variant has been reported in all the studies in Ghana (Table 1). *CYP2C8*2* variant may have the potential implication for the metabolism of a number of therapeutic agents, such as amodiaquine, dapsone, ibuprofen and morphine on the GEML. *CYP2C8*2* variant has been associated with a decrease in enzymatic activity which leaves more Amodiaquine to turn into a toxic metabolite. These metabolites can cause leucopenia and liver toxicities as side effects.

Table 2: Allele frequencies of Phase II genes in Ghanaian population

Gene	Allele	No	Variant	Reference
Phase II enzymes				
COMT	1947A	195	0.06	40
TPMT	*3C *3C *8 719G	217 116 863	0.148 0.025 0.034 0.065	41 42 16
UGT1A1	-3156A	853	0.34	16
NAT2	*6 *14	850 800	0.27 0.10	16 16
GSTP1	I105V	837	0.50	16
Transporters				
ABCB1	3435T 3435T 3435T 3435T	194 206 172 861	0.11 0.17 0.17 0.12	36 43 44 16
ABCG2	Q141K	919	0.01	16
SDR5A2		129	0.19	38
Others				
TYMS	1494del	799	0.44	16
TNFα	-238A	850	0.02	16
SGK1	I6C E8T	112	0.317 0.045	45

Two other phase 1 enzymes, CYP2A6 and CYP2B6, have been associated with efavirenz plasma concentration in HIV-infected patients. *CYP2A6*9B* and

*CYP2A6*17* have been identified as slow metaboliser variants.[46,47] and have been reported at a frequency of 5% and 12% respectively in Ghana (Table 1). CYP2B6 c.516G>T mutation has also been associated with reduced enzyme activity and higher efavirenz concentration.[48,49] This has also been detected in 45% of the Ghanaian population (Table 1). It was suggested by the authors that genotyping CYP2A6 and CYP2B6 enzymes may be useful in accurately predicting efavirenz concentration in HIV-infected patients which will enhance treatment.

TPMT is one of the phase II enzymes that alter drug response in humans. *TPMT*2*, *TPMT*3A* and *TPMT*3C* are common variants associated with decreased enzyme activity.[50] *TPMT*3C* was detected between 6.5% and 14.8% among the Ghanaian population[16, 41, 42] (Table 2). Patients who inherit two non-functional TPMT alleles will accumulate excessive amounts of the metabolites and can suffer severe to fatal toxicity from drugs such as azathiopurine and 6-mecaptopurine therapy.

IMPLICATIONS FOR GHANA

An ideal situation will be to genotype each individual for relevant genetic variants before treatment to maximise the outcome of therapeutics. However, due to financial constraints in developing countries such as Ghana, this option remains unfeasible at the moment. Allele frequency data from a national population can be used as an alternative for individual genotyping. Although this option may not be the best, it is the most practicable and technologically feasible option at the moment.

Pharmacogenetic data can be used in a variety of ways. It can be used retrospectively to investigate ADRs or the basis of drug resistance. A polymorphic analysis of ADR cases or drug resistant cases can be compared with a population pharmacogenetic profile to determine if there are significant genetic differences between the ADR patients and the general population. Based on the results from such studies, drug dosages can be adjusted to achieve a better therapeutic outcome or the treatment plan for the patient changed.

Knowledge of the genetic profile of a population can also be a useful guide in making National policy decisions for example adding new drugs to the Essential Medicines List. New drugs can be evaluated in light of the scope and profile of the pharmacogenetic polymorphisms of the drug ADME genes. Treatment policy decisions can be made based on the potential risk of ADRs, therapeutic benefits of the drug and the availability of viable alternative treatments.

Integrating pharmacogenetics data into patient management plan requires that all healthcare professionals (Doctors, Pharmacists, Nurses and laboratory technicians) be familiar with the tests available, the interpretation of pharmacogenetic data and be confident enough to use it. Currently healthcare professionals in Ghana and other health workers at the Ghana Health Service may not be aware of the availability of some these pharmacogenetic information on the Ghanaian population.

THE WAY FORWARD

The benefits of pharmacogenetics in individualising patient care has been shown, however, its deployment is beset with considerable challenges. In view of competing demands in the healthcare, it is not easy to allocate huge resources to this important field. The need to prioritise which drugs or disease areas would benefit most is important. Pharmacogenetics has the potential of providing opportunities for improving drug efficacy and safety. However, some areas of the world especially indigenous African populations have scarce information in the current pharmacogenetics research[51, 52]. There is the need to increase research in the area of pharmacogenetics for it to make a meaningful impact on genetically tailored treatment in Ghana. Each country has to determine their own national genotype data since it has been established that interethnic variations do exist and African populations do have relatively high genetic diversity.

Training institutions of health professionals have to include pharmacogenetics in their curriculum at undergraduate and post graduate levels. Pharmacogenetics can also be included in the continuous education programmes for Clinicians and Pharmacists who are already practicing. This will adequately equip these health professionals in public health, national formulary decisions, applied genetics, medicine, pharmacy, and related disciplines on the need to integrate of genetic information into public health decision making and provide guidelines for medical prioritization using pharmacogenetic information.

To address some of these scarcity of allele frequency data on clinically relevant SNPs, International HapMap project (www.hapmap.org) and the Pharmacogenetics for Every Nation Initiative (www.pgeni.com) are setting the pace by including African samples in their analysis.

CONCLUSION

Ghana is one of the few countries in Africa whose population has been genotyped to some degree. However, there is the need to increase research in the area of pharmacogenetics. Available pharmacogenetic data has also not been compiled into a database for easy access by health professionals. Relevant pharmacogenetic information available in Ghana has to be considered when making decisions for the national drug formulary.

For healthcare professionals to appreciate the value of pharmacogenetic tests and interpretation of the results, all schools of Medicine and Pharmacy would have to integrate pharmacogenetics into their curriculum if not already present. Including a pharmacogenetics course in the continuing education of the health professionals already practicing will also help in creating pharmacogenetics awareness. Pharmacogenetics has made significant progress in the developed world. We in Ghana need to prepare to take advantage of the promises which the future holds for the country, doctors, pharmacists and patients by maximising the benefits of drug use and experiencing fewer adverse events

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