Pharmacogenetics: the path to personalized prescribing

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The fact that different patients may show dissimilar responses to the same drug, has been recognised for several years, and many variables, such as age, gender and body weight have been identified to contribute to this observation. The last half century has seen a rise in research concerning a new variable – genetic variation – which has been recognised to offer a major contribution to this phenomenon. Pharmacogenetics research has today established itself as an important arm of pharmacology, and has key applications in drug development and clinical therapeutics. The advent of high throughput methodologies coupled with new data derived from the human genome sequencing project, has helped to powerfully mobilise the developmental pace of this research work, and to introduce the concept of genome-wide pharmacogenetic studies, or *pharmacogenomics*. The eventual development of pharmacogenetic tests, able to identify patients who are most likely to adequately respond to specific therapies from those who are not, will be a landmark in the history of therapeutics, and coupled to the development of new drugs for specific pharmacogenetically-stratified patient populations, will provide a markedly enhanced toolkit for the optimization of the benefit-risk ratio in prescribing.

Introduction

Pharmacogenetics and pharmacogenomics are terms which are today soundly entrenched within pharmacological and pharmaceutical literature. The term *pharmacogenetics* was used for the first time by Friedrich Vogel in 1959[1], who coined it to describe the influence of genetic factors on the response to drugs. In the following years, the number of peer-reviewed scientific publications dealing with this area, started to show a steady rise, while the last 10 years has suddenly seen an exponential increase. This is a reflection of the research explosion which has recently been occurring in this area. A cursory look at the Medical Subject Heading (MeSH) fields of the National Library of Medicine Pubmed database, which to-date indexes over 11 million articles[2] gives evidence to this (Fig. 1). Rubin and his workgroup recently reported on their use of an automated system, based on an algorithm designed to specifically data-mine biomedical literature databases for pharmacogenetics knowledge in order to extract specific reference lists which are more focused to a specific topic, than manual Boolean operator-linked multiple field search methods can provide.[2]

This article will review the relevance of this research area, and its implications to pharmacological therapeutics.

Pharmacogenetics and pharmacogenomics

The advent of novel research technologies, allowing high throughput screening of large numbers of biomolecules has ushered us into the –omics era of new methodologies such as *transcriptomics* (the large-scale study of the cell transcriptosome), *metabolomics* (the large-scale study of metabolite profiles), *proteomics* (the large-scale study of proteins) and in 1995, *pharmacogenomics*.[3] Unfortunately, throughout the recent past, *pharmacogenomics* has often been used interchangeably with *pharmacogenetics*, blurring the large-scale gene-study implications inferred by the former term. The Nuffield Council on Bioethics, UK, defines pharmacogenetics as "the study of the effects of genetic differences between individuals in their response to medicines" and pharmacogenomics as "the examination

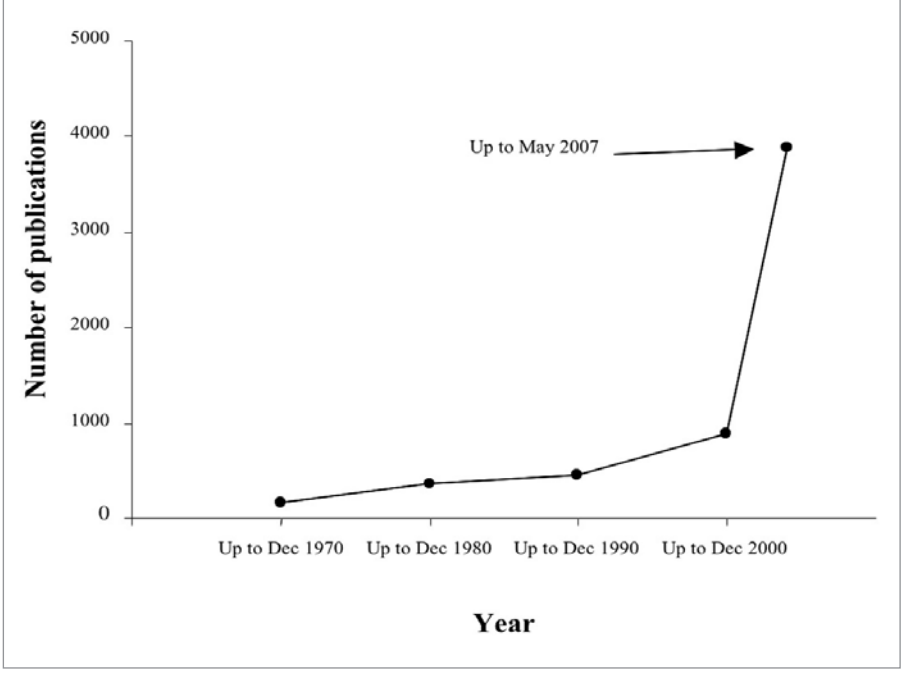
of whole genomes or substantial numbers of genes in order, for example, to identify putative targets for medicines or to identify large-scale differences in the patterns of gene expression in response to chemical compounds."[4] The National Centre for Biotechnology Information (NCBI), USA, uses a similar distinction between the terms and defines pharmacogenetics as "the study of inherited differences (variation) in drug metabolism and response" and pharmacogenomics as "the general study of all of the many different genes that determine drug behaviour."[5] Table 1 lists various definitions as given by different official bodies, and it is evident, that even now, the distinction between both terms is not completely exclusive. Indeed, the International Union of Basic and Clinical Pharmacology (IUPHAR) states that "...there is no internationally accepted consensus depicting any semantic differences between pharmacogenetics and pharmacogenomics."[8] However, while *pharmacogenetics* has been with us since Vogel's first use of the term, pharmacogenomic research is mainly the fruit of the post-human genome sequencing era.

Pharmacogenetically-influenced drug responses

Inter-individual variations in drug responses may be influenced by a plethora of variables. These factors do not only influence therapeutic drug responses such as the degrees of efficacy and potency, but also the propensity to develop specific adverse effects. Some of these variables such as age, gender and body weight are well known, and are regularly factored into algorithms used for drug dosing. Pharmacogenetic profiling fills in the gap for another variable, and its relevance is particularly accentuated in those instances where it is a primary factor in influencing patient-to-patient variability. In its simplest form, pharmacogenetic data may be used to identify patients in whom a drug shows adequate efficacy, from patients in whom the same drug does not. This information may be used to assist the selection of which drug to administer to which patient, and to establish a relevant dosing schedule; in other words, to administer the right drug to the right patient at the right dose. Table 2 shows a sample list of genes for which specific variants have been shown to exert an influence on particular drug responses. Changes in drug responses may be influenced by one particular genetic polymorphism alone, but more commonly, pharmacogenetically-influenced variations are the result of several gene variants interacting together and also with environmental factors, and this is one of the major challenges faced by researchers today.[11,12]

Adverse drug reactions (ADRs) are estimated to be responsible for up to 7% of hospital admissions in the UK, with an estimated annual direct cost amounting to EUR 400 million.[13-15] In addition, 10% of drugs which had been approved by the FDA between 1975 and 1999 were removed from the US market due to the appearance of new ADRs which were identified during the post-marketing surveillance stage. Besides known factors such as age, renal and liver function, disease status and lifestyle variables such as tobacco and alcohol consumption, genetic factors are also recognised to significantly modify the risk for development of ADRs.[16] The classical example consists of genetic variation which decreases the activity of a drug metabolizing enzyme, resulting in a "slow-metabolizer" phenotype for a particular drug or group of drugs. Such patients exhibit higher blood concentrations when administered the drug at conventional doses, since they take longer to metabolize it, often resulting in gradual accumulation to toxic levels. Primary amongst the enzyme systems which have been studied in this respect, are the cytochrome P450 (CYP) group, of which there are more than 30 gene families in humans. One of the most studied CYP enzymes is CYP2D6 which is responsible for the metabolism of more than 100 drugs, which derive from diverse pharmacological groups. Examples of these include propranolol, flecainide, amitriptyline, nortriptyline, clomipramine, fluoxetine, haloperidol, thioridazine, codeine, debrisoquine, dextromethorphan, phenformin and tramadol. The CYP2D6 gene exhibits significant variability, and more than 75 alleles have been identified to date.[17] Some of these produce an enzyme with normal activity, some alleles produce an enzyme with high activity and some

Figure 1: The number of publications retrieved using a Pubmed search (http://www.pubmed.gov) for the terms "pharmacogenetics OR pharmacogenomics" in the MeSH field. The data shown is cumulative, at intervals of 1 decade, and highlights the explosion in research publications which occurred since the start of this millennium. (MeSH: Medical Subject Headings)



produce a low-activity CYP2D6 enzyme. In addition, individuals with multiple copies of functional CYP2D6 genes have been described, with resultant high enzyme expression and high CYP2D6 metabolic activity. Patients may be classified as poor, normal, rapid or ultrarapid metabolisers with respect to CYP2D6 metabolic activity, and this may have significant clinical implications. For example, the doses of nortriptyline required to attain a therapeutic response, may vary by over 20-fold between poor and ultrarapid CYP2D6 metabolizers. If poor metabolisers are administered "normal" doses, they are more likely to develop ADRs due to slow elimination with consequential potential accumulation, while conversely, ultrarapid metabolisers may not show any therapeutic response at all.[18]

Other pharmacogenetically-related ADRs may be related to membrane transporter proteins. The Adenosine triphosphate-Binding Cassette (ABC) genes code for a number of transmembrane proteins which are responsible for translocating drugs across extra- and intracellular cell membranes. Examples of such drugs include anticancer drugs, digoxin, immunosuppressants and some antiretroviral agents. Digoxin bioavailability, for example, is known to be influenced by variants of the ABCB1 gene.[19]

Drug hypersensitivity may also be influenced by pharmacogenetic variation. For example, abacavir, an anti-retroviral drug used in the management of HIV infection, exhibits a five-fold greater risk of hypersensitivity in patients with the HLA-B*5701 allele, and some medical centres in the USA are today HLA-typing patients before prescribing the drug.[20]

Personalized medicine and drug development

The ultimate goal of pharmacogenetics and pharmacogenomics research is to enable prescribers to utilize a patient's genetic data (pharmacogenetic profile) in order to enable the selection of *the* drug from the applicable therapeutic repertoire, which would exhibit the greatest efficacy and the least adverse effects in that particular patient, and the prescription of that drug at a *dose* that is appropriate for that patient; that is, *genotype-guided prescribing,* or as it has been more universally termed, *personalized medicine.*[20] This goal, although often considered by the practitioner community to still be a distant vision, is advancing rapidly, and pharmaceutical companies are today already integrating pharmacogenomic aspects into the drug development process.

This integration raises issues of a commercial interest. The "niching" of drugs to selected genetic groups may restrict their potential markets, and may appear to disadvantage pharmaceutical companies. However, the identification, during drug development, of a genetically-determined target population in which the drug offers superior benefit than currently available medication, may potentially rescue an otherwise unmarketable drug into a marketable one. Additionally, phase III trials of such a drug, may fail to indicate its superiority, unless they are performed in a genetically-selected population.[21]

For what drugs may personalized medicine be expected to be available first? Several variables may influence this, but the following may offer some insight:

a) drugs which show a high inter-individual variation in efficacy and/or potency.
b) drugs which possess a narrow therapeutic window and have to be used in conjunction with therapeutic drug monitoring. Both the starting dose, as well as subsequent dosage adjustments may be made with greater accuracy, if the patient's pharmacogenetic profile is included into the equation.
c) drugs which demonstrate a clinical effect only several days after initiation of administration. The risk of having to substitute such a prescribed drug for another due to ineffective clinical outcome, or of having to alter the dose of the same drug, several days after therapy has been initiated, may be

Table 1: The terms *pharmacogenetics* and *pharmacogenomics* as defined by different official organisations

Nuffield Council on Bioethics, UK[4]	
Pharmacogenetics	The study of the effects of genetic differences between individuals in their response to medicines.
Pharmacogenomics	The examination of whole genomes or substantial numbers of genes in order, for example, to identify putative targets for medicines or to identify large-scale differences in the patterns of gene expression in response to chemical compounds.
The National Centre for Biotechnology Information (NCBI), USA[5]	
Pharmacogenetics	The study of inherited differences (variation) in drug metabolism and response.
Pharmacogenomics	The general study of all of the many different genes that determine drug behaviour.
Food and Drug Administration (FDA), USA[6]	
Pharmacogenetics	The influence of variations in DNA sequence on drug response
Pharmacogenomics	The investigation of variations of DNA and RNA characteristics as related to drug response.
European Medicines Agency (EMEA), UK[7]	
Pharmacogenetics	The study of interindividual variations in DNA sequence related to drug response.
Pharmacogenomics	The study of the variability of the expression of individual genes relevant to disease susceptibility as well as drug response at cellular, tissue, individual or population level. The term is broadly applicable to drug design, discovery, and clinical development.
International Union of Basic and Clinical Pharmacology (IUPHAR), USA[8]	
Pharmacogenetics	The science about how heritability affects the response to drugs.
Pharmacogenomics	How the systematic identification of all the human genes, their products, interindividual variation, intraindividual variation in expression and function over time may be used both to predict the right treatment in individual patients and to design new drugs.

minimized if the genetic influence on the efficacy and dose-requirement of the drug can be predicted for a particular patient. This is especially important in diseases where optimum therapy has to be instituted as early as possible in order to optimize clinical prognosis.

d) drugs which are known to have the propensity to exhibit serious adverse effects, even if the incidence of such effects is low.

Regulatory issues

Currently both the Food and Drug Administration (FDA), as well as the European Medicines Agency (EMEA) regulations do not require pharmacogenetic data to be submitted as part of a new drug licensing application. However, the FDA is asking pharmaceutical companies conducting drug development programs to consider providing pharmacogenomic data to the Agency on a voluntary basis. In this respect, the FDA has recently established an Interdisciplinary Pharmacogenomic Review Group (IPRG) to review voluntary pharmacogenomic data submissions (VGDSs) and provide feedback to submitters, provide guidance to the relevant FDA reviewing divisions and work on ongoing pharmacogenomic data submission policy development.[22]

At the same time, the EMEA Committee for Medicinal Products for Human Use (CHMP) established the Pharmacogenetics Working Party (PgWP), which currently meets four times a year in London and of which Malta is currently a member. The primary PgWP's mandate is to provide for a technical multidisciplinary forum to the CHMP pharmacogenetics experts network and applicants. It accomplishes this by hosting workshops and briefing meetings to share experience on pharmacogenetics-related issues, preparing, reviewing and updating guidelines for the preparation and assessment of the pharmacogenetics parts of regulatory submissions, providing advice to the CHMP on general and product-specific matters relating to pharmacogenetics and liaising with interested parties and providing advice, through the CHMP, to the European Commission on pharmacogenetics-related issues.[23] Since their inception, The PgWP and the IPRG have established collaborative links between themselves, and have already had the opportunities to provide joint advice to pharmaceutical companies.

Table 2: A non-exhaustive list of genes for which specific variants have been shown to have clinical implications for specific pharmacological therapies. This list has been compiled from reviews by Frueh and Gurwitz (2004),[9] and Evans and Relling (2004).[10]

Gene	Drug affected	Effect
CYP2C9	warfarin	Increased anticoagulant effects of warfarin
	tolbutamide	Hypoglycemia
	phenytoin	Toxicity
CYP2C19	Omeprazole	Peptic ulcer response to omeprazole
	Diazepam	Prolonged sedation, toxicity
CYP2D6	Nortriptyline, fluoxetine	Increased antidepressant toxicity
	codeine	Decreased codeine analgesia
CYP3A4/3A5/3A7	tacrolimus	Decreased efficacy of tacrolimus in organ transplantation
Dihydropyrimidine dehydrogenase	Fluorouracil	Increased neurotoxicity
Glutathione transferase GSTM1, M3, T1	Several anticancer agents	Increased response in breast cancer, more toxicity and poorer outcome in acute myeloid leukaemia
Thiopurine methyltransferase	Mercaptopurine, thioguanine, azathioprine	Increased haematopoietic toxicity
UGT1A1	Irinotecan	Increased gastrointestinal toxicity
ABCB1 (MDR-1)	Digoxin, HIV protease inhibitors	Decreased digoxin bioavailability Decreased CD4 response in HIV-infected patients,
$ß_2$-adrenoceptor	$ß_2$-adrenergic agonists (eg. salbutamol, terbutaline)	Decreased bronchodilation response
$ß_1$-adrenoceptor	$ß_1$-adrenergic antagonists	Decreased cardiovascular response
Gs_α subunit	$ß_1$-adrenergic antagonists	Decreased antihypertensive effect
ALOX5	Leukotriene receptor antagonists	Less improvement in FEV_1 (forced expiratory volume in 1 second)
Serotonin transporter (5-HTT)	fluoxetine and other anti-depressants	Decreased antidepressant response
Human leukocyte antigen (HLA)	Abacavir	Increased liklihood of hypersensitivity
N-Acetyl-transferase 2 (NAT2)	Isoniazid	Exaggerated drug response, toxic metabolites
Sulfonylurea receptor	Tolbutamide	Decreased insulin response

Interpretation and ethical aspects

The concept of pharmacogenetic testing carries significant ethical implications. Issues which may be affected include the design of research studies and clinical trials, the pricing of medicines, and the accessibility of pharmacogenetic information by third parties.[24] In 2003, the Nuffield Council on Bioethics, London, published a 132-page document[4] which identified and presented issues relating to the correct use and interpretation of pharmacogenetic information and the implications of population stratification based on this data. The following highlights some of the main issues discussed in this document.

Development of new medicines

The report encourages regulators to promote the collection and storage of samples derived from clinical trials such that they could be subjected to pharmacogenetic analysis either during the trial, or later. This approach could permit re-analysis of data based on pharmacogenetic profile stratification,

and could identify smaller groups in whom the trial results are more robust, and who would be better candidates for the medicine being tested. The issue of population stratification presents as a double-edged blade in terms of commercial development. Some potentially valuable new medicines may not be developed if, as a result of genetic stratification, the number of patients who would benefit is too small for the venture to be commercially viable. However, stratification may also enable some medicines to be developed that would otherwise have failed because the subgroup in which the medicine is effective can now be distinguished.

Improvement of existing medicines

Pharmacogenetics could be used to improve the prescribing of existing medicines, for example either by predicting individualized dosing and thus reducing the incidence of adverse reactions, or by restricting prescription to those patients likely to benefit. Some potential examples include clozapine and warfarin for which sufficient data exists to make these strong candidates. The Nuffield Council recommended that efforts should be made to encourage pharmacogenetic research on existing medicines, where there is reason to believe that such research could significantly improve efficacy or safety, and that funding and support should be made available within the public sector and public–private partnerships should be encouraged.

Withdrawn medicines

The most common reason for medicines to be withdrawn from the market once they have been licensed is the subsequent occurrence of serious adverse reactions, which were either unsuspected at the time of marketing authorisation or occur more frequently than was expected. If some adverse reactions can be explained by genetic variation, pharmacogenetic analysis might enable some withdrawn medicines to be reinstated, by restricting their licensed used to a genetically-defined group of patients. This may be especially relevant in cases where there is currently no alternative treatment available to replace a withdrawn medicine.

Key Points

- The major aim of pharmacogenetic and pharmacogenomic research is to enable prescribers to administer the right drug to the right patient at the right dose, i.e. to enable the establishment of personalized medicine.
- Dugs which are strong candidates are those which (a) show high inter-patient variability, (b) have a narrow therapeutic window, (c) demonstrate a clinical effect several days after initiation of administration, and/or (d) may exhibit serious adverse reactions.
- FDA and EMEA do not mandate pharmacogenetic data submissions as part of a new drug licensing application, but both organisations recommend it and both have established expert committees to evaluate this data.
- In drug development, pharmacogenetic research may aid in the development of new medicines for specific genetically-defined groups, it may improve existing medicines by identifying the patients in whom they show the highest benefit and it may re-instate some withdrawn medicines by restricting their licensed use to a genetically-defined subgroup of patients.
- For some drugs, pharmacogenetic tests will not unequivocally delineate patients who would and would not benefit from their use, but would rather predict the likelihood of each patient's response. Adequate training must be provided for clinicians and pharmacists to enable them to correctly interpret such tests and advise patients accordingly.

Cost

The incorporation of pharmacogenetic studies in drug development, would be likely to influence the cost of the final product. This has pharmacoeconomic implications and might adversely influence cost-benefit issues, possibly also presenting a barrier to medicine access.

Information, training and education

The results of a pharmacogenetic test may not be as easily interpretable as other clinical tests, and the way in which the data may be best used, may not be immediately evident. In a number of instances, pharmacogenetic tests will not draw a clear line between a patient being a responder / non-responder to a particular drug, but will rather predict the *likelihood* of that's patient's response. The prescriber may have to consider other factors besides pharmacogenetic data, while taking a decision, especially when bringing dosage regimen into the equation. Adequate training must be provided for clinicians and pharmacists to enable them to interpret such pharmacogenetic tests correctly and to advise patients accordingly. The Nuffield Council recommended that such testing should not be made available directly to the patient but only to trained health care professionals. However, in the case of pharmacogenetic tests which are able to provide a clear cut *responder/non-responder* result, patients could be provided with the means to directly request such testing themselves. The selection of tests which could be made available in this way should be decided by the relevant Health Authority.

Ethnicity

Particular genetic variation may often be clustered to specific ethnic populations. Although ethnicity alone should not be used as a replacement for a pharmacogenetic test, this situation could make the commercialization of some drugs only viable within certain ethnic groups. This could cause serious concerns where, for example, solely due to commercial interests, whole countries could be denied the availability of these drugs, even though specific individuals may test pharmacogenetically positive for their use.

Drug licensing

Even if it will improve the likelihood of receiving a safe and effective treatment, some patients might have an aversion to taking a pharmacogenetic test, either, for example because it might become more difficult to obtain health insurance,

or because it might indirectly reveal information about a medical condition which cannot be effectively treated. A question arises regarding whether these patients will still have the option to receive treatment without taking an associated test, or whether the drug licensing conditions will mandate it. This may also be relevant in developing countries which do not have recourse to testing, thus effectively making any use of such a drug in these countries, fall under off-label prescribing.

Use by insurers

Pharmacogenetic information could be of relevance to insuring companies, especially those providing types of healthcare insurance such as private medical insurance and long-term care insurance, as well as life insurers. Such genotyping may be used to classify individuals as "more expensive" or "less expensive" to treat and could be used to define premiums for people applying for policies, as well as to adjudicate claims in order to make decisions about payment to policy-holders. The Nuffield Council strongly advocates in favour of the setting up of regulations that would deny insurers any right to request genetic information.

Conclusion

Half a century from the Watson and Crick's identification of DNA structure, and 5 years from the completion of the Human Genome Sequence, the implications of genetic research have infiltrated our daily lives. Pharmacogenetic-based individualized drug therapy aims to provide a safer and personalized therapeutic option for patients, with better clinical outcomes and disease prognosis. As new high throughput research methodologies are developed, and further automation is introduced into research laboratories, the development and commercialization of pharmacogenetic tests may become a reality sooner rather than later. Roses, in 2002[25] had already speculated that a pharmacogenetic test kit could be developed by a pharmaceutical company, validated and commercialized within a time frame as short as 2 to 3 years, and more recently, Lesko (2007)[12] suggested that a pharmacogenetic kit could be commercialized for point-of-care use by the prescriber himself at a cost of only around USD50 per test. Now is the time for health care professionals to start seeking the knowledge and training that will prepare them for the introduction of pharmacogenetics/pharmacogenomics into the framework of pharmacological management and patient care.

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