Pharmacogenetics and pharmacogenomics

Pharmacogenetics has been defined as the study of variability in drug response due to heredity [1]. More recently, with the fashion for adding the suffix '... omics' to areas of research, the term 'pharmacogenomics' has been introduced. While the former term is largely used in relation to genes determining drug metabolism, the latter is a broader based term that encompasses all genes in the genome that may determine drug response [2]. The distinction however, is arbitrary and both terms can be used interchangeably. Over the last 12–18 months, a large number of articles have appeared on pharmacogenomics in various journals. In addition, three new journals with the term 'pharmacogenomics' in their title have been launched (*Pharmacogenomics, The American Journal of Pharmacogenomics and The Pharmacogenomics Journal*). This is because pharmacogenomics is viewed as a highly important area for improving drug therapy and prescribing in the future. Whether this promise is fulfilled and to what extent will only become evident with time.

In this issue of the *Journal*, we start a new review series of articles concentrating on the area of pharmacogenetics/pharmacogenomics to provide readers with the state of the art in relevant aspects of this area, which we hope will help them assess for themselves the importance (or not) of this area with respect to both their clinical practice and research.

The history of pharmacogenetics stretches as far back as 510 B.C. when Pythagoras noted that ingestion of fava beans resulted in a potentially fatal reaction in some, but not all, individuals [1]. Since then there have been numerous landmarks (Table 1) that have shaped this field of research, and have led to the current wave of interest. Variation within the human genome is seen about every 500–1000 bases [3]. Although there are a number of different types of polymorphic markers, most attention recently has focused on single nucleotide polymorphisms (SNPs, pronounced snips), and the potential for using these to determine the individual drug response profile.

Table 1 Historical overview of pharmacogenetics and pharmacogenomics

Year	*Individual(s)*	*Landmark*
510 BC	Pythagoras	Recognition of the dangers of ingesting fava beans, later characterized to be due to deficiency of G6PD [1]
1866	Mendel	Establishment of the rules of heredity [11]
1906	Garrod	Publication of '*Inborn Errors of Metabolism*' [12]
1932	Snyder	Characterization of the 'phenylthiourea nontaster' as an autosomal recessive trait [13]
1956	Carson *et al.*	Discovery of glucose-6-phosphate dehydrogenase deficiency [14]
1957	Motulsky	Further refined the concept that inherited defects of metabolism may explain individual differences in drug response [15]
1957	Kalow & Genest	Characterization of serum cholinesterase deficiency [16]
1957	Vogel	Coined the term pharmacogenetics [17]
1960	Price Evans	Characterization of acetylator polymorphism [18]
1962	Kalow	Publication of '*Pharmacogenetics – Heredity and the Response to Drugs*' [19]
1977/79	Mahgoub *et al.* and Eichelbaum *et al.*	Discovery of the polymorphism in debrisoquine hydroxylase sparteine oxidase [20, 21]
1988	Gonzalez *et al.*	Characterization of the genetic defect in debrisoquine hydroxylase, later termed *CYP2D6* [22]
1988–2000	Various	Identification of specific polymorphisms in various phase I and phase II drug metabolizing enzymes, and latterly in drug transporters
2000	Public-private partnership	Completion of the first draft of the human genome [23, 24]
2000	The International SNP Map Working Group	Completion of map of human genome sequence variation containing 1.42 million SNPs [5]

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SNPs occur at a frequency of 1% or greater in the population [4]. A consortium between the pharmaceutical industry and charities such as the Wellcome Trust was formed to create a library of 300 000 SNPs; this project was always well ahead of the intended schedule, and has recently resulted in the publication of a SNP map comprising 1.42 million SNPs at an average density of one SNP every 1.9 kilobases [5]. The database is publicly available (http://snp.cshl.org). Theoretically, this could be used to create individual SNP profiles that correlate with individual drug response. Currently, we prescribe drugs according to the model that 'one dose fits all' [6]. Using SNP profiling, it may possible to tailor drug prescription and drug dosage to the individual, thereby maximizing efficacy and minimizing toxicity [3, 7, 8]. The promise of personalized medicines is also of obvious interest and importance to the pharmaceutical industry since it may allow streamlining of the drug development, drug testing and drug registration process, reducing the time from chemical synthesis to introduction into clinical practice, and therefore the cost of the drug development process [3].

With the completion of the first draft of the human genome, articles have generally been rather sceptical of its importance in unravelling the complex genetics of polygenic diseases [9]. By contrast, articles about pharmacogenomics have almost entirely been upbeat [3, 7]. It has also been suggested that it may be easier for general practitioners to understand pharmacogenetic information than genetic principles, and since primary care is the major area of drug prescribing, this may serve to be a greater driving force for implementing genetic medicine into primary care [10]. However, before we all start espousing the importance of pharmacogenomics, there are many issues that need to be resolved. Prominent amongst these are whether SNP genotyping technologies will be affordable and readily available, and even if they are, whether patient outcomes will be changed by genotyping prior to commencement of drug therapy. These are important issues that will require clinical pharmacological expertise to investigate, and will be covered in articles in this series. Inevitably, it is likely that many of our expectations may be unrealistic, and what may eventually be realized is somewhere in between the viewpoints of the optimists and pessimists.

The series begins with articles concentrating on individual drug metabolizing enzyme gene polymorphisms, which classically fit in with the term pharmacogenetics. Over the course of the year, broader 'pharmacogenomic' articles that concentrate on disease categories, study design and the role of genotyping in clinical trials and clinical practice will also appear. Acknowledged authorities in the field have written all the articles. Clearly, this is a field that is developing rapidly, and as new advances are made, more articles will be commissioned to keep the readership informed and up to date.

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