



***Vive la difference* – genetic variation and drug development**

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Genetic data from individual patients can be obtained for less cost and in less time than ever before. Such information may predict drug safety and efficacy in particular segments of the population. Therefore the data may affect drug development strategies in pharmaceutical companies and drug prescription patterns in clinical practice. Here we outline some of the broad implications of availability of information on genetic variations in human patients.

Introduction

Part of the disease burden of humanity may be thought of as the consequence of human genes interacting with environmental agents such as toxins or pathogens. For example, some human genes direct the expression of particular proteins on the surface of cells in the respiratory passages; airborne viruses can use those proteins to enter cells; and consequently humans suffer from respiratory diseases such as influenza. Unsurprisingly, human genetic variability will mean that some populations are more prone to the effects of particular environmental agents than are others (pale-skinned populations are more prone to skin cancers than are dark-skinned populations). In just the same way, genetic variation may affect the way in which particular groups respond to drugs, such that a given drug will be safer for some populations than for others, and more efficacious for some than for others.

Sometimes these differences in safety and efficacy can be causally linked to a genetic variation (mutation) in a given gene. For example, a protein encoded by a mutated gene may interact with a drug less efficiently than do non-mutant proteins. Alternatively, the relationship between an observed mutation and the patient's response to a drug may be one of correlation rather than causation. Thus, a given mutation may be associated with a particular clinical outcome simply because it is found in a chromosomal location close to the gene variant which is the real primary cause of the clinical outcome, and therefore the two variants are normally inherited together.

In practise, the important point is that a given genetic variation is predictive of a given clinical outcome, regardless of whether the link is causal or correlative. Those individuals with genomes bearing a mutation associated with poor response to a drug will comprise a population in which the drug in question will, in general, be less efficacious than it is in non-mutant populations. The size of the population is irrelevant; a very rare genetic variant may only exist as a 'population' of one, while some variants are found in millions of individuals. The study of the effect of genetic variants on drug safety and efficacy is known as pharmacogenetics, and may have significant implications both for drug development and for healthcare.

Spot the difference - DNA profiling technologies

Identification of genetic variation has relatively little utility in itself, but becomes useful when the variants are correlated with particular clinical outcomes in the context of treatment with a given drug. Therefore two types of data are required, namely (i) identification of the DNA mutations exhibited by particular patients, and (ii) records of the 'clinical phenotypes' of these patients, in other words the response of the patients to the drug in question.

Uncovering the genetic mutations exhibited by thousands of individual patients requires a cost-effective means of extracting and analysing their DNA. This usually involves not only technology for recognising DNA sequences, but also robotics technology to automate laboratory procedures, and informatics software to capture, manage and analyse the information provided by DNA sequencing. The trend is for DNA sequencing to become progressively faster and cheaper through the application of high-throughput, miniaturised systems and sophisticated software.

In terms of the broad technical approach that is applied, one can either search for mutations in a few specific genes which are thought to be involved in (for example) the metabolism of the drug or the pathogenesis of the disease, or one can look for mutations in the entire genome (every single gene) of the patient. The former approach requires less DNA sequencing and therefore would be expected to be faster and cheaper, but requires some understanding of the molecular biology of the disease and the drug action, and in any case may only identify a subset of the mutations that could be correlated with the observed response. The latter approach would be expected to be more time-consuming and expensive, but should identify all mutations, causative as well as correlative.

A number of different technologies have been developed to allow rapid sequencing / identification of mutations. These include microarray technologies focusing on the rapid identification of a few known variants, and new techniques which are proposed to allow low cost sequencing of the entire genome of a patient in a matter of days. Application of technologies such as these will allow small genetic variations between individuals to be rapidly and reliably identified and catalogued. There are many companies offering technologies and services in these areas, and several pharmaceutical companies developing in-house systems. A discussion of the relative merits and weaknesses of the various different approaches is beyond the remit of this article.

Value the difference - clinical profiling and clinical trial design

Genetic variations are relatively meaningless unless they are correlated with response to a drug, either in terms of efficacy (was the drug of benefit to the patient) or in terms of safety (did the drug harm the patient). Where patient DNA and clinical outcomes are available from historical trials, a retrospective analysis may be rapidly performed to identify the extent to which specific genetic variations are correlated with efficacy and / or safety, or to discover new, correlative genetic variants.

Once such information has been acquired, ie once a correlation has been found between a mutation and a clinical response, it may be used to inform the design of future clinical trials. In circumstances where, for example, data from a Phase II trial suggests that some patients respond well to the drug, whereas others do not respond at all, identification of mutations which correlate with a good response may have a significant effect on the design of the subsequent Phase III trial. Specifically, they will enable future recruitment of trial patients to be limited to those with mutations correlated with a good response. This has two effects; firstly it will make the success of the Phase III trial more likely, and secondly, by limiting the trial to a segment of the population, it may be possible to perform the trial with fewer patients, which will make it faster and less costly.

Furthermore, pharmacogenetic information may prevent a potentially useful drug from being scrapped during development. For example, a drug which is found in early clinical trials to work in only a proportion of patients, normally may not get taken to Phase III because the risks associated with development would be perceived as too great. However, the acquisition of pharmacogenetic correlative markers (diagnostics) that identify the segment of the patient population in which the drug appears to be safest or most effective may allow continued 'low risk' development of the drug for a given population.

Therefore pharmacogenetics is perceived by some companies as a means to decrease the risk, time and cost associated with the critical Phase III part of the drug development process. Since clinical trials, and Phase III trials in particular, are often the most expensive part of the drug development process, any method which can decrease the high cost and risk of trials is

likely to be of great interest. Indeed, success or failure in Phase III can significantly affect a company's share price, and can make or break smaller companies. Hence, a number of biotechnology and diagnostics companies are addressing this general area, generating information on genetic mutations relevant to clinical outcome and developing tests to identify the presence of such mutations.

Pharmacogenetic fears; *plus ca change....*

It has been suggested that there may be economic disadvantages associated with the application of pharmacogenetics. For example, even where the population with a 'responder' mutation is large enough to make drug development economically feasible, it has been suggested that revenues and return on investment will unavoidably be lower than for non-targeted drugs. This is because the patient population for whom the drug is suitable will be smaller than the total patient population for whom non-targeted drugs would be suitable. Indeed, there has been a certain amount of speculation that the advent of pharmacogenetics will spell the end of the 'blockbuster drug' (drugs with sales of \$1 billion per year or more). Different drugs will need to be developed for specific, smaller patient populations, and therefore each drug will address smaller market segments, and generate lower revenues.

There may also be less obvious disadvantages associated with the use of pharmacogenetic data. For example, few genetic variants will be perfectly, 100% predictive of poor response to a drug or of side effects of a drug. Correlation is simply an expression of probability, not an absolute guarantee of a particular outcome. But if drugs are approved for only a certain population bearing the 'responder' genotypes, then it is likely that some patients with 'non-responder' genotypes will be effectively denied access to the drug who in fact would benefit from its use.

More insidiously, where particular genetic variations are correlated with ethnic groups, it is suggested that there might arise perceptions of racial overtones in the provision of healthcare. Indeed, there are fears that the increasing use of pharmacogenetic data to direct the drug development process will eventually result in groups of 'orphan' patients who are untreatable by any available medications, either because appropriate medications are not available, or because the patients with the genetic variation in question represent populations that are too small to repay the investment in drug development.

.....*plus c'est la meme chose*

However, these fears are simply restatements of the human situation. There are already many rare diseases which are unlikely ever to attract the attention of the pharmaceutical industry. Some of these diseases are more common in some populations than in others. Patients with such diseases are not being victimised, unless they are victims of a blind providence; they are just unfortunate. Pharmacogenetics simply brings into sharper focus the natural genetic variations in human populations and the consequent variations in the incidence and molecular pathology of disease. These variations always have and always will exist, and the application of pharmacogenetics enables us to account for such variation and to design safer and more effective drugs. In this context we should remember that, in the US alone, there are about 100,000 deaths per year due to adverse drug reactions, a proportion of which no doubt could be avoided by treating patients according to their genotype.

Similarly, the extent to which the stratification of patient populations into smaller groups will have implications for the economics of drug development, and kill off the blockbuster product, sometimes may be overstated. For example, if a responder mutation is present in the majority of patients, and if a drug targeted to these patients is perceived to be safer or more effective than non-targeted drugs, then premium pricing for a product that still addresses a significant population may make up for any revenue loss due to exclusion of a minority of patients from the market. Furthermore, if the application of pharmacogenetics can indeed reduce the size, time and therefore the cost of clinical trials, then the investment required for drug development will be smaller and time to market speedier, which of course has obvious implications for return on investment.

In addition, extra revenues could be gained from the sale of supplementary products. The segmentation of the patient population might require development of a diagnostic test to identify the relevant genetic mutations in the DNA of each patient. This test would be applicable to all patients with a given disease, ie would address the type of broad market previously aspired to by the blockbuster drugs. Indeed, it has been suggested that in some cases, the diagnostic test could be the main revenue generator, and the drug could be almost given away “free” with the test. However, it should be noted that, so long as the drug is safe, regulatory bodies may not enforce the use of a diagnostic test. Indeed, it is notable that some medicines are approved on the basis of eliciting a useful response in less than 50% of the population, and are prescribed without any means of distinguishing the patients that will respond.

Future trends?

It is clear that pharmacogenetics will affect the pharmaceutical industry, although the precise extent of this effect is debatable. The most obvious effect will be the stratification of patient populations into subsets which may require different therapeutic approaches. This represents no more than a recognition of the relevance of inherent variations in humankind to disease development and drug response.

It may be that not all of the implications of patient stratification in drug development and drug prescription have yet become apparent, due to lack of clinical experience with drugs that have been developed for specific genetic variants. For example, it is possible that undertaking clinical trials with smaller numbers of patients, in whom a good response is most assured, may obscure identification of drug-related side-effects, for example if it turns out that the correlation does not hold for all populations. In such cases, drug-induced adverse events might not become apparent until the post-marketing stage. This might drive regulatory bodies to require more intense post-marketing scrutiny of the drug, and greater control over off-label prescribing.

The most likely near-term applications of pharmacogenetics will be in diseases where not all patients respond to the available drug, and where the therapeutic index of the drug is narrow (ie the danger of side effects is great). One such area is cancer therapy, and pharmacogenetic data has already had a significant impact in this field. Genetic analysis may allow identification of cancer patients who are most likely to respond, and at the same time spare other patients from the side-effects of a course of treatment which would be unlikely to help them. We will examine the applications of pharmacogenetics for cancer therapy in more depth in a future article.

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