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The genetics of human drug response

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The genetics of variable drug response appears to be a more tractable complex trait than common disease predisposition. This has implications for prioritizing research and for experimental design, and in particular argues for extensive use of candidate gene based approaches in pharmacogenetic association studies. Eventually, when whole genome scanning becomes feasible, it may be appropriate to consider weighting schemes that assign higher prior probabilities of variants in genes related to the mode of action of metabolism of medicines.

Keywords: drug response; pharmacogenetics

The tools and information emerging from the Human Genome Project are rapidly maturing, allowing more systematic investigation of how human genetic variation influences common disease predisposition and variable responses to their treatment. Although it has long been recognized that genetic differences among people may influence their drug responses, the larger-scale academic research efforts have been much more orientated towards disease predisposition than the genetics of drug response. While there is some overlap between these research enterprises, they are not the same and I argue here that the genetics of drug response is generally a more tractable phenotype than common disease predisposition. For this reason, it seems likely that research efforts on the genetics of drug response will provide quicker returns in terms of improved therapies than direct study of common disease predisposition. This is not to say that common disease predisposition should not be studied. It clearly should be, and is. But it is to say that the academic community should do considerably more work on the genetics of drug response than it currently is.

Here, I discuss some differences between variable drug response and common disease predisposition. Next, I suggest some possible implications of these differences for research strategies.

First, a note on nomenclature. Pharmacogenetics is often considered to have emerged as a field when Arno Motulsky (1957) assembled examples of variable drug responses, and argued that in many cases the genetic differences among individuals responsible for drug response may have little phenotypic consequence until the challenge with the given medicine occurs. Many of the variants that we now know about that influence drug response clearly follow Motulsky's prediction. Pharmacogenetics emerged as a discipline dedicated to identifying such variants, characterizing their effects and assessing their pattern of global geographic variation. Pharmacogenetics research through most of its history however focused most of its attention on drug metabolizing enzymes, and the development of assays to assess how variants might influence enzyme activity. It is fair to say that pharmacogenetics to date has had very little clinical consequence. Although some of the classical variants are very likely of some clinical significance, most of them have not been carefully assessed in outcomes based studies.

More recently, interest has developed in more systematic studies in which the starting point is a variable drug response of clinical significance and likely candidate genes are investigated for any variants that are associated with the variable response. These efforts tend to tap into genomic methodologies, such as haplotype tagging and expression profiling. For this reason, some authors have suggested the term pharmacogenomics as a replacement for pharmacogenetics. While the change in research methods is beyond question, the precise distinction between pharmacogenetics and pharmacogenomics remains undecided. For this reason, I will here use the term pharmacogenetics to refer to the research effort dedicated to finding and using genetic and genomic differences among patients that correlate with drug response.

The first point I would like to make is that pharmacogenetics is more tractable than disease predisposition. This tractability has two main components, as discussed below.

1. OBVIOUS CANDIDATE GENES

In pharmacogenetics, obvious candidate genes often do carry gene variants relevant to drug response (Goldstein *et al.* 2003). Of the 42 variants that were identified in the literature had been significantly associated with a drug response in at least two studies, 34 of them are in genes that are either the target of the drug or are enzymes that are involved in metabolizing the drug (or in the relevant pathway) or one of its principal metabolites (Goldstein *et al.* 2003). This is highly suggestive, but suffers an obvious ascertainment bias in that the field has mainly concentrated until

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recently on characterizing variation in genes expected to be relevant (e.g. those that metabolize many prescription drugs). It is therefore important to ask what happens when a given drug response phenotype is studied. Here too, the results are suggestive that obvious candidate genes often carry gene variants associated with drug response. Tate *et al.* (2005) recently studied dosing of the anti-epileptic drugs carbamazepine and phenytoin. As an obvious starting point, Tate *et al.* considered one of the genes encoding the target of both drugs (the *SCN1A* gene, encoding the alpha subunit of the sodium channel), a transporter thought to act on both drugs (*ABCB1*), and the principal enzyme responsible for the metabolism of phenytoin into inactive metabolites. From these very obvious starting points, Tate *et al.* found that a well known low activity allele of the *CYP2C9* gene is associated with the maximum dose that patients are exposed to in the regular clinical use of phenytoin. More interestingly, Tate *et al.* also found that a previously unknown and apparently functional variant in the *SCN1A* gene is associated with the maximum dose patients are exposed to of both phenytoin and carbamazepine. Because the *SCN1A* polymorphism has not been previously characterized, these results will require independent replication for confirmation. But it would appear that these obvious candidate genes do carry variants that influence patient response in a manner that causes clinicians to prescribe in a way that is correlated with genotype. In a similar example, after the target of warfarin was identified a number of studies documented that variation in the gene has an important role (e.g. D'Andrea *et al.* 2005).

This means that in the short term there is a strong case for candidate gene studies in pharmacogenetics. In the longer term, as genome-wide association becomes more economical, there may be a case for assigning higher *a priori* probabilities to the obvious categories of candidates.

2. PHARMACOGENETIC VARIANTS ARE OFTEN COMMON

Of the 42 variants identified as significantly associated with drug response in at least two studies, a majority of them have minor allele frequencies greater than 10% (Goldstein *et al.* 2003). One practical implication of this is that such variants are easier to find using linkage disequilibrium mapping than variants that are more rare (see Ahmadi *et al.* 2005). A second implication is that once found common variants obviously apply to a larger fraction of the population. This makes good sense in light of Motulksy's original insight. Many of the variants important in drug response may have little effect, except when an environmental challenge is presented (i.e. drug administration). Because drug administration is very recent in our history, this means that evolution may have been effectively blind to variants that have very major effects (on drug response), which therefore may be maintained in the population at high frequency. This is in sharp contrast to common disease predisposition. Except in cases when the conditions presents late in life (e.g. late onset dementia), any variant having a major effect on a common disease would be selected against in the population.

3. CLINICAL RELEVANCE

Finally, and perhaps most importantly, when pharmacogenetic variants are identified, there is often a clear direction for clinical relevance. For example, a diagnostic indicating a greater likelihood of efficacy for an anti-hypertensive might suggest trying that anti-hypertensive in individuals of the relevant genotype before alternative categories of anti-hypertensive are tried. Or, as in the examples above, a pharmacogenetic diagnostic might indicate optimum dosing strategies as a function of genotype. It should be emphasized that clinical relevance cannot be assumed on the basis of an association observed in a retrospective study design. Rather, the clinical utility of a diagnostic must be assessed in a prospective outcome-based trial. Unfortunately, such studies are rare. If pharmacogenetics is to deliver on its potential, explicit clinical evaluation of potential diagnostics will need to become much more common. Nonetheless, the potential relevance remains more clear than in the study of disease predisposition. In the case of disease predisposition, it is not unusual for an association to be of little or no (apparent) relevance, either because the gene in question is already a target for drug development, or because there is no obvious therapeutic intervention that can be suggested on the basis of genotype (e.g. APOE4 and dementia).

4. CONCLUSIONS

It may be relevant to note that genomics has for many years been cast as clinically applied research. In the US context major funding is provided by the National Institutes of Health (NIH) for example as opposed to the National Science Foundation (NSF). It is not unreasonable to assume that an expectation has been generated that research will lead to clinically relevant advances, and in the absence of such advances, there is a reasonable expectation of a negative reaction among both politicians and the public. It seems likely that the promise of clinical relevance may be more readily delivered by an increased effort in pharmacogenetics. There are compelling reasons to argue for a marked increase in public-sector research in pharmacogenetics making use of the most recent advances in genomics.

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