

Expectations, validity, and reality in pharmacogenetics

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Abstract

In this review, we discuss the potential expectations, validity, predictive ability, and reality of pharmacogenetics in (1) titration of medication dose, (2) prediction of intended (efficacy) drug response, and (3) dose prediction of unintended (adverse) drug response. We expound on what these potential genetic predictors tell us and, more importantly, what they cannot tell us.

Although pharmacogenetic markers have been hailed as promising tools, these proclamations are based mainly on associations rather than their evaluation as predictors. To put the expectations of the promise of pharmacogenetics in a realistic perspective, we review three examples. First, warfarin pharmacogenetics, wherein although the validity of the genetic variant dose is established and there is a validity of genetic variant–hemorrhage association, the clinical utility of testing is not clear. Second, the strong and clinically relevant HLA–Stevens–Johnson syndrome/toxic epidermal necrolysis association highlights the role of ethnicity. Third, the influence of *CYP2D6* on tamoxifen efficacy, a model candidate with potential clinical utility but unclear validity.

These examples highlight both the challenges and opportunities of pharmacogenomics. First, establishing a valid association between a genetic variation and drug response; second, doing so for a clinically meaningful outcome; and third, providing solid evidence or rationale for improvement in patient outcomes compared with current standard of care. © 2010 Elsevier Inc. All rights reserved.

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1. Introduction

It has long been recognized that patients have varied responses to drugs, both beneficial and adverse. Serious adverse drug reactions represent an important clinical issue and are an important cause of hospital admissions [1–3], whereas lack of response to drug therapy, although not uncommon, leads to inefficient use of health care resources and delay in patients receiving appropriate alternative therapies.

Our increasing understanding of influences, such as environmental exposures, nutritional status, comorbidities, severity of disease, and concomitant medications has helped explain heterogeneity in drug response. In addition, the profound contribution of genetics has been appreciated for some time and is receiving greater emphasis. The

technological advances spearheaded by the Human Genome Project now offer the opportunity for using genetic information to predict disease risk and drug response. Pharmacogenetics is the study of how genetic differences affect variation in response to medication. The promise (expectation) of pharmacogenetics is to be able to deliver “personalized medicine” by making decisions that optimize patient health outcomes based on a patient’s genetic makeup [4].

Despite this promise, as with disease genetics, various widely cited pharmacogenomic association studies have not been reproduced and confirmed. For example, one study indicated a significant relationship between an alpha-adducin gene variant and diuretic antihypertensive response [5], but several recent, larger studies failed to confirm such an association [6–8], and the association between the CETP polymorphisms and statin therapy outcomes has been widely studied, but a recent meta-analysis failed to validate the association [9]. Furthermore, several pharmacogenomic associations that have not been consistently replicated to date, including ACE gene polymorphisms and antihypertensives [10], beta-receptor polymorphisms and both asthma [11,12] and heart failure medications [13], and serotonin transporters and antidepressants [14,15].

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The importance of sound epidemiological approaches in assessing genetic associations has been verified by these experiences, including appropriately powered studies, assessment of potential selection bias and confounding, adjustment for multiple comparisons, careful assessment of phenotypes, and caution regarding publication bias [16–18]. More importantly, the recognition of the promise of genotype-guided therapy has fostered the development of multicenter, multinational consortiums, such as the International Warfarin Pharmacogenomics Consortium (IWPC) [19]. Such large efforts will continue to serve as a critical mechanism for providing the necessary sample sizes to identify and validate pharmacogenomic associations and evaluate their predictive ability.

Herein, we discuss the potential expectations, validity, predictive ability, and reality of pharmacogenetics in (1) titration of medication dose; (2) prediction of intended (efficacy) drug response; and (3) dose prediction of unintended (adverse) drug response. We expound on what these potential genetic predictors can tell us and, more importantly, what they cannot tell us based on the current evidence and how this knowledge can set the research direction in informing the development of novel therapeutics. To this end, we review several examples to highlight pharmacogenetic associations from an epidemiological perspective. First, warfarin pharmacogenetics, wherein although the validity of the gene dose (surrogate endpoint) is established and there is a validity of gene–outcome (hemorrhage) association, the clinical utility of testing is not clear. Second, the strong and clinically relevant HLA–Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) association highlights the role of ethnicity. Third, the association of *CYP2D6* with the efficacy of tamoxifen highlights a model candidate with unclear validity but potential for clinical utility.

2. The long road from association to prediction

The extensive research efforts undertaken over the past decade have identified several genetic markers that are strongly associated with outcomes of interest. Although these pharmacogenetic markers have been hailed as promising tools, these proclamations are based mainly on associations rather than their evaluation as predictors. Therefore, the expectations of their performance, and ultimately, the ability to improve drug therapy, patient outcomes, and health care spending need to be put in a realistic perspective.

At the crux of this debate are three questions:

1. Can a genetic risk factor (genetic marker) associated with an adverse (or beneficial) outcome be a clinically useful predictor of that outcome? (clinical validity)
2. Can incorporation of the genetic factor predict risk of the outcome more accurately than existing clinical models? (clinical utility)

3. Will the risks predicted for individuals be sufficiently different to warrant a change in treatment decisions? (degree of clinical utility)

Evaluating the relationship between variation in genetic factors and outcomes can be particularly challenging because of the varying study designs, differences in outcomes evaluated, and variation in outcome definitions. Therefore, the readers should familiarize themselves with evaluation of epidemiological studies with regard to potential sources of error: chance, bias, and confounding. The readers should also understand the characteristics of predictive tests (sensitivity, specificity, positive predictive value, and negative predictive value) and summary of statistical measures that enable assessment of improvement in the predictive ability [20].

3. Pharmacogenetics as a tool for predicting drug dosage

Most of the early research in pharmacogenetics focused on drug metabolizing enzymes and identified common polymorphisms in patients exhibiting unusual adverse drug response to conventional doses. Many of these gene–dose associations have been replicated in independent populations and provide, perhaps, the greatest potential for realization of the “personalized medicine” promise.

There are relatively few examples of genetic variation influencing drug dosage that are well validated across different racial/ethnic/geographic groups as with the case of warfarin. The effect of cytochrome P450 2C9 (*CYP2C9*, the principal enzyme in warfarin metabolism) and vitamin K epoxide reductase complex 1 (*VKORC1*, the target protein inhibited by warfarin to produce therapeutic anticoagulation) variants on warfarin dose requirements is probably the most well studied [21].

Current warfarin dosing practice involves administration of a standard “one size fits all” starting dose (e.g., 5 mg/d) or estimation of initial dose based on clinical characteristics (age, gender, medications, liver function, and others). Dose adjustment is then based on anticoagulation (as measured by the international normalized ratio; INR) response with the goal of maintaining INR in the target range. However, these dosing strategies result in over-anticoagulation or under-anticoagulation in a significant proportion of patients. Therefore, the ability to improve the accuracy of dose prediction could potentially improve anticoagulation control and decrease the risk of thrombotic or hemorrhagic events associated with under-anticoagulation or over-anticoagulation.

CYP2C9 genotype alone accounts for 2–10% of the variance in warfarin dose [22,23], *VKORC1* genotype alone accounts for 10–25%, and nongenetic factors (including age, body size, and concomitant medications) account for 20–25%. Integration of these factors further improves the explanatory power, accounting for up to 60% of the

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