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Genome-wide approaches in pharmacogenomics: heritability estimation and pharmacoethnicity as primary challenges

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The ultimate aim of pharmacogenomics is the identification of genetic variants that underlie interindividual variation in drug response. The furious pace of technological advances [1], such as DNA sequencing and genotyping technologies [2], has begun to enhance our understanding of human diversity in pharmacologic traits. Meanwhile, methodological advances, such as the genome-wide association study (GWAS) approach, have facilitated the discovery of genetic variation with considerable clinical relevance [3]. The *sine qua non* of the rapidly developing field of pharmacogenomics is the translation of genomic information from these convergent developments into individualized patient care. Exciting promises of the new science abound, including the possibilities of optimized drug therapy, adverse-effect risk prediction, and improved drug discovery and development. The purpose of this article is to explore two of the major challenges to pharmacogenomic progress despite the substantial advances in genome-wide approaches that have already been made.

The central premise is also the ‘gap’ in pharmacogenomic studies

The central premise of every pharmacogenomic study is that the pharmacologic trait under investigation is under appreciable genetic control. Indeed, studies in search of pharmacogenes are, in many instances, conducted without the prerequisite studies to confirm the heritability of the trait. The premise is implicit and, to a large extent, untested.

The challenges of quantifying the heritability of a pharmacologic trait are well recognized. Although twin and family studies have for a long time been part of the human geneticist’s standard toolkit to quantify the relative contribution of the genetic component to human

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pathophysiology, it is nearly impossible to generate drug response phenotype data in related individuals with the same disease phenotype. Consequently, there is a general paucity of estimates of heritability of drug action.

To overcome this challenge, some heritability studies are conducted in healthy, drug-naive related individuals to quantify the extent of variation in drug response attributable to familial relatedness. For example, in a study of clopidogrel response [4] as defined by ADP-stimulated platelet aggregation in 429 healthy Amish individuals, it was found that platelet response is a highly heritable trait (heritability estimate = 0.73). Notably, a single allele, the common loss-of-function variant *CYP2C19*2*, was observed to account for 12% of the variation in clopidogrel response.

Highly toxic drugs, such as chemotherapeutic agents, present a different type of challenge with heritability estimation. The unsuitability of these drugs in healthy human subjects and the exceptionality of shared tumor type in related individuals [5] render traditional approaches lacking. Thus, an *ex vivo* familial genetics approach [5] has been utilized to evaluate the extent of genetic contribution to chemotherapeutic susceptibility. Furthermore, a number of groups have shown the utility of preclinical cell-based models to identify genetic predictors that can be validated in prospective clinical trials [6,7]. For example, the HapMap lymphoblastoid cell lines have been adopted as a model system for human genotype–phenotype relationships [8–10], yielding notable advances in our understanding of the genetics of gene regulation [11,12], as well as considerable insights into the impact of genetic variation on the pharmacodynamic effect of drugs and other xenobiotics [5,13]. As these studies illustrate, cellular pharmacogenomics [14] may well provide an effective approach to overcome the limitations of clinical studies to manipulate environmental exposures *in vivo* [15].

Prior to the advances in high-throughput genome-wide technologies [16], pharmacogenetic studies focused primarily on candidate genes within *a priori* implicated pathways. In general, classic pharmacogenetic studies were restricted to pharmacologic traits in which a small number of variants (frequently, in a single candidate gene) had a large effect on drug response [17]. For example, pharmacogenetic markers were identified for the dosing of warfarin (*VKORC1*) [18] and irinotecan (*UGT1A1*) [19], which have become iconic examples of successful pharmacogenetic discoveries, as these findings have been incorporated into drug labeling by the US FDA. Given the function of *CYP2C9* in the hydroxylation of (*S*)-warfarin and the drug's therapeutic effect in the inhibition of *VKORC1*, genetic variants in these genes have been reproducibly implicated in the adverse effect and therapeutic response of this anticoagulant. Importantly, polymorphisms in *CYP2C9* and *VKORC1* have been found to account for at least 30% of the variation in warfarin dose in individuals of European descent [20].

The advent of genome-wide approaches has had a transformative influence on the study of genetic variation contributing to variability in drug response. GWAS have identified thousands of SNPs that are reproducibly associated with complex traits, including common disease and quantitative traits [3]. However, as has been lamented by some [21], the associated SNPs explain only a small proportion of the heritability to these traits. The 'missing heritability' phenomenon [22] has led some to call into question the utility of the GWAS approach, or to reconsider the totality of the GWAS results [23].

A comprehensive, manually curated catalog [24] now lists several hundred pharmacogenetic associations that have been identified with varying levels of evidence. One important question that arises is the extent to which common genetic variation underlies drug response phenotypes. Recent developments in the complex traits genetics of disease susceptibility

may be particularly relevant. A study of 3322 European individuals with schizophrenia and 3587 controls supports a polygenic basis to disease risk wherein the emerging picture is of a genetic architecture that involves thousands of common alleles of small effect [25]. As interindividual variation in most clinically administered drugs is likely to be due to multiple genetic variants with small independent effects, the approaches characterized in this and related studies [26] may be broadly relevant to characterizing the genetic architecture of pharmacologic traits.

Although methodological and technological advances promise to facilitate further pharmaco-genomic progress that builds on the earlier notable successes (e.g., warfarin and irinotecan), the relative paucity of heritability studies on drug response traits may well limit, adversely, the impact of pharmacogenomics on clinical practice. In particular, the contribution of genetics to drug response is crucially dependent on the environmental condition of the administration of the drug. Thus, heritability studies of pharmacologic traits may need to be conducted within a gene–environment interaction context. This distinctive feature may necessitate the development of novel methods for heritability estimation that take into account this particularity of drug response phenotypes.

Pharmacoethnicity enhances pharmacogenomic research

Health disparities exist on various sides of the ethnic or racial divide. The sources are complex [27], spanning socioeconomic, cultural and environmental causal factors, and any approach to alleviate the disparities may well be difficult or even controversial. Furthermore, race, ethnicity and ancestry are highly discordant categories with complex social histories, and an overemphasis on the connections of these categories with research on the genetic basis of complex human traits is fraught with hazards, not the least of which is the downplaying of the environmental and socioeconomic causes of health status disparities [28].

Nevertheless, a genuine understanding of the genetic contribution to health disparities and of contributory environmental factors holds promise for optimal therapy and disease risk prediction. Race- and ethnicity-based disparities are increasingly being implicated in interindividual variation in complex traits, raising the question of an underlying genetic component [29]. For the pharmacogenomics researcher, ethnically divergent drug response phenotypes may provide a powerful means to identify the underlying genetic etiology, which may otherwise be difficult to detect. Regrettably, most pharmacogenomic studies to date have been conducted in populations of European descent only, with potentially far-reaching implications for both pharmacogenetic discovery and therapeutic benefit.

The extension of pharmacogenomic research to diverse worldwide populations has the potential to lead to genuine advances in our understanding of the genetic causal factors, but also promises to make the fruits of these advances more widely available [30]. Genetic studies in admixed populations can facilitate the fine-mapping and identification of causal variants in regions of the genome first identified in studies involving European samples [31]. Furthermore, genetic risk factors identified in European samples may not extend to non-European populations given that genetic variants are likely to differ in allele frequency between populations. For example, the polymorphisms in *VKORC1* and *CYP2C9* (namely, *VKORC1* -1639, *CYP2C9*2* and *CYP2C9*3*) that account for at least 30% of the variation in warfarin dose in populations of European descent explain only 10% of the variation in African–Americans [32]; the difference in explained proportion of variation is not surprising given that the SNPs occur at much lower frequencies in African–Americans. These genetic variants are associated with low doses of warfarin, while African–Americans consistently require higher doses than other ethnicities. Furthermore, the International Warfarin

Pharmacogenetics Consortium warfarin dosing algorithm, which incorporated several clinical variables as well as the *VKORC1* and *CYP2C9* SNPs, could account for 25.9% of the variation in dose in the admixed population [20]. By contrast, it was shown that the inclusion of both known African–American-specific *CYP2C9* variants and novel variants to an ethnicity-specific model increased the explained *are* proportion of variation to 40%, with specific benefit to high-dose individuals [32].

Conclusion

In this exciting era of genome-wide approaches, two important challenges face the pharmacogenomics community, namely the problem of the heritability of drug response traits and the new opportunities from studies of pharmacoethnicity. Future investigations in these areas are likely to play a crucial role in determining the impact of pharmacogenomics on clinical practice.

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