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Warfarin Pharmacogenetics: An Illustration of the Importance of Studies in Minority Populations

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Abstract

Translation of pharmacogenetics to clinical practice is increasingly common. However, most data arise in people of European ancestry, so clinical translation in non-Europeans can be challenging. Depending on the population being assessed, a polymorphism's effect can differ in magnitude or be absent. Studies in minorities are therefore essential as they present opportunities for discovery that would be missed through European-only studies, and they ensure that all populations benefit from clinical pharmacogenetics.

Introduction

The goal of pharmacogenomics is to provide safer and more effective pharmacotherapy through the application of genetic information to guide drug therapy decisions. There are well documented examples of genetic contributions to drug response from candidate gene studies and more recently from genome-wide association studies (GWAS). For an increasing number of medications, these data have progressed to the point of supporting clinical implementation of pharmacogenetics. Accordingly, the Clinical Pharmacogenetics Implementation Consortium provides guidelines on how to apply genetic test results to optimize therapy for at least 11 drugs or drug classes, with others on the way. In some cases, genotype may aid in choosing appropriate drug therapy, such as deciding which oral antiplatelet therapy is likely to be most effective based on *CYP2C19* genotype. In other cases, genotype is useful in choosing safe and effective drug doses, such as for mercaptopurine or warfarin.

With the recognition that genetic information can better inform prescribing, along with the availability of expert consensus guidelines on how to apply genotype results to drug therapy decisions, several academic medical centers are now clinically implementing pharmacogenetics. However, a major limitation within pharmacogenetics is that most of the

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data informing guidelines and implementation efforts are from populations of European descent. In fact, many studies exclude non-Europeans as to eliminate the confounding effect of population admixture on pharmacogenetic associations. Consequently, less is known about genetic influences of drug response in minority populations.

If pharmacogenetics is to have its full clinical impact, all populations must be able to benefit. This will not be possible without sufficient data in non-European populations. Accumulation of these data will require an increased focus on pharmacogenetics studies in minorities, especially given the differences in allele frequencies and linkage disequilibrium (LD) by ancestry. Not only will such studies increase the clinical utility of pharmacogenetics, but they also provide the potential for identifying novel associations with drug response. The literature on warfarin pharmacogenetics provides numerous examples of the importance of pharmacogenetics studies in non-European populations.

The challenges and benefits of studies in more diverse genomes

People of African ancestry and Hispanics (Latinos) are the largest and most rapidly growing minority populations in the United States. However, these populations are under-represented in studies aimed at identifying variation that affects drug phenotypes. As we move toward broader integration of genetic information into clinical care, accounting for population specific genetic variation will be important for optimizing outcomes when translating pharmacogenomics findings to the clinic.

Although functional SNPs translate across populations, differences in the variant frequencies by ancestry may result in different contributions to the drug phenotype, with a large contribution in one population but less in another with a lower variant allele frequency. This is the case with the *VKORC1* -1639G>A SNP and warfarin dose requirements, where the SNP provides greater contribution to the variability in dose among Europeans than non-Europeans, a difference that is largely explained by the greater variant allele frequency in the former population(1).

African populations have been in existence the longest and thus have more genetic variation, specifically greater amounts of rare variation. The differences between African and non-African ancestry result from human migration, with populations formed from migrations out of Africa in the last 100,000 years giving rise to unique variants between populations(2). Consequently, functional SNPs might be found almost exclusively in a single population, and thus those that are unique to non-Europeans will be missed through investigations focused in Europeans. Because of the age of the African population, this is the population where unique functional variants will most likely be discovered. For example, the *CYP2C9*5*, **6*, **8*, and **11* alleles, which have important implications for the disposition of CYP2C9 substrates, were identified in African populations. appear to be essentially absent in non-African populations. The greater amount of genetic variation in the African genome is further highlighted by Freimuth *et al*., who resequenced 51 pharmacogenetic candidate genes(3). They found that samples from persons of African descent contained the greatest number of variants and had the most population-specific variants, compared to European and Asian samples, with 30% of all variants found only in African samples. Studies such as

these highlight the need for genome-wide association studies in populations outside of Europe.

The age of the African population has also led to greater numbers of recombination events, and thus a decrease in LD, meaning fewer SNPs are correlated with one another in genomes of people with African ancestry as compared to other populations. Because of population differences in LD, in the absence of evidence that a SNP has biological function, one cannot assume that its association with drug response in one population will translate into a similar association in another population. In particular, GWAS studies often find that the most highly associated SNP is not the causative SNP, but more likely in LD with the SNP that has biological function. If the functional SNP is not yet known, it is important to determine if the GWAS results replicate in other populations in whom the associated SNP may or may not be in LD with the functional SNP.

A recent GWAS limited to African Americans highlights the importance of conducting genome-wide studies in minority populations(4). The GWAS revealed a novel association between the rs12777823 variant, located on chromosome 10 near CYP2C18, and warfarin dose requirements. Subsequent analysis showed an association between the variant and reduced warfarin clearance in this population. The rs12777823 variant occurs in up to 40% of African Americans, and thus, failure to account for this variant could lead to over-dosing a significant portion of African American patients with warfarin. Interestingly, the rs12777823 variant is not associated with warfarin dose requirements in Europeans or Asians, suggesting the rs12777823 variant is not the causal variant. Rather, the data suggest that the rs12777823 variant is in LD with one or more yet unknown functional (causal) variants in African Americans, but not in either European or Asian populations.

On the other hand, the decreased LD in the African genome can be an advantage to the discovery of causal variants. Because African Americans have shorter stretches of LD, there are few SNPs correlated to the associated SNP in which to determine causality. The lower levels of LD in African ancestry populations allowed for the more precise definition of the functional variant in *VKORC1* (5). Specifically, the -1639G>A, but not the 1542G>C, variant is associated with warfarin dose requirements in African Americans, while both are associated in Europeans. This led to the discovery that only the -1639G>A variant (which in in strong LD with 1542G>C in Europeans but not African Americans) is functional. This discovery that would not have been possible with only Asian and European LD information.

Warfarin pharmacogenetic studies are also beginning to emerge in Hispanics, who are even less well studied than African Americans. Pharmacogenetic studies in Hispanics are complicated by differences in genetic ancestry depending on the region of origin, with greater Native American ancestry in persons from Mexico and greater West African ancestry in Puerto Ricans. As such, it will be important to consider genetic ancestry in studies of Hispanics in order to better explain any differences in pharmacogenetic associations that may arise among different Hispanic groups.

Based on the warfarin examples above, it is clear that without pharmacogenomic studies in minority populations, important variants would be missed and the clinical benefits of

pharmacogenetic-guided therapy will be lower in non-Europeans. Examples of differences in pharmacogenetic associations by ancestry with other drugs in other therapeutic areas are beginning to emerge. However, there is still much to be learned about pharmacogenetics in minority populations. Identifying genetic variants with important pharmacogenetic contributions across populations is essential to ensure global benefit from genotype-guided therapies.

Editors and reviewers also must recognize the importance of research in minority populations, including pharmacogenetics research. Specifically problematic is bias regarding studies in minority populations, where there is a tendency to consider such data less important if pharmacogenetic data already exist in Europeans. However, in the absence of data in minority groups, either confirming what is seen in those of European ancestry, or documenting differences from Europeans, minority populations cannot obtain the full benefits from pharmacogenetics. Nonetheless, studies in minority populations are often perceived as “me too” research and criticized as lacking sufficient clinical importance or novelty. By perpetuating this bias, both the basic and translational science communities continue to proceed with a “one genotype fits all” mentality. As such, African Americans and other minority populations will never reach the same “playing field” in terms of the benefits of personalized medicine and health disparities are perpetuated. This can be avoided by increased research, including pharmacogenetics research, in minorities. Investigators, grant and manuscript reviewers and editors alike are encouraged to remain diligent of the risks of research that does not benefit a global population, and in avoiding these risks, thereby making personalized medicine accessible to all.

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