Population Heterogeneity and Genomic Admixture: Relevance for Global Pharmacogenetics

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Editorial

The use of clinical algorithms derived by linear regression analyses is a standard method in medicine, but the empirical and descriptive nature of this kind of model also results in a number of limitations and drawbacks, exemplified by the COAG and EU-PACT trials (ClinicalTrial.gov identifier NCT00839657 and NCT01119300, respectively). Regression-based models are data-driven and, therefore, population-dependent. Accordingly, they are expected to be only valid in the same patient population on which they were originally derived (i.e., mostly in Caucasians) [1-3].

Indeed, such data-driven methods are at increasing risk of overfitting the data, giving rise to a so-called “prediction” model that is not generalizable to other datasets or populations [4]. In addition, statistical analysis used to this purpose can be biased by linkage disequilibrium (LD) structure, admixture patterns and differences in minor allele frequencies (MAF) between and within populations. Population specificity is the most likely explanation to the poor predictability found in African-Americans in the COAG trial. It is becoming increasingly clear that many of the currently available pharmacogenetic-guided algorithms for warfarin dosing predictions do not work well in people with substantial African heritage. This poor predictability seems to be related to the omission of some important variants in the models (e.g., CYP2C9*5, *6, *8 and *11), which have proven to be clinically relevant in Africans [5-8]. Consequently, any extrapolation to a different, poorly characterized population with remarkable heterogeneity (e.g., African-Americans, Amerindians or admixed Hispanics) will be flawed. It is important to mention that none of these two clinical trials recruited a significant portion of Hispanics.

I agree with authors of the COAG trial [9] as to their results suggested no improvements on anticoagulation control in patients starting warfarin therapy by using a genotype-guided versus a clinically-driven dosing algorithm. Despite the fact that this trial showed non-superiority (but also non-inferiority) of genotyping over standard clinical procedures (i.e., to stabilize patients on warfarin during the first 4-weeks of therapy), a significant interaction between race and dosing strategy was found. Noteworthy, the primary outcome slightly improved among non-blacks in the genotype-guided group versus those in the clinical group (49% vs. 46%; adjusted mean difference 2.8%, p=0.15) [9]. Furthermore, authors of the EU-PACT trial found a moderate but significantly better control of anticoagulation in the genotype-guided dosing group (adjusted difference of 7%; p<0.001) [10]. In this trial, ~99% of patients enrolled are Whites from Europe. There were also significantly fewer incidences of excessive anticoagulation, as measured by INR>4 levels, in the pharmacogenetically controlled group. Based on their results, both the COAG and the EU-PACT trial [9,10] provided further evidence in favor of a need to develop and test more comprehensive, multi-ethnic pharmacogenetic-based dosing algorithms in order to draw valid conclusions and make adequate recommendations about the potential clinical utility of genotyping patients on warfarin.

A measure of ancestral admixture proportions needs to be included as a critical predictor in order to expand the pharmacogenetic-guided prediction models to mixed populations. Admixture is cardinal for a proper adoption of the clinical pharmacogenetic paradigm in medical practice as multi-gene algorithms are developed to predict variability of certain phenotypes or quantitative traits (e.g., differences in dose requirements). Our group has extensively assessed the role of admixture in the pharmacogenetics of Caribbean Hispanics [11-13]. Human genetic diversity has long been considered a major topic in biomedical sciences. Admixture is a surrogate for ethno-geographic genetic diversity not measured by common polymorphisms on target pharmacogenes and, therefore, it can capture a significant proportion of the missing “genetic heritability” in genotype-guided drug prescribing algorithms. Moreover, failure to control for the effect of population stratification by admixture may give rise to a confounder in pharmacogenetic studies. A previous work on the effect of NQO1*B and CYP4F2 V133M genotypes on warfarin dose requirements in Hispanic and African Americans successfully incorporated ancestry measurements as a predictor of dose variability [14]. Other studies have also considered measures of ancestry in the pharmacogenetics of warfarin by using PCA metrics [4]. The utility of genetic ancestry and admixture measures has been postulated early, emphasizing the need to be cautious when extrapolating genetic results from a homogeneous population to admixed ones [15-17].

On the other hand, differences in LD by ancestry can alter associations of well-known genetic markers with warfarin dose requirements across populations. Differential association suggests that certain genetic variants on relevant loci (i.e., some highly prevalent in Caucasians) are not causal mutations but rather in LD with functional variants (e.g., rs12777823 in African Americans and VKORC1-1639G>A in Asians) that occur preferentially in a particular ethnic group. Given the unique pattern of mixture, LD/ haplotype architecture and recombination events occurred in admixed population like Caribbean Hispanics, it is expected that some new putative markers or association signals arise from these events.

There are, of course, other elements to consider in the interpretation of negative results from the COAG trial. First, the clinical value of a pharmacogenetic test decreases when our current predictive ability is high (e.g., INR). Secondly, regression analyses usually fail to explain

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causality in the observed association between dose variability in the patient population and any of the clinical or genetic variables used as regressors. A further limitation is that they are usually derived originally from patients stable on warfarin (i.e., maintenance doses), to then be used for a priori predictions of initial doses. Additionally, regression analysis only address variability in extent, but not rate of response or the well-known time-delay between the pharmacokinetic and pharmacodynamic effects of warfarin. Accordingly, they cannot explain temporal aspects of warfarin response (e.g., anticoagulation control over time as measured by the mean percentage of time in the therapeutic INR range). Finally, common genetic variants included in the pharmacogenetic model of this trial only accounted for sensitivity but not for resistant phenotypes.

A more optimal philosophy for global pharmacogenetics is to guide medical predictions by using DNA-guided algorithms that also accounts for the effect of admixture. Experimental designs with measures of admixture included will propel the full potential of implementing genetically-guided drug therapies to advance global health. The conclusion of the COAG study is valid for the average patient within the context of the study design and its limitations, but not necessarily remains true for a global, admixture-adjusted, multi-ethnic algorithm. A clinical benefit will only be tangible for those individuals thoroughly represented in the derivation cohort of the prediction model. Recruitment of individuals from multiple ethnic groups, including admixed ones, will definitely be a challenge but a better understanding of the real utility of genotyping patients on warfarin can be gained.

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