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A Conceptual Framework for Pharmacodynamic Genome-wide Association Studies in Pharmacogenomics

Rongling Wu¹, Chunfa Tong¹, Zhong Wang¹, David Mauger¹, Kelan Tantisira², Stanley J. Szeffler³, Vernon M. Chinchilli¹, and Elliot Israel²

¹Division of Biostatistics, Pennsylvania State University, Hershey, PA

²Channing Laboratory, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

³National Jewish Health and University of Colorado School of Medicine, Denver, CO

Summary

Genome-wide association studies (GWAS) have emerged as a powerful tool to identify loci that affect drug response or susceptibility to adverse drug reactions. However, current GWAS based on a simple analysis of associations between genotype and phenotype ignores the biochemical reactions of drug response, thus limiting the scope of inference about its genetic architecture. To facilitate the inference of GWAS in pharmacogenomics, we sought to undertake the mathematical integration of the pharmacodynamic process of drug reactions through computational models. By estimating and testing the genetic control of pharmacodynamic and pharmacokinetic parameters, this mechanistic approach does not only enhance the biological and clinical relevance of significant genetic associations, but also improve the statistical power and robustness of gene detection. This report discusses the general principle and development of pharmacodynamics-based GWAS, highlights the practical use of this approach in addressing various pharmacogenomic problems, and suggests that this approach will be an important method to study the genetic architecture of drug responses or reactions.

Introduction

It has been recognized that there exists a great variability among different individuals in response to a particular drug, with a large proportion determined by genes [1,2]. The term pharmacogenetics or pharmacogenomics was proposed to investigate the effects of individual genes on drug disposition and drug response. With the rapid development of high-throughput genotyping techniques, genome-wide association studies (GWAS) using multiple single nucleotide polymorphisms (SNPs) to test association with a phenotype have revolutionized the study of the comprehensive genetic architecture of complex traits. In the last three years, this approach has been increasingly applied to search for genetic influences

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Corresponding author: Rongling Wu, rwu@hes.hmc.psu.edu.

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on drug response [3-9] or adverse drug reactions [10-12]. Many GWAS studies identified significant genetic associations that display potential clinical implications in practice [13].

Despite benefits in identifying genetic variants for complex traits, GWAS also raises questions. One of the most important is why the identified variants account for so little heritability [14,15]. When applied to pharmacogenomics, GWAS can raise additional challenges [2]. First, since it is challenging to obtain adequate numbers of cases for pharmacogenomics GWAS, there is insufficient power to detect small or moderately sized genetic effects. This sharply contrasts with complex-disease GWAS studies in which a sample size with a large population is common [16]. Second, in order to determine an optimal dose for individual patients, phenotypic response is often measured at a range of drug doses, leading to the longitudinal feature of drug response. Third, longitudinal trajectories of drug response in clinical trials may be sampled at sparsely distributed doses, with dose levels varying from subject to subject; the measurements may be affected by noise and are dependent within the same subject. To better study the genetic etiology of drug response, therefore, a special analytical model should be derived by considering these characteristics.

The purpose of this report is to introduce a dynamic model for pharmacogenomics GWAS through incorporating repeated measures of drug response. Although we will show that statistical modeling of multiple measurements increases the power of gene detection, this treatment also exhibits a significant biological relevance. Normally, when a drug is administered to a patient, it must be absorbed, distributed to its site of action, interact with its targets, undergo metabolism, and finally be excreted [17]. This process, called pharmacokinetics (PK), influences the concentration of a drug reaching its target, and it interacts with another process associated with the drug target, called pharmacodynamics (PD), to determine drug response. By modeling the effects of a drug over a range of doses, the pharmacodynamic response can be quantified. The incorporation of PK and PD models to map quantitative trait loci for drug response has proven to be powerful for gene identification [18-20]. More recently, new insight has been provided for the mechanistic basis of interactions between genes and drug reactions by dissecting drug response as a dynamic system in which the coordination of various biochemical components is modeled by a series of differential equations [21]. We propose that integrating pharmacodynamic processes into GWAS will facilitate the mechanistic elucidation of the genetic architecture of drug response.

Dynamic Pattern of Pharmacogenetic Control

It has been recognized that specific genes are involved in regulating drug response via PK and PD processes of medications [22,23]. In Figure 1, a gene is assumed to determine inherited differences in drug disposition (e.g., metabolizing enzymes and transporters), expressed as PK reactions (top, Fig. 1), and in regulating drug targets (e.g., receptors), expressed as PD reactions (middle, Fig. 1) [22]. Patients are different in drug clearance (or the area under the plasma concentration-time curve) and receptor sensitivity, depending on their genotypes. The patients who are homozygous for the wild-type allele (*WT/WT*) tend to depose a less amount of drug in time course than those who are homozygous for the variant

allele (*V/V*) and heterozygous (*WT/V*). Also, the clinical efficacy (favorable effect) of the drug is more pronounced for the *WT/WT* patients than for the *WT/V* and *V/V* patients, although the toxicity (adverse effect) of the drug displays no difference among different genotypes.

An increasing body of genetic studies has shown that genes responsible for drug response operate in different ways [20]. Figure 2 elucidates three possible types of genes for drug effect as a function of dose. Assuming that there are two different genotypes at a gene, these three types of genes can be described as follows:

1. **Faster-slower genes** (Fig. 2A), which control variation in the dose at which drug effect is maximal. While one genotype at a gene (faster) has maximal drug effect at higher dose levels, the other (slower) has maximal drug effect at lower doses. The faster-slower gene determines how quickly patients reach their physiological limits in drug response.
2. **Higher-lower genes** (Fig. 2B), which determine variation in the maximum drug effect reached. A higher genotype can tolerate higher physiological limits than a lower genotype.
3. **Earlier-later genes** (Fig. 2C), which are responsible for variation in the dose at which drug effect increases exponentially. One genotype responds to lower dose levels more quickly than to higher dose levels (earlier), whereas the genotype responds to higher dose levels more quickly than to earlier dose levels (later).

It is possible that these three types of genes may exist simultaneously in the same population so that such a population may contain mixtures of genotypes that vary along different axes of analysis. Also, a single gene may be characterized by these three features of expression. A central challenge is to quantify how different types of genetic variation controlled contribute to the total genetic variation for response-dose curves in a population. This can be addressed by integrating pharmacodynamic principles into GWAS.

Integrating Pharmacodynamic Principles into GWAS

Study Design

Suppose there is a group of patients who differ in age, race, sex, body mass index (BMI), and other demographics, recruited from a natural population to study their response to a particular drug. If the drug is administered with a series of doses, each patient is measured for some phenotypes that reflect drug effect. Let $C_i = (C_{i1}, \dots, C_{iT_i})$ denote dose levels administered to subject i and $y_i = [y_i(C_{i1}), \dots, y_i(C_{iT_i})]$ denote the vector of effect phenotypes at T_i at different doses for this subject. All these patients are genotyped for genome-wide SNPs, aimed to identify significant genetic variants with drug response. Let us first consider a SNP with three different genotypes *AA*, *Aa*, and *aa*. The observations of these three genotypes are n_1 , n_2 , and n_3 , respectively. If these genotypes differ significantly in a response phenotype, detected by a likelihood-ratio test as described below, then this SNP is thought to be associated with drug response.

Dissecting Drug Response

Drug response is multifactorial, affected by genetic, demographic and environmental factors. The phenotype of drug response for subject i can be expressed as a function of these factors, with demographic factors included in covariates, i.e.,

$$y_i(C_{i\tau}) = \sum_{k=1}^3 z_{ik} g_k(C_{i\tau}) + \sum_{r=1}^R \alpha_r u_{ir} + \sum_{s=1}^S \sum_{l=1}^{L_s} x_{isl} v_{sl} + e_i(C_{i\tau}) \quad (1)$$

where $y_i(C_{i\tau})$ is the phenotypic value of drug response for subject i at dose $C_{i\tau}$, $g_k(C_{i\tau})$ is the genotypic value at dose $C_{i\tau}$ of subject i who carries SNP genotype k ($k = 1$ for AA , 2 for Aa , and 3 for aa), z_{ik} is an indicator variable of subject i defined as 1 if this subject carries a genotype considered and 0 otherwise, u_{ir} ($r = 1, \dots, R$) is the value of the r th continuous covariate, such as age and BMI, for subject i , α_r is the effect of the r th continuous covariate, v_{sl} ($l = 1, \dots, L_s$, $s = 1, \dots, S$) is the effect of the l th level for the s th discrete covariate, such as race, gender, and treatment, with $\sum_{l=1}^{L_s} v_{sl} = 0$ where L_s is the number of levels for the s th discrete covariate, x_{isl} is an indicator variable of subject i who receives the l th level of the s th discrete covariate, and $e_i(C_{i\tau})$ is a random error.

Pharmacodynamic Model

The effects of a drug at different doses reflect its pharmacodynamic process in a human body, which can be described by the Emax model [24], i.e.,

$$E(C) = E_0 + \frac{E_{\max} C^H}{EC_{50}^H + C^H}, \quad (2)$$

where E_0 is the baseline, $E_{\max}$ is the asymptotic (limiting) effect, EC_{50} is the drug concentration that results in 50% of the maximal effect, and H is the slope parameter that determines the slope of the concentration-response curve. The larger H , the steeper the linear phase of the log-concentration effect curve. If the data is normalized so that the baseline is removed, only the remaining three parameters are needed to describe drug effect.

In equation (1), the genotypic value of subject i for dose-dependent drug effects can be approached by the Emax model. For a particular SNP genotype k , we need to estimate PD parameters (E_{0k} , $E_{\max k}$, EC_{50k} , H_k) to illustrate its effect-dose curve. If these parameters are different among the three genotypes, this means that this SNP is associated with drug response. In practice, we often normalize the data of drug response by removing the baseline effect, leading to three PD parameters arrayed as $\Omega_k = (E_{\max k}, EC_{50k}, H_k)$.

Covariance Function

For subject i , its phenotype vector $\mathbf{y}_i$ is regarded to follow a multivariate normal distribution so that its random error vector $\mathbf{e}_i$ is distributed as $N(0, \Sigma_i)$ where Σ_i is a longitudinal covariance matrix for subject i . The covariance structure can be modeled parametrically by various statistical approaches, such as autoregressive, antedependence, autoregressive

moving average, Brownian motion, and Ornstein-Uhlenbeck process. For each of these approaches, it is important to determine its optimal order to model covariance structure. A model selection procedure was proposed to determine the most parsimonious approach.

Assuming that the simplest first-order autoregressive (AR(1)) model, in which variances and covariances are stationary, is used to model the covariance structure, we estimate two parameters, σ^2 , the residual variance at a dose, and ρ ($-1 < \rho < 1$), the proportion parameter with which the correlation decays with dose lag. For the AR(1), we estimate parameters $\Omega_v = (\sigma^2, \rho)$.

Likelihood and Estimation

The likelihood of all unknowns $\Theta = (\{\Omega_k\}_{k=1}^3, \Omega_v)$ given the SNP genotype ($\mathbf{M}$) and phenotype data ($\mathbf{y}$) is formulated by

$$L(\Theta|\mathbf{M}, \mathbf{y}) = \prod_{i=1}^{n_1} f_1(\mathbf{y}_i) \prod_{i=1}^{n_2} f_2(\mathbf{y}_i) \prod_{i=1}^{n_3} f_3(\mathbf{y}_i) \quad (3)$$

where $f_k(\mathbf{y}_i)$ is a multivariate normal distribution for genotype k with subject-specific mean vector

$$\mu_{ik} = \left\{ \frac{E_{\max} C_{i\tau}^H}{EC_{50}^H + C_{i\tau}^H} + \sum_{r=1}^R \alpha_r u_{ir} + \sum_{s=1}^S \sum_{l=1}^{Ls} x_{isl} v_{sl} \right\}_{\tau=1}^{T_i} \quad (4)$$

and subject-specific covariance matrix Σ_i fitted by the AR(1) model.

The mean vectors of different genotypes are modeled by the Emax model, whereas the covariance modeled by an appropriate approach such as AR(1). To obtain the maximum likelihood estimates (MLEs) of the unknown parameters in equation (3), we apply a hybrid of the Nelder-Mead Simplex and least squares methods. The MLEs of the covariate effects are obtained by a least square method, whereas the Emax parameters of three genotypes and covariance-structuring parameters are estimated by the Simplex method. If the AR(1) model is used, the MLE of parameter ρ can be estimated by an exhausting search in the interval (0, 1) or (−1, 0), depending on whether the correlation between different dose levels is positive or negative.

Model Selection

Full Model—The significance of the association between the SNP and drug response can be expressed in different ways. If all three genotypes at a SNP, *AA*, *Aa*, and *aa*, are different from one another in drug response, these differences can be tested by a full model (3) based on the following hypotheses:

$$\begin{aligned} H_0: \Omega_1 = \Omega_2 = \Omega_3 &\equiv \Omega \\ H_1: &\text{at least one of the equalities above does not hold} \end{aligned} \quad (5)$$

where the H_0 corresponds to the reduced model in which the data is fitted by a single curve and the H_1 corresponds to the full model in which there exist at least two curves to fit the data. The log-likelihood ratio of the full model over the reduced model is applied to test the above hypotheses

$$LR = -2 \log \left[\frac{L_0(\hat{\Theta})}{L(\hat{\Theta})} \right] \quad (6)$$

where $\hat{\Theta}$ and $\tilde{\Theta}$ denote the MLEs of the unknown parameters under H_1 and H_0 , respectively. Generally the LR is distributed as a chi-square distribution with 6 degrees based on the large sample theory. However, if the large sample theory does not hold for a typical small-sized pharmacogenomic study permutation tests can be used to determine the critical threshold. The LR of a SNP with a p -value less than 0.05 can indicate that this SNP is associated with a significant effect. However, in GWAS testing of SNPs at the same time, multiple testing should be performed to reduce false-positive rates. A commonly used FDR approach is employed to adjust for multiple comparison, in which the conventional p -value is multiplied by the number of tests performed and divided by its rank from small to large [25].

Additive Model—If the genotypic difference of a SNP is due to its allelic effect, we formulate an additive model to specify this pattern. The additive model describes the difference between alleles A (carried by all genotype AA and a half of genotype Aa) and a (carried by all genotype aa and a half of genotype Aa). The likelihood for the additive model is expressed as

$$L(\Theta_a | \mathbf{M}, \mathbf{y}) = \prod_{i=1}^{n_1 + \frac{1}{2}n_2} f_A(\mathbf{y}_i) \prod_{i=1}^{n_3 + \frac{1}{2}n_2} f_a(\mathbf{y}_i) \quad (7)$$

where Θ_a contains allele-specific curve parameters in $f_A(\mathbf{y}_i)$ and $f_a(\mathbf{y}_i)$, respectively.

Dominant and Recessive Models—The genotypic difference of a SNP can also arise from the dominance of one allele over the other. If allele A is dominant to allele a , genotypes AA and Aa collapse into the same group (A_{-}). Relative to this dominant model, the recessive model describes the case in which allele A is recessive to allele a so that genotypes Aa and aa are in the same group ($_{-}a$). The likelihood for the dominant or recessive model is expressed as

$$L(\Theta_d | \mathbf{M}, \mathbf{y}) = \begin{cases} \prod_{i=1}^{n_1+n_2} f_{A_{-}}(\mathbf{y}_i) \prod_{i=1}^{n_3} f_{aa}(\mathbf{y}_i) & \text{when } A \text{ is dominant to } a \\ \prod_{i=1}^{n_1} f_{AA}(\mathbf{y}_i) \prod_{i=1}^{n_2+n_3} f_{_{-}a}(\mathbf{y}_i) & \text{when } a \text{ is dominant to } A \end{cases} \quad (8)$$

where Θ_d contains curve parameters specifying the dominant relationships.

Like the full model (3), the parameters are estimated for reduced models (7) and (8), respectively. For a practical data set, the optimal model that explains it is unknown. Using commonly used criteria, such as AIC or BIC, we can identify an optimal model that best fits the data.

Model Validation

To investigate the statistical behavior of the pharmacodynamic model for GWAS, we performed simulation studies for a genomic region derived from a GWAS dataset and calculated the mean genotypic curves under an additive genetic model. The simulation studies mimicked a pharmacogenomic trial of asthma [26], reflecting a general design used for practical pharmacogenomic studies in terms of sample size, dose level, and demographical attributes of participants. The phenotypic longitudinal data of drug response were simulated using parameters estimated for SNP rs10481450 from a trial called the Dose of Inhaled Corticosteroids with Equisystemic Effects (DICE) [26] by assuming the autoregressive structure of residual covariance matrix. The estimates of genotype-specific pharmacodynamic parameters and covariate effects as well as the standard errors of all the estimates from 1000 simulation replicates are described in Table 1. In general, a modest sample size (say 100) provides reasonably good estimates of the parameters. When sample size is doubled or tripled, the precision of parameter estimates increases strikingly. In Figure 1, we illustrate the estimated and true curves for drug response, demonstrating that the model provides reasonably accurate estimates of response curves, especially when a larger sample is used.

We conducted additional simulation studies to compare the power of our dynamic model and traditional single-trait GWAS models with different sample sizes (Table 2). If drug effects at individual doses are analyzed separately by traditional models, the power for association detection is low, although higher doses have increasing power due to increasing variability at these doses. However, when all doses are analyzed simultaneously using our new pharmacodynamic model, the power increases remarkably. By simulating and analyzing phenotypic data based on a single curve of drug response, we examined the false positive rates (FPR) of the model. With a modest sample size, the FPR is below 0.05.

Discussion

Drug reactions can be better described as a coordinated network of genes, proteins and biochemical reactions [27]. However, traditional pharmacogenetic or pharmacogenomics studies merely consider the associations between genes and final outcomes of pharmacological parameters. By incorporating the pharmacodynamic and pharmacokinetic mechanisms through mathematical equations, the statistical method proposed for genome-wide association studies (GWAS) will provide a computational tool for identifying genetic variants associated with drug response and, ultimately, obtaining a better insight into the multifactorial and mechanistic basis of this important phenotype.

The new pharmacodynamic model dissects the control mechanisms of genes for drug response into its underlying PD processes, thus a network of genetic control is identified for

key steps of biochemical pathways that cause the outcome of drug response. Specific genes and their interactions can be modeled and tested for different aspects of drug response including drug efficacy, drug toxicity, and chronobiology. The impact of genes on the optimal window of dosage over which a drug is used can be investigated.

The new model was validated using simulation studies that can theoretically examine the statistical behavior of the model. By mimicking a real data structure of asthma genetic study [26], we found that parameters that define the model can be reasonably well estimated even with a modest sample size. Furthermore, the model displays acceptable power to detect significant SNPs and, also has low false positive rates, when a modest sample size is used. It has also been shown that the pharmacodynamic model is much more powerful than a traditional model based on individual doses. Finally and not least, the pharmacodynamic model shows a unique robustness for irregular, uneven-spaced, and subject-specific longitudinal measurements, which are common in clinical trials.

The model was derived on the basis of single SNP or single SNP-pair analyses. Such analyses using a SNP or a SNP pair at one time, with the significance level adjusted for multiple comparisons of all SNPs throughout the genome, are simple and accepted in current GWAS, but may fail to precisely characterize a comprehensive picture of the genetic control for drug response. However, considering all SNPs and all their possible interactions is difficult, given the extremely high dimension of the GWAS data. A powerful statistical technique, called LASSO, can be used to reduce the dimension of independent variables and obtain sparse results of significant main and interaction effects. This technique has produced promising results in analyzing GWAS data [28]. In addition, joint modeling of pharmacodynamic and pharmacokinetic processes has proven to be effective for unraveling the biochemical machineries for drug response [29,30]. It is worthwhile to apply a joint PK-PD model, coupled with systems biology [27], into the GWAS setting, further improving our understanding of pharmacogenetic variability of drug response.

In conclusion, our approach for combining longitudinal analyses and pharmacodynamic principles is a powerful way for identifying novel pharmacogenetic markers through GWAS. While early studies identified genetic variants for drug response through a static model, future advances depend on the more difficult challenge of elucidating pharmacodynamic and pharmacokinetic determinants of drug response. Our model that integrates genomic tests with extensive phenotypic analyses of uniformly treated patients shows unique power to define the inherited nature of drug effects and fully understand the contribution of polymorphisms to individual differences in drug effects, ultimately facilitating the translation of genomics into clinical practice.

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Figure 1.

Three genotypes (WT/WT, WT/V, and V/V) associated with different curves for drug metabolism and drug receptor, showing the pattern of genetic control of drug response through pharmacokinetics and pharmacodynamics. AUC is the area under the concentration-time curve. Adapted from ref [22].

Figure 2.
Hypothetical patterns of variation in response-dose curves.

Figure 3. Pharmacodynamic curves of drug response estimated from a simulation study that mimicking a real pharmacogenetic trial (broken), in a comparison with true curves (solid), under an additive model of two genotypic groups. The consistency between the broken and solid curves under different sample sizes (**A**, 100; **B**, 200; **C**, 400) indicates the accuracy of pharmacodynamic response by our dynamic model.

Table 1

Means of the estimates of parameters for the pharmacodynamic model and their standard errors (in parentheses) from simulated data by mimicking the DICE data structure with different sample sizes based on 1000 simulation replicates. An additive model is assumed, with two groups of genotypes at a specific SNP.

Parameter	True Value	Estimate (SE)		
		100	200	400
Favorable allele				
$E_{\max 1}$	2.19	2.39(0.71)	2.38(0.62)	2.34(0.52)
$EC_{50(1)}$	15.43	18.57(3.55)	16.65(3.50)	16.34(3.46)
H_1	0.26	0.28(0.11)	0.26(0.08)	0.26(0.05)
Unfavorable allele				
$E_{\max 2}$	18.04	18.13(2.44)	18.16(1.82)	18.19(1.28)
$EC_{50(2)}$	29.81	31.60(3.53)	29.52(3.51)	29.20(3.46)
H_2	0.12	0.13(0.02)	0.13(0.01)	0.13(0.01)
Covariates				
α_1	-0.10	-0.09(0.11)	-0.09(0.07)	-0.10(0.05)
α_2	0.15	0.14(0.14)	0.14(0.09)	0.14(0.06)
ν_{11}	0.05	0.08(1.53)	0.03(1.10)	0.01(0.74)
ν_{12}	-0.45	-0.40(1.80)	-0.42(1.33)	-0.43(0.86)
ν_{13}	-3.73	-3.73(1.80)	-3.71(1.26)	-3.70(0.90)
ν_{14}	3.14	3.06(2.09)	3.12(1.50)	3.13(1.07)
ν_{21}	3.6	3.50(2.16)	3.52(1.25)	3.63(0.83)
ν_{22}	-2.18	-2.24(2.62)	-2.30(1.51)	-2.19(1.07)
ν_{23}	1.21	1.22(3.04)	1.22(1.89)	1.17(1.31)
ν_{31}	-0.62	-0.60(0.88)	-0.62(0.67)	-0.60(0.44)
Covariance structure				
ρ	0.77	0.75(0.03)	0.76(0.02)	0.76(0.02)
σ^2	82.15	77.28(7.47)	79.71(5.42)	80.81(4.00)

Note: In this simulation example, we consider the following covariates: α_1 is the effect due to age, α_2 is the effect of body mass, $\nu_{11}, \dots, \nu_{14}$ are the effects of five different treatment groups with restriction $\nu_{15} = -\nu_{11} - \dots - \nu_{14}$, $\nu_{21}, \dots, \nu_{23}$ are effects of four different races, with $\nu_{24} = -\nu_{21} - \dots - \nu_{23}$, and ν_{31} is the effect of two genders, with $\nu_{32} = -\nu_{31}$.

Table 2

Power of significance detection by the traditional model for analyzing data at individual doses and our dynamic model combining all doses in an integral way. The sample size used is 100 and the number of simulation replicates is 1000.

Dose Level	Power
Traditional Model	
1	0.002
2	0.259
3	0.170
4	0.180
Dynamic Model	
All	0.804