Title
Pharmacodynamic genome-wide association study identifies new responsive loci for glucocorticoid intervention in asthma

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Asthma is a chronic lung disease that has a high prevalence. The therapeutic intervention of this disease can be made more effective if genetic variability in patients’ response to medications is implemented. However, a clear picture of the genetic architecture of asthma intervention response remains elusive. We conducted a genome-wide association study (GWAS) to identify drug response-associated genes for asthma, in which 909 622 SNPs were genotyped for 120 randomized participants who inhaled multiple doses of glucocorticoids. By integrating pharmacodynamic properties of drug reactions, we implemented a mechanistic model to analyze the GWAS data, enhancing the scope of inference about the genetic architecture of asthma intervention. Our pharmacodynamic model observed associations of genome-wide significance between dose-dependent response to inhaled glucocorticoids (measured as %FEV1) and five loci ($P = 5.315 \times 10^{-7}$ to $3.924 \times 10^{-9}$), many of which map to metabolic genes related to lung function and asthma risk. All significant SNPs detected indicate a recessive effect, at which the homozygotes for the mutant alleles drive variability in %FEV1. Significant associations were well replicated in three additional independent GWAS studies. Pooled together over these three trials, two SNPs, chr6 rs69248008 and chr11 rs1353649, display an increased significance level ($P = 6.661 \times 10^{-16}$ and $5.670 \times 10^{-11}$). Our study reveals a general picture of pharmacogenomic control for asthma intervention. The results obtained help to tailor an optimal dose for individual patients to treat asthma based on their genetic makeup.

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family-based data\textsuperscript{25–29} and has recently been applied to asthma treatment response.\textsuperscript{30} However, the vast majority of clinical trials of drug response do not involve DNA collection in non-trial family participants. Here, we present an alternative approach by incorporating the pharmacodynamic principle of drug response into a pharmacogenetic GWAS. The basic idea of such incorporation is to model drug effect-dose relationships through mathematical equations based on repeated measures of drug response at multiple dosages.\textsuperscript{31–34} By estimating and testing those mathematical parameters that define the effect-dose curves, one can determine how a specific gene affects drug effects at each dose or across a range of doses. Because of its statistical parsimony, that is, the number of curve parameters is always less than the number of doses,\textsuperscript{31–34} the incorporation of mathematical equations can potentially increase the power of detecting significant associations, compared with traditional GWAS analysis based on a simple phenotype-genotype relationship. Although the theory of this incorporation has well been established in the previous studies,\textsuperscript{30–34} here we have for the first time reported a systematic implication of this theory for practical pharmacogenetic studies in asthma intervention.

The pharmacodynamic approach was applied to analyze a pharmacological GWAS trial derived from SNP Health Association Asthma Resource projects (SHARP),\textsuperscript{35–37} leading to the identification of five significant SNPs responsible for pulmonary response after asthma treatment. Associations between these SNPs and the same phenotype were well confirmed by analyzing three additional GWAS. To investigate how small sample sizes, characteristic of pharmacogenomics studies, impact on the estimation of genetic effects and the power of gene detection, we performed computer simulation by mimicking the data structure of SHARP. We found that the implementation and use of a pharmacodynamic model can overcome, to some extent, the limitation of small sample sizes in pharmacological GWAS.

**MATERIALS AND METHODS**

**Statistical Consider**

Consider a clinical trial composed of \( n \) participants used for a pharmacological GWAS, in which each of the participants is genotyped for SNPs throughout the entire genome. These participants receive the administration of a drug under a multitude of doses, at each of which a pharmacological parameter that reflects drug effect is measured. Under this design, each participant (say \( i \)) has a series of dose-dependent pharmacological phenotypic data, expressed as \( y_i = (y_i(C_0), \ldots, y_i(C_{n_m})) \), where \( C_0, \ldots, C_{n_m} \) are \( M \) doses of administration participant \( i \) receives. We allow different participants to possibly receive different number of doses in the clinical trial.

It is likely that drug response as a complex trait is controlled by many genes, each with a different effect. The GWAS is motivated to identify all possible genes and estimate each gene’s effects on drug response. Assuming that there is such a gene with three genotypes and, also, the number of curve parameters is always less than the number of doses,\textsuperscript{31–34} the incorporation of mathematical equations can potentially increase the power of detecting significant associations, compared with traditional GWAS analysis based on a simple phenotype-genotype relationship. Although the theory of this incorporation has well been established in the previous studies,\textsuperscript{30–34} here we have for the first time reported a systematic implication of this theory for practical pharmacogenetic studies in asthma intervention.

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predict. During enrollment, AM (before 0930 hours) plasma cortisol concentration of $\geq 5$ mcg dl$^{-1}$ need to be attained. After a 1-week run-in period, participants were randomized to one of six active inhaled corticosteroid (ICS) delivery systems (or the corresponding placebo). After each week of treatment, participants remained at the study center for an overnight stay and then received a medication supply with a doubled dose for the subsequent week. This process continues until there are a total of four dosages. At each of the dosages, participants were measured for morning plasma cortisol levels and the FEV$_1$ in 1s (%FEV$_1$).

### RESULTS

#### Gene detection

We used the pharmacodynamic model to identify genes for drug response (%FEV$_1$) to inhaled corticosteroids for asthma treatment by jointing estimating the effect due to covariates, age, BMI, race, gender and drug type. Dose levels of drugs were normalized to a common 6-week run-in period on inhaled corticosteroid therapy (Table 1). At the end of the run-in period, the milder patients were allocated to SOCS (FEV$_1 \geq 80\%$ predicted, PEF variability $\approx 200$ ml improvement following albuterol $\pm$ inhaled corticosteroids for asthma treatment) and the more moderate patients allocated to SLIC. The %FEV$_1$ was measured for the three trials above.

In four trials, DICE, IMPACT, SOCS and SLIC, subjects were genotyped for 909,622 SNPs throughout the entire genome. Genotyping was performed on Affymetrix 6.0 arrays. SNP genotypes were obtained after stringent quality-control filters.

#### Pharmacogenomic control for asthma intervention

Table 1. Population characteristics of the longitudinal DICE trial and other three independent trials

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DICE</th>
<th>IMPACT</th>
<th>SOCS</th>
<th>SLIC</th>
<th>SOCS/SLIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>120</td>
<td>251</td>
<td>79</td>
<td>106</td>
<td>31</td>
</tr>
<tr>
<td>Inhaled glucocorticoid</td>
<td>Budesonide</td>
<td>1) Budesonide+Zafirlukast</td>
<td>Triamcinolone</td>
<td>1) Triamcinolone+Salmetrol+Triamcinolone</td>
<td>Triamcinolone</td>
</tr>
<tr>
<td>Age (year)</td>
<td>30.6 $\pm$ 8.1</td>
<td>34.2 $\pm$ 10.8</td>
<td>30.4 $\pm$ 10.9</td>
<td>35.9 $\pm$ 12.4</td>
<td>32.7 $\pm$ 11.4</td>
</tr>
<tr>
<td>Sex no. subject(%)</td>
<td>Male</td>
<td>51 (56.7%)</td>
<td>57 (39.0%)</td>
<td>30 (41.1%)</td>
<td>43 (45.3%)</td>
</tr>
<tr>
<td>Female</td>
<td>39 (43.3%)</td>
<td>89 (61.0%)</td>
<td>43 (58.9%)</td>
<td>52 (54.7%)</td>
<td>10 (47.6%)</td>
</tr>
<tr>
<td>Baseline FEV$_1$ (%) of predicted</td>
<td>79.0 $\pm$ 7.4</td>
<td>88.8 $\pm$ 13.3</td>
<td>85.6 $\pm$ 14.0</td>
<td>67.6 $\pm$ 10.9</td>
<td>73 $\pm$ 15.9</td>
</tr>
<tr>
<td>Change in FEV$_1$ (%) of predicted</td>
<td>6.5 $\pm$ 10.3</td>
<td>1.3 $\pm$ 7.4</td>
<td>7.3 $\pm$ 11.8</td>
<td>4.5 $\pm$ 9.8</td>
<td>2.6 $\pm$ 16.6</td>
</tr>
</tbody>
</table>

Table 2. Power to correctly identify the pattern of pharmacological inheritance by the pharmacodynamic model

<table>
<thead>
<tr>
<th>Sample size</th>
<th>True model</th>
<th>Estimated model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Full</td>
<td>Recessive</td>
</tr>
<tr>
<td>100</td>
<td>Full</td>
<td>887</td>
</tr>
<tr>
<td></td>
<td>Recessive</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Dominant</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Additive</td>
<td>4</td>
</tr>
<tr>
<td>200</td>
<td>Full</td>
<td>991</td>
</tr>
<tr>
<td></td>
<td>Recessive</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Dominant</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Additive</td>
<td>9</td>
</tr>
<tr>
<td>400</td>
<td>Full</td>
<td>1000</td>
</tr>
<tr>
<td></td>
<td>Recessive</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Dominant</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Additive</td>
<td>2</td>
</tr>
</tbody>
</table>

The data were simulated by mimicking the DICE data structure and the estimates obtained by BIC from 1000 simulation replicates.

five significant SNPs were detected by the genotypic (Supplementary Figure 1A) and recessive model (Supplementary Figure 1D). The additive and dominant models did not identify significant associations (Supplementary Figure 1B and 1C). Two SNPs on chromosomes 8 and 11 were detected by both genotypic and recessive models, but, according to BIC values calculated, both SNPs conform to the recessive model better than the genotypic model. The following loci produce associations of genome-wide significance with physiological response to glucocorticoid therapy for asthma (Table 2): rs6924808 on chromosome 6 with wild-type allele C and mutant T ($P = 3.924 \times 10^{-4}$), rs10481450 on chromosome 8 with wild-type allele A and mutant T ($P = 5.315 \times 10^{-5}$), rs1353649 on chromosome 11 with wild-type allele G and mutant A ($P = 1.798 \times 10^{-6}$), and rs2230155 on chromosome 15 with wild-type allele C and mutant T ($P = 107.3 \times 10^{-6}$). To evaluate the influence of population stratification, we calculated the ratio of the median of the log-likelihood ratio among all SNPs analyzed over the critical value of the $\chi^2$ distribution at the 0.05 significance level. If this ratio is near, or slightly less than, 1.0, this indicates that the effect due to population stratification is ignorable. The ratios calculated are 0.82–0.88 for the genotypic, additive and dominant models used, suggesting that our results are not largely affected by population structure.
Pharmacodynamic pattern of genetic effects

The pharmacodynamic model allows the estimates of genotype-specific curve parameters ($E_{\text{max}}$, $EC_{50}$, $H$) that define drug response (see Supplementary Table 1 for the maximum likelihood estimates of the parameters and the s.d. of the estimates). Each of these parameters differs strikingly between two groups of genotypes, the homozygote for the mutant allele, and a mix of the homozygote for the wild-type allele and the heterozygote for the two different alleles, at significant SNPs. The overall influence of these parameters on variability in glucocorticoid response curve can be seen from response curves drawn for each genotype group (Figure 1). It can be observed that individual SNPs fit raw longitudinal data reasonably well and also different SNPs affect drug response in different ways.

At all significant SNPs, the wild-type allele is dominant over the mutant for their actions in affecting glucocorticoid response, as revealed by the recessive model. For chr6 rs6924808, the homozygote (CC) for the wild-type allele C and the heterozygote (CT) for the wild-type allele and mutant T are more responsive to changing doses of glucocorticoids than the homozygote (TT) for the mutant (Figure 1a). At chr8 rs10481450 and chr11 rs1353649, the homozygotes for the mutant display remarkably greater sensitivity to drug dose than the genotypes containing the wild-type alleles (Figures 1b and c). Chr15 rs12438740 and chr15 rs2230155 are located closely together on the same chromosome, with a high linkage disequilibrium ($r = 0.99$), exhibit a similar dynamic pattern of genetic effect (Figures 1d and e); the homozygote for the mutant do not respond until a particular dose level is reached, whereas the genotypes containing the wild-type allele appear to be resistant to increasing dose. Figure 1 shows that some SNPs capture a wide variation like rs10481450 and rs1353649, whereas the others explain a narrow variation like rs6924808, rs12438740 and rs2230155. Some SNPs are sensitive to a small change in low doses of drug, such as rs6924808, and some display variation after a certain level of dose is reached, such as rs10481450 and rs12438740. The common feature of all the SNPs is that different groups of genotypes start to diverge at a lower level of dose and stabilize their variation during a wide range of dose.

In sum, the mutant allele produces a pronounced increase in lung function after glucocorticoid treatment as compared with the wild-type allele for all SNPs, except for chr6 rs6924808. Overall, subjects who are homozygous for the mutant allele are 30–300% larger for %FEV1 values at an intermediate dose of glucocorticoids than those who are homozygous for the wild-type allele and heterozygous for the two alleles (Figure 2; Supplementary Table 2). The differences between these two groups of genotypes are 30–245% of the mean of all treated subjects. There are striking differences in the heritability of %FEV1 response to glucocorticoid therapy explained by individual SNPs (Figure 3). Chr11 rs1353649 accounts for 19–26% of the phenotypic variation, whereas these

Figure 1. Changes in pulmonary response to varying doses of inhaled corticosteroids as defined as prebronchodilator %FEV1 for two different groups of genotypes (i.e., the mutant homozygote, MM and a mix of the homozygote for the wild-type allele and the heterozygote for the two different alleles, W_) at five significant SNPs, chr6 rs6924808 (a), chr8 rs10481450 (b), chr11 rs1353649 (c), chr15 rs12438740 (d) and chr15 rs2230155 (e), for the DICE trial detected by the recessive model. Blue thin lines in background are response curves of individual participants to varying dosages. The original data were normalized by removing the baselines and plotted against relative scales of corticosteroid dosages.
values are 8–20% for chr8 rs10481450 and chr6 rs6924808 and 2–5% for chr15 rs12438740 and chr15 rs2230155. All SNPs display a dynamic change of heritability over dose.

Cross validation

We performed an additional analysis to cross-validate the results detected by randomly splitting the population into two equally sized sub-groups. In Supplementary Table 3, we summarized the results about the estimates of parameters from 100 resampling replicates for each subgroup at a significant SNP rs10481450, in a comparison with those from the whole population. The parameter estimates of each subgroup are quite consistent, and they are consistent with those using the whole population. Although s.e. values of the estimates for some parameters are large due to a small sample size, they are reasonably within the space of estimates.

Computer Simulation

The statistical properties of the pharmacodynamic model to analyze GWAS data were investigated through computer simulation. The simulation mimicked the DICE trial in terms of sample size, dose level and demographic attributes of participants. The phenotypic data of drug response on the DICE trial in terms of sample size, dose level and demographic attributes of participants. The phenotypic data of drug response were simulated using parameters estimated for SNP rs10481450 detected from the DICE trial by assuming normally distributed residuals. The data were simulated using the genotypic, additive, dominant and recessive models and then analyzed by each model.

The pharmacological model has good power to detect a correct pattern of genetic action (Table 2). When a correct model was used, genotype-specific pharmacodynamic parameters and covariate effects can be reasonably estimated. Table 3 gives the estimates of parameters and their sampling errors under different sample sizes when the genotypic model is assumed. In Supplementary Table 4, estimates of parameters by the dominant, recessive and additive models are given. The estimates of three pharmacological parameters, \( F_{\text{max}} \), \( \text{EC50} \) and \( H \), each have a reasonably small sampling error for each genotype, even when the sample size is modest (100). The estimation precision of these parameters increases markedly when sample size increases to 200 or 400.

Because humans cannot be controlled, like plants or animals, it is unavoidable to include many covariates, such as different demographic factors, in human GWAS. These covariates would often confound the identification of significant genes. However, the deployment of a multiple regression model that incorporates covariate effects can filter some of these confounders. As shown in Table 4, the estimates of genotype-specific pharmacodynamics parameters are not affected by covariates. Furthermore, model (1) can provide an estimate of the effects of each covariates including continuous and discrete. Estimates of some of the covariate effects are not very precise under a small sample size (100), but this situation can improve dramatically when the sample size increases to 400.

Wu et al.30 showed that the pharmacodynamics model displays increased power of gene detection compared to traditional GWAS.

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Figure 4. Changes of %FEV1, mean (± s.e.) by the mutant homozygote (MM) over a mix of the homozygote for the wild-type allele and the heterozygote for the two different alleles (W_) at an intermediate dose of glucocorticoids for significant SNPs, chr6 rs6924808 (a), chr8 rs10481450 (b), chr11 rs1353649 (c), chr15 rs12438740 (d), and chr15 rs2230155 (e), for pooled IMPACT, SOCS and SLIC trials detected by the recessive model. Notice that %FEV1 was not normalized because these trials contain only one dose of glucocorticoids.

Table 4. Significant SNPs detected for inhaled corticosteroid drug response to asthma treatment from the DICE trials and confirmed in three additional trials

<table>
<thead>
<tr>
<th>Model</th>
<th>SNP</th>
<th>Chr</th>
<th>Position</th>
<th>Alleles</th>
<th>MAF</th>
<th>DICE</th>
<th>IMPACT</th>
<th>SOCS</th>
<th>SLIC</th>
<th>Pooled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recessive</td>
<td>rs6924808</td>
<td>6</td>
<td>98465296</td>
<td>C/T</td>
<td>0.477 (T)</td>
<td>5.315 × 10^{-7}</td>
<td>5.908 × 10^{-11}</td>
<td>0.034</td>
<td>0.001</td>
<td>6.661 × 10^{-16a}</td>
</tr>
<tr>
<td>Recessive</td>
<td>rs10481450</td>
<td>8</td>
<td>9835656</td>
<td>A/T</td>
<td>0.310 (T)</td>
<td>2.614 × 10^{-8}</td>
<td>0.072</td>
<td>0.057</td>
<td>1.154 × 10^{-6}</td>
<td>0.023</td>
</tr>
<tr>
<td>Recessive</td>
<td>rs13353649</td>
<td>11</td>
<td>20210175</td>
<td>A/G</td>
<td>0.320 (A)</td>
<td>3.924 × 10^{-9}</td>
<td>0.003</td>
<td>0.089</td>
<td>0.024</td>
<td>5.670 × 10^{-11a}</td>
</tr>
<tr>
<td>Recessive</td>
<td>rs12438740</td>
<td>15</td>
<td>57303035</td>
<td>C/T</td>
<td>0.348 (T)</td>
<td>4.499 × 10^{-8}</td>
<td>0.004</td>
<td>0.0003</td>
<td>2.883 × 10^{-5}</td>
<td>0.040</td>
</tr>
<tr>
<td>Recessive</td>
<td>rs2230155</td>
<td>15</td>
<td>57297481</td>
<td>C/T</td>
<td>0.350 (T)</td>
<td>1.798 × 10^{-7}</td>
<td>0.043</td>
<td>0.211</td>
<td>0.056</td>
<td>0.132</td>
</tr>
</tbody>
</table>

The chromosomal positions, alleles, minor allele (in parentheses) frequencies (MAF), and significance levels of these SNPs are given. *These P-values were obtained from an optimal model, genotypic model.

The pharmacodynamic model has successfully detected five loci of significant effects on response curves of corticosteroids for asthma by integrating the biochemical processes of drug response into GWAS. This integration has proven to be statistically more powerful for gene detection than traditional approaches based on a single dose.30 The identification of significant SNPs by our model has been validated by resampling and simulation studies. Furthermore, these five SNPs demonstrate good replication in three independent clinical trial populations for the same phenotype. In general, the mutant alleles at most SNPs tend to increase pulmonary function of asthma participants by 30–300% after inhaled glucocorticoid treatment relative to the wild-type alleles, although the expression of the mutant may be masked by the wild-type allele. In another study, Tantisira et al.29 found that the mutant homozygote at chr7 rs37972 displays 120–330% decrease of lung function through glucocorticoid treatment compared with the wild-type homozygote. In both studies by us and Tantisira et al., the heritabilities of glucocorticoid response explained by individual SNPs are much larger than those detected for disease and physiological traits.8–11 This may be due to the fact that drug response is evolutionarily a 'young' trait, which has not experienced yet a long history of natural selection as the other traits have.12

High heritability detection should benefit from the statistical merit of our pharmacodynamic model that was derived from parsimonious modeling of the mean-covariance structures for longitudinal data of drug response across a series of doses. For example, four parameters are needed to describe drug response of a genotype at four dose levels if traditional approaches are used, while the pharmacodynamic model only uses three parameters to do the same thing. Moreover, the pharmacodynamic model, such as the Emax model35 and differential equations,44,45 contains biologically meaningful aspects of drug response in terms of body–drug interactions. Applied to GWAS of response to corticosteroids for asthma intervention, this model can not only facilitate the interpretation and elucidation of the pharmacogenomics architecture of this important clinical problem, but also increase the statistical power of significant association detection.

Except for SNP rs6924808 on chromosome 6, the other four detected are located in the vicinity of candidate genes associated with cellular functions. It appears that SNP rs10481450 on chromosome 8 is related to gene TNKS, a PARP member localized predominantly in the cytosol, that regulates cellular viability and NAD(+) metabolism46 and gene MSRA that has a function to repair oxidative damage to proteins to restore biological activity.47 SNP rs13353649 on chromosome 11 is nearby many candidate genes, such as DBX1,48 NAV2,49 HTATIP250 and PRMT3,51 some of which

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**DISCUSSION**

The pharmacodynamic model has successfully detected five loci of significant effects on response curves of corticosteroids for asthma by integrating the biochemical processes of drug response into GWAS. This integration has proven to be statistically more powerful for gene detection than traditional approaches based on a single dose.30 The identification of significant SNPs by our model has been validated by resampling and simulation studies. Furthermore, these five SNPs demonstrate good replication in three independent clinical trial populations for the same phenotype. In general, the mutant alleles at most SNPs tend to increase pulmonary function of asthma participants by 30–300% after inhaled glucocorticoid treatment relative to the wild-type alleles, although the expression of the mutant may be masked by the wild-type allele. In another study, Tantisira et al.29 found that the mutant homozygote at chr7 rs37972 displays 120–330% decrease of lung function through glucocorticoid treatment compared with the wild-type homozygote. In both studies by us and Tantisira et al., the heritabilities of glucocorticoid response explained by individual SNPs are much larger than those detected for disease and physiological traits.8–11 This may be due to the fact that drug response is evolutionarily a 'young' trait, which has not experienced yet a long history of natural selection as the other traits have.12

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**Replication**

Here, we used three other trials to validate the results. These trials are the IMProving Asthma Control Trial (IMPACT),35 Salmeterol Off CorticoSteroids (SOCS) trial,36 and Salmeterol ± Inhaled Corticosteroids (SLIC) trials.37 Because of one single dose of corticosteroid used, we analyzed associations between %FEV1 values and five significant SNPs detected from DICE using a univariate model (Table 4). All the five SNPs were found to be significant in the three trials, except for chr15 rs2230155 being non-significant for SOCS and chr8 rs10481450 and chr11 rs13353649 being marginally significant for IMPACT and SOCS, respectively (Table 4). Pooled together over IMPACT, SOCS, and SLIC of a similar design, all SNPs, except for chr15 rs2230155, display significant associations with glucocorticoid response. Figure 4 compares the differences of %FEV1 between two groups of genotypes, the mutant homozygote and a mix of the homozygote for the wild-type allele and the heterozygote for the two different alleles, at each SNP for the pooled three trials. For chr6 rs6924808 and chr11 rs13353649, such differences have different directions between the pooled trials and DICE. When an optimal model, i.e., genotypic model, was used, these two SNPs produce a very high level of significance for associations (P = 6.661 × 10^{-16} and 5.670 × 10^{-11}; Table 4).

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determine nicotine dependence. MYO1E is also a nicotine dependence-related gene in which two associated SNPs, rs12438740 and rs2230155, on chromosome 15 were identified. A modest sample size used may overestimate genetic effects of SNPs. However, our pharmacodynamic model makes use of the longitudinal feature of phenotypic data measured repeatedly for the same subjects, which has proven to be powerful for increasing the precision of parameter estimation. Our finding here shows a promise to utilize the genetic results obtained to predict individual patients’ performance in asthma intervention. Recent studies showed that asthma may be affected by DNA methylation through regulating gene expression. It is straightforward to integrate methylation variants into the model to better reveal the genetic and epigenetic basis of asthma intervention. To the end, by incorporating our new model with genetic and epigenetic observations for asthma and associated alteration in lung function by asthma, we may better determine and design the optimal doses for individual patients, maximizing drug efficacy for optimal pulmonary function response while minimizing drug toxicity.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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