Published in final edited form as:
Am J Med Genet B Neuropsychiatr Genet. 2008 September 5; 147B(6): 712–719. doi:10.1002/ajmg.b.30669.

Identification of Pharmacogenetic Markers in Smoking Cessation Therapy

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Abstract

Pharmacogenetic clinical trials seek to identify genetic modifiers of treatment effects. When a trial has collected data on many potential genetic markers, a first step in analysis is to screen for evidence of pharmacogenetic effects by testing for treatment-by-marker interactions in a statistical model for the outcome of interest. This approach is potentially problematic because i) individual significance tests can be overly sensitive, particularly when sample sizes are large; and ii) standard significance tests fail to distinguish between markers that are likely, on biological grounds, to have an effect, and those that are not. One way to address these concerns is to perform Bayesian hypothesis tests (Berger 1985; Kass and Raftery 1995), which are typically more conservative than standard uncorrected frequentist tests, less conservative than multiplicity-corrected tests, and make explicit use of relevant biological information through specification of the prior distribution. In this article we use a Bayesian testing approach to screen a panel of genetic markers recorded in a randomized clinical trial of bupropion versus placebo for smoking cessation. From a panel of 59 single-nucleotide polymorphisms (SNPs) located on 11 candidate genes, we identify four SNPs (one each on *CHRNA5* and *CHRNA2* and two on *CHAT*) that appear to have pharmacogenetic relevance. Of these, the SNP on *CHRNA5* is most robust to specification of the prior. An unadjusted frequentist test identifies seven SNPs, including these four, none of which remains significant upon correction for multiplicity. In a panel of 43 randomly selected control SNPs, none is significant by either the Bayesian or the corrected frequentist test.

Keywords

Bayes factor; Bayesian hypothesis test; bupropion; importance sampling; pharmacogenomics; single-nucleotide polymorphism

Introduction

The emerging field of pharmacogenomics seeks to link genetic polymorphisms in drug targets and metabolizing enzymes with efficacy and toxicity phenotypes (Eichelbaum et al. 2006). When a polymorphism is recorded on subjects in a clinical trial, a natural approach to assessing its importance is to test the treatment-by-polymorphism interaction in a statistical model for the trial outcome. Although such an approach potentially oversimplifies the complexity of the

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polygenic drug response phenotype (Need et al. 2005), nevertheless it can be valuable in identifying markers that are worthy of further study.

A potential problem with this approach is that classical significance tests are overly sensitive, especially in large samples. This is because they assess departures from the null rather than comparing the fits of the null and alternative models. The problem is compounded when one conducts many tests, as failure to correct for multiplicity can lead to an excess of false positives. One can adapt variants of the Bonferroni method to construct adjusted tests whose family-wise type I error rates are acceptably low (Hochberg 1988), but these methods are extremely conservative. Moreover, in screening large numbers of markers one should be able to use available biological information. In particular, markers that are thought likely, *a priori*, to have a pharmacogenetic effect should be held to a lower standard of evidence than those that are unlikely to have such an effect. That classical statistical tests do not permit the incorporation of prior information is often touted as an indication of their "objectivity".

A possible alternative approach is to screen the markers using Bayesian hypothesis testing (Berger 1985). This involves calculating for each marker a Bayes factor, or weight of evidence, that measures the plausibility of the null hypothesis of no interaction versus the alternative that there is an interaction (Kass and Raftery 1995). Bayesian tests are generally more conservative than classical tests and therefore potentially more suitable for screening panels of markers. Moreover Bayesian tests make explicit use of contextual biological information through specification of the prior distribution, which in this setting refers to the analyst's *a priori* degree of belief that a particular marker is pharmacogenetically active. Until fairly recently, the computation of Bayesian analyses in all but the simplest models was prohibitively expensive, but improvements in computing technology have largely eliminated this obstacle. Thus, applications of Bayesian analysis in genetics have become increasingly common (Desai and Emond 2004; Tadesse et al. 2005; Zhao et al. 2005; Gottardo et al. 2006; Kitchen et al. 2007).

In this article we conduct an explicitly Bayesian analysis of a panel of candidate genetic markers collected in a clinical trial of bupropion for smoking cessation. Pharmacotherapy for smoking cessation provides an ideal case study given the public health significance of tobacco dependence, the relatively modest effectiveness of currently available drugs, and emerging data supporting associations of genetic polymorphisms with response to nicotine replacement therapies (Johnstone et al. 2004; Lerman et al. 2006; Lerman et al. 2004; Malaiyandi et al. 2006; David et al. 2007) and bupropion (Swan et al. 2005; Berrettini et al. 2007; Lee et al. 2006; Lerman et al. 2004).

Our analysis focuses on 59 single-nucleotide polymorphisms (SNPs) on 11 genes in the nicotinic acetylcholine receptor (nAChR) family. *In vitro* binding experiments have demonstrated that bupropion is a non-competitive antagonist at the $\alpha 3\beta 4\alpha 5\pm\beta 2$ subtype of nAChR (Fryer and Lukas 1999; Slemmer et al. 2000; Bondarev et al. 2003; Alkondon and Albuquerque 2005). Bupropion blocks the hypothermic and antinociceptive effects of nicotine (Slemmer et al. 2000; Damaj et al. 2004), as well as dopamine and norepinephrine release from striatal synaptical vesicles, most likely via antagonism at these nAChRs (Miller et al. 2002). Several human genetic studies have also nominated nAChRs in the etiology of tobacco dependence (Feng et al. 2004; Li et al. 2005; Greenbaum et al. 2006; Beirut et al. 2007; Saccone et al. 2007), although not all results have been positive (Silverman et al. 2000; Lueders et al. 2002).

In this article we apply Bayesian hypothesis testing to SNP data and clinical outcomes from the bupropion trial. Our analyses moreover compare the Bayesian approach to standard unadjusted and adjusted frequentist analyses.

Materials and Methods

The bupropion trial

The data are from a placebo-controlled randomized pharmacogenetic trial of bupropion for smoking cessation; the design and main findings have been published previously (Lerman et al. 2004). Briefly, the study enrolled 599 smokers between April 1999 and October 2001 at Georgetown University and SUNY Buffalo. Participants were aged 18 or older and had smoked at least 10 cigarettes per day for the preceding 12 months. Exclusion criteria included pregnancy, a history of DSM-IV axis I psychiatric disorder, seizure disorder, substance abuse, and current use of psychotropic medications. Participants were randomized to receive either bupropion or placebo for 10 weeks, plus 7 sessions of behavioral group smoking cessation counseling. The primary outcome measure was 7-day point prevalence smoking cessation at the end of treatment (8 weeks following the target quit date), which was biochemically verified using cotinine (<15ng/ml to confirm smoking cessation). To reduce potential bias from ethnic admixture, we restrict our genetic analyses to the 436 participants of European ancestry in the intention-to-treat population.

All participants provided DNA for the pharmacogenetic evaluation. The data analysis described here focuses on a panel of 59 SNPs in seven nAChR α-subunit genes (*CHRNA2–CHRNA7*, *CHRNA10*), three nAChR β-subunit genes (*CHRNB2–CHRNB4*), and choline acetyltransferase (*CHAT*). As a negative control, we included a panel of 43 SNPs, randomly selected from throughout the genome, that had been used to test for population stratification (Lerman et al. 2004). Although all subjects provided DNA, valid data were not available on all SNPs for all subjects. The number of available cases ranged from 290 to 428 among the candidate SNPs and 334 to 424 among the control SNPs, with 75% of all SNPs having at least 411 available cases.

The study was approved by the appropriate institutional review boards.

Statistical model

For each SNP we assume a dominant model in that a subject who has at least one copy of the rarer allele is considered positive for the polymorphism. Because the outcome is binary, our basic model is a logistic regression predicting quit success from treatment arm, SNP status, and the treatment-by-SNP interaction:

$$\Pr(Y_i=1|D_i,G_i)=h(\beta_0+\beta_T D_i+\beta_G G_i+\beta_I D_i G_i),$$

where

$$h(u)= \exp(u)/(1+\exp(u));$$

$$Y_i=\begin{cases}1 & \text{if subject } i \text{ was abstinent at EOT,}\\ 0 & \text{otherwise;}\end{cases}$$

$$D_i=\begin{cases}1/2 & \text{if subject } i \text{ was assigned to bupropion,}\\ -1/2 & \text{if subject } i \text{ was assigned to placebo;}\end{cases}$$

$$G_i=\begin{cases}1/2 & \text{if subject } i \text{ was positive for the polymorphism,}\\ -1/2 & \text{otherwise.}\end{cases}$$

In this model β_0 is the logit of the overall quit rate; β_T is the log odds ratio for treatment; β_G is the log odds ratio for the polymorphism; and β_I is the interaction, or the difference of treatment log odds ratios between subjects who are positive and negative for the polymorphism.

Priors for Bayesian hypothesis testing

In Bayesian hypothesis testing one must specify a prior, or distribution over the space of the model parameters, that attaches a point mass to the null hypothesis (in this case, $\{\beta: \beta_I = 0\}$) and spreads the remainder of the prior probability over the set of alternative hypotheses. For the bupropion trial, we set the prior $f_I(\beta_I)$ for the interaction parameter β_I to be a mixture of a point null and a continuous density:

$$f_I(\beta_I)=\rho I_0(\beta_I)+(1-\rho)(1-I_0(\beta_I))g(\beta_I),$$

where ρ is the prior probability that the null is true (i.e., that the interaction is 0), $I_0(x)$ is an indicator that $x = 0$, and $g(\beta_I)$ is a prior density over the set of alternative (non-zero) values of β_I. We moreover assume that the other parameters β_0, β_T and β_G are *a priori* independent of each other and of β_I.

For convenience, we take our priors for the β coefficients to be normal, choosing their means and variances to match information from the literature. In a previous randomized, placebo-controlled trial of bupropion in smoking cessation (Tønnesen et al. 2003), the average of abstinence fractions in the two groups on the logit scale was −0.69, which we use as the prior mean of β_0. Taking the variance estimates from the Tønnesen study, transforming to the logit scale, and inflating by 50% to account for between-trial variability, we arrive at a prior standard deviation (SD) for β_0 of 0.148. Also adapting estimates from the Tønnesen study, we take the prior of β_T to be normal with mean 1.037 and SD 0.315. Assuming that most SNPs will have no more than a modest main effect on abstinence, we take the prior for β_G to be normal with mean 0 and SD equal to that of β_T.

The prior for β_I contains both a continuous and a discrete part. To compute Bayes factors it is not necessary to specify the prior probability of the null hypothesis ρ, so we allow this number to vary in the range (0, 1). We take $g(\beta_I)$, the density of β_I over the alternative space, to be normal with mean 0 and SD equal to twice that of β_T (i.e., 0.632). As $g(\beta_I)$ is the component of the prior that is least well informed by data, we conducted a sensitivity analysis in which we varied its SD in the range (0, 9).

Posterior probabilities and Bayes factors

Given the data x and the model assumptions, the posterior probability that the null hypothesis is true is

$$\Pr(\beta_I=0|x)=\frac{\rho m_0(x)}{\rho m_0(x)+(1-\rho)m_1(x)},$$

where

$$m_0(x)=\int L(\beta_0,\beta_T,\beta_G,0)\pi_{0TG}(\beta_0,\beta_T,\beta_G)d(\beta_0,\beta_T,\beta_G),$$
$$m_1(x)=\int L(\beta_0,\beta_T,\beta_G,\beta_I)\pi_{0TG}(\beta_0,\beta_T,\beta_G)g(\beta_I)d(\beta_0,\beta_T,\beta_G,\beta_I),$$

π_{0TG} is the joint prior for the parameters β_0, β_T and β_G, and $L(\beta)$ is the likelihood function. One can think of $m_0(x)$ and $m_1(x)$ as the marginal likelihoods for the null and alternative hypotheses, respectively. The marginal likelihood reflects how well the model hypothesis explains the observed data.

We calculate $m_0(x)$ and $m_1(x)$ by importance sampling (Hammersley and Handscomb 1964), a simulation method that takes advantage of the fact that although the posterior density itself is generally unavailable, it is typically easy to compute a function that is proportional to the posterior density — specifically, the product of the prior and the likelihood. In importance sampling one takes a large number of draws from an approximate posterior, known as the *proposal distribution*, that one can easily simulate from and whose density is available in closed form (the asymptotic normal approximation to the sampling distribution of the MLE is a common choice). One then calculates importance weights, which are the ratios of the unscaled true posterior density to the proposal density evaluated at the sampled parameters. Averages of functions of the sampled parameters, weighted by the importance weights, approximate the posterior expectations of those functions. SPlus code for an implementation of importance sampling in the pharmacogenetic model is available from the first author.

A summary of the weight of evidence against the null is the Bayes factor (BF), defined as the ratio of the posterior odds that the null is true to the prior odds that the null is true:

$$\mathrm{BF}=\frac{m_0(x)}{m_1(x)}.$$

Note that the BF does not depend on the prior probability of the null hypothesis, ρ, which cancels out when one takes the ratio of posterior to prior odds. BF does depend on the priors for the parameters under the null and the alternative hypotheses, however, because these functions enter into the calculation of $m_0(x)$ and $m_1(x)$, respectively.

To use BF as a screening tool, we adopt the Jeffreys scale of evidence, which interprets a value of BF < 1/3 as moderate evidence for the alternative hypothesis (Kass and Raftery 1995). For example, a BF of this magnitude implies evidence strong enough to transform a prior odds of 3 (prior probability equal to 75%) to a posterior odds of 1 or less (posterior probability 50% or less).

Comparison with a frequentist analysis

We have also calculated p values for the hypothesis of no interaction using a likelihood-ratio test (LRT) and a multiplicity-adjusted LRT based on the permutation step-down min-*P* procedure of Westfall and Young (1993). This method controls the family-wise error rate in the strong sense; that is, it controls the error rate for any combination of true and false hypotheses. We have used it here because it is valid even if the individual tests are not independent, as is the case in our data.

Results

Table 1 lists the 59 candidate SNPs, sorted by BF, with the corresponding LRT unadjusted and adjusted p values for the test of no treatment-by-SNP interaction. The criterion BF < 1/3 identifies four SNPs, on genes *CHRNA5*, *CHAT* (two SNPs) and *CHRNA2*, that have potential pharmacogenetic associations. To assess robustness we varied the alternative-hypothesis prior SD of the interaction β_I and found that the BF for the *CHRNA5* SNP remained less than 1/3 for prior SDs in the range (0.4, 3.6), suggesting modest sensitivity to the prior. The other SNPs have BFs under 1/3 in the ranges (0.5, 3.3), (0.5, 1.9) and (0.6, 1.4), respectively, suggesting greater sensitivity. Thus we consider the *CHRNA5* SNP to be significant in a robust Bayesian sense (Berger and Berry 1988). By comparison, the unadjusted LRT p value criterion identifies seven SNPs as potentially pharmacogenetically active (column 5 of Table 1). None of these p values remains significant in the adjusted procedure that controls the FWE rate at 0.05 (column 6).

Table 2 shows the BFs and unadjusted and adjusted p values for the treatment-by-SNP interaction tests for the 43 randomly selected SNPs. None of these is identified as significant by either the Bayesian or adjusted frequentist criteria, and only one is identified as significant by the unadjusted frequentist test. As one would expect to find two or more p values of .05 or less in a list of 43 p values, we consider it likely that this lone significant finding is a type I error.

Table 3 shows the posterior probability of the null hypothesis of no interaction as a function of its prior probability for the top four candidate and control SNPs. Note, for instance, that for the second- and third-ranked control SNPs, whose BFs are nearly 1 (Table 2), the prior and posterior probabilities are practically equal. For each SNP, the posterior probability of the null increases monotonically as ρ (the prior probability of the null) increases from 0.1 to 0.9. A potential use of the prior probabilities in screening a large number of markers (for example in a SNP array) would assign some value $\rho \leq 0.5$ to candidate SNPs and some $\rho \geq 0.5$ to control SNPs, in which case the top four candidate SNPs would all have posterior probabilities of the null no greater than 24%, whereas even the top four control SNPs would have posterior probabilities of the null in excess of 44%.

The last four columns of Tables 1 and 2 present the raw probabilities of 7-day abstinence at EOT, cross-classified by SNP type and treatment, for the candidate and control SNPs, respectively. Note that for the top SNP, rs871058 on *CHRNA5*, there is a modest treatment effect (24% quit on placebo vs. 26% on bupropion) for subjects who possess the rare allele but a large effect for those who do not (19% vs. 44%). The same is true for rs1917810 on *CHAT* and rs2565065 on *CHRNA2*, the third and fourth most significant SNPs. The opposite holds for the second-lowest-BF SNP, rs2269338 on *CHAT*, where the bupropion effect is large for positives and modest for negatives. Thus a potential use of rs871058, rs1917810 and rs2565065 in clinical practice would be to prescribe bupropion treatment to subjects who are heterozygous for the common allele, and some other treatment, perhaps nicotine replacement therapy or varenicline, for the others. One would use an opposite approach with rs2269338.

Note that interaction effects are generally more modest for the control SNPs (Table 2) and that in both the candidate and control SNPs the strength of the interaction declines as one progresses down the columns.

Discussion

We have developed a Bayesian hypothesis test to screen for genetic modifiers of patient response to bupropion pharmacotherapy for smoking cessation. Our method is more conservative than a conventional frequentist test, but less so than the frequentist test adjusted for multiplicity. The method identified one strongly robust pharmacogenetic marker from a panel of candidate SNPs in nAChR genes. Neither the Bayesian test nor the adjusted frequentist test identified any of a panel of randomly selected control SNPs as likely to be pharmacogenetically informative.

The most strongly significant marker is rs871058, a SNP in the first intron of *CHRNA5*, which codes for the nAChR α5 subunit. In the human genome, *CHRNA5* lies in a three-gene cluster *CHRNA5-CHRNA3-CHRNB4* (Duga et al. 2001) that comprises a single haplotype block (HapmapDatabase 2007). The α5 subunit binds to either the $\alpha 3\beta 4$ or $\alpha 3\beta 2$ subunits to form a pentamer (Conroy et al. 1992; Conroy and Berg 1995), and inclusion of the α5 subunit increases the efficacy of nicotine's actions on these receptors (Wang et al. 1996). The α5 subunit is also a component of $\alpha 4\beta 2$, the most abundant nAChR in the brain, and inclusion of α5 increases conductance of these receptors and causes a higher rate of desensitization (Ramirez-Latorre et al. 1996). Moreover, pre-clinical studies have demonstrated that bupropion is a non-

competitive antagonist at the $\alpha 3\beta 4\alpha 5$ and $\alpha 3\beta 2\alpha 5$ subunits (Fryer and Lukas 1999; Bondarev et al. 2003), and thus it is plausible that genetic variation in *CHRNA5* influences bupropion's efficacy for treatment of tobacco dependence. Further, a non-synonymous SNP (rs16969968) on *CHRNA5* emerged as the strongest risk variant in a nicotine dependence association study of over 3,000 SNPs in over 300 candidate genes (Saccone et al. 2007). This polymorphism is located about 24kb downstream from rs871058, and these two SNPs lie in the same haplotype block. Although the functional significance of these SNPs is unknown, there is a high degree of linkage disequilibrium across *CHRNA5* (see Figure 1) that matches the Hapmap data, and the intronic SNP identified in the current analysis could be in linkage with an unknown functional variant that alters the subunit properties (Hapmap Database 2007). We obtained sufficient coverage of *CHRNA5* with the seven SNPs spanning 26kb of its total 28kb, and pairwise linkage disequilibrium between the markers was high.

On the whole the BF and p value give similar answers. When they do not, it is a matter of the data fitting poorly under the alternative-hypothesis prior. For example, candidate SNP rs2292975 on *CHRNA2*, ranked 10 in Table 1, has a significant LRT p value but a BF that does not meet the 1/3 cutoff. Under the null model, the treatment effect was moderate ($\hat{\beta}_T = 0.585$), whereas under the alternative model the treatment effect was reduced substantially (away from the prior mean) to $\hat{\beta}_T = 0.368$, with a very large interaction term ($\hat{\beta}_I = 1.07$). The net result was that although the interaction model fits better in the sense of the LRT, the estimated parameters are more remote from the prior mean because of the small treatment effect and large interaction. This is the effect of the alternative-hypothesis prior, which allows for interaction terms but at the same time discounts large interactions. Note that this situation occurs when bupropion has a positive treatment effect for SNP carriers but a negative effect for non-carriers. The same pattern occurs for the SNP with the 14th-smallest BF, rs2292974 on *CHRNA2*.

As suggested in the preceding paragraph, a potential concern with Bayesian tests is their dependence on the assumed prior distribution. Although in general one should select a prior that most faithfully reflects existing knowledge about the actions of the treatment in question, inevitably there will be aspects of the prior that existing data cannot address precisely — specifically, the size of the interaction. Our sensitivity analysis reveals a modest effect of the assumed prior SD of the interaction coefficient with the strongest BF; more elaborate sensitivity analyses are possible and may be desirable in some cases.

Other related problems that can benefit from Bayesian analysis of this type include specification of the optimal genetic model (dominant, recessive, additive or general) and identification of combinations of SNPs that best predict treatment outcome (Kitchen et al. 2007). Because such models are not generally *nested* — i.e., they do not form a sequence of sub-models — they are not amenable to comparison by classical frequentist tests but nevertheless can readily be tested using Bayes factors.

The current model allows for testing of SNPs individually but does not take account of potential correlation between SNPs. Such correlation is likely to obtain in cases, like this one, where SNPs on several related genes may together affect a complex phenotype. A more comprehensive approach would specify a model including a treatment effect, main effects of all the SNPs, their interactions with treatment, and also possibly SNP-by-SNP and other higher-order interactions. This is a potentially large and complicated model involving hundreds of parameters even in an application where, like ours, only a few dozen genetic markers are in play. A comprehensive model of this kind would allow us not only to more efficiently screen markers but to identify parsimonious models describing the simultaneous effects of treatment and genetic factors on the outcome. We are working to build such models in further research with the bupropion data.

The Bayesian approach measures the weight of evidence for an hypothesis from a single data set, unlike frequentist tests that seek to achieve target values for long-term error rates in hypothetical replications of an experiment. Bayesian tests are typically more conservative than frequentist tests, as our example illustrated. Thus Bayesian tests may to some extent mitigate the multiplicity problem that arises when one tests a large number of hypotheses with a single set of data. It does not follow, however, that the Bayesian test, considered as a screening procedure, is free of multiplicity concerns (Westfall et al. 1997). That is, one can evaluate the Bayesian test in terms of its power and type I error rate, which will, as in any frequentist test, depend on the number of markers being assessed. Thus to set the significance criterion for the BF in a screening context one should consider both the number of markers to be screened and the likely distribution of alternative-hypothesis interaction effects. For example, in screening a larger panel of markers, one may wish to use a stricter criterion for significance such as BF < 1/20. Methodology for the selection of this criterion is an object for further empirical research.

Acknowledgements

The USPHS supported this research under grants P50 CA084718 from the National Cancer Institute and National Institute on Drug Abuse, R01 CA063562 and R01 CA116723 from the National Cancer Institute, and P20 RR020741 from the National Center for Research Resources. We are grateful to Jinbo Chen, Edward George and Stephen Kimmel for helpful comments and support.

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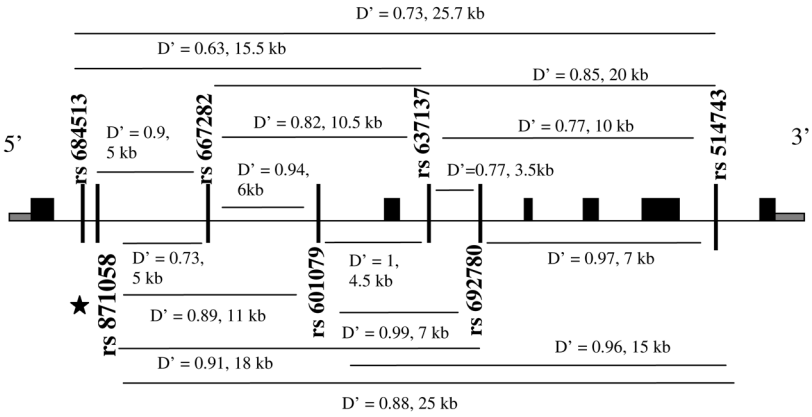

Figure 1.

Diagram of the *CHRNA5* gene indicating the genotyped SNPs. The darker shaded boxes represent the exons and the lighter shaded boxes represent the untranslated regions (kb = kilobases, D′= linkage disequilibrium estimate). Figure is not drawn to scale.

Table 1

Tests for treatment-by-SNP interaction effect on 7-day point prevalence of smoking cessation at end of treatment, SNPs on candidate genes.

							Percent Abstinent at EOT (# of subjects)			
							SNP=0		SNP=1	
Rank	RS Number	Gene	Bayes Factor	LRT p	Adjusted LRT p	Prevalence, SNP=1 (%)	Placebo	Bupropion	Placebo	Bupropion
1	rs871058	*CHRNA5*	0.200	0.019	0.699	59.2	19(88)	44(84)	24(109)	26(141)
2	rs2269338	*CHAT*	0.251	0.031	0.838	19.9	24(157)	29(170)	15(34)	45(47)
3	rs1917810	*CHAT*	0.293	0.029	0.828	65.9	16(64)	39(76)	26(127)	30(144)
4	rs2565065	*CHRNA2*	0.313	0.027	0.812	51.2	18(102)	38(104)	26(96)	27(120)
5	rs3793798	*CHAT*	0.390	0.048	0.934	64.7	16(67)	39(79)	24(127)	29(141)
6	rs3743077	*CHRNA3*	0.396	0.058	0.963	63.7	17(75)	38(74)	26(117)	29(145)
7	rs1878399	*CHRNA3*	0.406	0.059	0.963	64.5	18(74)	39(76)	25(122)	29(151)
8	rs1948	*CHRNB4*	0.442	0.073	0.980	56.9	20(98)	41(83)	23(98)	27(141)
9	rs1878399	*CHRNA3*	0.468	0.077	0.982	65.7	18(72)	40(75)	23(128)	29(153)
10	rs2292975	*CHRNA2*	0.474	0.029	0.828	68.2	25(59)	22(76)	19(139)	37(150)
11	rs601079	*CHRNA5*	0.483	0.079	0.983	62.8	18(73)	39(72)	26(108)	31(137)
12	rs3743075	*CHRNA3*	0.547	0.106	0.995	60.8	21(86)	41(80)	23(110)	27(147)
13	rs8023462	*CHRNB4*	0.594	0.094	0.992	54.5	18(97)	37(86)	25(92)	30(127)
14	rs2292974	*CHRNA2*	0.621	0.045	0.926	68.6	25(59)	23(74)	20(139)	37(151)
15	rs692780	*CHRNA5*	0.713	0.161	1.000	60.8	21(86)	41(81)	22(113)	28(146)
16	rs2231532	*CHRNA10*	0.717	0.071	0.978	63.7	24(67)	23(86)	21(128)	38(140)
17	rs3743074	*CHRNA3*	0.738	0.163	1.000	60.9	20(83)	40(81)	23(114)	28(141)
18	rs3743073	*CHRNA3*	0.890	0.197	1.000	52.2	18(89)	39(96)	22(88)	30(114)
19	rs514743	*CHRNA5*	0.896	0.207	1.000	53.4	19(78)	38(78)	24(76)	30(103)
20	rs2741868	*CHRNA10*	0.972	0.225	1.000	47.9	22(99)	27(121)	21(99)	38(103)
21	rs3824103	*CHRNA2*	1.011	0.695	1.000	5.2	22(186)	32(215)	18(11)	36(11)
22	rs2377871	*CHAT*	1.062	0.692	1.000	6.4	22(185)	33(211)	17(12)	33(15)
23	rs4953	*CHRNB3*	1.063	0.755	1.000	7.3	21(175)	31(206)	25(16)	43(14)
24	rs3735757	*CHRNA2*	1.114	0.130	0.999	27.1	18(141)	34(163)	27(51)	29(62)
25	rs1316971	*CHRNB4*	1.290	0.690	1.000	26.8	21(125)	30(159)	26(50)	41(54)
26	rs2229958	*CHRNA2*	1.361	0.608	1.000	74.0	16(45)	27(62)	24(148)	33(157)
27	rs2072659	*CHRNB2*	1.361	0.626	1.000	16.5	23(172)	33(183)	15(26)	30(44)

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Rank	RS Number	Gene	Bayes Factor	LRT p	Adjusted LRT p	Prevalence, SNP=1 (%)	Percent Abstinent at EOT (# of subjects)			
							SNP=0		SNP=1	
							Placebo	Bupropion	Placebo	Bupropion
28	rs2273505	*CHRNA4*	1.364	0.941	1.000	13.3	21(163)	32(195)	24(29)	35(26)
29	rs938682	*CHRNA3*	1.370	0.737	1.000	26.5	21(135)	30(168)	25(56)	40(53)
30	rs3793792	*CHAT*	1.371	0.445	1.000	59.2	21(78)	34(93)	23(116)	30(132)
31	rs3743078	*CHRNA3*	1.420	0.688	1.000	31.7	20(128)	30(163)	24(71)	39(64)
32	rs2304298	*CHRNA6*	1.430	0.554	1.000	30.8	23(137)	33(153)	19(59)	33(70)
33	rs7177514	*CHRNA3*	1.446	0.803	1.000	26.2	21(97)	31(117)	29(34)	38(42)
34	rs8040868	*CHRNA3*	1.457	0.717	1.000	70.9	21(56)	36(64)	21(135)	31(158)
35	rs868437	*CHRNA7*	1.472	0.654	1.000	45.7	20(89)	34(96)	22(68)	32(88)
36	rs2236196	*CHRNA4*	1.489	0.634	1.000	42.4	20(100)	29(128)	21(84)	36(84)
37	rs748281	*CHRNA2*	1.527	0.973	1.000	20.7	20(152)	32(177)	23(39)	36(47)
38	rs684513	*CHRNA5*	1.548	0.670	1.000	21.9	20(138)	28(166)	32(44)	37(41)
39	rs8027814	*CHRNA7*	1.557	0.640	1.000	49.2	22(102)	30(114)	22(95)	35(114)
40	rs1917814	*CHAT*	1.560	0.564	1.000	13.8	22(169)	34(192)	19(26)	22(32)
41	rs2292977	*CHRNA2*	1.567	0.582	1.000	26.7	20(142)	34(163)	22(51)	30(60)
42	rs637137	*CHRNA5*	1.568	0.532	1.000	26.5	17(126)	30(157)	27(56)	35(46)
43	rs2565061	*CHRNA2*	1.569	0.554	1.000	22.5	21(155)	34(172)	21(43)	27(52)
44	rs2741864	*CHRNA10*	1.577	0.759	1.000	70.6	16(56)	29(65)	22(134)	35(156)
45	rs891400	*CHRNA2*	1.608	0.673	1.000	23.3	22(154)	33(171)	20(45)	26(54)
46	rs6495308	*CHRNA3*	1.622	0.925	1.000	30.0	20(132)	31(165)	26(66)	38(61)
47	rs11637630	*CHRNA3*	1.637	0.790	1.000	26.4	19(135)	30(164)	26(53)	37(54)
48	rs2565055	*CHRNA2*	1.657	0.911	1.000	43.2	18(104)	28(134)	25(91)	38(90)
49	rs733722	*CHAT*	1.666	0.750	1.000	27.3	20(142)	32(165)	25(55)	35(60)
50	rs885834	*CHAT*	1.683	0.980	1.000	54.7	22(89)	35(98)	20(102)	31(124)
51	rs892413	*CHRNA6*	1.684	0.884	1.000	34.2	23(126)	32(147)	22(64)	32(78)
52	rs13280604	*CHRNB3*	1.689	0.959	1.000	37.7	20(120)	30(141)	23(73)	35(85)
53	rs2177370	*CHAT*	1.690	0.600	1.000	64.1	26(72)	33(75)	20(118)	31(144)
54	rs2072661	*CHRNB2*	1.699	0.997	1.000	38.0	25(118)	38(140)	15(74)	24(84)
55	rs7175581	*CHRNA7*	1.699	0.820	1.000	68.9	25(68)	36(64)	20(130)	32(163)
56	rs2304297	*CHRNA6*	1.705	0.714	1.000	38.3	19(119)	31(135)	24(71)	33(87)
57	rs1880676	*CHAT*	1.723	0.648	1.000	39.4	20(119)	32(130)	25(69)	33(93)

							Percent Abstinent at EOT (# of subjects)			
							SNP=0		SNP=1	
Rank	**RS Number**	**Gene**	**Bayes Factor**	**LRT p**	**Adjusted LRT p**	**Prevalence, SNP=1 (%)**	**Placebo**	**Bupropion**	**Placebo**	**Bupropion**
58	rs883473	*CHRNA7*	1.760	0.900	1.000	50.8	21(100)	32(108)	22(99)	33(116)
59	rs747111	*CHRNA2*	1.767	0.961	1.000	55.8	19(81)	28(107)	24(118)	35(119)

Table 2

Tests for treatment-by-SNP interaction effect on 7-day point prevalence of smoking cessation at end of treatment, SNPs on randomly selected genes.

							Percent Abstinent at EOT (# of subjects)			
							SNP=0		SNP=1	
Rank	RS Number	Gene	Bayes Factor	LRT p	Adjusted LRT p	Prevalence, SNP=1 (%)	Placebo	Bupropion	Placebo	Bupropion
1	rs2839290	*DIP2A*	0.656	0.208	1.000	22.4	22(141)	29(177)	20(51)	41(41)
2	rs638732	*VGCNL1*	0.699	0.159	0.999	63.4	18(76)	36(74)	24(118)	29(142)
3	rs741441	*MGC35440*	0.728	0.041	0.850	71.3	31(58)	29(63)	17(140)	33(160)
4	rs2828759	Unidentified	0.758	0.055	0.920	64.4	28(79)	29(69)	17(118)	35(150)
5	rs256875	Unidentified	0.832	0.176	1.000	23.2	25(139)	34(152)	13(38)	34(50)
6	rs2750097	Unidentified	0.865	0.244	1.000	66.5	17(76)	35(63)	24(119)	31(157)
7	rs1909118	*NFLA*	0.908	0.256	1.000	25.6	23(145)	30(158)	14(49)	31(55)
8	rs1024766	Unidentified	0.940	0.281	1.000	68.6	19(47)	36(58)	25(110)	30(119)
9	rs588981	*UNC93A*	0.953	0.196	1.000	58.4	15(87)	32(85)	27(108)	35(133)
10	rs1910412	*LASS3*	0.968	0.086	0.976	71.6	30(57)	30(61)	18(137)	34(160)
11	rs1467200	*GRK7*	1.072	0.306	1.000	36.6	22(125)	29(143)	20(74)	37(81)
12	rs907444	Unidentified	1.094	0.206	1.000	35.8	25(103)	35(127)	11(62)	29(66)
13	rs1691251	*AHCTF1*	1.102	0.437	1.000	74.4	23(43)	41(59)	22(146)	30(151)
14	rs2611611	Unidentified	1.127	0.320	1.000	56.3	20(88)	37(93)	23(105)	30(128)
15	rs2009866	*EFCAB3*	1.244	0.579	1.000	21.7	22(152)	32(179)	20(46)	35(46)
16	rs1534596	*FMN1*	1.245	0.378	1.000	62.0	17(80)	33(80)	25(118)	33(143)
17	rs1468158	Unidentified	1.312	0.298	1.000	49.9	26(101)	34(107)	16(94)	31(113)
18	rs736737	*CCDC105*	1.417	0.429	1.000	47.6	26(99)	33(120)	17(98)	30(101)
19	rs2031633	*ZC3H13*	1.433	0.409	1.000	46.2	26(108)	34(120)	17(90)	30(106)
20	rs2054213	*SETD1A*	1.452	0.459	1.000	45.5	21(108)	28(116)	21(87)	35(100)
21	rs1330106	*LOC728727*	1.452	0.459	1.000	45.5	21(108)	28(116)	21(87)	35(100)
22	rs1939810	*KIAA1826*	1.488	0.466	1.000	61.8	22(68)	28(93)	22(129)	35(132)
23	rs878451	*LOC152485*	1.502	0.540	1.000	50.8	21(85)	31(97)	20(85)	36(103)
24	rs1365057	Unidentified	1.529	0.449	1.000	42.5	26(121)	36(120)	14(76)	27(102)
25	rs2036943	Unidentified	1.531	0.624	1.000	50.4	20(89)	34(93)	22(85)	32(100)
26	rs2208056	*C20orf23*	1.567	0.604	1.000	59.3	22(76)	30(93)	21(120)	33(126)
27	rs2190184	Unidentified	1.581	0.521	1.000	46.5	25(100)	33(121)	17(93)	29(99)

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							Percent Abstinent at EOT (# of subjects)			
							SNP=0		SNP=1	
Rank	RS Number	Gene	Bayes Factor	LRT p	Adjusted LRT p	Prevalence, SNP=1 (%)	Placebo	Bupropion	Placebo	Bupropion
28	rs2054255	*NUDCD1*	1.637	0.543	1.000	58.8	22(86)	30(88)	21(110)	34(138)
29	rs1885423	Unidentified	1.650	0.978	1.000	66.1	20(64)	30(79)	23(133)	34(146)
30	rs1906810	Unidentified	1.653	0.877	1.000	66.4	24(62)	35(78)	20(133)	31(144)
31	rs136501	Unidentified	1.670	0.667	1.000	30.2	20(142)	32(151)	24(55)	32(72)
32	rs2052584	*PHLPPL*	1.686	0.787	1.000	29.7	22(140)	34(154)	22(55)	30(69)
33	rs829864	Unidentified	1.688	0.993	1.000	65.8	23(66)	34(77)	21(131)	32(144)
34	rs2294693	*UNC5CL*	1.703	0.737	1.000	42.0	19(109)	31(137)	24(89)	34(89)
35	rs719674	Unidentified	1.705	0.667	1.000	63.5	27(74)	37(79)	18(123)	29(143)
36	rs288259	*DNAJC10*	1.717	0.937	1.000	57.8	22(82)	31(80)	21(101)	31(121)
37	rs1106499	*ZNF445*	1.721	0.862	1.000	53.0	24(90)	35(106)	19(104)	30(117)
38	rs2605141	*SMCR7*	1.735	0.918	1.000	56.5	22(78)	34(105)	20(119)	31(119)
39	rs1359719	Unidentified	1.740	0.992	1.000	48.0	21(104)	31(115)	23(93)	33(109)
40	rs2598108	*EPDR1*	1.753	0.871	1.000	58.3	20(83)	31(89)	21(112)	34(128)
41	rs2802853	*NFASC*	1.758	0.976	1.000	58.9	21(85)	33(85)	22(111)	34(133)
42	rs946778	*ZFYVE27*	1.762	0.835	1.000	45.3	18(103)	29(126)	26(94)	36(96)
43	rs1998505	*CEP110*	1.766	0.987	1.000	52.2	18(88)	28(112)	25(106)	36(112)

Table 3

Posterior probability (× 100) of the null hypothesis of no interaction for the top four candidate and randomly selected SNPs, as a function of the prior probability ρ.

	RS number	Gene	ρ = 0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
Candidate SNPs	rs871058	*CHRNA5*	2	5	8	12	16	23	31	44	64
	rs2269338	*CHAT*	3	6	10	14	20	28	37	50	70
	rs1917810	*CHAT*	3	7	11	17	23	31	41	55	73
	rs2565065	*CHRNA2*	3	7	12	17	24	32	42	56	74
Randomly selected SNPs	rs2839290	*DIP2A*	8	16	25	34	44	54	64	76	87
	rs638732	*VGCNL1*	10	20	31	41	51	61	71	80	90
	rs741441	*MGC35440*	11	21	32	42	52	62	72	81	91
	rs2828759	Unidentified	11	22	33	43	53	63	73	82	91

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