Dopamine D4 receptor gene variation moderates the efficacy of bupropion for smoking cessation

AM Leventhal1, SP David2, M Brightman1, D Strong3, JE McGeary3, RA Brown3, EE Lloyd-Richardson4, M Munafo5, GR Uhl6 and R Niaura7

1Department of Preventive Medicine, University of Southern California Keck School of Medicine, Los Angeles, CA, USA; 2Department of Family and Community Medicine, Stanford University School of Medicine, Palo Alto, CA, USA; 3Department of Psychiatry and Human Behavior, Alpert Medical School of Brown University, Providence, RI, USA; 4Department of Psychology, University of Massachusetts Dartmouth, Dartmouth, MA, USA; 5Department of Experimental Psychology, University of Bristol, Bristol, UK; 6Molecular Neurobiology Research Branch, National Institute on Drug Abuse Intramural Research Program, Baltimore, MD, USA and 7Schroder Institute, American Legacy Foundation, Washington, DC, USA

Correspondence: Dr AM Leventhal, Department of Preventive Medicine, University of Southern California Keck School of Medicine, 2250 Alcazar Street, CSC 240, Los Angeles, CA 90033, USA. E-mail: adam.leventhal@usc.edu

Introduction

Identifying genetic factors that predict smoking cessation outcomes and response to smoking cessation treatments may be important in advancing the state of the science because of the low efficacy of current pharmacotherapies. Furthermore, such data may inform the development of personalized treatment approaches to tobacco addiction and elucidate the underlying mechanisms of nicotine dependence.

A variable number of tandem repeats (VNTR) polymorphism in exon III of the dopamine D4 receptor (DRD4) gene (11p15.5) that is putatively functional has been shown to be involved in phenotypes relevant to addiction.1 Although there are alternate classification schemes for this polymorphism,2 alleles have been grouped into ‘long’ (L; seven or more repeats) or ‘short’ (S; six or fewer) most consistently in the literature.1-6 Compared with the S allele, the L allele of this polymorphism has been associated with reduced ligand binding,7 decreased gene expression in vitro and attenuation of cyclic AMP formation when dopamine is bound to the receptor.8-10 Thus, L allele carriers may show low overall dopaminergic tone in areas of the mesolimbic pathway where D4 receptors appear to be distributed,11,12 although the exact localization of D4 receptors in the human brain is still under investigation.13,14
Previous research suggests that the L allele of the \textit{DRD4} exon III VNTR is associated with personality traits that may transmit risk for addiction,\cite{15,16} response to medications for alcohol abuse\cite{17,18} and enhanced reactivity to substance-related cues\cite{19,20}, including smoking-related stimuli among cigarette smokers.\cite{5,18,21} Furthermore, L allele carriers may have lower tobacco use quit rates and poorer smoking cessation outcomes in some populations.\cite{22,23} In addition, a recent study of smokers of European ancestry participating in a placebo controlled trial of transdermal nicotine replacement showed that possession of at least one copy of the L allele was associated with lower abstinence rates at 12-week follow-up, but this effect was not observed at the 26-week follow-up.\cite{3} Nicotine patch was associated with higher abstinence rates than placebo in that study; however, \textit{DRD4} genotype did not moderate treatment effects. It is possible that medications that directly target the dopaminergic system may perhaps be more likely to show differential efficacy by \textit{DRD4} genotype.

Sustained-release bupropion is a first-line treatment for smoking cessation, which inhibits dopamine and norepinephrine reuptake and has partial nicotinic receptor agonist properties.\cite{24,25} Previous reports indicate that variation in the dopamine D2 receptor gene region influences the efficacy of bupropion for smoking cessation.\cite{26,27} Conversely, a study of 1295 single nucleotide polymorphisms (SNPs) in 58 genes found that none of the 11 SNPs in \textit{DRD4} that were analyzed moderated the effects of bupropion on smoking cessation outcomes.\cite{28} Similarly, a genome-wide SNP association analysis of pooled samples, including this study's sample, found no evidence that SNPs within \textit{DRD4} influenced bupropion response.\cite{29}

To the best of our knowledge, we are unaware of any published study that has examined whether copy number repeat variants within \textit{DRD4}, such as the exon III VNTR, moderate the efficacy of bupropion for smoking cessation. Accordingly, we conducted the present pharmacogenetic analysis to investigate whether the \textit{DRD4} exon III VNTR polymorphism moderates the effects of bupropion (vs placebo) on smoking cessation outcomes.

\section*{Materials and methods}

\subsection*{Participants}

Participants were 524 individuals recruited through advertisements to take part in a $2 \times 2$ smoking cessation trial comparing bupropion vs placebo crossed with standard smoking cessation counseling (ST) vs enhanced counseling incorporating cognitive behavioral therapy for depression.\cite{30} Exclusion criteria included pregnancy; a history of mood or thought disorder, based on the \textit{Diagnostic and Statistical Manual of Mental Disorders}, 4th edition;\cite{31} seizure disorder; current use of psychotropic medications; history of seizures or eating disorders; previous use of L-dopa or monoamine oxidase inhibitors; age less than 18 years; or score less than 5 on a 10-point Likert scale of willingness to quit; and smoking less than 10 cigarettes per day. The final sample for analysis included only those who consented for genotyping and reported being of white European descent to reduce potential bias due to racial admixture ($N = 331$). Subjects contributing DNA had significantly higher proportions of women, were older and had been smoking longer.

\subsection*{Procedure}

Following screening and intake procedures, which have been detailed previously,\cite{30} participants were randomized in double-blind manner to bupropion or placebo, according to gender, current depressive symptoms and levels of nicotine dependence, using the urn randomization technique. Bupropion treatment was delivered according to the standard therapeutic dose (150 mg per day for the first 3 days, followed by 300 mg per day) for 12 weeks. Medication was delivered concurrently along with the two randomly assigned counseling conditions (ST vs cognitive behavioral therapy), both of which involved 12 two-hour sessions (see Brown et al.\cite{30} for more details about the counseling interventions). Counseling condition did not moderate genotype or medication effects, thus it was not retained in the analysis.

\subsection*{Measures}

\textbf{Genotyping.} Blood samples were separated and frozen on the day of receipt. Plasma and buffy coat lymphocytes were stored at 80 °C at the Miriam Hospital (Providence, RI, USA) and the Primary Care Genetics Laboratory and Translational Research Center at Memorial Hospital of Rhode Island (Pawtucket, RI, USA) until required for analysis. DNA was extracted using standard techniques described elsewhere.\cite{32} DNA was genotyped at the National Institute on Drug Abuse Molecular Neurobiology Laboratory (Baltimore, MD, USA) using methods previously described and briefly summarized here. The \textit{DRD4} VNTR was amplified by polymerase chain reaction (PCR) using primers and methods previously described.\cite{10,33} After separation by electrophoresis for 3 h on a 2.5% agarose gel, the PCR products (2 to 8- or 10-repeat units) were sized using a 50 bp ladder.

This polymorphism involves a 48 bp sequence that is repeated between 2 and 11 times with the most common versions being two, four and seven repeats. \textit{DRD4} VNTR alleles were classified as long (L) if they consisted of seven or more repeats, and short (S) if they consisted of six or fewer repeats, and participants were grouped into those with at least one copy L allele (SL + LL genotypes) vs those with no copies (SS genotypes), consistent with previous studies.\cite{1,3} Genotype frequencies were not significantly different across treatment conditions and did not deviate from Hardy–Weinberg proportions. Genotype frequencies by treatment condition are reported in the top of Table 1.

\textbf{Baseline characteristics.} Gender, education, marital status, age, ethnic ancestry and smoking history variables (cigarettes per day, age started smoking, years smoking, number of serious quit attempts) were assessed by self-report during the pretreatment assessment visit. Depressive symptoms were measured on the same visit using the
Center for Epidemiologic Studies Depression Scale, a well-validated tool for assessing depressive symptom severity among nonpsychiatric populations. Baseline nicotine dependence severity was assessed using the Fagerström test of nicotine dependence, a widely used and well-validated measure.

Smoking outcomes. Consistent with the previous reports, 7-day point-prevalence abstinence (that is, 7 continuous days without any smoking), verified biochemically on the basis of cotinine levels (classified as abstinent) at end of treatment (EOT) and at 2, 6 and 12 months after EOT, was the primary outcome. This approach does not account for brief lapses back to smoking following quit day and treats participants who undergo lapses and then reinitiate and maintain abstinence in between outcome assessments as successful abstainers. Participants lost to follow-up were classified as smokers for all outcome analyses, consistent with previous investigations and established practice. Continuous abstinence at EOT, 6- and 12-month follow-up was analyzed as a secondary outcome.

Analyses
Preliminary analyses involved $\chi^2$-tests (for categorical variables) and analyses of variance (for continuous variables), which compared baseline characteristics listed in Table 1 across treatment conditions and across genotype within each treatment condition. Consistent with reported recommendations, the primary analysis involved generalized estimating equations (GEE) with unstructured covariance matrices specified. Baseline GEE models including Genotype (SL+LL vs SS), Treatment (bupropion vs placebo) and Time (EOT, 2-, 6- and 12-month follow-up) as predictors and 7-day point-prevalence abstinence (abstinent vs non-abstinent) as the outcome were first tested. Full GEE models, which added the Genotype $\times$ Treatment interaction to the baseline models, were then performed. Additional GEE models showed that Genotype $\times$ Time and Genotype $\times$ Treatment $\times$ Time interactions were nonsignificant and were therefore dropped. Significant Genotype $\times$ Treatment interactions were followed up with simple-effect models, which tested the treatment effect separately across subsamples stratified by Genotype. Results of GEE models are reported as odds ratios (ORs) with 95% confidence intervals (CIs). All models were tested both unadjusted and adjusted for all demographic and clinical characteristics listed in Table 1.

For continuous abstinence outcomes, Genotype, Treatment and the Genotype $\times$ Treatment interaction were predictors in separate logistic regression models for each outcome time point in unadjusted models and models adjusting for baseline demographic and clinical characteristics. For descriptive purposes, logistic regression models predicting abstinence rates by treatment condition for each follow-up point within each genotype group were performed and ORs (95% CIs) are reported; $\alpha$ level was set to 0.05 for all the analyses.

Results
Baseline characteristics
Baseline characteristics by genotype and treatment group are presented in Table 1. There were no significant differences in demographics, smoking characteristics or depressive symptoms across treatment condition nor were
there any differences across genotype within each treatment group.

7-day point-prevalence outcomes
Results of GEE models predicting 7-day point-prevalence outcomes are reported in Table 2. In comparison to placebo, bupropion was associated with increased odds of abstinence in both the unadjusted and adjusted baseline models. The main effect of Genotype in the overall sample was not significant.

There was a significant Genotype × Treatment interaction in both the unadjusted and adjusted full GEE models (Figure 1; Table 2). As illustrated in Table 2, simple-effect GEE analyses indicated that bupropion (vs placebo) was associated with increased odds of abstinence in SL+LL participants (n=102), but did not have a significant effect in SS participants (n=229). This overall pattern of results remained consistent when adjusting for demographics, smoking characteristics and depressive symptoms. In all GEE analyses, there was a significant main effect of time indicating that abstinence rates were higher at earlier outcome assessments.

Abstinence rates by genotype and treatment are reported in Figure 1. Among SL+LL participants, logistic regression models predicting 7-day point-prevalence abstinence at each assessment point indicated significantly higher abstinence rates in the bupropion compared with the placebo condition at EOT (OR = 5.70, 95% CI 2.39–13.62, \( P \leq 0.0001 \)), 2-month (OR = 5.50, 95% CI 2.14–14.16, \( P = 0.0004 \)) and 6-month (OR = 10.36, 95% CI 2.80–38.31, \( P \leq 0.0001 \)).

### Table 2: Results of generalized estimating equation analyses of point-prevalence abstinence

|                  | Unadjusted | P         | Adjusted* | P         |
|------------------|------------|-----------|------------|-----------|
| **Baseline model** |            |           |            |           |
| Time             | 0.91 (0.89–0.93) | <0.0001   | 0.91 (0.89–0.92) | <0.0001   |
| Genotype         | 0.94 (0.87–1.02) | 0.13      | 0.95 (0.87–1.03) | 0.28      |
| Treatment        | 1.13 (1.05–1.22) | 0.001     | 1.16 (1.07–1.26) | 0.0004    |
| **Full model**   |            |           |            |           |
| Genotype × Treatment | 1.25 (1.07–1.46) | 0.005     | 1.24 (1.05–1.46) | 0.014     |
| **Simple effect in SS (n=229)** |            |           |            |           |
| Treatment        | 1.06 (0.96–1.16) | 0.23      | 1.09 (0.99–1.21) | 0.08      |
| Time             | 0.91 (0.89–0.93) | <0.0001   | 0.90 (0.88–0.93) | <0.0001   |
| **Simple effect in SL+LL (n=102)** |            |           |            |           |
| Treatment        | 1.32 (1.16–1.49) | <0.0001   | 1.34 (1.17–1.54) | <0.0001   |
| Time             | 0.92 (0.89–0.95) | <0.0001   | 0.91 (0.87–0.95) | <0.0001   |

Abbreviations: CESD, Center for Epidemiologic Studies Depression Scale; FTND, Fagerström test of nicotine dependence; SL+LL \( \geq 1 \) copy of long allele; SS, homozygous for short allele.

Bupropion: SS (n=116), SL+LL (n=46); placebo: SS (n=113), SL+LL (n=56); variable coding: abstinence (abstinent vs nonabstinent), genotype (SL+LL vs SS), treatment bupropion vs placebo.

*Adjusted for age, sex, employment, education, FTND, CESD, age started smoking, years smoking, no. of previous quit attempts, cigarettes per day.

![Figure 1](image_url)  
Seven-day point prevalence abstinence percentages (± s.e.) by treatment and genotype. SS = homozygous for short allele, SL+LL ≥1 copy of long allele. Placebo vs bupropion comparisons: *\( P < 0.10 \), **\( P < 0.05 \), ***\( P < 0.0005 \), ****\( P < 0.0001 \).
\(P = 0.0005\) follow-ups, and a nonsignificant trend favoring bupropion at the 12-month follow-up (OR = 2.83, 95% CI 0.89–9.00, \(P = 0.08\)). In SS participants, treatment differences were significant only at EOT (OR = 1.79, 95% CI 1.06–3.02, \(P = 0.03\)) and nonsignificant at 2-month (OR = 1.58, 95% CI 0.92–2.73, \(P = 0.10\)), 6-month (OR = 1.12, 95% CI 0.61–2.05, \(P = 0.72\)) and 12-month (OR = 0.92, 95% CI 0.48–1.74, \(P = 0.79\)) follow-ups.

On the basis of inspection of abstinence rates, we carried out additional unplanned simple-effect GEE analyses predicting point prevalence abstinence from genotype within each treatment group. In those randomized to placebo \((n = 169)\), SS + SL (vs LL) was significantly associated with reduced odds of abstinence in unadjusted (OR = 0.85, 95% CI 0.77–0.93, \(P = 0.0006\)) and adjusted (OR = 0.88, 95% CI 0.80–0.97, \(P = 0.0009\)) models. In those randomized to bupropion \((n = 162)\), genotype was not associated with abstinence in unadjusted (OR = 1.06, 95% CI 0.93–1.19, \(P = 0.38\)) or adjusted (OR = 1.06, 95% CI 0.93–1.21, \(P = 0.39\)) model.

**Continuous abstinence outcomes**

Logistic regression models predicting continuous abstinence showed near-significant or significant Genotype \(\times\) Treatment interactions at EOT (Wald \(\chi^2 = 3.7, P = 0.054\)), 6-month (Wald \(\chi^2 = 9.8, P = 0.002\)) and 12-month (Wald \(\chi^2 = 4.2, P = 0.04\)) follow-ups. Adjusting for baseline demographic and clinical characteristics did not substantially alter the effects of Genotype \(\times\) Treatment interactions (EOT: Wald \(\chi^2 = 3.5, P = 0.06\); 6 months: Wald \(\chi^2 = 8.7, P = 0.003\); and 12 months: Wald \(\chi^2 = 3.6, P = 0.06\)). Continuous abstinence rates in the SL + LL group, by treatment (bupropion vs placebo), were as follows: EOT (41 vs 11%, OR = 5.86, 95% CI 2.09–16.43, \(P = 0.0088\)), 6-month (35 vs 4%, OR = 14.40, 95% CI 3.10–66.90, \(P = 0.0007\)) and 12-month (17 vs 4%, OR = 5.68, 95% CI 1.14–28.27, \(P = 0.03\)) follow-ups. Continuous abstinence rates in the SL + LL group, by treatment, were: EOT (35 vs 23%, OR = 1.83, 95% CI 1.02–3.27, \(P = 0.04\)), 6-month (22 vs 21%, OR = 1.02, 95% CI 0.54–1.92, \(P = 0.95\)) and 12-month (14 vs 15%, OR = 0.90, 95% CI 0.43–1.89, \(P = 0.79\)) follow-ups.

**Discussion**

The **DRD4** exon III VNTR polymorphism moderated the effects of bupropion (vs placebo) on smoking cessation outcomes in this study. Participants with at least one copy of the L allele had increased abstinence rates following bupropion (vs placebo) treatment, whereas bupropion evidenced minimal efficacy beyond placebo among smokers with SS genotypes. Additional simple-effect analyses also showed that L allele carriers treated with placebo showed a higher risk of relapse than participants with the SS genotype, and this risk was offset by bupropion treatment. This pattern of findings was generally consistent across multiple outcomes (that is, point prevalence and continuous abstinence) and in adjusted models that accounted for the effects of demographic and clinical characteristics.

The present results are concordant with previous pharmacogenetic analyses showing that polymorphisms related to dopaminergic activity are associated with smoking cessation outcomes and that such variants may moderate the efficacy of bupropion.\(^{26,27,38}\) Furthermore, they add to an emerging literature indicating the **DRD4** exon III VNTR polymorphism is associated with addiction-related phenotypes, including smoking cessation.\(^{1,2,22,23}\)

To the best of our knowledge this is the first published pharmacogenetic investigation of the **DRD4** exon III VNTR and bupropion treatment for smoking cessation. In a previous pharmacogenetic study of this gene and nicotine patch (vs placebo) treatment, carriers of the L allele showed greater relapse risk at the 12-week follow-up,\(^3\) which parallels the pattern of results in the placebo arm of this study. By contrast, the exon III VNTR polymorphism did not predict outcome at 26 weeks follow-up in that study, nor did it interact with nicotine replacement therapy to predict outcome. Furthermore, the C→T position S21 SNP in **DRD4** also did not predict outcomes in that study. Similarly, multigene and genome-wide SNP association studies using more stringent type I error corrections found that SNPs within **DRD4** do not have a significant main effect on nor significantly interact with bupropion treatment to predict smoking cessation outcomes.\(^{28,29}\)

The L allele of this VNTR polymorphism may produce structural changes to the length of the protein in the third cytoplasmic loop of D4 receptor, which is associated with reduced receptor-binding affinity and diminished signaling in response to dopamine binding.\(^7\)–\(^10\) There is also suggestive evidence that the L allele is associated with reduced gene expression in human brain tissue,\(^39\) potentially through its effect on RNA stability or translational efficiency.\(^40\) Given the potential functional effects of the **DRD4** exon III VNTR, one may speculate why this polymorphism moderated efficacy of bupropion in this study, but did not moderate the efficacy of nicotine replacement therapy in the study by David et al.\(^3\) One explanation is that the L allele results in low dopaminergic tone, which may in turn increase relapse risk, and bupropion is better able to ameliorate this deficit than nicotine replacement therapy because it exerts its effect more directly on the dopaminergic system. Although this explanation would be consistent with recent findings indicating that variants in the catechol-O-methyltransferase gene that may result in low dopaminergic tone are associated with better bupropion response,\(^38\) it is unclear how to integrate these findings with other evidence indicating that polymorphisms linked with low D2 receptor availability may be associated with poorer bupropion response.\(^26,27\) On the basis of the current finding and the results of David et al.,\(^3\) one hypothesis is that, in the context of smoking cessation treatment, L allele carriers of European descent may perhaps benefit more from bupropion as opposed to nicotine replacement therapy. However, because the two studies sampled from distinct populations and had other methodological differences, a direct comparison of smokers prospectively genotyped for **DRD4** and then experimentally randomized either to bupropion or nicotine
replacement therapy by genotype is required to evaluate this prediction systematically.

A Genotype × Treatment interaction and an association between the L allele and abstinence outcomes within the placebo arm were found in this study. Accordingly, one might expect that, provided there is sufficient sample size, a main effect of genotype could also be apparent when averaged across treatment groups, albeit this effect would be weakened by the lack of genotype effect in the bupropion condition. However, the main effect of genotype in the overall sample was not statistically significant (unadjusted GEE model: OR = 0.94, 95% CI 0.87–1.02, \( P = 0.13 \)). One possible explanation for the lack of the significant main effect of genotype is that our sample was not large enough to detect such an effect. Indeed, placebo-controlled nicotine replacement pharmacogenetic analysis performed by David et al. required a sample that was twice as large as the current sample (\( N = 720 \)) to show a main effect of the \( DRD4 \) exon III VNTR on 12-week cessation outcomes (\( P = 0.034 \)).

The Genotype × Treatment interaction did not significantly vary by time. Follow-up analyses among L allele carriers suggested relatively robust bupropion vs placebo effects that endured through the 6-month follow-up, and were weakened at the 12-month follow-up (ORs ranging 2.83–10.36 across all assessments). By contrast, treatment effects for participants with the SS genotype were comparatively weaker across all assessments and became nonsignificant after the EOT assessment (ORs \( \leq 1.52 \) across all assessments). Similar patterns of abstinence rates by treatment and genotype over time have been shown in an analysis of the \( DRD2 \) Taq1A polymorphism and bupropion for smoking cessation.\(^{27}\) Extant research suggests that the L allele is associated with greater craving,\(^{41}\) attentional capture\(^{5}\) and brain activation\(^{6}\) in response to smoking-related stimuli, suggesting that incentive sensitization processes triggered by smoking-paired cues may potentially contribute to relapse among L allele carriers. There is some evidence to suggest that bupropion\(^{62}\) (but not nicotine patch)\(^{63}\) diminishes cue-induced craving, which could help to extinguish the condition craving response and possibly render smoking-associated stimuli less potent following active treatment. Speculatively, bupropion may buffer L allele carriers from the relapse-producing effects of cue exposure even after active treatment is terminated, which could account for the persistent treatment effects in smokers with the L allele. However, further research is required to determine whether this putative mechanism accounts the pharmacogenetic effects of \( DRD4 \) on bupropion efficacy.

Some limitations should be noted. A small portion of participants did not contribute DNA. These individuals were different from members of the primary sample on some baseline variables, which may have altered the generalizability of the present sample. We only included participants who reported being from white European descent in analyses to reduce potential bias due to racial admixture. Genotyping ancestry informative markers would have been preferable, given the limitations of self-report. In addition, we did not have a large enough sample of non-Europeans for multi-subgroup analyses, leaving unclear whether these findings will extend across other ancestral groups. It should be noted that three other genes have been analyzed in this sample.\(^{26,27}\) Thus, a more conservative approach would have been to adjust the \( \alpha \) level for multiple tests. Given the small sample, we retained the standard \( \alpha \) level of .05 to increase power to detect potential effects. Even if we adopted a more stringent significance level of 0.0125 (0.05/4 total genes tested in this sample), most of the primary findings would have retained significance, with the exception of the Gene × Treatment interaction in the adjusted model that yielded a \( P \)-value of .014. Finally, as mentioned above, this sample may have been too small to provide sufficient power to detect a main effect of genotype in the overall sample.

In sum, this investigation suggests that individuals who carry the L allele of the exon III \( DRD4 \) VNTR polymorphism show a better clinical response to bupropion (vs placebo) for smoking cessation than noncarriers. If replicated and extended, these findings may eventually lead to clinical applications of genetically tailored smoking cessation therapy using bupropion with the \( DRD4 \) gene.

**Conflict of interest**

The authors declare no conflict of interest.

**Acknowledgments**

This research was supported by NIH grants DA025041 (AML), HL32318 and CA84719 (RN), DA08511 (RAB), DA14276 and DA27331 (SPD) and NIDA-IRP.

**References**

1. McGeary J. The \( DRD4 \) exon 3 VNTR polymorphism and addiction-related phenotypes: a review. *Pharmacol Biochem Behav* 2009; 93: 222–229.
2. Wang E, Ding YC, Flodman P, Kidd JR, Kidd KK, Grady DL et al. The genetic architecture of selection at the human dopamine receptor D4 (\( DRD4 \)) gene locus. *Am J Hum Genet* 2004; 74: 931–944.
3. David SP, Munafo MR, Murphy MF, Proctor M, Walton RT, Johnstone EC. Genetic variation in the dopamine D4 receptor (\( DRD4 \)) gene and smoking cessation: follow-up of a randomised clinical trial of transdermal nicotine patch. *Pharmacogenomics J* 2008; 8: 122–128.
4. Munafo MR, Clark TG, Moore LR, Payne E, Walton R, Flint J. Genetic polymorphisms and personality in healthy adults: a systematic review and meta-analysis. *Mol Psychiatry* 2003; 8: 471–484.
5. Munafo MR, Johnstone EC. Smoking status moderates the association of the dopamine D4 receptor (\( DRD4 \)) gene VNTR polymorphism with selective processing of smoking-related cues. *Addict Biol* 2008; 13: 435–439.
6. Munafo MR, Yalcin B, Willis-Owen SA, Flint J. Association of the dopamine D4 receptor (\( DRD4 \)) gene and approach-related personality traits: meta-analysis and new data. *Biol Psychiatry* 2008; 63: 197–206.
7. Asghari V, Schoots O, van Kats S, Ohara K, Jovanovic V, Guan HC et al. Dopamine D4 receptor repeat: analysis of different native and mutant forms of the human and rat genes. *Mol Pharmacol* 1994; 46: 364–373.
8. Asghari V, Sanjal S, Buchwaldt S, Paterson A, Jovanovic V, Van Tol HH. Modulation of intracellular cyclic AMP levels by different human dopamine D4 receptor variants. *J Neurochem* 1995; 65: 1157–1165.
9. Van Tol HH, Wu CM, Guan HC, Ohara K, Bunzow JR, Civelli O et al. Multiple dopamine D4 receptor variants in the human population. *Nature* 1992; 358: 149–152.
25 Fryer JD, Lukas RJ. Noncompetitive functional inhibition at diverse, human nicotinic acetylcholine receptor subtypes by bupropion, phenycyclidine, and ibogaine. J Pharmacol Exp Ther 1999; 288: 88–92.

26 David SP, Brown RA, Papandonatos GD, Kahler CW, Lloyd-Richardson EE, Munafo MR et al. Pharmacogenetic clinical trial of sustained-release bupropion for smoking cessation. Nicotine Tob Res 2007; 9: 821–833.

27 David SP, Strong DR, Munafo MR, Brown RA, Lloyd-Richardson EE, Willeto PE et al. Bupropion efficacy for smoking cessation is influenced by the DRD2 Taq1A polymorphism: analysis of pooled data from two clinical trials. Nicotine Tob Res 2007; 9: 1251–1257.

28 Conti DV, Lee W, Li D, Liu J, Van Den Berg D, Thomas PD et al. Nicotinic acetylcholine receptor beta2 subunit gene implicated in a systems-based candidate gene study of smoking cessation. Hum Mol Genet 2008; 17: 2834–2848.

29 Uhl GR, Liu QR, Drogan T, Johnson C, Walther D, Rose JE et al. Molecular genetics of successful smoking cessation: convergent genome-wide association study results. Arch Gen Psychiatry 2008; 65: 683–693.

30 Brown RA, Niaura R, Lloyd-Richardson EE, Strong DR, Kahler CW, Abrantes AM et al. Bupropion and cognitive-behavioral treatment for depression in smoking cessation. Nicotine Tob Res 2007; 9: 721–730.

31 American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV. 4th edn. American Psychiatric Association: Washington, DC, 1994.

32 Lerman C, Caporaso NE, Audrain J, Main D, Bowman ED, Lockshin B et al. Evidence suggesting the role of specific genetic factors in cigarette smoking. Psychol Bull 1999; 125: 14–20.

33 Lichter JB, Barr CL, Kennedy JL, Van Tol HH, Kidd KK, Livak KJ. A hypervariable segment in the human dopamine receptor D4 (DRD4) gene. Hum Mol Genet 1993; 2: 767–773.

34 Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. Appl Psychol Meas 1977; 1: 385–401.

35 Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom K-O. The Fagerstrom test for nicotine dependence: a revision of the Fagerstrom tolerance questionnaire. Br J Addict 1991; 86: 1119–1127.

36 Hughes J, Stead L. Antidepressants for smoking cessation. Cochrane Database Syst Rev 2004: CD000831.

37 Hall SM, Delucchi KL, Velicer WF, Kahler CW, Rangner-Moore J, Hedeker D et al. Statistical analysis of randomized trials in tobacco treatment: longitudinal designs with dichotomous outcome. Nicotine Tob Res 2001; 3: 193–202.

38 Berrettini WH, Willeto EP, Epstein L, Restine S, Hawk L, Shields P et al. Catechol-O-methyltransferase (COMT) gene variants predict response to bupropion therapy for tobacco dependence. Biol Psychiatry 2007; 61: 111–118.

39 Simpson J, Vetuz G, Wilson M, Brookes KJ, Kent L. The DRD4 receptor exon 3 VNTR and 5' SNP variants and mRNA expression in human post-mortem brain tissue. Am J Med Genet B Neuropsychiatr Genet (in press).

40 Schoots O, Van Tol HH. The human dopamine D4 receptor repeat sequences modulate expression. Pharmacogenomics 2003; 3: 343–348.

41 Hutchison KE, LaChance H, Niaura R, Bryan A, Smolen A. The DRD4 VNTR polymorphism influences reactivity to smoking cues. J Abnorm Psychol 2002; 111: 134–143.

42 Brody AL, Mandelknr MA, Lee G, Smith E, Sadeghi M, Saxena S et al. Attenuation of cue-induced cigarette craving and anterior cingulate cortex activation in bupropion-treated smokers: a preliminary study. Psychol Res 2004; 130: 269–281.

43 Ferguson SG, Shiffman S. The relevance and treatment of cue-induced cravings in tobacco dependence. J Subst Abuse Treat 2009; 36: 235–243.