Analysis of 34 candidate genes in bupropion and placebo remission

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Abstract

There is considerable variability in the rate of response and remission following treatment with antidepressant drugs or placebo in depression patients. No pharmacogenetic studies of bupropion response have been done. We investigated 532 tagging single nucleotide polymorphisms (SNPs) in 34 candidate genes for association with remission and response to either bupropion (n = 319) or placebo (n = 257) in patients with major depressive disorder. Analyses were performed using conditional logistic regression. Significant association (gene-wide correction) was observed for remission following treatment with bupropion for a SNP within the serotonin receptor 2A gene (HTR2A rs2770296, \( p_{\text{corrected}} = 0.02 \)). Response to bupropion treatment was significantly associated with a SNP in the dopamine transporter gene (rs6347; \( p_{\text{corrected}} = 0.013 \)). Among the patients who received placebo, marginal association for remission was observed between a SNP in HTR2A (rs2296972, \( p_{\text{corrected}} = 0.055 \)) as well as in the serotonin transporter gene (5-HTT or SLC6A4; rs4251417, \( p_{\text{corrected}} = 0.050 \)). Placebo response was associated with SNPs in the glucocorticoid receptor gene (NR3C1; rs1048261, \( p_{\text{corrected}} = 0.040 \)) and monoamine oxidase A gene (MAOA; rs6609257, \( p_{\text{corrected}} = 0.046 \)). Although the above observations were significant after gene-wide corrections, none of these would be significant after a more conservative study-wide correction for multiple tests. These results suggest a possible role for HTR2A in remission to bupropion treatment. In accordance with bupropion pharmacology, dopamine transporter may play a role in response. The MAOA gene may be involved in placebo response.

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Key words: Association, bupropion, dopamine, placebo, response, serotonin.

Introduction

Major depressive disorder (MDD) is one of the most serious illnesses affecting at least one in six individuals in the United States during their lifetime (Kessler et al. 2005). Antidepressants are the cornerstone in treating depression; however, about 50–70% of patients respond to therapy and <40% of patients achieve full remission (Thase et al. 2005). Therefore, a reliable tool to predict the efficacy of the prescribed antidepressant is required. Pharmacogenetics offers one such alternative, wherein genetic factors associated with response to a specific drug can be used to identify individuals who may not respond to that treatment option. In family studies, concordance for antidepressant response suggests a possible role of genetic factors in treatment response (Franchini et al. 1998).

Candidate gene studies have reported several polymorphisms in genes from the serotonergic, dopaminergic and hypothalamic–pituitary–adrenal (HPA) pathways to be associated with antidepressant response (Kato & Serretti, 2010). Genetic polymorphisms in the serotonin transporter (5-HTT or SLC6A4; Drago et al. 2009; Hu et al. 2007; Serretti et al. 2007), serotonin receptor 2A (HTR2A; McMahon et al. 2006; Uher et al. 2009) and in FK506 binding protein 51 (FKBP5; Binder et al. 2004) have been reported to be associated with antidepressant treatment response. Recently, association of a polymorphism in the interleukin 11 gene with escitalopram response and a polymorphism in the uronyl 2-sulphotransferase gene with nortriptyline response has also been reported (Uher et al. 2010). Similarly, single nucleotide polymorphisms (SNPs) in the vicinity of the ubiquitin protein ligase E3C and bone morphogenetic protein 7 genes and in the intron of the retinoic acid receptor-related orphan receptor A gene have also been associated with response to citalopram (Garriock et al. 2010a). Thus, several putative genetic markers associated with response to antidepressants have been identified.

Placebo response has been a major concern for drug trials as well as genetic studies (Walsh et al. 2002). In a recent meta-analysis, placebo effect was reported to account for 67.6% of the efficacy observed in antidepressant...
treatment (Rief et al. 2009). No common mechanism for placebo response has been identified. However, brain mechanisms such as reward expectation and conditioning have been reported to play an important role (Benedetti et al. 2011; de la Fuente-Fernandez, 2009). In depression, regions associated with reward, including prefrontal cortex and anterior cingulate, were activated in response to placebo treatment (Mayberg et al. 2002). Increased quantitative electroencephalogram cordance in the prefrontal region in placebo responders, but not in antidepressant responders, has also been reported (Leuchter et al. 2002). To our knowledge, a relatively large scale genetic study has not yet been carried out to investigate the genetic determinants of placebo response in depression. There is a report of association \( n = 52 \) of the high activity GG or G genotype of the monoamine oxidase-A (MAOA) polymorphism \( rs6323, T > G \) and a trend of association of the Met/Met low activity genotype of catechol-O-methyltransferase (COMT) polymorphism \( Val^{158}Met; rs4680 \) with poor response to placebo treatment (Leuchter et al. 2009).

In this study, we aim to conduct the first comprehensive association study to investigate whether polymorphisms in candidate genes from the monoaminergic pathways and HPA axis are associated with bupropion as well as placebo treatment remission and response. The precise mechanism of action of bupropion is unknown; however, it is a weak dual norepinephrine and dopamine reuptake inhibitor and a non-competitive antagonist of several nicotinic acetylcholine receptors (Arias et al. 2009).

**Materials and method**

**Subjects**

Subjects for the present study are bupropion- or placebo-treated patients from four different clinical trials (AK130926, Clayton et al. 2006; AK130927, Clayton et al. 2006; AK130931, Jefferson et al. 2006; WXL100368, Thase et al. 2006). Diagnosis was made according to the Diagnostic and Statistical Manual of Mental disorders (DSM-IV) criteria by an investigator experienced in diagnosing and treating MDD. Approval from the institutional review boards and informed consent was obtained from all the subjects. Studies AK130926 (NCT00051259) and AK130927 (NCT0051272) were multi-centre, double-blind, randomized, placebo-controlled trials evaluating effects of extended-release bupropion hydrochloride (300–450 mg/d), escitalopram (10–20 mg) and placebo on sexual functioning in out-patients with moderate to severe major depression [Hamilton rating scale for depression (HAMD\(_{17}\)) \( \geq 19 \)] over an 8-wk treatment period (Clayton et al. 2006). Study AK130931 (NCT00064467) was also a multi-centre, double-blind, randomized, placebo-controlled comparison of the efficacy and safety of flexible dose extended-release bupropion (HCl) 300–450 mg/d vs. placebo, administered for 8 wk for the treatment of adult out-patients with MDD reporting symptoms of decreased energy, pleasure and interest (Jefferson et al. 2006). Patients with a minimum score of 25 on the 30-item Inventory of Depressive Symptomatology measured using interactive voice response were included. Study WXL100368 (NCT00316160) compared the effects of bupropion hydrochloride extended-release (Wellbutrin XL, 150–450 mg/d) and extended-release venlafaxine (Effexor XR, 75–225 mg/d) on sexual functioning in subjects with MDD (HAMD\(_{17}\) \( \geq 17 \)). This was a 12-wk, multi-centre, randomized, double-blind, double-dummy, parallel-group, active controlled study (Thase et al. 2006). The exclusion criteria for these studies were current diagnosis of bipolar disorder or schizophrenia, or other significant psychiatric disorder, a diagnosis of anorexia nervosa or bulimia, a diagnosis of panic disorder, obsessive–compulsive disorder, post-traumatic stress disorder or acute stress disorder. Other exclusions included alcohol or substance abuse, unstable medical conditions, seizure disorder or brain injury. No psychotropic drugs were allowed within 2 wk of baseline visit.

The studies AK130926, AK130927 and WXL100368 used the HAMD\(_{17}\) while study AK130931 reported measures using Inventory of Depressive Symptoms–clinician rated (IDS-C). The IDS-C scores were converted to equivalent HAMD\(_{17}\) scores using the modified formula \( \text{HAMD}_{17} = \frac{\text{IDS-C}}{2} \) (Rush et al. 2003). Percent change in HAMD\(_{17}\) and the converted IDS-C from baseline score was used in all the quantitative analyses.

In this study, we included patients who had received either bupropion or placebo and gave written informed consent to participate in genetic research. A total of 582 subjects who completed at least 4 wk of study were included in the genetic association analysis. Similar cut-off points have been used in the large STAR*D (42 d exposure to citalopram; see Binder et al. 2010; Garriock et al. 2011b) and in other studies in the literature. The most common reason for premature withdrawal from the bupropion clinical trials was loss of contact during follow-up or the emergence of mild or moderate adverse events. The dependent variables for association analysis were remission and response to antidepressant or placebo treatment. Patients were classified as remitters if the HAMD\(_{17}\) score was \( \leq 7 \) (studies AK130926, AK130927 and WXL100368) or IDS-C score of \( \leq 13 \) at exit/end of the study (AK130931). Similarly, patients with \( \geq 50\% \) reduction in HAMD\(_{17}\) or IDS-C from randomization were classified as responders. Last observation carried forward (LOCF) was used to include subjects who completed at least 4 wk but dropped out before the end of the study. The demographic characteristics of the study population, by the treatment groups, bupropion or placebo, are provided in Table 1 (clinical study specific summaries are provided in Supplementary Table S1).
Table 1. Demographic characteristics of the study samples stratified by treatment (n = 576)

<table>
<thead>
<tr>
<th></th>
<th>Bupropion</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>European ancestry (N = 251)</td>
<td>African ancestry (N = 41)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>38.90 ± 12.6</td>
<td>37.98 ± 11.4</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>164 (65.3)</td>
<td>25 (61.0)</td>
</tr>
<tr>
<td>Male</td>
<td>87 (34.7)</td>
<td>16 (39.0)</td>
</tr>
<tr>
<td>Remission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-remitter</td>
<td>150 (59.8)</td>
<td>24 (58.5)</td>
</tr>
<tr>
<td>Remitter</td>
<td>101 (40.2)</td>
<td>17 (41.5)</td>
</tr>
<tr>
<td>Response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-responder</td>
<td>101 (40.2)</td>
<td>18 (43.9)</td>
</tr>
<tr>
<td>Responder</td>
<td>150 (59.8)</td>
<td>23 (56.1)</td>
</tr>
<tr>
<td>Baseline HAMD&lt;sub&gt;17&lt;/sub&gt; score</td>
<td>23.39 ± 4.0</td>
<td>25.5 ± 4.6</td>
</tr>
<tr>
<td>Change in HAMD&lt;sub&gt;17&lt;/sub&gt; score (%)</td>
<td>−54.81 ± 29.5</td>
<td>−53.49 ± 27.8</td>
</tr>
</tbody>
</table>

*Baseline Hamilton Rating Scale for Depression (HAMD<sub>17</sub>) score for the African ancestry patients was significantly higher than the patients from European ancestry (p = 0.003). Values shown in bold indicate p < 0.05.
Statistical analyses

Statistical analyses were performed using SAS v.9.1.3 and the PLINK software 1.06 (Purcell et al. 2007). Categorical variables were tested using a \( \chi^2 \) test and the continuous variables were tested using analysis of covariance. Association between SNPs and the treatment outcome, remission or response, was tested using conditional logistic regression (CLR) assuming an additive genetic model. We decided a priori that the additive model would be the association-determining test. CLR was used because we were pooling data from four clinical trials (three for placebo arm of the study). CLR is an extension of logistic regression that takes into account the differences between clinical trials. CLR gives us an average across trials of the within-trial effects, after accounting for differences between the trials. Details of model assumptions are provided in Supplementary Information. Odds ratio (OR) with 95% confidence interval (CI) are reported.

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Association was tested using LOCF as well as the sensitivity analysis using only the subjects who completed the clinical trials of the within-trial effects, after accounting for differences between the trials. Details of model assumptions are provided in Supplementary Information. Odds ratio (OR) with 95% confidence interval (CI) are reported.

Percent change in HAMD\(_{17}\) from baseline was further evaluated for SNPs that were statistically significant using analysis of covariance. Linkage disequilibrium (LD) and haplotypic association were determined using Haploview 4.1 (Barrett et al. 2005). Since this was a candidate gene-based association study, effective number of independent tests (\( M_{\text{eff}} \)) was calculated taking into account the LD between the SNPs in the same gene (SNPSpD; Li & Ji, 2005; Nyholt, 2004, Supplementary Table S2). The effective number of tests varied from 10 to 30 and these values were used for the calculation of the multiple tests corrected \( p \) value for each gene separately (\( p \) value \( \times M_{\text{eff}} = p_{\text{corrected}} \)). This method has accuracy similar to permutation testing and efficiently controls for false-positive results (Li & Ji, 2005; Nyholt, 2004). The power of our study to identify moderate genetic effects was calculated using Quanto 1.2.4. (Gauderman & Morrison, 2006). With the placebo-treated sample set, we had \( \sim 80\% \) power to detect genetic effects with \( OR \geq 1.9 \). Similarly for the bupropion treatment response and remission sample sets, we had \( \sim 80\% \) power to detect OR \( \geq 1.8 \) (assuming a log-additive model and a minor allele frequency of 20\%).

Results

Patients in study AK130931 had a higher mean age, lower mean baseline HAMD\(_{17}\), a lower rate of placebo response and a lower remission rate compared to the other studies (Supplementary Table S1). However, the rate of response and remission in bupropion-treated subjects was similar across the clinical studies. Gender distribution was also significantly different in patients treated with bupropion (Table 1). Because there is significant heterogeneity in the study data, we tested for genotype effect after adjusting for the effect of age, severity of MDD (baseline HAMD\(_{17}\) score), ancestry and gender. In total, 84.95\% of patients on bupropion completed the duration of the clinical trials for bupropion (271 of 319) and 88.33\% of patients on placebo (227 of 257). The list of genes investigated is provided in Supplementary Table S2.

Association of SNPs with remission and response to bupropion (n = 319)

Of the 532 SNPs tested, rs2770296 in HTR2A was significantly associated with remission in bupropion-treated patients (\( p_{\text{corrected}} = 0.02 \), Table 2, Supplementary Table S3). Suggestive associations were also observed with two other SNPs in HTR2A, two SNPs in solute carrier 18 A2 (SLC18A2 or VMAT2) and one SNP each in angiotensin converting enzyme (ACE) and dopamine \( \beta \)-hydroxylase (DBH). As the majority of patients are of European ancestry, repeating the analysis on a subset of patients of European ancestry provided similar association results (Table 2 and Supplementary Table S3). In addition, an allelic analysis of SNPs in HTR2A gene in patients of European ancestry showed significant allelic association of rs2770296 and rs9526240 with remission (\( P \) permutation corrected = 0.0274 and 0.0151, respectively). Nominal association of the haplotype block including rs9526240 was also observed (Supplementary Fig. S2, block 5, \( P \) permutation corrected = 0.05). The haplotype block containing rs2770296 was not significant after correction for multiple comparisons (\( P \) permutation corrected = 0.488, uncorrected \( p \) value 0.029).

Response to bupropion treatment was significantly associated with rs6347 in the dopamine transporter [DAT1 or SLC6A3; \( OR = 1.85 (1.28–2.69); P_{\text{corrected}} = 0.013 \)]. Suggestive associations (\( p_{\text{corrected}} < 0.1 \)) were observed with rs363225 in SLC18A2 [\( OR = 0.59 (0.41–0.85), P_{\text{corrected}} = 0.059 \)], and rs17614642 in FKBP5 [\( OR = 3.14 (1.36–7.24), P_{\text{corrected}} = 0.065 \); Table 2, Supplementary Table S3].

The genetic associations mentioned above were also further supported by the observations that carriers of the minor alleles of the polymorphisms rs2770296 in HTR2A and rs8075924 in ACE, for example, showed significant differences in percentage change in HAMD\(_{17}\) from baseline in patients of European ancestry (Table 3). Patients who carry the ‘GG’ genotype of rs2770296 had significant reduction in HAMD\(_{17}\) score following treatment, suggesting better response and/or remission to bupropion. On the other hand, carriers of the TT genotype of rs8075924 showed less improvement and is associated with non-remission/non-response (Table 3).

We also performed an association analysis in subjects who had completed the duration of the clinical trials (\( n = 271 \), Table 4, Supplementary Table S4). The SNP rs2770296 in HTR2A, similar to the above analysis, was still significantly associated with remission following treatment with bupropion (\( p_{\text{corrected}} = 0.027 \); Table 4).
**Table 2.** Results of association analysis between SNPs and remission or response during bupropion (\(n=319\)) or placebo treatment (\(n=257\)) after correcting for multiple comparisons (Li & Ji, 2005; Nyholt, 2004)

<table>
<thead>
<tr>
<th>Chr</th>
<th>Gene</th>
<th>SNP</th>
<th>Minor allele</th>
<th>Total (European ancestry only)</th>
<th>Bupropion remission</th>
<th>Placebo remission</th>
<th>Bupropion response</th>
<th>Placebo response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(N)</td>
<td>(p) value (^a)</td>
<td>(p_{corrected} (^b)</td>
<td>OR (CI)</td>
<td>(N)</td>
</tr>
<tr>
<td>13</td>
<td>HTR2A</td>
<td>rs2770296</td>
<td>G</td>
<td>317</td>
<td>0.00075</td>
<td>0.0204</td>
<td>1.95 (1.32–2.87)</td>
<td>251</td>
</tr>
<tr>
<td>13</td>
<td>HTR2A</td>
<td>rs985933</td>
<td>T</td>
<td>317</td>
<td>0.00215</td>
<td>0.0587</td>
<td>1.71 (1.21–2.42)</td>
<td>251</td>
</tr>
<tr>
<td>13</td>
<td>HTR2A</td>
<td>rs9526240</td>
<td>T</td>
<td>318</td>
<td>0.00228</td>
<td>0.0620</td>
<td>1.86 (1.25–2.77)</td>
<td>251</td>
</tr>
<tr>
<td>17</td>
<td>ACE</td>
<td>rs8075924</td>
<td>T</td>
<td>319</td>
<td>0.00621</td>
<td>0.0536</td>
<td>0.54 (0.35–0.84)</td>
<td>251</td>
</tr>
<tr>
<td>9</td>
<td>DBH</td>
<td>rs2873804</td>
<td>T</td>
<td>317</td>
<td>0.00378</td>
<td>0.0796</td>
<td>0.61 (0.43–0.85)</td>
<td>250</td>
</tr>
<tr>
<td>10</td>
<td>SLC18A2</td>
<td>rs363226</td>
<td>G</td>
<td>317</td>
<td>0.00410</td>
<td>0.0574</td>
<td>1.74 (1.19–2.55)</td>
<td>249</td>
</tr>
<tr>
<td>10</td>
<td>SLC18A2</td>
<td>rs363225</td>
<td>T</td>
<td>313</td>
<td>0.00632</td>
<td>0.0884</td>
<td>0.61 (0.43–0.87)</td>
<td>247</td>
</tr>
<tr>
<td>5</td>
<td>SLC6A3</td>
<td>rs6347</td>
<td>G</td>
<td>316</td>
<td>0.00119</td>
<td>0.0130</td>
<td>1.85 (1.28–2.69)</td>
<td>249</td>
</tr>
<tr>
<td>10</td>
<td>SLC18A2</td>
<td>rs363225</td>
<td>T</td>
<td>313</td>
<td>0.00427</td>
<td>0.0598</td>
<td>0.59 (0.41–0.85)</td>
<td>247</td>
</tr>
<tr>
<td>6</td>
<td>FKBP5</td>
<td>rs17614642</td>
<td>G</td>
<td>308</td>
<td>0.00713</td>
<td>0.0647</td>
<td>3.14 (1.36–7.24)</td>
<td>244</td>
</tr>
<tr>
<td>13</td>
<td>HTR2A</td>
<td>rs2296972</td>
<td>T</td>
<td>256</td>
<td>0.00201</td>
<td>0.0548</td>
<td>0.47 (0.29–0.76)</td>
<td>196</td>
</tr>
<tr>
<td>17</td>
<td>SLC6A4</td>
<td>rs4251417</td>
<td>A</td>
<td>257</td>
<td>0.00718</td>
<td>0.0502</td>
<td>2.73 (1.31–5.68)</td>
<td>197</td>
</tr>
<tr>
<td>13</td>
<td>HTR2A</td>
<td>rs622337</td>
<td>C</td>
<td>256</td>
<td>0.00294</td>
<td>0.0802</td>
<td>0.49 (0.31–0.87)</td>
<td>196</td>
</tr>
<tr>
<td>5</td>
<td>NR3C1</td>
<td>rs10482616</td>
<td>A</td>
<td>257</td>
<td>0.00305</td>
<td>0.0396</td>
<td>0.45 (0.27–0.76)</td>
<td>197</td>
</tr>
<tr>
<td>X</td>
<td>MAOA</td>
<td>rs6609257</td>
<td>G</td>
<td>246</td>
<td>0.00351</td>
<td>0.0456</td>
<td>1.85 (1.22–2.80)</td>
<td>187</td>
</tr>
</tbody>
</table>

CI, Confidence interval (95%).

\(^{a}\)Additive model.

\(^{b}\)\(p\) value corrected for multiple independent comparisons (gene-wide; Li & Ji, 2005; Nyholt, 2004). The effective number of independent comparisons was calculated \(M_{eff}\) and the corrected \(p\) value \(\left(p_{corrected}\right)\) was calculated \(\left(M_{eff} \times \left.M_{RIL} \times p\right)\). Association statistics for the total sample was calculated using conditional logistic regression with gender, age, baseline Hamilton Rating Scale for Depression score and ancestry as covariates.

Single nucleotide polymorphisms (SNPs) associated with either remission or response \(\left(p_{corrected} \leq 0.1\right)\) in the total sample are presented. The odds ratios (OR) are with regard to remission/response.
Table 3. Percentage change in HAMD_{17} scores from baseline compared across genotypic categories in patients of European ancestry, with age, gender and baseline HAMD_{17} score used as covariates

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Gene</th>
<th>SNP</th>
<th>Genotype</th>
<th>Change in HAMD_{17} (%, mean ± s.e., n)</th>
<th>p value^c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupropion</td>
<td>HTR2A</td>
<td>rs2770296</td>
<td>AA</td>
<td>−50.99 ± 2.7 (119)</td>
<td>0.018</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AG</td>
<td>−56.11 ± 2.7 (114)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GG</td>
<td>−71.71 ± 6.9 (18)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ACE</td>
<td>rs8075924</td>
<td>CC</td>
<td>−54.69 ± 2.2 (180)</td>
<td>0.010</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CT</td>
<td>−59.37 ± 3.7 (61)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TT</td>
<td>−28.94 ± 9.2 (10)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DBH</td>
<td>rs2873804</td>
<td>CC</td>
<td>−63.25 ± 3.3 (79)</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CT</td>
<td>−50.57 ± 2.7 (118)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TT</td>
<td>−50.99 ± 4.0 (53)</td>
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</tr>
<tr>
<td></td>
<td>SLC6A3</td>
<td>rs6347</td>
<td>AA</td>
<td>−50.88 ± 2.6 (130)</td>
<td>0.108</td>
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<td>AG</td>
<td>−58.72 ± 2.9 (97)</td>
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<tr>
<td></td>
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<td>GG</td>
<td>−59.11 ± 6.3 (22)</td>
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<tr>
<td></td>
<td>SLC18A2</td>
<td>rs363225</td>
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<td>−66.4 ± 4.3 (45)</td>
<td>0.008</td>
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<td>CT</td>
<td>−54.17 ± 2.6 (130)</td>
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<td></td>
<td>TT</td>
<td>−49.28 ± 3.4 (72)</td>
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<td></td>
<td></td>
<td>rs363226</td>
<td>CC</td>
<td>−50.52 ± 2.6 (124)</td>
<td>0.018</td>
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<td>CG</td>
<td>−57.26 ± 2.8 (109)</td>
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<td>TT</td>
<td>−37.03 ± 7.7 (18)</td>
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<tr>
<td></td>
<td>SLC6A4</td>
<td>rs4251417</td>
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<td>−42.64 ± 2.5 (158)</td>
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<td>−57.97 ± 5.1 (38)</td>
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<td>−96.68 ± 31.5 (1)</td>
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<td></td>
<td>NR3C1</td>
<td>rs10482616</td>
<td>GG</td>
<td>−49.69 ± 2.6 (145)</td>
<td>0.005^a</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>GG</td>
<td>−49.53 ± 4.2 (59)</td>
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HAMD_{17}, Hamilton Rating Scale for Depression; SNP, single nucleotide polymorphism.

^a Calculated for GG vs. GA + AA as the cell values for the AA genotype is low.

^b AA vs. AG + GG, p = 0.021.

c Uncorrected p value.

A trend of association was observed with rs2873804 in DBH (p_{corrected} = 0.059), rs363225 in SLC18A2 (p_{corrected} = 0.092) and rs8075924 in ACE (p_{corrected} = 0.078). Response to bupropion in this subsample was associated with a SNP in corticotropin releasing hormone receptor 2 (rs1076292, p_{corrected} = 0.046) after corrections for multiple tests. The SNP rs17614642 in FKBP5 showed a trend of association with response (p_{corrected} = 0.072).

Association of SNPs with placebo response and remission (n = 257)

A SNP rs2296972 in the HTR2A gene showed suggestive association with placebo remission (p_{corrected} = 0.055, Table 2 and Supplementary Table S3). Carriers of the minor T allele were more likely to be non-remitters [OR 2.12 (1.32–3.45)]. Similarly, rs4251417 in the 5-HTT or SLC6A4 gene was marginally associated with remission in patients receiving placebo treatment (p_{corrected} = 0.0502, Table 2). Patients who carry the minor A allele of this polymorphism were 2.7 times more likely to be a remitter.

Placebo response was associated with a polymorphism in the glucocorticoid receptor gene (NR3C1, rs10482616, OR 2.22, p_{corrected} = 0.039); carriers of the minor A allele were more likely to be non-responders. Conversely, carriers of the minor G allele of MAOA, SNP rs6609257, (OR 1.85, p_{corrected} = 0.046) were more likely to be responders compared to non-carriers (Table 2).

In the subjects who completed the clinical studies (n = 227), rs4251417 in SLC6A4 (p_{corrected} = 0.029) was significantly associated with placebo remission (Table 4,
Table 4. Results of association analysis between SNPs and remission or response during bupropion (n = 271) or placebo treatment (n = 227) in the patients who completed the clinical studies

<table>
<thead>
<tr>
<th>Chr</th>
<th>Gene</th>
<th>SNP</th>
<th>Minor allele</th>
<th>Total</th>
<th>N</th>
<th>p value</th>
<th>p_corrected</th>
<th>OR (CI)</th>
<th>N</th>
<th>p value</th>
<th>p_corrected</th>
<th>OR (CI)</th>
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<tbody>
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<td></td>
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</tr>
<tr>
<td>Bupropion remission</td>
<td>13</td>
<td>HTR2A</td>
<td>rs2770296</td>
<td>G</td>
<td>269</td>
<td>0.00098</td>
<td>0.02680</td>
<td>2.05 (1.34–3.14)</td>
<td>218</td>
<td>0.00147</td>
<td>0.04018</td>
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<td></td>
<td>9</td>
<td>DBH</td>
<td>rs2873804</td>
<td>T</td>
<td>270</td>
<td>0.00284</td>
<td>0.05980</td>
<td>0.57 (0.39–0.82)</td>
<td>217</td>
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<td>0.11081</td>
<td>0.56</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>SLC6A2</td>
<td>rs11649505</td>
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<td>270</td>
<td>0.00030</td>
<td>0.06918</td>
<td>0.56 (0.38–0.82)</td>
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<td>0.07801</td>
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<td>0.09484</td>
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<td>rs1076292</td>
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<td>0.00415</td>
<td>0.04596</td>
<td>0.56 (0.38–0.83)</td>
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<td></td>
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<td>0.06858</td>
<td>2.20 (1.26–3.83)</td>
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<td>0.10016</td>
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<td>3.21 (1.44–7.12)</td>
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<td>0.09088</td>
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<td>0.09925</td>
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<td>1.88 (1.21–2.93)</td>
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<td>176</td>
<td>0.00876</td>
<td>0.06131</td>
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</table>

CI, Confidence interval (95%).

a p value corrected for multiple independent comparisons (gene-wide; Li & Ji, 2005; Nyholt, 2004). The effective number of independent comparisons was calculated (M_{eff}) and the corrected p value (p_{corrected}) was calculated (M_{eff} \times p value).

Association statistics was calculated using conditional logistic regression with gender, age, baseline Hamilton Rating Scale for Depression score and ancestry as covariates. Single nucleotide polymorphisms (SNPs) associated with either remission or response (p_{corrected} < 0.1) in the total sample is presented. The odds ratios (OR) are with regard to remission/response.

Supplementary Table S4). A trend of association was observed with the SNP rs622337 in HTR2A (p = 0.10). The SNP rs2296972 in HTR2A did not reach significance (p_{corrected} = 0.124). Placebo response showed a trend of association with rs609257 in MAOA (p_{corrected} = 0.065) and rs4251417 in SLC6A4 (p_{corrected} = 0.09). The SNP rs10482616 in NR3C1 was not significantly associated with placebo response (p_{corrected} = 0.688).

Remission and HTR2A SNPs

A number of polymorphisms in the HTR2A gene were associated with remission in both bupropion- and placebo-treated patients. Therefore, we fitted a conditional logistic regression model including the treatment × genotype interaction term using a combined set of bupropion- and placebo-treated subjects (LOCF). Assuming an additive genetic model, the treatment × genotype interaction term was statistically significant for SNP rs2770296 (p = 0.0092). In particular, patients homozygous for the G allele of rs2770296 were ~ 5-fold more likely to be remitters (CI 1.89–12.87), while patients heterozygous (AG) were ~ 2-fold more likely to achieve remission (CI 1.40–3.68) following bupropion treatment. This relationship between remission following bupropion treatment and rs2770296 is not observed in patients who received placebo. The treatment × genotype interaction term for SNP rs2296972 in HTR2A associated with placebo response was only marginally significant (p = 0.050). Carriers of the TT [OR 3.57 (1.46–8.74)] and the TG genotype [OR 2.04 (1.29–3.23)] were more likely to be placebo remitters (Supplementary Table S5). These data suggest that remission rates may be differentially modulated in bupropion and/or placebo treatment.

Discussion

Bupropion remission and response

To our knowledge, this is the first study investigating the association of genes with bupropion remission and response. The HTR2A gene has been associated with response to other antidepressants in several studies (Kato & Serretti, 2010; McMahon et al. 2006; Uher et al. 2009). In this investigation, although several polymorphisms in HTR2A showed suggestive association with remission,
the intronic SNP rs2770296 survived gene-wide correction for multiple testing (Tables 2 and 4, Supplementary Fig. S2a,b, Supplementary Tables S3 and S4). Furthermore, the treatment × genotype interaction for SNP rs2770296 is statistically significant, with a strong bupropion remission effect, but not in the placebo-treated group (Supplementary Table S5). Bupropion is not known to bind to the 5-HT$_{1A}$ receptor but has been shown to decrease 5-HT$_{1A}$ mRNA levels in the frontal cortex of a depressive rat model (Kitamura et al. 2008) and 5-HT$_{1A}$ receptor activation has been reported to stimulate dopaminergic activity (Alex & Pehek, 2007). Therefore, it is plausible that, in MDD patients, a low dopaminergic tone can lead to compensatory increase in 5-HT$_{1A}$ receptor expression. Treatment with bupropion increases extracellular dopamine levels, potentially leading to normalization of 5-HT$_{1A}$ expression. Genetic variation influencing 5-HT$_{1A}$ expression could therefore alter the efficacy of bupropion. Although rs2770296 is intronic with no reported functional effect, it might be in LD with an as yet unknown functional variation(s). Association of other intronic HTR2A polymorphisms with response has been reported in the STAR*D (rs7997012, citalopram) as well as the GENDEP (rs9316233, escitalopram) studies (McMahon et al. 2006; Uher et al. 2009). These two intronic polymorphisms are not associated with either remission or response in the present study (Supplementary Table S6) and they are in low LD and $r^2$ value with rs2770296 (Supplementary Fig. S2b). These results suggest that the HTR2A gene is involved in antidepressant remission but the exact functional site is not yet clear.

A SNP, rs8075924, located in the intron (or downstream region due to alternative splicing) of the ACE gene was also nominally associated with remission after gene-wide correction for multiple testing (Tables 2 and 4). Similarly, single polymorphisms in the DBH (rs2873804) and VMAT2 (rs363225) genes were also nominally associated with remission (Tables 2 and 4). These genes, as well as the ACE gene, which has been associated with antidepressant response (Baghai et al. 2004; Bondy et al. 2005), unipolar depression (Baghai et al. 2006), the ability to cope with stressful conditions (Heck et al. 2009) and modulation of serotonergic and dopaminergic turnover (Annerbrink et al. 2010), could play an important role in treatment response. Decreased DBH activity has been observed in depressed patients, which normalizes following antidepressant treatment (Paclt et al. 2009). Bupropion causes a rapid, reversible and dose-dependent increase in vesicular dopamine uptake by cellular redistribution of VMAT2 protein following inhibition of DAT (Rau et al. 2005). In addition to DAT increasing extracellular dopamine, VMAT2 may increase the presynaptic pool of dopamine available for release, possibly contributing to bupropion treatment efficacy (Dwoskin et al. 2006).

Nominal association of rs17614642 in the FKB5 with bupropion response was also observed (Tables 2 and 4). This SNP is intronic with no reported functional significance. FKB5 regulates glucocorticoid receptor sensitivity and is a co-chaperone of hsp90 (Horstmann & Binder, 2009). Binder et al. (2004) reported association of rs1360780 in FKB5 with antidepressant response; however, our study of bupropion showed no association with response or remission. Association of rs6347 DAT1 (or SLC6A3) with response to bupropion treatment and nominal association of rs363225 in VMAT2 (or SLC18A2) was also observed (Table 2). The associations with DAT1 and VMAT2 are intriguing as bupropion is a dual norepinephrine and dopamine reuptake inhibitor (Arias et al. 2009). However, rs6347 and rs363225 were not significantly associated in the analysis with subjects who completed the study. This could be due to reduced power in the smaller completer-only sample and indicates that further exploration of these associations is needed in larger independent samples.

Overall remission per se following bupropion treatment appears to be associated with HTR2A. These results, taken at face value, suggest that remission to antidepressants, irrespective of the class of drug, may be determined by serotonergic mechanisms.

**Placebo remission and response**

This is the largest study to date investigating genetic determinants of placebo response and remission in MDD. The only other published study investigated two polymorphisms, rs6323 in MAOA and Val105Met in COMT, in a sample of 52 MDD patients (Leuchter et al. 2009).

We observed nominal association of SNPs in the HTR2A gene with remission to placebo treatment (Table 2). These SNPs are located in the 3′ half of intron 3 (or intron 2 due to alternative splicing). The location of this association signal is distinct from those observed with bupropion remission and is located beyond a region of high recombination in a different part of intron 3 (Supplementary Fig. S2b). Furthermore, the minor allele of these polymorphisms is associated with placebo non-remission as opposed to the association of the minor allele of rs2770296 with bupropion remission. It may be that a single common functional variant is in high LD with the SNPs associated with placebo remission while a different variant is involved with bupropion remission. Re-sequencing of HTR2A may help in identifying new relevant variants. Nominal association of a SNP in 5-HTT (rs4251417, G>A) was also observed. Interestingly, a haplotype ‘C-A’ of SNPs rs4251417 and rs202934 is known to be correlated with the short allele of serotonin transporter-linked polymorphic region (5-HTTLPR; $r^2=0.72$; Wray et al. 2009). The long allele of 5-HTTLPR is associated with better response to antidepressant treatment in Caucasians (Drago et al. 2009) and, recently, this long allele has also been associated with placebo response in social anxiety disorder patients (Furmark et al. 2008). Although we did not investigate rs202934 mentioned...
above, if we assume that the correlation of the C allele with the short allele holds true in our sample set, then our association of the A allele with remission in placebo treatment might be related to the long allele of 5-HTTLPR, in line with the literature. The association of rs4251417 with placebo remission was also observed in subjects who completed the study, further supporting the importance of this observation. Our observations also support the hypothesis that placebo and medication may both activate the same disease-related pathway to achieve response and remission (Benedetti et al. 2011).

We observed association of placebo response with rs6609257 located 6.6 kb downstream of the MAOA gene (Table 2). In the completers-only analysis, rs6609257 showed a trend of association with placebo response ($P_{\text{corrected}} = 0.065$). This SNP rs6609257 was significantly associated with placebo response in the sub-analysis of females separately (Supplementary Table S7). Several markers in the MAOA gene were nominally associated with placebo response (Supplementary Tables S3 and S4 and Supplementary Fig. S3). Association of the SNP rs6323 with placebo response was recently reported by Leuchter et al. (2009). Although we did not assay variant rs6323 directly, we analysed the SNP rs2235186, which is in complete LD with rs6323 (HapMap, $r^2 = 1.0$). We observed the minor allele of rs2235186 to be nominally associated with placebo response (Supplementary Tables S3 and S4) similar to that of Leuchter et al. who observed that the minor allele of rs6323 confers better placebo response. MAOA is expressed in the presynaptic terminal mainly on the outer mitochondrial membrane and is involved in the metabolism of serotonin, norepinephrine and, to a lesser extent, dopamine. Placebo response has been associated with activation of the reward pathway. Reward has primarily been associated with dopamine signalling; however, recent research suggests an important modulating role of serotonin in the reward pathway (Kranz et al. 2010). The activity of the serotonergic neurons in the dorsal raphae nucleus has been associated with the value of rewards specifically in motivation and liking (hedonia), which are key deficits in MDD (Kranz et al. 2010). Therefore, any variation in MAOA activity could alter the turnover of serotonin and norepinephrine and thereby modulate the patient’s response to placebo treatment. In addition, individuals with the lower expressing MAOA-L promoter variant demonstrate greater emotional reactivity, particularly in response to negative social cues (Buckholtz & Meyer-Lindenberg, 2008). It is possible that a physician writing a prescription for a patient constitutes a powerful social cue that leads the MAOA-L person to amplify their symptomatic response to placebo. An assessment of personality traits in placebo-treated patients can help us to better understand the factors influencing response to treatment in these patients.

In terms of potential limitations, population stratification (assessed in our sample using STRUCTURE) is unlikely to lead to our association signals (see Supplementary Fig. S1). Although our sample had sufficient power to detect moderate effects (ORs $\sim 1.8$), we may have missed smaller genetic effects. Another limitation of the present study is that none of the observations is significant after correcting for all the tests conducted in the study. However, it should be noted that our study is hypothesis driven and not hypothesis free; therefore, a gene-based correction is more appropriate than a study-wide correction. The present sample does not have enough power to conduct a genome-wide association study. However, additional biologically relevant genes may be investigated in the future.

In conclusion, our association findings with HTR2A in bupropion remission provide further evidence in support of an important role for the HTR2A gene in remission to antidepressant treatment. This is the largest study to date of genetic factors in placebo response and remission. We provide evidence that the HTR2A gene could be important for remission, supporting the long-held view that placebo and antidepressant treatment remission occurs through similar pathways.

Supplementary material
For supplementary material accompanying this paper, visit http://dx.doi.org/10.1017/S1461145712000843

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Statement of Interest
J.L.K. has been a consultant to GSK, Sanofi-Aventis and Dainippon-Sumitomo and received honoraria from Eli Lilly.
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