Clinical response to antipsychotic drug treatment: Association study of polymorphisms in six candidate genes

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Abstract
Pharmacogenetic studies have demonstrated significant associations between several candidate genes (DRD2, DRD3, 5HTR2A and 5HTR2C, COMT and MTHFR) and antipsychotic drug response. The present study investigates the effect of nine polymorphisms in these genes for an association with antipsychotic treatment response. 329 Caucasian patients with a non-affective psychotic disorder using antipsychotics were included. All patients participated in the longitudinal GROUP-study in The Netherlands. We genotyped 9 SNPs in 6 candidate genes (DRD2: TaqI_A, -141C; DRD3: Ser9Gly; HTR2A: 102-T/C, His452Tyr; HTR2C: Cys23Ser; COMT: Val158Met;...
1. Introduction

Since their introduction in the 1950s antipsychotic drugs play a key role in the treatment of psychotic disorders. However, almost half of patients with schizophrenia display insufficient response to antipsychotic treatment and many patients show low compliance as a result (Lacro et al., 2002). In turn, this may cause clinical deterioration including psychotic relapse. Factors that influence the variation in response to antipsychotic drug treatment have not been well elucidated. Inter-individual and inter-racial variability in response to drug treatment may possibly reflect genetic heterogeneity and the presence of modifier genes (Tsuang et al., 1990).

Several genetic association studies have been performed showing positive associations between response and polymorphisms in genes coding for the dopaminergic, serotonergic, and several other systems. In this study we focus on polymorphisms associated with antipsychotic drug response (positive or global symptoms) in Caucasian patients only.

Dopamine D2 receptor blockade is a property of all antipsychotics. The polymorphisms Taq1A, located downstream of the dopamine receptor D2 gene (DRD2), and -141C Ins/Del, located in the promoter region of DRD2, are linked to D2 receptor density at the level of the striatum (Jonsson et al., 1999; Laakso et al., 2005; Pohjalainen et al., 1998). Several studies have associated Taq1A and -141C with response to first (FGA) and second generation antipsychotics (SGA) (Hwang et al., 2005; Lencz et al., 2006; Schafer et al., 2001). The affinity of certain antipsychotics for the D3 receptor may reflect a part of their action, although affinity for the D3 receptor may differ among them (Schwartz et al., 2000). The Ser9Gly polymorphism of DRD3 is an amino-acid substitution in the N-terminal extracellular part of the receptor and might influence the membrane expression of this receptor by modifying its intracellular maturation (Reynolds et al., 2001). A positive relation between response to SGA and the presence of the Gly allele was found in three studies (Staddon et al., 2002; Szekeres et al., 2004; Scharfetter et al., 1999).

Alterations in the serotonergic system have been implicated in the mechanisms of action of antipsychotics, having antagonistic properties (particularly SGA) on serotonergic receptors, especially the serotonin 2A and 2C receptors. Two SNPs (His452Tyr and 102-T/C) of the 5HT2A (serotonin receptor 2A) gene were the subject of several association studies on the response to clozapine. Results were conflicting (Masellis et al., 1995, 1998; Malhotra et al., 1996; Joober et al., 1999; Jonsson et al., 1996; Arranz et al., 1995, 1996, 1998a, 1998b). The 102-T/C SNP does not entail amino acid substitution, but in Caucasian patients it is in complete linkage disequilibrium with variant -1438A/G, which is located in the gene promoter. The A allele of this polymorphism would increase the in-vitro activity of the receptor (Parsons et al., 2004). The His452Tyr polymorphism brings about functional modifications of the receptor, the Tyr variant would decrease the receptor’s ability to activate C and D phospholipases (Hazelwood and Sanders-Bush, 2004). The serotonin 2C receptor is suggested to play a moderate role in the effect of antipsychotics on particularly negative symptoms (Sodhi et al., 1995; Reynolds et al., 2005; Arranz et al., 2000a; Lieberman et al., 1998). The Cys23Ser polymorphism of the 5HT2C (serotonin receptor 2C) gene was associated in one study with global response on clozapine (Sodhi et al., 1995). The consequences of the involved amino acid substitution are unknown.

COMT (catechol-O-methyltransferase) is involved in the degradation of dopamine in the prefrontal cortex. The COMT gene has a relevant Val158Met polymorphism (sometimes referred to as Val158/108Met). The Met allele was associated with a better response in two studies (Anttila et al., 2004; Bertolino et al., 2004). The MTHFR (methylene-tetrahydrofolate reductase) enzyme is required for the synthesis of 5-MTHF, a cosubstrate for the conversion of homocysteine into methionine. Elevated plasma homocysteine concentrations has been suggested as a risk factor for schizophrenia but the causality is still unclear. The MTHFR gene has a missense mutation 677-C/T. Patients possessing a copy of the T allele showed a better treatment response (Joober et al., 2000a).

In the present study we tested above mentioned nine polymorphisms for their association with response on positive symptoms in a sample of Caucasian patients with a psychotic disorder. We focused on polymorphisms associated with response on positive symptoms because antipsychotics are mainly effective for treating positive symptoms.

2. Experimental procedures

2.1. Sample

A sample of 329 in- and outpatients using antipsychotic medication was drawn from the participants in the ongoing longitudinal Genetic Risk and Outcome of Psychosis (GROUP) study. In GROUP, patients
were identified in selected representative geographical areas in the Netherlands and Belgium. Inclusion criteria for GROUP were: (i) age range 16 to 50 years, (ii) DSM-IV diagnosis of non-affective psychotic disorder and (iii) good command of Dutch language. For the present analysis the following extra inclusion criteria were applied: (iv) use of antipsychotic medicine at the time of assessment for at least one month and (v) Caucasian ethnicity of Northern European ancestry. The study was approved by the Ethics Committee of the University Medical Center Utrecht and by the institutional review boards of all other participating hospitals. All subjects gave written informed consent in accordance with the committee’s guidelines.

### 2.2. Genotyping

A total of 9 polymorphisms in 6 candidate genes were selected for the current study: DRD2 TaqI_A and -141C; DRD3 Ser9Gly; HTR2A: 102_T/C and His452Tyr; HTR2C: Cys223Ser; COMT: Val158Met; MTHFR: 677_C/T. These polymorphisms were chosen a priori based on findings in other association studies and determined by Seque- nom (Hamburg, Germany) using the Sequenom MassARRAY iPLEX platform at the facilities of the manufacturer. Quality check for genotyping was performed in the overall GROUP study, which encompassed exclusion of polymorphisms and individuals based on missingness and based on departure from Hardy–Weinberg equilibrium in a sample of 398 controls without a psychotic disorder.

### 2.3. Phenotyping

All patients were evaluated by their attending psychiatrist with the Clinical Global Impression - Improvement (CGI-I) scale at one point in time. This instrument was used to score the change in positive symptoms since the start of the current antipsychotic medication on a seven point scale (1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; or 7, very much worse). Response was dichotomized for some of the analyses: improvement was defined as a CGI-I score of very much improved or much improved. Attending psychiatrists were blinded to patient's genotype. Other clinical variables that were measured in this study were DSM-IV diagnosis, duration of illness, and antipsychotic medication and dose. Haloperidol dose equivalents were subsequently calculated using power formulas as outlined by Andreasen et al. (2010). To assess DSM-IV diagnosis one of the two structured diagnostic instruments was used: the Compre- hensive Assessment of Symptoms and History (CASH (Andreasen et al., 1992)) or the SCAN Schedules for Clinical Assessment for Neuro- psychiatry (SCAN 2.1 (Wing et al., 1990)). All raters were trained psychologist or psychiatrist, with extensive clinical experience. They had completed training in the CASH or SCAN. Diagnostic consen- sus was achieved in the presence of an independent psychiatrist. Psychiatric diagnosis was established according to the criteria of DSM-IV. Haloperidol dose equivalents were subsequently calculated using power formulas as outlined by Andreasen et al. (2010).

### 2.4. Statistical analysis

Age, duration of illness and haloperidol dose equivalents were com- pared between patients with and without response and were tested for statistical significance using a Mann–Whitney test or t-test when appropriate. We compared response between the most frequently pre- scribed antipsychotics and between diagnoses and tested differences for statistical significance using the χ² test. Ordinal regression (Scott et al., 1997), with the logit link function, was used to quantify the association between the highly skewed CGI-I score on positive symptoms and polymorphisms, while adjusting for age and gender. Sequential low prevalent outcome groups were pooled to fulfill the assumptions of ordinal regression, i.e. high enough cell counts in each genotype/ outcome group (minimum of 1). The null hypothesis of parallel lines was tested for each polymorphism using χ² tests. We considered initial- ly an additive model with the number of minor alleles as independent variable for all polymorphisms. When genotype/outcome group cell counts were too low, a dominant model for the polymorphism was con- sidered. Polymorphisms positioned on the X-chromosome were tested in a dominant model only. All statistical analyses were performed using SPSS 16.0 for Windows. Since all nine polymorphisms were based on earlier positive association studies in Caucasian patients, we refrained from adjusting for the multiple testing. The significance level of this study was set at 0.05, two-sided. Replication was established when the effect was in the same direction as in the original study and statistically significant.

### 3. Results

Descriptive statistics of our study sample are presented in Table 1 according to response on positive symptoms. Patients with response had a two years higher age (Mann Whitney P value 0.031) and a two months longer treatment period of the current antipsychotic (Mann Whitney P value 0.039) than patients without response. Haloperidol equivalents, duration of illness, DSM-IV diagnoses and type of antipsychotic were not significantly different between response groups.

All polymorphisms were validated and had a missing genotype rate below 10% in the total sample. No polymorphism deviated from Hardy–Weinberg equilibrium. The allele and genotype fre- quencies are shown in Table 2. Due to the low prevalence of scores 4, 5, 6 and 7 on the CGI-I, we used three ordinal groups of re- sponse: a CGI-I score of 1, 2, and 3 or higher. Rs6314 and rs1799732 showed too low cell counts when tested additive, and were subsequently tested dominantly. The null hypothesis of par- allel lines was not rejected for any of the polymorphisms tested. In Table 3 the associations with response are depicted. Two of the nine polymorphisms showed a significant association with response on positive symptoms. The Gly (C) allele of Ser9Gly of the DRD3 gene was associated with more improvement on positive symptoms (P value 0.034). The T-allele of 677-C/T of the MTHFR gene also showed more improvement (P value 0.019). Both results were in the same direction as the previous associa- tion studies reporting on these polymorphisms (Staddon et al., 2002; Szekeres et al., 2004; Scharfetter et al., 1999; Joober et al., 2000a). The Gly-allele and T-allele showed odds ratios of 1.39 (95% CI 1.03–1.90) and 1.45 (95% CI 1.06–1.98) for being in a better response category, respectively.

### 4. Discussion

In this study we aimed to replicate previously reported sig- nificant findings from candidate gene studies on positive symptoms improvement in patients with psychotic disorders treated with antipsychotics. Of the nine tested polymorphisms two were tested significantly: Ser9Gly of the DRD3 gene and 677-C/T of the MTHFR gene.

Previous positive association studies with Ser9Gly of DRD3 in Caucasian patients were performed in prospective studies with patients using clozapine (Scharfetter et al., 1999), olanza- pine (Staddon et al., 2002), and several SGA (Szekeres et al., 2004). In all three studies the Gly allele was associated with better response. All three studies used different symptom scales and treatment duration varied between 12 weeks and 6 months. Three other studies (two clozapine and one FGA) with Caucasian patients showed no significant association
In vitro studies indicate that the Gly variant is associated with higher dopamine binding affinity (Lundstrom and Turpin, 1996). However, the biological function is hard to interpret since the Gly variant was mostly associated with poor response in Chinese populations (Reynolds et al., 2005; Lane et al., 2005). This different direction of association with response may be explained by a linkage disequilibrium status with another functional polymorphism.

Only one study has been performed regarding 677-C/T of MTHFR and antipsychotic response (Joober et al., 2000a). The T allele was found more often in responders compared to non-responders, all having FGA. The 677-C/T polymorphism is functional (Frosst et al., 1995) and is possibly associated with risk of schizophrenia itself (Shi et al., 2008; Allen et al., 2008). MTHFR is required for the synthesis of 5-methyltetrahydrofolate, the primary circulatory form of folate and the carbon donor for homocysteine remethylation to methionine. Homozygous individuals (TT) have around one third of the expected MTHFR enzyme activity, and heterozygotes (CT) have around two third activity, compared to the most common genotype CC (Frosst et al., 1995). Some patients with homocysteinuria, an inborn error of metabolism that can be caused by rare and severe mutations in the MTHFR gene, have exhibited schizophrenia-like symptoms (Freeman et al., 1975). Furthermore, high levels of homocysteine have been

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**Table 1** Descriptive statistics of 329 Caucasian patients using antipsychotics, stratified by improvement on positive symptoms.

<table>
<thead>
<tr>
<th></th>
<th>Improvement (n=247)</th>
<th>No improvement (n=82)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (range)</td>
<td>27 (16–47)</td>
<td>25 (16–42)</td>
<td>0.031</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>197 (80%)</td>
<td>63 (77%)</td>
<td>0.52</td>
</tr>
<tr>
<td>Duration of illness (years), median (range)</td>
<td>3.4 (0.2–21.4)</td>
<td>3.2 (0.2–12.0)</td>
<td>0.99</td>
</tr>
<tr>
<td>Duration of current treatment (months), median (range)</td>
<td>4 (1–60)</td>
<td>6 (1–110)</td>
<td>0.039</td>
</tr>
<tr>
<td>Current dose (haloperidol equivalents&lt;sup&gt;a&lt;/sup&gt;), median (range)</td>
<td>4.8 (0.6–18.2)</td>
<td>6.6 (0.6–21.0)</td>
<td>0.33</td>
</tr>
<tr>
<td>DSM-IV diagnosis</td>
<td></td>
<td></td>
<td>0.45</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>163 (66%)</td>
<td>57 (70%)</td>
<td></td>
</tr>
<tr>
<td>Schizoaffective disorder</td>
<td>37 (15%)</td>
<td>9 (11%)</td>
<td></td>
</tr>
<tr>
<td>Schizophreniform disorder</td>
<td>6 (2%)</td>
<td>3 (4%)</td>
<td></td>
</tr>
<tr>
<td>Psychotic disorder NOS</td>
<td>28 (11%)</td>
<td>9 (11%)</td>
<td></td>
</tr>
<tr>
<td>Delusional disorder</td>
<td>6 (2%)</td>
<td>4 (5%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>7 (3%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Antipsychotic</td>
<td></td>
<td></td>
<td>0.24</td>
</tr>
<tr>
<td>Risperidone</td>
<td>55 (22%)</td>
<td>20 (24%)</td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>68 (28%)</td>
<td>12 (15%)</td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>14 (6%)</td>
<td>4 (5%)</td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td>22 (9%)</td>
<td>8 (10%)</td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td>19 (8%)</td>
<td>5 (6%)</td>
<td></td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>2 (1%)</td>
<td>3 (4%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>16 (7%)</td>
<td>6 (7%)</td>
<td></td>
</tr>
<tr>
<td>Multiple antipsychotics</td>
<td>25 (10%)</td>
<td>12 (15%)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>26 (11%)</td>
<td>12 (15%)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Calculated as outlined by Andreasen et al. (2010).

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**Table 2** Frequencies of alleles and genotypes of polymorphisms in 329 Caucasian patients with a non-affective psychotic disorder.

<table>
<thead>
<tr>
<th>Gene</th>
<th>rs-id</th>
<th>Chromosome</th>
<th>Variant name</th>
<th>Alleles&lt;sup&gt;a&lt;/sup&gt;</th>
<th>MAF&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Genotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>position</td>
<td></td>
<td></td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>DRD2</td>
<td>rs1800497</td>
<td>Chr11:113270827</td>
<td>Taq1_A</td>
<td>C/T</td>
<td>0.17</td>
<td>228 (69%)</td>
</tr>
<tr>
<td></td>
<td>rs1799732</td>
<td>Chr11:113346252</td>
<td>-141C</td>
<td>C/ Del</td>
<td>0.11</td>
<td>262 (80%)</td>
</tr>
<tr>
<td>DRD3</td>
<td>rs6280</td>
<td>Chr3:113890814</td>
<td>Ser9Gly</td>
<td>T/C</td>
<td>0.32</td>
<td>150 (46%)</td>
</tr>
<tr>
<td>HTR2A</td>
<td>rs6314</td>
<td>Chr13:47409033</td>
<td>His452Tyr</td>
<td>C/T</td>
<td>0.1</td>
<td>255 (80%)</td>
</tr>
<tr>
<td></td>
<td>rs6311</td>
<td>Chr13:4741477</td>
<td>102-T/C</td>
<td>C/T</td>
<td>0.45</td>
<td>92 (28%)</td>
</tr>
<tr>
<td>HTR2C</td>
<td>rs3813929</td>
<td>X:113818519</td>
<td>-759C_T</td>
<td>C/T</td>
<td>0.18</td>
<td>244 (83%)</td>
</tr>
<tr>
<td></td>
<td>rs6318</td>
<td>X:113965734</td>
<td>Cys23Ser</td>
<td>G/C</td>
<td>0.16</td>
<td>249 (84%)</td>
</tr>
<tr>
<td>COMT</td>
<td>rs4680</td>
<td>Chr22:19951270</td>
<td>Val158Met</td>
<td>A/G</td>
<td>0.46</td>
<td>91 (28%)</td>
</tr>
<tr>
<td>MTHFR</td>
<td>rs1801133</td>
<td>Chr1:11856378</td>
<td>677-C/T</td>
<td>C/T</td>
<td>0.32</td>
<td>153 (47%)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Major allele given first.

<sup>b</sup> MAF = minor allele frequency.

<sup>c</sup> Carriers of variant allele, polymorphism positioned on X-chromosome.
observed in schizophrenia patients (Regland et al., 1995). Several reports link a high plasma level of homocysteine to various neurological conditions also, such as pregnancies complicated by neural tube defects (Bakker and Brandjes, 1997) and neurological conditions also, such as pregnancies complicated by neural tube defects (Bakker and Brandjes, 1997) and migraine (Oterino et al., 2010). Together with the association we replicated, this points out that MTHFR may be involved in the interaction with antipsychotic medication.

In this study we did not replicate seven of the previously associated polymorphisms with response on positive symptoms. When a more conservative correction for multiple testing was applied, such as Bonferroni, even the two replications would not be significant. An important question regards the explanation of our findings. A likely explanation for the variation in results from pharmacogenetic studies is the explanation of our findings. A likely explanation for the variation in results from pharmacogenetic studies is the heterogeneity in the definition and characterization of the phenotype as well as in the characterization of the genetic variability. This concerns the present study as well. An important difference of our study from other studies is the inclusion of all antipsychotics. Our study does not suffer from heterogeneity with regard to ethnicity as we have a homogeneous group of Caucasian patients.

Compared to most other candidate studies we have a relatively large sample size of more than 300 patients using antipsychotics. These polymorphisms may be of clinical value if their added value to other clinical predictors of response can be demonstrated in future research.

### Table 3 Results of association analyses between polymorphisms and clinical improvement on positive symptoms in 329 Caucasian patients with a non-affective psychotic disorder.

<table>
<thead>
<tr>
<th>Gene</th>
<th>rs-id</th>
<th>Variant name</th>
<th>Alleles</th>
<th>Beta</th>
<th>Odds ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRD2</td>
<td>rs1800497</td>
<td>Taq1_A</td>
<td>C/T</td>
<td>-0.24</td>
<td>0.79</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>rs1797932</td>
<td>-141C</td>
<td>C/Del</td>
<td>-0.36</td>
<td>0.70</td>
<td>0.17</td>
</tr>
<tr>
<td>DRD3</td>
<td>rs6280</td>
<td>Ser9Gly</td>
<td>T/C</td>
<td>-0.33</td>
<td>0.72</td>
<td>0.034</td>
</tr>
<tr>
<td>HTR2A</td>
<td>rs6314</td>
<td>His452Tyr</td>
<td>C/T</td>
<td>-0.17</td>
<td>0.84</td>
<td>0.53</td>
</tr>
<tr>
<td></td>
<td>rs6311</td>
<td>T102C</td>
<td>C/T</td>
<td>0.10</td>
<td>1.11</td>
<td>0.53</td>
</tr>
<tr>
<td>HTR2C</td>
<td>rs3813929</td>
<td>-759C_T</td>
<td>C/T</td>
<td>0.08</td>
<td>1.08</td>
<td>0.79</td>
</tr>
<tr>
<td></td>
<td>rs6318</td>
<td>Cys23Ser</td>
<td>G/C</td>
<td>-0.47</td>
<td>0.63</td>
<td>0.13</td>
</tr>
<tr>
<td>COMT</td>
<td>rs4680</td>
<td>Val158Met</td>
<td>A/G</td>
<td>0.08</td>
<td>1.08</td>
<td>0.62</td>
</tr>
<tr>
<td>MTHFR</td>
<td>rs1801133</td>
<td>677-C/T</td>
<td>C/T</td>
<td>-0.37</td>
<td>0.69</td>
<td>0.019</td>
</tr>
</tbody>
</table>

a Ordinal regression analysis with CGI-I improvement as dependent variable, and the number of minor alleles (0, 1 or 2) of the polymorphism as independent variable (additive model), corrected for age and gender. A negative beta or odds ratio <1 means more improvement (lower CGI score) per extra minor allele. Significant results (p < 0.05) are shown in bold.

b Major allele first given.

c Polymorphisms tested in a dominant model.

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Site Groningen: University Medical Center Groningen, Lentis, GGZ Friesland, GGZ Drenthe, Dimence, Mediant, GGZ Yulius and Parnassia Bavo Group; Site Maastricht: Maastricht University Medical Center, GGZ Eindhoven, GGZ Midden-Brabant, GGZ Oost-Brabant, GGZ Noord- Midden Limburg, Mondriaan Zorggroep, Prins Clauscentrum Sittard, RIAGG Roermond, Universitair Centrum Sint-Jozef Kortenberg, CAPRI University of Antwerp, PC Ziekeren Sint-Truiden, PZ Sancta Maria Sint-Truiden, GGZ Overpelt, OPZ Rekem).

ZonMW – or any of the Mental Health Care organizations – had no further role in the study design; in the analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Contributors

All authors designed the study. The GROUP investigators wrote the study protocol. Author Vehof managed the literature searches (together with GROUP investigators and Al Hadithy) and statistical analyses (together with Burger, Snieder and Alizadeh). All authors contributed to and have approved the final manuscript.

Conflict of interest

The authors declare no conflict of interest.

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