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Serotonin transporter gene: a new polymorphism may affect response to antidepressant treatments in major depressive disorder

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Running title: serotonergic genes in response to antidepressants and psycotherapy

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Abstract

Objective: Several gene variants have been related to major depressive disorder (MDD) treatment outcomes, however few studies investigated a possible different effect on pharmacotherapy and brief psychotherapy response.

Methods: 137 MDD patients were randomized to either inter-personal counseling (IPC n=40) or antidepressant pharmacological treatment (n=97). Outcomes were remission, response, and symptom improvement at week 8. Five genetic variants were investigated (*5HTR2A* rs6314, *BDNF* rs6265, *SLC6A4* rs8076005, *CREB1* rs2253206, and *TPH2* rs11179023) as possible modulators of outcomes.

Results: *SLC6A4* rs8076005 AA genotype and A allele were associated with response rate in the antidepressant group (p=0.015 and p=0.005, respectively) and in the whole sample (p=0.03 and p=0.02, respectively). In the IPC group a non significant trend in the same direction was observed. *TPH2* rs11179023 A allele showed a marginal association with symptom improvement only in the IPC group. Other gene variants did not impact on outcomes in any treatment group.

Conclusion: Our study suggests that rs8076005 in *SLC6A4* gene may be a modulator of antidepressant response especially when pharmacological treatment is used.

Keywords: antidepressant, psychotherapy, *HTR2A*, *BDNF*, serotonin transporter, *SLC6A4*, *CREB1*, *TPH2*, gene, polymorphism, pharmacogenetics, major depressive disorder.

Key Points

- The role in treatment response of five genes involved in the modulation of the serotonergic system (*HTR2A*, *BDNF*, *SLC6A4*, *CREB1*, and *TPH2)* was examined in 137 major depressive disorder patients treated with inter-personal counseling (IPC) or antidepressant drugs.
- Our findings supported the association of *SLC6A4* rs8076005 with response in both treatment groups.
- A marginal association between *TPH2* rs11179023 and symptom improvement was observed only in the IPC group.

1. Introduction

Major depressive disorder (MDD) is one of the most common psychiatric disorder (life time prevalence: 12.8%) [1], and ~~major depression will be the leading cause of disability by 2030~~it is among the major causes of worldwide disability [2]. The heavy personal and socio-economic burden of MDD is partly due to the still unsatisfactory response and remission rates (47 and 33%, respectively) [3]. Antidepressant drugs and psychotherapy are thought to be equally efficacious in moderate MDD [4, 5]. However, predictors of response to antidepressant treatments to guide treatment choice in the individual patient are not available. Among predictors of clinical outcomes, genetic variants are estimated to contribute substantially to the interindividual variability [6-9]. Serotonergic genes represent ideal candidates since current antidepressant drugs mainly act by the modulation of the serotonergic system.

The serotonin receptor gene 2A *(HTR2A)* is expressed in all neocortex, hippocampus, and prefrontal cortex [10]. 5HT-induced Ca^{2+} response in platelets was found to be enhanced in MDD [11] after remission during imipramine treatment [12]. The missense T allele of *HTR2A* rs6314 showed lower Ca^{2+} response to 5-HT than those without the mutation [13]. Following studies found that this polymorphism may predict SSRIs efficacy [14, 15].

Serotonin transporter *(SLC6A4* gene*)* plays a pivotal role in the regulation of serotonin concentration in the synaptic cleft and extrasynaptic sites. Promoter polymorphisms (5-HTTLPR and rs25531) have been extensively investigated, leading to replicated even if not univocal results [16]. The intronic rs8076005 has been previously associated with IL-6 levels in MDD and depressive symptom severity [17], but has not been studied as possible modulator of treatment response.

Tryptophan hydroxylase *(TPH)* catalyzes the rate-limiting step in synthesis of 5-HT. *TPH2* is the main isoform expressed in the CNS, but studies focused on its role in antidepressant response reported inconsistent results [18-33]. *TPH2* rs1179023 variation has not been investigated in the field before, thus represents a new candidate within a gene with strong biological rationale of involvement in antidepressant action.

During antidepressant treatment, the enhancement of 5-HT availability increases brain-derived neurotrophic factor *(BDNF)* synthesis and signaling, a major event in the stimulation of adult neurogenesis [34]. *BDNF* serum levels are associated with MDD and antidepressant response [35]. The rs6265 (Val66Met) was associated with *BDNF* secretion [36], *BDNF* serum levels [37], and antidepressants response [38-40].

Cyclic AMP response element-binding protein1 *(CREB1)* is a transcription factor activated by a number of signals, among which neuronal growth factors and stress-induced signals [41, 42]. *CREB1* gene has been associated with recurrent early-onset MDD [43, 44]. The G allele of the promoter polymorphism rs2253206 has been associated with lower promoter activity [45] and the same SNP may affect the risk of MDD, depression severity [46], and risk of treatment resistant depression [47].

Given the data supporting the involvement of these genes in antidepressant action, the present paper aims to study the role of *HTR2A* rs6314, *BDNF* rs6265, *SLC6A4* rs8076005, *CREB1* rs2253206, and *TPH2* rs11179023 in a sample 137 MDD Italian patients treated with IPC or antidepressants in a multicenter randomized trial.

2. Methods

2.1. Sample

Subjects aged 18 years or older with diagnosis of MDD (DSM-IV TR**)** were recruited. Inclusion and exclusion criteria were detailed elsewhere [48]. Eligible patients were divided into inter-personal counseling (IPC, a brief psychotherapy derived from Interpersonal Psychotherapy [49-51]) or into pharmacological antidepressant treatment [52]. Subjects were collected in three centers (Neuroscience Department, Turin University; Department of Health Sciences, University of Pavia; and Institute of Psychiatry, Bologna University), as previously reported [48]. All patients recruited at Bologna University were treated with antidepressant drugs. Despite the design of the study has been planned as randomized, the failure in developing a psychotherapy arm at Bologna University (the centre that recruited the higher number of patients) resulted in different size between the two treatment arms. In all cases of pharmacological treatment, antidepressant was chose and titrated according to current guidelines up to the effective dose range within the first week of treatment. Ethical approval was obtained from the ethic committees of all participating centers.

2.2. Evaluations

All subjects were evaluated with both structured and unstructured interviews to obtain diagnoses assigned by two independent experienced psychiatrists. Depressive states were assessed at baseline and after 8 weeks through Hamilton Depression Rating Scale (HDRS, 21 items version). Assessments were performed by trained psychiatrists and inter-rater reliability was k=0.8. A monitoring of treatment adherence through drug plasma level determination was not performed, but treatment adherence was assessed weekly by a trained psychiatrist and side effects were monitored weekly using the Dosage Record & Treatment Emergent Symptom scale (DOTES) [53]. Thus, we can suppose that non-responders at week 8 were not false non-responders due to overlooked side effects and poor treatment adherence.

2.3. Outcomes

The primary outcome was remission at week 8, defined according to standard criteria (HDRS score ≤ 7), and the secondary outcomes were response (at least 50% reduction in HDRS score) and HDRS percent improvement at week 8.

2.4. Polymorphism selection

The genotyped SNPs were selected according to the following criteria: 1) tagging approach (R2=0.08); 2) reported prevalence of at least 5% for the minor allele among Caucasians (data from http://hapmap.ncbi.nlm.nih.gov/); 3) availability of a validated assay in our laboratory; and 4) previous literature findings. In detail, the Tagger software was used to test SNPs downloaded from HapMap (Rel 28 PhaseII+III, August 2010, NCBI B36 assembly, dbSNP b126) and that satisfied some quality criteria (maximum number of Mendel errors=1; p value for Hardy-Weinberg equilibrium >0.001, MAF>5%). The Tagger program was used to identify SNPs that tagged at least other 2 SNPs with r2 and LOD thresholds of 0.8 and 3, respectively. The selected polymorphisms ~~were~~ are shown in Supplementary Table 1 together with polymorphisms in complete linkage disequilibrium (R2>0.8) with them. ~~the following SNPs: *TPH2* rs11179023 with rs12229394 and rs1487278; *SLC6A4* rs8076005 with rs12150214, rs11080122, rs8071667, rs2020936, rs25528, and rs6354; *BDNF* rs6265 with rs2030323.~~

2.5. Genotyping

DNA was purified from whole blood using the QIAamp DNA Blood Kit (Qiagen, CA, USA), according to the manufacturer's protocol. rs6314 (*HTR2A*, Chr 13q14-q21), rs6265 (*BDNF*, Chr 11p13), rs8076005 (*SLC6A*4, Chr 17q11.2), rs2253206 (*CREB1*, Chr 2q34), rs11179023 (*TPH*2, Chr 12q21.1) were genotyped by High Resolution Melting (HRM)-PCR. All the experiments were performed by the Rotor Gene Q instrument (Qiagen, CA, USA), using the Type-it HRM PCR kit (Qiagen, CA, USA). All primers were designed by Beacon Designer v. 7.9 (PREMIER Biosoft, CA, USA). After an initial step of enzyme activation at 95°C for 5 min, PCRs were carried out by 40 cycles as follows: denaturation at 95°C for 10 sec and annealing at 60°C for 30 sec. The HRM analysis was performed with a temperature resolution of 0.1°C and a temperature range between 70°C and 85°C. Data collection and genotype calls were obtained by the Rotor-Gene 6000 series software v. 1.7 (QIAGEN, CA, USA) using as reference genotypes DNA samples sequenced by ABI Prism® 310 Genetic Analyzer (Applied Biosystems, CA, USA).

2.6. Statistical analysis

The effect of genotypes and alleles on response and remission ~~rates~~ was tested by Pearson's chi-squared tests. A Multivariate Analysis of Variance (MANOVA) ~~One-way ANOVA~~ was used ~~within a linear regression model~~ to study the effect of genotypes and alleles on improvement at week 8 adjusting for center, gender, age, and baseline severity. Analyses were carried out only in completers, in the two individual treatment groups and in the whole sample.

Despite ~~The level of significance was conservatively set to 0.05 since~~the selected candidate genes show a strong biological rationale for involvement in antidepressant mechanisms of action~~, thus~~ and the pre-test probability of association is favorable, Bonferroni correction was applied to reduce the risk of false

positives. Thus, alpha value was set to 0.005 considering 5 independent polymorphisms that were tested in two independent groups of patients (IPC- and antidepressant-treated). The whole sample was not considered as an independent group, as well as the three analyzed phenotypes (response, remission and symptom improvement) were considered as highly related one to each other. Further, we stated only remission as primary outcome (see paragraph 2.3.).

Our whole sample setting alpha value to 0.005 two tailed provides a power of 0.80 to detect a risk allele (for non-remission) with OR ≥ 4.0~~observe a difference between two variants with effect size d=0.26~~ (Gpower 3.1 software)~~, which corresponds to a difference of at least 1.5 points in the HDRS at week 8 and to an explained variance of 2.2%~~.

3. Results

SCL6A4 rs8076005 slightly deviated from Hardy-Weinberg equilibrium (HWE) (p=0.03), while the other polymorphisms satisfied HWE (*HT2A* rs6314: p=0.61; *BDNF* rs6265: P=0.34; *CREB1* rs2253206: P=0.52; *TPH2* rs11179023: P=0.45). For 1 subject in the IPC group and 2 in the antidepressant group genotyping was not successful thus they were excluded from the analysis.

Clinical-demographic characteristics of the sample were reported in Table 1. The major part of patients was treated with SSRIs (80.4%). Further clinical data were reported in a previous paper [48]. Non completers (12.74%) did not show any difference in age, gender, and baseline severity when compared to the 8 week-completers [48]. As previously reported [48], no difference was observed in clinical outcomes between the two treatment groups (Table 1). In the IPC group the number of remitters ~~remission rate~~ was slightly higher than that of responders ~~the response rate~~ because the IPC group had lower baseline severity than the antidepressant group. Nevertheless, the difference was not so pronounced to be clinically relevant and analyses were adjusted for baseline severity.

Effect of polymorphisms on outcomes

SLC6A4 rs8076005 ~~AA genotype and~~ A allele ~~were~~ reached the significance threshold for association with ~~associated with~~ better response in the antidepressant group (~~p=0.015 and~~ p=0.005~~, respectively~~) and showed a consistent trend in the whole sample (~~p=0.03 and~~ p=0.02~~, respectively~~) (Tables 2 and 3). Further, rs8076005 A allele carriers showed a trend of higher symptom improvement at week 8 in the whole sample (F=3.29, df=2, p=0.04). The association between rs8076005 AA genotype-A allele ~~(genotypes and alleles)~~ and response was ~~still observed~~more evident after correction for age, gender, baseline severity and center in the antidepressant group (Z=2.81, p=0.005; Z=3.10, p=0.002, respectively), ~~as well as~~while trends were found in the whole group (Z= 2.51, p=0.012; Z=2.54, p=0.011, respectively).

TPH2 rs11179023 A allele showed a mild trend of selective association with symptom improvement in the IPC group (F=4.29, df=1, p=0.042), but no effect was found on response and remission ~~rates in any group analyzed~~. The other investigated polymorphisms did not show evidence or trends of impact on ~~affect~~ clinical outcomes nor in individual treatment groups neither in the whole sample (Tables 2 and 3; data pertaining % improvement not shown).

4. Discussion

This study investigated the effect of five serotonergic polymorphisms on clinical outcomes of a brief psychotherapy, IPC, versus antidepressant pharmacotherapy. As previously reported in this sample [48], IPC is effective in the treatment of mild-moderate MDD as well as antidepressants.

SLC6A4 rs8076005 AA genotype and A allele were associated with response ~~rates~~ in the antidepressant group ~~as well as in the whole sample (Table 2 and 3)~~, with consistent trends in the whole sample (Table 2 and 3). Rs8076005 has been previously suggested as a risk factor for MDD through the neural-immune interaction~~, particularly IL-6 levels~~ [17], even if this does not necessarily imply an impact of the SNP on antidepressant response. In detail, rs8076005 G allele carriers showed higher depressive symptom severity and higher IL-6 levels, as well as demonstrated for the minor allele of SNPs that are in linkage disequilibrium (LD) with rs8076005 (rs12150214, rs11080122, rs8071667, rs2020936, rs25528, and rs6354). Interestingly, IL-6 levels were previously demonstrated to negatively affect antidepressant response [54-56]. Two SNPs in LD with rs8076005 (rs6354 and rs2020936) were associated with anxiety, MDD and neuroticism [57].

On the other hand, rs8076005 A allele did not affect clinical outcomes in the IPC group, that instead may be influenced by TPH2 rs11179023. Inconsistent results were found about the role of *TPH2* variants in antidepressant response [14, 20, 29, 31, 32, 58], but rs11179023 has not been investigated previously. In this study, rs11179023 A allele ~~was associated with~~showed a trend of higher symptom improvement at week 8 only in the IPC group, while the genotypic analysis could not be performed since only 1 subject carried the AA genotype. Clearly, the present result did not allow to trace any statement but suggested a new polymorphism within a known candidate gene for further investigation~~confirmation of the result in a larger sample is needed~~.

In the present study, *HTR2A* rs6314 was not associated with antidepressants or IPC outcomes. Despite some inconsistent results, previous studies suggested that this polymorphism may be associated with SSRIs response [14, 15, 59]. Thus, the use of different treatments in our study or the small sample size may partly explain the reported negative findings.

In this study, also *BDNF* rs6265 did not affect treatment outcomes. Recent meta-analyses reported that the heterozygous genotype may be a predictor of better antidepressant response [38-40], but negative findings

have been reported as well [60-71]. The inconsistency in previous results may be at least partly due to different rs6265 allele and genotype distribution across populations. Indeed, the frequency of the Met allele is higher in Asians than in Caucasians, and the Met allele may be protective against MDD and associated with better antidepressant response only in Asian subjects [38, 40, 72].

Phosphorylation of CREB is related to cellular resilience and neuroplasticity [73]. Phosphorylated CREB (pCREB) is positively correlated with antidepressant and interpersonal psychotherapy (IPT) response in MDD [73, 74]. Previous association studies suggested that the *CREB1* gene may show a selective effect on the risk of treatment resistance in MDD [47] and paroxetine response [71]. Our negative results are line with other studies focused on response to mixed antidepressant treatments [61, 75].

Among the limitations of the present study, the first is the limited statistical power compared to current pharmacogenetic studies, particularly in the IPC group. Thus, the present findings should be cautiously considered. Anyway, the low sample size mainly affects the risk of false negative findings given the lack of power to find small effect sizes. Further, the choice of candidate genes with strong biological plausibility for involvement in antidepressant mechanisms of action contributes to reduce the risk of false positives. Others limitations are represented by the use of the present sample in a previous pharmacogenetic study [48] and the recruitment of patients in different centers (even if center of recruitment was used as covariate and inter-rater reliability was good). Another issue is the deviation of *SLC6A4* rs8076005 from HWE, despite the MAF was in line with that reported in the HapMap database for the CEU population (0.22 in our study and 0.18 according to HapMap Phase III release on NCBI B36 assembly, dbSNP b126). The availability of more evaluation time points could have provided information about response timing in the two treatment groups. Finally, the use of a naturalistic setting in the pharmacological arm of the study could be seen as a limitation, but also provided a perspective that is more near to the real clinical practice and the major part of patients were treated with SSRIs.

Despite these limitations, the present study is among the few that have investigated the impact of genetic variants on brief psychotherapy response. Previous studies were mainly focused on the effect of genetic variants on personality characteristics that may in turn affect psychotherapy outcome. Further genetic studies directly focused on the efficacy of psychological interventions in MDD are clearly needed. Personality features should be considered as modulators. However, in the present sample the comorbidity with personality disorders did not affect IPC outcomes [48], as found by an independent study [76].

5. Conclusion

Our study suggests that *SLC6A4* rs8076005 may impact on antidepressant response ~~rate~~ at week 8, especially in patients treated with antidepressant drugs. *TPH2* may be a selective modulator of IPC response, even if this result is even more preliminary given the limited size of the IPC-treated group and non-significance of the finding after Bonferroni correction. IPC, an effective treatment in mild-moderate MDD, is worthy of further investigation in genetic studies.

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Disclosure statement

Dr Serretti is or has been a consultant/ speaker for: Abbott, Astra Zeneca, Clinical Data, Boheringer, Bristol Myers Squibb, Eli Lily, GlaxoSmithkline, Janssenn, Lundbeck, Pfizer, Sanofi, and Servier. Other authors have no conflicts of interest.

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