Brief report

Variation in the HTR1A and HTR2A genes and social adjustment in depressed patients

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1. Introduction

Patients with mood disorders have impaired levels of social functioning, in particular during the acute phase of the disorder (Bauwens et al., 1991; Blairy et al., 2004). Although an improvement in functioning is expected during remission, social adjustment problems also persist in the euthymic phase (Serretti et al., 1999). The Social Adjustment Scale (SAS) (Weissman and Bothwell, 1976; Weissman et al., 2001) has been extensively used to assess this area as a predictor of the depressive course. For example, social maladjustment was considered to be a risk factor for recurrent affective episodes (Bauwens et al., 1998; Grunebaum et al., 2010) and was associated with the recurrence of depressive symptoms in depressed patients treated with antidepressants (Reinherr et al., 2001). Social adjustment has also been examined as an outcome in depressive disorders. In a prospective study of a depressed cohort, characteristics of the depressive episode, such as severity, recurrence before baseline and during follow-up, lack of full remission, and episode duration predicted current levels of social adjustment (Rytisalā et al., 2006). Consequently, social maladjustment has been implicated both as a consequence and as a cause of depression.

Current research on etiological mechanisms implicates both genetic and environmental variables as major contributors of depression. Research on the genetics of mood disorders has focused on the serotonergic system as a reasonable source of...
candidate genes, since this system is implicated in antidepressant pharmacodynamics, challenged by tryptophan depletion methods, and consequently affects mood states (Cowan, 2008). Variation in the serotonin transporter promoter polymorphism (5-HTTLPR) has been associated with levels of social adjustment in healthy controls and bipolar patients (Serretti et al., 2005). The 5-HT1A receptor gene (HTR1A) has a polymorphism (rs6295) in the promoter region, which has been associated with depression (Savitz et al., 2009). Furthermore, within the 5-HT2A receptor gene (HTR2A), the rs7997012 polymorphism has been mainly investigated in relation to treatment response (Kato and Serretti, 2010). The purpose of this study was to investigate whether variations in the HTR1A and HTR2A genes were associated with social adjustment levels (SAS) of depressed patients.

2. Methods

2.1. Participants and assessments

One hundred and sixty five patients with a major depressive disorder were recruited. Of the 165 patients, 94 (56.97%) were recruited in the context of the European multicenter project “Patterns of treatment resistance and switching strategies in unipolar affective disorder”. Data was collected from the following centers: (1) Department of Psychiatry and Psychotherapy, Medical University Vienna, Austria; (2) Department of Psychiatry, Chaim Sheba Medical Center, Tel-Hashomer, Israel; (3) Department of Psychiatry, Ness Ziona, Israel, (4) Department of Psychiatry, Erasme Hospital, Universite Libre de Bruxelles, Brussels, Belgium. The sample has been described in detail elsewhere (Souvey et al., 2007). In brief, the main inclusion criterion was to be affected by a primary mood disorder (i.e. mood disorder preexisting to any primary mood disorder). Exclusion criteria were: a mood disorder secondary to any primary ‘non affective’ psychiatric condition. Only patients with a major depressive disorder (MDD) diagnosis were included in this report. Diagnoses were obtained using the Mini International Neuropsychiatric Interview (MINI) version 5.0.0.

Of the 165 patients, 71 patients (43.03%) were recruited from the outpatient unit at the Institute of Psychiatry of Bologna University, Italy. Inclusion criterion was a primary MDD diagnosis as assessed with the MINI.

Both samples completed the Hamilton Rating Scale for Depression (HAM-D) and the SAS (Weissman and Bothwell, 1976). The SAS is a 54-item self-report scale, subdivided into the following subareas: (1) work; (2) leisure; (3) extended family; (4) marital role; (5) children; (6) family unit; and (7) finance. Social adjustment is assessed for each area (item range: 1–5). Higher scores reflect poorer adjustment. The scale contains “skip-outs”, so that non-applicable items were not considered (Weissman et al., 2001). Scores for each area were calculated by averaging the scores for all answered items within that area, and the total score was calculated by averaging all the applicable items (Weissman et al., 2001). The SAS was administered during the treatment sessions of the episode; for the majority of patients SAS was administered after at least 4 weeks of adequate antidepressant treatment (5 (5.3%) patients from the multicentre sample and 15 (21.1%) patients from the Bologna sample had not received at least 4 weeks of treatment). The ethical committees of all participating centers approved the study protocol and all participants gave written informed consent.

2.2. Genotype analyses

Single nucleotide polymorphisms (SNPs) of the HTR1A (rs6295) and HTR2A (rs7997012) genes were genotyped. Please refer to supplementary material for details.

2.3. Statistical analyses

Descriptive characteristics were assessed with correlations, chi-square tests or one-way ANOVAs as appropriate. Differences between genotype and allele groups on SAS scores were assessed using analysis of co-variance (ANCOVA). Socio-demographic and clinical variables that could influence the outcome were included as covariates. In the whole sample, we had sufficient power (0.80) to detect an effect size of 0.22, with an alpha level of 0.05, that, as an example, corresponds to a final difference in the total SAS score of 1.8 points between subjects carrying GG and AG genotypes of rs7997012. For other SNPs power was lower (data not shown). Genotype frequencies were consistent with Hardy Weinberg Equilibrium (rs7997012: AA = 13, AG = 82, GG = 70, x^2(1) = 2.72, p = 0.10; rs6295: CC = 32, CG = 72, GG = 61, x^2(1) = 1.63, p = 0.20). There were no differences in genotype frequencies between European and Israeli samples (rs7997012: x^2(2) = 3.85, p = 0.15; rs6295: x^2(2) = 0.02, p = 0.99). Minor Allele Frequencies (MAFs) were in accordance with those reported for Caucasian populations (rs7997012 MAF:0.33; rs6295 MAF: 0.41). A Cochran-Mantel-Haenszel test (McDonald, 2009) showed that there was no difference in allele frequencies between the samples as well: rs7997012: x^2(1) = 0.16, p = 0.69; rs6295: x^2 (1) = 2.59, p = 0.11).

3. Results

Demographic and clinical characteristics of the sample can be observed in Table 1. Genotypic data were available for 165 patients. Of those, 156 patients also filled in the SAS. SAS levels were not related to age, education level, occupation status, marital status or number of episodes (all p>0.05), but only to gender and current level of symptoms (HAM-D). Women reported higher levels of social dysfunction on areas of work, leisure and marital relationships (all p<0.05). Higher levels of symptoms were related to higher impairment in areas of work (r = 0.54, p<0.001), leisure (r = 0.46, p<0.001), family (all r = 0.19 p = 0.02) and finances (r = 0.18, p = 0.02). The duration of the received antidepressant treatment was marginally related to the “family unit” area (r = -0.19, p = 0.05).

<p>| Table 1 Sociodemographic and clinical characteristics of the sample(s). |
|-------------------------------|-------------------------------|-------------------------------|-------------------------------|</p>
<table>
<thead>
<tr>
<th>Total sample</th>
<th>Multicenter sample</th>
<th>Bologna sample</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 165</td>
<td>n = 94</td>
<td>n = 71</td>
<td></td>
</tr>
<tr>
<td>M±SD/N (%)</td>
<td>M±SD/N (%)</td>
<td>M±SD/N (%)</td>
<td></td>
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<td>----------------</td>
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</tr>
<tr>
<td>Age</td>
<td>53.15±16.72</td>
<td>52.16±14.99</td>
<td>54.67±19.12</td>
</tr>
<tr>
<td>Gender: females</td>
<td>118 (71.5%)</td>
<td>69 (73.4%)</td>
<td>49 (69.0%)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>33 (20.0%)</td>
<td>17 (20.0%)</td>
<td>16 (25.0%)</td>
</tr>
<tr>
<td>Married</td>
<td>84 (50.9%)</td>
<td>54 (63.5%)</td>
<td>30 (46.9%)</td>
</tr>
<tr>
<td>Separated</td>
<td>22 (13.3%)</td>
<td>13 (15.3%)</td>
<td>9 (14.1%)</td>
</tr>
<tr>
<td>Living together</td>
<td>1 (0.6%)</td>
<td>1 (1.2%)</td>
<td>na</td>
</tr>
<tr>
<td>Widowed</td>
<td>9 (5.3%)</td>
<td>na</td>
<td>9 (14.1%)</td>
</tr>
<tr>
<td>Education*</td>
<td></td>
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</tr>
<tr>
<td>School not completed</td>
<td>30 (18.2%)</td>
<td>15 (17.0%)</td>
<td>15 (24.2%)</td>
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<tr>
<td>Technical degree</td>
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<tr>
<td>University</td>
<td>79 (47.9%)</td>
<td>50 (56.8%)</td>
<td>29 (46.8%)</td>
</tr>
<tr>
<td>Employed</td>
<td>41 (24.8%)</td>
<td>23 (26.1%)</td>
<td>18 (29.0%)</td>
</tr>
<tr>
<td>Treatment (weeks)</td>
<td>10.30±9.74</td>
<td>9.87±10.16</td>
<td>10.85±9.24</td>
</tr>
<tr>
<td>HAM-D</td>
<td>14.51±6.55</td>
<td>17.73±8.97</td>
<td>10.24±8.05</td>
</tr>
<tr>
<td>Number of episodes</td>
<td>3.50±6.56</td>
<td>4.18±7.15</td>
<td>2.20±5.05</td>
</tr>
</tbody>
</table>

Abbreviations: HAM-D—Hamilton Depression Rating Scale; M—Mean; SD—Standard Deviation.

* P value represents differences between Bologna and Multicenter samples.

* Original data have been re-computed into new variables for comparison.
We examined differences on social adjustment areas among the three genotype groups of the HTR1A-rs6295 and HTR2A-rs7997012 SNPs. The GG genotype group reported lower social maladjustment in the areas of “work” (F[2,112]=3.99, p=0.02), and “family unit” (F[2,119]=3.96, p=0.02) (Table 2). Controlling for center, depressive symptoms and treatment duration (weeks) did not influence these results (“work”: F(2,97)=5.88, p=0.004; “family unit”: F(2,96)=4.47, p=0.01). For consistency purposes, we repeated the analysis, examining the two samples separately. In the first sample (n=94), observations remained (p<0.05); in the second sample (n=71), differences failed to reach statistical significance but a similar pattern was observed. Allelic analyses showed no differences between the A and G alleles on SAS “work” and “family unit” scores.

Furthermore, we examined whether genotype variation in the rs7997012 is related to other clinical characteristics, which may partly explain the relationship with social maladjustment. Genotype groups did not differ on the level of depression severity (HAM-D) (p=0.75) (Means±SD: AA: 14.46±8.85, AG: 15.05±9.76, GG: 13.89±9.03). Differences in the number of prior depressive episodes did not reach significance as well (p=0.40), but GG genotype carriers reported a lower number of episodes (AA: 5.91±4.94, AG: 3.54±6.55, GG: 2.96±5.87). Nevertheless, since the subsamples showed differences in marital status, employment status and depressive symptoms (Table 1), we also re-run the initial analysis controlling for age, marital status, employment status, HAM-D total score, participating center, and number of episodes. The association was maintained between rs7997012 and SAS “work” [F(2,73)=8.06, p=0.001] (same direction, AA: 2.85±1.35, AG: 3.03±1.28, GG: 2.37±0.89). No association was found, however, between rs7997012 and SAS “family unit” [F(2,71)=6.13, p=0.54]. Since not all covariate data were available for all the participants, the covariate analysis for SAS “work” included 82 patients, instead of 127 patients, and 80 patients instead of 124 for SAS “family unit”. Due to the small sample sizes of the genotype groups the positive genotypic association (GG genotype carriers reporting lower scores) should be interpreted with caution.

Finally, there was no association between HTR1A-rs6295 and social adjustment (data not shown).

4. Discussion

The present study provides some evidence that variation in the HTR2A rs7997012 SNP is associated with SAS social adjustment levels, with the GG genotype carriers showing lower social maladjustment in areas of work and family. Although not statistically significant, but potentially clinically relevant, this genotype group reported a lower number of recurrent episodes compared to the other groups. Prior research has shown that impaired work adjustment has been associated with recurrent episodes in bipolar and unipolar patients (Bauwens et al., 1998). Furthermore, previous studies examining social adjustment in relation to genetic vulnerability have shown that variation in the 5-HTTLPR was associated with levels of social adjustment in healthy controls and bipolar patients (Serretti et al., 2005). Bipolar patients homozygous for the 5-HTTLPR A allele reported poor familial adjustment (Serretti et al., 2005), similar to the AA homozygous depressed patients in the present study.

Interestingly, the G allele of the rs7997012 SNP has been previously associated with a higher rate of antidepressant response and remission (Lucae et al., 2010). However, McMahon et al. (2006) observed that AA genotype carriers had a reduced risk of non-response to treatment, compared to GG patients. Furthermore, the rs7997012-AA genotype was associated with treatment resistance in another study (Noro et al., 2010). Along the same lines, we observed that variation in this gene is associated with social adjustment in the areas of work and family in depressed patients.

The most important limitation of the present research is that the observed associations did not survive correction for multiple testing, therefore the chance of observing false positive findings cannot be ruled out. Since the results of genetic studies have shown a hyperinflation of false positive observations during the last years, a replication of the present findings in an independent sample is clearly warranted in order to draw any conclusions on the topic. Furthermore, the sample size is limited and the main results were only based on small sub-group of individuals (small genotype groups) and any positive observation should be interpreted with caution. The data were collected from different samples and although population stratification is unlikely (allele frequencies were homogeneous and in HWE), it cannot be ruled out. Furthermore, we cannot exclude the possibility that our observations may be due to other unknown variations. Additional studies are necessary to clarify the role of the HTR2A-rs7997012 in treatment-related phenotypes of depression.

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Conflict of interest

The authors declare no conflict of interest.

Acknowledgement

None.
Appendix A. Supplementary information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jad.2013.02.036.

References


