Genetic variability in the endocannabinoid system and 12-week clinical response to citalopram treatment: the role of the CNR1, CNR2 and FAAH genes

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What is This?
Genetic variability in the endocannabinoid system and 12-week clinical response to citalopram treatment: the role of the CNR1, CNR2 and FAAH genes

Marina Mitjans¹, Cristóbal Gastó²,³, Rosa Catalán²,³, Lourdes Fañanás¹,³ and Bárbara Arias¹,³

Abstract
First line treatment of major depression is based on selective serotonin re-uptake inhibitors (SSRIs) that enhance serotonergic neurotransmission by blocking the serotonin transporter. However, clinical response is a complex phenomenon in which other systems such as the endocannabinoid system could be involved. Given the evidence for the role of the endocannabinoid system in the pathogenesis of depression as well as in the mediation of antidepressant drug effects, the aim of this study was to analyze genetic variability in the endocannabinoid system genes (CNR1, CNR2 and FAAH genes) and their role in clinical response (at week 4) and remission (at week 12) in SSRI (citalopram) treatment in a sample of 154 depressive outpatients, all of Spanish origin. All patients were treated with citalopram and followed over 12 weeks. Severity of depressive symptomatology was evaluated by means of the 21-item Hamilton Depression Rating Score (HDRS). No differences were found in any of the genotype distributions according to response or remission. The longitudinal study showed that (i) the CNR1 rs1049353-GG genotype conferred a better response to citalopram treatment in the subgroup of male patients and (ii) G allele carriers (CNR2 rs2501431) presented higher HDRS scores in the follow-up than AA homozygous allele carriers. Our results seem to suggest the involvement of CNR1 and CNR2 genes in clinical responses to citalopram treatment.

Keywords
Major depression, pharmacogentics, endocannabinoid system, SSRI, molecular variation

Introduction
Major depressive disorder has been described as a clinically heterogeneous disease that results from the interplay of multiple genes interacting with environmental factors such as early stressful life events (Caspí et al., 2003). Treatment of major depression is principally based on selective serotonin re-uptake inhibitors (SSRIs) that enhance serotonergic neurotransmission by blocking the serotonin transporter. However, clinical response to drug treatment in depression is a highly complex biological phenomenon in which several factors are involved, some of them genetic (Klengel and Binder, 2011; Uher, 2011). SSRIs were developed as drugs with high selectivity for the target molecule, the serotonin transporter, and have constituted one of the most important advances in the pharmacological treatment of depression since the late 80s (Martin et al., 1997). Although SSRIs exert their action by basically modifying the serotonergic system, previous studies have shown the modulating action of this system on other neurotransmission systems such as the dopaminergic or glutamatergic systems (Arias et al., 2006, 2009; Domschke et al., 2008; Drago et al., 2011; Kato and Serretti, 2010; Porcelli et al., 2011).

In addition, recent evidence suggests that other systems like the endocannabinoid system can also have a role in modulating the serotonergic system (Horstmann and Binder, 2011). In this sense, the endocannabinoid system is expressed in both the brain and at the periphery. It consists of two cannabinoid receptors (CB1 and CB2), their natural ligands and specific enzymes for their biosynthesis and inactivation. It has recently been suggested that the endocannabinoid system may be implicated in the pathophysiology of depression (Hill and Gorzalka, 2005a). This is supported by evidence showing that the cannabinoid receptors and enzymes involved in the synthesis and degradation of endocannabinoid ligands are highly expressed in the neuroanatomical structures and circuits involved in depression, including the prefrontal cortex, hippocampus, amygdala, hypothalamus and forebrain monoaminergic circuits (Herkenham, 1991). Moreover, experimental data showed that the blockade of the endocannabinoid system is a risk factor in the pathogenesis of depression as well as anxiety disorders (Hill and Gorzalka, 2005c; Martin et al., 2002).

The CB1 receptor is coded by the CNR1 gene located on chromosome 6 (6q14-15). It is considered the most abundant G

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protein-coupled receptor expressed in the CNS of mammalian brain (Herkenham, 1991) and, to a lesser extent, in peripheral tissues (Galiegue et al., 1995; Kumar et al., 2001). The CB1 receptor is mainly located in GABAergic and glutamatergic neurons suggesting a modulating role of synapses of a different nature (Rodríguez de Fonseca et al., 2005). Several studies demonstrate the role of CB1 receptors in the modulation of monoaminergic neurotransmission such as the serotonergic one (Bambico et al., 2007; Gobbi et al., 2005). CB1 receptors are present and function on 5-HT systems (Balazsa et al., 2008) and human genetic studies have provided evidence for interaction among the CB1 receptor gene, the serotonin receptor gene (SERT), and anxiety (Lazary et al., 2009, 2011). Also, a study of Hill et al. (2006) shows that the expression of CB1 receptor in the hippocampus and the hypothalamus is up-regulated by chronic tricyclic antidepressant treatment which exerts part of its antidepressant action on the serotonergic system.

A recent study shows that CNR1 rs1049353 A allele also confers increased risk for neuroticism and depression especially in haplotypic combination (Juhasz et al., 2009). In addition, a decrease of CB1 receptor density has been detected in grey matter glial cells in post mortem brains of patients with major depression (Koethe et al., 2007). In this context, a meta-analysis has reported the anxiogenic and depressive effects when the CB1 receptor is blocked by antagonist-like rimonabant, a drug for obesity treatment (Christensen et al., 2005; Hill and Linnet, 1996). Although, on the contrary, other studies have showed the potential indication of CB1 receptor antagonists in the treatment of depressive symptomatology (Witkin et al., 2005).

On the other hand, the CB2 receptor is basically highly expressed in the periphery and the presence of this receptor has been recently demonstrated in neurons of the brainstem and cerebellum (Onaivi, 2006; Suarez et al., 2008). The CB2 receptor is encoded by the CNR2 gene located on chromosome 1 (1p36.1). Animal and clinical studies have provided evidence of the participation of CB2 receptor in mood disorders. Recent results based on mice models with a genetically-modified CB2 receptor have suggested that this receptor is involved in the regulation of emotional behaviour (Ortega-Alvaro et al., 2011; Racz et al., 2008a, 2008b).

The CB1 and CB2 receptors are activated by endogenous ligands such as anandamide and 2-arachidonoylglycerol (2-AG). Hydrolysis of endogenous ligands is controlled by two enzyme systems, fatty acid amide hydrolase (FAAH) (Cravatt et al., 1996) and monoacylglycerol lipase (Dinh et al., 2002). The FAAH is coded by the FAAH gene located on chromosome 1 (1p35-34). It has been reported by experimental data that the administration of CB1 receptor agonists, endogenous cannabinoid re-uptake inhibitors or inhibitors of the FAAH enzyme resulted in antidepressant-like effects and in an increased efficacy of fluoxetine in animal models (Adamczyk et al., 2008; Gobbi et al., 2005; Hill and Gorzalka, 2005b).

Taking into account the strong evidence of the role of the endocannabinoid system in the pathogenesis of depression as well as in the mediation of antidepressant drug effects, the aim of this study was to analyze genetic variability in the CB1 receptor gene (CNR1 rs1049353 G/A), CB2 receptor gene (CNR2 rs2501431 G/A) and fatty acid amide hydrolase gene (FAAH rs324420 C/A) and their role on clinical response (four weeks) and clinical remission (12 weeks) after SSRI (citalopram) treatment in major depression.

Methods and materials
Sample
The sample consisted of 154 depressive outpatients (122 females and 32 males; mean age: 39.5±12.19 years) from the Centre de Salud Mental of the Hospital Clinic de Barcelona who were recruited between 1999 and 2002 and followed during at least 12 weeks by experienced psychiatrists. All patients suffered an active episode of major depression diagnosed following DSM-IV-TR criteria (APA, 1994) at the time of inclusion in the study. All cases were diagnosed using the Spanish version of the Structured Clinical Interview (SCID-I) (Spitzer et al., 1990). Detailed data about the severity of clinical features was collected from the medical records of the patients, and data on the presence of melancholic features (n=49 (33.3%)), psychotic symptoms (n=27 (18.5%)), seasonal pattern (n=69 (47.6%)) or previous suicide attempts (n=24 (16.7%)) was also collected (Arias et al., 2009). No patients with bipolar I or II disorder were included in this sample. Patients with drug abuse and dependence, mental retardation or with a medical disease that impairs evaluation have been excluded from the study.

All patients were treated with citalopram (20–40 mg/day). Patients were initially evaluated for the severity of their symptoms using the 21-item Hamilton Rating Scale for Depression (HDRS) (mean initial HDRS: 24.7±4.74). A new HDRS was assessed for all patients every four weeks until the completion of the follow-up at week 12. A positive clinical response to citalopram treatment was considered when a decrease of at least 50% in the baseline score was observed at week 4 (Baumann et al., 1996). Remission for the index episode was considered when HDRS scores were equal or lower seven by the end of week 12 (Frank et al., 1991). Plasma levels of citalopram were determined at week 6 using high performance liquid chromatography (HPLC) (Olesen and Linnet, 1996).

All participants were of Spanish ancestry (Caucasian), thereby reducing the possibility of confounding genetic differences by population stratification (Fredman et al., 2004). Ethical approval was obtained from local research ethic committees. Patients provided written informed consent before inclusion in the study.

Selection of gene variants and genetic analysis
Genetic variants were selected according to their role in depression or antidepressant response based on previous publications. Firstly, the genetic variant CNR1 rs1049353 has been reported to confer an increased risk of antidepressant treatment resistance, particularly in female patients (Domschke et al., 2008). Secondly, the CNR2 rs2501431 variant was selected because this polymorphism has been reported to be associated with risk for major depression in Japanese population (Onaivi et al., 2008). Thus, we hypothesize that the polymorphism could also have an involvement in the treatment response. Finally, the FAAH-rs324420 variant has functional effects producing a 50% reduced activity of the FAAH enzyme.
(Chiang et al., 2004). Animal models show that inhibition of the FAAH enzyme has antidepressant effects (Gobbi et al., 2005).

Genomic DNA was extracted from blood samples using a conventional phenol-chloroform extraction protocol. The rs1049353 (CNR1 gene), rs2501431 (CNR2 gene) and rs324420 (FAAH gene) polymorphisms were analyzed using Applied Biosystems (AB) Taqman technology (Applied Biosystems, Foster City, California, USA). All the probes for genotyping were ordered through the TaqMan® SNP Genotyping assays AB assay-on-demand service. The final volume of the polymerase chain reaction (PCR) was 5 mL, which contained 10 ng of genomic DNA, 2.5 mL of TaqMan Master Mix, and 0.125 mL of 40x genotyping assay. The cycling parameters were as follows: 95°C for 10 min followed by 40 cycles of denaturation at 92°C for 15 sec and annealing/extension at 60°C for 1 min. Polymerase chain reaction plates were read on an ABI PRISM 7900HT instrument with SDS v2.1 software (Applied Biosystems).

Genotype determinations were performed blind to clinical condition. A randomized 10% of the individuals were retested for their genotypes to confirm the pattern reproducibility. Table 1 shows the final genetic sample. Of the total sample, 90.25% was successfully genotyped for the CNR1 rs2501431 polymorphism, the 96.1% for the CNR2 rs2501431 polymorphism and the 95.45% for the FAAH rs324420 polymorphism.

### Statistical analysis

Hardy-Weinberg equilibrium for genotype frequencies in patients sample were calculated using chi-square tests (Epi Info v3.5.1; Dean et al., 1991). Simple chi-squared tests of independence were performed to confirm the presence or absence of allele or genotype associations. Odds ratios (OR) with 95% confidence intervals (CI) were estimated for the effects of high-risk genotypes. The combined study group had an 80% power (95% CI) to detect OR equal or greater than 2.93–2.98 for No-RP or No-RM according to the allele frequencies of the different polymorphisms analyzed in our sample (Cohen, 1988).

The longitudinal study based on HDRS change scores during the 12 weeks of citalopram treatment was performed using analysis of variance (ANOVA) with repeated measures (genotype and gender as fixed factor, time point as a repeated measure and a number of covariates: see below). Covariates were included in these multivariable ANOVA models if they showed an impact on treatment response (4 weeks). All data were processed using SPSS 17.0 (SPSS for Windows; SPSS Inc., Chicago, Illinois, USA).

### Results

#### Sociodemographic and clinical measures

The genotype distribution of all single nucleotide polymorphisms (SNP) was found to be in Hardy-Weinberg equilibrium in the overall sample (rs1049353: $\chi^2=0.76$, df=2, $P=0.68$; 2501431: $\chi^2=0.14$, df=2 $P=0.93$; rs324420: $\chi^2=0.09$, df=2, $P=0.95$).

In our sample, 101 patients (65.6%) were considered responders (RP) and 53 (34.4%) were classified as no-responders (No-RP) according to the decrease of their HDRS scores at week 4. Considering the remission criteria at week 12, 99 patients (64.7%) were classified as remitters (RM) and 54 (35.3%) as no-remitters (No-RM).

#### Table 1. Genotype and allele distribution of the CNR1, CNR2 and FAAH polymorphisms in major depression patients according to treatment response at week 4 and remission at week 12.

<table>
<thead>
<tr>
<th></th>
<th>Response (week 4)</th>
<th>Remission (week 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (88)</td>
<td>No (51)</td>
</tr>
<tr>
<td></td>
<td>No (51)</td>
<td>No (51)</td>
</tr>
<tr>
<td>rs1049353 (CNR1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>139 (76.4)</td>
<td>52 (76.5)</td>
</tr>
<tr>
<td>G</td>
<td>98 (75.7)</td>
<td>38 (76.5)</td>
</tr>
<tr>
<td>C</td>
<td>41 (31.4)</td>
<td>14 (27.5)</td>
</tr>
<tr>
<td>Alleles (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G/G</td>
<td>38 (62.2)</td>
<td>39 (72.5)</td>
</tr>
<tr>
<td>G/C</td>
<td>30 (46.8)</td>
<td>20 (38.5)</td>
</tr>
<tr>
<td>C/C</td>
<td>22 (34.8)</td>
<td>13 (25.5)</td>
</tr>
<tr>
<td>Genotypes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G/G/G</td>
<td>12 (17.6)</td>
<td>6 (11.5)</td>
</tr>
<tr>
<td>G/G/C</td>
<td>24 (36.5)</td>
<td>14 (27.5)</td>
</tr>
<tr>
<td>G/C/C</td>
<td>12 (17.6)</td>
<td>6 (11.5)</td>
</tr>
<tr>
<td>C/C/C</td>
<td>4 (6.0)</td>
<td>2 (3.9)</td>
</tr>
<tr>
<td>N</td>
<td>Yes (87)</td>
<td>No (51)</td>
</tr>
<tr>
<td>rs2501431 (CNR2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>139 (76.4)</td>
<td>52 (76.5)</td>
</tr>
<tr>
<td>A</td>
<td>98 (75.7)</td>
<td>38 (76.5)</td>
</tr>
<tr>
<td>G</td>
<td>41 (31.4)</td>
<td>14 (27.5)</td>
</tr>
<tr>
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<tr>
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<td></td>
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</tr>
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<td>A/G/G</td>
<td>12 (17.6)</td>
<td>6 (11.5)</td>
</tr>
<tr>
<td>G/G/G</td>
<td>4 (6.0)</td>
<td>2 (3.9)</td>
</tr>
</tbody>
</table>

*P* values are shown when *P* < 0.01.
We compared RP vs No-RP and RM vs No-RM according to sociodemographical variables (sex and age) and clinical features (age at onset, presence of anxiety, melancholic symptoms, suicide attempts, seasonal pattern, psychotic symptoms and citalopram levels at the sixth week) (Table 2). These variables were selected on the basis of previous literature that showed their possible influence on the evolution of response to antidepressant treatment (Arranz and Kapur, 2008; Nierenberg, 2003).

Our result showed that the presence of suicide attempts was associated with No-RP at week 4 ($\chi^2=3.75$, df=1, $P=0.046$) and No-RM at week 12 ($\chi^2=10.204$, df=1, $P=0.002$). Also, our results showed that lower citalopram levels at week 6 were associated with No-RP at week 4 ($F=4.72$, df=1, $P=0.032$). Therefore, these variables were considered as covariates in multivariable ANOVA procedures.

**Pharmacogenetics of Response (week 4) and Remission (Week 12)**

As described in Table 1, we tested whether there was any difference in genotype and allele distribution according to citalopram response at week 4 and remission at week 12. We did not find any statistical difference when comparing response/no response or remission/no remission for rs1049353 (CNR1), 2501431 (CNR2) and rs324420 (FAAH) polymorphisms.

**Pharmacogenetics of the longitudinal study**

We performed a two-way repeated measure ANOVA on HDRS scores to evaluate the effect of the rs1049353 polymorphism (CNR1 gene) on the 12-week clinical follow-up of the patients treated with citalopram. Our results showed that rs1049353-GG carriers presented a better response to antidepressant treatment compared to the rs1049353-A allele carriers ($F_{(2.74,284.98)}=2.914$, $P=0.038$) (Figure 1(a)). Stratification for gender revealed that this effect is originated by the subgroup of male patients ($F_{(2.78, 270.41)}=5.85$, $P=0.001$) that showed a better outcome in response to citalopram treatment (Figure 1(b)).

When we consider the rs2501431 polymorphism (CNR2 gene), we detected a significant decrease of HDRS scores along time ($F_{(1.23, 264.98)}=137.262$, $P<0.001$) and a significant effect of genotype ($F_{(1,104)}=11.432$, $P=0.001$) but a non significant effect of genotype x time interaction ($F_{(2.74, 284.98)}=0.412$, $P=0.72$). Thus, we observed significant effect of genotype, indicating that the homozygous AA presented higher scores on the HDRS scale than carriers of the G allele along the follow up (Figure 2).

Finally, when we analyzed the effect of the rs324420 polymorphism in the FAAH gene we did not find any significant influence of this polymorphism in the outcome of the depressive episode treated with citalopram (data not shown).

**Discussion**

Our results showed that genetic variability in endocannabinoid receptors could play a role in the understanding of clinical response. Specifically, molecular variation at CNR1 gene seems to differentiate response to citalopram according to sex and the results on CNR2 gene showed a possible involvement of this gene in the severity of the disease.

The analyses of response and remission criteria according to clinical features have shown an effect of suicide attempts on both lack of response at week 4 and remission at week 12. In this sense, it has been proposed that a history of suicide attempts could be a correlate of severe depressive disorder and that suicide attempters could represent a particular subtype of subjects suffering from major depressive disorder (Gilmer et al., 2008; Zisook et al., 2007). Particularly, it has been previously reported that depressive patients with a history of suicidal attempts presented, among other features, a worse response to antidepressant as it has been shown by our study (Claassen et al., 2007; Forman et al., 2004; Hansen et al., 2003; Roy, 1993).

With respect to the effect of the rs1049353 polymorphism (CNR1 gene) on the 12-week clinical follow-up, our results showed that rs1049353-GG presented a better response to antidepressant treatment compared to the rs1049353-A allele carriers. This effect was stronger when the sample was stratified for gender, revealing that GG-men showed better outcome in response to citalopram treatment than A-carrier men or all women. However, it has recently reported that being an rs1049353-G carrier confers an increased risk of resistance to antidepressant treatment, particularly in female patients with major depression and high comorbid anxiety (Domschke et al., 2008). In this sense, it seems that the CNR1 gene is involved in the antidepressant response; however, the contradictory results related to the rs1049353 polymorphism...
will require replication and have to be interpreted with caution. Moreover, it is unclear the role that it would play in relation to differential gender response. In this sense, the results referring to differential response mediated by gender still remain controversial (Serretti et al., 2008; Vermeiden et al., 2010). It might be hypothesized that gender differences in the response could also reflect the differences that are found in the etiology of major depression as physiological and epidemiological studies have shown (Biver et al., 1996; Kendler et al., 2001; Legato, 2010; Nishizawa et al., 1997; Weissman et al., 1996).

As the CB2 receptor has been recently shown to be expressed in CNS, a possible role in brain disorders has still to be established. Thus, no studies have been published in relation to the CNR2 gene and response to antidepressant treatment. However, a recent study found an association between a genetic variant of the rs2501432 polymorphism in the CNR2 gene and increased risk for depression in the Japanese population (Onaivi et al., 2008).

These results suggest study of this gene in both depressive illness and response to antidepressants.

The results of the longitudinal study did not show an influence of the polymorphism analyzed in the CNR2 gene on the response to treatment. However, we observed a significant effect of genotype, indicating that homozygous AA carriers presented higher scores on the HDRS scale than carriers of the G allele during the follow-up. This result shows that AA homozygous carriers present a more severe type of depression than G carriers. Thus, this gene appears to be more associated with severity of outcome of the disease than with response to treatment.
Both CNR1 rs1049353 and CNR2 rs2501431 are synonymous in not altering amino acid residues. The rs1049353 has an A to G change at the third position of codon 453 Thr (National Center for Biotechnology Information (NCBI) Protein Database: NP_057167.2) while in rs2501431 there is an A to G change at the third position of codon 155 Gly (NCBI Protein Database: NM_001841.2). Although synonymous SNPs have often been described as silent or unable to affect functional changes, recent reports indicate that there are several mechanisms by which synonymous mutations could bring about such changes. These studies pointed out the value of analyzing a priori silent polymorphism suggesting that altered translation kinetics of a defined mRNA due to synonymous codon substitutions might drive the in vivo folding of the same polypeptide chain into different conformations (Komar, 2007; Sauna et al., 2007). These may have important implications in biology and in the diagnosis and treatment of human diseases. Alternatively, these polymorphisms might not constitute the actual causative variant, but rather reflect association of other polymorphisms in linkage disequilibrium with this locus.

The FAAH-rs324420 predicts a substitution of threonine for highly-conserved proline residue (129 P/T). Expression studies have shown that individuals carrying this polymorphism may have approximately half of the enzymatic activity of FAAH (Chiang et al., 2004). This reduction in the activity of FAAH might increase levels of the endogenous cannabinoids AEA and 2-AG, thereby increasing the activity of the endocannabinoid system. Animal models show that the inhibition of the FAAH enzyme has antidepressant effects (Gobbi et al., 2005) but there are no studies relating the FAAH gene to response and remission to antidepressant treatment. Moreover, a recent case-control study in the Caucasian population did not find any significant difference between the genotype and allele frequencies of this polymorphism between patients with major depression and healthy controls (Monteleone et al., 2010). Following this line of investigation, our results do not suggest that this polymorphism has a role in the response and remission with citalopram treatment.

Our study has some limitations. Firstly, the relatively small size of our pharmacogenetic sample limits the power to detect small differences. However, we have enough power to detect small–medium size effects. Moreover, we investigated only one SNP of each gene (CNR1, CNR2 and FAAH) and the possible functional effects of the markers are still under investigation. We consider that multiple testing corrections are likely to be excessively exclusive in the context of the present study since the selection of the genetic polymorphisms, the sample size and the analyses performed had a directional hypothesis based on previous findings (Cardon and Bell, 2001). However, it should be taken into account that when we consider correction for multiple testing based on the false discovery rate (Benjamini and Hochberg, 1995), most of our significant results do not survive the correction. Secondly, we have not controlled for a possible placebo effect at response time (fourth week). However, the 12-week longitudinal analysis could overcome, in part, this limitation.

In conclusion, our results suggest a role of the endocannabinoid system in antidepressant response. However, further studies will be needed in order to analyze in depth the molecular variability associated with endocannabinoid genes in larger samples. New data could help to improve knowledge about the treatment response to antidepressants and also the etiology of major depression.

Conflict of interest

The authors declare that they do not have any conflict of interest.

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