OXFORD

International Journal of Neuropsychopharmacology, (2016) 19(4): 1–12

doi:10.1093/ijnp/pyv135
Advance Access Publication December 30, 2015
Research Article

RESEARCH ARTICLE

Glucocorticoid Receptors, Brain-Derived Neurotrophic Factor, Serotonin and Dopamine Neurotransmission are Associated with Interferon-Induced Depression

M Udina, MD, PhD; R Navinés, MD, PhD; E Egmond, PhD Fellow; G Oriolo, MD; K Langohr, PhD; D Gimenez; M Valdés, MD, PhD; E Gómez-Gil, MD, PhD; I Grande, MD, PhD; M Gratacós, MD, PhD; F Kapczinski, MD, PhD; F Artigas, PhD; E Vieta, MD, PhD; R Solà, MD, PhD; R Martín-Santos, MD, PhD

Department of Psychiatry, Hospital Clínic, Institut d'Investigacions Biomèdiques de Barcelona (IDIBAPS), Spain (Drs Udina, Navinés, Egmond, Oriolo, Valdés, Gómez-Gil, Grande, Vieta, and Martín-Santos); Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Barcelona, Spain (Drs Navinés, Grande, Artigas, Vieta, and Martín-Santos); Department of Psychiatry and Clinical Psychobiology, University of Barcelona, Spain (Drs Oriolo, Valdés, Vieta, and Martín-Santos); Liver Section, Parc de Salut Mar, UAB, Barcelona, Spain (Drs Navinés, Gimenez, and Solà); Department of Clinical and Health Psychology, Universitat Autónoma de Barcelona (UAB), Barcelona, Spain (Egmond); Departament d'Estadística, Investigació Operativa, Universitat Politècnica de Catalunya and Research programme in Neurosciences, Hospital del Mar Medical Research Institute (IMIM), Barcelona, Spain (Dr Langohr); Center of Genomic Regulation, Parc de Recerca Biomèdica de Barcelona, Barcelona, Spain (Dr Gratacós); National Institute for Translational Medicine, Hospital de Clinicas de Porto Alegre, Federal University of Rio Grande do Sul, Porto Alegre, Brazil (Dr Kapczinski); Department of Neurochemistry and Neuropharmacology, Institute d'Investigacions Biomèdiques de Barcelona (IBB-CSIC-IDIBAPS), Spain (Dr Artigas)

Correspondence: Rocio Martin-Santos, MD, PhD, Head of Section Department of Psychiatry and Psychology, Hospital Clínic, UB, IDIBAPS, CIBERSAM. Villarroel, 170, 08036-Barcelona, Spain (rmsantos@clinic.ub.es)

Abstract

Background: The role of inflammation in mood disorders has received increased attention. There is substantial evidence that cytokine therapies, such as interferon alpha (IFN-alpha), can induce depressive symptoms. Indeed, proinflammatory cytokines change brain function in several ways, such as altering neurotransmitters, the glucocorticoid axis, and apoptotic mechanisms. This study aimed to evaluate the impact on mood of initiating IFN-alpha and ribavirin treatment in a cohort of patients with chronic hepatitis C. We investigated clinical, personality, and functional genetic variants associated with cytokine-induced depression.

Methods: We recruited 344 Caucasian outpatients with chronic hepatitis C, initiating IFN-alpha and ribavirin therapy. All patients were euthymic at baseline according to DSM-IV-R criteria. Patients were assessed at baseline and 4, 12, 24, and 48 weeks after treatment initiation using the Patient Health Questionnaire (PHQ), the Hospital Anxiety and Depression Scale (HADS), and the Temperament and Character Inventory (TCI). We genotyped several functional polymorphisms of

Received: July 20, 2015; **Revised:** November 24, 2015; **Accepted:** December 11, 2015

interleukin-28 (*IL28B*), indoleamine 2,3-dioxygenase (*IDO-1*), serotonin receptor-1A (*HTR1A*), catechol-O-methyl transferase (COMT), glucocorticoid receptors (*GCR1* and *GCR2*), brain-derived neurotrophic factor (BDNF), and FK506 binding protein 5 (FKBP5) genes. A survival analysis was performed, and the Cox proportional hazards model was used for the multivariate analysis.

Results: The cumulative incidence of depression was 0.35 at week 24 and 0.46 at week 48. The genotypic distributions were in Hardy-Weinberg equilibrium. Older age (p = 0.018, hazard ratio [HR] per 5 years = 1.21), presence of depression history (p = 0.0001, HR = 2.38), and subthreshold depressive symptoms at baseline (p = 0.005, HR = 1.13) increased the risk of IFN-induced depression. So too did TCI personality traits, with high scores on fatigability (p = 0.0037, HR = 1.17), impulsiveness (p = 0.0200 HR = 1.14), disorderliness (p = 0.0339, HR = 1.11), and low scores on extravagance (p = 0.0040, HR = 0.85). An interaction between *HTR1A* and COMT genes was found. Patients carrying the G allele of *HTR1A* plus the Met substitution of the COMT polymorphism had a greater risk for depression during antiviral treatment (HR = 3.83) than patients with the CC (*HTR1A*) and Met allele (COMT) genotypes. Patients carrying the *HTR1A* CC genotype and the COMT Val/Val genotype (HR = 3.25) had a higher risk of depression than patients with the G allele (*HTR1A*) and the Val/Val genotype. Moreover, functional variants of the *GCR1* (GG genotype: p = 0.0436, HR = 1.88) and *BDNF* genes (Val/Val genotype: p = 0.0453, HR = 0.55) were associated with depression.

Conclusions: The results of the study support the theory that IFN-induced depression is associated with a complex pathophysiological background, including serotonergic and dopaminergic neurotransmission as well as glucocorticoid and neurotrophic factors. These findings may help to improve the management of patients on antiviral treatment and broaden our understanding of the pathogenesis of mood disorders.

Keywords: 5HT1A, COMT, depression, GCR1, genetic, hepatitis C, inflammation pathways, personality traits, risk factors

Background

The role of inflammation in mood disorders has received increased attention (Dowlati et al., 2010; Moylan et al., 2013; Zhang et al., 2015). Indeed, depression is prevalent in patients with inflammatory medical conditions, including cardiovascular diseases, rheumatoid arthritis, autoimmune disorders, obesity, or chronic hepatitis C (CHC; Evans et al., 2005). Moreover, there is substantial evidence that cytokine therapies can induce depressive symptoms (Martín-Santos et al., 2008; Raison et al., 2009; Huckans et al., 2015). Not only is antiviral treatment for CHC associated with a high incidence of fatigue, insomnia, irritability and low mood, but full major depressive episodes (MDE) are also observed in around 25% of patients (Udina et al., 2012).

Given that some patients are more likely to present depression during treatment with cytokines such as interferon alpha (IFN-alpha), research has focused on identifying social, clinical, and biological factors that may lead to neuropsychiatric side effects (Smith et al., 2012). Previous studies and meta-analyses have shown several risk factors for IFN-induced depression, including clinical factors such as subthreshold depressive symptoms at baseline, a history of depression, and certain personality traits, as well as sociodemographic factors such as female gender and low educational level (Raison et al., 2005a; Castellvi et al., 2009; Udina et al., 2012; Martin-Santos et al., 2015).

Although the exact neurobiological basis of cytokine-induced depression is not known, there is evidence that administration of an exogenous cytokine such as IFN-alpha modulates the function of cytokines such as interleukin-6 (IL-6) or interleukin-28 (IL-28; Fernández-Rodriguez et al., 2013). In turn, this may result in both the treatment-induced antiviral response (Jimenez-Sousa et al., 2013) and antiviral-induced neuropsychiatric side effects (Udina et al., 2013). Cytokine-induced alterations within the central nervous system (CNS) may depend on various mechanisms, including the passage of cytokines through leaky regions of the blood-brain barrier and activation of nervous pathways (Anisman, 2009). A high concentration of pro-inflammatory cytokines with activity in the CNS may modulate monoamine neurotransmission (Raison et al., 2009), alter the glucocorticoid axis, and dysregulate apoptotic mechanisms (Cai et al., 2005; Asnis and De La Garza, 2006; Raison et al., 2010a), which are factors related with the onset of clinical depression (Anisman, 2009). Specifically, immunological mechanisms may modulate the function of indoleamine 2,3-dioxygenase (IDO-1; Kim et al., 2012), serotonin receptors (5HT1A; Cai et al., 2005; Le Francois et al., 2008), and catechol-O-methyl transferase (COMT; Tchivileva et al., 2009), and thereby alter serotonin and dopamine neurotransmission in certain brain regions involved with the pathogenesis of depression (Frisch et al., 1999). Equally, chronic activation of the immune system is known to cause increased plasma cortisol levels by desensitizing glucocorticoid receptors (GCR1 and GCR2; Cai et al., 2005; Silverman and Sternberg, 2012) that may be modulated by proteins such as FK506-binding protein 5 (FKBP5), which is a co-chaperone of the glucocorticoid receptors (Menke et al., 2013; Höehne et al., 2014). Lastly, high concentrations of cytokines in the CNS have been associated with dysregulation of brain apoptotic mechanisms, such as the brain-derived neurotrophic factor (BDNF), and with increases in the levels of several oxidative factors (Gibney et al., 2013).

In view of this evidence, the study of biological factors that may lead to IFN-induced neuropsychiatric symptoms is of potential interest, as it may help to improve the management of patients receiving antiviral treatment and illuminate the pathogenesis of depression. Thus, we aimed to investigate the association between IFN-induced depression and functional genetic variants in immunological factors (IL28), monoamine neurotransmission (IDO, 5HT1A, COMT), and the glucocorticoid axis (GCR1, GCR2, FKBP5), and neurotrophic factors (BDNF) in patients with CHC.

Methods

Selection of Patients

All consecutive Caucasian outpatients with CHC infection who were candidates for combination treatment with pegylated interferon-alpha (PegIFN alpha) and ribavirin (RBV) were recruited between 2005 and 2009 at the Liver Unit of a general teaching hospital (Parc de Salut Mar) in Barcelona. The exclusion

criteria for the study were as follows: unable to understand the Catalan or Spanish languages, the presence of concomitant liver disease, decompensated cirrhosis or hepatocarcinoma, current drug or alcohol abuse, and any depressive episode within a 24-week period before starting treatment. The sample in this study partially overlapped with that described in a previous article (Udina et al., 2013). The institutional review board at our hospitals (Parc de Salut Mar and Hospital Clínic) approved the study protocol and all participants provided written informed consent, including consent for genetic study.

Study Design

This study used a prospective cohort design. All patients were interviewed at baseline using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; First et al., 1995) to assess their current and past history of psychiatric disorders. At baseline, all patients also completed the Patient Health Questionnaire (PHQ; Spitzer et al., 1999), the Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith, 1983), and the revised Temperament and Character Inventory (TCI-R; Cloninger and Svrakic, 1997).

Patients started treatment with PegIFN alpha-2a (180 μg subcutaneously, per week) and RBV (800–1200 mg orally, per day) for 24 or 48 weeks according to the Hepatitis C virus (HCV) genotype. After 4, 12, 24, and 48 weeks of treatment, patients again completed the HADS and the PHQ. If, at any point during the study, patients met the criteria for any depressive disorder according to the PHQ they were referred to a senior psychiatrist on the same day. After a full clinical assessment, the psychiatrists confirmed or rejected the diagnosis of depression, and initiated psychopharmacological treatment if needed.

Clinical Assessment

The validated Spanish version of the PHQ is designed to screen depressive and other psychiatric disorders in primary care and other medical settings (Diez-Quevedo et al., 2001; Navines et al., 2012). The items on the PHQ correspond to the symptom criteria for each disorder as outlined in the DSM-IV. The depression module (PHQ-9) has nine items with four response options: "Not at all," "Several days," "More than half the days," and "Nearly every day." We have also developed a categorical algorithm in which major depression is diagnosed if five or more of these criteria have been present at least "more than half the days" in the past 2 weeks, and if one of the symptoms is depressed mood or anhedonia; other depressive disorders are diagnosed if two, three, or four depressive symptoms have been present at least "more than half the days" in the past 2 weeks, and if one of the symptoms is depressed mood or anhedonia. The PHQ has good accuracy (95.2%) for detecting any depressive disorder in patients with CHC (Navines et al., 2012). Moreover, the diagnosis of any depressive disorder through the PHQ has convergent validity with the scores of the depression subscale of the HADS (Navines et al., 2012).

The HADS is a self-administered questionnaire with 14 items scored on a four-point Likert scale over depression and anxiety subscales (HADS-D and HADS-A). It is particularly useful for patients with comorbid medical conditions, as it excludes somatic or vegetative symptoms from the depression subscale. In this study, the validated Spanish version of the HADS was used (Herrero et al., 2003).

The TCI-R (Cloninger and Svrakic, 1997) is a 240-item, five-point Likert scale, self-report questionnaire that measures seven personality dimensions. The biopsychosocial model by Cloninger et al. (1993) proposed that personality is formed by four temperament dimensions (harm avoidance, novelty seeking, reward dependence, and persistence) and three character dimensions (self-directedness, cooperativeness, and self-transcendence). Each dimension has three to five subscales measuring specific personality traits. The validated Spanish version of the TCI-R questionnaire (Gutierrez-Zotes et al., 2004) was used in this study.

HCV RNA levels were measured by COBAS AMPLICOR HCV (Roche) at weeks 4, 12, and 24 and at week 48 in patients with genotype 1, and at week 24 after completion of antiviral treatment to evaluate sustained virological response.

Genetic Variant Selection

We selected one variant in each of the following genes: interleukin-28 (IL28B; rs8099917); indoleamine 2,3-dioxygenase (*IDO-1*; rs3824259); 5-hydroxytryptamine (serotonin) receptor 1A (*HTR1A*; rs6295); COMT (rs4860); nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor; *NR3C1*; rs6196); nuclear receptor subfamily 3, group C, member 2 (NR3C2; rs5522); BDNF (rs6265); and FK506 binding protein 5 (*FKBP5*; rs1360780). To do so, we selected eight single nucleotide polymorphisms (SNPs) with a minor allele frequency higher than 10% in Caucasian populations that had previously been reported in the literature to be involved in psychiatric disorders or to be potentially functional in a public dbSNP database (http://www.ncbi.nlm.nih.gov/SNP/). Overall descriptions of each polymorphism are shown in Table 1.

SNP Genotyping

SNPs were genotyped using a custom VeraCode GoldenGate Genotyping Assay (Illumina) according to the manufacturer's protocols (http://www.illumina.com). We used the Bead Studio software (Illumina) to process raw data, and genotypes were inferred via a genotyping cluster. For statistical analyses, we selected the SNPs with a minimum genotyping rate of 95% and in Hardy–Weinberg equilibrium ($p > 0.05$; see Table 1).

Statistical Analysis

To study possible risk factors for the incidence of any depressive disorder, we used a survival analysis approach; a logistic model was inappropriate since the time under study was different between patients. Instead, the time from treatment start until the onset of the depression was chosen as the response variable of interest. Hence, right-censored data were given in the case of patients without depression during the study period, and the time to incidence was interval-censored between the last medical visit without depressive syndrome and the first after the onset, in all other cases. At a univariate level, the role of categorical variables was studied with the Fleming–Harrington test for interval-censored data based on a score vector distribution (Gómez et al., 2009), and the role of continuous variables by univariate Weibull regression models. All variables with a corresponding p-value below 0.25 were initially considered for the multivariate Weibull regression model, which is equivalent to the Cox proportional hazards model. The final model was obtained following the variable selection approach proposed by Hosmer and Lemeshow (2000). Possible interactions were considered between all variables of the resulting model. The cumulative incidence of depression at weeks 24 and 48 was

Table 1. Description of the Genetic Variants Included in the Study

dbSNP ID*	Gene	Chr.	Position**	Alleles	Function/Location in gene	Genotyping Rate (%)	MAF	HWE
rs6295	HTR1A	5	63294321	C/G	5' upstream	99.1	0.47	0.33
rs4680	COMT	22	18331271	G/A	Coding non-synonymous Val158Met	100.0	0.48	0.2
rs6196	NR3C1	5	142641683	A/G	Coding synonymous	99.7	0.10	1.0
rs5522	NR3C2	4	149576925	A/G	Coding non-synonymous Val180Ile	99.7	0.09	0.75
rs6265	BDNF	11	27636492	C/G	Coding non-synonymous Val66Met	100	0.47	0.33
rs3824259	IDO	8	39888750	T/G	5' upstream	100	0.48	0.33
rs1360780	FKBP5	6	35715549	C/T	Intronic	100	0.29	0.29
rs8099917	IL28B	19	44435005	T/G	5' upstream	99.7	0.21	0.62

*Based in dbSNP 135 (http://www.ncbi.nlm.nih.gov/projects/SNP)
**Mapped to Genome Build 36.3
BDNF = brain-derived neurotrophic factor; Chr = chromosome; COMT = Catechol-O-methyl transferase; FKBP5 = FK506 binding protein 5; HWE = Hardy-Weinberg equilibrium; HTR1A = 5-hydroxytryptamine (serotonin) receptor 1A; IDO = indoleamine 2,3-dioxygenase; IL28B = interleukin-28; MAF = minor allele frequency; NR3C1 = nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor); NR3C2 = nuclear receptor subfamily 3, group C, member 2.

estimated using the Turnbull estimator for interval-censored data (Turnbull, 1976). All statistical analyses were carried out with the statistical software package R (The R Foundation for Statistical Computing), version 3.2.1; in particular, we used the contributed packages survival (https://cran.r-project.org/web/packages/survival/index.html), FHtest (https://cran.r-project.org/web/packages/FHtest/index.html), and Icens (http://www.bioconductor.org/packages/release/bioc/html/Icens.html).

Results

Sample Characteristics

The clinical and sociodemographic characteristics of the 344 patients included in the study are displayed in Table 2.

Incidence of IFN-Induced Depression

The cumulative incidence of depression was 0.35 at week 24 and 0.46 at week 48 (see Figure 1). Some patients received treatment over 24 weeks and others over 48 weeks, depending on virus genotype and other medical criteria: the mean and median time under treatment were 37.3 and 47.8 weeks, respectively. The mean HADS-D score rate at the time of the first diagnosis of depression was 8.7 (standard deviation = 4.2). No suicidality was detected in the sample during the time of the study.

Predictive Variables of IFN-Induced Depression

Table 2 shows all the variables that were evaluated and the results of univariate analysis. All variables with a corresponding *p*-value below 0.25 were initially included in the multivariate analysis.

The multivariate model showed that older age ($p = 0.018$, HR associated to a 5-year increase = 1.21), a history of depression ($p = 0.0001$, HR = 2.38), and subthreshold depressive symptoms at baseline ($p = 0.0050$, HR = 1.13) increased the risk of IFN-alpha–induced depression. Concerning personality traits measured with the TCI-R, high scores on fatigability ($p = 0.0037$, HR associated to a 5-point increase = 1.17), impulsiveness ($p = 0.0200$, HR associated to a 5-point increase = 1.14), disorderliness ($p = 0.0339$, HR associated to a 5-point increase = 1.11), and low scores on extravagance ($p = 0.0040$, HR associated to a 5-point increase = 0.85) were risk factors for depression during antiviral treatment. A history of anxiety ($p = 0.0955$) and human immunodeficiency virus (HIV) infection ($p = 0.0781$) showed a trend toward an association with depression (see Table 3).

With regard to genetic polymorphisms, the following were risk factors for depression during antiviral treatment: being homozygous for the A allele of the GCR1 polymorphism ($p = 0.029$, HR = 1.88) and the genotype GG of the BDNF polymorphism ($p = 0.0453$ HR = 1.53; see Table 3).

Interaction Between Variables

In addition, we found an interaction between the *HTR1A* and COMT genes: patients carrying the *HTR1A* G allele had a higher risk of depression than those with the CC genotype if they also carried the A allele (Met/Met or Val/Met) of the COMT polymorphism (HR = 3.83). The G allele was not a risk factor in patients with the GG genotype (Met/Met) of COMT (HR = 0.45). Among patients with the *HTR1A* CC genotype, those patients carrying the COMT GG genotype were at a higher risk of depression during antiviral treatment than patients carrying the A allele (HR = 3.25), whereas the GG allele was not a risk factor in patients with the HTR1AC G genotype (HR = 0.39; see Table 3 and Figure 2). No other interactions were found between any other variables studied.

Discussion

We evaluated the impact on mood of initiating IFN-alpha and ribavirin treatment in a cohort of 344 euthymic patients with CHC. We found a higher incidence of depression in elderly patients, those with a history of depression, and those with depressive symptoms at baseline, as well as with certain personality traits. In addition, significant associations were found with functional variants of genes, such as *GCR1* and BDNF, and with combinations of *HTR1A* and COMT genes. Notably, the incidence of depression was higher in patients carrying both the Met substitution in COMT and the G allele in *HTR1A* and in those carrying both the Val/Val substitution in COMT and the CC genotype *HTR1A*. To our knowledge, this is the first report of an association between a *GCR1* gene polymorphism and IFN-alpha treatment-related depression.

The cumulative incidence of depression during antiviral treatment was similar to previous reports (Robaeys et al., 2007; Castellvi et al., 2009). Some authors, however, have observed a lower incidence of IFN-induced depression (Schäfer et al., 2007; Raison et al., 2010b), probably due to the exclusion of patients with a history of depression or concomitant viral infections such as HIV.

According to our results, a previous history of depression and the presence of subthreshold depressive symptoms at baseline were both predictors of IFN-induced depression. A history of anxiety and HIV infection only showed a trend toward

Table 2. Sample description and univariate analysis of variables

	Whole sample n = 344	Euthymic n = 209	Depression n = 135	
Qualitative variables	n (%)	n (%)	n (%)	*p*-Value
Gender				
Female	113 (32.8)	69 (33)	44 (32.6)	0.962
Male	231 (67.2)	140 (67)	91 (67.4)	
Civil status				
Engaged/married	239 (69.5)	145 (69.4)	94 (69.6)	0.996
Single	62 (18)	37 (17.7)	25 (18.5)	
Widow/divorced	43 (12.5)	27 (12.9)	16 (11.9)	
Education				
Primary	151 (43.9)	80 (38.3)	71 (52.6)	0.005
Medium	137 (39.8)	92 (44)	45 (33.3)	
Superior	56 (16.3)	37 (17.7)	19 (14.1)	
Immigrant				
No	269 (78.2)	165 (78.9)	104 (77)	0.706
Yes	75 (21.8)	44 (21.1)	31 (23)	
Job				
Active	257 (75.4)	161 (77.8)	96 (71.6)	0.169
Unemployed/retired	84 (24.6)	46 (22.2)	38 (28.4)	
Viral Genotype				
1	194 (56.4)	122 (58.4)	72 (53.3)	0.410
2	16 (4.7)	12 (5.7)	4 (3)	
3	98 (28.5)	57 (27.3)	41 (30.4)	
4	36 (10.5)	18 (8.6)	18 (13.3)	
HIV infection				
No	275 (79.9)	179 (85.6)	96 (71.1)	0.004
Yes	69 (20.1)	30 (14.4)	39 (28.9)	
Methadone treatment				
No	330 (96.2)	199 (95.7)	131 (97)	0.396
Yes	13 (3.8)	9 (4.3)	4 (3)	
Depression History				
No	212 (62.7)	155 (76)	55 (42.5)	0.000
Yes	126 (37.3)	49 (24)	77 (57.5)	
Anxiety History				
No	248 (73.4)	163 (79.9)	85 (63.4)	0.001
Yes	90 (26.6)	41 (20.1)	49 (36.6)	
Cocaine abuse history				
No	252 (74.6)	158 (77.5)	94 (70.1)	0.206
Yes	86 (25.4)	46 (22.5)	40 (29.9)	
Alcohol abuse history				
No	273 (80.8)	171 (83.8)	102 (76.1)	0.060
Yes	65 (19.2)	33 (16.2)	32 (23.9)	
Opioid abuse history				
No	242 (71.6)	154 (75.5)	88 (65.7)	0.116
Yes	96 (28.4)	50 (24.5)	46 (34.3)	
General psychiatric history				
No	180 (52.8)	126 (61.2)	54 (40)	0.000
Yes	161 (47.2)	80 (38.8)	81 (60)	
Family psychiatric history				
No	219 (64.6)	134 (65)	85 (63.9)	0.797
Yes	120 (35.4)	72 (35)	48 (36.1)	
Antidepressants at baseline				
No	302 (87.8)	189 (90.4)	113 (83.7)	0.064
Yes	42 (12.2)	20 (9.6)	22 (16.3)	
Quantitative variables	Mean (SD)	Mean (SD)	Mean (SD)	
Age	44 (10.4)	43.6 (10.4)	44.8 (10.3)	0.219
HADS depression baseline	2.5 (2.8)	1.9 (2.2)	3.5 (3.2)	0.000
Body mass index	25.1 (4.5)	25.3 (4.2)	24.7 (4.9)	0.403
N° previous IFN treatments	1.2 (0.5)	1.2 (0.6)	1.2 (0.5)	0.730

Table 2. *Continued*

Quantitative variables	Whole sample n = 344 Mean (SD)	Euthymic n = 209 Mean (SD)	Depression n = 135 Mean (SD)	
HADS anxiety baseline	4.5 (3.3)	3.9 (3.1)	5.5 (3.4)	0.000
TCI-R Novelty Seeking	50.3 (9.9)	50.3 (9.7)	50.2 (10.3)	0.684
Exploratory excitability	48.9 (10.4)	50.1 (10.2)	47 (10.4)	0.010
Impulsiveness	50.7 (10.2)	49.8 (9.8)	52.3 (10.7)	0.035
Extravagance	51.2 (10.2)	51.6 (10.2)	50.5 (10.1)	0.163
Disorderliness	49.9 (10.5)	49.2 (9.7)	51.2 (11.6)	0.151
TCI-R Harm Avoidance	52.6 (10.4)	50.9 (10.3)	55.4 (9.9)	0.000
Anticipatory worry	51 (9.9)	49.6 (10)	53.3 (9.3)	0.001
Fear of uncertainty	50.9 (10.6)	50.4 (10.4)	51.7 (10.7)	0.213
Shyness	51.8 (10.1)	51 (9.7)	53 (10.6)	0.071
Fatigability	54.2 (11.4)	51.8 (10.7)	58 (11.4)	0.000
TCI-R Reward Dependence	48.8 (9.5)	48.9 (8.8)	48.5 (10.7)	0.846
Sentimentality	47.9 (10.7)	47.7 (10)	48.2 (11.7)	0.570
Openness to warm communication	49 (13.7)	49 (12.6)	49 (15.2)	0.918
Attachment	49.3 (9.9)	49.2 (9.8)	49.4 (10.3)	0.886
Dependence	49.8 (10.6)	50.6 (10.4)	48.5 (10.8)	0.104
TCI-R Persistence	48.6 (10.9)	48.4 (10.5)	49 (11.5)	0.509
Eagerness of effort	49.3 (11.1)	49.6 (10.8)	49 (11.5)	0.854
Work hardened	47.7 (10.3)	47.7 (10.4)	47.7 (10.3)	0.954
Ambitious	49.1 (12.1)	48.6 (11.4)	49.9 (13.1)	0.330
Perfectionism	49 (10.6)	48.6 (10.6)	49.8 (10.7)	0.250
TCI-R Self-directedness	50.4 (10.5)	52.3 (10)	47.5 (10.7)	0.000
Responsibility	50.1 (11.3)	51.9 (10.3)	47.3 (12.3)	0.000
Purposefulness	49.3 (11.4)	50.6 (10.6)	47.2 (12.3)	0.007
Resourcefulness	50 (10.9)	51.1 (9.9)	48.3 (12.1)	0.019
Self-acceptance	50.3 (10.4)	51.5 (9.7)	48.4 (11.1)	0.014
Enlightened second nature	51.2 (10.9)	52.4 (11)	49.4 (10.5)	0.027
TCI-R Cooperativeness	49.5 (9.8)	50.8 (10)	47.5 (9.1)	0.010
Social acceptance	50 (9.8)	51.1 (9.7)	48.1 (9.7)	0.010
Empathy	49.6 (9.6)	50.1 (9.3)	48.8 (9.9)	0.303
Helpfulness	48.7 (9.7)	49.6 (9.5)	47.3 (9.9)	0.066
Compassion	49.2 (10.3)	50.1 (9.9)	47.8 (10.8)	0.080
Poor-hearted consciousness	50.6 (11.2)	51.5 (11)	49.3 (11.4)	0.080
TCI-R Self-Transcendence	51.3 (11)	50.7 (11)	52.2 (11.1)	0.218
Self-forgetful	50.6 (11.1)	50 (10.9)	51.5 (11.3)	0.231
Transpersonal identification	50.8 (10.9)	50.6 (10.6)	51.1 (11.4)	0.511
Spiritual acceptance	51.8 (11)	51.1 (10.8)	52.8 (11.4)	0.264

HADS, Hospital Anxiety and Depression Scale; INF, interferon; SD, standard deviation; TCI-R, Temperament and Character Inventory, revised

association. These have consistently been reported as risk factors in previous clinical studies and meta-analyses (Raison et al., 2005b; Castellvi et al., 2009; Udina et al., 2012).

Our finding of an association between certain personality traits and IFN-induced depression was also interesting. Previous studies have reported that high harm-avoidance, low self-direction, and high neuroticism may be related to IFN-induced depression (Lotrich et al., 2007; Castellvi et al., 2009). In our study, all traits associated with depression (fatigability, impulsiveness, disorderliness, extravagance) were from two temperamental dimensions of the TCI-R: harm avoidance and novelty seeking. Temperamental dimensions assess differences in automatic emotional responses to stimuli, define personality style, and are influenced by different neurotransmitter systems. Harm avoidance refers to a tendency to shyness and anxiety, and has been associated with serotonergic function (Tuominen et al., 2013), while novelty seeking reflects reward system activity and has been related to mesolimbic and mesocortical dopaminergic projections (Buskila et al., 2004; Tournier et al., 2013). However, despite these overall trends, we found no interactions between these variables and the functional polymorphisms examined.

The current study also found an association between the *HTR1A* polymorphism and IFN-alpha induced depression. The results are in agreement with those reported by Kraus et al. (2007), where patients carrying the G allele of the *HTR1A* gene were at a higher risk of depression during antiviral treatment. Moreover, the same polymorphism has previously been associated with panic disorder, neuroticism, depression, and reduced response to antidepressant treatment (Le Francois et al., 2008). We found that the G allele in *HTR1A* only predicted depression in patients also carrying the A allele (Met substitution) in the COMT gene (n = 141). Interestingly, a small group of patients (n = 33) carrying the GG genotype in the COMT polymorphism (Val/Val substitution) together with the CC genotype in the *HTR1A* polymorphism also showed a higher incidence of depression. Importantly, both patient subgroups had more than a three-fold higher risk of depression during interferon treatment than those without this combination. The risk for these patients

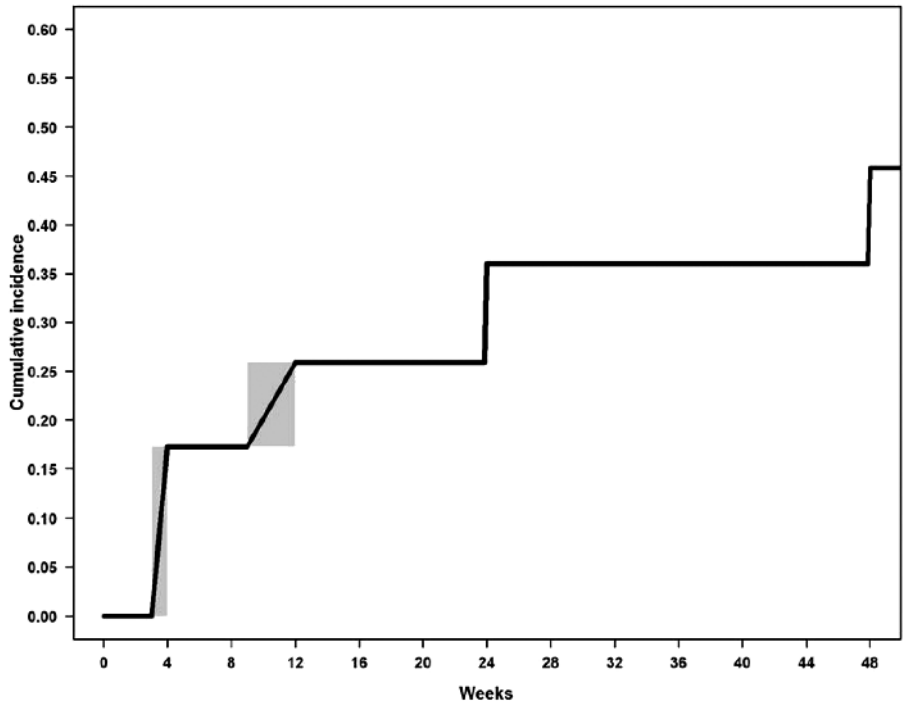

Figure 1. Estimated cumulative incidence of depression during antiviral treatment. Shaded areas indicate that the estimation of the cumulative incidence is not defined in the corresponding intervals, but only known to increase monotonically.

Table 3. Multivariate Analysis

	Value	Standard error	CI (2.5- 97.5)		*p*	HR
Age	0.0652	0.0209	0.106	0.024	0.0018	1.21*
HIV infection	-0.7146	0.4057	0.080	-1.510	0.0781	1.51
History of mood disorder	-1.5142	0.3944	-2.287	-0.741	0.0001	2.38
History of anxiety disorder	-0.6375	0.3824	-1.387	0.112	0.0955	1.44
HADS score at baseline	-0.2195	0.0781	-0.373	-0.066	0.0050	1.13
TCI HA: Fatigability	-0.0552	0.0190	-0.092	-0.018	0.0037	1.17**
TCI NS: Impulsiveness	-0.0468	0.0201	-0.086	-0.007	0.0200	1.14**
TCI NS: Extravagance	0.0551	0.0192	0.018	0.093	0.0040	0.85**
TCI NS: Disorderliness	0.0374	0.0176	-0.072	-0.003	0.0339	1.11**
5HT1A: G	-2.3443	0.5966	-3.514	-1.175	<0.0001	-
COMT: GG (Val/Val)	-2.0613	0.9225	-3.869	-0.253	0.0254	-
GCR1: G	1.0495	0.5201	0.030	2.069	0.0436	0.55
BDNF: GG (Val/Val)	-0.7460	0.3726	-1.476	-0.016	0.0453	1.53
5HT1A * COMT	3.7231	1.0943	1.578	5.868	0.0007	
- Val/Val: G vs. CC						0.45
- Met: G vs. CC						3.83
- CC:Val/Val vs. Met						3.25
- G:Val/Val vs. Met						0.39

Variables included in the analysis and with $p < 0.1$.
*Hazard ratio associated to a 5 years' increase
**Hazard ratios associated to a 5 points' increase
BDNF, brain-derived neurotrophic factor; CI, confidence interval; COMT, catechol-O-methyl transferase; HA, harm avoidance; HADS, Hospital Anxiety and Depression Scale; HR, hazard ratio; NS, novelty seeking; TCI, Temperament and Character Inventory

was even higher than in patients with a history of depression (HR 2.35), which is the most replicated and strongest risk factor for developing IFN-induced depression (Castellvi et al., 2009; Fransen Van De Putte et al., 2009; Udina et al., 2012).

Overall, these results suggest that both serotonin and dopamine pathways are important in the development of depression during antiviral treatment for CHC. On the one hand, the G allele of *HTR1A* may alter transcription in serotonergic and non-serotonergic neurons and confers a higher susceptibility to depression and suicide (Lemonde et al., 2003). Specifically, the G allele up-regulates 5-HT_{1A} autoreceptor expression, which reduces serotonergic function in the forebrain and may also alter dopaminergic neurotransmission (Vollenweider et al., 1999; Albert et al., 2011). Furthermore, 5-HT_{1A} receptors modulate the activity of dopaminergic neurons in the ventral tegmental area and regulate mesocortical dopamine release (Diaz-Mataix et al.,

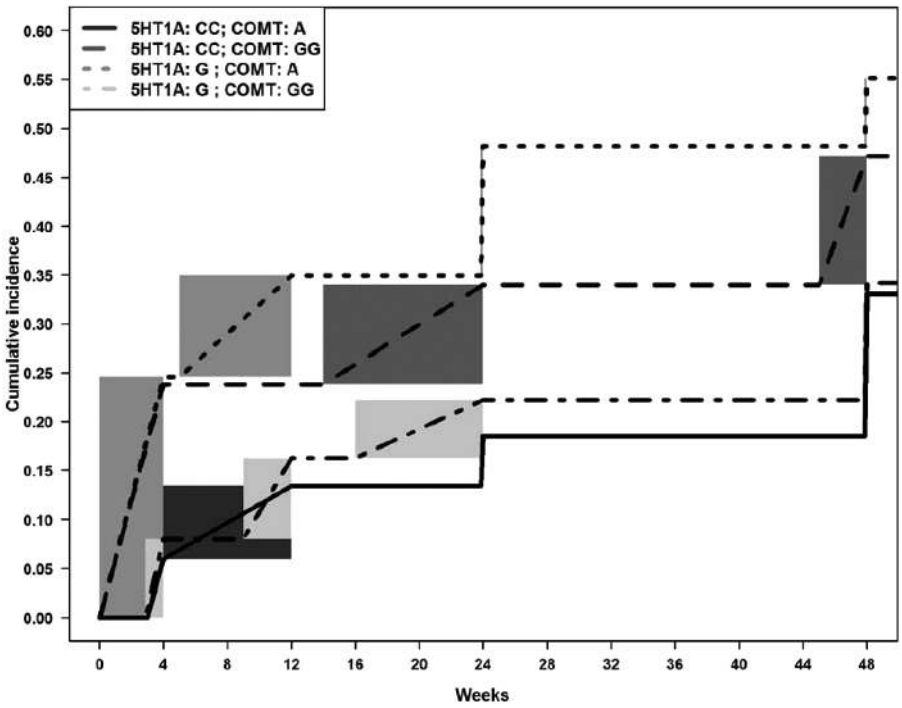

Figure 2. Estimated cumulative incidence of depression according to genotypes of *HTR1A* and COMT genes. Shaded areas indicate that the estimation of the cumulative incidence is not defined in the corresponding intervals, but only known to increase monotonically.

2005). Capuron et al. (2012) also reported alterations in dopaminergic neurons after IFN-alpha administration that might be associated with anhedonia, fatigue, and other behavioral changes. On the other hand, dopamine plays a critical role in prefrontal cortex function in an inverted U-shaped manner, with both too much and too little dopamine being associated with a higher risk of depression (Meyer-Lindenberg et al., 2005; Honea et al., 2009). Such a phenomenon might explain the interaction between the COMT and *HTR1A* polymorphisms. The A allele (Met/Met or Val/Met) in the COMT polymorphism is related to lower activity of the enzyme, and therefore probably to a higher concentration of dopamine in the prefrontal cortex (Chen et al., 2004). Moreover, the G allele of the *HTR1A* polymorphism may be associated with an up-regulation of $5HT_{1A}$ receptor expression in the prefrontal cortex and a further release of dopamine. Therefore, patients carrying both alleles (COMT A and *HTR1A* G) may develop abnormally high concentrations of dopamine in the prefrontal cortex, leading to a higher risk of IFN-induced depression. Alternatively, patients who simultaneously carry the GG genotype (Val/Val) in the COMT gene and the CC genotype in the *HTR1A* polymorphism may have abnormally low concentrations of dopamine that also result in a higher risk for depression. This theory is biologically plausible because patients with the other genotypes would have intermediate levels of dopamine and would therefore be at a lower risk of developing depression.

A novel association between GCR1 and antiviral-induced depression is worthy of note. Genetic variants of the *GCR1* gene have been associated with changes in corticosteroid resistance (Krupoves et al., 2011), major depressive disorders (Szczepankiewicz et al., 2011; Galecka et al., 2013), and a predominance of depression in the course of bipolar disorder (Szczepankiewicz et al., 2011). This observation may be related to the cytokine-induced activation of the hypothalamic-pituitary-adrenal axis, a physiological condition often related to depression (Vreeburg et al., 2009; Lok et al., 2012). Specifically, chronic administration of IFN-alpha is associated with a desensitization of the hypothalamic-pituitary-adrenal axis, leading to a reduced negative feedback regulation and increased plasma cortisol levels (Capuron et al., 2003; Cai et al., 2005; Silverman and Sternberg, 2012). Hence, a reduction in glucocorticoid receptor mRNA levels has been reported in patients with major depression (Webster et al., 2002; Perlman et al., 2004). Interestingly, IFN-alpha markedly down-regulated HTR1A and GCR1 receptors in cell lines *in vitro*, an effect that was attenuated by the administration of antidepressants (Cai et al., 2005). In this line, clinical studies showed that prophylactic administration of antidepressants reduces the incidence of IFN-induced depression (Udina et al., 2014).

Lastly, we found an association between the BDNF polymorphism and depression during antiviral treatment. It is possible that activation of cytokines and inflammatory mediators in the brain could produce excitotoxicity and alterations in neurotrophic factors. Indeed, cytokines may stimulate the release of glutamate from glial cells and alter glutamate reuptake through glutamate transporters (Muller and Schwarz, 2007). The subsequent excessive activation of N-methyl-D-aspartate receptors by glutamate could then cause oxidative stress by producing reactive species of oxygen and nitrogen, thereby altering the expression of trophic factors such as BDNF (Muller and Schwarz, 2007; Capuron and Miller, 2011). According to our results, the Val genotype of BDNF was associated with IFN-induced depression. In addition, this genotype was also associated with higher neurotic scores and with anxiety- and depression-related personality traits, suggesting a relationship with depression (Sen et al., 2003; Lang et al., 2005). Conversely, some studies have reported an association between the Met genotype and increased serum concentrations of BDNF (Lang et al., 2009) and with a risk factor for anxiety disorders, major depression (Jiang et al., 2005), and even INF-induced depression (Lotrich et al., 2012). Gratacos et al. (2007) reported that the Met allele increases the risk of

eating disorders and schizophrenia, while reducing the risk of substance-related disorders. Castren et al. (2007) showed that increased BDNF concentrations in the hippocampus mimic the effects of antidepressants on behavior, but that injection of BDNF into the mesolimbic dopamine pathway produces an opposing response. As described in previous studies and meta-analyses, the association between the BDNF Val66Met polymorphism and different psychiatric conditions is complex (Groves, 2007; Verhagen et al., 2010). It is likely that neurotrophic factors themselves do not control mood, but that they may be crucial to the modulation of neural networks involved in the pathogenesis of depression, including serotonergic or dopaminergic pathways (Castren et al., 2007; Groves, 2007).

This study has some strengths and limitations. We controlled for potential confounding variables at baseline, such as antidepressant use, a history of depression, and other relevant sociodemographic variables, and did not find an interaction between these variables and the polymorphisms examined. Although we did not control for antidepressant therapy being initiated during antiviral treatment, we doubt that this would influence our conclusions because therapy was only initiated after the clinical diagnosis of depression.

Sample size and the all-Caucasian population are also limitations. To our knowledge, only two genetic studies evaluating patients with CHC under antiviral treatment have had larger samples; however, neither study used a standardized clinician-administered assessment to establish the diagnosis of depression (Pierucci-Lagha et al., 2010; Smith et al., 2011), which we believe is a strength of our study. Nevertheless, it should be noted that antiviral treatment can induce two overlapping syndromes: a specific psychiatric syndrome of mood alterations, cognitive complaints, and anxiety, and a non-specific syndrome of neurovegetative symptoms (Raison et al., 2005a). In this study, we only assessed patients using the HADS scale, which specifically excludes neurovegetative symptoms and avoids overlapping with other depression symptoms; this may be somewhat counterbalanced by the fact that the mean HADS-D score was 8.7 at the onset of depression, suggesting the presence of a depressive episode with high sensitivity and specificity (Olsson et al., 2005). Another limitation of the study is that specific neuropsychiatric symptoms of depression were not evaluated, which may be important. For example, insomnia has been associated with increased cytokine concentrations and with a polymorphism in the serotonin transporter gene (Lotrich et al., 2012).

Lastly, we did not find an association between the *IDO*, *IL28*, *FKBP5*, and *GCR2* genetic variants. However, these results should be interpreted with care due to the small number of polymorphisms evaluated. For example, a previous study showed an association between another *IDO* gene variant (rs9657182) and IFN-induced depression, suggesting that IDO may have an important role in cytokine-induced behavioral changes (Smith et al., 2011).

In conclusion, this study supports the notion that IFN-induced depression is a complex pathophysiological process in which specific factors interact with physiological changes that are associated with depressive symptoms. Consistent with previous reports, the serotonin pathway was important in the development of depression. However, factors such as the integrity of dopamine neurotransmission, vulnerability to glucocorticoid resistance, and neurotrophin function may also be crucial.

Moreover, the results of the study should help to optimize the managment of patients with CHC, detecting those at high risk to present IFN-induced depression. In fact, recent guidelines recommend multidisciplinary monitoring for psychiatric symptoms during antiviral treatment for CHC in all cases (Schaefer, 2012; Carrion et al., 2013). However, those in high risk to present depression may well benefit from certain interventions such as prophilactical treatment with antidepressants (Udina et al., 2014). Although interferon-free regimens with direct-acting antivirals are recent options, currently interferon-alpha is still widely used in CHC in most countries (Ermis and Senocak Tasci, 2015).

Acknowledgments

This study was funded by the following Spanish grants: Instituto de Carlos III, Fondo de Investigaciones Sanitarias PSICOCIT-VHC-P110/01827 and PSIGEN-VHC-EC08/00201 (Dr Martín-Santos). It was co-financed by the ERDF, European Union "One way to make Europe," Ministerio de Economía y Competitividad (MTM2012-38067-C02-01), and the support of the Generalitat de Catalunya (SGR2009/1435/SGR2014/1411; Dr Martín-Santos). Dr Grande has received a research grant from Río Hortega Contract (CM12/00062), Instituto de Salud Carlos III, Spanish Ministry of Economy and Competiveness.

Statement of Interest

Dr Solà reports receiving consulting fees from Roche Pharma, Bristol Myers Squibb, Gilead Sciences, Novartis, Roche/Genentech, Jansen Cilag, and Abbvie; lecture fees from Bristol Myers Squibb, Gilead Sciences, Novartis, Roche/Genentech, Jansen, and Abbvie; grant support from Gilead Sciences, Roche/Genentech and Schering-Plough/Merck. Dr Grande reports receiving consulting fees for Ferrer and as a speaker for AstraZeneca, Ferrer, and Janssen-Cilag. Dr Artigas has received consulting and educational honoraria from Lundbeck and he is PI of grants from Lundbeck. He is also member of the scientific advisory board of Neurolixis.

The other authors do not have conflicts of interest.

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