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Risk for depression during interferon-alpha treatment is affected by the serotonin transporter polymorphism

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Abstract

Background—Major depression (MDD) occurs in a subset of patients receiving interferon-alpha treatment, although many are resilient to this side effect. Genetic differences in the serotonin reuptake transporter promoter (5-HTTLPR) may interact with the inflammatory system and may influence depression risk.

Methods—A cohort of 71 non-depressed hepatitis C patients about to receive interferon-alpha was prospectively followed, employing a diagnostic structured clinical interview (SCID; DSM-IV) and self-report questionnaires. Patients were genotyped for the 5-HTTLPR (L_G, L_A, and S) and the variable number of tandem repeats (VNTR) polymorphism in the second intron. Kaplan-Meier analyses were used to compare major depression incidence. Genotype effects on sleep quality (Pittsburgh Sleep Quality Index) and Beck Depression Inventory (BDI) were assessed using mixed-effect repeated-measure analyses.

Results—The L_A allele was associated with a decreased rate of developing MDD (Mantel-Cox Log Rank Test $p < 0.05$) with the L_A/L_A genotype being the most resilient. This genotype was also associated with better sleep quality ($F_{(61,2,2)} = 3.3$ $p < 0.05$). The ability of baseline sleep quality to predict depression incidence disappeared when also including genotype in the model. Conversely, the relationship of neuroticism with depression incidence ($B = 0.07$ SE = 0.02 $p < 0.005$) was not mitigated when including genotype.

Conclusions—Using a prospective design, 5-HTTLPR is associated with MDD incidence during interferon-alpha treatment. Preliminary evidence that this effect could be mediated by effects on sleep quality was observed. These findings provide support for a possible interaction between inflammatory cytokine (interferon-alpha) exposure and 5-HTTLPR variability in MDD.

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Disclosures

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Keywords

Depression; cytokine; polymorphism; serotonin; interferon; prospective

Introduction

Although major depression (MDD) is common (1), determining the role of genetic vulnerability is complicated. There is difficulty with depression measurement and heterogeneity (2,3), and the power of prospective studies is limited by an incidence of about 1–3% per year (4). Nonetheless, meta-analyses (5) and large association studies (6) indicate that the short/short (S/S) genotype in the serotonin transporter length promoter region (5-HTTLPR) increases MDD risk. 5-HTTLPR likely interacts with ‘stressful life events’ to influence MDD (7–9), though this is not universally replicated (10).

One approach to prospectively examining the role of genetics is to focus on specific, homogenous depression-inducing incidents. As one example, a potent MDD trigger is interferon-alpha (IFN- α), an inflammatory cytokine, with the occurrence of depression ranging up to 30–50%, depending upon study design (11–15). For some individuals, depression symptoms develop over the first few months of therapy and include sadness, anhedonia, irritability, anxiety, social withdrawal, and suicidal ideation. IFN- α -induced depression can respond to antidepressant treatments, ranging from selective serotonin reuptake inhibitors to electroconvulsive therapy (16), and is distinct from general somatic effects such as fatigue and aching (12,14). Abnormalities in endogenous cytokines have been associated with idiopathic MDD, prompting speculation regarding their involvement in MDD’s etiology (17–19). Although the mechanism is unknown, IFN- α may affect frontal lobe and anterior cingulate function (20,21), influence transcription of multiple genes (22,23), and involve neurotransmitters including dopamine (24), glutamate (25,26), apoptotic systems (27), and multiple targets in the 5-HT system (28–31).

We therefore examined 5-HTTLPR in patients without current MDD but who were about to be treated with IFN- α for hepatitis C. 5-HTTLPR has been associated with transcriptional efficiency (32), serotonin 1A receptor binding (33), activity in the amygdala (34), and connective interaction between the amygdala and anterior cingulate (35). Thus, 5-HTTLPR could influence resiliency when facing a depressogenic trigger such as an inflammatory cytokine like IFN- α .

A polymorphism within the L allele (L_G) may result in lower transcription efficiency, functionally comparable to the S allele (7,36), warranting its inclusion in our analyses. We also assessed another polymorphism in 5-HTT that may affect transcriptional regulation (37), a variable number of tandem repeats (VNTR) polymorphism in the second intron (5). We additionally examined both sleep quality and neuroticism. Neurotic traits and poor sleep quality may be influenced by 5-HTTLPR (38,39); and both are risk factors for MDD (40,41) and IFN-induced MDD (12,42).

Methods

Seventy-eight non-depressed patients with Hepatitis C were started on pegylated-IFN- α 2 and oral ribavirin and followed for four months of treatment. Using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID), patients were excluded from this study if they had active mood, anxiety, psychotic, or drug/alcohol use disorders within six months prior to starting IFN- α . Subjects could have a resolved, past history of mood or substance use disorder. Seven participants who were euthymic but taking antidepressants were excluded, as

antidepressant use may confound the results. The study was approved by the University of Pittsburgh Institutional Review Board.

An abbreviated SCID specifically focused on mood disorders was used to diagnose categorical MDD during IFN- α treatment. It was obtained either monthly (by F.L. or a single research assistant) or sooner at the request of the treating hepatologist (requesting that the psychiatrist (F.L.) promptly evaluate the patient). Once MDD was diagnosed, immediate psychiatric intervention was provided (typically starting an antidepressant, or sometimes discontinuing IFN- α treatment). A subset of patients also developed severe irritability with depression symptoms. Although they did not meet formal criteria for MDD, psychiatric intervention to prevent potentially injurious behavior was deemed ethically appropriate and therefore instituted. Thus, time until intervention for any 'mood disorder' was a secondary endpoint. Although, diagnoses were made blind to genotype, independent raters were not used.

The Beck Depression Inventory-II (BDI) assessed depressive symptoms. Sleep quality was measured with the Pittsburgh Sleep Quality Index (PSQI) (43), a well-validated 19-item questionnaire consisting of 7 components that yield a global score (0–21; higher numbers indicating poorer sleep quality). Both were administered prior to IFN- α , and at weeks 2, 4, 8, 12, and 16 during treatment. Neuroticism from the NEO-Five Factor Inventory (44) and medical illness burden (Cumulative Illness Rating Scale-Geriatric) (45) were assessed at baseline.

Genetics

DNA was isolated from blood lymphocytes using the PureGene™ kit (Gentra Systems, Minneapolis, MN). The serotonin transporter gene (SLC6A4) promoter polymorphism was typed by DNA amplification (PCR) using flanking primers 5'-TCCTCCGCTTTGGCGCCTCTTCC-3' (forward) and 5'-TGGGGGTTGCAGGGGAGATCCTG-3' (reverse) (46). The L allele was subtyped for rs25531. This A>G single nucleotide polymorphism was concurrently detected by digesting the amplified fragments with MspI (New England Biolabs, Beverly, Massachusetts), where the A>G substitution creates an additional MspI site. Amplification products were simultaneously resolved by electrophoresis on 3.5% agarose gels. For the second intron VNTR, PCR used the following primers: 5'-GGGCAATGTCTGGCGCTTCCCCTACATA-3' (forward) and 5'-TTCTGGCCTCTCAAGAGGACCTACCAGC-3' (reverse), examining the 10/10 10/12 or 12/12 repeat genotypes -- where we combined the rare 9s with 10s.

Data Analysis

We used SPSS 16.0 for all analyses. Based on equivalence of function (36), the S and L_G alleles were grouped together for analyses, unless otherwise indicated (7% of the L alleles were L_G and 93% were L_A). Baseline measures were assessed using ANOVA or chi-square tests (Table 1). Kaplan-Meier survival analyses using the Mantel-Cox log-rank test, initially stratifying by race and comparing factors pooled over strata, was used to examine MDD incidence. For the survival analyses, eight participants were censored before 16 weeks for either discontinuing or holding IFN- α treatment; seven for medical complications and one for severe fatigue.

To assess the relationship between genotype and symptoms (BDI and PSQI), we used repeated-measures mixed-effects models, with last observation carried forward. Because of the repeated measure design, a first-order ante-dependence covariance structure was used. Cox proportional hazards models were then employed in exploratory analyses, and included baseline neuroticism, BDI, or PSQI in conditional stepwise regression models with genotype.

Results

The 5-HTTLPR genotypes were in Hardy-Weinberg equilibrium, with no significant differences between subjects at baseline (Table 1). There was a non-significant trend for L_A to be associated with lower PSQI scores (Table 1).

The L_A allele was associated with lower rates of MDD (Mantel-Cox Log Rank $\chi^2_{(1)} = 4.3$; $p < 0.05$), with the S/S genotype being the least resilient (Figure 1). Pair-wise comparisons indicated that L_A/L_A was different from S/S but not from S/ L_A . Notably, the overall pattern was similar for both Caucasians and the nine African-Americans, with the L_A/L_A genotype being the most resilient and S/S the most vulnerable in both groups. However, when solely examining Caucasians, the results only trended towards significance ($\chi^2_{(1)} = 3.12$; $p = 0.077$). When specifically comparing the S/S genotype vs. L_A in just Caucasians, the results were again significant ($\chi^2_{(1)} = 4.5$; $p < 0.05$), consistent with association studies in which the S/S genotype is the most vulnerable (5,6).

Given uncertainty regarding the functional role of the rs25531 G allele, we combined L_A and L_G together. MDD incidence was similar ($\chi^2_{(1)} = 4.06$; $p < 0.05$) comparing 22 L/L 37 S/L and 12 S/S. Thus, rs25531 may have a small but present role. The effect was significantly mitigated when solely examining Caucasians ($\chi^2_{(1)} = 2.46$; $p = 0.12$). There was no relationship between the second intron VNTR and MDD incidence (Mantel-Cox Log Rank $\chi^2_{(1)} = 0.005$; n.s.).

We next examined BDI scores using a mixed-effect repeated-measures analysis. Individuals developing MDD received antidepressant treatment and/or had their INF- α held, potentially limiting any further increase in symptoms over time and resulting in a likely 'ceiling' effect. Despite this limitation, time was highly significant ($F_{(137,8,5)} = 3.7$; $p < 0.005$) with BDI increasing in all three genotypes during treatment (Figure 2A). Genotype was not significantly influential ($F_{(75,8,2)} = 1.7$), nor was the interaction.

Conversely, when assessing sleep quality (Figure 2B), genotype was influential ($F_{(61,2,2)} = 3.3$; $p < 0.05$), but time was not ($F_{(95,5,5)} = 1.7$), nor was the interaction. That is, sleep did not significantly worsen during interferon-alpha treatment, but those with the L_A/L_A genotype had better sleep quality throughout the study (Figure 2B).

Using Cox Regression analysis, we confirmed that genotype was related to MDD incidence ($B=0.62$ SE=0.27 $p < 0.05$). We also confirmed that baseline neuroticism was strongly associated with MDD incidence ($B=0.07$ SE = 0.02 $p < 0.005$). When genotype was included with neuroticism in the Cox Regression, both continued to be significantly associated with MDD incidence; with both neuroticism's ($B=0.07$ SE = 0.02 $p < 0.005$) and genotype's ($B=0.53$ SE = 0.27 $p < 0.05$) relationship relatively unchanged, indicating that neuroticism does not mediate the effect of 5-HTTLPR. Clinically, neuroticism could predict MDD ($\chi^2_{(2)} = 9.7$ $p < 0.005$; -2 Log Likelihood = 233.04), and genotyping slightly improved this predictive ability ($\chi^2_{(4)} = 14.23$ $p < 0.005$; -2 Log Likelihood = 228.41).

In Cox Regression analyses, both baseline PSQI and BDI were also associated with MDD incidence (PSQI: $B=0.153$ SE = 0.074 $p < 0.05$ and BDI: $B=0.067$ SE = 0.034 $p < 0.05$). When either PSQI or BDI was included with genotype using stepwise Cox Regression (both forward and backward conditional LR), only genotype remained significant ($B = 0.73$ SE = .37 $p < 0.05$). Forcing all three into the same model, again only genotype remained associated ($B=0.66$ SE = 0.34 $p < 0.05$), with the effects of PSQI ($B=0.08$ SE = 0.05 n.s.) and BDI ($B=0.02$ SE = 0.03 n.s.) no longer remaining. However, because baseline PSQI only trended toward a significant association with genotype (Table 1), actual mediation could not be concluded.

To ensure that we weren't biasing our analyses by focusing purely on a DMS-IV based MDD diagnosis, we next examined the rate of development of all diagnosed "mood disorders" combined. After starting IFN- α , 24% ultimately developed categorical MDD by month four, but 45% total developed mood symptoms severe enough to prompt treatment (including one episode of mania). This group had "subsyndromal depression/irritability" as they did not have grandiosity, racing thoughts, increased goal-oriented activity, or decreased need for sleep – but did have insomnia, elevated anger, and irritability. When stratified by race; the L_A allele remained dose-dependently associated with resiliency to this broader diagnosis ($\chi^2_{(1)} = 5.74$ $p < 0.05$). This association remained when examining solely Caucasians ($\chi^2_{(1)} = 4.8$ $p < 0.05$), but was lost when ignoring the role of the rs25531A/G SNP ($\chi^2_{(1)} = 2.96$ $p = 0.085$).

Discussion

The L_A allele was associated with a lower rate of depression development during IFN- α treatment. This relationship was notable despite heterogeneity in presentation and diagnosis used (i.e. MDD or 'subsyndromal depression with irritability'). The S/S genotype was the least resilient. Thus, with a homogenous influence (IFN- α treatment), in a uniform set of patients (non-depressed patients with hepatitis C), followed prospectively, the effects of genotype can be discernable, even with a relatively small sample size ($n=71$). Nonetheless, given the sample size, these results require replication.

Neuroticism may also influence development of MDD (12). However, neuroticism does not appear to mediate the effect of 5-HTTLPR; as both lower neuroticism and 5-HTTLPR were independently associated with MDD. Conversely, 5-HTTLPR was associated with sleep quality, a relationship observed by others (39), and consistent with serotonin's role as a regulator of sleep. Poor sleep may predict future depression (41). In the current study, the relationship between PSQI scores and MDD disappeared when 5-HTTLPR was included in the model. However, (i) we do not have the statistical power to test a mediation model, (ii) PSQI baseline scores only trended towards an association with genotype, and (iii) the PSQI is a self-report rather than direct measure of sleep. The results are therefore only suggestive that poor sleep could potentially mediate the influence of 5-HTTLPR, and require further examination. We did not assess whether increased stress, interpersonal conflict, or changes in social support during treatment could have mediated the influence of interferon-alpha. These possibilities also await further examination. Also, whether 5-HTTLPR may influence a variety of phenotypes relevant to mental health, or a single widely influential factor such as sleep is not yet determined (38).

The findings were more pronounced when including L_G and S together as low expressing alleles, consistent with observations in the literature (7,36), although the actual role of the L_G remains under debate (47). Moreover, we cannot rule out the possibility the 5-HTTLPR is simply in linkage with another nearby functional region. But we did not find any trend toward association of the second intron VNTR with MDD risk, ruling out this site. We did observe that the relationship between 5-HTTLPR and MDD risk was similar in both Caucasians and African-Americans, making racial differences less likely contributors to the findings. Nonetheless, the results will need to be confirmed in a larger sample that includes genomic control.

A study recently reported that 5-HTTLPR and Hospital Anxiety and Depression Scale (HADS) scores in IFN- α patients were not associated (48), using a cross-tabs χ^2 analysis. It was not stated whether any patients were on antidepressants before or during IFN- α treatment. Other differences with that study relate to patient population (whether patients with a past history of MDD were included is not indicated), and depression diagnosis (SCID vs. a HADS cutoff).

Regardless, this study is consistent with a growing literature on the relationship between inflammatory cytokines and the central 5-HT system. IFN- α and other cytokines can alter expression of the 5-HT transporter *in vitro* (49) and affect central 5-HT efflux *in vivo* (50). IFN- α can affect expression of 5-HT_{1A} receptors (28), consistent with 5-HT_{1A} findings in depressed humans (33). In humans, IFN- α also decreases peripheral tryptophan levels, an effect correlated with depression (51). Abnormalities in the inflammatory system can also be observed in many depressed patients (17,18), prompting the biologically plausible possibility for an interaction between endogenous IFN- α and 5-HT variability in the pathogenesis of depression.

In summary, in a cohort of patients at risk for depression because of exposure to exogenous IFN- α , the role of 5-HTTLPR in influencing resiliency was demonstrable. 5-HTTLPR influenced MDD incidence independently from neuroticism. Exploratory analyses suggested that poor sleep quality at baseline could potentially mediate this genetic effect. Regardless, one pathogenic pathway towards the development of depression may involve an interaction between the 5-HT system and increases in inflammatory cytokines such as IFN- α . Explicating the details underlying this interaction may be informative in delineating the pathophysiologic pathways that lead to MDD.

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Figure 1.
Development of MDD in patients starting interferon-alpha treatment.

Figure 2. Development of increased BDI and PSQI self-report scores in patients starting interferon-alpha treatment. (Means $\pm$ S.E.M. L_A/L_A = circles; S/L_A or L_A/L_G = squares; S/S or S/L_G=triangles).

Table 1Baseline characteristics of subjects (mean $\pm$ S.D.)

	L_A/L_A N=18	S/L_A or L_G/L_A N=39	S/S or S/L_G N=14	
Age	47.6 $\pm$ 12.2	49.0 $\pm$ 11.0	47.7 $\pm$ 13.5	n.s.
Percent female	33.3%	20.5%	35.7%	n.s.
Percent African-American	11.1%	12.8%	14.3%	n.s.
History of mood disorder	33%	23%	43%	n.s.
History of drug/alcohol disorder	50%	56%	57%	n.s.
Beck Depression Inventory	6.3 $\pm$ 6.2	6.0 $\pm$ 5.1	8.6 $\pm$ 7.5	n.s.
Pittsburgh Sleep Quality Index	4.4 $\pm$ 2.0	7.1 $\pm$ 3.9	8.1 $\pm$ 6.1	p<0.1
Neuroticism	15.3 $\pm$ 8.3	14.9 $\pm$ 6.8	18.5 $\pm$ 8.0	n.s.
Cumulative Illness Rating Scale	2.8 $\pm$ 1.2	3.7 $\pm$ 2.1	3.1 $\pm$ 1.6	n.s.

(n.s. indicates p>0.1 in either ANOVA or chi-square tests)