IL28B Polymorphism Is Associated with Both Side Effects and Clearance of Hepatitis C During Interferon-Alpha Therapy

Francis E. Lotrich,¹ Jennifer M. Loftis,² Robert E. Ferrell,³ Mordechai Rabinovitz,⁴ and Peter Hauser⁵

Interferon- α (IFN- α) treatment for hepatitis C virus (HCV) is complicated by depression and related neurovegetative side effects. Recent genome-wide scans identified *IL28B* gene polymorphisms that associated with HCV clearance. Whether the *IL28B* polymorphism is also associated with these adverse effects of IFN- α would affect its clinical usefulness. One hundred thirty-three patients were prospectively examined using the Beck Depression Inventory-II and a Structured Clinical Interview for Diagnostic and Statistical Manual-IV (DSM-IV) during IFN- α treatment. The candidate C/T single-nucleotide polymorphism upstream from *IL28B* (rs1297860) was genotyped and assessed for association with individual items from the Beck Depression Inventory-II. We confirmed that the *IL28B* polymorphism was associated with differences in sustained viral response ($F = 3.38$; $P < 0.05$), with the T/T genotype faring worst. However, the T/T genotype was associated with less appetite ($P < 0.05$), energy ($P < 0.05$), and sleep complaints ($P < 0.05$) during treatment. Only 3.1% of patients with T/T developed major appetite complaints, whereas 10.1% and 8.9% of those with the C/T and C/C genotype did, respectively. Only 10.8% of patients with T/T developed major sleep complaints, whereas 16.1% and 20.7% of those with the C/T and C/C genotype did. However, *IL28B* genotype did not predict development of major depressive disorder ($\chi^2 = 0.12$; $P = 0.94$). The allele (C) was associated with both better viral clearance and more subjective appetite, energy, and sleep complaints. This has implications for the management of patients with HCV. If genotyping is used to better target therapy, this may co-enrich the population for likelihood of also suffering from these side effects.

Introduction

THE PRIMARY RECOMMENDED treatment of chronic hepatitis C virus (HCV) infection consists of pegylated (PEG) interferon- α (IFN- α) and ribavirin (Manns and others 2001; Witthoft and others 2007). However, sustained viral response (SVR) is only achieved in ~40%–50% of those with HCV genotype 1 and 75%–80% with HCV genotypes 2/3. Although multiple genes potentially mediate antiviral activity (Tan and others 2005), recent genome-wide association studies have specifically identified polymorphisms in the *IL28B* gene to be predictive of SVR (Ge and others 2009; Suppiah and others 2009; Tanaka and others 2009). *IL28B* encodes for IFN-lambda-3 (IFN- λ -3), which is potentially involved in the inflammatory pathway, and an upstream

polymorphism from *IL28B* was associated with a 2-fold difference in the rate of SVR (Ge and others 2009).

However, successful IFN- α -based therapy is also complicated by adverse side effects ranging from severe psychiatric symptoms (including major depression [MDD] and suicidal behavior) (Janssen and others 1994) to neutropenia, loss of appetite, and fatigue (Fried 2002). Poor antiviral efficacy during IFN- α therapy may result from dose reduction and/or premature discontinuation of treatment. In fact, the development of psychiatric side effects has been associated with decreased viral clearance (Maddock and others 2005; Raison and others 2005), and it is possible that both viral clearance and risk for side effects may share similar influences (Loftis and others 2004, 2005). Risk for side effects during IFN- α treatment may be influenced by genetic polymorphisms, including those

¹University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania.

²Department of Psychiatry, Research and Development Service, Portland Veteran Affairs Medical Center, Oregon Health and Science University, Portland, Oregon.

³Department of Human Genetics, University of Pittsburgh, Pittsburgh, Pennsylvania.

⁴Division of Gastroenterology and Hepatology, University of Pittsburgh, Pittsburgh, Pennsylvania.

⁵VISN 22 Network Office, Long Beach, California.

affecting the serotonin system (Kraus and others 2007; Lotrich and others 2009), other cytokines such as IL-6, the receptor for IFN- α (Yoshida and others 2005), and phospholipase A2 (Su and others 2010). Predicting and preventing these adverse effects is important for successful completion of IFN- α -based therapy and for better quality of life. We thus explored whether a candidate polymorphism in *IL28B* could be related to depression, fatigue, sleep problems, and/or changes in appetite, in addition to its influence on SVR.

Methods

We followed subjects recruited from the Center for Liver Disease at the University of Pittsburgh Medical Center ($N=111$), and the Portland, OR and Long Beach, CA Veterans Affairs Medical Centers ($N=14$ and $N=8$, respectively). All were prescribed PEG-IFN- α and ribavirin and then prospectively monitored as described previously (Lotrich and others 2009; Prather and others 2009). In brief, chronic HCV patients without MDD initiating PEG IFN- α 2 (PEG-IFN- α 2a: 135 μ g/week or PEG-IFN- α 2b: 120 or 150 μ g/week) and oral ribavirin (1,000–1,200 mg/day) were examined pretreatment and then prospectively for the initial 16 weeks of therapy. Subsequently, end-of-treatment viral response was defined as undetectable HCV RNA (polymerase chain reaction) within 1 week of the last dose of IFN- α , and SVR was defined as undetectable HCV RNA at least 6 months following the completion of treatment. None of these patients had active mood, anxiety, psychotic, or drug/alcohol disorders within 6 months prior to starting IFN- α therapy. The study was approved by the Institutional Review Boards of the University of Pittsburgh and the Veterans Affairs Medical Centers in Portland, OR and Long Beach, CA.

Categorical MDD during therapy was diagnosed using the Structured Clinical Interview for Diagnostic and Statistical Manual-IV (DSM-IV) Axis I Disorders focusing on mood disorders (First and others 1995). It was also used to retrospectively assess a history of either mood or substance use disorder. The 21-item Beck Depression Inventory-II (BDI) (Beck and others 1988) was used to assess specific individual depressive symptoms at baseline, at week 2, and during monthly visits (but could be returned by mail if the participant was unable to attend the scheduled appointment). Because IFN- α may induce somatic side effects that are distinct from depression-specific effects (Capuron and others 2002)—and energy or appetite-specific scales were not included in the assessments—we specifically focused on individual BDI questions pertaining to sleep, appetite, and loss of energy. Item scores range from 0 (no complaints) to 3 (severe symptoms).

Genomic DNA was isolated from lymphocytes using the PureGene kit (Gentra Systems) or from whole blood using the QuickGene-Mini-80 kit (Fujifilm Life Science; www.autogen.com). For genotyping of the C/T single-nucleotide polymorphism (rs1297860), we utilized the fluorescence polarization method (Chen and others 1999), with DNA sequence-based controls included in each assay.

All statistics employed SPSS 17.0. Analysis of variances were used to compare viral responses in the 3 genotypes, employing Scheffe's *post-hoc* analyses. Repeated-measure mixed-effect analyses were used to compare changes in subjective symptoms over time, including age, gender, and self-identified race as covariates. Unstructured covariance models were used as they provided the best fit for this (determined by

the least -2 log likelihood). Because *IL28B* genotype is associated with race, we also repeated these analyses solely in Caucasian subjects. Kaplan–Meier survival analyses examining time until MDD development were compared using the Mantel–Cox log rank test. Although hypothesis driven, the analyses are secondary and, therefore, were not corrected for multiple testing. Results are presented as the mean $\pm$ standard deviation, unless otherwise indicated.

Results

Replication of recent findings that *IL28B* is associated with viral response

The *IL28B* genotype was associated with end-of-treatment viral response ($F_{(2)}=6.23$; $P=0.002$) as well as with SVR ($F_{(2)}=3.38$; $P=0.038$). Consistent with prior studies, *post-hoc* analyses indicate that the T/T genotype was associated with a lower SVR than the C/C genotype ($P<0.05$; Fig. 1). We did not have enough power to assess SVR solely in the 18 African-Americans; however, the association with SVR was replicable when analyses were solely limited to Caucasian-American patients ($F_{(2)}=3.1$; $P=0.049$). This is important because genotype frequency was related to race. Thirty-nine percent of African Americans had the T/T genotype, which was higher than in Caucasians ($F_{(2)}=4.2$; $P=0.017$). The influence of *IL28B* was specifically in those infected with HCV genotype 1 (Fig. 1). Of the subjects with HCV genotype 1 who completed 48 weeks of treatment, SVR was observed in 61% of C/C, 47% of C/T, and 20% of T/T *IL28B* genotypes. Most (89%) patients with genotype 2/3 had sustained clearance of HCV, regardless of *IL28B* genotype.

Lack of association of *IL28B* with MDD

As anticipated, average total BDI scores increased over time during treatment as assessed using the repeated-measure mixed-effect analysis [$F(5, 48.2)=5.35$; $P=0.01$]. As noted in Table 1 (the results of the repeated-measure analyses), many individual symptoms ranging from pessimism and suicidal thoughts to poor sleep and fatigue worsen over time during IFN- α treatment. About 14% developed categorical MDD. However, *IL28B* genotype was not associated with the total BDI score [$F(2, 80.7)=0.81$; $P=0.45$] or with the development of categorical MDD during IFN- α therapy ($\chi^2=0.12$; $P=0.94$).

FIG. 1. Sustained viral response was associated with *IL28B* genotype, whether measuring all subjects, only Caucasian subjects, or only subjects infected with HCV genotype 1. HCV, hepatitis C virus.

TABLE 1. REPEATED-MEASURE MIXED-EFFECT ANALYSIS RESULTS, ASSESSING INDIVIDUAL ITEMS FROM THE BECK DEPRESSION INVENTORY-II

Question	Time	Genotype
No. 2 Pessimism	$F(5,33.7) = 11.3; P < 0.001$	$F(2,83.6) = 0.1; P = 0.93$
No. 3 Past failure	$F(5,18.2) = 5.6; P = 0.003$	$F(2,68.0) = 0.4; P = 0.69$
No. 6 Punishment feelings	$F(5,45.0) = 2.4; P = 0.048$	$F(2,48.0) = 1.2; P = 0.30$
No. 8 Self-criticalness	$F(5,32.6) = 3.5; P = 0.012$	$F(2,62.2) = 0.8; P = 0.46$
No. 9 Suicidal thoughts	$F(5,152.1) = 3.0; P = 0.001$	$F(2,113.3) = 0.6; P = 0.47$
No. 13 Indecisiveness	$F(5,39.8) = 3.5; P = 0.01$	$F(2,69.5) = 0.6; P = 0.56$
No. 17 Irritability	$F(5,48.0) = 6.1; P < 0.001$	$F(2,67.7) = 1.7; P = 0.19$
No. 20 Fatigue	$F(5,55.7) = 7.3; P < 0.001$	$F(2,79.6) = 1.0; P = 0.37$
No. 21 Loss of libido	$F(5,50.2) = 3.9; P = 0.005$	$F(2,90.9) = 0.1; P = 0.87$
No. 15 Loss of energy	$F(5,89.0) = 3.2; P = 0.01$	$F(2,90.9) = 3.6; P = 0.03$
No. 16 Sleep	$F(5,56.2) = 2.3; P = 0.05$	$F(2,82.3) = 4.1; P = 0.02$
No. 18 Change in appetite	$F(5,48.1) = 5.4; P = 0.001$	$F(2,83.2) = 3.4; P = 0.04$
No. 1 Sadness	$F(5,36.3) = 1.6; P = 0.19$	$F(2,79.6) = 0.2; P = 0.87$
No. 4 Loss of pleasure	$F(5,34.0) = 1.8; P = 0.14$	$F(2,84.6) = 1.4; P = 0.25$
No. 5 Guilty feelings	$F(5,35.9) = 0.9; P = 0.49$	$F(2,63.8) = 0.5; P = 0.60$
No. 7 Self-dislike	$F(5,88.1) = 1.2; P = 0.34$	$F(2,72.3) = 0.3; P = 0.74$
No. 10 Crying	$F(5,36.8) = 1.0; P = 0.43$	$F(2,58.7) = 0.2; P = 0.84$
No. 11 Agitation	$F(5,57.4) = 2.0; P = 0.097$	$F(2,68.6) = 1.0; P = 0.49$
No. 12 Loss of interest	$F(5,43.8) = 2.4; P = 0.056$	$F(2,86.6) = 0.3; P = 0.75$
No. 14 Worthlessness	$F(5,3.1) = 2.1; P = 0.29$	$F(2,34.5) = 1.3; P = 0.27$
No. 19 Concentration	$F(5,50.0) = 0.98; P = 0.44$	$F(2,76.0) = 0.74; P = 0.48$

Twelve of the 21 symptoms worsened over time (bold in first column). Three of the items were associated with the IL28B genotype (bold in second column), and all 3 were worse in those with the C allele.

Association of IL28B with specific depression symptoms

In the repeated-measure mixed-effect analyses, 3 specific somatic symptoms on the BDI were associated with *IL28B* genotype, namely loss of energy, worsened sleep, and change in appetite (Table 1, column 2). In all cases, the C allele was associated with more somatic symptoms. These findings did not change and remained significant when solely assessing Caucasian subjects. In terms of effect sizes during treatment, only 3.1% of T/T, 10.1% C/T, and 8.9% C/C had appetite changes of "much less" or "no appetite"; 3.1% of T/T, 16.3% C/T, and 14.5% C/C indicated not having enough energy "to do very much" or "to do anything"; 10.8% T/T, 16.1% C/T, and 20.7% C/C reported "a lot less" sleep or worse.

Potential association of IL28B with baseline liver disease

There was a trend for *IL28B* genotype to be related to hepatic activity index and ALT levels, with the C/C genotype demonstrating more severe liver inflammation (Table 2), although this did not meet criteria for statistical significance. The only factors associated with SVR were race, *IL28B* genotype, and HCV viral genotype; other potential influences on SVR such as age, fibrosis stage, and viral load trended in the expected direction but did not reach statistical significance (Table 3).

Discussion

Recent findings that genetic variation in *IL28B* has an influence on SVR were replicated in this study. The absolute

TABLE 2. A COMPARISON OF INDICES OF LIVER FUNCTION AMONG *IL28B* GENOTYPES

	CC	CT	TT	P value
Baseline BDI-II	7.8 ± 7.1	6.9 ± 7.6	6.2 ± 4.3	0.70
SSRI RX during treatment	48.9%	39.5%	46.7%	0.68
Any treatment interruption	10.2%	15.4%	5.0%	0.44
Viral count (million)	6.05 ± 14.1	4.18 ± 7.11	2.52 ± 2.26	0.43
AST (IU/L)	79.9 ± 51.6	63.5 ± 38.4	79.2 ± 52.2	0.19
HCV genotype	40% genotype 2/3	23% genotype 2/3	9.1% genotype 2/3	0.069
ALT (IU/L)	135.7 ± 125.7	90.6 ± 64.6	90.5 ± 68.9	0.052
Platelets (thousand/μL)	216.6 ± 75.4	229.3 ± 74.2	213.6 ± 78.1	0.63
Hepatic activity index	6.7 ± 3.2	5.3 ± 1.3	5.4 ± 1.7	0.050
Fibrosis score	2.8 ± 1.9	2.7 ± 1.6	3.5 ± 1.9	0.48
Fibrosis score of 5 or 6	26.7%	16.7%	36.4%	0.36

There is a nonsignificant trend for the C/C genotype to have higher ALT levels and a greater hepatic activity index at baseline. HCV, hepatitis C virus; BDI, Beck Depression Inventory-II.

TABLE 3. POTENTIAL PREDICTORS OF SUSTAINED VIRAL RESPONSE WERE COMPARED

	SVR	No SVR	P value
<i>IL28B</i> rs12979860	54.3% CC; 39.2% CT; 6.5% TT	32.6% CC; 45.7% CT; 21.7% TT	0.038
Gender	71.8% male	78.6% male	0.49
Race	3 African-American	15 African American	0.006
	59 Caucasian	56 Caucasian	
Age (years)	47.0 ± 12.0	51.6 ± 9.4	0.063
Hepatic activity index	5.4 ± 1.6	6.5 ± 2.9	0.12
Fibrosis score	2.4 ± 1.8	3.1 ± 1.7	0.20
Fibrosis score of 5 or 6	13%	29%	0.13
AST (IU/L)	77.8 ± 53.9	67.9 ± 41.0	0.36
ALT (IU/L)	123.2 ± 110.9	87.4 ± 71.3	0.11
Platelets (thousand/ μ L)	226.9 ± 57.0	205.6 ± 82.7	0.20
HCV genotype	31 genotype 1	67 genotype 1	<0.0001
	31 genotype 2/3	4 genotype 2/3	
Brand	31 PEG-IFN- α -2b	41 PEG-IFN- α -2b	0.44
	31 PEG-IFN- α -2a	30 PEG-IFN- α -2a	
Baseline BDI-II score	5.7 ± 5.5	6.6 ± 6.3	0.50
SSRI during treatment	42.5% prescribed an SSRI	41.5% prescribed an SSRI	0.93

The 3 predictors meeting statistical significance (bold) in this group are *IL28B* genotype, viral genotype, and race. IFN, interferon; SVR, sustained viral response; PEG, pegylated.

rates of SVR, as associated with rs1297860, are very similar to those reported by Ge and others (2009). In addition, rs1297860 was associated with various somatic symptoms including decrements in appetite, worsened sleep, and loss of energy. In particular, the C allele was associated with both improved SVR and also more somatic complaints. Consequently, if *IL28B* genotyping is used to select individuals most likely to respond to IFN- α treatment, then this selection will concurrently choose patients most likely to suffer from these somatic symptoms. However, our study is the first to examine this and requires replication.

Unfortunately, there is a limited clinical evidence base for treating these 3 symptoms in HCV patients. These somatic side effects are distinct from MDD (Lotrich and others 2007) and are not responsive to antidepressant treatment (Capuron and others 2002). Further work is critical, particularly if genetic *IL28B* testing is used to target treatment populations. Behavioral or pharmacological treatments have been suggested for managing insomnia (Sockalingam and others 2010). Antiemetic agents such as compazine have been traditionally used for emesis, with limited data supporting cannabinoid-containing medications for anorexia (Sylvestre and others 2006; Costiniuk and others 2008). A very small study of 12 subjects found that a combination of exercise and methylphenidate was helpful for loss of energy during IFN- α treatment (Schwartz and others 2002). Fortunately, most subjects did not experience severe increases in these symptoms. A score of 2 or 3 (the maximal score on individual BDI items) was uncommon in those with the T/T genotype (3.1% with severe loss of appetite and 10.8% with very poor sleep), but was also present in a minority of subjects with the C allele (8.9% with severe loss of appetite and 20.7% with very poor sleep). However, when present, these symptoms can interfere with both successful continuation of IFN- α -based treatment and quality of life and, therefore, require addressing.

One important caveat to our study is that there are limitations to using individual items from self-report scales. Loss of energy could be related to neurophysiologic effects, ane-

mia, and/or direct musculature effects. Similarly, effects on appetite, nausea, and gastrointestinal disturbance are likely to be complex. Another limitation is that we elected to examine only one polymorphism in the *IL28B* gene. This polymorphism was chosen as a plausible candidate given its recent association with SVR (Ge and others 2009), but linkage studies indicate that it could be in linkage with nearby polymorphisms that are more causally related to SVR (Ge and others 2009; Suppiah and others 2009; Tanaka and others 2009). Very little is known about the expression patterns of IFN- λ -3, its function in various tissues, its role during viral infection, or influences on its expression.

We and others have found that other genetic polymorphisms can influence psychiatric side effects (Yoshida and others 2005; Kraus and others 2007; Lotrich and others 2009, 2010; Su and others 2010). Interestingly, different genes influence different effects. A polymorphism in TNF- α appears to influence fatigue and irritability but not depression (Lotrich and others 2010), whereas the serotonin transporter polymorphism is more specific for depression and sleep (Lotrich and others 2009). Thus, it is notable that the *IL28B* polymorphism was not associated with depression per se, indicating that IFN- λ -3 may play less of a role in mediating many of the central nervous system effects of IFN- α , whereas fatigue and poor appetite may be the consequence of enhanced inflammation peripherally.

Placing these *IL28B* findings in context, many other variables have moderate associations with SVR, including adherence (Jen and others 2001; Rodriguez-Torres and others 2008), baseline viral load, age, gender, race, liver fibrosis, and weight (Shirakawa and others 2008). The risk for side effects during IFN- α treatment is likely influenced by additional genetic polymorphisms (Bull and others 2008). Thus, predictions of both SVR and adverse events may require examining more than a single gene such as *IL28B*.

Regardless, our findings replicate the finding that the C allele of the *IL28B* polymorphism rs1297860 is associated with improved viral clearance, and we report for the first

time an effect on fatigue, appetite, and sleep during IFN- α therapy. Improved attention of these 3 sets of symptoms may increasingly be important, and better therapies to address them are required. This may become particularly relevant if future clinical testing for the *IL28B* genotype is used to help target patients for IFN- α -based therapies.

Acknowledgments

This study was funded by NIMH K23MH074012 (to F.E.L.) and VA#08-1904 (to P.H.).

Authors Contributions

Francis E. Lotrich: concept and design, data acquisition, analysis and interpretation, manuscript drafting, statistical analysis, and obtained funding; Jennifer M. Loftis: data acquisition, analysis and interpretation, and manuscript drafting; Robert E. Ferrell: manuscript drafting and technical and material support for genotyping; Mordechai Rabinovitz: concept and design, data acquisition, analysis and interpretation, and manuscript drafting; Peter Hauser: data acquisition, analysis and interpretation, manuscript drafting, and obtained funding.

Author Disclosure Statement

No conflict of interest exists. The agencies that funded this work did not participate in the design, analysis, collection, or interpretation of data.

References

- Beck A, Steer R, Garbin M. 1988. Psychometric properties of the Beck Depression Inventory: twenty-five years of evaluation. *Clin Psychol Rev* 8:77–100.
- Bull SJ, Huezio-Diaz P, Binder EB, Cubells JF, Ranjith G, Maddock C, Miyazaki C, Alexander N, Hotopf M, Cleare AJ, Norris S, Cassidy E, Aitchison KJ, Miller AH, Pariante CM. 2008. Functional polymorphisms in the interleukin-6 and serotonin transporter genes, and depression and fatigue induced by interferon- α and ribavirin treatment. *Mol Psychiatry* 14:1095–1104.
- Capuron L, Gummnick JF, Musselman DL, Lawson DH, Reemsnyder A, Nemeroff CB, Miller AH. 2002. Neurobehavioral effects of interferon- α in cancer patients: phenomenology and paroxetine responsiveness of symptom dimensions. *Neuropsychopharmacology* 26:643–652.
- Chen X, Levine L, Kwok PY. 1999. Fluorescence polarization in homogeneous nucleic acid analysis. *Genome Res* 9:492–498.
- Costiniuk CT, Mills E, Cooper CL. 2008. Evaluation of oral cannabinoid-containing medications for the management of interferon and ribavirin-induced anorexia, nausea and weight loss in patients treated for chronic hepatitis C virus. *Can J Gastroenterol* 22:376–380.
- First MB, Spitzer RL, Williams JBW, and others. 1995. Structured Clinical Interview for DSM-IV (SCID-I) (Users Guide and Interview) Research Version, American Psychiatric Press, Washington, D.C.
- Fried MW. 2002. Side effects of therapy of hepatitis C and their management. *Hepatology* 36:S237–S244.
- Ge D, Fellay J, Thompson AJ, Simon JS, Shianna KV, Urban TJ, Heinzen EL, Qiu P, Bertelsen AH, Muir AJ, Sulkowski M, McHutchison JG, Goldstein DB. 2009. Genetic variation in *IL28B* predicts hepatitis C treatment-induced viral clearance. *Nature* 461:399–401.
- Janssen H, Brouwer J, van der Mast R, Schalm S. 1994. Suicide associated with alfa-interferon therapy for chronic viral hepatitis. *J Hepatol* 21:241–243.
- Jen JF, Glue P, Ezzet F, Chung C, Gupta SK, Jacobs S, Hajian G. 2001. Population pharmacokinetic analysis of pegylated interferon alfa-2b and interferon alfa-2b in patients with chronic hepatitis C. *Clin Pharmacol Ther* 69:407–421.
- Kraus MR, Al-Taie O, Schefer A, Pfersdorff M, Lesch KP, Scheurlen M. 2007. Serotonin-1A receptor gene (HTR1A) variation predicts interferon-induced depression chronic hepatitis C. *Gastroenterology* 132:1279–1286.
- Loftis JM, Hauser P, Rifai MA. 2005. The association between viral clearance and depression in patients with hepatitis C receiving interferon- α and ribavirin. *Brain Behav Immun* 19:271–272.
- Loftis JM, Socherman RE, Howell CD, Whitehead AJ, Hill JA, Dominitz JA, Hauser P. 2004. Association of interferon- α -induced depression and improved treatment response in patients with hepatitis C. *Neurosci Lett* 365:87–91.
- Lotrich FE, Ferrell RE, Rabinovitz M, Pollock BG. 2009. Risk for depression during interferon- α treatment is affected by the serotonin transporter polymorphism. *Biol Psychiatry* 65:344–348.
- Lotrich FE, Ferrell RE, Rabinovitz M, Pollock BG. 2010. Labile anger during interferon- α treatment is associated with a polymorphism in tumor necrosis factor- α . *Clin Neuropharmacol* 33(4):191–197.
- Lotrich FE, Rabinovitz F, Girona P, Pollock BG. 2007. Depression following pegylated interferon- α : characteristics and vulnerability. *J Psychosom Res* 63:131–135.
- Maddock C, Landau S, Barry K, Maulayah P, Hotopf M, Cleare A, Norris S, Pariante CM. 2005. Psychopathological symptoms during interferon- α and ribavirin treatment: effects on virologic response. *Mol Psychiatry* 10:332–333.
- Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, Goodman ZD, Koury K, Ling M-H. 2001. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 358:958–965.
- Prather AA, Rabinovitz M, Pollock BG, Lotrich FE. 2009. Cytokine-induced depression during IFN- α treatment: the role of IL-6 and sleep quality. *Brain Behav Immun* 23:1109–1116.
- Raison CL, Broadwell SD, Borisov AS, Manatunga AK, Capuron L, Woolwine BJ, Jacobson IM, Nemeroff CB, Miller AH. 2005. Depressive symptoms and viral clearance in patients receiving interferon- α and ribavirin for hepatitis C. *Brain Behav Immun* 19:23–27.
- Rodriguez-Torres M, Rios-Bedoya CF, Ortiz-Lasanta G, Purcell-Arevalo D, Marxuach-Cuetara A, Jimenez-Rivera J. 2008. Weight affect relapse rates in latinos with genotype 2/3 chronic hepatitis C (CHC) treated with peg IFN alfa-2a (Pegasys) 180 mcg/week and 800 mg daily of ribavirin for 24 weeks. *J Med Virol* 80:1576–1580.
- Schwartz AL, Thompson JA, Masood N. 2002. Interferon-induced fatigue in patients with melanoma: a pilot study of exercise and methylphenidate. *Oncol Nurs Forum* 29:E85–E90.
- Shirakawa H, and others. 2008. Pretreatment prediction of virological response to peginterferon plus ribavirin therapy in chronic hepatitis C patients using viral and host factors. *Hepatology* 48:1753–1760.
- Sockalingam S, Abbey SE, Alosaimi F, Novak M. 2010. A review of sleep disturbance in Hepatitis C. *J Clin Gastroenterol* 44(1):38–45.

- Su K-P, Huang S-Y, Peng C-Y, Lai H-C, Huang C-L, Chen Y-C, Aitchison KJ, Pariente CM. 2010. Phospholipase A2 and cyclooxygenase 2 genes influence the risk of interferon- α -induced depression by regulating polyunsaturated fatty acids levels. *Biol Psychiatry* 67:550–557.
- Suppiah V, Moldovan M, Ahlenstiel G, Berg T, Weltman M, Abate ML, Bassendine M, Spengler U, Dore GJ, Powell E, Riordan S, Sheridan D, Smedile A, Fragomeli V, Müller T, Bahlo M, Stewart GJ, Booth DR, George J. 2009. IL28B is associated with response to chronic hepatitis C interferon- α and ribavirin therapy. *Nat Genet* 41:1100–1104.
- Sylvestre DL, Clements B, Malibu Y. 2006. Cannabis use improves retention and virological outcomes in patients treated for hepatitis C. *Eur J Gastroenterol Hepatol* 18:1057–1063.
- Tan H, and others. 2005. Global transcription profiling combination of type I and type II demonstrates that interferon enhances antiviral and immune responses at clinically relevant doses. *J Interferon Cytokine Res* 25:632–649.
- Tanaka Y, Nishida N, Sugiyama M, Kurosaki M, Matsuura K, Sakamoto N, Nakagaw M, Korenaga M, Hino K, Hige S, Ito Y, Mita E, Tanaka E, Mochida S, Murawaki Y, Honda M, Sakai A, Hiasa Y, Nishiguchi S, Koike A, Sakaida I, Imamura M, Ito K, Yano K, Masaki N, Sugauchi F, Izumi N, Tokunaga K, Mizokami M. 2009. Genome-wide association of IL28B with response to pegylated interferon- α and ribavirin therapy for chronic hepatitis C. *Nat Genet* 41:1105–1109.
- Witthoft T, Moller B, Wiedmann KH, Mauss S, Link R, Lohmeyer J, Lafrenz M, Gelbmann CM, Huppe D, Niederau C, Alshuth U. 2007. Safety, tolerability and efficacy of peginterferon alpha-2a and ribavirin in chronic hepatitis C in clinical practice: The German Open Safety Trial. *J Viral Hepat* 14:788–798.
- Yoshida K, Alagbe O, Wang X, Woolwine B, Thornbury M, Raison CL, Miller AH. 2005. Promoter polymorphisms of the interferon- α receptor gene and development of Interferon-induced depressive symptoms in patients with chronic hepatitis C: preliminary findings. *Neuropsychobiology* 52:55–61.

Address correspondence to:

Dr. Francis E. Lotrich

University of Pittsburgh Medical Center

Western Psychiatric Institute and Clinic

3811 Ohara St.

Pittsburgh, PA 15213

E-mail: lotrichfe@upmc.edu

Received 2 July 2010/Accepted 20 August 2010