ORIGINAL ARTICLE

Association Between Treatment-Emergent Suicidal Ideation With Citalopram and Polymorphisms Near Cyclic Adenosine Monophosphate Response Element Binding Protein in the STAR*D Study

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Context: A small subset of patients with depression exhibit new or worsening suicidal thoughts or behavior during short-term treatment with antidepressants. Because cyclic adenosine monophosphate response element binding (CREB) protein has been implicated in both antidepressant mechanisms and suicide, the *CREB1* gene represents a gene that possibly influences the risk for treatment-emergent suicidality.

Objective: To examine polymorphisms that span *CREB1*, which was previously associated with anger expression in men with major depressive disorder, for association with new or worsening suicidality.

Design: Nested case-control study derived from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, a multicenter, prospective, open, 12-week effectiveness trial from July 1, 2001, to September 30, 2006.

Setting: Outpatient primary care and psychiatric clinics.

Patients: Individuals with nonpsychotic major depressive disorder for whom DNA was available and who did not report suicidal ideation at study entry were subsequently treated with citalopram hydrobromide for up to 12 weeks.

Main Outcome Measure: Emergent suicidal ideation, defined as a score of 2 or higher on any postbaseline visit for participants whose baseline score was 0 or 1 on the 16-item Quick Inventory of Depressive Symptomatology–Clinician Rated suicide item.

Results: Of 1447 participants, 124 (8.6%) subsequently reported suicidality on at least 1 visit; these individuals were compared with the remaining 1324 participants. Of 5 single nucleotide polymorphisms (SNPs) examined, none were significantly associated with treatment-emergent suicidality overall. However, 2 SNPs revealed a gene-by-sex interaction with suicidality. Among the 539 men, these 2 SNPs and 2 of the 5 SNP haplotypes were significantly associated with new-onset suicidality.

Conclusions: Polymorphisms that span *CREB1* were associated with treatment-emergent suicidality among men with depression, extending an observation of association with male anger expression in a prior independent cohort. If replicated, this finding would suggest that pharmacogenetic testing could facilitate the identification of the small subset of individuals at greater risk during short-term antidepressant treatment.

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DESPITE A NUMBER OF EARLY case reports indicating emergence or worsening of suicidal thinking or behavior after initiation of desipramine hydrochloride[1] and selective serotonin reuptake inhibitors,[2-8] several meta-analyses of antidepressant medication trials in major depressive disorder (MDD) found no significant difference in risk relative to placebo.[9-12] Indeed, an examination of health-plan data found a *decrease* in suicide risk after initiation of treatment with antidepressants.[13]

On the other hand, although most individuals are helped by antidepressant medication, a subgroup may still experience symptomatic worsening.[14-16] This concern led the Food and Drug Administration to mandate a labeling change for antidepressants.[17] Regardless of treatment specificity, nearly all antidepressant medication studies find that some patients experience suicidality after treatment initiation. For example, in a large open study of fluoxetine hydrochloride, 14% of patients reported emergence of suicidal thoughts after treatment initiation.[18] Identification of this subpopulation before treatment would have tremendous clinical utility.

Family studies reviewed by Brent and Mann[19] indicate that suicide attempts and completed suicide show familial aggregation, which persists even after adjustment for the presence of psychiatric dis-

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order. Based on large twin registry studies, estimates of the heritability of suicidal behavior are in the range of 30% to 55%.[20-22] We hypothesized that, as with suicidal behavior in general, propensity to develop suicidal thinking during antidepressant treatment might itself be genetically influenced. In particular, converging lines of evidence implicate the transcription factor cyclic adenosine monophosphate (cAMP) response element binding (CREB) protein, coded by the *CREB1* gene, in antidepressant response[23-25] and suicide,[26-28] as well as mood disorders in general.[29,30] In addition, we have recently observed[31] that single nucleotide polymorphisms (SNPs) near this gene are associated with variation in anger expression among male patients with MDD, a trait that has been associated with suicidality.[32-36] Therefore, we examined the possible association between polymorphisms near *CREB1* and emergence of suicidal thoughts and behavior during antidepressant treatment in a cohort from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, a large multicenter study of patients treated openly with citalopram hydrobromide for 12 to 14 weeks.[37-39]

METHODS

CLINICAL METHODS

STAR*D was a multicenter trial in which patients initially received first-line treatment with the selective serotonin reuptake inhibitor citalopram. The methods of the STAR*D study are described in detail elsewhere[37-39] and are summarized herein.

STUDY ORGANIZATION

The STAR*D study was conducted at 14 regional centers that oversaw 41 sites that consisted of 18 primary care and 23 psychiatric care settings across the United States. Research outcomes were collected by telephone interviews conducted by a small team of trained research outcome assessors masked to treatment and by telephone-based interactive voice response. The research outcome assessors received extensive training in the administration of efficacy measures, with interrater reliability assessed periodically.

STUDY POPULATION

This report presents data from the 1879 participants who entered level 1 (citalopram) treatment in the STAR*D study for whom DNA was available. The study recruited only individuals who sought treatment at the clinical sites; advertising to recruit participants was not permitted. Participants were informed of all risks, benefits, and adverse events associated with each study treatment, and they provided written informed consent before study entry. Participants were not required to participate in the genetic portion of the protocol, which was initiated approximately 12 months after study initiation. The study protocol was approved by institutional review boards at all participating regional centers, the national coordinating center, and the data coordinating center. The study was overseen by the National Institute of Mental Health data and safety monitoring board.

Participants met broadly inclusive and minimally exclusive criteria to enroll a representative sample. Men and women outpatients aged 18 to 75 years with a *DSM-IV* diagnosis of nonpsychotic MDD, with a baseline score of 14 or higher on the 17-item Hamilton Rating Scale for Depression ($HRSD_{17}$)[40] determined by the clinical research coordinator, and for whom the treating physician had determined that outpatient antidepressant treatment was safe and appropriate were enrolled. Exclusion criteria included a well-documented history of nonresponse or intolerability in the current major depressive episode to adequate doses[41] of 1 or more medications used in the first 2 treatment steps; lifetime diagnosis of MDD with psychotic features, schizophrenia, schizoaffective disorder, or bipolar disorder; a current primary diagnosis of eating disorder or obsessive-compulsive disorder; presence of severe, unstable concurrent psychiatric conditions likely to require hospitalization within 6 months (eg, severe alcohol dependence with recent detoxification admissions); presence of concurrent medical or psychiatric conditions or concomitant medications that contraindicate a protocol treatment; and pregnancy or intent to conceive within the 9 months subsequent to study entry.

RESEARCH OUTCOME ASSESSMENTS

The clinical research coordinator at each study site completed the $HRSD_{17}$ at baseline, reviewed inclusion and exclusion criteria, and completed the 16-item Quick Inventory of Depressive Symptomatology ($QIDS\text{-}C_{16}$),[42-45] a clinician-rated scale that assesses 9 diagnostic symptoms and domains of MDD, at each visit. The research outcome assessor conducted a telephone interview with study participants within 72 hours of the baseline and subsequent visits to complete the baseline $HRSD_{17}$ and the 30-item Inventory of Depressive Symptomatology–Clinician Rated ($IDS\text{-}C_{30}$).[46]

INTERVENTION

All participants received citalopram hydrobromide using dosing guidelines that advised beginning at 20 mg/d and then increasing to 40 mg/d by week 4 and to 60 mg/d by week 6. Dose adjustments were based on guidelines that reflect duration of treatment at current dose, symptom changes, and adverse effect burden, with flexibility allowed based on clinician impression of patient status. The protocol advised treatment visits at 2, 4, 6, 9, and 12 weeks (with an optional visit at week 14 if needed). Patients could discontinue use of citalopram before 12 weeks in the event of intolerable adverse effects that required change in medication, inability to increase to an optimal dose because of adverse effects or patient preference, or presence of significant depressive symptoms (defined as QIDS-C score ≥ 9) after 9 weeks at the maximum tolerated dose. Concomitant treatments for current general medical conditions; for associated symptoms of depression, including insomnia, anxiety, and agitation; and for citalopram adverse effects were permitted based on clinical judgment. However, stimulants, anticonvulsants, antipsychotics, alprazolam, nonprotocol antidepressants other than trazodone (≤ 200 mg) at bedtime for insomnia, and psychotherapies for depressive symptoms were not permitted.[39]

GENOTYPING METHODS

We first identified all validated SNPs in a region that included *CREB1* and flanking regions (115 kilobases in all) using the International HapMap Project Phase Ic database (http://www.hapmap.org), which yielded a total of 44 SNPs. The Tagger program (http://www.broad.mit.edu/mpg/tagger/),[47] which examines pairwise and multiallelic linkage disequilibrium to determine the minimum set of SNPs necessary to capture all common genetic variation in a region, identified 5 tags sufficient to capture all exonic or putative promoter-region HapMap SNPs in *CREB1*, with a minimum r^2 of 0.8 (mean r^2 of 0.93). Subse-

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quently, HapMap Phase II was released, and we again used Tagger to examine the efficiency of the 5 tag SNPs in capturing known HapMap SNPs. All but 2 SNPs with minor allele frequency greater than 0.05 (one in the promoter of an adjacent gene, *LOC151194*, and the other in the 3′ untranslated region of *CREB1*) were captured with minimum r^2 greater than or equal to 0.8 (http://massgeneral/.org/chgr/faculty_perlis.htm/publications).

Genotyping was performed using the methods previously described.[48] Primers were designed using SpectroDESIGNER software (Sequenom, San Diego, Calif). Polymerase chain reaction was performed followed by homogeneous MassEXTEND reaction. Samples were analyzed in automated mode by a MassARRAY RT mass spectrometer (Sequenom).[49] The resulting spectra were analyzed by SPECTROTYPER software (Sequenom) after baseline correction and peak identification. In the present study, the 5 SNPs yielded pass rates of 95% or higher and did not deviate significantly from Hardy-Weinberg equilibrium. Concordance for duplicate DNAs was 100%; previous work in our laboratory with intraplate and interplate control samples yielded error rates less than 0.1%.

ANALYTIC METHODS

Participants were grouped according to baseline score on the suicide item (item 12) of the QIDS-C_{16}, which captures suicidal thinking or behavior in the prior week. The QIDS-C completed by the clinical research coordinators was used rather than the IDS-C completed by the research outcome assessors, because it was completed at a face-to-face interview rather than by telephone and as a result was more complete than that available from telephone assessments.[39] For consistency with prior work, including our own,[18] we considered a score of 2 or greater to indicate suicidality. Specifically, a score of 2 corresponds to "thinks of suicide/death several times a week for several minutes" and a 3 to "thinks of suicide/death several times a day in depth, or has made specific plans, or attempted suicide." The risk set was considered to be those participants without suicidality at the baseline visit (ie, QIDS-C item 12 score was 0 or 1); the primary outcome was whether individuals from this group reported the emergence of suicidality (score of 2 or 3) on at least 1 postbaseline visit. Follow-up analyses examined emergence of suicidality in 3 epochs separately: 0 to 30 days, 30 to 60 days, and greater than 60 days; individual cases were censored if they had no visits in the epoch in question.

SINGLE SNP ANALYSES

We used the software package WHAP (developed by S.P., available at http://pngu.mgh.harvard.edu/purcell/WHAP/) to perform the basic single SNP association tests with treatment-emergent suicidality. The regression-based method implemented in WHAP is described in the article by Sham et al[50] and was recently found to perform well in a comprehensive simulation study that compared different haplotype-based methods for case-control association analysis.[51] For each SNP, we calculated asymptotic significance values based on a Wald test and empirical significance values based on 50 000 permutations. Empirical significance values ensure that any deviation from normality or small sample size will not cause false-positive results; further, by comparing each observed Wald statistic to the maximum of all 5 Wald statistics for each permuted data set, we can obtain a set of significance values that control for the multiple testing of 5 correlated SNPs. Analyses were adjusted for the presence or absence of baseline hopelessness as measured by a score of 1 on the QIDS-C_{16} suicide item (item 12) because this was identified as a potential confounder in univariate analyses in this cohort and in a prior report.[18]

In light of previous analyses that indicate sex-specific effects of *CREB1* in depression liability, which show an association in women but not men,[29] as well as anger expression,[31] which show an association in men but not women, we also used WHAP to formally test for sex-related heterogeneity in the effect of *CREB1* (ie, a gene-by-sex interaction). When this test result was statistically significant, we proceeded as planned to examine within-sex associations separately. This gene-by-sex interaction was the only subgroup analysis specified a priori.

Although permutation accounts for testing multiple correlated SNPs within a gene (ie, controls α at the genewise level), *P* values for single-marker associations are otherwise reported without correction for multiple comparisons; because 2 primary sets of tests were performed (the sample as a whole and male cohort alone), Bonferroni correction would require $P<.025$ for statistical significance, although since the tests are not truly independent, this represents a conservative threshold.

HAPLOTYPE AND CONDITIONAL TESTING

Haplotype analyses were also conducted using WHAP. The initial haplotype test is an omnibus test for any joint effect of all haplotypes observed (minor allele frequency, $\geq$0.01). WHAP accounts for any potential ambiguity in inferred haplotypes by using a weighted likelihood approach to test for association conditional on the posterior distribution of possible haplotypic phases given the multilocus genotype for each individual. When the omnibus test result was statistically significant, we then performed haplotype-specific tests (ie, 1- *df* tests of each haplotype vs all others). Because HapMap data indicated a single block of linkage disequilibrium that spanned the 5 markers, haplotypes that used all 5 markers were examined.

ADDITIONAL ANALYSES

Comparisons of clinical features between groups used *t* tests or χ^2 tests, as appropriate. To generate Kaplan-Meier survival curves for illustrative purposes, participant data were censored at time of dropout, completion of 90 days, or after emergence of suicidality. For examination of the effects of covariates such as cotreatment with a sedative or hypnotic, logistic regression was used. These analyses were performed using Stata statistical software, version 9.0 (Stata Inc, College Station, Tex).

RESULTS

Participants who provided DNA were generally similar to the total STAR*D population in sociodemographic and clinical features, as has been reported elsewhere.[52] However, since the DNA sample collection began months after study initiation, those providing DNA samples were more likely to have been in follow-up and to have achieved a good outcome. **Figure 1** shows how the analytic sample was generated. Of 1879 individuals for whom DNA was available, 38 did not remain in the study for at least 1 week, leaving 1841 in the risk set (none of these 38 are known to have made a suicide attempt). Among these 1841, 394 scored 2 or higher on item 12 at study entry, which left 1447 in the risk set. Of these 1447, 123 (8.5%) scored 2 or higher on item 12 (ie, reported suicidal ideation) on at least 1 postbaseline visit.

Those who did or did not develop suicidal ideation during treatment were generally similar in baseline characteristics (**Table 1**). Individuals who developed suicidal ideation were significantly more likely to report

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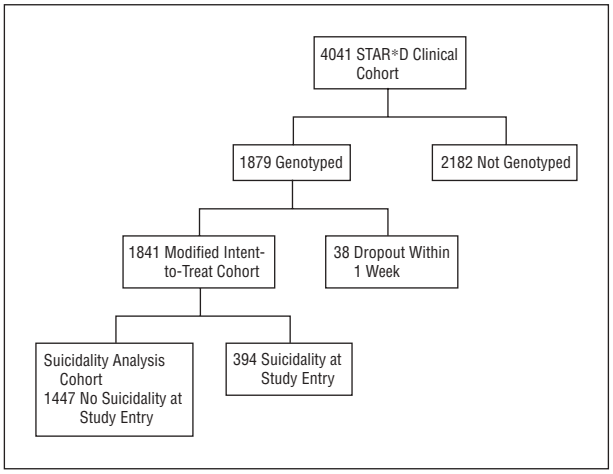

Figure 1. CONSORT diagram of Sequenced Treatment Alternatives to Relieve Depression (STAR*D) genetics and suicidality cohort. Of 1879 individuals in the STAR*D cohort from whom DNA was available, 1447 remained in the study for at least 1 week and did not express suicidal ideation at study entry. These 1447 represent the risk cohort examined in subsequent genetic analyses.

hopelessness (QIDS-C_{16} item 12 score, 1) at study entry, to have made a prior suicide attempt, and to have more severe depression at study entry as measured by the $HRSD_{17}$, IDS-C_{30}, or QIDS-C_{16}.

For the genotyped SNPs, minor allele frequencies are given in **Table 2**. For the sample as a whole, no SNP showed a significant association with emergence of suicidality (Table 2 and **Figure 2**). Results of an omnibus test of all haplotypes were likewise not statistically significant. Two SNPs, however, showed significant evidence of inhomogeneity of odds ratios (ORs) (ie, gene-by-sex interaction with suicidality).

Of the 539 men without suicidal ideation at the screen or baseline visit, 54 (10%) developed new suicidal ideation at some point during short-term treatment of up to 12 weeks. Of these 54, 51 scored a 2 on QIDS-C item 12, 2 reported a QIDS-C score of 3 (active suicidal ideation), and 1 made a suicide attempt. Among the men, the *rs7569963* and *rs4675690* SNPs showed a significant association with suicidality (Table 2 and Figure 2) with permuted $P=.005$; results were essentially unchanged by inclusion of history of suicide attempt or overall depression severity as measured by the IDS-C30, QIDS-C_{16}, or $HRSD_{17}$, as a covariate (results not shown). Likewise, when the analysis was restricted to the 426 white participants, results were similar (permuted *P* value was .005 for *rs4675690* and .004 for *rs7569963*).

For illustrative purposes, a Kaplan-Meier estimated time course of suicidal ideation emergence among men, censored at time of study discontinuation or dropout, with curves separated by genotype at *rs4675690*, is displayed in **Figure 3**. Overall, 19 (16%) of those 118 individuals homozygous for the T allele at *rs4675690* experienced emergence of suicidality vs 8 (5%) of those 164 homozygous for the C allele.

In the male participants, an initial haplotype analysis that incorporated all 5 SNPs in an omnibus test for any joint effect of the 5-marker haplotypes observed was statistically significant ($P=.04$); therefore, we performed haplotype-specific tests (ie, eight 1-*df* tests of each haplotype vs all others) (Table 2 and Figure 2). These tests indicated that 2 of 8 haplotypes were significantly associated ($P=.004$ and $P=.009$). The most common haplotype appears to be protective (ie, to be underrepresented among those who developed suicidal ideation).

The primary analyses indicated a sex-specific association between 2 SNPs that flanked *CREB1* and treatment-emergent suicidality. To examine the possibility that *CREB1* polymorphisms were associated with proneness to suicidality before treatment, rather than treatment-emergent suicidality in particular, men with and without suicidality at study entry were compared. No statistically significant association was noted between any SNP and the presence or absence of baseline suicidality. Likewise, no evidence of association was noted between any SNP and history of lifetime suicide attempt.

We also examined the potential confounding effect of sedative or hypnotic use during citalopram treatment, as allowed by the protocol. Among the male participants, 111 (21%) of 539 received sedative or hypnotic cotreatment, including 92 (19%) of 485 with no suicidality and 19 (35%) of 54 with suicidality ($\chi^2_2=7$; $P=.008$). Individuals who received sedative or hypnotic cotreatment were significantly more likely to experience suicidality ($P=.02$; OR, 2.3; 95% confidence interval [CI], 1.2-4.5). However, in a regression model, *rs4675690* remained significantly associated with suicidality after adjustment for presence or absence of cotreatment (OR, 1.91; 95% CI, 1.3-2.9).

Finally, because previous studies[16,18] have suggested that antidepressant-associated suicidality often occurs in the first month of treatment, we performed a secondary analysis in which suicidality was divided by epoch (ie, new suicidality occurring within 30 days, between 30 and 60 days, and beyond 60 days). For the initial 30 days, statistically significant association ($P<.003$; OR, 2.3; 95% CI, 1.3-3.9) remained between *rs4675690* and new suicidality. However, for suicidality emerging after 30 days, no statistically significant association was evident ($P>.05$).

COMMENT

In this analysis of 1447 outpatients with MDD without suicidality who initiated citalopram treatment, 8.6% subsequently reported emergence of such ideation during short-term antidepressant treatment. Among men, risk of emergence of suicidality was associated with 2 SNPs that flanked *CREB1* that were previously implicated in a measure of anger expression in an independent cohort of men with MDD.[31] The present finding therefore partially replicates and extends the initial association with a quantitative trait in our previous cohort. Notably, the risk alleles in our cohort correspond to those associated with lower outward expression of anger in a previous cohort with MDD,[31] consistent with models associating suicidality with inwardly rather than outwardly directed anger, particularly among men.[53,54] To our knowledge, this finding represents the first association between a genetic polymorphism and antidepressant-associated suicidality. The STAR*D study cohort is one of few with sample sizes sufficient to allow examination of this uncommon but clinically important outcome.

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Table 1. Clinical Features of Genotyped STAR*D Participants Without Suicidality at Study Entry

Treatment-Associated Suicidality	No (n = 1324)	Yes (n = 124)	Total (N = 1447)	Significance Test	*P* Value
Mean (SD)*					
Current age, y	42.5 (13.4)	42.3 (13.20)	42.5 (13.4)	0.3	.80
Age at first episode, y	26.7 (14.8)	24.4 (13.80)	26.5 (14.8)	1.7	.10
Baseline $HRSD_{17}$ score	19.0 (6.3)	21.0 (6.40)	19.2 (6.3)	–3.3	<.001
Baseline IDS-C score	34.0 (11.1)	37.9 (11.60)	34.3 (11.2)	–3.6	<.001
Baseline QIDS-C score	15.6 (3.1)	17.0 (3.30)	15.7 (3.1)	–4.9	<.001
No. (%)†					
Male	486 (36.7)	54 (43.6)	539 (37.3)	2.3	.10
White	1050 (79.3)	94 (75.8)	1143 (79.0)	0.8	.40
Recurrent depression	913 (74.8)	95 (82.6)	1007 (75.5)	3.4	.10
Hopelessness, baseline‡	692 (52.3)	99 (80.5)	791 (54.7)	36.2	<.001
History of suicide attempt	150 (11.4)	22 (17.70)	124 (8.6)	4.4	.04

Abbreviations: $HRSD_{17}$, 17-item Hamilton Rating Scale for Depression; IDS-C, Inventory of Depressive Symptomatology–Clinician Rated; QIDS-C, Quick Inventory of Depressive Symptomatology–Clinician Rated.
*t test.
†χ^2_2 test.
‡Hopelessness was defined as a QIDS-C item 12 score of 1.

Table 2. Single Marker and Haplotype Test Results for Association With Treatment-Emergent Suicidality for All Participants and a Male-Only Subset

	rs2709376	*rs2253206*	*rs7569963*	*rs7594560*	*rs4675690*	Freq (Males)	Freq (Males: SI+)	Freq (Males: SI–)	Empirical *P* Value (Males)
Hap1	C	A	A	T	C	0.25	0.14	0.26	.004
Hap2	C	G	G	T	T	0.23	0.28	0.22	.16
Hap3	C	G	G	T	C	0.19	0.15	0.19	.21
Hap4	C	A	G	T	T	0.09	0.16	0.08	.009
Hap5	C	G	G	C	T	0.08	0.07	0.08	.45
Hap6	C	A	G	T	C	0.07	0.09	0.07	.55
Hap7	T	A	G	T	C	0.03	0.04	0.03	.84
Hap8	T	A	G	C	T	0.03	0.05	0.03	.16
Hap9	T	A	G	T	T	0.01	0.03	0.01	.10
Hap10	C	G	A	T	T	0.01	0.01	0.01	.68
Minor allele	T	G	A	C	T				Omnibus .04
MAF (all participants)	0.08	0.5	0.28	0.11	0.46				
Empirical *P* value (all participants)	.21	.86	.14	.86	.13				
SNP-by-sex *P* value	.76	.79	.02	.39	.007				
MAF (all males)	0.09	0.49	0.28	0.1	0.46				
MAF (males: SI+)	0.11	0.49	0.17	0.09	0.59				
MAF (males: SI–)	0.08	0.5	0.29	0.1	0.44				
Empirical *P* value (males)	0.36	0.87	0.005	0.70	0.005				

Abbreviations: Freq, haplotype frequency; MAF, minor allele frequency; SI+, emergence of suicidality; SI–, no suicidality; SNP, single nucleotide polymorphism.

The rate of suicidal ideation emergence is similar to or slightly less than that observed in other studies. For example, in a previous group of 400 fluoxetine-treated patients, 14.3% subsequently had emergence or worsening of suicidality on at least at 1 subsequent visit throughout 12 weeks. Similarly, a previous meta-analysis[9] that included fluoxetine found worsening of the suicidal ideation score ($HRSD_3$ score increasing by any amount) in 15.3%. Of note, only 1 participant in the STAR*D genetics cohort made a suicide attempt, and there were no completed suicides.

In addition to multiple linkage peaks identified in a genomewide linkage survey,[55] a number of candidate gene studies have reported associations with suicide or suicide attempts, although most have not been replicated; these include studies of the serotonin transporter,[56,57] tryptophan hydroxylase,[58-62] and other monoaminergic genes.[63-70] Association studies such as this one may yield false-positive results when the prior probability of association is low. Importantly, therefore, *CREB1* represented a particularly appealing functional candidate gene because its product is known to be associated with antidepressant effects and suicide. Region-specific alterations in CREB protein activity have been observed in animal models of antidepressant treatment.[23-25] In humans, changes in CREB protein expression and phosphorylation have been demonstrated in those committing suicide,[26-28] and the *CREB1* region has been linked to MDD.[29,71] Finally, we recently observed an association between the same *CREB1* poly-

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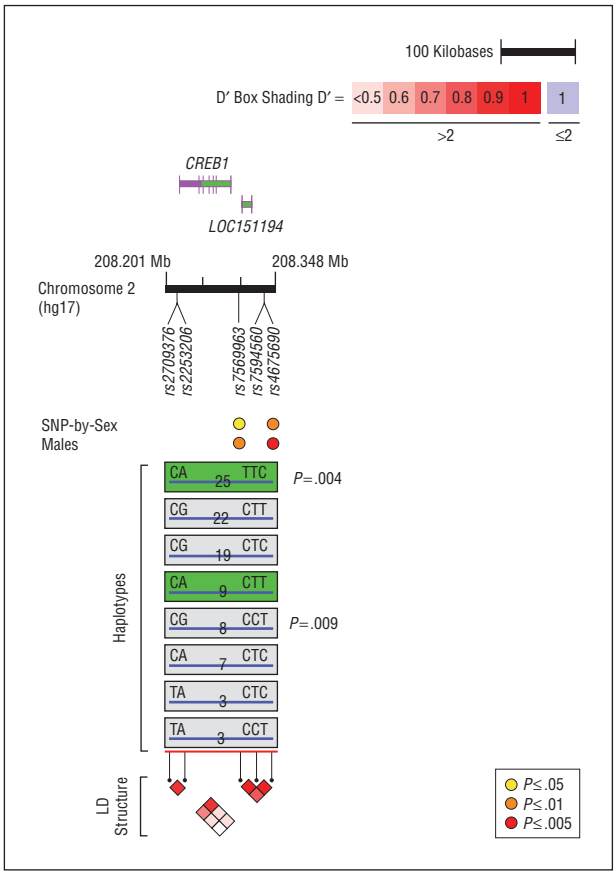

Figure 2. Location of single nucleotide polymorphisms (SNPs) that span the *CREB1* gene, SNP × sex interactions, and strength of association with treatment-emergent suicidality. hg17 indicates Human Genome Sequence 17 (Single Nucleotide Polymorphisms database, National Center for Biotechnology Information, build 35, May 2004); LD, linkage disequilibrium; and Mb, megabases.

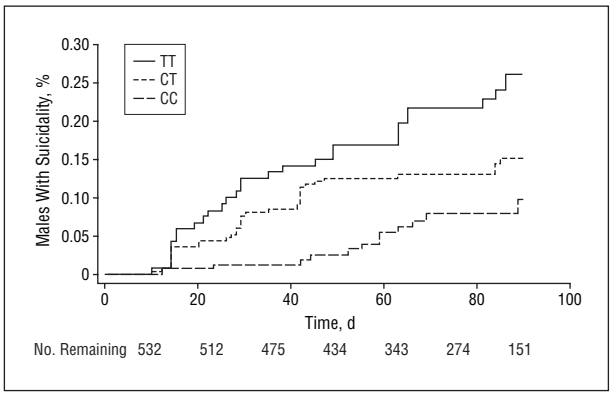

Figure 3. Kaplan-Meier failure curve for emergence of suicidality among males with depression treated with citalopram by genotype (*rs4675690*).

morphisms and a measure of anger expression among males but not females in a sample of 94 patients with MDD[31]; hostility and anger expression have also been associated with suicide.[36,72] We thus hypothesized that antidepressant treatment might provide an additional stress in a subset of male patients with MDD with an underlying diathesis and that this diathesis would be associated with *CREB1* polymorphisms.

An important question in interpreting these results is their treatment specificity, that is, to what extent might they reflect risk associated with the antidepressant citalopram vs natural fluctuation in illness severity or placebo response. Without a placebo comparator, we cannot directly address this question. Notably, patients often initiate antidepressant treatment when their symptoms are most severe, which could contribute to an apparently elevated early risk of suicidality.[16] However, we note that the SNPs associated with treatment-emergent suicidality did not demonstrate association with suicidality at baseline.

A key limitation in the present study is the reliance on a single rating scale item that captures suicidal ideation. Of note, similar single-item measures exhibit excellent interrater reliability[73] and correlate well with the Beck Scale for Suicide Ideation.[74] Such a measure also has predictive validity: a 20-year prospective study[75] found that individuals who scored 2 or higher on item 3 of the $HRSD_{17}$ were 4.9 times as likely to commit suicide as individuals scoring lower than 2; other studies also support the predictive role, even if imperfect, of suicidal thoughts.[76,77]

We also note that neither of the 2 SNPs with evidence of association lie in coding regions; *rs4675690* is 3′ to the coding region of *CREB1*, adjacent to a second gene (*LOC151194*, similar to hepatocellular carcinoma–associated antigen HCA557b, which is known to be expressed in the brain), whereas *rs7569963* is in the 3′ untranslated region for both genes. Although a less likely a priori candidate, *LOC151194* cannot be excluded as mediating the observed association (eTable). Our SNPs tagged (with r_2>0.8) all but 2 of the known HapMap SNPs in the region with minor allele frequency greater than or equal to 0.05 (Single Nucleotide Polymorphism database of the National Center for Biotechnology Information, build 125: http://www.ncbi.nlm.nih.gov/SNP/index.html). There is currently only 1 known (noncoding) exonic SNP in CREB in this database. Thus, if *CREB1* influences treatment-emergent suicidality, the causal variant remains to be determined, because none of the polymorphisms directly assayed here are known to affect *CREB1* expression or function. Of note, the tagging approach captures common variations but may not account for SNPs not included in HapMap or those with low (<5%) minor allele frequency. Finally, we cannot entirely exclude the possibility of spurious association arising from population stratification,[78] despite the persistence of association when the cohort is limited to white individuals.

The sex-specific nature of the association is intriguing and merits further study. We hypothesized a gene-by-sex interaction based on evidence from a prior study of *CREB1* and anger expression in MDD.[31] Interestingly, Zubenko et al[79] reported linkage between the *CREB1* region and recurrent, early-onset MDD in women but not men. Female patients with depression may express lower levels of anger or irritability in general; in the same way, their antidepressant response phenotype may differ from that of men.[80]

Regardless of specificity, the associations noted between symptoms and suicidal thinking have potential

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clinical implications in identifying a higher-risk subgroup among depressed patients; interventions that benefit most patients may still be associated with worsening in a small subset.[14,15] The ability to identify this group could allow both patients and clinicians to proceed with antidepressant use with greater confidence or focus more attention on the high-risk group. Before consideration of clinical application of these findings, the confirmation in other antidepressant trial data sets, particularly those with placebo control, will be critical to clarify their specificity and generalizability.

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