Published in final edited form as:
Am J Psychiatry. 2010 December ; 167(12): 1499–1507. doi:10.1176/appi.ajp.2010.10040541.

Genome-Wide Association Study of Suicide Attempts in Mood Disorder Patients

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Abstract

Objective—Family and twin studies suggest that liability for suicide attempts is heritable and distinct from mood disorder susceptibility. The authors therefore examined the association between common genomewide variation and lifetime suicide attempts.

Method—The authors analyzed data on lifetime suicide attempts from genomewide association studies of bipolar I and II disorder as well as major depressive disorder. Bipolar disorder subjects were drawn from the Systematic Treatment Enhancement Program for Bipolar Disorder cohort, the Wellcome Trust Case Control Consortium bipolar cohort, and the University College London cohort. Replication was pursued in the NIMH Genetic Association Information Network bipolar disorder project and a German clinical cohort. Depression subjects were drawn from the Sequential Treatment Alternatives to Relieve Depression cohort, with replication in the Netherlands Study of Depression and Anxiety/Netherlands Twin Register depression cohort.

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Results—Strongest evidence of association for suicide attempt in bipolar disorder was observed in a region without identified genes (rs1466846); five loci also showed suggestive evidence of association. In major depression, strongest evidence of association was observed for a single nucleotide polymorphism in *ABI3BP*, with six loci also showing suggestive association. Replication cohorts did not provide further support for these loci. However, meta-analysis incorporating approximately 8,700 mood disorder subjects identified four additional regions that met the threshold for suggestive association, including the locus containing the gene coding for protein kinase C-epsilon, previously implicated in models of mood and anxiety.

Conclusions—The results suggest that inherited risk for suicide among mood disorder patients is unlikely to be the result of individual common variants of large effect. They nonetheless provide suggestive evidence for multiple loci, which merit further investigation.

Epidemiologic studies indicate that mood disorders are associated with a marked increase in risk for suicide and suicide attempts, with one such study suggesting a 20-fold greater risk of death from suicide compared with the general population (1). The familiality of suicide risk is well-established (for a review, see Brodsky et al. [2]) and not accounted for solely by familial transmission of mood disorders (3–5). For example, a family-based study of a large, bipolar disorder cohort suggested that lifetime suicide attempts were among the more strongly familial features of the disorder (6). That risk for suicide attempt in particular is heritable is supported by twin studies (7, 8), with heritability estimates ranging from 30%–50%, intermediate between major depressive disorder and bipolar disorder. Adoption studies suggest that this risk cannot be explained solely by shared environment (9).

Individual candidate-gene studies have implicated genes of the serotonergic or noradrenergic system (10–14), hypothalamic-pituitary-adrenal axis (15,16), renin-angiotensin system (17), and neuronal development (18–20) and function (21) in the propensity for suicide, using a variety of case and control definitions (for a review, see Brezo et al. [22]). However, given the limited understanding of pathophysiology, prioritizing candidates for study has been difficult and likely accounts for the near absence of consistent replication. The emergence of low-cost approaches for characterizing common genetic variation across the genome facilitates an alternate approach, which may lead to identification of truly novel risk factors, as has been the case in nonpsychiatric disorders (23).

Therefore, we analyzed data from multiple genomewide association studies to identify variations associated with suicide risk. To minimize the potential heterogeneity introduced by pooling mood disorder subjects, cohorts with bipolar disorder and major depression were examined separately and then combined for meta-analysis. In all, data from >8,700 mood disorder subjects were used to detect and replicate associations.

Method

Study Design, Genotyping, Quality Control, and Imputation

The cohorts examined in the present study are summarized in Table 1. For bipolar disorder, genomewide association data were derived from three nonoverlapping cohorts of bipolar I or II patients, all of which were included in a previously reported meta-analysis of disease liability (24). These bipolar disorder cohorts were from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) (25, 26), the Wellcome Trust Case Control Consortium (27), and the University College London. Details of sample ascertainment and genotyping have been previously described by Ferreira et al. (24). Quality control and imputation using MACH (28) are described in the original reports (summarized

in the data supplement accompanying the online version of this article), yielding 1,922,309 single nucleotide polymorphisms (SNPs) in 3,117 subjects.

Follow-up analyses examined the most significant SNPs from these cohorts in pooled data from the following three additional bipolar disorder cohorts: the initial Genetic Association Information Network (GAIN) bipolar disorder project and the Translational Genomics Research Institute samples (29), both drawn from the five waves of sample collection in the NIMH Bipolar Disorder Genetics Initiative (30), and a sample of German individuals collected at the Universities of Bonn and Heidelberg (31). Genotyping, quality control, and imputation are described by Smith et al. (29) and McMahon et al. (31).

Table 1 also lists the major depression cohorts included in primary and replication analyses, which were the Systematic Treatment Alternatives to Relieve Depression (STAR*D) cohort (32) and the GAIN depression cohort that was derived from the Netherlands Study of Depression and Anxiety (33)/Netherlands Twin Register (34) cohorts (35). The former data set was used in initial analyses, with replication pursued in the latter. Details of genotyping and quality control for the STAR*D cohort have been previously described by Garriock et al. (36) (for additional quality control steps and imputation using MACH, see the data supplement), yielding 1,954,455 SNPs in 1,273 subjects. For the Netherlands Study of Depression and Anxiety/Netherlands Twin Register, methods are described by Sullivan et al. (35). Imputation was performed using IMPUTE (http://mathgen.stats.ox.ac.uk/impute/impute.html), with a threshold of 70% confidence.

Identification of Lifetime Suicide Attempts

For the STEP-BD cohort, determination of lifetime suicide attempts was conducted using all available sources of information, including the Affective Disorders Evaluation (37), which incorporates questions from the Structured Clinical Interview for DSM-IV Axis I Disorders (38) at study entry, as well as data regarding suicide attempt during the study period documented as serious adverse effect or hospitalization. In the Wellcome Trust Case Control Consortium, lifetime suicide attempts were identified with a semistructured diagnostic psychiatric interview. Assessment of the University College London cohort was conducted utilizing the Schedule for Affective Disorders and Schizophrenia–Lifetime version (39), which includes questions about the presence or absence of lifetime suicide attempt. Among the replication cohorts, the GAIN and Translational Genomics Research Institute samples were assessed using the Diagnostic Interview for Genetic Studies (40), which includes questions regarding lifetime suicide attempt. Assessment of the German university cohorts also incorporated structured interview and review of psychiatric history.

In the STAR*D cohort, lifetime history of suicide attempts was assessed at the initial study visit by the study clinician (41); suicidality was not exclusionary, provided the patient did not require hospitalization for stabilization. Finally, lifetime suicide attempt in the Netherlands Study of Depression and Anxiety/Netherlands Twin Register group was determined at diagnostic interview, which included the Composite International Diagnostic Interview, version 2.1 (42).

Analysis

Primary analyses were performed with logistic regression of the presence or absence of suicide attempt on single SNP allelic dosage, adjusted for the first four components from the aforementioned multidimensional scaling plot, to address the possibility of confounding by population substructure. Analyses were conducted using PLINK, version 1.07 (43). Results were not meaningfully different with inclusion of the first 10 indices of ancestry.

The bipolar disorder and major depression cohorts were initially analyzed independently as discovery data sets, based on the hypothesis that suicide susceptibility could be diagnosis-specific so that pooling across mood disorders would increase heterogeneity and diminish power to detect association. All available data sets were initially pooled, rather than holding some out to allow for a replication cohort. Therefore, to examine suicide liability among patients diagnosed with bipolar disorder, combined data from the STEP-BD, Wellcome Trust Case Control Consortium, and University College London cohorts were analyzed jointly. For replication, any SNP with a p value $<1\times10^{-3}$ in this combined cohort was then examined in the combined GAIN, Translational Genomics Research Institute, and German cohorts. In parallel, STAR*D data were analyzed for association with suicide attempts among individuals with major depression. For replication, any SNP associated with a p value $<1\times10^{-3}$ was then examined in the Netherlands Study of Depression and Anxiety/ Netherlands Twin Register cohorts. Power to detect association at the nominal threshold for replication ($p<1\times10^{-3}$) in the bipolar discovery cohort was >95% for a minor allele frequency of 20% and genotypic risk ratio of 1.25, corresponding to a genotypic odds ratio of approximately 1.36. For depression, power under the same conditions decreased to 33%.

Finally, to examine the hypothesis that suicide liability arises from variation common to depression and bipolar disorder, random effects meta-analysis was used to examine any SNP implicated in either bipolar disorder or depression with a p value $<1\times10^{-3}$ across all mood disorder subjects, using PLINK. For the combined cohorts, power was >90% to detect association at a p value $<5\times10^{-8}$ for a minor allele frequency of 20% and genotypic risk ratio of 1.2, which in the present study corresponds to a genotypic odds ratio of approximately 1.3.

For descriptive purposes, a set of candidate genes was identified based upon previous reports of association. Candidates were selected based on a MEDLINE search, performed in June 2010, using the terms “suicide,” “genetic,” and “association,” followed by manual review of abstracts under the name of the corresponding author of the articles identified. Any gene with at least one report of significant association with suicide attempt was included, even if such association was identified only in a subset of subjects. This search yielded 19 regions. We performed gene-based tests by combining the single-SNP p values, using a weighted-inverse chi-square method that accounts for correlation between tests (44), implemented in PLINK. We used the correlation between alleles (i.e., linkage disequilibrium) in the Caucasian-European (Centre d’Etude du Polymorphisme Humain from Utah) phase II HapMap project to estimate the correlation between tests, which performed well in simulation experiments. For descriptive purposes, the minimum p value for any SNP within the gene or 20-kb flanking regions was also identified.

Results

In the bipolar disorder cohort, 1,295 out of 3,117 subjects (41.5%) reported a history of suicide attempts. Figures 1 and 2 in the data supplement show Q-Q and Manhattan plots for suicide attempts in this cohort (λ=1.003). A total of five loci included SNPs with a p value $<1\times10^{-5}$; the minimum p value was 1.98×10^{-6} (rs1466846, with no known gene within 400 kb) (Table 2 [also see Table 1 in the data supplement]). None of these loci yielded a nominal p value <0.05 in the bipolar disorder replication cohort, which included 2,698 subjects, of whom 1,201 (44.5%) reported a lifetime history of suicide attempts.

Among 1,273 subjects with major depression, 176 (9.9%) reported a history of suicide attempts. Q-Q and Manhattan plots for this cohort are presented in Figure 3 and Figure 4 in the data supplement (λ=1.017). A total of six loci included SNPs with a p value $<1\times10^{-5}$; the minimum p value was 2.55×10^{-8} (rs2576377 in gene ABI3BP) (Table 3 [also see Table

2 in the data supplement]). However, none of these regions yielded a p value <0.05 in a second depression cohort of 1,649 subjects, including 133 individuals (8.1%) with a history of suicide attempts.

We also examined association results in 19 genes previously suggested to be associated with suicide attempts in at least one prior report. Table 4 lists the results of a gene-based test for association, which accounts for correlation between tests (SNPs) within a gene. Two genes, *FKBP5* and *NGFR* (p75NTR), showed nominal evidence of association in bipolar disorder subjects (uncorrected p<0.05) but did not survive correction for 19 comparisons (see Table 4 in the data supplement). Minimum single-SNP p values for each gene (with 20-kb flanking regions) are presented in the data supplement.

Lastly, we examined any SNP with a p value $<1\times10^{-3}$ in either the major depression or bipolar disorder discovery cohort, using random-effects meta-analysis across all available mood disorder subjects (N=8,737). None of the aforementioned loci identified were more strongly implicated by meta-analysis. Table 5 shows all SNPs with a p value $<1\times10^{-5}$ in the overall meta-analysis (complete results are shown in Table 3 of the data supplement). The 10 SNPs that met this threshold are in four loci, including SNPs in genes coding for sorbin and SH3-domain containing-1 (*SORBS1*) and protein kinase C-epsilon (*PRKCE*).

Discussion

We examined and then attempted to replicate associations with suicide attempt liability among a total of approximately 2,900 subjects with major depression and approximately 5,800 subjects with bipolar disorder. One region, with multiple intronic SNPs in Abl-interactor family member 3 binding protein (*ABI3BP* or *TARSH*) (45), met our threshold for genomewide significance in suicide attempt liability among individuals with depression but failed to replicate in a second cohort. This gene is known to be expressed in brain as well as multiple other organ systems, but its function is not well-characterized, although it may have effects in apoptosis and senescence (46–48). While the most likely explanation for this nonreplication remains a type I error, we also note that heterogeneity between STAR*D and the Netherlands Study of Depression and Anxiety/Netherlands Twin Register has been suggested as another explanation for nonreplication of significant associations with variants in the Piccolo (*PCLO*) region in depression liability (35). Other regions with suggestive evidence of association in depression include *SLC4A4*, coding for a sodium bicarbonate cotransporter, which is also widely expressed (and believed to interact with inositol triphosphate signaling [49]); hyaluronan synthase-1 (*HAS1*), important in synthesis of extracellular matrix and brain inflammatory response (50, 51); adenosine diphosphateribosylation factor-like-6-interacting protein-2 (*ARL6IP2*), whose expression is influenced by nitric oxide signaling (52); and the putative leucinerich repeat-containing protein 44 (*LRRC44* or *LRRIQ3*) (53).

Among the most regions with the greatest evidence of association in bipolar disorder were the transducin beta-like receptor 1 (*TBL1XR1*), implicated in gene activation by nuclear receptors (for example, based upon presence in histone deacetylase-3 (*HDAC3*) complexes [54]); Iroquois homeobox protein 2 (*IRX2*), important in embryonic pattern formation, including brain development (55); and calpain-13 (*CAPN13*), part of a class of cysteine proteases with multiple functions, including synaptic plasticity (56). Once again, no single SNP showed evidence of replication in a second cohort. Examination of candidate regions using a gene-based test provided modest support for two loci, *FKBP5* and *NGFR* (p75NTR), identified in previous investigations of suicide attempt (19, 20), although neither results survived correction for the 19 tests performed.

Meta-analysis of association data across mood disorders did not provide further support for the novel loci identified in the discovery cohorts. However, SNPs in two genes were associated with a p value $<1\times10^{-5}$. The first, *SORBS1*, has been implicated in insulin signaling (57); its product was also shown to interact with ataxin-7, the site of a trinucleotide repeat causing spinocerebellar atrophy type 7 (58). The second, *PRKCE*, is most notable because *PRKCE* null mice have been shown to exhibit reduced anxiety behavior and lower levels of multiple stress hormones, with increased sensitivity to neurosteroids that modulate gamma-aminobutyric acid type A receptors (59). A recent postmortem study found differences in expression of multiple protein kinases, including *PRKCE*, in individuals with depression relative to comparison subjects (60). Overall, this examination of approximately 8,700 mood disorder subjects may provide a framework for considering future association results.

While our results provide some support for multiple novel regions of potential interest, they also suggest that individual common variants of large effect are unlikely to account for the known heritability of suicide risk, leading to the problem of missing heritability. A recent review described multiple potential explanations for the observed paucity of common variants of large effect, noting the potential importance of epistatic or epigenetic effects, for example, among many others (61). Notably, the absence of large effects also does not preclude SNPs in aggregate accounting for a substantial proportion of disease risk, which may be the case in schizophrenia, for example (62). However, it also bears consideration that suicide liability should detract from reproductive fitness, with the pressure of purifying selection acting to keep risk variants rare, which might argue for more aggressive pursuit of rare variants (61).

Several features of our analytic approach bear consideration. We prioritized a within-disorder analysis to minimize the potential heterogeneity introduced by combining mood disorder subjects in the absence of strong evidence of cross-disorder risk. Pooling both disorders could have improved our power to detect association but at the cost of reducing power because of heterogeneity. Similarly, while we initially analyzed all samples available to us (rather than holding some out in order to allow for replication), we were later able to identify replication data sets, but not to fully pool results. Thus, the final design included discovery followed by replication. We pursued a replication-discovery design.

We elected to assess the harder endpoint of suicide attempt rather than lifetime suicidal ideation for two reasons. First, the latter is difficult to assess retrospectively, while recall and other biases are less likely to impact reporting of suicide attempt, particularly where sources of collateral information, such as emergency room visits or hospital discharge summaries, are available. Retrospective suicidal ideation was not assessed in STEP-BD or STAR-D. Second, twin studies suggest that while much of the heritability of thoughts of suicide may be accounted for by familial transmission of disease liability, risk for suicidal behavior may be more distinctly heritable (2). An important caveat in considering these results is that lifetime suicide attempt was not the primary phenotype of interest in these cohorts and was assessed by one or a few items on a scale. Thus, it is likely that suicide attempt was underreported in these cohorts, which would lead to misclassification error and diminish our power to detect association. In addition, while many mood disorder subjects make a suicide attempt early in their illness course, we cannot exclude the possibility that some subjects labeled as nonattempters would ultimately go on to make an attempt, leading to further misclassification.

Also of note, to minimize type I error, we did not consider any subphenotypes. Investigations of suicide often focus on the nature of the suicide attempt, in terms of degree of aggression or violence involved; more violent or more potentially lethal attempts have

been suggested to represent a subgroup with greater homogeneity (63). However, the majority of cohorts examined in the present study did not distinguish this phenotype. We also did not conduct sex-stratified analyses. While suicidal behavior may differ by sex, we could not identify a strong rationale for positing sex differences in heritability and were mindful of the hazards of this sort of subanalysis (64).

Some prior investigations of suicide have compared suicide attempters with healthy comparison subjects. In the present study, we elected instead to contrast attempters with nonattempters among a single disorder, which allowed us to distinguish genes conferring suicide risk beyond that conferred by the disorder itself. That is, rather than a case-control association study of the putative subtype of bipolar-plus-suicide attempt, we focused on suicide liability per se.

Taken together, our results suggest an absence of common variants of large effect mediating suicide liability in mood disorders. A recent investigation of bipolar disorder and schizophrenia liability suggested that a substantial portion of risk for these disorders may be highly polygenic (62). The observation of an excess of SNPs with p values approximately $\geq 1\times10^{-3}$, apparent in both Q-Q plots but particularly in that of the depression cohort, would be consistent with this model. For the effect sizes observed in our meta-analysis (i.e., odds ratio of approximately 1.2), approximately 7,000 suicide attempt cases (with matched nonattempting comparison subjects) would be required for 80% power to identify SNPs with a minor allele frequency of 20% and a p value $<5\times10^{-8}$. Thus, analysis of even larger cohorts, in the context of consortia such as the Psychiatric Genomewide Association Study Consortium (65), and consideration of alternate models of heritability—for example, using polygenic models or considering rarer variants of larger effect—may be required to identify loci that confer risk for suicide in mood disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Dr. Perlis has received research support from Eli Lilly and Elan/Ei-sai; he has received advisory/consulting fees from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, and Pfizer; he has received speaking fees or honoraria from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Glaxo-SmithKline, and Pfizer; and he has equity holdings and patents with Concordant Rater Systems. Dr. Fava has received research support from Abbott Laboratories, Alkermes, Aspect Medical Systems, Astra-Zeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly, Forest Pharmaceuticals, GlaxoSmithKline, J and J Pharmaceuticals, Lichtwer Pharma GmbH, Lorex Pharmaceuticals, Novartis, Organon, Pamlab, Pfizer, Pharmavite, Roche, Sanofi/Synthelabo, Solvay Pharmaceuticals, and Wyeth-Ayerst Laboratories; he has received advisory/consulting fees from Aspect Medical Systems, AstraZeneca, Bayer AG, Biovail Pharmaceuticals, BrainCells, Bristol-Myers Squibb, Cephalon, Compellis, Cypress Pharmaceuticals, Dov Pharmaceuticals, Eli Lilly, EPIX Pharmaceuticals, Fabre-Kramer Pharmaceuticals, Forest Pharmaceuticals, GlaxoSmithKline, Grunenthal GmbH, Janssen Pharmaceutica, Jazz Pharmaceuticals, J and J Pharmaceuticals, Knoll Pharmaceutical, Lundbeck, MedAvante, Neuronetics, Novartis, Nutrition 21, Organon, Pamlab, Pfizer, PharmaStar, Pharmavite, Roche, Sanofi/Synthelabo, Sepracor, Solvay Pharmaceuticals, Somaxon, Somerset Pharmaceuticals, and Wyeth-Ayerst Laboratories; he has received speaking fees from AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Cephalon, Eli Lilly, Forest Pharmaceuticals, GlaxoSmith-Kline, Novartis, Organon, Pfizer, PharmaStar, and Wyeth-Ayerst Laboratories; and he is a share holder with Compellis and MedAvante. Dr. Rush has served as a consultant for AstraZeneca, Bristol-Myers Squibb/Otsuka, Merck, and Otsuka Pharmaceuticals; he has also received royalties from Guilford Publications and Healthcare Technology Systems. Dr. Smoller has served as a consultant to Eli Lilly; he has received honoraria from Hoffman-La Roche, Enterprise Analysis, and MPM Capital; and he has served on an advisory board for Roche Diagnostics Corporation. Dr Sullivan receives unrestricted research funding from Eli Lilly for genetic research in schizophrenia.

Supported by National Institute of Mental Health grant R01MH-086026 (Dr. Perlis). Drs. McMahon and Schulze are supported by the NIMH Intramural Research Program.

The authors thank the patients who participated in the genetic studies summarized in this article, including participants in STEP-BD, the Wellcome Trust Case Control Consortium, the University College London, the Genetic Association Information Network, the Translational Genomics Research Institute, and the Netherlands Study of Depression and Anxiety/Netherlands Twin Register.

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TABLE 1

Mood Disorder Cohorts Included in Suicide Attempt Analyses

			Suicide Attempt	
Disorder Cohort	**Study Cohort**	**N**	**N**	**%**
Bipolar disorder				
Discovery	STEP-BD; Wellcome Trust Case Control Consortium; University College London	3,117	1,295	41.5
Replication	GAIN bipolar disorder project; Translational Genomics Research Institute; Universities of Bonn/Heidelberg	2,698	1,201	44.5
Major depressive disorder				
Discovery	STAR*D Caucasian	1,273	176	9.9
Replication	Netherlands Study of Depression and Anxiety/Netherlands Twin Register	1,649	133	8.1
Combined		8,737	2,805	32.1

TABLE 2

Loci Showing Strongest Evidence of Association With Suicide Attempt in Bipolar Disorder Discovery Cohort

Chromosome	SNP	p	Additional SNPs (p<0.0001)	Nearest Gene	Distance	Replication (p)
3	rs1466846	1.98E-06	7	*TBL1XR1*	417,958 Base pairs downstream	0.19
5	rs924134	6.12E-06	6	*IRX2*	278,504 Base pairs upstream	0.37
2	rs6548036	7.37E-06	12	*CAPN13*	Intron 21	0.07
8	rs1457463	8.45E-06	8	*ZNF406*	390,253 Base pairs upstream	0.31
3	rs11130703	9.37E-06	0	*FLJ42117*	322,475 Base pairs downstream	0.23

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TABLE 3

Loci Showing Strongest Evidence of Association With Suicide Attempt in Major Depressive Disorder Discovery Cohort

Chromosome	SNPs	p	Additional SNPs (p<0.0001)	Nearest Gene	Distance	Replication (p)
3	rs2576377	2.55E-08	39	*ABI3BP*	Intron 34	0.70
4	rs2602098	8.80E-07	1	*SLC4A4*	Intron 3	0.39
1	rs1417259	3.17E-06	38	*LRRC44*	73,264 Base pairs upstream	0.77
4	rs7655668	4.16E-06	17	*SLC4A4*	Intron 1	0.22
19	rs12462673	8.85E-06	0	*HAS1*	17,710 Base pairs upstream	0.07
2	rs6737169	8.86E-06	13	*ARL6IP2*	Intron 12	0.24

TABLE 4

Gene-Based Tests of Association for 19 Candidate Loci

	Bipolar Disorder		Major Depression	
Gene	**Single Nucleotide Polymorphisms**	**Gene (p)**	**Single Nucleotide Polymorphisms**	**Gene (p)**
ACE	11	0.30	21	0.38
ADRA2A	10	0.81	16	0.44
AKT1	9	0.81	11	0.57
COMT	48	0.18	43	0.62
CRHBP	20	0.15	18	0.18
CRHR1	66	0.38	65	0.41
CRHR2	26	0.37	26	0.48
DRD2	92	0.71	98	0.67
FKBP5	41	0.04	41	0.20
HTR1A	12	0.09	12	0.88
HTR2A	120	0.29	122	0.47
LSAMP	417	0.06	414	0.82
NGFR	12	0.03	12	0.65
NOS1	111	0.17	113	0.54
NTRK2	316	0.85	341	0.47
SLC6A4	37	0.09	36	0.06
TAAR6	65	0.72	64	0.71
TPH1	40	0.28	40	0.37

TABLE 5

Loci Showing Strongest Evidence of Association With Suicide Attempt in Meta-Analysis of All Mood Disorder Subjects

Chromosome	Base Pair	SNP	A1	A2	Random Effects (p)	Odds Ratio (random-effects model)	Cochrane's Q Statistic (p)	Heterogeneity Index (I^2)	Annotation
10	97112231	rs4918918	C	T	3.28E-06	0.8456	0.81	0	*SORBS1*(0), *PDLIM1* (+71.46 kb)
10	97113875	rs955760	A	G	4.87E-06	0.8513	0.52	0	*SORBS1*(0), *PDLIM1* (+73.1 kb)
10	97109039	rs7900095	C	T	5.58E-06	0.8501	0.81	0	SORBS1(0), *PDLIM1* (+68.27 kb)
21	39943622	rs10854398	C	T	6.06E-06	1.178	0.62	0	*IGSF5*(−95.58 kb), *B3GALT5* (−7.501 kb)
10	97109583	rs7079293	C	T	6.19E-06	0.8507	0.79	0	*SORBS1*(0), *PDLIM1* (+68.81 kb)
21	39947754	rs8132770	A	T	7.15E-06	0.8559	0.62	0	*IGSF5*(−95.45 kb), *B3GALT5* (−3.369 kb)
10	30530710	rs2462021	C	T	8.30E-06	1.1755	0.43	0	
10	97106209	rs7076888	C	T	8.62E-06	1.1696	0.39	0	*SORBS1*(0), *PDLIM1* (+65.44 kb)
10	30527766	rs1360550	A	G	8.95E-06	0.8511	0.43	0	*PRKCE*(0)
2	46174598	rs12373805	A	G	9.20E-06	1.2169	0.91	0	