Depressed mood is the predominant feature in the diagnosis of mood disorders (e.g., major depressive disorder, dysthmic disorder, bipolar disorder) and is an important clinical component of many psychiatric, neurological, and physical syndromes (1). Mood disorders are one of the leading causes of disability worldwide (2,3), with an estimated lifetime risk of 20% in the US population (4). Most mental disorders are thought to arise from the combination of multiple genes and environmental factors (5). Large, genetically informative, population-based longitudinal studies (6–8) indicate that the personality trait neuroticism strongly reflects the genetic vulnerability to major depression, sharing an estimated 50% of the genetic liability, and consistently predicts which individuals are at greater risk for depressive illness (6,7,9). These findings suggest shared genetic basis underlying the continuum from personality traits to psychopathology.

In this study, we performed two genome-wide association (GWA) scans to search across the genome for common variants that contribute to depression vulnerability. We tested for association between trait depression and over 2 million genotyped or imputed single nucleotide polymorphisms (SNPs) in a large and homogeneous sample from Sardinia, Italy, and in a sample of participants with European ancestry from a US longitudinal study. To increase power, we meta-analytically combined the results from the two samples. Rather than focus on strong signals in one sample that might not replicate in the other sample, we looked for consistent effects across samples. This approach has been successful in identifying genetic variants that are reliably associated with quantitative traits, such as height, and diseases, such as diabetes (25,26).

In the field of psychiatry, there is a growing number of GWA studies for bipolar disorder (26,27), major depression (9,28,29), and trait neuroticism (16–18). This is the first GWA study for the depression facet of personality. The accumulating evidence across multiple GWA studies is providing replicable associations (30,31), even when the primary studies did not reach statistical significance (e.g., CACNA1C) (26,27,32).

Methods and Materials

Sample Description: Sardinia

For the Sardinia study, we recruited 6148 individuals from a cluster of four towns in the Lanusei Valley, Sardinia, Italy (11). The only exclusion criteria were being younger than 14 years old and being from regions other than Sardinia. The sample included over
62% of the population aged 14 to 102 years; further recruitment and longitudinal testing are ongoing. Inhabitants of this area are a known founder population, descending from few ancestors with minimal admixture with other populations. Even today, most subjects are native born, and at least 95% of the Sardinia sample have all grandparents born in the same province (11). This population was chosen because of its high genetic homogeneity, which should increase power in genetic association studies. During the first wave of assessment (2001–2004), valid personality data were obtained from 5669 subjects, of whom 3972 were part of the GWA scan. The sample included 57% women and ranged in age from 14 to 90 years (M = 42.8, SD = 17). Additional information on the sample has been reported elsewhere (11,33). Genome-wide association analyses for neuroticism and the other four domains of the Five-Factor Model in this Sardinia sample have been previously reported for roughly 360K SNPs (17). The project was approved by institutional review boards in Italy and the United States.

Sample Description: Baltimore Longitudinal Study Of Aging

The Baltimore Longitudinal Study of Aging (BLSA) is an ongoing multidisciplinary study of community-dwelling volunteers. The GWA analysis was restricted to subjects with European ancestry to reduce population stratification biases. A total of 839 subjects (46% women) of European descent were successfully genotyped and completed the personality questionnaire at least once. In this sample, age at first assessment ranged from 20 to 93 years (M = 58.5; SD = 17). Personality traits were assessed between 1989 and 2008, and multiple assessments were available for most participants. Although personality traits are generally stable over time (13,34), we reduced variability due to temporary effects and random error, thereby obtaining more reliable and robust personality score estimates. The BLSA study was approved by the local institutional review board.

Trait Depression Assessment

Trait depression was assessed using the English (19) and Italian (35) versions of the Revised NEO Personality Inventory. The depression scale consists of eight items, including two reversed scored items to reduce the effects of acquiescence. The items are answered on a five-point Likert scale, from strongly disagree to strongly agree. Scores followed a normal distribution and were standardized (M = 50, SD = 10) using American combined gender norms (19). The depression scores ranged from 29 to 86 (M = 54, SD = 9) in the Sardinia sample and from 27 to 86 (M = 48, SD = 10) in the BLSA sample, both of which are in the range observed in nonscience populations. No structured psychiatric evaluation was available in either sample.

There is a large body of evidence that personality scores are both reliable and valid across cultures (10,36). Indeed, the Revised NEO Personality Inventory has a robust factor structure that has been replicated in Italy (35) and in more than 50 cultures (36), even at the genetic level (11,33). In both samples, the depression facet scale had good psychometric properties: internal consistency reliability was .73 in the Sardinia sample and .80 in the BLSA sample. In the BLSA, available longitudinal data (13) indicate that corrected stability coefficient for the depression facet is .86 over an interval of 10 years.

Genetic Assays and Imputation

The DNA was extracted from blood. Genotyping was performed in the BLSA sample with the 550K Illumina (San Diego, California) platform and in the Sardinia sample with the 10K and 500K Affymetrix (Santa Clara, California) Mapping Array Set (see below and previous reports for additional information) (17,25). The genotype calling algorithm used was the Bayesian Robust Linear Model with Mahalanobis distance classifier (Affymetrix) for the Sardinia sample and the Beadstudio (Illumina) for the BLSA sample. Genotype data from both samples passed quality controls. For the Sardinia cohort, sample call rate was >95%, and SNP exclusions criteria were Hardy-Weinberg equilibrium ≤ 10⁻⁶, SNP call rate ≤ .90%, and minor allele frequency < 5%. For the BLSA cohort, sample call rate was >98.5%, SNP exclusions criteria were Hardy-Weinberg equilibrium < 10⁻⁴, SNP call rate < .99%, and minor allele frequency < 5%.

The genotyping approach used in the Sardinia study takes advantage of the large number of multigenerational families in this relatively homogeneous sample from a founder population. Related individuals, such as siblings and parents/offspring, share long multi-megabase stretches of chromosome. If these shared stretches are genotyped with high-density array in only a few individuals, the information from these individuals can be propagated to their relatives who inherited shared chromosome stretches with them (37–39). Thus, data from Sardinian individuals genotyped with the Affymetrix Mapping 500K Array Set (n = 1412) were used to infer missing genotypes in their offspring or siblings genotyped with the 10K Array Set (n = 2893), for a total of 4305 samples available for GWA analyses (personality data were available for 3972 of these participants). This within-family imputation method, based on identical-by-descent sharing and implemented by the MERLIN program (http://www.sph.umich.edu/csg/abecasis/merlin/) (38), has enabled full GWA scans in the Sardinia sample. The results from the Sardinia sample have been combined successfully with other GWA studies of physical and mental traits, such as height, weight, lipid levels, and cigarette smoking (25,40–42).

To combine the data from the different array sets in the two cohorts and to increase the overall coverage of the genome to up to 2.5 million SNPs, we imputed autosomal SNPs reported in the HaploType Mapping Project (http://www.hapmap.org) CEU sample, using the imputation program MACH v1.015 (http://www.sph.umich.edu/csg/abecasis/MACH/index.html). Markers showing low imputation quality (r² ≤ .3) were discarded from the analysis.

Statistical Analyses

To account for family structure in the Sardinia sample, we used the program MERLIN (38) to evaluate the additive effect of all genotyped or imputed SNPs on trait depression. Imputed SNP dosages were coded using fractional counts between 0 and 2 according to the estimated number of copies of each allele. In MERLIN, regression coefficients are estimated in the context of a variance component model to adjust for relatedness among individuals (38). The same association test was carried out in the BLSA sample. An inverse normal transformation was applied to personality traits to avoid inflated type I error. Sex, age, and age squared were included as covariates in all analyses to account for sex and age differences in personality traits (34,43).

In the Sardinia sample, we checked the genomic control value for our genome-wide association analyses (44), and we did a principal component analysis of genome-wide SNP data in a subset of unrelated individuals (45). Neither analysis suggested evidence of population substructure or genetic outliers. Analyses in the BLSA were restricted to the European-American subsample. Self-reported ethnicity was confirmed by comparisons between the BLSA and HaploType Mapping Project genomic data. To account for population structure, in the BLSA we further adjusted for the first two
Results

Genome-wide association analyses for the depression personality trait were carried out on 3972 individuals from the Sardinia sample and on 839 individuals from the BLSA sample, all of European ancestry. The quantile-quantile plot (Figure 1) indicate that there may be an excess of significant associations in the BLSA ($\lambda = 1.08$) but not in the Sardinia sample ($\lambda = 1.01$). To identify SNPs associated with trait depression, we combined the results from the GWA analyses in the Sardinia and BLSA samples in a meta-analysis (total $n = 4811$). There were no genome-wide significant findings (threshold: $p < 5 \times 10^{-8}$). The top 25 SNPs, ranked by $p$ value, are presented in Table 1. In addition, the SNPs with $p \leq 10^{-4}$ are presented in Table S1 in Supplement 1.

The meta-analysis indicates that the SNP with the lowest $p$ value maps within an intron of the RORA gene (rs12912233; $p = 6 \times 10^{-7}$). As shown in Figure 2, a number of other SNPs within RORA show strong associations with trait depression. Some of these SNPs had a stronger association in the Sardinia sample (e.g., rs12912233, rs4775340), but for others the effects were quite similar across the two samples (e.g., rs8028646, rs8023563). For rs12912233 and most of the other significant SNPs in RORA, the allele with the lower frequency was associated with roughly .15 SD higher depression scores (Table 1).

Among the top hits, the most biologically plausible finding was the association between trait depression and SNPs within the metabotropic glutamate receptor type 8 gene (GRM8) (Figure 3). The strongest effect was observed for the intronic SNP rs17864092 ($p = 5.5 \times 10^{-10}$); the allele T (frequency 90% in both Sardinia and BLSA samples) was associated with lower depression scores. In terms of effect size, individuals with the risk allele (C) scored roughly two T-score points (.2 SD) higher on depression, compared with the homozygous TT. Interestingly, a pharmacogenetic study of antipsychotic response implicated rs17864092 in verbal fluency scores (46). Other SNPs in GRM8 that were associated with trait depression in our two samples (e.g., rs17867725, $p = 4.2 \times 10^{-5}$; rs11563409, $p = .019$) are associated with cognitive phenotypes of psychotic patients (46). In addition, other GRM8 SNPs (rs2299495, rs1361995, rs10487457, rs10487459) that show some evidence of association in either the Sardinia or the BLSA sample have been associated with alcohol dependence and other psychiatric disorders in previous research (47).

Other SNPs in Table 1 were strongly associated in the Sardinia sample but showed weak or nonsignificant $p$ values in the BLSA. Although many of these SNPs mapped within or near genes of unknown function (e.g., SLFN12L and FAM155A), in the Sardinia sample we found strong associations between the depression personality trait and SNPs within the CDH13 gene (rs10514585) and near the CDH18 gene (rs349475). These cadherin genes encode for cell adhesion proteins, which may play a role in regulating synapse formation, function, and plasticity (48 –50). The CDH13 gene is expressed in the heart and several brain tissues, whereas CDH18 is...
Table 1. Sardinia and Baltimore Longitudinal Study of Aging Meta-Analysis of Association Results for Trait Depression

<table>
<thead>
<tr>
<th>Single Nucleotide Polymorphisms</th>
<th>Gene</th>
<th>Chr</th>
<th>Position</th>
<th>Effect-Allele</th>
<th>Imputation Quality (r²)</th>
<th>Effect-Allele Frequency</th>
<th>Effect Size</th>
<th>p Value</th>
<th>Meta-Analysis</th>
</tr>
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<tr>
<td>rs12912233</td>
<td>RORA</td>
<td>15</td>
<td>59.05</td>
<td>T/C</td>
<td>.54 .96</td>
<td>.46 .46</td>
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<td>rs8070473</td>
<td>SLFN12L</td>
<td>17</td>
<td>30.87</td>
<td>T/G</td>
<td>.81 .99</td>
<td>.32 .32</td>
<td>-.16 -.07</td>
<td>1.1 x 10⁻⁶</td>
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</tr>
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<td>CDH19a</td>
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<td>T/C</td>
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<td>.29 .29</td>
<td>.18 .02</td>
<td>2.4 x 10⁻⁷</td>
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<td>T/G</td>
<td>.37 .GN</td>
<td>.04 .04</td>
<td>-.38 -.08</td>
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</tr>
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<td>C/G</td>
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<td>.32 .32</td>
<td>-.15 -.08</td>
<td>4.4 x 10⁻⁶</td>
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<td>106.58</td>
<td>A/G</td>
<td>.66 .GN</td>
<td>.24 .24</td>
<td>-.16 -.06</td>
<td>3.5 x 10⁻⁶</td>
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</tr>
<tr>
<td>rs1054585</td>
<td>CDH13</td>
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<td>81.84</td>
<td>A/G</td>
<td>GN .99</td>
<td>.31 .31</td>
<td>.15 .06</td>
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<td>2.8 x 10⁻⁴</td>
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<td>ITGB1a</td>
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<td>A/G</td>
<td>.86 .96</td>
<td>.17 .17</td>
<td>.16 .16</td>
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<td>2.3 x 10⁻²</td>
</tr>
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<td>rs17864092</td>
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<td>.90 .90</td>
<td>-.17 -.25</td>
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<td>2.2 x 10⁻³</td>
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<tr>
<td>rs9634463</td>
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<td>13</td>
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<td>T/G</td>
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<td>.24 .24</td>
<td>-.16 -.05</td>
<td>2.5 x 10⁻⁶</td>
<td>3.7 x 10⁻¹</td>
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<td>A/G</td>
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<td>.75 .75</td>
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<td>2.5 x 10⁻⁶</td>
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<td>T/G</td>
<td>.91 .90</td>
<td>.25 .25</td>
<td>-.16 -.05</td>
<td>2.6 x 10⁻⁶</td>
<td>3.7 x 10⁻¹</td>
</tr>
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<td>A/G</td>
<td>.55 .GN</td>
<td>.43 .43</td>
<td>.14 .09</td>
<td>2.1 x 10⁻⁵</td>
<td>6.5 x 10⁻²</td>
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<tr>
<td>rs1449984</td>
<td>—</td>
<td>2</td>
<td>23.33</td>
<td>A/G</td>
<td>.96 .72</td>
<td>.72 .72</td>
<td>-.15 -.06</td>
<td>6.7 x 10⁻⁷</td>
<td>2.0 x 10⁻¹</td>
</tr>
<tr>
<td>rs9301191</td>
<td>FAM155Aa</td>
<td>13</td>
<td>106.57</td>
<td>T/G</td>
<td>.85 .90</td>
<td>.79 .79</td>
<td>-.17 -.05</td>
<td>2.9 x 10⁻⁶</td>
<td>3.9 x 10⁻¹</td>
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<tr>
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<td>59</td>
<td>A/T</td>
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<td>.25 .25</td>
<td>-.14 -.15</td>
<td>1.6 x 10⁻⁴</td>
<td>4.6 x 10⁻³</td>
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<tr>
<td>rs1924397</td>
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<td>.96 .96</td>
<td>.32 .15</td>
<td>2.0 x 10⁻⁵</td>
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<td>.68 .63</td>
<td>.63 .63</td>
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<td>.92 .92</td>
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<tr>
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<td>70.34</td>
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<td>.92 .92</td>
<td>-.22 -.20</td>
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<td>T/G</td>
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<td>.08 .08</td>
<td>-.21 -.21</td>
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<tr>
<td>rs8023563</td>
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<td>59</td>
<td>A/T</td>
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<td>-.13 -.15</td>
<td>2.9 x 10⁻⁴</td>
<td>5.4 x 10⁻³</td>
</tr>
</tbody>
</table>

The first allele in the Effect-Allele column is the reference allele for allele frequency and effect size direction. BLSA, Baltimore Longitudinal Study of Aging; Chr, chromosome; GN, genotyped.

*Nearest gene.

expressed specifically in the brain (51,52). Genome-wide association studies have implicated SNPs within the large CDH13 gene in several traits and diseases, such as introversion (17), substance abuse (53,54), and attention-deficit/hyperactivity disorder (55).

Discussion

We report results from the first GWA study of the depression personality trait, the facet of neuroticism most closely related to the core component of mood disorders. We genotyped or imputed over 2 million SNPs in a large homogeneous sample from Sardinia,
Italy, and in a longitudinal sample from the United States, for a total of 4811 individuals. The imputation of genetic information is now a common practice in GWA studies (25–27,30,56), but it was not used in our previous GWA study of the five major dimensions of personality (17) or by the previous GWA studies of neuroticism (16,18). Although we found no genome-wide statistical significant associations, our GWA results point to genes involved in brain function, behavior, and psychopathology, and can provide useful insight in the biology of depression. Specifically, we found the SNPs most strongly associated with trait depression were within the RORA and GRM8 genes.

The strongest meta-analytic signal was found for a number of closely linked SNPs within the RORA gene, particularly in the Sardinian sample. The RORA gene, or retinoic acid receptor-related orphan receptor alpha, is a member of the nuclear hormone receptor superfamily. In the mouse nervous system, RORA is localized in the cerebellum, thalamus, cerebral cortex, superchiasmatic nucleus, and other structures (57). The function of this gene appears to be complex. Deletion within the RORA gene causes the staggerer mouse phenotype, which is characterized by severe cerebellar ataxia due to a defect in the development of Purkinje cells (58). The RORA gene also seems to play a role in immunity (59) and has emerged as an important component of mammalian circadian rhythms (60,61). As recently reviewed (62), multiple lines of evidence from animal models, GWA, and linkage studies converge on variants in the RORA gene that may be linked to bipolar disorder. A recent study that examined circadian candidate genes in a Swedish population-based sample also found RORA to be associated with clinical depression (63). This evidence, together with our GWA results, supports a role of RORA in trait depression, and given its function as a circadian gene, may be implicated in the cyclic nature of mood disorders, especially seasonal and bipolar disorder (64,65).

Glutamate is a widespread excitatory neurotransmitter involved in multiple brain functions (e.g., synaptic plasticity) and has been implicated in neuropathology (e.g., Alzheimer’s disease, addictions) (47,66,67). Glutamate activates a number of ionotropic (NMDA, AMPA) and metabotropic glutamate (mGlu) receptors. In this study, the strongest effect was found for GRM8 (or mGlue8), a group III metabotropic glutamate receptor, a subgroup known to modulate glutamatergic neurotransmission via presynaptic inhibition of glutamate release (68). The group III metabotropic receptors are part of the control system that maintains glutamate levels within normal boundaries, as excessive levels of glutamate in the synaptic space have excitotoxic effects, triggering cellular damage, neuronal atrophy, and loss. Growing evidence suggests that the glutamatergic system plays a major role in the pathophysiology of neuropsychiatric disorders; glutamate receptors are seen as promising therapeutic targets (67–70). In animal models, agonists for type III mGlue receptors produce anxiolytic-like effects, but the evidence is mixed for the antidepressant-like effects across behavioral tests (70–72). In addition, a GRM8 agonist has been shown to suppress alcohol self-administration and cue-induced reinstatement of alcohol-seeking behaviors (73). At the genetic level, GRM8 has been tested as a candidate gene for schizophrenia (74) and alcohol-dependence phenotypes (47) and was part of a network of glutamate receptor genes that emerged from a GWA study of cigarette smoking (56). Thus, the results of our GWA study that implicate GRM8 suggest that genetic variants in a key component of the glutamate neurotransmission system may contribute to risk of depression and other psychiatric disorders.

The GRM8 and the RORA are promising candidate genes, but larger samples are required to obtain definitive evidence. Consistent with most other studies of quantitative traits and disorders (16–18,25,53–55), the variants we identified explained a small portion of variance (1% or less), which suggests that common SNPs with large effects on trait depression are unlikely to exist. Although GWA has been successful in identifying common variants associated with various complex traits, the full genetic component of complex traits will require the examination of other types of variants, such as rare variants and copy number variants. Large-scale sequencing projects are one approach to address some of the limitations of the current GWA studies and move the field forward. Sequence data would provide virtually complete genetic coverage and allow the assessment of the effect of rarer variants. Other approaches are also needed to investigate epigenetic effects and the role of environmental factors that contribute to psychiatric disorders. Epigenetic regulations of gene expression, such as DNA methylation, histone modifications, DNA rearrangement, and RNA inhibition, have been implicated in complex behaviors and psychiatric disorders (75,76). Still, the role of epigenetic phenomena is complex and will require new methods to fully evaluate the biological mechanisms that contribute to the etiology of complex disorders. To date, the GWA can provide an unbiased examination across the genome for common variants that contribute to quantitative traits and diseases. Even small effects can point to genes that may harbor rarer variants with larger effects and may elucidate the role of biological pathways.

Our top results are likely to be enriched with SNPs that are truly associated with the depression personality trait and can contribute to the accumulation of evidence in support or against any particular gene in association with depression and related phenotypes. If these findings are confirmed, they would support the hypothesis behind GWA studies that common variants contribute to disease liability. There is also growing evidence that different psychiatric disorders share common genetic loci (30–32). This study extends these findings, suggesting that common variants associated with psychiatric disorders in clinical studies contribute to individual differences on trait depression in the general population.

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We thank Sardinia study participants for their volunteerism and the local civil and religious authorities in Sardinia for their support. We thank Professor Antonio Cao for his leadership of the Sardinia project. Antonio Terracciano had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Supplementary material cited in this article is available online.


