Published in final edited form as:
Biol Psychiatry. 2010 November 1; 68(9): 811–817. doi:10.1016/j.biopsych.2010.06.030.

Genome-wide association scan of trait depression

Antonio Terracciano[1,*], **Toshiko Tanaka**[1,4], **Angelina R. Sutin**[1], **Serena Sanna**[2], **Barbara Deiana**[2], **Sandra Lai**[2], **Manuela Uda**[2], **David Schlessinger**[1], **Gonçalo R. Abecasis**[3], **Luigi Ferrucci**[1], and **Paul T. Costa Jr.**[1]

[1] National Institute on Aging, NIH, DHHS, Baltimore, MD, USA

[2] Istituto di Neurogenetica e Neurofarmacologia, Consiglio Nazionale delle Ricerche, Monserrato, Cagliari, Italy

[3] Center for Statistical Genetics, Department of Biostatistics, University of Michigan, Ann Arbor, MI, USA

[4] Medstar Research Institute, Baltimore, MD, USA

Abstract

Background—Independent of temporal circumstances, some individuals have greater susceptibility to depressive affects, such as feelings of guilt, sadness, hopelessness, and loneliness. Identifying the genetic variants that contribute to these individual differences can point to biological pathways etiologically involved in psychiatric disorders.

Methods—Genome-wide association scans (GWA or GWAS) for the Depression scale of the Revised NEO Personality Inventory (NEO-PI-R) in community-based samples from a genetically homogeneous area of Sardinia, Italy (N = 3,972) and from the Baltimore Longitudinal Study of Aging in the US (N = 839).

Results—Meta-analytic results for genotyped or imputed single nucleotide polymorphisms (SNPs) indicate that the strongest association signals for trait depression were found in *RORA* (rs12912233; $p= 6 \times 10^{-7}$), a gene involved in circadian rhythm. A plausible biological association was also found with SNPs within *GRM8* (rs17864092; $p = 5 \times 10^{-6}$), a metabotropic receptor for glutamate, a major excitatory neurotransmitter in the central nervous system.

Conclusions—These findings suggest shared genetic basis underlying the continuum from personality traits to psychopathology.

Keywords

GWA or GWAS; depression; neuroticism; *RORA*; *GRM8* or mGlu8

[*]Corresponding author: Antonio Terracciano, Laboratory of Personality & Cognition, National Institute on Aging, NIH, DHHS 251 Bayview Blvd, Baltimore, MD 21224, Phone: 410 558-8358; Fax: 410 558-8690; Terraccianoa@mail.nih.gov.

Financial disclosure: Paul T. Costa, Jr., receives royalties from the Revised NEO Personality Inventory. All other authors report no biomedical financial interests or potential conflicts of interest.

Introduction

Depressed mood is the predominant feature in the diagnosis of mood disorders (e.g., major depressive disorder, dysthymic 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 links, along with evidence that personality traits are heritable (6,10,11) and highly stable in adulthood (12–14), indicate that Neuroticism-related personality traits are a promising endophenotype (15) for mood and other psychiatric disorders (16–18).

Neuroticism is a broad dimension that reflects the tendency to experience a wide spectrum of negative emotions. This heterogeneous trait is composed of several lower-order facets, including depression, anxiety, hostility, self-consciousness, impulsivity, and vulnerability to stress (19). These more circumscribed facets are also heritable (10,11) and have greater predictive power for specific behavioral and health outcomes than the broader domain-level Neuroticism (20,21).

The depression facet captures the core aspects of depressed mood, with items that assess susceptibility to feelings of sadness, hopelessness, worthlessness, discouragement, guilt, and loneliness. As such, this facet measures the characteristic psychic component of depression, not its physical symptoms (22). This enduring disposition increases vulnerability to depressive states, but also may be one common denominator underlying comorbidities among psychiatric disorders. Indeed, both clinically depressed and other psychiatric patients tend to score higher on depression compared to the other facets of Neuroticism (23,24). Identifying genetic variants associated with trait depression may be informative not only for this personality trait, but for a wide range of psychiatric disorders that share a mood component. Moreover, as a more circumscribed facet, trait depression measures a narrower phenotype, which can increase statistical power by reducing phenotypic variability, and might thus prove advantageous in genetic association studies.

In this study, we performed two genome-wide association scans (GWA or GWAS) 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, 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

Sample description: SardiNIA

For the SardiNIA study, we recruited 6,148 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 includes over 62% of the population aged 14 to 102 years; further recruitment and longitudinal testing is 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 5,669 subjects, of whom 3,972 were part of the genome-wide association (GWA) scan. The sample includes 57% women and ranged in age from 14 to 90 (M = 42.8, SD = 17). Additional information on the sample has been reported elsewhere (11,33). GWA 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 USA.

Sample description: BLSA

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 (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 combined all available assessments for each individual, for a total of 3,507 assessment points. By averaging across multiple time points, we reduce 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 (NEO-PI-R). The Depression scale consists of 8 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 non-clinical 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 NEO-PI-R 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 has 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

DNA was extracted from blood. Genotyping was performed in the BLSA sample with the 550k Illumina platform, and in the SardiNIA sample with the 10K and 500K Affymetrix mapping array set (see below and previous reports for additional information)(17,25). The genotype calling algorithm used was the BRLMM for the SardiNIA sample and the Beadstudio for the BLSA sample. Genotype data from both samples passed quality controls. For the SardiNIA cohort, sample call rate was > 95%, and SNPs exclusions criteria were Hardy-Weinberg equilibrium (HWE) <= 10^{-6}, SNP call rate <= 90%, and minor allele frequency (MAF) < 5%. For the BLSA cohort, sample call rate was > 98.5%, SNPs exclusions criteria were HWE < 10^{-4}, SNP call rate < 99%, and MAF < 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 inherit shared chromosome stretches with them (37–39). Thus, data from Sardinian individuals genotyped with the Affymetrix Mapping 500K Array Set (N = 1,412) was used to infer missing genotypes in their offspring or siblings genotyped with the 10K Array Set (N =2,893), for a total of 4,305 samples available for GWA analyses (personality data were available for 3,972 of these participants). This within-family imputation method, based on "identical-by-descent" sharing and implemented by the MERLIN program (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 HapMap CEU sample, using the imputation program MACH v1.015 (http://www.sph.umich.edu/csg/abecasis/MACH/index.html). Markers showing low imputation quality ($r^2 \leq 0.3$) 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 HapMap genomic data. To account for population structure, in the BLSA we further adjusted for the first two principal components derived from an EIGENSTRAT analysis utilizing ~10,000 randomly selected SNPs from the 550K SNP panel (45).

A weighted z score based fixed effects meta-analysis method was used to combine results from the SardiNIA and BLSA samples using the program METAL

(http://www.sph.umich.edu/csg/abecasis/metal/). In brief, for every SNP, a reference allele was identified and a z statistic summarizing the magnitude of the P-value for the association and direction of effect was generated in each sample. An overall z statistic was then computed as a weighted average of the individual statistics, and a corresponding P-value for that statistic was computed. The weights were proportional to the square root of the number of individuals in each study and scaled such that the squared weights summed to 1. Genomic control correction was applied to the test statistics in each study when appropriate. A Bonferroni corrected p-value of $5x10^{-8}$ was considered genome-wide significant.

Results

GWA analyses for the depression personality trait were carried out on 3,972 individuals from the SardiNIA sample and on 839 individuals from the BLSA sample, all of European ancestry. The Q-Q plots (Figure 1) indicate that there may be an excess of significant associations in the BLSA (λ=1.08), but not in the SardiNIA sample (λ=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 = 4,811). There were no genome-wide significant findings (threshold: $P < 5x10^{-8}$). 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 Supplement: Table S1.

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 0.15 SD higher depression scores (see 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* or mGlu8)(see Figure 3). The strongest effect was observed for the intronic SNP rs17864092 ($p = 5.5x10^{-6}$); 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 (0.2 SD) higher on depression, compared to 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, $p = 4.2x10^{-4}$; 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 non-significant 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). *CDH13* is expressed in the heart and several brain tissues, whereas *CDH18* is expressed specifically in the brain (51,52). GWA 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 US, for a total of 4,811 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 SardiNIA sample. *RORA*, 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). *RORA* 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, kainate, and delta) and metabotropic (mGlu) receptors. In this study, the strongest effect was found for *GRM8* (or mGlu8), 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 maintain 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 mGlu 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 have 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 effect 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We would like to thank SardiNIA study participants for their volunteerism and the local civil and religious authorities in Sardinia for their support. We thank Prof. 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. Funding: This research was supported in part by the Intramural Research Program of the NIH, National Institute on Aging.

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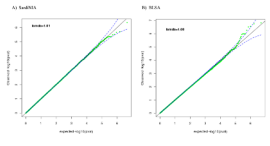

Figure 1.
Quantile-Qualtile plot of observed vs expected log P-value for the SardiNIA (A) and the Baltimore Longitudinal Study of Aging (B).

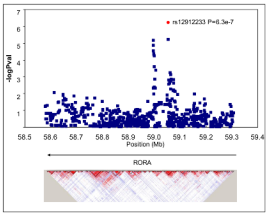

Figure 2.
Plot of -$\log_{10}$ P values for depression trait meta-analysis for SNPs mapping within the *RORA* gene. Bottom panel presents patterns of linkage disequilibrium (r^2) for the region in the HapMap CEPH population.

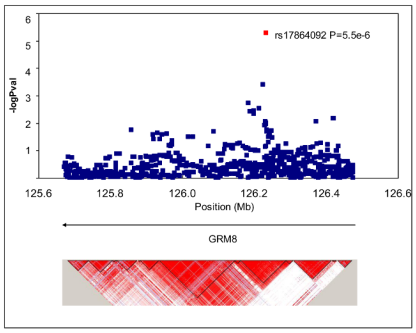

Figure 3.
Plot of -$\log_{10}$ P values for depression trait meta-analysis for SNPs mapping within the *GRM8* gene. Bottom panel presents patterns of linkage disequilibrium (r^2) for the region in the HapMap CEPH population.

Table 1

SardiNIA and BLSA meta-analysis of association results for trait depression.

					Imputation quality (r^2)		Effect-allele frequency		Effect size		p-value		
SNP	**Gene**	**chr**	**position**	**Effect-allele**	**SardiNIA**	**BLSA**	**SardiNIA**	**BLSA**	**SardiNIA**	**BLSA**	**SardiNIA**	**BLSA**	**Meta-analysis**
rs12912233	*RORA*	15	59.05	T/C	0.54	0.96	.46	.46	0.15	0.09	1.8×10^{-6}	6.1×10^{-2}	6.3×10^{-7}
rs8070473	*SLFN12L*	17	30.87	T/G	0.81	0.99	.32	.32	−0.16	−0.07	1.1×10^{-6}	2.3×10^{-1}	1.5×10^{-6}
rs349475	*CDH18**	5	19.48	T/C	0.66	0.86	.29	.29	0.18	0.02	2.4×10^{-7}	7.3×10^{-1}	2.4×10^{-6}
rs12420464	*EIF3F*	11	7.97	T/G	0.37	GN	.04	.04	−0.38	−0.08	1.3×10^{-6}	3.8×10^{-1}	3.3×10^{-6}
rs8068353	*SLFN12L*	17	30.86	C/G	0.78	0.93	.32	.32	−0.15	−0.08	4.4×10^{-6}	1.6×10^{-1}	3.4×10^{-6}
rs1927745	*FAM155A**	13	106.58	A/G	0.66	GN	.24	.24	−0.16	−0.06	3.5×10^{-6}	2.4×10^{-1}	4.7×10^{-6}
rs10514585	*CDH13*	16	81.84	A/G	GN	0.99	.31	.31	0.15	0.06	3.1×10^{-6}	2.8×10^{-1}	4.9×10^{-6}
rs11009175	*ITGB1**	10	33.33	A/G	0.86	0.96	.17	.17	0.16	0.16	4.2×10^{-5}	2.3×10^{-2}	5.4×10^{-6}
rs17864092	*GRM8*	7	126.23	T/C	0.65	GN	.90	.90	−0.17	−0.25	1.9×10^{-4}	2.2×10^{-3}	5.5×10^{-6}
rs9634463	*FAM155A**	13	106.57	T/C	0.89	0.90	.24	.24	−0.16	−0.05	2.5×10^{-6}	3.7×10^{-1}	5.7×10^{-6}
rs7329003	*FAM155A**	13	106.57	A/G	GN	0.90	.75	.75	−0.16	−0.05	2.5×10^{-6}	3.7×10^{-1}	5.8×10^{-6}
rs713548	*FAM155A**	13	106.57	T/G	0.91	0.90	.25	.25	−0.16	−0.05	2.6×10^{-6}	3.7×10^{-1}	5.9×10^{-6}
rs4775340	*RORA*	15	59.06	A/G	0.55	GN	.43	.43	0.14	0.09	2.1×10^{-5}	6.5×10^{-2}	6.3×10^{-6}
rs1449984	-	2	23.33	A/G	0.96	GN	.72	.72	−0.15	−0.06	6.7×10^{-6}	2.0×10^{-1}	6.6×10^{-6}
rs9301191	*FAM155A**	13	106.57	T/C	0.85	0.90	.79	.79	−0.17	−0.05	2.9×10^{-6}	3.9×10^{-1}	7.1×10^{-6}
rs8028646	*RORA*	15	59	A/T	GN	0.99	.25	.25	−0.14	−0.15	1.6×10^{-4}	4.6×10^{-3}	7.2×10^{-6}
rs1924397	*FAM155A**	13	105.41	A/C	0.54	0.80	.96	.96	0.32	0.15	2.0×10^{-5}	8.3×10^{-2}	7.6×10^{-6}
rs10744304	-	12	126.34	A/G	0.68	GN	.63	.63	−0.15	−0.05	5.0×10^{-6}	3.2×10^{-1}	8.7×10^{-6}
rs2017305	*DDX21**	10	70.38	A/G	1.00	0.97	.92	.92	−0.22	−0.21	6.9×10^{-5}	2.3×10^{-2}	9.0×10^{-6}
rs3740596	*DDX50*	10	70.34	A/G	1.00	0.97	.92	.92	−0.22	−0.20	6.8×10^{-5}	2.6×10^{-2}	9.5×10^{-6}
rs12638201	*CCR9*	3	45.91	A/G	0.82	GN	.14	.14	0.17	0.19	4.9×10^{-5}	4.9×10^{-2}	1.1×10^{-5}
rs4796093	*SLFN12L*	17	30.87	A/G	0.89	GN	.64	.64	−0.14	−0.06	9.3×10^{-6}	2.6×10^{-1}	1.2×10^{-5}
rs4885589	-	13	78.45	T/C	0.86	0.96	.60	.60	0.10	0.18	1.1×10^{-3}	2.4×10^{-4}	1.3×10^{-5}
rs1539163	*DDX21*	10	70.41	T/C	1.00	0.96	.08	.08	−0.21	−0.21	1.1×10^{-4}	2.4×10^{-2}	1.4×10^{-5}

					Imputation quality (r^2)		Effect-allele frequency		Effect size		p-value		
SNP	**Gene**	**chr**	**position**	**Effect-allele**	**SardiNIA**	**BLSA**	**SardiNIA**	**BLSA**	**SardiNIA**	**BLSA**	**SardiNIA**	**BLSA**	**Meta-analysis**
rs8023563	*RORA*	15	59	A/T	GN	0.98	.76	.76	−0.13	−0.15	2.9×10^{-4}	5.4×10^{-3}	1.5×10^{-5}

* Nearest gene. GN = Genotyped. The first allele in the Effect-allele column is the reference allele for allele frequency and effect size direction.