RESEARCH ARTICLE

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Genome-Wide Association Uncovers Shared Genetic Effects Among Personality Traits and Mood States

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Measures of personality and psychological distress are correlated and exhibit genetic covariance. We conducted univariate genome-wide SNP (~2.5 million) and gene-based association analyses of these traits and examined the overlap in results across traits, including a prediction analysis of mood states using genetic polygenic scores for personality. Measures of neuroticism, extraversion, and symptoms of anxiety, depression, and general psychological distress were collected in eight European cohorts (n ranged 546–1,338; maximum total n = 6,268) whose mean age ranged from 55 to 79 years. Meta-analysis of the cohort results was performed, with follow-up associations of the top SNPs and genes investigated in independent cohorts (n = 527–6,032). Suggestive association ($P = 8 \times 10^{-8}$) of rs1079196 in the *FHIT* gene was observed with symptoms of anxiety. Other notable associations ($P < 6.09 \times 10^{-6}$) included SNPs in five genes for neuroticism (*LCE3C*, *POLR3A*, *LMAN1L*, *ULK3*, *SCAMP2*), *KIAA0802* for extraversion, and *NOS1* for general psychological distress. An association between symptoms of depression and rs7582472 (near to *MGAT5* and *NCKAP5*) was replicated in two independent samples, but other replication findings were less consistent. Gene-based tests identified a significant locus on chromosome 15 (spanning five genes) associated with neuroticism which replicated ($P < 0.05$) in an independent cohort. Support for common genetic effects among personality and mood (particularly neuroticism and depressive symptoms) was found in terms of SNP association overlap and polygenic score prediction. The variance explained by individual SNPs was very small (up to 1%) confirming that there are no moderate/large effects of common SNPs on personality and related traits.

Key words: GWAS; extraversion; neuroticism; anxiety; depression

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INTRODUCTION

Personality traits are influenced in part by one's genetic make-up, with around 50% of their variation being genetic [Bouchard and Loehlin, 2001]. They are related to health and other life characteristics, and predict many aspects of psychiatric illness. In particular, neuroticism is associated with anxiety and depression [Brandes and Bienvenu, 2006]. Therefore, a better understanding of the genetic basis of psychiatric disease and more widespread, milder forms of psychological distress will be gained by studying stable personality traits alongside psychiatric symptoms. Such symptoms, while state-dependent, surface against a background of predisposing personality traits, primarily high neuroticism, and, to a lesser extent, low extraversion. In this study, we measure the effect of single nucleotide polymorphisms (SNPs) and genes, with an emphasis on shared effects on personality trait and mood state measures.

Twin studies have confirmed that substantial genetic effects are shared between neuroticism and both anxiety and depression, and to a lesser extent, extraversion with depression [Middeldorp et al., 2005; Kendler and Myers, 2010]. Such findings provided the impetus for candidate gene studies to investigate pleiotropic gene

effects on personality traits and psychological distress. For example, variants in *GAD1* have been associated with neuroticism and anxiety/mood disorder measured in the same sample [Hettema et al., 2006]. Genome-wide association studies (GWAS) have not systematically compared results of personality traits and mood. However, cross-disorder GWAS analysis has proved informative for uncovering pleiotropic effects on schizophrenia, bipolar disorder, and major depressive disorder [Huang et al., 2010]. The finding that genetic risk scores for neuroticism predicted major depressive disorder in an independent sample [Middeldorp et al., in press] is relevant to the present study, which hypothesizes that genetic prediction scores for stable personality traits will be related to mood states.

The largest personality GWAS to date [de Moor et al., 2011] (n = 17,375) failed to replicate associated SNPs from the first GWAS of personality which had shown some of their top SNPs to be within/near genes putatively involved in psychiatric illness; nor did this study confirm previously reported associations for neuroticism. Neuroticism is a strong risk factor for anxiety, but no GWAS of general anxiety has been published yet. Various GWAS for major depression exist, the largest included 5,763 cases and 6,901 controls [Wray et al., 2012]. No SNPs exceeded genome-wide significance, but there was some support for *ADCY3*, *GAL*, and *CAGNA1C* genes. Genetic studies based on continuous measures of depressive symptoms in normal populations have also had some success. A linkage study of the depression subscale of the Hospital Anxiety and Depression Scale reported a potentially linked chromosomal region on 11q which their follow-up population-based association analysis suggested was partly explained by the *OPCML* or *APLP2* genes [Schol-Gelok et al., 2010]. The present study is the first GWAS of symptoms of anxiety and depression sampled from the general population.

The aim of the present study is to compare the results of genome-wide SNP and gene-based analyses for neuroticism and extraversion personality traits, and symptoms of anxiety, depression, and general psychological distress. These measures were all based on continua, sampled from population-based cohorts living in Europe. Whereas the cohorts varied in age, personality is largely stable across the lifetime and these stable effects in later life are predominantly genetic in origin [Johnson et al., 2005]; so, too, are the genetic determinants of anxiety and depression [Gillespie et al., 2004]. It is this stable genetic variance that is of interest to the present study. Replication cohorts were available from Australia, Germany, and The Netherlands.

MATERIALS AND METHODS

Sample

CROATIA-Vis and CROATIA-Korcula. Adults living in the Croatian villages of Komiza and Vis (island of Vis) and from Korcula (island of Korcula) were recruited within a larger epidemiological study of genetically isolated populations [Rudan et al., 1999]. The CROATIA-Vis study comprised 536 women and 388 men aged 18–93 years (mean = 56.4 ± 15.5). The CROATIA-Korcula study comprised 573 women and 325 men aged 18–98 years (mean = 56.3 ± 13.9).

Lothian birth cohorts 1921 (LBC1921) and 1936 (LBC1936). These relatively healthy older individuals, living in the Lothian region of Scotland, were born in 1921 or 1936 and assessed on psychological and medical traits from the age of 79 (LBC1921) or 70 (LBC1936) years [Luciano et al., 2010]. In the LBC1921, genotype and phenotype data were available for 426 (personality) and 517 (depression, anxiety) participants (58% female); mean age of ~81 years (range = 80–82) when personality was assessed and 79 ± 0.6 years (range = 77–81) when depression and anxiety symptoms were measured. In the LBC1936, 880 (personality) and 1,003 (depression, anxiety) individuals (50% female) had genotype and phenotype data; mean age of 69.5 ± 0.8 years (range = 67–71).

Orkney Complex Disease Study (ORCADES). This is a family-based, cross-sectional study in the isolated Scottish archipelago of Orkney. Genetic diversity in this population is decreased compared to mainland Scotland [McQuillan et al., 2008]. Data from 445 healthy volunteers (57% female) from a subgroup of 10 islands, aged 18–84 years (mean = 54.9 ± 13.8) with known Orcadian ancestry, were available. Personality assessments were collected during 2005–2007.

Manchester and Newcastle. The University of Manchester Longitudinal Study of Cognition [Rabbitt et al., 2004] includes individuals from Greater Manchester and Newcastle-upon-Tyne. We focus on first-test wave data where the sample size was the largest. Manchester participants (n = 796) were 41–84 years (mean = 64.6 ± 6.2) when assessed on personality, and 41–82 years (mean = 62.8 ± 6.1) when measured for depression. Newcastle participants (n = 751) were 51–86 years (mean = 65.8 ± 6.0) when assessed on personality, and 50–84 years (mean = 62.7 ± 6.3) when measured for depression. Women comprised ~71% of the samples.

Nijmegen biomedical study. This is a population-based survey conducted by the Radboud University Nijmegen Medical Centre [Wetzels et al., 2007] in Nijmegen, a town in the eastern part of The Netherlands. Age- and sex-stratified randomly selected adult inhabitants received an invitation to fill out a postal questionnaire on lifestyle and medical history. Genotype and phenotype data were available for 1,338 participants (50.5% female), aged 27–78 years (mean = 61.5 ± 10.3).

All studies conformed to the ethical guidelines of the 1975 Declaration of Helsinki and were approved by appropriate ethics boards with participants signing informed consent prior to participation.

Measures

CROATIA-Vis and CROATIA-Korcula. Participants completed a translated version [Ivkovic et al., 2007] of the Eysenck Personality Questionnaire-Revised (short form; EPQ-R) and the General Health Questionnaire 30 (GHQ). The EPQ-R is a self-report inventory with each scale tested by 12 items requiring a binary "yes/no" response [Eysenck and Eysenck, 1975]. The GHQ is a 30-item, self-report questionnaire of recent psychological distress with 4-response categories [Goldberg and Williams, 1988].

LBC1921 and LBC1936. Personality was measured by the International Personality Item Pool Big-Five 50-item inventory [Goldberg, 1999], consisting of 10 items for each trait. Anxiety and

depression symptoms were quantified using the Hospital Anxiety and Depression Scale [Zigmond and Snaith, 1983], containing seven items each for anxiety and depression, the total score giving a general measure of psychological distress.

ORCADES. EPQ-R (short form) was used to measure personality.

Manchester and Newcastle. The respective personality and depression scales were the EPQ and the Beck Depression Inventory [BDI, Beck et al., 1961]. The BDI is a 21-question multiple-choice self-report inventory in which the severity of each symptom is rated on a 4-point scale.

Nijmegen biomedical study. Neuroticism and extraversion (12 items/scale) were measured using the Dutch version of the EPQ-R Short Scale [Sanderman et al., 1991]. Depressive symptoms were measured using the BDI and anxiety symptoms via a Dutch version of the Symptom Checklist 90 [Arrindell and Ettema, 1986], a self report inventory which includes 10 items from the anxiety scale which are rated on a 5-point scale of symptom distress.

Genotyping and imputation. DNA was extracted from blood samples. Genotyping of CROATIA-Vis, LBC, and English samples were conducted by the Genetics Core Laboratory at the Wellcome Trust Clinical Research Facility, Western General Hospital, Scotland. CROATIA-Korcula and ORCADES genotyping was undertaken by Helmholtz Zentrum München, GmbH, Neuherberg, Germany, and the Nijmegen Biomedical Study genotyping was performed by deCODE Genetics, Iceland. For genotype quality control (QC) procedures see Supplementary Table S1. Standard checks for gender discrepancies, individual relatedness (in the non-isolate cohorts only), and non-Caucasian descent were done—with necessary exclusions made. Population stratification factors were estimated via multidimensional scaling (MDS) using an identity-by-state distance matrix; the first three MDS components were covaried for in the association analysis.

Due to differences in SNP arrays used between cohorts, genomic coverage was extended to ~2.5 M common SNPs by imputation using the HapMap phase II CEU data (NCBI build 36 (UCSC hg18)) as the reference sample and MACH software. SNPs with low imputation quality ($r^2 < 0.30$) were removed.

Statistical Analysis

GWAS analyses of autosomes were conducted in each study using linear regression of standardized traits adjusted for the effects of sex, age, and population stratification. Dosage analysis accounted for differential imputation quality of SNPs. In the CROATIA-Vis, CROATIA-Korcula, and ORCADES cohorts, analyses were performed using the *ABEL suite of software [Aulchenko et al., 2007] making adjustments for pedigree structure. For the other cohorts, association analyses were performed in mach2qtl [Li et al., 2009]. A weighted inverse variance method in METAL [Willer et al., 2010] was used to meta-analyze the results. A genome-wide significance level of $P < 5 \times 10^{-8}$ [Dudbridge and Gusnanto, 2008] and a suggestive significance level of 6.09×10^{-6} [Duggal et al., 2008] was adopted.

To further assess pleiotropic SNP effects, prediction analyses were performed in which polygenic scores for extraversion and neuroticism were used to predict phenotypic variation in mood measures. Because anxiety, depression, and psychological distress symptoms were available in a subset of cohorts, polygenic scores for personality were estimated from GWAS meta-analysis results based on cohorts who did not have the mood measure under investigation. Thus, the prediction cohort was independent of the cohort in which polygenic scores were based. Polygenic scores were calculated [in PLINK; Purcell et al., 2007] by summing across all genotyped SNPs, where the number of reference alleles (0, 1, or 2) at that SNP was multiplied by the effect size of that SNP. Each of the personality polygenic scores was correlated with each of the mood traits, controlling also for the number of SNPs used in the scoring. This was done separately for each cohort; a meta-analysis of the correlations was conducted in META 5.3 [Schwarzer, 1989]. For the replication cohorts, personality polygenic scores were estimated from all the Discovery cohorts, with personality predicted in the Australian cohort and mood states predicted in the German and NTR cohorts.

A gene-based test was performed using VEGAS [Liu et al., 2010]. Such tests can be more powerful than individual level SNP association because weaker signals from multiple causal variants in a gene will contribute evidence to gene significance whereas in GWAS these would likely be inseparable from random noise. Meta-analysis SNP *P*-values were used as the input, with the program assigning them to genes, and assessing the combined effect of all SNPs within a gene while accounting for SNP linkage disequilibrium. Almost 18,000 genes were tested, annotated to positions on the UCSC Genome Browser (hg18 assembly) which include regulatory regions located ±50 kb of 5′ and 3′ untranslated regions. Bonferroni significance was set at $P < 2.8 \times 10^{-6}$ based on a correction for the number of genes tested.

Replication Cohorts

Personality. Neuroticism data (n = 6,032) were drawn from three Australian cohorts of twin families measured in 1980, 1989, and 2002 on the EPQ 23- (1980 cohort) or 12-item scale (1989 and 2002 cohorts) at a mean age of 32.5 ± 11.8 years (62.9% female). Extraversion data (n = 5,443) were available from the 1980 and 1989 cohorts, based on respective 21- and 12-items of the EPQ; the mean age was 31.6 ± 12 years (64.7% female). For details on cohort ascertainment and measure reliability see Birley et al. [2006]. Participants were genotyped on an Illumina SNP microarray chip (317K, 370K-array, 370-Quad, 610-Quad, or humanCNV370-Quadv3) in different genotyping centers with imputation to ~2.5 million SNPs using Hap Map Phase II data and MACH. QC procedures were applied separately to each project [Wray et al., 2012]. Association analysis included sex, age, cohort, and the population stratification components as covariates; a variance components approach accounted for relatedness among individuals in MERLIN [Chen and Abecasis, 2007].

Mood

Germany. Anxiety and depression symptoms [measured by the Profile of Mood States, McNair et al., 1992] were available in a population cohort aged 52 ± 16 years. General psychological

distress was indexed by a composite score of anxiety and depression. GWAS data (Illumina HumanHap300 chip) were available for 527 (54% females) participants. For QC of the GWAS data see Stefansson et al. [2008]. A linear regression was performed including the covariates age, sex and the first three MDS components in PLINK [Purcell et al., 2007].

Netherlands Twin Register (NTR). Longitudinal data have been collected since 1991 in twins/their family members registered in the NTR. In 1993 and 1997, depression was measured with the BDI [Beck et al., 1974]. Anxious depression (comparable to psychological distress) was measured with the (young) Adult Self Report [Achenbach and Rescorla, 2003] in 1991, 1995, 1997, 2000, 2002, and 2009. BDI data comprised the 1997 dataset complemented with 1993 data, and the psychological distress dataset used the 2009 dataset complemented with data from the other time-points. The numbers of unrelated individuals (>18 years) with genotype and phenotype data were 2,685 (psychological distress) and 1,383 (depression); mean age was 45.1 (SD 14.9) and 37.5 years (SD 12.3), respectively. Genome-wide genotyping was performed in a selection of subjects as part of six projects, including around 40% of the sample who participated in one of two Major Depressive Disorder GWAS studies [Sullivan et al., 2009; Wray et al., 2012]. Affymetrix 6.0, Affymetrix Perlegen 5.0, Illumina 370, Illumina 660 and Illumina Omni Express 1M platforms were used. Following exclusions based on standard QC [Psychiatric Genetics Network, 2009], data were merged and imputed against the reference set using IMPUTE v2. After imputation, genotype dosage was calculated if the highest genotype probability was above 90%.

RESULTS

Raw score descriptive statistics for the GWAS cohorts are shown in Table I. Analyses were performed on standardized scores for measure compatibility. Correlations among the measures within each cohort were significant (Supplementary Table S2). *P*-values from meta-analysis are presented in Manhattan and Q-Q plots (Supplementary Figs. S1 and S2). No SNPs surpassed genome-wide significance. Effect size statistics and *P*-values for SNPs reaching suggestive significance are shown in Table II. The top 100 SNPs for each measure appear in Supplementary Table S3, whereas these do not pass the stringent significance tests of GWAS, they may lie in existing candidate genes.

For neuroticism, seven independent SNPs in five genes showed suggestive significance. Four SNPs showed suggestive association with extraversion, with two in the same locus. Five SNPs were identified for depression symptoms: three located in genes (*RAVER1*, *WWOX*, *FAM190A*) and two near genes. Three SNPs passed suggestive significance for anxiety symptoms: two located in *FHIT* and one nearby *ZNF438*. For psychological distress symptoms, four SNPs showed suggestive association: three were near *TNFRSF21* and the other located in *NOS1*. Nominally significant associations with the other correlated variables for each of the suggestively associated SNPs are reported in Table II. Pleiotropic effects with other variables were indicated for all the top SNPs except those for extraversion. The extraversion polygenic score significantly predicted psychological distress variation ($r = 0.03$, $P = 0.04$), and the neuroticism polygenic score significantly predicted depression symptoms ($r = 0.03$, $P = 0.03$).

Results for the top 10 most significant genes from the gene-based analysis are reported in Table III. Significant gene associations at the Bonferroni-corrected significance level were observed for neuroticism. These associated genes included *C15orf17, POLR3A*, *MPI*, *SCAMP2*, *ULK3*, *COX5A*. With the exception of *POLR3A*, they were located in a region on chromosome 15 in very tight LD, so the assignment of the same SNP to multiple genes at this locus occurred where gene boundaries overlapped. Only one of these genes showed nominal significance for the other traits: *POLR3A* was associated with depression symptoms ($P = 0.026$). The most significant genes for the other traits included: *PNMA1* for extraversion ($P = 6 \times 10^{-6}$), *GRAP* for depression symptoms ($P = 1.9 \times 10^{-5}$), *RTTN* for anxiety symptoms ($P = 1 \times 10^{-4}$), and *ARID3A* for psychological distress symptoms ($P = 2.1 \times 10^{-5}$). We checked the gene-based *P*-value for genes in which suggestively-associated SNPs from the GWAS were located. For extraversion, the *KIAA0802* gene showed a *P*-value of 0.051. All the neuroticism top SNPs were in the top 10 gene list, including three genes that were genome-wide significant. For anxiety symptoms, the *FHIT* gene was not nominally significant ($P = 0.44$). For depression symptoms, *FAM190A* was not tested, but *WWOX* and *RAVER1* showed respective *P*-values of 0.08 and 0.50. For psychological distress symptoms, *NOS1* was nominally significant ($P = 0.005$).

Suggestively associated SNPs from the GWAS meta-analysis were examined in replication cohorts (Table IV). Four SNPs showed association (two with neuroticism, one with depressive symptoms, and two with psychological distress symptoms) at a significance level of 0.05. One of these, rs7582472, was associated with depressive symptoms in German ($P = 0.013$) and NTR ($P = 0.006$) cohorts, and showed allelic effects in the same direction as the meta-analysis result. Replication results for the genes associated with neuroticism (Table III) were nominally significant for the five genes in LD on chromosome 15. Polygenic scores of personality were significant predictors of trait scores of personality ($P < 0.05$) in the Australian cohort, but they explained very little variance (0.1%) in extraversion and neuroticism. In the German cohort, genetic profile scores of extraversion were negatively correlated with symptoms of anxiety ($r = -0.09$; $P = 0.044$), depression ($r = -0.10$; $P = 0.022$) and psychological distress ($r = -0.10$; $P = 0.021$). In the NTR cohort, genetic profile scores of neuroticism predicted psychological distress ($r = 0.04$; $P = 0.045$).

DISCUSSION

Several SNPs in known genes showed suggestive association with measures of neuroticism, extraversion, symptoms of anxiety, depression, and general psychological distress. One of these (rs7582472) was associated with symptoms of depression in two independent cohorts. One of the top SNPs (and a gene, *POLR3A*, from the gene-based test) for neuroticism showed pleiotropic effects for symptoms of depression, whereas for extraversion no such effects were observed. Genetic profile scores for extraversion predicted mood state phenotypes in the expected direction in one of the replication cohorts, indicating genetic overlap between the traits. A gene-based test identified six genes associated with

TABLE I. Mean Raw Scores of Personality and Psychological Distress Traits in the Croatian, Scottish, English, and Dutch Cohorts, Stratified Across Sex, and Their Correlations With Age

		Total sample		Men		Women		
	N	Mean	SD	Mean	SD	Mean	SD	Correlation with age
CROATIA-Vis								
1. EPQ extraversion	878	8.20	2.79	8.47	2.65	7.99	2.87	−0.22
2. EPQ neuroticism	881	5.37	3.35	4.43	3.12	6.07	3.36	0.18
3. GHQ total	911	58.12	11.20	55.32	9.96	60.15	11.62	0.18
CROATIA-Korcula								
1. EPQ extraversion	809	8.55	2.61	8.87	2.41	8.37	2.71	−0.14
2. EPQ neuroticism	808	4.85	3.21	3.92	2.92	5.39	3.25	0.18
3. GHQ total	876	56.64	9.79	55.20	9.03	57.47	10.11	0.24
ORCADES								
1. EPQ extraversion	445	6.31	3.41	6.30	3.51	6.49	3.28	−0.12
2. EPQ neuroticism	445	3.22	2.86	2.79	2.91	3.86	2.83	−0.19
LBC1921								
1. IPIP extraversion	427	20.67	7.55	19.95	7.81	21.18	7.33	0.01
2. IPIP emotional stability	430	24.37	8.02	24.69	8.39	24.15	7.76	−0.02
3. HADS—anxiety	523	5.19	3.30	4.59	3.04	5.62	3.42	0.02
4. HADS—depression	523	3.50	2.31	3.56	2.23	3.45	2.37	0.00
5. HADS—total	523	8.69	4.71	8.15	4.54	9.07	4.80	0.02
LBC1936								
1. IPIP extraversion	880	21.31	7.08	20.96	7.28	21.65	6.87	−0.01
2. IPIP emotional stability	877	24.62	7.68	25.51	7.59	23.74	7.68	−0.03
3. HADS—anxiety	1,003	4.88	3.20	4.19	2.88	5.59	3.37	−0.02
4. HADS—depression	1,000	2.80	2.25	2.91	2.35	2.69	2.14	0.02
5. HADS—total	1,000	7.67	4.58	7.10	4.40	8.26	4.68	−0.01
Manchester								
1. EPQ extraversion	694	11.58	5.07	10.26	5.22	12.10	4.92	−0.01
2. EPQ neuroticism	694	9.76	5.58	8.37	5.22	10.31	5.66	−0.12**
3. BDI—depression	836	6.38	5.53	4.93	4.65	6.99	5.75	−0.05
Newcastle								
1. EPQ extraversion	795	11.63	5.06	10.83	5.03	11.95	5.03	−0.08*
2. EPQ neuroticism	795	10.35	5.41	8.82	4.94	10.96	5.47	−0.06
3. BDI—depression	828	7.21	5.80	5.83	5.39	7.77	5.88	0.01
Nijmegen[a]								
1. EPQ extraversion	1,328	6.60	3.58	6.14	3.59	7.05	3.50	−0.20***
2. EPQ neuroticism	1,338	3.22	2.71	2.68	2.51	3.74	2.80	−0.08*
3. SCL90—anxiety	1,314	11.61	2.77	11.21	2.30	12.00	3.10	−0.05
4. BDI—depression	1,338	5.24	4.67	4.81	4.34	5.64	4.94	0.08*

[a]Non parametric correlation between age and dependent measures.
*$P < 0.05$.
**$P < 0.001$.
***$P < 0.0001$.

neuroticism; five were located in a region of high LD on chromosome 15 and replicated in an independent cohort.

Phenotypic correlations among neuroticism, anxiety, and depression symptoms were substantial; therefore, we expected overlap in the association results. Shared genetic association effects can represent: correlated type 1 error, true genetic pleiotropy, or direct effects of a gene on one trait that indirectly influences the other through a causal pathway. For top neuroticism associations, we observed nominally significant associations with depressive symptoms for SNPs in the *POLR3A* gene. For extraversion, none of the top hits showed nominal significance for any other trait (but this correlated less strongly with the other measures). The prediction analyses confirmed phenotypic variance in depression/psychological distress attributed to polygenic neuroticism scores. In line with findings that showed pleiotropy was characteristic of 17% of genes and 5% of SNPs associated with diseases/disease traits [Sivakumaran et al., 2011], we interpret our overlapping results across traits as evidence of genetic pleiotropy; alternatively, indirect genetic effects on the correlated trait might be operating. It is also possible that they instead reflect shared type 1 error, although the partly non-overlapping nature of the samples across traits (e.g., the GWAS for depressive symptom scores was a subset of the GWAS

TABLE II. SNPs Showing Suggestive GWAS Significance ($P < 6.09 \times 10^{-6}$) in the Meta-Analysis for Extraversion, Neuroticism, and Symptoms of Anxiety, Depression, and Psychological Distress

	Ch	Position[a]	Effect allele (EA)	Other allele	EA frequency range	Gene/Closest gene (*SNP located in a gene)	Effect	Effect SE	*P*-value	Direction of Effect	$P < 0.05$ for other traits (effect size, *P*-value)
Personality traits											
Extraversion (E) N = 6,256											
rs6782143	3	5768262	T	A	0.93–0.97	AC027119.1	0.251	0.052	1.19×10^{-6}	++++++++	None
rs2470646	3	5775765	T	C	0.92–0.96	AC027119.1	0.211	0.045	2.91×10^{-6}	++++++++	None
rs9598027	13	34297478	C	A	0.97–0.99	RP11-141M1.3	0.361	0.078	4.09×10^{-6}	++++?−?+	None
rs4798680	18	8730726	A	G	0.39–0.47	*KIAA0802**	0.086	0.019	5.39×10^{-6}	++++++++	None
Neuroticism (N) N = 6268											
rs12067374	1	152568230	C	G	0.27–0.33	*LCE3C* (4 kb)	0.114	0.024	2.72×10^{-6}	+++++−++	None
rs7905170	10	79738238	G	A	0.18–0.20	*POLR3A**	0.105	0.023	5.32×10^{-6}	++++++++	D (0.06 ± 0.03, $P = 0.02$)
rs11634474	15	75116184	C	G	0.26–0.31	*LMAN1L**	0.097	0.021	2.28×10^{-6}	−+++++++	E (−0.04 ± 0.02, $P = 0.04$)
rs936229	15	75132319	A	G	0.23–0.26	*ULK3**	0.110	0.022	9.97×10^{-7}	−+++++++	None
rs3765066	15	75140854	G	A	0.29–0.37	*SCAMP2**	0.096	0.020	8.93×10^{-7}	−+++++++	E (−0.04 ± 0.02, $P = 0.05$)
rs1869959	15	75147332	A	C	0.25–0.32	*SCAMP2**	0.099	0.020	1.18×10^{-6}	−+++++++	E (−0.04 ± 0.02, $P = 0.04$)
rs11630918	15	75155896	C	T	0.39–0.54	*SCAMP2**	0.095	0.019	4.22×10^{-7}	−+++++++	None
Mood states											
Anxiety (A) N = 2,840											
rs1079196	3	59806778	A	G	0.19–0.21	*FHIT**	0.179	0.033	8.00×10^{-8}	+++	PD (0.08 ± 0.03, $P = 0.01$)
rs10428174	3	59814048	G	A	0.21–0.23	*FHIT**	0.160	0.032	5.33×10^{-7}	+++	PD (0.07 ± 0.03, $P = 0.01$)
rs2793109	10	31379846	A	T	0.48–0.53	*ZNF438* (59 kb)	0.132	0.027	1.47×10^{-6}	+++	PD (0.07 ± 0.02, $P = 4 \times 10^{-3}$)
Depression (D) N = 4,525											
rs7582472	2	134644794	C	T	0.17–0.19	*MGAT5* (367 kb), *NCKAP5* (318 kb)	0.132	0.028	1.59×10^{-6}	+++++	PD (0.06 ± 0.03, $P = 0.04$)
rs2141848	4	92395356	A	C	0.44–0.46	*FAM190A**	0.100	0.021	2.64×10^{-6}	+++++	PD (0.09 ± 0.03, $P = 6 \times 10^{-4}$)
rs3808900	9	124992764	A	G	0.74–0.76	*LHX6* (1,745 bp)	0.115	0.025	2.89×10^{-6}	+++++	PD (0.06 ± 0.03, $P = 0.03$); N (0.06 ± 0.02, $P = 3 \times 10^{-3}$); E (-0.04 ± 0.02, $P = 0.04$)
rs4888786	16	78394040	G	A	0.62–0.66	*WWOX**	0.102	0.022	5.52×10^{-6}		
rs10410977	19	10443254	A	C	0.01–0.02	*RAVER1**	0.693	0.139	6.75×10^{-7}	+++++	PD (0.67 ± 0.20, $P = 1 \times 10^{-3}$)
Psychological distress (PD) N = 3,310											
rs10948347	6	47311898	T	C	0.93–0.96	*TNFRSF21* (34 kb)	0.269	0.058	4.01×10^{-6}	++++	A (0.21 ± 0.07, $P = 2 \times 10^{-3}$)
rs9381534	6	47313491	G	A	0.95–0.97	*TNFRSF21* (36 kb)	0.297	0.064	2.88×10^{-6}	++++	D (0.13 ± 0.06, $P = 0.02$); A (0.17 ± 0.07, $P = 0.02$)
rs4374821	6	47355493	G	A	0.94–0.90	*TNFRSF21* (78 kb)	0.259	0.053	1.07×10^{-6}	++++	D (0.12 ± 0.05, $P = 0.01$); A (0.21 ± 0.06, $P = 4 \times 10^{-4}$)
rs7298903	12	117747210	T	C	0.86–0.91	*NOS1**	0.185	0.041	5.39×10^{-6}	++++	None

The number of cohorts included in each meta-analysis ranges between four (for anxiety) to eight (for personality).
Ch, chromosome.
Significant SNPs in strong linkage disequilibrium ($r^2 > 0.80$ in HapMap phase 2/3 CEU sample or our own cohorts) with those in the table are not presented, they include: Extraversion: rs6782143 with rs17043388, rs1811510; rs2470646 with rs2470644, rs7621135, rs7618793, rs1452713; rs9598027 with rs2182058, rs9315242, rs9598025, rs9598026, rs9598029, rs9592004, rs10507414, rs7318085, rs7319180, rs17079650; Neuroticism: rs7905170 with rs4979936, rs4979937; rs11630918 with rs7497393, rs11072511, rs7495739, rs1127796, rs1130741, rs4886636, rs11072512, rs1133322, rs1133323, rs11856413, rs11072514, rs11072513; rs3765066 with rs11072518; rs936229 with rs1378938, rs7176022, rs7162232, rs9210, rs8031937, rs6495126, rs8042694, rs936230, rs6495127; Depression: rs7582472 with rs13429789; rs2141848 with rs7675583, rs10007512, rs6845679 Anxiety: rs10428174 with rs4679614, rs1872495, rs4679615; Psychological Distress: rs9381534 with rs9369675, rs6918220, rs9357529, rs3905310, rs9395248.
[a]NCBI dbSNP Human Build 131 (GRCh37).

TABLE III. Top 10 Most Significant Genes for Extraversion and Neuroticism, and Symptoms of Anxiety, Depression, and Psychological Distress, as Evaluated by VEGAS

Gene	Chromosome	Start position	Stop position	No. of SNPs	*P*-value
Extraversion					
PNMA1	14	73248238	73250881	77	6.00×10^{-6}
C14orf43	14	73251577	73323649	124	3.00×10^{-5}
DNAL1	14	73181330	73238402	104	6.10×10^{-5}
CRTC3	15	88874201	88989581	184	1.38×10^{-4}
KIAA0146	8	48336094	48811028	94	1.78×10^{-4}
SLC35F1	6	118335381	118745532	487	3.88×10^{-4}
SLC7A11	4	139304697	139382953	88	6.83×10^{-4}
PCBP1	2	70168204	70169836	52	7.57×10^{-4}
PAP2D	1	99128388	99243037	207	8.18×10^{-4}
ASPRV1	2	70040727	70042901	72	8.41×10^{-4}
Neuroticism					
C15orf17 [a]	15	72979380	72986515	30	1.00×10^{-6} (0.048)
POLR3A	10	79405909	79459265	55	1.00×10^{-6} (0.588)
MPI [a]	15	72969462	72977618	34	1.00×10^{-6} (0.046)
SCAMP2 [a]	15	72924249	72952723	55	1.00×10^{-6} (0.049)
ULK3 [a]	15	72915511	72922605	53	1.00×10^{-6} (0.047)
COX5A	15	72999669	73017548	31	2.00×10^{-6} (0.046)
CPLX3	15	72906003	72911189	53	3.00×10^{-6}
LMAN1L	15	72892246	72905152	63	7.00×10^{-6}
RPP25	15	73034495	73036828	32	7.00×10^{-6}
CSK	15	72861477	72882592	67	1.70×10^{-5}
Anxiety					
RTTN	18	65822020	66023942	251	1.02×10^{-4}
ST8SIA1	12	22237591	22378915	261	2.45×10^{-4}
FAM110B	8	59069666	59224831	261	3.57×10^{-4}
KMO	1	239762302	239825567	135	3.75×10^{-4}
MMRN1	4	91035074	91094803	128	6.28×10^{-4}
RPS28	19	8292383	8293280	41	6.28×10^{-4}
KANK3	19	8293467	8314146	45	7.12×10^{-4}
CHML	1	239858789	239865855	66	7.57×10^{-4}
OPN3	1	239823074	239870324	121	7.61×10^{-4}
FAM82B	8	87553693	87590125	117	8.32×10^{-4}
Depression					
GRAP	17	18864714	18891061	23	1.90×10^{-5}
ARMC1	8	66677627	66708986	89	4.50×10^{-5}
MTFR1	8	66719527	66785340	98	4.70×10^{-5}
TTRAP	6	24758183	24775094	126	6.30×10^{-5}
THEM2	6	24775253	24809921	127	6.80×10^{-5}
NDE1	16	15651604	15726491	85	1.00×10^{-4}
KIAA0430	16	15595744	15644510	54	1.18×10^{-4}
KIAA0319	6	24652310	24754362	229	2.35×10^{-4}
PDE7A	8	66793866	66916297	84	2.70×10^{-4}
FAM83G	17	18815105	18848785	59	3.23×10^{-4}
Psychological distress					
ARID3A	19	877036	923803	79	2.10×10^{-5}
GRIN3B	19	951436	960723	75	2.60×10^{-5}
WDR18	19	935327	945569	70	3.20×10^{-5}
VGLL2	6	117693413	117701421	116	7.50×10^{-5}
C19orf6	19	960649	972141	71	8.40×10^{-5}
EPOR	19	11349474	11356019	36	1.84×10^{-4}
HMGB2	4	174489361	174492167	51	2.54×10^{-4}
C19orf39	19	11346382	11348627	37	2.87×10^{-4}
RGL3	19	11366000	11391004	41	2.87×10^{-4}
KISS1R	19	868341	872015	54	2.96×10^{-4}

Genome-wide significant genes (in bold) were tested in an independent Australian cohort (replication *P*-value is shown in parentheses).
[a]The best-SNP association was rs11630918.

TABLE IV. Replication Results for Personality Traits (Tested in an Australian Cohort, n = 6,032) and Mood [Tested in GERMAN (n = 527) and NTR (n = 1,383–2,685) Cohorts]

	Ch	Increaser effect allele	Effect allele frequency	Effect	Effect SE	*P*-value
Extraversion						
rs6782143	3	T	0.97	−0.121	0.074	0.103
rs2470646	3	T	0.96	−0.089	0.061	0.146
rs9598027	13	C	0.98	−0.096	0.117	0.41
rs4798680 (in *KIAA0802*)	18	A	0.40	−0.020	0.022	0.35
Neuroticism						
rs12067374	1	C	0.28	0.026	0.029	0.36
rs7905170 (in *POLR3A*)	10	G	0.19	0.024	0.027	0.38
rs11634474 (in *LMAN1L*)	**15**	**C**	**0.27**	**−0.051**	**0.025**	**0.038**
rs936229 (in *ULK3*)	15	A	0.25	−0.043	0.027	0.11
rs3765066 (in *SCAMP2*)	15	G	0.32	−0.039	0.023	0.089
rs1869959 (in *SCAMP2*)	**15**	**A**	**0.27**	**−0.062**	**0.024**	**0.011**
rs11630918 (in *SCAMP2*)	15	C	0.43	−0.030	0.022	0.17
Anxiety						
rs1079196 (in *FHIT*)	3	A	0.19	−0.345	0.249	0.167
rs10428174 (in *FHIT*)	3	A	0.79	0.226	0.241	0.347
Depression						
rs7582472 (Germany)	**2**	**C**	**0.20**	**1.288**	**0.501**	**0.010**
rs7582472 (NTR)		**C**	**0.20**	**0.131**	**0.048**	**0.006**
rs1922230 (proxy for rs2141848 in *FAM190A*—Germany)[a]	4	G[d]	0.37	−0.436	0.412	0.291
rs2141848 (NTR)		A	0.46	−0.021	0.038	0.585
rs3808900 (Germany)	9	A	0.75	−0.240	0.453	0.596
rs3808900 (NTR)		A	0.75	−0.027	0.049	0.576
rs7184686 (proxy for rs4888786 in *WWOX*—Germany)[b]	16	G[d]	0.41	0.264	0.420	0.529
rs4888786 (NTR)		A	0.37	−0.011	0.039	0.78
Psychological distress						
rs10948347 (German)	6	T	0.95	0.132	1.298	0.919
rs10948347 (NTR)		**T**	**0.94**	**0.157**	**0.073**	**0.038**
rs11068447 (proxy for rs7298903 in *NOS1* - German)[c]	**12**	**C[d]**	**0.116**	**2.378**	**0.871**	**0.006**
rs7298903 (NTR)		T	0.09	0.059	0.050	0.233
rs4374821 (NTR)	6	G	0.94	0.102	0.057	0.073

Significant results ($P < 0.05$) are indicated in bold.
Ch, chromosome.
For mood traits, some SNPs were not genotyped and no suitable tagging SNP available for the German cohort.
[a]Distance between markers: 22,029 kb, $r^2 = 0.63$.
[b]Distance between markers: 21,598 kb, $r^2 = 0.93$.
[c]Distance between markers: 477 kb, $r^2 = 0.97$.
[d]Allele corresponds to minor or major allele proxy equivalent.

sample for neuroticism) should have the effect of reducing correlated error variance.

Our most significant GWAS finding was for SNPs in *FHIT* (fragile histidine triad gene which codes for a protein involved in purine metabolism) influencing anxiety symptoms. These SNPs were also associated with psychological distress, which taps anxiety, depression, and social dysfunction. SNPs nearby/in the *FHIT* gene have been associated with recurrent early-onset major depressive disorder in a GWAS [Shi et al., 2011]. Importantly, 35% of the cases in their study showed a co-morbid anxiety disorder diagnosis. Our top *FHIT* SNPs were not in LD with rs10514718, their associated marker (located 176 kb from *FHIT*). In our study, rs10514718 fell short of association with anxiety; the C allele conferred a 0.12 SD decrease in scores ($P = 0.08$).

For depressive symptoms, the most interesting genes—*MGAT5* (mannosyl (alpha-1,6-)-glycoprotein beta-1,6-*N*-acetyl-glucosaminyltransferase) and *NCKAP5/NAP5* (Nck-associated protein 5)—were located 300–400 kb 5′ to a SNP replicated in the German and NTR cohorts. Mgat5 mouse knockouts exhibit lower depression-like behaviors especially under stress-induced conditions [Soleimani et al., 2008]; and a GWAS of bipolar disorder reported *NAP5* as a gene/region worthy of further study [Smith et al., 2009]. Our associated SNP is some distance from these genes and, and in the CEU population, is located in a recombination hotspot, making it less likely that this variant relates to these genes. Additionally, gene-based testing did not show significant associations of these two genes with depression symptoms.

TNFRSF21 (tumor necrosis factor receptor superfamily, member 21) was the closest (~34 kb downstream) gene to eight intergenic SNPs reaching suggestive significance for psychological distress. Whereas *TNFRSF21* presents as a good candidate gene for anxiety and depression—due to its role in inflammation and immune regulation—our SNPs were not in LD with SNPs in *TNFRSF21*. A SNP located in *NOS1* (encoding nitric oxide synthase 1) was suggestively associated with psychological distress, but unlike the SNPs located near *TNFRSF21*, this SNP showed no association with anxiety/depression symptoms. In rodent models of stress, nitric oxide levels in plasma and brain affect stress-induced neurobehavioral measures and stress susceptibility [Gilhotr et al., 2010]. In humans, haplotypes in *NOS1* have been associated with suicidal behavior [Rujescu et al., 2008].

The gene-based test identified six genes associated with neuroticism. Five (*C15orf17*, *MPI*, *SCAMP2*, *ULK3*, *COX5A*) were located in a region of tight LD, which was replicated in the Australian cohort. SNPs in *ULK3* and *SCAMP2* passed suggestive significance in the GWAS—and one in *SCAMP2* was significant (albeit in the opposite direction) in the Australian cohort. *SCAMP2* (secretory carrier membrane protein 2) was an interesting candidate because SCAMP2 plays a role in plasmalemmal norepinephrine transporter function, a drug target of mood disorder [Matthies et al., 2009]. While not reaching corrected significance, *NDE1* (nudE nuclear distribution gene E homolog 1) was nominally associated with symptoms of depression, and has been related to major depression. This gene encodes a protein involved in microtubal organization, mitosis and neuronal migration. Variants in NDE1 affect expression levels of genes targeted by drugs for bipolar disorder and major depression [Hennah and Porteous, 2009]. There was good agreement between the top SNP associations (i.e., those located in genes) and the gene-based tests. That *FHIT* and *RAVER1* were not significant in the gene-based test indicates that the SNP associations within these genes are possibly type 1 error, are in LD with another important gene, or have very specific effects on gene functioning, for instance if they are exonic SNPs.

The main limitation of the present study was the relatively small sample size, particularly for the measurement of anxiety. Using the more conservative alpha level, power calculations for our varying sample sizes ranged 45–99% to detect an effect size of 1%. This resulted in insufficient power to attain genome-wide significance for some associations that were suggestive. However, it has been shown that most borderline GWAS significant results (i.e., $P > 5 \times 10^{-8}$ and $P \leq 10^{-7}$) are potentially genuine associations [Panagiotou and Ioannidis, 2011]. Thus, we can place confidence in several of our SNP and gene-based test findings because of the replication support we found. The use of different psychological scales across cohorts is considered advantageous because the meta-analysis results will invariably detect associations that relate to reliable trait variance (i.e., variance that is common across tests that purportedly measure the same underlying trait).

In summary, our strongest GWAS finding was for a SNP near *MGAT5* and *NCKAP5*, which was suggestively associated with depression symptoms and replicated in two cohorts. Our gene based test identified a locus on chromosome 15 associated with neuroticism, and this region was also replicated. Single SNP results often generalized across multiple traits, particularly neuroticism and depression, and by using genetic personality profile scores we were able to predict (in the hypothesized direction) symptoms of depression from neuroticism polygenic scores. In the replication cohorts, all mood states were predicted by extraversion polygenic scores (in the German cohort) and psychological distress from neuroticism polygenic scores (in the NTR). Future work should encompass multivariate genetic association analysis of personality traits and mood states because the covariance among these variables might more reliably index people at greater genetic predisposition to psychological distress by removing environmental variance affecting mood. Some of our results have been linked previously to clinical psychiatric traits, suggesting that personality and mood traits sampled in the general population may be relevant to clinical pathology of mood.

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