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Genetic variants associated with subjective well-being, depressive symptoms, and neuroticism identified through genome-wide analyses

Very few genetic variants have been associated with depression and neuroticism, likely because of limitations on sample size in previous studies. Subjective well-being, a phenotype that is genetically correlated with both of these traits, has not yet been studied with genome-wide data. We conducted genome-wide association studies of three phenotypes: subjective well-being (n = 298,420), depressive symptoms (n = 161,460), and neuroticism (n = 170,911). We identify 3 variants associated with subjective well-being, 2 variants associated with depressive symptoms, and 11 variants associated with neuroticism, including 2 inversion polymorphisms. The two loci associated with depressive symptoms replicate in an independent depression sample. Joint analyses that exploit the high genetic correlations between the phenotypes ($|\hat{\rho}| \approx 0.8$) strengthen the overall credibility of the findings and allow us to identify additional variants. Across our phenotypes, loci regulating expression in central nervous system and adrenal or pancreas tissues are strongly enriched for association.

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Subjective well-being—as measured by survey questions on life satisfaction, positive affect, or happiness—is a major topic of research in psychology, economics, and epidemiology. Twin studies have found that subjective well-being is genetically correlated with depression (characterized by negative affect, anxiety, low energy, bodily aches and pains, pessimism, and other symptoms) and neuroticism (a personality trait characterized by easily experiencing negative emotions such as anxiety and fear)[1–3]. Depression and neuroticism have received much more attention than subjective well-being in genetic association studies, but the discovery of genetic variants associated with either of them has proven elusive[4,5].

Here we report a series of separate and joint analyses of subjective well-being, depressive symptoms, and neuroticism, which identify 16 genome-wide significant associations across the three phenotypes. In our two joint analyses, we exploit the high genetic correlation between subjective well-being, depressive symptoms, and neuroticism (i) to evaluate the credibility of the associations from our initial genome-wide association study (GWAS) and (ii) to identify new associations (beyond those identified by the GWAS). In achieving the first aim, we investigate whether SNPs associated with subjective well-being 'quasi-replicate' by testing them for association with depressive symptoms and neuroticism. We similarly examine the quasi-replication records of the loci associated with depressive symptoms and neuroticism by testing them for association with subjective well-being. We find that the quasi-replication record closely matches what would be expected, given our statistical power, if none of the genome-wide significant associations were chance findings. These results strengthen the credibility of most of the original associations. For our second aim, we use a 'proxy-phenotype' approach[6]: we treat the set of loci associated with subjective well-being at $P < 1 \times 10^{-4}$ as candidates and test them for association with depressive symptoms and neuroticism.

In designing our study, we faced a tradeoff between analyzing a smaller sample with a homogeneous phenotype measure versus attaining a larger sample by jointly analyzing data from multiple cohorts with heterogeneous measures. For example, in our analysis of subjective well-being, we included measures of both life satisfaction and positive affect, even though these constructs are conceptually distinct[7,8]. In the **Supplementary Note** and **Supplementary Figure 1**, we present a theoretical framework for evaluating the costs and benefits of pooling heterogeneous measures. In our context, given the high genetic correlation across measures, the framework predicts that pooling increases statistical power to detect variants. This prediction is supported by our results.

RESULTS

GWAS of subjective well-being

Following a prespecified analysis plan, we conducted a sample-size-weighted meta-analysis using data from 59 cohorts (n = 298,420 individuals) of cohort-level GWAS summary statistics. The phenotype measure was life satisfaction, positive affect, or (in some cohorts) a measure combining life satisfaction and positive affect. We confirmed previous findings[9] of high pairwise genetic correlation between life satisfaction and positive affect using bivariate LD Score regression[10] ($\hat{\rho}$ = 0.981 (s.e.m. = 0.065); **Supplementary Table 1**). Details on the 59 participating cohorts, their phenotype measures, genotyping, quality control filters, and association models are provided in the Online Methods, **Supplementary Note**, and **Supplementary Tables 2–6**.

As expected under polygenicity[11], we observed inflation of the median test statistic (λ_{GC} = 1.206). The estimated intercept from LD Score regression (1.012) suggests that nearly all of the inflation is due to polygenic signal rather than bias. We also performed family-based analyses that similarly suggested minimal confounding due to

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population stratification (Online Methods). Using a clumping procedure (**Supplementary Note**), we identified three approximately independent SNPs reaching genome-wide significance ('lead SNPs'). These three lead SNPs are indicated in the Manhattan plot (**Fig. 1a**) and are listed in **Table 1**. The SNPs had estimated effects in the range of 0.015–0.018 s.d. per allele (each $R^2 \approx 0.01\%$).

We also conducted separate meta-analyses of the components of our subjective well-being measure—life satisfaction (n = 166,205) and positive affect (n = 180,281) (Online Methods). Consistent with our theoretical conclusion that pooling heterogeneous measures increases power, in our context, the life satisfaction and positive affect analyses yielded fewer signals across a range of P-value thresholds than our meta-analysis of subjective well-being (**Supplementary Table 7**).

GWAS of depressive symptoms and neuroticism

We conducted auxiliary GWAS of depressive symptoms and neuroticism (see the Online Methods, **Supplementary Note**, and **Supplementary Tables 8–12** for details on the cohorts, phenotype measures, genotyping, association models, and quality control filters). For depressive symptoms (n = 180,866), we performed meta-analysis on publicly available results from a study performed by the Psychiatric Genomics Consortium (PGC)[12] together with new results from analyses of the initial release of UK Biobank (UKB) data[13] and the Resource for Genetic Epidemiology Research on Aging (GERA) cohort (database of Genotypes and Phenotypes (dbGaP), phs000674.v1.p1). In the UKB cohort (n = 105,739), we constructed a continuous phenotype measure by combining responses to two questions asking about the frequency in the past 2 weeks with which the respondent experienced feelings of unenthusiasm or disinterest and feelings of depression or hopelessness. The other cohorts had ascertained case–control data on major depressive disorder (GERA, n_{cases} = 7,231, $n_{controls}$ = 49,316; PGC, n_{cases} = 9,240, $n_{controls}$ = 9,519).

For neuroticism (n = 170,911), we pooled summary statistics from a published study by the Genetics of Personality Consortium (GPC)[4] with results from a new analysis of UKB data. GPC (n = 63,661) harmonized different neuroticism batteries. In the UKB cohort (n = 107,245), our measure was the respondent's score on a 12-item version of the Eysenck Personality Inventory Neuroticism[14].

In both the depressive symptoms and neuroticism GWAS, the heterogeneous phenotypic measures were highly genetically correlated (**Supplementary Table 1**). As in our subjective well-being analyses, there was substantial inflation of the median test statistics (λ_{GC} = 1.168 for depressive symptoms and 1.317 for neuroticism), but the estimated LD Score intercepts (1.008 and 0.998, respectively) suggest that bias accounts for little or none of the inflation.

For depressive symptoms, we identified two lead SNPs, indicated in the Manhattan plot (**Fig. 1b**). For neuroticism, our meta-analysis yielded 16 loci that were independent according to our locus definition (**Fig. 1c**). However, six of these reside within a well-known inversion polymorphism[15] on chromosome 8. We established that all genome-wide significant signals in the inversion region were attributable to the inversion, and we confirmed that the inversion was associated with neuroticism in both of our neuroticism data sets, the GPC and the UKB (Online Methods and **Supplementary Note**). In our list of lead SNPs (**Table 1**), we only retain the most strongly associated SNP from these six loci to tag the chromosome 8 inversion.

Another lead SNP associated with neuroticism, rs193236081, is located within a well-known inversion polymorphism on chromosome 17. We established that this association was attributable to the inversion polymorphism (Online Methods and **Supplementary Note**).

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Figure 1 Manhattan plots of GWAS results. (**a**–**c**) Results are shown for subjective well-being (n = 298,420) (**a**), depressive symptoms (n = 180,866) (**b**), and neuroticism (n = 170,911) (**c**). The x axis shows chromosomal position, and the y axis shows association significance on a $-\log_{10}$ scale. The upper dashed line marks the threshold for genome-wide significance ($P = 5 \times 10^{-8}$), and the lower dashed line marks the threshold for nominal significance ($P = 1 \times 10^{-5}$). Each approximately independent genome-wide significant association (lead SNP) is marked by a red **×**. Each lead SNP is the SNP with the lowest P value within the locus, as defined by our clumping algorithm (**Supplementary Note**).

Because this inversion yielded only one significant locus and is genetically complex[16], we hereafter simply use its lead SNP as a proxy for it. Our neuroticism GWAS therefore identified 11 lead SNPs, 2 of which tag inversion polymorphisms. A concurrent neuroticism GWAS using a subset of our sample reported similar findings[17].

The estimated effects of all lead SNPs associated with depressive symptoms and neuroticism were in the range of 0.020–0.031 s.d. per allele ($R^2 \approx 0.02$–0.04%) (**Table 1**). In the UKB cohort, we estimated the effect of an additional allele of the chromosome 8 inversion polymorphism itself on neuroticism to be 0.035 s.d. (**Supplementary Table 13**). The inversion explains 0.06% of variance in neuroticism (roughly the same as the total variance explained jointly by the six SNPs in the inversion region).

Genetic overlap across subjective well-being, depressive symptoms, and neuroticism

The three pairwise genetic correlations between our phenotypes, estimated using bivariate LD Score regression[10], are substantial: −0.81 (s.e.m. = 0.046) between subjective well-being and depressive symptoms, −0.75 (s.e.m. = 0.034) between subjective well-being and neuroticism, and 0.75 (s.e.m. = 0.027) between depressive symptoms and neuroticism (**Fig. 2a**). Using height as a negative control, we also examined pairwise genetic correlations between each of our phenotypes and height and, as expected, found all three to be modest, for example, 0.07 with subjective well-being (**Supplementary Table 1**). The high genetic correlations between subjective well-being, depressive symptoms, and neuroticism may suggest that the genetic influences on these phenotypes are predominantly related to processes common across the phenotypes, such as mood, rather than being phenotype specific (**Fig. 2**).

Quasi-replication and Bayesian credibility analyses

We assessed the credibility of our findings using a standard Bayesian framework[18,19] in which a positive fraction of SNPs have null effects and a positive fraction of SNPs have non-null effects (Online Methods). For each phenotype, the non-null effect sizes are assumed to be drawn from a normal distribution whose variance is estimated from the GWAS summary statistics. As a first analysis, for each lead SNP's association with its phenotype, we calculated the posterior probability of null association after having observed the GWAS results.

Table 1 Summary of polymorphisms identified across analyses

Genome-wide significant associations									
Subjective well-being (n = 298,420)									
SNP ID	Chr.	Position (bp)	EA	EAF	β (s.e.m.)	R^2 (%)	P value	n	Quasi-replication[d]
rs3756290	5	130,951,750	A	0.24	−0.0177 (0.0031)	0.011	9.6×10^{-9}	286,851	
rs2075677	20	47,701,024	A	0.76	0.0175 (0.0031)	0.011	1.5×10^{-8}	288,454	DS**
rs4958581	5	152,187,729	T	0.66	0.0153 (0.0027)	0.011	2.3×10^{-8}	294,043	DS***
Neuroticism (n = 170,911)									
SNP ID	Chr.	Position (bp)	EA	EAF	β (s.e.m.)	R^2 (%)	P value	n	Quasi-replication
rs2572431[a]	8	11,105,077	T	0.59	0.0283 (0.0035)	0.039	4.2×10^{-16}	170,908	SWB*
rs193236081[b]	17	44,142,332	T	0.77	−0.0284 (0.0043)	0.028	6.3×10^{-11}	151,297	
rs10960103	9	11,699,270	C	0.77	0.0264 (0.0042)	0.024	2.1×10^{-10}	165,380	$D^*_{23andMe}$
rs4938021	11	113,364,803	T	0.66	0.0233 (0.0037)	0.024	4.0×10^{-10}	159,900	$D^*_{23andMe}$, SWB*
rs139237746	11	10,253,183	T	0.51	−0.0204 (0.0034)	0.021	2.6×10^{-9}	170,908	
rs1557341	18	35,127,427	A	0.34	0.0213 (0.0037)	0.021	5.6×10^{-9}	165,579	$D^*_{23andMe}$
rs12938775	17	2,574,821	A	0.53	−0.0202 (0.0035)	0.020	8.5×10^{-9}	163,283	SWB*
rs12961969	18	35,364,098	A	0.2	0.0250 (0.0045)	0.020	2.2×10^{-8}	156,758	
rs35688236	3	34,582,993	A	0.69	0.0213 (0.0038)	0.019	2.4×10^{-8}	161,636	
rs2150462	9	23,316,330	C	0.74	−0.0217 (0.0039)	0.018	2.7×10^{-8}	170,907	
rs12903563	15	78,033,735	T	0.50	0.0198 (0.0036)	0.020	2.9×10^{-8}	157,562	$D^*_{23andMe}$,SWB*
Depressive symptoms (n = 180,866)									
SNP ID	Chr.	Position (bp)	EA	EAF	β (s.e.m.)	R^2 (%)	P value	n	Quasi-replication/replication
rs7973260	12	118,375,486	A	0.19	0.0306 (0.0051)	0.029	1.8×10^{-9}	124,498	$D^*_{23andMe}$
rs62100776	18	50,754,633	A	0.56	−0.0252 (0.0044)	0.031	8.5×10^{-9}	105,739	$D^*_{23andMe}$, SWB*
SNPs identified via proxy-phenotype analyses of subjective well-being loci with $P < 1 \times 10^{-4}$									
Depressive symptoms in non-overlapping cohorts									
SNP ID	Chr.	Position (bp)	EA	EAF	β_{DS} (SE_{DS})	R^2 (%)	P_{DS}	Bonferroni	n_{DS}
rs4346787[c]	6	27,491,299	A	0.113	−0.023 (0.0059)	0.011	9.8×10^{-5}	0.0160	142,265
rs4481363	5	164,483,794	A	0.524	0.014 (0.0038)	0.009	3.1×10^{-4}	0.0499	142,265
Neuroticism in non-overlapping cohorts									
SNP ID	Chr.	Position (bp)	EA	EAF	β_{neuro} (SE_{neuro})	R^2 (%)	P_{neuro}	Bonferroni	n_{neuro}
rs10838738	11	47,663,049	A	0.49	0.0178 (0.0039)	0.016	5.0×10^{-6}	0.0009	131,864
rs10774909	12	117,674,129	C	0.52	−0.0150 (0.0039)	0.011	1.2×10^{-4}	0.0203	131,235
rs6904596	6	27,491,299	A	0.09	−0.0264 (0.0072)	0.012	2.5×10^{-4}	0.0423	116,335
rs4481363	5	164,474,719	A	0.49	0.0151 (0.0040)	0.011	1.9×10^{-4}	0.0316	122,592

Chr., chromosome; EA, effect allele; EAF, effect allele frequency (all effect sizes are reported in units of s.d. per allele); SWB, subjective well-being; DS, depressive symptoms; D, depression; SE, standard error.

[a]Inversion-tagging polymorphism on chromosome 8. [b]Inversion-tagging polymorphism on chromosome 17. [c]Proxy for rs6904596 (r^2 = 0.98). [d]Phenotypes with which a SNP was found to be nominally associated in quasi-replication analyses conducted in independent samples: *, significant at the 5% level; **, significant at the 1% level; ***, significant at the 0.1% level.

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Figure 2 Genetic correlations. Correlations were estimated using bivariate LD Score (LDSC) regression. (**a**) Genetic correlations between subjective well-being, depressive symptoms, and neuroticism ('our three phenotypes'), as well as between our three phenotypes and height. (**b**) Genetic correlations between our three phenotypes and selected neuropsychiatric phenotypes. (**c**) Genetic correlations between our three phenotypes and selected physical health phenotypes. In **b** and **c**, we report the negative of the estimated correlation with depressive symptoms and neuroticism (but not subjective well-being). Error bars represent 95% confidence intervals.

We found that, for any assumption about the fraction of non-null SNPs in the range 1–99%, the probability of true association always exceeded 95% for all 16 loci (and always exceeded 98% for 14 of them).

To further probe the credibility of the findings, we performed quasi-replication exercises (Online Methods) in which we tested the subjective well-being lead SNPs for association with depressive symptoms and neuroticism. We similarly tested the depressive symptoms lead SNPs and the neuroticism lead SNPs for association with subjective well-being. Below, we refer to the phenotype for which the lead SNP was identified as the first-stage phenotype and the phenotype used for the quasi-replication as the second-stage phenotype. To avoid sample overlap, for each quasi-replication analysis, we omitted any cohorts that contributed to the GWAS of the first-stage phenotype.

Results of the quasi-replication of the three subjective well-being lead SNPs are shown in **Figure 3a**. The reference allele for each association in the figure is chosen such that the predicted sign of the second-stage estimate is positive. We found that two of the three subjective well-being lead SNPs were significantly associated with depressive symptoms (P = 0.004 and P = 0.001) in the predicted direction. For neuroticism, where the second-stage sample (n = 68,201) was about one-half as large, the allele increasing subjective well-being had the predicted sign for all three SNPs, but none reached significance.

We also show the results for the depressive symptoms (**Fig. 3b**) and neuroticism (**Fig. 3c**) lead SNPs. In each panel, the blue crosses depict results from the quasi-replications where subjective well-being was the second-stage phenotype. We found that the two depressive symptoms lead SNPs had the predicted sign for subjective well-being, and one was nominally significant (P = 0.04). Finally, of the 11 neuroticism lead SNPs, 9 had the predicted sign for subjective well-being. Four of the 11 had nominally significant association with subjective well-being, all with the predicted sign. One of the four is the SNP tagging the inversion on chromosome 8 (ref. 15). That SNP's association with neuroticism (and likely with subjective well-being) was driven by its correlation with the inversion (**Supplementary Fig. 2**).

To evaluate what these quasi-replication results imply about the credibility of the 16 GWAS associations, we compared the observed quasi-replication record to the quasi-replication record expected given our statistical power. We calculated statistical power using our Bayesian framework, under the hypothesis that each lead SNP has a non-null effect on both the first- and second-stage phenotypes. Our calculations take into account both the imperfect genetic correlation between the first- and second-stage phenotypes and inflation of the first-stage estimates due to the well-known problem of winner's curse (Online Methods). Of the 19 quasi-replication tests, our calculations imply that 16.7 would be expected to yield the anticipated sign and 6.9 would be significant at the 5% level. The observed numbers were 16 and 7. Our quasi-replication results are thus consistent with the hypothesis that none of the 16 genome-wide significant associations are chance findings and in fact strengthen the credibility of our GWAS results (**Supplementary Table 14**).

Lookup of depressive symptoms and neuroticism lead SNPs

Investigators of an ongoing large-scale GWAS of major depressive disorder (n = 368,890) in the 23andMe cohort shared association results for the loci identified in our depressive symptoms and neuroticism analyses (Online Methods and **Supplementary Table 15**; C.L. Hyde, M.W. Nagle, C. Tian, X. Chen, S.A. Paciga *et al.*, unpublished data). Because the depression sample overlaps with our subjective well-being sample, we did not request a lookup of the SNPs associated with subjective well-being.

In **Figure 3b**,**c**, the results are depicted as green crosses. For interpretational ease, we chose the reference allele so that positive coefficients imply that the estimated effect is in the predicted direction. All 13 associations had the predicted sign. Of the 11 neuroticism polymorphisms, 4 were significantly associated with depression at the 5% level. Both of the depressive symptoms lead SNPs replicated (P = 0.004 and P = 0.015), with effect sizes (0.007 and −0.007 s.d. per allele) close to those predicted by our Bayesian framework (0.008 and −0.006) (**Supplementary Tables 14** and **15**).

The top part of **Table 1** summarizes the results for the 16 lead SNPs identified across our separate genome-wide association analyses of the three phenotypes. The rightmost column summarizes the statistical significance of the quasi-replication and depression lookup analyses of each SNP.

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Figure 3 Quasi-replication and lookup of lead SNPs. (**a**–**c**) In quasi-replication analyses, we examined whether lead SNPs identified in the subjective well-being meta-analyses are associated with depressive symptoms or neuroticism (**a**), whether lead SNPs identified in the analyses of depressive symptoms are associated with subjective well-being (**b**), and whether lead SNPs identified in the analyses of neuroticism are associated with subjective well-being (**c**). The quasi-replication sample was always restricted to non-overlapping cohorts. In a separate lookup exercise, we examined whether lead SNPs for depressive symptoms and neuroticism are associated with depression in an independent sample of 23andMe customers (n = 368,890). The results from this lookup are depicted as green crosses in **b** and **c**. Error bars represent 95% confidence intervals (not adjusted for multiple testing). For ease of interpretation, we chose the reference allele such that positive coefficients imply that the estimated effect is in the predicted direction. Listed below each lead SNP is the nearest gene or chromosomal region.

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Proxy-phenotype analyses

To identify additional SNPs associated with depressive symptoms, we conducted a two-stage 'proxy-phenotype' analysis (Online Methods). In the first stage, we ran a new GWAS of subjective well-being to identify a set of candidate SNPs. Specifically, from each locus exhibiting suggestive evidence of association ($P < 1 \times 10^{-4}$) with subjective well-being, we retained the SNP with the lowest P value as a candidate. In the second stage, we tested these candidates for association with depressive symptoms at the 5% significance threshold, Bonferroni adjusted for the number of candidates. We used an analogous two-stage procedure to identify additional SNPs associated with neuroticism. The first-stage subjective well-being sample differed across the two proxy-phenotype analyses (and from the primary subjective well-being GWAS sample) because we assigned cohorts across the first and second stages so as to maximize statistical power for the overall procedure.

For depressive symptoms, there were 163 candidate SNPs. Of these, 115 (71%) had the predicted direction of effect on depressive symptoms, 20 were significantly associated at the 5% significance level (19 in the predicted direction), and 2 remained significant after Bonferroni adjustment. For neuroticism, there were 170 candidate SNPs. Of these, 129 (76%) had the predicted direction of effect, all 28 SNPs significant at the 5% level had the predicted sign, and 4 of these remained significant after Bonferroni adjustment (**Supplementary Fig. 3** and **Supplementary Tables 16** and **17**). Two of the four were SNPs also identified in the proxy-phenotype analysis for depressive symptoms.

The four SNPs in total identified by the proxy-phenotype analyses are listed in **Table 1**.

Biological analyses

To shed some light on possible biological mechanisms underlying our findings, we conducted several analyses.

We began by using bivariate LD Score regression[10] to quantify the amount of genetic overlap between each of our three phenotypes and ten neuropsychiatric and physical health phenotypes. The estimates for subjective well-being and the negative of the estimates for depressive symptoms and neuroticism (as subjective well-being is negatively genetically correlated with depressive symptoms and neuroticism) are shown in **Figure 2b**,**c**. Subjective well-being, depressive symptoms, and neuroticism had strikingly similar patterns of pairwise genetic correlation with the other phenotypes.

We examined five neuropsychiatric phenotypes: Alzheimer disease, anxiety disorders, autism spectrum disorder, bipolar disorder, and schizophrenia (**Fig. 2b**). For four of these phenotypes, genetic correlations with depression (but not neuroticism or subjective well-being) were reported in Bulik-Sullivan *et al.*[10]. For schizophrenia and bipolar disorder, our estimated correlations with depressive symptoms, 0.33 and 0.26, are substantially lower than the point estimates of Bulik-Sullivan *et al.* but are contained within their 95% confidence intervals. By far, the largest genetic correlations we estimated were with anxiety disorders: −0.73 with subjective well-being, 0.88 with depressive symptoms, and 0.86 with neuroticism. To our knowledge, genetic correlations estimated from GWAS data have not previously been reported for anxiety disorders.

We also examined five physical health phenotypes that are known or believed to be risk factors for various adverse health outcomes: body mass index (BMI), ever-smoker status, coronary artery disease, fasting glucose levels, and triglyceride levels (**Fig. 2c**). The estimated genetic correlations were all small in magnitude, consistent with earlier work, although the greater precision of our estimates allowed us to reject null effects in most cases. The signs were generally consistent with those of the phenotypic correlations reported in earlier work between our phenotypes and outcomes such as obesity[20], smoking[21,22], and cardiovascular health[23].

Next, to investigate whether our GWAS results are enriched in particular functional categories, we applied stratified LD Score regression[24] to our meta-analysis results. In our first analysis, we report estimates for all 53 functional categories included in the 'baseline model'; the results for subjective well-being, depressive symptoms, and neuroticism were broadly similar (**Supplementary Tables 18**–**20**) and are in line with what has been found for other phenotypes[24]. In our second analysis, the categories were groupings of SNPs likely to regulate gene expression in cells of a specific tissue. The estimates for subjective well-being, depressive symptoms, and neuroticism are similar to each other and different from those for height, which was again included as a benchmark[25] (**Fig. 4a** and **Supplementary Table 21**).

We found significant enrichment of central nervous system for all three phenotypes and, perhaps more surprisingly, enrichment of adrenal/pancreas for subjective well-being and depressive symptoms. The cause of the adrenal/pancreas enrichment is unclear, but we note that the adrenal glands produce several hormones, including cortisol, epinephrine, and norepinephrine, known to have important roles in

Figure 4 Results from selected biological analyses. (**a**) Estimates of the expected increase in the phenotypic variance accounted for by a SNP due to the SNP's being in a given category (τ_c), divided by the LD Score heritability of the phenotype (h^2). Each estimate of τ_c comes from a separate stratified LD Score regression, controlling for the 52 functional annotation categories in the baseline model. Error bars represent 95% confidence intervals (not adjusted for multiple testing). To benchmark the estimates, we compare them to those obtained from a recent study of height[25]. (**b**) Inversion polymorphism on chromosome 8 and the seven genes for which the inversion is a significant *cis*-eQTL at false discovery rate (FDR) < 0.05. The upper half of the figure shows the Manhattan plot for neuroticism for the inversion and surrounding regions. The bottom half shows the squared correlation between the SNPs and the principal component that captures the inversion (PC1). The inlay plots the relationship, for each SNP in the inversion region, between the SNP's significance and its squared correlation with the principal component that captures the inversion.

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the bodily regulation of mood and stress. It has been robustly found that blood serum levels of cortisol in patients afflicted by depression are elevated relative to those in controls[26].

Whereas the above analyses use genome-wide data, we also conducted three analyses (Online Methods) restricted to the 16 GWAS and 4 proxy-phenotype SNPs in **Table 1**. In brief, we ascertained whether each SNP (or a variant in strong linkage disequilibrium (LD) with it) fell into any of the following three classes: (i) resides in a locus for which genome-wide significant associations with other phenotypes have been reported (**Supplementary Table 22**), (ii) is nonsynonymous (**Supplementary Table 23**), and (iii) is an expression quantitative trait locus (eQTL) in blood or in 1 of 14 other tissues (although the non-blood analyses are based on smaller samples) (**Supplementary Table 24**). Here we highlight a few particularly interesting results.

We found that 5 of the 20 SNPs are in loci in which genome-wide significant associations have previously been reported. Two of these five are loci associated with schizophrenia. Interestingly, one of them harbors the gene *DRD2*, which encodes the D_2 subtype of the dopamine receptor, a target for antipsychotic drugs[27] that is also known to have a key role in neural reward pathways[28]. Motivated by these findings, as well as by the modest genetic correlations with schizophrenia (**Fig. 2b**), we examined whether the SNPs identified in a recent study of schizophrenia[29] are enriched for association with neuroticism in our non-overlapping UKB sample (n = 107,245). We conducted several tests and found strong evidence of such enrichment (**Supplementary Note**). For example, we found that the P values of the schizophrenia-associated SNPs tended to be much lower than the P values of a randomly selected set of SNPs matched on allele frequency ($P = 6.50 \times 10^{-71}$).

Perhaps the most notable pattern that emerged from our biological analyses is that the inversions on chromosomes 8 and 17 were implicated consistently across all analyses. The inversion-tagging SNP on chromosome 8 is in LD with SNPs that have previously been found to be associated with BMI[30] and triglyceride levels[31] (**Supplementary Table 22**). We also conducted eQTL analyses in blood for the inversion itself and found that it is a significant *cis*-eQTL for seven genes (**Supplementary Table 24**). All seven genes are positioned in close proximity to the inversion breakpoints (**Fig. 4b**), suggesting that the molecular mechanism underlying the inversion's effect on neuroticism could involve the relocation of regulatory sequences. Two of the genes (*MSRA* and *MTMR9*) are known to be highly expressed in tissues and cell types that belong to the nervous system, and two (*BLK* and *MFHAS1*) are known to be highly expressed in the immune system. In the tissue-specific analyses, we found that the SNP tagging the inversion is a significant eQTL for two genes, *AF131215.9* (in tibial nerve and thyroid tissue analyses) and *NEIL2* (in tibial nerve tissue), both of which are also located near the inversion breakpoint.

The SNP tagging the chromosome 17 inversion is a significant *cis*-eQTL for five genes in blood and is an eQTL in all 14 other tissues (**Supplementary Table 24**). It alone accounts for 151 of the 169 significant associations identified in the 14 tissue-specific analyses. Additionally, the SNP is in near-perfect LD ($r^2 > 0.97$) with 11 missense variants (**Supplementary Table 23**) in three different genes, one of which is *MAPT*. *MAPT*, which is also implicated in both blood and other tissue-specific analyses, encodes a protein important in the stabilization of microtubules in neurons. Associations have previously been reported between SNPs in *MAPT* (all of which are in strong LD with our inversion-tagging SNP) and neurodegenerative disorders, including Parkinson disease[32] and progressive supranuclear palsy[33], a rare disease whose symptoms include depression and apathy.

DISCUSSION

The discovery of genetic loci associated with subjective well-being, depression, and neuroticism has proven elusive. Our study identified several credible associations for two main reasons. First, our analyses had greater statistical power than previous studies because ours were conducted in larger samples. Our GWAS findings—3 loci associated with subjective well-being, 2 loci associated with depressive symptoms, and 11 loci associated with neuroticism—support the view that GWAS can successfully identify genetic associations with highly polygenic phenotypes in sufficiently large samples[5,34]. A striking finding is that two of our identified associations are with inversion polymorphisms.

Second, our proxy-phenotype analyses further boosted power by exploiting the strong genetic overlap between our three phenotypes.

These analyses identified two additional loci associated with neuroticism and two additional loci associated with both depressive symptoms and neuroticism. Through our quasi-replication tests, we also demonstrated how studying genetically overlapping phenotypes in concert can provide evidence on the credibility of GWAS findings. Our direct replication of the two genome-wide significant associations with depressive symptoms in an independent depression sample provides further confirmation of these findings (**Fig. 2b** and **Supplementary Table 15**).

We were able to assemble much larger samples than previous work in part because we combined data across heterogeneous phenotype measures. Our results reinforce the conclusions from our theoretical analysis that doing so increases statistical power, but our strategy also has drawbacks. One is that mixing different measures may make any discovered associations more difficult to interpret. Research studying higher-quality measures of the various facets of subjective well-being, depressive symptoms, and neuroticism is a critical next step. Our results can help facilitate such work because, if the variants we identify are used as candidates, studies conducted in the smaller samples in which more fine-grained phenotype measures are available can be well powered.

Another limitation of mixing different measures is that doing so may reduce the heritability of the resulting phenotype, if the measures are influenced by different genetic factors. Indeed, our estimates of SNP-based heritability[10] for our three phenotypes are quite low: 0.040 (s.e.m. = 0.002) for subjective well-being, 0.047 (s.e.m. = 0.004) for depressive symptoms, and 0.091 (s.e.m. = 0.007) for neuroticism. We correspondingly find that polygenic scores constructed from all measured SNPs explain a low fraction of variance in independent samples: ~0.9% for subjective well-being, ~0.5% for depressive symptoms, and ~0.7% for neuroticism (Online Methods). The low heritabilities imply that, even when polygenic scores can be estimated using much larger samples than ours, they are unlikely to attain enough predictive power to be clinically useful.

According to our Bayesian calculations, the true explanatory power (corrected for winner's curse) of the SNP with the largest posterior R^2 is 0.003% for subjective well-being, 0.002% for depressive symptoms, and 0.011% for neuroticism (**Supplementary Table 14**). These effect sizes imply that, to account for even a moderate share of heritability, hundreds or (more likely) thousands of variants will be required. They also imply that our study's power to detect variants of these effect sizes was not high—for example, our statistical power to detect the lead SNP with the largest posterior R^2 value was only ~13%—which in turn means it is likely that there exist many variants with effect sizes comparable to those for our identified SNPs that evaded detection. These estimates suggest that many more loci will be found in studies with sample sizes realistically attainable in the near future. Consistent with this projection, when we perform meta-analysis on the 54 SNPs reaching $P < 1 \times 10^{-5}$ in our analyses of depressive symptoms together with the 23andMe replication sample for depression, the number of genome-wide significant associations increases from two to five (**Supplementary Table 15**).

URLs. Genotype-Tissue Expression Portal, http://www.GTExportal.org/; Social Science Genetic Association Consortium (SSGAC), http://www.thessgac.org/#!data/kuzq8.

METHODS

Methods and any associated references are available in the online version of the paper.

Accession codes. For neuroticism and depressive symptoms, we provide meta-analysis results from the combined analyses for all variants. For subjective well-being, meta-analysis results for all variants are provided for the full sample excluding 23andMe, for which only up to 10,000 SNPs can be reported. Therefore, for the subjective well-being meta-analysis, we provide results for 10,000 SNPs. Meta-analysis results can be downloaded from the SSGAC website.

Note: Any Supplementary Information and Source Data files are available in the online version of the paper.

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AUTHOR CONTRIBUTIONS

M.B., D.J.B., D.C., J.-E.D.N., P.D.K., and R.F.K. designed and oversaw the study. A.O. and B.M.L.B. were responsible for quality control and meta-analyses. Bioinformatics analyses were carried out by J.P.B., T.E., M.A.F., J.R.G., J.J.L. S.F.W.M., M.G.N., and H.-J.W. Other follow-up analyses were conducted by M.A.F., J.P.B., P.T., A.O., B.M.L.B., and R.K.L. Especially major contributions to writing and editing were made by M.B., D.J.B., J.P.B., D.C.C., J.-E.D.N., P.D.K., A.J.O., and P.T. All authors contributed to and critically reviewed the manuscript.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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ONLINE METHODS

GWAS of subjective well-being. Genome-wide association analyses were performed at the cohort level according to a prespecified analysis plan. Genotyping was performed using a range of common, commercially available genotyping arrays. The analysis plan instructed cohorts to upload results imputed using the HapMap 2 CEU (r22.b36) reference sample[35]. We performed meta-analysis on summary association statistics from 59 contributing cohorts with a combined sample size of 298,420 individuals. Before meta-analysis, a uniform set of quality control procedures were applied to the cohort-level summary statistics, including but not limited to the EasyQC[36] protocol. All analyses were restricted to European-ancestry individuals.

We performed a sample-size-weighted meta-analysis of the cohort-level summary statistics. To adjust standard errors for non-independence, we inflated them using the square root of the estimated intercept from an LD Score regression[10]. We also performed secondary, separate meta-analyses of positive affect (n = 180,281) and life satisfaction (n = 166,205) and a *post hoc* genome-wide analysis of subjective well-being in cohorts with 1000 Genomes Project–imputed data (n = 229,883) (**Supplementary Figs. 4–6**).

Detailed cohort descriptions, information about cohort-level genotyping and imputation procedures, cohort-level measures, and quality control filters are shown in **Supplementary Tables 2–6**. Association results from the following four meta-analyses are reported: the primary subjective well-being analysis, the life satisfaction analysis, the positive affect analysis, and the *post hoc* subjective well-being analysis (**Supplementary Table 7**). For each phenotype, we provide association results for the set of approximately independent SNPs that attained a P value smaller than 1×10^{-5}. We identify these SNP using the same clumping algorithm as for the lead SNPs but with the P-value threshold set at 1×10^{-5} instead of genome-wide significance.

GWAS of depressive symptoms and neuroticism. Our auxiliary genome-wide association studies of depressive symptoms and neuroticism were conducted in 1000 Genomes Project–imputed data, combining new genome-wide association analyses with publicly available summary statistics from previously published studies. We applied a similar quality control protocol to that used in our primary subjective well-being analysis. In the depressive symptoms meta-analysis (n = 180,866), we weighted the UKB analysis by sample size and the two case–control studies by effective sample size. In the neuroticism meta-analysis (n = 170,911), we performed a sample-size-weighted fixed-effects meta-analysis of the UKB data and the publicly available summary statistics from a previous GWAS of neuroticism.

Detailed cohort descriptions, information about cohort-level genotyping and imputation procedures, and quality control filters are provided in **Supplementary Tables 8–12**. Quantile–quantile plots of the neuroticism and depressive symptoms meta-analysis results are shown in **Supplementary Figure 7**. Association results for the set of approximately independent SNPs that attained a P value smaller than 1×10^{-5} are supplied in **Supplementary Table 25**.

Population stratification. To quantify the fraction of the observed inflation of the mean test statistic that is due to bias, we used LD Score regression[10]. The estimated LD Score regression intercepts were all close to 1, suggesting no appreciable inflation of the test statistics attributable to population stratification in any of our subjective well-being, depressive symptoms or neuroticism meta-analyses (**Supplementary Fig. 8**). For all three phenotypes, our estimates suggest that less than 2% of the observed inflation of the mean test statistic was accounted for by bias.

In our primary GWAS of subjective well-being, we also used two family-based analyses to test for and quantify stratification biases. These analyses used within-family estimates, the coefficients from regressing the difference in phenotype across siblings on the difference in siblings' genotype (and controls). These within-family estimates are not biased by population stratification because siblings share their ancestry entirely, and therefore differences in siblings' genotypes cannot be due to the siblings being from different population groups. We performed meta-analysis on association statistics from within-family analyses conducted in four cohorts.

In the first analysis, we estimated the fraction of SNPs for which the signs of the within-family estimates were concordant with the signs of the estimates obtained from a GWAS identical to our primary subjective well-being GWAS except with the four family cohorts excluded. For the 112,884 approximately independent SNPs considered, we found a sign concordance of 50.83%, which is significantly greater than 50% ($P = 1.04 \times 10^{-8}$). Under the null hypothesis of no population stratification, the observed sign concordance nearly perfectly matches the expected rate after adjustment for winner's curse at 50.83% (**Supplementary Fig. 9**).

The second analysis used the within-family regression coefficient estimates (that is, not only their signs) to estimate the amount of stratification bias. For each SNP j, let $\hat{\beta}_j$ denote the GWAS estimate and let $\hat{\beta}_{\mathrm{WF},j}$ denote the within-family estimate. Under the assumption that the causal effect of each SNP is the same within families as in the population, we can decompose the estimates as

$$\hat{\beta}_j = \beta_j + s_j + U_j$$
$$\hat{\beta}_{\mathrm{WF},j} = \beta_j + V_j$$

where β_j is the true underlying GWAS parameter for SNP j, s_j is the bias due to stratification (defined to be orthogonal to β_j and U_j), and U_j and V_j are the sampling variances of the estimates with $\mathrm{E}(U_j) = \mathrm{E}(V_j) = 0$. Whenever $s_j \neq 0$, the GWAS estimate of $\hat{\beta}_j$ is biased away from the population parameter β_j. The proportion of variance in the GWAS coefficients accounted for by true genetic signals can be written as

$$\frac{\mathrm{var}(\beta_j)}{\mathrm{var}(\beta_j) + \mathrm{var}(s_j)}$$

In the **Supplementary Note**, we show that, with estimates $\hat{\beta}_j$ and $\hat{\beta}_{\mathrm{WF},j}$ (and their standard errors) from independent samples, it is possible to consistently estimate the above ratio. The 95% confidence interval for the ratio implies that between 72% and 100% of the signal in the GWAS estimates is a result of true genetic effects on subjective well-being rather than stratification.

Analyses of inversion polymorphisms. Two genome-wide significant SNPs for the neuroticism analysis are located within well-known inversion polymorphisms, on chromosomes 8 and 17. Using the genotypic data available for UKB participants, we called the inversion genotypes for UKB participants using a principal-components analysis (PCA)–mixture method. For both inversions, the method clearly distinguishes three clusters of genotypes, corresponding to inversion genotypes (**Supplementary Fig. 10**). We validated the PCA–mixture procedure using existing methods designed to call inversion genotypes[37] (**Supplementary Table 26**).

For each inversion, we established that the inversion-tagging SNPs were always located in close proximity to the inversion region (**Fig. 3b** and **Supplementary Figs. 10** and **11**). We list the 20 variants that most strongly correlate with the principal components that capture the inversion polymorphisms on chromosomes 8 (**Supplementary Table 27**) and 17 (**Supplementary Table 28**). In additional analyses, we confirmed that the inversion is associated with neuroticism and subjective well-being in independent cohorts (**Supplementary Figs. 12** and **13** and **Supplementary Tables 29** and **30**).

Proxy-phenotype analyses. In these analyses, we used a two-stage approach that has been successfully applied in other contexts[6]. In the first stage, we conducted a meta-analysis of our first-stage proxy phenotype and used our clumping procedure to identify the set of approximately independent SNPs at the P-value threshold of 1×10^{-4}. In the second stage, we tested SNPs identified in stage 1 (or high-LD proxies for them) for association with a second-stage phenotype in an independent (non-overlapping) sample. In our analyses, we used our primary phenotype of subjective well-being as the proxy phenotype. We conducted one analysis with depressive symptoms as the second-stage phenotype and one analysis with neuroticism as the second-stage phenotype. In the analyses, we omitted cohorts from the first or second stage as needed to ensure that the samples in the two stages were non-overlapping. The cohort restrictions imposed are listed in **Supplementary Table 31**. These cohort restrictions, as well as the P-value threshold of 1×10^{-4}, were chosen before the data were analyzed on the basis of statistical power calculations.

To test for cross-phenotype enrichment, we used a non-parametric procedure that tests whether lead SNPs are more strongly associated with the

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second-stage phenotype than randomly chosen sets of SNPs with a similar distribution of allele frequencies (**Supplementary Note**).

To test the individual lead SNPs for experiment-wide significance, we examined whether any of the lead SNPs (or their high-LD proxies) were significantly associated with the second-stage phenotype at the Bonferroni-adjusted significance level of 0.05/number of SNPs tested.

Genetic correlations. We used bivariate LD Score regression[10] to quantify the amount of genetic heterogeneity among the phenotypic measures pooled in each of our three separate meta-analyses. For subjective well-being, we estimated a pairwise correlation of 0.981 (s.e.m. = 0.065) between life satisfaction and positive affect, 0.897 (s.e.m. = 0.017) between well-being (our measure that combines life satisfaction and positive affect) and life satisfaction, and 1.031 (s.e.m. = 0.019) between positive affect and well-being. For depressive symptoms, we estimated a genetic correlation of 0.588 (s.e.m. = 0.242) between GERA and PGC, 0.972 (s.e.m. = 0.216) between GERA and UKB, and 0.797 (s.e.m. = 0.108) between UKB and PGC. Finally, we estimated a genetic correlation of 1.11 (s.e.m. = 0.14) between the measures of neuroticism in the UKB analyses and the summary statistics from a previously published meta-analysis[4].

Bayesian credibility analyses. To evaluate the credibility of our findings, we use a standard Bayesian framework[18] in which our prior distribution for any SNP's effect is

$$\beta \sim \begin{cases} N(0, \tau_j^2) & \text{with probability } \pi \\ 0 & \text{otherwise} \end{cases}$$

Here π is the fraction of non-null SNPs and τ_j^2 is the variance of the non-null SNPs for trait $j \in$ {subjective well-being, depressive symptoms, neuroticism}. In this framework, credibility is defined as the probability that a given SNP is non-null.

We begin with univariate analyses of the GWAS results that do not incorporate the additional information from the quasi-replication analyses of the 16 lead SNPs reported in **Table 1**. We use the three subjective well-being-associated SNPs to illustrate our approach, but we use analogous procedures when analyzing depressive symptoms and neuroticism. We calculate credibility for each value $\pi \in \{0.01, 0.02, \ldots, 0.99\}$. For each assumed value of π, we estimate τ^2_{SWB} by maximum likelihood (**Supplementary Note**). For each SNP, we use Bayes' rule to obtain a posterior estimate of credibility for each of the assumed values of π. For all considered values of π and all three SNPs, the posterior probability that the SNP is null is below 1% (**Supplementary Fig. 14**). Similar analyses of the depressive symptoms and neuroticism SNPs show that the posterior probability never exceeds 5%.

In our joint analyses, we consider two phenotypes with genetic correlation r_g. We make the simplifying assumption that the set of null SNPs is the same for both phenotypes. The joint distribution of a SNP's effect on the two phenotypes is then given by

$$\begin{bmatrix} \beta_1 \\ \beta_2 \end{bmatrix} \sim \begin{cases} N\left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \tau_1^2 & \tau_1\tau_2 r_g \\ \tau_1\tau_2 r_g & \tau_2^2 \end{bmatrix} \right) & \text{with probability } \pi \\ \begin{bmatrix} 0 \\ 0 \end{bmatrix} & \text{otherwise} \end{cases}$$

With coefficient estimates, $\hat{\beta}_1$ and $\hat{\beta}_2$, obtained from non-overlapping samples, the variance–covariance matrix of the estimation error will be diagonal. We denote the diagonal entries of this matrix, which represent the variances of the estimation error in the two samples, by σ_1^2 and σ_2^2. This gives us the joint prior distribution

$$\begin{bmatrix} \hat{\beta}_1 \\ \hat{\beta}_2 \end{bmatrix} \sim \begin{cases} N\left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \tau_1^2 & \tau_1\tau_2 r_g \\ \tau_1\tau_2 r_g & \tau_2^2 \end{bmatrix} + \begin{bmatrix} \sigma_1^2 & 0 \\ 0 & \sigma_2^2 \end{bmatrix} \right) & \text{with probability } \pi \\ N\left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \sigma_1^2 & 0 \\ 0 & \sigma_2^2 \end{bmatrix} \right) & \text{otherwise} \end{cases}$$

To select parameter values for the prior, we use the estimates of r_g reported in **Supplementary Table 1**, and we estimate the parameters π, τ_1^2, and τ_2^2 from GWAS summary statistics using a maximum-likelihood procedure. For this procedure, we make the standard assumption[10,38] that the variance in a SNP's effect size is inversely proportional to the variance of its genotype, 2 × MAF × (1 – MAF), where MAF is the minor allele frequency.

The credibility estimates follow from applying Bayes' rule to calculate either the probability that the SNP is non-null (an event denoted C) given only the first-stage estimate, $P\left(C \mid \hat{\beta}_1\right)$, or the probability that the SNP is non-null conditional on the results of both the first-stage GWAS and the quasi-replication analysis, $P\left(C \mid \hat{\beta}_1, \hat{\beta}_2\right)$. Credibility estimates for our lead SNPs are in **Supplementary Table 14**.

To calculate the expected record of a replication or quasi-replication study, we assume that the SNP is non-null for both phenotypes. (This is analogous to a standard power calculation for a single phenotype, in which the SNP is assumed to be non-null.) Under this assumption, $\hat{\beta}_1$ and $\hat{\beta}_2$ are jointly normally distributed, implying that the conditional distribution of $\hat{\beta}_2$ given $\hat{\beta}_1$ is

$$\left(\hat{\beta}_2 \mid \hat{\beta}_1, C\right) \sim N\left[\frac{\tau_1\tau_2 r_g}{\tau_1^2 + \sigma_1^2}\hat{\beta}_1, \frac{\left(\tau_1^2 + \sigma_1^2\right)\left(\tau_2^2 + \sigma_2^2\right) - \tau_1^2\tau_2^2 r_g^2}{\tau_1^2 + \sigma_1^2} \right]$$

Using this equation, we can calculate the probability that the GWAS estimates will have concordant signs across the two phenotypes, or that the GWAS estimate of the second-stage phenotype will reach some level of significance. These probabilities can be summed over the set of lead SNPs to generate the expected number of SNPs meeting the criterion.

To obtain effect size estimates for a SNP that are adjusted for winner's curse (**Supplementary Table 32**), we use the mean of the posterior distribution of the SNP's effect, conditional on the quasi-replication result and the SNP being non-null. We derive the posterior distribution and expected R^2 in the **Supplementary Note**.

Lookup of SNPs associated with depressive symptoms and neuroticism in an independent depression study. We partnered with the investigators of an ongoing large-scale GWAS of major depressive symptoms (n = 368,890) to follow up on the associations identified in the depressive symptoms and neuroticism analyses. The participants of the study were all European-ancestry customers of 23andMe, a personal genomics company, who responded to online survey questions about mental health. We did not request results for the SNPs identified in the subjective well-being or proxy-phenotype analyses because these were both conducted in samples that overlap with the 23andMe's depression sample. For details on association models, quality control filters, and the ascertainment of depression status, we refer to the companion study (C.L. Hyde, M.W. Nagle, C. Tian, X. Chen, S.A. Paciga *et al.* unpublished data). The P values we report are based on standard errors that have been adjusted using the intercept from an LD Score regression[10].

Polygenic prediction. To evaluate the predictive power of a polygenic score derived from the subjective well-being meta-analysis results, we used two independent withheld cohorts: the Health and Retirement Study (HRS)[39] and the Netherlands Twin Register (NTR)[40,41]. To generate the weights for the polygenic score, we performed meta-analyses of the pooled subjective well-being phenotype excluding each of the withheld cohorts, applying a minimum-sample-size filter of 100,000 individuals (**Supplementary Note**). The results from these analyses are reported in **Supplementary Table 33** and depicted in **Supplementary Figure 15**.

Biological annotation. For biological annotation of the 20 SNPs in **Table 1**, we generated a list of LD partners for each of the original SNPs. A SNP was considered to be an LD partner for the original SNP if (i) its pairwise LD with the original SNP exceeded r^2 = 0.6 and (ii) it was located within 250 kb of the original SNP. We also generated a list of genes residing within loci tagged by our lead SNPs (**Supplementary Table 34**).

We used the NHGRI GWAS catalog[42] to determine which of our 20 SNPs (and their LD partners) were in LD with SNPs for which genome-wide

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significant associations have previously been reported. Because the GWAS catalog does not always include the most recent GWAS results available, we included additional recent GWAS studies. We used the tool HaploReg[43] to identify nonsynonymous variants in LD with any of the 20 SNPs or their LD partners.

We examined whether the 20 polymorphisms in **Table 1** were associated with gene expression levels (**Supplementary Table 24** and **Supplementary Note**). The *cis*-eQTL associations were performed in 4,896 peripheral blood gene expression and genome-wide SNP samples from two Dutch cohorts measured on the Affymetrix U219 platform[40,41,44]. We also performed eQTL lookups of our 20 SNPs in the Genotype-Tissue Expression Portal[45,46]. We restricted the search to the following trait-relevant tissues: hippocampus, hypothalamus, anterior cingulate cortex (BA24), putamen (basal ganglia), frontal cortex (BA9), nucleus accumbens (basal ganglia), caudate (basal ganglia), cortex, cerebellar hemisphere, cerebellum, tibial nerve, thyroid, adrenal gland, and pituitary.

Finally, using a gene coexpression database[47], we explored the predicted functions of genes colocating with the 20 SNPs in **Table 1** (**Supplementary Table 35**).

Further details appear in a **Supplementary Note**.

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