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The Genetic Architecture of Depression in Individuals of East Asian Ancestry
A Genome-Wide Association Study

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IMPORTANCE Most previous genome-wide association studies (GWAS) of depression have used data from individuals of European descent. This limits the understanding of the underlying biology of depression and raises questions about the transferability of findings between populations.

OBJECTIVE To investigate the genetics of depression among individuals of East Asian and European descent living in different geographic locations, and with different outcome definitions for depression.

DESIGN, SETTING, AND PARTICIPANTS Genome-wide association analyses followed by meta-analysis, which included data from 9 cohort and case-control data sets comprising individuals with depression and control individuals of East Asian descent. This study was conducted between January 2019 and May 2021.

EXPOSURES Associations of genetic variants with depression risk were assessed using generalized linear mixed models and logistic regression. The results were combined across studies using fixed-effects meta-analyses. These were subsequently also meta-analyzed with the largest published GWAS for depression among individuals of European descent. Additional meta-analyses were carried out separately by outcome definition (clinical depression vs symptom-based depression) and region (East Asian countries vs Western countries) for East Asian ancestry cohorts.

MAIN OUTCOMES AND MEASURES Depression status was defined based on health records and self-report questionnaires.

RESULTS There were a total of 194 548 study participants (approximate mean age, 51.3 years; 62.8% women). Participants included 15 771 individuals with depression and 178 777 control individuals of East Asian descent. Five novel associations were identified, including 1 in the meta-analysis for broad depression among those of East Asian descent: rs4656484 ($\beta = -0.018$, SE = 0.003, $P = 4.43 \times 10^{-8}$) at 1q24.1. Another locus at 7p21.2 was associated in a meta-analysis restricted to geographically East Asian studies ($\beta = 0.028$, SE = 0.005, $P = 6.48 \times 10^{-9}$ for rs10240457). The lead variants of these 2 novel loci were not associated with depression risk in European ancestry cohorts ($\beta = -0.003$, SE = 0.005, $P = .53$ for rs4656484 and $\beta = -0.005$, SE = 0.004, $P = .28$ for rs10240457). Only 11% of depression loci previously identified in individuals of European descent reached nominal significance levels in the individuals of East Asian descent. The transancestry genetic correlation between cohorts of East Asian and European descent for clinical depression was $r = 0.413$ (SE = 0.159). Clinical depression risk was negatively genetically correlated with body mass index in individuals of East Asian descent ($r = -0.212$, SE = 0.084), contrary to findings for individuals of European descent.

CONCLUSIONS AND RELEVANCE These results support caution against generalizing findings about depression risk factors across populations and highlight the need to increase the ancestral and geographic diversity of samples with consistent phenotyping.

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Supplemental content

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Depression affects an estimated 300 million people[1] and represents a leading cause of health-related disabilities. More than 80% of the global burden affects low- and middle-income countries.[2,3] To date, 102 genetic variants have been associated with depression liability.[4-7] However, most previous genetic studies have been conducted in European ancestry cohorts.[8] Extending this work to other population groups can yield new biological insights pertinent to specific populations and facilitate improved genetic risk prediction across ancestry groups.[9,10]

The manifestation of depression varies. In China, the disorder traditionally associated with serious stress is neurasthenia, characterized by strong physical and psychological fatigue.[11] Depression-like presentations are becoming more common in recent times.[12] However, somatic symptoms tend to be emphasized over emotional and cognitive symptoms.[13] Previous studies of US individuals of European descent have reported the absence of high-arousal positive emotions, such as excitement or enthusiasm, as a main feature of depression, while presentations in Chinese individuals emphasize the absence of low-arousal positive states, such as peacefulness.[14-16] Consequently, different items on depression scales tend to be useful markers of depression across populations and ethnic groups,[17-19] raising questions about what depression means and how best to assess it cross-culturally for research.

In this study, we have combined data from the China, Oxford, and Virginia Commonwealth University Experimental Research on Genetic Epidemiology (CONVERGE) consortium,[20] China Kadoorie Biobank (CKB), and the Taiwan-Major Depressive Disorder (MDD) study, as well as studies conducted in the US and UK that included participants of East Asian ancestry, to carry out the first (to our knowledge) large GWAS meta-analysis of depression among 194 548 individuals with East Asian ancestry. We aimed to identify novel depression loci, assess the transferability of genetic risk factors between individuals of European and East Asian descent, characterize the genetic architecture associated with different depression definitions, and compare the findings between ancestry cohorts.

Key Points

Question Are the genetic risk factors for depression the same in individuals of East Asian and European descent?

Findings In this genome-wide association meta-analysis of depression in 194 548 individuals with East Asian ancestry, 2 novel genetic associations were identified, one of which is specific to individuals of East Asian descent living in East Asian countries. There was limited evidence for transferability with only 11% of depression loci previously identified in individuals of European descent reaching nominal significance levels in the individuals of East Asian descent.

Meaning Caution is advised against generalizing findings about genetic risk factors for depression beyond the studied population.

Methods

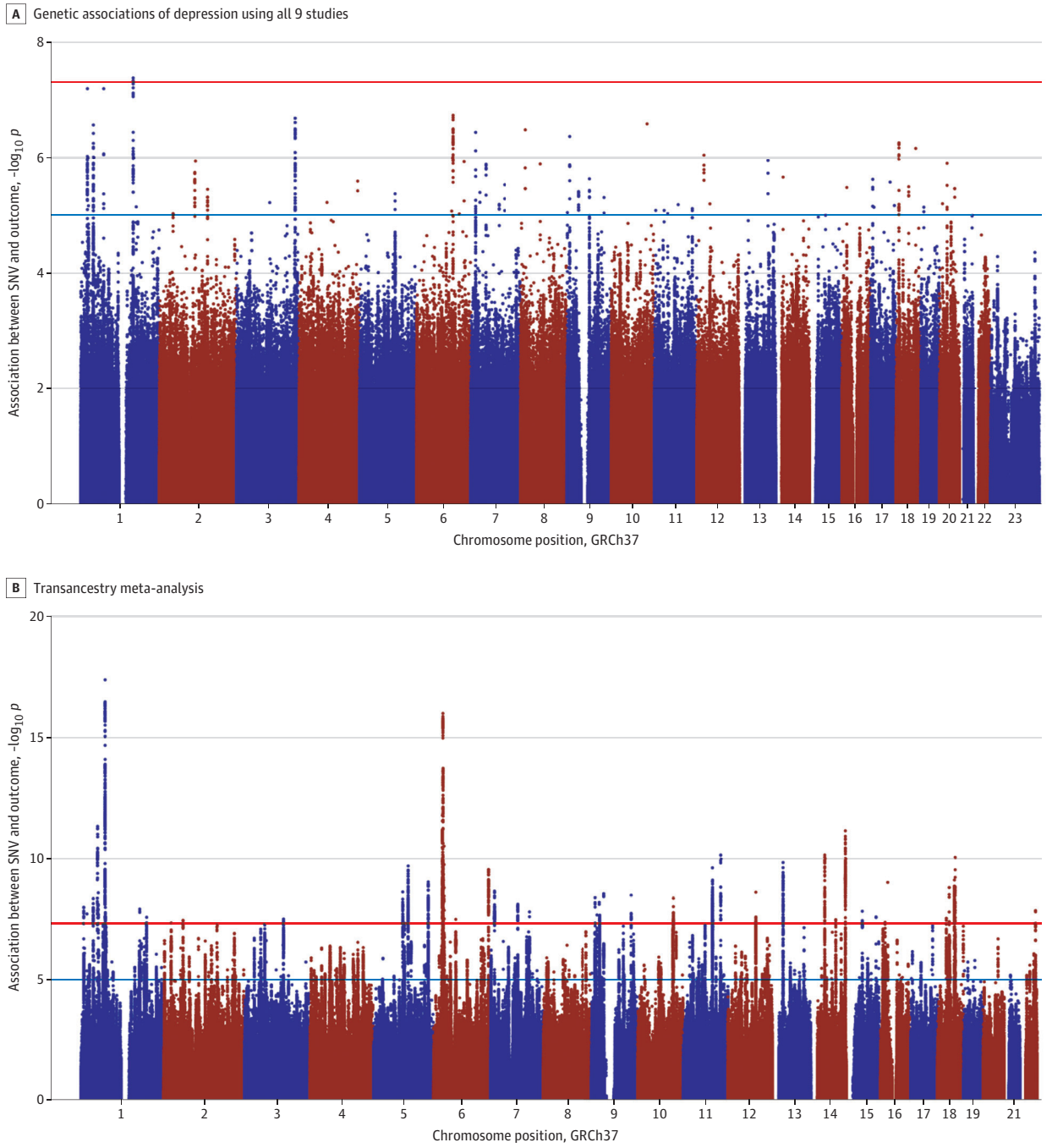
Participating Studies and Depression Definitions

This genome-wide association study was conducted between January 2019 and May 2021. We included data from CKB, CONVERGE, and the Taiwan-MDD study, as well as US- and UK-based cohorts with DNA samples of individuals of East Asian descent: 23andMe Inc, Women's Health Initiative (WHI), Mount Sinai Bio*Me* Biobank, Intern Health Study (IHS), the Study to Assess Risk and Resilience in Servicemembers (Army-STARRS), and UK Biobank (UKB). The data for WHI presented in the current publication are based on the use of study data downloaded from the dbGaP website, under phs000200.v12.p3. Details about these cohorts and data sets are available in eTable 1 in Supplement 1 and eAppendix 1 in Supplement 2. All participants provided written informed consent, and each study obtained approval from local ethical review boards. Genotyping data were exported from China to the Oxford CKB International Coordinating Centre under Data Export Approvals 2014-13 and 2015-39 from the Office of Chinese Human Genetic Resource Administration. The CKB analyses were conducted under project 2018-0018 as approved by the CKB Research Committee. Details of each cohort have been previously described.[20-30] This study followed the Strengthening the Reporting of Genetic Association Studies (STREGA) reporting guideline.

This investigation was based on data from individuals with East Asian ancestry as defined by the investigators based on genetic information. For each study, a principal component analysis was carried out based on the genetic similarity of pairs of individuals. Individuals that clustered around a reference group with confirmed East Asian ancestry were included in this analysis.

We used a range of measures to define depression, including structured clinical interviews, medical health care records, symptom questionnaires, and self-completed surveys in a broad discovery association analysis of 15 771 depression cases and 178 777 controls (eTable 1 in Supplement 1). We also split the sample to perform outcome-specific analyses based on clinical depression or symptom-based depression. For the analysis based on clinical depression, participants reporting lifetime symptoms that were likely to fulfill *DSM* criteria for MDD and individuals diagnosed with a depressive disorder based on medical records from primary and secondary health care were classified as having depression. In this analysis (8223 patients with depression and 85 370 control participants), we combined data from CONVERGE, Taiwan-MDD study, UKB, Army-STARRS, Bio*Me*, and CKB. The symptom-based depression analysis used short questionnaires to identify those with self-reported depression symptoms in general population cohorts, including the CKB (CIDI-trigger symptoms), WHI, and IHS (6124 individuals with depression, 73 095 control participants). We conducted additional association analyses in which cohorts were regrouped by region: cohorts in East Asian countries (12 027 individuals with depression and 83 727 control participants) vs cohorts with participants of East Asian descent in the US and UK studies (3744 individuals with depression, 95 050 control participants) (eTable 1 in Supplement 1).

Figure 1. Manhattan Plot of the Genetic Associations With Depression in Ancestrally East Asian Samples Using All 9 Studies and the Transancestry Meta-analysis Between East Asian and European Ancestry Samples



The y-axes show the $-\log_{10}P$ values of the association between each single-nucleotide variant and the outcome. The x-axes show the chromosomal position (GRCh37). The red line represents the genome-wide significance threshold of 5×10^{-8} and the blue line, 10^{-5}.

Genetic Association Analyses and Meta-analyses

Genotyping and quality control are described in eAppendix 1 and eTable 2 in Supplement 2. Single-nucleotide variant (SNV)–level associations with depression were assessed using logistic regression in the 23andMe, Taiwan-MDD study, Army-STARRS, UKB, WHI, and IHS cohorts. Linear-mixed models were used in the association analysis for CONVERGE (FastLMM, version 2.06.20130802)[31] as well as CKB and Bio*Me* (SAIGE, version 0.36.1)[32] to adjust for population structure and relatedness. We assessed an additive per-allele model. Unstandardized β estimates and standard errors (SEs) were calculated. Age, sex, principal components, and study-specific covariates (eg, study arm in WHI) were included as covariates.

Table. Association Results With Depression for Novel Loci With $P < 5 \times 10^{-8}$ Based on Fixed-Effects Meta-analyses

rs-id[a]	CHR:position	EA/OA	Cohort	No. of individuals with depression; No. of control participants	EAF	β (SE)	OR (95% CI)[b]	*P* value
Discovery set: East Asian ancestry GWAS of broad depression								
rs4656484	1:166145466	C/G	EAS[c]	15 771; 178 777	0.63	−0.018 (0.003)	0.94 (0.91-0.97)	4.43×10^{-8}
			EUR[d]	170 756; 329 443	0.76	−0.003 (0.005)	1.00 (0.99-1.01)	.53
Discovery set: studies conducted in East Asian countries								
rs10240457	7:15431149	A/G	East Asia[e]	12 027; 83 727	0.65	0.028 (0.005)	1.08 (1.05-1.12)	6.48×10^{-9}
			EUR[d]	170 756; 329 443	0.50	−0.005 (0.004)	1.00 (0.99-1.00)	.28
Discovery set: meta-analysis combining ancestrally East Asian and European samples								
rs7548487	1:177025098	A/G	EAS+EUR[f]	186 527; 508 220	0.90	−0.013 (0.002)	0.96 (0.95-0.98)	1.29×10^{-8}
			EAS[c]	15 771; 178 777	0.95	−0.016 (0.007)	0.95 (0.89-1.01)	.02
			EUR[d]	170 756; 329 443	0.88	−0.035 (0.007)	0.97 (0.96-0.97)	1.26×10^{-7}
rs547488	18:26481463	C/G	EAS+EUR[f]	186 527; 508 220	0.54	0.008 (0.001)	1.02 (1.01-1.03)	3.25×10^{-8}
			EAS[c]	15 771; 178 777	0.78	0.011 (0.004)	1.05 (1.01-1.08)	.003
			EUR[d]	170 756; 329 443	0.45	0.020 (0.004)	1.02 (1.01-1.03)	3.12×10^{-6}
rs12160976	22:46438246	A/G	EAS+EUR[f]	186 527; 508 220	0.25	−0.009 (0.002)	0.98 (0.97-0.98)	1.55×10^{-8}
			EAS[c]	15 771; 178 777	0.02	−0.026 (0.011)	0.91 (0.81-1.03)	.02
			EUR[d]	170 756; 329 443	0.34	−0.024 (0.005)	0.98 (0.97-0.99)	2.40×10^{-7}

Abbreviations: CHR, chromosome; EA, effect allele; EAF, effect allele frequency; EAS, East Asian descent; EUR, European descent; OA, other allele; OR, odds ratio.

[a] Only the lead variant of each locus is included. The association results for these variants in European ancestry samples from the largest published meta-analysis for depression are also shown.[7]

[b] Based on an inverse-variance–weighted meta-analysis of the regression coefficients for EAS and EAS+EUR.

[c] East Asian ancestry GWAS of broad depression outcome.

[d] Published results from depression GWAS with European ancestry samples.

[e] Depression GWAS restricted to studies conducted in East Asian countries.

[f] Meta-analysis between East Asian GWAS[c] and European ancestry GWAS.[d]

We performed a *z*-score weighted meta-analysis using METAL, version 2011-03-25[33] for 13 163 200 genetic variants (eFigure 1 in Supplement 2). For all meta-analyses, results were restricted to variants present in at least 2 studies. We also performed a *z*-score weighted meta-analysis combining results from our analysis of individuals of East Asian descent and the publicly available summary statistics from the largest published GWAS of participants of European descent.[7]

Reproducibility of Established Depression Loci

We assessed whether the associations of 102 established depression loci from the largest published European ancestry GWAS[7] were reproducible in samples from individuals with East Asian ancestry. We compared this to the absolute number of associations out of the 102 that we are powered to observe if the effect size estimates in individuals of East Asian ancestry are consistent with the effect size estimates from the European ancestry studies. For benchmarking, we also assessed the reproducibility of these established loci in ancestry-matched cohorts. We used independent European ancestry GWAS for depression with different sample sizes (Bio*Me*, BioVU, FinnGen, 23andMe).

Heritability and Genetic Correlations

We estimated the SNV heritability (h^2) using linkage disequilibrium score regression[33] and bivariate genome-based restricted maximum likelihood (GREML) implemented in the GCTA software version 1.92[34] for the 2 large Chinese data sets, CONVERGE and CKB (symptom-based definition). For this analysis we applied several prevalence estimates, ranging from 6.5%[35] to 15%.[6]

We estimated transancestry genetic correlations between depression in cohorts of East Asian descent and European descent using POPCORN, version 1.0.[36] We only present genetic correlation estimates where the standard error was less than 0.3. For clinical depression in individuals of European descent, we used the summary statistics from 45 396 individuals with a *DSM*-based diagnosis of major depressive disorder and 97 250 control participants included in the latest GWAS,[7] excluding UKB and 23andMe. Additionally, we generated a symptom-based definition for individuals of European descent using the Patient Health Questionnaire 9 and a cutoff score of 10.[25,37,38]

Results

Genome-Wide Association Meta-analysis of Depression in Individuals of East Asian Descent

Participants included 15 771 individuals with depression and 178 777 control participants from 9 different studies[20-30,39,40] (eTable 1 in Supplement 1). The meta-analysis yielded results for 9 223 944 variants with 1 region associated at genome-wide significance (**Figure 1**A; eTable 3 in Supplement 3). Variant rs4656484 at a previously unreported locus, 1q24.1, was associated with depression (β for C allele = −0.018, SE = 0.003, effect allele frequency [EAF] = 0.635, $P = 4.4 \times 10^{-8}$) (**Table**). It had consistent effect sizes across all studies except UKB (133

individuals with depression and 366 control participants) (eFigure 2 in Supplement 2). In the UK Brain Expression Consortium resource (UKBEC),[41] rs4656484 was associated with expression of *LMX1A* (OMIM 600298), which has been linked to dopamine neuron development.[42] The tissue group showing the strongest eQTL association was frontal cortex ($P = 1.1 \times 10^{-4}$).[42]

Association Analyses by Geographic Region and Depression Definition

We further investigated associations by geographic region and by depression definition. We carried out separate meta-analyses in the studies conducted in East Asian countries (12 027 individuals with depression and 83 727 control participants)[20-22] and in studies with ancestrally East Asian participants conducted in the US and the UK (3744 individuals with depression and 95 050 control participants)[23-30,39,40] (eTable 4 in Supplement 4). A novel locus at 7p21.2 was associated with depression at genome-wide significance in the analysis of the studies conducted in East Asia (Table). The lead SNV, rs10240457 (EAF = 0.646, β for A allele = 0.028, SE = 0.005, $P = 5.0 \times 10^{-9}$) is intronic to *AGMO* (OMIM 613738). This gene cleaves the O-alkyl bond of ether lipids, which are essential components of brain membranes and function in cell-signaling and other critical biological processes. This variant did not display evidence of association in the samples from studies conducted in the US and UK (β = 0.001, SE = 0.005, $P = .79$) (eFigure 3 in Supplement 2). No other associations were observed at genome-wide significance (eTable 4 in Supplement 4).

We also split the sample to perform outcome-specific analyses (ie, those with clinical diagnosis of depression vs those with self-reported symptoms of depression). No variants were associated at genome-wide significance in the meta-analysis for clinical diagnosis (8223 individuals with depression and 85 370 control participants) nor for symptom-based depression (6124 individuals with depression and 73 095 control participants) (eTable 1 in Supplement 1 and eTable 5 in Supplement 5).

Meta-analysis of Studies of Participants of East Asian Descent and Studies of Participants of European Descent

We carried out a meta-analysis for the broad depression outcome in cohorts of East Asian descent and the largest GWAS of depression in cohorts of European descent[7] (Figure 1B; eFigure 4 in Supplement 2). Variants at 43 loci were associated at genome-wide significance. Out of these, 3 loci had not been previously reported, nor did they reach genome-wide significance in either the analysis of European descent cohorts or East Asian descent cohorts alone (Table; eTable 6 in Supplement 6). There was no significant heterogeneity for any of the lead variants at the newly identified loci. The lead variant at 1q25.2, rs7548487 (β for A allele = −0.013, SE = 0.002, $P = 1.29 \times 10^{-8}$), is located in an intron of *ASTN1* (OMIM 600904). Astrotactin is a neuronal adhesion molecule required for glial-guided migration of young postmitotic neuroblasts in cortical regions of the developing brain.[43] The C allele of the lead variant at 18q12.1, rs547488, had a β of 0.008 (SE = 0.001) and $P = 3.3 \times 10^{-8}$. This variant is located downstream of *CDH2* (OMIM 114020), which encodes N-cadherin and has been shown to play a role in the development of the nervous system and be associated with neurodevelopmental disorders.[44] The third locus is 22q13.31 with lead variant rs12160976 (β for A allele = −0.009, SE = 0.002, $P = 1.6 \times 10^{-8}$).

Reproducibility of Depression-Associated Loci

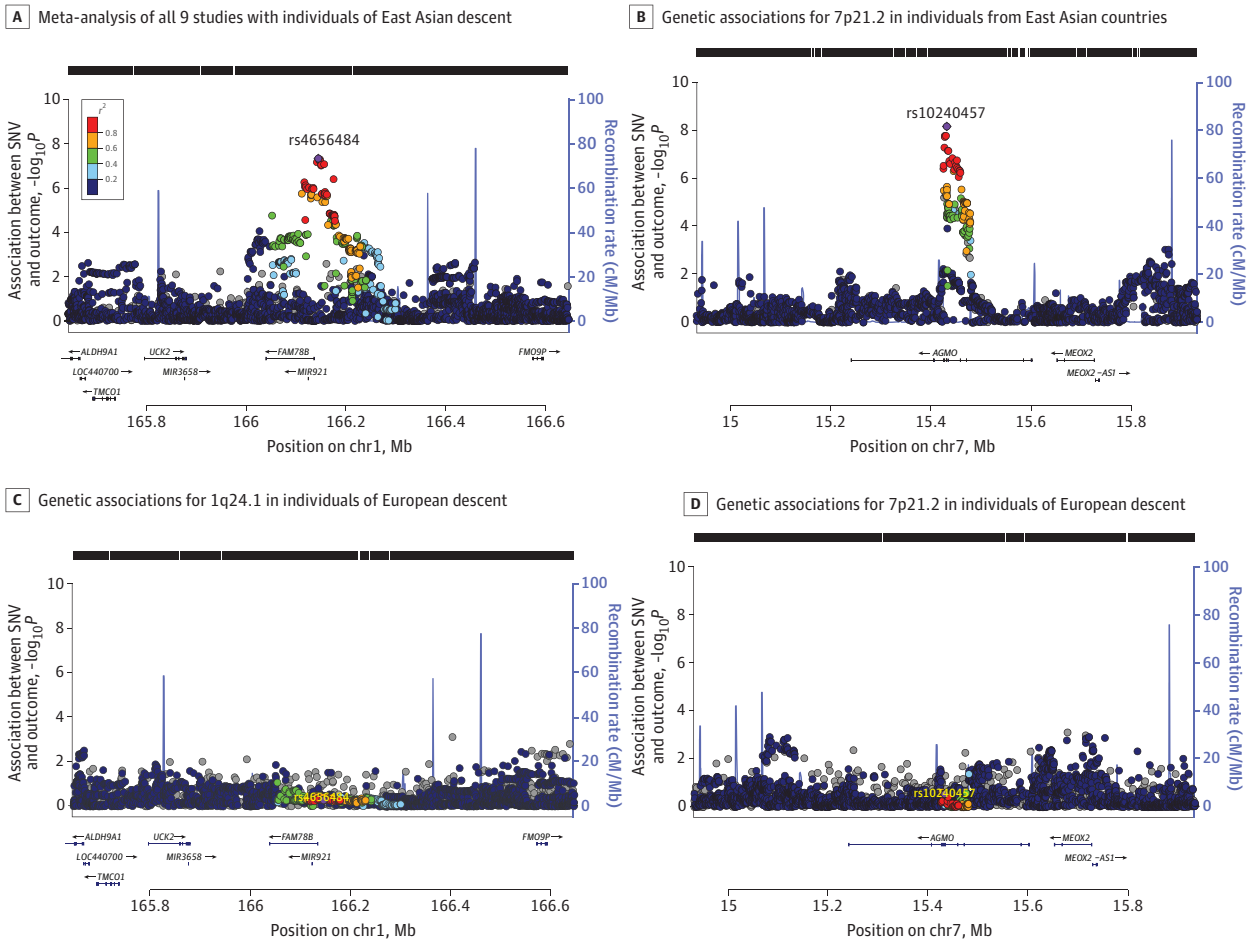
Although the lead variants of both novel associations from the meta-analyses of individuals of East Asian descent were common in individuals of European descent (EAF = 0.76 and EAF = 0.65 in 1000 Genomes Project phase 3 of individuals of European descent for rs4656484 and rs10240457, respectively), they were not associated with depression in the largest published meta-analysis of depression among individuals of European descent,[7] and effect sizes similar to those in cohorts of East Asian descent can be ruled out (Table). None of the variants in the credible sets displayed evidence of association at nominal significance levels in the meta-analysis of European ancestry cohorts (**Figure 2**).

We assessed evidence for reproducibility of previously reported loci for depression. The 2 genome-wide significant loci previously identified in the CONVERGE study[20] did not show evidence of association in any of the other data sets of cohorts with East Asian ancestry included in this study (eFigure 5 and eTable 7 in Supplement 2). It is worth noting that the effect sizes of these loci in the largest published meta-analysis of depression among individuals of European descent[7] (eTable 7 in Supplement 2) were also close to 0 for both variants, and the 95% CIs did not overlap with those from CONVERGE (eg, rs12415800 in CONVERGE: β = 0.152; 95% CI = 0.097 to 0.207; European ancestry GWAS: β = −0.004; 95% CI = −0.041 to 0.033).[20]

Of the 102 genetic variants that were independently associated with depression risk in individuals with European ancestry,[7] 94 lead variants were present in the data for individuals of East Asian ancestry (eTable 8 in Supplement 7). Of these variants, 63 variants (67%) had consistent direction of effect sizes in the European and East Asian ancestry GWASs, more than expected by chance ($P = .001$). Only 11% of these variants were associated with depression at nominal significance in the meta-analysis of cohorts of East Asian descent, although our study was powered to observe 43% under the assumption that the effect sizes are consistent between the cohorts of East Asian descent and the cohorts of European descent (eFigure 6 in Supplement 2). There was no evidence for enrichment of associations at more stringent *P* value thresholds.

For comparison, we also tested how many of the 102 established loci were reproducible in ancestry-matched studies, using several independent European ancestry GWASs with different depression definitions. The expected reproducibility rates varied widely, reflecting the differences in power. The largest data set from 23andMe had a reproducibility rate of 84%, which compared to an expected value of 99% (ratio = 0.86) (eTable 9 in Supplement 2). The lowest reproducibility relative to the expected value was observed for FinnGen, with a ratio of 0.40. However, this was still considerably higher than the ratio of observed vs expected reproducibility for the meta-analysis of cohorts of East Asian ancestry (ratio = 0.25).

Figure 2. Regional Association Plots of the Depression Associations for 1q24.1 and 7p21.2



The y-axes show the $-\log_{10}P$ values of the association between each SNV and the outcome. The x-axes show the chromosomal position (GRCh37). A Genetic associations for 1q24.1 in the meta-analysis of all 9 studies with ancestrally East Asian samples. B, Genetic associations for 7p21.2 in studies conducted in East Asian countries. C, Genetic associations for 1q24.1 in the largest European depression GWAS.[8] D, Genetic associations for 7p21.2 based on the largest European depression GWAS.[8] The purple diamond shows the lead SNV in each region; the color coding depicts the linkage disequilibrium with the lead SNV based on the 1000 Genomes East Asian reference panel.

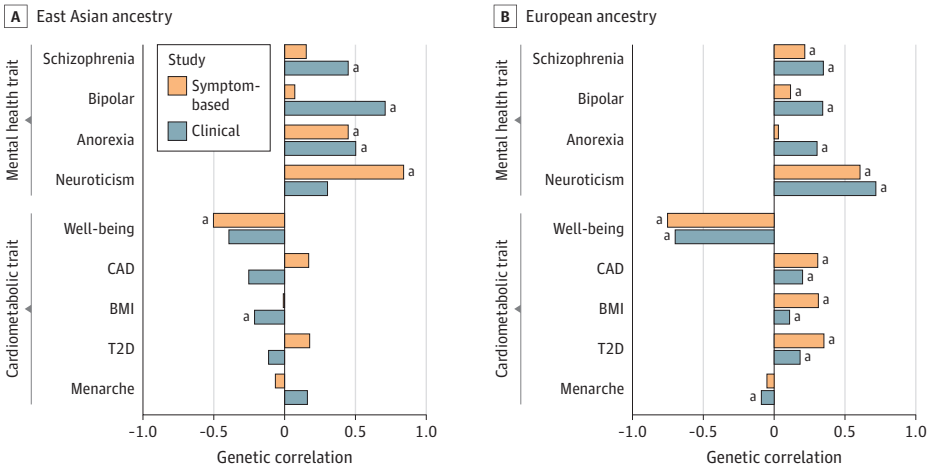
Heritability and Genetic Correlations

The SNV heritability in CONVERGE was 26.2% (SE = 0.03) on the liability scale and 6.4% (SE = 0.02) for CKB based on a prevalence of 6.5%. The clinical diagnosis and symptom-based depression meta-analyses in individuals of East Asian descent had h^2 estimates of 6.8% (SE = 0.02) and 3.8% (SE = 0.04), respectively (eTable 10 in Supplement 2). However, it is likely that depressive symptoms were more common in the population than clinical depression. When we assumed a prevalence estimate of 15%, as in analyses of individuals of European descent, all heritability estimates were significantly increased.

The transancestry genetic correlation between cohorts of East Asian and European descents for clinical depression was r = 0.413 (SE = 0.159). We also compared the clinical definition in cohorts of East Asian descent with the symptom-based definition for cohorts of European descent, and the genetic correlation was lower: r = 0.223 (SE = 0.181). When using the symptom-based definition for the cohorts of both East Asian and of European descents, we found a correlation of r = 0.433 (SE = 0.281). The highest estimate was observed for the comparison of symptom-based depression in individuals of East Asian descent with clinical depression in individuals of European descent: r = 0.558 (SE = 0.221). For benchmarking, we also summarized genetic correlations between independent cohorts of East Asian and European descents for other traits and diseases, such as cholesterol, breast cancer, and age at menarche (eTable 11 in Supplement 2). The estimates from large GWASs were consistently higher than the estimates for depression. The genetic correlations for studies with at least 2000 cases ranged from 0.7 to 1. The genetic correlation from the largest study of schizophrenia was r = 0.98 (SE = 0.03),[45] and for bipolar disorder, the correlation was r = 0.718 (SE not reported).[46]

We also assessed the sharing of genetic risk factors between depression in individuals of East Asian descent with

Figure 3. Genetic Correlations for Clinical and Symptom-Based Depression With Cardiometabolic and Mental Health Traits



Correlations are shown for samples with East Asian ancestry (A) and European ancestry (B) for the depression studies. For the cardiometabolic and mental health traits, publicly available summary statistics from studies with European ancestry samples were used. Blue bars represent the clinical outcome definition, and orange bars the symptom-based outcome. BMI indicates body mass index; CAD, coronary artery disease; T2D, type 2 diabetes.

[a] Genetic correlations statistically different from zero.

other diseases and traits from published summary statistics of studies of individuals of European descent (eTables 12 and 13 in Supplement 2). For clinical depression in individuals of East Asian descent, the highest genetic correlation was observed for bipolar disorder (r = 0.710 [SE = 0.153]) (**Figure 3**).[47] Clinical depression also had significant positive genetic correlations with other psychiatric disorders, including anorexia nervosa (r = 0.502 [SE = 0.158]) and schizophrenia (r = 0.449 [SE = 0.109]).[48,49] For symptom-based depression, the highest correlation was observed for the personality trait of neuroticism (r = 0.840 [SE = 0.216]). Symptom-based depression was also negatively correlated with subjective well-being (r = −0.502 [SE = 0.195]).[50]

Depression in individuals of European descent has been reported to be genetically correlated with unfavorable cardiometabolic profiles.[6] However, we observed the opposite for body mass index (BMI) in this study. For clinical depression in individuals of East Asian descent, there was a statistically significant negative genetic correlation with BMI from a GWAS of individuals of European descent (r = −0.212 [SE = 0.084]).[51] The transancestry correlations with type 2 diabetes (T2D) and coronary artery disease were also negative, but not significantly different from 0: r = −0.113 (SE = 0.113) and r = −0.253 (SE = 0.160, respectively).[52,53]

For a subset of these traits, results for large GWASs of cohorts of East Asian descent were also available. We used these to validate the genetic correlations for depression in individuals of East Asian descent (eFigure 7 and eTable 14 in Supplement 2). For clinically diagnosed depression in individuals of East Asian descent, the estimates were highly consistent for correlations with schizophrenia (r = 0.447 [SE = 0.085]), BMI (r = −0.147 [SE = 0.061]), and T2D (r = −0.143 [SE = 0.072]).[45,54,55] Correlations between symptom-based depression and the aforementioned traits in individuals of East Asian descent were in the same direction but weaker: schizophrenia (r = 0.189 [SE = 0.137]); BMI (r = −0.082 [SE = 0.098]); and T2D (r = −0.088 [SE = 0.120]).

Discussion

Herein, we present results of the largest (to our knowledge) GWAS for depression in samples with East Asian ancestry (15 771 individuals with depression and 178 777 control participants). Our results demonstrate the value of combining data from studies with different outcome definitions and study designs, as the increased sample size can empower the discovery of novel associations. Variant rs4656484 at 1q24.1 was associated in studies of individuals of East Asian descent that used different definitions for depression, which suggests that this locus may be linked to the part of the genetic predisposition that is shared between different depression outcomes. Furthermore, by combining GWASs of cohorts of East Asian and European descents, we identified 3 additional novel associations that were not significant in analyses of either the East Asian ancestry cohorts or the European ancestry cohorts alone.

We also observed differences by ancestry, depression outcome definition, and geographic region that highlight the heterogeneity underlying depression. Several depression loci were not transferable between studies of cohorts of East Asian and European ancestry. The newly identified variant rs4656484 was not associated with depression in a previous GWAS of individuals of European descent[7] (β = 0.003; SE = 0.005; P = .53), and an effect size similar to that observed in individuals of East Asian descent can be ruled out. Conversely, only 11% of the established depression loci from studies of participants of European descent were associated with depression at nominal significance in the meta-analysis of individuals of East Asian descent, although the study was powered to observe 43%. The ratio of observed to expected reproducibility was 0.25 for our meta-analysis of individuals of East Asian descent, which was lower than the ratios for several independent ancestry-matched depression GWASs (ratios ranged from 0.40 to 0.86). In line with this, we found moderate transancestry genetic

correlations between the depression outcomes in studies of cohorts of East Asian and European descents, ranging from 0.223 to 0.558, consistent with previous findings.[56] These results are considerably lower than transancestry correlation estimates for other psychiatric traits, such as schizophrenia (r = 0.98).[45] Low transferability could limit downstream applications of depression genetics in transancestry settings, for example in genetic risk prediction.

We also identified a novel depression association at 7p21.2 in studies conducted in East Asian countries. The lead variant was not associated with depression in the US and UK-based data sets, suggesting that nongenetic factors may play an important role for the transferability of loci.[57] In the context of the growing number of transancestry GWAS meta-analyses, this highlights the importance of considering geographic region as well as genetic ancestry.

Although the genetic risk factors overlap between different depression definitions, their genetic architecture differs, as demonstrated by previous research based on studies of individuals of European descent.[58] We estimated SNV heritability to be 0.26 in CONVERGE (for severe recurrent depression)[59] and 0.06 in CKB (for symptom-based depression), which is similar to the previously reported range for different studies of cohorts of European descent of 0.09 to 0.26.[6] The estimate for CKB supports the hypothesis that lower heritability estimates are linked to less stringent outcome definitions.[58] However, 0.06 is likely to be an underestimation because the underlying prevalence rate should be higher. In the absence of widely accepted prevalence rates for each of these outcomes in China due to the wide variation in estimates,[60] we applied the same prevalence estimate for symptom-based and clinical diagnosis definitions of depression.

To account for the differences between clinical and symptom-based depression, we also split our sample and carried out separate association analyses. The genetic correlations with other diseases and traits identified shared and outcome-specific patterns. For clinical depression in individuals of East Asian descent, the highest genetic correlation was observed for bipolar disorder (r = 0.710), which was stronger than the respective transancestry genetic correlation with clinical depression in individuals of European descent (r = 0.413). For symptom-based depression, on the other hand, the strongest correlation was observed for the personality trait neuroticism (r = 0.840). There were also population-specific patterns. The genetic correlations of clinical depression in individuals of East Asian descent with metabolic traits were opposite to that observed for individuals of European descent. European ancestry studies have provided some evidence that BMI is a causal risk factor for major depression.[6] It is a matter of ongoing research to establish whether this link is due to shared metabolic mechanisms between the 2 phenotypes.[61] The recruitment strategy in the CONVERGE study, with a high proportion of melancholia subtype and exclusively female participants, may have contributed to the inverse correlation. However, it is unlikely to explain it fully. Symptom-based depression was also inversely correlated with BMI in CKB, but this correlation was not statistically significant. The opposite direction of effect of this risk factor across populations could suggest that the link between depression and weight is social rather than metabolic in nature. This hypothesis is supported by previous work using favorable adiposity genetic variants as an instrument to try to separate the potential biological and social effects of higher adiposity in Europeans.[61] Genetic variants that are associated with higher adiposity but a more favorable metabolic profile (ie, lower T2D, CAD, and dyslipidemia) were associated with higher odds of depression, suggesting it is not solely the metabolic consequences of higher BMI that drive the association.

In terms of its genetic architecture, major depressive disorder has been shown to be one of the most polygenic outcomes across a wide range of studied phenotypes in cohorts of individuals of European descent[62] (ie, its potential genetic effects are small and distributed across a very large number of variants in the genome). This is linked to heterogeneity of depression in terms of presentation as well as etiology that results from the complex interplay between genetic and environmental factors.[63,64] Our results suggest that nongenetic factors, such as cultural differences and other factors, may further add to the heterogeneity of depression and thereby impact on its genetic architecture. First, the spectrum of depression manifestations may overlap but not be identical between cultural contexts of different ancestral groups and geographic regions. Second, many risk factors for depression are determined within a given cultural context and can themselves be heritable, which may modify genetic associations through gene-environment interactions. For example, genetic variants predisposing to higher weight would be associated with depression only in societies where obesity is stigmatized.

Limitations

This study has some limitations. The data sets we included used different outcome definitions, which can lead to heterogeneity in the meta-analysis. Outcome definitions based on help-seeking behavior may result in a different case group than outcome definitions that fulfill *DSM* criteria for major depressive disorder. More fine-grained conclusions will require greater depth of mental health phenotyping for large samples in future studies. This necessitates global studies in clinical settings as well as general population cohorts with improved mental health phenotyping to address this gap in the future. Some of the studies included in this GWAS meta-analysis used DNA microarrays that were designed for samples from individuals of European descent. These arrays may have lower coverage of the genetic variation present in populations of East Asian descent. General limitations of GWAS apply, as described by Tam et al.[65] There is a high multiple testing burden. Only a fraction of the heritability is explained by GWAS. Further work is needed to identify the causal variants of the novel associations. Not all genetic determinants of depression can be identified through GWAS. GWAS have largely failed to identify gene-gene interactions. Genetic associations may be influenced by population stratification. The clinical value of GWAS is limited.

Conclusions

Overall, this study implies caution against generalizing findings about genetic and other risk factors for depression beyond the studied population. It highlights the need for more diverse samples with consistent phenotyping. Increased representation of different populations will benefit locus discovery, fine mapping for potential causal variants, and polygenic risk score profiling and could help address health disparities.[57,66-69]

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Supplementary Online Content

Giannakopoulou O, Lin K, Meng X, et al; for the 23andMe Research Team, China Kadoorie Biobank Collaborative Group, and Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium. The genetic architecture of depression in individuals of East Asian ancestry. Published online September 29, 2021. *JAMA Psychiatr*. doi:10.1001/jamapsychiatry.2021.2099

eTable 6. Variants Associated With Depression ($P<5x10^{-8}$) in the Meta-Analysis of the Broad Depression Outcome in East Asian Ancestry Samples and the Largest Depression GWAS in European Ancestry Samples (Howard et al., 2019) *provided in the separate excel file*

eTable 7. The Two Genome-Wide Significant Depression Loci in CONVERGE and the Relevant Results in the Other East Asian Ancestry Datasets of the Current Study and the Two Largest European Studies

eTable 8. The Association of Previously Reported Variants for Depression With $P<5x10^{-8}$ in European Ancestry Samples (Howard et al., 2019) in the East Asian Discovery Meta-Analysis *provided in the separate excel file*

eTable 9. Reproducibility of Established Depression Loci From Howard et al.,2019 in Independent Samples of European Ancestry and in the East Asian Depression GWAS

eTable 10. SNP-Heritabilities for the Different Depression-Definition Outcomes Considered in This Study

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eTable 13. Genetic Correlations of Clinical and Symptom-Based Depression in European Datasets With Other Traits

eTable 14. Genetic Correlations of Clinical and Symptom-Based Depression in East Asian Datasets With Other Traits, Based on East Asian Studies

eReferences

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix 1. Additional Information

Supplementary Methods

Raw genotype data were available for China Kadoorie Biobank (CKB), UK Biobank (UKB), Intern Health Study (IHS), Women's Health Initiative (WHI) and Army Study To Assess Risk and Resilience in Service members (Army-STARRS) study. Summary statistics were available for China Oxford and VCU Experimental Research on Genetic Epidemiology (CONVERGE) study, Bio*Me*, Taiwan-Major Depressive Disorder (MDD) study and 23andMe cohort. We did not assess whether there is sample overlap between studies because given their different design and area of recruitment sample overlap is extremely unlikely.

This investigation was based on EAS participants which was defined by the investigators based on genetic information. For each study a principal component analysis was carried out based on the genetic similarity of pairs of individuals. Individuals that clustered around a reference group with confirmed East Asian ancestry were included in this analysis.

Studies description

A. China Kadoorie Biobank (CKB)

The CKB is a large population dataset of more than 510,000 individuals from 10 geographically defined regions of China, with extensive clinical, lifestyle, dietary, medical history and genetic data[1]. All the participants were interviewed at the baseline by trained staff, while periodic re-surveys have been conducted in ~25,000 surviving participants. Health outcomes of the participants provided through linkages with established registries and health insurance databases are also available.

A total of 17,723 participants reported that had experienced at least one Composite International Diagnostic Interview (CIDI) -A trigger symptom (i.e., feeling sad/depressed, loss of appetite, loss of interest or feeling worthless) for two or more weeks during the past year and were categorized as having "symptom-based" depression in our analyses. These participants were further assessed for major depression (MD) using the Chinese version of the CIDI-short form by trained clinicians at study clinics. Participants were defined as having past year MD if they had felt sad, blue, or depressed for ≥2 weeks during the past 12 months, accompanied by at least 3 of 7 additional symptoms, including weight/appetite change, sleep problems, loss of interest and pleasure, loss of energy or fatigue, concentration problems, feelings of guilt or worthlessness, and thoughts of suicide. In our analysis, 4,500 participants who fulfilled the past year MD CIDI-criteria, had at least one relevant medical record (ICD10 F32, F33, F34.1, F38.1 codes) during the follow-up period or reported at resurvey 2 that have been ever diagnosed by a doctor with depression were classified as having "lifetime diagnosis of MD". Participants that had never been diagnosed with MDD (either diagnosed by CIDI-A questionnaire, self-reported depression or had a medical diagnosis of depression (F32, F33, F34.1, F38.1)) or with neurasthenia and did not report any MDD symptoms constituted the control group (~70,000) in all our analyses. Further exclusions from both cases and controls groups included participants with a medical diagnosis for dementia, psychosis, bipolar disorder, mental retardation and pervasive developmental disorders.

A total of 102,783 participants have been genotyped using 2 custom-designed Affymetrix Axiom arrays including up to 803,000 variants, optimised for genome-wide coverage in Chinese populations. Stringent quality control (QC) included SNP call rate > 0.98, plate effect $P > 10^{-6}$, batch effect $P > 10^{-6}$, Hardy-Weinberg Equilibrium (HWE) deviations $P > 10^{-6}$ (combined 10df $\chi 2$ test from 10 regions), biallelic, Minor Allele Frequency (MAF) difference from 1000 Genomes East-Asian frequencies < 0.2, sample call rate > 0.95, heterozygosity < mean + 3 standard deviation (SD), no sex chromosomes aneuploidy, genetically-determined sex concordant with database, resulting in genotypes for 532,415 variants present on both array versions. Genotypes were imputed to the 1,000 Genomes Phase 3 reference (EAS MAF > 0) using SHAPEIT version 3 and IMPUTE version 4.

A total of 5,376 symptom-based depression cases (1,305 participants with lifetime diagnosis) and 69,998 controls have been genotyped. A linear mixed model (SAIGE) was implemented for the association with depression, adjusting

for age, sex, principal components (PCs) and recruitment region. After filtering variants with effective sample size (Neff) < 50[2] and poorly imputed variants (info<0.7), 10,834,708 variants were included in the downstream analyses.

B. China, Oxford and Virginia Commonwealth University Experimental Research on Genetic Epidemiology cohort (CONVERGE)

The CONVERGE cohort of Han Chinese women has been previously described[3]. Briefly, ~5,000 cases of recurrent MDD (≥2 episodes), established with the CIDI, which used DSM-IV criteria, were analysed against an equal number of controls. Cases with medical history of bipolar disorder, psychosis, mental retardation and/or drug or alcohol abuse before their first depressive episode were excluded from the study.

CONVERGE samples underwent whole-genome sequencing, as previously described[3]. In brief, after genotyping calling, two rounds of imputation were performed: first without a reference panel and then using the 1000Genomes Phase 1 Asian haplotypes. Variants with a) a P-value for violation HWE < 10^{-6}, b) information score < 0.9 and c) MAF in CONVERGE < 0.5% were excluded from the GWAS, resulting in a final set of 5,987,610 SNPs. The GWAS was conducted with a mixed-linear model including a genetic relationship matrix (FastLMM version 2.06.20130802) as random effect and PCs from eigen-decomposition of this matrix as fixed effects. We further filtered the publicly available GWAS summary statistics by removing variants with Neff less than 50.

C. 23andMe cohort

The GWAS dataset of personal genetic company 23andMe, Inc. (Sunnyvale, CA) that included in this meta-analysis, encompassed 2,729 depression cases and 90,310 controls of East Asian ancestry. All participants provided informed consent and answered surveys online according to 23andMe's human subject protocol, which was received and approved by Ethical & Independent Review Services, an AAHRPP-accredited institutional review board. As part the medical history survey, participants were asked if they have ever received a clinical diagnosis or treatment for depression (binary variable).

DNA extraction and genotyping were performed on saliva samples by National Genetics Institute (NGI), a CLIA licensed clinical laboratory and a subsidiary of Laboratory Corporation of America. Samples were genotyped on one of five genotyping platforms. The v1 and v2 platforms were variants of the Illumina HumanHap550+ BeadChip, including about 25,000 custom SNPs selected by 23andMe, with a total of about 560,000 SNPs. The v3 platform was based on the Illumina OmniExpress+ BeadChip, with custom content to improve the overlap with our v2 array, with a total of about 950,000 SNPs. The v4 platform was a fully customized array, including a lower redundancy subset of v2 and v3 SNPs with additional coverage of lower-frequency coding variation, and about 570,000 SNPs. The v5 platform (68.4% of the samples in the East-Asian dataset), is an Illumina Infinium Global Screening Array (~640,000 SNPs) supplemented with ~50,000 SNPs of custom content. This array was specifically designed to better capture global genetic diversity and to help standardize the platform for genetic research.

Imputation was performed with Minimac3 using a reference panel combining the May 2015 release of the 1000 Genomes Phase 3 haplotypes with the UK10 imputation reference panel. The association testing was performed by logistic regression assuming additive allelic effects, adjusting for age, sex, the top five principal components to account for residual population structure and indicators for genotype platforms to account for genotype batch effects. The association analysis and the downstream quality control was conducted separately for the genotyped and the imputed SNPs.

Genotyped GWAS results were filtered for: SNPs that were only genotyped on "v1" and/or "v2" platforms due to small sample size, SNPs on chrM or chrY, SNPs that failed a test for parent-offspring transmission, SNPs with fitted $\beta<0.6$ and $P<10^{-20}$ for a test of $\beta<1$, SNPs with a Hardy-Weinberg $P<10^{-20}$, or a call rate of <90%, SNPs with genotype date effects (determined as $P<10^{-50}$ by ANOVA of SNP genotypes against a factor dividing genotyping date into 20 roughly equal-sized buckets), SNPs with large sex effect (ANOVA of SNP genotypes, r2>0.1), SNPs with probes matching multiple genomic positions in the reference genome and variants with minor allele counts in the controls less than 50.

For imputed GWAS results, SNPs with poor imputation quality (rsq<0.7), Neff less than 50 and SNPs that had strong evidence of a platform batch effect were excluded from the downstream analysis. The batch effect test is an F test from an ANOVA of the SNP dosages against a factor representing v4 or v5 platform ($P<10^{-50}$).

Across all results, further filtering was performed on SNPs that have an available sample size of less than 20% of the total GWAS sample size, logistic regression results that did not converge due to complete separation, identified by abs(effect)>10 or stderr>10 on the log odds scale.

D. Taiwan-Major Depressive Disorder (MDD) Study

MDD patients were included from a family study of mood disorders in Taiwan. Patients aged between 18 to 70 years, who met diagnostic criteria of MDD using the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) were consecutively referred by psychiatrists in clinical settings. Exclusion criteria include patients diagnosed with schizophrenia, schizoaffective or substance-induced mood disorders. The community-recruited Taiwan Biobank Dataset was used as the control group. The control group was further filtered by excluding subjects who have self-reported bipolar disorder (BPD), postpartum depression, alcoholism or drug addiction, schizophrenia, Parkinson's disease or dementia. Moreover, subjects in Taiwan Biobank Data who had self-reported diagnosis of MDD were classified into case (MDD) group. Sample collection procedures and detailed information about Taiwan Biobank were described elsewhere[4]. Both MDD and control subjects were Han Chinese.

Genotyping for Taiwan MDD cases was obtained using Affymetrix CHB Array with 642,832 genetic variants, Affymetrix TWB1.0 Array with 642,545 variants, Illumina Human Omni Express Exiome Beadchips with 949,974 variants and Affymetrix TWB2.0 Array with 689,688 variants. Genotyping for Taiwan Biobank controls was obtained using Affymetrix TWB1.0 Array with 646,735 variants and Affymetrix TWB2.0 Array with 686,439 variants. Owing to Affymetrix TWB2.0 is a very unique array specifically designed for Taiwanese, which is very different from other platforms, imputation was performed separately. One set of imputation was done for Affymetrix TWB2.0 array only, the other set of the imputation was done with combining all other arrays, including Affymetrix CHB, TWB1.0, and Illumina arrays using common SNPs across platforms. The overlapping variants of Affymetrix TWB2.0 array and all other platforms were around 28,000. Imputation was conducted by Michigan Imputation Server using 1000G phase 3 v5 as a reference panel, Eagle v2.3 for phasing, and EAS population for QC. Samples that did not meet the 95% threshold of call rate, kinship-pairs and outliers in population stratification were removed. Genetic variants with call rate <95%, MAF <0.01, p-value of HWE $<10^{-6}$ were also excluded. The GWAS was performed using PLINK 1.9 and adjusted for 5 ancestry principal components. The GWA analysis was conducted separately by platforms with (1) Affymetrix TWB2.0 and (2) all other platforms combined together. In the latter, variants significantly associated (P<0.005) with genotyping platforms were excluded from downstream analysis. We also used a stricter imputation threshold for filtering (info<0.9 instead of 0.7).

E. Women's Health Initiative study (WHI)

The WHI study is a long-term national health study in U.S conducted in postmenopausal women, enrolled either in a clinical trial or an observational study[5]. We analysed data from 3,492 women with Asian ancestry who were genotyped as part of the WHI – Population Architecture using Genomics and Epidemiology (PAGE) sub-study. These participants had agreed their data to be included in the database of Genotypes and Phenotypes (dbGaP). The genotype and phenotype data were assessed vid dbGaP study accession phs000200.v12.p3. Depressive symptoms in the past week were assessed in the baseline visit with a 6-item Center for Epidemiological Studies Depression Scale (CES-D) form. Based on Smoller et al., definitions[6], participants with a score of 5 or more were considered as depression cases, while participants not classified as currently depressed (6-item CES-D), without medical history of depression (2-item Diagnostic Interview Schedule) and not on antidepressant therapy constituted the control group.

The dataset of Asian participants of WHI included in our analyses, have been genotyped with CardioMetaboChip, as part of the NHGRI's PAGE project. Samples and variants with a call rate lower than 95%, typed variants with different missingness rates between case and control group > 0.2 and variants with MAF < 0.05 were excluded from downstream analysis. A logistic regression analysis was performed (PLINK2), adjusting for age, sex, 20 PCs and study subgroup.

F. Intern Health Study (IHS)

We also considered participants from IHS, a multi-institutional longitudinal cohort study of medical interns in U.S. The study design has been previously described[7]. Depressive symptoms were measured through the PHQ-9 questionnaire, a self-report component of the primary care evaluation of mental disorders inventory. Subjects were asked to complete the questionnaire assessing PHQ-9 depressive symptoms in the baseline survey, as well as at months 3, 6, 9 and 12 of their internship year. Participants with a PHQ-9 score of 10 or greater[8] during their internship were considered as depression cases in this study. A total of 294 depression cases and 544 controls were considered in this association study.

IHS samples were genotyped on Illumina Infinium CoreExome v1.0 or v1.1 array. Quality control steps and imputation were performed using the Ricopili Rapid Imputation Consortium Pipeline[9]. Study samples were assigned into distinct ancestry groups based on PCs derived from the study samples combined with 1000Genomes reference panel. In brief, samples with call rate < 98% or samples with a gender mismatch between genotype and reported data were excluded. For duplicated samples and up to third-degree relatives, the sample with higher call rate was selected. Variants with call rate < 98%, missing difference > 0.20 were also excluded prior imputation. Genotypes were imputed to the Haplotype Reference Consortium (HRC) reference panel using EAGLE and IMPUTE2 for the phasing and the imputation respectively. A logistic regression analysis was performed (PLINK2) in genotype dosages, adjusting for age, sex, 20 first PCs. Variants with MAF < 0.05 and imputation info score < 0.7 were excluded from downstream analysis, resulting in a dataset of 4,626,568 variants.

G. UK Biobank (UKB)

UKB is a well-characterized cohort of more than 500,000 individuals recruited at UK between 2006-2010 with linked health and genetic data[10]. A subset of participants has also completed the mental-health questionnaire. We used a combination of hospital diagnoses (ICD10 codes) and lifetime CIDI (A. prolonged feelings of depression OR prolonged loss of interest in normal activities AND B. affected more than half of the day during worst episode of depression AND C. the frequency of depressed days during worst episode was at almost every day/every day AND D. these problems interfered with your life/activities (study/employment, childcare and housework, leisure pursuits) somewhat/a lot) to define our cases. Gender mismatches, missingness/heterozygosity outliers, participants with excessive genetic relatedness, no quality control metrics, individuals that have withdrawn their consent and up to 2nd degree relatives (PC-Relate) were excluded before the analysis.

UKB genotyping was conducted by Affymetrix using two similar arrays; Applied Biosystems™ UK BiLEVE Axiom™ Array, consisting of 807,411 genetic variants and a bespoke UK Biobank Axiom™ array, including 825,927 genetic variants. All genetic data was quality controlled by UKBB bioinformatics team, both at sample and marker level, resulting in a dataset of 488,377 samples and 805,426 variants from both arrays. The genetic data was subsequently imputed by UKB to over 90 million SNPs, indels and large structural variants, using haplotypes of both British, European and diverse-ancestry populations. For this study, we used data imputed with both the HRC and the merged UK10K and 1000Genomes Phase 3 reference panels[10]. To assign individuals in ancestry groups based on their genetic information, we implemented the PC-AiR method to perform a PC analysis for the detection of population structure[11]. A logistic regression analysis was performed in imputed genetic dataset (PLINK2), adjusting for age, sex, genotyping array and PCs that were calculated based on the subset of genetically defined EAS participants. Downstream analysis was restricted in the subset of common (MAF > 0.05) and well-imputed (> 0.7) variants. The analysis conducted under UK Biobank application 51119.

H. Army Study To Assess Risk and Resilience in Service members (Army STARRS) study

Data from the Army-STARRS, a study conducted in army members in USA, were also assessed in the current analysis. Army STARRS includes the New Soldier Study (NSS) and the Pre/Pst Deployment Study (PPDS). Detailed information about the design of the study have been published previously[12]. Depression outcomes were measured with the CIDI screening scales and evaluated for concordance with DSM-IV diagnoses within the Army STARRS clinical reappraisal study[13].

The genotyping and imputation of Army-STARRS, New Soldier Study (NSS) samples has been described previously[14]. In brief, samples were genotyped using the Illumina OmniExpress and Exome array and were imputed on a reference multi-ancestry panel from the 1000G Genomes Project (phase1). Samples and genetic variants with a call rate less than 95% and 98% respectively were filtered out. A logistic regression analysis was performed in common and well-imputed variants (PLINK2), adjusting for age, sex and the 20 first PCs.

I. Bio*Me*

Bio*Me* is an electronic medical record-linked biobank of more than 50,00 participants from the Mount Sinai Health System[15]. Bio*Me* cases were individuals with a medical depression diagnosis (ICD9 296.2, 296.3, 296.82, 298.0, 300.4, 301.12, 311; ICD10 F32, F33, F34.1, F38.1). Participants diagnosed with dementia, bipolar or manic disorder, developmental disorders, intellectual disability, psychotic disorder, personality disorder were excluded from this study.

Bio*Me* samples were genotyped with the Infinium Global Screening Array (GSA) BeadChip. Individuals with population-specific heterozygosity rate that surpassed +/- 6 standard deviations of the population-specific mean, along with individuals with a call rate of <95%, individuals with discordant reported and genetic sex and with phenotypically intermediate sex were not considered in the analysis. In cases of duplicates, the sample of each pair with the lower missingness rate in the exomic data was preferentially excluded. Genetic variants exclusions included a call rate <95% and HWE $p < 10^{-5}$. The resulting dataset was imputed to the 100Genomes Phase 3 reference panel. The GWAS was performed with a binary mixed model (SAIGE). The first 20 PCs were calculated using PLINK (v1.9) and a genomic relationship matrix (GRM) was calculated using the KING (v1.4) software (-ibs). The PCA and GRM calculations were restricted to common (MAF>0.01), autosomal sites. Additionally, variants with MAF<0.05 and info<0.07 were excluded before the meta-analysis.

Data availability statement

Summary statistics for the combined EAS meta-analysis excluding the 23andMe study are available through the PGC website (http://www.med.unc.edu/pgc/downloads). The genome-wide summary statistics for CONVERGE and the European meta-analysis are also available on the PGC website. Uploading and sharing of individual genetic data from CKB are subject to restrictions according to the Interim Measures for the Administration of Human Genetic Resources administered by the Human Genetic Resources Administration of China (HGRAC). Summary data including allele frequencies and GWAS summary statistics are available by application and restricted to research-related purposes. Other individual-level CKB data are available through www.ckbiobank.org, subject to completion of a Material Transfer Agreement, either through Open Access or on application. CKB data access is subject to oversight by an independent Data Access Committee. Analyses using CKB data were conducted under research approval 2018-0018. Data from 23andMe, Inc were made available under a data use agreement that protects participant privacy. Please visit https://research.23andme.com/collaborate/#dataset-access for more information and to apply to access the data. The raw genetic and phenotypic UK Biobank data used in this study, which were used under license (application number 51119), are available from: http://www.ukbiobank.ac.uk/. The genotype and phenotype data for the WHI study can be requested via dbGaP study accession phs000200.v12.p3.

Genotyping

The genotyping of each study has been previously described [3, 4, 10, 14, 16]. To optimise genome-wide coverage in EAS populations, genotyping was carried out using two custom-designed Affymetrix Axiom arrays in CKB and the Affymetrix TWB2.0 array for a subset of the Taiwan-Major Depressive Disorder study samples [1, 4]. CONVERGE used whole-genome sequencing with a mean depth of 1.7[3]. More detail for all studies is provided in the studies description above.

Quality control

Quality control and association analyses were carried out separately for each study as described in the studies description and Supplementary Table 2. Genotypes were imputed to 1000 Genomes Project reference panel, except IHS where the Haplotype Reference Consortium (HRC) was used, 23andMe and UKB where the 1000 Genomes data were combined with the UK10K and HRC imputation reference panel, respectively. In the meta-analysis, we included only well-imputed variants (imputation accuracy > 0.7) with effective sample size (N_{eff}) equal or higher than 50^2 in the larger datasets (CONVERGE, CKB, 23andMe), and with minor allele frequency (MAF)>=0.05 in the other studies. For the Taiwan-MDD study an imputation accuracy threshold of 0.9 was used.

Meta-analysis

We performed a Z-score weighted meta-analysis using METAL[33] for 13,163,200 genetic variants (Supplementary Figure 1). For all meta-analyses, results were restricted to variants present in at least two studies. We also performed a Z-score weighted meta-analysis combining results from our EAS analysis and the publicly available summary statistics from the largest published GWAS in EUR samples[17]. Variants associated at genome-wide significance in this trans-ancestry meta-analysis were considered novel if they were located outside ±250kb either side of the lead variants from the published GWAS of depression in EUR and if the Linkage Disequilibrium (LD) with the lead variant was <0.01 [17]. We calculated betas for the meta-analyses using the formula from Zhu et al.[18]. Odds ratios were based on an inverse-variance weighted meta-analysis of the study betas, where for CONVERGE we used results from a logistic regression in Plink instead of FastLMM.

Functional annotation and gene-based association analysis

We functionally annotated the lead variants and their proxies ($r^2 \geq 0.8$). Gene-based association analysis was performed using MAGMA (v1.08), implemented in FUMA, with default settings[19, 20]. SNPs were mapped to 19,575 protein coding genes from Ensembl build 85. Significance for the gene-based analysis was defined as the Bonferroni corrected threshold ($P=2.6x10^{-6}$).

We functionally annotated the lead SNPs in the genomic regions associated with increased risk for depression using HaploReg v4[21] and Open Targets Genetics Platfrom[22]. Candidate genes for each locus associated with depression were selected based on their proximity to the lead variant and/or the evidence of eQTL associations for a gene in that region. Open Targets Genetics interrogates various data sources to link genetic variation to genetic expression. The GeneCards database was used to obtain summary information of the identified genes, while NCBI's PubMed database was used to interrogate literature related to gene function and association with other human traits/diseases. We queried the identified variants and their proxies in PhenoScanner[23] and the NHGRI-EBI GWAS catalogue[24] to investigate trait pleiotropy.

Reproducibility of established depression loci

We assessed whether the associations of 102 established depression loci from the largest published EUR GWAS [17] were reproducible in samples with EAS ancestry. Since the lead SNP might not be the causal variant nor correlated with it in other ancestry groups due to LD differences, we also formed credible sets that are likely to include the causal variant. These were based on all variants in LD with the lead variant of a locus ($r^2>0.6$) based on an ancestry matched reference (1000 Genomes Project v3 EUR samples). We assessed whether any variant in the credible set displayed evidence of association in the target study. As these credible sets contained multiple SNPs, we used a p-value threshold of P<0.01 to indicate reproducibility. While this p-value threshold might not provide conclusive evidence of reproducibility for individual loci, we used it to test reproducibility rates across sets of loci.

We estimated the number of associations out of the 102 established loci that were expected to replicate. We accounted for the sample size of our study and the allele frequency in EAS populations. First, we calculated the power[25] to observe an association in the EAS meta-analysis for each of the 102 loci at alpha error of 0.05 using the effect estimate from the EUR discovery study[8], the allele frequency for EAS samples from 1000 Genomes and the sample size available in the EAS meta-analysis. By summing up the probabilities across the 102 loci, we derived the absolute number of associations out of the 102 we are powered to observe if the effect estimates in EAS are consistent with the ones from the EUR studies. For benchmarking, we also assessed the reproducibility of these established loci in ancestry-matched cohorts. We used independent EUR GWAS for depression with different sample sizes (Bio*Me*, BioVU, FinnGen[26], 23andMe).

Heritability and genetic correlations

We estimated the SNP heritability (h^2) for each depression phenotype in EAS (meta-analysed cohorts) using used LD score (LDSC) regression[27]. We also used bivariate GREML implemented in the GCTA software[28] to estimate h^2 for the two large Chinese datasets, CONVERGE and CKB (symptom-based definition), that contribute the majority of samples in our analysis for which genotype data were available. For this we excluded, related individuals and used hard-calls for variants with call rate>0.95 and MAF>0.01. For this analysis we used a variety of prevalence estimates, ranging from 6.5%[29] to 15%[30].

To characterise the genetic architecture of depression, we estimated genetic correlations between depression in EAS and EUR studies. For clinical depression in EUR samples, we used the summary statistics from 45,396 cases with DSM-based diagnosis of major depressive disorder and 97,250 controls from a meta-analysis of 33 independent cohorts included in the latest GWAS[17], excluding UKB and 23andMe. Additionally, we generated a symptom-based definition for EUR samples using the PHQ-9 questionnaire and a cut-off score of 10[31], yielding 6,510 affected individuals and 116,697 controls from UK Biobank[10, 32].

To assess the sharing of genetic risk factors for depression across the genome between the two populations, we estimated trans-ancestry genetic correlations using POPCORN[33]. We estimated the genetic effect correlation which compares effects independent of allele frequency differences between the two populations. LDSC was also used to estimate genetic correlations between different outcomes within each ancestry group. The default LD Scores computed using 1000 Genomes EAS data were used as a reference for the LD estimates. We also assessed the genetic overlap with other traits using publicly available summary statistics (PGC, NHGRI-EBI GWAS catalogue) from EAS and EUR populations, using LDSC and POPCORN respectively, as described above. We only present genetic correlation estimates where the standard error (SE) was less than 0.3.

To aid interpretation of the trans-ancestry genetic correlations, we also gathered estimates for other traits. We extracted genetic correlations between EUR and EAS from publications[34-37]. Additionally, we used publicly available summary statistics from Biobank Japan[38, 39] and EUR GWASs to estimate correlations for coronary artery disease (CAD)[40], breast cancer[41] and age at menarche[42] using POPCORN as outlined above.

Supplementary results

Characterisation of novel loci

Variant rs4656484 at a previously unreported locus, 1q24.1, was associated with depression with $P=4.4x10^{-8}$ (beta for C allele=-0.018, SE=0.003, effect allele frequency (EAF)=0.635) (Table 1). In the UK Brain Expression Consortium resource (UKBEC)[43] rs4656484 was associated with expression of *LMX1A* (LIM Homeobox Transcription Factor 1 Alpha), which has been linked to dopamine neuron development[44]. The tissue group showing the strongest eQTL association was frontal cortex ($P=1.1x10^{-4}$). In GTEx and ROSMAP[45], rs4556484 showed significant eQTL association with *FAM78B* (Family with sequence similarity 78 member B) in thyroid (GTEx, $P=7.7x10^{-5}$), cortex

(GTEx, P=0.046) and brain (ROSMAP, P=0.001). FAM78B forms a ribonucleoprotein complex, which shuttles RNA between the nucleus and cytosol[46].

A novel locus at 7p21.2 was associated with depression at genome-wide significance in the analysis of the East Asia based studies (Table 1). The lead SNP, rs10240457 (EAF=0.646, beta for A-allele=0.028, SE=0.005, $P=5.0x10^{-9}$) is intronic to *AGMO* (Alkylglycerol Monooxygenase). This gene cleaves the O-alkyl bond of ether lipids which are essential components of brain membranes and function in cell-signalling and other critical biological processes.

We carried out a meta-analysis for the broad depression outcome in EAS and the largest GWAS of depression in EUR samples[17] (Figure 1B , Supplementary Figure 4). The lead variant at 1q25.2, rs7548487, (beta for A allele= -0.013, SE=0.002, $P=1.29x10^{-8}$) is located in an intron of *ASTN1* (astrotactin 1). Astrotactin is a neuronal adhesion molecule required for glial-guided migration of young postmitotic neuroblasts in cortical regions of the developing brain[47]. The C-allele of the lead variant at 18q12.1, rs547488 had beta 0.008 (SE=0.001) and $P=3.3x10^{-8}$. It is located downstream of *CDH2* (cadherin 2) and is nominally associated with the expression of *CDH2* in the brain (UKBEC, P=0.03) and from BrainSeq[48] (P=0.027). CDH2 encodes N-cadherin, which expresses broadly in multiple tissues and has been shown to play a role in the development of the nervous system and be associated with neurodevelopmental disorders[49]. The third locus is 22q13.31 with lead variant rs12160976 (beta for A allele=-0.009, SE=0.002, $P=1.6x10^{-8}$).

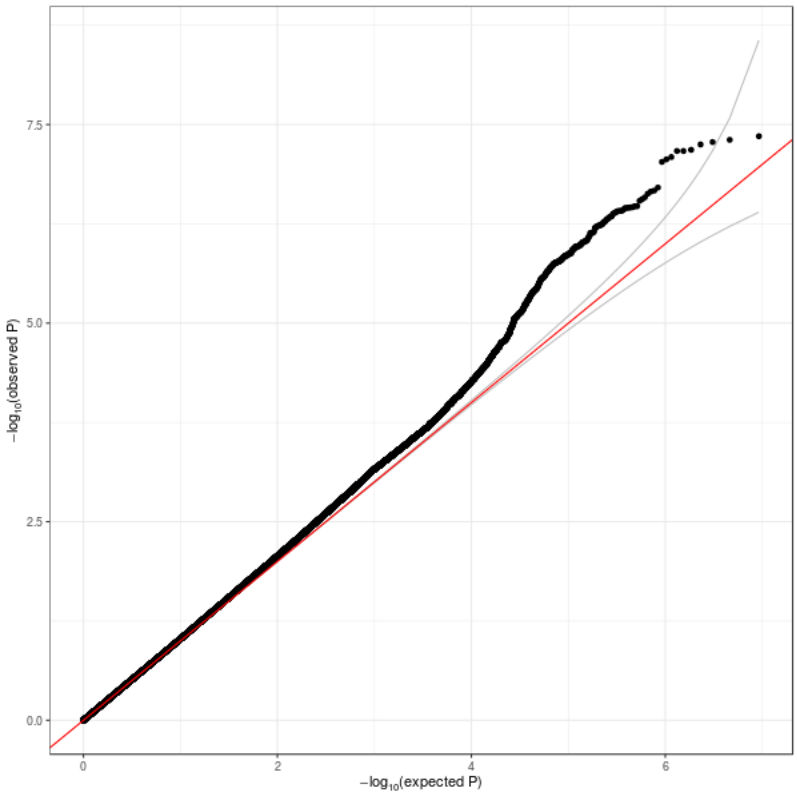
Gene-based analysis

We also performed a gene-level aggregate test based on the meta-analysis summary statistics using MAGMA (v1.08), as implemented in FUMA[20]. The ETS Variant Transcription Factor 5 (3q27.2) gene, was the only gene that passed the significance threshold ($P=6.9x10^{-6}$). It has been previously associated with depression risk in an EUR study[50].

Reproducibility

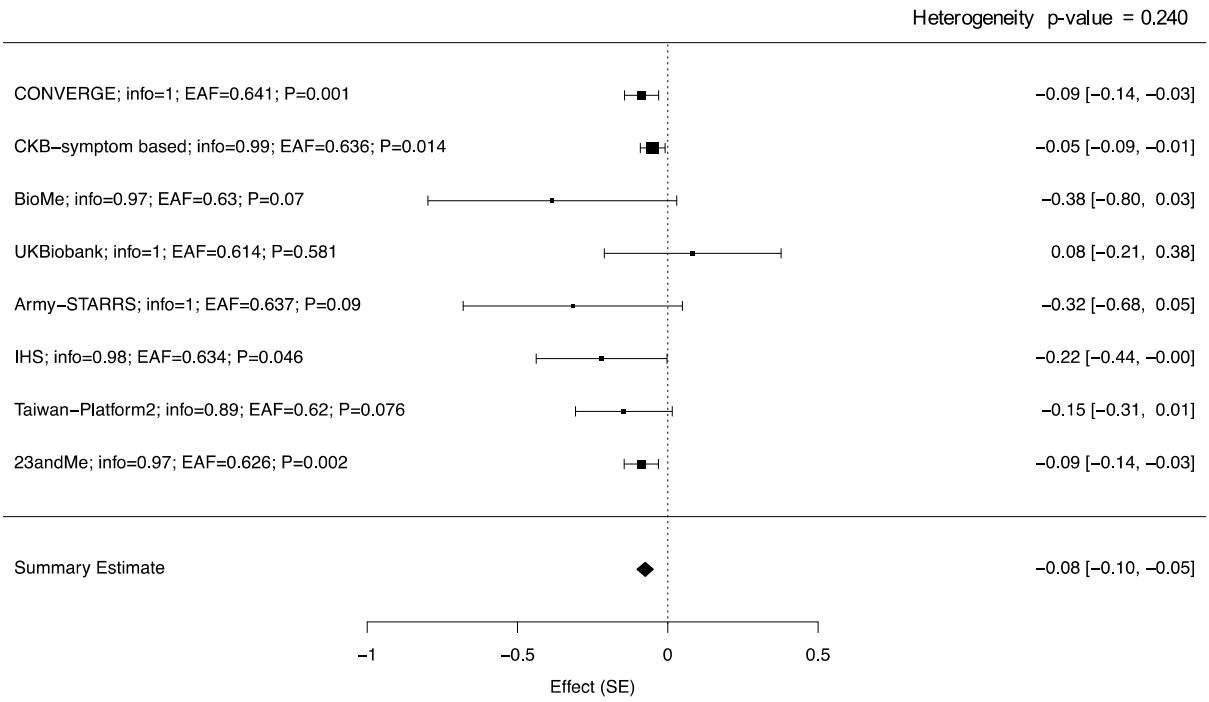
In addition to the comparisons described in the main manuscript, to rule out that the low reproducibility rates are due to differences in LD patterns between the ancestry groups, we created credible sets of SNPs that are likely to contain the causal variants and assessed their associations in the EAS data. Of the 102 credible sets, 13 (12.7%) contained variant(s) with P<0.01 in the EAS association analysis with depression. We also assessed a high-confidence set of loci from the largest EUR meta-analysis that were replicated in an independent dataset of 23andMe[8]. Out of the 86 which were available in the EAS meta-analysis, 13 (15.1%) of the credible sets contained a variant with P<0.01.

eFigure 1. Quantile-quantile Plot Illustrating the GWAS Meta-Analysis for Depression in 15,771 Individuals With Depression and 178,777 Controls with East Asian Ancestry



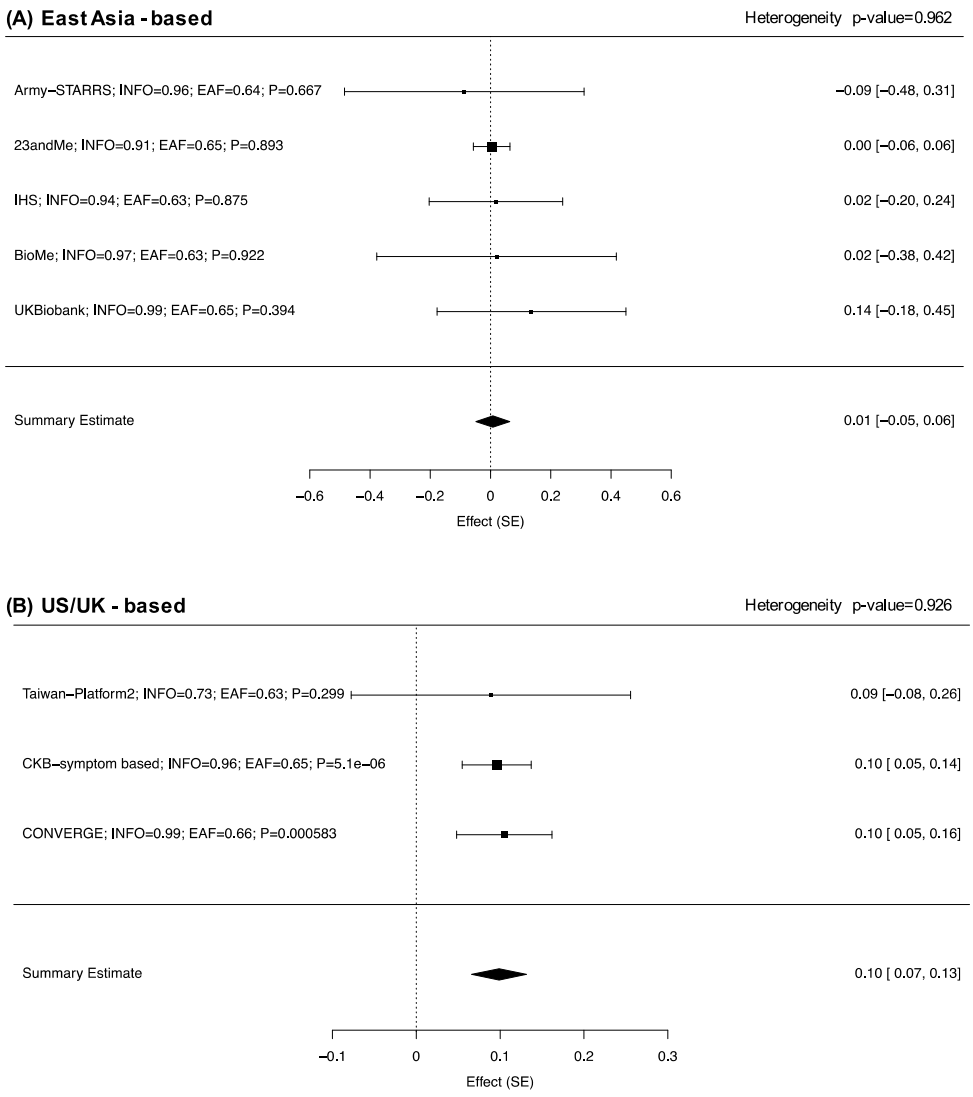
It shows the deviation of association test statistics (black dots) from the distribution expected under the null hypothesis (red line). The grey lines indicated the lower and upper 95% confidence bands. The inflation statistic was λ=1.035 and λ_{1000}=1.001 when scaled to a sample size of 1000 cases and 1000 controls (LDSC intercept 1.01 (0.01)).

eFigure 2. Forest Plot for rs4656484 Which Was Genome-Wide Significant in the Depression East Asian Meta-Analysis Based on all Studies



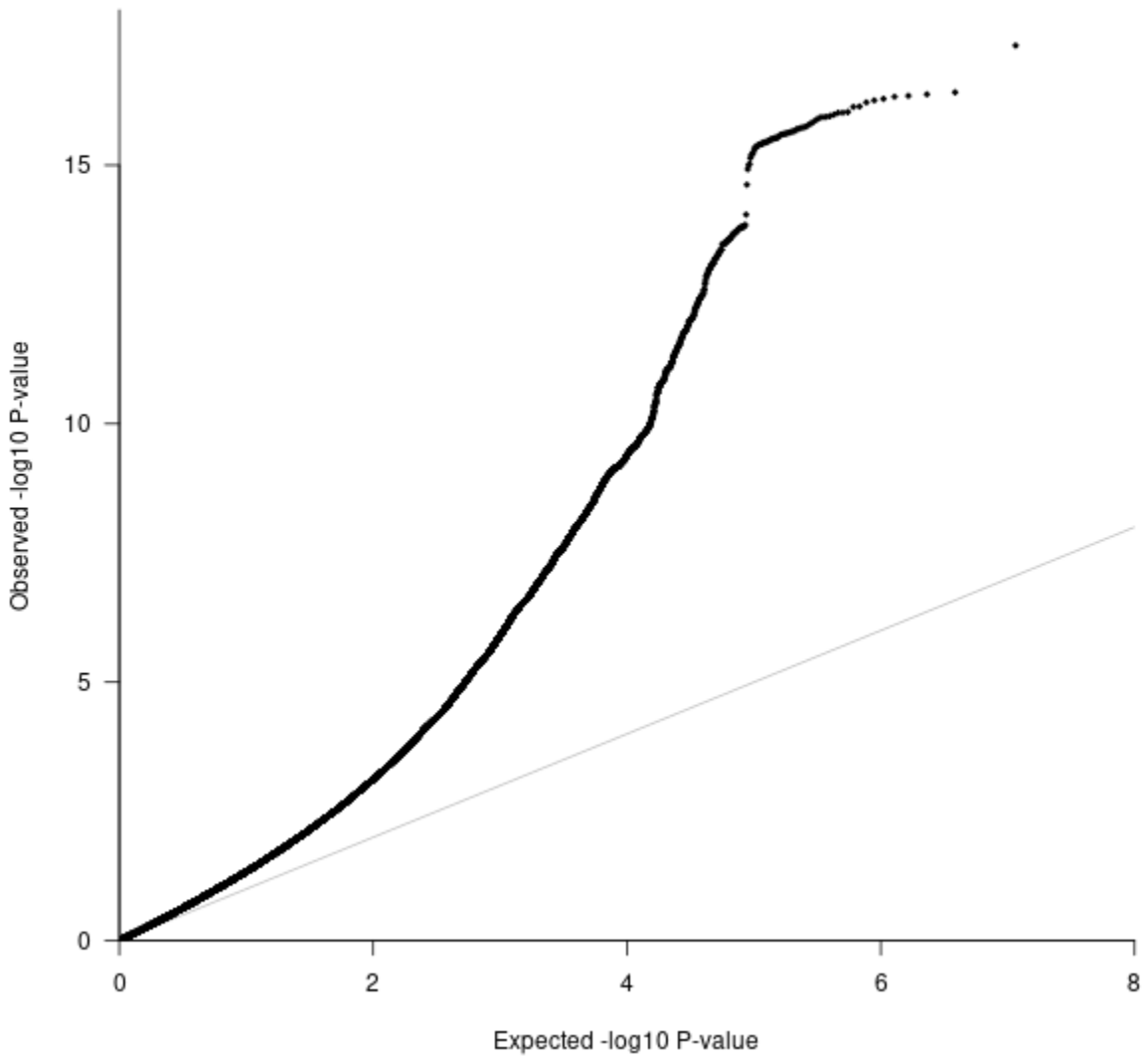
The plot shows the effect size estimates and associated confidence interval for each of the studies. The variant was not available in the Women's Health Initiative and Taiwan-Platform 1 datasets due to insufficient imputation quality. IHS=Intern Health Study; CKB=China Kadoorie Biobank (symptom-based depression outcome). INFO=imputation accuracy score; EAF=effect allele frequency, P=p-value for the association with depression in the study.

eFigure 3. Forest Plots of rs10240457 Which Was Genome-Wide Significant in the Depression Meta-Analysis of Studies Based in East Asian Countries



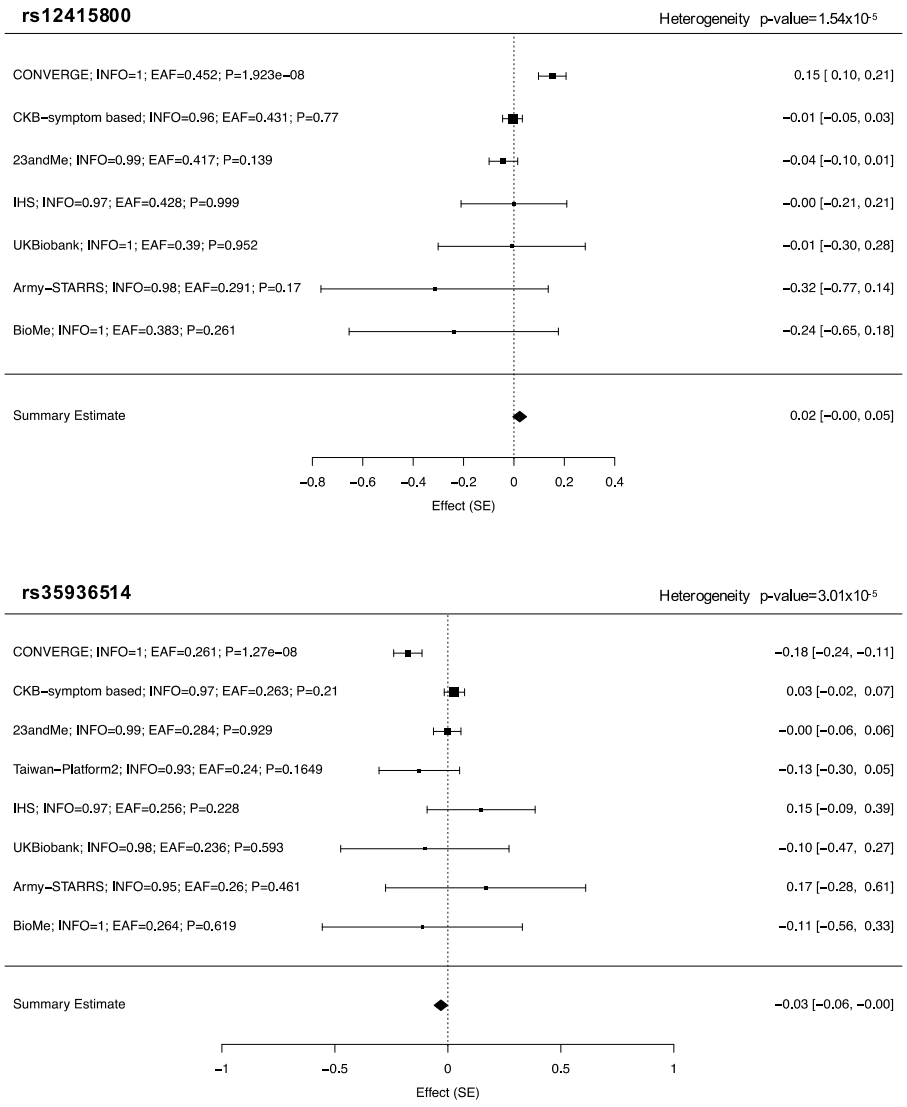
(A) effect size estimates and confidence interval for each of the studies in the East-Asia based meta-analysis and (B) results for the US/UK based studies with ancestrally East Asian samples. The variant was not available in WHI and Taiwan-Platform 1 datasets. IHS=Intern Health Study; CKB=China Kadoorie Biobank (symptom-based depression outcome).

eFigure 4. Quantile-Quantile Plot Illustrating the Meta-Analysis of East Asian Results for Depression With the Largest GWAS in Europeans (Howard et al., 2019)



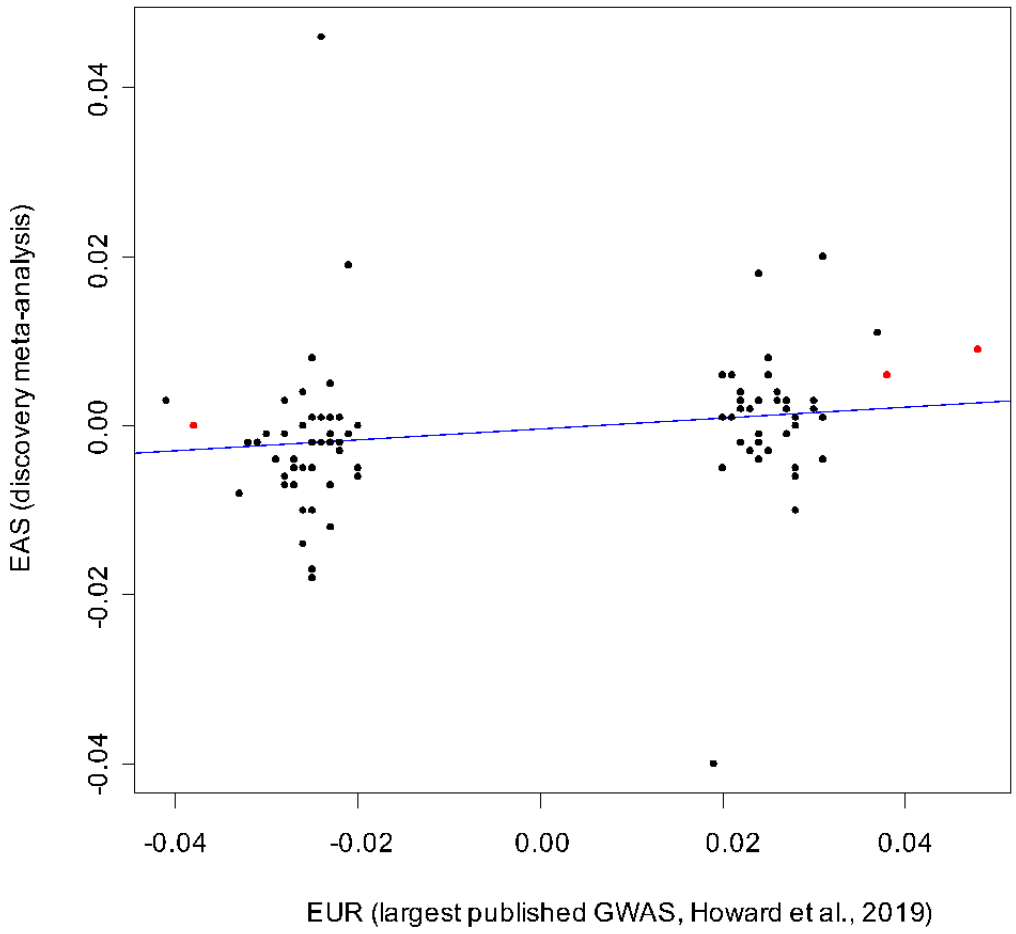
The inflation factor war λ = 1.383, λ_{1000} = 1.001.

eFigure 5. Forest Plots for the Two Previously Reported Depression Loci Based on the Chinese CONVERGE Study



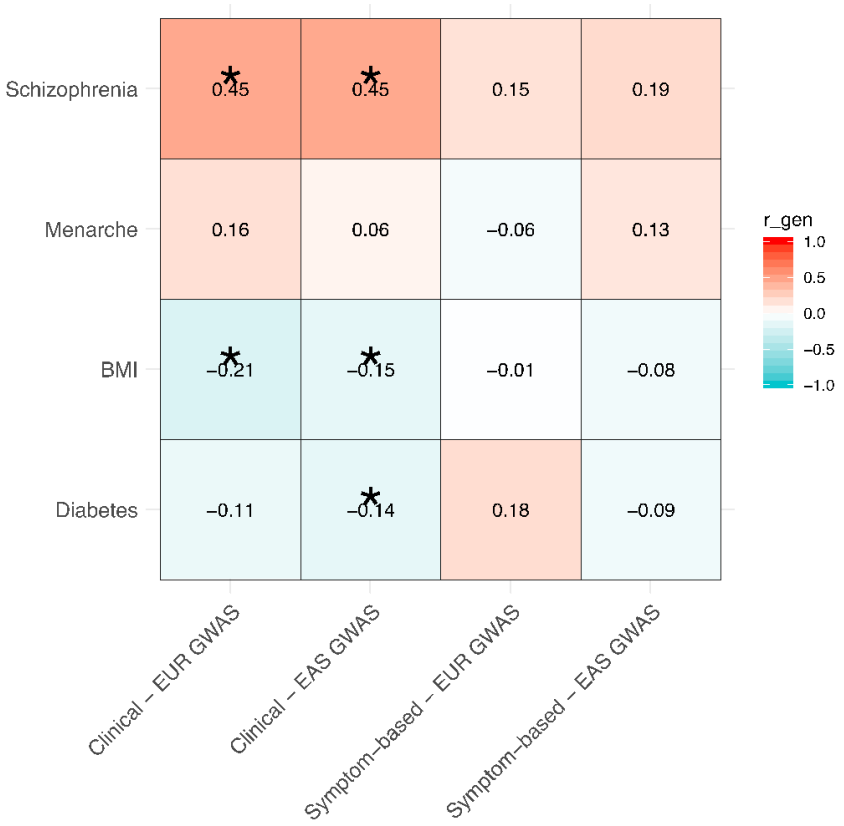
The plot shows the effect size estimates and associated confidence interval for each of the studies. IHS=Intern Health Study; CKB=China Kadoorie Biobank (symptom-based depression outcome).

eFigure 6. Effect Estimates for Depression of Previously Reported Depression Loci in the Discovery European Study vs in the East Asian Meta-Analysis



The effects are presented in log odds ratios. Variants with more than 80% power to replicate in the EAS analysis are coloured in red. The slope for regression between effect sizes is 0.065. EAS=East-Asian ancestry samples (current study), EUR=European-ancestry samples[17].

eFigure 7. Genetic Correlations Between the Clinical and Symptom-Based Depression Phenotypes in East Asians and Other Traits in Europeans



For this analysis we used published summary statistics for schizophrenia, age of menarche, body mass index (BMI) and type 2 diabetes, from European (EUR) GWAS (LDSC) and East Asian (EAS) GWASs (POPCORN). Colours correspond to direction and strength of the genetic correlations (r_{gen}). Statistically significant genetic correlations are indicated by a star (*).

eTable 2. Details of the Genotyping for Each Dataset Included in the Discovery East Asian Meta-Analysis for Depression

Study	Genotyping Array	Imputation panel	Inflation factor (λ)	N cases	N controls	N markers (included in the meta-analysis)
CKB	Custom-designed Affymetrix	1000Genomes	1.000	5376	69998	10,834,708
CONVERGE	Low-depth Whole Genome Sequencing	1000Genomes Phase 1 Asian panel	1.075	5303	5337	5,987,610
23andMe	Illumina HumanHap550+ BeadChip, Illumina OmniExpress+ BeadChip, a custom-designed array and Illumina Infinium Global Screening Array	1000 Genomes Phase 3 haplotypes with the UK10 imputation reference panel	1.024	2729	90310	9,072,919
Taiwan MDD study - Platform 1	Affymetrix CHB Array, Affymetrix TWB1.0 Array, Illumina Human Omni Express Exiome Beadchip*	1000Genomes Phase 3	0.945	988	6075	551,251
Taiwan MDD study - Platform 2	Affymetrix TWB2.0 Array	1000Genomes Phase 3	1.013	360	2317	4,390,026
IHS	CoreExome	Haplotype Reference Consortium panel	1.023	294	544	4,626,568
WHI	CardioMetabochip	-	1.045	454	2553	94,527
UKB	UKBB Axiom & BiLEVE	1000Genomes Phase 3 + Haplotype Reference Consortium	1.039	133	366	8,037,956
Army STARRS	Illumina OmniExpress + Exome array	1000Genomes	1.06	74	442	6,591,199
Bio*Me*	Infinium Global Screening Array-24 v2.0	1000Genomes Phase 3	0.995	60	835	6,336,224
Meta-analysis	**-**	**-**		**15,771**	**178,777**	

*Due to the differences in genotyping arrays, imputation and meta-analysis was performed separately. Samples genotyped with Affymetrix TWB2.0 array were considered a separate dataset, while the other samples were combined in a different set. CKB=China Kadoorie Biobank; MDD=Major Depressive Disorder; IHS=Intern Health Study; WHI=Women's Health Initiative; UKB=UK Biobank

eTable 7. The Two Genome-Wide Significant Depression Loci in CONVERGE and the Relevant Results in the Other East Asian Ancestry Datasets of the Current Study and the Two Largest European Studies

rs12415800								
Study	**EA**	**OA**	**EAF**	**BETA**	**SE**	**P**	**Ncases/ Ncontrols**	**Power**
CONVERGE	A	G	0.452	0.152	0.028	0.00000001923	5303/5337	0.127
CKB-Symptom based	A	G	0.431	-0.006	0.020	0.77	5376/69998	1.000
CKB-Lifetime diagnosis	A	G	0.431	-0.024	0.041	0.55	1305/69998	0.942
23andMe	A	G	0.417	-0.042	0.029	0.139	2729/90310	0.999
Taiwan MDD Study - Platform 1	NA	NA	NA	NA	NA	NA	988/6075	NA
Taiwan MDD Study - Platform 1	NA	NA	NA	NA	NA	NA	360/2317	NA
WHI	NA	NA	NA	NA	NA	NA	454/2553	NA
IHS	A	G	0.428	-0.0001	0.107	0.999	294/544	0.292
UK Biobank	A	G	0.390	-0.009	0.149	0.952	133/366	0.179
Army STARRS	A	G	0.291	-0.315	0.230	0.170	74/442	0.119
BioMe	A	G	0.383	-0.239	0.212	0.261	60/835	0.115
PGC Major Depression Study (Wray et al., 2018)*	A	G	0.027	-0.004	0.039	0.797	59851/113154	1.000

Depression (Howard et al., 2019)*	A	G	0.016	-0.004	0.019	0.843	179756/329443	1.000
rs35936514								
Study	**EA**	**OA**	**EAF**	**BETA**	**SE**	**P**	**Ncases/Ncontrols**	**Power**
CONVERGE	T	C	0.261	-0.177	0.032	0.0000000127	5303/5337	0.142
CKB-Symptom based	T	C	0.263	0.029	0.023	0.21	5376/69998	1.000
CKB-Lifetime diagnosis	T	C	0.263	0.063	0.046	0.17	1305/69998	0.972
23andMe	T	C	0.284	-0.003	0.031	0.929	2729/90310	1.000
Taiwan MDD Study - Platform 1	NA	NA	NA	NA	NA	NA	988/6075	NA
Taiwan MDD Study - Platform 1	T	C	0.240	-0.126	0.091	0.1649	360/2317	0.495
WHI	NA	NA	NA	NA	NA	NA	454/2553	NA
IHS	T	C	0.256	0.147	0.122	0.228	294/544	0.334
UK Biobank	T	C	0.236	-0.102	0.190	0.593	133/366	0.199
Army STARRS	T	C	0.260	0.167	0.226	0.461	74/442	0.148
BioMe	T	C	0.264	-0.113	0.226	0.619	60/835	0.132
PGC Major Depression Study (Wray et al., 2018)*	T	C	0.057	-0.009	0.019	0.293	59851/113154	1.000
Depression (Howard et al., 2019)*	T	C	0.048	-0.010	0.011	0.356	179756/329443	1.000

The effect sizes (beta coefficients) are reported for the effect allele. The power calculations are based on the natural log of the combined Odds Ratios in the discovery study (Cai et al., 2015), the EAF of each variant in each individual study, as well as the sample size of each study. The * denotes the studies conducted in studies with European ancestry samples. EA=Effect Allele; OA=Other Allele; EAF=EA frequency; SE=Standard Error; CKB=China Kadoorie Biobank; MDD=Major Depressive Disorder; WHI=Women's Health Initiative; IHS=Intern Health Study; PGC=Psychiatric Genetics Consortium

eTable 9. Reproducibility of Established Depression Loci From Howard et al.,2019 in Independent Samples of European Ancestry and in the East Asian Depression GWAS

Cohort Name	Ancestry	Phenotype definition	N cases	N controls	N variants	Observed (%)	Expected (%)	Observed /expected
BioMe	EUR	EHR	1,456	8,304	102	6.86%	9.28%	0.74
BioVU	EUR	HER	7,757	24,723	71	18.31%	28.17%	0.65
FinnGen	EUR	EHR	17,794	156,611	92	21.74%	55%	0.40
23andMe	EUR	self-reported	105,114	1,757,384	96	84.38%	99.79%	0.86
EAS GWAS	EAS	broad	15,771	178,777	94	10.6%	42.5%	0.25

*N variants: number of lead variants from genome-wide significant loci in Howard et al which were present in the look up study
EUR: European ancestry samples
EAS: East Asian ancestry samples
EHR: Medical diagnosis of major depressive disorder from Electronic Healthcare Records

eTable 10. SNP-Heritabilities for the Different Depression-Definition Outcomes Considered in This Study

Study	Observed h^2 (SE)	Liability scale h^2 (SE)		
		K=6.5%	K=12%	K=15%
Broad depression, EAS meta-analysis	0.009 (0.002)	2.9% (0.01)	3.5% (0.01)	3.8% (0.01)
Clinical depression, EAS meta-analysis	0.024 (0.006)	6.7% (0.02)	8.2% (0.02)	8.8% (0.02)
Symtom-based depression, EAS meta-analysis	0.012 (0.006)	3.8% (0.02)	4.6% (0.03)	4.6% (0.02)
CONVERGE	0.284 (0.032)	26.2% (0.03)	31.7% (0.04)	34.1% (0.04)
China Kadoorie Biobank (symptom-based definition)	0.045 (0.017)	6.4% (0.02)	7.8% (0.03)	8.4% (0.03)
Clinical depression, EUR meta-analysis (PGC)	0.073 (0.005)	7.4% (0.01)	9% (0.01)	9.7% (0.01)
Symptom-based depression, UK Biobank European dataset (PHQ9)	0.028 (0.004)	12.2% (0.02)	14.8% (0.02)	15.9% (0.02)

EAS=East Asian ancestry; SE=Standard error

eTable 11. Transancestry Genetic Correlation Estimates for Diverse Phenotypes Between Samples With East Asian and European Ancestry

Trait	PMID	N EAS (cases) a	N EUR (cases)	Country b	Genetic correlation	Standard error	*P* value c
Schizophrenia	31740837	58,140 (22,778)	82,315 (35,476)	Multiple	0.98	0.03	>0.05
Schizophrenia	30285260	9,348 (1,940)	77,096 (33,640)	Japan	0.577	-	1.83*10-13
Bipolar disorder	30285260	64,851 (2,964)	16,731 (7,481)	Japan	0.718	-	3.65*10-3
Smoking initiation	31089300	165,436 (83,810)	359,751(297, 127)	Japan	0.717	0.035	2.2*10-16
HDL cholesterol	31551420	162,255	188,577	Japan	0.999	0.081	
HDL cholesterol	31551420	21,295	188,577	China	0.999	-	
LDL cholesterol	31551420	162,255	188,577	Japan	0.959	0.138	
LDL cholesterol	31551420	21,295	188,577	China	0.778	0.300	
Triglyceride levels	31551420	162,255	188,577	Japan	0.961	0.066	
Triglyceride levels	31551420	21,295	188,577	China	0.999	-	
Coronary artery disease	32514122 (EAS), 28714975 (EUR)	212,453 (29,319)	332,477 (71,602)	Japan	0.908	0.083	0.27
Breast cancer	32514122 (EAS), 29059683 (EUR)	95,283 (5,552)	119,014 (69,980)	Japan	0.761	0.196	0.22
Age at menarche	29773799 (EAS), 28436984 (EUR)	67,029	252,000	Japan	0.0801	0.0688	0.0036

a. Number of East Asians (EAS) in calculation with number of Europeans (EUR) in brackets; b. Country where the East Asian samples were collected; c. P value for whether the genetic correlation is different from 1.

eTable 12. Transancestry Genetic Correlations of Clinical and Symptom-Based Depression in East Asian Datasets With Other Traits, Based on European Studies

Trait	PMID	Genetic correlation	Standard error	Confidence Intervals
		Clinical depression		
Body mass index (BMI)*	30124842	-0.212	0.084	-0.378, -0.047
Coronary artery disease (CAD)	28714975	-0.253	0.160	-0.567, 0.06
Age of menarche	28436984	0.161	0.099	-0.033, 0.356
Smoking (ever vs never)	30643251	-0.156	0.089	-0.331, 0.019
Subjective well-being	27089181	-0.393	0.198	-0.781, -0.004
Type 2 diabetes (T2D)	30054458	-0.113	0.113	-0.334, 0.108
Alcohol dependence (AD)	30482948	-0.045	0.298	-0.629, 0.54
Alcohol consumption (drinks per week)	30643251	-0.022	0.110	-0.237, 0.194
Attention-Deficit/Hyperactivity Disorder (ADHD)	30478444	-0.063	0.150	-0.356, 0.231
Alzheimer's disease	24418058	NA	NA	NA
Anorexia nervosa*	31308545	0.502	0.158	0.193, 0.811
Anxiety	26754954	NA	NA	NA
Autism	30804558	0.130	0.171	-0.205, 0.465
Bipolar disorder*	31043756	0.710	0.153	0.41, 1.009
Neuroticism	27089181	0.303	0.150	0.009, 0.596
Schizophrenia*	31740837	0.449	0.109	0.234, 0.664
Depressive symptoms	27089181	0.311	0.212	-0.103, 0.726
Symptom-based depression (UKB)	30305743	0.223	0.181	-0.131, 0.577
Clinical depression (PGC)*	29700475	0.413	0.159	0.101, 0.725

		Symptom-based depression		
Body mass index (BMI)	30124842	-0.009	0.100	-0.206, 0.187
Coronary artery disease (CAD)	28714975	0.170	0.158	-0.14, 0.479
Age of menarche	28436984	-0.065	0.106	-0.273, 0.144
Smoking (ever vs never)	30643251	-0.172	0.126	-0.419, 0.075
Alcohol dependence (AD)	30482948	NA	NA	NA
Alcohol consumption (drinks per week)	30643251	-0.002	0.140	-0.276, 0.273
Attention-Deficit/Hyperactivity Disorder (ADHD)	30478444	-0.115	0.148	-0.404, 0.175
Alzheimer's disease	24418058	NA	NA	NA
Anorexia nervosa*	31308545	0.449	0.193	0.07, 0.827
Anxiety	26754954	NA	NA	NA
Autism	30804558	0.182	0.219	-0.247, 0.611
Bipolar disorder	31043756	0.072	0.161	-0.243, 0.388
Neuroticism	27089181	0.840	0.216	0.417, 1.263
Schizophrenia	31740837	0.153	0.142	-0.126, 0.431
Subjective well-being*	27089181	-0.502	0.195	-0.885, -0.119
Type 2 diabetes (T2D)	30054458	0.177	0.166	-0.148, 0.503
Depressive symptoms	27089181	NA	NA	NA
Symptom-based depression (UKB)	30305743	0.433	0.281	-0.118, 0.985
Clinical depression (PGC)	29700475	0.558	0.221	0.124, 0.992

The * denotes the significance, based on the confidence intervals. The traits that did not provide robust results (Standard Error > 0.3) are not presented (Not Available (NA)).

eTable 13. Genetic Correlations of Clinical and Symptom-Based Depression in European Datasets With Other Traits

Trait	PMID	rg	SE	Z	P-value
		Clinical depression - Psychiatric Genetics Consortium			
Symptom-based depression	30305743	0.814	0.080	10.168	2.77E-24
Attention-Deficit/Hyperactivity Disorder (ADHD)	30478444	0.570	0.040	14.139	2.19E-45
Alcohol dependence (AD)	30482948	0.583	0.119	4.915	8.89E-07
Alzheimer's disease	24418058	0.041	0.079	0.515	6.07E-01
Anorexia nervosa	31308545	0.305	0.047	6.473	9.60E-11
Anxiety	26754954	0.855	0.168	5.094	3.51E-07
Autism	30804558	0.417	0.047	8.918	4.76E-19
Bipolar disorder	31043756	0.345	0.038	9.129	6.95E-20
Alcohol consumption (drinks per week)	30643251	0.090	0.036	2.511	1.20E-02
Depressive symptoms	27089181	0.964	0.043	22.342	1.45E-110
Neuroticism	27089181	0.720	0.046	15.712	1.25E-55
Schizophrenia	31740837	0.349	0.030	11.772	5.44E-32
Age at menarche	28436984	-0.091	0.031	-2.902	3.70E-03
Body Mass Index (BMI)	30124842	0.111	0.025	4.368	1.26E-05
Smoking (ever vs never)	30643251	0.321	0.032	10.156	3.10E-24
Subjective wellbeing	27089181	-0.697	0.053	-13.092	3.67E-39
Type 2 diabetes (T2D)	30054458	0.185	0.031	5.926	3.11E-09
Coronary Artery Disease (CAD)	28714975	0.203	0.037	5.463	4.68E-08

Trait	PMID	rg	SE	Z	P-value
		Clinical depression - Psychiatric Genetics Consortium			
Broad depression (self-reported help-seeking behaviour for mental health difficulties or diagnosis of a depressive mood disorder from linked hospital admission records)	29662059	0.878	0.038	23.160	1.17E-118
ICD-coded MDD (hospital admission diagnosis)	29662059	0.907	0.070	13.021	9.26E-39
Probable MDD (cardinal symptoms + broad depression)	29662059	0.840	0.085	9.925	3.26E-23
Depression	30718901	0.946	0.022	43.498	0
		Symptom-based depression - UK Biobank			
Clinical depression	29700475	0.814	0.080	10.168	2.77E-24
Attention-Deficit/Hyperactivity Disorder (ADHD)	30478444	0.520	0.070	7.388	1.49E-13
Alcohol dependence (AD)	30482948	0.375	0.140	2.682	7.31E-03
Alzheimer's disease	24418058	-0.065	0.108	-0.601	5.48E-01
Anorexia nervosa	31308545	0.032	0.073	0.441	6.59E-01
Anxiety	26754954	0.596	0.211	2.826	4.72E-03
Autism	30804558	0.315	0.097	3.263	1.10E-03
Bipolar disorder	31043756	0.118	0.055	2.155	3.12E-02
Alcohol consumption (drinks per week)	30643251	-0.063	0.053	-1.202	2.29E-01
Depressive symptoms	27089181	0.894	0.091	9.873	5.47E-23
Neuroticism	27089181	0.608	0.095	6.427	1.30E-10

Trait	PMID	rg	SE	Z	P-value
		Symptom-based depression - UK Biobank			
Schizophrenia	31740837	0.218	0.049	4.481	7.44E-06
Age at menarche	28436984	-0.051	0.039	-1.314	1.89E-01
Body Mass Index (BMI)	30124842	0.314	0.041	7.700	1.36E-14
Smoking (ever vs never)	30643251	0.290	0.044	6.683	2.34E-11
Subjective wellbeing	27089181	-0.750	0.086	-8.722	2.73E-18
Type 2 diabetes (T2D)	30054458	0.353	0.063	5.603	2.11E-08
Coronary Artery Disease (CAD)	28714975	0.310	0.057	5.464	4.67E-08
Broad depression (self-reported help-seeking behaviour for mental health difficulties or diagnosis of a depressive mood disorder from linked hospital admission records)	29662059	0.681	0.061	11.254	2.22E-29
ICD-coded MDD (hospital admission diagnosis)	29662059	0.817	0.109	7.521	5.44E-14
Probable MDD (cardinal symptoms + broad depression)	29662059	0.724	0.103	7.019	2.23E-12
Depression	30718901	0.708	0.059	11.925	0

rg= genetic correlation; SE= standard error

eTable 14. Genetic Correlations of Clinical and Symptom-Based Depression in East Asian Datasets With Other Traits, Based on East Asian Studies

Trait	PMID	rg	SE	Z	P-value
		Clinical depression			
Schizophrenia	31740837	0.447	0.085	5.256	1.47E-07
Type 2 diabetes (T2D)	30718926	-0.143	0.072	-1.997	0.046
Body Mass Index (BMI)	28892062	-0.147	0.061	-2.402	0.016
Age at menarche	29773799	0.060	0.087	0.687	0.492
High-density lipoprotein (HDL)	28334899	0.093	0.154	0.605	0.545
Low-density lipoprotein (LDL)	28334899	0.177	0.134	1.323	0.186
Triglycerides (TG)	28334899	-0.073	0.165	-0.441	0.660
Total cholesterol (TC)	28334899	0.127	0.116	1.097	0.273
		Symptom-based depression			
Schizophrenia	31740837	0.189	0.137	1.380	0.168
Type 2 diabetes (T2D)	30718926	-0.088	0.120	-0.734	0.463
Body Mass Index (BMI)	28892062	-0.082	0.098	-0.832	0.405
Age at menarche	29773799	0.130	0.134	0.971	0.332
High-density lipoprotein (HDL)	28334899	0.145	0.219	0.660	0.509
Low-density lipoprotein (LDL)	28334899	0.133	0.226	0.587	0.557
Triglycerides (TG)	28334899	-0.321	0.235	-1.368	0.172
Total cholesterol (TC)	28334899	0.085	0.208	0.411	0.681

rg= genetic correlation; SE= standard error

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