

Genome-wide association study of major anxiety disorders in 122,341 European-ancestry cases identifies 58 loci and highlights GABAergic signaling

Received: 22 July 2024

Accepted: 12 December 2025

Published online: 3 February 2026

 Check for updates

A list of authors and their affiliations appears at the end of the paper

The major anxiety disorders (ANX; including generalized anxiety disorder, panic disorder and phobias) are highly prevalent, often onset early and cause substantial global disability. Although distinct in their clinical presentations, they probably represent differential expressions of a dysregulated threat–response system. Here, we present a genome-wide association meta-analysis comprising 122,341 European ancestry ANX cases and 729,881 controls. We identified 58 independent genome-wide significant risk variants and 66 genes with robust biological support. In an independent sample of 1,175,012 self-report ANX cases and 1,956,379 controls, 51 out of the 58 associations replicated. As predicted by twin studies, we found substantial genetic correlation between ANX and depression, neuroticism and other internalizing phenotypes. Follow-up analyses demonstrated enrichment in all major brain regions and highlighted GABAergic signaling as one potential mechanism implicated in ANX genetic risk. These results advance our understanding of the genetic architecture of ANX and prioritize genes for functional follow-up studies.

Fear and anxiety are critical survival responses; thus, ANX may result from dysregulation of the brain's threat–response circuits. Although perturbations in various neurotransmitter systems, such as serotonin or gamma-aminobutyric acid (GABA), have been proposed as a basis of their etiology, no reliable biomarkers have yet been identified¹. The major ANX, including generalized anxiety disorder (GAD), panic disorder and phobias (specific phobia, social phobia and agoraphobia), represent different clinical presentations of that underlying common diathesis^{2–4}. Up to 25% of the population will develop an ANX at some point during their lifetime^{5–7}. These disorders tend to onset early in life, are persistent and are highly comorbid with other psychiatric conditions for which they often present as a predisposing risk factor; for example, major depressive disorder (MDD) and substance-use disorders^{6,8–10}. ANX are also associated with other medical conditions, such as neurological, cardiovascular and gastrointestinal disorders as well as cancers^{11–14}. These features make ANX a leading source of worldwide disability^{15,16}.

Each ANX aggregates in families (odds ratio, 4–6) primarily owing to genetic risk factors¹⁷. Estimates from twin studies indicate that ANX

are moderately heritable ($h^2 = 30–50\%$)^{2,17}, similar to other common psychiatric disorders like MDD but lower than less prevalent disorders like schizophrenia and bipolar disorder. Different ANX exhibit overlapping clinical features and strong comorbidity, which may be a result of shared genetic susceptibility^{17–19} and environmental risk factors^{20–22}. Research implicates mechanisms that affect the structure and functional capacity of brain networks involved in emotion and cognition^{23–25}. Twin studies report substantial genetic correlations between ANX and other psychiatric conditions, particularly MDD²⁶, helping to explain their high comorbidity. In addition, ANX and depression both share genetic risk with heritable personality traits such as neuroticism^{27,28}. Anxiety symptoms often precede suicidal behaviors²⁹, with possible causal implications³⁰. Therefore, examining the genetic relationship between ANX and related phenotypes on the internalizing spectrum is essential.

The combination of high prevalence, extensive comorbidity and high polygenicity makes it particularly difficult to identify genetic variants underlying risk for ANX. Prior genome-wide association studies (GWAS) have identified a handful of genetic loci with inconsistent

✉ e-mail: deckert_j@ukw.de; thalia.eley@kcl.ac.uk; manuel.mattheisen@dal.ca; hetteema@tamu.edu

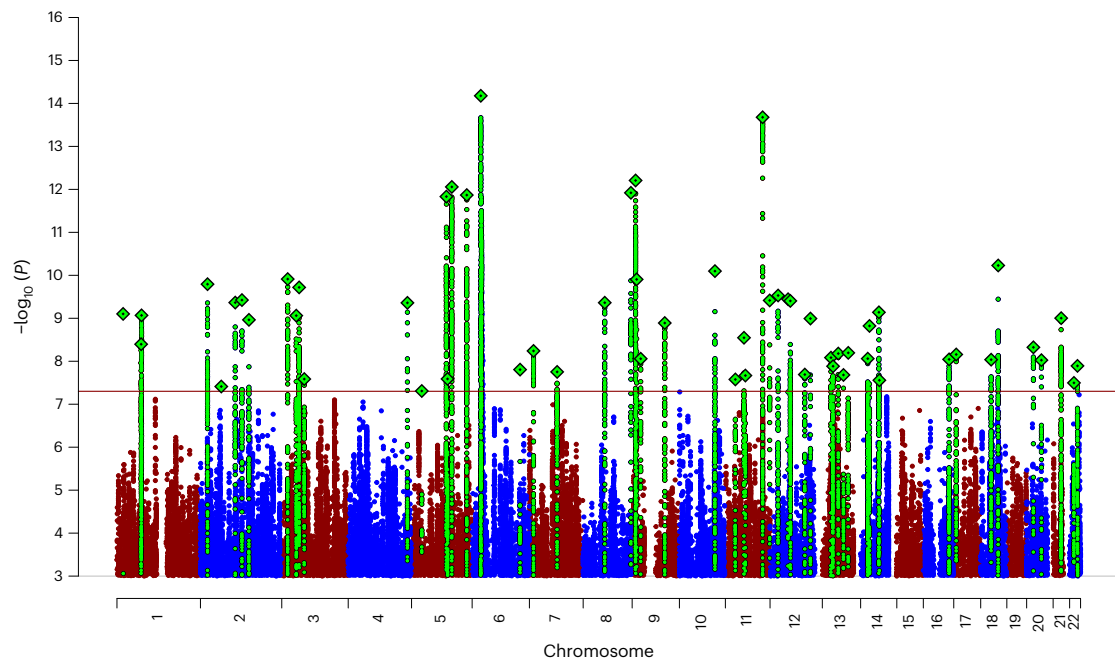


Fig. 1 | Manhattan plot of the main ANX GWAS showing 58 GWS loci. The x axis shows the position in the genome (chromosomes 1 to 22), and the y axis represents $-\log_{10}(P)$ values (two-sided, not adjusted for multiple testing) for the association of variants with ANX using an inverse-variance weighted fixed effects model (122,341

ANX cases and 729,881 unaffected controls). The horizontal red line shows the threshold for GWS ($P = 5 \times 10^{-8}$). Dots represent each SNP that was tested in the GWAS, with a green diamond indicating the lead SNP of a GWS locus and green dots below representing SNPs within the locus with high levels of LD with the lead SNP.

results^{31–36}. A recent meta-analysis using five publicly available datasets reported ten additional novel associations³⁷. Genome-wide single nucleotide polymorphism (SNP)-based heritability estimates range from 10–28%, supporting that ANX have a polygenic basis. Consistent with twin studies, previous psychiatric GWAS have demonstrated that ANX polygenic risk is highly correlated with that of MDD and neuroticism^{38–42}. Similar to other complex genetic phenotypes, sufficiently large samples are required to achieve the necessary power to detect the small effects of common variants.

Here, we present a GWAS meta-analysis from the Anxiety Disorders Working Group of the Psychiatric Genomics Consortium (PGC-ANX), consisting of 122,341 individuals diagnosed with any ANX and 729,881 controls, all of European (EUR) ancestry. We analyzed the data at the level of variant, gene, pathway/gene set and tissue by using both functionally informed and functionally agnostic methods. Subsequently, these results were compared with those of other phenotypes and investigated for possible molecular mechanisms and avenues for drug repurposing.

Results

GWAS meta-analysis

We performed a GWAS meta-analysis of 36 case-control cohorts (122,341 ANX cases and 729,881 controls; Supplementary Table 1). Details about phenotype, quality control and GWAS analysis for each individual cohort are provided in Supplementary Note 2. Among the 7.2 million autosomal SNPs analyzed, we identified 58 independent, genome-wide significant (GWS) SNPs associated with ANX (Fig. 1 and Table 1; further information is provided in Supplementary Table 2, Supplementary Fig. 1 (quantile-quantile plot) and Supplementary Figs. 2–56 (regional association plots of each significant SNP and forest plots indicating each cohort's effect size)). Estimates of the genomic inflation factor ($\lambda = 1.41$, $\lambda_{1000} = 1.00$), linkage disequilibrium (LD) score regression (LDSC) intercept (1.05, standard error (s.e.) = 0.01), and attenuation ratio (0.082, s.e. = 0.014) suggest that inflation was probably caused by polygenicity and not by cryptic population structure. LDSC estimates a SNP-based heritability of 10.1% (s.e. = 0.004), assuming a 20% population prevalence.

A series of sensitivity analyses, including GWAS Cochran's Q (Supplementary Fig. S7) and I^2 statistics (forest plots in Supplementary Figs. 2–56), revealed no substantial genome-wide heterogeneity across the 36 cohorts. Furthermore, we performed subgroup-specific meta-analyses, subdividing our study cohorts based on (1) their ascertainment strategy (five subgroups: clinical, comorbidity, community, biobanks and self-reported professional diagnosis (SRPD); Manhattan and quantile-quantile plots in Supplementary Figs. 58–62) and (2) their assessment strategy (three subgroups: interview, ICD-10 codes and SRPD; Manhattan and quantile-quantile plots in Supplementary Figs. 63–66). We then used confirmatory factor analysis in GenomicSEM⁴³ to test whether these subgroups fit a one-factor model. In both cases, a single latent factor best explained the genetic covariance between the subgroups (ascertainment fit statistics: CFI = 1, SRMR = 0.04; assessment fit statistics: CFI = 1, SRMR = 3.67×10^{-9}). The factor loadings across both subgroup models were high (0.75–1), with the factor explaining 81.8% and 95.6% of the total genomic variance in the ascertainment and assessment models, respectively (see Supplementary Note 3 for details on the subgrouping and Supplementary Table 5 and Supplementary Fig. 67a,b for GenomicSEM results). Using parallel analysis based on multivariate LDSC (paLDSC⁴⁴), we identified one non-spurious dimension in exploratory genomic factor analysis, including 14 cohorts with more than 10,000 individuals and at least 1,000 cases. This finding supports our hypothesis that the genetic association signals were generally consistent across samples and study designs and tapped into a common underlying ANX genetic vulnerability.

Replication and validation of GWAS SNPs

We conducted two replication analyses of the 58 significant loci: one in a large independent EUR ANX GWAS from 23andMe, and the other in an African-American (AFR) ancestry ANX GWAS from the Veterans Affairs Million Veteran Program (MVP). The 23andMe sample consisted of 1,175,012 ANX self-report cases and 1,956,379 controls (see Methods for details). Among the 58 SNPs identified in the discovery GWAS, all but one (**rs7121169**) were available for replication testing in the 23andMe genotype platform. Two additional variants failed quality

Table 1 | List of the 58 independent GWS SNPs of the main ANX GWAS meta-analysis

Locus	Index SNP	CHR	Position (bp)	Pvalue	OR	s.e.	A1/A2	Freq. cases	Freq. controls	Closest genes (distance kb)
1	rs34579341	1	72,745,962	4.01×10^{-9}	0.964	0.006	G/A	0.18	0.17	NEGR1
2	rs11580539	1	73,896,218	8.55×10^{-10}	0.971	0.005	G/A	0.60	0.61	LINC01360 (−41.7)
3	rs5015511	2	22,546,852	1.61×10^{-10}	0.032	0.005	A/G	0.52	0.54	–
4	rs79556790	2	63,480,537	3.87×10^{-8}	0.881	0.023	A/C	0.98	0.98	WDPCP
5	rs7570682	2	104,983,267	4.31×10^{-10}	0.036	0.006	A/G	0.23	0.23	LOC100287010
6	rs2165077	2	124,932,847	3.77×10^{-10}	0.032	0.005	T/C	0.48	0.47	CNTNAP5
7	rs17407658	2	145,703,652	1.09×10^{-9}	0.972	0.005	G/A	0.50	0.52	TEX41
8	rs9867083	3	18,804,734	1.22×10^{-10}	0.034	0.005	C/T	0.70	0.69	SATB1-AS1 (−183.1)
9	rs2888367	3	44,242,929	8.67×10^{-10}	0.032	0.005	A/G	0.33	0.34	TOPAZ1
10	rs2710323	3	52,815,905	1.91×10^{-10}	0.971	0.005	C/T	0.48	0.49	NEK4, ITIH1, ITIH3, ITIH4, ITIH4-AS1
11	rs4856929	3	68,030,736	2.59×10^{-8}	0.047	0.008	T/C	0.87	0.88	SUCLG2-AS1, TAF41
12	rs72704544	4	176,853,286	4.37×10^{-10}	0.043	0.007	G/A	0.21	0.21	GPM6A
13	rs2066928	5	30,843,787	4.92×10^{-8}	0.974	0.005	A/G	0.49	0.51	–
14	rs77960	5	103,964,585	1.47×10^{-12}	0.037	0.005	A/G	0.32	0.31	–
15	rs288160	5	107,364,269	2.58×10^{-8}	0.973	0.005	T/C	0.32	0.33	FBXL17
16	rs11241568	5	120,140,556	8.77×10^{-13}	0.037	0.005	C/T	0.33	0.34	PRR16 (−67.5)
17	rs10476497	5	164,588,817	1.36×10^{-12}	0.034	0.005	A/G	0.54	0.55	–
18	rs58825580	6	26,365,679	6.64×10^{-15}	0.943	0.008	G/T	0.12	0.11	BTN3A2, BTN2A2, BTN3A1
19	rs9373363	6	143,150,043	1.57×10^{-8}	0.969	0.006	G/A	0.26	0.28	HIVEP2
20	rs12699332	7	12,269,762	5.75×10^{-9}	0.028	0.005	T/G	0.41	0.39	TMEM106B
21	rs2371365	7	82,506,898	1.77×10^{-8}	0.028	0.005	C/T	0.38	0.37	PCLO
22	rs4395923	8	65,569,387	4.34×10^{-10}	0.031	0.005	A/G	0.59	0.61	CYP7B1
23	rs4976976	8	143,311,653	1.20×10^{-12}	0.965	0.005	A/G	0.40	0.41	LINC00051, TSNARE1
24	rs10959883	9	11,519,984	6.21×10^{-13}	0.959	0.006	C/T	0.20	0.20	–
25	rs10961649	9	14,670,949	1.24×10^{-10}	0.033	0.005	T/C	0.32	0.31	ZDHHC21
26	rs13287777	9	26,719,411	8.74×10^{-9}	0.960	0.007	T/G	0.18	0.18	–
27	rs28474857	9	98,247,204	1.29×10^{-9}	0.048	0.008	T/C	0.10	0.11	PTCH1, LOC100507346
28	rs11599236	10	106,454,672	7.99×10^{-11}	0.968	0.005	C/T	0.41	0.42	SORCS3, SORCS3-AS1
29	rs2071754	11	31,812,582	2.65×10^{-8}	0.968	0.006	T/C	0.78	0.79	ELP4, PAX6, PAX6-AS1, PAUPAR
30	rs7121169	11	57,452,543	2.84×10^{-9}	0.034	0.006	A/G	0.33	0.34	MIR130A, YPEL4, CLP1, ZDHHC5, MED19, TMX2, TMX2-CTNND1
31	rs174560	11	61,581,764	2.15×10^{-8}	0.033	0.006	C/T	0.32	0.34	TMEM258, MIR611, FEN1, FADS1, MIR1908, FADS2
32	rs7110863	11	112,843,138	2.10×10^{-14}	0.039	0.005	G/A	0.44	0.49	LOC101928847, NCAM1
33	rs73034295	11	133,822,133	3.84×10^{-10}	0.963	0.006	A/G	0.22	0.24	IGSF9B
34	rs78120929	12	24,139,063	6.84×10^{-10}	0.955	0.008	C/T	0.11	0.11	SOX5
35	rs989657	12	24,166,426	2.95×10^{-10}	0.031	0.005	C/T	0.56	0.56	SOX5
36	rs61928096	12	53,780,633	3.60×10^{-10}	0.100	0.015	A/G	0.04	0.03	SP7, SP1, AMHR2
37	rs4382947	12	60,475,057	3.94×10^{-10}	0.969	0.005	A/G	0.42	0.41	–
38	rs6539062	12	103,552,910	2.04×10^{-8}	0.027	0.005	A/C	0.51	0.54	LOC101929058 (also known as C12orf42-AS1)
39	rs3847960	12	120,271,100	1.02×10^{-9}	0.036	0.006	A/T	0.63	0.64	CIT
40	rs544271348	12	120,320,793	2.09×10^{-8}	0.930	0.013	T/G	0.96	0.97	CIT
41	rs9534593	13	47,879,549	8.23×10^{-9}	0.973	0.005	G/A	0.44	0.44	–
42	rs7997746	13	54,020,455	1.31×10^{-8}	0.973	0.005	A/C	0.46	0.46	–
43	rs36119415	13	69,579,612	6.62×10^{-9}	0.954	0.008	T/G	0.10	0.10	–
44	rs870764	13	84,973,006	2.08×10^{-8}	0.031	0.006	A/G	0.73	0.74	LINC00333 (non-coding)
45	rs9556979	13	99,241,507	6.38×10^{-9}	0.032	0.005	G/T	0.32	0.32	STK24, STK24-AS1
46	rs61990288	14	42,074,726	8.70×10^{-9}	0.973	0.005	A/G	0.50	0.49	LRFN5
47	rs3007061	14	47,238,606	1.51×10^{-9}	0.031	0.005	C/T	0.62	0.63	–

Locus	Index SNP	CHR	Position (bp)	Pvalue	OR	s.e.	A1/A2	Freq. cases	Freq. controls	Closest genes (distance kb)
48	rs12588874	14	75,254,073	7.26×10^{-10}	0.029	0.005	A/G	0.53	0.51	FCF1, YLPM1
49	rs6574271	14	76,580,655	2.77×10^{-8}	0.973	0.005	C/T	0.45	0.46	IFT43, GPATCH2L
50	rs616695	16	77,105,587	9.03×10^{-9}	0.973	0.005	T/G	0.43	0.44	–
51	rs2289590	17	8,110,764	6.95×10^{-9}	0.029	0.005	A/C	0.59	0.61	VAMP2, TMEM107, SNORD118, MIR4521, BORCS6, AURKB, LINCOO324, CTC1, PFAS
52	rs8091977	18	31,359,414	9.18×10^{-9}	0.029	0.005	C/T	0.46	0.47	ASXL3
53	rs4801024	18	52,396,321	5.90×10^{-11}	0.038	0.006	G/T	0.75	0.74	RAB27B (49.4)
54	rs6047130	20	20,868,094	4.74×10^{-9}	0.958	0.007	T/C	0.12	0.13	–
55	rs12624433	20	44,680,853	9.43×10^{-9}	0.033	0.006	A/G	0.26	0.25	MMP9, SLC12A5-AS1, SLC12A5, NCOA5
56	rs2070865	21	40,715,519	9.93×10^{-10}	0.972	0.005	T/C	0.47	0.50	BRWD1, BRWD1-AS2, BRWD1-AS1, HMGN1, GET1, WRB-SH3BGR
57	rs7290074	22	30,922,642	3.19×10^{-8}	0.095	0.016	A/G	0.02	0.03	SDC4P, SEC14L4, SEC14L6, GAL3ST1, PES1
58	rs13056300	22	41,408,754	1.28×10^{-8}	0.032	0.006	C/T	0.27	0.28	RBX1, SNORD140 (10.9)

Index SNP, rs number of variant; CHR, chromosome; BP, base pair position (hg19); OR, odds ratio for allele 1; s.e., standard error; A1/A2, allele 1 and allele 2; Freq. cases, frequency of A1 in cases; Freq. controls, frequency of A1 in controls; Closest genes (distance kb), closest genes to the SNP with distance in kilobases in parentheses (if the SNP lies within the gene, no distance is given).

control procedures (rs72704544 and rs11599236). Considering the remaining 55 loci tested, all showed the same direction of effect as the primary GWAS, and 51 were significant at a Bonferroni-corrected P value of $P = 0.0009$ ($0.05 / 55$) (Supplementary Table 6). At the time of this analysis, only the MVP had published an ANX GWAS in a reasonably sized non-EUR sample (MVP-AFR: military ascertainment, AFR ancestry; 5,664 cases and 26,410 controls)³⁴. Analyzing those data, we compared the direction of effect and P values of association for our 58 lead SNPs to examine consistency with our EUR results (Supplementary Table 7). Among the 53 SNPs available in MVP-AFR, only 27 (50.9%) showed the same sign. Given differences in LD and allele frequency between EUR and AFR genomes, we also searched for the most significant SNP in a 50-kb window around each lead SNP in the MVP-AFR cohort. A total of 36 of these SNPs were nominally associated, but only two were significantly associated after adjustment for multiple testing.

We further compared our associations with those reported in previous ANX case–control GWAS^{31–34,37} (Supplementary Table 8). A recent GWAS using broader anxiety-related case–control and symptom-based phenotypes reported 40 EUR-ancestry significant SNPs⁴⁵; all but one showed the same direction of effect, while ten were also GWS in our analysis. Importantly, most of the associations in our GWAS are novel discoveries, with only 15 reported in prior ANX GWAS. We note that some of the previously identified SNPs are in LD with each other, and all previously published ANX GWAS partially overlap with our samples. Therefore, these are not independent replications but demonstrate the consistency of results when additional samples are incorporated.

To study the generalizability of our results across different ancestral groups, we tested the extent to which polygenic risk scores (PRS) derived from our GWAS (excluding UK datasets) predicted ANX in the UK Biobank for participants of EUR, AFR and South Asian ancestry (see Supplementary Table 9). The PRS predicted 2.27% of the variance ($P < 2.0 \times 10^{-16}$) in ANX liability for those of EUR ancestry, assuming a prevalence of 20%. The variance explained for those of South Asian and AFR ancestries was 1.94% ($P = 6.37 \times 10^{-5}$) and 0.54% ($P = 0.051$), respectively, revealing significant polygenic overlap across EUR and South Asian ancestries.

Characterization and functional annotation of GWAS SNPs

To identify potential causal variants, we conducted statistical fine mapping of our GWS loci using FINEMAP (v1.3.1) with stringent inclusion thresholds⁴⁶. This process identified six credible SNP sets defined as having a posterior probability of >0.95 and five or fewer SNPs per credible

set to avoid excessive false positive rates (Supplementary Table 10). The lead SNPs of these credible sets were located at the following chromosomal positions: 3:67,895,104 (within *SUCLG2-GT*), 10:104,654,873 (within *SORCS3*), 17:8,187,590 (near *TRI-AAT-5*) and 20:20,876,379 (near *KIZ*); and two within the major histocompatibility complex (MHC) region: 6:28,329,086 (within *ZSCAN3I*) and 6:30,170,699 (within *TRIM15*).

To examine the biological relevance of our GWS SNPs, we performed functional annotation in FUMA (v1.6.1) to link our GWS SNPs with expression quantitative trait loci (eQTL) and brain chromatin interaction (Hi-C) data. The results suggest that most of the identified loci were associated with established gene regulatory mechanisms (circos plots in Supplementary Figs. 68–87). Although these results on their own do not provide enough evidence for involvement of respective genes in the etiology of ANX, they add to a broader picture that includes our summary-data-based Mendelian randomization (SMR) and other analyses (Supplementary Table 20).

We conducted stratified LDSC to partition the heritability into different functional genetic annotations and cell types. As noted in Supplementary Table 11, the association signal is highly conserved across species and significantly enriched for introns, monomethylated and polyacetylated histone marks (H3K4me1 and H3K4ac) and DNase I hypersensitivity sites in both adult and fetal tissues. Similar to other psychiatric GWAS, our findings are enriched for certain non-coding features rather than coding regions. Cell-type-specific enrichment was observed for central nervous system structures, including multiple cortical and subcortical areas, as well as cervical spine.

We also examined whether genetic associations with ANX were enriched among transcriptomic profiles of human tissues and/or individual cell types, using FUMA (v1.6.1)⁴⁷. Tissue-enrichment analyses for general tissue types using data from the GTEx (v.8) consortium suggested that the expression patterns related to brain and pituitary tissues were significantly associated with the genetic risk of ANX ($P = 1.18 \times 10^{-13}$ and $P = 6.50 \times 10^{-5}$, respectively; Supplementary Table 12a and Supplementary Fig. 88). All individual brain tissues showed significant enrichment (Supplementary Table 12b and Supplementary Fig. 89), with cortex overall ($P = 2.62 \times 10^{-12}$) as well as frontal and anterior cingulate cortices and nucleus accumbens as most significant. At the level of individual cell types, we found a consistent association of GABAergic neurons with genetic variation associated with ANX (Supplementary Fig. 90). Our strongest association ($P = 3.24 \times 10^{-8}$) was found with GABAergic neuroblasts (via GSE76381)⁴⁸.

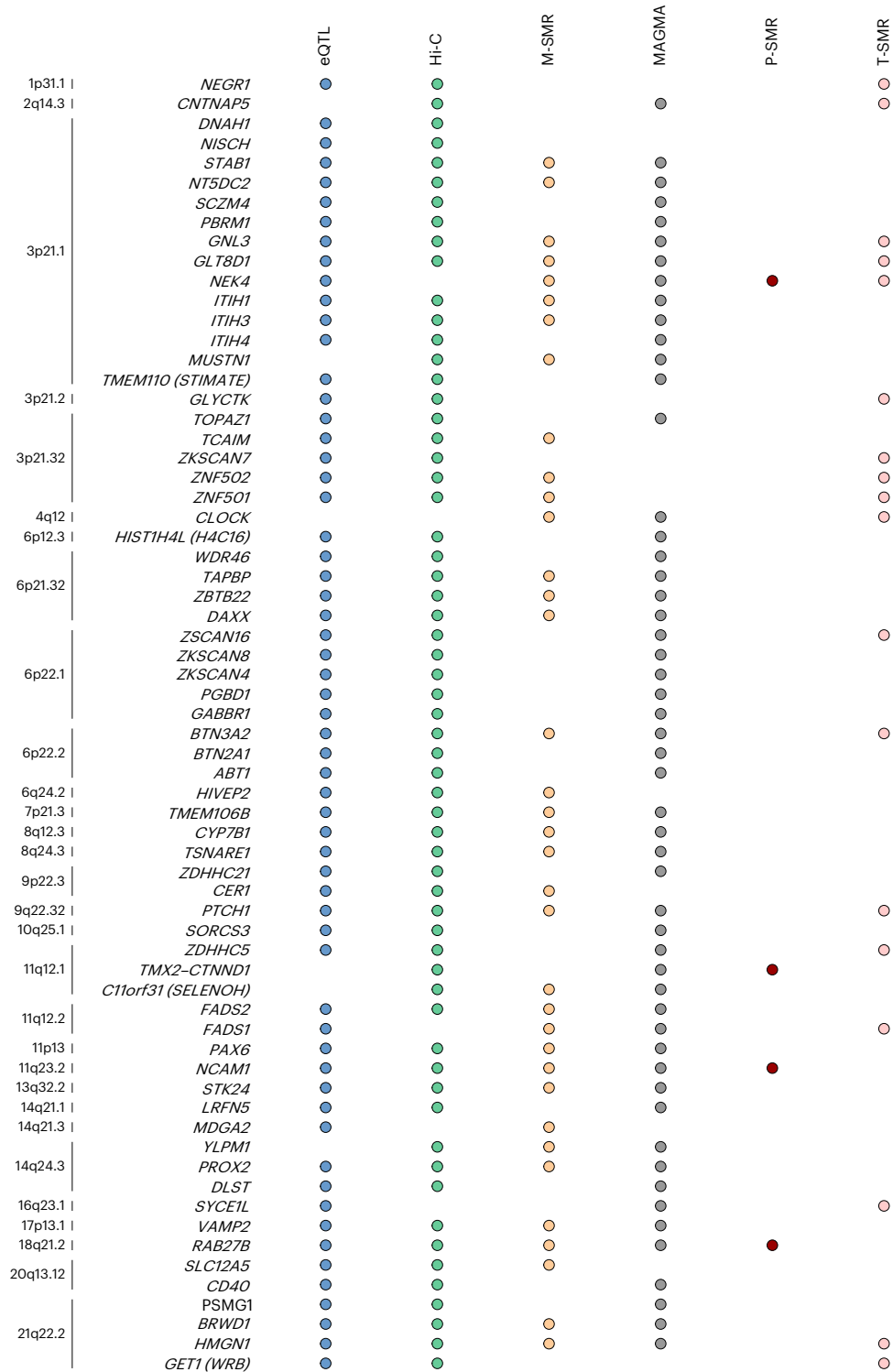


Fig. 2 | List of 66 most highly supported ANX genes. Genes that were implicated in at least three of the six SNP-based (eQTL, Hi-C) or gene-based (MAGMA, M-SMR, P-SMR, T-SMR) tests. The left side indicates the position of the gene in the genome. Significance is indicated by a colored dot. eQTL (blue dots) compares results from brain-related eQTL studies for overlap in significance between our GWAS and the eQTL studies. Hi-C (green dots) uses brain-related Hi-C information available through FUMA to functionally annotate our results.

MAGMA (gray dots) tests genetic associations at the gene level for the combined effect of SNPs in or near protein-coding genes. M-SMR, P-SMR and T-SMR (yellow, red and pink dots, respectively) refer to transcriptome-wide, proteome-wide and methylome-wide analyses that assessed likely causal associations between traits and genes, proteins and genomic regions by inferring the association between the trait and gene expression, protein concentration and methylation, as predicted from genomic data.

Gene-based association and enrichment

Using MAGMA (v.1.08)⁴⁹, we identified 91 significantly associated genes (adjusted $P < 0.05 / 18,490 = 2.7 \times 10^{-6}$; Supplementary Table 13). Historically interesting candidates include *CLOCK*, *GABBR1*, *PCLO*, *NCAM1* and *DRD2*.

To test whether our loci significantly co-localize with known functional QTLs, we used SMR⁵⁰ to conduct transcriptome-wide, proteome-wide and methylome-wide analyses (T-SMR, P-SMR and M-SMR, respectively). We used the largest available eQTL, protein QTL and

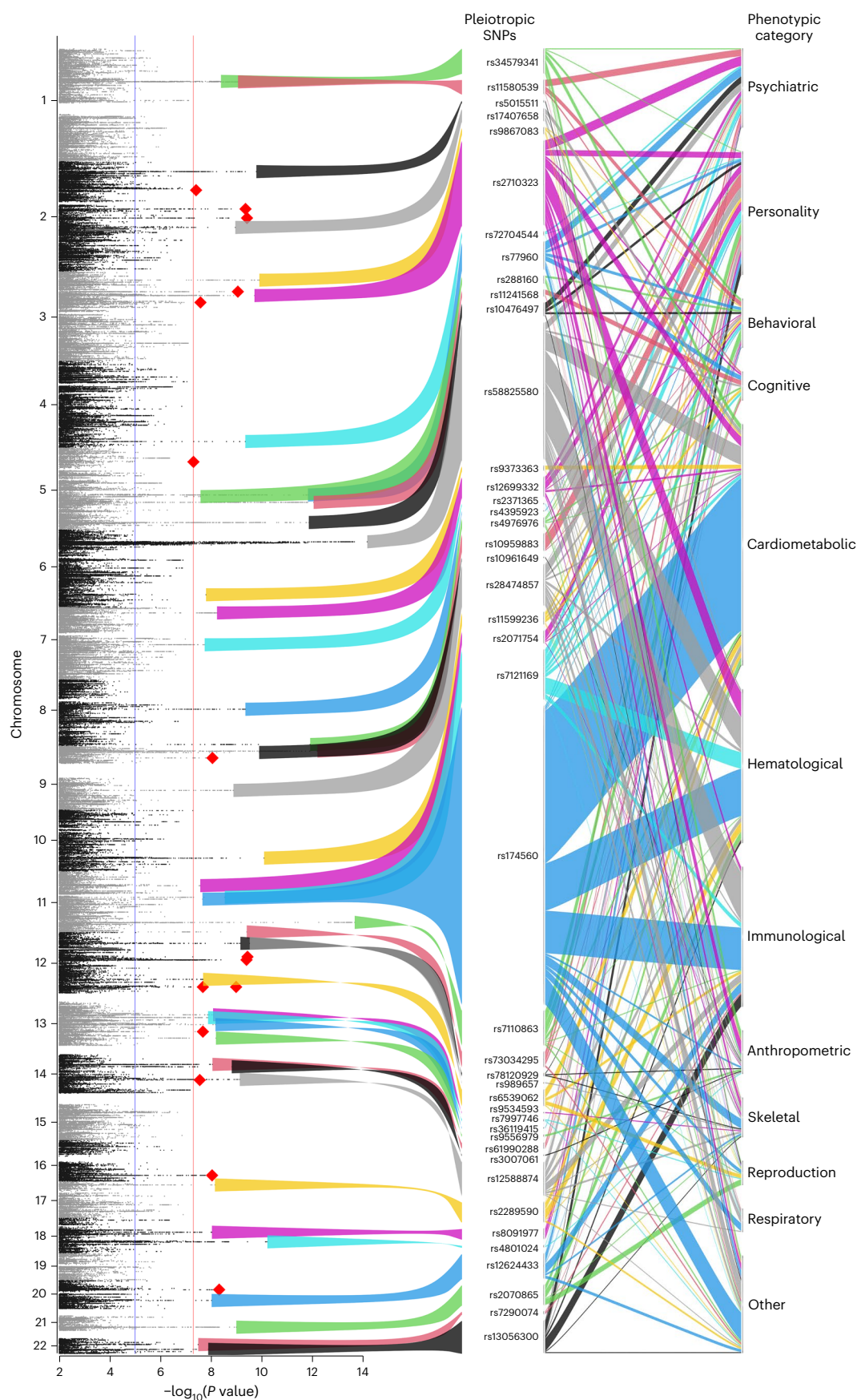


Fig. 3 | Overview of SNP associations with other phenotypes. The (rotated) Manhattan plot of the $-\log_{10}(P)$ values of the ANX meta-analysis (left; as in Fig. 1) and PheWAS alluvial plot of potentially pleiotropic variants (right). The colored ribbons depict variants that are associated with at least one other published

GWAS finding and correspond with the color of the ribbon in the alluvial plot. The red diamonds in the Manhattan plot depict the most significant variant in the region corresponding with potentially ANX-specific SNPs; that is, a variant that reached the GWS threshold for ANX but not in any other published GWAS.

methylation QTL reference datasets, respectively, for both brain and blood tissues (Supplementary Table 14). By using the conservative *P* values adjusted for the HEIDI test (see Methods), we detected 27 Bonferroni-corrected significant genes or isoforms in the brain associated with changes in the methylome, 16 in the transcriptome and seven in the proteome (Supplementary Tables 15–17). To improve signal detection in brain transcriptome and methylome data, we used Primo⁵¹ to jointly analyze blood and brain statistics (see ref. 52). We did not jointly analyze proteome data because of the low number of brain probes. These between-tissue concordance analyses yielded 22 significant ANX signals (posterior probability of >0.95) for the transcriptome and 133 for the methylome (Supplementary Tables 18 and 19). *BTN3A2* remains a leading signal in both analyses, and interesting sub-threshold genes from single-tissue analyses become strong findings in the joint T-SMR (*ZDHC5*, *FURIN* and *NEGR1*).

To highlight genes for which there was the strongest support, we summarized the findings across multiple (equally weighted) analyses in Supplementary Table 20, which includes an expanded set of 151 genes associated with ANX susceptibility. Starting with the 91 significant associations from MAGMA, we added genes supported by joint T-SMR or joint M-SMR with a posterior probability of >0.95. We annotated these using additional support from P-SMR, eQTL and Hi-C data. Figure 2 lists the 66 genes with three or more sources of support (score of ≥3). Most of these have prior reported associations with one or more psychiatric phenotypes, possibly suggesting gene-based pleiotropy, while a small proportion appear specific to ANX risk (reviewed in the Discussion).

To test whether pre-existing gene sets are enriched for our ANX risk loci, we examined 10,894 gene sets obtained from MsigDB (v.5.2) (curated gene sets, 4,728; Gene Ontology terms, 6,166). Specifically, we used MAGMA to test for enrichment of our ANX signals (see Supplementary Table 21). Overall, one gene set was significant after correction for multiple testing: *dawson_methylated_in_lymphoma_tcl1* ($P = 1.71 \times 10^{-6}$), including 57 genes that are hypermethylated in at least one of the lymphoma tumors in transgenic mice overexpressing *TCL1* in germinal center B lymphocytes; the top three genes were also supported by T-SMR or M-SMR (*NCAM1*, *HMGNI* and *ZDHC5*). On the surface, it is difficult to appreciate the relevance of this cancer gene pathway for anxiety etiology. We also note that the overlap between this gene set and MAGMA gene signals is small (three out of 54; namely, *NCAM1*, *HMGNI* and *ZDHC5*). Among the next highly associated sets were genes related to commissural neuron axon guidance ($P = 5.24 \times 10^{-5}$) and GABAergic synapse ($P = 9.67 \times 10^{-5}$), the latter with 66 genes, including *GABBR1*, *DRD2*, *CDH13* and *LRFN5*.

Gene–drug associations

To reveal possible drug repurposing opportunities for ANX, we used DrugTargetor⁵³ (v.1.3) with our main ANX summary statistics. Among the 161 drug classes analyzed, several that are already successfully being used for ANX treatment demonstrated significant associations (q value_{BF} < 0.05; Supplementary Table 22): psycholeptics (drugs with a calming effect) and psychoanaleptics (mostly antidepressants), as well as other sedating drugs like antihistamines, antipsychotics, general anesthetics and opioids. However, none of the more than 1,500 individual compounds cataloged in ChEMBL⁵⁴ and DgiDB⁵⁵ yielded a significant signal (Supplementary Table 23), possibly because of the moderate power of this GWAS.

Genetic overlap between ANX and other phenotypes

To examine the overlap between our ANX association signals and other phenotypes, we conducted a phenome-wide association study (PheWAS). Of the 58 SNPs significantly associated with ANX, 15 were deemed ANX-specific (red diamonds in Fig. 3); that is, variants not reported as GWS in other extant GWAS. A total of 43 variants were associated with at least one other phenotype. We note that the higher number of overlapping associations with cardiometabolic, hematological

and immunological outcomes reflects both the robust genetic architectures of these phenotypes and the number of GWAS that have been published in these domains. Overlap of ANX-related SNPs with cardiometabolic and hematological traits was heavily skewed towards a subset of variants (*rs2710323*, *rs58825580* and *rs174560*). Figure 4 depicts a dendrogram-based heatmap showing the association with psychiatric or personality traits among 24 possibly pleiotropic SNPs (other heatmaps for cognitive and behavioral domains are found in Supplementary Figs. 91 and 92). Not surprisingly, more ANX SNPs overlap with internalizing phenotypes (neuroticism, depression) than with psychotic disorders (schizophrenia, bipolar disorder).

We used bivariate LDSC to estimate the genetic correlations between ANX and a wide variety of other traits. We included 112 previously published GWAS on various traits, including psychiatric, substance use, cognition or socioeconomic status, personality, psychological, neurological, autoimmune, cardiovascular, anthropomorphic, dietary and fertility phenotypes. After false discovery rate correction, we found that 82 traits showed significant genetic correlation with ANX (Fig. 5 and Supplementary Table 24). Among the psychiatric disorders and traits, ANX showed the strongest correlations with MDD ($r_g = 0.91$), followed by childhood internalizing symptoms ($r_g = 0.76$), mood disturbance ($r_g = 0.76$), symptoms of depression ($r_g = 0.71$), post-traumatic stress disorder (PTSD) ($r_g = 0.71$), psychosis ($r_g = 0.68$), mania ($r_g = 0.66$), suicide attempt ($r_g = 0.58$) and obsessive–compulsive disorder ($r_g = 0.41$). Genetic correlations were also high with total neuroticism score ($r_g = 0.70$) and its various clusters and items. We found somewhat lower correlations with other psychiatric and substance-use disorders. ANX genetic risk was also modestly correlated with that of several neurological disorders, as well as adult-onset asthma and heart disease (positive) and inflammatory bowel diseases (negative). As shown in Supplementary Figs. 93 and 94 and Supplementary Table 24, the different ANX data subgroups show a variable but overall similar pattern of correlations.

These results highlight the complex interrelations between the three internalizing phenotypes that also have the highest genetic correlations with ANX: MDD⁵⁶, PTSD⁵⁷ and neuroticism³⁹. To examine potential directional effects underlying these correlations, we applied bi-directional generalized SMR (GSMR)⁵⁸ with the latest available GWAS summary statistics. These results (Supplementary Table 25) indicate a highly significant bi-directional effect between ANX and each of these phenotypes. Based on beta-values, the strength of reverse (MDD → ANX = 0.657) and forward (ANX → MDD = 0.545) effects are similar between ANX and MDD. However, both PTSD (PTSD → ANX = 0.891 vs ANX → PTSD = 0.239) and neuroticism (neuroticism → ANX = 1.25 vs ANX → neuroticism = 0.17) effects on ANX are stronger than the reverse.

Discussion

In this GWAS meta-analysis, we identified 58 independent genome-wide loci associated with anxiety risk by including data from a composite phenotype created from five lifetime anxiety disorders (36 cohorts including 122,341 ANX cases and 729,881 controls; $n_{\text{effective}} = 390,560$). Three-quarters of the identified variants are novel, with only 15 reported in prior anxiety GWAS. A total of 51 of these SNPs were replicated in an independent EUR-ancestry sample from 23andMe, strengthening their relevance. These results represent a major advance in identifying validated susceptibility loci for anxiety disorders.

The SNP-based heritability estimated at 10.1% captures approximately one-quarter of the broad-sense heritability from twin studies of adult ANX¹⁷, similar to other complex traits like MDD⁴⁰. We divided the cohorts into subgroups based on ascertainment and assessment strategies and conducted separate GWAS as a sensitivity test. We observed moderate to high genetic correlations between these subgroups, supporting our decision to combine all samples into a single meta-analysis. SNP-based heritability varied from 23.7% in the clinical subgroup to 6.9% in the community subgroup (ascertainment) and from 7.7% in

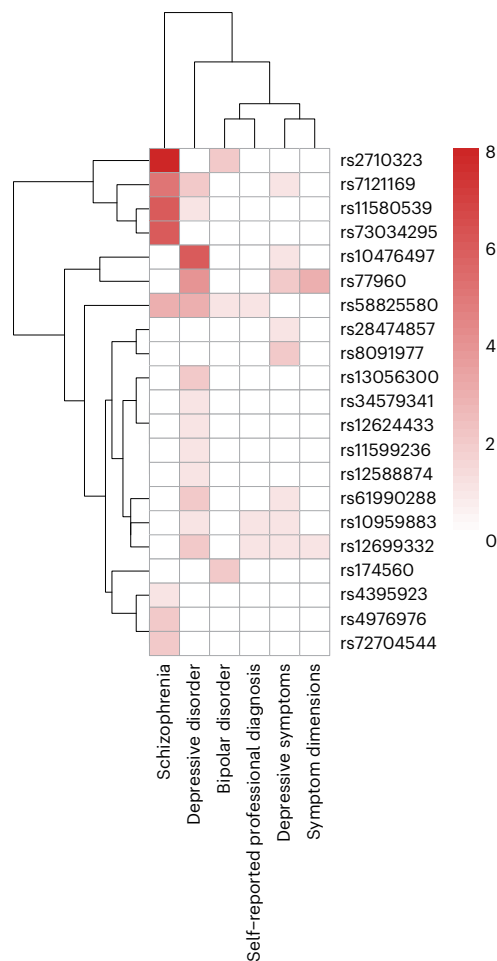


Fig. 4 | Heatmap of SNP associations with other psychiatric and personality traits. Dendrogram-based heatmap indicating the number of unique GWAS associations with psychiatric or personality traits among 24 SNPs that reach significance for multiple such phenotypes. Shading indicates the number of GWAS reporting associations between a specific SNP and the outcomes. Symptom dimensions (mood disturbance, mania, psychosis) and self-reported professional diagnoses (depression, anxiety, distress) are from the UK Biobank.

the interview subgroup to 13.2% in the ICD-10 subgroup (assessment), consistent with the hypothesis that more severe syndromes have higher heritability^{59–61}. The overall meta-analytic SNP heritability is probably diminished by the effects of heterogeneity across these subgroups.

Along with replication in an independent EUR cohort from 23andMe (51 loci replicated at a Bonferroni-corrected *P* value), we tested the transferability of our results. First, we examined replication in the MVP-AFR ancestry sample, in which nominally significant proxy loci were identified for 36 lead SNPs, but only two showed significant association after Bonferroni adjustment. This is not surprising given both ancestry and ascertainment differences. Second, we applied PRS to estimate the variance explained in ANX liability. The PRS explained 2.27% of the variance in EUR individuals, which is comparable to PRS reports of MDD⁴⁰. We then tested whether our findings would generalize to non-EUR samples. The EUR-ANX PRS explained 1.94% of the variance in the South Asian subsample of UK Biobank (significant) but only 0.54% for the AFR subsample (non-significant), in line with the low replication in the MVP-AFR ancestry cohort. This shows that for anxiety, as for other phenotypes, genetic liability estimated from EUR samples more closely reflects that of South Asian than AFR ancestry³¹. These findings stress the need for more diverse ancestry inclusion in future ANX GWAS.

Using LDSC, we found that, consistent with prior twin studies and extant GWAS, ANX shares the largest genetic overlap with MDD

($r_g = 0.91$), with which it has the highest lifetime comorbidity. This is followed by PTSD ($r_g = 0.71$), which is expected given their high comorbidity and the prior classification of PTSD among anxiety disorders⁶²; however, this correlation is over twice that estimated in an early twin study²⁸. The genetic correlation with neuroticism was similarly high ($r_g = 0.7$), reflecting that neuroticism is an important predisposing personality trait for both ANX and MDD. In addition, ANX shows moderate genetic correlations with ADHD ($r_g = 0.42$), obsessive-compulsive disorder ($r_g = 0.41$), schizophrenia ($r_g = 0.41$), bipolar disorder ($r_g = 0.34$) and anorexia nervosa ($r_g = 0.33$). ANX also correlates with childhood internalizing symptoms ($r_g = 0.76$), reflecting genetic continuity across development^{63,64}. Notably, ANX shows a substantial genetic correlation with suicide attempt ($r_g = 0.58$). This may be partly driven by comorbid depression, although ANX also independently increases suicide risk⁶⁵.

Follow-up Mendelian randomization (MR) analyses suggest bi-directional genetic effects between ANX and its strongest correlates: MDD, PTSD and neuroticism. Although ANX onset tends to precede MDD^{66,67}, some studies show mutual prediction over time^{68,69}. Our MR analyses support a stronger genetic causation of neuroticism on ANX, reflecting the stability of this personality trait⁷⁰ and its persistent relationship with psychiatric disorders⁷¹. Unexpectedly, MR suggests that PTSD is more likely to cause ANX, potentially owing to confounding (for example, diagnostic misclassification), ascertainment bias (PTSD presents with more severe symptoms) or because trauma can impact both disorders. These findings align with clinical experience that comorbid internalizing disorders exacerbate each other.

Gene-set and single-cell RNA expression analyses support GABAergic signaling as one potential mechanism underlying ANX genetic risk, supported by the efficacy of drugs like barbiturates and benzodiazepines in enhancing GABA neurotransmission. Indeed, the results of our gene-drug analysis included several classes of drugs that are already successfully used to relieve anxiety.

The PheWAS revealed that 43 SNPs identified in prior GWAS of other phenotypes overlap with ANX, highlighting extensive genetic sharing. The loci clustered into three categories: those affecting multiple medical, physiological and behavioral outcomes; those linked to psychiatric and behavioral phenotypes; and a small set specific to anxiety. Given the high comorbidity and genetic overlap of ANX with phenotypes like MDD or neuroticism, it is unsurprising that many of our loci have been reported in prior GWAS. However, most prior psychiatric GWAS did not exclude ANX, which may have influenced their findings. Notably, several loci—including four genes (*PAX6*, *PROX2*, *VAMP2* and *HMGNI*)—show strong evidence of association in our study but have not been reported in prior psychiatric GWAS (further discussed in Supplementary Note 4).

Seven of the 66 protein-coding genes associated with ANX risk (*ZNF502*, *ZNF501*, *STAB1*, *NTSDC2*, *GNL3*, *GLT8D1* and *NEK4*) are located on chromosome 3p21, a region previously linked to depression⁵⁶, schizophrenia⁷², bipolar disorder⁷³, suicide⁷⁴, amyotrophic lateral sclerosis⁷⁵ and neuroticism³⁹, making it a ‘hot spot’ for overall neuropsychiatric susceptibility. Although little is known about these seven genes in addition to their basic cellular functions, some are implicated in anxiety-like behaviors in rodents⁷⁶. Three genes (*TAPBP*, *ZBTB22* and *DAXX*) of the MHC region (chromosomal band 6p21.32) were also associated with ANX. These findings do not represent a definitive set of anxiety risk genes but instead provide a high-level summary of findings from multiple post-GWAS approaches, serving as a starting point for future studies.

Given similarly high lifetime prevalence, moderate twin-based heritability and extensive comorbidity, our ANX genetic results should be most comparable to those for MDD among all psychiatric diagnoses. Indeed, the authors of a previous publication⁴⁰ describe results from their PGC-MDD2 analyses that are highly similar to ours regarding the number of GWAS SNPs identified per effective sample size, SNP-based heritability, enrichment of non-exonic classes of variants and proportion of variance explained by PRS. These highly polygenic internalizing disorders require

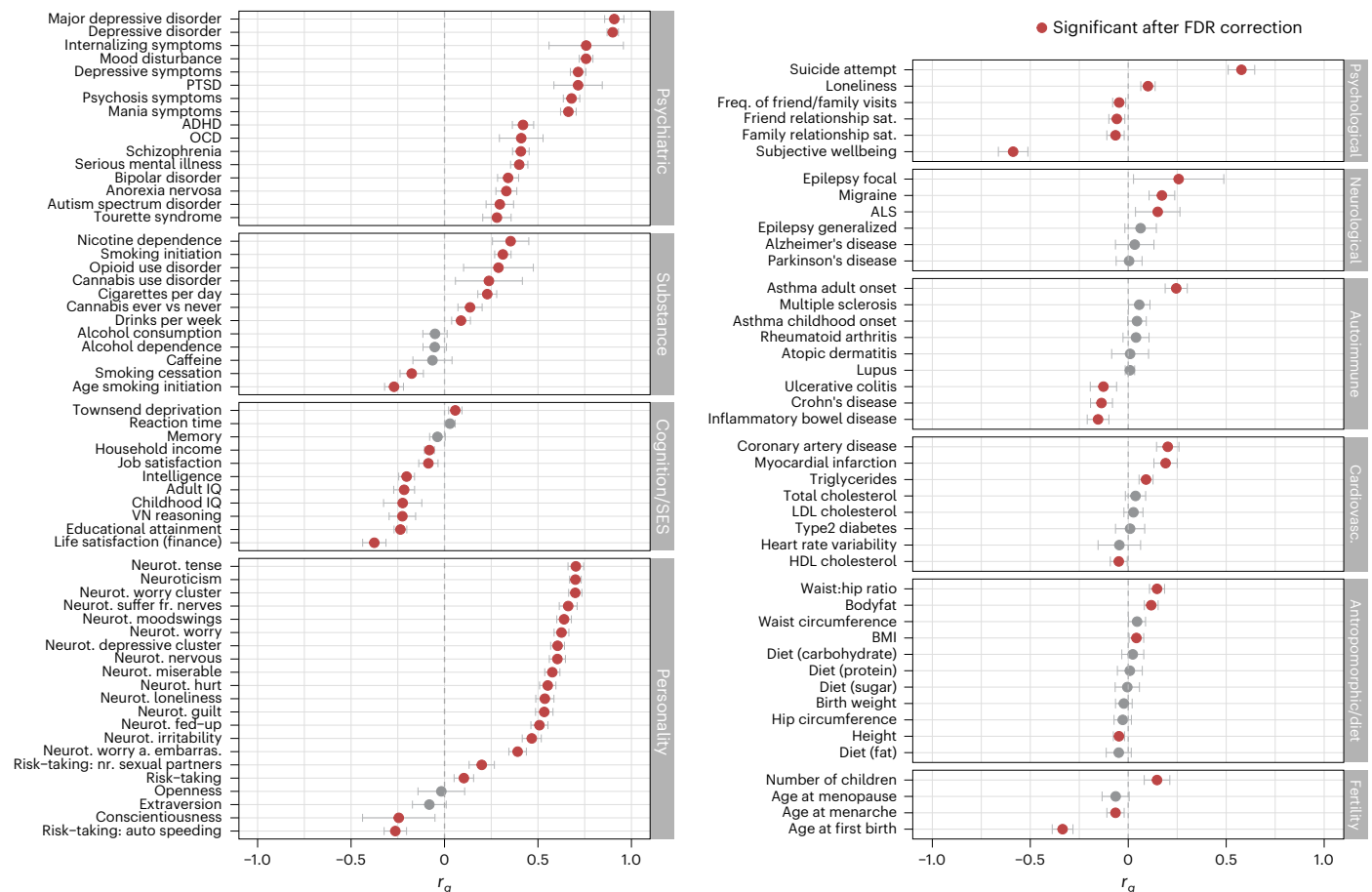


Fig. 5 | Genetic correlations (r_g) between the main ANX GWAS and 112 phenotypes. Genetic correlations (r_g) between ANX and psychiatric, substance use, cognition/socioeconomic status (SES), personality, psychological, neurological, autoimmune, cardiovascular, anthropomorphic/diet, fertility and other phenotypes. References and sample sizes of the corresponding summary statistics of the GWAS studies can be found in Supplementary Table 24. The ANX summary statistics are of the main meta-analysis ($n_{\text{cases}} = 122,341$; $n_{\text{controls}} = 729,881$). Red circles indicate significant associations with a P value

adjusted for multiple testing with the Benjamini–Hochberg procedure to control the false discovery rate (FDR < 0.05). Black circles indicate associations that are not significant. Error bars represent 95% confidence intervals for the genetic correlation estimates. ADHD, attention-deficit hyperactivity disorder; ALS, amyotrophic lateral sclerosis; BMI, body mass index; embarrass., embarrassment; freq., frequency; fr., from; HDL, high-density lipoprotein; LDL, low-density lipoprotein; neurot., neuroticism; nr., number; OCD, obsessive-compulsive disorder; sat., satisfaction.

massive sample sizes to detect association signals from the small effects of many common SNPs. From what we have learned about MDD and other complex psychiatric phenotypes, the 58 loci we report herein are probably ‘the tip of the iceberg’ among the many hundreds of loci presumed to underlie individual differences in ANX risk. Therefore, further genomic discovery efforts for ANX will demand even larger sample sizes.

This study has several potential limitations. First, heterogeneity in ANX case phenotype assessments—from structured psychiatric interviews to ICD clinical assignments to self-report diagnoses—limits the validity and power to detect susceptibility variants. There is often a trade-off between clinical validity and sample size^{61,77}, as seen in our largest samples, which had the lowest depth of phenotyping. Second, by collapsing across all five of the adult anxiety diagnoses, we increased phenotypic heterogeneity, making it impossible to pinpoint the genetic signals specific to any particular disorder. Future studies with large, well-phenotyped samples of individual diagnoses are needed to address this limitation. Additionally, genetic contributions to ANX may change over the lifespan, highlighting the importance of longitudinal studies. We allowed comorbid mood disorders in ANX cases but excluded them from controls. Although this was justifiable because of the strong genetic sharing between ANX and depression, it could indirectly inflate their genetic associations and complicate inferences of pleiotropy. Finally, limiting our meta-analysis to EUR

data reduces generalizability. We are working to aggregate data across ancestries for future multi-ancestry GWAS.

In summary, this study advances our understanding of the genetic basis of ANX by providing a foundation for future research into the biological mechanisms behind anxiety syndromes. It is our sincere hope that this opens new lines of investigation for expanding the clinical armamentarium of the next generation of clinicians who treat individuals affected by these conditions.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at <https://doi.org/10.1038/s41588-025-02485-8>.

References

1. Bandelow, B. et al. Biological markers for anxiety disorders, OCD and PTSD: a consensus statement. Part II: neurochemistry, neurophysiology and neurocognition. *World J. Biol. Psychiatry* **18**, 162–214 (2017).
2. Ask, H. et al. Genetic contributions to anxiety disorders: where we are and where we are heading. *Psychol. Med.* **51**, 2231–2246 (2021).

3. Ressler, K. J. Translating across circuits and genetics toward progress in fear- and anxiety-related disorders. *Am. J. Psychiatry* **177**, 214–222 (2020).
4. Craske, M. G. et al. Anxiety disorders. *Nat. Rev. Dis. Primers* **3**, 17024 (2017).
5. Hasin, D. S. & Grant, B. F. The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) Waves 1 and 2: review and summary of findings. *Soc. Psychiatry Psychiatr. Epidemiol.* **50**, 1609–1640 (2015).
6. Kessler, R. C., Petukhova, M., Sampson, N. A., Zaslavsky, A. M. & Wittchen, H.-U. Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. *Int. J. Methods Psychiatr. Res.* **21**, 169–184 (2012).
7. McGrath, J. J. et al. Age of onset and cumulative risk of mental disorders: a cross-national analysis of population surveys from 29 countries. *Lancet Psychiatry* **10**, 668–681 (2023).
8. Beesdo, K., Knappe, S. & Pine, D. S. Anxiety and anxiety disorders in children and adolescents: developmental issues and implications for DSM-V. *Psychiatr. Clin. North Am.* **32**, 483–524 (2009).
9. Rice, F., van den Bree, M. B. & Thapar, A. A population-based study of anxiety as a precursor for depression in childhood and adolescence. *BMC Psychiatry* **4**, 43 (2004).
10. Lemyre, A., Gauthier-Légaré, A. & Bélanger, R. E. Shyness, social anxiety, social anxiety disorder, and substance use among normative adolescent populations: a systematic review. *Am. J. Drug Alcohol Abuse* **45**, 230–247 (2019).
11. Kuhnt, S. et al. Twelve-month and lifetime prevalence of mental disorders in cancer patients. *Psychother. Psychosom.* **85**, 289–296 (2016).
12. Celano, C. M., Daunis, D. J., Lokko, H. N., Campbell, K. A. & Huffman, J. C. Anxiety disorders and cardiovascular disease. *Curr. Psychiatry Rep.* **18**, 101 (2016).
13. Zamani, M., Alizadeh-Tabari, S. & Zamani, V. Systematic review with meta-analysis: the prevalence of anxiety and depression in patients with irritable bowel syndrome. *Aliment. Pharmacol. Ther.* **50**, 132–143 (2019).
14. Delpino, F. M. et al. Prevalence of anxiety during the COVID-19 pandemic: a systematic review and meta-analysis of over 2 million people. *J. Affect. Disord.* **318**, 272–282 (2022).
15. Meier, S. M. et al. Increased mortality among people with anxiety disorders: total population study. *Br. J. Psychiatry* **209**, 216–221 (2016).
16. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* **392**, 1789–1858 (2018).
17. Hettema, J. M., Neale, M. C. & Kendler, K. S. A review and meta-analysis of the genetic epidemiology of anxiety disorders. *Am. J. Psychiatry* **158**, 1568–1578 (2001).
18. Hettema, J. M., Prescott, C. A., Myers, J. M., Neale, M. C. & Kendler, K. S. The structure of genetic and environmental risk factors for anxiety disorders in men and women. *Arch. Gen. Psychiatry* **62**, 182–189 (2005).
19. Waszczuk, M. A., Zavos, H. M. S., Gregory, A. M. & Eley, T. C. The phenotypic and genetic structure of depression and anxiety disorder symptoms in childhood, adolescence, and young adulthood. *JAMA Psychiatry* **71**, 905–916 (2014).
20. Carr, C. P., Martins, C. M. S., Stingel, A. M., Lemgruber, V. B. & Jurueña, M. F. The role of early life stress in adult psychiatric disorders: a systematic review according to childhood trauma subtypes. *J. Nerv. Ment. Dis.* **201**, 1007–1020 (2013).
21. Baldwin, J. R., Coleman, O., Francis, E. R. & Danese, A. Prospective and retrospective measures of child maltreatment and their association with psychopathology: a systematic review and meta-analysis. *JAMA Psychiatry* **81**, 769–781 (2024).
22. Zhang, J., Wiecek, P., Sami, S. & Meiser-Stedman, R. Association between panic disorder and childhood adversities: a systematic review and meta-analysis. *Psychol. Med.* **53**, 2585–2595 (2023).
23. Savage, J. E., Sawyers, C., Roberson-Nay, R. & Hettema, J. M. The genetics of anxiety-related negative valence system traits. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* **174**, 156–177 (2017).
24. Zavos, H. M. S., Rijdsdijk, F. V., Gregory, A. M. & Eley, T. C. Genetic influences on the cognitive biases associated with anxiety and depression symptoms in adolescents. *J. Affect. Disord.* **124**, 45–53 (2010).
25. Harrewijn, A. et al. Cortical and subcortical brain structure in generalized anxiety disorder: findings from 28 research sites in the ENIGMA-Anxiety Working Group. *Transl. Psychiatry* **11**, 502 (2021).
26. Mosing, M. A. et al. Genetic and environmental influences on the co-morbidity between depression, panic disorder, agoraphobia, and social phobia: a twin study. *Depress. Anxiety* **26**, 1004–1011 (2009).
27. Roy, M.-A., Neale, M. C., Pedersen, N. L., Mathé, A. A. & Kendler, K. S. A twin study of generalized anxiety disorder and major depression. *Psychol. Med.* **25**, 1037–1049 (1995).
28. Hettema, J. M., Neale, M. C., Myers, J. M., Prescott, C. A. & Kendler, K. S. A population-based twin study of the relationship between neuroticism and internalizing disorders. *Am. J. Psychiatry* **163**, 857–864 (2006).
29. Doering, S. et al. Anxiety symptoms preceding suicide: a Swedish nationwide record review. *J. Affect. Disord.* **355**, 317–324 (2024).
30. Campos, A. I. et al. Genomics-driven screening for causal determinants of suicide attempt. *Aust. N. Z. J. Psychiatry* **57**, 423–431 (2023).
31. Otowa, T. et al. Meta-analysis of genome-wide association studies of anxiety disorders. *Mol. Psychiatry* **21**, 1391–1399 (2016).
32. Purves, K. L. et al. A major role for common genetic variation in anxiety disorders. *Mol. Psychiatry* **25**, 3292–3303 (2020).
33. Meier, S. M. et al. Genetic variants associated with anxiety and stress-related disorders: a genome-wide association study and mouse-model study. *JAMA Psychiatry* **76**, 924–932 (2019).
34. Levey, D. F. et al. Reproducible genetic risk loci for anxiety: results from ~200,000 participants in the Million Veteran Program. *Am. J. Psychiatry* **177**, 223–232 (2020).
35. Hettema, J. M. et al. Genome-wide association study of shared liability to anxiety disorders in Army STARRS. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* **183**, 197–207 (2020).
36. Erhardt, A. et al. TMEM132D, a new candidate for anxiety phenotypes: evidence from human and mouse studies. *Mol. Psychiatry* **16**, 647–663 (2011).
37. Li, W. et al. Genome-wide meta-analysis, functional genomics and integrative analyses implicate new risk genes and therapeutic targets for anxiety disorders. *Nat. Hum. Behav.* **8**, 361–379 (2024).
38. Smith, D. J. et al. Genome-wide analysis of over 106 000 individuals identifies 9 neuroticism-associated loci. *Mol. Psychiatry* **21**, 749–757 (2016).
39. Nagel, M. et al. Meta-analysis of genome-wide association studies for neuroticism in 449,484 individuals identifies novel genetic loci and pathways. *Nat. Genet.* **50**, 920–927 (2018).
40. Wray, N. R. et al. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nat. Genet.* **50**, 668–681 (2018).
41. Forstner, A. J. et al. Genome-wide association study of panic disorder reveals genetic overlap with neuroticism and depression. *Mol. Psychiatry* **26**, 4179–4190 (2021).

42. Morneau-Vaillancourt, G. et al. The genetic and environmental hierarchical structure of anxiety and depression in the UK Biobank. *Depress. Anxiety* **37**, 512–520 (2020).
43. Grotzinger, A. D. et al. Genomic structural equation modelling provides insights into the multivariate genetic architecture of complex traits. *Nat. Hum. Behav.* **3**, 513–525 (2019).
44. Fürtjes, A. E. et al. General dimensions of human brain morphometry inferred from genome-wide association data. *Hum. Brain Mapp.* **44**, 3311–3323 (2023).
45. Friligkou, E. et al. Gene discovery and biological insights into anxiety disorders from a large-scale multi-ancestry genome-wide association study. *Nat. Genet.* **56**, 2036–2045 (2024).
46. Benner, C. et al. FINEMAP: efficient variable selection using summary data from genome-wide association studies. *Bioinformatics* **32**, 1493–1501 (2016).
47. Watanabe, K., Taskesen, E., van Bochoven, A. & Posthuma, D. Functional mapping and annotation of genetic associations with FUMA. *Nat. Commun.* **8**, 1826 (2017).
48. La Manno, G. et al. Molecular diversity of midbrain development in mouse, human, and stem cells. *Cell* **167**, 566–580.e19 (2016).
49. de Leeuw, C. A., Mooij, J. M., Heskes, T. & Posthuma, D. MAGMA: generalized gene-set analysis of GWAS data. *PLoS Comput. Biol.* **11**, e1004219 (2015).
50. Zhu, Z. et al. Integration of summary data from GWAS and eQTL studies predicts complex trait gene targets. *Nat. Genet.* **48**, 481–487 (2016).
51. Gleason, K. J., Yang, F., Pierce, B. L., He, X. & Chen, L. S. Primo: integration of multiple GWAS and omics QTL summary statistics for elucidation of molecular mechanisms of trait-associated SNPs and detection of pleiotropy in complex traits. *Genome Biol.* **21**, 236 (2020).
52. Gedik, H. et al. Identifying potential risk genes and pathways for neuropsychiatric and substance use disorders using intermediate molecular mediator information. *Front. Genet.* **14**, 1191264 (2023).
53. Gaspar, H. A., Hübel, C. & Breen, G. Drug Targetor: a web interface to investigate the human druggome for over 500 phenotypes. *Bioinformatics* **35**, 2515–2517 (2019).
54. Zdrazil, B. et al. The ChEMBL Database in 2023: a drug discovery platform spanning multiple bioactivity data types and time periods. *Nucleic Acids Res.* **52**, D1180–D1192 (2024).
55. Freshour, S. L. et al. Integration of the Drug–Gene Interaction Database (DGIdb 4.0) with open crowdsourcing efforts. *Nucleic Acids Res.* **49**, D1144–D1151 (2021).
56. Howard, D. M. et al. Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. *Nat. Neurosci.* **22**, 343–352 (2019).
57. Maihofer, A. X. et al. Enhancing discovery of genetic variants for posttraumatic stress disorder through integration of quantitative phenotypes and trauma exposure information. *Biol. Psychiatry* **91**, 626–636 (2022).
58. Zhu, Z. et al. Causal associations between risk factors and common diseases inferred from GWAS summary data. *Nat. Commun.* **9**, 224 (2018).
59. Low, N. C. P., Cui, L. & Merikangas, K. R. Community versus clinic sampling: effect on the familial aggregation of anxiety disorders. *Biol. Psychiatry* **63**, 884–890 (2008).
60. Wang, R., Snieder, H. & Hartman, C. A. Familial co-aggregation and shared heritability between depression, anxiety, obesity and substance use. *Transl. Psychiatry* **12**, 108 (2022).
61. Flint, J. The genetic basis of major depressive disorder. *Mol. Psychiatry* **28**, 2254–2265 (2023).
62. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders* 5th edn (American Psychiatric Publishing, 2013).
63. Kendler, K. S., Gardner, C. O., Annas, P. & Lichtenstein, P. The development of fears from early adolescence to young adulthood: a multivariate study. *Psychol. Med.* **38**, 1759–1769 (2008).
64. Waszczuk, M. A., Zavos, H. M. S., Gregory, A. M. & Eley, T. C. The stability and change of etiological influences on depression, anxiety symptoms and their co-occurrence across adolescence and young adulthood. *Psychol. Med.* **46**, 161–175 (2016).
65. Sareen, J. Anxiety disorders and risk for suicide: Why such controversy? *Depress. Anxiety* **28**, 941–945 (2011).
66. Wittchen, H. U., Kessler, R. C., Pfister, H. & Lieb, M. Why do people with anxiety disorders become depressed? A prospective-longitudinal community study. *Acta Psychiatr. Scand. Suppl.* **2000**, 14–23 (2000).
67. Kessler, R. C. et al. Comorbidity of DSM-III-R major depressive disorder in the general population: results from the US National Comorbidity Survey. *Br. J. Psychiatry Suppl.* **1996**, 17–30 (1996).
68. Kessler, R. C. et al. Lifetime co-morbidity of DSM-IV disorders in the US National Comorbidity Survey Replication Adolescent Supplement (NCS-A). *Psychol. Med.* **42**, 1997–2010 (2012).
69. Copeland, W. E., Shanahan, L., Costello, E. J. & Angold, A. Childhood and adolescent psychiatric disorders as predictors of young adult disorders. *Arch. Gen. Psychiatry* **66**, 764–772 (2009).
70. Viken, R. J., Rose, R. J., Kaprio, J. & Koskenvuo, M. A developmental genetic analysis of adult personality: extraversion and neuroticism from 18 to 59 years of age. *J. Pers. Soc. Psychol.* **66**, 722–730 (1994).
71. Jeronimus, B. F., Kotov, R., Riese, H. & Ormel, J. Neuroticism's prospective association with mental disorders halves after adjustment for baseline symptoms and psychiatric history, but the adjusted association hardly decays with time: a meta-analysis on 59 longitudinal/prospective studies with 443 313 participants. *Psychol. Med.* **46**, 2883–2906 (2016).
72. Trubetskoy, V. et al. Mapping genomic loci implicates genes and synaptic biology in schizophrenia. *Nature* **604**, 502–508 (2022).
73. Stahl, E. A. et al. Genome-wide association study identifies 30 loci associated with bipolar disorder. *Nat. Genet.* **51**, 793–803 (2019).
74. Han, S. et al. Whole-genome sequencing analysis of suicide deaths integrating brain-regulatory eQTLs data to identify risk loci and genes. *Mol. Psychiatry* **28**, 3909–3919 (2023).
75. Cooper-Knock, J. et al. Mutations in the glycosyltransferase domain of GLT8D1 are associated with familial amyotrophic lateral sclerosis. *Cell Rep* **26**, 2298–2306.e5 (2019).
76. Goulding, D. R. et al. Inter- α -inhibitor deficiency in the mouse is associated with alterations in anxiety-like behavior, exploration and social approach. *Genes Brain Behav.* **18**, e12505 (2019).
77. Cai, N. et al. Minimal phenotyping yields genome-wide association signals of low specificity for major depression. *Nat. Genet.* **52**, 437–447 (2020).

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

© The Author(s) 2026

Nora I. Strom^{1,2,3,4,134}, Brad Verhulst^{5,134}, Silviu-Alin Bacanu^{6,134}, Rosa Cheesman⁷, Kirstin L. Purves⁸, Hüseyin Gedik^{9,10,11}, Brittany L. Mitchell^{12,13}, Alex S. Kwong^{14,15}, Annika B. Faucon¹⁶, Kritika Singh^{17,18}, Sarah Medland¹², Lucia Colodro-Conde^{12,19}, Kristi Krebs²⁰, Per Hoffmann^{21,22}, Stefan Herms^{21,22,23}, Jan Gehlen²⁴, Stephan Ripke^{25,26}, Swapnil Awasthi²⁵, Teemu Palviainen²⁷, Elisa M. Tasanko²⁸, Roseann E. Peterson^{6,9}, Daniel E. Adkins²⁹, Andrey A. Shabalin²⁹, Mark J. Adams³⁰, Matthew H. Iveson³⁰, Archie Campbell³¹, Laurent F. Thomas^{32,33,34,35}, Bendik S. Winsvold^{36,37,38}, Ole Kristian Drange^{39,40,41,42,43}, Sigrid Børte^{37,44,45}, Abigail R. ter Kuile^{8,46,47}, Joonas Naamanka^{48,49}, Tan-Hoang Nguyen¹¹, Sandra M. Meier⁵⁰, Elizabeth C. Corfield^{51,52}, Laurie Hannigan^{51,52,53}, Daniel F. Levey^{54,55}, Darina Czamara⁵⁶, Heike Weber⁵⁷, Karmel W. Choi^{58,59}, Giorgio Pistis⁶⁰, Baptiste Couvy-Duchesne^{12,61,62}, Sandra Van der Auwera⁶³, Alexander Teumer^{63,64}, Robert Karlsson⁶⁵, Miguel Garcia-Argibay^{65,66}, Donghyung Lee⁶⁷, Rujia Wang⁶⁸, Ottar Bjerkset^{39,69}, Eystein Stordal^{39,70}, Julia Bäckman³, Giovanni A. Salum^{71,72}, Clement C. Zai^{73,74,75,76,77}, James L. Kennedy^{73,74,75}, Gwyneth Zai^{73,74,75}, Arun K. Tiwari^{73,74,75}, Stefanie Heilmann-Heimbach²¹, Børge Schmidt⁷⁸, Jaakko Kaprio²⁷, Martin M. Kennedy⁷⁹, Joseph Boden⁸⁰, Alexandra Havdahl^{71,4,51,53}, Christel M. Middeldorp^{81,82}, Fabiana L. Lopes^{83,84}, Nirmala Akula⁸⁵, Francis J. McMahon^{85,86}, Elisabeth B. Binder⁵⁶, Lydia Fehm⁸⁷, Andreas Ströhle⁸⁸, Enrique Castelao⁶⁰, Henning Tiemeier^{89,90}, Dan J. Stein⁹¹, David Whiteman⁹², Catherine Olsen⁹², Zachary Fuller⁹³, Xin Wang⁹³, Naomi R. Wray^{62,94}, Enda M. Byrne⁸¹, Glyn Lewis⁹⁵, Nicholas J. Timpson^{14,53}, Lea K. Davis¹⁷, Ian B. Hickie⁹⁶, Nathan A. Gillespie⁶, Lili Milani²⁰, Johannes Schumacher²⁴, David P. Woldbye⁹⁷, Andreas J. Forstner^{21,24,98}, Markus M. Nöthen²¹, Iiris Hovatta⁹⁹, John Horwood⁸⁰, William E. Copeland¹⁰⁰, Hermine H. Maes^{6,11,101}, Andrew M. McIntosh³⁰, Ole A. Andreassen^{41,42,102}, John-Anker Zwart^{37,44,45}, Ole Mors^{103,104}, Anders D. Børghlum^{4,104,105}, Preben B. Mortensen¹⁰⁶, Helga Ask^{7,51}, Ted Reichborn-Kjennerud^{41,51}, Jakob M. Najman¹⁰⁷, Murray B. Stein^{108,109}, Joel Gelernter^{55,110,111}, Yuri Milaneschi¹¹², Brenda W. Penninx¹¹², Dorret I. Boomsma^{113,114}, Eduard Maron^{115,116}, Angelika Erhardt-Lehmann^{56,117}, Christian Rück³, Tilo T. Kircher¹¹⁸, Christiane A. Melzig^{119,120}, Georg W. Alpers¹²¹, Volker Arolt¹²², Katharina Domschke^{123,124}, Jordan W. Smoller^{58,59}, Martin Preisig⁶⁰, Nicholas G. Martin¹², Michelle K. Lupton^{12,13,125}, Annemarie I. Luik¹²⁶, Andreas Reif¹²⁷, Hans J. Grabe⁶³, Henrik Larsson^{65,66}, Patrik K. Magnusson⁶⁵, Albertine J. Oldehinkel¹²⁸, Catharina A. Hartman¹²⁸, Jerome Breen⁸, Anna R. Docherty^{6,129,130}, Hilary Coon¹²⁹, Rupert Conrad¹³¹, Kelli Lehto²⁰, Veterans Affairs Million Veteran Program*, FinnGen*, 23andMe Research Team*, Jürgen Deckert^{117,135}✉, Thalia C. Eley^{8,135}✉, Manuel Mattheisen^{2,132,133,135}✉ & John M. Hettema^{5,135}✉

¹Department of Psychology, Humboldt-Universität zu Berlin, Berlin, Germany. ²Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Munich, Germany. ³Centre for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet & Stockholm Health Care Services, Region Stockholm, Stockholm, Sweden. ⁴Department of Biomedicine, Aarhus University, Aarhus, Denmark. ⁵Psychiatry and Behavioral Sciences, Texas A&M University, College Station, TX, USA. ⁶Psychiatry, Virginia Commonwealth University, Richmond, VA, USA. ⁷PROMENTA Centre, Department of Psychology, University of Oslo, Oslo, Norway. ⁸Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK. ⁹Institute for Genomics in Health, Department of Psychiatry and Behavioral Sciences, State University of New York Downstate Health Sciences University, Brooklyn, NY, USA. ¹⁰Life Sciences, Integrative Life Sciences Doctoral Program, Virginia Commonwealth University, Richmond, VA, USA. ¹¹Human and Molecular Genetics, Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University, Richmond, VA, USA. ¹²Brain and Mental Health Program, QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia. ¹³Faculty of Medicine, Queensland University, Brisbane, Queensland, Australia. ¹⁴Bristol Medical School, Population Health Sciences, MRC Integrative Epidemiology Unit, University of Bristol, Bristol, UK. ¹⁵Centre for Clinical Brain Sciences, Division of Psychiatry, University of Edinburgh, Edinburgh, UK. ¹⁶Division of Medicine, Human Genetics, Vanderbilt University, Nashville, TN, USA. ¹⁷Division of Genetic Medicine, Vanderbilt University Medical Center, Nashville, TN, USA. ¹⁸Vanderbilt Genetics Institute, Vanderbilt University Medical Center, Nashville, TN, USA. ¹⁹School of Psychology, The University of Queensland, Brisbane, Queensland, Australia. ²⁰Estonian Genome Centre, Institute of Genomics, University of Tartu, Tartu, Estonia. ²¹Institute of Human Genetics, University of Bonn, School of Medicine & University Hospital Bonn, Bonn, Germany. ²²Department of Biomedicine, Human Genomics Research Group, University of Basel; University Hospital Basel, Basel, Switzerland. ²³Institute of Medical Genetics and Pathology, Medical Faculty, University Hospital Basel, Basel, Switzerland. ²⁴Center for Human Genetics, University of Marburg, Marburg, Germany. ²⁵Department of Psychiatry and Psychotherapy, Charité - Universitätsmedizin, Berlin, Germany. ²⁶Analytic and Translational Genetics Unit, Massachusetts General Hospital, Boston, MA, USA. ²⁷Helsinki Institute of Life Science, Institute for Molecular Medicine Finland - FIMM, University of Helsinki, Helsinki, Finland. ²⁸Faculty of Medicine, Department of Psychology and Logopedics, SleepWell Research Program, University of Helsinki, Helsinki, Finland. ²⁹School of Medicine, Department of Psychiatry, University of Utah, Salt Lake City, UT, USA. ³⁰Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK. ³¹College of Medicine and Veterinary Medicine, Institute of Genetics and Cancer; Centre for Genomic and Experimental Medicine, University of Edinburgh, Edinburgh, UK. ³²Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway. ³³HUNT Center for Molecular and Clinical Epidemiology, Department of Public Health and Nursing, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway. ³⁴BioCore - Bioinformatics Core Facility, Norwegian University of Science and Technology, Trondheim, Norway. ³⁵Clinic of Laboratory Medicine, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway. ³⁶Division of Clinical Neuroscience, Department of Research and Innovation, Oslo University Hospital, Oslo, Norway. ³⁷Department of Public Health and Nursing, HUNT Center for Molecular and Clinical Epidemiology, Norwegian University of Science and Technology, Trondheim, Norway. ³⁸Department of Neurology, Oslo University Hospital, Oslo, Norway. ³⁹Department of Mental Health, Norwegian University of Science and Technology, Trondheim, Norway. ⁴⁰Division of Mental Health, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway. ⁴¹NORMENT Centre, University of Oslo, Oslo, Norway. ⁴²Centre of Precision Psychiatry, Division of Mental Health and Addiction, Oslo University Hospital and University of Oslo, Oslo, Norway. ⁴³Department of Psychiatry, Sørlandet Hospital, Kristiansand, Norway. ⁴⁴Division of Clinical Neuroscience, Department of

Research and Innovation; Musculoskeletal Health, Oslo University Hospital, Oslo, Norway. ⁴⁵Faculty of Medicine, Institute of Clinical Medicine, University of Oslo, Oslo, Norway. ⁴⁶National Institute for Health and Care Research (NIHR) Maudsley Biomedical Research Centre, South London and Maudsley NHS Foundation Trust, London, UK. ⁴⁷Department of Clinical, Educational and Health Psychology, University College London, London, UK. ⁴⁸Hector Institute for Artificial Intelligence in Psychiatry, Central Institute of Mental Health, Mannheim, Germany. ⁴⁹SleepWell Research Program, Faculty of Medicine, University of Helsinki, Helsinki, Finland. ⁵⁰Psychiatry, Dalhousie University, Halifax, Nova Scotia, Canada. ⁵¹PsychGen Centre for Genetic Epidemiology and Mental Health, Norwegian Institute of Public Health, Oslo, Norway. ⁵²Nic Waals Institute, Lovisenberg Diaconal Hospital, Oslo, Norway. ⁵³Bristol Medical School, Population Health Sciences, University of Bristol, Bristol, UK. ⁵⁴Department of Psychiatry, Division of Human Genetics, Yale University School of Medicine, New Haven, CT, USA. ⁵⁵Psychiatry, Research, Veterans Affairs Connecticut Healthcare System, West Haven, CT, USA. ⁵⁶Department of Genes and Environment, Max Planck Institute of Psychiatry, Munich, Germany. ⁵⁷Department of Psychiatry, Psychosomatics and Psychotherapy, University Hospital of Würzburg, Würzburg, Germany. ⁵⁸Psychiatry, Center for Precision Psychiatry, Massachusetts General Hospital, Boston, MA, USA. ⁵⁹Psychiatry, Psychiatric and Neurodevelopmental Genetics Unit, Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA, USA. ⁶⁰Psychiatric Epidemiology and Psychopathology Research Center, Department of Psychiatry, Lausanne University Hospital and University of Lausanne, Prilly, Switzerland. ⁶¹ARAMIS laboratory, Paris Brain Institute, Paris, France. ⁶²Institute for Molecular Bioscience, University of Queensland, Brisbane, Queensland, Australia. ⁶³Department of Psychiatry and Psychotherapy, University Medicine Greifswald, Greifswald, Germany. ⁶⁴Institute for Community Medicine, University Medicine Greifswald, Greifswald, Germany. ⁶⁵Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden. ⁶⁶School of Medical Sciences, Faculty of Medicine and Health, Örebro University, Örebro, Sweden. ⁶⁷Department of Statistics, Miami University, Oxford, OH, USA. ⁶⁸Social, Genetic, and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK. ⁶⁹Faculty of Nursing and Health Science, Nord University, Levanger, Norway. ⁷⁰Department of Psychiatry, Hospital Namsos, Nord-Trøndelag Health Trust, Namsos, Norway. ⁷¹Department of Psychiatry, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil. ⁷²Child Psychiatry, National Institute of Developmental Psychiatry, São Paulo, Brazil. ⁷³Tanenbaum Centre for Pharmacogenetics, Molecular Brain Sciences Department, Campbell Family Mental Health Institute, Centre for Addiction and Mental Health, Toronto, Ontario, Canada. ⁷⁴Department of Psychiatry, Division of Neurosciences and Clinical Translation, University of Toronto, Toronto, Ontario, Canada. ⁷⁵Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada. ⁷⁶Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario, Canada. ⁷⁷Stanley Center for Psychiatric Research, Broad Institute of Harvard and MIT, Cambridge, MA, USA. ⁷⁸Institute for Medical Informatics, Biometry and Epidemiology, University Hospital of Essen, University of Duisburg-Essen, Essen, Germany. ⁷⁹Pathology and Biomedical Science, University of Otago, Christchurch, New Zealand. ⁸⁰Psychological Medicine, University of Otago, Christchurch, New Zealand. ⁸¹Child Health Research Centre, University of Queensland, Brisbane, Queensland, Australia. ⁸²Child and Youth Mental Health Service, Children's Health Queensland Hospital and Health Service, Brisbane, Queensland, Australia. ⁸³National Institute of Mental Health, Human Genetics Branch, National Institutes of Health, Bethesda, MD, USA. ⁸⁴Department of Psychiatry and Human Behavior, Alpert Medical School of Brown University, Providence, RI, USA. ⁸⁵National Institute of Mental Health, Genetic Basis of Mood and Anxiety Disorders, National Institutes of Health, Bethesda, MA, USA. ⁸⁶Psychiatry & Behavioral Sciences, Johns Hopkins University, Baltimore, MA, USA. ⁸⁷Department of Psychology, Zentrum für Psychotherapie, Humboldt-Universität zu Berlin, Berlin, Germany. ⁸⁸Department of Psychiatry and Psychotherapy, Campus Charité Mitte, Charité - Universitätsmedizin Berlin, Corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany. ⁸⁹Social and Behavioral Science, T.H. Chan School of Public Health, Harvard University, Boston, MA, USA. ⁹⁰Child and Adolescent Psychiatry, Erasmus University Medical Center, Rotterdam, Netherlands. ⁹¹SAMRC Unit on Risk & Resilience in Mental Disorders, Department of Psychiatry & Neuroscience Institute, University of Cape Town, Cape Town, South Africa. ⁹²Population Health Program, QIMR Berghofer Medical Research Institute, Brisbane, Australia. ⁹³23andMe, Sunnyvale, CA, USA. ⁹⁴Department of Psychiatry, University of Oxford, Oxford, UK. ⁹⁵UCL Division of Psychiatry, University College London, London, UK. ⁹⁶Brain and Mind Centre, University of Sydney, Sydney, New South Wales, Australia. ⁹⁷Department of Neuroscience, Laboratory of Neural Plasticity, University of Copenhagen, Copenhagen, Denmark. ⁹⁸Institute of Neuroscience and Medicine (INM-1), Research Center Jülich, Jülich, Germany. ⁹⁹Faculty of Medicine, Department of Psychology and Logopedics and SleepWell Research Program, University of Helsinki, Helsinki, Finland. ¹⁰⁰UVM Medical Center, Department of Psychiatry, University of Vermont, Burlington, VT, USA. ¹⁰¹Massey Cancer Center, Virginia Commonwealth University, Richmond, VA, USA. ¹⁰²K. G. Jebsen Center for Neurodevelopmental disorders, University of Oslo, Oslo, Norway. ¹⁰³Department of Psychiatry, Psychosis Research Unit, Aarhus University Hospital, Aarhus, Denmark. ¹⁰⁴The Lundbeck Foundation Initiative for Integrative Psychiatric Research, iPSYCH, Aarhus University, Aarhus, Denmark. ¹⁰⁵Center for Genomics and Personalised Medicine, Aarhus University, Aarhus, Denmark. ¹⁰⁶The National Centre for Register-based Research, Aarhus University, Aarhus, Denmark. ¹⁰⁷Faculty of Medicine, School of Public Health, University of Queensland, Herston, Queensland, Australia. ¹⁰⁸Psychiatry, University of California San Diego, La Jolla, CA, USA. ¹⁰⁹School of Public Health, University of California San Diego, La Jolla, CA, USA. ¹¹⁰Psychiatry Research, Veterans Affairs Connecticut Healthcare System, West Haven, CT, USA. ¹¹¹Departments of Genetics and Neuroscience, Yale University of Medicine, New Haven, CT, USA. ¹¹²Amsterdam Neuroscience; Amsterdam Public Health, Amsterdam University Medical Center, Amsterdam, The Netherlands. ¹¹³Twin Register and Department of Complex Trait Genetics, Center for Neurogenomics and Cognitive Research, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands. ¹¹⁴Amsterdam Public Health, Amsterdam University Medical Center, Amsterdam, The Netherlands. ¹¹⁵Centre for Digital Health: Department of Health Technologies, Tallinn University of Technology, Tallinn, Estonia. ¹¹⁶Department of Medicine, Centre for Neuropsychopharmacology, Division of Brain Sciences, Imperial College London, London, UK. ¹¹⁷Department of Psychiatry, Psychosomatics and Psychotherapy, Center of Mental Health, University Hospital Würzburg, Würzburg, Germany. ¹¹⁸Department of Psychiatry, University of Marburg, Marburg, Germany. ¹¹⁹Psychology, Clinical Psychology, Experimental Psychopathology and Psychotherapy, University of Marburg, Marburg, Germany. ¹²⁰Psychology, Biological and Clinical Psychology, University of Greifswald, Greifswald, Germany. ¹²¹School of Social Sciences, Department of Psychology, University of Mannheim, Mannheim, Germany. ¹²²Department of Mental Health, Institute for Translational Psychiatry, University of Muenster, Muenster, Germany. ¹²³Department of Psychiatry and Psychotherapy, Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany. ¹²⁴German Center for Mental Health (DZPG), Partner Site Berlin, Berlin, Germany. ¹²⁵Faculty of Health, Queensland University of Technology, Brisbane, Queensland, Australia. ¹²⁶Epidemiology, Erasmus University Medical Center, Rotterdam, The Netherlands. ¹²⁷Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, University Hospital Frankfurt - Goethe University, Frankfurt, Germany. ¹²⁸Psychiatry, Interdisciplinary Center Psychopathology and Emotion Regulation, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands. ¹²⁹School of Medicine, Psychiatry, University of Utah, Salt Lake City, UT, USA. ¹³⁰School of Medicine, Psychiatry; Huntsman Mental Health Institute, University of Utah, Salt Lake City, UT, USA. ¹³¹Department of Psychosomatic Medicine and Psychotherapy, University Hospital Münster, Münster, Germany. ¹³²Community Health and Epidemiology, Dalhousie University, Halifax, Nova Scotia, Canada. ¹³³Computer Science, Dalhousie University, Halifax, Nova Scotia, Canada. ¹³⁴These authors contributed equally: Nora I. Strom, Brad Verhulst, Silviu-Alin Bacanu. ¹³⁵These authors jointly supervised this work: Jürgen Deckert, Thalia C. Eley, Manuel Mattheisen, John M. Hettema. *A list of authors and their affiliations appears at the end of the paper. ✉e-mail: deckert_j@ukw.de; thalia.eley@kcl.ac.uk; manuel.mattheisen@dal.ca; hettema@tamu.edu

Veterans Affairs Million Veteran Program

Daniel F. Levey^{54,55}, Murray B. Stein^{108,109} & Joel Gelernter^{55,110,111}

FinnGen

Joonas Naamanka^{48,49}, Teemu Palviainen²⁷, Elisa M. Tasanko²⁸, Jaakko Kaprio²⁷ & Iiris Hovatta⁹⁹

23andMe Research Team

Zachary Fuller⁹³ & Xin Wang⁹³

Methods

Ethics

All relevant ethics approvals have been obtained by the respective cohort's institutions, and a list of all respective approvals can be found in Supplementary Note 1.

Samples

To maximize sample size and power, we assigned the composite Any Anxiety case status if a participant had at least one of five core adult ANX across their lifetime: GAD, panic disorder, social phobia, agoraphobia or specific phobias. This amounts to identifying common genetic effects shared across these disorders. We did not exclude comorbid mood or other anxiety-related disorders in the cases. Controls had no lifetime anxiety disorder. Owing to the genetic overlap between ANX and depression^{78,79}, we excluded controls if they had a lifetime comorbid mood disorder like MDD or bipolar disorder. We excluded individuals with a diagnosis of severe mental health conditions such as schizophrenia, autism or intellectual disability. As much as possible, we uniformly applied these criteria across the 36 samples included in this study (Supplementary Table 1). However, like most large-scale psychiatric GWAS, these samples were ascertained and assessed with variable approaches that introduce known and cryptic sources of heterogeneity (see Supplementary Note 2 for details of each study). With the aim to address phenotypic heterogeneity, we classified each of the 36 cohorts into five ascertainment subgroups (clinical, biobank, community, SRPD and comorbid) and three assessment subgroups (interview, ICD-10, biobank); see Supplementary Table 1 and Supplementary Note 3.

Our subsequent analyses fall into six categories, which are described in detail below. These include (1) core GWAS, SNP heritability and sensitivity analyses including differences between ascertainment and assessment groups; (2) replication and validation of the GWAS SNPs; (3) characterization and functional annotation of the significant SNPs, (4) gene-based associations and enrichment; (5) gene–drug associations; and (6) genetic associations and pleiotropy shared with other traits.

GWAS, SNP-based heritability and sensitivity analyses

Genetic data processing and individual GWAS analyses. Each dataset was imputed using either the Haplotype Reference Consortium⁸⁰ or the 1000 Genomes Project Phase 3 (ref. 81) reference panels, and a GWAS was conducted for each (Supplementary Note 2 for details). The results from the individual GWAS were then harmonized and transformed to ‘daner’ file format following Rapid Imputation and COMputational PIPEline for GWAS (RICOPILI)⁸² specifications. Details of harmonization, alignment and filtering can be found at the end of Supplementary Note 2. Sumstats further used DENTIST as a quality control measure⁸³.

GWAS meta-analysis. The GWAS meta-analysis was performed on over 7.2 million autosomal SNPs across the 36 cohorts using inverse-variance weighting in METAL⁸⁴ within RICOPILI. Heterogeneity between the studies was evaluated using Cochran's Q and I^2 statistics (see Supplementary Note 2). To distinguish polygenicity from other causes of genomic inflation, we calculated the LDSC⁸⁵ intercept using the summary statistics for the high-quality common SNPs (INFO score of >0.9) from the meta-analysis. The GWS threshold for association was set at $P < 5 \times 10^{-8}$. Automated LD-based ‘clumping’ of GWS SNPs was conducted in RICOPILI using PLINK to facilitate identification of independently associated loci. We defined LD-independent SNPs as those with low LD ($r^2 < 0.1$) to a more significantly associated SNP within a 500-kb window. When loci contained several significant SNPs, the SNP with the lowest P value in each locus was selected as the lead SNP reported here. In addition to the main meta-analysis, we meta-analyzed similar datasets together according to the subgroup assignments described above.

Internal consistency of the ANX phenotype—sensitivity analyses of ANX ascertainment and assessment subgroups. *SNP-based heritability estimation and genetic correlations.* We used LDSC⁸⁶ to calculate the SNP-based heritability of the overall meta-analysis and the subgroup meta-analyses. Additionally, we used cross-trait LDSC to compute pairwise genetic correlations among the subgroups. SNP-based heritability was estimated from the slope of the LDSC on the liability scale, assuming a 20% population prevalence of ANX. To avoid a downward bias in our liability scale heritability estimates, the effective sample size across the contributing cohorts was calculated and used as the input sample size for LDSC⁸⁷. The sample prevalence was then specified as 0.5 for the conversion to the liability scale. Genetic correlation is calculated by estimating the slope from regressing the product of the Z -scores from two separate GWAS onto the LD score. It reflects the genetic covariation between two traits that is captured by all SNPs included in the GWAS. For both heritability estimation and genetic correlation analysis, we used pre-calculated LD scores from samples of EUR in the 1000 Genomes Project, which were filtered for SNPs present in the HapMap3 reference panel.

paLDSC. The paLDSC function⁴⁴ in GenomicSEM was used to determine the number of non-spurious dimensions in exploratory genomic factor analysis. This is achieved by comparing the eigenvalues obtained from the eigendecomposition of the LDSC genetic correlation matrix to those derived from a Monte Carlo-simulated null correlation matrix, whereby random noise is drawn from the multivariate LDSC sampling distribution. The suggested number of factors to be extracted corresponds with an eigenvalue exceeding a pre-specified percentile from the corresponding distribution of eigenvalues generated under the null.

GenomicSEM 1-factor model. To extend the genetic correlation analysis, we used genomic structural equation modeling (GenomicSEM)⁴³ to model the genetic architecture of the ascertainment and assessment subgroups. We conducted an exploratory factor analysis first, followed by a confirmatory factor analysis. To conduct these analyses, first, the summary statistics were harmonized and filtered (with the munge-function) using HapMap3 as the reference file, with the effective sample size as the input sample size and SNPs filtered to INFO > 0.9 and MAF > 0.01 . Second, multivariable LDSC was run to obtain the genetic covariance matrix and corresponding sampling covariance matrix using pre-computed EUR-ancestry LD scores. Third, we conducted exploratory factor analysis followed by confirmatory factor analysis using the pre-packaged common factor model in GenomicSEM using diagonally weighted least squares estimation.

Replication and validation of GWAS SNPs

Replications. Lead SNPs from the primary GWAS were tested for replication in the 23andMe commercial database using 1,175,012 self-reported ANX cases and 1,956,379 controls. Self-reported ANX cases were individuals who checked ‘anxiety’ in response to either of the following survey questions: “Have you ever been diagnosed with any of the following...” or “What mental health problems have you had? Please check all that apply”. This GWAS excluded close relatives (excluded cases, 13,801; excluded controls, 21,454) and an additional 35,255 samples (1.1%) because of consent restrictions (as of June 9, 2023). We performed logistic regression, assuming an additive model for allelic effects after covarying for age, sex, the first five principal components and genotyping platform. Previous work has demonstrated that the first five principal components in the 23andMe dataset explain more variance than the first ten principal components from the UK BioBank⁸⁶. The P values were adjusted using the standard genomic control procedure⁸⁸ in which the chi-squared test statistic is divided by the genome-wide estimated lambda inflation factor, $\lambda = 1.491$ (s.e. = 0.024). The estimated SNP heritability was $h^2 = 0.088$ (s.e. = 0.002), consistent with the estimate from our discovery GWAS.

Furthermore, we conducted a replication analysis of our 58 ANX-associated SNPs in an independent AFR sample from MVP comprising 5,664 ANX cases and 26,410 controls. Initially, we assessed the association results of the same 58 SNPs that reached significance in our main EUR-ancestry GWAS. Recognizing that the lead SNP might not necessarily be the causal SNP in this region and considering the differing LD structures between the EUR and AFR ancestry groups, we anticipated that the same SNP might not exhibit significant association. However, the genomic region might still be associated in AFR samples. Therefore, we performed a second look-up to identify the most significant SNP within a 50-kb window (± 25 kb) to accommodate potential differences in LD across EUR and AFR ancestries (proxy loci). LD between AFR and EUR populations was evaluated using r^2 and D' metrics (as reported on <https://ldlink.nih.gov>). We considered replication significant at a Bonferroni-corrected significance threshold of 8.62×10^{-4} ($0.05/58$).

To evaluate the consistency of previously reported ANX-associated SNPs, we performed a look-up of those SNPs in our main GWAS meta-analysis. We restricted the look-up to prior findings from case-control GWAS (as opposed to dimensional, symptom-based GWAS). Of note is that none of the previously published ANX GWAS are completely independent of our sample but are partially overlapping.

PRS analyses. We validated our results with PRS analyses in independent UK Biobank samples after removing all UK-based samples (UK Biobank and Generation Scotland) from the primary GWAS. We defined ANX cases as meeting one of the following three criteria: (1) a likely lifetime DSM-IV GAD diagnosis based on the anxiety-related questions from the Composite International Diagnostic Interview short-form questionnaire⁸⁹ and the first UK Biobank Mental Health Questionnaire⁹⁰; (2) SRPD of one of the five core anxiety disorders (GAD, panic disorder, social phobia, agoraphobia, specific phobia; first and second UK Biobank Mental Health Questionnaires); or (3) having a GAD-7 score⁹¹ of ≥ 10 , reflecting anxiety symptoms over the past 2 weeks (first and second UK Biobank Mental Health Questionnaires). Controls were defined in the same ways as the primary GWAS. We grouped individuals into three ancestry groups: EUR, AFR and South Asian.

We calculated PRS using MegaPRS⁹² within the GenoPred⁹³ pipeline, which implements polygenic scoring approaches using the LDKA heritability model, whereby the variance explained by each SNP depends on its allele frequency, LD and functional annotations. Logistic regression was run to estimate the PRS prediction effect for ANX, adjusting for genotyping batch, assessment center and ten genetic principal components.

Characterization and functional annotation of GWAS SNPs

We conducted variant fine-mapping and functional annotation (described in detail below). Note that although some gene prioritization approaches (for example, MAGMA, eQTL-based analyses, T-SMR) use different underlying statistical algorithms, they rely on overlapping expression datasets such as GTEx and PsychENCODE. Although eQTL uses only significant functional signals, T-SMR also incorporates sub-threshold functional signals that can better inform causal inference. These shared data sources mean that significant findings across methods are not fully independent. Given the challenges and biases associated with weighting schemes⁹⁴, we chose to prioritize genes supported by three or more analyses, acknowledging the varying strengths of evidence but avoiding arbitrary weighting.

Variant fine mapping. We conducted statistical fine mapping using FINEMAP (v.1.3.1)⁴⁶. Only variants located in a region of 1 Mb around index variants were included in the analyses. We used the default $k = 5$ maximum number of SNPs in credible sets, and the significant (suggestive) threshold for signals was set at 95% (50%) total posterior probability for the variants in credible sets (see Supplementary Table 10).

FUMA: functional annotation (eQTL/Hi-C). We used FUMA (v.1.6.1) to examine the functional significance of our GWS loci. We compared results from brain-related eQTL studies to identify overlap in significance between our GWAS SNPs and the eQTL results. Furthermore, we used brain-related Hi-C information available through FUMA to functionally annotate our results. Standard settings were applied and results visualized using FUMA's built-in circo plot routine. More information about the individual third-party datasets (available through the FUMA website) included in the analyses can be found in the Code Availability section or online in FUMA's tutorial (<https://fuma.ctglab.nl/tutorial>).

Stratified LDSC. Two stratified LDSC analyses were conducted. First, the overall SNP heritability was partitioned into 53 overlapping functional genomic categories⁹⁵. Second, SNP heritability was partitioned into 220 cell-type-specific regulatory elements based on GTEx data and data from the Franke Lab⁹⁶. In both partitioned heritability analyses, we regressed the χ^2 from the meta-analysis summary statistics onto LD scores downloaded from <https://console.cloud.google.com/storage/browser/broad-alkesgroup-public-requester-pays>. EUR allele frequencies derived from the 1000 Genome Project data were used as the reference genomes in both analyses. The enrichment of a functional or cell-type-specific category was defined as the proportion of SNP heritability in the category divided by the proportion of SNPs in that category.

FUMA: cell-type and tissue enrichment. We used MAGMA (v.1.08)⁴⁹ as implemented in FUMA (v.1.6.1)⁴⁷ to perform tissue-enrichment and cell-type-enrichment analyses. For tissue-enrichment analyses, we considered a set of 30 tissue groupings (average enrichment across all tissues in these groups) and 54 individual tissues (with 13 individual tissues from the 'Brain' group). Default settings were applied for all above-mentioned analyses. More information about the individual third-party datasets (available through the FUMA website) included in the analyses can be found in the Code Availability section or online in FUMA's tutorial (<https://fuma.ctglab.nl/tutorial>).

Gene-based associations and enrichment

MAGMA: gene-based GWAS and gene-set analysis. We performed gene-based and gene-set analyses using MAGMA⁴⁹ (v.1.08) as implemented in FUMA⁴⁷ (v.1.6.1). To test genetic associations at the gene level for the combined effect of SNPs in or near protein-coding genes, we applied default settings (SNP-wise model for gene-based analysis and competitive model for gene-set analysis). Gene-based P values were computed by mapping SNPs to their corresponding gene(s) based on their position in the genome. Positional mapping was based on ANNOVAR annotations, and the maximum distance between SNPs and genes was set to 10 kb (default). A multiple regression model was used while accounting for LD between the markers. The 1000 Genomes phase 3 reference panel⁸¹, excluding the MHC region, was used to adjust for gene size and LD across SNPs. Using the result of the gene-based analysis (gene-level P values), competitive gene-set analysis was performed with default parameters: 15,496 gene sets were tested for association. Gene sets were obtained from MSigDB (v.7.0) (see www.gsea-msigdb.org for details), including 'Curated gene sets' consisting of nine data resources, including KEGG, Reactome and BioCarta, and 'GO terms' consisting of three categories (biological processes, cellular components and molecular functions).

T-SMR, P-SMR and M-SMR. SMR methods are MR tests for assessing (causal) colocalization between significant trait association signals and significantly accurate predictions of molecular mediators or regulators (transcriptomic, proteomic and methylomic) that often use multiple variants, some of which, unlike classical colocalization methods, might possess only suggestive signals. If both trait and molecular mediator QTL signals are statistically significant, the SMR and classical

colocalization methods are equivalent. However, the SMR methods accommodate (combinations of) non-significant QTLs that accurately predict molecular mediators, a situation still encountered for many genes owing to the low sample sizes for the reference molecular mediator-genetic data⁹⁷.

We performed T-SMR, P-SMR and M-SMR studies using SMR (v.1.03)⁵⁰ in conjunction with the largest available external blood and brain xQTL reference datasets (Supplementary Table 16). When protein QTL summary statistics from reference data were not available (blood and brain protein QTL) in the SMR-required input binary file format (that is, .besd), we processed them into the required format. One advantage of SMR over competing tools is the inclusion of the HEterogeneity In Dependent Instruments (HEIDI) test, which can be used as a proxy for likely causality.

SMR analyses were based on *cis*-xQTLs (SNPs with $P < 5 \times 10^{-8}$ within 2 Mb of the probe). We also used the default maximum (20) and minimum (3) number of xQTLs selected for the HEIDI test. We set the significance threshold as $P < 1.57 \times 10^{-3}$ for xQTL and the mismatch of minimum allele frequency among input files as <15%. For the HEIDI test, SNPs with LD > 0.9 and <0.05 with the top associated xQTL SNP were pruned.

To prioritize genes and perform pathway analyses, we adjusted probe (RNA, protein, CpG) SMR P value (P_{SMR}) for the HEIDI test P value (P_{HEIDI}) by combining the two P values into a single one by requiring that P_{SMR} was not penalized when P_{HEIDI} was above 0.01 and P_{SMR} was penalized by the amount P_{HEIDI} fell below 0.01. Consequently, we adjusted P_{SMR} to $P'_{\text{SMR}} = \frac{P_{\text{SMR}}}{\min(\frac{P_{\text{HEIDI}}}{0.01}, 1)}$. We used this approach instead of filtering by $P_{\text{HEIDI}} < 0.01$ because a misalignment between the GWAS cohort population and the EUR LD reference panel used by SMR might yield very low P_{HEIDI} . We previously arrived at this compromise between the two types of SMR P values when applying this approach to many psychiatric disorders⁵², for example, the well-known SCZ *C4A* signal yielded a T-SMR $P_{\text{HEIDI}} = 5.94 \times 10^{-4}$ but a much lower P_{SMR} . However, for researchers who prefer to use the more conservative approach based on strict P_{HEIDI} thresholds described in the SMR paper⁵⁰, we also provide gene P_{HEIDI} values for all SMR analyses, as documented in Supplementary Tables 15–17.

Gene–drug associations

To uncover potential repurposing of existing drugs to ANX, we conducted gene–drug interaction analyses by applying the DrugTargetor³³ method (v.1.3) to ANX summary statistics. DrugTargetor assesses the association of individual drugs or small-molecule-related gene sets and drug class enrichment. The method used two drug–gene interaction databases: ChEMBL^{54,98} and DgiDB⁵⁵. The analysis used the following settings: (1) hypothesized action for the nervous system; (2) both drug class and single drug; and (3) 1,500 maximum number of unique drugs and 200 maximum classes of drugs. Please see Supplementary Tables 22 and 23 and the README tab for the source databases used to accumulate the gene sets. Analyses were run using MAGMA (v.1.10)⁴⁹ using gene flanks of –35 kb 5' and +10 kb 3' (ref. 99). Drug class enrichment was calculated using the area under the curve defined by the percent of drug class gene sets versus their rank in all the gene sets¹⁰⁰.

Genetic overlap between ANX and other phenotypes

PheWAS. Using the identified 58 GWS SNPs, we conducted a PheWAS to identify the variants that have been significantly associated with other psychiatric, physiological, medical and behavioral traits in prior GWAS, using the phewas function from the R packages ieugwas¹⁰¹. The R package uses publicly available GWAS data from over 10,000 studies compiled by the IEU Open GWAS Project^{101,102}. The PheWAS used the following databases:

- ebi-a: datasets that satisfy minimum requirements imported from the EBI database of complete GWAS summary data;
- finn-b: FinnGen study Data Freeze 5;

- ieu-a: GWAS summary datasets generated by many different consortia that have been manually collected and curated, initially developed for MR-Base;
- ieu-b: GWAS summary datasets generated by many different consortia that have been manually collected and curated, initially developed for MR-Base (round 2);
- ubm-a: complete GWAS summary data on brain region volumes as described by Elliott et al.¹⁰³;
- ukb-d: Neale lab analysis of UK Biobank phenotypes, round 2.

This combination of databases provides the maximum coverage of published GWAS summary statistics that could be used for the PheWAS while minimizing duplication. To increase the accuracy of the PheWAS and consistency of the results across analyses for psychiatric disorders and related behavioral phenotypes, we supplemented the default GWAS summary statistics from the IEU Open GWAS Project for the traits we curated for the genetic correlation analyses. Curating the primary psychiatric and behavioral studies removed duplication from sequential GWAS analyses of the key disorders. We required that a SNP's P value was GWS in both the current ANX GWAS and the alternative GWAS. Figure 2a was constructed using edited combinations of the following packages in R: alluvial¹⁰⁴, qqman¹⁰⁵ and pheatmap¹⁰⁶.

Cross-trait genetic correlations. We used cross-trait LDSC to compute genetic correlations between the ANX meta-analysis and 112 selected disorders and traits with publicly available summary statistics. The sources of GWAS summary statistics can be found in Supplementary Table 24. Details of cross-trait LDSC can be found in the section “SNP-based heritability estimation and genetic correlations” (Methods). As a follow-up, we also calculated genetic correlations between the 112 phenotypes and each ascertainment-specific sub-cohort and compared the genetic correlation patterns between the four groups.

GSMR. We performed bi-directional GSMR⁵⁸ analyses for trait pairs (ANX with MDD¹⁰⁷, PTSD⁵⁷ and neuroticism³⁹) using GSMR (v.1.1.1), available in the GSMR R package. We used commonly applied parameters: (1) a 5×10^{-8} threshold for GWS signals; (2) the original HEIDI outlier method; (3) single-SNP and multi-SNP HEIDI outlier $P = 0.01$; (4) LD threshold for selecting MR SNP instruments of 0.05; and (5) false discovery rate threshold of 0.05. LD between SNPs with significant signals in at least one trait were computed using GCTA¹⁰⁸ (v.1.94.1) based on the 1000 Genome Project⁸¹ EUR genetic data.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

Summary statistics excluding 23andMe are made available on the PGC data-download page (<https://pgc.unc.edu/for-researchers/download-results>). The replication GWAS summary statistics for the 23andMe data will be made available through 23andMe to qualified researchers under an agreement with 23andMe that protects the privacy of the 23andMe participants. Datasets will be made available at no cost for academic use. Please visit <https://research.23andme.com/research-innovation-collaborations> for more information and to apply to access the data.

Code availability

Core analysis code for RICOPILI can be found at <https://sites.google.com/a/broadinstitute.org/ricopili>. This includes PLINK (<https://www.cog-genomics.org/plink2>), EIGENSOFT (<https://www.hsph.harvard.edu/alkes-price/software>), Eagle2 (<https://alkesgroup.broadinstitute.org/Eagle>), Minimac3 (<https://genome.sph.umich.edu/wiki/Minimac3>), SHAPEIT3 (https://mathgen.stats.ox.ac.uk/genetics_software/

shapeit/shapeit.html), METAL (https://genome.sph.umich.edu/wiki/METAL_Documentation) and LDSC (<https://github.com/bulik/ldsc>). MAGMA can be found at <https://ctg.cncr.nl/software/magma>. GenomicSEM, specifically the tutorial 'Models without Individual SNP effects', can be found at <https://github.com/GenomicSEM/GenomicSEM/wiki/3.-Models-without-Individual-SNP-effects>. Additional code for data processing (for example, harmonization of summary statistics) can be found at <https://zenodo.org/records/17478061>.

References

78. Kendler, K. S., Neale, M. C., Kessler, R. C., Heath, A. C. & Eaves, L. J. Major depression and phobias: the genetic and environmental sources of comorbidity. *Psychol. Med.* **23**, 361–371 (1993).
79. Kendler, K. S., Neale, M. C., Kessler, R. C., Heath, A. C. & Eaves, L. J. Major depression and generalized anxiety disorder. Same genes, (partly) different environments? *Arch. Gen. Psychiatry* **49**, 716–722 (1992).
80. McCarthy, S. et al. A reference panel of 64,976 haplotypes for genotype imputation. *Nat. Genet.* **48**, 1279–1283 (2016).
81. Auton, A. et al. A global reference for human genetic variation. *Nature* **526**, 68–74 (2015).
82. Lam, M. et al. RICOPILI: Rapid Imputation for COnsortias PipeLine. *Bioinformatics* **36**, 930–933 (2020).
83. Chen, W. et al. Improved analyses of GWAS summary statistics by reducing data heterogeneity and errors. *Nat. Commun.* **12**, 7117 (2021).
84. Willer, C. J., Li, Y. & Abecasis, G. R. METAL: fast and efficient meta-analysis of genomewide association scans. *Bioinformatics* **26**, 2190–2191 (2010).
85. Bulik-Sullivan, B. et al. An atlas of genetic correlations across human diseases and traits. *Nat. Genet.* **47**, 1236–1241 (2015).
86. Watanabe, K. et al. Genome-wide meta-analysis of insomnia prioritizes genes associated with metabolic and psychiatric pathways. *Nat. Genet.* **54**, 1125–1132 (2022).
87. Grotzinger, A. D., de la Fuente, J., Privé, F., Nivard, M. G. & Tucker-Drob, E. M. Pervasive downward bias in estimates of liability-scale heritability in genome-wide association study meta-analysis: a simple solution. *Biol. Psychiatry* **93**, 29–36 (2023).
88. Devlin, B. & Roeder, K. Genomic control for association studies. *Biometrics* **55**, 997–1004 (1999).
89. Kessler, R. C., Andrews, G., Mroczek, D., Ustun, B. & Wittchen, H.-U. The World Health Organization Composite International Diagnostic Interview short-form (CIDI-SF). *Int. J. Methods Psychiatr. Res.* **7**, 171–185 (1998).
90. Davis, K. A. S. et al. Mental health in UK Biobank—development, implementation and results from an online questionnaire completed by 157 366 participants: a reanalysis. *BJPsych Open* **6**, e18 (2020).
91. Spitzer, R. L., Kroenke, K., Williams, J. B. W. & Löwe, B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch. Intern. Med.* **166**, 1092–1097 (2006).
92. Zhang, Q., Privé, F., Vilhjálmsson, B. & Speed, D. Improved genetic prediction of complex traits from individual-level data or summary statistics. *Nat. Commun.* **12**, 4192 (2021).
93. Pain, O. et al. Evaluation of polygenic prediction methodology within a reference-standardized framework. *PLoS Genet.* **17**, e1009021 (2021).
94. Moore, A. et al. Evaluating 17 methods incorporating biological function with GWAS summary statistics to accelerate discovery demonstrates a tradeoff between high sensitivity and high positive predictive value. *Commun. Biol.* **6**, 1199 (2023).
95. Finucane, H. K. et al. Heritability enrichment of specifically expressed genes identifies disease-relevant tissues and cell types. *Nat. Genet.* **50**, 621–629 (2018).
96. Ernst, J. & Kellis, M. Large-scale imputation of epigenomic datasets for systematic annotation of diverse human tissues. *Nat. Biotechnol.* **33**, 364–376 (2015).
97. Zuber, V. et al. Combining evidence from Mendelian randomization and colocalization: review and comparison of approaches. *Am. J. Hum. Genet.* **109**, 767–782 (2022).
98. Gaulton, A. et al. ChEMBL: a large-scale bioactivity database for drug discovery. *Nucleic Acids Res.* **40**, D1100–D1107 (2012).
99. Network and Pathway Analysis Subgroup of Psychiatric Genomics Consortium. Psychiatric genome-wide association study analyses implicate neuronal, immune and histone pathways. *Nat. Neurosci.* **18**, 199–209 (2015).
100. Gaspar, H. A. & Breen, G. Drug enrichment and discovery from schizophrenia genome-wide association results: an analysis and visualisation approach. *Sci. Rep.* **7**, 12460 (2017).
101. Elsworth, B. et al. The MRC IEU OpenGWAS data infrastructure. Preprint at <https://doi.org/10.1101/2020.08.10.244293> (2020).
102. Hemani, G. et al. The MR-Base platform supports systematic causal inference across the human phenome. *eLife* **7**, e34408 (2018).
103. Elliott, L. T. et al. Genome-wide association studies of brain imaging phenotypes in UK Biobank. *Nature* **562**, 210–216 (2018).
104. Brunson, J. C. ggalluvial: layered grammar for alluvial plots. *J. Open Source Softw.* **5**, 2017 (2020).
105. Turner, S. D. qqman: an R package for visualizing GWAS results using Q-Q and Manhattan plots. *J. Open Source Softw.* **3**, 731 (2018).
106. Kolde, R. pheatmap: pretty heatmaps, version 1.0.12. <https://cran.r-project.org/web/packages/pheatmap/index.html> (2024).
107. Als, T. D. et al. Depression pathophysiology, risk prediction of recurrence and comorbid psychiatric disorders using genome-wide analyses. *Nat. Med.* **29**, 1832–1844 (2023).
108. Yang, J., Lee, S. H., Goddard, M. E. & Visscher, P. M. GCTA: a tool for genome-wide complex trait analysis. *Am. J. Hum. Genet.* **88**, 76–82 (2011).

Acknowledgements

We thank all research participants and staff for their valuable time and involvement in our research studies. We are extremely grateful to all the families who took part in the ALSPAC study, the midwives for their help in recruiting them and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists and nurses. Part of this data was collected using REDCap (<https://projectredcap.org/resources/citations>). The UK Medical Research Council and Wellcome (grant ref. 217065/Z/19/Z) and the University of Bristol provide core support for ALSPAC. GWAS data were generated by Sample Logistics and Genotyping Facilities at Wellcome Sanger Institute and LabCorp (Laboratory Corporation of America) using support from 23andMe. A comprehensive list of grant funding is available on the ALSPAC website. Vanderbilt University Medical Center's BioVU is supported by institutional funding, private agencies and federal grants. These include the National Institutes of Health (NIH)-funded Shared Instrumentation Grant S10RR025141 and CTSA grants UL1TR002243, UL1TR000445 and UL1RR024975. Genomic data are also supported by investigator-led projects that include U01HG004798, R01NS032830, RC2GM092618, P50GM115305, U01HG006378, U19HL065962 and R01HD074711; additional funding sources listed at <https://vict.vumc.org/biovu-funding>. We are grateful to the individuals and families who took part in Generation Scotland and generously donated their time and data, as well as the general practitioners and the Scottish School of Primary care for their help in recruiting them. Generation Scotland received core funding from the Chief Scientist Office of the Scottish Government Health Directorate CZD/16/6 and the Scottish Funding Council HR03006. Genotyping of

Generation Scotland samples was carried out by the Genetics Core Laboratory at the Wellcome Trust Clinical Research Facility, Edinburgh, Scotland and was funded by the Medical Research Council and the Wellcome Trust (104036/Z/14/Z, 220857/Z/20/Z). This work made use of the resources provided by the Edinburgh Compute and Data Facility (<http://www.ecdf.ed.ac.uk>). This study includes data from the Norwegian Mother, Father and Child Cohort Study (MoBa) conducted by the Norwegian Institute of Public Health (NIPH). MoBa is supported by the Norwegian Ministry of Health and Care Services and the Ministry of Education and Research. We are grateful to all the participating families in Norway who take part in this on-going cohort study. We thank the NIPH for generating high-quality genomic data. This research is part of the HARVEST collaboration, supported by the Research Council of Norway (RCN) (229624). We also thank the NORMENT Centre for providing genotype data, funded by the RCN (223273), South East Norway Health Authority (SENHA) and KG Jebsen Stiftelsen. We further thank the Center for Diabetes Research, the University of Bergen, for providing genotype data and performing quality control and imputation of the data funded by the ERC AdG project SELECTIONPREDISPOSED, Stiftelsen Kristian Gerhard Jebsen, Trond Mohn Foundation, RCN, Novo Nordisk Foundation, University of Bergen and Western Norway Health Authorities. The RCN supported H.A., E.C.C and T.R.-K. (274611, 324620). A.H., L.H. and E.C.C. were supported by SENHA (2020022, 2018058, 2021045). Partial support for all datasets housed within the Utah Population Data Base is provided by the Huntsman Cancer Institute (HCI; <http://www.huntsmancancer.org>) and HCI Cancer Center Support Grant P30CA42014 from the National Cancer Institute. DNA extraction was performed by the University of Utah Center for Clinical and Translational Science supported by the National Center for Advancing Translational Sciences of the NIH (grant no. UL1TR002538). We acknowledge The Swedish Twin Registry for access to data. The Swedish Twin Registry is managed by Karolinska Institutet and receives funding through the Swedish Research Council under grant 2017-00641. We are grateful to all VTSABD study participants who contributed to this work, and to leadership and guidance offered by the former principal investigator, L. J. Eaves. The Gedi study was supported by the National Institute on Drug Abuse (U01DA024413, R01DA11301), the National Institute of Mental Health (NIMH) (R01MH063970, R01MH063671, R01MH048085, K01MH093731 and K23MH080230), National Alliance for Research on Schizophrenia and Depression (NARSAD) and the William T. Grant Foundation. We are grateful to all the GSMS and CCC study participants who contributed to this work. GEDI-VTSABD research was supported by the National Institute on Drug Abuse (U01DA024413, R01DA025109) and the NIMH (R01MH045268, R01MH068521). We are grateful to all the VTSABD study participants who contributed to this work. The Christchurch Health and Development Study has been supported by funding from the Health Research Council of New Zealand, the National Child Health Research Foundation (Cure Kids), the Canterbury Medical Research Foundation, the New Zealand Lottery Grants Board, the University of Otago, the Carney Centre for Pharmacogenomics, the James Hume Bequest Fund, NIH grant MH077874 and National Institute on Drug Abuse grant R01DA024413. SHIP-START is part of the Community Medicine Research net of the University of Greifswald, Germany, which is funded by the Federal Ministry of Education and Research (BMBF) (grant nos. 01ZZ9603, 01ZZ0103 and 01ZZ0403), the Ministry of Cultural Affairs as well as the Social Ministry of the Federal State of Mecklenburg-West Pomerania, and the network 'Greifswald Approach to Individualized Medicine (GANI_MED)' funded by the BMBF (grant 03IS2061A). Genome-wide data have been supported by the BMBF (grant no. 03ZIK012) and a joint grant from Siemens Healthineers, Erlangen, Germany and the Federal State of Mecklenburg-West Pomerania. The University of Greifswald is a member of the Caché Campus program of the InterSystems. We are

thankful to the participants and investigators of the Panic-Net I and II studies, the staff of the recruiting centers and the BMBF for funding. Thanks to S. Marrington (Project Manager) and G. Shuttlewood (Data Manager) who supervised the day-to-day management of the study. We also extend our thanks to the mothers and children who have continued to participate in the study. Panic-Net I and II cohorts were recruited as part of the German multicenter trial "Mechanisms of Action in CBT (MAC)". The MAC study was funded by the BMBF (project no. 01GV0615) as part of the BMBF Psychotherapy Research Funding Initiative. The Trøndelag Health Study (HUNT) is a collaboration between HUNT Research Centre (Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology (NTNU)), Trøndelag County Council, Central Norway Regional Health Authority and the NIPH. Genotyping was financed by the NIH, University of Michigan, RCN and Central Norway Regional Health Authority and the Faculty of Medicine and Health Sciences, NTNU. Genotype quality control and imputation was conducted by the K.G. Jebsen Center for Genetic Epidemiology, Department of Public Health and Nursing, Faculty of Medicine and Health Sciences, NTNU. The iPSYCH team was supported by grants from the Lundbeck Foundation (R102-A9118, R155-2014-1724, R248-2017-2003), NIH/NIMH (1U01MH109514-01, 1R01MH124851-01 to A.D.B.) and the Universities and University Hospitals of Aarhus and Copenhagen. The Danish National Biobank resource was supported by the Novo Nordisk Foundation. High-performance computer capacity for handling and statistical analysis of iPSYCH data on the GenomeDK HPC facility was provided by the Center for Genomics and Personalized Medicine and the Centre for Integrative Sequencing, iSEQ, Aarhus University, Denmark (grant to A.D.B.). The infrastructure for the NESDA study (www.nesda.nl) is funded through the Geestkracht program of the Netherlands Organization for Health Research and Development (ZonMw) (grant no. 10-000-1002) and financial contributions by participating universities and mental health care organizations (VU University Medical Center, GGZ inGeest, Leiden University Medical Center, Leiden University, GGZ Rivierduinen, University Medical Center Groningen, University of Groningen, Lentis, GGZ Friesland, GGZ Drenthe, Rob Giel Onderzoekscentrum). The generation and management of GWAS genotype data for the Rotterdam Study (RS I, RS II, RS III) was executed by the Human Genotyping Facility of the Genetic Laboratory of the Department of Internal Medicine, Erasmus MC, Rotterdam, Netherlands. The GWAS datasets are supported by Netherlands Organisation of Scientific Research (NWO) Investments (nos. 175.010.2005.011, 911-03-012), the Genetic Laboratory of the Department of Internal Medicine, Erasmus MC, the Research Institute for Diseases in the Elderly (RIDE) (014-93-015; RIDE2), Netherlands Genomics Initiative/NWO Netherlands Consortium for Healthy Aging (project no. 050-060-810). We thank P. Arp, M. Jhamai, M. Verkerk, L. Herrera, M. Peters and C. Medina-Gomez for their help in creating the GWAS database, and K. Estrada, Y. Aulchenko and C. Medina-Gomez for the creation and analysis of imputed data. We are grateful to the study participants, the staff from the Rotterdam Study and the participating general practitioners and pharmacists. The CoLauS|PsyCoLauS study was supported by unrestricted research grants from GlaxoSmithKline, the Faculty of Biology and Medicine of Lausanne, the Swiss National Science Foundation (grants 3200BO-105993, 3200BO-118308, 33CSO-122661, 33CS30-139468, 33CS30-148401, 33CS30-177535, 3247730_204523 and 320030_220190) and the Swiss Personalized Health Network (grant 2018DRI01). The BLTS and QIMR adult samples were collected using grant funding awarded from many grant funding bodies, including the Australian National Health and Medical Research Council (NHMRC) (241944, 339462, 389927, 389875, 389891, 389892, 389938, 442915, 442981, 496675, 496739, 552485, 552498, 613608), the FP-5 GenomEUtwin Project (QLG2-CT- 2002-01254), the NIH (AA07535, AA10248, AA13320, AA13321, AA13326, AA14041, MH66206, DA12854, DA019951) and the

Center for Inherited Disease Research, Baltimore. This also incorporated updated data collected as a part of the PISA study. PISA is funded by an NHMRC Boosting Dementia Research Initiative Team Grant (APP1095227). The QIMR twin samples are made available through the generous and willing participation of twins and their families registered at the Australian Twin Registry. We thank D. Statham (sample collection); L. Wallace, A. Caracella and staff of the Molecular Epidemiology Laboratory (DNA processing); and D. Smyth, H. Beeby and D. Park (IT support). We are also indebted to all participants of the Australian Genetics of Depression Study for giving their time to contribute to this study. We thank everyone who helped with the conception, implementation, media campaign and data cleaning. We thank R. Parker, S. Cross and L. Sullivan for their valuable work coordinating all administrative and operational aspects of the AGDS project. The AGDS was primarily funded by the NHMRC of Australia (grant 1086683). This work was further supported by NHMRC grants 1145645, 1078901, 1113400 and 1087889 and the NIMH. The QSkin study was funded by the NHMRC (grant nos. 1073898, 1058522 and 1123248). N.G.M. is supported through NHMRC investigator grants (1172917, 1173790 and 1172990). PISA is funded by a NHMRC Boosting Dementia Research Initiative Team Grant (APP1095227). The Rotterdam Study is funded by Erasmus MC and Erasmus University, Rotterdam, ZonMw, RIDE, the Ministry of Education, Culture and Science, the Ministry for Health, Welfare and Sports, the European Commission (DG XII) and the Municipality of Rotterdam. This research is part of the TRacking Adolescents' Individual Lives Survey (TRAILS). Participating centers of TRAILS include the University Medical Center and University of Groningen, the University of Utrecht, the Radboud Medical Center Nijmegen and the Parnassia Bavo group, all in The Netherlands. TRAILS has been financially supported by various grants from NWO (Medical Research Council program grant GB-MW 940-38-011; ZonMW Brainpower grant 100-001-004; ZonMW Risk Behavior and Dependence grant 60-60600-97-118; ZonMW Culture and Health grant 261-98-710; Social Sciences Council medium-sized investment grants GB-MaGW 480-01-006 and GB-MaGW 480-07-001; Social Sciences Council project grants GB-MaGW 452-04-314 and GB-MaGW 452-06-004; NWO large-sized investment grant 175.010.2003.005; NWO Longitudinal Survey and Panel Funding 481-08-013 and 481-11-001; NWO Vici 016.130.002 and 453-16-007/2735; NWO Gravitation 024.001.003), the Dutch Ministry of Justice, the European Science Foundation (EuroSTRESS project FP-006), the European Research Council (ERC-2017-STG-757364 en ERC-CoG-2015-681466), Biobanking and Biomolecular Resources Research Infrastructure BBMRI-NL (CP 32), the Gratama foundation, the Jan Dekker foundation, the participating universities and Accare Centre for Child and Adolescent Psychiatry. Thanks to the study participants who have continued to participate in the study and to the MUSP study team. MUSP was funded by grants received from the NHMRC and Australian Research Council (ARC). We thank the veterans who participate in the VA MVP. The FinnGen project is funded by two grants from Business Finland (HUS 4685/31/2016 and UH 4386/31/2016) and the following industry partners: AbbVie, AstraZeneca UK, Biogen MA, Bristol Myers Squibb (and Celgene Corporation & Celgene International II Sàrl), Genentech, Merck Sharp & Dohme, Pfizer, GlaxoSmithKline Intellectual Property Development, Sanofi US Services, Maze Therapeutics, Janssen Biotech, Novartis and Boehringer Ingelheim International. We are grateful to the Ministry of Research and Innovation of Ontario for funding the IMPACT project. We also thank L. and J. Tanenbaum for their generous support in creating the Tanenbaum Centre for Pharmacogenetics, which is advancing research for the Centre for Addiction and Mental Health (CAMH) Pharmacogenetic Program. We are grateful to everyone who participated in this research or worked on this project to make it possible. We thank UK Biobank volunteers for their participation. We thank the National Institute for Health Research (NIHR), National

Health Service (NHS) Blood and Transplant and Health Data Research UK as part of the Digital Innovation Hub Programme. This work was partially funded by the NIHR Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. Patient and public involvement groups and services were provided by the NIHR KCL-Maudsley Biomedical Research Centre. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care. We acknowledge the participants and investigators of the FinnGen study. Following biobanks are acknowledged for delivering biobank samples to FinnGen: Auriia Biobank (www.auria.fi/biopankki), THL Biobank (www.thl.fi/biobank), Helsinki Biobank (www.helsinginbiopankki.fi), Biobank Borealis of Northern Finland (<https://www.ppshp.fi/Tutkimus-ja-opetus/Biopankki/Pages/Biobank-Borealis-briefly-in-English.aspx>), Finnish Clinical Biobank Tampere (www.tays.fi/en-US/Research_and_development/Finnish_Clinical_Biobank_Tampere), Biobank of Eastern Finland (www.ita-suomenbiopankki.fi/en), Central Finland Biobank (www.ksshp.fi/fi-FI/Potilaalle/Biopankki), Finnish Red Cross Blood Service Biobank (www.veripalvelu.fi/verenluovutus/biopankkitoiminta), Terveystalo Biobank (www.terveystalo.com/fi/Yritystietoa/Terveystalo-Biopankki/Biopankki) and Arctic Biobank (<https://www oulu.fi/en/university/faculties-and-units/faculty-medicine/northern-finland-birth-cohorts-and-arctic-biobank>). All Finnish Biobanks are members of the BBMRI.fi infrastructure (<https://www.bbMRI-eric.eu/national-nodes/finland>). Finnish Biobank Cooperative (FINBB; <https://finbb.fi>) is the coordinator of BBMRI-ERIC operations in Finland. Finnish biobank data can be accessed through the Fingenious services (<https://site.fingenious.fi/en>) managed by FINBB. We are thankful to all Estonian Biobank participants for their contribution and to the Estonian Biobank Research Team (A. Metspalu, T. Esko, R. Mägi, M. Nelis and G. Hudjashov) for data collection, genotyping, quality control and imputation. We thank the research participants and employees of 23andMe for making this work possible. This work was supported by NIH grant R01MH113665 (principal investigator, J.M.H.) and PGC4 grant 5R01MH124847 (main principal investigator, P. F. Sullivan). T.C.E. is supported by the UK Medical Research Council (MR/V012878/1 and previously MR/M021475/1). M.K.L. is supported by a Boosting Dementia Leadership Fellowship (APP1140441). S.-A.B. is funded by grants MH113665 and MH118239. R. Cheesman. is funded by the Jacobs Foundation (no. 2023-1510-00) and the RCN (288083). A.B.F. is funded by T32GM080178. S.M. is funded by the NHMRC (APP1172917). S.R. is funded by 1U01MH109528 01. S.A. has received money from the Stanley Center Gift 2020. R.E.P. is supported by the NIMH (R01MH125938) and the Brain & Behavior Research Foundation (BBRF) (NARSAD grant 28632P&S). M.H.I. was supported by a Wellcome Trust Mental Health award (226770/Z/22/Z), a Medical Research Council Mental Health Data Pathfinder award (MRC-MC_PC_17209) and by the UK Research and Innovation-funded DATAMIND project (MR/W014386/1). B.S.W. was supported by the South-Eastern Norway Regional Health Authority (grant no. 2020034). A.R.t.K. was funded by the NIHR Maudsley Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care. D.F.L. was supported by an NARSAD Young Investigator Grant from the BBRF and a Career Development Award CDA-2 from the Veterans Affairs Office of Research and Development (1IK2BX005058-01A2). B.C.-D. is supported by a CJ Martin Fellowship, awarded by the NHMRC (app. 1161356). S.V.d.A. was supported by the BMBF (grant no. 01KU2004) under the frame of ERA PerMed (TRAJECTOME project, ERAPERMED2019-108). A.T. was funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) (542489987). G.A.S. is supported by the National Institute of Developmental Psychiatry for Children and Adolescents, São Paulo, with grants from the São Paulo Research Foundation (Fapesp

2014/50917-0, 2013/08531-5) and the Brazilian National Council for Scientific and Technological Development (CNPq 465550/2014-2). J.L.K. is supported by the Tanenbaum Family Foundation. C.C.Z. is supported by the BBRF (NARSAD) and the CAMH Foundation. G.Z. is supported by the BBRF, the Physicians' Services Incorporated Foundation, the International OCD Foundation, the University of Toronto Department of Psychiatry Academic Scholars Award and the CAMH AFP Innovation Fund. A.K.T. is supported by the Ministry of Research and Innovation of Ontario, CAMH foundation and Canadian Institutes of Health Research. J.K. is supported by the Academy of Finland (grant 312073). J. Boden is supported by the Health Research Council of New Zealand (Programme Grant 16/600). C.M.M. was funded by grants received from the NHMRC and ARC. F.L.L. is supported by the NIMH (R25 MH101076). F.J.M. and N.A. are supported in part by the Intramural Research Program of the NIMH (ZIAMH002843). F.J.M. used the computational resources of the NIH HPC Biowulf cluster. We thank the Mass General Brigham Biobank for providing samples, genomic data and health information data. H.T. was supported by grant 016.VICI.170.200 from ZonMw. N.R.W. was supported by the NHMRC (1113400, 1173790). E.M.B. was supported by the NHMRC (grant 1145645). G.L. was supported by the Wellcome Trust 084268/Z/07/Z. UCLH BRC. N.J.T. is a Wellcome Trust Investigator (202802/Z/16/Z) and the principal investigator of the Avon Longitudinal Study of Parents and Children (MRC & WT 217065/Z/19/Z). N.J.T. is also supported by the University of Bristol NIHR Biomedical Research Centre (BRC-1215-2001), the MRC Integrative Epidemiology Unit (MC_UU_00011/1) and works within the CRUK Integrative Cancer Epidemiology Programme (C18281/A29019). L.K.D. CTSA (SD, Vanderbilt Resources) was supported by the National Center for Research Resources (Grant UL1R024975-01) and the National Center for Advancing Translational Sciences (Grant 2 UL1TR000445-06). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. N.A.G. was supported by grant R00DA023549. Work by K.K., L.M. and K.L. was funded by the European Union through the European Regional Development Fund (Project No. 2014-2020.4.01.15-0012 GENTRANSMED) and the Estonian Research Council (PRG184, PSG615). Data analysis was carried out in part in the High-Performance Computing Center of University of Tartu. A.J.F. received funding from the Else Kröner-Fresenius-Stiftung (2019_A127). M.M.N. is a member of the DFG-funded Excellence Cluster ImmunoSensation2 (EXC 2151-390873048). I.H. and E.M.T. have received support from the Sigrid Jusélius Foundation. H.H.M. was supported by the National Institute on Drug Abuse (U01DA024413, R01DA025109, R01DA054313) and the NIMH (R01MH045268, R01MH068521). A.M.M. is supported by the Wellcome Trust (104036/Z/14/Z, 216767/Z/19/Z, 220857/Z/20/Z, 223165/Z/21/Z, 226770/Z/22/Z) and UKRI MRC (MC_PC_17209, MR/S035818/1). This work is part of a project that has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement no. 847776. O.A.A. has received support from KG Jebsen Stiftelsen (SKGJ-MED-021), RCN (223273, 324252, 324499), UiO LifeScience Program and NordForsk (164218). T.R.K. is supported by the RCN (274611, principal investigator, T.R.-K.). J.M.N. is supported by the NHMRC. M.B.S. is supported by the US Department of Defense, Army and NIMH. J. Gelernter is supported by the Department of Veterans Affairs Office of Research and Development (USVA grant I01CX001849). D.I.B. is supported through the Royal Netherlands Academy of Science Award (KNAW PAH/6635). NWO 480-15-001/674: Netherlands Twin Registry Repository; Biobanking and Biomolecular Research Infrastructure (NWO BBMRI-NL, 184.033.111); NWO/SPI 56-464-14192, Genetic Association Information Network (GAIN) of the Foundation for the National Institutes of Health, Rutgers University Cell and DNA Repository (NIMH U24 MH 068457-06), the Avera Institute, Sioux Falls (USA) and the NIH (R01HD042157-01A1, MH081802, Grand Opportunity grants 1RC2

MH089951 and 1RC2 MH089995) and European Research Council (ERC-230374). C.R.K. is supported by the Swedish Research Council (2018-02487), Swedish Research Council for Health, Working Life and Welfare (2018-00221 and 2021-00132). T.K. and G.W.A. were funded by the BMBF. V.A. was supported by the BMBF and was funded by EU Horizon 2020 (Project MOODSTRATIFICATION). J.W.S. was supported by grant NIMH R01 MH085542. A.R. is supported by DFG TR CRC 58, BMBF Panic-Net. G.B. and T.E. are supported by MR/V012878/1. T.E. was partly funded by the NIHR Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. The Panic-Net I and II studies have been funded by the BMBF. A.R.D. is supported by R01MH123619 and R01MH123489. H.C. is supported by R01MH122412 and R01MH123489. K.L. is supported by the Estonian Research Council (grant no PSG615). J.D. has received support by the EU, BMBF and DFG. T.-H.N. is supported by the NIAAA (K25AA030072) and the BBRF (NARSAD grant 28599). B.M. was supported by an Australian NHMRC Investigator Grant (APP2017176). A.S.F.K. was supported by an Economics and Social Research Council Postdoctoral Fellowship (ES/V011650/1). B.W.P. is supported by the research project 'Stress in Action', financially supported by the Dutch Research Council and the Dutch Ministry of Education, Culture and Science (NWO gravitation grant number 024.005.010). Full lists of researchers involved in the three listed consortia (23andMe, Veterans Affairs MVP and FinnGen) can be found in Supplementary Note 5.

Author contributions

J.M.H., M.M., T.C.E. and J.D. designed and directed the study. N.I.S., M.M., B.V., S.-A.B., R. Cheesman, K.L.P., H.G., R.W. and T.-H.N. conducted data analysis. B.L.M., A.S.K., A.B.F., K.S., S.M., L.C.-C., K.K., P.H., S.H., J. Gehlen, S.R., S.A., T.P., E.M.T., R.E.P., D.E.A., A.A.S., M.J.A., M.H.I., A.C., L.F.T., B.S.W., O.K.D., S.B., A.R.t.K., J.N., S.M.M., E.C.C., L.H., D.F.L., D.C., H.W., K.W.C., G.P., B.C.-D., S.V.d.A., A.T., R.K., M.G.-A., D.L., O.B., E.S., J. Bäckman, G.A.S., C.C.Z., J.L.K., G.Z., A.K.T., S.H.-H., B.S., J.K., M.M.K., J. Boden, A.H., C.M.M., F.L.L., N.A., F.J.M., E.B.B., L.F., A.S., E.C., H.T., D.J.S., D.W., C.O., Z.F., X.W., N.R.W., E.M.B., G.L., N.J.T., L.K.D., I.B.H., N.A.G., L.M., J.S., D.P.W., A.J.F., M.M.N., I.H., J.H., W.E.C., H.H.M., A.M.M., O.A.A., J.-A.W., O.M., A.D.B., P.B.M., H.A., T.R.-K., J.M.N., M.B.S., J. Gelernter, Y.M., B.W.P., D.I.B., E.M., A.E.-L., C.R., T.T.K., C.A.M., G.W.A., V.A., K.D., J.W.S., M.P., N.G.M., M.K.L., A.I.L., A.R., H.J.G., H.L., P.K.M., A.J.O., C.A.H., G.B., A.R.D., H.C., R. Conrad, K.L., J.D., T.C.E., M.M. and J.M.H. provided samples and/or processed individual cohort data. J.M.H., N.I.S., M.M., J.D., B.V., S.-A.B. and T.C.E. wrote the paper and formed the core revision group. All authors discussed the results and approved the final version of the manuscript.

Competing interests

P.H. receives salary from the Life & Brain. J.L.K. is a member of the Scientific Advisory Board for Myriad Neuroscience. I.B.H. was an inaugural commissioner on Australia's National Mental Health Commission (2012–2018). He is the Co-Director, Health and Policy at the Brain and Mind Centre (BMC), University of Sydney. The BMC operates early-intervention youth services at Camperdown under contract to Headspace. He is the Chief Scientific Advisor to, and a 5% equity shareholder in, InnoWell. InnoWell was formed by the University of Sydney (45% equity) and PwC (Australia; 45% equity) to deliver the \$30M Australian Government-funded Project Synergy (2017–2020; a 3-year program for the transformation of mental health services) and to lead transformation of mental health services internationally through the use of innovative technologies. A.M.M. has received research support from Eli Lilly, Janssen and The Sackler Trust. A.M.M. has also received speaker fees from Illumina and Janssen. M.B.S. has, in the past 3 years, received consulting income from Acadia Pharmaceuticals, Aptinyx, atai Life Sciences,

Boehringer Ingelheim, Bionomics, BioXcel Therapeutics, Clexio, Eisai, EmpowerPharm, Engrail Therapeutics, Janssen, Jazz Pharmaceuticals and Roche/Genentech. M.B.S. has stock options in Oxeia Biopharmaceuticals and EpiVario. He is paid for his editorial work on Depression and Anxiety (Editor-in-Chief), Biological Psychiatry (Deputy Editor) and UpToDate (Co-Editor-in-Chief for Psychiatry). He has also received research support from the NIH, Department of Veterans Affairs and Department of Defense. He is on the scientific advisory board for the BBRF and the Anxiety and Depression Association of America. J. Gelernter is named as an inventor on PCT patent application no. 15/878,640, entitled “Genotype-guided dosing of opioid agonists”, filed 24 January 2018 and issued 26 January 2021 as US Patent No. 10,900,082; he is also paid for editorial work for the journal “Complex Psychiatry”. I.H. received speaker’s honoraria from Lundbeck. O.A.A. received speaker’s honorarium from Lundbeck and Sunovion and served as a consultant for Cortechs.ai and Precision Health. K.D. has been a member of the Steering Committee of Neurosciences, Janssen, until 2022 and is currently a member of the Board of the German National Society of Psychiatry (DGPPN) and the Neurotorium Editorial Board of the Lundbeck Foundation. J.W.S. is a member of the Scientific Advisory Board of Sensorium Therapeutics (with equity) and has received an honorarium for an internal seminar at Tempus Labs. He is the principal investigator of a collaborative study of the genetics of depression and bipolar disorder sponsored by 23andMe, for which 23andMe provides analysis time as in-kind support but no payments. E.M. has received research support and has

also received speaker fees from Lundbeck. H.J.G. has received travel grants and speaker’s honoraria from Indorsia, Neuraxpharm, Servier and Janssen Cilag. H.L. has served as a speaker for Evolan Pharma, Medici and Shire/Takeda and has received research grants from Shire/Takeda; all outside of the submitted work. G.B. is an advisory board member for Compass Pathways. J.D. is a member of the board of the German Society of Biological Psychiatry and is on the scientific advisory boards of non-profit organizations and foundations. V.A. worked as an advisor for Sanofi-Adventis Germany. Z.F. and X. Wang are employees of 23andMe and hold stock or stock options in 23andMe. All other authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41588-025-02485-8>.

Correspondence and requests for materials should be addressed to Jürgen Deckert, Thalia C. Eley, Manuel Mattheisen or John M. Hettema.

Peer review information *Nature Genetics* thanks Kazutaka Ohi and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

Reprints and permissions information is available at www.nature.com/reprints.

Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our [Editorial Policies](#) and the [Editorial Policy Checklist](#).

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a Confirmed

- ☐ ☒ The exact sample size (n) for each experimental group/condition, given as a discrete number and unit of measurement
- ☐ ☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
- ☐ ☒ The statistical test(s) used AND whether they are one- or two-sided
Only common tests should be described solely by name; describe more complex techniques in the Methods section.
- ☐ ☒ A description of all covariates tested
- ☐ ☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
- ☐ ☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
- ☐ ☒ For null hypothesis testing, the test statistic (e.g. F , t , r) with confidence intervals, effect sizes, degrees of freedom and P value noted
Give P values as exact values whenever suitable.
- ☒ ☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
- ☒ ☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
- ☐ ☒ Estimates of effect sizes (e.g. Cohen's d , Pearson's r), indicating how they were calculated

Our web collection on [statistics for biologists](#) contains articles on many of the points above.

Software and code

Policy information about [availability of computer code](#)

- | | |
|-----------------|---|
| Data collection | This is fully described in the Methods, associated Supplementary Information, and original GWAS publications. In brief, individual level imputed data and summary statistics from previous publications and additional ANX case-control studies were re-evaluated in a meta-analysis for association with ANX. |
| Data analysis | This is fully described in the Online Methods and associated Supplementary Information. In brief: Quality control and genetic association analyses was performed either using the Ricopili (v 1118b) pipeline: https://github.com/Nealelab/ricopili , which relies on the following software: Eigensoft 6.0.1 (incl. smartPCA), Plink 1.9, METAL 2011-03-25 or in some samples with comparable software tools and approaches (more details can be found in the Supplemental Table S1 and the Supplemental Text). MegaPRS polygenic risk scores were estimated using the GenoPred (92) pipeline. SNP-based finemapping was performed using FINEMAP v.1.3.1. Genomic SEM v 0.04 was used to conduct structural equation modeling. LDSC (v 1.0.1; https://github.com/bulik/ldsc) was used to estimate heritability and bivariate genetic correlations. We used FUMA v1.6.1 to examine the functional significance of loci. Gene-based analyses were performed using MAGMA (38) v1.08 as implemented in FUMA. Tissue and cell-type enrichment of GWAS association signals was conducted using MAGMA (v1.08). We performed transcriptome/proteome/methylome -wide association studies using SMR (v.1.03). We conducted gene-drug interaction analyses by applying the DrugTargetor method. We performed bi-directional generalized summary-data based mendelian randomization using GSMR v1.1.1 available in the GSMR R package. R v3.4 was used in general for statistical analyzes and plotting (https://www.Rproject.org). |

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio [guidelines for submitting code & software](#) for further information.

Data

Policy information about [availability of data](#)

All manuscripts must include a [data availability statement](#). This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our [policy](#)

Upon manuscript publication, the primary meta-analyzed summary statistics will be made available via the Psychiatric Genomics Consortium Download page (<https://www.med.unc.edu/pgc/download-results/>).

Research involving human participants, their data, or biological material

Policy information about studies with [human participants or human data](#). See also policy information about [sex, gender \(identity/presentation\), and sexual orientation](#) and [race, ethnicity and racism](#).

Reporting on sex and gender	For most samples, the number of female and male cases or controls was not provided as part of this project and therefore not reported. Sex and/or gender based analyses were not performed
Reporting on race, ethnicity, or other socially relevant groupings	Primary analyses are limited to European ancestry samples, and no race, ethnicity or other socially relevant groupings have been shared for this project. We conducted secondary analyses (replication or polygenic risk scoring) in participants of African descent in the MVP and UK Biobank samples and participants of South Asian descent in the UK Biobank sample as officially designated in those datasets.
Population characteristics	Data from many different samples were included. See above and below and details in the manuscript and Supplement.
Recruitment	Details are provided in the Supplemental material and vary for the different studies that are part of the meta-analysis. In brief, samples were either ascertained in a clinical setting, a community setting, as part of larger biobanking efforts, or as part of studies looking into comorbid phenotypes (such as MDD, ASD, and ADHD). Our replication dataset was collected in 23andMe.
Ethics oversight	The details of the IRB/oversight body that provided approval or exemption for the research described are given below for 23andMe and in the Supplement for all the primary samples. 23andMe replication dataset: Participants provided informed consent and volunteered to participate in the research online, under a protocol approved by the external AAHRPP-accredited IRB, Ethical & Independent (E&I) Review Services. As of 2022, E&I Review Services is part of Salus IRB (https://www.versitclinicaltrials.org/salusirb).

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see [nature.com/documents/nr-reporting-summary-flat.pdf](https://www.nature.com/documents/nr-reporting-summary-flat.pdf)

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Sample sizes are provided for each contributing study and summed for the overall meta-analysis. We also estimated an effective sample size.
Data exclusions	Within each analyzed cohort except one we aimed at analyzing genetically homogeneous samples of unrelated individuals. Related individuals were excluded based on Identity by State analyses and genetic outliers were excluded based on principal component analyses. (The exception was the QIMR family-based samples which were analyzed using SAIGE that is able to account for relatedness between individuals through fitting a genetic relatedness matrix to the model.)
Replication	After identifying GWS associations in the primary GWAS, lead SNPs were tested for replication in the commercial database of 23andMe using 1,175,012 ANX self-report cases and 1,956,379 controls of European ancestry.
Randomization	This was not a clinical outcomes study, so randomization was not applied.
Blinding	Due to the different ascertainment strategies, blinding was dealt with differently across the different studies. More information can be found in the Supplemental information.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Plants

Seed stocks	N/A
Novel plant genotypes	N/A
Authentication	N/A