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REGULAR ARTICLE

Identification of novel genomic loci for anxiety symptoms and extensive genetic overlap with psychiatric disorders

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Aims: Anxiety disorders are prevalent and anxiety symptoms (ANX) co-occur with many psychiatric disorders. We aimed to identify genomic loci associated with ANX, characterize its genetic architecture, and genetic overlap with psychiatric disorders.

Methods: We included a genome-wide association study of ANX (meta-analysis of UK Biobank and Million Veterans Program, $n = 301{,}732$), schizophrenia (SCZ), bipolar disorder (BIP), major depression (MD), attention-deficit/hyperactivity disorder (ADHD), and autism spectrum disorder (ASD), and validated the findings in the Norwegian Mother, Father, and Child Cohort ($n = 95{,}841$). We employed the bivariate causal mixture model and local analysis of covariant association to characterize the genetic architecture including overlap between the phenotypes. Conditional and conjunctional false discovery rate analyses were performed to boost the identification of loci associated with anxiety and shared with psychiatric disorders.

Results: Anxiety was polygenic with 12.9k genetic variants and overlapped extensively with psychiatric disorders (4.1k–11.4k variants) with predominantly positive genetic correlations between anxiety and psychiatric disorders. We identified 119 novel loci for anxiety by conditioning on the psychiatric disorders, and loci shared between anxiety and MD ($n = 47$), BIP ($n = 33$), SCZ ($n = 71$), ADHD ($n = 20$), and ASD ($n = 5$). Genes annotated to anxiety loci exhibit enrichment for a broader range of biological pathways including cell adhesion and neurofibrillary tangle compared with genes annotated to the shared loci.

Conclusions: Anxiety is highly polygenic phenotype with extensive genetic overlap with psychiatric disorders, and we identified novel loci for anxiety implicating new molecular pathways. The shared genetic architecture may underlie the extensive cross-disorder comorbidity of anxiety, and the identified molecular underpinnings may lead to potential drug targets.

Keywords: *anxiety, genetic loci, genetic overlap, psychiatric disorder.*

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Anxiety, characterized by excessive fear, anxiousness, or avoidance behaviors, is a core feature of anxiety disorders.[1] Anxiety disorders are among the leading causes of global disease burden.[2] The extensive overlap and comorbidity among anxiety disorders[3] have led to a growing view of them as a continuum rather than discrete categories.[4,5] Epidemiological data show frequent comorbidity between anxiety disorders and other psychiatric disorders,[3] including depressive disorders,[6] bipolar disorder (BIP),[7,8] schizophrenia (SCZ),[9] autism spectrum disorder (ASD),[10] and attention-deficit/hyperactivity disorder (ADHD).[11,12] Further, anxiety symptoms (ANX), not meeting the criteria for an anxiety disorder, frequently co-occur with other psychiatric disorders.[13,14] Comorbid anxiety disorders and ANX have been linked with greater disease burden, poorer course and outcome, and lower quality of life.[15–19] The relevance of co-occurring ANX is highlighted by its inclusion as the 'with anxious distress' specifier in major depression (MD) and BIP diagnoses.[1]

The cause of anxiety disorders is not clearly understood; however, genetic and environmental factors are involved.[1,3,4,20,21] Genetic susceptibility plays a role in anxiety disorders and traits,[21] with heritability estimates from twin studies ranging between 30% and 50%.[22] Genome-wide association studies (GWAS) have identified genetic loci for anxiety disorders,[21,23,24] ANX,[25] and the latent factor of ANX.[26] Genetic correlation analyses support that there is shared genetic

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liability between psychiatric disorders and both anxiety disorders and ANX.[23,25] However, genetic correlations do not provide a comprehensive overview of the shared genetic architecture between two phenotypes as genetic variants with the same and opposite effect directions cancel each other out.[27,28] The identification of novel genetic loci for anxiety phenotypes and a better understanding of the shared genetic landscape with other psychiatric disorders can unveil new biological pathways underlying anxiety traits and disorders.[29,30] This is crucial for the development of effective treatments against anxiety disorders and comorbid conditions. Advances in statistical genetics have improved genetic discoveries for complex diseases.[31,32] Novel analytical methods in characterizing the genetic architecture of anxiety disorders and their overlap with psychiatric disorders can enhance our understanding of the underlying biological mechanisms.

A common method to evaluate shared heritability in complex disorders is to estimate genetic correlation using linkage disequilibrium score regression.[33] However, genetic correlation, a genome-wide summary measure,[32,34] may conceal shared genetic architecture involving a mixture of concordant and discordant effect directions and does not capture specific overlapping loci and relevant genes.[27,28,35] These characteristics are captured by bivariate causal mixture model (MiXeR)[27] and local analysis of covariant association (LAVA).[35] Genetic overlap can be exploited to boost the discovery of genetic loci for a phenotype[32] and loci shared with other phenotypes using conditional false discovery rate (condFDR) and conjunctional FDR (conjFDR) analyses, respectively.[31,36]

Given the high comorbidity between ANX and psychiatric disorders, we aimed to quantify their genetic overlap. To this end, we applied univariate MiXeR to characterize the polygenic architecture of ANX. We also employed bivariate MiXeR and LAVA to assess the genetic overlap with other psychiatric disorders. To identify genetic loci associated with ANX, we performed a meta-analysis of two GWAS ($n = 301{,}732$) and applied the condFDR method. We then performed conjFDR to identify loci shared between ANX and the psychiatric disorders. Finally, we tested whether polygenic liability to the psychiatric disorders predicted anxiety disorder status in an independent sample.

Methods

Genome-wide association for anxiety

We obtained quantitative anxiety trait (ANX) data from the UK Biobank (UKB) measured using the seven-item Generalized Anxiety Disorder (GAD-7) scale in 2016. Genotype data for white British, unrelated participants ($n = 126{,}569$) was used for the GWAS. The mean age of the participants was 64.3 years (SD, 7.6 years), and 55.9% were female.

GWAS summary statistics data

We obtained GWAS summary statistics for ANX measured as a quantitative trait using the Generalized Anxiety Disorder 2-item scale (GAD-2) from the Million Veterans Program (MVP; United States) ($n = 175{,}163$).[25] The ANX GWAS summary statistics were accessed through the Database of Genotype and Phenotype (dbGaP; phs001672). We obtained GWAS summary statistics for BIP, ADHD, and SCZ from the Psychiatric Genomics Consortium (PGC),[37–39] and MD from a meta-analysis of the PGC and 23andMe, Inc.[40] Similarly, those of ASD were obtained from The Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH) and PGC.[41] The GWAS comprised populations of only European ancestry (Table 1 and Supplementary Methods in Supplement 1).

Target sample for polygenic risk score

We obtained genotype data for a total of 130,992 population-based cohort of mothers and fathers from the Norwegian MoBa (Mother, Father, and Child Cohort Study).[42] MoBa was conducted by the Norwegian Institute of Public Health, and participants were enrolled from all over Norway from 1999 to 2008. The details of sample collection, genotyping, and quality control are provided elsewhere.[43,44] We obtained *ICD-10* psychiatric diagnoses from the Norwegian Patient Registry until June 2022. Data on 95,841 (58.2% females) unrelated participants of European Ancestry were used in the analyses. The mean age of the participants was 49.0 years (SD, 5.5 years). The cases of anxiety disorder ($n = 4469$; 4.7%) comprised agoraphobia (F40.0, $n = 900$; 0.94%), social phobia (F40.1, $n = 1345$; 1.4%), specific phobia (F40.2 = 432; 0.45%), panic disorder (F41.0, $n = 1343$; 1.4%), and generalized anxiety disorder (F41.1, $n = 1742$; 1.8%).

Ethics approval and consent to participate

The MoBa cohort has initially been approved by the Norwegian Data Protection Agency and The Regional Committees for Medical and Health Research Ethics in Norway and is currently regulated by the Norwegian Health Registry Act. The use of MoBa data for this work was approved under (REK 2016/1226). Informed consent was obtained. Individual studies comprising the published data sets have been approved by their respective ethical approval committees. This research was conducted according to the Declaration of Helsinki.

Statistical analysis

GWAS and meta-analysis

We performed GWAS of ANX (GAD-7 scores) among unrelated individuals of European ancestry in the UKB (project number 27412). The GWAS was run using PLINK and applied the following filters: minor allele frequency >0.001, Hardy–Weinberg equilibrium *P*-value >1.0e−09, and genotyping missingness rate <0.1. Age, sex, and the first 20 genotype principal components (PCs) were included as covariates.

We performed a fixed-effects inverse variance–weighted meta-analysis of the anxiety (ANX) GWAS from the MVP and UKB using METAL.[45] The resulting summary statistics ($n = 301{,}732$) were used to investigate genetic overlap and identify ANX loci and shared loci between ANX and psychiatric disorders.

Assessing genetic overlap

We performed MiXeR analyses to investigate the genetic architecture of ANX and its genetic overlap with MD, BIP, SCZ, and ADHD.[27] The ASD GWAS data were not powered for MiXeR analysis. First, we conducted univariate MiXeR analyses to estimate the number of trait-influencing variants explaining 90% of single nucleotide polymorphism (SNP)–based heritability after controlling for linkage disequilibrium (LD). These were followed by bivariate MiXeR analyses to estimate the number of SNPs shared between pairs of phenotypes irrespective of effect direction. We also determined the estimated proportion of shared SNPs between two phenotypes out of the total number of SNPs estimated to influence both phenotypes (Dice coefficients) and the fraction of SNPs with concordant effects in the shared component.[27] Detailed information about MiXeR models is provided in the supplement (Supplementary Methods in Supplement 1).

We employed LAVA to estimate local genetic correlations between ANX and MD, BIP, SCZ, and ADHD.[35] LAVA estimates local genetic correlations across 2495 semi-independent genomic regions of approximately 1 Mb and identifies shared genetic regions with their effect directions.[35] It accounts for sample overlap from the genetic covariance intercept.[33] Also, LAVA estimates the heritability for each genomic region with respect to the phenotypes and then estimates the local genetic covariance between pairs of phenotypes.

Conditional and conjunctional FDRs

We generated quantile–quantile (Q–Q) plots where the *P*-values of SNPs in ANX were plotted conditional on three different cutoffs of *P*-values in the secondary phenotypes (i.e. one of MD, BIP, SCZ, ASD, and ADHD). Q–Q plots with successive leftward and upward deviation compared with the null indicated cross-trait enrichment.[31] We performed condFDR analyses to identify loci associated with ANX. Next, we applied conjFDR analyses to identify loci shared between ANX and the secondary phenotypes.[31,36] In condFDR analysis, the SNP *P*-values in the ANX GWAS summary statistics were re-ranked based on their *P*-values in the GWAS summary statistics of

Table 1. GWAS summary statistics data used for investigation of genetic overlap, discovery of genomic risk loci, and polygenic risk prediction

Phenotype	Number of cases	Number of controls	Effective sample size	Source of data
MVP-ANX[†]	-	-	175,163	MVP[25]
UKB-ANX[†,‡]	-	-	126,569	UKB
META-ANX[†]			301,732	MVP + UKB
MD	246,363	561,190	684,817	PGC-MD + 23andMe[40]
BIP	41,917	371,549	150,670	PGC-BIP[39]
SCZ	53,386	77,258	126,282	PGC-SCZ[38]
ADHD	38,691	186,843	128,214	PGC-ADHD[37]
ASD	18,381	27,969	44,367	iPSYCH + PGC[41]
All ANX[§]	37,517	482,693	150,058	FinnGen

[†]Quantitative trait without case-control dichotomy.
[‡]Project number 27412.
[§]Replication data set comprising genome-wide association studies (GWAS) of various anxiety-related disorders.
ADHD, attention-deficit/hyperactivity disorder; ANX, anxiety symptoms; ASD, autism spectrum disorder; BIP, bipolar disorder; FinnGen, the Finnish Biobank; iPSYCH, the Lundbeck Foundation Initiative for Integrative Psychiatric Research; MD, major depression; META-ANX, Meta-Analysis of the MVP-ANX and UKB-ANX; MVP, Million Veterans Program; PGC, Psychiatric Genomics Consortium; SCZ, schizophrenia; UKB, UK Biobank.

the secondary phenotype. CondFDR leverages the SNPs' association with the secondary phenotype to boost the power to identify novel SNPs associated with the primary phenotype (i.e. anxiety).[31] This boost in power is contingent on the extent of genetic overlap between the two phenotypes.[31,46]

We then performed inverse condFDR analyses with MD, BIP, SCZ, ASD, and ADHD as primary phenotypes, and ANX as the secondary phenotype. We used pairs of condFDR results in conjFDR analyses. The conjFDR value for an SNP is the greater of the condFDR and inverse condFDR values for a pair of phenotypes.[31] A threshold of 5% was used as significant for both condFDR and conjFDR *P*-values. We excluded SNPs within the extended major histocompatibility complex region and chromosome 8p23.1 inversion (genome build 19 positions of chr6:25,119,106–33,854,733 and chr8:7,200,000–12,500,000, respectively) from the condFDR model fit procedure, but not from the discovery analyses.[47] All of the *P*-values were corrected for inflation using a genomic inflation control procedure as previously described (Supplementary Methods in Supplement 1).[36]

Definition of genomic loci

We designated independent genomic loci according to the functional mapping and gene annotation (FUMA) protocol.[48] We specified candidate SNPs as any SNP with condFDR or conjFDR <0.05, and candidate SNPs with LD $r^2 < 0.6$ with each other as independent significant SNPs. Lead SNPs were defined as independent SNPs with LD $r^2 < 0.1$. The candidate SNPs in LD $r^2 \geq 0.6$ with a lead SNP delineated the boundaries of a genomic locus. We defined candidate SNPs positioned within the boundaries of a genomic locus to correspond to an independent genomic locus. We obtained LD information from the 1000 Genomes Project European reference panel.[49] In conjFDR, we compared the *z* scores of each lead SNP for locus in GWAS summary statistics corresponding to the phenotypes. We defined novel risk loci as genomic loci not identified in the GWAS catalog for ANX and anxiety disorder (accessed in January 2024) and in published GWAS.[21,24–26,50–57]

Consistency of genetic effects in an independent sample

We performed a left-sided binomial test of lead SNPs for concordant effect directions in the discovery (GWAS used for condFDR) and independent data set from the Finnish population (FinnGen, https://r10.finngen.fi/). The independent data set comprised GWAS summary statistics of lifetime anxiety disorders based on *ICD-10* diagnoses (Table 1).

Functional annotations and gene set analyses

We performed functional gene mapping for lead SNPs from cond/conjFDR using the OpenTargets platform (https://genetics.opentargets.org/).[58] For each lead SNP, the gene with the highest overall score was selected. We used the mapped genes for gene set analyses conducted using the GENE2FUNC analyses in FUMA. We also obtained Combined Annotation Dependent Depletion (CADD) scores, which show how deleterious the SNP is on protein function,[59] and RegulomeDB scores, which predicted the regulatory function of the SNP from FUMA.[60] We obtained the expression of genes identified in 54 different human tissues using Genotype-Tissue Expression project.[61]

Polygenic risk scores

In MoBa, we restricted the polygenic risk score (PRS) analyses to individuals of European ancestry selected based on genotype PCs as described elsewhere.[62] We used a kinship coefficient >0.05 to exclude one of the related pairs while prioritizing individuals with anxiety disorders. When two related individuals had anxiety disorder, one of them was selected randomly. We used PRSice[63] to calculate PRSs at different *P*-value thresholds (i.e. 5e−8, 1e−6, 1e−5, 1e−4, 1e−3, 1e−2, 5e−2, 1e−1, 5e−1, 1) using the GWAS summary statistics for ANX, MD, BIP, ADHD, ASD, and SCZ (Table 1). Subsequently, we extracted the first PC for each PRS across all *P*-value thresholds.[64] Next, we used logistic regression to estimate PRS association with anxiety disorder using models that included the PRS of the disorder, and age, sex, and the first 10 genotype PCs as covariates. The combined model included PRSs for all six psychiatric phenotypes, and covariates: age, sex, and the first 10 genotype PCs.

Results

Polygenicity and genetic overlap

MiXeR analyses showed that ANX is a polygenic trait with 12.9k ± 1.2k (mean ± SD) trait-influencing variants contributing to 90% of its heritability (Supplement 2: Table S1). The estimated SNP heritability of ANX was 5.1 ± 0.3% (Table 2). The other psychiatric disorders are also polygenic, each with the following numbers of trait-influencing variants: MD 13.9k ± 0.4k, BIP 8.6k ± 0.2k, SCZ 9.6k ± 0.2k, and ADHD 7.7k ± 0.4k (Supplement 2: Tables S2–S5), as previously reported.[28,37]

Table 2. SNP heritability and genetic correlation parameters between anxiety and psychiatric disorders from LD score regression analyses

		Genetic correlation (r_g, [SE]; *P*-value)				
Phenotypes	SNP heritability (h^2, [SE]; *P*-value*)	ANX	MD	BIP	SCZ	ADHD
ANX	0.051 (0.003); 4.1e−65	1.00		-		
MD	0.065 (0.002); 5.3e−232	0.66 (0.02); 6.45e−193	1.00			
BIP	0.198 (0.008); 1.5e−135	0.24 (0.03); 4.19e−17	0.45 (0.02); 5.7e−117	1.00		
SCZ	0.384 (0.013); 4.6e−192	0.30 (0.03); 5.07e−32	0.35 (0.02); 4.7e−76	0.70 (0.02); 0.0	1.00	
ADHD	0.167 (0.008); 4.5e−97	0.37 (0.03); 6.32e−33	0.49 (0.02); 8.3e−99	0.23 (0.03); 7.4e−17	0.20 (0.02); 1.2e−17	1.00
ASD	0.210 (0.016); 9.7e−38	0.18 (0.05); 2.00e−04	0.40 (0.03); 1.6e−42	0.22 (0.04); 5.1e−08	0.26 (0.03); 7.5e−14	0.53 (0.04); 7.7e−38

*Computed using the cumulative distribution function for one-tailed test using the formula: *P*-value = pnorm(0, h^2, SE).
ADHD, attention-deficit/hyperactivity disorder; ANX, anxiety symptoms; ASD, autism spectrum disorder; BIP, bipolar disorder; LD, linkage disequilibrium; MD, major depression; r_g, genetic correlation; SCZ, schizophrenia; SE, standard error; SNP, single nucleotide polymorphism.

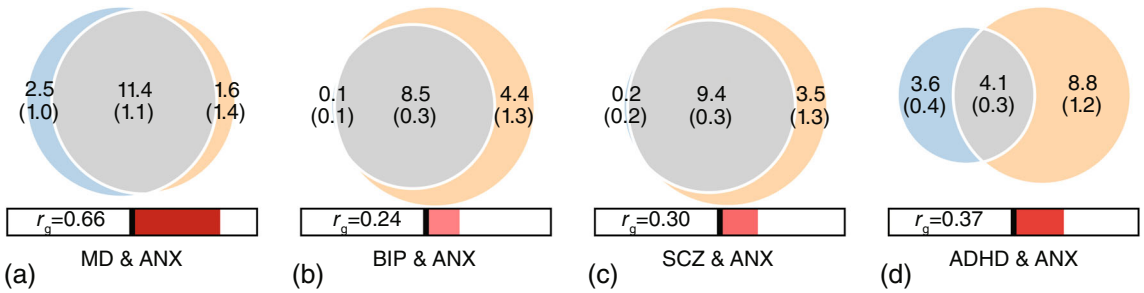

Fig. 1 (a–d) Bivariate causal mixture model (MiXeR): genome-wide genetic overlap between anxiety symptoms (ANX) and major depression (MD), bipolar disorder (BIP), schizophrenia (SCZ), and attention-deficit/hyperactivity disorder (ADHD). r_g, genetic correlation. The numbers indicate estimates of trait-influencing variants in the thousands. Colors: gray, shared variants; orange, variants unique to ANX; and blue, variants unique to MD, BIP, SCZ, or ADHD.

In bivariate MiXeR analyses, ANX exhibited a large genetic overlap with psychiatric disorders as demonstrated by the number of shared variants with MD (11.4k ± 1.1k), BIP (8.5k ± 0.3k), SCZ (9.4k ± 0.3k), and ADHD (4.1k ± 0.3k) (Fig. 1a–d). The Dice coefficients also indicated substantial overlap with MD (84.7%), BIP (79.3%), SCZ (84.0%), and to a lesser extent ADHD (39.7%). Most variants shared between ANX, and the psychiatric disorders had concordant effect directions, with 92% for ADHD, 82% for MD, 60% for BIP, and 61% for SCZ (Supplement 2: Tables S6–S9). The GWAS summary statistics for ASD lacked statistical power for MiXeR. Genome-wide genetic correlations using LD score regression showed positive genetic correlations (r_g) between ANX and all five psychiatric disorders (Table 2). Further, ANX[25] had a significant positive genetic correlation with anxiety disorders[21] ($r_g = 0.69, \mathrm{SE} = 0.05, P = 1.9e^{-40}$).

LAVA also showed that several regions had positive genetic correlations between ANX and MD ($n = 17$), SCZ ($n = 6$), ADHD ($n = 3$), and BIP ($n = 1$) after Bonferroni correction. Only one region identified had a significant negative genetic correlation between ANX and SCZ (Fig. 2a–d; Supplement 2: Table S10).

Cross-trait polygenic enrichment

The Q–Q plots SNP *P*-values for ANX exhibited upward and leftward deviation when conditioned on progressively smaller *P*-value thresholds from each of MD, BIP, SCZ, ASD, and ADHD (Supplement 1: Fig. S1). The pattern of Q–Q plots was consistent with cross-trait polygenic enrichment between ANX and each of the psychiatric disorders.

Identification of genetic loci for anxiety

The meta-analysis identified 11 loci associated with ANX, of which four were novel (Fig. 3, Table 3). Further, we leveraged the cross-trait enrichment and genetic overlap between ANX and psychiatric disorders to identify genomic loci for ANX. The condFDR analyses identified 184 unique loci associated with ANX (condFDR <0.05), of which 119 (64%) were novel (Supplement 3: Tables S11–S15). When tested collectively, the lead SNPs of ANX loci showed a significant concordance of effect directions in the independent GWAS of lifetime anxiety disorders (Table 4).

Genomic loci shared between anxiety and psychiatric disorders

We identified 117 loci shared between ANX and psychiatric disorders (conjFDR <0.05). Notably, ANX and MD had 47 jointly associated loci with concordant effect direction. There were 71 loci shared between ANX and SCZ with 52 having a concordant effect. Twenty-four of the 33 shared loci between ANX and BIP, 19 of the 20 loci shared between ANX and ADHD, and four of the five loci shared between ANX and ASD had concordant effects (Supplement 3: Tables S16–S20).

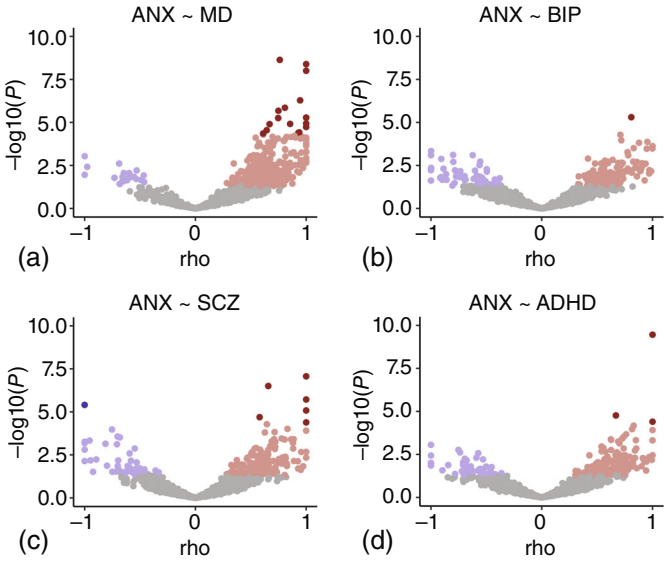

Fig. 2 (a–d) Local analysis of covariant association (LAVA): volcano plots of local genetic correlation coefficients (rho) with $-\log_{10}P$ values for each locus. Dark red dots represent significantly correlated loci after Bonferroni correction. ADHD, attention-deficit/hyperactivity disorder; ANX, anxiety symptoms; BIP, bipolar disorder; MD, major depression; SCZ, schizophrenia.

Many of the joint loci were shared across different pairs of traits in conjFDR analysis (Supplement 1: Fig. S2).

Functional annotations and gene set analyses

The lead SNPs for the four novel ANX loci identified in the meta-analysis were intronic and included rs3103257 (*NPPC*), rs6961970 (*FOXP2*), rs143042901 (*PLEKHA1*), and rs11841641 (*DIAPH3*) (Table 3). Two lead SNPs, rs3103257 (*NPPC*) and rs6961970 (*FOXP2*), may have functional significance, as indicated by high CADD (Supplement 3: Table S21). Most lead SNPs in the ANX loci identified from condFDR were either intronic or intergenic, while four of them were exonic: rs3825393 (*MYO1H*), rs4969391 (*BAIAP2*), rs1468291 (*SERGEF*), and rs61753077 (*TACC2*) (Supplement 3: Tables S11–S15). Lead SNPs shared between ANX and MD (rs3793577 and rs3825393), ANX and BIP (rs10497655, rs4702 and rs34961470), ANX and SCZ (rs10497655, rs4702, rs564, rs898031 and rs13262595), ANX and ASD (rs2668653), and ANX and ADHD (rs61687445 and rs56403421) had a CADD score >12.37 (Supplement 3: Tables S16–S20).

Gene set analyses of genes annotated to ANX loci with condFDR revealed enrichment of biological processes relevant to neurodevelopment such as neurogenesis (Supplement 4: Table S22). The top enriched cellular components for genes annotated to loci identified for ANX and those shared with psychiatric disorders converged to the synapse, synaptic membrane, and site of polarized growth. ANX loci were also enriched for pathways relevant to cell adhesion and neurofibrillary tangle (Supplement 4: Tables S23 and S24).

Enrichment analysis of the genes annotated to ANX loci showed differential expression in the brain, cardiovascular, gastrointestinal, genitourinary and adipose tissues, and the adrenal gland. In contrast, enrichment analysis of the genes annotated to the loci shared between ANX and the psychiatric disorders showed differential expression in the brain and cardiovascular tissues (Supplement 1: Figs. S3,S4).

Polygenic risk scores

The PRS for each of the psychiatric disorders and ANX were positively associated with anxiety disorders ($P < 5.8e{-}05$, Bonferroni-corrected). MD PRS had a larger effect estimate than all other PRSs. Nagelkerke R^2 showed that MD PRS explained the largest proportion of liability for anxiety disorders (1.51%) followed by ANX PRS (0.41%) (Fig. 4a,b; Supplement 5: Table S25). In a multiple regression model, the estimates for the associations remained significant for all except PRS of ASD and BIP (Supplement 5: Table S26).

Discussion

Here, we showed that ANX are highly polygenic with nearly 13,000 trait-influencing genetic variants, with extensive genetic overlap with other psychiatric disorders. Overlapping variants were the largest for ANX and MD, BIP, and SCZ, and a relatively smaller overlap between ANX and ADHD. The proportion of variants with concordant effects within the shared component was the highest for ADHD (92%) and lowest for BIP (60%). LAVA revealed predominantly positively correlated regions. We identified 119 novel ANX loci and 117 loci shared between ANX and psychiatric disorders, with most loci having concordant effects. Consistent with these, polygenic liabilities for the different psychiatric disorders predicted a lifetime clinical diagnosis of anxiety disorders in the independent sample, further supporting a shared genetic risk.

The observed high polygenicity of ANX is important as common genetic variants contribute to much of its heritability.[21] We also show that variants in ANX exhibit low discoverability and hence require studies with large sample sizes for genome-wide discoveries. This may partly explain the observed difference between the SNP heritability we found or that reported in other GWAS[21,25] and the PRS performance. Our comprehensive characterization of genetic overlap between ANX and MD, BIP, SCZ, and ADHD using methods agnostic to effect directions, enhances our understanding beyond genetic correlations.[25] Genetic correlations alone are high for ANX and other internalizing disorders,[25] whereas our results from MiXeR revealed extensive overlap with externalizing disorders as well. Further, the higher genetic correlation between ANX and ADHD, despite a smaller genetic overlap compared with ANX and BIP, is likely attributable to similar effect directions for most shared genetic variants with ADHD.[27] The local genetic correlations are consistent with those previously reported.[65] However, we found more correlated genomic regions between ANX and MD, SCZ, and ADHD probably because of the larger statistical power of GWAS data used in this study.

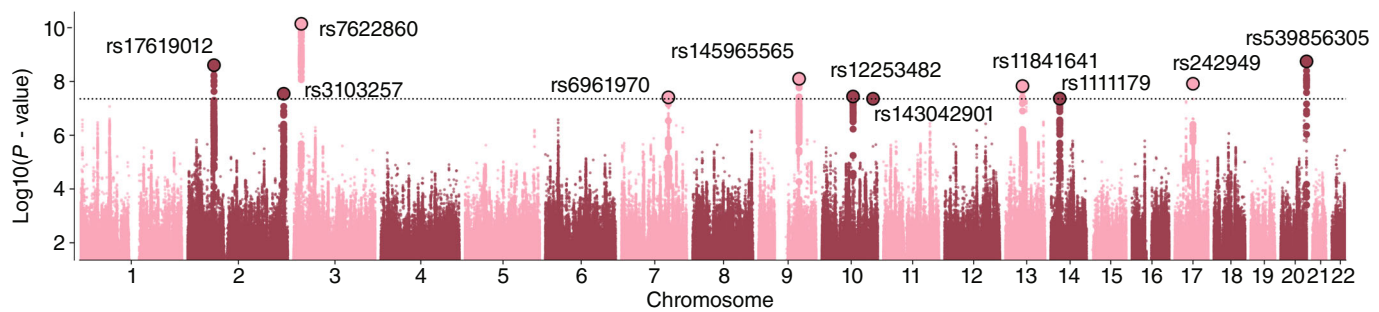

Fig. 3 Manhattan plot. Genomic risk loci associated with anxiety. Circled dots indicate the lead single nucleotide polymorphisms with genome-wide significance.

Table 3. Genetic risk loci for anxiety identified from a meta-analysis of GWAS

CHR: Position[†]	SNP	A1	A2	Gene[‡]	Function	Beta (SE)	*P*-value
2: 63893589	rs17619012	T	G	*WDPCP*	intergenic	−0.023 (0.0039)	2.80e−09
2: 233005775	rs3103257	A	G	*NPPC*	intronic	0.020 (0.0036)	3.23e−08
3: 18795765	rs7622860	A	C	*SATB1*	ncRNA_intronic	0.023 (0.0036)	8.09e−11
7: 113901132	rs6961970	A	C	*FOXP2*	intronic	0.021 (0.0038)	4.40e−08
9: 98273305	rs145965565	T	G	*PTCH1*	intronic	−0.032 (0.0056)	8.99e−09
10: 75496130	rs12253482	A	G	*CAMK2G*	ncRNA_intronic	0.018 (0.0033)	4.09e−08
10: 124012277	rs143042901	A	G	*PLEKHA1*	intronic	−0.050 (0.0092)	4.98e−08
13: 60362163	rs11841641	T	C	*DIAPH3*	intronic	0.040 (0.007)	1.67e−08
14: 42075952	rs1111179	T	G	*LRFN5*	upstream	−0.018 (0.0032)	4.90e−08
17: 43911716	rs242949	T	G	*MAPT*	intronic	−0.019 (0.0033)	1.37e−08
20: 62714171	rs539856305	T	G	*OPRL1*	intronic	0.034 (0.0057)	2.02e−09

[†]Based on genome build hg19.

[‡]Genes annotations were based on the highest overall score in OpenTargets.

The rows with novel loci are shaded in gray.

A1, effect allele; A2, other allele; CHR, chromosome; GWAS, genome-wide association studies; SE, standard error; SNP, single nucleotide polymorphism.

Table 4. Collective test of concordance of effect directions between genetic variants identified for ANX (condFDR) and corresponding variants in independent GWAS of anxiety disorders from the Finnish population (FinnGen)

CondFDR Phenotype pairs	ANX loci (*n*)	SNPs in the replication data set (*n*)	SNPs with concordant effects, *n* (%)	*P*-value*
ANX|MD	81	79	69 (87)	2.77e−12
ANX|BIP	61	60	49 (82)	3.78e−07
ANX|SCZ	105	105	88 (84)	4.98e−13
ANX|ADHD	57	57	47 (82)	3.76e−07
ANX|ASD	34	32	26 (81)	2.68e−04

*One-sided binomial test.

ADHD, attention-deficit/hyperactivity disorder; ANX, anxiety symptoms; ASD, autism spectrum disorder; BIP, bipolar disorder; condFDR, conditional false discovery rate; FDR, false discovery rate; FinnGen, the Finnish Biobank; GWAS, genome-wide association study; MD, major depression; SCZ, schizophrenia; SNP, single nucleotide polymorphism.

The substantial genetic overlap with psychiatric disorders enabled us to identify numerous ANX loci. Thorp *et al.*,[26] using different methods, reported a boost in the discovery of ANX loci by leveraging related traits. The identification of novel loci revealed biological pathways potentially involved in the pathophysiology of ANX.[48] Genes annotated to the ANX loci were enriched for pathways linked to neurodevelopment and cellular components related to the synapse implicating neurodevelopmental factors in the pathophysiology of anxiety phenotypes.[66] Pathways related to synaptic biology are relevant to discovering potential drug targets.[67] The shared loci between ANX and psychiatric disorders and the enriched biological pathways suggest shared mechanisms related to neurotransmission. We speculate that such shared biological pathways may underlie the high prevalence of ANX among individuals with psychiatric disorders. The relatively higher number of loci shared between ANX and SCZ, despite only a moderate genetic correlation, could be attributed to the greater statistical power of SCZ GWAS compared with that of MD. Also, the small number of shared loci for ANX and ASD may be attributable to the low power of ASD GWAS data.

Identifying novel loci offers valuable insight into the biology of ANX and their potential molecular mechanisms, especially regarding comorbid conditions. For example, *FOXP2* encodes a transcription factor involved in regulation of gene expression in the human brain.[68] Mutations in the gene have been associated with speech-language disorders[69] and a heightened risk of anxiety and depressive disorders.[70] Similarly, *NPPC*, which encodes a preproprotein for natriuretic peptides, may contribute to the association between anxiety disorders and cardiovascular diseases.[71] Natriuretic peptides can alleviate panic attacks,[72] suggesting a potential therapeutic avenue for anxiety disorders.[73,74] Additionally, one study has found an inverse correlation between plasma levels of atrial natriuretic propeptide and anxiety in patients with severe heart failure.[75] The protein-coding gene *DIAPH3*, involved in cell adhesion and motility, is known to play a critical role in cortical neurogenesis,[76,77] further highlighting its relevance to mental disorders. Furthermore, *PLEKHA1* has been implicated in both depressive symptoms and type 2 diabetes indicating pleiotropy.[78] The majority of identified loci are in noncoding regions that are implicated in various diseases,[79] highlighting the role of gene regulatory elements in the biology of ANX. Overall, these findings align with observations that anxiety disorders frequently coexist with various psychiatric and somatic conditions. They provide novel insight into the

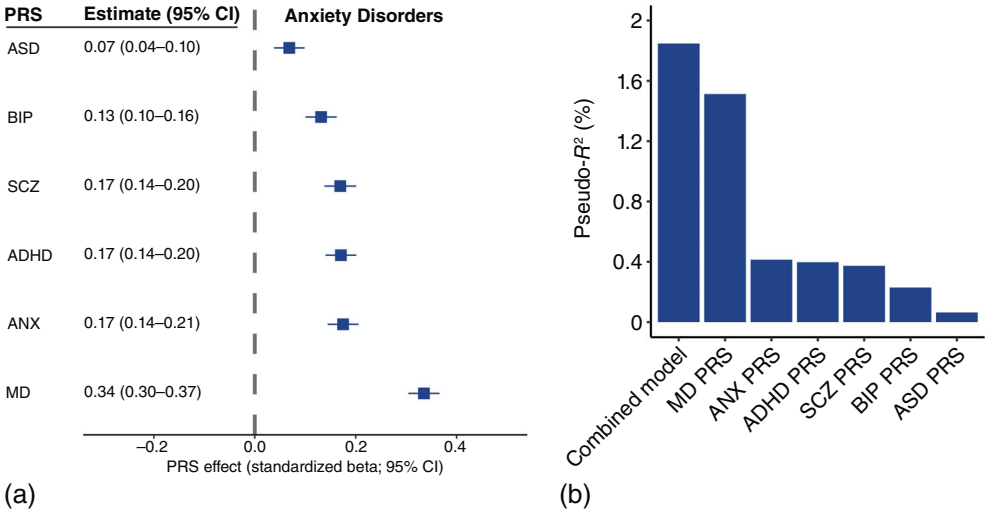

Fig. 4 (a,b) Logistic regression: the association between polygenic risk scores (PRS) of various psychiatric disorders and anxiety disorders in MoBa (Mother, Father, and Child Cohort Study) parents. (a) Models for the PRS of anxiety symptoms (ANX), attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), bipolar disorder (BIP), major depression (MD), schizophrenia (SCZ), and covariates. (b) Nagelkerke R^2 showing the difference in the percentage of prediction of anxiety traits by each PRS over a base model that includes age, sex, and genotype principal components. CI, confidence interval.

underlying shared molecular pathways and may assist in improving the treatment of comorbid anxiety disorders, as well as symptoms of anxiety.

Notably, the genes annotated to ANX loci showed differential tissue expression in a broad range of tissues including the brain, gastrointestinal, cardiovascular, and endocrine tissues. While these may be caused by comorbidity between anxiety disorders and medical conditions,[80,81] we argue that ANX has a stronger somatic component involving various organ systems than other psychiatric disorders. Also, the genetic risk for ANX may influence risk through a more diverse set of tissues than other psychiatric disorders, as demonstrated in animal models.[82]

The measures of ANX, i.e. the GAD-7 and its shorter version GAD-2, are well-established tools with comparable psychometric properties.[83] ANX as a dimensional trait in GWAS may have the advantage of capturing several of the anxiety disorders, as well as subsyndromal ANX,[83] both of which have important clinical implications. The recognition of co-occurring symptoms of anxiety is highlighted by the diagnostic specifier 'anxious distress' in *DSM-5*.[1,84,85] Anxious distress can adversely affect the severity and clinical outcome of primary psychiatric disorders.[84,86] Our findings suggest that concurrent ANX across diagnostic categories can partly be attributed to shared genetic underpinnings. As more powered GWAS data for ASD become available, applying statistical tools for further investigation of its shared genetic architecture becomes possible.

The primary GWAS phenotype ANX is a dimensional trait defined based on self-reported GAD-2 or GAD-7 and refers to symptoms experienced in the preceding 2 weeks rather than a lifetime clinical diagnosis of anxiety disorders. This may have contributed to the low proportion of polygenic liability for lifetime anxiety disorders explained by the ANX PRS. Further underestimation may arise from the low prevalence of anxiety disorders in the target sample, a limitation of patient registry data that do not account for individuals with anxiety disorders who do not seek help. Since individuals with a history of diagnosis of depression were not excluded from the ANX GWAS, the genetic overlap between ANX and MD could partly be attributed to comorbidity. We conducted our analyses on GWAS data from populations of European ancestry, thus the results may not be generalizable to other ancestries. As multiancestry GWAS data become available, our methods can then be applied to improve genetic discoveries for anxiety.

In conclusion, our investigation of the genetic architecture of ANX revealed a high polygenicity and low discoverability. We found a large genetic overlap between anxiety and psychiatric disorders, which enabled the identification of 119 novel ANX loci and 117 shared loci. The shared genetic architecture may underlie the high burden of ANX in individuals with other psychiatric disorders. The genetic risk for anxiety may involve pathophysiology in neurodevelopment and neurotransmission. The genes annotated to ANX loci implicated a broad range of biological pathways and differential tissue expression in diverse tissues. Our findings advance our understanding of the pathophysiology of ANX across psychiatric disorders and may help in the identification of potential drug targets. Further research is needed to investigate the genetic underpinnings of specific types of anxiety disorders.

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Disclosure statement

O.A.A. is a consultant for Cortechs.ai and Precision Health, and has received speaker's honoraria from Lundbeck, Janssen, Otsuka, and Sunovion. S.D. has received speaker's honoraria from Lundbeck. A.M.D. is Founding Director, holds equity in CorTechs Labs, Inc. (DBA Cortechs.ai), and serves on its Board of Directors and the Scientific Advisory Board. He is an unpaid consultant for Oslo University Hospital. The terms of these arrangements have been reviewed and approved by the University of California, San Diego, in accordance with its conflict-of-interest policies. O.F. is a consultant for Precision Health. P.P. has received conference travel support from the Digital Life Norway Research School, supported by the Research

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Author contributions

M.T., K.S.O., and O.A.A. conceived and designed the analysis. K.S.O., Z.R., O.F., A.M.D., and O.A.A. contributed to analysis tools. M.T., P.J., K.S.O., D.V.M., and A.S. performed the analyses. M.T. wrote the first draft of the manuscript. All authors contributed to the interpretation of the findings, provided critical intellectual content, and approved the final manuscript.

Data availability statement

MVP anxiety GWAS can be accessed at https://www.ncbi.nlm.nih.gov/gap/, (dbGaP: phs001672). The GWAS summary statistics for ANX based on data from the UKB can be accessed at https://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90429001-GCST90430000/GCST90429699/. PGC data are available at https://www.med.unc.edu/pgc/download-results/. GWAS summary statistics for the 23andMe DEP dataset will be available through 23andMe to qualified researchers under an agreement with 23andMe that protects the privacy of the 23andMe participants. Interested investigators should email dataset-request@23andme.com and reference this paper for more information. Access to the MoBa data can be obtained by applying to the Norwegian Institute of Public Health (NIPH). Restrictions apply regarding the availability of the MoBa data, and therefore, it is not publicly available. Access can be given after approval provided that the applications are consistent with the consent provided by participants. Detailed information on the application can be found on the NIPH website at https://www.fhi.no/en/studies/moba/. The cond/conjFDR and MiXeR codes are freely available online at https://github.com/precimed/pleiofdr and https://github.com/precimed/mixer, respectively.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section at the end of this article.