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Dissecting the shared genetic basis of migraine and mental disorders using novel statistical tools

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Migraine is three times more prevalent in people with bipolar disorder or depression. The relationship between schizophrenia and migraine is less certain although glutamatergic and serotonergic neurotransmission are implicated in both. A shared genetic basis to migraine and mental disorders has been suggested but previous studies have reported weak or non-significant genetic correlations and five shared risk loci. Using the largest samples to date and novel statistical tools, we aimed to determine the extent to which migraine’s polygenic architecture overlaps with bipolar disorder, depression and schizophrenia beyond genetic correlation, and to identify shared genetic loci.

Summary statistics from genome-wide association studies were acquired from large-scale consortia for migraine (n cases = 59 674; n controls = 316 078), bipolar disorder (n cases = 20 352; n controls = 31 358), depression (n cases = 170 756; n controls = 328 443) and schizophrenia (n cases = 40 675, n controls = 64 643). We applied the bivariate causal mixture model to estimate the number of disorder-influencing variants shared between migraine and each mental disorder, and the conditional/conjunctive false discovery rate method to identify shared loci. Loci were functionally characterized to provide biological insights.

Univariate MiXeR analysis revealed that migraine was substantially less polygenic (2.8K disorder-influencing variants) compared to mental disorders (8100–12 300 disorder-influencing variants). Bivariate analysis estimated that 800 (SD = 300), 2100 (SD = 100) and 2300 (SD = 300) variants were shared between bipolar disorder, depression and schizophrenia, respectively. There was also extensive overlap with intelligence (1800, SD = 300) and educational attainment (2100, SD = 300) but not height (1000, SD = 100). We next identified 14 loci jointly associated with migraine and depression and 36 loci jointly associated with migraine and schizophrenia, with evidence of consistent genetic effects in independent samples. No loci were associated with migraine and bipolar disorder. Functional annotation mapped 37 and 298 genes to migraine and each of depression and schizophrenia, respectively, including several novel putative migraine genes such as *L3MBTL2*, *CACNB2* and *SLC9B1*. Gene-set analysis identified several putative gene sets enriched with mapped genes including transmembrane transport in migraine and schizophrenia.

Most migraine-influencing variants were predicted to influence depression and schizophrenia, although a minority of mental disorder-influencing variants were shared with migraine due to the difference in polygenicity. Similar overlap with other brain-related phenotypes suggests this represents a pool of ‘pleiotropic’ variants that influence vulnerability to diverse brain-related disorders and traits. We also identified specific loci shared between migraine

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and each of depression and schizophrenia, implicating shared molecular mechanisms and highlighting candidate migraine genes for experimental validation.

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Abbreviations: cond/conjFDR = conditional/conjunctional false discovery rate; GWAS = genome-wide association study; LD = linkage disequilibrium; MiXeR = bivariate causal mixture model; SNP = single nucleotide polymorphism

Introduction

People with migraine are three times more likely to suffer from bipolar disorder or depression than the general population and vice versa.^{1–5} The clinical overlap between schizophrenia and migraine is less well delineated. Epidemiological studies report positive,⁶ negative⁷ or no association,⁸ but are limited by small or non-representative samples. Nonetheless, several neurobiological systems are implicated in both disorders, including serotonergic⁹ and glutamatergic dysfunction.¹⁰ It has been hypothesized that a shared genetic basis contributes to the phenotypic and patho-aetiological overlap observed between migraine and mental disorders.¹¹

Although the aetiologies of all four disorders remain elusive,^{12–15} twin studies have revealed strong genetic influences, with broad-sense heritabilities of ~40% for migraine and between 40% and 80% for mental disorders.^{16–19} Genome-wide association studies (GWAS), which test for association between a disorder and

millions of common single nucleotide polymorphisms (SNPs), have since demonstrated that approximately half of the total heritability for each disorder is due to common genetic variants.^{20–23} GWAS have also identified 38, 30, 102 and 176 genetic risk loci for migraine, bipolar disorder, depression and schizophrenia, respectively, with the latest migraine GWAS implicating a predominance of genes expressed in vascular tissues.^{20–23} However, thousands of variants are predicted to influence their risk with small effects, the majority of which have not been discovered.²⁴ The discovery of disorder-influencing variants (also referred to as 'causal variants') is further complicated by the tendency for physically approximate alleles to be inherited together, termed linkage disequilibrium (LD). SNP effect sizes are therefore highly correlated across blocks of SNPs, effectively concealing disorder-influencing variants among large numbers of correlated SNPs.

Traditional methods investigating genetic overlap include genetic correlation and polygenic risk scores, which return a single estimate of genome-wide genetic overlap. A significant positive

genetic correlation of 0.32 has been reported between migraine and depression but not bipolar disorder or schizophrenia.²⁵ This implies that increased genetic risk of migraine increases risk of depression and vice versa, possibly contributing to their comorbidity, but not for bipolar disorder or schizophrenia. An increased polygenic risk score for schizophrenia was also associated with reduced risk of migraine, although this study was limited by small sample sizes.¹⁰ An important limitation to genetic correlation and polygenic risk scores, however, is that they require a predominant correlation of effect sizes across all SNPs between two traits, which may not be the case with brain-related traits where genetic effects with a mixture of same and opposite effect directions have been reported in several cross-GWAS analyses (Fig. 1).^{27–29} In contrast, the bivariate causal mixture model (MiXeR) provides a ‘bird’s eye view’ of genetic overlap by first inferring the total number of disorder-influencing variants beyond the confounding effect of LD. This is a key advance on standard frameworks such as linkage disequilibrium score regression (LDSR), which are based on the infinitesimal model that assumes that all variants have an infinitesimally small effect on all phenotypes.³⁰ Bivariate analysis next estimates the total number of shared and unique variants influencing two traits regardless of effect direction.³¹ This has enabled the discovery of extensive genetic overlap between brain-related traits with non-significant genetic correlation and a mixture of variants with same and opposite effect directions.^{26,29,32,33} While this indicates that genetic risk for one disorder does not correlate with risk for the second at the genome-wide level, this is nevertheless biologically relevant since it may suggest shared molecular mechanisms.³⁴ It is important to note, however, that MiXeR only estimates the number of disorder-influencing variants, without identifying genomic loci hosting those variants.

Identifying genetic overlap at the individual locus level is therefore essential to obtain biological insights. Previously, cross-GWAS analysis identified three SNPs associated with migraine and depression, two of which mapped to the *ANKK1B* and *KCNK5* genes, respectively.³⁵ However, standard cross-GWAS techniques rely on family-wise error rate-based methods, requiring massive correction for multiple testing which limits the statistical power to discover shared genetic loci.³⁶ In contrast, the conditional/conjunctive false discovery rate method (cond/conjFDR) uses a Bayesian approach that leverages information from two GWAS to identify shared loci without the same loss in statistical power, thus increasing the yield in comparison to standard approaches.^{32,36}

Despite their comorbidity, there have been few attempts to investigate genetic overlap between migraine and bipolar disorder, depression and schizophrenia, which possess overlapping symptom profiles, large proportions of overlapping common genetic variants,^{26,31} and moderate-to-strong positive genetic correlation ($r_g = 0.3–0.7$).²⁵ Understanding how migraine’s genetic determinants relate to this clinico-genetic spectrum may offer insights into the landscape of shared genetic architecture across brain-related traits and highlight putative shared aetiological processes, with potential applications to personalized treatment. It can also form the basis for follow-up experimental studies to determine the biological significance of the overlapping regions.

We therefore applied MiXeR and cond/conjFDR to GWAS summary statistics to (i) describe the shared genetic architecture of migraine and mental disorders beyond genetic correlations; (ii) identify and characterize specific shared genomic loci; and (iii) identify novel risk loci for migraine.

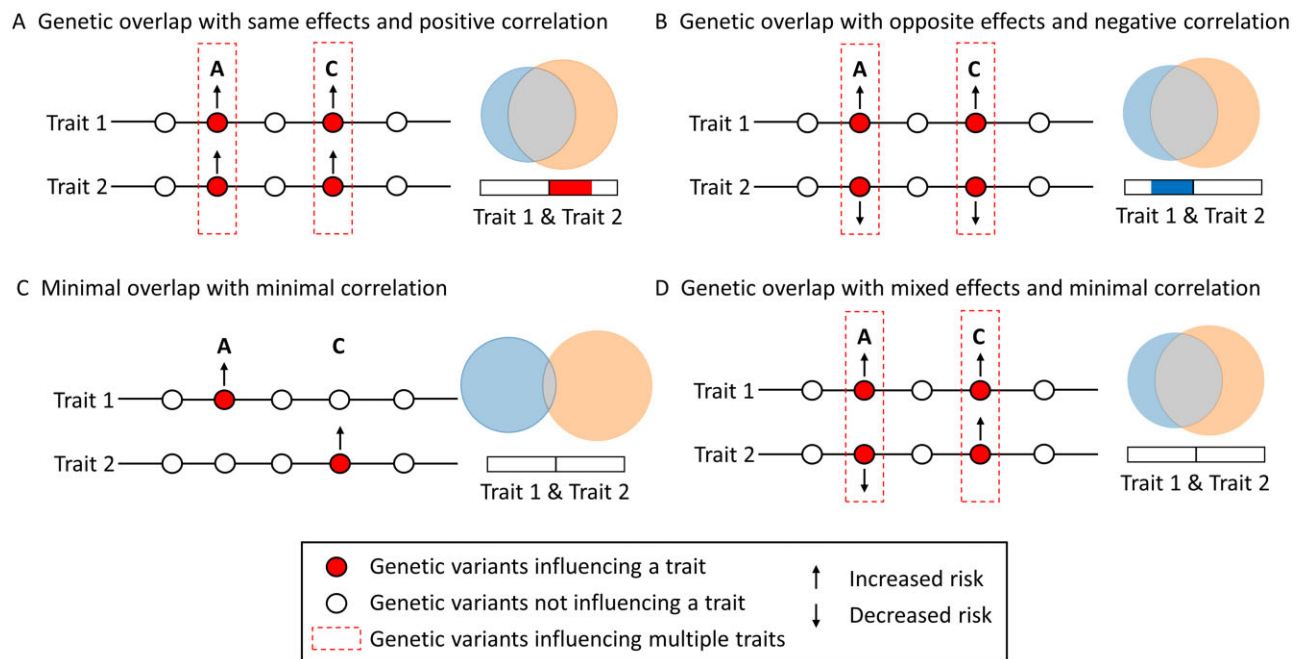


Figure 1 Conceptual figure illustrating MiXeR’s ability to characterise genetic overlap beyond genetic correlation adapted from Smeland et al.²⁶ Four scenarios of genetic overlap (A–D) with corresponding MiXeR Venn diagrams and genetic correlations. Genetic overlap with a preponderance of shared variants with the same (A) or opposite (B) effect directions results in either positive (A, red bar) or negative (B, blue bar) genetic correlation. However, since genetic correlation provides an estimate of the correlation of effect sizes between two traits, it is unable to discriminate between scenarios C and D, both of which return minimal genetic correlations. In contrast, since MiXeR estimates the number of shared variants regardless of effect direction, MiXeR successfully estimates more extensive genetic overlap in D compared to C, represented by the larger shared component (grey).

Materials and methods

Samples

We acquired summary statistics for migraine, comprising 59 674 cases and 316 078 controls, including self-reported migraine²¹ and a replication sample comprising 18 682 cases and 362 593 controls.^{37,38} The bipolar disorder sample comprised 20 352 cases and 31 358 controls,²⁰ the depression sample 170 756 cases and 328 443 controls,^{39,40} and the schizophrenia sample 40 675 cases and 64 643 controls.⁴¹ Studies were published between June 2016 and May 2019 and selected to maximize available sample size. For further details, including data availability and additional replication samples, see the [Supplementary material](#). Full genotyping procedures are detailed in the original publications. The Regional Committee for Medical and Health Research Ethics South-East Norway evaluated the protocol and found that no additional ethical approval was required because no individual data were used.

Data analysis

We applied MiXeR v.1.3 to quantify polygenic overlap between migraine and mental disorders.³¹ We constructed a univariate mixture model to estimate the number of disorder-influencing SNPs based on the distributions of the primary GWAS test statistics (i.e. SNPs underlying the association with the disorder beyond LD, also termed ‘casual SNPs’). Next, a bivariate gaussian mixture model was constructed to quantify the additive effect of four components: (i) SNPs not influencing either phenotype; SNPs uniquely influencing either the (ii) primary; or (iii) secondary phenotype (unique disorder-influencing SNPs); and (iv) SNPs influencing both phenotypes (shared disorder-influencing SNPs). Results were presented as Venn diagrams displaying the proportion of unique and shared SNPs. Model fit was based on likelihood maximization of signed test statistics (GWAS z-scores), the Akaike Information Criterion (AIC) and predicted versus observed conditional quantile–quantile (Q-Q) plots ([Supplementary material](#)). We also calculated LD score regression based genetic correlations.⁴²

We next applied cond/conjFDR, which leverages polygenic overlap between two traits to boost statistical power to identify novel loci associated with a single trait (condFDR) and loci jointly associated with two traits (conjFDR).³⁶ Cross-trait enrichment of SNP associations between migraine and each mental disorder was visualized using conditional Q-Q plots. The condFDR value of each SNP was computed for migraine conditional on mental disorders and vice versa. CondFDR represents the probability that a SNP is not associated with the primary trait given that the P-values in the primary and conditional trait are as small or smaller than the observed P-values. The conjFDR value for each SNP was next calculated as the maximum of the two condFDR values (i.e. migraine conditional on bipolar disorder and vice versa). This represents a conservative estimate of the FDR for the association between each SNP with both traits. SNPs with a cond/conjFDR < 0.05 were assigned statistical significance.³⁶ Further details are provided in [Supplementary material](#) and previous publications.^{36,43}

Genomic loci definition

Because of the confounding effect of LD and in line with previous literature, significantly associated SNPs were clumped into discrete ‘genomic loci’ defined by their cond/conjFDR value, LD structure (r^2 -value) and physical proximity.⁴⁴ Each locus comprised: a lead SNP—the most significantly associated SNP; independent significant SNPs—significant SNPs (cond/conjFDR < 0.05) which are not in LD with each other (r^2 < 0.6) but physically approximate (<250 kb apart); and candidate SNPs—in LD with independent

significant SNPs ($r^2 \geq 0.6$) and with evidence of association with the primary trait/traits (cond/conjFDR < 0.1). In line with previous literature, the candidate SNP cond/conjFDR thresholds were lowered to maximize the probability that putative disorder-influencing SNPs were captured within each locus.³⁴ Novel loci were identified by cross-referencing candidate SNPs against the NHGRI-EBI catalogue and minimum and maximum base pair positions with loci reported in original GWAS publications and secondary GWAS analyses of migraine and mental disorders.^{20,21,28,39,41,45–47}

Replication of conditional FDR and conjunctive FDR significant loci in independent samples

Since the probability of replicating individual loci at genome-wide significance is low due to weak genetic effects, we first tested for *en masse* sign concordance of effect direction in primary and replication samples, in line with previous literature.^{48–50} For condFDR analyses, there was sign concordance if the lead SNP had concordant effect directions in the primary and replication migraine samples. For conjFDR, there was sign concordance if the lead SNP possessed concordant effect directions for both phenotypes. If lead SNPs were missing in the independent datasets for conjFDR analyses, we replaced them with the next most significant candidate SNP which was present in the independent datasets. We employed a one-sided exact binomial test of significance under the null hypothesis that sign concordance was randomly distributed.^{48–50} We also identified lead SNPs (or the next most significant candidate SNPs) that were nominally significant at $P < 0.05$ in each independent sample.^{48,50}

Functional annotation

Candidate SNPs were functionally annotated to characterize their biological significance ([Supplementary material](#)), identify SNPs with pathogenic potential [Combined Annotation Dependent Depletion (CADD) scores > 12.37]⁵¹ and highlight putative causal genes. Genes were mapped using three strategies: (i) positional mapping—SNP mapped to all genes within 10 kb distance; (ii) expression quantitative trait locus (eQTL) mapping—SNPs mapped to genes whose expression has been associated with the SNPs allelic variation by one of three eQTL resources ([Supplementary material](#)); and (iii) chromatin interaction mapping—SNPs mapped to genes with which they are predicted to physically interact by 3D modelling of chromatin structure.⁴⁴

On each set of mapped genes, we performed gene-set enrichment analysis within the Gene Ontology classification system, corrected for multiple testing using Benjamini–Hochberg FDR.⁴⁴ The Gene Ontology resource is a comprehensive database of computationally or biologically derived gene sets.^{52,53} We also constructed spatiotemporal heat maps of gene-expression levels across 11 brain tissues at 11 developmental time points in the R package ‘cerebroViz’ using BrainSpan RNA sequencing data.^{54–56} Expression across brain tissues was clustered using unsupervised hierarchical cluster analysis. We tested for overrepresentation of mapped genes within pathways derived from 12 public resources, collated by ConsensusPathDB and corrected for multiple testing using the q -value.⁵⁷

Data availability

Data supporting the findings of this study are openly available from an online repository or are available on request from study authors. For further details, refer to the [Supplementary material](#). All code is freely available at <https://github.com/precimed> and <https://github.com/bulik/ldsc>. Analyses were conducted in Python

v.3.5, MATLAB R2020b and R v.3.6.3. Locus definition, functional annotation and gene-set analysis were performed using FUMA (<https://fuma.ctglab.nl/>).⁴⁴

Results

Quantifying polygenic overlap

Univariate MiXeR estimated that mental disorders were 2.9–4.4 times more polygenic relative to migraine, with 8100, 12 300 and 9700 variants estimated to influence bipolar disorder, depression and schizophrenia, respectively, compared to 2800 in migraine.

Bivariate MiXeR analysis revealed substantial polygenic overlap of migraine-influencing variants with each of depression and schizophrenia, and less overlap with bipolar disorder (Fig. 2). Of the 2800 migraine-influencing variants, 2100 (SD = 100) and 2300 (SD = 300) were also predicted to influence depression and schizophrenia, respectively, compared to 800 (SD = 0.3) predicted to influence bipolar disorder. This is despite minimal negative genetic correlation between migraine and each of schizophrenia ($r_g = -0.077$, standard error (SE) = 0.027, $P = 0.0046$) and bipolar disorder ($r_g = -0.035$, SE = 0.037, $P = 0.35$) and moderate positive genetic correlation between migraine and depression ($r_g = 0.33$, SE = 0.030 $P = 8.31 \times 10^{-28}$), replicating previous findings.²⁵ The difference in polygenicity between migraine (2800) and mental disorders (8100–12 300) limits the overlap between migraine and each mental disorder, demonstrated by the difference in the number of migraine-specific variants (500–2000) and mental disorder-specific variants (7300–10 200).

The AIC demonstrated adequate power for all analyses, but model fit was suboptimal for depression and bipolar disorder (Supplementary material, Supplementary Table 1 and Supplementary Fig. 1). These findings must therefore be interpreted with caution.

Identifying shared loci

ConjFDR analysis identified 14 loci jointly associated with depression and migraine and 36 loci associated with schizophrenia and migraine (Table 1, Fig. 3, Supplementary Tables 2 and 3 and Supplementary Fig. 2). Five loci were identified across both analyses, four of which had the same lead SNP. Furthermore, 71% of lead SNPs (10/14) had the same effect direction on depression and migraine compared to 42% for schizophrenia and migraine (15/36), consistent with the moderate positive genetic correlation between depression and migraine and minimal negative genetic correlation

between schizophrenia and migraine. There were no loci jointly associated with bipolar disorder and migraine.

The boost in power derived from condFDR analysis provided a total of 138 unique novel loci associated with migraine conditional on bipolar disorder ($n = 56$), depression ($n = 84$) and schizophrenia ($n = 119$). Forty-nine were identified across all three analyses (Supplementary material, Supplementary Tables 4–9 and Supplementary Figs 3 and 4).

Consistency of genetic effects in independent samples

For 176 unique loci associated with migraine across condFDR and conjFDR analyses, 153 lead SNPs showed sign concordance ($P = 1.30 \times 10^{-27}$) and 76 (43%) had nominal $P < 0.05$ in the independent migraine datasets. Among the conjFDR loci, 11 of 14 loci jointly associated with migraine and depression had lead SNPs or next most significant candidate SNPs with concordant effects in primary and independent samples for both migraine and depression ($P = 0.0292$). Three of 14 had nominally significant P -values in the independent depression sample and one in the independent migraine sample, none of which were nominally significant in both samples. For schizophrenia and migraine, three loci had neither lead SNPs nor secondary lead SNPs present in the schizophrenia replication sample, leaving 33 conjFDR lead SNPs. Twenty-seven of 33 lead SNPs had concordant effect directions in the primary and independent samples in both migraine and schizophrenia ($P = 0.00016$). Nineteen lead SNPs were nominally significant in the independent migraine cohort and eight in the independent schizophrenia sample. Five lead SNPs were nominally significant in both independent samples. The consistency of associations in independent datasets is comparable to that of other GWAS on complex polygenic phenotypes,^{48,50} supporting the validity of these findings. Complete condFDR replication analyses are presented in the Supplementary material.

Genetic overlap between migraine and other brain and non-brain-related phenotypes

We performed *post hoc* analyses to test the specificity of the observed overlaps. Compared to schizophrenia and depression, there was similar MiXeR estimated polygenic overlap between migraine and intelligence (1800, SD = 300) and educational attainment (2100, SD = 300). In contrast, there were fewer shared

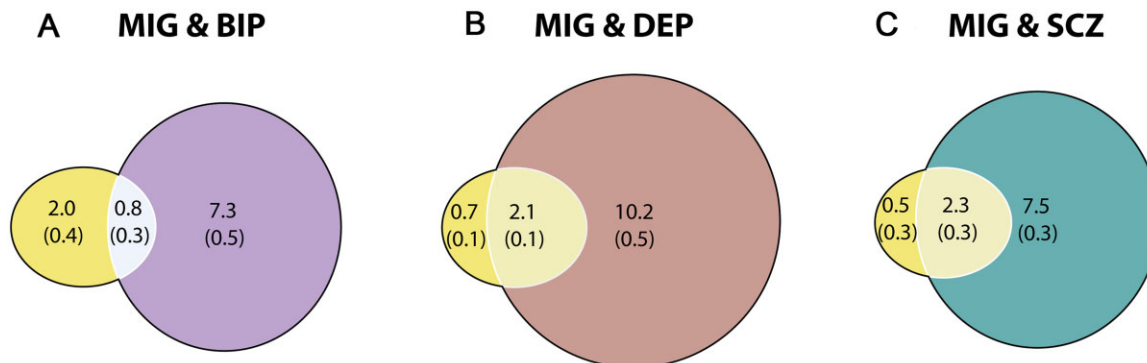


Figure 2 Total number of shared and unique variants estimated to influence migraine and mental disorders. Results from the MiXeR analysis for migraine (MIG) and each of (A) bipolar disorder (BIP), (B) depression (DEP) and (C) schizophrenia (SCZ). Venn diagrams representing the unique and shared variants associated with migraine and each of bipolar disorder, depression and schizophrenia. Polygenic overlap is represented in a lighter shade, migraine in yellow, bipolar disorder in purple, depression in brown and schizophrenia in green. The numbers indicate the estimated number of variants in thousands per component with standard deviations in parentheses. The size of the circle reflects the extent of polygenicity for each disorder.

Table 1 Top 10 most strongly associated loci with migraine and each of depression (depression) and schizophrenia (schizophrenia)

Chr	Min-max base pairs	Lead SNPs	ConjFDR	Psych			Migraine			Overlapping
				Effect size (OR)	P-value	Novel	Effect size (Beta)	P-value	Novel	
Migraine and depression										
1	73 458 846–74 108 971	rs11210247	<0.001	1.06	6.62×10^{-9}	No	-0.04	1.69×10^{-7}	No	Yes
2	208 017 033–208 088 987	rs7592120	0.03	0.94	4.46×10^{-8}	No	-0.03	4.78×10^{-5}	Yes	Yes
5	92 362 700–92 538 853	rs10514370	0.02	0.96	9.39×10^{-6}	Yes	-0.03	2.95×10^{-5}	Yes	No
8	64 496 159–64 624 581	rs1217091	0.03	0.95	1.23×10^{-5}	Yes	0.04	3.93×10^{-5}	Yes	Yes
8	131 030 628–131 361 477	rs143725649	0.03	1.04	5.85×10^{-5}	Yes	-0.04	6.08×10^{-5}	Yes	No
9	23 736 400–23 737 627	rs10119773	0.03	0.95	7.70×10^{-8}	No	-0.03	5.02×10^{-5}	Yes	No
9	37 045 825–37 406 391	rs10973193	0.03	1.08	4.96×10^{-8}	No	0.04	3.85×10^{-5}	Yes	No
9	98 191 712–98 314 415	rs10512249	0.02	1.07	3.28×10^{-5}	No	0.05	1.48×10^{-5}	Yes	No
15	47 615 220–47 685 504	rs281264	0.03	0.96	2.25×10^{-5}	No	-0.03	4.26×10^{-5}	Yes	No
22	41 408 754–41 713 111	rs71327107	0.01	0.95	4.02×10^{-6}	No	-0.04	1.45×10^{-5}	Yes	Yes
Migraine and schizophrenia										
1	73 305 593–74 161 292	rs11210247	<0.001	1.07	1.92×10^{-11}	No	-0.04	1.69×10^{-7}	No	Yes
1	115 677 183–115 763 649	rs12134493	0.002	1.08	6.29×10^{-7}	Yes	0.11	1.01×10^{-22}	No	No
3	16 947 451–16 972 211	rs11128810	0.008	1.04	8.66×10^{-6}	No	-0.04	3.39×10^{-6}	No	No
4	103 618 023–103 975 060	rs6810668	0.008	1.04	8.04×10^{-6}	No	-0.03	1.04×10^{-5}	Yes	No
8	64 496 159–64 842 662	rs1217112	0.004	1.06	2.94×10^{-6}	No	-0.04	4.60×10^{-6}	Yes	Yes
11	46 257 757–47 371 598	rs7932866	<0.001	0.92	1.06×10^{-10}	No	0.05	6.36×10^{-7}	Yes	No
12	57 331 741–57 527 283	rs324015	<0.001	0.93	1.42×10^{-10}	No	0.05	1.26×10^{-8}	No	No
16	4 447 771–4 596 447	rs4786505	0.001	0.95	2.85×10^{-7}	No	-0.04	1.07×10^{-6}	Yes	No
17	78 442 650–78 738 796	rs112821038	0.006	0.93	5.51×10^{-6}	No	0.06	4.76×10^{-6}	No	No
22	41 408 754–41 713 111	rs71327107	0.009	0.93	3.71×10^{-10}	No	-0.04	1.45×10^{-5}	Yes	Yes

For the complete list of loci please refer to [Supplementary Tables 2 and 3](#). Chromosome (Chr), minimum and maximum base pairs, lead SNPs and conjFDR statistic are presented from each conjFDR analysis. Effect sizes [either odds ratio (OR) for depression and schizophrenia or beta for migraine] and P-values are presented from the original mental disorder (psych) and migraine GWAS. The novelty of each locus for migraine, depression and schizophrenia in relation to previous GWAS and conjFDR studies is indicated by Yes (novel) or No (not novel). 'Overlapping' indicates loci that were physically overlapping across both migraine and depression, and migraine and schizophrenia analyses.

variants with coronary artery disease (1300, SD = 100) and more unique migraine variants (1500, SD 200), although the shared variants represented a large proportion coronary artery disease-influencing variants (1300/1400 variants). Migraine shared the fewest variants with height (1000K, SD = 100) ([Supplementary Fig. 5](#)). Other neurological and non-neurological disorders were not suitable for MiXeR analysis due to small sample sizes and the inability of MiXeR to accurately model less polygenic phenotypes. However, *post hoc* conjFDR analysis identified multiple shared loci between migraine and educational attainment (34), intelligence (29), Parkinson's disease (2), multiple sclerosis (4) and prostate cancer (2), alongside previously identified loci between migraine and coronary artery disease (3).⁴⁷ Interestingly, 15 loci associated with either depression and migraine and/or schizophrenia and migraine were physically overlapping with loci associated with migraine and educational attainment (5), intelligence (8) and Parkinson's disease (1), but not multiple sclerosis, prostate cancer or coronary-artery disease ([Supplementary material and Supplementary Figs 6 and 7](#)).

Biological insights from shared loci

We mapped 298 and 37 protein-coding genes to candidate SNPs jointly associated with migraine and each of schizophrenia and depression, respectively ([Supplementary Tables 10 and 11](#)). Among genes mapped to depression and migraine loci, PAX5, a transcription factor involved in neurogenesis,⁵⁸ ELAVL2, a regulator of neurodevelopmental and synaptic genes,⁵⁹ and L3MBTL2, a transcriptional repressor, were all mapped to probable pathogenic SNPs from novel migraine loci, and have all previously been linked to both depression and schizophrenia.^{58,60–63} Notably, L3MBTL2 was mapped to a locus that was nominally significant in the

depression replication sample, and was mapped by both positional and eQTL mapping, with evidence of differential expression in the anterior cingulate cortex and frontal cortex. With regards to schizophrenia and migraine, several genes have previously been linked to both disorders, including LRP1, ASTN2, HPSE2 and IGSF9B. Among the genes mapped to novel migraine loci, CSNK1G2 was mapped by chromatin interaction mapping within foetal and adult cortex. CSNK1G2 is a casein kinase that has previously been implicated in schizophrenia.⁶⁴ It is also a paralogue of CSNK1D, a monogenic cause of familial advanced sleep phase syndrome with migraines and a component of the circadian clock.⁶⁵ Additionally, KLF10 was positionally mapped to a probable pathogenic lead SNP (CADD score > 12.37). KLF10 is a transcriptional repressor that also plays a role in the circadian clock.⁶⁶ There were also several genes coding transmembrane ion channel proteins including the calcium channel subunit CACNB2, which has been strongly linked to schizophrenia,⁶⁷ and the sodium/hydrogen exchanger SLC9B1 which was mapped using all three strategies, including eQTL mapping to brain tissue in two independent datasets. Both CACNB2 and SLC9B1 were mapped to loci that were nominally significant in both migraine and schizophrenia replication samples. Further functional annotation analyses are described in the [Supplementary material and Supplementary Fig. 6](#).

We conducted gene-set analyses on each set of mapped genes. While there were no significantly enriched depression and migraine gene sets, 27 gene sets were enriched with mapped genes for schizophrenia and migraine with a predominance of gene sets related to transmembrane transport (e.g. 'GO_TRANSPORTER_ACTIVITY'), mitochondria (e.g. 'GO_MITOCHONDRIA') and neuron structure (e.g. 'GO_SOMATODENDRITIC_COMPARTMENT') gene sets ([Supplementary Table 12](#)).

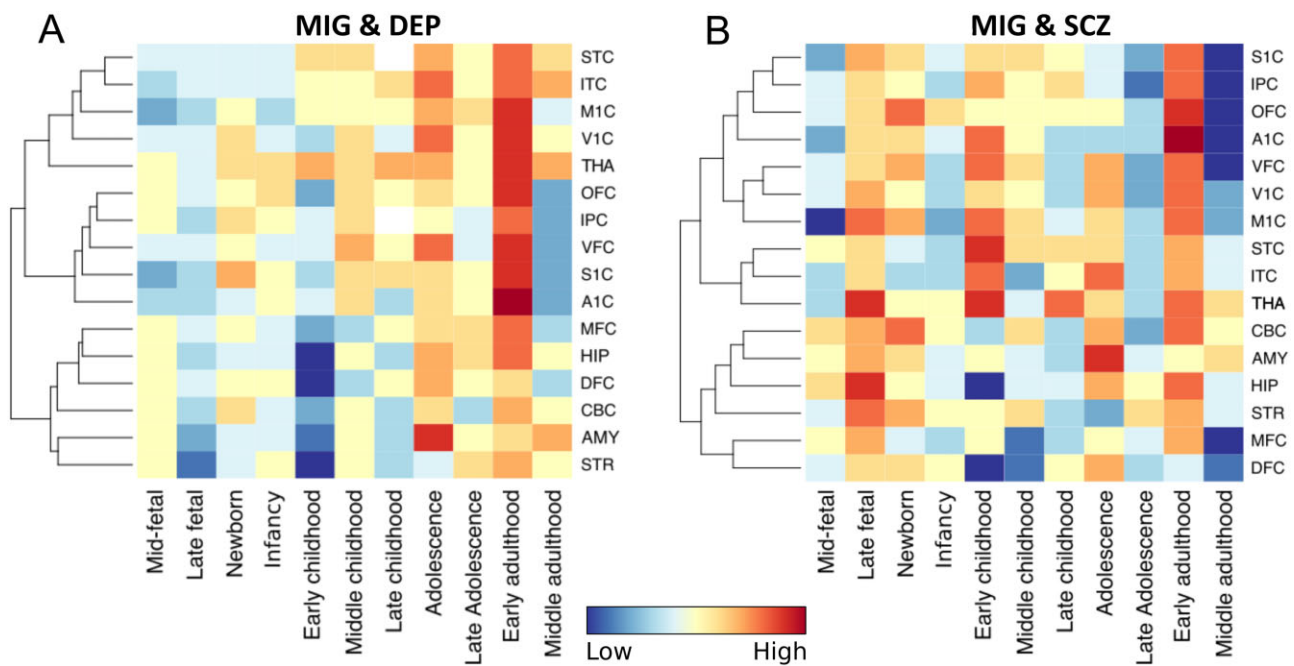


Figure 4 Spatiotemporal gene expression of all mapped genes. Dendrogram and heat map showing spatiotemporal gene expression of all mapped genes for (A) migraine (MIG) and depression (DEP) and (B) migraine and schizophrenia (SCZ) using RNA sequencing data from BrainSpan over 11 developmental periods (columns) and 16 brain regions (rows). Global expression of mapped genes for depression and migraine was low from the mid-fetal stage to early childhood, increasing from middle childhood to early adulthood with highest expression during early adulthood. Expression of mapped genes for schizophrenia and migraine was more distributed, with highest expression during the late foetal stage, early childhood and early adulthood. Highest expression of mapped genes for both migraine and depression and migraine and schizophrenia occurred in the primary auditory cortex (A1C) during early adulthood, during which there was also high expression in the primary sensory (S1C), primary motor (M1C), primary visual (V1C), inferior temporal (ITC), ventrolateral prefrontal (VFC), orbitofrontal cortices (OFC) and thalamus (THA) for both sets of genes. There was also high expression in the thalamus at several developmental stages from late foetal to early adulthood for schizophrenia and migraine, while expression in the thalamus increased steadily from the newborn stage to early adulthood for depression and migraine. Brain regions were clustered using unsupervised hierarchical cluster analysis. Gene expression is indicated from high (red) to low (blue). AMY = amygdala; CBC = cerebellum; DFC = dorsolateral prefrontal cortex; HIP = hippocampus; IPC = inferior parietal cortex; MFC = medial prefrontal cortex; STC = superior temporal cortex; STR = striatum. Refer to the [Supplementary material](#) for more details.

disorder-specific variants with limited overlap across disorders and traits. While extensive overlap is increasingly recognized across mental disorders, our findings indicate this also encompasses migraine. In addition to the overlapping loci identified across migraine, mental disorders, educational attainment, intelligence and Parkinson's disease, recent evidence has also revealed genetic overlap between Parkinson's disease and schizophrenia.³⁴ Taken together, this is suggestive of a subset of 'pleiotropic' variants associated with a general vulnerability to brain disorders and influence several brain-related traits. This may also encompass brain structure, which has recently been associated with several hundreds of loci with distributed genetic effects.⁶⁹ If there are few specific genetic variants, the specificity of genetic risk for a given disorder could instead be determined by the differing effect sizes and directions of the variants on each phenotype and disorder-specific gene \times gene or gene \times environment interactions.²⁶ This also places greater emphasis on identifying disease-specific and rare variants, which may be of high relevance for understanding pathological processes and improving diagnosis and treatment.

Our findings also contribute to ongoing debate over the aetiology of migraine.⁷⁰ Migraine was previously thought to be a vascular disorder, supported by the association with cardiovascular events and GWAS findings showing association with vascular genes.^{21,70,71} An alternative theory implicates a primary neurological origin, related to inappropriate activation in the hypothalamus, midbrain ventral tegmentum and noradrenergic and serotonergic nuclei.⁷¹ These regions are proposed to modulate cerebral blood flow leading to secondary alterations in vasculature.

Our finding that ~75% of genetic risk for migraine overlaps with both schizophrenia and depression, alongside the identification of multiple shared genetic risk loci, could support the latter theory. Vascular dysfunction is not prominent in schizophrenia or depression, while dysfunction of neurotransmitter-based systems, such as serotonin^{72,73} and glutamate,^{74,75} as well as cortical excitability are implicated in all three disorders.^{76,77} This is supported by the finding that transmembrane transporter gene sets were enriched with genes mapping to schizophrenia and migraine loci, and that several putative causal genes coded for ion channel subunits. However, previous studies have also reported genetic overlap between cardiovascular disease phenotypes and both migraine and mental disorders. Interestingly, our *post hoc* analysis found that most coronary-artery influencing variants were shared with migraine, but in addition there was a large number of unique migraine variants.^{47,78} It is therefore tempting to speculate that migraine possesses a spectrum of genetic overlap with psychiatric, neurological and cardiovascular disorders, possibly indicating distinct 'neurological' and 'vascular' components of genetic risk. Larger sample sizes and improved statistical modelling will enable more complete cross-disorder comparisons.

When comparing migraine to mental disorders, there was a substantial difference in polygenicity, which may reflect greater neurobiological heterogeneity. For example, the quality and laterality of migraine pain may be more directly linked to specific underlying neurobiological mechanisms than anhedonia or low energy in depression, which may represent multiple phenomena with similar phenotypic expression. This could mean that migraine maps to a more distinct underlying neurobiological

substrate, whereas mental disorders encompass several, overlapping neurobiological processes. This interpretation is supported by the finding of less genetic correlation between neurological disorders than between mental disorders.²⁵ Moreover, MiXeR has previously demonstrated extensive overlap across bipolar disorder, depression and schizophrenia, and almost complete overlap with autism spectrum disorder.²⁶ It is therefore possible that the subset of migraine-influencing variants shared with mental disorders represent a specific neurobiological subset of genetic risk in mental disorders. The shared loci identified by conjFDR, which have the strongest joint effects, provide some insights into the neurobiological mechanisms that this subset may relate to. However, the biological significance of this will gain clarity once a greater proportion of shared variants are discovered.

The smaller overlap and lack of genetic correlation between bipolar disorder and migraine, alongside the failure of conjFDR to identify any shared loci, is surprising given the evidence of increased rates of bipolar disorder among migraine patients and vice versa.^{1,3} It is important to note that the suboptimal MiXeR model fit means that this result should be interpreted with caution, particularly considering the extensive overlap observed between migraine and each of intelligence and educational attainment. Furthermore, the primary reason for the absence of conjunctive loci is likely to be sample size (bipolar disorder $n = 51\,720$ versus schizophrenia $n = 105\,318$ and depression $n = 375\,752$). However, this may also relate to the fact that migraine is more strongly associated with bipolar-II than bipolar-I.^{79,80} Bipolar-II, a less severe form of bipolar disorder, is underrepresented in the current cohort ($n = 3421$) despite an equivalent prevalence to bipolar-I.⁸¹ There may therefore be a genetic basis to the association with bipolar-II patients that is not captured given the current sample make-up. Additionally, bipolar-I patients with migraine have been hypothesized to represent a distinct neurobiological subset, since they differ significantly from those without migraine in several key clinical features.⁸¹ A follow-up analysis of bipolar subtypes would be of great interest.

The extent of MiXeR estimated polygenic overlap between depression and migraine is striking despite phenotypic correlation and previously reported positive genetic correlation.²⁵ Furthermore, our identification of 14 shared loci, 10 of which had concordant effects and 10 of which had P -values < 0.05 in an independent sample, provides detail to their shared genetic basis beyond genetic correlation.³⁵ A single conjunctive lead SNP also met genome-wide significance in the combined GWAS of Yang et al.,³⁵ but missed genome-wide significance in the original migraine GWAS and hence was not reported as shared. Among the 37 mapped genes for depression and migraine, we highlight *PAX5*,⁵⁸ *ELAVL2*⁵⁹ and *L3MBTL2* that mapped to probable pathogenic SNPs, and so may be of high interest for *in vitro* and *in vivo* validation and have potential for drug discovery. In contrast, the extensive overlap with schizophrenia and the 36 shared loci represent entirely novel findings given the dearth of previous genetics studies.¹⁰ The prominence of ion channel subunit genes and gene sets related to transmembrane transport was particularly striking. Ion channel dysfunction has been suggested to play a key role in migraine pathophysiology, while GWAS have previously implicated calcium channels in schizophrenia.^{82,83} These findings suggest possible mechanistic convergence between these distinct brain-related disorders, although further experimental studies are required to validate this.

While gene-set and pathway analyses provided insights into putative shared mechanisms, our spatiotemporal gene-expression analysis identified brain regions and developmental time periods during which these processes may impact disorder risk. Interestingly, global expression was highest during early adulthood

for both sets of shared genes, while there was an additional period of high gene expression during the late foetal stage for migraine and schizophrenia. This widespread increase in expression during early adulthood broadly maps on to the clinical manifestation of all three disorders, with prevalence increasing from adolescence through to early adulthood.⁸⁴ There is also extensive evidence implicating disturbances of early neurodevelopment in schizophrenia, including changes in gene expression.^{85,86} In contrast, few studies have explored the relationship between neurodevelopment and migraine risk.⁸⁷ Evidence of increased rates of migraine in autism spectrum disorder, a common neurodevelopmental disorder, however, suggest this may be of relevance.⁸⁸ The fact that gene expression during this time period was highest in the thalamus and the hippocampus, two subcortical structures implicated in the precipitation of migraines,⁷¹ is particularly intriguing, possibly indicating that altered expression of migraine risk genes during early development within these core structures may result in a predisposition to migraine later in life.

There were limitations to the current study. First, due to available sample sizes, we were unable to include multi-ancestral data for migraine or depression. Efforts to boost trans-ancestral samples and the development of statistical techniques to translate findings across ancestral groups are crucially important. Second, a subset of migraine and depression diagnoses were by self-report. Given that 20% of self-report migraines do not meet diagnostic criteria,⁸⁹ it is possible that the genetic overlap is driven by a non-specific mental trait related to self-reporting rather than a specific migraine-signal. Similarly, the depression phenotype included self-report diagnoses and a 'broad definition' of depression.⁴⁰ Nonetheless, this is weighed against the extra power for discovery offered by studies with self-report measures. These analyses should be repeated once larger samples of strictly defined depression and migraine are achieved. Third, although MiXeR explicitly models genetic effects beyond the confounding influence of LD, it is possible that uncontrolled environmental confounders could influence our findings. This limitation is inherited from the primary GWAS, and LDSR intercept estimates and genomic inflation factors indicated minimal effects of non-genetic confounders in all four studies.^{20,21,23,41} Despite this, further *in vitro* studies are required to confirm the causative effects of the genetic associations identified. Fourth, the comorbidity between migraine and bipolar disorder and depression may confound our findings since the rate of migraine among the cases is likely to be higher than controls, and vice versa. However, if this was a significant confounder, we would expect to see more substantial overlap with bipolar disorder and less overlap with schizophrenia, which does not have the same evidence of migraine comorbidity as bipolar disorder and depression. Nonetheless, individual level data with deeper phenotyping are required to confirm these findings, similar to other studies of genetic overlap.^{25,27,90–92} Finally, while functionally annotating candidate SNPs reduces the probability of missing causal variants, this approach increases the number of false positives to the gene-mapping, gene-set enrichment and gene-expression analyses. Further work will be required to refine functional annotation once larger primary GWASs are achieved.

To conclude, we have found substantial polygenic overlap of migraine-influencing variants with both schizophrenia and depression, and moderate overlap with bipolar disorder. These findings have implications for how the genetic risk of complex polygenic brain disorders is conceptualized, indicate the presence of a subset of highly pleiotropic genetic variants that influence diverse brain-related disorders and traits and provide biological insights into the shared variants with strongest effects on migraine, depression and schizophrenia.

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Competing interests

O.A.A. has received speaker's honorarium from Sunovion, and Lundbeck and is a consultant for Healthlytix. A.M.D. is a founder of and holds equity interest in CorTechs Labs and serves on its scientific advisory board. He is also a member of the Scientific Advisory Board of Healthlytix and receives research funding from General Electric Healthcare (GEHC). 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. All other authors have no conflicts of interest to declare.

Appendix I

Full details of the HUNT All-In Headache members are provided in the [Supplementary material](#).

HUNT all-in headache

Amy E. Martinsen, Anne Heidi Skogholt, Ben Brumpton, Cristen J. Willer, Erling Tronvik, Espen Saxhaug Kristoffersen, John-Anker Zwart, Jonas Bille Nielsen, Knut Hagen, Kristian Bernhard Nilsen, Kristian Hveem, Lars Jacob Stovner, Lars G. Fritsche, Laurent F. Thomas, Linda M. Pedersen, Maiken E. Gabrielsen, Marianne Bakke Johnsen, Marie Udnesseter Lie, Oddgeir Holmen, Sigrid Børte, Synne Øien Stensland, Wei Zhou.

Supplementary material

[Supplementary material](#) is available at *Brain* online.

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