Blood pressure (BP) was inconsistently associated with migraine and the mechanisms of BP-lowering medications in migraine prophylaxis are unknown. Leveraging large-scale summary statistics for migraine ($N_{\text{cases}}/N_{\text{controls}} = 59,674/316,078$) and BP ($N = 757,601$), we find positive genetic correlations of migraine with diastolic BP ($r_g = 0.11, P = 3.56 \times 10^{-06}$) and systolic BP ($r_g = 0.06, P = 0.01$), but not pulse pressure ($P = -0.01, P = 0.75$). Cross-trait meta-analysis reveals 14 shared loci ($P \leq 5 \times 10^{-08}$), nine of which replicate ($P < 0.05$) in the UK Biobank. Five shared loci ($ITGB5$, $SMG6$, $ADRA2B$, $ANKDD1B$, and $KIAA0040$) are reinforced in gene-level analysis and highlight potential mechanisms involving vascular development, endothelial function and calcium homeostasis. Mendelian randomization reveals stronger instrumental estimates of DBP (OR [95% CI] = 1.20 [1.15–1.25]/10 mmHg; $P = 5.57 \times 10^{-25}$) on migraine than SBP (1.05 [1.03–1.07]/10 mmHg; $P = 2.60 \times 10^{-07}$) and a corresponding opposite effect for PP (0.92 [0.88–0.95]/10 mmHg; $P = 3.65 \times 10^{-07}$). These findings support a critical role of DBP in migraine susceptibility and shared biology underlying BP and migraine.
Migraine is a chronic intermittent neurological disorder affecting up to 14.7% people worldwide and ranks as the second leading cause of disability, responsible for 5.6% of all years lived with disability. The link between migraine and the vascular system has been substantiated by an array of physiologic and epidemiologic evidence, including migraine comorbidities with other vascular conditions including stroke, coronary artery disease (CAD), and cervical vascular development, endothelial structure, and smooth muscle function. Loci mapping to the END1/PHACTRI, LP1, and FHLS genes in particular are shared by migraine and CAD or cervical artery dissection.

Blood pressure (BP) has been associated not only with vascular disease but also with migraine. In contrast to highly consistent associations of increased BP with increased susceptibility to vascular disease, associations of BP with migraine are not consistent. For example, some studies have found associations between elevated systolic BP (SBP) or diastolic BP (DBP) and lower prevalence of migraine, whereas some have found inverse associations only for SBP. One study suggested that migraine was associated with higher DBP but lower SBP. Still other reports focused on pulse pressure (PP), defined as the difference between SBP and DBP, consistently showed an inverse relationship between PP and migraine. The relationship is further complicated by longitudinal studies suggesting that migraine may increase the risk of incident hypertension, whereas BP has been found to be inversely related to onset of headache and migraine. Regardless, BP-lowering medications notably provide prophylactic benefit for many migraineurs, and the choice of antihypertensive appears to be related to comorbidities, cost, availability, or side effect profile rather than the specific mechanism of BP-lowering.

Recently developed but widely accepted genetic methods leveraging only GWAS summary statistics, including cross-trait meta-analysis and transcriptome-wide association study (TWAS), may be used to identify specific shared genetic components and pathophysiology between BP and migraine. Instrumental genetic analysis, i.e. Mendelian randomization, may suggest causality and directionality of effects of BP on migraine, or the reverse, i.e. migraine influences on BP. Therefore, in the current study, we leverage large-scale genetic summary-level data and the preceding genetic methods to gain insight into mechanistic links between BP and migraine.

### Results

#### Shared heritability between migraine and blood pressure

There was a positive overall genetic correlation of migraine with DBP ($r_g = 0.11$, Wald test $P = 3.56 \times 10^{-06}$) and SBP ($r_g = 0.06$, Wald test $P = 0.01$), but not PP ($r_g = 0.01$, Wald test $P = 0.75$) using linkage disequilibrium (LD) score regression (LDSC) (Table 1). When extended to the migraine subtypes: migraine with aura (MA) and migraine without aura (MO), DBP was consistently correlated with both MA ($r_g = 0.17$, Wald test $P = 1.50 \times 10^{-03}$) and MO ($r_g = 0.14$, Wald test $P = 1.20 \times 10^{-03}$), whereas SBP was only marginally correlated with MA ($r_g = 0.10$, Wald test $P = 0.04$). Findings for genetic covariance analyzer (GNOVA), which included SNPs with lower minor allele frequency (MAF) than LDSC, were similar with $r_g = 0.12$ (Wald test $P = 3.45 \times 10^{-07}$), $0.07$ (Wald test $P = 4.64 \times 10^{-03}$), and $0.00$ (Wald test $P = 0.94$) for DBP, SBP, and PP, respectively (Table 1). Partitioned genetic correlation did not reveal strong contrasts but suggested that shared effects were concentrated in some chromosomes with the

| Method | Trait 1 | Trait 2 | $r_g$ | $P^*$ | gcov | gcov_se |
|--------|---------|---------|------|-------|------|---------|
| LDSC   | Any migraine | DBP | 0.11 | $3.56 \times 10^{-06}$ | 0.018 | 0.009 |
|        |         | SBP | 0.06 | 0.01  | 0.004 | 0.009 |
|        |         | PP  | $-0.01$ | 0.75  | $-0.009$ | 0.008 |
|        | Migraine with aura | DBP | 0.17 | $1.50 \times 10^{-03}$ | $-0.006$ | 0.008 |
|        |         | SBP | 0.10 | 0.04  | $-0.014$ | 0.008 |
|        |         | PP  | 0.00 | 0.92  | $-0.015$ | 0.007 |
|        | Migraine without aura | DBP | 0.14 | $1.20 \times 10^{-03}$ | 0.014  | 0.008 |
|        |         | SBP | 0.03 | 0.43  | 0.010  | 0.008 |
|        |         | PP  | $-0.08$ | 0.06  | 0.002  | 0.007 |
| GNOVA  | Any migraine | DBP | 0.12 | $3.45 \times 10^{-07}$ | 0.009  | 0.002 |
|        |         | SBP | 0.07 | $4.64 \times 10^{-03}$ | 0.005  | 0.002 |
|        |         | PP  | 0.00 | 0.94  | 0.000  | 0.002 |
|        | Migraine with aura | DBP | 0.15 | $1.90 \times 10^{-05}$ | 0.008  | 0.002 |
|        |         | SBP | 0.10 | $2.57 \times 10^{-03}$ | 0.006  | 0.002 |
|        |         | PP  | 0.03 | 0.33  | 0.002  | 0.002 |
|        | Migraine without aura | DBP | 0.13 | $1.86 \times 10^{-04}$ | 0.008  | 0.002 |
|        |         | SBP | $-0.02$ | 0.66  | $-0.001$ | 0.002 |
|        |         | PP  | $-0.12$ | $2.12 \times 10^{-04}$ | 0.006  | 0.002 |

$r_g$ Genetic correlation, gcov genetic covariance, gcov_se standard error of genetic covariance. LDSC LD score regression, GNOVA genetic covariance analyzer, DBP diastolic blood pressure, SBP systolic blood pressure, PP pulse pressure.

*P*-value was calculated for the genetic correlation in LDSC and for the genetic covariance in GNOVA. *P*-values are based on two-sided Wald test.
Fig. 1 Local genetic correlation between migraine and BP traits at reported migraine loci using p-HESS and GWAS-PW. Colors represent the significance level of local genetic correlation between migraine and blood pressure (BP) traits (DBP, SBP, and PP) using p-HESS (p-HESS based on Wald test), red for positive genetic correlation and blue for negative genetic correlation at the corresponding locus. Dots represent the estimated posterior probability (PPA_3 > 0.9, see details in Supplementary Table 2).

strongest positive genetic correlation observed at chr22 (r_g = 0.47, Wald test P = 1.37 × 10^{-04}) between migraine and DBP, and the strongest negative genetic correlation observed at chr19 (r_g = −0.32, Wald test P = 1.28 × 10^{-03}) between migraine and PP (Supplementary Figs. 10–21).

The local genomic regions around individual migraine loci from GWAS showed signals of genetic overlap with BP (Fig. 1). Accounting for multiple testing, there was genome-wide significant local genetic correlation between migraine and BP at three regions (chr6: 94441175..97093511 harboring previous migraine locus FHLS; chr7: 39862670..42001811 harboring previous migraine locus C7orf10; and chr10: 95396368..96221243 harboring previous migraine locus PLCE1) using heritability estimation from summary statistics (p-HESS) (Fig. 1 and Supplementary Table 1, P < 0.05/1703). The genetic correlation between migraine and SBP was negative in the chromosome 7 region despite being positive across the whole genome (Fig. 1). For PP, although the overall genome-wide genetic correlation with migraine was null, there were significant local genetic correlations at chromosome 6 (Wald test P = 3.20 × 10^{-06}) and 7 (Wald test P = 3.98 × 10^{-08}), which were also significantly correlated for the other BP measures. Results were consistent for these regions with the alternative pairwise traits analysis of GWAS (GWAS-PW) approach (i.e. PPA_3 > 0.9, Fig. 1 and Supplementary Table 2).

Taken together, although the overall genetic correlations between BP traits and migraine were relatively modest compared to more closely related phenotypes, e.g. among psychiatric disorders (r_g ~ 0.6) or between lipids and CAD (r_g ~ 0.25)22, they nevertheless indicate potential shared genetic etiologies, especially at certain chromosomes or regions, and are therefore worthy of additional investigation into potential mechanisms using cross-trait analysis and expression-trait analysis.

Cross-trait meta-analysis of migraine with BP measurements. We conducted cross-trait meta-analysis to identify individual SNPs that may share association with BP and migraine using the Cross Phenotype Association (CPASSOC) package. Thirty-three independent loci reached genome-wide significance for combined statistics (P_{CPASSOC} ≤ 5 × 10^{-08}) and suggestive trait-specific significance (P_{GWAS} ≤ 1 × 10^{-05}) for migraine and at least one BP measurement (Supplementary Tables 3–5), 19 of which were previously reported migraine loci, including PHACTR1, LRPI, FHLS, C7orf10, and PLCE1, after controlling for multiple testing (P_{p-HESS} < 0.05/1703, see details in Supplementary Table 1) and with high estimated posterior probability (PPA_3 > 0.9, see details in Supplementary Table 2).

Among the candidate migraine loci, lead SNP rs62155750 was most significant (chr2q11.1, P_{CPASSOC} = 5.42 × 10^{-34} for DBP based on S_{Het} statistic). Rs62155750 was a significant expression quantitative trait locus (eQTL) for its nearby gene ADRA2B (Supplementary Table 7), encoding the subtype B of the α2-adrenergic receptor that regulates neurotransmitter release from sympathetic nerves and adrenergic neurons in the central nervous system23. Interestingly, this locus was related to migraine (P = 0.02 based on S_{Het} statistic) but not broadly defined headache (P = 0.55 based on S_{Het} statistic) in the replication dataset (Supplementary Table 6). The second strongest signal overall was lead SNP rs10484838 (at chr17p13.3) that was associated with both SBP (P_{CPASSOC} = 9.29 × 10^{-27} based on S_{Het} statistic) and PP (P_{CPASSOC} = 5.13 × 10^{-28} based on S_{Het} statistic). Rs10484838 mapped to SMG6 that encodes a nonsense-mediated mRNA decay factor, and is a significant eQTL for the nearby gene SSR (Serine Racemase, Supplementary Table 8), which is responsible for transforming l-serine to d-serine, a key co-agonist with glutamate at N-methyl-d-aspartate (NMDA) receptors24. Lead SNP rs6438857 (at chr3q21.2, P_{CPASSOC} = 2.64 × 10^{-22}, 1.77 × 10^{-23}, 2.55 × 10^{-14} for DBP, SBP, and PP, respectively based on S_{Het} statistic) implicating ITGB5 was the only locus that was shared between migraine and all the three BP measurements. ITGB5 encodes a beta subunit of integrin (integrin alpha-V/beta-5), which is a member of integrin family of heterodimeric transmembrane cell surface receptors and has a role in vascular permeability induced by vascular endothelial growth factor (VEGF) in the systemic circulation25. COL4A1 at chr13q34 was shared between migraine and DBP (lead SNP rs13260, P_{CPASSOC} = 8.69 × 10^{-15} based on S_{Het} statistic) as well as PP (lead SNP rs12875271, P_{CPASSOC} = 6.29 × 10^{-12} based on S_{Het} statistic). COL4A1 encodes a type IV collagen alpha protein, and COL4A1 mutations may present with small vessel disease and stroke, both
### Table 2: Candidate migraine loci from cross-trait meta-analysis between migraine and blood pressure using CPASSOC.

| Trait 1 | Trait 2 | SNP       | POS       | A1 | A2 | MAF | Trait 1 BETA | Trait 1 P  | Trait 2 BETA | Trait 2 P  | P_{CPASSOC} | Genes                                      |
|---------|---------|-----------|-----------|----|----|-----|--------------|-----------|--------------|-----------|------------|-------------------------------------------|
| Any migraine | DBP     | rs72663521 | chr1p34.3 | A  | G  | 0.19 | 0.04 | 194 × 10^{-6} | 0.13       | 1.42 × 10^{-08} | 2.22 × 10^{-12} | BMP8A, KIAA0754, MACF1, PABPC4, PPIEL, SNORA55, KIAA0040, ADRA2B, ARID5A, ASTL, CIAO1, CMMNA4, DUSP2, FAH2D2, FAH2D2C, FER1L5, GATA2, ITPRP1L, KANS3, KONP3, LINC00342, LMAN21L, NCAPH, NEU1L, PROM2, SNRPN200, STARD7, STARD7-AS1, TMM127, TRIM43, TRIM43B |
|         |         | rs3766694  | chr1q25.1  | T  | C  | 0.39 | -0.03 | 1.26 × 10^{-06} | 0.11       | 4.07 × 10^{-10} | 3.17 × 10^{-14} | |
|         |         | rs62155750 | chr2q11.1  | A  | G  | 0.31 | -0.04 | 4.42 × 10^{-07} | 0.22       | 8.27 × 10^{-09} | 5.42 × 10^{-34} | |
| SBP     | PP      | rs6438857  | chr3q21.2  | T  | C  | 0.43 | -0.03 | 8.92 × 10^{-07} | 0.15       | 1.50 × 10^{-17} | 2.64 × 10^{-22} | |
|         |         | rs688648   | chr5q13.3  | A  | C  | 0.37 | -0.04 | 4.76 × 10^{-07} | 0.17       | 5.06 × 10^{-21} | 3.43 × 10^{-26} | |
|         |         | rs1271309  | chr1q24.31 | A  | G  | 0.17 | -0.04 | 8.56 × 10^{-06} | 0.20       | 1.45 × 10^{-16} | 2.04 × 10^{-20} | |
|         |         | rs13260    | chr13q34   | T  | G  | 0.09 | 0.06 | 6.60 × 10^{-07} | 0.20       | 1.66 × 10^{-10} | 8.69 × 10^{-15} | |
|         |         | rs8008129  | chr14q23.1 | T  | G  | 0.34 | -0.03 | 3.91 × 10^{-06} | 0.09       | 1.37 × 10^{-06} | 7.22 × 10^{-10} | |
|         |         | rs28451064 | chr21q22.11| A  | G  | 0.13 | -0.06 | 2.69 × 10^{-07} | 0.13       | 1.54 × 10^{-06} | 1.96 × 10^{-10} | |
|         |         | rs6438857  | chr3q21.2  | T  | C  | 0.43 | -0.03 | 8.92 × 10^{-07} | 0.27       | 3.33 × 10^{-10} | 1.77 × 10^{-23} | |
|         |         | rs1048483  | chr7p13.3  | T  | C  | 0.49 | -0.03 | 1.31 × 10^{-06} | 0.30       | 6.49 × 10^{-23} | 9.29 × 10^{-27} | |
|         |         | rs8080108  | chr17q21.32| T  | C  | 0.30 | -0.03 | 3.74 × 10^{-06} | 0.30       | 3.15 × 10^{-20} | 1.22 × 10^{-23} | |
| PP      | PP      | rs6438857  | chr3q21.2  | T  | C  | 0.43 | -0.03 | 8.92 × 10^{-07} | 0.13       | 9.00 × 10^{-10} | 2.55 × 10^{-14} | |
|         |         | rs974819   | chr1q22.3  | T  | C  | 0.29 | -0.03 | 1.00 × 10^{-05} | 0.11       | 4.15 × 10^{-07} | 1.67 × 10^{-10} | |
|         |         | rs12875271 | chr13q34   | A  | G  | 0.09 | -0.06 | 5.15 × 10^{-07} | 0.19       | 1.18 × 10^{-07} | 6.29 × 10^{-12} | |
|         |         | rs28577186 | chr16p13.3 | A  | G  | 0.35 | -0.04 | 1.44 × 10^{-06} | 0.14       | 8.39 × 10^{-10} | 3.77 × 10^{-14} | |
|         |         | rs104843   | chr17p13.3 | T  | C  | 0.49 | -0.03 | 1.31 × 10^{-06} | 0.20       | 1.47 × 10^{-22} | 5.13 × 10^{-28} | |
|         |         | rs1800470  | chr19q13.2 | A  | G  | 0.40 | 0.04  | 4.97 × 10^{-07} | -0.15      | 1.76 × 10^{-12} | 1.49 × 10^{-17} | |
|         |         | rs9982601  | chr21q22.11| T  | C  | 0.13 | -0.05 | 1.78 × 10^{-07} | -0.21      | 7.51 × 10^{-12} | 3.38 × 10^{-17} | |

Position is under build 37/hg19.

All these loci were candidate genes to migrate with genome-wide significant (P < 5 × 10^{-8}) for cross-trait meta-analysis (using heterogenous version of CPASSOC, SHet) and P < 1 × 10^{-5} for single trait GWAS. P-values are based on SShet statistic. POS position, MAF minor allele frequency, DBP diastolic blood pressure, SBP systolic blood pressure, PP pulse pressure.
of which also have migraine as a clinical feature. TGFB1 at chr19q13.2 (lead SNP rs1800470, \( P_{\text{CPASSOC}} = 1.49 \times 10^{-17} \) based on \( S_{\text{let}} \) statistic) was shared between migraine and PP alone and encodes a transforming growth factor-beta 1 protein (TGF-\( \beta \)) family member.

Cross-trait meta-analysis between migraine subtypes (MA and MO) and BP showed that previous reported migraine loci, including PHACTR1, LRPI, and FHL5, were shared between both migraine subtypes and BP while locus rs4141663 implicating ITGB5 was genome-wide significant in cross-trait meta-analysis between MO and BP measurements, but not MA (Supplementary Tables 9–14).

**Transcriptome-wide association studies.** We performed TWAS to identify gene-level genetic overlap between BP and migraine. There were 76 TWAS genes that were transcriptome-wide significant for both migraine and at least one BP trait, most of which were identified from gene expression in tissues of cardiovascular and nervous system (Fig. 2). Restricting this list to shared genes with independent signals (see Methods), we identified 23 genes that were TWAS significant for both migraine and at least one of the BP traits from tissues including artery, nerve, skin, esophagus mucosa, and whole blood (Supplementary Tables 15–17), among which 12 were migraine candidate genes. Five of these 12 genes were also identified by the cross-trait meta-analysis (ITGB5, SMG6, ADRA2B, ANKKD1B, and KIAA00400). ITGB5, SMG6, and ADRA2B are described above. Data on ANKKD1B and KIAA00400 were limited, but ANKKD1B was previously suggested to have a shared role between migraine and major depressive disorder (MDD)28. Other gene-level genetic overlap between migraine and BP included genes (CISS2, DMPK, and C12orf5) that were related to regulation of calcium homeostasis and reactive oxygen species (ROS)29,30. TWAS genes with independent effects shared by subtypes of migraine and BP were consistent with findings for overall migraine at ITGB5, while identifying additional associations at HMOX2 for MA and BP, and HVCN1 and MANBA for MO and BP (Supplementary Figs. 22–27, Supplementary Tables 18–23).

**Instrumental variable analysis.** Finally, we used bi-directional MR instrumental analysis to develop evidence for causality in the relationship between BP and migraine. Genetically instrumented elevated DBP and SBP, and decreased PP were associated with increased risk of having migraine with odds ratios (OR) of 1.20 (95% confidence interval [CI] = 1.15–1.25; Wald test \( P = 5.01 \times 10^{-24} \)) and 1.05 (95% CI = 1.03–1.07; Wald test \( P = 2.34 \times 10^{-06} \)) per 10 mmHg increment of DBP and SBP, and 1.09 (95% CI = 1.05–1.14; Wald test \( P = 3.29 \times 10^{-06} \)) per 10 mmHg decrement of PP (Table 3). There were also significant instrumental variable estimates from migraine to BP. Reverse MR showed significant negative instrumental effects per doubling odds of migraine on SBP (estimate = 0.67 mmHg decrement, Wald test \( P = 1.01 \times 10^{-10} \)) and PP (estimate = 0.55 mmHg decrement, Wald test \( P = 3.21 \times 10^{-15} \)), but not DBP (estimate = 0.08 mmHg decrement, Wald test \( P = 0.45 \)). All heterogeneity P-values were non-significant (\( P_{\text{HET}} > 0.01 \)) indicating at worst only subtle heterogeneity among retained instruments. In conditional analysis to distinguish effects mediated by DBP from those mediated by SBP, there was an increase in the instrumental association of high DBP on migraine with conditioning on SBP (OR [95% CI] = 1.38 [1.30–1.46], Wald test \( P = 4.16 \times 10^{-37} \)), while an opposite effect of high SBP on migraine with conditioning on DBP (OR [95% CI] = 0.86 [0.83–0.90], Wald test \( P = 2.08 \times 10^{-22} \)). The diverging instrumental effects of DBP and SBP on migraine were also supported by restricting analysis to SNP instruments that were non-significant (\( P > 0.05 \)) for one measure but highly significant (\( P < 1 \times 10^{-5} \)) for the other (Supplementary Fig. 28). For significance thresholds of \( P < 5 \times 10^{-8} \) or smaller, the instrumental effects of DBP and SBP for migraine were associated respectively with increased and decreased migraine susceptibility. The instrumental variable analysis revealed consistent associations of

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**Fig. 2** Number of shared TWAS significant genes between migraine and BP traits across 48 GTeX tissues (version 7). The X axis shows the count of genes from tissues in the GTEx database meeting significance thresholds for multiple testing for migraine and for each of the BP measures as indicated. The Y axis lists GTEx tissues. Colors represent different tissue categories. The null hypothesis of TWAS is no expression-trait association (or genetic correlation between expression and a trait) conditional on the observed GWAS statistics at the corresponding locus. The total number of TWAS gene-tissue pairs being tested is 206,397 across 48 GTEx tissues. TWAS transcriptome-wide association studies, BP blood pressure, DBP diastolic blood pressure, SBP systolic blood pressure, PP pulse pressure, No. number.
elevated DBP and decreased PP with MO (OR [95% CI] = 1.34 [1.21–1.47], Wald test $P = 1.24 \times 10^{-09}$, OR [95% CI] = 1.16 [1.05, 1.28], Wald test $P = 5.80 \times 10^{-03}$, respectively), whereas no significant association was observed for MA after controlling for multiple testing (Table 3). Sensitivity analysis for the main MR analysis using inverse-variance weighted (IVW), weighted median, and MR-Egger procedures suggested there was no systematic bias due to pleiotropy (Supplementary Table 25). Taken together, the instrumental analyses suggest a potential causal role of elevated DBP on migraine susceptibility, whereas conditional on DBP, SBP may be causally protective. These relationships are also reflected in a potential inverse causal relationship between PP and migraine.

We also applied MR to explore the potential role of causality in anti-hypertensives for migraine prophylaxis effect by only examining lead variants in targets of BP-lowering medications (i.e. beta blocker: ADRB1, ACE inhibitor: ACE, calcium channel blockers: CACNB2, CACNA1D, and CACNA1C$^{31}$). Instrumental associations at these SNPs were directionally consistent with the preceding findings but none was significant alone or in combination (all $P_{MR-Steiger} > 0.05$). Together, the instrumental analyses suggest a potential causal role of elevated DBP on migraine susceptibility, whereas conditional on DBP, SBP may be causally protective. These relationships are also reflected in a potential inverse causal relationship between PP and migraine.

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### Discussion

The conclusions from our genetic analyses were highly consistent and generally support observational associations of positive correlation between BP and migraine$^{32}$ but also qualify these associations in important ways. We find the strongest association between elevated DBP and increased migraine susceptibility. Weaker genetic relationships of elevated SBP with migraine were largely explained by effects on DBP, and conditional on DBP, genetically determined SBP was inversely related to migraine susceptibility. The latter relationship was supported by SNP instruments exclusively associated with SBP and the reverse direction instrumental variable analysis. Consistent with distinct effects of SBP and DBP, greater genetically determined PP was inversely related to migraine susceptibility. The latter relationship was supported by SNP instruments exclusively associated with SBP and the reverse direction instrumental variable analysis. Consistent with distinct effects of SBP and DBP, greater genetically determined PP was inversely related to migraine susceptibility. The latter relationship was supported by SNP instruments exclusively associated with SBP and the reverse direction instrumental variable analysis. Consistent with distinct effects of SBP and DBP, greater genetically determined PP was inversely related to migraine susceptibility. The latter relationship was supported by SNP instruments exclusively associated with SBP and the reverse direction instrumental variable analysis. Consistent with distinct effects of SBP and DBP, greater genetically determined PP was inversely related to migraine susceptibility. The latter relationship was supported by SNP instruments exclusively associated with SBP and the reverse direction instrumental variable analysis. Consistent with distinct effects of SBP and DBP, greater genetically determined PP was inversely related to migraine susceptibility. The latter relationship was supported by SNP instruments exclusively associated with SBP and the reverse direction instrumental variable analysis. Consistent with distinct effects of SBP and DBP, greater genetically determined PP was inversely related to migraine susceptibility. The latter relationship was supported by SNP instruments exclusively associated with SBP and the reverse direction instrumental variable analysis. Consistent with distinct effects of SBP and DBP, greater genetically determined PP was inversely related to migraine susceptibility. The latter relationship was supported by SNP instruments exclusively associated with SBP and the reverse direction instrumental variable analysis. Consistent with distinct effects of SBP and DBP, greater genetically determined PP was inversely related to migraine susceptibility. The latter relationship was supported by SNP instruments exclusively associated with SBP and the reverse direction instrumental variable analysis. Consistent with distinct effects of SBP and DBP, greater genetically determined PP was inversely related to migraine susceptibility. The latter relationship was supported by SNP instruments exclusively associated with SBP and the reverse direction instrumental variable analysis. Consistent with distinct effects of SBP and DBP, greater genetically determined PP was inversely related to migraine susceptibility. The latter relationship was supported by SNP instruments exclusively associated with SBP and the reverse direction instrumental variable analysis. Consistent with distinct effects of SBP and DBP, greater genetically determined PP was inversely related to migraine susceptibility.
relationships between BP and migraine from observational epidemiology. In fact, the findings from genetics are concordant with at least one of the prior observational studies.

Meanwhile, 9 replicating SNPs from cross-trait association analysis as well as 12 genes from TWAS of both migraine and BP suggested potential functions relevant to migraine. The five loci identified in both SNP and TWAS analysis revealed potential shared biological mechanisms in migraine and BP regulation involving vascular development and endothelial function, neurogenic inflammation, calcium homeostasis through proteins encoded by ITGB5, SMG6, ADRA2B, ANKDD1B, and KIAA0040 and, in particular, functions of the α2-adrenergic receptor type B encoded by ADRA2B. Neurotransmitters, such as glutamate, serotonin (5-HT), dopamine (DA), noradrenaline (NE), substance P, and calcitonin gene-related peptide (CGRP), have all been identified as contributing causally to migraine, as well as potential therapeutic targets, and all are related with the α2-adrenergic receptor regulation. Therefore, our results support the role of α2-adrenergic receptor in migraine mechanisms.

In contrast to the results for the genetic effects of DBP and PP on migraine, the genetic association between BP and cardiovascular events was driven by SBP, consistent with the results from observational studies. This suggests that different mechanisms may underlie BP associations with migraine compared to CVD. Thus, observational associations of migraine with cardiovascular events likely do not involve BP-based etiology in a trivial way, a conclusion further supported by the larger MR effects of BP on cardiovascular events compared to the MR effects of BP on migraine. However, it is also possible that potential genetic heterogeneity in migraine or misclassification due to changes in migraine presentation over time may have attenuated the MR association between BP and migraine.

This study comprehensively investigates the genetic-based association between migraine and BP. The main strengths of our study include large-scale genetic data (sample size up to 757,601), independent replication of migraine candidate loci from cross-trait meta-analysis, the use of multiple MR sensitivity analysis for outliers, horizontal pleiotropy, and reverse causation, and the use of exclusive SNP instruments for DBP or SBP that were significant for one trait (P < 1.00 × 10^{-5}) but non-significant (P > 0.05) for the other. However, we acknowledge limitations. First, our conclusions are limited to a general susceptibility of migraine and its major subtypes MA and MO but may not extend to different migraine traits over time or forms of migraine that may not arise from the common, population-based genetic susceptibilities implicit in our datasets, e.g. familial forms of migraine. Second, although the instrumental analysis focused on genetic variation in targets of BP-lowering medications (beta blocker, ACE inhibitor, and calcium channel blocker) was not significant, it may also have been underpowered. Based on the combined effects of SNPs in these genes on BP, we estimated there was only <50% power at nominal significance to detect such instrumental effects on migraine in our datasets. Third, although our analysis points to tissues and genes relevant to migraine susceptibility and BP, more work is needed to identify individual cell types and more detailed molecular mechanisms with the goal of developing potential therapeutic strategies.

Nevertheless, the findings further our understanding of the long-standing debate about the role of BP in migraine susceptibility, reveal the prominent genetic-based role of DBP in migraine susceptibility, and identify shared genetic components including ADRA2B, all of which may provide insight into future migraine therapies.

### Methods

#### Summary statistics from GWAS for migraine and blood pressure.

We used the most recent GWAS summary-level data from International Headache Genetics Consortium (IHGC) for migraine (any migraine and two subtypes of migraine: migraine with aura [MA] and migraine without aura [MO]) and from the International Consortium of Blood Pressure-Genome Wide Association Studies (ICBP) and UK Biobank (UKB) for three BP traits (SBP, DBP, and PP). The migraine meta-analysis summary statistics combined 59,674 cases and 316,078 controls from 22 cohort level GWASs, whereas the BP meta-analysis summary statistics combined 757,601 participants from the UKB (N = 458,577) and ICBP (N = 299,024 across 77 cohorts). In the original GWASs, migraine and its two sub-forms (MA and MO) were defined by diagnostic criteria from the International Headache Society and the summary statistics were adjusted for age, sex, and principle components where applicable in each sub-cohort, whereas BP summary statistics (including three traits: SBP, DBP, and PP) were adjusted for age, sex, and body mass index (BMI) in the parent study, and all sub-cohorts corrected for hypertension treatment (~15/10 mmHg in the presence of any hypertensive medication). All of the participants were of European descent with only a small fraction of overlapping samples (N = 39,199, proportion of overlapping samples is ~10% for migraine summary statistics, and ~5% for BP summary statistics) between migraine and BP traits. Analysis in the current study was restricted to SNPs, at most ~7 million, which were common to GWASs for migraine and the BP traits. To compare the instrumental effects of BP traits on migraine and two migraine cardiovascular comorbidities, coronary artery disease (CAD) and stroke, we used publicly available GWAS summary statistics from European descent individuals for CAD and stroke from CARDIoGRAM and MEGASTROKE, respectively. To minimize the bias from overlapping samples when conducting the instrumental analyses of BP with CAD and stroke, we used BP GWAS

### Table 4 Instrumental estimates between blood pressure and cardiovascular diseases (stroke and CAD) using GSMR.

| Exposure | Outcome | Direction | GSMR | Conditional GSMR |
|----------|---------|-----------|------|------------------|
|          |         |           |      | Covariates       |
|          |         |           |      | Instrumental     |
|          |         |           |      | estimates        |
|          |         |           |      | se               |
|          |         |           |      | P                |
| DBP      | AS      | Forward   | 0.50 | 0.03             |
| SBP      | Forward | 0.31      | 0.02 | 9.49E-61         |
| DBP      | IS      | Forward   | 0.49 | 0.04             |
| SBP      | Forward | 0.30      | 0.02 | 2.36E-51         |
| DBP      | LAS     | Forward   | 0.59 | 0.06             |
| SBP      | Forward | 0.56      | 0.05 | 9.90E-11         |
| DBP      | CES     | Forward   | 0.27 | 0.07             |
| SBP      | Forward | 0.17      | 0.04 | 4.36E-06         |
| DBP      | SVS     | Forward   | 0.75 | 0.09             |
| SBP      | Forward | 0.39      | 0.02 | 2.62E-17         |
| DBP      | CAD     | Forward   | 0.59 | 0.04             |
| SBP      | Forward | 0.34      | 0.02 | 3.87E-71         |

GSMR: Generalized summary-data-based Mendelian randomization; se: standard error; DBP: diastolic blood pressure; SBP: systolic blood pressure; AS: any stroke; IS: ischemic stroke; CAD: coronary artery disease. 
P-values are based on two-sided Wald test.

*The instrumental estimate is corresponding to 10 mmHg increment of blood pressure on the corresponding outcome.

Conditional GSMR was performed by conditioning the exposure on the corresponding covariates (using mtCDIO), then used the conditional summary statistics to infer the instrumental estimates from the exposure to the outcome.
summary statistics ($N = 361,194$) from the UK Biobank, which is publicly available at http://www.nealelab.is/uk-biobank/. All participants provided written informed consent to each of the sub-cohorts of the consortium.

**Genetic correlation analysis.** To evaluate genetic correlation between migraine and BP, we used conventional cross-trait linkage disequilibrium (LD) score regression (LDSC) and the more recent genetic covariance analyzer (GNOVA). For LDSC, we used precomputed LD-scores derived from $\sim$1.2 million common- and well-imputed SNPs in European populations as represented in the HapMap panel excluding the HLA region. With GNOVA, which is potentially more powerful than LDSC, we estimated the genetic correlation across $\sim$5 million well-imputed SNPs in the 1000 Genomes Project and partitioned the estimates among categories of SNPs defined by 11 functional categories, quartiles of MAF, and regions implicated in transcription for seven broadly-defined tissue types. Both LDSC and GNOVA controlled for potential overlapping samples between each pair of traits.

**Local genetic correlation.** We estimated local genetic correlations between migraine and BP traits in 1703 pre-specified LD-independent segments with both p-HES5 and GWAS-PW. Both methods are designed to identify small contiguous regions of the genome in which the genetic associations with two traits are locally concordant. However, they use different approaches. p-HESS quantifies the local genetic covariance (and correlation) and $P$-values ($P_{HESS}$) between pairs of traits at local regions, while GWAS-PW uses a Bayesian framework to estimate the posterior probability ($PP_A_3$) that genetic associations with the two traits co-localize using priors that are learned from the data. BP and migraine were considered to have genetic correlation at local regions if $P_{HESS}$ was significant after correcting for multiple testing ($P_{HESS} < 0.05/1703$) and $PP_A_3$ from GWAS-PW was larger than 0.9.

**Cross-trait meta-analysis between migraine and BP traits.** We conducted pairwise cross-trait meta-analysis using Cross Phenotype Association (CPASSOC) through the statistic $S_{HES}$ that implements a sample size-weighted, fixed effect meta-analysis of the association statistics from the individual traits while modeling genetic covariance from all sources. In these analyses, we used total sample size values directly from the summary statistics file for BP and an average effective sample size for migraine. The cross-trait meta-analysis was not inflated by observing a mean ratio of LDSC intercept-1/($\text{mean}(\chi^2) - 1$) at 0.05 (Supplementary Figs. 1–9). Replication of migraine candidate associations from CPASSOC was performed using an independent dataset from UK Biobank (using data from data field 20002 and 6159 for migraine and recent headache, respectively, see details in Supplementary Note 1).

**Transcriptome-wide association studies.** To identify genes whose expression pattern across tissues implicates etiology or biological mechanisms shared by migraine and the BP measures, we performed TWAS. With TWAS, we compared gene-based models of genetic effects on tissue-specific gene expression from GTex v.7 for migraine and the BP measures from the GWAS summary statistics to estimate strength of association between concordant gene-based genetic influences on gene expression on migraine or BP. In total, we performed 48 TWAS for each trait, one tissue–trait pair at a time. The null hypothesis of TWAS is no expression trait association (or genetic correlation between expression and a trait) conditional on the observed GWAS statistics at the locus. In practice, a permutation test based on 1000 resampling iterations was run for each TWAS gene to ensure that the TWAS false positive rate was well controlled. We applied Bonferroni correction to identify significant expression-trait associations adjusted for multiple comparisons for all gene–tissue pairs tested for each trait ($\sim$200,000 gene–tissue pairs in total), significant expression–trait associations were defined as $P_{\text{Bonferroni}} < 0.05$, and then identified genes that had Bonferroni significant associations for both migraine and BP. We further tested for conditional relationships among the shared genes to identify an independent set of gene-based genetic models using an extension of TWAS that leverages previous methods for joint/conditional tests of SNPs using summary statistics (Supplementary Note 2).

**Generalized summary-data-based Mendelian randomization.** To examine evidence for potential causal relationships between migraine and BP, we conducted instrumental variable analysis using bi-directional MR implemented in generalized summary-data-based Mendelian randomization (GSMR). GSMR applies strict criteria to select independent SNP instruments and extends conventional MR by accounting for the sampling variance in the genetic effects on both exposure ($b_0$) and outcome ($b_3$) in estimating the instrumental effect. Further, as pleiotropy is an important potential confounder that could bias the estimates and possibly result in an inflated test-statistic in MR, we used heterogeneity criteria in HEIDI (heterogeneity in dependent instruments, $P_{HEIDI} < 0.01$) in the GSMR package to exclude likely pleiotropic SNPs from the analysis. To evaluate separate effects of SBP and DBP on migraine, we performed conditional instrumental analysis using mtCOJO (multi-trait-based conditional and joint analysis), also within GSMR, with a two-step procedure requiring only the GWAS summary statistics. SNP effects on SBP ($\beta_1$) were adjusted for effects on DBP ($\beta_2$) (or vice-versa) obtained from GSMR step 1, and then the adjusted instruments were used to derive the conditional instrumental estimate in step 2. $P$-values were corrected for multiple testing using Bonferroni criteria. We conducted sensitivity analyses using conventional inverse-variance weighted (IVW) MR, weighted median, simple median, MR-egger (Egger regression), and MR-Steiger (Supplementary Note 3). As migraine is a binary variable, we interpreted the reverse causal estimates as the average change in BP per doubling (twofold increase) in the odds of migraine, which could be obtained by multiplying the reverse causal estimate by $0.693$ ($\log_2(2)$).

**Reporting summary.** Further information on research method is available in the Nature Research Reporting Summary linked to this article.

**Data availability**

Summary-level data for CAD (CARDIoGRAM), Stroke (MEGASTROKE), and BP (International Consortium of Blood Pressure genetics [ICBP] and the UK Biobank [UKBi]) are publicly available at: http://www.cardiogrampluscldc.org/data-downloads/ and http://www.megastroke.org/download.html; and http://www.nealelab.is/uk-biobank/. Summary-level data ($P < 1 \times 10^{-5}$) from International Headache Genetics Consortium (IHGC) for migraine are available here: http://www.headachege genetics.org/content/datasets-and-cohorts. Individual level data from UK Biobank (UKB) are available upon application: https://www.ukbiobank.ac.uk/.

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