Shared genetic basis for migraine and ischemic stroke

A genome-wide analysis of common variants

Rainer Malik, PhD
Tobias Freilinger, MD
Bendik S. Winsvold, PhD
Verneri Anttila, PhD
Jason Vander Heiden, MSc
Matthew Traylor, PhD
Boukje de Vries, PhD
Elizabeth G. Holliday, PhD
Gisela M. Terwindt, MD, PhD
Jonathan Sturm, PhD
Joshua C. Bis, PhD
Jemma C. Hopewell, PhD
Michel D. Ferrari, MD, PhD
Kristiina Rannikmae, MD
Maija Wessman, PhD
Mikko Kallela, MD, PhD
Christian Kubisch, MD
Myriam Fornage, PhD
James F. Meschia, MD
Terho Lehtimäki, MD
Cathie Sudlow, FRCP
Robert Clarke, FRCP
Daniel I. Chasman, PhD
Braxton D. Mitchell, PhD
Jane Maguire, PhD
Jaakko Kaprio, MD, PhD
Martin Farrall, FRCPath
Olli T. Raitakari, MD, PhD
Tobias Kurth, MD, ScD
M. Arfan Ikram, MD
Alex P. Reiner, PhD
W.T. Longstreth, Jr., MD
Peter M. Rothwell, FMedSci
David P. Strachan, MD
Pankaj Sharma, PhD

Author list continued on next page

ABSTRACT

Objective: To quantify genetic overlap between migraine and ischemic stroke (IS) with respect to common genetic variation.

Methods: We applied 4 different approaches to large-scale meta-analyses of genome-wide data on migraine (23,285 cases and 95,425 controls) and IS (12,389 cases and 62,004 controls). First, we queried known genome-wide significant loci for both disorders, looking for potential overlap of signals. We then analyzed the overall shared genetic load using polygenic scores and estimated the genetic correlation between disease subtypes using data derived from these models. We further interrogated genomic regions of shared risk using analysis of covariance patterns between the 2 phenotypes using cross-phenotype spatial mapping.

Results: We found substantial genetic overlap between migraine and IS using all 4 approaches. Migraine without aura (MO) showed much stronger overlap with IS and its subtypes than migraine with aura (MA). The strongest overlap existed between MO and large artery stroke (LAS; $p = 6.4 \times 10^{-28}$ for the LAS polygenic score in MO) and between MO and cardioembolic stroke (CE; $p = 2.7 \times 10^{-20}$ for the CE score in MO).

Conclusions: Our findings indicate shared genetic susceptibility to migraine and IS, with a particularly strong overlap between MO and both LAS and CE pointing towards shared mechanisms. Our observations on MA are consistent with a limited role of common genetic variants in this subtype. *Neurology*® 2015;84:2132–2145

GLOSSARY

CE = cardioembolic stroke; **CPSM** = cross-phenotype spatial mapping; **GWAS** = genome-wide association studies; **IHGC** = International Headache Genetics Consortium; **IS** = ischemic stroke; **LAS** = large artery stroke; **LD** = linkage disequilibrium; **MA** = migraine with aura; **MO** = migraine without aura; **SNP** = single nucleotide polymorphism; **SVD** = small vessel disease.

Migraine is a primary headache disorder characterized by recurrent attacks of severe, often throbbing, headache associated with autonomic dysfunction. Although the majority of patients have migraine without aura (MO), one third have headaches preceded by transient neurologic disturbances (migraine with aura [MA]).[1] Ischemic stroke (IS) is etiologically heterogeneous and a leading cause of premature death and disability.[2]

Results of epidemiologic studies show increased risk of IS in migraine patients.[3] A large meta-analysis of case-control and observational cohort studies reported an increased risk of IS for patients with MO and MA,[4] whereas more recent meta-analyses reported the association to be restricted to MA.[3,5,6] Pathophysiology linking these neurovascular disorders remains poorly understood; suggested mechanisms include cortical spreading depression,[7] endothelial dysfunction,[8] enhanced platelet activation,[9] and vasoconstriction.[10]

Recent genome-wide association studies (GWAS) identified common genetic variants associated with migraine[11] and its subtypes MO[12] and MA.[13] Similarly, GWAS results point to variants associated with IS subtypes such as large artery atherosclerotic[14,15] and cardioembolic.[16] We combined GWAS from the International Headache Genetics Consortium (IHGC)[11] and METASTROKE[15] to assess shared genetic bases for migraine and IS. We first

Author affiliations are provided at the end of the article.

Coinvestigators are listed on the *Neurology*® Web site at Neurology.org.

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Sudha Seshadri, MD
Lydia Quaye, PhD
Lynn Cherkas, PhD
Markus Schürks, MD, MSc
Jonathan Rosand, MD
Lannie Ligthart, PhD
Giorgio B. Boncoraglio, MD
George Davey Smith, DSc
Cornelia M. van Duijn, PhD
Kari Stefansson, MD, PhD
Bradford B. Worrall, MD, MSc
Dale R. Nyholt, PhD
Hugh S. Markus, FRCP
Arn M.J.M. van den Maagdenberg, PhD
Chris Cotsapas, PhD
John A. Zwart, MD, PhD
Aarno Palotie, MD
For the International Headache Genetics Consortium
Martin Dichgans, MD
For the METASTROKE Collaboration of the International Stroke Genetics Consortium

Correspondence to Dr. Dichgans: martin.dichgans@med.uni-muenchen.de

examined known genome-wide risk loci in the respective phenotypes. Using 2 methodologies, we then evaluated shared genetic risk for migraine with IS: (1) analysis of shared polygenic risk with subsequent estimation of genetic correlation between phenotypes and (2) detailed investigation of overlapping regions.

METHODS

Standard protocol approvals, registrations, and patient consents. ***Ethics statement.*** For all study cohorts, all participants gave informed consent and local research ethics boards approved all protocols.[11,15]

Cohorts. Investigators of the IHGC study, a meta-analysis of GWAS data, enrolled 23,285 patients with migraine and 95,425 population-based or headache-free controls from 29 studies.[11] When possible, researchers considered subclassifications of migraine with (MA: 5,118 cases vs 74,239 controls) or without aura (MO: 7,107 cases vs 69,427 controls). The METASTROKE study consists of combined data from 15 GWAS of IS (12,389 cases vs 62,004 controls).[15] We used TOAST criteria[17] to classify IS as large artery stroke (LAS) (2,167 cases/49,159 controls from 11 studies), cardioembolic stroke (CE) (2,365 cases/56,140 controls from 13 studies), and small vessel disease (SVD) (1,894 cases/51,976 controls from 12 studies) (tables e-1 and e-2 on the *Neurology*® Web site at Neurology.org).[11,15] We removed overlapping controls between the migraine and stroke samples from deCODE, WTCCC2 (B58C and KORA), and the Rotterdam studies from the stroke datasets for polygenic score analyses, cross-phenotype spatial mapping (CPSM), and correlation analyses to avoid inflation of statistics.

Genome-wide association studies. Both the IHGC migraine[11] and METASTROKE[15] studies consisted of independently performed genome-wide single nucleotide polymorphism (SNP) genotyping using standard technologies and imputation to HapMap release 21 or 22 CEU phased genotype[18] or 1000 Genome reference panels. Investigators contributed summary statistical data from association analyses using frequentist additive models for meta-analysis after application of appropriate quality control measures (e-Methods). Subtle differences in allele frequencies between migraine and stroke could lead to deviation from the expected test statistic. Thus, as a final quality control step, we meta-analyzed results from the IHGC study and the METASTROKE study and constructed quantile-quantile plots (figure e-1).

Statistical analysis. For analysis of previously discovered risk loci for IS or migraine, we extracted relevant loci from the literature and the 2 described consortia.[11,15] We examined all SNPs within a window of ±50 kb surrounding the original reported risk SNP (coordinates from human genome build hg18) and reported the most significant p values of all genotyped or imputed SNPs within this window. We applied Bonferroni correction for association, integrating all tested SNPs for IS risk loci (650 tested SNPs), migraine risk loci (1,175 tested SNPs), and MO risk loci (213 tested SNPs) with resulting p value thresholds of 7.69E-5, 4.25E-5, and 2.30E-4, respectively.

Polygenic scores reveal combined effects of multiple nonsignificant variants derived from a derivation sample and tested in an independent replication sample. We derived polygenic scores for multiple p value cutoffs (0.5, 0.25, 0.1, 0.05, 0.01, 0.001, and 0.0001) in derivation samples. Further, we performed testing on summary statistics using the grs.summary function of the gtx package for *R*, a technique previously used in multiple studies, which estimates the polygenic component with high reliability.[19] We use the term replication to describe analyses across phenotypes.

Use of linkage disequilibrium (LD) pruned data ($r^2 > 0.25$) ensured approximate independence of SNPs. We retained the SNP with the lowest p value in an independent region and calculated the proportion of variance explained in the testing set by the polygenic scores using Nagelkerke's pseudo R^2. Outcome measures include the p value of the association of the polygenic score in the testing dataset and the variance explained.

CPSM identifies genomic windows exhibiting similar association patterns across 2 phenotypes using a signal processing approach. CPSM allows analysis of pleiotropy across multiple diseases. Peak heights serve as an intuitive measure for description of shared risk loci in different phenotypes. This method corrects for background noise in the p value distribution and is thus superior to comparisons of single p values. We computed Pearson covariance between p values from 2 traits across a 60-kb sliding window. In each iteration, the window slides to the next SNP; thus, we obtained a covariance coefficient for each SNP in the analysis. We then detected signal peaks across the genome in the covariance trace and calculated the signal s_n for a given SNP with index n, position b_n (base pairs), and association p values $p1_{,n}$, $p2_{,n}$ for 2 phenotypes as follows:

$$x = -\log(10)p_{1,j}, \ldots. -\log(10)\,p_{1,k}$$

$$y = -\log(10)p_{2,j}, \ldots\ldots -\log(10)\,p_{2,k}$$

$$w = \left[1 - \frac{|b_j - b_n|}{b_k - b_j}, \ldots, 1 - \frac{|b_k - b_n|}{b_k - b_j}\right]$$

$$w' = \frac{1}{\sum_{i=j}^{k} w_i}.w$$

$$s_n = \frac{\sum_{i=j}^{k} w'_i x_i y_i}{1 - \sum_{i=j}^{k} w'^2_i},$$

where each $b_i \in b_j, \ldots b_k$ is the position of SNP_i within the window of $SNPs_{j,\ldots,k}$ containing SNPn. For a given window size d (base pairs), the window of $SNPs_{j,\ldots,k}$ is defined such that j is the smallest SNP index where $b_n - b_j \leq \frac{d}{2}$ and k is the largest SNP index where $b_k - b_n \leq \frac{d}{2}$.

After constructing the CPSM signal for all SNPs, we corrected for strong associations identified in only one phenotype by permuting the association p values for one phenotype 1,000 times while holding the other phenotype constant, and then recalculating CPSM signals. From the total set of 2,000 permutation signals (1,000 per phenotype), we subtracted the upper 0.95 quantile at each SNP as the background signal threshold from the observed covariance as a correction. We then identified regions of shared association as peaks above the 99.95 (approximately corresponding to a height of 1.5) percentile of the covariance signal. We highlighted regions with a height >2.5 (corresponding to approximately 99.985 percentile) and with a height >5 (corresponding to approximately 99.998 percentile). CPSM only provides a signal when the effect in 2 traits is the same, implying shared causality in the discovered regions.

Utilizing a recently developed framework for polygenic analyses and based on the number of SNPs, the dataset sample sizes, and estimates of disease prevalence and pseudo-heritability, we estimated the power to detect an association indexing on a given degree of genetic correlation between the 2 phenotypes. We used the same framework, including p values from polygenic analysis, to estimate the overall degree of genetic correlation between each of the IS and migraine phenotypes, a posteriori to the polygenic

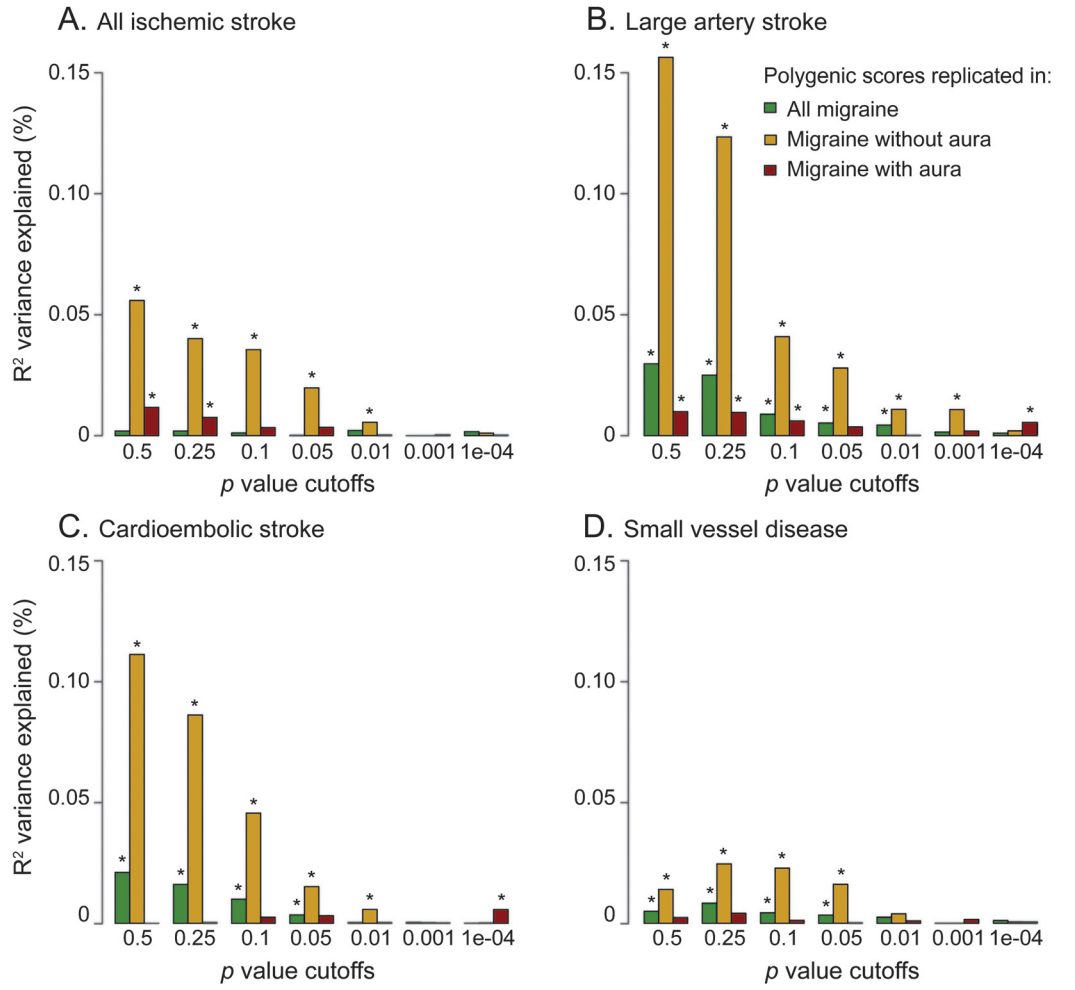
Supplemental data at Neurology.org

analysis. We estimated genetic correlation in both the forward direction (using results from polygenic analysis of IS and subtypes as a discovery sample and migraine and subtypes as a replication sample) and the reverse direction (using results from the polygenic analysis from migraine and subtypes as a discovery sample and stroke and subtypes as a replication sample) to evaluate consistency of results using the estimateCorrFromP method. An implementation of the procedure was downloaded from http://sites.google.com/site/fdudbridge. This method approximates SNP correlation from cross-disorder applications of polygenic scores and can be compared to GREML-SNP genetic correlation. All analyses used *R* statistical software (http://www.R-project.org). Using stroke prevalence data from the British Heart Foundation for IS[20] (1.7% in the United Kingdom) and the proportional incidence of IS events from all stroke events in the OXVASC study[21] (59%), we estimated the prevalence of IS (~1%). We then used the proportion of IS subtypes (CE, LAS, or SVD) from a meta-analysis of population-based incidence studies[22] to estimate the prevalence of each subtype. We estimated stroke heritability on a liability scale.[23] Although we acknowledge that migraine prevalence may vary across countries, we estimated migraine prevalence to be 17% for all migraine, 11% for MO, and 5% for MA based on published data.[1,24] Migraine heritability estimates vary in the literature, with MA being highest. We chose heritability measures of 0.65 for MA[25] and 0.61 for MO[26] and a more conservative measure of 0.57 for all migraine.

RESULTS Information on clinical subtypes was available for 12,225 (52.5%) of the migraine and for 6,426 (51.9%) of the IS patients (tables e-1 and e-2). We identified 38,338 potentially overlapping controls and excluded them from analyses where necessary. QQ plots revealed no inflation of test statistics (lambda inflation factors below 1.05 in all analyses of migraine subtypes vs all IS; figure e-1 and e-Methods).

All migraine. We first evaluated risk loci identified in previous GWAS on IS or its subtypes,[15] in all migraine[11] and vice versa. Although we identified several variants reaching nominal association ($p < 0.05$), when controlling for all tested SNPs, none of the

Figure 1 Results from polygenic score analysis using ischemic stroke as a discovery phenotype



(A) All ischemic stroke. (B) Large artery stroke. (C) Cardioembolic stroke. (D) Small vessel disease. Migraine was used as a replication phenotype. The x-axis describes the *p* value cutoffs used in the polygenic score; the y-axis describes the pseudo-R^2 variance explained by the score. Asterisks on top of a bar designate *p* values < 0.05. Raw values can be found in table e-5.

tested variants surpassed Bonferroni-corrected *p* value thresholds (tables e-3 and e-4).

Polygenic scores. Scores derived from LAS, CE, and SVD each showed significant associations with all migraine (figure 1, tables 1 and e-5) with replication *p* values ranging from 2.7E-9 for LAS to 0.017 for SVD. Explained variance ranged from 0.005% to 0.03% (figure 1, table 1). Conversely, polygenic scores derived from all migraine significantly associated with LAS, CE, and SVD (figure 2, tables 1 and e-5) with replication *p* values between 8E-9 (replication in LAS) and 0.03 (replication in SVD) and an explained variance between 0.008% and 0.065% (figure 2, tables 1 and e-5). Calculated estimates of genetic correlation between all migraine and IS ranged from approximately 3% for correlation with all IS to 38% for correlation with LAS (table 2).

CPSM analysis. The most significant loci reaching an arbitrary peak height cutoff of 2.5 for CPSM are summarized in table 3 (full results, table e-6). Using this height cutoff, there were 5 shared loci for all IS and all migraine with the strongest signal at chromosome 12q24 (height = 7.2). For LAS and all migraine, we found 3 shared loci, with the *LMOD2-WASL* region on chromosome 7q31 showing the strongest signal (height = 7.2). CE and SVD showed 8 and 3 shared loci with all migraine, respectively (maximum height, 4.94 for CE and all migraine; 3.99 SVD and all migraine).

Migraine without aura (MO). A single variant in the 9p21 region, previously associated with LAS,[14] surpassed the Bonferroni-corrected threshold for association with MO (p = 4.0E-5). Focusing on 2

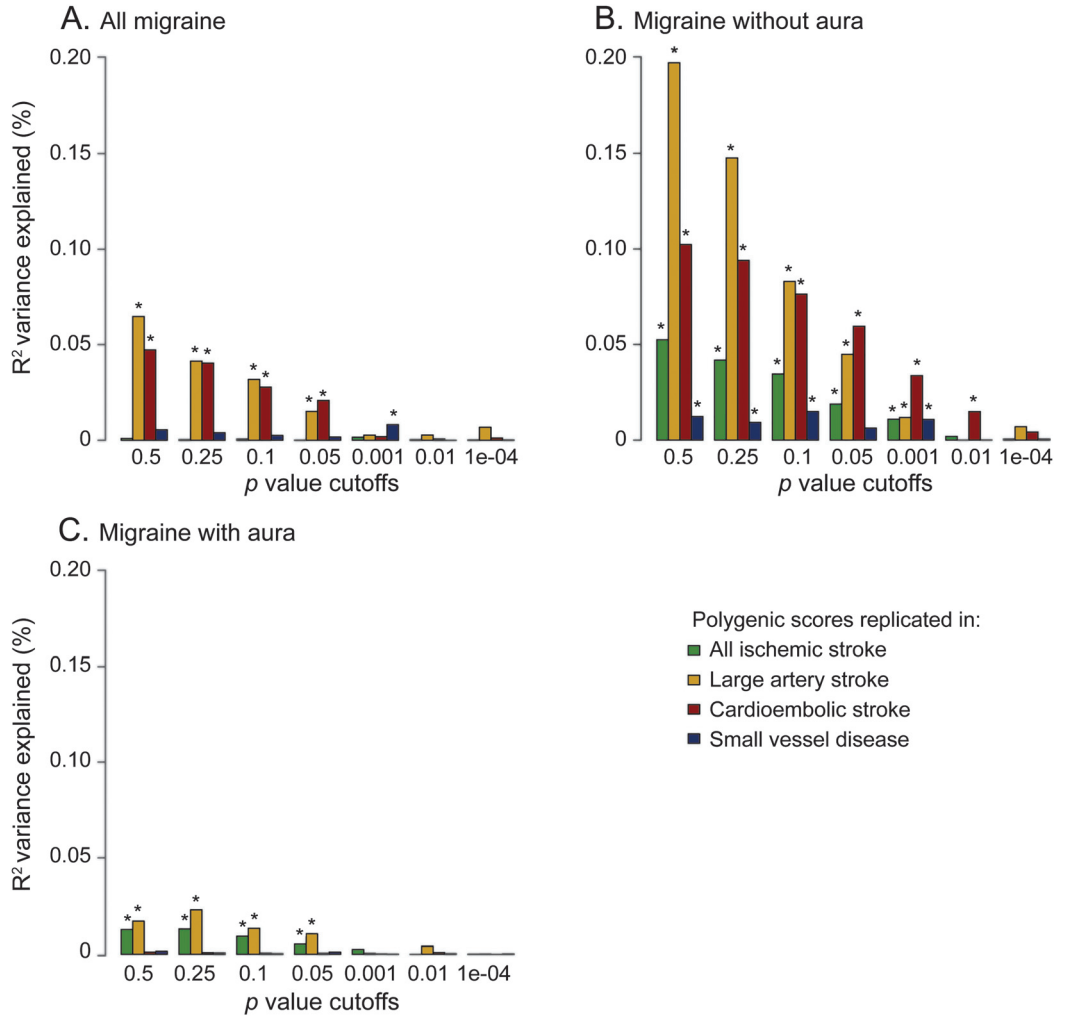
Table 1 Polygenic score results

Discovery set	Replication set	p Value cutoff	No. SNPs	p Value replication set	R^2 variance explained, %	OR replication set (95% CI)
All migraine	All IS	0.5	88,479	0.384178	0.0010	1.003 (0.996-1.009)
All migraine	LAS	0.5	88,479	7.99E-9	0.0650	1.041 (1.027-1.055)
All migraine	CE	0.5	88,479	1.46E-7	0.0473	1.035 (1.022-1.049)
All migraine	SVD	0.5	88,479	0.082929	0.0056	1.013 (0.998-1.028)
MO	All IS	0.5	87,163	3.89E-10	0.0526	1.011 (1.008-1.015)
MO	LAS	0.5	87,163	6.59E-24	0.1978	1.039 (1.031-1.046)
MO	CE	0.5	87,163	9.10E-15	0.1026	1.028 (1.021-1.035)
MO	SVD	0.5	87,163	0.00970	0.0124	1.010 (1.003-1.018)
MA	All IS	0.5	87,674	0.001920	0.0129	0.995 (0.992-0.998)
MA	LAS	0.5	87,674	0.002842	0.0174	1.010 (1.003-1.017)
MA	CE	0.5	87,674	0.4001	0.0012	1.003 (0.996-1.009)
MA	SVD	0.5	87,674	0.3432	0.0017	1.003 (0.996-1.010)
All IS	All migraine	0.5	84,947	0.13043	0.0019	1.003 (0.999-1.006)
All IS	MO	0.5	84,947	6.02E-11	0.0559	1.021 (1.015-1.028)
All IS	MA	0.5	84,947	0.00227	0.0117	0.989 (0.982-0.996)
LAS	All migraine	0.5	84,258	2.67E-9	0.0298	1.005 (1.003-1.007)
LAS	MO	0.5	84,258	6.43E-28	0.1566	1.017 (1.014-1.020)
LAS	MA	0.5	84,258	0.00489	0.0010	1.005 (1.001-1.008)
CE	All migraine	0.5	82,187	5.94E-7	0.0209	1.005 (1.003-1.006)
CE	MO	0.5	82,187	2.74E-20	0.1112	1.016 (1.012-1.019)
CE	MA	0.5	82,187	0.92492	1.12E-5	1.000 (0.996-1.004)
SVD	All migraine	0.5	81,946	0.01640	0.0049	1.002 (1.000-1.004)
SVD	MO	0.5	81,946	0.001091	0.0139	1.005 (1.002-1.008)
SVD	MA	0.5	81,946	0.17365	0.0023	1.002 (0.999-1.006)

Abbreviations: CE = cardioembolic; CI = confidence interval; IS = ischemic stroke; LAS = large artery stroke; MA = migraine with aura; MO = migraine without aura; OR = odds ratio; SNP = single nucleotide polymorphism; SVD = small vessel disease.

The results for a *p* value cutoff of 0.5 are shown. For full results, see table e-5. *p* Value is the *p* value of the 1 *df* test of the risk score in the replication set. R^2 variance explained is the pseudovariance explained by the risk score model in the replication dataset (×100 to display percentage). Odds ratios were calculated from the estimated coefficient for regressing the response onto the risk score and are given as an increase of 1 standard deviation of the polygenic score.

Figure 2 Results from polygenic score analysis using migraine as a discovery phenotype



(A) All migraine. (B) Migraine without aura. (C) Migraine with aura. Stroke was used as a replication phenotype. The x-axis describes the *p* value cutoffs used in the polygenic score; the y-axis describes the pseudo-R^2 variance explained by the score. Asterisks on top of a bar designate *p* values < 0.05. Raw values can be found in table e-5.

loci previously known to be associated with MO but not MA,[11] we identified no variants surpassing the Bonferroni-corrected *p* value threshold (table e-4).

Polygenic scores. Scores derived from all IS, LAS, CE, and SVD each showed significant associations with MO (figure 1, tables 1 and e-5); replication *p* values ranged from 6.43E-28 for LAS polygenic score to 1.47E-5 for SVD polygenic score. The highest percentage of explained variance occurred for scores derived from LAS and CE (0.157% and 0.111%, respectively), and was higher in MO than in all migraine across all *p* value cutoffs (figure 1, B and C). Conversely, polygenic scores derived from MO significantly associated with all IS, LAS, CE, and SVD (figure 2, tables 1 and e-5) with replication *p* values between 6E-24 (replication in LAS) and 0.004 (replication in SVD) and an explained variance between 0.015% and 0.198% (figure 2, tables 1 and e-5). Estimates of genetic correlation with IS were markedly higher than observed for all migraine (estimates ranged from 25% for correlation with all IS to 83% for correlation with LAS; table 2).

CPSM analysis. Using a cutoff of 2.5, we detected 4 shared loci between MO and all IS. MO and LAS shared 3 loci, with the strongest signal at chromosome 9p21 (signal height, 7.7). CE and MO shared 6 loci (maximum height = 3.87), and MO and SVD shared 4 loci (2 loci reaching maximum heights of 6.7 and 6.3). The former was near the *CISD2* gene on chromosome 4q24, the latter in a gene-rich region on chromosome 17q21 including the *Tau* locus (tables 3 and e-6).

Migraine with aura (MA). None of the variants previously associated with IS surpassed the Bonferroni-corrected *p* value threshold of 7.69E-5 when tested for association with MA. There were no genome-wide significant loci[11] for MA.

Table 2 Estimation of genetic correlation with the Dudbridge Method

Stroke subtype	Migraine subtype	Forward estimated genetic correlation, % (95% CI)	Reverse estimated genetic correlation, % (95% CI)
All IS	All migraine	4.47 (0.007–10.26)	2.96 (0.007–9.63)
All IS	MO	25.83 (18.09–33.56)	25.68 (17.64–33.72)
All IS	MA	14.39 (5.15–23.64)	15.28 (5.45–24.18)
LAS	All migraine	33.98 (22.79–45.17)	38.47 (25.41–51.53)
LAS	MO	83.55 (68.61–98.47)	81.06 (65.33–96.78)
LAS	MA	25.64 (7.79–43.53)	28.80 (9.88–47.71)
CE	All migraine	29.32 (17.81–40.83)	36.19 (22.71–49.68)
CE	MO	72.40 (57.04–87.76)	64.26 (48.02–80.49)
CE	MA	8.83 (0.007–19.26)	8.37 (0.007–27.85)
SVD	All migraine	20.82 (3.81–37.82)	17.17 (0.007–37.7)
SVD	MO	37.86 (15.14–60.58)	31.77 (7.69–55.84)
SVD	MA	18.84 (0.007–45.92)	13.95 (0.007–42.85)

Abbreviations: CE = cardioembolic; CI = confidence interval; IS = ischemic stroke; LAS = large artery stroke; MA = migraine with aura; MO = migraine without aura; SVD = small vessel disease.
Genetic correlation is estimated using results from polygenic score analysis, taking into account the number of single nucleotide polymorphisms used, number of subjects in the analysis, and prevalences and heritability estimates of the 2 phenotypes. The forward experiment uses the stroke subtype as the discovery set and the migraine subtype as the testing set. The reverse experiment uses the migraine subtype as the discovery set and the stroke subtype as the testing set.

Polygenic scores. Scores derived from IS, LAS, and CE all showed significant associations with MA (figure 1, tables 1 and e-5) with replication p values ranging from 0.002 for the all IS polygenic score to 0.04 for the CE polygenic score. Explained variance ranged from 0.010% (LAS) to 0.012% (IS). Polygenic scores derived from MA significantly associated with all IS and LAS (figure 2, tables 1 and e-5) with replication p values of 0.0017 and 0.0005, and an explained variance of 0.013% and 0.023%, respectively. Estimates of genetic correlation ranged from 8% for correlation with CE to 28% for correlation with LAS (table 2).

CPSM analysis. We found several shared regions between MA and stroke subtypes. Using a cutoff of 2.5, we found 2 shared loci between all IS and MA with a maximum height of 3.15 and 2 loci shared between LAS and MA with a maximum height of 3.53 in the *LMOD2/WASL* gene region. CE and MA shared no loci using this cutoff and SVD and MA shared 1 locus with a maximum height of 2.83 (tables 3 and e-6).

DISCUSSION We demonstrated that the combined contributions of common genetic variants at a number of loci influence risk for both migraine and IS. This is supported by results from 4 investigative approaches: (1) analysis of common variants at loci reaching genome-wide significance for potential signal overlap; (2) investigation of shared genetic load using polygenic score models; (3) estimation of genetic correlation between disease subtypes using data derived from these models; and (4) highlighting regions of shared risk by analysis of covariance patterns between phenotypes using CPSM. We found stronger signal overlap between MO and IS than between MA and IS; overlap is stronger for LA and CE stroke than for SVD. Finally, we identified several individual loci with a strong signal for association with both phenotypes.

Polygenic scores, estimates of genetic correlation, and CPSM results all demonstrated a stronger genetic overlap of IS with MO compared to MA. Polygenic scores from MO replicated in overall IS and IS subtypes across a wide range of p value cutoffs, while scores derived from IS behaved similarly when tested in MO. Scores derived from MA demonstrated weaker association with IS. The variance explained by polygenic scores of each IS subtype was consistently higher for MO (figures 1 and 2). Also, estimates of genetic correlation with IS and its subtypes were consistently higher for MO than for MA (table 2).

Unexpectedly, CPSM revealed that the number of loci reaching a peak height >2.5 was larger for MO and IS than for MA and IS (table 3). Recent epidemiologic studies suggest an association between IS risk and MA but not MO,[3,6] but other data suggest that patients with MO are at increased risk of IS.[4] One potential explanation is that genetic risk for MA may be more restricted to rare variants not captured by GWAS strategies as suggested by the larger number of genome-wide significant loci for MO compared to MA despite comparable sample sizes.[11] However, estimated heritability for MA is as least as high as for MO.[25,26] Larger samples together with sequencing efforts or rare variant assays might help to determine whether rare variants indeed influence MA risk and whether the same variants also contribute to IS risk. The same might be true for SVD, for which there are no existing identified genome-wide loci. Hence, we might have underestimated genetic overlap between migraine subtypes and SVD.

We found particularly strong genetic overlap for migraine with LAS and CE. Polygenic scores analyses showed the strongest overlap with LAS for all forms of migraine regardless of whether polygenic scores were derived from LAS and tested in migraine or vice versa. In a recent small population-based study of 360 migraineurs and 617 controls, researchers reported no association between migraine and intima media thickness,[27] but more advanced stages of atherosclerosis were not assessed. Most previous studies examining the relationship between migraine and IS did not distinguish among stroke subtypes. Migraineurs display enhanced platelet aggregation,[9] which together with other factors might contribute to overlap with LAS.

Table 3 Most significant loci detected by the cross-phenotype spatial mapping method

Migraine phenotype	Stroke phenotype	Chr band	Position, Mb	Locus size	Peak SNP	Same directional effect[a]	Peak height	Genes within locus
All migraine	All IS	5p14.1	29.0-29.1	126 kB	rs1692345	Y	4.18	—
		6q16.1	96.9-97.2	206 kB	rs12213426	N	2.82	*KIAA0776, FHL5*
		12q24.11[b]	110.2-111.5[b]	1.26 MB[b]	rs7962138[b]	Y[b]	7.20[b]	*CUX2, SH2B3, ATXN2, BRAP, ACAD10, ALDH2, MAPKAPK5, TMEM116, ERP29, nap1, TRAFD1, RPL6, PTPN11*[b]
		14q13.2	35.2-35.4	190 kB	rs10141289	N	3.17	*GARNL1, BRMS1L*
		21q21.2	23.0-23.1	107 kB	rs7280779	Y	2.80	—
	LAS	7q31.32[b]	123.0-123.2[b]	203 kB[b]	rs1008539[b]	N[b]	7.18[b]	*ASB15, LMOD2, WASL*[b]
		10q24.1	99.1-99.2	85 kB	rs2297668	Y	3.06	*RRP12, PGAM1, EXOSC1*
		10q24.33	104.9-105.1	237 kB	rs1063461	N	3.94	*INA, PCGF6, TAF5, USMG5, PDCD11*
	CE	2q32.2	190.2-190.4	169 kB	rs7571089	Y	2.54	*ANKAR, OSGEPL1, ORMDL1, PMS1*
		6q16.1	97.0-97.1	67 kB	rs12207471	Y	3.16	*KIAA0776*
		10q22.1	73.8-74.0	218 kB	rs7918099	Y	3.03	*DNAJB12, CBARA1*
		12q13.12	48.2-48.5	257 kB	rs4641552	Y	3.07	*SPATS2, KCNH3, MCRS1, FAM186B, PRPF40B, FMNL3, TMBIM6*
		14q13.2	35.1-35.4	377 kB	rs4981309	N	4.83	*GARNL1, BRMS1L*
		14q23.2	62.9-63.0	108 kB	rs7140274	Y	4.12	*PPP2R5E*
		17p13.1	7.3-7.4	129 kB	rs9890920	N	4.94	*TMEM102, FGF11, CHRNB1, ZBTB4, POLR2A, TNFSF12*
		20p11.21	25.8-24.9	112 kB	rs6050070	Y	2.62	—
	SVD	1q22	154.7-154.8	113 kB	rs1171561	Y	3.99	*MEF2D, IQGAP3*
		4q24	103.9-104.2	322 kB	rs11722779	Y	3.78	*MANBA, UBE2D3, CISD2, SLC9B1, SLC9B2*
		12q24.12	110.5-110.9	411 kB	rs11066090	N	2.81	*ATXN2, BRAP, ACAD10, ALDH2, MAPKAPK5, TMEM116*
MO	All IS	5p14.1	29.0-29.1	125 kB	rs606408	Y	4.47	—
		6q16.1	96.9-97.2	226 kB	rs12210146	N	4.07	*KIAA0776, FHL5*
		12q24.11	109.8-110.0	192 kB	rs4378452	N	4.02	*MYL2, CUX2*
		12q24.12	110.2-111.5	1.26 MB	rs6490294	N	3.78	*CUX2, SH2B3, ATXN2, BRAP, ACAD10, ALDH2, MAPKAPK5, TMEM116, ERP29, nap1, TRAFD1, RPL6, PTPN11*
	LAS	9p21.3[b]	21.9-22.1[b]	179 kB[b]	rs9632884[b]	Y[b]	7.67[b]	*CDKN2A/B*[b]
		9q33.2	122.4-122.6	169 kB	rs1886337	N	2.99	*MEGF9*
		10q22.1	72.6-72.6	78 kB	rs10999709	Y	3.00	*UNC5B*
	CE	2q13	112.5-112.6	104 kB	rs7583755	Y	2.67	*TMEM87B, FBLN7*
		2q32.2	190.2-190.5	297 kB	rs920427	Y	3.87	*ANKAR, OSGEPL1, ORMDL1, PMS1*
		6q16.1	97.0-97.1	48 kB	rs12207471	Y	2.55	*KIAA0776*
		9q33.2	122.4-122.6	162 kB	rs10491784	N	2.95	*MEGF9*
		10q22.1	73.8-74.0	190 kB	rs10823921	Y	2.60	*CBARA1*
		20p11.21	24.7-24.9	227 kB	rs6083652	Y	3.19	—
	SVD	1q22	154.7-154.8	97 kB	rs3790455	Y	2.64	*MEF2D, IQGAP3*
		4q24[b]	103.8-104.2[b]	455 kB[b]	rs223308[b]	Y[b]	6.65[b]	*MANBA, UBE2D3, CISD2, SLC9B1, SLC9B2*[b]
		5q31.1	132.4-132.5	85 kB	rs4321746	Y	2.85	*HSPA4*
		17q21.31[b]	40.9-42.3[b]	1.4 MB[b]	rs2463519[b]	Y[b]	6.33[b]	*ARHGAP27, PLEKHM1, CRHR1, MAPT, KIAA1267, LRRC37A, ARL17P1, ARL17, NSF*[b]
MA	All IS	3q11.2	96.6-96.8	228 kB	rs4498047	Y	2.50	—
		9q22.32	98.2-98.4	182 kB	rs7857261	Y	3.15	*SLC35D2, ZNF367, HABP4, CDC14B*

Continued

Table 3 Continued

Migraine phenotype	Stroke phenotype	Chr band	Position, Mb	Locus size	Peak SNP	Same directional effect[a]	Peak height	Genes within locus
	LAS	7q31.32	123.0-123.2	174 kB	rs3815458	N	3.53	*ASB15, LMOD2, WASL*
		8p21.2	24.0-24.1	138 kB	rs6996722	Y	3.07	—
	SVD	4q24	103.9-104.2	323 kB	rs3974608	Y	2.83	*MANBA, UBE2D3, CISD2, SLC9B1, SLC9B2*

Abbreviations: CE = cardioembolic; LAS = large artery stroke; IS = ischemic stroke; MA = migraine with aura; MO = migraine without aura; SNP = single nucleotide polymorphism; SVD = small vessel disease.
All loci with a height >2.5 are shown. For full results, refer to table e-6. Note that coordinates are mapped to NCBI36/hg18. The IS and migraine subtype where the calculation was performed as well as chromosomal band, chromosomal location, peak SNP, and peak height are displayed. Genes in the region denote all genes found within the specified region.
[a] Direction of effect is given for the peak SNP.
[b] All loci with height >5.

Analysis of loci previously shown to reach genome-wide significance for association with migraine showed several variants nominally associated with IS or its subtypes and vice versa. In fact, single variants reached a high threshold of statistical significance, e.g., variants on 9p21, a major risk locus for LAS[14,15] reaching very low p values in MO (table e-3). However, in all instances index SNPs for the tested phenotype were in poor LD ($r^2 < 0.4$) with published risk SNPs making it unlikely that the same variants confer risk to both stroke and migraine.

CPSM analysis revealed several chromosomal regions with strong evidence for genetic overlap between migraine and IS pointing to shared biological mechanisms, including loci already shown to be associated with either migraine or stroke such as a chromosome 12 locus previously implicated in IS, coronary artery disease, hypertension, diabetes, and blood cell traits including platelet count.[19,28–30] Interestingly, *MRVI1* on chr11, another locus previously associated with platelet aggregation,[31] showed genetic overlap between migraine and IS, adding to previous data suggesting a shared role of platelet dysfunction in migraine and IS.[9] Mendelian randomization studies and interventional studies are needed to determine the exact role of platelets in mediating such genetic risk. We also demonstrated genetic overlap between migraine and IS at chromosome 9p21 especially for LAS.

There was genetic overlap at loci not reaching genome-wide significance in migraine or stroke GWAS. A shared locus for all migraine and LAS on 7q31.32 includes the *LMOD2-WASL* gene region. *LMOD2* encodes leiomodin2 that antagonizes tropomodulin, an actin-capping protein.[32] *WASL* is implicated in stabilizing endothelial adherens junctions,[33] and is important for synapse development.[34] We also found overlapping regions for SVD with MO including a locus on 4q24 that encompasses *MANBA*, which encodes β-mannosidase. Mutations in *MANBA* are associated with epileptic encephalopathy[35] and leukoencephalopathy.[36] This region also contains *SLC9B2,* previously associated with essential hypertension,[37] a major risk factor for SVD. A second shared risk locus between MO and SVD points to *MAPT*, the gene encoding tau protein on chromosome 17.

We used the largest collections of GWAS data currently available for migraine[11] and IS,[15] with 4 different but complementary approaches for analysis of genetic overlap including novel methodology (CPSM).[38] Polygenic scores reflect multiple variants with very small effect sizes distributed across the whole genome whereas our analysis of known loci and CPSM analysis focus on specific broader regions with highly correlated p values. Overall, results were remarkably consistent. Estimates of genetic correlation between phenotypes were similar in forward and reverse direction as were results of polygenic scores.

Our study also has limitations. First, some patients with MA might have been misdiagnosed with IS and vice versa. However, this should have shifted the results towards a stronger overlap between IS and MA, whereas we found stronger overlap for MO. Thus, diagnostic misclassification is unlikely to contribute substantially to our results. Second, some patients may have had both conditions. We can largely exclude ascertainment bias favoring the selection of patients with comorbidity substantiated by differences in age structure between migraineurs and stroke patients. Third, lacking individual level data, we cannot exclude some overlap in controls. We carefully checked for any potential overlap in controls and excluded samples where appropriate. Bias resulting from overlapping controls would not explain the differences observed between clinical subphenotypes. Finally, we are missing information on clinical subtypes for a substantial proportion of patients, reducing power in subgroup analyses, but this should not result in systematic bias to explain observed differences. Future studies on larger samples should further explore genetic overlap with rare causes of IS such as dissections, which were not considered separately in this study.

Our data provide genetic insights from GWAS meta-analyses into shared mechanisms of migraine and IS and may in part explain the relationship between these 2 common neurovascular disorders.

AUTHOR AFFILIATIONS

From the Institute for Stroke and Dementia Research (R.M., T.F., M.D.), Ludwig-Maximilians-Universität München, Munich; Abteilung Neurologie mit Schwerpunkt Epileptologie und Hertie Institut für Klinische Hirnforschung (T.F.), Universitätsklinikum Tübingen, Germany; the Department of Neurology and FORMI (B.S.W., J.A.Z.), Oslo University Hospital and University of Oslo, Norway; the Analytical and Translational Genetics Unit, Department of Medicine (B.S.W., V.A., A.P.), the Department of Neurology (J.R., A.P.), and the Psychiatric & Neurodevelopmental Genetics Unit, Department of Psychiatry (A.P.), Massachusetts General Hospital, Boston; the Program in Medical and Population Genetics (V.A., J.R.) and the Stanley Center for Psychiatric Research (V.A., A.P.), Broad Institute of MIT and Harvard, Cambridge; Harvard Medical School (V.A., D.I.C., T.K., J.R.), Boston, MA; the Interdepartmental Program in Computational Biology and Bioinformatics (J.V.H.), Yale University, New Haven, CT; the Department of Clinical Neurosciences (M.T., H.S.M.), University of Cambridge, UK; the Departments of Human Genetics (B.d.V., A.M.J.M.v.d.M.) and Neurology (G.M.T., M.D.F., A.M.J.M.v.d.M.), Leiden University Medical Center, the Netherlands; the University of Newcastle and Hunter Medical Research Institute (E.G.H., J.M.), Newcastle; the Faculty of Health, School of Health Sciences (J.S.), Faculty of Health and Medicine, School of Nursing and Midwifery (J.M.), and the Centre for Translational Neuroscience and Mental Health (J.M.), University of Newcastle; the Department of Neurosciences (J.S.), Central Coast Health District, Gosford, Australia; the Cardiovascular Health Research Unit, Department of Medicine (J.C.B.), and the Departments of Neurology and Epidemiology (W.T.L.), University of Washington, Seattle; the Clinical Trial Service Unit & Epidemiological Studies Unit (J.C.H., R.C.), the Wellcome Trust Centre for Human Genetics (M. Farrall), the Department of Cardiovascular Medicine (M. Farrall), and the Stroke Prevention Research Unit, Nuffield Department of Clinical Neuroscience (P.M.R.), University of Oxford; the Division of Clinical Neurosciences, Centre for Clinical Brain Sciences (K.R., C.S.), University of Edinburgh, UK; the Institute of Genetics (M.W.), Folkhälsan Research Center, Helsinki; the Institute for Molecular Medicine Finland (FIMM) (M.W., J.K., A.P.) and the Department of Public Health (J.K.), University of Helsinki; the Department of Neurology (M.K.), Helsinki University Central Hospital, Finland; the Institute of Human Genetics (C.K.), University Medical Center Hamburg-Eppendorf, Hamburg; the Institute of Human Genetics (C.K.), University of Ulm, Germany; the University of Texas Health Science Center at Houston (M. Fornage), Houston; the Department of Neurology (J.F.M.), Mayo Clinic, Jacksonville, FL; the Department of Clinical Chemistry (T.L.), Fimlab Laboratories and School of Medicine, University of Tampere, Finland; the Division of Preventive Medicine (D.I.C., T.K., M.S.), Brigham and Women's Hospital, Boston, MA; the Department of Medicine (B.D.M.), University of Maryland School of Medicine, Baltimore; the Department of Mental Health and Alcohol Research (J.K.), National Institute for Health and Welfare, Helsinki; the Department of Clinical Physiology and Nuclear Medicine and Research Centre of Applied and Preventive Cardiovascular Medicine (O.T.R.), University of Turku and Turku University Hospital, Finland; the INSERM Research Center for Epidemiology and Biostatistics (U897), Team Neuroepidemiology (T.K.), Bordeaux; the College of Health Sciences (T.K.), University of Bordeaux, France; the Departments of Epidemiology (M.A.I., C.M.v.D.), Neurology (M.A.I.), and Radiology (M.A.I.), Erasmus MC University Medical Center, Rotterdam; the Netherlands Consortium for Healthy Ageing (M.A.I., C.M.v.D.), Leiden, the Netherlands; the Division of Public Health Sciences (A.P.R.), Fred Hutchinson Cancer Research Center, Seattle, WA; the Division of Population Health Sciences and Education (D.P.S.), St George's, University of London; Imperial College Cerebrovascular Research Unit (ICCRU) (P.S.), Imperial College London, UK; the Department of Neurology (S.S.), Boston University School of Medicine, MA; the Department of Twin Research and Genetic Epidemiology (L.Q., L.C.), King's College London, UK; the Department of Neurology (M.S.), University Hospital Essen, Germany; the Center for Human Genetic Research and Division of Neurocritical Care and Emergency Neurology, Department of Biological Psychology (L.L.), VU University, Amsterdam, the Netherlands; the Department of Cerebrovascular Disease (G.B.B.), Fondazione Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Istituto Neurologico Carlo Besta, Milan, Italy; the MRC Integrative Epidemiology Unit at the University of Bristol (G.D.S.), UK; deCODE genetics (K.S.), Reykjavík, Iceland; the Departments of Neurology and Public Health Sciences (B.B.W.), University of Virginia School of Medicine, Charlottesville; the Neurogenetics Laboratory (D.R.N.), QIMR Berghofer, Brisbane, Australia; the Department of Neurology (C.C.), Yale School of Medicine, New Haven, CT; the Wellcome Trust Sanger Institute (A.P.), Wellcome Trust Genome Campus, Cambridge, UK; and the Munich Cluster for Systems Neurology (SyNergy) (M.D.), Germany.

AUTHOR CONTRIBUTIONS

Rainer Malik: drafting/revising the manuscript for content, study concept or design, analysis or interpretation of data, acquisition of data, statistical analysis, accepts responsibility for conduct of research and final approval. Tobias Freilinger: drafting/revising the manuscript for content, study concept or design, acquisition of data, accepts responsibility for conduct of research and final approval. Bendik S. Winsvold: drafting/revising the manuscript for content, acquisition of data, accepts responsibility for conduct of research and final approval. Verneri Anttila: drafting/revising the manuscript for content, acquisition of data, accepts responsibility for conduct of research and final approval. Jason Vander Heiden: drafting/revising the manuscript for content, acquisition of data, accepts responsibility for conduct of research and final approval. Matthew Traylor: drafting/revising the manuscript for content, acquisition of data, accepts responsibility for conduct of research and final approval. Boukje de Vries: drafting/revising the manuscript for content, acquisition of data, accepts responsibility for conduct of research and final approval. Elizabeth G. Holliday: drafting/revising the manuscript for content, acquisition of data, accepts responsibility for conduct of research and final approval. Gisela M. Terwindt: drafting/revising the manuscript for content, acquisition of data, accepts responsibility for conduct of research and final approval. Jonathan Sturm: drafting/revising the manuscript for content, accepts responsibility for conduct of research and final approval. Joshua C. Bis: drafting/revising the manuscript for content, acquisition of data, accepts responsibility for conduct of research and final approval. Jemma C. Hopewell: drafting/revising the manuscript for content, acquisition of data, accepts responsibility for conduct of research and final approval. Michel D. Ferrari: drafting/revising the manuscript for content, accepts responsibility for conduct of research and final approval. Kristiina Rannikmae: drafting/revising the manuscript for content, acquisition of data, accepts responsibility for conduct of research and final approval. Maija Wessman: drafting/revising the manuscript for content, accepts responsibility for conduct of research and final approval. Mikko Kallela: drafting/revising the manuscript for content, accepts responsibility for conduct of research and final approval. Christian Kubisch: drafting/revising the manuscript for content, accepts responsibility for conduct of research and final approval. Myriam Fornage: drafting/revising the manuscript for content, accepts responsibility for conduct of research and final approval. James F. Meschia: drafting/revising the manuscript for content, accepts responsibility for conduct of research and final approval. Terho Lehtimäki: drafting/revising the manuscript for content, accepts responsibility for conduct of research and final approval. Cathie Sudlow: drafting/revising the manuscript for content, accepts responsibility for conduct of research and final approval. Robert Clarke: drafting/revising the manuscript for content, accepts responsibility for conduct of research and final approval. Dan I. Chasman: drafting/revising the manuscript for content, accepts responsibility for conduct of research and final approval. Braxton D. Mitchell: drafting/revising the manuscript for content, accepts responsibility for conduct of research and final approval. Jane Maguire: drafting/revising the manuscript for content, accepts responsibility for conduct of research and final approval. Jaakko Kaprio: drafting/revising the manuscript for content, accepts responsibility for conduct of research and final approval. Martin Farrall: drafting/revising the manuscript for content, accepts responsibility for conduct of research and final approval. Olli T. Raitakari: drafting/revising the manuscript for content, accepts

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Comment: Tackling shared genetic underpinnings of migraine and ischemic stroke

In this large collaborative effort, Malik et al.[1] explore shared genetic variation underlying 2 common conditions: migraine and ischemic stroke (IS). Numerous studies have shown an increased risk of stroke in patients with migraine, but the contribution of genetic factors to this relationship is unclear.[2] The authors used the 2 largest existing meta-analyses of genome-wide association studies (GWAS) for both phenotypes.

First, they tested whether genetic variants showing genome-wide significant association with migraine also influence the risk of IS and vice versa. Second, they constructed a polygenic risk score, combining genetic variants associated with one disease at lower significance levels, and tested whether it predicts an increased risk of the other disease. Third, they used cross-phenotype spatial mapping (CPSM) to identify genomic regions exhibiting similar association patterns across phenotypes.

Although only one genome-wide significant locus for IS (in the chromosome 9p21 region) was associated with migraine, the CPSM approach showed various genomic regions affecting both the risk of IS and migraine. An important result emerging from the polygenic and CPSM approaches is that more shared genetic variation was observed between IS and migraine without aura (MO) than between IS and migraine with aura (MA). This is surprising, as phenotypic associations between migraine and IS were shown to be stronger for, or even restricted to, MA.[2] One potential explanation is that rare variants that are not captured by genome-wide chips may be influencing the risk of MA and its genetic correlation with IS. This is consistent with the fact that GWAS failed to reveal a large number of risk loci for MA, while numerous loci were discovered for MO.[3] Nongenetic factors may also contribute to the association between IS and MA.

While more data are needed to unravel the specific biological pathways underlying the association between IS and migraine, this study sheds new light on the pattern by which common variants jointly contribute to both diseases and their subtypes.

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Stéphanie Debette, MD, PhD

From the Department of Neurology, University Hospital of Bordeaux and INSERM Center U897, University of Bordeaux, France.

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DISCLOSURE

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