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Migraine, Stroke, and Cervical Arterial Dissection

Shared Genetics for a Triad of Brain Disorders With Vascular Involvement

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Abstract

Background and Objectives

Migraine, stroke, and cervical artery dissection (CeAD) represent a triad of cerebrovascular disorders with pairwise comorbid relationships and vascular involvement. Larger samples and recent advances in methodology invite systematic exploration of their shared genetics.

Methods

Genetic analyses leveraged summary statistics from genome-wide association studies of the largest available samples of each disorder, including subtypes of stroke (ischemic stroke, large artery stroke, small vessel stroke, and cardioembolic stroke) and migraine (with aura and without aura). For each pair of disorders, genetic correlation was assessed both on a genome-wide basis and within independent segments across the genome including known specific loci for each disorder. A cross-trait meta-analysis was used to identify novel candidate loci. Finally, potential causality of migraine susceptibility on stroke and CeAD was assessed by Mendelian randomization.

Results

Among all pairs of disorders, genome-wide genetic correlation was observed only between CeAD and migraine, particularly MO. Local genetic correlations were more extensive between migraine and CeAD than those between migraine and stroke or CeAD and stroke and revealed evidence for novel CeAD associations at rs6693567 (*ADAMTSL4/ECM1*), rs11187838 (*PLCE1*), and rs7940646 (*MRVI1*) while strengthening prior subthreshold evidence at rs9486725 (*FHL5*) and rs650724 (*LRP1*). At known migraine loci, novel associations with stroke had concordant risk alleles for small vessel stroke at rs191602009 (*CARF*) and for cardioembolic stroke at rs55884259 (*NKX2-5*). Known migraine loci also revealed novel associations but with opposite risk alleles for all stroke, ischemic stroke, and small vessel stroke at rs55928386 (*HTRA1*), for large artery stroke at rs11172113 (*LRP1*), and for all stroke and ischemic stroke at rs1535791 and rs4942561 (both *LRCH1*), respectively. rs182923402 (near *PTCH1*) was a novel concordant locus for migraine and cardioembolic stroke. Mendelian randomization supported potential causal influences of migraine on CeAD (odds ratio [95% confidence interval] per doubling migraine prevalence = 1.69 [1.24–2.3], p = 0.0009) with concordant risk, but with opposite risk on large artery stroke (0.86 [0.76–0.96], p = 0.0067).

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Glossary

ρHESS = Heritability Estimation from Summary Statistics; **AS** = all stroke; **CE** = cardioembolic stroke; **CeAD** = cervical artery dissection; **CI** = confidence interval; **GNOVA** = Genetic Covariation Analyzer; **GWAS** = genome-wide association study; **GWAS-PW** = GWAS-pairwise; **IS** = ischemic stroke; **IVW** = inverse variance–weighted; **LAS** = large artery stroke; **LD** = linkage disequilibrium; **LDSc** = linkage disequilibrium score regression; **MA** = migraine with aura; **MR** = Mendelian randomization; **MO** = migraine without aura; **MTAG** = multitrait analysis of GWAS; **OR** = odds ratio; **PPA3** = posterior probability of association in mode 3; **SNV** = single nucleotide variation; **SVS** = small vessel stroke; **WGHS** = Women's Genome Health Study.

Discussion

The findings emphasize shared genetic risk between migraine and CeAD while identifying loci with likely vascular function in migraine and shared but opposite genetic risk between migraine and stroke subtypes, and a central role of *LRP1* in all 3 cerebrovascular disorders.

Migraine, stroke, and extracranial cervical artery dissection (CeAD) represent a triad of brain disorders with vascular involvement and pairwise comorbid relationships that are pertinent to risk assessment and clinical care.[1] While the shared clinical features of all 3 disorders point to vasculature as the basis of the comorbidity, precise underlying mechanisms are not established. Understanding the shared and distinct biological mechanisms has the potential to clarify the basis of shared risk while also informing potential prophylactic and treatment strategies.

From this perspective, previous investigations have leveraged the unique properties of human genetics to reveal shared biology among the 3 disorders while limiting the potential influence of reverse causality and confounding that may arise in conventional observational epidemiology. One study found that genome-wide genetic overlap with migraine was most significant for large artery stroke and significant for cardioembolic stroke (CE), contrary to observational associations that had linked migraine to small vessel disease.[2,3] Associations were stronger for migraine without aura (MO) than those for either overall migraine or migraine with aura (MA), though the latter is a stronger risk factor of ischemic stroke (IS).[4-6] Similarly, genetic associations at specific loci diverged from conventional observational associations. At the 9p21 locus, associations with stroke and MO had concordant direction, but there was no association with MA, and there remained uncertainty about whether the causal variants for MO and stroke at the locus were the same.[3] At the *FHL5* locus on chromosome 6, the associations with stroke and migraine were in opposite directions, while the same locus has been noted for a concordant association between migraine and CeAD, the latter from a genome-wide association study (GWAS) at subgenome-wide significance.[7] The GWAS of CeAD also noted concordant effects with migraine at loci implicating the *PHACTR1/EDN1* and *LRP1* genes,[8] but only the former was replicated in an independent follow-up sample.

Recent GWASs of stroke and migraine incorporating much larger samples than previously available (therefore with much greater power), as well as novel genetic methods and the lack of a systematic comparison among all 3 cerebrovascular disorders, invite a new genetic analysis toward resolving several outstanding questions. First, what is the extent of shared genetics among the 3 disorders? Second, which specific susceptibility loci are shared on a genome-wide basis? Finally, does human genetics support causal relationships underlying the increased risk of stroke and CeAD among individuals susceptible to migraine?

Methods

Overview

Pairwise genetic relationships among migraine, CeAD, and subtypes of stroke were examined using 4 analytic strategies. Genome-wide genetic correlations were calculated to assess for overall genetic sharing. Local genetic correlations were calculated to assess shared genetics within disjoint segments across the genome and at specific candidate loci previously identified for association with at least one of the disorders. A genome-wide cross-trait association analysis was implemented to identify novel variant associations for each trait. Finally, the Mendelian randomization (MR) analysis was performed to assess potential causal influences of migraine on the other cerebrovascular disorders.

Summary Statistics

Analyses used discovery summary statistics from published, consortium-based GWASs of migraine,[9] CeAD,[7] and stroke.[10] The total numbers of samples included in these summary statistics were as follows: any migraine (59,674 cases/316,078 controls), MA (6,332 cases/144,883 controls), MO (8,348 cases/139,622 controls), CeAD (carotoid and vertebral, 1,393 cases/14,416 controls), all stroke (AS) (40,584 cases/406,111 controls), IS (34,217 cases/406,111 controls), large artery stroke (LAS) (4,373 cases/297,290 controls), CE (7,193 cases/355,4468 controls), and small vessel stroke (SVS) (5,386 cases/343,560 controls). All summary statistics were derived from study populations exclusively with European ancestry. The migraine and stroke GWASs were based on 1000 Genomes Project imputed data (hg19) and included approximately 8 million single nucleotide variations ([SNVs], formerly SNPs), while the CeAD GWAS was based on HapMap

(hg18) and 1000 Genomes Project (August 2010 release) imputed data and included approximately 6.6 million SNVs. The Women's Genome Health Study (WGHS)[11] provided a substantial proportion of cases and controls to the GWAS for MA (1,177 WGHS cases/6,332 total cases) and MO (1,826 WGHS cases/8,348 total cases) while also contributing a smaller proportion of cases to overall migraine (N = 5,122 WGHS cases/59,674 total cases) and stroke (N = 422 cases of all stroke/22,795 controls) GWASs. Other cohorts may have contributed smaller numbers of samples to the GWAS for migraine and stroke. Potential bias due to this overlap was addressed in 2 ways. First, migraine summary statistics from a meta-analysis were as described but omitted the WGHS contribution.[9] Second, the genetic correlation and cross-trait association methods intrinsically account for any minimal residual overlap.[12-14]

Summary statistics for the 23andMe cohort were obtained under an agreement with 23andMe that protects the privacy of the 23andMe participants. The participants of 23andMe provided informed consent and participated in the research under a protocol approved by the external AAHRPP-accredited IRB, Ethical & Independent Review Services. The full GWAS summary statistics for the 23andMe discovery data set will be made available through 23andMe to qualified researchers under an agreement with 23andMe that protects the privacy of the 23andMe participants. Information about access the data from 23andMe can be found at research.23andme.com/collaborate/#dataset-access/. Use of other summary statistics wass consistent with the local IRBs of each of the contributing cohorts or samples. All genomic coordinates refer to genome build hg19.

Genome-wide Genetic Correlation

Two established methods were used to estimate a genome-wide genetic correlation with the GWAS summary statistics: the conventional approach, linkage disequilibrium (LD) score regression (LDSc, version 1.0.0), and a similar but potentially more powerful approach, Genetic Covariation Analyzer (GNOVA) (downloaded in December 2017).[12,13] An analysis with LDSc incorporated precomputed LD measures for approximately 1.3 million common SNVs based on the HapMap with minimum minor allele frequency of approximately 10%[12] and shared across all of the summary statistics. An analysis with GNOVA included a step to calculate LD relationships among individuals with European ancestry in the 1000 Genomes reference panel including approximately 6.1 million SNVs with minimum minor allele frequency 5%. Genome-wide genetic correlation is the principal estimate in LDSc. By contrast, genetic covariance is the principal estimate in GNOVA, and genetic correlation is derived by scaling with the single-trait heritability estimates. As such, p values refer to the genetic correlation in LDSc and to the genetic covariance in GNOVA. Both LDSc and GNOVA have options to compute genetic correlation or covariance while adjusting for potential sample overlap or other potential causes of inflation. These options were invoked in all analyses. Although LDSc and GNOVA are substantially similar methods and the use of both provides cross-validation, differences in the minor allele frequency thresholds are expected to influence genetic correlation estimates and significance to some extent.

Locally Shared Genetic Effects

Local (as opposed to genome-wide) genetic correlation was estimated by 2 approaches, applied initially to approximately 1,704 prespecified disjoint segments across the genome with minimal intersegment LD within the GWAS summary statistics.[15] One approach, ρ Heritability Estimation from Summary Statistics (ρHESS) (version 0.5),[16] provided a frequentist estimate of the local covariance of genetic effects, while the other approach, GWAS-pairwise (GWAS-PW) (version 0.21),[14] provided a posterior probability of a locally shared genetic association (posterior probability of association in mode 3 [PPA3]) within each segment in an empirical Bayes framework based on GWAS p values. Genome-wide significance across the prespecified segments was 2.9×10^{-5} (=0.05/1,704) in ρHESS and PPA3 >0.9 in GWAS-PW. Candidate genes were assigned for regions showing PPA3 >0.9 based on proximity to potentially shared causal variants. ρHESS was also adapted to examine candidate segments surrounding genome-wide significant loci for stroke or migraine, as previously performed.[16] In this study, candidate segments were defined to include the SNVs neighboring each of GWAS index SNV, such that all SNVs outside of the segment had LD $r^2 < 0.1$ to the index SNV. Testing 69 candidate loci for each pairwise comparison, $p < 7 \times 10^{-4}$ (=0.05/69) was considered significant. As needed, pairwise SNV LD was estimated using a European ancestry panel from the 1000 Genomes Project with PLINK or LDlink.[17-19]

A Cross-Trait Association Analysis With a Multitrait Analysis of GWAS

A cross-trait association analysis was performed using a multitrait analysis of GWAS (MTAG, version 1.0.7), which leverages the pairwise genome-wide trait genetic correlation to boost power in association testing.[20] In MTAG, LDSc provided the estimates of pairwise genetic correlation. The significance threshold in the MTAG required $p_{MTAG} < 1.67 \times 10^{-8}$ ($=5.00 \times 10^{-8}/3$ phenotypes) but was also restricted to SNVs that also had nominal significance ($p < 0.05$) for each phenotype separately in the preexisting univariate GWAS.

MR Instrumental Analysis

Genetic instrumental variable analysis with MR was performed using the 2-sample method, prioritizing the random-effects inverse variance–weighted (IVW) estimator within the package TwoSampleMR in the R computing environment.[21,22] Sensitivity analysis included MR-weighted median, MR-Egger, MR-Egger bootstrap, MR-robust adjusted profile score, and MR-PRESSO.[23-26] The latter detects and excludes instruments that are consistent with horizontal pleiotropy, a violation of assumptions underlying MR, and then evaluates an overall estimate with the remaining instruments using the IVW method. Pleiotropy was also assessed with Cochran Q for heterogeneity and the MR-Egger intercept as recommended.[25] MR was limited to effects of migraine on the other disorders because (1) only the GWAS of any migraine, i.e., not the other disorders, had a sufficient number of genome-wide significant SNVs (N ≥

10) for use as exposure instruments and (2) because migraine typically precedes stroke or CeAD, potential causal effects of migraine on the other disorders are most consistent with temporal plausibility. Because migraine is a binary exposure, MR effect estimates were scaled by 0.693 for reporting to represent the odds of the outcome for a doubling of the odds of the exposure.[27]

Standard Protocol Approvals, Registrations, and Patient Consents

The GWAS summary statistics were all derived by a meta-analysis. Participants who contributed to cohort-level summary statistics constituting the meta-analyses provided written informed consent, and each of the cohort protocols was approved by a local institutional review board.

Data Availability

This study used only GWAS summary statistics from published reports as described earlier. The availability of these data or procedures for accessing them is documented in the cited publications. Summary statistics for the GWAS of migraine lacking contribution from the WGHS will be made available by sending an application to the International Headache Genetics Consortium via the corresponding author using the same procedure that governs access to the summary statistics for the published migraine study.[9]

Results

Genome-wide Genetic Correlation

Genetic correlations involving CeAD and stroke or migraine were generally positive (i.e., concordant) and comparable between LDSc and GNOVA, but significant only with GNOVA for the combinations of migraine (r_g [ρ (ρ SE)] = 0.22 [0.048 (0.012)], p = 4.9e-05) or MO (0.29 [0.051 (0.016)], 0.0017) with CeAD, after accounting for multiple testing (Table 1). The estimated genetic correlations were larger but only nominally significant with LDSc (r_g = 0.45 and 0.41, respectively).

Local Genetic Correlation

At the experiment-wide significance threshold (PPA3 >0.9), GWAS-PW implicated novel locally concordant associations of migraine and CE on chromosome 9q22.32 (top SNV rs113154802 near *PTCH1*) (Table 2). The remaining significant segments all include loci previously recognized by GWAS for 1 or more of the disorders, although many are newly implicated for an additional disorder (indicated in bold). These loci were *ADAMTSL4/ECM1*: **CeAD**-migraine, *CARF*: **SVS**-migraine, *NKX2*: **migraine**-CE, *HDAC9*: **migraine**-AS/IS, *ARMS2*: **AS**/**IS**/**SVS**-migraine, *LRCH1*: **migraine**-AS/IS, and *COL4A1*: **migraine**-AS. At *COL4A1*, neither migraine nor AS is genome-wide significant in the summary statistics used in this study, which are derived from population of European ancestry alone, but the locus has been recently identified for stroke by a trans-ancestry meta-analysis with index SNV rs9521634.[28] However, this variant is not in LD (r^2 = 0.02, D′ = 0.52) with the top SNV for the joint analysis of stroke and migraine, rs650724, which is also the top SNV for stroke alone in the current summary statistics derived from European ancestry and in high LD (r^2 = 0.86, D′ = 0.94) with the top SNV for migraine alone (rs2000660). Identification of shared, concordant associations involving CeAD in segments encompassing *LRP1* and *FHL5* is consistent with strong, subgenome-wide significant associations in these regions previously noted.[7] Although already known for any migraine, these 2 loci are newly implicated in both MA and MO. None of the segments was significant for combinations of CeAD and stroke. In contrast to the GWAS-PW method, local genetic covariance assessed with ρHESS did not meet experiment-wide significance for any pairwise combination of the cerebrovascular disorders (all p for local $r_g > 2.9 \times 10^{-5}$ [=0.05/1704]).

However, with ρHESS, local genetic covariance was also assessed at candidate regions defined by LD r^2 >0.1 around the 69 known genome-wide significant loci for each of the disorders (Methods, Table 3).[16] Local genetic covariance was concordant and met significance thresholds for candidate analysis (p < 0.0007 [=0.05/69]) between migraine and CeAD at *PHACTR1/EDN1* and *LRP1* as previously suggested but not formally demonstrated.[7] At nominal significance (p < 0.05), concordant covariance was observed similarly not only at these candidate loci between CeAD and MO but also at *FHL5* between CeAD and both any migraine and MO. The nominal associations also suggested shared signals between migraine and various stroke subtypes at known migraine loci mapping to *PRDM16* (SVS, opposite directionality), *ARMS2/HTRA1* (AS and IS, opposite), *LRP1* (LAS, opposite), *LRCH1* (AS and IS, opposite), and *RNF213* (IS, opposite); and between migraine and CeAD at *PLCE1* (concordant) and *FGF6* (opposite). None of the nominally significant local correlations implicated MA.

Novel Genome-wide Significant SNVs in Cross-Trait Association Analysis

MTAG, which leverages pairwise genome-wide genetic correlations to boost univariate association signals, identified novel genome-wide signals among SNVs that were also nominally significant in single-trait analysis (Methods, Table 4). Combining migraine with CeAD, there were novel associations for CeAD at SNVs mapping to the *PLCE1* (chr. 10, rs57866767) and *MRVI1* (chr 11, rs7940646) genes. The former was also nominally significant in the candidate local genetic correlation analysis (previous section). MTAG associations also recapitulated the findings from GWAS-PW for CeAD at *FHL5* (chr. 6, rs2971603 or rs9486725), *LRP1* (chr. 12, rs11172113), and at *ADAMTSL4/ECM1* (chr. 1, rs6693567) for SNVs that were previously genome-wide significant for migraine. Two SNVs in moderately high LD (R^2 = 0.5, D′ = 1.0), rs2971603 and rs9486725, represent the top associations at *FHL5*, the former more significant with any migraine and the latter with CeAD. Combining migraine and stroke, MTAG identified 2 novel stroke loci: *LRP1* (chr. 12, rs11172113) for LAS at a SNV shared with CeAD (and migraine, opposite

Table 1 Genome-wide Genetic Correlations Between Pairs of Brain Disorders

Pheno 1	Pheno 2	LDSc r_g (SE), p value	GNOVA r_g (cov [cov SE]), p value
Any migraine	AS	0.062 (0.049), 0.20	0.042 (0.001 [0.00077]), 0.20
	IS	0.062 (0.047), 0.19	0.037 (0.00089 [0.00074]), 0.23
	LAS	−0.36 (0.41), 0.38	−0.097 (−0.0028 [0.001]), 0.006
	CE	0.05 (0.069), 0.46	0.014 (0.00035 [0.00087]), 0.69
	SVS	0.049 (0.093), 0.60	0.071 (0.0018 [0.00095]), 0.064
MO	AS	−0.036 (0.089), 0.68	−0.037 (−0.00073 [0.0011]), 0.50
	IS	−0.03 (0.089), 0.74	−0.065 (−0.0013 [0.0011]), 0.24
	LAS	−0.72 (0.67), 0.28	−0.15 (−0.0035 [0.0014]), 0.013
	CE	−0.18 (0.11), 0.11	−0.092 (−0.0019 [0.0012]), 0.13
	SVS	−0.065 (0.16), 0.69	0.069 (0.0014 [0.0012]), 0.26
MA	AS	0.059 (0.10), 0.57	0.098 (0.0019 [0.001]), 0.06
	IS	0.061 (0.10), 0.54	0.078 (0.0015 [0.001]), 0.13
	LAS	−0.64 (0.73), 0.39	−0.018 (−0.00042 [0.0014]), 0.76
	CE	−0.16 (0.13), 0.19	−0.014 (−0.00029 [0.0012]), 0.81
	SVS	−0.23 (0.20), 0.25	0.12 (0.0024 [0.0014]), 0.075
CeAD	AS	0.27 (0.15), 0.081	0.13 (0.018 [0.0095]), 0.062
	IS	0.22 (0.16), 0.15	0.13 (0.018 [0.01]), 0.076
	LAS	0.35 (0.67), 0.61	0.16 (0.025 [0.013]), 0.046
	CE	0.11 (0.20), 0.58	0.075 (0.011 [0.01]), 0.30
	SVS	0.16 (0.34), 0.64	0.093 (0.013 [0.013]), 0.30
	Any migraine	0.45 (0.17), 0.0077	0.22 (0.048 [0.012]), 4.9e-05
	MA	0.097 (0.23), 0.67	−0.11 (−0.018 [0.015]), 0.24
	MO	0.41 (0.21), 0.05	0.29 (0.051 [0.016]), 0.0017

Abbreviations: AS = all stroke; CE = cardioembolic stroke; CeAD = cervical artery dissection; IS = ischemic stroke; LAS = large artery stroke; MA = migraine with aura; MO = migraine without aura; SVS = small vessel stroke.
Multiple testing significance threshold p = 0.002 (=0.05/23). Both LDSc and GNOVA values, corrected for estimated potential sample overlap and other potential sources of bias.

effect), and *CARF* (chr. 2, rs191602009) for SVS also previously genome-wide significant for migraine (concordant effect). No locus was genome-wide significant for CeAD in combination with any of the stroke outcomes.

Mendelian Randomization

In MR analysis (i.e., genetic instrumental analysis), liability to migraine was supported as causal for increased CeAD risk (odds ratio [OR] [95% confidence interval (CI)] = 1.69 [1.24–2.3], p = 0.0009) but protective for LAS (0.86 [0.76–0.96], p = 0.007) (Figure 1). There were no significant effects on either AS or other stroke subtypes, including all IS. There was significant heterogeneity detected for the migraine-CeAD effect (Cochran Q = 109, df = 39, $p = 1.48 \times 10^{-8}$), which was diminished but not eliminated by exclusion of 2 clearly pleiotropic SNVs, rs11172113 (*LRP1*) and rs9349379 (*PHACTR1/EDN1*) (Q = 65, df = 37, p = 0.003), leading to an attenuated but still nominally significant effect (OR [95% CI] = 1.33 [1.02–1.73], p = 0.04) (eTables 1 and 2, links.lww.com/NXG/A511). The MR-Egger intercept test for directional pleiotropy was null (p = 0.85), as suggested also by the largely consistent estimates of the effect in the sensitivity analyses (eTable 3, links.lww.com/NXG/A511). By contrast, there was no significant heterogeneity in the effect of migraine on LAS (Cochran Q = 46, df = 39, p = 0.21), and sensitivity analyses for pleiotropy yielded consistent and significant estimated protective effects of migraine, with the exception of MR-Egger (1.01 [0.73–1.39], p = 0.97). However, the effect obtained from the MR-Egger bootstrap test (0.85 [0.66–1.08], p = 0.091) was directionally consistent with the primary analysis, suggesting a potential undue influence of outliers on the estimate from MR-Egger when including all instruments without bootstrapping.

Table 2 Local Prespecified Segments With Significant Joint GWAS-PW Association Among Cerebrovascular Conditions

		Segment							Segment top SNV					
											P(heno) *Z*-score		Novel locus for pheno no.	Locus candidate gene(s)
Pheno 1	Pheno 2	Chr	Start bp	End bp	PPA1[a]	PPA2[a]	PPA3[a]	PPA4[a]	rsID	bp	P1	P2		
Any migraine	CeAD	1	149788928	151538412	0.06	0.00	0.94	0.01	rs6693567	150510660	5.70	3.19	2	Near *ADAMTSL4/ECM1*
Any migraine	SVS	2	202819643	205799152	0.00	0.00	0.99	0.00	rs191602009	203795717	−5.72	−4.93	2	*CARF*
Any migraine	CE	5	171074292	172677991	0.00	0.00	1.00	0.00	rs55884259	172642370	4.95	5.12	1	*NKX2-5*
Any migraine	CeAD	6	11791351	13209144	0.00	0.00	1.00	0.00	rs9349379	12903957	−9.64	−6.09		*PHACTR1/EDN1*
MO	CeAD				0.00	0.00	1.00	0.00			−5.99	−6.09		
Any migraine	CeAD	6	94441595	97093400	0.02	0.00	0.98	0.00	rs9486725	97061159	10.59	4.34		*FHL5*
MA	CeAD				0.00	0.00	0.94	0.01			4.42	4.34	1	
MO	CeAD				0.00	0.00	1.00	0.00			7.11	4.34	1	
Any migraine	IS	7	16902510	19481290	0.00	0.02	0.96	0.01	rs2107595	19049388	−3.37	6.68	1	*HDAC9/TWIST1*
Any migraine	AS				0.00	0.03	0.95	0.02			−3.37	6.64	1	
Any migraine	CE	9	96671698	98921816	0.01	0.00	0.97	0.00	rs182923402	98299677	4.91	4.38	1, 2	Near *PTCH1*
Any migraine	IS	10	123901203	125869042	0.02	0.00	0.95	0.02	rs55928386	124220667	−5.32	4.32	2	*ARMS2, HTRA1*
Any migraine	AS				0.01	0.00	0.96	0.04	rs2284665	124226630	4.73	−5.42	2	
Any migraine	SVS				0.08	0.00	0.91	0.01	rs72631113	124213449	5.15	−4.48	2	
Any migraine	CeAD	12	55665948	57548466	0.00	0.00	1.00	0.00	rs11172113	57527283	−14.72	−5.45		*LRP1*
MA	CeAD				0.00	0.00	1.00	0.00			−4.87	−5.45	1	
MO	CeAD				0.00	0.00	1.00	0.00			−8.14	−5.45	1	
Any migraine	IS	13	46496025	47430602	0.00	0.02	0.96	0.02	rs4942561	47209347	3.51	−5.65	1	*LRCH1*
Any migraine	AS				0.00	0.02	0.96	0.02	rs1535791	47165458	3.62	−5.95	1	
Any migraine	AS	13	109815112	111231864	0.01	0.00	0.97	0.00	rs650724	110804809	4.44	−4.75	1, 2	*COL4A1*

Abbreviations: AS = all stroke; bp = base pair; CE = cardioembolic stroke; CeAD = cervical artery dissection; GWAS = genome-wide association study; IS = ischemic stroke; MA = migraine with aura; MO = migraine without aura; SNV = single nucleotide variation; SVS = small vessel stroke.
[a] Posterior probability in the segment of association of phenotype 1 only (PPA1), phenotype 2 only (PPA2), shared association of both phenotypes (PPA3), and independent associations of both phenotypes (PPA4).

Discussion

The preceding analysis was undertaken to investigate the etiologic basis of comorbidity among each pair of 3 brain disorders with known vascular involvement through the unique properties of genetics. Both genome-wide and at specific loci, the findings emphasized extensive sharing of biology between migraine and CeAD. Genetic sharing was less for migraine and stroke but still implicated a few loci, while still less sharing was detected for stroke and CeAD. Figure 2 summarizes the significant pairwise associations from all analyses.

Table 3 Nominally Significant Local Genetic Covariance (ρ_g) at 69 Candidate Loci From Previous GWAS

			Candidate region					
Locus known phenotype(s)	**Pheno 1**	**Pheno 2**	**Chr**	**Start**	**End**	**N SNVs**	**Local ρ_g, p value[a]**	**Candidate gene(s)**
Any migraine	Any migraine	SVS	1	3065568	3116361	97	−1.1E-04, 0.04584	*PRDM16*
Any migraine/CeAD	Any migraine	CeAD	6	12758654	13119871	486	2.3E-03, 0.00021	*PHACTR1/EDN1*
Any migraine	MO	CeAD					2.2E-03, 0.01023	
Any migraine	Any migraine	CeAD	6	96682566	97082880	562	2.1E-03, 0.00080	*FHL5*
Any migraine	MO	CeAD					2.5E-03, 0.00337	
Any migraine	Any migraine	CeAD	10	95952031	97039458	1737	1.6E-03, 0.04244	*PLCE1*
Any migraine	Any migraine	AS	10	123910423	124326089	891	−1.3E-04, 0.02415	*ARMS2/HTRA1*
Any migraine	Any migraine	IS					−1.2E-04, 0.03811	
Any migraine	Any migraine	CeAD	12	4446116	4570190	232	−1.0E-04, 0.03432	*FGF6*
Any migraine	Any migraine	CeAD	12	57256380	57545756	360	3.1E-03, 0.00003	*LRP1*
Any migraine	MO	CeAD					2.3E-03, 0.00932	
Any migraine	Any migraine	LAS					−1.6E-04, 0.02121	
Stroke	Any migraine	AS	13	47062093	47323718	502	−8.3E-05, 0.03039	*LRCH1*
Stroke	Any migraine	IS					−8.1E-05, 0.03382	
Any migraine	Any migraine	IS	17	78235300	78384523	255	−7.9E-05, 0.04741	*RNF213*

Abbreviations: AS = all stroke; bp = base pair; CeAD = cervical artery dissection; GWAS = genome-wide association study; IS = ischemic stroke; LAS = large artery stroke; MO = migraine without aura; SNV = single nucleotide variation; SVS = small vessel stroke.
[a] Multiple testing significance threshold is $p < 0.0007$ (=0.05/69).

While the challenge of recruiting large samples of CeAD cases for genome-wide genetic analysis had limited power for previous genome-wide analysis, local genetic correlation with migraine boosted genetic signals to highlight novel candidate loci for CeAD and reinforced existing candidates, all with concordant effects on migraine. Novel genomic regions on at chr.1q21.3 (*ADAMTSL4/ECM1* candidate genes), chr10q23.33 (*PLCE1*), and chr11p15.4 (*MRVI1*) were all previously associated with migraine[9] and are now implicated also with CeAD. All reached genome-wide significance in the MTAG, and the chromosome 1 and 10 loci were further supported by GWAS-PW and ρHESS analyses, respectively. The extracellular matrix protein 1 (*ECM1*) gene at the chr1q21.3 locus has been suggested for involvement in vascular development.[29] The association at the *MRVI1* gene, encoding murine retrovirus integration site 1 homolog, a tumor suppressor, arose previously as a candidate influencing both migraine and IS.[3] The lead SNV, rs7940646, and its LD proxies associated with migraine in the region are also associated with blood pressure, arterial stiffness, airway inflammatory diseases, platelet aggregation, brain region volume, and measures for white matter integrity.[30-34] *PLCE1* encodes the phospholipase C, epsilon 1 protein, at which GWAS has implicated other vascular conditions including CVD and blood pressure.[33,35] The remaining CeAD loci shared with migraine at the *PHACTR1/EDN1*, *LRP1*, and *FHLS* genes were all noted in the original CeAD GWAS (*FHLS* at suggestive significance), but only *PHACTR1/EDN1* was formally genome-wide significant in replication, again likely due to limited sample.[7] All have been previously annotated as playing a role in vascular development or function.[29] At the *PHACTR1/EDN1* locus, recent functional work has not fully resolved which of 2 candidate genes may underlie the functional effects.[8,36] Though there is no strong genetic overlap between stroke and CeAD, the genetic overlap involving *LRP1* implicates both with migraine. Owing to the vascular etiology of CeAD and stroke, the preceding shared loci may be particularly relevant to vascular etiologies of migraine.

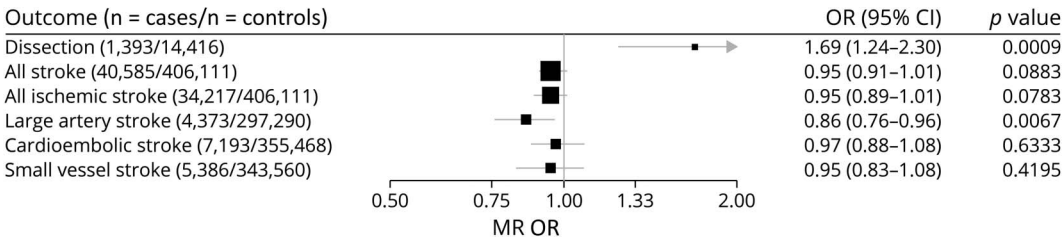
Despite the modest genome-wide correlations, local comparisons with GWAS-PW revealed potential new candidate loci with concordant effects for various stroke subtypes and any migraine. *CARF* (rs191602009), a known migraine locus encoding the calcium-response transcription factor, likely mediates calcium signaling in neurons, including regulation of the brain-derived neurotrophic factor,[37] and was implicated in SVS; *NKX2-5* (rs55884259), a known CE stroke locus encoding a homeobox protein for which variations cause congenital heart defects, was implicated in migraine; and *PTCH1* (rs182923402), encoding patched 1, is a member of a protein family of receptors that are ligands for sonic hedgehog signaling peptides in development and was implicated in both migraine and CE. Other pairwise shared loci revealed novel associations for 1 disorder but with opposite risk alleles

Table 4 Pairwise MTAG Genome-wide Significant Associations That Are Also Nominally Significant in Original GWAS

							GWAS association (*Z* score, *p* value)		MTAG association (beta [SE], p_{MTAG})			
Pheno 1	**Pheno 2**	**SNV rsID**	**Chr**	**bp**	**Segment (bp)[a]**	**Coded/ref allele**	**Pheno 1**	**Pheno 2**	**Pheno 1**	**Pheno 2**	**Novel locus for pheno no.**	**Candidate gene**
Any migraine	CeAD	rs6693567	1	150510660	150065704–150714741	C/T	5.7, 1.2E-08	3.2, 1.4E-03	0.016 (0.003), 3.1E-09	0.163 (0.028), 3.4E-09	2	*ADAMTSL4/ECM1*
Any migraine	SVS	rs191602009	2	203795717	203439395–204264839	G/A	−5.7, 1.1E-08	−4.9, 8.2E-07	−0.022 (0.004), 6.9E-09	−0.025 (0.004), 8.1E-09	2	*ALS2CR8 (CARF)*
Any migraine	CeAD	rs9349379	6	12903957	12568218–13148388	G/A	−9.6, 5.8E-22	−6.1, 1.2E-09	−0.024 (0.002), 6.2E-24	−0.251 (0.024), 1.8E-25		*PHACTR1/EDN1*
MO	CeAD	rs9349379	6	12903957	12681855–13145093	G/A	−6.0, 2.1E-09	−6.1, 1.2E-09	−0.026 (0.004), 1.2E-12	−0.257 (0.031), 8.0E-17		
Any migraine	CeAD	rs2971603	6	97035418	96319657–97267047	T/C	10.8, 2.8E-27	3.4, 6.4E-04	0.031 (0.003), 5.8E-28	0.267 (0.028), 8.8E-22	2	*FHL5*
Any migraine	CeAD	rs9486725	6	97061159	96319657–97267047	T/C	10.6, 3.5E-26	4.3, 1.4E-05	0.027 (0.002), 2.4E-27	0.251 (0.025), 1.4E-23	2	
MO	CeAD	rs9486725	6	97061159	96643134–97267047	T/C	7.1, 1.3E-12	4.3, 1.4E-05	0.030 (0.004), 4.5E-15	0.245 (0.032), 2.7E-14	1, 2	
Any migraine	CeAD	rs57866767	10	96023077	95798179–96274157	C/T	−7.6, 2.3E-14	−2.1, 3.6E-02	−0.018 (0.002), 1.3E-14	−0.157 (0.024), 4.9E-11	2	*PLCE1*
Any migraine	CeAD	rs11187838	10	96038686	95798179–96274157	A/G	−7.6, 3.0E-14	−2.4, 1.8E-02	−0.018 (0.002), 1.4E-14	−0.161 (0.024), 1.8E-11	2	
Any migraine	CeAD	rs7940646	11	10669228	10454911–10899696	T/C	−7.5, 5.0E-14	−2.6, 1.0E-02	−0.019 (0.002), 1.9E-14	−0.174 (0.026), 1.1E-11	2	*MRVI1*
Any migraine	CeAD	rs11172113	12	57527283	57057912–57745756	C/T	−14.7, 5.6E-49	−5.4, 5.1E-08	−0.035 (0.002), 8.5E-51	−0.328 (0.024), 9.2E-42	2	*LRP1*
Any migraine	LAS	rs11172113	12	57527283	57056380–57745756	C/T	−14.0, 1.9E-44	2.9, 3.8E-03	−0.034 (0.002), 3.6E-44	0.023 (0.003), 4.4E-13	2	
MO	CeAD	rs11172113	12	57527283	57302981–57734912	C/T	−8.1, 4.3E-16	−5.4, 5.1E-08	−0.033 (0.004), 1.2E-19	−0.282 (0.031), 1.0E-19	1, 2	

Abbreviations: bp = base pair; CeAD = cervical artery dissection; GWAS = genome-wide association study; LAS = large artery stroke; MO = migraine without aura; MTAG = multi-trait analysis of GWAS; SNV = single nucleotide variation; SVS = small vessel stroke.
[a] Span of genome-wide significant MTAG associations for either phenotype and maximum distance 200 kb.

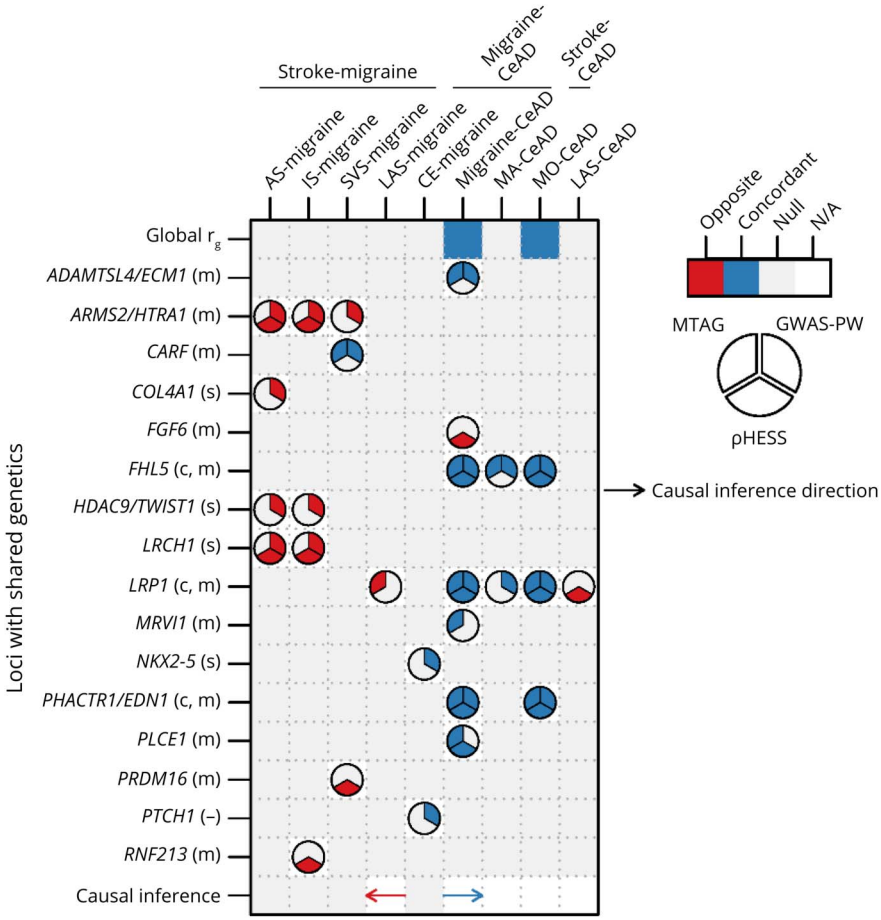
Figure 1 Instrumental Effects by MR of Migraine on the Other Cerebrovascular Disorders



MR was performed using the random-effects inverse variance–weighted method. ORs and 95% CIs are scaled to reflect the effect of migraine liability on CeAD and stroke per doubling of migraine prevalence (see Methods). CeAD = cervical artery dissection; CI = confidence interval; MR = Mendelian randomization; OR = odds ratio.

compared with the known association at the second disorder: (1) *HDAC9/TWIST1* (rs2107595), a known LAS locus for which the candidate gene is not yet definitively identified,[38,39] is implicated in migraine; (2) *ARMS2/HTRA1* (3 SNVs [all D′ = 1, low R^2 with each other and with rs10490924]), a known a migraine locus for which *HTRA1* encoding a serine peptidase may be the best candidate gene, is implicated in AS, IS, and SVS, reinforcing previous subthreshold associations.[10] Mendelian associations with small vessel disease also support this association because monogenic variations in *HTRA1* lead to a rare autosomal dominant form of SVD, CARASIL[40,41]; (3) *LRCH1* (2 SNVs, LD R^2 = 1), a migraine locus, is now implicated in AS and IS; and (4) *COL4A1* (rs650724), encoding collagen type 4 alpha 1, is now implicated in migraine having been previously identified for stroke by GWAS and Mendelian genetics of SVD.[10,42] Signals at

Figure 2 Summary of Pairwise Genetic Comparisons for the 3 Disorders



Only pairs with significant associations are shown. For Mendelian randomization, the direction of each arrow indicates whether the direction of inferred causality is from the first disorder of each pair to the second (rightward arrow) or the opposite (leftward arrow) with concordant (blue) or opposite (red) functional relationship. Symbols following gene name labels for each locus refer to the disorder(s) for which association has been previously reported, if any, as follows: m = migraine, c = CeAD, s = stroke, and - = no known association. CeAD = cervical artery dissection; GWAS-PW = genome-wide association study-pairwise; MTAG = multitrait analysis of GWAS; ρHESS = ρ Heritability Estimation from Summary Statistics.

ARMS2/HTRA1 and *LRCH1* were also supported at nominal significance by the ρHESS candidate local genetic correlations, while the signal at rs191602009 (*CARF*) was supported in the MTAG.

The less extensive genetic sharing of migraine (particularly MA) and IS across the genome is contrary to their strong comorbidity in epidemiologic studies.[4] Genome-wide genetic correlations were not only modest but also emphasized an opposite relationship rather than concordance, particularly between migraine and LAS. Similarly, causality in an opposite relationship of migraine liability to LAS was supported by the instrumental analysis. This finding is consistent with prior MR analyses, which identified opposite instrumental relationships of migraine liability with coronary artery disease, a disorder that shares pathophysiology with LAS.[43] Similarly, the findings are reminiscent of previous analysis of shared genetics between migraine, especially MO, and stroke that also found overlap, especially for large artery and CE types.[3] Although the genetic correlation of migraine with SVS, which has been suspected in the mechanism of migraine comorbidity,[2] was concordant with findings from conventional epidemiology and with migraine being an important feature of monogenic forms of small vessel disease, the estimate was only marginally significant. This observation may be qualified, however, by the low power of GWAS for IS subtypes, as well as likely imperfect ascertainment of SVS in many studies. The genetic relationship between migraine and small vessel disease deserves further investigation using more specific MRI markers of SVD, such as white matter hyperintensity burden.[44]

An MTAG-based genome-wide significant association at rs11172113 for LAS that was supported by local correlation at nominal significance in ρHESS with migraine implicates *LRP1*, which is the only locus influencing risk of all 3 cerebrovascular disorders, although opposite in its effect on stroke compared with that on migraine or CeAD. This same locus has recently also been implicated in aortic and coronary dissection and abdominal aortic aneurysm with the same directionality for CeAD and migraine, placing *LRP1* at the center of shared biology and deserving further study.[45-47] *LRP1*, a member of the LDL receptor family, has been implicated by GWAS also in pulmonary function and CHD, the latter likely related in pathophysiology to the association with LAS.[33,48,49] LRP1 protein is involved in endocytosis of a wide variety of ligands, including lipoproteins, and understanding mechanism(s) of its contribution to the shared susceptibilities will require further research.[50]

The strengths of this study are the very large sample sizes and therefore power represented by the GWAS summary statistics for migraine and stroke. The study is limited in its restriction to populations of European ancestry, although multiancestry meta-analysis for stroke subtypes supports the top loci, implying that relevant biological functions are shared among European and other ancestries. However, it remains possible that genetic relationships in non-European ancestries among the 3 disorders would highlight additional relationships, including those that may contribute to health disparities. The study is also limited by the modest sample size underlying the summary statistics for CeAD, a consequence of the challenge in accumulating genome-wide genetic data for extremely low prevalence events. The incidence of CeAD is only on the order of approximately 2.6 per 100,000 per year.[51] Similarly, despite the relatively large total sample for the stroke GWAS, heterogeneity in stroke mechanism and intrinsic difficulties in assigning stroke subclassifications may have limited the ability to detect genetic overlap with either migraine or CeAD. An additional consequence of the limitations in the CeAD and stroke GWASs was an insufficient number of qualifying instruments to perform MR for assessing potential causal effects of liability to these disorders on migraine.

Taken together, the results thus provide novel support for the contribution of vascular functions to migraine and enhance understanding of the comorbidity among migraine, CeAD, and stroke. Future functional studies prioritizing specific loci identified through this genetic analysis may reveal deeper insights into corresponding vascular mechanisms leading to susceptibility to the 3 brain disorders.

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