Genetic analysis for a shared biological basis between migraine and coronary artery disease

ABSTRACT

Objective: To apply genetic analysis of genome-wide association data to study the extent and nature of a shared biological basis between migraine and coronary artery disease (CAD).

Methods: Four separate methods for cross-phenotype genetic analysis were applied on data from 2 large-scale genome-wide association studies of migraine (19,981 cases, 56,667 controls) and CAD (21,076 cases, 63,014 controls). The first 2 methods quantified the extent of overlapping risk variants and assessed the load of CAD risk loci in migraineurs. Genomic regions of shared risk were then identified by analysis of covariance patterns between the 2 phenotypes and by querying known genome-wide significant loci.

Results: We found a significant overlap of genetic risk loci for migraine and CAD. When stratified by migraine subtype, this was limited to migraine without aura, and the overlap was protective in that patients with migraine had a lower load of CAD risk alleles than controls. Genes indicated by 16 shared risk loci point to mechanisms with potential roles in migraine pathogenesis and CAD, including endothelial dysfunction (PHACTR1) and insulin homeostasis (GIP).

Conclusions: The results suggest that shared biological processes contribute to risk of migraine and CAD, but surprisingly this commonality is restricted to migraine without aura and the impact is in opposite directions. Understanding the mechanisms underlying these processes and their opposite relationship to migraine and CAD may improve our understanding of both disorders. Neurol Genet 2015;1:e10; doi: 10.1212/NXG.0000000000000010

GLOSSARY

CAD = coronary artery disease; CARDIoGRAM = Coronary ARtery Disease Genome-Wide Replication And Meta-Analysis; CPSM = Cross-Phenotype Spatial Mapping; GWAS = genome-wide association studies; IHGC = International Headache Genetics Consortium; LD = linkage disequilibrium; MA = migraine with aura; MO = migraine without aura; SNP = single nucleotide polymorphism

Migraine affects 19% of women and 11% of men worldwide and causes more years lost to disability than any other neurologic disorder.1,2 In about one-third of patients, headache attacks are preceded by transient neurologic symptoms termed migraine aura, and migraine with and without aura (MA and MO, respectively) are believed to have a partially distinct pathogenic basis.3 It has long been assumed that the vascular system is involved in migraine pathogenesis, but little is known of the specific biological processes involved, and the relative importance of neuronal and vascular mechanisms remains controversial.3-6 Supporting a vascular basis, epidemiologic studies have found an increased risk for stroke among patients with migraine, most pronounced for MA.7 Some recent studies indicate a similar risk increase for coronary artery disease (CAD), the most common vascular disorder, although the association is less certain than for stroke.8-11 This raises the question of whether migraine and cardiovascular disease have a shared biological basis.

Both migraine and CAD have a strong genetic determination, and recent genome-wide association studies (GWAS) have identified risk variants for each. If migraine and CAD have a shared biological basis, one might anticipate that they will also share genetic variants that affect their risk. In this study, we utilized data from 2 large-scale nonoverlapping GWAS meta-analyses of migraine (the International Headache Genetics Consortium, IHGC)12 and CAD (Coronary ARtery Disease Genome-Wide Replication And Meta-Analysis, CARDIoGRAM)13 to quantify shared genetic risk.

METHODS Study cohorts. Summary statistics (p value and effect size) at single nucleotide polymorphism (SNP) level from 2 recently performed meta-analyses of genome-wide association data on migraine (IHGC)12 and CAD (CARDIoGRAM)13 were used in

*These authors contributed equally to the manuscript.

Author affiliations are provided at the end of the article.

Funding information and disclosures are provided at the end of the article. Go to Neurology.org/ng for full disclosure forms. The Article Processing Charge was paid by the authors.

The CARDIoGRAM Consortium and the International Headache Genetics Consortium co-investigators are listed at Neurology.org/ng.
Evaluating extent of overlapping signals. To assess whether more association signals were shared between the migraine and CAD studies than would be expected by chance, we used a set of 2,342,101 overlapping SNPs that were directly typed or imputed in both studies. Following the same procedure as described in a previous study,14 we first sorted the SNPs by association \( p \)-value to migraine. Starting from the top of the list, all subsequent SNPs with linkage disequilibrium \( (LD) R^2 > 0.05 \) (based on HapMap CEU release 27) were removed. This process was repeated until a set of 92,654 SNPs in approximate linkage equilibrium remained. For each of 5 separate \( p \)-value cutoffs \( (1 \times 10^{-2}, 1 \times 10^{-3}, 1 \times 10^{-4}, 1 \times 10^{-5}, \) and \( 1 \times 10^{-6} \)), we counted the number of SNPs above and below the cutoff in each of the 2 studies, resulting in one 2 x 2 table for each \( p \)-value cutoff. The Fisher exact test was used to estimate deviation from the expected distribution, and false discovery rate correction was performed on all 6 tests using the \( p \)-adjunct function in \( R \).15 A corrected Fisher \( p < 0.01 \) was taken to indicate an excess of overlapping signals. In order to obtain a more robust estimate of the significance of the observed overlap, this was also assessed through permutations. In each permutation cycle, the relation of \( p \)-values to SNPs was randomized within each of the LD-pruned migraine and CAD data sets, and a Fisher \( p \) for overlap was calculated for each \( p \)-value cutoff. We generated 100,000 permutations to produce an empirical null distribution of \( p \)-values.

In an equivalent manner, secondary analyses were performed for MO (83,373 overlapping SNPs after LD pruning) and MA (88,031 overlapping SNPs after LD pruning).

Polymorphic risk score analysis. If shared genetic risk variants are in part or fully responsible for comorbidity between migraine and CAD, we would expect an accumulation of CAD risk alleles in migraineurs. To test this hypothesis, we used the 6 migraine cohorts in which individual-level genotype data were available for analysis (6,350 migraineurs vs 15,069 controls; figure 1). For each migraine case or control, we calculated a CAD polygenic risk score based on a previously published method.16 We first generated 3 sets of CAD risk SNPs by selecting SNPs with strong \( p < 5 \times 10^{-8} \) (149 SNPs), moderate \( p < 1 \times 10^{-5} \) (1,631 SNPs), or weak \( p < 1 \times 10^{-3} \) (36,384 SNPs) association to CAD among the 2,342,101 SNPs with information in both migraine and CAD studies. As suggested in the original description of the method,16 the analysis was based on non-LD-pruned SNP sets in order to optimize sensitivity. Using each set of CAD risk SNPs, we calculated a per-individual CAD polygenic risk score by summing the number of CAD risk alleles (or expected allele counts for imputed SNPs), each weighted by the log odds ratio from the CAD study. We subsequently assessed whether CAD polygenic risk score was associated with migraine status by applying a logistic regression model of the effect of CAD polygenic risk score (continuous) on migraine status (case, control), adjusted for sex and dummy-coded covariates representing the 6 individual migraine study cohorts.

Identifying shared risk loci. In order to identify shared risk loci between migraine and CAD, we applied a novel method, Cross-Phenotype Spatial Mapping (CPSM; see e-Methods for an overview). This method compares 2 sets of \( p \)-values from GWAS in order to find groups of SNPs at which they are correlated and thus identify shared patterns of association. We applied this method to the 2,342,101 overlapping SNPs from the migraine and CAD studies and selected genomic regions with signal above the 99.95th percentile of 1,000 permutations for further analysis. Potential effects of the shared association loci on regional gene expression (cis effect) were examined using an existing expression quantitative trait locus database from peripheral blood.17

RESULTS Comparing nominally significant SNPs from the migraine and CAD GWASs, we found an overlap of association signals in excess of what would be expected by chance (table 1). An overlap of signals was seen for SNPs with \( p \)-values \( \leq 1 \times 10^{-2} \), \( 1 \times 10^{-4} \), and \( 1 \times 10^{-6} \). This was supported by permutation testing, which indicated a sharing of association signals at \( p \)-value cutoff \( 1 \times 10^{-2} \) as well. For reference, the full list of SNPs with association \( p \)-value \( \leq 1 \times 10^{-2} \) to both CAD and migraine is given in table e-3. Secondary analyses by migraine subtype revealed an overlap of association signals between MO and CAD at all \( p \)-value cutoffs \( (1 \times 10^{-2}, 1 \times 10^{-3}, 1 \times 10^{-4}, 1 \times 10^{-5}, \) and \( 1 \times 10^{-6} \)), while no overlap was seen between MA and CAD at any of the \( p \)-value cutoffs. The direction of effect for overlapping association signals did not consistently agree between migraine and CAD, as evidenced by nonsignificant binomial \( p \)-values for concordance (table 1).

To examine this further, the second analysis compared the load of genetic risk variants for CAD between migraineurs and controls, using individual-level data. The results indicated that a high CAD polygenic risk score was associated with a reduced risk of migraine (figure 2, further details in table e-4). For migraine overall, this association was seen for only the moderate CAD risk SNP set \( (p = 0.007) \). Secondary analyses revealed a similar, but more pronounced, association between CAD polygenic risk score and
MO ($p = 1.5 \times 10^{-4}$ and $5.1 \times 10^{-4}$ for the moderate and strong CAD risk SNP sets, respectively). No association was seen for MA. In the analysis of the weak CAD risk SNP set, there was no association to CAD genetic risk score for either migraine category, indicating that the observed associations were driven by a fairly limited number of loci that are at least moderately associated with CAD. These findings were consistent across men and women (figure e-2) and across individual independent cohorts within the same migraine subtype (figure e-3).

CPSM yielded 16 loci that overlapped between migraine and CAD (table 2; figure e-4). Details of the most significant migraine and CAD SNPs at each locus are given in table e-5. The strongest evidence of shared association was seen at 6p24 (locus no. 2), where both CAD and migraine showed genome-wide significant signals within the PHACTR1 gene (CAD: rs4714955, $p = 9.8 \times 10^{-11}$; migraine: rs9349379, $p = 5.9 \times 10^{-9}$). The second strongest overlapping signal was on 17q21 (locus no. 2), where the lead CAD SNP (rs46522, $p = 2.6 \times 10^{-7}$) was intragenic in UBE2Z, whereas the lead migraine SNP (rs11079844, $p = 3.1 \times 10^{-9}$) was intergenic between SNF8 and GIP. It is interesting that both lead SNPs are in high LD ($r^2 > 0.9$) with 2 functional variants in GIP: Ser103Gly (rs2291725) and a splice site variant (rs2291726) that is predicted to lead to a prematurely truncated transcript18 (table e-6). The locus was also found to have a potential effect on the expression level of UBE2Z (table e-7). Lead SNPs in 5 loci were in high LD ($r^2 > 0.8$) with nonsynonymous or splice site variants in nearby genes (table e-6). Ten of the 16 loci showed opposite direction of effect for migraine and CAD. In the secondary analyses, 12 of the 16 lead migraine SNPs had a lower association $p$ value in MO than in MA (2-tailed binomial $p = 0.08$), and all 16 SNPs
had the same effect direction in each of the 2 migraine subtypes. Local Manhattan plots and covariance plots for the identified loci are given in figure e-4.

When considering previously reported risk loci for migraine and CAD, 3 CAD risk SNPs were associated to migraine at study-wide significance, and 2 migraine risk SNPs were associated to CAD (table 3). These correspond to loci no. 1, 2, 3, 11, and 14 as identified by the CPSM method and corroborate the evidence for shared genetic risk at these loci.

**DISCUSSION**

In this study, we used data from 2 recently performed large-scale nonoverlapping GWAS to examine shared genetic risk between migraine and CAD. We found that association signals overlapped in excess of what would be expected by chance. Stratifying by migraine subtype further revealed that MO and MA behaved differently. MO had a genetic overlap with CAD, whereas MA did not. These results are unexpected, given the epidemiologic evidence that comorbidity with CAD is more common in MA than MO. Patients with MA were found to have a 2-fold increased risk for CAD, and an increased risk for CAD-related mortality, although one cross-sectional study failed to find an association between

| Table 1 Analysis of the extent of overlapping signals between migraine and CAD |

<table>
<thead>
<tr>
<th>Signal definition (p value cutoff)</th>
<th>Overlapping SNPs</th>
<th>p Value for overlap (Fisher exact test)a</th>
<th>p Value for overlap (permutation test)b</th>
<th>Concordance of overlapping SNPsb</th>
<th>Binomial p value for concordance</th>
</tr>
</thead>
<tbody>
<tr>
<td>All migraine (total no. SNPs: 92,654)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1E-2</td>
<td>146</td>
<td>1 E-05c</td>
<td>6 E-05c</td>
<td>0.534</td>
<td>0.18</td>
</tr>
<tr>
<td>1E-3</td>
<td>7</td>
<td>0.099</td>
<td>0.056</td>
<td>0.571</td>
<td>0.23</td>
</tr>
<tr>
<td>1E-4</td>
<td>2</td>
<td>9.3 E-03c</td>
<td>7.9 E-03c</td>
<td>0</td>
<td>0.75</td>
</tr>
<tr>
<td>1E-5</td>
<td>1</td>
<td>0.014</td>
<td>2.1 E-04c</td>
<td>0</td>
<td>0.50</td>
</tr>
<tr>
<td>1E-6</td>
<td>1</td>
<td>5.2 E-03c</td>
<td>3.5 E-03c</td>
<td>0</td>
<td>0.50</td>
</tr>
<tr>
<td>Migraine without aura (total no. SNPs: 83,373)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1E-2</td>
<td>113</td>
<td>1.6 E-04c</td>
<td>1.5 E-05c</td>
<td>0.510</td>
<td>0.87</td>
</tr>
<tr>
<td>1E-3</td>
<td>8</td>
<td>1.3 E-03c</td>
<td>1.1 E-04c</td>
<td>0.442</td>
<td>0.86</td>
</tr>
<tr>
<td>1E-4</td>
<td>3</td>
<td>2.0 E-04c</td>
<td>1.5 E-05c</td>
<td>0.250</td>
<td>0.88</td>
</tr>
<tr>
<td>1E-5</td>
<td>1</td>
<td>8.5 E-03c</td>
<td>1.5 E-05c</td>
<td>0</td>
<td>0.50</td>
</tr>
<tr>
<td>1E-6</td>
<td>1</td>
<td>3.0 E-03c</td>
<td>1.5 E-05c</td>
<td>0</td>
<td>0.50</td>
</tr>
<tr>
<td>Migraine with aura (total no. SNPs: 88,031)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1E-2</td>
<td>107</td>
<td>0.13</td>
<td>0.11</td>
<td>0.523</td>
<td>0.28</td>
</tr>
<tr>
<td>1E-3</td>
<td>1</td>
<td>1.0</td>
<td>0.64</td>
<td>0.523</td>
<td>0.50</td>
</tr>
<tr>
<td>1E-4</td>
<td>0</td>
<td>1.0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>1E-5</td>
<td>0</td>
<td>1.0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>1E-6</td>
<td>0</td>
<td>1.0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: CAD = coronary artery disease; NA = not applicable; SNP = single nucleotide polymorphism.

*a False discovery rate corrected p values.

*b Proportion of overlapping association signals having the same direction of effect in migraine and CAD.

* c p < 0.01.

Figure 2 Association between coronary artery disease polygenic risk score and the presence of migraine

Results are given as odds ratios with 95% confidence intervals. Separate lines are shown for all migraine (blue), migraine without aura (green), and migraine with aura (red). The coronary artery disease (CAD) polygenic risk score was calculated based on single nucleotide polymorphisms (SNPs) with weak (p < 1 x 10^-2), moderate (p < 1 x 10^-4), or strong (p < 5 x 10^-8) association to CAD in the Coronary ARtery Disease Genome-Wide Replication And Meta-Analysis study.
Table 2 Overlapping association loci between migraine and CAD as identified by CPSM analysis

<table>
<thead>
<tr>
<th>Locus no.</th>
<th>Chr band</th>
<th>Position (Mb)b</th>
<th>Locus</th>
<th>Peak SNP</th>
<th>Peak height</th>
<th>Genes within locusc</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6p24</td>
<td>12.929</td>
<td>13.187</td>
<td>257.386</td>
<td>rs7454157</td>
<td>PHACTRI</td>
</tr>
<tr>
<td>2</td>
<td>17q21</td>
<td>44.282</td>
<td>44.512</td>
<td>230.813</td>
<td>rs12601858</td>
<td>CALCOCO2, ATP5G1, UBE2Z, SNF8, GIP, IGF2BP1</td>
</tr>
<tr>
<td>3</td>
<td>6q16</td>
<td>96.917</td>
<td>97.188</td>
<td>271.548</td>
<td>rs12529248</td>
<td>UFL1, FHL5</td>
</tr>
<tr>
<td>4</td>
<td>12q24</td>
<td>110.241</td>
<td>111.064</td>
<td>823.633</td>
<td>rs7962138</td>
<td>CUX2, FAM109A, SH2B3, ATXN2, BRAP, ACAD10, ALDH2, MAPKAP5-5-AS1, MAPKAP5-5, ADAM1A, TMEM116, ERp29, NAA25, TRAFD1</td>
</tr>
<tr>
<td>5</td>
<td>17p11</td>
<td>17.603</td>
<td>17.992</td>
<td>389.086</td>
<td>rs9890341</td>
<td>RA11, SMCR5, SREBF1, MR3B3, TOM1L2, LRR2C4B, ATPAF2, GID4, DRG2, MYO1S</td>
</tr>
<tr>
<td>6</td>
<td>16q23</td>
<td>72.182</td>
<td>72.403</td>
<td>220.605</td>
<td>rs12207845</td>
<td>BCAI1, CFD1P1, TMEM170A, CHST6</td>
</tr>
<tr>
<td>7</td>
<td>10q24</td>
<td>104.823</td>
<td>105.178</td>
<td>354.585</td>
<td>rs7067970</td>
<td>CNNM2, NTSC2, LOC729020, INA, PCG6F, TAF5, USM55, MIR1307, PDCD11</td>
</tr>
<tr>
<td>8</td>
<td>2q33</td>
<td>203.375</td>
<td>203.52</td>
<td>145.53</td>
<td>rs6435169</td>
<td>ICA11, WDR12, ALS2CR8</td>
</tr>
<tr>
<td>9</td>
<td>10q24</td>
<td>104.569</td>
<td>104.785</td>
<td>216.416</td>
<td>rs1538204</td>
<td>CYP17A1, C10orf32, C10orf32-AS3MT, AS3MT, CNNM2</td>
</tr>
<tr>
<td>10</td>
<td>6q13</td>
<td>72.182</td>
<td>72.403</td>
<td>220.605</td>
<td>rs12207845</td>
<td>LINCO0472</td>
</tr>
<tr>
<td>11</td>
<td>8p21</td>
<td>89.53</td>
<td>89.69</td>
<td>160.492</td>
<td>rs1352317</td>
<td>None</td>
</tr>
<tr>
<td>12</td>
<td>19q13</td>
<td>46.543</td>
<td>46.664</td>
<td>120.921</td>
<td>rs3810174</td>
<td>TGFBI, B9D2, TMEM91, EXOSC5C, BCKDHA, B3GNT8, ATP5SL, C19orf69, LOC1005050495</td>
</tr>
<tr>
<td>13</td>
<td>12q24</td>
<td>109.501</td>
<td>109.714</td>
<td>213.015</td>
<td>rs16940933</td>
<td>PPTC7, TCTN1, HVACN1, PPP1CC</td>
</tr>
<tr>
<td>14</td>
<td>8p21</td>
<td>89.382</td>
<td>89.525</td>
<td>143.754</td>
<td>rs6984041</td>
<td>MMP16</td>
</tr>
<tr>
<td>15</td>
<td>16q24</td>
<td>88.099</td>
<td>88.191</td>
<td>91.257</td>
<td>rs17775174</td>
<td>SPG7, RPL13, SNORD68, CPNE7</td>
</tr>
<tr>
<td>16</td>
<td>9p21</td>
<td>23.429</td>
<td>23.505</td>
<td>75.25</td>
<td>rs10811931</td>
<td>None</td>
</tr>
</tbody>
</table>

Abbreviations: Chr – chromosome; CAD – coronary artery disease; CPSM – Cross-Phenotype Spatial Mapping; peak height – value of covariance signal at apex of the peak; SNP – single nucleotide polymorphism.

*Sorted by decreasing peak height.

bPositions refer to build NCBI36/hg18.

cRefSeq genes.
### Table 3  Cross-analysis of loci previously reported to show genome-wide significant association with migraine or CAD

<table>
<thead>
<tr>
<th>Lead SNP</th>
<th>Chr band</th>
<th>Reported gene(s)</th>
<th>CAD p Value</th>
<th>Migraine p Value</th>
<th>Migraine without aura p Value</th>
<th>Migraine with aura p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead SNP</td>
<td>Chr band</td>
<td>Reported gene(s)</td>
<td>p Value</td>
<td>Odds ratio (SE)</td>
<td>p Value</td>
<td>Odds ratio (SE)</td>
</tr>
<tr>
<td>rs9349379</td>
<td>6p24</td>
<td>PHACTR1</td>
<td>8.97E-08(^a)</td>
<td>11 (0.019)</td>
<td>5.88E-09</td>
<td>1.09 (0.015)</td>
</tr>
<tr>
<td>rs10504861</td>
<td>8q21</td>
<td>MMP16</td>
<td>1.96E-03(^b)</td>
<td>1.06 (0.02)</td>
<td>1.71E-03</td>
<td>1.05 (0.017)</td>
</tr>
<tr>
<td>rs13208321</td>
<td>6q16</td>
<td>FHL5</td>
<td>2.53E-03(^b)</td>
<td>1.05 (0.018)</td>
<td>1.41E-10</td>
<td>1.1 (0.016)</td>
</tr>
</tbody>
</table>

### Abbreviations:

- Chr: chromosome
- CAD: coronary artery disease
- SNP: single nucleotide polymorphism

Only SNPs with significant association to the other phenotype after Bonferroni correction are shown (p < 0.0038 for previously reported migraine loci in the CAD sample, and p < 0.0023 for previously reported CAD loci in the migraine sample). p values may differ from those reported in the original studies since overlapping samples were excluded in the current study.

\(^a\) Direction of effect: SNPs with the same effect direction for association to CAD and migraine are marked as plus (+), opposing effect direction is marked as minus (-).

\(^b\) Significant cross-phenotype p value.

*It is possible that MA is a more heterogeneous disorder or is influenced by rare and low-frequency variants not captured by current sequencing studies.*
more in-depth analyses, including analysis for potential gene-gene interactions or identification of CAD risk loci specific to migraineurs. Third, considerable effort was devoted to the careful avoidance of shared controls between studies, and stringent quality control measures within each data set were enforced to reduce the risk of spurious results resulting from biases within the data sets. Nevertheless, we cannot rule out subtle biases that could affect the current results. Two such concerns are the effects of migraine on survival and the possibility that migraineurs may be more likely to seek medical treatment and therefore be under closer surveillance with regards to other disorders. Future efforts should aim to replicate these findings in sufficiently large prospective data sets where both phenotypes are measured in the same individuals.

Our study provides novel insights into the relationship between migraine and CAD. Intriguingly, and unexpectedly, there was no genetic overlap between MA and CAD, for which epidemiologic studies suggest comorbidity, but there was compelling evidence for a genetic overlap between MO and CAD, where the impact of risk variants overall was in opposite direction for the 2 disorders. The results do not demonstrate that shared common genetic risk factors drive comorbidity between the 2 disorders. However, dissecting the mechanisms underlying the shared risk loci may improve our understanding of both disorders.

**AUTHOR AFFILIATIONS**

From the Department of Neurology (B.S.W., J.-A.Z.) and FORMI (B.S.W., L.M.J., L.M.P., J.-A.Z.), Oslo University Hospital, Oslo, Norway; Institute of Clinical Medicine (B.S.W., J.-A.Z.), University of Oslo, Norway; Wellcome Trust Sanger Institute (B.S.W., P.G., V. Anntila, P.P., E.H., A.P.), Wellcome Trust Genome Campus, Cambridge, United Kingdom; Department of Cardiovascular Sciences (C.P.N., N.J.S.), University of Leicester, Clinical Sciences Wing and National Institute for Health Research Leicester Biomedical Research Unit in Cardiovascular Disease (C.P.N., N.J.S.), Glenfield Hospital, Leicester, United Kingdom; Institute for Smoke and Dementia Research (R. Malik, T.F., M.D.), Klinikum der Universität München, Ludwig-Maximilians-Universität, Munich, Germany; Munich Cluster for Systems Neurology (SyNergy) (R. Malik, M.D.), Munich, Germany; Program in Medical and Population Genetics (P.G., V. Anntila, H.-H.W., S.K., C.C., A.P.) and Stanley Center for Psychiatric Research (V. Anntila, A.P.), Broad Institute, Cambridge, MA; Psychiatric & Neurodevelopmental Genetics Unit (P.G., A.P.), Department of Psychiatry, Analytic and Translational Genetics Unit (V. Anntila, A.P.), Department of Medicine, Center for Human Genetic Research (H.-H.W., S.K.), Cardiovascular Research Center (H.-H.W., S.K.), and Department of Neurology (A.P.), Massachusetts General Hospital, Boston, MA; Division of Preventive Medicine (T. Kurth, D.I.C.), Brigham and Women’s Hospital and Department of Medicine (V. Anntila, H.-H.W., S.K.), Harvard Medical School, Boston, MA; Department of Genetics (J.Y.H., C.C.) and Department of Neurology (C.C.), Yale University School of Medicine, New Haven, CT; Wellcome Trust Centre for Human Genetics (K.S.E.), University of Oxford, United Kingdom; Department of Public Health (J.K.), High Institute and Institute for Molecular Medicine Finland (P.P., E.H., J.K., M.W., A.P.), University of Helsinki, Finland; Department of Epidemiology (N.A., M.A.L., C.-D.), Department of Radiology (M.A.L.), and Department of Neurology (M.A.L.), Erasmus University Medical Centre, Rotterdam, the Netherlands; Department of Human Genetics (B.d.V., A.M.J.M.v.d.M.) and Department of Neurology (M.D.F., G.M.T., A.M.J.M.v.d.M.), Leiden University Medical Centre, Leiden, the Netherlands; Department of Neurology and Epileptology and Hertie-Institute for Clinical Brain Research (T.F.), University of Tübingen, Germany; Deutsches Herzzentrum München (T. Kesler, H.S.), Technische Universität München, Munich, Germany; DZHK (German Centre for Cardiovascular Research) (T. Kesler, H.S.), Partner Site Munich Heart Alliance, Munich, Germany; Institute of Health Sciences (M. Koitmann, M.-R.J.) and BioCenter Oulu (M.-R.J.), University of Oulu, Finland; Department of Biological Psychology (L.L., D.I.B.), VU University and EGMO+ Institute for Health and Care Research (L.L.), VU University Medical Centre, Amsterdam, the Netherlands; Medical Research Council (MRC) Integrative Epidemiology Unit at the University of Bristol (G.M., G.D.S.), United Kingdom; Institut für Integrative und Experimentelle Genomik (C.W., J.E.), Universitätsklinikum zu Lübeck, Lübeck, Germany; DZHK (German Research Centre for Cardiovascular Research) (C.W., J.E.), Partner Site Hamburg/Lübeck/Kiel, Lübeck, Germany; Department of Neurology (J.O.), Glosstrup Hospital, University of Copenhagen, Denmark; Department of Neurology (V. Arto, M. Kallais), Helsinki University Central Hospital, Helsinki, Finland; Department of Medicine (T.L.A.), Stanford University School of Medicine, Stanford, CA; Medizinische Klinik und Poliklinik (S.B.), Universitätsmedizin Mainz, Johannes-Gutenberg-Universität Mainz, Germany; Department of Twin Research and Genetic Epidemiology (L.C., L.Q.), King’s College London, United Kingdom; MedStar Heart Institute (S.E.F.), Washington Hospital Center, Washington, DC; Kiel Pain and Headache Center (H.G.), Kiel, Germany; Division of Cardiovascular and Neuronal Remodelling (A.S.H.), Multidisciplinary Cardiovascular Research Centre, Leids Institute of Health, and Therapeutics, University of Leeds, United Kingdom; Department of Children, Young People and Families (M.-R.J.) and Department of Mental Health and Substance Abuse Services (J.K.), National Institute for Health and Welfare, Helsinki, Finland; Department of Epidemiology and Biostatistics (M.-R.J.), School of Public Health, MRC–Health Protection Agency (HPA) Centre for Environment and Health, Faculty of Medicine, Imperial College, London, United Kingdom; Unit of Primary Care (M.-R.J.), Oulu University Hospital, Oulu, Finland; Department of Clinical Chemistry (T.L.), Fimlab Laboratories, Tampere, Finland; University of Tampere School of Medicine (T.L.), Finland; The John and Jennifer Ruddy Canadian Cardiovascular Genetics Centre (R. McPherson, R.R., A.F.R.S.) and Atherogenomics Laboratory (R. McPherson), University of Ottawa Heart Institute, Ottawa, Canada; Synlab Center of Laboratory Diagnostics Heidelberg (W.M.), Heidelberg, Germany; Clinical Institute of Medical and Chemical Laboratory Diagnostics (W.M.), Medical University of Graz, Austria; Institute of Public Health (W.M.), Social and Preventive Medicine, Medical Faculty Mannheim, University of Heidelberg, Germany; Institute of Health and Biomedical Innovation (D.R.N.), Queensland University of Technology, Brisbane, Australia; National Heart, Lung, and Blood Institute’s Framingham Heart Study (C.J.O.), Framingham, MA; Department of Medicine, Institute for Translational Medicine and Therapeutics, and Cardiovascular Institute (D.J.R.), University of Pennsylvania, Philadelphia, PA; Department of Clinical Physiology and Nuclear Medicine (O.R.), Turku University Hospital, Turku, Finland; Research Centre of Applied and Preventive Cardiovascular Medicine (O.R.), University of Turku, Finland; Department of Neurology (M.S.), University Hospital Essen, Essen, Germany; dCODE genetics (U.T.), Reykjavik, Iceland; Faculty of Medicine (U.T.), University of Iceland, Reykjavik, Iceland; Institute of Genetics (M.W.), Folkhälsovårdslära Research Center, Helsinki, Finland; Institut National de la Santé et de la Recherche Médicale (INserm) Research Center for Epidemiology and Biostatistics (U897) Team–Neuroepidemiology (T. Kurth), Bordeaux, France; University of Bordeaux (T. Kurth), France; and Institute of Human Genetics (C.K.), University Medical Center Hamburg-Eppendorf, Hamburg, Germany.

**AUTHOR CONTRIBUTIONS**

Bendik S. Winrold and Christopher P. Nelson: performed statistical analysis; conceived and designed the study; analyzed and interpreted the data; contributed data; drafted/revised the manuscript for content. Rainer Malik: conceived and designed the study; analyzed and interpreted the data; contributed data; drafted/revised the manuscript for content. Padraig Gormley, Verneri Anntila, Jason Vander Heiden, Katherine S. Elliott, Line M. Jacobsen, and Priti Palta: analyzed and interpreted the data; contributed data; drafted/revised the manuscript for content. Najaf
Amin, Boule de Vries, Eija Hämäläinen, Tobias Fredinger, M. Arfan Ikram, Thorsten Kessler, Markku Koiranen, Lannie Ligthart, George McMahon, Linda M. Pedersen, Christina Willenborg, and Hong-Hee Won: contributed data; drafted/revised the manuscript for content. Jes Olesen: analyzed and interpreted the data; contributed data; drafted/reviewed the manuscript for content. Ville Arto, Themistocles L. Assimes, Stefan Blankenberg, Dorrett I. Boomsma, Lynne Cherkas, George Davey Smith, Stephen E. Epstein, Jeanette Erdmann, Michel D. Ferrari, Harmut Gobel, Alastair S. Hall, Mary-Rita Jarvelin, Mikko Kallela, Jarkko Kaprio, Sakari Karhunen, Terho Lehikoinen, Ruth McPherson, Winfried Mütze, Dale R. Nyholt, Christopher J. O’Donnell, Lydia Quayle, Daniel J. Rader, Olli Raitakari, Robert Roberts, Heribert Schunkert, Markus Schürk, Alexandre F.R. Stewart, Gisela M. Terwindt, Unnur Thorsteinsdóttir, Arn M.J.M. van den Maagdenberg, Cornelia van Duijn, and Maija Wessman: contributed data; drafted/revised the manuscript for content. Tobias Kurth and Christian Kubisch: analyzed and interpreted the data; contributed data; drafted/reviewed the manuscript for content. Daniel I. Chaussion and Chris Costapas: analyzed and interpreted the data; contributed data; drafted/revised the manuscript for content. Martin Dichgans: conceived and designed the study; analyzed and interpreted the data; contributed data; drafted/revised the manuscript for content. Daniel I. Chaussion and Christopher Costapas: analyzed and interpreted the data; contributed data; drafted/revised the manuscript for content. John-Anker Zwart, Niles H. Samani, and Arno Palotie: conceived and designed the study; jointly supervised research; analyzed and interpreted the data; contributed data; drafted/revised the manuscript for content. All authors accept responsibility for conduct of research and will give final approval.

ACKNOWLEDGMENT

P.F. was supported by the European Commission FP7 project no. 261123 (gEUVDAS). C.K. and H.G. were funded by the German Federal Ministry of Education and Research (BMBF) within the framework of the National Genome Research Network (NGFN-Plus; grants 01GS08120 and 01GS1103 [to C.K.]) and the Deutsche Forschungsgemeinschaft (DFG). The Academy of Finland (grant 139795 to M.W.); the Folkhälso Research Foundation (to M.W.); the Medicinska Understödsföreningen Liv & Hälsa (to M.W.); the Orion Farmos Research Foundation (to Y. Antrila); and the Helsinki University Central Hospital (to M. Koiranen and V. Arto). The Women’s Genome Health Study (WGPS) is supported by HL043851 and HL080467 from the National Heart, Lung, and Blood Institute and CA047988 from the National Cancer Institute, with collaborative scientific support and funding for genotyping provided by Amgen. Genetic analyses of migraine in WGPS have been supported by NS061836 from the National Institute of Neurological Disorders and Stroke. The Nord-Trondelag Health Study (The HUNT Study) is a collaboration between HUNT Research Centre (Faculty of Medicine, Norwegian University of Science and Technology, NTNU), Nord-Trøndelag Health Study.—The HUNT Study is a collaboration between HUNT Research Centre (Faculty of Medicine, Norwegian University of Science and Technology, NTNU), Nord-Trøndelag Health Study.—The Nord-Trøndelag Health Study (The HUNT Study) is a collaboration between HUNT Research Centre (Faculty of Medicine, Norwegian University of Science and Technology, NTNU), Nord-Trøndelag County Council, Central Norway Health Authority, and the Norwegian University of Science and Technology, NTNU, Nord-Trøndelag County Council, Central Norway Health Authority, and the Norwegian University of Science and Technology, NTNU.—The Young Finns Study has been financially supported by the Academy of Finland: grants 104781, 120315, 129269, 1114194, 24300796, Center of Excellence in Center of Excellence in Complex Disease Genetics and Salve, Oulu University Hospital, Finland, Biocenter, University of Oulu, Finland 75617, 24002054, University of Oulu, Finland (grants 24000692 and 24500283: Well-being and health in the Northern Finland Birth Cohorts 1966 and 1986, Phenotypic and Genomic analyses). NIH/NHLBI NHLBI grant 5R01HL087679-02 through the STAMPEDE program (R1L1MH083268-01). NHLBI Consortium for Neuropsychiatric Phenomics Co-ordinating Center (R1R01HL087679-01). NIH/NIMH NIH/NIMH grant 2R01MH63706-02, United States. ENGAGE project and grant agreement HEALTH-F4-20027-201413. Medical Research Council (grant G1002319). The DNA extractions, sample quality controls, biobank upkeep, and aliquoting were performed in the National Public Health Institute, Biocenter Helsinki, Finland and supported financially by the Academy of Finland and Biocentre Helsinki. The authors thank Ms. Outi Tornwall and Ms. Ministu Jusila (DNA biobanking).

STUDY FUNDING

This work was supported by Academy of Finland (grant 251704 to A.P.), Sigrid Juselius Foundation (to A.P.), SynSys (to A.P.), the Wellcome Trust (grant 098051 to A.P.), EU FP7-242167 (to A.P.), NIH/RFAL-HL-12-007, Genomic and Metabolomic Profiling of Finnish Familial Dyslipidemia Families (to A.P.), the South-Eastern Norway Regional Health Authority (grants 2010075 and 2011083 to B.S.W., L.M.J., and J.-A.Z.), the Research Council of Norway (grant 251187/F20 to B.S.W.), and the NIHHLBI NHLBI grant 1R01HL087615-02, United States. ENGAGE project and grant agreement HEALTH-F4-20027-201413. Medical Research Council (grant G1002319). The DNA extractions, sample quality controls, biobank upkeep, and aliquoting were performed in the National Public Health Institute, Biocenter Helsinki, Finland and supported financially by the Academy of Finland and Biocentre Helsinki. The authors thank Ms. Outi Tornwall and Ms. Minna Jusila (DNA biobanking).

DISCLOSURE

Bendik S. Winsvold has received research support from the Research Council of Norway, the South-Eastern Norway Regional Health Authority, and Forboks’ and Auli Endowment. Christopher P. Nelson, Rainer Malik, and Padhraig Gormley report no disclosures. Verner Anttila has received travel support from Orion Farmos Research Foundation. Jason Vander Heiden has received funding for travel and/or speaker honoraria from New England Biolabs; and has received research support from National Library of Medicine and the United States-Israel Binational Science Foundation. Katherine S. Elliott reports no disclosures. Line M. Jacobsen is employed by AstraZeneca. Prit Palta has received

© 2015 American Academy of Neurology. Unauthorized reproduction of this article is prohibited.
research support from the Finnish Cultural Foundation. Najaf Amin has received research support from the Netherlands Brain Foundation. Boukje de Vries and Eija Hamalainen report no disclosures. Tobias Freilinger has received funding for travel and/or speaker honoraria from Boehringer Ingelheim and Allergan; and has received research support from Deutsche Forschungsgemeinschaft (DFG). M. Arfan Ikram has received funding for travel and/or speaker honoraria from Kaizo, Ltd.; has served on the editorial boards of Neuropeptidology, PLoS One, and Journal of Alzheimer Disease; and has received research support from Jansen Prevention Center, Netherlands Organization for Health Research and Development, the Netherlands Heart Foundation, Internationa1 Parkinson Fonds, Internationale Stichting Alzheimer Onderzoek, and the Alzheimer Association. Thorsten Kessler and Markku Koiranen report no disclosures. Lannie Lighart has received research support from EFIC-Grüntenthal. George McMahon, Linda M. Pedersen, Christina Willenborg, and Hong-Hee Won report no disclosures. Jes Olsen has consulted for Janssen Pharmaceutical Products; and has served on speakers’ bureaus for Allergan. Ville Arto has received funding for travel and/or speaker honoraria from Boehringer Ingelheim, Orion, Menarini, Migraine Trust, and Bayer; and has received research support from the Finnish Medical Foundation and Helsinki University Central Hospital. Themistocles L. Assimes has served on the editorial board of Frontiers in Cardiovascular Medicine; has consulted and received research support from Telomere Diagnostics, Inc.; and has received research support from NHLBI, Stefan Blankenbarg, Dorit L. Boomsma, Lynn Cherka, and George Davey Smith report no disclosures. Stephen E. Epstein has received research support from MedStar Heart and Vascular Institute, MedStar WA Hospital Center; and holds stock/stock options and/or receives Board of Directors Compensation for CardioCell. Jeanette Erdmann reports no disclosures. Michel D. Ferrari has served on the editorial board of Cephalalgia; and has received research support from the Netherlands Organization for Scientific Research (NWO), European Community, ZonMW, and the Dutch Heart Foundation. Hartmut Gobel has served on Scientific Advisory Boards for Allergan, Bayer Vital, and St. Jude Medical; has received funding for travel and/or speaker honoraria from Amgen, Allergan, Hormosan, Klosterfrau, MSD, Mundi, pharma, St. Jude Medical, and Teva; has served on the editorial board of Der Schmerz, Pain Research and Treatment; has served on speakers’ bureaus for Allergan, Hormosan, Klosterfrau, MSD, Mundipharma, St. Jude Medical, and Teva; and has received research support from St. Jude Medical. Alistair S. Hall and Marjo-Riitta Jarvelin report no disclosures. Mikko Kallela has served on Advisory Boards for MSD and Allergan; has received funding for travel and/or speaker honoraria from MSD, Allergan, TEVA, Novartis, and Genzyme; has received compensation for producing educational material from TEVA and Allergan; has served on research support from Helsinki University Central Hospital; and holds stock/stock options and/or has received Board of Directors compensation from Helsinki Headache Center. Jaakko Kaprio has served on an Advisory Board for Copenhagen University; has received funding for travel and/or speaker honoraria; and has consulted for Pfizer Ltd. Sekar Kathiresan has served on scientific advisory boards for Regeneron, Merck, Eli Lilly, Aegerion, Catabasis, Amarin, and Novartis; and has received research support from Regeneron, Aegerion, Merck, NIH, and Fondation Leducq. Terho Lehtimaki reports no disclosures. Ruth McPherson has served on the editorial board of Arteriosclerosis, Thrombosis & Vascular Biology; and has received research support from Canadian Institutes of Health Research and Heart & Stroke Foundation of Canada. Winfried Mai has served on Scientific Advisory Boards and speakers’ bureaus and consulted for Aegerion Pharmaceuticals, AMGEN, Danone Research, Sanofi/Genzyme, Hoffmann LaRoche, MSD, Synageva, Eli Lilly, and BASF; has received funding for travel and/or speaker honoraria from Aegerion Pharmaceuticals, AMGEN, Danone Research, Sanofi/ Genzyme, Hoffmann LaRoche, MSD, Synageva, Eli Lilly, and BASF; has served on the editorial boards of European Heart Journal and Journal of Laboratory Medicine; has been employed by and holds stock/stock options and/or Board of Directors compensation from Synlab Services GmbH; and has received research support from Aegerion Pharmaceuticals, AMGEN, Danone Research, Sanofi/Genzyme, Hoffmann LaRoche, MSD, Synageva, Eli Lilly, BASF, European Union, German Ministry of Research, German Ministry of Commerce, and Wissenschaftsinitiative Oberhein. Dale R. Nyholt reports no disclosures. Christopher J. O’Donnell is employed by and has received research support from National Institutes of Health. Lydia Quaye reports no disclosures. Daniel J. Rader has served on the scientific advisory boards of Arteriosclerosis, Thrombosis & Vascular Biology; and has received research support from NIH and the Leducq Foundation. Olli Raidakari and Robert Roberts report no disclosures. Hersibert Schunkert has served on scientific advisory boards, consulted for, received funding for travel and/or honoraria, and/or received research support from AstraZeneca, AMGEN, MSD SHARP & DOHME, Bayer Vital, Boehringer Ingelheim, Medtronic, Novartis, Pfizer, Sanofi-Aventis, St. Jude, Boston Scientific, and Daiichi Sankyo. Markus Schürks has served on the editorial boards of The Journal of Headache and Pain, and BMC Neurology; and consults Bayer HealthCare Pharmaceuticals. Alexandre F.R. Stewart has served on the editorial board of Frontiers in Cardiovascular Medicine—Cardiovascular Genetics. Gisela M. Terwindt has received research support from the Netherlands Organisation for Scientific Research (NWO). Unnur Thorsteinsdottir is an employee of deCODE genetics/Amgen. Arn M.J.M. van den Maagdenberg and Cornelia van Duijn report no disclosures. Maaja Wessman has received research support from Folkhälsan Research Foundation, Academy of Finland, and Medicinska Understödsföreningen Liv och Halsa. Tobias Kurth has served on editorial boards for BMJ and Cephalalgia; and has received research support from the French National Research Agency and the University of Bordeaux. Christian Kubisch reports no disclosures. Martin Dichgans has served on editorial boards for Stroke, The International Journal of Stroke, Cerebrovascular Diseases, and Journal of Neuroscience; has consulted for Bayer Vital, Boehringer Ingelheim, Bristol-Myers Squibb, and Heel; and has received research support from Wellcome Trust, European Union, and German Federal Ministry of Education and Research. Daniel I. Chaushman has served on the editorial board for Arteriosclerosis, Thrombosis, and Vascular Biology; and has received publishing royalties for Protein Structure: Determination, Analysis, and Applications for Drug Discovery (Marcel Dekker, 2003). Chris Cotsapas has served on the editorial board for PLoS Genetics; and has received research support from NINDS, NIAID, and RE Childen’s Consortium. John-Anker Zwart reports no disclosures. Nilesh J. Samani has served on editorial boards for Circulation: Cardiovascular Genet ics and Heart; and has received research support from British Heart Foundation and National Institute for Health Research. Aaro Palotie has been a member of the Pfizer Genetic Scientific Advisory Panel; has received travel expenses and/or honoraria for lectures or educational activities not funded by industry; and has received research support from the Finnish Academy, European Union NIH, NINDS, Janssen Foundation, and the Finnish Foundation for Cardiovascular Research. Go to Neurology.org for full disclosure forms.

Received April 4, 2015. Accepted in final form May 27, 2015.

REFERENCES


Genetic analysis for a shared biological basis between migraine and coronary artery disease

Bendik S. Winsvold, Christopher P. Nelson, Rainer Malik, et al.

*Neurol Genet* 2015:1;
DOI 10.1212/NXG.0000000000000010

*This information is current as of July 2, 2015*