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. 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. 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. Supporting a vascular basis, epidemiologic studies have found an increased risk for stroke among patients with migraine, most pronounced for MA. 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. 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) and CAD (Coronary ARtery Disease Genome-Wide Replication And Meta-Analysis, CARDIoGRAM) 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) and CAD (CARDIoGRAM) were used in

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MO (p = 1.5 × 10^{-4} and 5.1 × 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 × 10^{-11}; migraine: rs9349379, p = 5.9 × 10^{-9}). The second strongest overlapping signal was on 17q21 (locus no. 2), where the lead CAD SNP (rs46522, p = 2.6 × 10^{-7}) was intragenic in UBE2Z, whereas the lead migraine SNP (rs11079844, p = 3.1 × 10^{-3}) 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 transcript^{18} (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

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**CPSM** = Cross-Phenotype Spatial Mapping.
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)*</th>
<th>p Value for overlap (permutation test)*</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>1.1E-05c</td>
<td>6.0E-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>9.3E-03c</td>
<td>7.9E-03c</td>
<td>0</td>
<td>0.75</td>
</tr>
<tr>
<td>1E-5</td>
<td>1</td>
<td>0.014</td>
<td>2.1E-04c</td>
<td>0</td>
<td>0.50</td>
</tr>
<tr>
<td>1E-6</td>
<td>1</td>
<td>5.2E-03c</td>
<td>3.5E-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>1.6E-04c</td>
<td>1.5E-05c</td>
<td>0.510</td>
<td>0.87</td>
</tr>
<tr>
<td>1E-3</td>
<td>8</td>
<td>1.3E-03c</td>
<td>1.1E-04c</td>
<td>0.442</td>
<td>0.86</td>
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<tr>
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<td>3</td>
<td>2.0E-04c</td>
<td>1.5E-05c</td>
<td>0.250</td>
<td>0.88</td>
</tr>
<tr>
<td>1E-5</td>
<td>1</td>
<td>8.5E-03c</td>
<td>1.5E-05c</td>
<td>0</td>
<td>0.50</td>
</tr>
<tr>
<td>1E-6</td>
<td>1</td>
<td>3.0E-03c</td>
<td>1.5E-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>1.0</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>1E-5</td>
<td>0</td>
<td>1.0</td>
<td>1.0</td>
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</tr>
<tr>
<td>1E-6</td>
<td>0</td>
<td>1.0</td>
<td>1.0</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

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

*False discovery rate corrected p values.

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 ($p < 1 \times 10^{-2}$), moderate ($p < 1 \times 10^{-4}$), or strong ($p < 5 \times 10^{-8}$) association to CAD in the Coronary ARtery Disease Genome-Wide Replication And Meta-Analysis study.
CAD and any migraine subtype. Studies not differentiating on migraine subtype have been less conclusive, with some but not others indicating an increased risk of CAD related to migraine overall.

For MO, we found a clear overlap of association signals with CAD, whichever value cutoff was used to define signals. Intriguingly, the impact was in the opposite direction, in that patients with MO had a lower load of CAD risk alleles than migraine-free controls. This association seemed to be driven by a limited number of loci. Only a proportion of the included migraine patients were phenotyped in sufficient detail to allow subclassification into MA or MO. When using the considerably larger set of all migraine patients, a similar association was seen as for MO, likely driven by this migraine subtype. While the results suggest that there are shared common risk variants between migraine and CAD, they do not indicate that these variants explain comorbidity between the 2 disorders.

The opposite direction of effect for some of the loci is consistent with a recent GWAS in which the migraine and CAD risk SNP rs9349379 (in PHACTRI) was associated with cervical artery dissection, with effect in the same direction as for migraine but opposite of CAD. Two further migraine SNPs showed evidence of association to cervical artery dissection with the same effect direction as for migraine (rs11172113 in LRPI and rs13208321 in FHL5, the latter identified as locus 3 in the current study) but opposite direction for CAD.

The significant sharing of risk loci between migraine and CAD may reflect that they involve some of the same biological processes. Experimental studies will be needed to clarify this and whether the shared risk loci can give information on vascular mechanisms involved in migraine pathogenesis.

The lack of overlapping association signals between MA and CAD may indicate that the 2 disorders have separate and nonrelated genetic backgrounds. However, it may also result from insufficient power to detect shared common genetic risk factors for this migraine subtype. This is consistent with the relative failure so far in identifying common risk variants for MA; despite at least as high heritability and comparable study sample sizes, only one genome-wide significant locus has been identified.
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</th>
<th>Migraine</th>
<th>Migraine without aura</th>
<th>Migraine with aura</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p Value</td>
<td>Odds ratio (SE)</td>
<td>p Value</td>
<td>Odds ratio (SE)</td>
<td>Dir.*</td>
<td>p Value</td>
</tr>
<tr>
<td>Previously reported loci for migraine in the CAD sample</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs9349379</td>
<td>6p24</td>
<td>PHACTR1</td>
<td>8.97E-08</td>
<td>1.1 (0.019)</td>
<td></td>
<td>5.88E-09</td>
</tr>
<tr>
<td>rs10504861</td>
<td>8q21</td>
<td>MMP16</td>
<td>1.96E-03</td>
<td>1.06 (0.02)</td>
<td></td>
<td>1.71E-03</td>
</tr>
<tr>
<td>rs13208321</td>
<td>6q16</td>
<td>FHL5</td>
<td>2.53E-03</td>
<td>1.05 (0.018)</td>
<td></td>
<td>1.41E-10</td>
</tr>
</tbody>
</table>

Previously reported loci for CAD in the migraine sample

| Lead SNP    | Chr band | Reported gene(s) | p Value      | Odds ratio (SE) | Dir.*     | p Value          | Odds ratio (SE) | Dir.*     |
|-------------|----------|------------------|--------------|-----------------|----------|                  |                |          |
| rs12526453  | 6p24     | PHACTR1          | 9.72E-09     | 1.09 (0.017)    |          | 8.18E-06     | 0.94 (0.013)    |          |
| rs46522     | 17q21    | UBE2Z            | 2.58E-07     | 0.93 (0.013)    |          | 1.24E-04     | 1.05 (0.013)    |          |

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.

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 (−).

Significant cross-phenotype p value.

sensitize the insulin response.38 It is also expressed in neuronal progenitor cells.39 Whether the brain, where it may be involved in proliferation of vasomotor dysfunctions has been implicated in migraine,36,37 and this locus offers a potential focus for future studies. Alternatively, the pleiotropic effects of this gene on both synaptic and vascular functions may give rise to independent causal pathways for the 2 disorders.

The second strongest overlapping region (locus 2) is a previously identified risk locus for CAD (rs11079444) and migraine variants (rs46522) and migraine variants are in strong LD (r² > 0.9) with 2 potentially functional variants (rs11079444 and rs46522). The lead SNP (rs11079444) is entirely intragenic in its potential overlap with cardiovascular disease.

Six of the overlapping loci have previously been associated with MA, compared to 9 for MO. It is possible that MA is a more heterogeneous disorder, or is influenced by rare and low-frequency variants not captured by current imputation panels. Larger studies that also interrogate rare variants will be needed to determine the genetic basis of MA and its potential overlap with cardiovascular disease.

This prevented us from performing another imputation and meta-analysis of the migraine GWAS data, which also interrogate rare variants.

PHACTR1 has been identified as a key regulator of endothelial function, including endothelial cell survival and angiogenesis.34 More recently, PHACTR1 has been shown to be expressed in the brain and its transcript is an important regulator of synaptic activity and dendritic morphology through the control of protein phosphatase 1 and actin binding protein phosphatase 1 and protein phosphatase 2A. It has also been associated with coronary artery calcification and stroke.31,32 PHACTR1 is highly expressed in the brain and its transcript is an important regulator of synaptic activity and dendritic morphology through the control of protein phosphatase 1 and actin binding protein phosphatase 1 and protein phosphatase 2A. It has also been associated with coronary artery calcification and stroke.31,32

CAUSE OF NOT FOUND 2 OF 2

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.

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 (−).
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 effects 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.

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