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Shared Genetics of Migraine and Gastrointestinal Disorders Implicates Underlying Neurologic Mechanisms Yet Heterogeneous Etiologies

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Abstract

Background and Objectives

Migraine is strongly comorbid with irritable bowel syndrome (IBS), one of several gastrointestinal (GI) conditions that are distinguished by symptomatic profiles that are partly overlapping. Potential shared mechanisms of migraine and the GI conditions were investigated by assessing shared genetics on a genome-wide basis.

Methods

Analyses leveraged genome-wide summary statistics from large-scale genetic studies for migraine, including by aura status, IBS, peptic ulcer disease (PUD), gastrointestinal reflux (GERD), functional dyspepsia (FD), diverticular disease (DD), and the immune-related inflammatory bowel disease (IBD) or its constituents, ulcerative colitis (UC) and Crohn disease (CD). Genetic correlation was evaluated on a genome-wide basis and at independent local regions, including those related to therapeutic targeting of serotonin and the calcitonin gene-related peptide. Genetic correlation was assessed for enrichment at genes according to tissue specificity of gene expression. Potential causality between migraine and the GI conditions was assessed by Mendelian randomization.

Results

Genetic correlation with migraine was strongly significant among the nonimmune GI disorders, maximally for IBS (rg [SE] = 0.37[0.04], $p = 10^{-21}$) and minimally for DD (0.18 (0.04), 7.5×10^{-7}), but null for IBD. There were distinct patterns of local genetic sharing with migraine across the GI conditions at 22 significant segments of the genome, 7 of which were novel for either migraine or GI or both. Enrichment analysis suggested involvement of the CNS in genetic overlap of GERD, IBS, and PUD with migraine. There was local genetic sharing with migraine at *CALCA/CALCB* (encoding calcitonin gene-related peptide [CGRP]) in an inverse sense for GERD and PUD, but with concordance and greater significance for DD, IBD, and UC. Mendelian randomization supported causal effects of PUD, GERD and particularly DD (OR [SE] = 1.90 (1.35–2.68, $p = 2.2 \times 10^{-4}$) on migraine, but not of migraine on any GI condition.

Discussion

Genetic sharing of migraine and non–immune-related GI disorders was extensive yet distinct across GI disorders that have overlapping symptoms, with enrichment signals that imply neurologic mechanisms. Causal effects of some GI conditions on migraine were supported. A concordant local correlation at *CALCA/CALCB* of migraine with both DD and the immune-related disorders suggests potential benefit to these conditions from repurposed migraine therapeutics targeting CGRP.

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Glossary

CD = Crohn disease; **CGRP** = calcitonin gene-related peptide; **DD** = diverticular disease; **FD** = functional dyspepsia; **GERD** = gastrointestinal reflux; **GI** = gastrointestinal; **GORD** = gastro-oesophageal reflux disease; **GWASs** = genome-wide association studies; **IBD** = inflammatory bowel disease; **IBS** = irritable bowel syndrome; **IHGC** = International Headache Genetics Consortium; **MR** = Mendelian randomization; **PUD** = peptic ulcer disease; **UC** = ulcerative colitis.

Introduction

Migraine is a highly debilitating condition, typically diagnosed by symptoms related to onset of recurrent but reversible headaches and the characteristics of these headaches. Although the mechanisms of migraine are only partly understood, susceptibility to migraine attacks and the initiating events of these attacks involve neurologic structures focused around the trigeminal ganglion complex, its neurologic projections, the hypothalamus, and the vascular system.[1] Genetic signals from genome-wide association studies (GWASs) of migraine support involvement of brain tissues, particularly the cerebellum, and the vasculature.[2-4]

Irritable bowel syndrome (IBS), a common gastrointestinal (GI) condition, is strongly comorbid with migraine.[5,6] This relationship is recognized in the International Classification of Headache Disorders reference criteria (1.6) for migraine that highlight IBS as a migraine-associated syndrome, although not formally among symptoms required for migraine diagnosis.[7] Moreover, tricyclic antidepressants (TCAs), used for migraine prophylaxis, are also used for the treatment of IBS, possibly exerting their benefit through serotonin-related pathways.[8,9] In medical insurance claims among 29 most common clinical conditions, genetic correlation between migraine and IBS in family structures was extremely strong.[10] It was estimated as r_g (SE) = 0.48 (0.03), despite the potential for etiologic heterogeneity in these data introduced by the breadth of symptoms that may have been considered in IBS diagnosis and the use of ICD codes as diagnosis proxies. Thus, understanding the genetics that may underlie the comorbidity between migraine and IBS may be revealing about the shared mechanism and, if so, whether it may imply therapeutic strategies for either or both.

IBS is one of several related GI conditions with partly overlapping symptomatic profiles suggesting both shared and distinct mechanisms. These conditions include gastroesophageal reflux disease, diverticular disease, and functional dyspepsia. All conditions involve interplay between neurologic etiologies and the physical structure (and, therefore, intrinsic function) of the GI system in various segments along its entire extent, with potential additional influence of microbiota. Peptic ulcer disease (PUD) also shares symptoms with the other GI conditions but primarily involves only structural aspects of the upper GI tract. The sharing of symptoms of these GI conditions, which presents a challenge for diagnosis, also implies that there is likely mechanistic heterogeneity within each class. Indeed, there is a high degree of comorbidity among these conditions.[11] Other GI conditions that may also share symptoms with the preceding conditions, including Crohn disease and ulcerative colitis and their composite inflammatory bowel disease, are characterized by additional etiologies based on immune-mediated mechanisms. Thus, 1 or more of 3 broad categories of mechanism are believed to underlie GI conditions potentially relevant to migraine: neurologic signaling, structural properties of the GI system, and immune-mediated pathways.

In this study, we perform genetic analysis to compare and contrast common genetic susceptibility to migraine, including both migraine with aura (MA) and migraine without aura (MO), with genetic susceptibility to the preceding series of GI conditions. We focus on whether there may be distinct patterns of genetic sharing between migraine and the GI conditions that informs mechanism despite broad overlap of their symptoms.

Methods

Data Sets

Analysis used published summary statistics from GWASs for migraine and each of the GI conditions that had been conducted in populations of European ancestry (eTable 1). Summary statistics for migraine were derived from a very large GWAS published by the International Headache Genetics Consortium (IHGC) (2016).[3] While an updated migraine GWAS was published recently by the IHGC (2022),[4] access to genome-wide summary statistics for the full sample was restricted and this study was only used when statistics were needed for the published GWAS index SNPs (rather than genome-wide SNPs), e.g., as instruments in the Mendelian randomization (mentioned further). Summary statistics for IBS1; PUD; gastro-oesophageal reflux disease (GORD [UK designation for UK Biobank data]); and a composite diagnosis of PUD, GORD, or a record of medications for either (PGM) were from a study performed exclusively in the UK Biobank.[11] Summary statistics for a second genetic study of IBS (designated as IBS2 throughout) combined genome-wide analysis from the UK Biobank and from a collection of cohorts in the Bellygenes consortium. Cases in the UK Biobank component used diagnostic criteria that differed from those in the IBS1 analysis in part by leveraging responses to a supplemental digestive health questionnaire incorporating Rome Foundation criteria, i.e., the accepted standard reference for

diagnosis, which were also used together with cohort-specific criteria for case ascertainment in the Bellygenes consortium.[8,12] Similarly, summary statistics for a second GWAS of gastroesophageal reflux disease (GERD [US designation throughout for US + UK data in that study]), which incorporates samples from the UK Biobank, the QSkin study, and 23andMe complemented the summary statistics from the UK Biobank alone (i.e., GORD mentioned above).[13] (Note: We preserve the 2 notations for the same reflux condition as they were published, GORD and GERD, to distinguish summary statistics from these 2 separate GWAS efforts.) Summary statistics for diverticular disease (DD), which involves formation of distended pouches in the large intestine, were from the UK Biobank.[14] Summary statistics for functional dyspepsia (FD), an upper GI condition with varied symptoms collectively labeled indigestion, were from a meta-analysis incorporating the UK Biobank, EGCUT, and MGI studies.[15] Finally, summary statistics for Crohn disease (CD), ulcerative colitis (UC), and the composite, inflammatory bowel disease (IBD), were from a large GWAS of clinic-based cases.[16]

Genetic Correlation

Global genetic correlation was performed using LDScore regression as described, with the 1,000-genome reference panel and precompiled partitions based on histone marks (H3K4me1, H3K4me3, H3K9ac, and H3K27ac) in groupings of cell types.[2,17,18] The primary local genetic correlation analysis was performed with SUPERGNOVA, which uses a random-effect formalism, applied to approximately 2,330 prespecified LD-independent segments across the genome.[19] An alternative approach, which uses a fixed-effect formalism, as implemented in LAVA, was used for validation.[20] Previous comparisons have suggested that estimates of local correlation are more likely to be out-of-bounds with SUPERGNOVA than LAVA, although estimates for both may exceed an absolute value of 1 because of error in estimating the local heritability scaling factor.[20] Therefore, candidate segments were selected on the basis of genome-wide significance for the SUPERGNOVA covariance ($p < 2.1 \times 10^{-5}$ [=0.05/2,330]) and then validated with LAVA requiring significance at either nominal ($p < 0.05$) or Bonferroni levels, accounting for the number of loci nominated by SUPERGNOVA. Gene expression in 53 tissues for genes mapping to each segment was derived from GTEx v.8[21] and dichotomized as either above or below the median expression (as estimated transcripts/cell) across all tissues. Tissue enrichment was based on the hypergeometric distribution, assessing the number of genes in a tissue with expression above median across all tissues and also mapping to a segment with a significant ($p < 0.05$) local correlation in SUPERGNOVA, compared with the number of genes with expression below median in a segment with significant local correlation and the number of genes with expression either above or below median and in a segment with nonsignificant ($p \geq 0.05$) local genetic correlation. Empirical p values for enrichment correcting for the 53 tissues were derived by random reassignment of genes to segments, iterated 10,000 times to derive null distributions.

Mendelian Randomization (MR)

The primary MR was performed with GSMR using HEIDI filtering, requiring at least 5 instruments selected with genome-wide significance ($p < 5 \times 10^{-8}$) and minor allele frequency >0.05 and clumping to enforce interinstrument LD < 0.1 within the 1,000-genome reference panel for European ancestry.[22] MR sensitivity analysis used instruments identified as independent, genome-wide significant lead variants in publications for the summary statistics and was performed with the MendelianRandomization package in R[23] that implements the inverse-variant weighted MR (MR-IVW)[24] and MR-Egger[25] and MR-median[26] methods among others and with the MR-PRESSO that excludes instruments inferred to be invalid.[27] Instrumental effects were scaled to reflect a doubling of the prevalence of the exposure.[28]

Standard Protocol Approvals, Registrations, and Participant Consents

All research was performed exclusively as secondary analysis of summary statistics from existing GWASs. No individual-level data were used. All GWAS summary statistics were derived from research that was approved by study-specific, local ethics committees with written participant consent. No experiments were performed on humans, live vertebrates, or higher invertebrates.

Artificial Intelligence Use Statement

No artificial intelligence applications were used to generate the source data for this investigation, to perform the analysis that is described, or to prepare the article.

Data Availability

All analyses were performed using existing genome-wide association study (GWAS) summary statistics described in previous publications with data availability provided in the given citations. Some analyses also used supporting publicly available data for genomic annotation, as cited in Methods. No new data were generated by this study.

Results

Analysis was performed with previously published summary statistics for migraine and the GI conditions (Methods, eTable 1).[3,11-16] For the GI conditions IBS and GERD, separate summary statistics were available from 2 studies each. For IBS, 1 study, herein termed "IBS1," ascertained cases in the UK Biobank solely on the basis of ICD coding.[11] The second study, herein termed "IBS2," was a meta-analysis of genome-wide association substudies in the Bellygenes consortium with cohort-level definition of cases largely consistent with Rome III criteria.[8,12] These substudies included an analysis in the UK Biobank that ascertained cases using a supplemental web-based digestive health

questionnaire, again incorporating the Rome III criteria. For GERD, 1 study solely used the UK Biobank resource.[11] This study is herein termed "GORD" to preserve the published designation, an acronym for the British spelling of the condition designated as GERD in the United States. The second study, herein termed "GERD," refers to a meta-analysis combining summary statistics from the UK Biobank with those from other samples.[13]

Global, i.e., genome-wide, genetic correlation was substantial and highly significant between migraine and all the GI conditions with the exception of those that are generally considered immune-mediated. The genetic correlation was strongest for IBS (r_g [SE], p: IBS1 = 0.37 [0.05] 6.6×10^{-15}, IBS2 = 0.37 [0.04], 1.0×10^{-21}), but only slightly weaker for gastroesophageal reflux (GERD = 0.34 [0.03], 2.2×10^{-31}, GORD = 0.31 [0.03], 3.8×10^{-22}), FD (0.34 [0.03], 2.2×10^{-31}), and PUD (0.29 [0.05], 5.4×10^{-9}) (Table 1, Methods). Migraine also had a strong correlation with the composite diagnosis that included GORD, PUD, or a record of medications for those conditions (PGM). The genetic correlation was less but still highly significant for DD (0.18 [0.04], 7.5×10^{-7}). These strong effects can be contrasted with the lack of genetic correlation with the immune-mediated GI conditions (CD, UC, and the composite IBD, all $p > 0.05$).

Power was comparatively limited for genetic overlap between the subtypes of migraine, i.e., MA and MO, and the GI conditions, but the overall patterns of correlations were similar to those for migraine overall (eTable 2). However, there was a much stronger genetic correlation of MO than MA with IBS as defined for IBS1, although this difference was not observed for IBS2. Conversely, genetic correlation of PUD was significant with MA but not MO.

Table 1 Global Genetic Correlation of Migraine[17] With GI Conditions

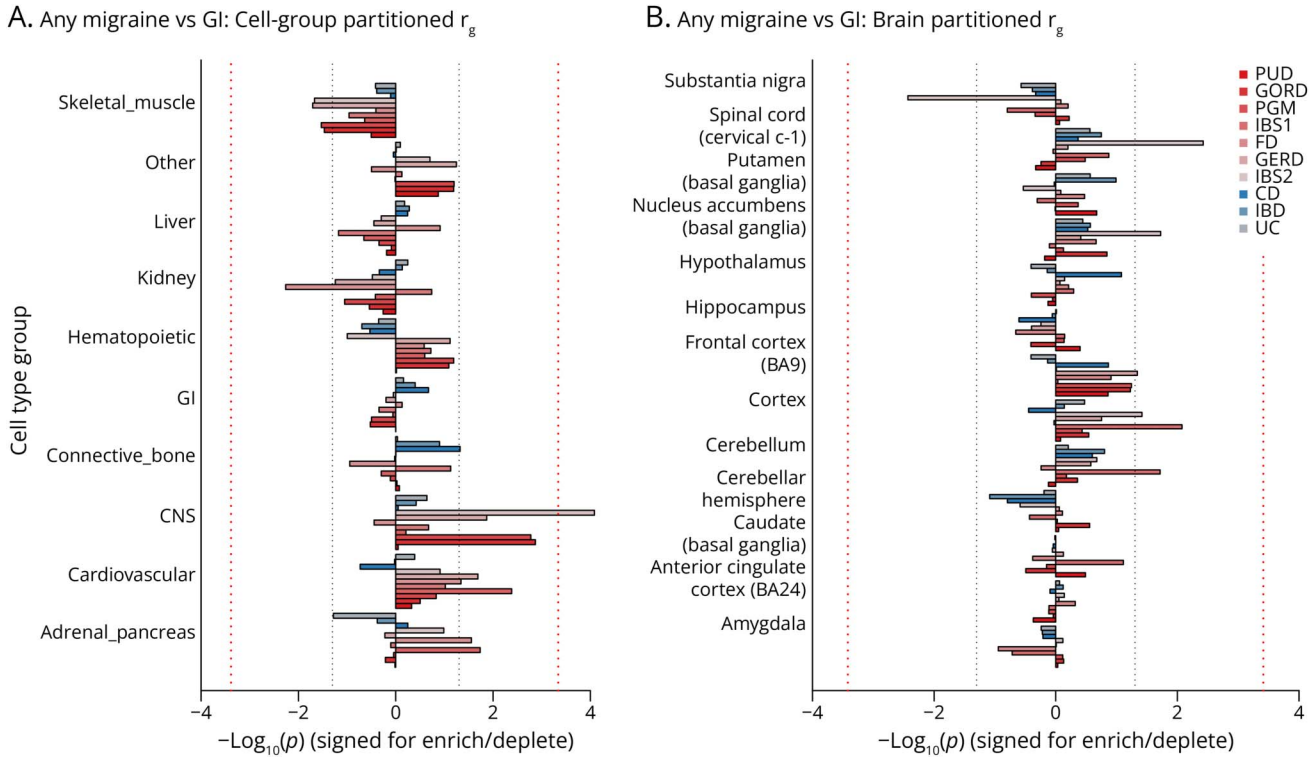
GI condition (abbreviation)	r_g (SE)	p Value
Irritable bowel syndrome (IBS2)[12]	0.37 (0.04)	1.0×10^{-21}
Irritable bowel syndrome (IBS1)[11]	0.37 (0.05)	6.6×10^{-15}
Gastroesophageal reflux disease (GERD)[13]	0.34 (0.03)	2.2×10^{-31}
Functional dyspepsia (FD)[15]	0.34 (0.03)	2.2×10^{-31}
Peptic ulcer, GORD, medication (PGM)[11]	0.34 (0.03)	9.2×10^{-32}
Gastro-oesophageal reflux disease UKB (GORD)[11]	0.31 (0.03)	3.8×10^{-22}
Peptic ulcer (PUD)[11]	0.29 (0.05)	5.4×10^{-9}
Diverticular disease (DD)[14]	0.18 (0.04)	7.5×10^{-7}
Inflammatory bowel disease (IBD)[16]	0.04 (0.04)	2.9×10^{-1}
Crohn's disease (CD)[16]	0.02 (0.04)	5.3×10^{-1}
Ulcerative colitis (UC)[16]	0.02 (0.05)	6.7×10^{-1}

Enrichment of the strong signal for genome-wide genetic correlations of migraine with non–immune-mediated GI conditions according to transcriptional activity in specific tissues was only observed at experiment-wide significance ($p < 5 \times 10^{-4}$) for IBS2 and CNS tissues (Figure 1A, eTable 3A). Genetic correlations with GERD, GORD, and the composite diagnosis PGM were nominally significantly ($p < 0.05$) enriched in CNS tissues. Enrichment was nominally significant for IBS1, GERD, and FD in cardiovascular tissues; for IBS1 and FD in adrenal/pancreas tissues; and for several other combinations of tissue and GI condition. Conversely, there was nominally significant depletion of the genetic correlation signal among genes expressed in the kidney for FD and in the skeletal muscle for GERD, GORD, IBS2, and PGM. Moreover, in GI-derived tissues, there was depletion (although nonsignificant) of the genetic correlation signal between migraine and the nonimmune disorders except PUD and FD.

A subanalysis of enrichment in brain tissues only had limited power but reached nominal significance in 6 of 13 brain subregions for IBS1 or IBS2, in comparison with only 2 of the 13 brain subregions in total for the remaining 9 GI conditions (Figure 1B, eTable 3B). Patterns of enrichment were similar for MO but diverged for MA, where the most significant (but still only nominally significant) enrichment was for GERD and hematopoietic tissues, although not all these analyses returned stable values likely because of the limited GWAS sample size (eFigure 1 and eTables 4 and 5).

Strong pairwise local genetic correlation, i.e., limited to specific segments, may augment insights from genome-wide genetic correlation analysis. Indeed, local genetic correlation using the primary analytic approach (Methods) revealed a total of 22 loci, 8 of which were significant using an alternative approach to local heritability ($p < 0.0023$ [=0.05/22]) and additional 4 of which met nominal significance ($p < 0.05$) (Table 2). The candidate loci could be grouped into largely distinct sets of loci shared between migraine and each of the various GI conditions (including the immune-mediated conditions) with very little overlap. Thus, the 3 loci shared by migraine and IBS1 were distinct from the 4 loci shared with GERD, PUD, or PGM, which were again distinct from 8 loci shared with DD. Of the total of 9 segments correlated between migraine and the immune-related disorders, only 2 were also correlated with another disorder (both DD). Another segment correlated between migraine and DD was also correlated with IBS1. Local genetic correlations implied concordant genetic effects between migraine and GI (i.e., same sign, "[+]," Table 2) at most of the loci, although there were inversions at 4 segments ("[-]," Table 2). Loci that had already been identified by GWASs for each trait alone (or their LD proxies) map to some of these shared segments, including top migraine variants rs10166942

Figure 1 Enrichment of Genome-Wide Genetic Correlation Between Any Migraine[3] and Various GI Conditions in Regions of the Genome With Transcriptionally Active Chromatin According to Tissue Type[2,11]



Disease designations are given in Methods and Table 1. (A) Tissue type defined by aggregated cell-type groupings. (B) Tissue type defined by subregions of the brain. The red dashed line indicates significance threshold consistent with multiple testing; the black dashed line indicates significance threshold for nominal significance. CD = Crohn disease; DD = diverticular disease; FD = functional dyspepsia; GERD = gastrointestinal reflux; GI = gastrointestinal; GORD = gastro-oesophageal reflux disease; IBD = inflammatory bowel disease; IBS = irritable bowel syndrome; PUD = peptic ulcer disease; UC = ulcerative colitis.

(w/IBS1), rs7511672 (w/GERD, PGM), and rs11153083 (w/UC and IBD, the composite of the immune-related GI conditions).[3,4] Additional loci for migraine had been prioritized recently through gene-based transcriptome-wide association testing (IHGC TWAS label) (eTable 6).[29] The 7 significant segments for which no GWAS locus is known identify novel candidate associations of migraine, IBS1, GERD/GORD, PUD, DD, and the immune-related GI disorders. Local genetic correlation with the migraine subtypes reflected much smaller samples and lower power than with migraine overall but nevertheless identified segments for MA (N = 7) or MO (N = 9) and the GI conditions, some of which coincided with known migraine or GI loci (eTables 1 and 7). However, only the signal between MA and CD on chromosome 5 was validated by the alternative local statistic after accounting for testing of the several candidates while additional 2 segments for MA and 3 segments for MO were validated at nominal significance.

Enrichment of the expression of genes mapping to segments with significant local genetic correlation highlighted tissues that may be relevant to genetic signals shared by migraine and the GI conditions (Table 3, Methods). The top enrichment involved expression in the pituitary of genes in segments shared by migraine and IBS1, with additional significant enrichments for the cerebellum and thyroid. For migraine and PUD, enrichment highlighted the prostate as most significant, followed by the pituitary, cerebellum, and skin. Other pairs had enrichment signals that met nominal significance, including pituitary and thyroid for the combination of migraine and GERD, but these enrichments were not significant after accounting for multiple testing. For local genetic correlation involving migraine subtypes, enrichment of the shared genetic signal in segments was most significant for the prostate (MA and IBD or FD) and pituitary (MO and IBD), although, again, these analyses had much less power than was available for migraine overall (eTable 8).

Genetic association at specific candidate loci involved in established treatments may provide additional insight into shared mechanisms (Table 4). Target protein(s) for TCAs, the class of drugs that are used to treat either IBS or migraine, have not been established and thus are not suitable for candidate genetic analysis. However, serotonin transactions, which are affected by TCAs, are believed to be important for both IBS and migraine. Moreover, treatment of some IBS cases may involve selective serotonin reuptake inhibitors (SSRIs) to target a solute transporter (*SLC6A4*) and its downstream effector the cholecystokinin B receptor

Table 2 Local Genetic Correlations Between Migraine and GI Conditions[a]

seg (chr:start-end)[b]	seg size (Mb)	Local correlation (GI [rho sign] rho *p* value)	LAVA replication	GWAS index SNP(s)[c]	mig candidate gene annotation[d]
2:234699366-235626316	0.93	IBS1 [+] 3.4e-08	*IBS1	rs10166942 ([-] 9.35e-51, mig)	*near TRPM8*
5:90504842-93602613	3.10	IBS1 [+] 5.2e-06	**IBS1	—	—
9:136429816-136979539	0.55	IBS1 [-] 2.6e-08	¯IBS1	—	—
1:65010679-66773349	1.76	PGM [+] 1.4e-05, GERD [+] 2.3e-06	*PGM, *GERD	rs7511672 ([-] 1.43e-09, mig), rs12064884 ([+] 5.2e-09, PGM)	*near LEPR*
2:156568806-158165818	1.60	PUD [+] 4.1e-06	**PUD	—	—
4:103388441-104802530	1.41	PGM [+] 1.2e-05, GERD [+] 2e-05	*GERD, ^{O}PGM	—	—
15:80637749-81604871	0.97	PGM [+] 1.7e-06, GERD [+] 5.5e-06	**GERD, ^{O}PGM	rs12708529 ([-] 8.11e-10, mig)	*ABHD17C*
2:202830132-204814896	1.98	DD [+] 2.8e-09, IBS2 [+]7.8e-08	**DD, *IBS	rs138556413 ([-] 4.15e-16, mig)	*CARF*
4:150634191-153226998	2.59	DD [+] 1e-06	**DD	—	—
5:121485609-122603725	1.12	DD [+] 3.9e-07	¯DD	rs11957829 ([+] 1.58e-09, mig), rs246326 ([+] 6.8e-10, mig), rs34126945 ([+] 1.2e-08, DD)	*near ZNF474, SNX24*
14:58449526-59135770	0.69	DD [-] 2.7e-07		rs28756401 ([-] 6.4e-09, mig)	*near ARID4A*
16:18065944-20054371	1.99	DD [+] 1.7e-06	**DD	—	—
16:74730819-75517115	0.79	DD [+] 4.4e-21, IBD [+] 1.9e-13, UC [+] 2.2e-18	*DD, ^{O}IBD, ^{O}UC	rs8046696 ([NA] 4.76e-14, mig)	*CFDP1*
17:6976284-7723513	0.75	DD [+] 1.1e-08	*DD	rs34914463 ([-] 2.41e-09, mig), rs12942267 ([-] 6.7e-11, DD)	*ZBTB4*
1:39537291-40933221	1.40	CD [+] 2.2e-06	¯CD	rs1472662 ([+] 1.75e-08, mig)	*MACF1*
3:18457304-18886128	0.43	IBD [+] 5.6e-06, CD [+] 7.2e-06	N/A	—	—
6:32424108-32682443	0.26	IBD [-] 1.7e-06	^{O}IBD	rs144614916 ([-] 0e+00, IBD)	
6:94920611-97093037	2.17	IBD [+] 5.2e-09, UC [+] 1.1e-09	*IBD, *UC	rs11153082 ([+] 7.26e-54, mig)	*FHL5*
7:2480729-2930941	0.45	UC [+] 1.3e-07	N/A	rs798502 ([+] 1.2e-08, UC)	—
9:4591655-5273194	0.68	IBD [+] 7.7e-06, IBD [+] 1.9e-08, CD [+] 3.1e-07, UC [+] 7.6e-07	N/A	rs36051895 ([-] 8.5e-10, IBD), rs10758669 ([-] 0e+00, IBD), rs10758669 ([-] 4.5e-11, CD), rs10758669 ([-] 4.1e-14, UC)	—
9:69576527-71968825	2.39	IBD [-] 1.7e-05, DD [-] 9.4e-11	**DD, ^{O}IBD	rs7034179 ([-] 1.6e-16, mig)	*TJP2*
18:55808692-56752598	0.94	IBD [-] 1.8e-05	^{O}IBD	—	—

Abbreviation: CD = Crohn disease; DD = diverticular disease; GERD = gastrointestinal reflux; GWASs = genome-wide association studies; GWASs = genome-wide association studies; IBD = inflammatory bowel disease; IBS = irritable bowel syndrome; PUD = peptic ulcer disease; UC = ulcerative colitis.
LAVA replication codes: *nominal significance ($p < 0.05$), **Bonferroni significance ($p < 0.002$), ¯not significant, and ^{O}no solution; N/A segment does not have significant migraine heritability in LAVA and not eligible for genetic correlation.
Disease designations are given in Methods and Table 1.
[a] Local correlation with migraine from SUPERGNOVA using summary statistics from the IHGC (2016).[3]
[b] Genome coordinates from build human genome GRCh37/hg19.
[c] GWAS index SNPs for migraine from the IHGC (2022)[4] or for GI conditions as indicated in eTable 1.
[d] Gene annotation for migraine from the IHGC (2022).[4]

(*CCKBR*) while abortive migraine treatment may involve triptans or ditans to target a serotonin receptor (*HTR1F*).[4,30] Variants at the *CCKBR*[11] and *SLC6A4*[31] loci have been identified in previous GWASs for several clinical measures, notably for GORD/GERD and PUD at CCKBR.[31] Neither *SLC6A4* nor *CCKBR* showed genetic association or local genetic correlation with migraine. Similarly, while *HTR1F* has a strong genetic signal in the GWAS

Table 3 GTEx Tissue Expression Enrichment in Significant Locally Correlated Segments With Any Migraine[3]

GI	Tissue	*p* Value[a]
IBS1	Pituitary	0.0021
	Brain...Cerebellum	0.0037
	Thyroid	0.0077
	Brain...Cerebellar.Hemisphere	0.0096
PUD	Prostate	0.0050
	Pituitary	0.0079
	Skin...Not.Sun.Exposed.Suprapubic	0.0182
	Brain…Cerebellum	0.0303
GERD	Pituitary	0.0155
	Thyroid	0.0196
IBD	Skin…Not.Sun.Exposed..Suprapubic	0.0250
	Skin…Sun.Exposed..Lower.leg	0.0368
CD	Spleen	0.0493

Abbreviations: CD = Crohn disease; GI = gastrointestinal; IBD = inflammatory bowel disease; IBS = irritable bowel syndrome; PUD = peptic ulcer disease.
[a] Empirical *p* value corrected for 54 GTEx tissues tested by 10,000-fold resampling (Methods). *p* Values <0.0045 (=0.05/11) are significant accounting for comparisons of migraine with the 11 GI conditions. Disease designations are given in Methods and Table 1.

of migraine,[4] there was no corresponding genetic signal for the GI conditions.

By contrast, candidate analysis in the calcitonin gene-related peptide (CGRP) pathway that is targeted for migraine revealed potential shared mechanisms (Table 4). Variant rs1003194 adjacent to the *CALCA/CALCB* genes, encoding CGRP, was associated with both migraine and several of the GI conditions, as noted previously,[14,32,33] and there was strong local genetic correlation in the segment encompassing this gene. For GORD, GERD, and IBS2, the local genetic correlations were inverse such that genetic variation that increases the risk of migraine decreases the risk of GI, as was also reflected by associations with GORD and GERD at the lead SNP. However, for DD, CD, UC, and the composite IBD, the associations were concordant and more significant, for both the lead SNP and the local correlation, exceeding significance thresholds consistent with multiple testing. Results for all 4 candidate loci were similar in analysis of the migraine subtypes MA and MO (eTable 9).

Although shared genetics of migraine and the GI conditions may suggest shared pathophysiology, genetic relationships may also imply causality, as formalized from Mendelian randomization (MR). At a significance threshold consistent with multiple testing, there was no MR signal to support liability to migraine as a causal influence on the GI outcomes (Table 5). However, the reverse relationship, i.e., liability to some GI conditions as a cause of migraine, was strongly supported, especially for PUD, GERD, PGM, and DD. The estimated odds ratio for increased migraine per doubling in the prevalence of these conditions was greatest for DD (OR [95%CI], p = 1.90 [1.35–2.68], 2.2×10^{-4}). The estimate of this effect was stronger for migraine with aura (MA) (4.15 [1.49–11.56], 0.0065) than any migraine or migraine without aura (MO) (1.66 [0.66–4.16], 0.28) (eTable 10). However, there was no effect of IBS. Strong associations were preserved in standard MR sensitivity analyses, although valid SNP instruments were not available for all comparisons (eTables 11 and 12). These strong positive associations were in sharp contrast to the lack of association for the immune-mediated GI conditions, as reported previously for IBD.[34]

Discussion

The very substantial comorbidity of migraine and non–immune-related GI conditions is here recapitulated in strong and highly significant genetic correlations on a population basis, as was previously shown for IBS in the family-based setting.[10] These genetic correlations were enriched most in genomic regions expressed in CNS, reaching experiment-wide significance for IBS2 (i.e., the most stringent definition for IBS), with additional nominally significant enrichments in cardiovascular and adrenal/pancreas tissues among others and some differences across the various GI conditions. However, there was uniformly no enrichment—or possibly even depletion—of genetic correlation signal in genomic regions that are expressed in GI tissues, including upper GI tissues. This finding was perhaps surprising because it has been previously shown that the migraine heritability signal is enriched in these regions.[3,4] It may imply that there are additional GI-related functions also involved in the genetics of migraine, with genetics separate from the GI conditions studied here. By contrast, the heritability signals for PUD, PGM, and GORD/GERD previously showed enrichment in regions expressed in CNS and/or adrenal/pancreas tissues but not GI tissues.[11] Together with the enrichment of the local genetic correlation signal in segments with elevated gene expression in the cerebellum, these observations point to a predominant role for neurologic function and perhaps the vasculature in the genetic correlations with migraine rather than intrinsic GI cellular function, e.g., smooth muscle function, which might be shared with the vasculature. However, there were clear differences among the relationships of migraine to the various GI disorders as delineated in the local genetic correlation analysis, including the candidate locus analysis, and in the Mendelian randomization. Such distinctions in shared genetics provide a unique dimension of support to the presence of several distinct etiologies, corresponding to the distinct GI diagnoses and potentially differential treatment recommendations, despite shared symptoms.[11] Known migraine or GI loci in shared segments may provide recognizable clues to relevant shared pathways while significant segments that do not include known

Table 4 Association and Genetic Covariance at Candidate Loci Between Any Migraine and the GI Conditions

	CCKBR		*SLC6A4*		*HTR1F*		*CALCA/CALCB* (*CGRP* gene)	
SNP	rs10500661 [C/T][a]		rs2020942 [T/C][a]		rs6795209 [A/G][a,b]		rs1003194 [A/G][a,b]	
chr:pos[c]	chr11:6273744		chr17:28546913		chr3:88210464		chr11:15126085	
seg[c]	6011761–6917273		27885675–29259899		87408634–88725583		14936943–16789155	
Trait	**SNP beta (SE), *p*[d]**	**rho *p*[e]**	**SNP beta (SE), *p*[d]**	**rho *p*[e]**	**SNP beta (SE), *p*[d]**	**rho *p*[e]**	**SNP beta (SE), *p*[d]**	**rho *p*[e]**
Any migraine	−0.0056 (0.0084), 0.50	NA	−0.0049 (0.007), 0.48	NA	0.03 (0.0097), 0.0024	NA	0.028 (0.0073), 1.3e-04	NA
MO	0.0044 (0.025), 0.86	NA	0.0029 (0.021), 0.89	NA	0.069 (0.031), 0.025	NA	0.061 (0.022), 6e-03	NA
MA	−0.0021 (0.023), 0.93	NA	0.019 (0.019), 0.33	NA	0.03 (0.027), 0.26	NA	0.037 (0.02), 0.065	NA
PUD	0.10 (0.013), 4.1e-14	[−] 0.04	0.002 (0.011), 0.86	[+] 0.87	−0.0093 (0.016), 0.55	[−] 0.44	−0.0084 (0.012), 0.47	[−] 0.42
GORD	0.024 (0.0079), 0.0021	[+] 0.96	0.0021 (0.0066), 0.75	[+] 0.78	0.015 (0.0089), 0.10	[+] 0.18	−0.015 (0.0067), 0.024	[−] 0.0012
PGM	0.043 (0.0064), 9.7e-12	[−] 0.95	0.00074 (0.0053), 0.89	[+] 0.78	0.0077 (0.0072), 0.28	[+] 0.77	−0.011 (0.0054), 0.049	[−] 0.01
IBS1	−0.019 (0.011), 0.076	[−] 0.85	0.01 (0.0088), 0.24	[+] 0.87	-3e-04 (0.012), 0.98	[+] 0.43	−3e-04 (0.009), 0.97	[+] 0.50
GERD	0.037 (0.0073), 3.6e-07	[−] 0.68	0.008 (0.006), 0.19	[+] 0.83	0.011 (0.0083), 0.20	[+] 0.77	−0.0078 (0.0061), 0.20	[−] 0.04
IBS2	−0.0041 (0.0088), 0.64	[+] 0.95	0.005 (0.007), 0.47	[+] 0.64	0.006 (0.011), 0.60	[+] 0.62	0.00 (0.007), 1.00	[−] 0.04
DD	−0.0013 (0.00067), 0.064	[+] 0.44	0.0011 (0.00055), 0.039	[+] 0.86	0.0011 (0.00075), 0.16	[+] 0.28	0.0019 (0.00056), 8.8e-04	[+] 0.0015
FD	NA, 0.56	[+] 0.16	NA, NA	[−] 0.93	NA, NA	[−] 0.26	NA, 0.61	[−] 0.46
IBD	−0.033 (0.02), 0.10	[−] 0.62	0.0091 (0.017), 0.60	[+] 0.91	0.0061 (0.023), 0.79	[−] 0.84	0.063 (0.018), 5.4e-04	[+] 0.00011
CD	−0.021 (0.028), 0.45	[−] 0.74	−0.019 (0.024), 0.41	[−] 0.98	0.043 (0.031), 0.16	[+] 0.33	0.05 (0.025), 0.043	[+] 0.02
UC	−0.044 (0.025), 0.082	[−] 0.50	0.027 (0.022), 0.21	[+] 0.88	−0.019 (0.029), 0.50	[−] 0.31	0.063 (0.023), 0.0058	[+] 0.002

Abbreviations: CD = Crohn disease; DD = diverticular disease; FD = functional dyspepsia; GERD = gastrointestinal reflux; GORD = gastro-oesophageal reflux disease; IBD = inflammatory bowel disease; IBS = irritable bowel syndrome; MA = migraine with aura; MO = migraine without aura; NA = not applicable or not available; PUD = peptic ulcer disease; UC = ulcerative colitis.
[a] Letters [A1/A2] refer to the coded (A1) and reference (A2) alleles.
[b] These SNPs reach genome-wide significance for migraine in the most recent GWAS, IHGC (2022).[4]
[c] Genome coordinates from GRCh37/hg19. Disease designations are given in Methods and Table 1.
[d] SNP associations from GWAS summary statistics (eTable 1).
[e] *p* Value (rho p) from the SUPERGNOVA analysis of segments containing candidate locus. Genetic correlation sign [+/−].

associations identify novel candidate loci for migraine, the GI conditions, or both.

Findings were substantially but not entirely concordant for IBS1 and IBS2, the 2 separate GWASs for IBS. For example, the estimates of the strong genetic correlation were comparable, but there were notable differences in the lack of enrichment for IBS1 in CNS tissues and the greater number of significant local segments for IBS1 that did not overlap with the single segment for IBS2. Despite high genetic correlation between IBS1 and IBS2 ($r_g = 0.86, p = 7 \times 10^{-96}$), differences in findings may be related to markedly different ascertainment of samples for GWASs. Cases in the IBS1 GWAS (no. of cases = 28,518) were derived solely from the UKB and based only on ICD10 code K58 for IBS while excluding individuals also coded for IBD. By contrast, the IBS2 GWAS was a meta-analysis combining summary statistics from the UKB and those from cohorts and other biobanks in the Bellygenes Initiative (no. of cases total = 53,400 as 40,548 [UKB] and 12,852 [Bellygenes]). IBS2 cases from the UKB were derived in large part from a supplemental web-based digestive health questionnaire implementing validated tools, including instruments capturing Rome III criteria (the recognized standard diagnostic criteria for IBS). ICD10 K58 was included as a criterion but only conditional on hospitalization and contributed only 10.4% of the UKB cases. Cases derived from Bellygenes used cohort-specific criteria. As such, and with 7 GWAS hits for IBS2 compared with only 2 for IBS1, genetic findings for the IBS2 GWAS may better capture IBS disease etiology.

The genetic correlation analysis in conjunction with MR may refine thinking about the mechanisms of comorbidity between migraine and GI conditions, at least from the perspective of genetic susceptibility. There was no evidence for a causal relationship, in either forward or reverse direction, between migraine and IBS despite the strong genetic correlation. This dichotomy suggests that the comorbidity is

Table 5 Bidirectional Mendelian Randomization Between Any Migraine and the GI Conditions

Exposure Outcome	Any migraine GI		GI Any migraine	
GI	**OR (CI)[a], *p***	**n SNPs**	**OR (CI)[a], *p***	**n SNPs**
IBS2	1.03 (1.00–1.06), 0.092	38	1.03 (0.93–1.13), 0.61	7
IBS1	1.03 (0.99–1.06), 0.15	38	NA	NA
PUD	1.01 (0.97–1.06), 0.61	38	1.08 (1.03–1.13), 0.0025	7
GORD	1.00 (0.97–1.03), 0.98	37	1.12 (1.02–1.22), 0.012	8
GERD	0.99 (0.97–1.02), 0.56	37	1.12 (1.06–1.18), 4.6e–05	28
PGM	1.01 (0.99–1.03), 0.46	37	1.14 (1.07–1.22), 8.7e–05	21
DD	1.00 (1.00–1.01), 0.023	35	1.90 (1.35–2.68), 2.2e–04	59
IBD	1.07 (0.99–1.14), 0.081	37	1.00 (0.99–1.00), 0.26	96
CD	1.07 (0.97–1.18), 0.15	37	0.99 (0.99–1.00), 0.02	73
UC	1.03 (0.94–1.12), 0.57	37	1.00 (0.99–1.01), 0.72	53

Abbreviations: CD = Crohn disease; DD = diverticular disease; FD = functional dyspepsia; GERD = gastrointestinal reflux; GI = gastrointestinal; GORD = gastro-oesophageal reflux disease; IBD = inflammatory bowel disease; IBS = irritable bowel syndrome; MA = migraine with aura; MO = migraine without aura; PUD = peptic ulcer disease; UC = ulcerative colitis.
[a] Odds ratio and 95% confidence interval [OR (CI)] for outcomes per doubling of the odds for the exposure.[28] NA = fewer than 5 independent SNP instruments available for the exposure. Disease designations are given in Methods and Table 1.

largely due to shared latent secondary etiologic pathways, rather than a primary etiologic pathway unique to either. In sharp contrast, for GERD/GORD, PUD, and DD, which also had strong genetic correlation with migraine, there was a strictly unidirectional MR signal supporting susceptibility mechanisms of the GI conditions as causes of migraine with no support for reverse causality. If there had been a primary shared neurologic cause, the findings might have been bidirectional. For example, potential shared neurologic pathways related to serotonin metabolism were not supported, although the serotonin pathway is targeted for treatment of migraine directly with triptans and ditans and the GI conditions indirectly with tricyclic antidepressants.[8,9] Similarly, bidirectional associations might have been expected if there had been a shared primary causal effect due to features of smooth muscle, e.g., in the GI and vascular systems. Enrichment of the local genetic correlation of GORD and PUD with migraine in thyroid and pituitary tissues may suggest a causal role of energy balance and/or homeostasis that, in turn, may underlie connections linked by diet or even the microbiota, both potential targets for therapeutic intervention, for example.[35] There were no such tissue enrichments in local correlation analysis for DD, whose inferred causal effect on migraine was almost twice as large (or larger for MA) as for GERD/GORD or PUD, reinforcing the theme of biological differences across the various GI conditions despite extensive comorbidity and shared symptoms. However, the strong genetic correlations of these same GI conditions with migraine likely imply additional shared etiologic susceptibilities beyond the unidirectional causal, i.e., from GI to migraine, relationships.

A new class of treatment of migraine targets the CGRP pathway, either through CGRP (a peptide) directly or its receptor, which is distributed across many tissues including the brain and GI system. Genetic associations at the CGRP locus (*CALCA/CALCB* genes) were inverse for migraine and the GI conditions that have concordant genome-wide genetic correlation, i.e., IBS2, GERD/GORD, PUD, PGM, as reflected in opposite signs of genetic associations at the lead SNP, rs1003194, and negative local genetic correlation in the segment including this locus. However, the signs were not only concordant but also more significant for both DD and the immune-related GI disorders that were otherwise not strongly linked by genetics to migraine. While this finding will require more research, it implies that inhibition of CGRP action may mitigate susceptibility to DD and the immune-mediated disorders. Such studies may need to consider that migraine monoclonal antibody therapeutics targeting CGRP can bind and block function of the 2 CGRP isotypes, α-CGRP and β-CGRP that differ at 3 amino acids, are encoded by neighboring genes *CALCA* and *CALCB*, and are primarily active in the CNS and in the enteric nervous system, respectively. Moreover, for migraine therapeutics targeting the primary CGRP receptor, *RAMP1/CLR*, there may be additional effects on signaling by other ligands of this receptor or an alternative receptor *RAMP1/CTR* (also termed the amylin [AMY1] receptor) that may also be activated by CGRP.[36,37]

The extent to which the findings present a comprehensive view of the shared genetics of migraine with the various GI conditions is limited primarily by the genetic variation that was available in the European ancestry populations used to

derive the summary statistics. Analysis incorporating other ancestries may identify additional relationships, particularly at specific loci that may harbor ancestry-specific variation contributing to risk of migraine and the GI conditions. Inclusion of additional ancestries may also enhance the general conclusions from the genome-wide analysis. However, given the limitation of sample ancestry, potential bias in the findings is likely minimal because the summary statistics were well controlled for population structure. A second limitation is the appreciably less power for the analyses targeting the subclasses of migraine, MA and MO, compared with migraine overall, given the much smaller samples of these subgroups.

To conclude, comparisons of GWAS summary statistics point to involvement of neurologic functions underlying strong genetic overlap between migraine and several non-immune–related conditions of the GI system while also identifying specific shared loci, including novel candidate shared loci. However, the nature of genetic sharing with migraine was distinct across the GI conditions and implied potential differentiated causal impacts of some GI conditions on migraine. Meanwhile, local genetic sharing of migraine and the immune-mediated GI conditions at the *CALCA/CALCB* locus implied potential administration of new migraine drugs targeting CGRP as therapeutics for DD and IBD.

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