

SUPPLEMENTARY NOTE

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Study phenotypes

We examined three phenotypes; all migraine, migraine with aura, and migraine without aura. Our primary analysis of all migraine cases incorporated study samples regardless of ascertainment and included individuals diagnosed with migraine by a doctor as well as those who self-reported migraine by questionnaire. This facilitated the inclusion of a large number of cases for our main analysis, possibly at the expense of some precision in phenotyping, but with the benefit of increased statistical power. Secondary analyses targeting the subtypes (migraine with aura and migraine without aura) included only those samples where individuals could be strictly diagnosed according to classification criteria standardized by the International Headache Society (IHS)¹. For the population-based study samples, this involved assessment of the diagnostic criteria from questionnaire data, whereas for the clinic-based study samples the diagnosis was assigned on the basis of a structured interview by telephone or in person. The stricter diagnosis was required for the subtypes because the migraine aura can be difficult to distinguish from other neurological features that can present as symptoms from unrelated conditions, especially in a questionnaire-based setting.

Study design

In order to detect common genetic variants with small effects on migraine risk, we prioritized collecting genome-wide association (GWA) study data from as many individuals as possible with available migraine information in order to maximize our power to detect associations. Thus, we jointly analyzed the summary statistics from 22 GWA studies provided by collaborators in the International Headache Genetics Consortium (IHGC). The 22 GWA studies were created by merging 33 population-matched case-control samples. All samples contained unrelated individuals of European ancestry and were obtained from six tertiary headache clinics and 27 population-based studies. A description of study design, ascertainment, and phenotyping for each GWA study included in the meta-analysis is given in the next section and summarized in **Supplementary Table 1**. Each study underwent quality control procedures to exclude poorly genotyped individuals and/or markers according to a pre-established IHGC protocol (details given in the following section and **Supplementary Table 3**).

All of the individual GWA studies have been published previously for migraine or other population-based phenotypes, except for the Danish Headache Center (1,771 new cases) and the Tromsø Study (660 new cases) datasets, which represent new data. The 23andMe GWA study dataset has been reported previously for other phenotypes, but not for migraine (30,465 new cases), as is similar for the dataset from the Estonian Genome Center, University of Tartu (813 new cases). The migraine GWA study results from the Swedish Twin Registry have been previously published but have not been included in previous meta-analyses of migraine (1,307 new cases). Several population-based samples were also able to identify new migraine cases within their existing samples since our previous IHGC meta-analysis in 2013² and were thus able to moderately increase the total number of cases they have provided for the current meta-analysis. Therefore, the meta-analysis described here includes data from over 35,000 migraine cases that have not been included in previously published genome-wide association studies.

Description of population-based studies

23andMe

For the 23andMe study, participants were drawn from the customer base of 23andMe Inc. (Mountain View, CA), a consumer genetics company^{3,4}. All participants included in the analyses provided informed consent and answered surveys online according to 23andMe's human subjects protocol, which was reviewed and approved by Ethical & Independent Review Services, a private institutional review board. Samples were genotyped on one of four genotyping platforms. The V1 and V2 platforms were variants of the Illumina HumanHap550+ BeadChip, including about 25,000 custom SNPs selected by 23andMe, with a total of about 560,000 SNPs.

Participants were restricted to a set of individuals who have >97% European ancestry, as determined through an analysis of local ancestry⁵. A maximal set of unrelated individuals was chosen for each analysis using a segmental identity-by-descent (IBD) estimation algorithm⁶. Individuals were defined as related if they shared more than 700 cM IBD, including regions where the two individuals share either one or both genomic segments identical-by-descent. This level of relatedness (roughly 20% of the genome) corresponds approximately to the minimal expected sharing between first cousins in an outbred population.

Participant genotype data were imputed against the March 2012 "v3" release of 1000 Genomes reference haplotypes, phased with Shapelt2⁷. Data were phased and imputed for each genotyping platform separately. Data were phased using a 23andMe developed phasing tool, Finch, which implements the Beagle haplotype graph-based phasing algorithm⁸, modified to separate the haplotype graph construction and phasing steps.

In preparation for imputation, phased chromosomes were split into segments of no more than 10,000 genotyped SNPs, with overlaps of 200 SNPs. SNPs with Hardy-Weinberg equilibrium $P < 10^{-20}$, call rate < 95%, or with large allele frequency discrepancies compared to European 1000 Genomes reference data were excluded. Frequency discrepancies were identified by computing a 2x2 table of allele counts for European 1000 Genomes samples and 2000 randomly sampled 23andMe research participants with European ancestry, and identifying SNPs with a chi squared $P < 10^{-15}$. Each phased segment was imputed against all-ethnicity 1000 Genomes haplotypes (excluding monomorphic and singleton sites) using Minimac2⁹, using five rounds and 200 states for parameter estimation.

After imputation and quality control, 30,465 migraine cases and 143,147 controls from the V1 and V2 platforms were available for analysis. The genetic association test was performed using logistic regression assuming an additive model for allelic effects and controlled for age, sex, and five principal components of genetic ancestry.

ALSPAC

The Avon Longitudinal Study of Parents and Children (ALSPAC)¹⁰ is a population-based birth cohort initially comprising of 14,541 mothers and their children recruited in the former County of Avon, UK between 1991 and 1992. Mothers indicated history of migraine via questionnaire during early pregnancy. Subjects were asked 'Have you ever had any of the following problems: migraine'. Controls subjects indicated the option "No never" and case subjects indicated either options "Yes had it recently" or "Yes in the past, not now". Please note that the study website contains details of all the data that is available through a fully searchable data dictionary (<http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/>).

Centre National de Génomage (CNG) carried out DNA genotyping on the Illumina Human660W-quadruplet array and genotypes were called with Illumina GenomeStudio. PLINK (v1.07) was used to carry out quality control measures on an initial set of 10,015 subjects and 557,124 directly genotyped SNPs. SNPs were removed if they displayed more than 5% missingness or a Hardy-Weinberg equilibrium *P*-value of less than 1×10^{-6} . Additionally SNPs with a minor allele frequency of less than 1% were removed. Samples were excluded if they displayed more than 5% missingness, had indeterminate X chromosome heterozygosity or extreme autosomal heterozygosity. Samples showing evidence of population stratification were identified by multidimensional scaling of genome-wide IBS pairwise distances using the four HapMap populations as a reference, and then excluded. Cryptic relatedness was assessed, in PLINK, using a π -hat of more than 0.125 which is expected to correspond to roughly 12.5% alleles shared IBD or a relatedness at the first cousin level.

8,237 subjects and 526,688 SNPs passed these quality control filters. We imputed this data against the 1000 genomes reference panel (Phase I, v3, March 2012 release) using minimac (v2012.11.16). Genome-wide SNP data was analyzed in a logistic regression in mach2dat (v1.0.18).

Ethical approval for the study was obtained from the ALSPAC Law and Ethics Committee and the Local Research Ethics Committees. All study participants provided informed consent.

ATM

The Australian Twin Migraine (ATM) GWA study includes data from Australian twins and their families. All cases and controls included in this study were unrelated individuals; one individual was selected from each family. The cases (*N* = 1,683; 466 [28%] male, 1,217 [72% female]) were preferentially selected from each family based on migraine severity. The population controls (*N* = 2,383; 1,225 [51%] male, 1,158 [49%] female) were randomly selected from families containing no known migraine cases. For the current study, two subsets of cases were identified: ATM1 encompassing 886 IHS MO cases (154 [17%] male, 732 [83% female]); and ATM2: encompassing 797 self-report (migraine "yes" or "no") cases (312 [39%] male, 485 [61% female]). To allow for potential differences in genetic risk for the different migraine definitions, we utilized a stratified analysis approach where the ATM1 and ATM2 cases were compared to a random selection of 1,586 and 797 of the 2,393 population controls, respectively. The mean

age at interview was 37.5 years (SD = 11.3). All subjects gave informed consent and approval to conduct the research was obtained from the QIMR Human Research Ethics Committee.

Case and control individuals were drawn from our QIMR GWA cohort of over 19,000 individuals genotyped using a variety of Illumina GWA arrays. After strict QC, the observed genotypes were imputed up to 1000 Genomes (Phase I, v3, March 2012 release) using the MaCH program¹¹. Association analysis of allelic dosage scores within a logistic regression framework including sex and strata (ATM1/ATM2) as covariates was performed using the PLINK program¹². For a detailed description of the QIMR 19K GWA cohort, including QC and imputation methodology, see Medland et al. (2009)¹³.

B58C

The British 1958 birth cohort is an ongoing follow-up of all persons born in England, Scotland and Wales during one week in 1958¹⁴. At age 33 years, a history of migraine ever was obtained by interview, whereas at 23 years of age, cohort members had been asked whether they had had migraine or recurrent sick headaches since their 16th birthday. For the purpose of this meta-analysis, cases were defined by a positive interview response for migraine ever at age 33. Controls were defined as cohort members who denied migraine ever at age 33, and reported no migraine or recurrent sick headaches since 16, when interviewed at age 23. Subjects who reported migraine or headaches between 16 and 23, but no history of migraine at age 33, were excluded from the analysis.

At the age of 44–45 years, the participants were followed up with a biomedical examination and blood sampling¹⁵, from which a DNA collection was established as a nationally representative reference panel. Three non-overlapping subsets of the DNA collection were genotyped as part of case-control studies by the Wellcome Trust Case-Control Consortium¹⁶, the Type 1 Diabetes Genetics Consortium¹⁷ and the GABRIEL asthma genetics consortium¹⁸. Imputations were performed using the 1000 Genomes (Phase I, v3, March 2012 release) reference panel by the MACH software¹¹. Within-cohort logistic regression analyses for migraine were performed using ProbABEL¹⁹. Written informed consent was obtained from all participants, and the local ethics committee approved the study.

DeCODE

Icelandic individuals suffering from migraine were recruited from three sources: (1) a list of patients provided by two neurologists (401 potential participants), (2) responses to an advertisement in the newsletter of the Icelandic Migraine Society (137 participants), and (3) responses to a brief screening questionnaire mailed to a random sample of 20,000 Icelanders, aged 18–50 years and living in the Reykjavik area. All recruits were diagnosed based on their answers to the third edition of the deCODE Migraine Questionnaire (DMQ3) for use in genetic studies²⁰. The DMQ3 is a comprehensive migraine questionnaire that was designed based on ICHD-II¹, and validated using a semi-structured, physician-conducted telephone interview as a gold standard. Approval for these studies was provided by the National Bioethics Committee

and the Icelandic Data Protection Authority, and informed consent was obtained from all participants.

EGCUT

The Estonian cohort is from the population-based biobank of the Estonian Genome Project of University of Tartu (EGCUT)²¹. The project is conducted according to the Estonian Gene Research Act, and all participants have signed the broad informed consent. The current cohort size is >51,515, 18 years of age and older, which reflects closely the age distribution in the adult Estonian population. Subjects were recruited by general practitioners (GP) and physicians in the hospitals were randomly selected from individuals visiting GP offices or hospitals. Each participant filled out a computer-assisted personal interview during 1–2 hours at a doctor's office, including personal data (place of birth, place(s) of living, nationality. etc.), genealogical data (three generation family history), educational and occupational history, and lifestyle data (physical activity, dietary habits, smoking, alcohol consumption, women's health, quality of life). For the current study, 813 migraine cases (after quality control) were compared to 9,850 controls from the population. Genotyping was performed on either the Illumina HumanHapCNV370 or OmniExpress array, according to the Illumina protocol (www.illumina.com) in the Estonian Biocenter Genotyping Core Facility.

Health 2000

The Health 2000 study is a national health survey undertaken in Finland consisting of a nationally representative sample of 10,000 persons drawn from the population aged 18 and over. Targets of the study were general health, major chronic conditions, functional ability and limitations, determinants of health, diseases, functional ability and limitations, health needs and service needs and their satisfaction (http://www.terveys2000.fi/background_001.html). Genotyping was performed on the Illumina 370k and after quality control, 136 migraine cases were available for comparison to 1,764 controls from the population. The study was approved by the co-ordinating ethical committee of the Helsinki University Hospital and all study participants provided informed consent.

HUNT

In total, 1,395 Norwegian migraine cases were recruited from the Nord-Trøndelag Health Study (HUNT), in which all inhabitants (age ≥20 years) of the Nord-Trøndelag county of Norway were invited to participate. Participants answered 13 headache questions designed to diagnose migraine according to a modified version of the ICHD criteria²², and to differentiate migraine with and without visual aura. This questionnaire-based classification has been validated by interview diagnoses, yielding positive and negative predictive values for ICHD migraine of 87% and 75% respectively²². The 1,011 Norwegian control samples were recruited from the same HUNT population study (see description above), and included 346 samples previously genotyped as part of a GWA study of lung cancer²³ and 542 samples genotyped as part of an ongoing GWA study of pre-eclampsia, in addition to 123 control samples genotyped for the

present study. Participants fulfilling criteria for migraine were excluded from the control population. Written informed consent was obtained from all participants, and the local ethics committee approved the study.

NFBC

Mothers expected to give birth in the two Northern provinces of Oulu and Lapland in 1966 were enrolled in the NFBC1966²⁴ (N = 12,058 live births). Primary clinical data collection on parents and the child occurred prenatally and at birth. Data collection on the child continued at ages six months, one year, 14 years (no data from one year or 14 years are included in this paper), 31 years, with assessment of a wide range of trait measures. Cohort members still living in Northern Finland and those who had moved to the capital area were invited to a clinical examination at age 31 years (N = 8,463). The attendees (71% response rate, N = 6,007) were adequately representative of the original cohort²⁵. Migraine was assessed based on the health questionnaire survey provided by the participants. The sample was originally genotyped for this study²⁶. The study was approved by the co-ordinating ethical committee of the Helsinki University Hospital and all study participants provided informed consent.

NTR/NESDA

The NTR/NESDA cohort includes participants of the Netherlands Twin Registry (NTR) and the Netherlands Study of Depression and Anxiety (NESDA). Data collection procedures for these studies are described in detail elsewhere^{27,28}. Written informed consent was obtained from all participants, and the local ethics committee approved the study. Individuals were classified as migraineurs based on questionnaire data if they reported enough migraine symptoms to qualify for a diagnosis according to ICHD-II criteria. The questionnaire started with a screening question (“do you ever experience headache attacks, for instance migraine?”). Individuals screening positive answered a set of more detailed questions on their headache symptomatology. Based on these symptom data, a diagnosis was made, following the ICHD-II criteria¹. Details on this procedure can be found in previous work²⁹. Individuals who did not complete the full headache questionnaire but reported a diagnosis of migraine were also classified as cases. The control group consisted of individuals who screened negative for headache. Individuals diagnosed with anxiety or depressive disorder (mostly NESDA participants) were excluded from the analyses

Buccal or blood DNA samples (N = 14,003) were collected for multiple NTR and NESDA projects. DNA extraction and purification of these samples were performed at various points in time, following several manufacturer specific protocols to obtain the best quality and concentration prior to SNP platform genotyping³⁰. Genotyping of several partly overlapping subsets was done on multiple platforms. Chronologically the following platforms have been used Affymetrix Perlegen 5.0, Illumina 370, Illumina 660, Illumina Omni Express 1M, and Affymetrix 6.0. After array specific data analysis, genotype calls were made with the platform specific software (BIRDSUITE, APT-GENOTYPER, BEADSTUDIO).

Quality control was done within and between platforms and subsets prior to imputation. For each platform, the individual SNP markers were lifted over to build 37 (HG19) of the Human reference genome, using the LiftOver tool. SNPs that were not mapped at all, SNPs that had ambiguous locations, and SNPs that did not have matching (or strand opposite alleles) were removed. Subsequently, the data were strand aligned with the 1000 Genomes GIANT phase1 release v3 20,101,123 SNPs INDELS SVS ALL panel. SNPs from each platform were removed if they still had mismatching alleles with this imputation reference set, if the allele frequencies differed more than 0.20 with the reference. From each platform, SNPs with a Minor Allele Frequency (MAF) <0.01 were removed, as well as SNPs that were out of Hardy–Weinberg Equilibrium (HWE) with $p < 0.00001$. Samples were excluded from the data if their expected sex did not match their genotyped sex, if the genotype missing rate was above 10% or if the Plink F inbreeding value was either >0.10 or <-0.10.

After these steps, the data of the individual arrays were merged into a single dataset using PLINK 1.07¹². Within the merged set, identity by state (IBS) sharing was calculated between all possible individual pairs and compared to the known family structure of the NTR study. Samples were removed if the data did not match their expected IBS sharing. DNA samples, which were typed on multiple platforms, were tested to ascertain that the concordance rate among overlapping SNPs exceeded 99.0%. If the concordance rate was lower, we removed all data of these samples. Subsequently, from each MZ twin pair a single DNA sample was selected. The HWE-, MAF- and the reference allele frequency difference <0.20 filters were re-applied in the combined data. As a final step, SNPs with C/G and A/T allele combinations were removed when the MAF was between 0.35 and 0.50 to avoid incorrect strand alignment.

Phasing of all samples and imputing cross-missing platform SNPs was done with MACH 1¹¹. The phased data were then imputed with MINIMAC³¹ in batches of around 500 individuals for 561 chromosome chunks obtained by the CHUNKCHROMOSOME program³². After imputation, DNA confirmed MZ twins were re-duplicated back into the data. The format of the data was transformed to the basic three probabilities SNPTEST gen.gz format, as this is the most general applicable format for the subsequent genomic analyses tools. The mean imputation quality R^2 metric is 0.38 (based on all 30,051,533 imputed autosomal SNPs).

GWA analysis was conducted in Plink, using logistic regression under an additive genetic model and adjusting for sex, genetic ancestry and batch and chip effects. Ancestry was accounted for by inferring ancestry principal components using the EIGENSOFT program³³, as described previously³⁴. In this study the first ancestry PC was included as a covariate. Plink's --family option was used to account for familial relatedness in the data. Genotype imputation uncertainty was accounted for by using allelic dosage.

Rotterdam III

This sample included participants of the Rotterdam Study, a prospective population based cohort study among persons 55 years or older who were living in Ommoord, a well-defined district of Rotterdam, the Netherlands³⁵. The aim of this study was to investigate causes of

frequent chronic diseases, with a focus on cardiovascular, neurologic, psychiatric, and ophthalmic diseases. The Medical Ethics Committee of Erasmus Medical Center approved of the study and all participants provided informed consent. The original cohort of the Rotterdam Study (7,983 participants) was expanded in 2000 ($N = 3,011$) and again in 2006 to include 3,919 persons who were 45 years of age or older. At study entry all participants underwent a structural interview and a physical examination, which was repeated every 3–4 years. The migraine questionnaire was introduced into the core study protocol in 2006 (response rate of 64.8%). For the current report, we used data from persons from the second cohort expansion (2006 to 2008) who completed the migraine questionnaire. Migraine data were available for 2,662 unrelated individuals, including 487 cases and 2,175 controls. The mean age of the sample was 55.37 years ($SD=4.51$)³⁶.

Swedish Twins

The Swedish Twin study consisted of 9,897 Swedish individuals collected by the Swedish Twin Registry³⁷. All experiments on human subjects, human material and human data were performed in accordance with the Declaration of Helsinki. All procedures were carried out with the adequate understanding and written consent of the subjects. Formal approval to conduct the experiments described has been obtained from the human subjects ethical review board of Stockholm (reference number 2007/644-31). The occurrence of migraine was self-assessed through a questionnaire using the criteria for migraine of the ICHD-II¹. Genotyping was done on the Illumina Omni Express chip at the SNP&SEQ Technology Platform, Uppsala University. We followed standard GWA study quality control procedures for missingness (max 0.03 genotypes missing per-SNP), low genotyping rate (max 0.03 genotypes missing per-individual), SNP frequency (minor allele frequency < 0.01), Hardy Weinberg equilibrium ($P \leq 1e-7$) and excluded individuals that were population outliers, heterozygosity outliers, or with incompatible sex assignment based on X chromosome homozygosity. After quality control, data from 642,402 single nucleotide polymorphisms (SNP) remained which we then imputed into the 1000 Genomes (phase I, v3, March 2012) reference panel. We selected one member from each twin pair for inclusion in the study (preferentially selecting cases) and excluded additional related individuals from the sample approximately greater than second cousins ($IBD > 0.185$). After quality control procedures, this resulted in 1,307 migraine cases and 4,182 unrelated control individuals available for analysis.

Tromsø

The Tromsø Study is a population based health study of the Tromsø municipality of Northern Norway. In the 6th wave of the study, which was used in the current study, 19,762 residents were invited and 12,984 (65.7%) participated (53% women, age range 30–87 years). 660 migraine cases and 2,407 controls were genotyped and included in this study. Migraine cases were defined as those who 1) reported suffering from headache during the last year, and satisfied ICHD criteria¹ for migraine, with the modification that instead of requiring "nausea and/or vomiting OR photophobia and phonophobia" as in the original criteria, we required "nausea and/or vomiting", since information on photophobia and phonophobia was not

available. This resulted in a slightly conservative definition of migraine for this group; or 2) self-reported previous or current migraine headache. Subjects who were not classified as migraine sufferers from these criteria were included as controls. Written informed consent was obtained from all participants, and the local ethics committee approved the study.

Twins UK

The study population comprised 4,809 individuals (428 males and 4,381 females) from the TwinsUK Adult Twin Registry³⁸. The twins were volunteers recruited through a national media campaign (www.twins.ac.uk), were not enriched for any particular disease or trait and were representative of the British general population³⁸. Volunteers provided informed consent and were administered a protocol approved by the St. Thomas' Hospital ethics committee. The twins were aged between 16 and 82 years with a standard deviation of 13 years and a mean age of 50 years. We selected 1 member from each twin pair, preferentially selecting cases, and excluded other relatedness within the sample by estimating IBD sharing. Migraine status was ascertained through questionnaires. 618 of the study participants fulfilled the IHS definition of migraine¹, and of these, 202 with typical aura with migraine headache. Samples were genotyped with a combination of Illumina arrays (HumanHap300, and HumanHap610Q). The genotype data was imputed with IMPUTE³⁹ version 2 using 1000 Genomes (Phase I, v3, March 2012 release) combined populations reference panel and the 610Q data was used as a reference panel for the HumanHap300 data. In total, there were 618 cases and 2,334 controls available for analysis after quality control. The imputed genotype data was analyzed with GWAF (Genome-wide association analyses for family data) to test for SNP association with adjustments for age⁴⁰. We used the equations option for logistic regression via generalized estimating of the GWAF software, which incorporates familial clustering.

WGHS

The Women's Genome Health Study (WGHS)⁴¹ is a prospective cohort of initially healthy, female North American health care professionals at least 45 years old at baseline representing participants in the Women's Health Study (WHS) who provided a blood sample at baseline and consent for blood-based analyses. The WHS was a 2x2 trial beginning in 1992–1994 of vitamin E and low dose aspirin in prevention of cancer and cardiovascular disease with about 10 years of follow-up. Since the end of the trial, follow-up has continued in observational mode. Additional information related to health and lifestyle were collected by questionnaire throughout the WHS trial and continuing observational follow-up. Written informed consent was obtained from all participants, and the local ethics committee approved the study.

Genotyping in the WGHS sample was performed using the HumanHap300 Duo “+” chips or the combination of the HumanHap300 Duo and iSelect chips (Illumina, San Diego, CA) with the Infinium II protocol. In either case, the custom SNP content was the same; these custom SNPs were chosen without regard to minor allele frequency (MAF) to saturate candidate genes for cardiovascular disease as well as to increase coverage of SNPs with known or suspected biological function, e.g. disease association, non-synonymous changes, substitutions at splice

sites, etc. For quality control, all samples were required to have successful genotyping using the BeadStudio v. 3.3 software (Illumina, San Diego, CA) for at least 98% of the SNPs. A subset of 23,230 individuals were identified with self-reported European ancestry that could be verified on the basis of multidimensional scaling analysis of identity by state using 1,443 ancestry informative markers in PLINK v. 1.06. In the final dataset of these individuals, a total of 339,596 SNPs were retained with MAF > 1%, successful genotyping in 90% of the subjects, and deviations from Hardy-Weinberg equilibrium not exceeding P -value = 1×10^{-6} in significance. Among these same 23,230 individuals of verified European ancestry, genotypes for a total of 30,052,423 (autosomes) + 1,264,493 (X) SNPs were imputed from the experimental genotypes and phase information from the 1000G phase I v.3 release (March 2012) ALL panel using MaCH (v. 1.0.16) and Minimac (release 5/29/2012). A total of 332,927 genotyped SNPs that were selected by HWE P -value > 1×10^{-6} but unrestricted by MAF could be reconciled with the 1000G ALL panel and were used for imputation.

Young Finns

The Young Finns study (YFS) cohort is a Finnish longitudinal population study sample on the evolution of cardiovascular risk factors from childhood to adulthood⁴². The first cross-sectional study was conducted in the year 1980 in five different centers. It included 3,596 participants in the age groups of 3, 6, 9, 12, 15, and 18, who were randomly chosen from the national population register. After the baseline in 1980 these subjects have been re-examined in 1983 and 1986 as young individuals, and in 2001, 2007 (aged 30–45 years) as older individuals. For the current analysis the latest follow-up was used. This study was carried out in accordance with the recommendations of the Declaration of Helsinki. All participants provided written informed consent and the study protocol was approved by the Ethics Committee.

Genomic DNA was extracted from peripheral blood leukocytes using a commercially available kit and Qiagen BioRobot M48 Workstation according to the manufacturer's instructions (Qiagen, Hilden, Germany). Genotyping was done for 2,556 samples using custom build Illumina Human 670k BeadChip at Wellcome Trust Sanger Institute. Genotypes were called using Illuminus clustering algorithm. 56 samples failed Sanger genotyping pipeline QC criteria (i.e., duplicated samples, heterozygosity, low call rate, or Sequenom fingerprint discrepancy). From the remaining 2,500 samples one sample failed gender check, three were removed due to low genotyping call rate (< 0.95) and 54 samples for possible relatedness (π -hat > 0.2). 11,766 SNPs were excluded based on Hardy-Weinberg equilibrium (HWE) test (P -value = 1×10^{-6}), 7,746 SNPs failed missingness test (call rate < 0.95) and 34,596 SNPs failed frequency test (MAF < 0.01). After quality control there were 2,443 samples and 546,677 genotyped SNPs available for further analysis⁴². Genotype imputation was performed using IMPUTE³⁹ version 2.1.2 and 1000 Genomes Interim Phase I June 2011 haplotypes as reference. Palindromic A/T and C/G SNPs were removed before imputation. After filtering SNPs with low Fisher information (info < 0.4) and MAF (< 0.001) there were 12,569,109 SNPs available.

Description of clinic-based studies

Danish HC

The Danish Headache Center (Danish HC) sample comprised 775 unrelated MA cases (cases with migraine with aura with or without a co-diagnosis of migraine without aura) and 996 unrelated MO cases (cases with migraine without aura only). All cases were recruited among patients at the Danish Headache Center in the years 1999–2002, 2005–2006 and 2010–2011^{43–45}. Migraine history and clinical data were obtained by a validated, extensive, semi-structured interview performed over the telephone or face-to face by a trained physician or a trained senior medical student⁴⁵. The migraine diagnoses adhere to the ICHD-2¹. The 1000 healthy and unrelated controls were recruited among volunteers in the Danish Blood Donor Study (DBDS)⁴⁶. Genotyping was carried out using Illumina HumanOmniExpress-12v1. Genotypes were phased and imputed into the 1000 Genomes phase 1 version 3 (Build 37HG19) using IMPUTE2. DNA extraction, genotyping and imputation was performed by deCODE Genetics, Reykjavik, Iceland. The study was approved by the Danish Ethical Standards Committee. Written informed consent was obtained from all participants.

Dutch MA

The Dutch MA study contains 879 Dutch MA patients that were available from the clinic-based Leiden University Migraine Neuro Analysis (LUMINA) study. After performing standard GWA study quality control procedures, 734 cases remained for analysis. Of the 734 MA cases, 138 (19%) were male and 596 (81%) were female. Self-reported migraineurs were recruited via the project's website (www.lumc.nl/hoofdpijn). A set of previously validated screening questions was used⁴⁷. Participants fulfilling the screening criteria then completed an extended questionnaire that focuses on signs and symptoms of migraine headache and aura as outlined in ICHD-II¹. Individual diagnoses were made using an algorithm based on these criteria and that was validated by a semi-structured telephone interview performed by experienced physicians or by well-trained medical students, when necessary in consultation with a neurologist specialized in headache (GMT)⁴⁸. A subset of the patients was asked to participate upon visiting the outpatient clinic. Population-matched controls (n=5,211 after QC) were obtained from the Rotterdam Study I³⁶. Written informed consent was obtained from all participants, and the local ethics committee approved the study.

Dutch MO

The Dutch MO study contains 1,115 Dutch MO patients, of which 163 (15%) were male and 952 (85%) were female, that were available from the clinic-based Leiden University Migraine Neuro Analysis (LUMINA) study. Self-reported migraineurs were recruited via the project's website (www.lumc.nl/hoofdpijn). A set of screening questions validated previously in a population-based study⁴⁷ was used. Participants fulfilling the screening criteria then completed an extended questionnaire that focuses on signs and symptoms of migraine headache and aura

(aura symptoms were absent in the selected patient group) as outlined in ICHD-II. Individual diagnoses were made using an algorithm based on these criteria, validated by a semi-structured telephone interview performed by experienced physicians or by well-trained medical students, when necessary in consultation with a neurologist specialized in headache (GMT)⁴⁸. A subset of the patients was asked to participate upon visiting the outpatient clinic. Population-matched controls (n=2,028 after QC) were obtained from the Rotterdam Study II (RSII)³⁶. Written informed consent was obtained from all participants, and the local ethics committee approved the study.

Finnish MA

1,032 Finnish patients (or 933 after QC) having either migraine with aura (MA) or migraine with and without aura (MA/MO) were collected nationwide from headache clinics and from the FinnTwin collection (<http://www.nationalbiobanks.fi/index.php/studies2/30-finnish-twin-cohort>). Each patient belongs to a multigenerational migraine family with at least three affected family members. All patients completed the validated Finnish Migraine Specific Questionnaire for Family Studies (FMSQ_{FS})⁴⁹ and all fulfilled the current International Headache Society diagnostic criteria (ICHD-II¹) for MA. In cases of insufficient or conflicting information, a follow-up interview was performed by telephone. 1,018 Finnish control subjects were obtained from FINRISK and 1,697 controls from the Helsinki Birth Cohort study⁵⁰. Written informed consent was obtained from all participants and the study was approved by the Helsinki University Central Hospital local ethics committee.

German MA

The German MA sample consists of 1,071 German patients with MA (after QC). The patients were recruited from a tertiary headache center in Northern Germany (Pain Clinic, Kiel), the University of Bonn, the University of Cologne, and the Department of Neurology at the Klinikum Großhadern of the Ludwig-Maximilians-University, Munich, Germany. All patients were diagnosed as having MA according to the ICHD-II¹ by experienced neurologists with a specialization in headache disorders, as described previously⁵¹. The diagnosis of MA was obtained either by face-to-face interviews or by telephone interviews.

German controls were obtained from the PopGen study⁵² (n = 645) and from the Heinz Nixdorf Recall (HNR) study (n = 365)⁵³, all genotyped on the Illumina 550K platform. Written informed consent was obtained from all participants, and the local ethics committee approved the study.

German MO

The German MO sample of 1,160 MO cases was recruited in Munich and Kiel and data were examined by a headache specialist at the Klinikum Großhadern of the Ludwig-Maximilians-University, Munich, and the Kiel Pain and Headache Center, Kiel. Phenotyping was based on a German translation of the FMSQ_{FS}⁴⁹. Particular emphasis was put on reliable exclusion of aura symptoms. In case of insufficient or conflicting information, an additional telephone interview

was performed. Information was obtained on all aspects of the ICHD-II¹ criteria as well as on other aspects (such as age at onset, prodromal symptoms, triggers, acute and prophylactic medication, family history, general past medical history, co-morbidity and place of birth).

Population-matched controls were obtained from pre-existing previously genotyped studies. German controls were available from the KORA S4/F4⁵⁴ (n = 801) as well as from the GSK⁵⁵ (n = 846). Written informed consent was obtained from all participants, and the local ethics committee approved the study.

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Ethics statement

All participating IHGC studies were approved by local research ethics committees and written informed consent was obtained from all study participants.

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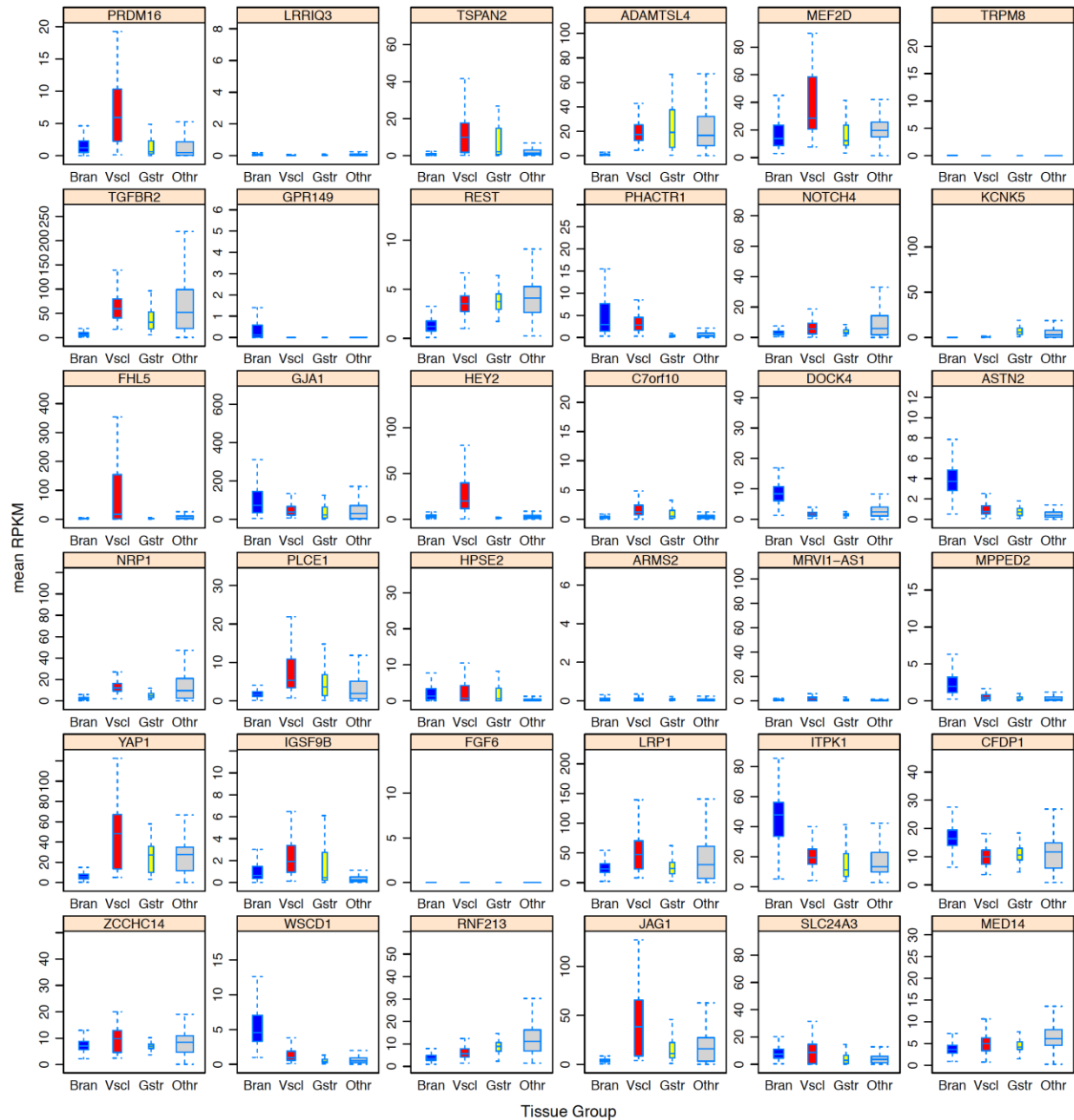
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SUPPLEMENTARY FIGURES

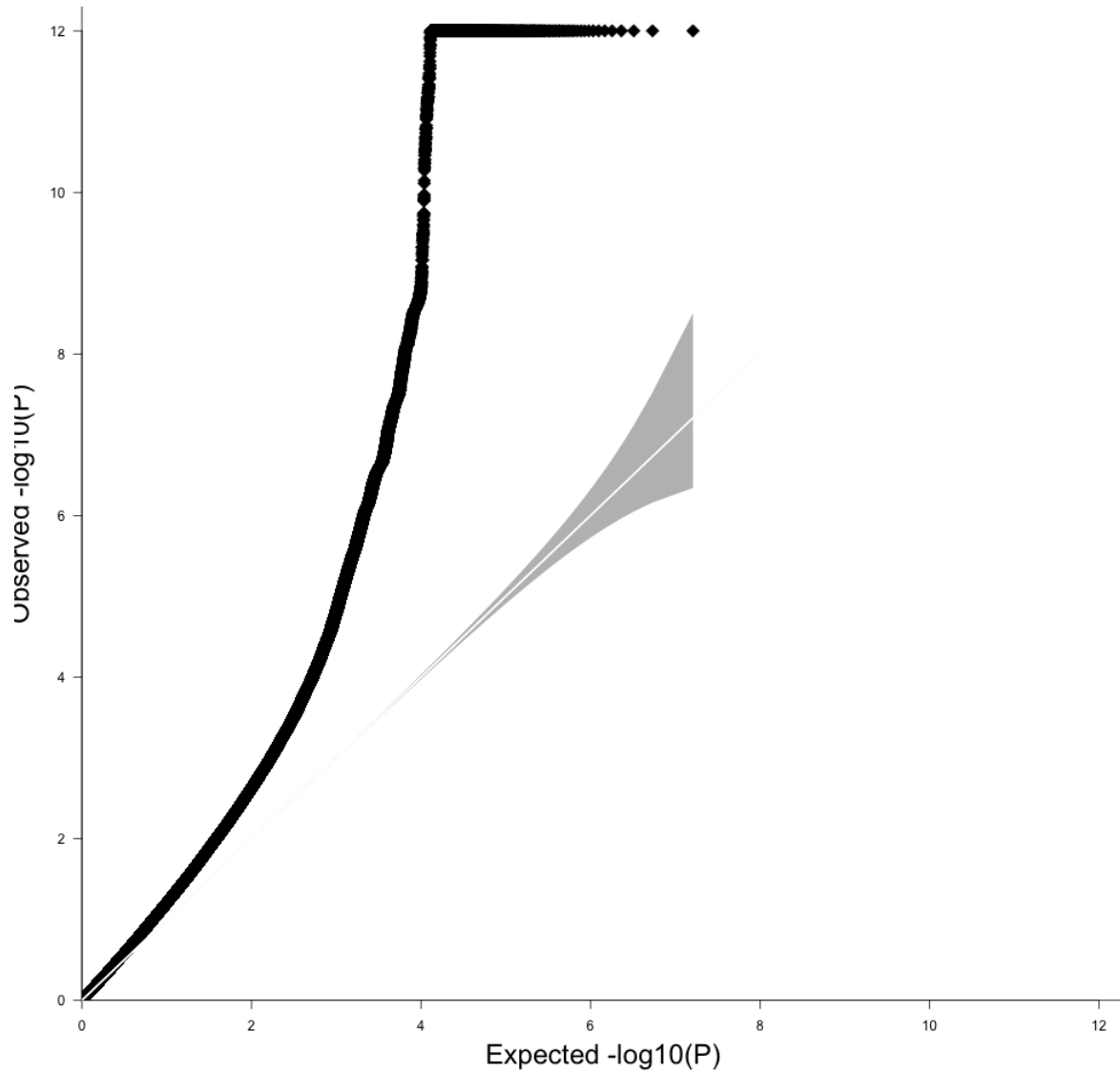
Supplementary Figure 1 (see separate PDF for figure). Forest plots of the 44 independently associated SNPs. For each SNP we plot the minor allele frequency for cases and controls (MAF[case] and MAF[ctrl] respectively) and the corresponding Odds Ratio (OR) from each of the 22 individual GWA studies. A value of “NA” means that the marker was filtered out of that particular study due to not passing genotyping or imputation quality control criteria. We also annotate each plot with the locus label, index SNP (and minor allele), chromosomal position (hg19 co-ordinates), combined meta-analysis association *P*-value, the heterogeneity index (i^2), and the *P*-value from Cochran’s Q test for heterogeneity.

Supplementary Figure 2 (see separate PDF for figure). Regional plots of the 38 genome-wide significant loci. Each point shows the significance level (left vertical axis) of each marker tested for association to migraine by logistic regression using an additive genetic model adjusted for sex. The index SNP for each locus is marked with a diamond and annotated with its corresponding *rs*-number. The solid blue line shows the recombination rate (right vertical axis) and the horizontal axis is the chromosomal position in megabases. The red line is the threshold for genome-wide significance ($p < 5 \times 10^{-8}$). Beneath the horizontal axis the track shows start-end co-ordinates from Gencode genes. Plots are ordered by genomic position.

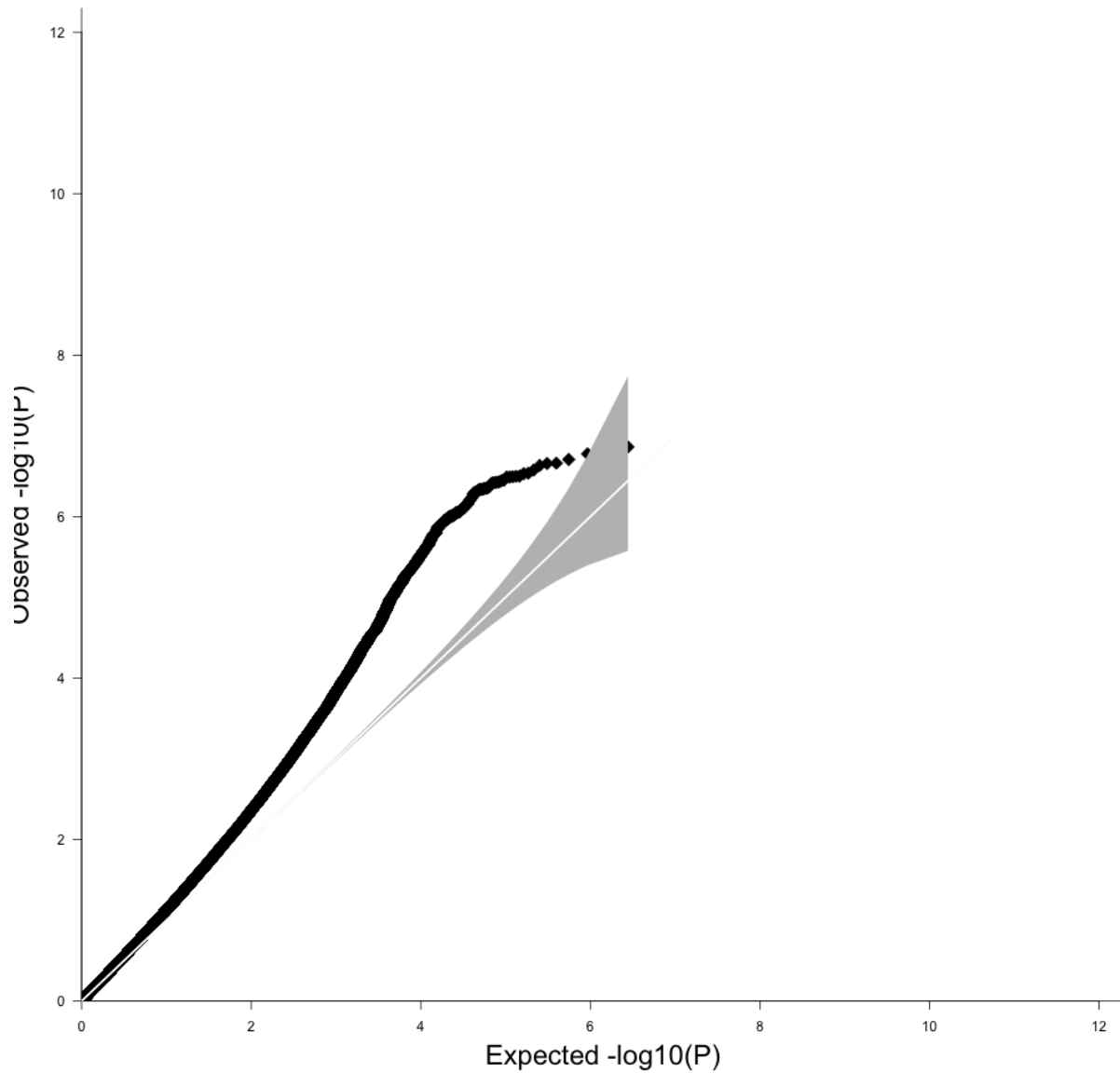
Supplementary Figure 3. Individual gene expression in GTEx tissues. Each panel shows the expression level, measured in reads per kilobase per million reads (RPKM), of the nearest gene to the index SNP at each migraine locus (intergenic loci *CCM2L* and *CARF* are not shown) in four tissue groups. The gene expression data was obtained from 1,641 samples across 42 tissues and three cell lines from the GTEx consortium. The four tissue groups are Brain (Bran), Gastrointestinal (Gastr), Vascular (Vscl), and Other (Othr). The center values of box-plots represent the median and the box itself outlines the interquartile range. These results are described further in **Supplementary Table 25**.



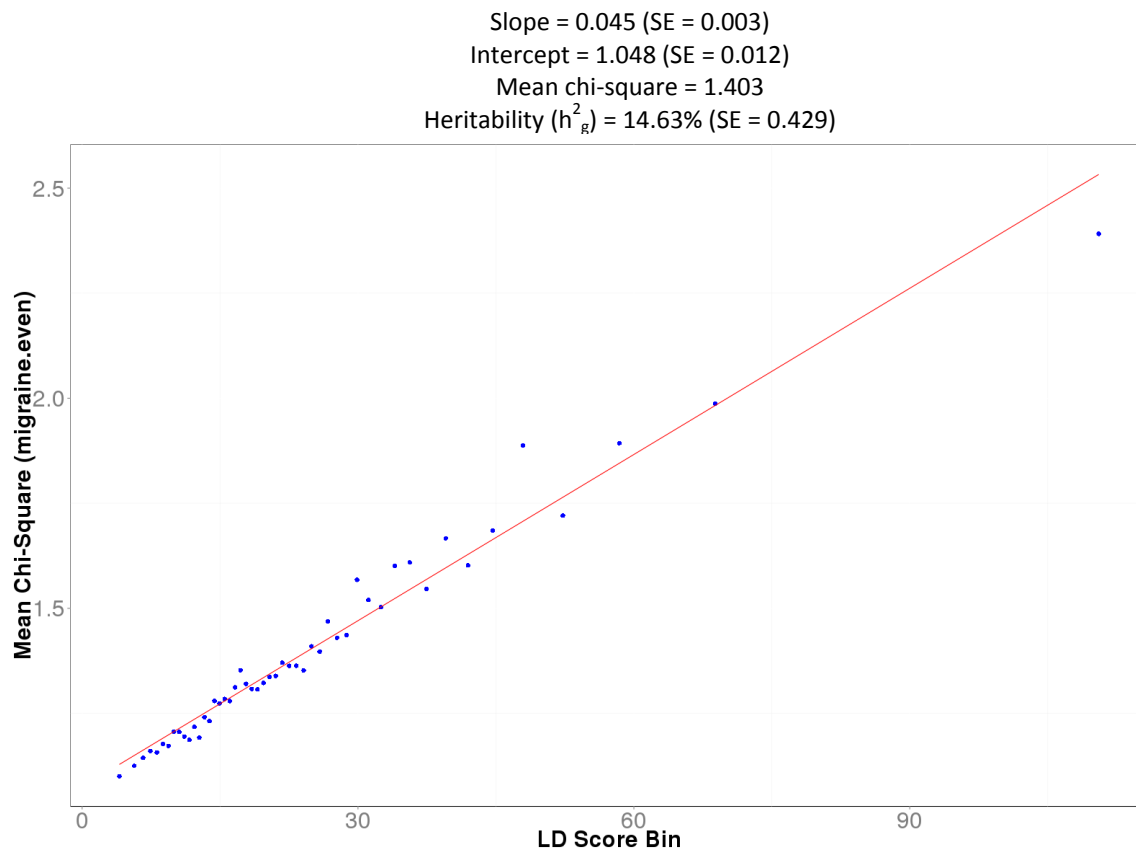
Supplementary Figure 4. QQ-plot of the primary analysis test statistics. In the analysis of all migraine (59,674 cases vs. 316,078 controls), $\lambda_{GC} = 1.24$. For clarity, the observed association P -values along the vertical axis have been limited to a minimum value of 1×10^{-12} . The shaded area represents the 95% confidence intervals of expected P -values under the null hypothesis.



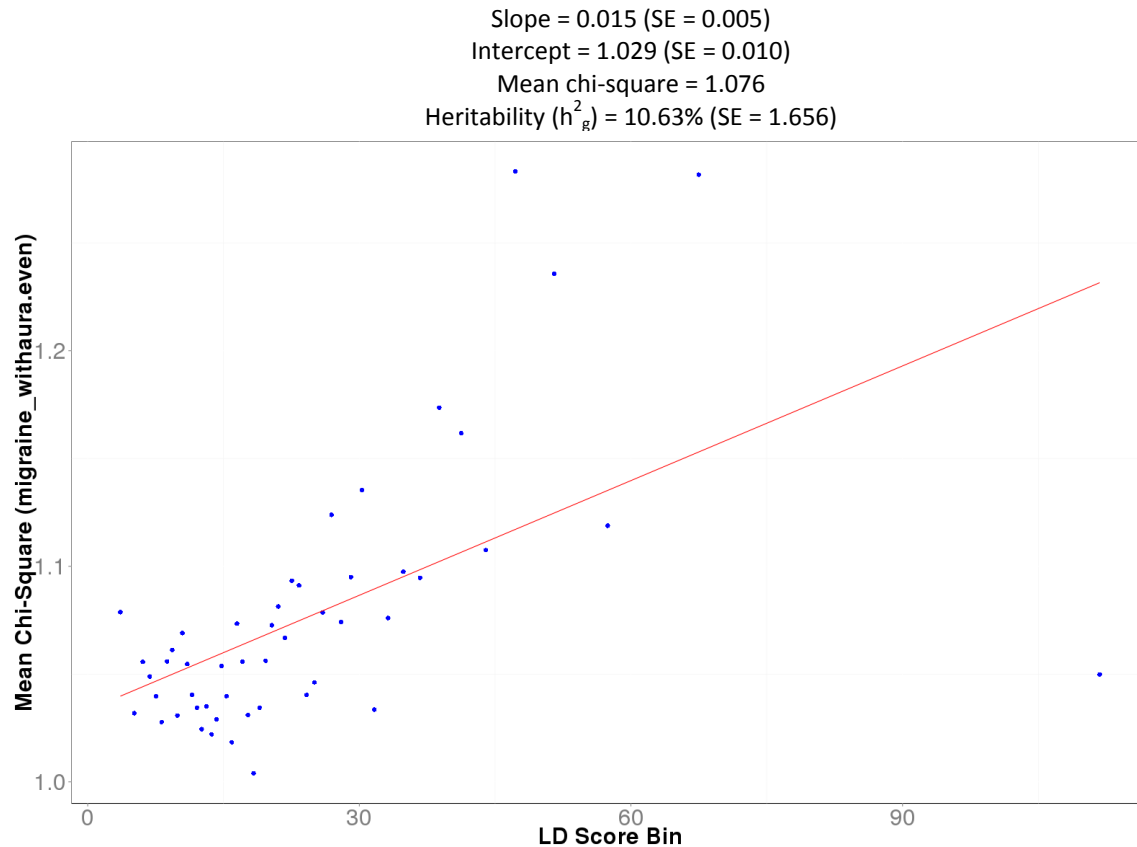
Supplementary Figure 5. QQ-plot of the primary analysis after LD-pruning. Re-plotting the test statistics for of all migraine (59,674 cases vs. 316,078 controls) after markers were pruned for LD-independence using a sliding window in PLINK and also removing all markers within our 38 associated loci means that now $\lambda_{GC} = 1.15$.



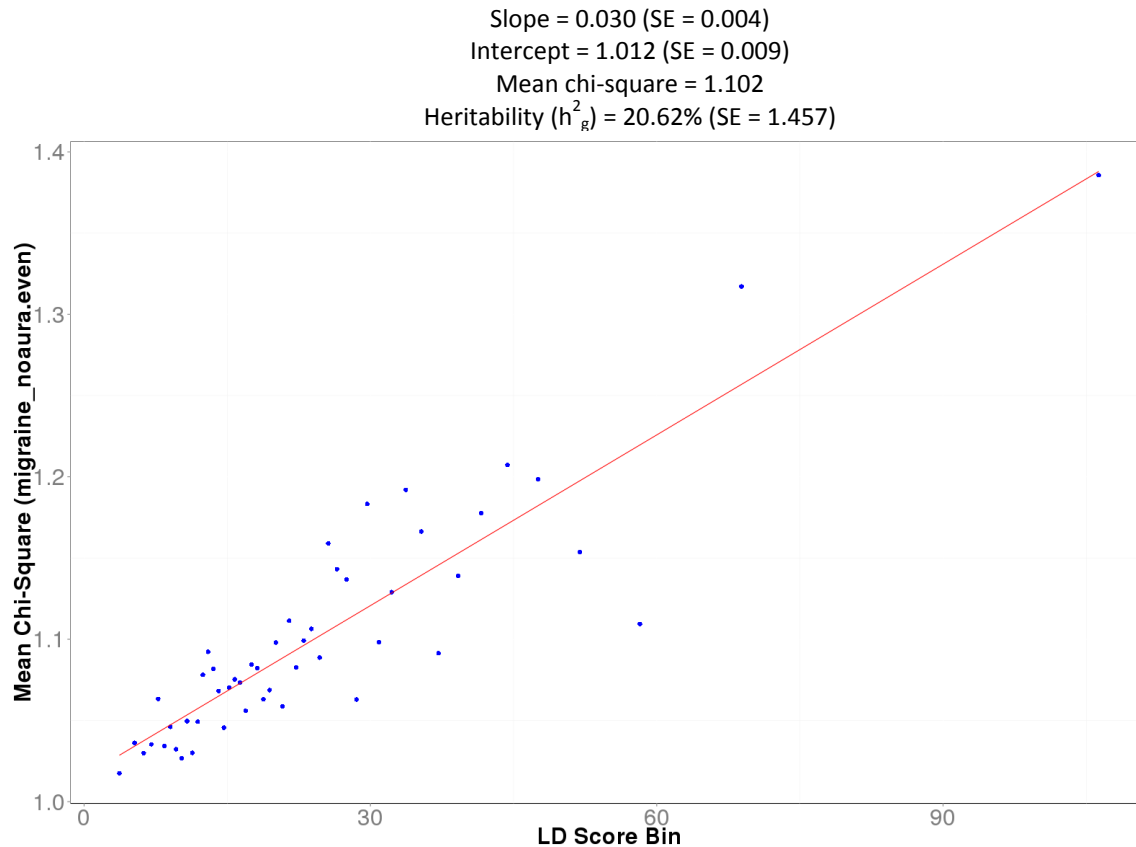
Supplementary Figure 6. LD-score regression plot for all migraine. The mean SNP association test statistics from the primary meta-analysis of all migraine were regressed against LD score by grouping SNPs in bins of equal LD-score rank (59,674 cases vs. 316,078 controls). The intercept estimates the inflation in test statistics contributed by confounding factors such as population structure or other systematic bias, and suggests that 88.2% (95%CI = 82.6–93.8) of the inflation we see is due to genuine polygenicity in migraine as a trait. Using a prevalence estimate of 16% for all migraine, we calculated the heritability (h^2_g) as 14.63% (95%CI = 13.79–15.47).



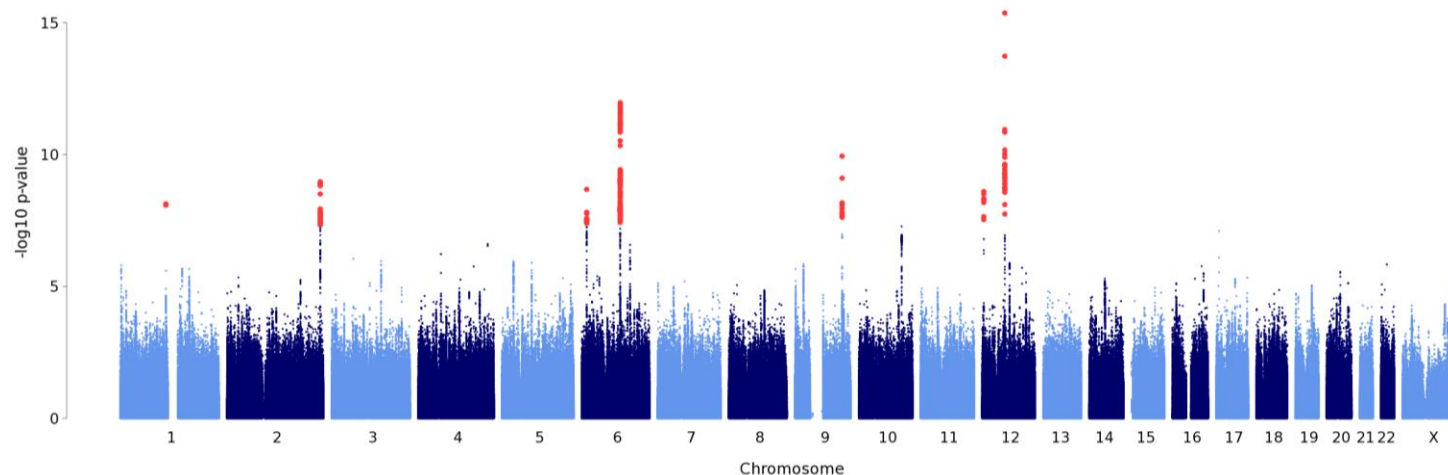
Supplementary Figure 7. LD-score regression plot for the MA subtype. The mean SNP association test statistics from the MA subset-analysis were regressed against LD score by grouping SNPs in bins of equal LD-score rank (6,332 cases and 144,883 controls). The intercept estimates the inflation in test statistics contributed by confounding factors such as population structure or other systematic bias, and suggests that 61.6% (95%CI = 36.3–86.9) of the inflation we see is due to genuine polygenicity in migraine as a trait. Using a prevalence estimate of 7.5% for MA, we calculated the heritability (h^2_g) as 10.63% (95%CI = 7.39–13.88).



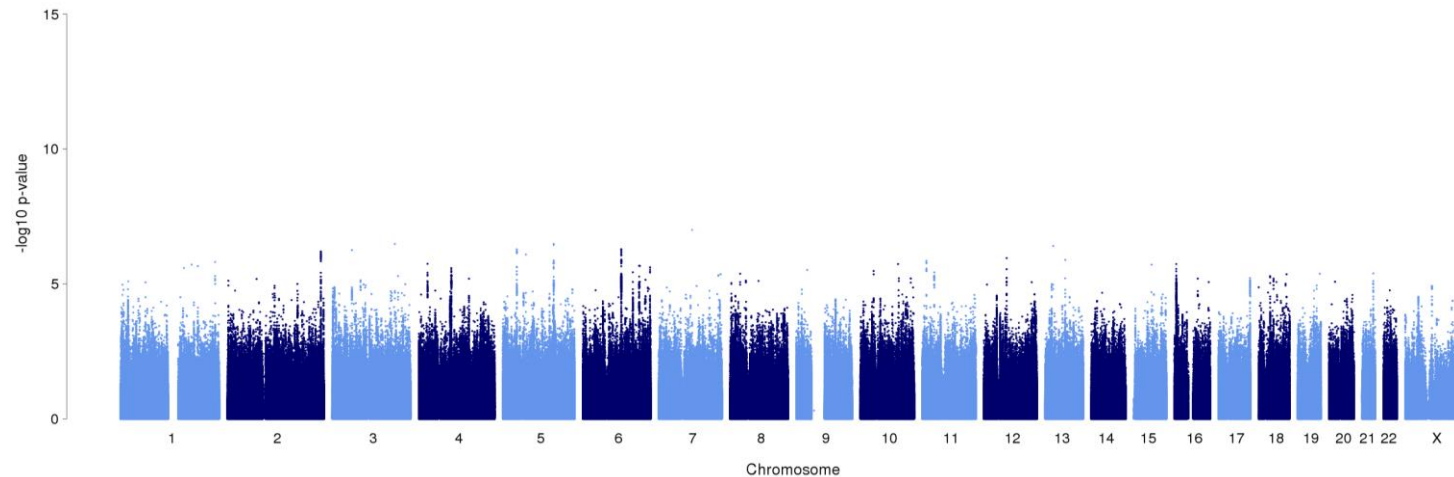
Supplementary Figure 8. LD-score regression plot for the MO subtype. The mean SNP association test statistics from the MO subset-analysis were regressed against LD score by grouping SNPs in bins of equal LD-score rank (8,348 cases and 139,622 controls). The intercept estimates the inflation in test statistics contributed by confounding factors such as population structure or other systematic bias, and suggests that 88.1% (95%CI = 71.3–100) of the inflation we see is due to genuine polygenicity in migraine as a trait. Using a prevalence estimate of 13% for MO, we calculated the heritability (h^2_g) as 20.62% (95%CI = 17.76–23.47).



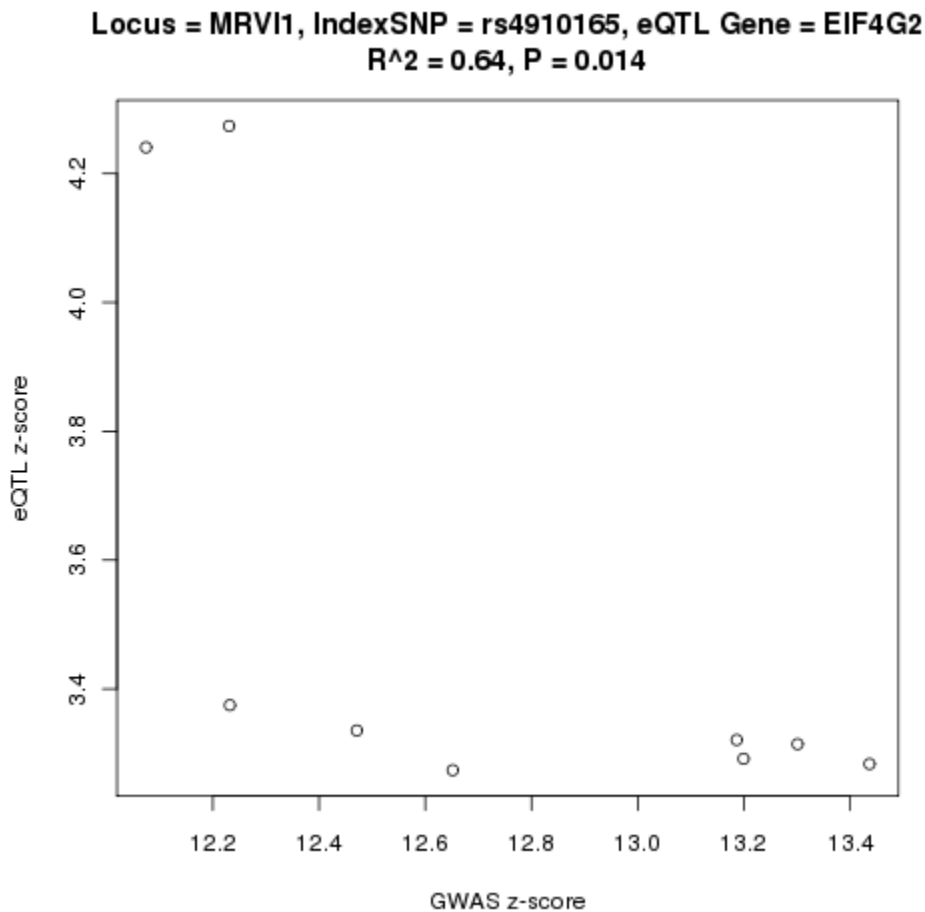
Supplementary Figure 9. Manhattan plot for the MO subset analysis. Each marker was tested for association using an additive genetic model by logistic regression adjusted for sex. A fixed-effects meta-analysis was then used to combine the association statistics from each GWA study with available MO sub-type data. The horizontal axis shows the chromosomal position and the vertical axis shows the significance of tested markers from logistic regression. Markers with test statistics that reach genome-wide significance ($P < 5 \times 10^{-8}$) are shown in red. In total there were 8,348 cases and 139,622 controls and seven genome-wide significant loci.



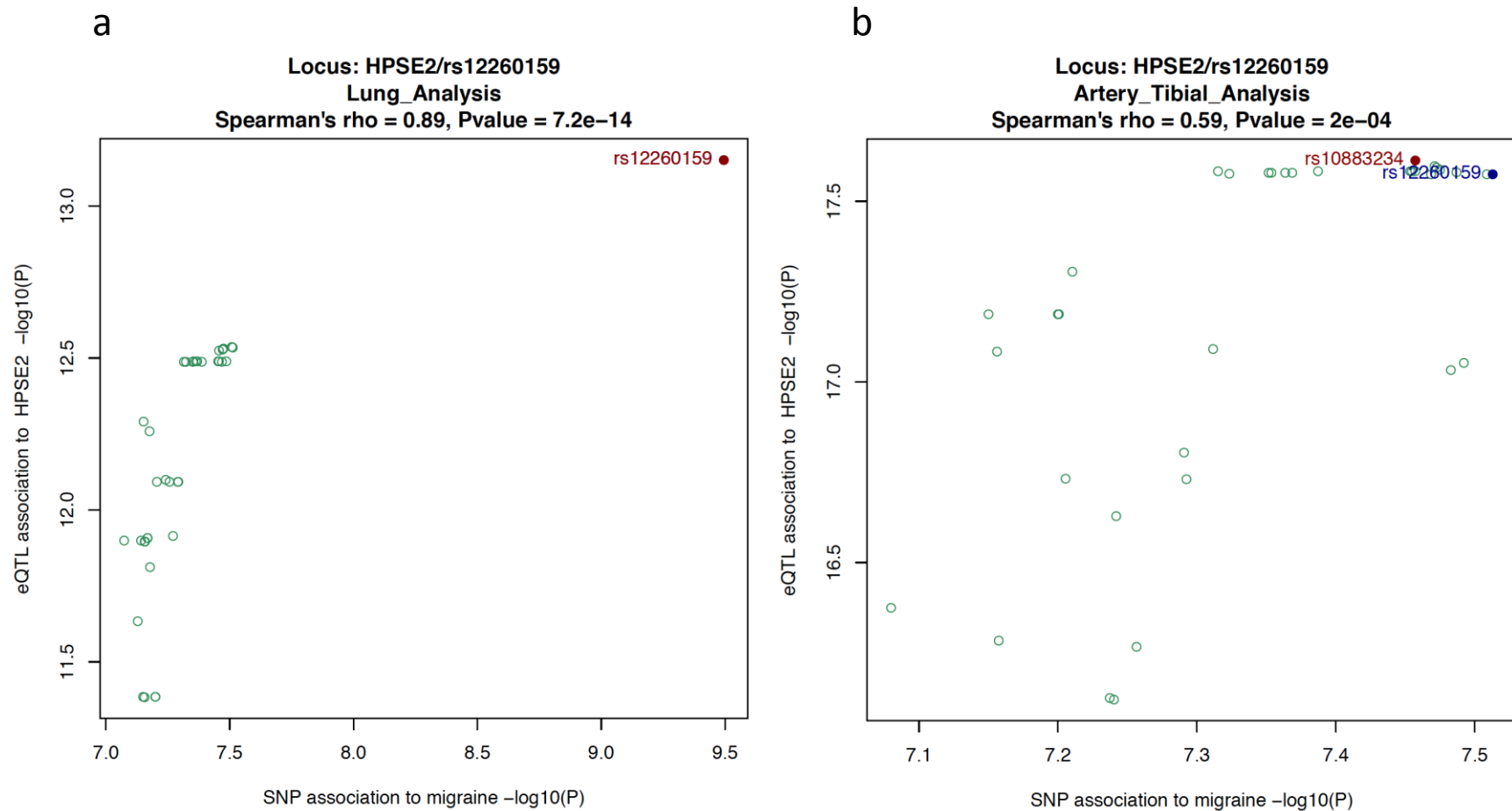
Supplementary Figure 10. Manhattan plot for the MA subset analysis. Each marker was tested for association using an additive genetic model by logistic regression adjusted for sex. A fixed-effects meta-analysis was then used to combine the association statistics from each GWA study with available MA sub-type data. The horizontal axis shows the chromosomal position and the vertical axis shows the significance of tested markers from logistic regression. Markers with test statistics that reach genome-wide significance ($P < 5 \times 10^{-8}$) are shown in red. In total there were 6,332 cases and 144,883 controls. No genome-wide significant loci were identified.

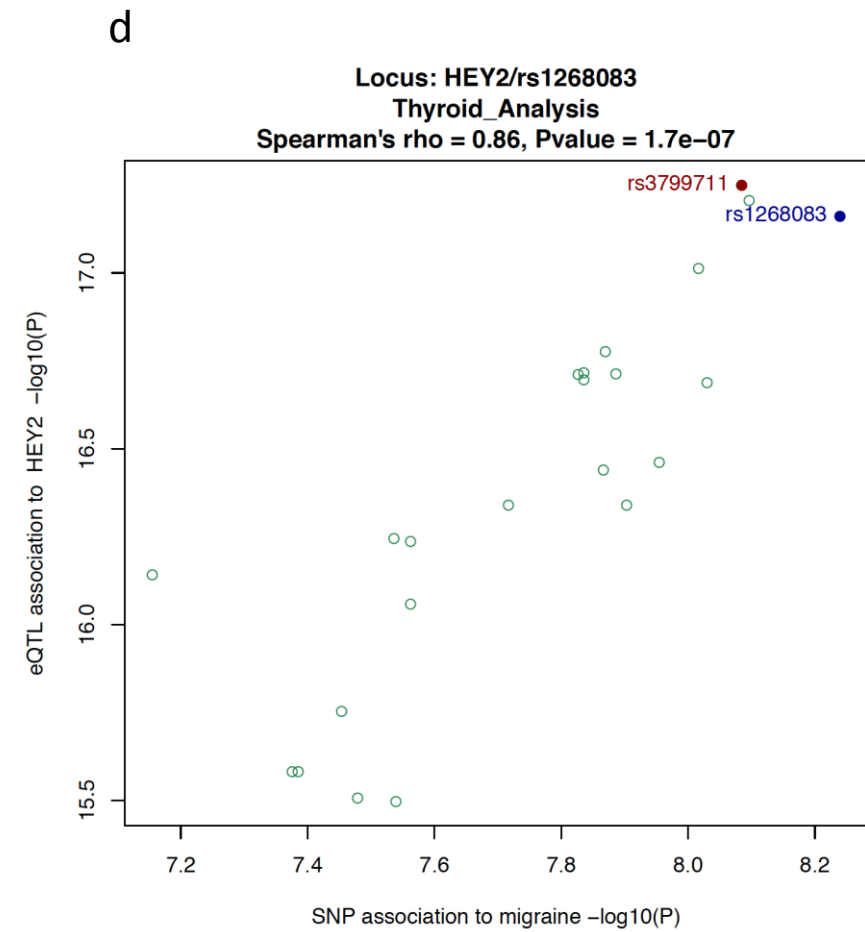
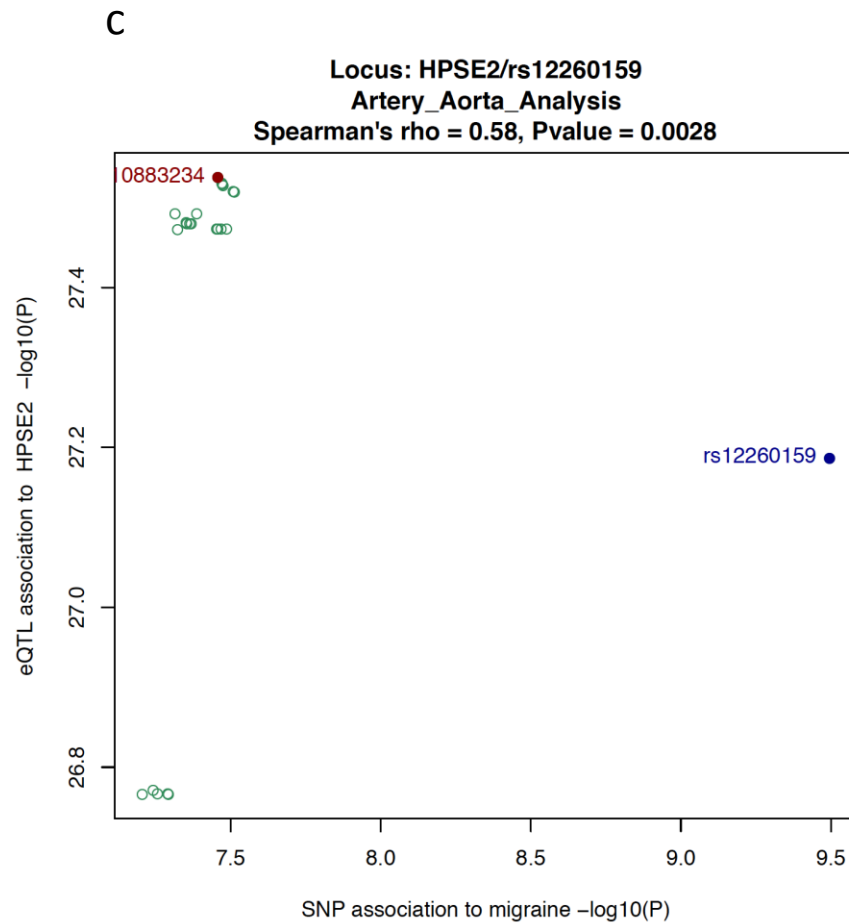


Supplementary Figure 11. Correlation of test statistics between migraine and eQTL SNPs at the *MRVI1* locus. For SNPs that were overlapping between the migraine locus credible set (at the *MRVI1* locus) and SNPs in the eQTL credible set for a probe to the *EIF4G2* gene (identified in 3,754 samples from peripheral venous blood), we tested whether there was a significant correlation (using Spearman's rank correlation) between the two sets of test statistics. The correlation was nominally significant ($P = 0.014$) but does not survive Bonferroni correction for multiple testing of the 23 identified eQTL signals in the peripheral blood data.

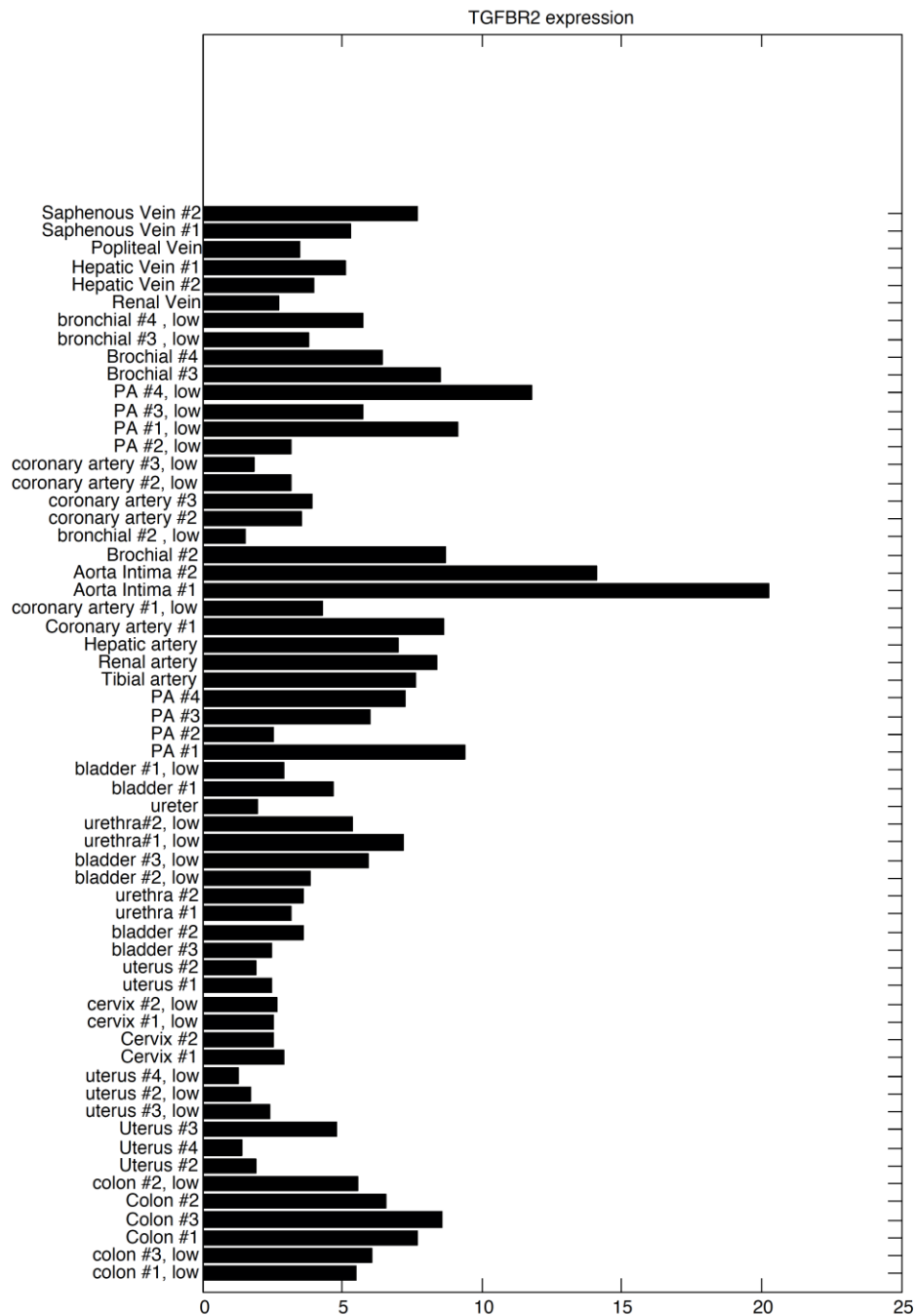


Supplementary Figure 12. eQTL credible sets in GTEx tissues with significant correlation to migraine loci credible sets. The figure shows four eQTL credible sets identified from expression data in GTEx tissues that were significantly correlated with the credible sets from migraine. We assessed significance using Spearman's rank correlation and adjusted for multiple testing using Bonferroni correction. The results implicate significant eQTLs in three tissues; **(a)** Lung, **(b)** Tibial Artery, and **(c)** Aorta for the *HPSE2* locus and one tissue; **(d)** Thyroid, for the *HEY2/NCOA7* locus. In each plot the migraine locus index SNP is annotated in blue and the eQTL locus index SNP is annotated in red. A summary of all tested credible sets is presented in **Supplementary Table 19**.

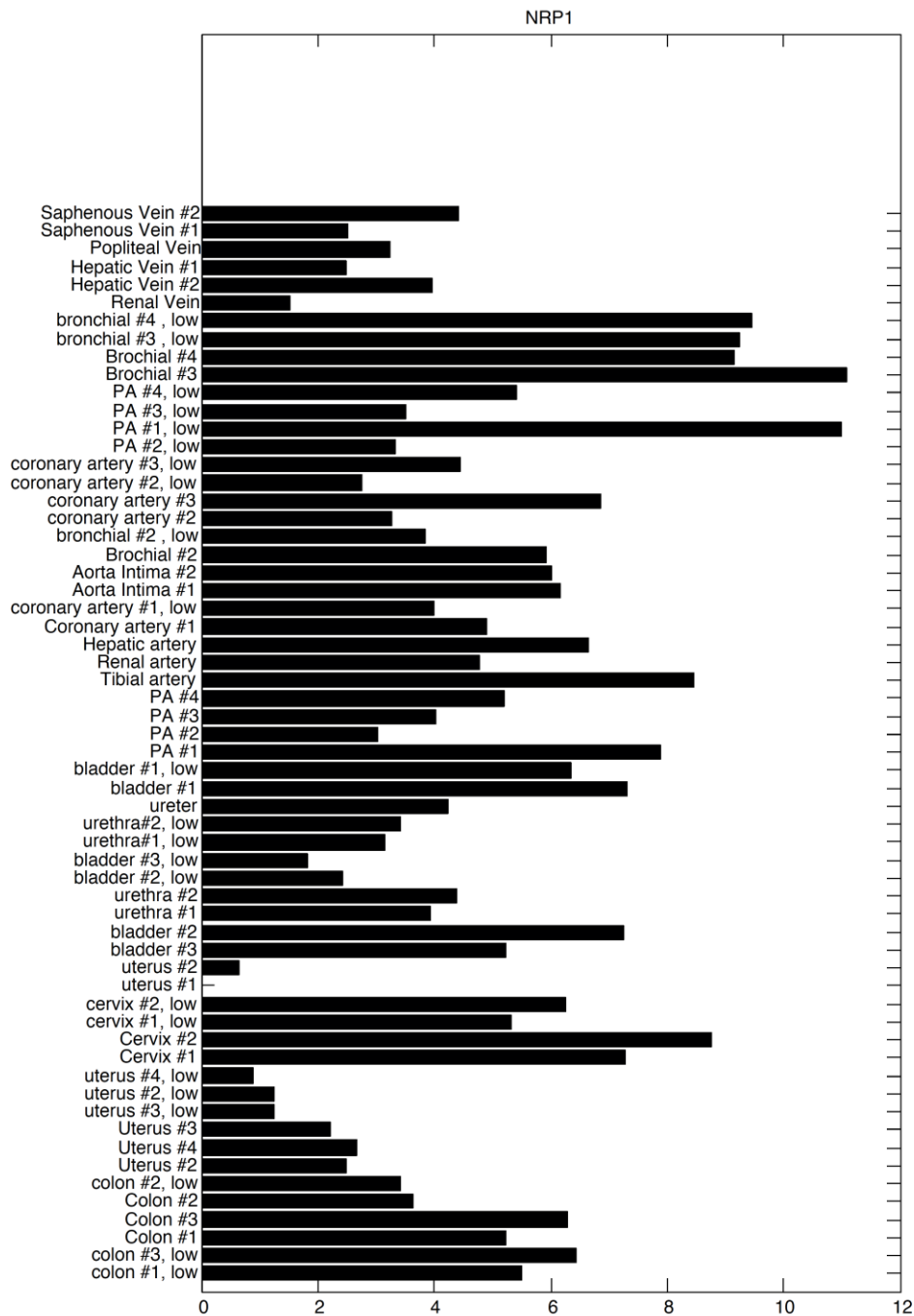




Supplementary Figure 14. Gene expression of *TGFBR2* in 60 types of smooth muscle tissue. The horizontal bars show gene expression levels per tissue. The top 31 tissues are vascular smooth muscle types while the bottom 29 tissues are visceral smooth muscle types. *TGFBR2* appears to be expressed in tissues across both smooth muscle types and shows particularly high expression in the aorta.



Supplementary Figure 15. Gene expression of *NRP1* in 60 types of smooth muscle tissue. The horizontal bars show gene expression levels per tissue. The top 31 tissues are vascular smooth muscle types while the bottom 29 tissues are visceral smooth muscle types. The expression of *NRP1* appears to be high in many tissues from both the vascular and visceral smooth muscle categories.



SUPPLEMENTARY TABLES

Supplementary Table 1. Design and characteristics of IHGC individual GWA studies. In the control definition column, “no migraine” means that individuals with known or possible migraine have been excluded from the controls, where as “pop.” stands for population-based controls that have not been screened for migraine. Where semi-colons separate the definitions, it means that more than one set of control samples has been combined for that study.

GWA Study	Full Name	Study Design	Control Samples	Ethnicity	Cases	Controls	Migraine %	ChrX	MA	MO	Migraine Definition	Control Definition	Study Ref. PMID
23andMe	23andMe Inc.	Population	Within population	European descent	30,465	143,147	17.5	30,465	-	-	Self-reported	No migraine	20585627 21858135
ALSPAC	Avon Longitudinal Study of Parents and Children	Population	Within population	European, British	3,134	5,103	38.0	3,134	-	-	Self-reported migraine, current or prior	No migraine or use of migraine medications; pop.	22507742
ATM	Australian Twin Migraine	Population	Within population	European descent	1,683	2,383	41.4	1,683	-	-	Modified ICHD-II criteria, current migraine	Pop.	20303062 18676988
B58C	1958 British Birth Cohort	Population	Within population	European, British	1,165	4,141	22.0	1,165	-	-	Self-reported migraine, current or prior	No migraine or severe recurrent headaches	16155052
Danish HC	Danish Headache Center	Clinic	Danish Blood Donor Study	European, Danish	1,771	1,000	63.9	1,771	775	996	ICHD-II	No migraine	-
DeCODE	deCODE Genetics Inc.	Population	Within population	European, Icelandic	3,135	95,585	3.2	3,135	366	608	Full ICHD-II criteria, current migraine	Pop.; no migraine	17038039
Dutch MA	Dutch migraine with aura	Clinic	Rotterdam I	European, Dutch	734	5,211	12.3	734	734	-	ICHD-II	Pop.	21914734 20802479 21877163
Dutch MO	Dutch migraine without aura	Clinic	Rotterdam II	European, Dutch	1,115	2,028	35.5	1,115	-	1,115	ICHD-II	Pop.	21914734 22683712 21877163
EGCUT	Estonian Genome Center, University of Tartu	Population	Within population	European, Estonian	813	9,850	7.6	-	76	94	Self-reported	No migraine	19424496
Finnish MA	Finnish migraine with aura	Clinic	Helsinki Birth Cohort (1,697); FINRISK pop controls (1,018)	European, Finnish	933	2,715	25.6	933	933	-	ICHD-II	Pop.; Pop.	11509082 20802479 16251536 19959603
German MA	German migraine with aura	Clinic	Heinz Nixdorf Recall study (365); PopGen (645)	European, German	1,071	1,010	51.5	1,071	1,071	-	ICHD-II	Pop.; Pop.	20802479 12177636 16490960

German MO	German migraine without aura	Clinic	KORA (801); GSK (846)	European, German	1,160	1,647	41.3	1,160	-	1,160	ICHD-II	Pop.; Pop.	22683712 16032514 19107115
Health2000	Health 2000	Population	Within population	European, Finnish	136	1,764	7.2	136	-	-	Self-reported	Mig-free pop.	20532202
HUNT	Nord-Trøndelag Health Study	Population	HUNT pop. controls; HUNT lung cancer; HUNT pre-eclampsia	European, Norwegian	1,395	1,011	58.0	1,395	290	980	Self-reported migraine or fulfilling modified ICHD-II criteria, current migraine	No migraine; pop.	10999674
NFBC	Northern Finnish Birth Cohort	Population	Within population	European, Finnish	756	4,393	14.7	756	-	-	Self-reported migraine, current or prior	No migraine	4911003
NTR/NESDA	Netherlands Twin Register and the Netherlands Study of Depression and Anxiety	Population	Within population	European, Dutch	1,636	3,819	30.0	1,636	544	615	Modified ICHD-II criteria, current migraine	No migraine or severe recurrent headache	17254420 16611468 18763692 20713558
Rotterdam III	Rotterdam Study III	Population	Within population	European, Dutch	487	2,175	18.3	-	106	381	Modified ICHD-II criteria, current migraine	No migraine	21877163
Swedish Twins	Swedish Twin Registry	Population	Within population	European, Swedish	1,307	4,182	23.8	1,307	-	-	Self-reported or fulfilling modified ICHD-II criteria	No migraine	24674449
Tromsø	The Tromsø Study	Population	Within population	European, Norwegian	660	2,407	21.5	660	-	-	Self reported or fulfilling modified ICHD-II criteria	No migraine	-
Twins UK	Twins UK	Population	Within population	European, British	618	2,334	20.9	-	202	416	Self-reported migraine or fulfilling Modified ICHD-II criteria, current or prior migraine	No migraine	22253318
WGHS	Women's Genome Health Study	Population	Within population	European descent	5,122	18,108	22.0	5,122	1,177	1,826	Self-reported migraine or fulfilling Modified ICHD-II criteria, current or prior migraine	No migraine	16849661 18070814
Young Finns	Young Finns	Population	Within population	European, Finnish	378	2,065	15.5	378	58	157	Full ICHD-II criteria, current migraine	No migraine	18263651

Supplementary Table 2. Evaluating heterogeneity from the 23andMe study. The table shows summary statistics for 12 SNPs that have been previously associated with migraine (Anttila et al 2013, PMID:23793025). The effect sizes and allele frequencies for 23andMe (where migraine was self-reported by questionnaire) can be compared to those of the other 15 population-based studies (self-reported migraine and structured questionnaires), and to those of the six best phenotyped clinic-based studies (where migraine was doctor-diagnosed or by telephone interview). The table shows that 23andMe effects are closely comparable to both ascertainment groups. After combining all population and clinic-based studies in meta-analysis, the table shows that the 23andMe study does not contribute substantial heterogeneity. Only one SNP (rs10915437) shows significant heterogeneity (correcting for 12 tests) but was already heterogeneous in the meta-analysis before including 23andMe. The *Q*-*P*val column is the *P*-value from Cochran's Q test for heterogeneity and i^2 is the heterogeneity index.

Locus	SNP	Allele	23andMe		Population-based (15 GWA studies)		Clinic-based (6 GWA studies)		Meta-analysis of Population & Clinic-based (excluding 23andMe)				Meta-analysis of all 22 GWA studies (including 23andMe)			
			MAF	OR [95% CI]	MAF	OR [95% CI]	MAF	OR [95% CI]	OR [95% CI]	P	Q Pval	i^2 (%)	OR [95% CI]	P	Q Pval	i^2 (%)
<i>PRDM16</i>	rs2651899	C	0.44	1.06 [1.04-1.08]	0.38	1.10 [1.07-1.12]	0.43	1.04 [0.99-1.09]	1.09 [1.07-1.11]	1.6E-15	0.01	46	1.07 [1.06-1.08]	2.4E-22	0.005	48
near <i>AJAP1</i>	rs10915437	G	0.36	1.00 [0.99-1.02]	0.34	1.00 [0.97-1.02]	0.37	0.90 [0.86-0.95]	0.98 [0.96-1.00]	5.9E-02	0.0006	56	0.99 [0.98-1.01]	3.9E-01	0.0004	56
near <i>TSPAN2</i>	rs12134493	A	0.11	1.10 [1.07-1.13]	0.12	1.13 [1.09-1.17]	0.12	1.15 [1.07-1.23]	1.13 [1.10-1.17]	6.6E-15	0.28	13	1.11 [1.09-1.13]	5.2E-24	0.28	13
<i>MEF2D</i>	rs2274316	C	0.34	1.07 [1.05-1.09]	0.36	1.06 [1.03-1.08]	0.36	1.16 [1.10-1.21]	1.08 [1.05-1.10]	1.9E-11	0.05	35	1.07 [1.06-1.09]	1.7E-21	0.07	32
<i>TRPM8</i>	rs7577262	A	0.11	0.91 [0.88-0.94]	0.10	0.89 [0.86-0.93]	0.10	0.78 [0.72-0.85]	0.87 [0.84-0.90]	1.5E-14	0.11	28	0.89 [0.87-0.91]	1.4E-22	0.09	29
near <i>TGFB2</i>	rs6790925	T	0.36	1.04 [1.02-1.06]	0.38	1.02 [0.99-1.04]	0.38	1.14 [1.09-1.20]	1.04 [1.02-1.06]	6.4E-04	0.01	45	1.04 [1.03-1.05]	4.2E-08	0.02	40
<i>PHACTR1</i>	rs9349379	G	0.41	0.93 [0.92-0.95]	0.41	0.94 [0.92-0.97]	0.39	0.89 [0.85-0.94]	0.93 [0.91-0.95]	1.0E-09	0.25	16	0.93 [0.92-0.95]	5.8E-22	0.26	14
<i>FHL5</i>	rs13208321	A	0.22	1.08 [1.06-1.11]	0.22	1.08 [1.05-1.11]	0.23	1.19 [1.12-1.26]	1.10 [1.07-1.13]	7.5E-14	0.03	38	1.09 [1.07-1.11]	1.4E-25	0.04	35
<i>C7orf10</i>	rs4379368	T	0.10	1.08 [1.05-1.11]	0.11	1.07 [1.03-1.11]	0.12	1.21 [1.13-1.30]	1.09 [1.06-1.13]	2.3E-08	0.27	14	1.09 [1.07-1.11]	8.4E-15	0.29	12
near <i>MMP16</i>	rs10504861	T	0.18	1.00 [0.98-1.02]	0.16	0.97 [0.94-1.00]	0.18	0.93 [0.88-0.99]	0.96 [0.93-0.99]	2.7E-03	0.46	0	0.98 [0.96-1.00]	4.6E-02	0.30	11
<i>ASTN2</i>	rs6478241	A	0.37	1.05 [1.03-1.07]	0.36	1.04 [1.02-1.07]	0.38	1.14 [1.09-1.20]	1.06 [1.04-1.08]	6.0E-08	0.07	33	1.05 [1.04-1.07]	1.2E-12	0.09	29
<i>LRP1</i>	rs11172113	C	0.40	0.90 [0.89-0.92]	0.44	0.90 [0.88-0.92]	0.40	0.90 [0.85-0.94]	0.90 [0.88-0.92]	2.0E-24	0.66	0	0.90 [0.89-0.91]	5.6E-49	0.71	0

Supplementary Table 3. Quality Control and imputation description of the individual GWA studies. The table lists genotyping platforms, software, and quality control metrics applied for each GWA study. The marker- and individual-level exclusion thresholds given are for minor allele frequency (MAF), Hardy-Weinberg equilibrium (HWE), genotyping call rate, identity-by-descent (IBD).

GWA Study	Full Name	GENOTYPING		IMPUTATION				ASSOCIATION ANALYSIS	
		Genotyping Platform	Quality Control	Imputation Reference Panel	MAF	Imputation Quality	Imputation Software	SNPs in meta-analysis	Analysis software
23andMe	23andMe Inc.	Illumina HumanHap550+ BeadChip (custom)	1) MAF > 0.01, 2) HWE > 1×10^{-20} , 3) Call Rate > 0.95 4) IBD < 0.125	1000G, Phase I, v3, March 2012	> 1%	> 0.6	Beagle, Minimac	8,668,133	mach2dat
ALSPAC	Avon Longitudinal Study of Parents and Children	Illumina human660W-quadruplet	1) MAF > 0.01 2) HWE > 1×10^{-6} 3) Call Rate > 0.95 4) IBD < 0.125	1000G, Phase I, v3, March 2012	> 1%	> 0.6	MACH, Minimac	8,343,543	mach2dat
ATM	Australian Twin Migraine	Illumina (various arrays)	1) MAF > 0.01, 2) HWE > 1×10^{-6} , 3) Call rate > 0.95, 4) IBD < 0.125	1000G, Phase I, v3, March 2012	> 1%	> 0.6	MACH, Minimac	7,439,352	PLINK
B58C	1958 British Birth Cohort	Illumina 550k Illumina 1.2M DuoCustom	1) MAF > 0.01, 2) HWE > 0.0001, 3) Call Rate > 95%, 4) Concordant allele frequencies across 3 deposits	1000G, Phase I, v3, March 2012	> 1%	> 0.6	MACH, Minimac	8,166,696	ProbABEL
Danish HC	Danish Headache Center	Illumina Human OmniExpress-12v1	1) MAF > 0.01 2) HWE > 1×10^{-6} , 3) Call rate > 95%, 4) IBD < 0.125	1000G, Phase I, v3, March 2012	> 1%	> 0.6	SHAPEIT, IMPUTE2	9,147,346	Custom software
DeCODE	deCODE Genetics Inc.	Illumina HumanHap 317K, 370K, 610K or 1M BeadArrays	1) MAF > 0.01, 2) HWE > 1×10^{-3} , 3) Geno/Sample Yield > 95%, 4) Inher error < 0.001, 5) No chip-chip freq diff, 6) Sample yield > 97%	Custom Icelandic, 2300 whole-genomes	> 1%	> 0.6	Custom software	9,119,069	Custom software
Dutch MA	Dutch migraine with aura	Illumina 550k	1) MAF > 0.01, 2) HWE > 1×10^{-6} , 3) Call Rate > 95%, 4) IBD < 0.185	1000G, Phase I, v3, March 2012	> 1%	> 0.6	SHAPEIT, IMPUTE2	9,047,309	SNPTEST
Dutch MO	Dutch migraine without aura	Illumina 550k	1) MAF > 0.01, 2) HWE > 1×10^{-6} , 3) Call Rate > 95%, 4) IBD < 0.185	1000G, Phase I, v3, March 2012	> 1%	> 0.6	SHAPEIT, IMPUTE2	9,037,120	SNPTEST
EGCUT	Estonian Genome Center, University of Tartu	Illumina HumanHapCNV370 OmniExpress array	1) MAF > 0.01, 2) HWE > 1×10^{-6} , 3) Call Rate > 95%, 4) IBD < 0.185	1000G, Phase I, v3, March 2012	> 1%	> 0.6	SHAPEIT, IMPUTE2	8,906,443	SNPTEST

Finnish MA	Finnish migraine with aura	Illumina 610k (Cases); Illumina 610k (HBC); Illumina HumanOmniExpress (FINRISK)	1) MAF > 0.01, 2) HWE > 1×10^{-6} , 3) Call Rate > 95%, 4) IBD < 0.185	1000G, Phase I, v3, March 2012	> 1%	> 0.6	SHAPEIT, IMPUTE2	8,859,953	SNPTEST
German MA	German migraine with aura	Illumina 610k	1) MAF > 0.01, 2) HWE > 1×10^{-6} , 3) Call Rate > 95%, 4) IBD < 0.185	1000G, Phase I, v3, March 2012	> 1%	> 0.6	SHAPEIT, IMPUTE2	9,092,253	SNPTEST
German MO	German migraine without aura	Illumina Human 610-Quad; Illumina Human 660W-Quad v1	1) MAF > 0.01, 2) HWE > 1×10^{-6} , 3) Call Rate > 95%, 4) IBD < 0.185	1000G, Phase I, v3, March 2012	> 1%	> 0.6	SHAPEIT, IMPUTE2	8,666,173	SNPTEST
Health2000	Health 2000	Illumina 610k	1) MAF > 0.01, 2) HWE > 1×10^{-6} , 3) Call Rate > 95%, 4) IBD < 0.185	1000G, Phase I, v3, March 2012	> 1%	> 0.6	SHAPEIT, IMPUTE2	9,419,974	SNPTEST
HUNT	Nord-Trøndelag Health Study	Illumina 670k (cases + pop controls); Illumina 310k (lung cancer); Illumina 550k (pre-eclampsia)	1) MAF > 0.01, 2) HWE > 1×10^{-6} , 3) Call Rate > 95%, 4) IBD < 0.185	1000G, Phase I, v3, March 2012	> 1%	> 0.6	SHAPEIT, IMPUTE2	8,961,818	SNPTEST
NFBC	Northern Finnish Birth Cohort	Illumina 370k	1) MAF > 0.01, 2) HWE > 1×10^{-6} , 3) Call Rate > 95%, 4) IBD < 0.185	1000G, Phase I, v3, March 2012	> 1%	> 0.6	SHAPEIT, IMPUTE2	9,331,341	SNPTEST
NTR/NESDA	Netherlands Twin Register and the Netherlands Study of Depression and Anxiety	Affymetrix Perlegen 5.0, Illumina 370, Illumina 660, Illumina Omni Express 1M, and Affymetrix 6.0	1) MAF > 0.01, 2) HWE > 1×10^{-5} , 3) Call Rate > 0.90, 4) $F < -0.10$ & $F > 0.10$	1000G, Phase I, v3, March 2012	> 1%	> 0.6	MACH, Minimac	7,656,469	PLINK
Rotterdam III	Rotterdam Study III	Illumina Human 610 Quad	1) MAF > 0.001, 2) HWE > 1×10^{-6} , 3) SNP call rate > 98% 4) IBD < 0.125	1000G, Phase I, v3, March 2012	> 1%	> 0.6	MACH, Minimac	8,052,185	mach2dat
Swedish Twins	Swedish Twin Registry	Illumina HumanOmniExpress	1) MAF > 0.01, 2) HWE > 1×10^{-6} , 3) Call Rate > 95%, 4) IBD < 0.185	1000G, Phase I, v3, March 2012	> 1%	> 0.6	SHAPEIT, IMPUTE2	9,209,621	SNPTEST
Tromsø	The Tromsø Study	Infinium HumanCoreExome BeadChip	1) MAF > 0.01, 2) HWE > 1×10^{-6} , 3) Call Rate > 98%, 4) IBD < 0.20	1000G, Phase I, v3, March 2012	> 1%	> 0.6	SHAPEIT, IMPUTE2	8,997,693	SNPTEST
Twins UK	Twins UK	Illumina HumanHap300 and HumanHap610Q	1) MAF > 0.01, 2) HWE > 1×10^{-6} , 3) Call Rate > 0.97, 4) IBD < 0.1875	1000G, Phase I, v3, March 2012	> 1%	> 0.6	IMPUTE2	8,674,998	GWAF
WGHS	Women's Genome Health Study	Illumina HumanHap300 Duo+ and iSelect	1) MAF > 0.01, 2) HWE > 1×10^{-6} , 3) Call Rate > 0.90	1000G, Phase I, v3, March 2012	> 1%	> 0.6	MACH, Minimac	7,670,940	mach2dat
Young Finns	Young Finns	Illumina Human 670k BeadChip	1) MAF > 0.01, 2) HWE > 1×10^{-6} , 3) Call Rate > 0.95,	1000G, Phase I, v3, March 2012	> 1%	> 0.6	SHAPEIT, IMPUTE2	9,394,411	SNPTEST



Supplementary Table 4. Covariates and genomic inflation for each individual GWA study. List of all covariates controlled for in each GWA study when estimating coefficients and association statistics using logistic regression. Sex was adjusted for in all studies. Age (if available) and other relevant covariates were used when necessary. Any principal components that were significantly associated with the phenotype were also used as covariates. Also listed is the genomic inflation factor (λ_{GC}), defined as the median ratio of the observed test statistic to the expected test statistic. A scaled version of λ_{GC} is also shown (λ_{1000}) which denotes the inflation estimated for the same study but rescaled for 1000 cases and 1000 controls (Freedman et al. 2004, PMID:15052270).

Study	Covariates	All migraine studies				MA studies				MO studies			
		Cases	Controls	λ_{GC}	λ_{1000}	Cases	Controls	λ_{GC}	λ_{1000}	Cases	Controls	λ_{GC}	λ_{1000}
23andMe	sex, age, PCs 1–5	30465	143147	1.157	1.003	-	-	-	-	-	-	-	-
ALSPAC	sex (females-only study)	3134	5103	1.008	1.002	-	-	-	-	-	-	-	-
ATM	sex	1683	2383	0.999	0.999	-	-	-	-	-	-	-	-
B58C	sex	1165	4141	1.003	1.002	-	-	-	-	-	-	-	-
Danish HC	sex	1771	1000	1.025	1.019	775	1000	1.020	1.023	996	1000	1.019	1.019
DeCODE	sex	3135	95585	0.994	0.999	366	95585	1.007	1.009	608	95585	0.995	0.996
Dutch MA	sex, PCs 1–10	734	5211	1.053	1.041	734	5211	1.053	1.041	-	-	-	-
Dutch MO	sex, PCs 1–10	1115	2028	1.046	1.032	-	-	-	-	1115	2028	1.046	1.032
EGCUT	sex, PCs 1–4	813	9850	1.027	1.018	76	9850	1.004	1.025	94	9850	1.010	1.054
Finnish MA	sex	933	2715	1.055	1.040	933	2715	1.055	1.040	-	-	-	-
German MA	sex	1071	1010	1.035	1.033	1071	1010	1.035	1.033	-	-	-	-
German MO	sex	1160	1647	1.028	1.021	-	-	-	-	1160	1647	1.028	1.021
Health 2000	sex	136	1764	1.013	1.050	-	-	-	-	-	-	-	-
HUNT	sex	1395	1011	1.015	1.013	290	1011	1.035	1.077	980	1011	1.002	1.002
NFBC	sex	756	4393	1.046	1.036	-	-	-	-	-	-	-	-
NTR/NESDA	sex, DNA (buccal/blood), PC1	1636	3819	1.026	1.011	544	3819	1.008	1.008	615	3819	1.026	1.025
Rotterdam III	sex	487	2175	1.023	1.028	106	2175	0.989	0.947	381	2175	1.018	1.027
Swedish Twins	sex	1307	4182	1.007	1.003	-	-	-	-	-	-	-	-
Tromsø	sex	660	2407	1.020	1.019	-	-	-	-	-	-	-	-
Twins UK	sex, age	618	2334	1.004	1.004	202	2334	1.010	1.026	416	2334	1.005	1.007
WGHS	sex (females-only study)	5122	18108	1.029	1.004	1177	18108	1.007	1.003	1826	18108	1.022	1.007
Young Finns	sex	378	2065	1.017	1.026	58	2065	1.029	1.253	157	2065	1.013	1.044
Combined	-	59674	316078	1.240	1.002	6332	144883	1.075	1.006	8348	139622	1.058	1.004

Supplementary Table 5. Validation of the migraine index SNPs by whole-genome sequencing. Concordance rates between the best-guess imputed genotypes and the genotypes obtained for the same individuals by whole-genome sequencing. Data from 3,919 whole-genome sequences (WGS) were available for comparison from three GWA studies; the Finnish MA ($N = 169$), DeCode ($N = 2,575$), and EGCUT ($N = 1,175$). Concordance was high ($> 90\%$) for 39 migraine-associated index SNPs. The remaining six SNPs with lower concordances were either multi-allelic or in repeat regions that can be problematic for correct alignment/calling in sequencing pipelines. For five of these we identified an alternative LD proxy ($R^2 > 0.6$) to the original SNP for validation instead; concordance of 100% for rs140467810 (proxy to rs140002913), 99.25% for rs2971606 (proxy to rs67338227), 98.16% for rs77410344 (proxy to rs186166891), 99.50% for rs6134000 (proxy to rs111404218), and 97.02% for rs76627106 (proxy to rs144017103). No suitable proxies were identified for the sixth SNP (rs2672599) therefore we consider it to not be validated.

Migraine SNPs from GWAS					Finnish MA			DeCode			EGCUT			Combined Validation	
Nearest Gene	Chr	SNP	Allele	EAF	Cases	Controls	Concordance	Cases	Controls	Concordance	Cases	Controls	Concordance	Total N	Concordance
<i>PRDM16</i>	1	rs10218452	G	0.22	72	92	95.73	89	1929	98.76	59	1116	96.31	3357	97.76
<i>PRDM16</i>	1	rs12135062	T	0.23	71	89	85.63	103	2170	96.88	59	1116	88.12	3608	93.53
<i>LRR1Q3</i>	1	rs1572668	A	0.52	70	92	100	112	2410	99.52	59	1116	98.69	3859	99.29
<i>TSPAN2</i>	1	rs2078371	C	0.12	73	94	99.40	115	2446	99.80	59	1116	98.88	3903	99.51
<i>NGF</i>	1	rs7544256	G	0.36	73	96	98.82	115	2383	98.92	59	1116	98.59	3842	98.82
<i>ADAMTSL4</i>	1	rs6693567	C	0.27	72	92	100	107	2344	97.10	59	1116	99.16	3790	97.87
<i>MEF2D</i>	1	rs1925950	G	0.35	72	95	99.40	111	2359	97.65	59	1116	99.51	3812	98.30
<i>CARF</i>	2	rs138556413	T	0.03	68	87	98.71	115	2456	99.69	59	1116	100	3901	99.74
<i>HJURP</i>	2	rs566529	T	0.15	72	96	99.40	112	2452	99.80	59	1116	99.60	3907	99.73
<i>TRPM8</i>	2	rs10166942	C	0.20	72	96	99.40	112	2440	99.88	59	1116	98.72	3895	99.51
<i>TGFBR2</i>	3	rs6791480	T	0.31	73	91	100	112	2415	99.80	59	1116	99.05	3866	99.58
<i>GPR149</i>	3	rs13078967	C	0.03	72	94	97.59	109	2404	98.29	59	1116	86.36	3854	94.62
<i>SPINK2</i>	4	rs7684253	T	0.55	69	93	98.77	107	2382	99.80	59	1116	99.33	3826	99.61
<i>PHACTR1</i>	6	rs9349379	G	0.41	72	94	99.40	101	2138	96.29	59	1116	98.93	3580	97.30
<i>NOTCH4</i>	6	rs140002913	A	0.06	73	96	98.22	104	2197	97.18	59	1116	59.38	3645	85.04
<i>KCNK5</i>	6	rs10456100	T	0.28	72	96	97.02	112	2375	99.60	59	1116	98.21	3830	99.06
<i>UFL1</i>	6	rs2223239	T	0.15	73	95	99.40	114	2433	99.49	59	1116	99.39	3890	99.46
<i>FHL5</i>	6	rs67338227	T	0.23	Not called in WGS			86	1859	56.50	59	1116	2.07	3120	36.00
<i>GJA1</i>	6	rs28455731	T	0.16	71	95	99.40	454	2460	99.65	59	1116	99.30	3915	99.54
<i>HEY2</i>	6	rs1268083	C	0.48	73	96	98.82	115	2446	99.80	59	1116	99.12	3905	99.56

<i>C7orf10</i>	7	rs186166891	T	0.11	25	34	98.31	106	2323	71.93	59	1116	74.15	3663	73.07
<i>DOCK4</i>	7	rs10155855	T	0.05	72	95	99.40	107	2328	99.92	59	1116	97.50	3777	99.14
<i>ASTN2</i>	9	rs6478241	A	0.36	69	90	100	113	2416	99.05	59	1116	98.19	3863	98.83
<i>NRP1</i>	10	rs2506142	G	0.17	72	95	99.40	114	2446	99.80	59	1116	98.68	3902	99.45
<i>PLCE1</i>	10	rs10786156	G	0.45	69	92	100	113	2382	99.64	59	1116	98.91	3831	99.43
<i>PLCE1</i>	10	rs75473620	T	0.04	71	95	98.19	113	2426	98.15	59	1116	94.62	3880	97.08
<i>HPSE2</i>	10	rs12260159	A	0.07	72	94	98.80	112	2415	99.17	59	1116	95.56	3868	98.06
<i>ARMS2</i>	10	rs2223089	C	0.08	73	95	99.40	114	2339	99.84	59	1116	98.21	3796	99.32
ARMS2	10	rs2672599*	C	0.54	14	21	77.14	72	1468	60.32	59	1116	61.41	2750	61.00
<i>MRVI1</i>	11	rs4910165	C	0.33	73	96	99.41	112	2353	99.76	59	1116	99.23	3809	99.58
<i>MPPED2</i>	11	rs11031122	C	0.24	70	94	100	112	2423	99.72	59	1116	98.51	3874	99.37
<i>YAP1</i>	11	rs10895275	A	0.33	71	92	100	111	2428	99.80	59	1116	98.67	3877	99.47
<i>IGSF9B</i>	11	rs561561	T	0.12	Not imputed in GWAS			104	2163	99.96	59	1116	98.95	3442	99.61
<i>FGF6</i>	12	rs1024905	C	0.53	73	96	100	112	2393	99.72	59	1116	98.95	3849	99.50
<i>SDR9C7</i>	12	rs7961602	T	0.41	72	92	98.78	109	2335	96.44	59	1116	93.71	3783	95.69
<i>LRP1</i>	12	rs11172113	C	0.42	73	95	99.40	103	2230	92.33	59	1116	99.09	3676	94.81
<i>ITPK1</i>	14	rs11624776	C	0.31	71	95	100	101	2061	99.31	59	1116	98.69	3503	99.13
<i>CFDP1</i>	16	rs77505915	G	0.55	66	79	93.79	103	2297	97.75	59	1116	94.91	3720	96.70
<i>ZCCHC14</i>	16	rs4081947	G	0.34	Not imputed in GWAS			106	2297	99.13	59	1116	99.22	3578	99.16
<i>WSCD1</i>	17	rs75213074	T	0.03	72	96	100	111	2388	99.92	59	1116	97.78	3842	99.27
<i>RNF213</i>	17	rs17857135	C	0.17	Not imputed in GWAS			106	2220	96.65	59	1116	89.18	3501	94.14
JAG1	20	rs111404218	G	0.34	Not called in WGS			86	1818	81.62	Not called in WGS			1904	81.62
<i>SLC24A3</i>	20	rs4814864	C	0.26	72	95	98.80	110	2414	99.88	59	1116	98.10	3866	99.29
<i>CCM2L</i>	20	rs144017103	T	0.02	73	94	97.01	105	2324	99.75	59	1116	61.76	3771	87.79
<i>MED14</i>	X	rs12845494	G	0.27	68	88	98.72	114	2372	97.30	59	1116	91.98	3817	95.72

*We were not able to validate this SNP (a secondary signal at the ARMS2 locus) or find any suitable proxy SNPs in LD. Therefore we do not report it in the paper as a significant association to migraine and remove it from all other analyses.

Supplementary Table 6. Previously reported loci not reaching genome-wide significance in the current meta-analysis. We tested 3 loci (near *AJAP1*, near *MMP16*, and near *MTDH*) that were previously reported to be associated with migraine subtypes through GWA studies. For each of the 3 previously reported index SNPs we show the effect sizes and association *P*-values obtained from our primary analysis of all migraine (59,674 cases and 316,078 controls), from the MA subset analysis (6,332 cases and 142,817 controls), from the MO subset analysis (8,348 cases and 136,758 controls), and from a meta-analysis of the six clinical samples only (6,784 and 13,611 controls). These loci are no longer significant ($P < 5 \times 10^{-8}$) in our current larger sample for any subsetting of the data. The 'Q pval' is the *P*-value from Cochran's Q test for heterogeneity.

Locus	Original PMID	SNP	Minor Allele	All migraine					MA subtype					MO subtype					Clinical samples only				
				MAF	OR [95% CI]	P	Q pval	i ²	MAF	OR [95% CI]	P	Q pval	i ²	MAF	OR [95% CI]	P	Q pval	i ²	MAF	OR [95% CI]	P	Q pval	i ²
near <i>AJAP1</i>	23793025	rs10915437	G	0.35	0.99 [0.98–1.01]	0.39	3.8×10 ⁻⁴	0.56	0.34	0.93 [0.89–0.98]	0.002	0.08	0.39	0.34	1.03 [0.99–1.07]	0.20	0.04	0.47	0.37	0.90 [0.86–0.95]	4.4×10⁻⁵	0.06	0.53
near <i>MMP16</i>	23793025	rs10504861	T	0.17	0.98 [0.96–1.00]	0.05	0.30	0.11	0.16	0.95 [0.90–1.00]	0.06	0.61	0	0.16	0.90 [0.86–0.95]	4.9×10⁻⁵	0.31	0.14	0.18	0.93 [0.88–0.99]	0.02	0.57	0
near <i>MTDH</i>	20802479	rs1835740	T	0.23	1.01 [0.99–1.02]	0.42	0.38	0.06	0.22	1.07 [1.02–1.13]	0.005	0.18	0.28	0.23	1.01 [0.97–1.06]	0.55	0.57	0	0.22	1.10 [1.04–1.17]	7.0×10⁻⁴	0.26	0.22

Supplementary Table 7. The 44 LD-independent SNPs significantly associated with migraine ($P < 5 \times 10^{-8}$). Effect sizes and association P -values were obtained from the primary meta-analysis of all migraine (59,674 cases and 316,078 controls). SNPs are ordered by chromosomal position and shaded rows represent SNPs within loci containing two associated SNPs that are LD-independent ($r^2 < 0.1$ in 1000 Genomes European samples). The P -value(FE) lists the P -values from a fixed-effects meta-analysis and the P -value(RE) gives the P -value from a random effects model at the four SNPs that showed evidenced for heterogeneity in Cochran's Q test for heterogeneity (Q P -value < 0.05). i^2 is the heterogeneity index and PAR is the population attributable risk contributed by each individual SNP. To estimate PAR we used $PAR_k = AF_k(OR_k - 1) / [1 + AF_k(OR_k - 1)]$ where AF_k is the frequency of the risk allele and OR_k is the corresponding odds ratio of the risk-increasing allele at the k^{th} SNP. Note PARs are difficult to interpret as applied to risk alleles in a population, as they tend to overestimate the predictive value of variants to a disease. The 'No. Samples' and 'No. Studies' columns show the total number of samples and studies respectively that had the marker present after quality control filtering.

Nearest Gene	Chr	Position	SNP	Minor Allele	MAF	OR [95% CI]	P -value (FE)	P -value (RE)	No. Samples	No. Studies	Q P -value	i^2	PAR (%)
<i>PRDM16</i>	1	3075597	rs10218452	G	0.22	1.11 [1.10–1.13]	5.3×10^{-38}	-	370,744	20	0.44	0.01	2.48
<i>PRDM16</i>	1	3103312	rs12135062	T	0.23	1.05 [1.04–1.07]	3.7×10^{-10}	-	374,810	22	0.58	0	1.17
<i>LRR1Q3</i>	1	73899742	rs1572668	G	0.48	1.04 [1.02–1.05]	2.1×10^{-08}	-	374,810	22	0.26	0.14	1.85
<i>TSPAN2</i>	1	115677183	rs2078371	C	0.12	1.11 [1.09–1.13]	4.1×10^{-24}	-	374,810	22	0.24	0.15	1.28
<i>NGF</i>	1	115824398	rs7544256	G	0.36	0.96 [0.95–0.97]	8.7×10^{-09}	-	374,810	22	0.26	0.14	2.64
<i>ADAMTSL4</i>	1	150510660	rs6693567	C	0.27	1.05 [1.03–1.06]	1.2×10^{-08}	-	374,810	22	0.15	0.23	1.23
<i>MEF2D</i>	1	156450740	rs1925950	G	0.35	1.07 [1.06–1.09]	9.1×10^{-22}	-	374,810	22	0.06	0.33	2.45
<i>CARF</i>	2	203832867	rs138556413	T	0.03	0.88 [0.84–0.92]	2.3×10^{-08}	-	346,121	14	0.94	0	11.56
<i>HJURP</i>	2	234756811	rs566529	T	0.15	0.94 [0.93–0.96]	2.5×10^{-09}	-	374,706	22	0.37	0.06	4.84
<i>TRPM8</i>	2	234825093	rs10166942	C	0.20	0.94 [0.89–0.99]	2.2×10^{-27}	2.2×10^{-27}	374,706	22	0.01	0.44	7.5
<i>TGFB2</i>	3	30480559	rs6791480	T	0.31	1.04 [1.03–1.06]	7.8×10^{-09}	-	374,706	22	0.43	0.02	1.34
<i>GPR149</i>	3	154289946	rs13078967	C	0.03	0.87 [0.83–0.91]	1.8×10^{-09}	-	374,705	22	0.89	0	13.11
<i>SPINK2</i>	4	57727311	rs7684253	C	0.45	0.96 [0.94–0.97]	2.5×10^{-09}	-	374,706	22	0.42	0.03	2.27
<i>PHACTR1</i>	6	12903957	rs9349379	G	0.41	0.93 [0.92–0.95]	5.8×10^{-22}	-	374,706	22	0.26	0.14	4.07
<i>NOTCH4</i>	6	32206049	rs140002913	A	0.06	0.91 [0.88–0.94]	3.8×10^{-08}	-	237,502	17	0.36	0.08	8.73
<i>KCNK5</i>	6	39183470	rs10456100	T	0.28	1.06 [1.04–1.07]	6.9×10^{-13}	-	374,705	22	0.84	0	1.57
<i>FUT9</i>	6	96853967	rs4839827	C	0.47	1.05 [1.03–1.06]	5.7×10^{-10}	-	374,706	22	0.42	0.03	2.11

<i>FHL5</i>	6	97042147	rs67338227	T	0.23	1.09 [1.08–1.11]	2.0×10^{-27}	-	374,706	22	0.05	0.33	2.09
<i>GJA1</i>	6	121846038	rs28455731	T	0.16	1.06 [1.04–1.08]	7.3×10^{-09}	-	374,706	22	0.17	0.21	0.9
<i>HEY2</i>	6	126049040	rs1268083	C	0.48	0.96 [0.95–0.97]	5.3×10^{-09}	-	374,706	22	0.24	0.16	2.1
<i>C7orf10</i>	7	40406876	rs186166891	T	0.11	1.09 [1.07–1.12]	9.7×10^{-16}	-	374,705	22	0.29	0.12	0.98
<i>DOCK4</i>	7	111328397	rs10155855	T	0.05	1.08 [1.05–1.12]	2.1×10^{-08}	-	374,706	22	0.15	0.23	0.45
<i>ASTN2</i>	9	119252629	rs6478241	A	0.36	1.05 [1.04–1.07]	1.2×10^{-12}	-	374,706	22	0.09	0.29	1.85
<i>NRP1</i>	10	33468124	rs2506142	G	0.17	1.06 [1.04–1.07]	1.5×10^{-09}	-	374,706	22	0.09	0.29	0.95
<i>PLCE1</i>	10	96014622	rs10786156	G	0.45	0.95 [0.94–0.96]	2.0×10^{-14}	-	374,706	22	0.08	0.30	2.95
<i>PLCE1</i>	10	96019029	rs75473620	T	0.04	0.89 [0.86–0.93]	5.8×10^{-09}	-	374,706	22	0.74	0	10.25
<i>HPSE2</i>	10	100702737	rs12260159	A	0.07	0.92 [0.89–0.94]	3.2×10^{-10}	-	374,706	22	0.65	0	7.92
<i>ARMS2</i>	10	124210160	rs2223089	C	0.08	0.93 [0.91–0.95]	3.0×10^{-08}	-	374,706	22	0.24	0.15	6.37
<i>MRVI1</i>	11	10674044	rs4910165	C	0.33	0.94 [0.91–0.98]	3.7×10^{-14}	2.9×10^{-11}	374,706	22	0.02	0.41	3.71
<i>MPPED2</i>	11	30547438	rs11031122	C	0.24	1.04 [1.03–1.06]	3.5×10^{-08}	-	374,706	22	0.62	0	1.06
<i>YAP1</i>	11	102083608	rs10895275	A	0.33	1.04 [1.03–1.06]	1.6×10^{-08}	-	374,706	22	0.79	0	1.35
<i>IGSF9B</i>	11	133829706	rs561561	T	0.12	0.94 [0.92–0.96]	3.4×10^{-08}	-	368,251	20	0.77	0	5.3
<i>FGF6</i>	12	4518140	rs1024905	G	0.47	1.06 [1.04–1.08]	2.1×10^{-17}	-	374,706	22	0.17	0.21	2.77
<i>SDR9C7</i>	12	57308260	rs11172055	T	0.48	1.04 [1.03–1.06]	1.3×10^{-09}	-	374,706	22	0.37	0.06	2.08
<i>LRP1</i>	12	57527283	rs11172113	C	0.42	0.90 [0.89–0.91]	5.6×10^{-49}	-	374,706	22	0.71	0	5.98
<i>ITPK1</i>	14	93595591	rs11624776	C	0.31	0.96 [0.94–0.97]	7.9×10^{-09}	-	374,706	22	0.39	0.05	2.99
<i>CFDP1</i>	16	75442143	rs77505915	T	0.45	1.05 [1.03–1.06]	3.3×10^{-10}	-	374,705	22	0.92	0	2.08
<i>ZCCHC14</i>	16	87579870	rs4081947	G	0.34	1.03 [1.00–1.06]	2.5×10^{-08}	2.5×10^{-09}	368,251	20	0.01	0.47	1.4
<i>WSCD1</i>	17	5612640	rs75213074	T	0.03	0.89 [0.86–0.93]	7.1×10^{-09}	-	374,706	22	0.86	0	10.2
<i>RNF213</i>	17	78262161	rs17857135	C	0.17	1.06 [1.04–1.08]	5.2×10^{-10}	-	364,185	18	0.20	0.20	1.06
<i>JAG1</i>	20	10684159	rs111404218	G	0.34	1.05 [1.03–1.07]	2.0×10^{-09}	-	374,705	22	0.56	0	1.65
<i>SLC24A3</i>	20	19469817	rs4814864	C	0.26	1.07 [1.06–1.09]	2.2×10^{-19}	-	374,706	22	0.41	0.04	1.83
<i>CCM2L</i>	20	30628982	rs144017103	T	0.02	0.85 [0.76–0.96]	4.3×10^{-08}	1.2×10^{-08}	317,252	16	0.03	0.42	16.72
<i>MED14</i>	23	40764757	rs12845494	G	0.27	0.96 [0.95–0.97]	1.7×10^{-08}	-	358,626	18	0.60	0	2.88

Supplementary Table 8. Gene overlap and NHGRI/OMIM database annotations for the 38 loci. Loci are rank-ordered by *P*-value of association and annotated with the nearest coding gene to the index SNP. The region column provides the left and right boundaries of all markers that are in LD with the index SNP (with an $r^2 > 0.6$). The size is the length of this LD region. Any other protein coding genes with transcripts overlapping this region (including a 20kb flank on each transcript) are given as they could also be relevant to migraine.

Rank	Top SNP	Allele	EAF	OR [95% CI]	P	Nearest coding gene	Region (hg19/b37)	Size (kb)	Protein-coding genes in region	NHGRI GWAS catalog	OMIM
1	rs11172113	C	0.42	0.9 [0.89-0.91]	5.6E-49	<i>LRP1</i>	chr12:57244168-57545756	301.6	<i>LRP1</i> , <i>STAT6</i> , <i>NAB2</i> , <i>TMEM194A</i> , <i>MYO1A</i> , <i>TAC3</i> , <i>ZBTB39</i> , <i>HBCBP</i> , <i>GPR182</i> , <i>RDH16</i> , <i>SDR9C7</i>		MYO1A Deafness, autosomal dominant 48; TAC3 Hypogonadotropic hypogonadism 10 with or without anosmia
2	rs10218452	G	0.22	1.11 [1.1-1.13]	5.3E-38	<i>PRDM16</i>	chr1:3065568-3112278	46.7	<i>PRDM16</i>		
3	rs67338227	T	0.23	1.09 [1.08-1.11]	2.0E-27	<i>FHL5</i>	chr6:96735298-97092478	357.2	<i>FHL5</i> , <i>UFL1</i>		
4	rs10166942	C	0.20	0.91 [0.89-0.92]	2.2E-27	<i>TRPM8</i>	chr2:234726966-234874402	147.4	<i>TRPM8</i> , <i>HJURP</i> , <i>MROH2A</i>	BP response pmid=24165912 p=3E-08; Bilirubin levels pmid=21646302 p=7E-23	
5	rs2078371	C	0.12	1.11 [1.09-1.13]	4.1E-24	<i>TSPAN2</i>	chr1:115084796-115829943	745.2	<i>NGF</i> , <i>TSPAN2</i> , <i>TSHB</i> , <i>SYCP1</i> , <i>SIKE1</i> , <i>CSDE1</i> , <i>NRAS</i> , <i>AMPD1</i> , <i>DENND2C</i> , <i>BCAS2</i>	Autism pmid=24189344 p=4E-08	NRAS Autoimmune lymphoproliferative syndrome type IV; NRAS Noonan syndrome 6; NRAS Epidermal nevus, somatic; NRAS Thyroid carcinoma, follicular, somatic; NRAS Colorectal cancer, somatic; NRAS Melanocytic nevus syndrome, congenital, somatic; NRAS Neurocutaneous melanosis, somatic; NRAS Schimmelpenning-Feuerstein-Mims syndrome, somatic mosaic; TSHB Hypothyroidism, congenital, nongoitrous 4; AMPD1 Myopathy due to myoadenylate deaminase deficiency; NGF Neuropathy, hereditary sensory and autonomic, type V
6	rs9349379	G	0.41	0.93 [0.92-0.95]	5.8E-22	<i>PHACTR1</i>	chr6:12768218-12948388	180.2	<i>PHACTR1</i>	CAD pmid=21846871 p=9E-	

										26; Coronary artery calcification pmid=22144573 p=4E-22; Cervical artery dissection pmid= 25420145 p=1E-11	
7	rs1925950	G	0.35	1.07 [1.06-1.09]	9.1E-22	MEF2D	chr1:156403681-156507704	104.0	IQGAP3, MEF2D, C1orf61		
8	rs4814864	C	0.26	1.07 [1.06-1.09]	2.2E-19	SLC24A3	chr20:19455203-19574290	119.1	SLC24A3		
9	rs1024905	C	0.53	0.94 [0.93-0.96]	2.1E-17	FGF6	chr12:4514858-4529272	14.4	FGF6		
10	rs186166891	T	0.11	1.09 [1.07-1.12]	9.7E-16	C7orf10	chr7:40360982-40477363	116.4	C7orf10		C7orf10 Glutaric aciduria III
11	rs10786156	G	0.45	0.95 [0.94-0.96]	2.0E-14	PLCE1	chr10:95976903-96823366	846.5	CYP2C8, CYP2C9, CYP2C19, CYP2C18, HELLS, TBC1D12, NOC3L, PLCE1	BP pmid=21909115 p=7E-16; HTN pmid=21909115 p=9E-09; Dengue shock syndrome pmid=22001756 p=3E-10; Esophageal cancer pmid=21642993 p=4E-20; Personality dimensions pmid=21368711 p=4E-08; Response to clopidogrel therapy pmid=19706858 p=2E-13; Response to SSRIs pmid=24528284 p=2E-16; Warfarin maintenance dose pmid=19300499 p=3E-79; Acenocoumarol maintenance dosage pmid=19578179 p=8E-12; Blood metabolite levels pmid=24816252 p=9E-65; Dehydroepiandrosterone sulphate levels pmid=21533175 p=2E-08	CYP2C19 Mephenytoin poor metabolizer; CYP2C19 Opremazole poor metabolizer; CYP2C19 Proguanil poor metabolizer; CYP2C19 Clopidogrel, impaired responsiveness to; PLCE1 Nephrotic syndrome, type 3; CYP2C8 Rhabdomyolysis, cerivastatin-induced; CYP2C9 Tolbutamide poor metabolizer; CYP2C9 Warfarin sensitivity
12	rs4910165	C	0.33	0.95 [0.93-0.96]	3.7E-14	MRVI1	chr11:10654911-10699750	44.8	MRVI1		
13	rs10456100	T	0.28	1.06 [1.04-1.07]	6.9E-13	KCNK5	chr6:39117698-39187886	70.2	KCNK5		
14	rs6478241	A	0.36	1.05 [1.04-1.07]	1.2E-12	ASTN2	chr9:119157030-119479868	322.8	TRIM32, ASTN2, PAPPA-AS1, PAPPA	Height pmid=20881960 p=7E-10	TRIM32 Muscular dystrophy, limb-girdle, type 2H; TRIM32 Bardet-Biedl syndrome 11
15	rs12260159	A	0.07	0.92 [0.89-0.94]	3.2E-10	HPSE2	chr10:100600946-100792984	192.0	HPSE2		HPSE2 Urofacial syndrome 1

16	rs77505915	G	0.55	0.95 [0.94-0.97]	3.3E-10	<i>CFDP1</i>	chr16:75304623-75504768	200.2	<i>CHST6, TMEM170A, CFDP1, BCAR1</i>	Pulmonary function pmid=21946350 p=2E-11	CHST6 Macular corneal dystrophy
17	rs17857135	C	0.17	1.06 [1.04-1.08]	5.2E-10	<i>RNF213</i>	chr17:78235300-78269111	33.8	<i>RNF213, SLC26A11</i>	Moyamoya disease pmid=21048783 p=2E-08	RNF213 Moyamoya disease 2
18	rs2506142	G	0.17	1.06 [1.04-1.07]	1.5E-09	<i>NRP1</i>	chr10:33464928-33468456	3.5	<i>NRP1</i>		
19	rs13078967	C	0.03	0.87 [0.83-0.91]	1.8E-09	<i>GPR149</i>	chr3:153891622-154438050	546.4	<i>GPR149, DHX36, ARHGEF26</i>		
20	rs111404218	G	0.34	1.05 [1.03-1.07]	2.0E-09	<i>JAG1</i>	chr20:10658917-10698494	39.6	<i>JAG1</i>	Bone mineral density pmid=22504420 p=3E-19	JAG1 Alagille syndrome; JAG1 Tetralogy of Fallot; JAG1 Deafness, congenital heart defects, and posterior embryotoxon
21	rs7684253	T	0.55	1.04 [1.03-1.06]	2.5E-09	<i>REST</i>	chr4:57727311-57761417	34.1	<i>REST</i>	ARMD pmid=21909106 p=2E-08	
22	rs1268083	C	0.48	0.96 [0.95-0.97]	5.3E-09	<i>HEY2</i>	chr6:125988964-126116953	128.0	<i>NCOA7, HEY2</i>	Brugada syndrome pmid=23872634 p=5E-17	
23	rs75213074	T	0.03	0.89 [0.86-0.93]	7.1E-09	<i>WSCD1</i>	chr17:5603221-5621884	18.7	<i>NLRP1-WSCD1*</i>		NLRP1 Vitiligo-associated multiple autoimmune disease susceptibility 1; NLRP1 Corneal intraepithelial dyskeratosis and ectodermal dysplasia
24	rs28455731	T	0.16	1.06 [1.04-1.08]	7.3E-09	<i>GJA1</i>	chr6:121782750-121860207	77.5	<i>GJA1</i>	Heart rate pmid=23583979 p=7E-12	GJA1 Oculodentodigital dysplasia; GJA1 Syndactyly, type III; GJA1 Hypoplastic left heart syndrome 1; GJA1 Atrioventricular septal defect 3; GJA1 Oculodentodigital dysplasia, autosomal recessive; GJA1 Craniometaphyseal dysplasia, autosomal recessive
25	rs6791480	T	0.31	1.04 [1.03-1.06]	7.8E-09	<i>TGFBR2</i>	chr3:30427287-30500279	73.0	<i>RBMS3-TGFBR2*</i>	Breast cancer pmid=23535729 p=2E-08	TGFBR2 Colorectal cancer, hereditary nonpolyposis, type 6; TGFBR2 Esophageal cancer, somatic; TGFBR2 Loeys-Dietz syndrome, type 2
26	rs11624776	C	0.31	0.96 [0.94-0.97]	7.9E-09	<i>ITPK1</i>	chr14:93591673-93596315	4.6	<i>ITPK1</i>	Platelet counts pmid=22139419 p=1E-10; Thyroid hormone levels pmid=23408906 p=2E-09	

27	rs6693567	C	0.27	1.05 [1.03-1.06]	1.2E-08	ADAMTSL4	chr1:150250636-150515021	264.4	ADAMTSL4-AS1, AL356356.1, ADAMTSL4, ECM1, TARS2, RPRD2, PRPF3, MRPS21, C1orf51, C1orf54, APH1A, CA14		TARS2 Combined oxidative phosphorylation deficiency 21; ADAMTSL4 Ectopia lentis, isolated, autosomal recessive; ADAMTSL4 Ectopia lentis et pupillae; ECM1 Urbach-Wiethe disease
28	rs10895275	A	0.33	1.04 [1.03-1.06]	1.6E-08	YAP1	chr11:101990252-102135427	145.2	YAP1	Polycystic ovary syndrome pmid=22885925 p=1E-22	YAP1 Coloboma, ocular, with or without hearing impairment, cleft lip/palate, and/or mental retardation; YAP1 Coloboma, ocular
29	rs12845494	G	0.27	0.96 [0.95-0.97]	1.7E-08	MED14	chrX:40744847-40794520	49.7	MED14-USP9X*		USP9X Mental retardation, X-linked 99
30	rs10155855	T	0.05	1.08 [1.05-1.12]	2.1E-08	DOCK4	chr7:111323799-111330237	6.4	IMMP2L-DOCK4*	CRP and white cell count pmid=22788528 p=7E-11	
31	rs1572668	A	0.52	0.96 [0.95-0.98]	2.1E-08	LRR1Q3	chr1:73458846-74098899	640.1	NEGR1-LRR1Q3*	Schizophrenia pmid=23974872 p=4E-10; BMI pmid=20935630 p=2E-22; Obesity pmid=23563607 p=2E-17	
32	rs138556413	T	0.03	0.88 [0.84-0.92]	2.3E-08	CARF	chr2:203591540-204352252	760.7	RAPH1, ABI2, CYP20A1, NBEAL1, CARF, WDR12, ICA1L, FAM117B	CAD pmid=21378990 p=1E-09; Total cholesterol pmid=24097068 p=2E-09; Butyrylcholinesterase levels pmid=21862451 p=4E-18	
33	rs4081947	G	0.34	1.04 [1.03-1.06]	2.5E-08	ZCCHC14	chr16:87576129-87579870	3.7	ZCCHC14-JPH3*		JPH3 Huntington disease-like 2
34	rs2223089	C	0.08	0.93 [0.91-0.95]	3.0E-08	ARMS2	chr10:124126358-124232915	106.6	HTRA1, ARMS2, PLEKHA1	ARMD pmid=23455636 p=400E-540	PLEKHA1 Age-related maculopathy; HTRA1 Macular degeneration, age-related, 7; HTRA1 Macular degeneration, age-related, neovascular type; HTRA1 CARASIL syndrome
35	rs561561	T	0.12	0.94 [0.92-0.96]	3.4E-08	IGSF9B	chr11:133813808-133846186	32.4	IGSF9B		

36	rs11031122	C	0.24	1.04 [1.03-1.06]	3.5E-08	<i>MPPED2</i>	chr11:30492070-30570596	78.5	<i>MPPED2</i>		
37	rs140002913	A	0.06	0.91 [0.88-0.94]	3.8E-08	<i>NOTCH4</i>	chr6:32200054-32206049	6.0	<i>NOTCH4</i>	Schizophrenia pmid=19571808 p=2E-10; Systemic sclerosis pmid=21779181 p=9E-21; Celiac disease pmid=23936387 p=5E-21; UC pmid=24837172 p=8E-10; RA pmid=21505073 p=2E-38; ARMD pmid=22694956 p=2E-11; Asthma pmid=21804548 p=4E-23; Nephropathy pmid=20595679 p=1E-09; Prostate cancer pmid=23535732 p=5E-09; Myeloperoxidase levels pmid=23620142 p=1E-08; Complement C3 and C4 levels pmid=23028341 p=4E-72	
38	rs144017103	T	0.02	0.83 [0.78-0.89]	4.3E-08	<i>CCM2L</i>	chr20:30610164-30628982	18.8	<i>HCK, CCM2L, XKR7</i>		

*Column 10 shows (1) all genes overlapping the locus after adding a 20kb flank to capture regulatory effects; or (2) if no overlapping genes in (1), the nearest upstream and downstream genes within 500kb are given (these loci are marked with an asterisk).

Column 11 shows intersections with the NHGRI GWAS catalog (<http://www.genome.gov/gwastudies>, downloaded February 2015) filtered for SNPs with $P < 5 \times 10^{-8}$ and retaining the SNP-phenotype entry with lowest P value. For each entry, the trait, PubMed identifier and P value are given.

Column 12 shows entries in the Online Mendelian Inheritance in Man (<http://omim.org>, downloaded February 2015), and gives gene name and corresponding disorder.

Abbreviations: ARMD=Age-related macular degeneration; BMI=Body mass index; BP=Blood pressure; CRP=C-reactive protein; HTN=Hypertension; RA=Rheumatoid arthritis; SSRI=Serotonin reuptake inhibitors; UC=Ulcerative colitis.

Supplementary Table 9. Genes in the 38 loci with previously reported associations to mechanisms or diseases that have hypothesized links to migraine. Genes are grouped by the previously hypothesized mechanism or disease and pubmed IDs are given for each relevant publication.

Mechanism/disease	Annotating only one gene per locus (the gene closest to index SNP)	Other genes in loci
Ion channels	<i>KCNK5</i> (PMID: 16239344) <i>TRPM8</i> (PMID: 23596210)	
Ion homeostasis	<i>KCNK5</i> (ion channel. PMID: 16239344) <i>TRPM8</i> (ion channel. PMID: 23596210) <i>SLC24A3</i> (exchanger. PMID: 11294880) <i>ITPK1</i> (ion flux regulator. PMID: 8816834) <i>GJA1</i> (Ca ²⁺ oscillations. PMID: 21654699)	<i>SLC26A11</i> (Cl ⁻ channel) <i>JPH3</i>
NO or oxidative stress	<i>REST</i> (Ox. stress PMID: 24670762) <i>GJA1</i> (Ox. stress PMID: 23456878) <i>YAP1</i> (Ox. stress PMID: 24810048) <i>PRDM16</i> (Ox. stress PMID: 20835244) <i>LRP1</i> (Ox. stress PMID: 21454812) <i>MRVI1</i> (NO PMID: 10724174)	<i>BCAR1</i> <i>USP9X</i> <i>IMMP2L</i> <i>HTRA1</i>
Vascular diseases	<i>PHACTR1</i> (PMID: 19198609 and 25420145) <i>TGFBR2</i> (PMID: 16885183) <i>LRP1</i> (AAA PMID: 22055160) <i>PRDM16</i> (Cardiomyopathy PMID: 23768516) <i>RNF213</i> (Moyamoya PMID: 24949311) <i>JAG1</i> (OMIMs PMID: 12427653) <i>HEY2</i> (Brugada Sy PMID: 23872634) <i>GJA1</i> (PMID: 25124494) <i>ARMS2</i> (Wet AMD. PMID: 20385826)	<i>HTRA1</i> (CARASIL)
Regulation of vascular tone	<i>MRVI1</i> (PMID: 20080989) <i>GJA1</i> (PMID: 17085540) <i>SLC24A3</i> (PMID 16617138) <i>NRP1</i> (PMID: 25659123)	<i>GPR182</i> <i>TAC3</i> <i>BCAR1</i>

Supplementary Table 10. NHGRI GWAS catalog SNPs correlated with the migraine SNPs. The table lists any National Human Genome Research Institute (NHGRI) GWAS catalog SNPs with previously reported associations ($P < 5 \times 10^{-8}$) to other diseases/traits that are also in high LD (allelic $R^2 > 0.8$) with any of the 44 associated SNPs identified for migraine. Also shown is the risk-increasing allele reported for both the migraine SNP and the GWAS catalog SNP and the corresponding risk allele frequencies (RAF). The allelic R^2 is the square of Pearson's correlation coefficient between alleles at both SNPs (estimated using 1000 Genomes European individuals). The GWAS catalog data was downloaded on Jan 28th 2016.

Locus	Migraine meta-analysis data					GWAS catalog data							
	Migraine SNP	Risk allele	RAF	OR [95% CI]	P-value	DISEASE/TRAIT	GWAS catalog SNP	Allelic R ²	Risk Allele	RAF	OR [95% CI]	P-value	PUBMED ID
PHACTR1	rs9349379	A	0.59	1.07 [1.06-1.09]	5.8×10 ⁻²²	Coronary artery calcification	rs9349379	1	A	0.59	1.22 [1.17-1.27]	4.0E-22	22144573
PHACTR1	rs9349379	A	0.59	1.07 [1.06-1.09]	5.8×10 ⁻²²	Cervical artery dissection	rs9349379	1	A	0.60	1.30 [1.20-1.39]	1.0E-11	25420145
PHACTR1	rs9349379	A	0.59	1.07 [1.06-1.09]	5.8×10 ⁻²²	Coronary heart disease	rs9349379	1	G	0.70	1.15 [1.10-1.21]	2.0E-09	22751097
near ITPK1	rs11624776	A	0.69	1.04 [1.03-1.06]	7.9×10 ⁻⁰⁹	Thyroid hormone levels	rs11624776	1	A	0.66	1.07 [1.04-1.09]	2.0E-09	23408906
LRP1/STAT6/SDR9C7	rs11172113	T	0.58	1.11 [1.09-1.13]	5.6×10 ⁻⁴⁹	Pulmonary function	rs11172113	1	T	0.61	1.03 [1.02-1.04]	1.0E-08	21946350
PRDM16	rs10218452	G	0.22	1.11 [1.10-1.13]	5.3×10 ⁻³⁸	Motion sickness	rs61759167	0.92	T	0.23	1.05 [1.03-1.06]	4.0E-13	25628336
CFDP1	rs77505915	T	0.45	1.05 [1.03-1.06]	3.3×10 ⁻¹⁰	Pulmonary function	rs2865531	0.81	T	0.42	1.03 [1.02-1.04]	2.0E-11	21946350
HEY2/NCOA7	rs1268083	T	0.52	1.04 [1.03-1.06]	5.3×10 ⁻⁰⁹	Brugada syndrome	rs9388451	0.81	C	0.50	1.58 [1.42-1.75]	5.0E-17	23872634

Supplementary Table 11 The seven loci associated with the MO subtype. Effect sizes and association *P*-values were obtained from the subset-analysis of the MO subtype (8,348 cases and 139,622 controls). The *Q* *P*-value is the *P*-value from Cochran's *Q* test for heterogeneity and the *i*² is the heterogeneity index. The 'No. Samples' column shows the total number of samples with each marker present after quality control filtering. Likewise, the 'No. Studies' column shows the total number GWA studies with each marker present after quality control filtering that could contribute data towards the final result.

Nearest Gene	Chr	Pos	Index SNP	Allele	MAF	OR [95%CI]	P	No. Samples	No. Studies	Q <i>P</i> -value	<i>i</i> ² (%)
<i>TSPAN2</i>	1	115677183	rs2078371	C	0.11	1.18 [1.12-1.25]	7.4E-09	144,801	11	0.61	0
<i>TRPM8</i>	2	234820578	rs6724624	G	0.20	0.86 [0.82-0.90]	1.1E-09	144,703	11	0.003	62.4
<i>PHACTR1</i>	6	12903957	rs9349379	G	0.41	0.88 [0.85-0.92]	2.1E-09	144,703	11	0.55	0
<i>FHL5</i>	6	97056979	rs7775721	T	0.33	1.15 [1.11-1.20]	1.1E-12	144,702	11	0.26	19.3
<i>ASTN2</i>	9	119252629	rs6478241	A	0.35	1.14 [1.09-1.18]	1.2E-10	144,703	11	0.50	0
<i>FGF6</i>	12	4518140	rs1024905	G	0.48	1.12 [1.08-1.16]	2.5E-09	144,703	11	0.65	0
<i>LRP1</i>	12	57527283	rs11172113	C	0.45	0.85 [0.82-0.89]	4.3E-16	144,703	11	0.77	0

Supplementary Table 12. Subsets of non-overlapping MA/MO samples used for the heterogeneity analysis. Listed are the two subsets created for MA and MO that contained no overlapping control individuals. The new MA subset consisted of 4,837 cases and 49,174 controls and the new MO subset consisted of 4,833 cases and 106,834 controls, as outlined in the table. These GWA studies from both subsets were then all combined together using a subtype-differentiated meta-analysis that allows for different allelic effects between the two groups. The results from this analysis are presented in **Supplementary Table 13**.

GWA study	<u>MA subset</u>		<u>MO subset</u>	
	Cases	Controls	Cases	Controls
Danish HC	-	-	996	1,000
DeCODE	-	-	608	95,585
Dutch MA	734	5,211	-	-
Dutch MO	-	-	1,115	2,028
EGCUT	76	7,300	-	-
Finnish MA	933	2,715	-	-
German MA	1,071	1,010	-	-
German MO	-	-	1,160	1,647
HUNT	302	1,011	-	-
NTR/NESDA	544	3,819	-	-
Rotterdam III	-	-	381	2,175
Twins UK	-	-	416	2,334
WGHS	1,177	18,108	-	-
YoungFinns	-	-	157	2,065
Total:	4,837	39,174	4,833	106,834

Supplementary Table 13. Testing for heterogeneity between MA and MO. Taking the 44 identified migraine SNPs, the table lists the results from a sub-type differentiated meta-analysis using non-overlapping subsets of the MA and MO samples (**Supplementary Table 12**). A fixed effects meta-analysis of these two subtypes is also provided in the table for comparison. The combined sample of all studies from both subsets shows the results from the sub-type differentiated meta-analysis and test for heterogeneity, as implemented in GWAMA. The seven SNPs highlighted in bold showed evidence of heterogeneity (Heterogeneity $P < 0.05$).

Nearest Gene	Chr	SNP	MA subtype			MO subtype			Combined Sample (MA and MO)				
			EAf	OR	P	EAf	OR	P	EAf	OR	P (fixed-effects)	P (rand-effects)	Heterogeneity P
<i>PRDM16</i>	1	rs10218452	0.25	1.11	2.2E-04	0.18	1.12	5.0E-04	0.20	1.11	3.9E-07	2.5E-06	8.5E-01
<i>PRDM16</i>	1	rs12135062	0.24	1.06	2.5E-02	0.21	1.05	9.9E-02	0.22	1.06	5.6E-03	2.1E-02	7.9E-01
<i>LRR1Q3</i>	1	rs1572668	0.49	1.00	9.7E-01	0.48	1.05	6.2E-02	0.48	1.02	2.0E-01	1.8E-01	1.8E-01
<i>MEF2D</i>	1	rs1925950	0.66	0.94	9.8E-03	0.63	0.86	4.2E-08	0.64	0.90	2.1E-08	1.0E-08	2.1E-02
<i>TSPAN2</i>	1	rs2078371	0.11	1.10	6.8E-03	0.11	1.20	3.4E-06	0.11	1.15	2.8E-07	5.2E-07	1.1E-01
<i>ADAMTSL4</i>	1	rs6693567	0.74	0.98	4.6E-01	0.70	0.92	4.1E-03	0.71	0.95	1.2E-02	1.2E-02	1.1E-01
<i>NGF</i>	1	rs7544256	0.36	0.94	2.0E-02	0.33	0.91	9.2E-04	0.34	0.93	8.0E-05	2.7E-04	3.6E-01
<i>TRPM8</i>	2	rs10166942	0.19	0.87	1.7E-05	0.21	0.86	1.4E-05	0.20	0.87	9.8E-10	7.3E-09	8.1E-01
<i>CARF</i>	2	rs138556413	0.03	0.99	9.0E-01	0.03	0.83	5.3E-02	0.03	0.89	1.2E-01	1.5E-01	2.4E-01
<i>HJURP</i>	2	rs566529	0.15	0.88	3.3E-04	0.14	0.90	3.4E-03	0.14	0.89	3.8E-06	2.2E-05	7.8E-01
<i>GPR149</i>	3	rs13078967	0.03	0.85	4.1E-02	0.03	0.85	7.0E-02	0.03	0.85	6.3E-03	2.4E-02	9.7E-01
<i>TGFBR2</i>	3	rs6791480	0.31	1.06	2.0E-02	0.31	1.07	2.2E-02	0.31	1.06	1.1E-03	4.8E-03	9.0E-01
<i>SPINK2</i>	4	rs7684253	0.54	0.99	6.2E-01	0.56	1.12	1.3E-05	0.55	1.05	1.1E-02	6.3E-05	3.3E-04
<i>KCNK5</i>	6	rs10456100	0.27	1.07	1.6E-02	0.30	1.08	7.9E-03	0.29	1.07	3.6E-04	1.6E-03	7.5E-01
<i>HEY2</i>	6	rs1268083	0.47	0.94	7.5E-03	0.49	0.97	2.1E-01	0.48	0.95	4.9E-03	1.3E-02	3.8E-01
<i>NOTCH4</i>	6	rs140002913	0.95	1.19	2.1E-02	0.95	1.15	5.6E-02	0.95	1.17	2.9E-03	1.1E-02	7.2E-01
<i>FUT9</i>	6	rs4839827	0.53	0.95	4.7E-02	0.51	0.95	7.5E-02	0.52	0.95	7.6E-03	2.8E-02	9.7E-01
<i>GJA1</i>	6	rs28455731	0.15	1.07	3.6E-02	0.18	1.14	2.4E-04	0.17	1.10	5.4E-05	1.3E-04	2.1E-01
<i>FHL5</i>	6	rs67338227	0.23	1.12	6.0E-05	0.22	1.18	8.4E-08	0.22	1.15	4.7E-11	1.8E-10	2.2E-01
<i>PHACTR1</i>	6	rs9349379	0.43	0.98	3.3E-01	0.40	0.88	3.7E-06	0.41	0.93	1.0E-04	1.4E-05	7.0E-03
<i>DOCK4</i>	7	rs10155855	0.05	1.08	1.4E-01	0.04	1.07	2.5E-01	0.04	1.08	6.0E-02	1.7E-01	8.5E-01
<i>C7orf10</i>	7	rs186166891	0.11	1.12	2.8E-03	0.10	1.18	9.6E-05	0.10	1.15	1.3E-06	5.7E-06	3.8E-01

ASTN2	9	rs6478241	0.64	0.94	1.7E-02	0.65	0.86	1.0E-08	0.64	0.90	1.8E-08	4.3E-09	9.3E-03
<i>PLCE1</i>	10	rs10786156	0.43	0.94	7.5E-03	0.45	0.92	1.7E-03	0.45	0.93	4.2E-05	2.0E-04	6.1E-01
<i>HPSE2</i>	10	rs12260159	0.07	0.97	5.3E-01	0.06	0.87	1.1E-02	0.06	0.92	3.1E-02	3.3E-02	1.4E-01
<i>ARMS2</i>	10	rs2223089	0.08	0.93	1.2E-01	0.08	0.90	3.4E-02	0.08	0.92	9.6E-03	3.0E-02	6.0E-01
<i>NRP1</i>	10	rs2506142	0.17	1.08	2.3E-02	0.16	1.09	1.8E-02	0.16	1.08	1.1E-03	4.7E-03	8.2E-01
PLCE1	10	rs75473620	0.04	0.79	7.0E-04	0.05	0.97	6.4E-01	0.05	0.87	6.7E-03	2.8E-03	3.6E-02
<i>YAP1</i>	11	rs10895275	0.33	1.02	3.6E-01	0.31	1.05	1.1E-01	0.31	1.03	8.1E-02	1.9E-01	5.7E-01
MPPED2	11	rs11031122	0.25	1.12	1.7E-05	0.22	0.98	5.2E-01	0.23	1.06	4.9E-03	7.8E-05	9.2E-04
<i>MRVI1</i>	11	rs4910165	0.68	1.10	1.6E-04	0.65	1.11	2.4E-04	0.66	1.11	1.4E-07	9.3E-07	8.8E-01
<i>IGSF9B</i>	11	rs561561	0.12	0.93	9.1E-02	0.14	0.88	5.9E-03	0.14	0.91	2.0E-03	5.4E-03	3.6E-01
<i>FGF6</i>	12	rs1024905	0.53	0.94	5.5E-03	0.51	0.91	2.6E-04	0.52	0.92	6.6E-06	2.7E-05	4.0E-01
<i>LRP1</i>	12	rs11172113	0.41	0.90	2.1E-05	0.46	0.84	7.1E-10	0.45	0.88	3.7E-13	6.5E-13	7.1E-02
<i>SDR9C7</i>	12	rs11172055	0.48	1.04	1.1E-01	0.46	1.08	7.6E-03	0.46	1.06	3.0E-03	8.1E-03	3.E-01
<i>ITPK1</i>	14	rs11624776	0.32	0.98	4.6E-01	0.29	0.95	7.8E-02	0.30	0.97	8.3E-02	1.6E-01	4.2E-01
<i>ZCCHC14</i>	16	rs4081947	0.34	1.01	7.5E-01	0.34	1.03	3.3E-01	0.34	1.02	3.7E-01	5.9E-01	6.1E-01
<i>CFDP1</i>	16	rs77505915	0.54	0.95	6.9E-02	0.56	0.93	1.2E-02	0.56	0.94	2.4E-03	8.1E-03	5.4E-01
<i>RNF213</i>	17	rs17857135	0.16	1.04	3.2E-01	0.18	1.14	6.9E-04	0.17	1.09	2.3E-03	1.9E-03	7.2E-02
<i>WSCD1</i>	17	rs75213074	0.04	0.85	2.1E-02	0.02	0.95	4.8E-01	0.03	0.90	3.2E-02	5.4E-02	2.6E-01
<i>JAG1</i>	20	rs111404218	0.32	1.06	2.8E-02	0.35	1.05	1.1E-01	0.34	1.06	7.2E-03	2.5E-02	7.1E-01
<i>CCM2L</i>	20	rs144017103	0.02	0.92	5.3E-01	0.02	0.77	1.8E-02	0.02	0.83	2.6E-02	4.9E-02	3.0E-01
<i>SLC24A3</i>	20	rs4814864	0.25	1.04	1.4E-01	0.25	1.09	3.9E-03	0.25	1.06	2.4E-03	5.1E-03	2.5E-01
MED14	X	rs12845494	0.73	1.07	7.4E-03	0.75	0.99	6.9E-01	0.74	1.04	6.5E-02	2.6E-02	4.7E-02

Supplementary Table 14. List of credible set SNPs in each locus. For each of the migraine loci, the table lists all SNPs included in the 99% credible sets that were calculated. The SNPs are ordered by posterior probability of being the causal SNP (highest first) with the corresponding posterior probability for each SNP given in brackets.

Locus Rank	Locus	Index SNP	No. Credible Set SNPs	List of Credible Set SNPs (posterior probability in brackets)
1	<i>LRP1/STAT6/SDR9C7</i>	rs11172113	1	rs11172113 (0.996),
2	<i>PRDM16</i>	rs10218452	8	rs10218452 (0.613), rs10797381 (0.288), rs7518255 (0.053), rs2075968 (0.011), rs10909886 (0.008), rs2376495 (0.007), rs61759167 (0.007), rs11587518 (0.004),
3	<i>FHL5/UFL1</i>	rs67338227	18	rs67338227 (0.240), rs2971603 (0.167), rs2983896 (0.099), rs9285393 (0.095), rs2971606 (0.090), rs3798293 (0.078), rs2983897 (0.075), rs2971608 (0.037), rs11751075 (0.034), rs11759769 (0.029), rs4486027 (0.013), rs3860229 (0.007), rs3860231 (0.007), rs3860230 (0.007), rs2971609 (0.005), rs6568392 (0.004), rs4265039 (0.004), rs4346856 (0.004),
4	<i>TRPM8/HJURP</i>	rs10166942	11	rs10166942 (0.142), rs1965629 (0.128), rs1985366 (0.128), rs10170399 (0.128), rs1003540 (0.118), rs6738979 (0.100), rs11563063 (0.084), rs6724624 (0.062), rs11892538 (0.050), rs4663983 (0.027), rs2362290 (0.025),
5	near <i>TSPAN2/NGF</i>	rs2078371	2	rs2078371 (0.560), rs12134493 (0.440),
6	<i>PHACTR1</i>	rs9349379	1	rs9349379 (1.000),
7	<i>MEF2D</i>	rs1925950	22	rs1925950 (0.089), rs3790454 (0.083), rs6700679 (0.065), rs4450010 (0.062), rs2282286 (0.061), rs6658120 (0.059), rs2274317 (0.057), rs2274319 (0.057), rs12131289 (0.055), rs3790455 (0.051), rs2274316 (0.049), rs2274320 (0.048), rs3818463 (0.048), rs11264486 (0.040), rs12038396 (0.030), rs3790459 (0.028), rs3790457 (0.025), rs10908505 (0.023), rs1050316 (0.023), rs10908504 (0.020), rs1342442 (0.017), rs12136856 (0.012),
8	<i>SLC24A3</i>	rs4814864	21	rs4814864 (0.159), rs4814863 (0.112), rs4814860 (0.109), rs6046139 (0.066), rs6035354 (0.054), rs4814861 (0.051), rs6046147 (0.046), rs1984571 (0.045), rs6035357 (0.044), rs6046144 (0.042), rs6046140 (0.042), rs6136756 (0.040), rs4814858 (0.032), rs6081613 (0.027), rs6046134 (0.025), rs6035353 (0.025), rs6081612 (0.023), rs3827986 (0.020), rs6046137 (0.014), rs3790228 (0.008), rs6035355 (0.007),
9	near <i>FGF6</i>	rs1024905	8	rs1024905 (0.284), rs10849061 (0.239), rs4766241 (0.163), rs2160875 (0.105), rs7957385 (0.097), rs1075550 (0.096), rs6489545 (0.006), rs7300066 (0.006),
10	<i>C7orf10</i>	rs186166891	42	rs186166891 (0.071), rs10234636 (0.049), rs77410344 (0.048), rs4723954 (0.039), rs12533531 (0.035), rs12532479 (0.034), rs12670267 (0.033), rs144002785 (0.032), rs11531504 (0.031), rs10435164 (0.031), rs80157425 (0.029), rs17171694 (0.027), rs77024938 (0.027), rs141208879 (0.026), rs147040642 (0.026), rs10951637 (0.025), rs17171696 (0.025), rs138268186 (0.025),

				rs1319467 (0.022), rs12669577 (0.021), rs79841539 (0.021), rs78017680 (0.020), rs17171705 (0.019), rs2190261 (0.019), rs17171703 (0.019), rs118103401 (0.019), rs12673516 (0.018), rs4434532 (0.017), rs4526265 (0.017), rs17171693 (0.017), rs77423178 (0.017), rs141633631 (0.016), rs117198283 (0.015), rs17171710 (0.014), rs78360249 (0.014), rs59682057 (0.013), rs12234460 (0.013), rs76206723 (0.012), rs11531505 (0.010), rs12538229 (0.009), rs12531683 (0.009), rs4379368 (0.008),
11	<i>PLCE1</i>	rs10786156	6	rs10786156 (0.235), rs57866767 (0.206), rs3891783 (0.166), rs11187838 (0.162), rs2274224 (0.131), rs7080472 (0.099),
12	<i>MRVI1</i>	rs4910165	9	rs4910165 (0.298), rs7940646 (0.220), rs4909945 (0.174), rs4442541 (0.169), rs10840457 (0.051), rs2052692 (0.034), rs6484437 (0.020), rs2098839 (0.019), rs1863243 (0.014),
13	<i>KCNK5</i>	rs10456100	4	rs10456100 (0.476), rs733701 (0.264), rs2815116 (0.180), rs9394578 (0.073),
14	<i>ASTN2</i>	rs6478241	3	rs6478241 (0.700), rs1040851 (0.226), rs10817898 (0.073),
15	<i>HPSE2</i>	rs12260159	59	rs12260159 (0.683), rs12266229 (0.017), rs112255710 (0.010), rs7919920 (0.008), rs7897140 (0.008), rs7071748 (0.008), rs11189905 (0.008), rs7070985 (0.008), rs7900872 (0.007), rs4917851 (0.007), rs7076651 (0.007), rs72836764 (0.007), rs10883234 (0.007), rs12258897 (0.007), rs11189909 (0.007), rs3897503 (0.007), rs3897501 (0.007), rs10883233 (0.006), rs7073636 (0.006), rs7075240 (0.006), rs1418255 (0.006), rs6584226 (0.006), rs4917850 (0.006), rs7084022 (0.005), rs4919264 (0.005), rs7087272 (0.005), rs146149652 (0.005), rs11189918 (0.005), rs947541 (0.005), rs6584225 (0.005), rs114665397 (0.005), rs74154360 (0.004), rs12243465 (0.004), rs7091740 (0.004), rs56220031 (0.004), rs151051295 (0.004), rs72836746 (0.004), rs12259692 (0.004), rs4469820 (0.004), rs7100093 (0.004), rs7924025 (0.004), rs7907604 (0.004), rs4919267 (0.004), rs7082605 (0.004), rs11189856 (0.004), rs7897719 (0.004), rs7912212 (0.004), rs12254075 (0.004), rs72838806 (0.004), rs7091149 (0.004), rs12260410 (0.004), rs9630091 (0.003), rs7908265 (0.003), rs7910906 (0.003), rs4919265 (0.003), rs1444802 (0.003), rs11189861 (0.003), rs17111066 (0.003), rs6584230 (0.003),
16	<i>CFDP1</i>	rs77505915	238	rs77505915 (0.034), rs11149826 (0.016), rs11149827 (0.016), rs4888378 (0.012), rs34624768 (0.012), rs12935787 (0.012), rs11640473 (0.010), rs3851738 (0.009), rs11646852 (0.008), rs1011121 (0.008), rs62059846 (0.008), rs6564259 (0.008), rs3784935 (0.007), rs11645329 (0.007), rs11864102 (0.007), rs7188604 (0.007), rs4887816 (0.007), rs62062565 (0.007), rs6564258 (0.006), rs11149815 (0.006), rs11648176 (0.006), rs4888412 (0.006), rs4888418 (0.006), rs4594277 (0.006), rs34841467 (0.006), rs3851734 (0.006), rs11861810 (0.006), rs11862684 (0.006), rs2285225 (0.006), rs62062572 (0.006), rs11642572 (0.006), rs4243112 (0.006), rs4887824 (0.006), rs8056236 (0.006), rs4888383 (0.006), rs11641801 (0.005), rs12444589 (0.005), rs2285222 (0.005), rs11860231 (0.005), rs17685540 (0.005), rs34673655 (0.005), rs7206541 (0.005), rs8048527 (0.005), rs2285224 (0.005), rs4888376 (0.005), rs4888411 (0.005), rs12924782 (0.005), rs11149833 (0.005), rs11149825 (0.005), rs11149830 (0.005), rs11149824 (0.005), rs11643410 (0.005), rs2285223 (0.005), rs3863446 (0.005), rs2903033 (0.005), rs11641587 (0.005), rs12930768 (0.005), rs4888400 (0.005), rs766521 (0.005), rs8050769 (0.005), rs10514393 (0.005), rs11642921 (0.005), rs2161648 (0.005), rs7200616 (0.005), rs11862582 (0.005), rs4888405 (0.005), rs6564252 (0.005), rs8050059 (0.005), rs12149063 (0.005), rs34296964 (0.005),

			rs35937717 (0.005), rs4888389 (0.005), rs7203157 (0.005), rs7199132 (0.005), rs4146809 (0.005), rs8046000 (0.005), rs4888414 (0.005), rs8051407 (0.005), rs1109342 (0.005), rs12051326 (0.005), rs12928722 (0.005), rs11149829 (0.005), rs12051111 (0.005), rs12928898 (0.005), rs1109341 (0.004), rs4888409 (0.004), rs12051136 (0.004), rs12443834 (0.004), rs11149828 (0.004), rs4888391 (0.004), rs12933281 (0.004), rs8057849 (0.004), rs11640674 (0.004), rs12599361 (0.004), rs35415181 (0.004), rs7184525 (0.004), rs3851737 (0.004), rs4887822 (0.004), rs8054769 (0.004), rs2865530 (0.004), rs17696696 (0.004), rs1895490 (0.004), rs35263058 (0.004), rs34222958 (0.004), rs4888403 (0.004), rs4887821 (0.004), rs11862719 (0.004), rs12924920 (0.004), rs1549306 (0.004), rs4888387 (0.004), rs4888390 (0.004), rs7185640 (0.004), rs1364077 (0.004), rs4888410 (0.004), rs11858992 (0.004), rs4993969 (0.004), rs1544810 (0.004), rs4887823 (0.004), rs11865004 (0.004), rs4993970 (0.004), rs11860284 (0.004), rs62059845 (0.004), rs11149832 (0.004), rs56343285 (0.004), rs11864587 (0.004), rs35552529 (0.004), rs8057203 (0.004), rs2113232 (0.004), rs2865531 (0.004), rs113251659 (0.004), rs4887820 (0.004), rs3863442 (0.004), rs4888408 (0.004), rs1030261 (0.004), rs4888379 (0.004), rs4888388 (0.004), rs4888392 (0.004), rs11646044 (0.004), rs11641532 (0.004), rs12445726 (0.004), rs11644741 (0.004), rs12917651 (0.004), rs4887815 (0.004), rs4888413 (0.004), rs71394207 (0.004), rs12448947 (0.004), rs4888416 (0.004), rs4888421 (0.004), rs1808434 (0.004), rs4888380 (0.004), rs35787595 (0.004), rs8057535 (0.004), rs10871311 (0.003), rs12929908 (0.003), rs11149822 (0.003), rs11643209 (0.003), rs7194129 (0.003), rs12922951 (0.003), rs3851733 (0.003), rs3863445 (0.003), rs62062564 (0.003), rs11644639 (0.003), rs67409275 (0.003), rs12449170 (0.003), rs4888420 (0.003), rs2865528 (0.003), rs34029337 (0.003), rs12930452 (0.003), rs4888415 (0.003), rs12927562 (0.003), rs59686216 (0.003), rs8060955 (0.003), rs11862095 (0.003), rs4638613 (0.003), rs4888407 (0.003), rs7188231 (0.003), rs1808436 (0.002), rs4888404 (0.002), rs10431974 (0.002), rs60730309 (0.002), rs4887818 (0.002), rs59155720 (0.002), rs4888386 (0.002), rs10459859 (0.002), rs35952313 (0.002), rs4888406 (0.002), rs8046109 (0.002), rs62062568 (0.002), rs72787160 (0.002), rs1808435 (0.002), rs11149818 (0.002), rs12443904 (0.002), rs35737321 (0.002), rs10781976 (0.002), rs4888385 (0.002), rs10514396 (0.002), rs6564260 (0.002), rs10871312 (0.002), rs11149820 (0.002), rs17696749 (0.002), rs12929673 (0.002), rs7499872 (0.002), rs4146810 (0.002), rs4243111 (0.002), rs35209155 (0.002), rs1364079 (0.002), rs1559339 (0.002), rs3863447 (0.002), rs8055974 (0.002), rs8056080 (0.002), rs11646677 (0.002), rs1364078 (0.002), rs2059256 (0.002), rs3743609 (0.002), rs2161684 (0.002), rs4888372 (0.002), rs35261357 (0.002), rs62062567 (0.002), rs34996006 (0.002), rs56004344 (0.001), rs1030262 (0.001), rs11865296 (0.001), rs4888425 (0.001), rs35214308 (0.001), rs7200053 (0.001), rs34021527 (0.001), rs4888426 (0.001), rs7202567 (0.001), rs12928036 (0.001), rs4887825 (0.001), rs7202596 (0.001), rs59465235 (0.001), rs4888422 (0.001), rs59867374 (0.001), rs1542864 (0.001), rs7198873 (0.001), rs7204984 (0.001), rs60937209 (0.001),
17	<i>RNF213</i>	rs17857135	16 rs17857135 (0.280), rs34397069 (0.085), rs73444339 (0.085), rs12942629 (0.077), rs17853989 (0.073), rs17853713 (0.068), rs35573434 (0.066), rs11651637 (0.056), rs17853714 (0.051), rs34155220 (0.043), rs12939230 (0.042), rs34801706 (0.039), rs55971860 (0.010), rs9909720 (0.007), rs9891691 (0.006), rs9890495 (0.005),

18	<i>NRP1</i>	rs2506142	7	rs2506142 (0.213), rs2474737 (0.199), rs2474735 (0.185), rs2506144 (0.113), rs2506140 (0.104), rs2474733 (0.092), rs2506143 (0.092),
19	near <i>GPR149</i>	rs13078967	5	rs13078967 (0.436), rs144029925 (0.276), rs34097149 (0.154), rs112346815 (0.120), rs71308496 (0.005),
20	near <i>JAG1</i>	rs111404218	4	rs111404218 (0.899), rs6134000 (0.048), rs2057053 (0.028), rs8183037 (0.025),
21	near <i>REST/SPINK2</i>	rs7684253	2	rs7684253 (0.922), rs2412771 (0.078),
22	<i>HEY2/NCOA7</i>	rs1268083	36	rs1268083 (0.080), rs9321054 (0.074), rs1269175 (0.053), rs3799709 (0.053), rs3799711 (0.052), rs7753038 (0.046), rs1159974 (0.045), rs1811852 (0.039), rs3966775 (0.035), rs2144224 (0.034), rs10457469 (0.033), rs9398787 (0.032), rs3757217 (0.032), rs1268070 (0.031), rs13209968 (0.030), rs7739566 (0.030), rs4897155 (0.029), rs1268065 (0.026), rs1268064 (0.026), rs980014 (0.023), rs9388451 (0.018), rs1028481 (0.016), rs7764016 (0.016), rs4897157 (0.015), rs9388453 (0.015), rs9401845 (0.013), rs2008027 (0.013), rs9398791 (0.012), rs9388454 (0.011), rs9388446 (0.011), rs7758115 (0.011), rs1268069 (0.010), rs10457467 (0.009), rs9375411 (0.008), rs4897156 (0.007), rs11154331 (0.007),
23	near <i>WSCD1/NLRP1</i>	rs75213074	7	rs75213074 (0.611), rs117584668 (0.179), rs79482790 (0.070), rs79022350 (0.064), rs76210292 (0.041), rs78383461 (0.018), rs111501524 (0.017),
24	near <i>GJA1</i>	rs28455731	14	rs28455731 (0.103), rs17083712 (0.098), rs9490315 (0.098), rs9320821 (0.096), rs34995334 (0.095), rs7757975 (0.080), rs9490310 (0.071), rs17083744 (0.065), rs9490314 (0.062), rs9490312 (0.061), rs9482172 (0.052), rs28581202 (0.050), rs9490308 (0.039), rs9490313 (0.023),
25	near <i>TGFBR2</i>	rs6791480	19	rs6791480 (0.191), rs7371912 (0.186), rs4131728 (0.088), rs4075748 (0.084), rs4075749 (0.076), rs4508823 (0.065), rs34130299 (0.057), rs12496164 (0.051), rs4955308 (0.040), rs6790925 (0.037), rs79617173 (0.033), rs7649804 (0.019), rs1994987 (0.019), rs4955309 (0.017), rs7640543 (0.017), rs11129403 (0.004), rs78631748 (0.004), rs11129402 (0.002), rs75407597 (0.002),
26	near <i>ITPK1</i>	rs11624776	3	rs11624776 (0.476), rs28540738 (0.448), rs2402246 (0.076),
27	near <i>ADAMTSL4/ECM1</i>	rs6693567	7	rs6693567 (0.758), rs78976593 (0.135), rs4970996 (0.041), rs698915 (0.022), rs1260387 (0.019), rs12740679 (0.008), rs9436117 (0.008),
28	<i>YAP1</i>	rs10895275	66	rs10895275 (0.065), rs10895276 (0.064), rs11608234 (0.059), rs11225165 (0.043), rs11225167 (0.041), rs10895274 (0.038), rs1820455 (0.035), rs10895277 (0.034), rs12786272 (0.033), rs7122907 (0.032), rs17097547 (0.031), rs4475891 (0.030), rs7124247 (0.030), rs10895273 (0.029), rs1893498 (0.023), rs3858420 (0.022), rs12787996 (0.021), rs17097560 (0.020), rs10895278 (0.020), rs2282652 (0.017), rs8504 (0.017), rs2187525 (0.015), rs11225160 (0.015), rs58751289 (0.014), rs12790399 (0.014), rs11225156 (0.014), rs4447144 (0.014), rs11605954 (0.014), rs12421242 (0.013), rs11225174 (0.013), rs12223991 (0.012), rs7931576 (0.012), rs12226331 (0.011), rs11225163 (0.009), rs4754041 (0.009), rs10895272 (0.009), rs7110557 (0.008), rs10895280 (0.007), rs11225177 (0.007), rs12420287 (0.007), rs11225170 (0.007), rs12807220 (0.005), rs57027482 (0.004), rs12793501 (0.004), rs1895916 (0.004), rs7104685 (0.004), rs12795624 (0.003), rs7110355 (0.003), rs1820454 (0.003), rs11225169 (0.003), rs10895270 (0.003), rs34083536 (0.003), rs10791569 (0.003), rs7942061 (0.002), rs718891

				(0.002), rs4420227 (0.002), rs61280272 (0.002), rs12787825 (0.002), rs2114308 (0.002), rs7112802 (0.002), rs7107909 (0.001), rs7120067 (0.001), rs12222063 (0.001), rs2846837 (0.001), rs4561174 (0.001), rs11225153 (0.001),
30	near <i>DOCK4/IMMP2L</i>	rs10155855	15	rs10155855 (0.201), rs11770473 (0.188), rs10262821 (0.152), rs57369558 (0.078), rs58145389 (0.075), rs7808745 (0.064), rs7789527 (0.031), rs10156055 (0.030), rs28626025 (0.029), rs10229093 (0.028), rs112078904 (0.027), rs10272370 (0.027), rs10263444 (0.025), rs57519933 (0.022), rs60103724 (0.022),
31	<i>1p31.1</i>	rs1572668	147	rs12037168 (0.020), rs1572668 (0.020), rs11210247 (0.020), rs11210251 (0.014), rs4113049 (0.014), rs4287126 (0.013), rs12747728 (0.013), rs4113050 (0.013), rs12033505 (0.013), rs35101879 (0.013), rs2095794 (0.013), rs4369181 (0.012), rs11210242 (0.012), rs11210244 (0.012), rs12026485 (0.012), rs6672225 (0.011), rs1923243 (0.011), rs61605983 (0.011), rs2341392 (0.011), rs12742409 (0.011), rs12718437 (0.011), rs6679389 (0.011), rs6669843 (0.011), rs10493517 (0.011), rs2173735 (0.010), rs7416650 (0.010), rs1338653 (0.010), rs7522217 (0.010), rs7532462 (0.010), rs12028720 (0.010), rs1021756 (0.010), rs61765512 (0.009), rs12406253 (0.009), rs7555507 (0.009), rs7553998 (0.009), rs1885250 (0.009), rs11210243 (0.008), rs1885251 (0.008), rs4463622 (0.008), rs10493518 (0.008), rs7528128 (0.008), rs11210276 (0.008), rs1338650 (0.008), rs11210232 (0.008), rs1316718 (0.008), rs12565386 (0.008), rs61765513 (0.008), rs11210266 (0.008), rs12039430 (0.007), rs1338647 (0.007), rs11210239 (0.007), rs1338648 (0.007), rs11210236 (0.007), rs1416266 (0.007), rs4636406 (0.007), rs1538376 (0.007), rs7519030 (0.007), rs11210235 (0.007), rs1538375 (0.007), rs1338656 (0.007), rs4354497 (0.007), rs61765511 (0.007), rs12562533 (0.007), rs1416274 (0.007), rs7521446 (0.007), rs10465868 (0.007), rs10465869 (0.007), rs1361244 (0.007), rs11210237 (0.007), rs4557913 (0.007), rs12044316 (0.007), rs1338649 (0.007), rs35641559 (0.007), rs11210263 (0.006), rs2340402 (0.006), rs11210261 (0.006), rs12759031 (0.006), rs911493 (0.006), rs7546305 (0.006), rs7549372 (0.006), rs6672818 (0.006), rs6424544 (0.006), rs10493515 (0.006), rs12077046 (0.006), rs12754690 (0.006), rs10890030 (0.006), rs4998957 (0.006), rs4361942 (0.005), rs1923226 (0.005), rs7513593 (0.005), rs11210218 (0.005), rs61765637 (0.005), rs11210191 (0.005), rs12033140 (0.005), rs12142515 (0.005), rs10890025 (0.005), rs10890029 (0.005), rs11210193 (0.005), rs12023347 (0.005), rs12044218 (0.005), rs6684341 (0.005), rs11210241 (0.005), rs2224494 (0.005), rs11210196 (0.005), rs11210259 (0.005), rs11210257 (0.005), rs3845343 (0.005), rs1120980 (0.005), rs10789368 (0.005), rs2180945 (0.005), rs35851404 (0.005), rs11210195 (0.004), rs11210258 (0.004), rs12564425 (0.004), rs12737087 (0.004), rs1923225 (0.004), rs1923217 (0.004), rs10890031 (0.004), rs12569115 (0.004), rs1923204 (0.004), rs7523734 (0.004), rs4406595 (0.004), rs12036558 (0.004), rs7513375 (0.003), rs1923240 (0.003), rs12239956 (0.003), rs11210188 (0.003), rs56060088 (0.003), rs12049376 (0.002), rs57578100 (0.002), rs6682579 (0.002), rs6692884 (0.002), rs12404978 (0.002), rs6684841 (0.002), rs8179409 (0.001), rs4129350 (0.001), rs138672342 (0.001), rs11210184 (0.001), rs4475699 (0.001), rs4650199 (0.001), rs4274014 (0.001), rs7518008 (0.001), rs4288548 (0.001), rs12034885 (0.001), rs11210177 (0.001), rs28585577 (0.001), rs13376454 (0.001),
32	<i>CARF</i>	rs138556413	2	rs138556413 (0.595), rs72926788 (0.405),

33	<i>ZCCHC14</i>	rs4081947	3	rs4081947 (0.504), rs8052831 (0.440), rs9929116 (0.050),
34	<i>ARMS2/HTRA1</i>	rs2223089	31	rs2223089 (0.251), rs7915081 (0.144), rs7898343 (0.097), rs80232578 (0.078), rs12571363 (0.074), rs78973239 (0.062), rs55928386 (0.041), rs117634244 (0.014), rs78438709 (0.014), rs75178961 (0.014), rs184800107 (0.014), rs74620354 (0.014), rs76568359 (0.013), rs2421015 (0.012), rs78986650 (0.012), rs76047227 (0.012), rs79581661 (0.012), rs4598609 (0.012), rs76432564 (0.011), rs12571218 (0.011), rs4551693 (0.011), rs78832427 (0.010), rs79508005 (0.009), rs41306858 (0.009), rs76797659 (0.008), rs80123520 (0.007), rs12571580 (0.006), rs111266031 (0.006), rs2281674 (0.006), rs74672221 (0.006), rs76579910 (0.006),
35	<i>IGSF9B</i>	rs561561	7	rs561561 (0.390), rs79071988 (0.192), rs493888 (0.169), rs678495 (0.104), rs12418760 (0.094), rs329661 (0.040), rs665448 (0.011),
36	<i>MPPED2</i>	rs11031122	17	rs11031122 (0.131), rs11031125 (0.099), rs11031126 (0.098), rs10835685 (0.088), rs11031127 (0.085), rs12361781 (0.077), rs35695296 (0.060), rs11031128 (0.058), rs11031129 (0.058), rs10835687 (0.050), rs11031133 (0.048), rs1458729 (0.028), rs12797142 (0.026), rs11606309 (0.025), rs11606078 (0.025), rs10835676 (0.021), rs61884730 (0.021),
37	near <i>NOTCH4</i>	rs140002913	15	rs140002913 (0.572), rs140467810 (0.036), rs116131534 (0.034), rs114097260 (0.034), rs143655257 (0.033), rs116807651 (0.033), rs115424290 (0.033), rs141370868 (0.033), rs151052195 (0.033), rs116637827 (0.032), rs140584153 (0.032), rs115741290 (0.032), rs145716761 (0.032), rs116322711 (0.015), rs115214125 (0.014),
38	near <i>CCM2L/HCK</i>	rs144017103	2	rs144017103 (0.506), rs76627106 (0.494),

Supplementary Table 15. Credible-set genic overlap analysis. Here we tested if SNPs in the 99% credible-sets from each locus overlapped with gene coding transcripts from Gencode. The ‘consequence’ columns indicate the most severe impact predicted for the variant out of all overlapping transcripts. SNPs highlighted in bold indicate variants that result in missense mutations. Three loci contain genes with credibly causal missense polymorphisms (*PLCE1*, *MRVI1*, and *RNF213*). Genes in each locus that were identified as significant (false discovery rate < 0.05) by DEPICT’s gene-prioritization function are also shown. Two prioritized genes match those with credibly causal missense variants (*PLCE1* and *MRVI1*).

Locus Index SNP	Index SNP genic overlap			Credible-Set genic overlap					DEPICT-prioritized genes		
	Nearest gene	Distance (kb)	Consequence	Total SNPs in Locus	No. SNPs in Credible-set	Overlapping genes	Consequence	Exonic credible-set SNPs	Gene	P-value	FDR
rs11172113	<i>LRP1</i>	0	Intronic	658	1	<i>LRP1</i>	Intronic	-	<i>LRP1</i>	0.00007	<0.005
rs10218452	<i>PRDM16</i>	0	Intronic	191	8	<i>PRDM16</i>	Intronic	-	<i>PRDM16</i>	0.004	0.01
rs67338227	<i>FHL5</i>	0	Intronic	851	18	<i>FHL5</i>	Intronic	-	-	-	-
rs10166942	<i>TRPM8</i>	1.0	Upstream	480	11	<i>TRPM8</i>	Intronic	-	-	-	-
rs2078371	<i>TSPAN2</i>	45.1	Intergenic	712	2	-	-	-	<i>NGF</i>	0.0007	<0.005
rs9349379	<i>PHACTR1</i>	0	Intronic	474	1	<i>PHACTR1</i>	Intronic	-	-	-	-
rs1925950	<i>MEF2D</i>	0	Synonymous	196	22	<i>MEF2D</i>	Synonymous	rs1925950, rs2274317	-	-	-
rs4814864	<i>SLC24A3</i>	0	Intronic	422	21	<i>SLC24A3</i>	Intronic	-	-	-	-
rs1024905	<i>FGF6</i>	19.2	Intergenic	41	8	-	-	-	<i>FGF6</i>	0.01	0.04
rs186166891	<i>C7orf10</i>	0	Intronic	223	42	<i>C7orf10</i>	Intronic	-	-	-	-
rs10786156	<i>PLCE1</i>	0	Intronic	206	6	<i>PLCE1</i>	Missense	rs2274224	<i>PLCE1</i>	0.0001	<0.005
rs4910165	<i>MRVI1</i>	0	Intronic	152	9	<i>MRVI1</i>	Missense	rs4909945	<i>MRVI1</i>	0.002	0.01
rs10456100	<i>KCNK5</i>	0	Intronic	283	4	<i>KCNK5</i>	Intronic	-	-	-	-
rs6478241	<i>ASTN2</i>	0	Intronic	950	3	<i>ASTN2</i>	Intronic	-	-	-	-
rs12260159	<i>HPSE2</i>	0	Intronic	372	59	<i>HPSE2</i>	Intronic	-	<i>HPSE2</i>	0.001	0.006
rs77505915	<i>CFDP1</i>	0	Intronic	745	238	<i>CFDP1</i> , <i>TMEM170A</i>	Intronic	-	-	-	-
rs17857135	<i>RNF213</i>	0	Missense	113	16	<i>RNF213</i>	Missense	rs17857135, rs17853714, rs17853989, rs17853713	-	-	-
rs2506142	<i>NRP1</i>	0	3-prime UTR	29	7	<i>NRP1</i>	3-prime UTR	-	<i>NRP1</i>	0.003	0.008
rs13078967	<i>GPR149</i>	142.4	Intergenic	527	5	-	-	-	<i>ARHGEF26</i>	0.008	0.03
rs111404218	<i>JAG1</i>	29.5	Intergenic	89	4	-	-	-	<i>JAG1</i>	0.00002	<0.005
rs7684253	<i>SPINK2</i>	39.4	Intergenic	186	2	-	-	-	<i>REST</i>	0.002	0.005
rs1268083	<i>HEY2</i>	19.8	Intergenic	291	36	<i>HEY2</i> , <i>NCOA7</i>	Intronic	-	<i>HEY2</i>	0.002	0.006
rs75213074	<i>WSCD1</i>	62.9	Intergenic	96	7	-	-	-	-	-	-

rs28455731	<i>GJA1</i>	75.2	Intergenic	255	14	-	-	-	<i>GJA1</i>	0.002	0.008
rs6791480	<i>TGFBR2</i>	167.4	Intergenic	218	19	-	-	-	<i>TGFBR2</i>	0.005	0.02
rs11624776	<i>ITPK1</i>	12.9	Intergenic	29	3	-	-	-	-	-	-
rs6693567	<i>ADAMTSL4</i>	11.2	Intergenic	766	7	<i>RPRD2</i>	Intronic	-	<i>ECM1</i>	0.003	0.01
rs10895275	<i>YAP1</i>	0	Intronic	285	66	<i>YAP1</i>	Intronic	-	<i>YAP1</i>	0.0009	0.007
rs12845494	<i>MED14</i>	169.6	Upstream	-	-	-	-	-	-	-	-
rs10155855	<i>DOCK4</i>	37.8	Intergenic	31	15	-	-	-	-	-	-
rs1572668	<i>LRRIQ3</i>	592.0	Intergenic	1176	147	-	-	-	-	-	-
rs138556413	<i>CARF</i>	0	Intronic	669	2	<i>CARF</i>	Intronic	-	<i>NBEAL1</i>	0.0005	<0.005
rs4081947	<i>ZCCHC14</i>	54.2	Intergenic	13	3	-	-	-	<i>ZCCHC14</i>	0.02	0.05
rs2223089	<i>ARMS2</i>	0.4	Upstream	295	31	<i>PLEKHA1, HTRA1</i>	Intronic	-	<i>HTRA1</i>	0.003	0.007
rs561561	<i>IGSF9B</i>	2.8	Upstream	111	7	<i>IGSF9B</i>	Intronic	-	-	-	-
rs11031122	<i>MPPED2</i>	0	Intronic	125	17	<i>MPPED2</i>	Intronic	-	-	-	-
rs140002913	<i>NOTCH4</i>	14.2	Intergenic	65	15	-	-	-	-	-	-
rs144017103	<i>CCM2L</i>	0.9	Intergenic	36	2	<i>CCM2L</i>	Intronic	-	<i>CCM2L</i>	0.0008	<0.005

Supplementary Table 16. Number of samples per tissue in the GTEx collection. Tissues with available gene expression data in the GTEx collection. The number of samples collected for individual tissue categories was sometimes small ($N < 10$) so we combined samples into four tissue groups: brain, vascular, gastrointestinal, and other.

Tissue group	Tissue label	Tissue full name	Sample N
Brain	BRNACC	Anterior cingulate cortex (BA24)	17
Brain	BRNAMY	Amygdala	23
Brain	BRNCDT	Caudate (basal ganglia)	36
Brain	BRNCHA	Cerebellum	30
Brain	BRNCHB	Cerebellar Cortex	24
Brain	BRNCTXA	Cortex	23
Brain	BRNCTXB	Frontal Cortex (BA9)	24
Brain	BRNHPP	Hippocampus	24
Brain	BRNHPT	Hypothalamus	23
Brain	BRNNCC	Nucleus accumbens	28
Brain	BRNPTM	Putamen	20
Brain	BRNSNG	Substantia nigra	25
Brain	BRNSPC	Spinal cord (Cervical C1)	16
Brain	PTTARY	Pituitary Gland	13
Vascular	ARTAORT	Aorta	24
Vascular	ARTCRN	Coronary Artery	9
Vascular	ARTTBL	Tibial Artery	112
Vascular	HRTAA	Heart - Atrial Appendage	25
Vascular	HRTLTV	Heart - Left Ventricle	83
Gastrointestinal	CLNTRN	Colon - Transverse	12
Gastrointestinal	ESPMCS	Esophageal Mucosa	18
Gastrointestinal	ESPMSL	Esophagus Muscularis	20
Gastrointestinal	LIVER	Liver	5
Gastrointestinal	PNCREAS	Pancreas	19
Gastrointestinal	STMACH	Stomach	12
Other	ADPSBQ	Adipose - Subcutaneous	94
Other	ADPVSC	Adipose - Visceral (Omentum)	19
Other	ADRNLG	Adrenal Gland	12
Other	BREAST	Mammary Tissue	27
Other	FIBRBLS	Skin Cells - Transformed Fibroblasts	14
Other	FLLPNT	Fallopian Tube	1
Other	KDNCTX	Kidney Cortex	3
Other	LCL	LCL	39
Other	LUNG	Lung	119
Other	MSCLSK	Skeletal Muscle	138
Other	NERVET	Nerve - Tibial	88
Other	OVARY	Ovary	6
Other	PRSTTE	Prostate	9

Other	SKINNS	Skin - not sun exposed	23
Other	SKINS	Skin - sun exposed	96
Other	TESTIS	Testis	14
Other	THYROID	Thyroid	105
Other	UTERUS	Uterus	7
Other	VAGINA	Vagina	6
Other	WHLBLD	Whole Blood	156

Supplementary Table 17. Overlap of the migraine and eQTL credible sets in peripheral blood. For each migraine locus we created credible sets of SNPs and then using blood eQTL data from 3,754 individuals, we searched for significant eQTLs ($P < 1 \times 10^{-4}$) found to genes within a 1Mb window of each migraine credible set. The table lists 23 migraine and eQTL loci that were found to have overlapping credible sets. We tested if there was a significant Spearman's Rank correlation between the association test-statistics in each migraine credible set compared to the expression test-statistics in each overlapping eQTL credible set. Only one eQTL credible set (highlighted in bold), was nominally significant ($P = 0.01$, **Supplementary Figure 11**) when tested for a significant correlation with the migraine credible set at the *MRVI1* locus but does not survive Bonferroni correction for 23 independent tests.

Migraine SNP nearest gene	Migraine index SNP	Migraine locus region	eQTL index SNP	eQTL locus region	eQTL Pval	eQTL Gene
<i>ADAMTSL4</i>	rs6693567	chr1:150250636-150515021	rs12131376	chr1:150262094-150514149	1.68E-10	<i>FAM63A</i>
<i>ADAMTSL4</i>	rs6693567	chr1:150250636-150515021	rs72700829	chr1:150345558-150776123	1.55E-15	<i>CTSS</i>
<i>ADAMTSL4</i>	rs6693567	chr1:150250636-150515021	chr1_150512316_D	chr1:150387139-150513534	9.20E-13	<i>RPRD2</i>
<i>ADAMTSL4</i>	rs6693567	chr1:150250636-150515021	rs145402324	chr1:150495327-150495327	8.34E-84	<i>MRPS21</i>
<i>MEF2D</i>	rs1925950	chr1:156403681-156507704	rs6662838	chr1:156403701-156467309	2.26E-05	<i>NTRK1</i>
<i>MEF2D</i>	rs1925950	chr1:156403681-156507704	rs115307473	chr1:156470422-156470422	1.60E-06	<i>GPATCH4</i>
<i>CARF</i>	rs138556413	chr2:203639395-204040296	rs34349435	chr2:203505125-203864114	4.17E-07	<i>ABI2</i>
<i>CARF</i>	rs138556413	chr2:203639395-204040296	rs145743318	chr2:203696281-203778245	1.36E-05	<i>ACO79354.1</i>
<i>TRPM8</i>	rs10166942	chr2:234726966-234874402	rs7596472	chr2:234722065-234737045	2.26E-06	<i>TRPM8</i>
<i>REST</i>	rs7684253	chr4:57727311-57761417	rs28545156	chr4:57709199-57939027	8.02E-17	<i>REST</i>
<i>PHACTR1</i>	rs9349379	chr6:12768218-12948388	rs6934996	chr6:12855262-12855262	5.46E-05	<i>EDN1</i>
<i>FHL5</i>	rs67338227	chr6:96767685-97092478	rs4240553	chr6:96854444-97067028	1.71E-27	<i>UFL1</i>
<i>DOCK4</i>	rs10155855	chr7:111323799-111330237	rs60607828	chr7:111269793-111387274	4.22E-05	<i>DOCK4</i>
<i>ASTN2</i>	rs6478241	chr9:119181794-119479868	rs809170	chr9:119266109-119469941	1.24E-06	<i>TRIM32</i>
<i>NRP1</i>	rs2506142	chr10:33464928-33468456	rs1015025	chr10:33423206-33485537	1.91E-05	<i>ITGB1</i>
<i>PLCE1</i>	rs10786156	chr10:95976903-96074157	rs35348430	chr10:96042893-96345888	5.96E-56	<i>NOC3L</i>
<i>ARMS2</i>	rs2223089	chr10:124126358-124232915	rs11200595	chr10:124127990-124198585	3.07E-147	<i>PLEKHA1</i>
<i>MRVI1</i>	rs4910165	chr11:10654911-10699750	rs1544861	chr11:10660840-10699750	2.97E-05	<i>EIF4G2</i>
<i>LRP1</i>	rs11172113	chr12:57249600-57545756	rs183314994	chr12:57272508-57272527	5.95E-05	<i>ERBB3</i>
<i>LRP1</i>	rs11172113	chr12:57249600-57545756	rs4559	chr12:57489648-57489648	<1.0E-147	<i>STAT6</i>
<i>CFDP1</i>	rs77505915	chr16:75304623-75504768	rs247451	chr16:75312136-75490409	1.05E-05	<i>TMEM170A</i>
<i>CFDP1</i>	rs77505915	chr16:75304623-75504768	rs4888397	chr16:75332603-75489026	3.81E-13	<i>CFDP1</i>
<i>CCM2L</i>	rs144017103	chr20:30610164-30628982	rs12479792	chr20:30593642-30645680	1.36E-09	<i>HCK</i>

Supplementary Table 18. Overlap of the migraine and eQTL credible sets in brain tissue. Here we used eQTL data from the human brain cortex of 550 individuals and searched for significant eQTLs ($P < 1 \times 10^{-4}$) for genes within a 1Mb window of each migraine credible set. The table lists 29 migraine and eQTL loci that had overlapping credible sets. We tested if there was a significant Spearman's Rank correlation between the test-statistics in each migraine credible set compared to the expression test-statistics in each overlapping eQTL credible set. None showed significant correlation when comparing the overlap of credible sets.

Migraine SNP nearest gene	Migraine index SNP	Migraine locus region	eQTL index SNP	eQTL locus region	eQTL Pval	eQTL Gene
<i>PRDM16</i>	rs10218452	chr1:3065568-3112278	rs2817140	chr1:3106397-3108496	6.01E-05	<i>MORN1</i>
<i>PRDM16</i>	rs10218452	chr1:3065568-3112278	rs116525159	chr1:3104972-3107384	2.31E-05	<i>CCDC27</i>
<i>TSPAN2</i>	rs2078371	chr1:115630981-115829943	rs147406142	chr1:115697124-115788614	1.73E-05	<i>CD2</i>
<i>ADAMTSL4</i>	rs6693567	chr1:150250636-150515021	rs7511649	chr1:150270791-150482738	7.78E-05	<i>ENSA</i>
<i>ADAMTSL4</i>	rs6693567	chr1:150250636-150515021	chr1_150375425_D	chr1:150247311-150512346	1.18E-06	<i>Rprd2</i>
<i>ADAMTSL4</i>	rs6693567	chr1:150250636-150515021	rs74335909	chr1:150266559-150470296	3.71E-05	<i>MRPS21</i>
<i>MEF2D</i>	rs1925950	chr1:156403681-156507704	rs114210236	chr1:156358051-156532657	7.19E-05	<i>DAP3</i>
<i>MEF2D</i>	rs1925950	chr1:156403681-156507704	rs7364455	chr1:156495177-156603422	3.08E-05	<i>KIAA0907</i>
<i>CARF</i>	rs138556413	chr2:203639395-204040296	rs182823259	chr2:203982049-203982049	3.96E-06	<i>CD28</i>
<i>CARF</i>	rs138556413	chr2:203639395-204040296	rs185726277	chr2:203904306-203904306	3.51E-05	<i>ORC2L</i>
<i>CARF</i>	rs138556413	chr2:203639395-204040296	rs190660781	chr2:203770182-203770182	1.64E-08	<i>BZW1</i>
<i>CARF</i>	rs138556413	chr2:203639395-204040296	rs182405143	chr2:204013299-204013299	1.93E-09	<i>FASTKD2</i>
<i>CARF</i>	rs138556413	chr2:203639395-204040296	rs182405143	chr2:204013299-204013299	6.72E-08	<i>WDR12</i>
<i>CARF</i>	rs138556413	chr2:203639395-204040296	rs182823259	chr2:203982049-203982049	1.86E-08	<i>C2orf69</i>
<i>KCNK5</i>	rs10456100	chr6:39117698-39187886	rs79894111	chr6:39091790-39130651	9.63E-06	<i>ZFAND3</i>
<i>KCNK5</i>	rs10456100	chr6:39117698-39187886	rs149096878	chr6:39089907-39152137	1.14E-06	<i>PTCRA</i>
<i>KCNK5</i>	rs10456100	chr6:39117698-39187886	rs13213552	chr6:39114475-39157865	6.47E-05	<i>KIF6</i>
<i>FHL5</i>	rs67338227	chr6:96767685-97092478	rs60752088	chr6:96702496-97040674	6.33E-05	<i>POU3F2</i>
<i>FHL5</i>	rs67338227	chr6:96767685-97092478	rs73488608	chr6:96702496-97040674	1.56E-05	<i>SFRS18</i>
<i>PLCE1</i>	rs10786156	chr10:95976903-96074157	rs35084709	chr10:96002360-96293504	1.37E-05	<i>NOC3L</i>
<i>HPSE2</i>	rs12260159	chr10:100600946-100792984	rs72838828	chr10:100610752-101042293	9.80E-06	<i>FRAT1</i>
<i>HPSE2</i>	rs12260159	chr10:100600946-100792984	rs147998049	chr10:100785193-100785193	8.58E-05	<i>ARHGAP19</i>
<i>HPSE2</i>	rs12260159	chr10:100600946-100792984	rs182329697	chr10:100773286-100835791	1.28E-06	<i>DHDPSL</i>
<i>IGSF9B</i>	rs561561	chr11:133813808-133846186	rs78510304	chr11:133843529-133843529	3.15E-05	<i>B3GAT1</i>
<i>LRP1</i>	rs11172113	chr12:57249600-57545756	rs10506346	chr12:57330858-57330858	4.57E-06	<i>INHBC</i>
<i>LRP1</i>	rs11172113	chr12:57249600-57545756	rs34484591	chr12:57290245-57764923	1.95E-05	<i>RAB5B</i>
<i>LRP1</i>	rs11172113	chr12:57249600-57545756	rs3024974	chr12:57399556-57492745	9.05E-06	<i>STAT6</i>
<i>LRP1</i>	rs11172113	chr12:57249600-57545756	rs7134373	chr12:57306224-57493727	9.77E-05	<i>ZBTB39</i>
<i>LRP1</i>	rs11172113	chr12:57249600-57545756	rs58801386	chr12:57272865-57394635	1.74E-05	<i>GDF11</i>

Supplementary Table 19. Overlap of the migraine and eQTL credible sets in GTEx tissues. The table lists the migraine loci whose credible set contained SNPs that overlapped with an eQTL credible set from any tissues in the GTEx catalog (42 tissues and 3 cell lines from 1,641 samples). We considered only significant ($P < 2 \times 10^{-13}$) *cis*-eQTLs identified in GTEx within a 1Mb window of each transcript and created credible sets for each eQTL locus identified in each tissue. We tested for a significant Spearman's Rank correlation between the meta-analysis test-statistics in each migraine credible set compared to the expression test-statistics in each overlapping eQTL credible set. After applying Bonferroni correction ($P < 7.1 \times 10^{-3}$) the correlation was significant from eQTLs to four tissues (Lung, Thyroid, Tibial Artery, and Aorta) at two migraine loci (*HPSE2* and *HEY2/NCOA7*). Companion plots of the four significantly correlated credible sets are presented in **Supplementary Figure 12**.

Locus	Chr	Locus Index SNP	Migraine P-value	eQTL Index SNP	eQTL P-value	eQTL Gene	GTEx Tissue	Spearman's rho	Correlation P-value
<i>HPSE2</i>	10	rs12260159	3.20×10^{-10}	rs12260159	7.07×10^{-14}	<i>HPSE2</i>	Lung	0.89	7.2×10^{-14}
<i>HEY2/NCOA7</i>	6	rs1268083	5.25×10^{-9}	rs3799711	5.63×10^{-18}	<i>HEY2</i>	Thyroid	0.86	1.7×10^{-7}
<i>HPSE2</i>	10	rs12260159	3.20×10^{-10}	rs10883234	2.44×10^{-18}	<i>HPSE2</i>	Artery; Tibial	0.59	2.0×10^{-4}
<i>HPSE2</i>	10	rs12260159	3.20×10^{-10}	rs10883234	2.90×10^{-28}	<i>HPSE2</i>	Artery; Aorta	0.58	2.8×10^{-3}
<i>ADAMTSL4/ECM1</i>	1	rs6693567	1.21×10^{-8}	rs6693567	4.65×10^{-33}	<i>ADAMTSL4</i>	Esophagus Mucosa	0.8	0.33
<i>HEY2/NCOA7</i>	6	rs1268083	5.25×10^{-9}	rs9401845	2.18×10^{-19}	<i>HEY2</i>	Testis	-0.38	0.09
<i>HPSE2</i>	10	rs12260159	3.20×10^{-10}	rs7091740	1.01×10^{-14}	<i>HPSE2</i>	Artery Coronary	0.06	0.71

Supplementary Table 20. DEPICT gene-expression enrichment in tissue annotations. Expression enrichment of genes from the migraine loci in any of 209 Medical Subject Heading (MeSH) tissue and cell type annotations. Expression data was obtained from 37,427 human microarray samples and then genes in the migraine loci were assessed for high expression in each of the annotation categories. Enrichment *P*-values were determined by comparing the expression pattern from the migraine loci to 500 randomly generated loci and the false discovery rate (FDR) was estimated to control for multiple testing (see **Online Methods**). A plot of these results is provided in the main text, **Figure 3**.

MeSH ID	Name	MeSH first level term	MeSH second level term	P value	FDR	Genes from associated loci
A07.231.114	Arteries	Cardiovascular System	Blood Vessels	1.58×10^{-5}	<0.033	HEY2 (2.02), FHL5 (1.73), BCAR1 (1.35), GJA1 (1.32), C1orf54 (1.3)
A03.556.875	Upper Gastrointestinal Tract	Digestive System	Gastrointestinal Tract	0.003	0.05	MRVI1 (1.57), CYP2C18 (1.55), ECM1 (1.04), CYP2C9 (1.01), IGSF9B (1.01)
A05.360.319.679.690	Myometrium	Urogenital System	Genitalia	0.003	0.03	FHL5 (2.73), SLC24A3 (2.55), TSPAN2 (2.52), CCM2L (2.38), MRVI1 (2.1)
A03.556.875.875	Stomach	Digestive System	Gastrointestinal Tract	0.003	0.04	MRVI1 (1.73), CYP2C18 (1.45), CYP2C9 (1.1), IGSF9B (1.03), KCNK5 (0.95)
A03.556.249.124	Ileum	Digestive System	Gastrointestinal Tract	0.009	0.19	MYO1A (4.92), CYP2C18 (2.23), KCNK5 (1.33), BCAR1 (1.26), CFDP1 (1.09)
A07.541.510.110	Aortic Valve	Cardiovascular System	Heart	0.01	0.18	CHST6 (2.82), HEY2 (2.24), C1orf54 (2.15), PLCE1 (1.9), RAPH1 (1.66)
A07.541.510	Heart Valves	Cardiovascular System	Heart	0.01	0.15	CHST6 (2.82), HEY2 (2.24), C1orf54 (2.15), PLCE1 (1.9), RAPH1 (1.66)
A05.360.319.887	Vulva	Urogenital System	Genitalia	0.01	0.22	SDR9C7 (3.38), ECM1 (1.47), GJA1 (1.41), CYP2C18 (1.26), SLC24A3 (1.01)
A10.615.789	Serous Membrane	Tissues	Membranes	0.01	0.19	MPPED2 (1.3), GJA1 (1.17), HTRA1 (1.03), C1orf54 (0.83), FHL5 (0.77)
A10.690.467	Muscle Smooth	Tissues	Muscles	0.01	0.18	PAPPA (2.43), C7orf10 (1.93), NGF (1.91), MRVI1 (1.58), C1orf54 (1.49)
A03.556.875.500	Esophagus	Digestive System	Gastrointestinal Tract	0.01	0.17	CYP2C18 (1.95), ECM1 (1.69), MRVI1 (1.43), CYP2C9 (0.95), PLEKHA1 (0.94)
A10.165.114	Adipose Tissue	Tissues	Connective Tissue	0.02	0.18	CCM2L (3.23), FHL5 (2.48), SLC24A3 (1.78), NRP1 (1.56), TGFB2 (1.49)
A14.549.167.646	Periodontium	Stomatognathic System	Mouth	0.02	0.21	CYP2C18 (3.82), SDR9C7 (3.46), SLC24A3 (2.14), ECM1 (1.71), FAM117B (1.44)
A10.165.114.830	Adipose Tissue White	Tissues	Connective Tissue	0.02	0.22	CCM2L (3.51), FHL5 (2.56), SLC24A3 (1.96), NRP1 (1.62), TGFB2 (1.52)
A10.165.114.830.750	Subcutaneous Fat	Tissues	Connective Tissue	0.02	0.20	CCM2L (3.51), FHL5 (2.56), SLC24A3 (1.96), NRP1 (1.62), TGFB2 (1.52)

A07.541	Heart	Cardiovascular System	Heart	0.02	0.21	HEY2 (2.52), CCM2L (2.48), PLCE1 (1.7), FHL5 (1.69), HPSE2 (1.65)
A07.231	Blood Vessels	Cardiovascular System	Blood Vessels	0.02	0.20	TGFBR2 (1.87), BCAR1 (1.64), CCM2L (1.48), DOCK4 (1.34), C1orf54 (1.29)
A03.556.124.684	Intestine Small	Digestive System	Gastrointestinal Tract	0.02	0.22	MYO1A (3.13), CYP2C18 (1.36), KCNK5 (1.0), BCAR1 (0.88), CYP2C9 (0.83)
A06.407.071.140	Adrenal Cortex	Endocrine System	Endocrine Glands	0.03	0.21	C7orf10 (1.74), GJA1 (1.36), ZCCHC14 (1.33), CCM2L (1.05), MRPS21 (0.95)
A05.360.319.679	Uterus	Urogenital System	Genitalia	0.03	0.23	MPPED2 (1.55), GJA1 (1.12), SLC24A3 (1.07), HEY2 (1.03), PLCE1 (0.98)
A05.360.319.679.256	Cervix Uteri	Urogenital System	Genitalia	0.03	0.22	GJA1 (1.08), CHST6 (0.85), YAP1 (0.71), HTRA1 (0.67), JAG1 (0.65)
A05.360	Genitalia	Urogenital System	Genitalia	0.03	0.23	MPPED2 (1.37), GJA1 (0.98), YAP1 (0.98), HTRA1 (0.84), HEY2 (0.75)
A05.810.890	Urinary Bladder	Urogenital System	Urinary Tract	0.04	0.23	MROH2A (1.27), TAC3 (1.25), GJA1 (1.03), BCAR1 (0.97), PLCE1 (0.95)
A10.165.114.830.500.750	Subcutaneous Fat Abdominal	Tissues	Connective Tissue	0.04	0.23	CCM2L (3.82), SLC24A3 (2.12), FHL5 (1.86), NRP1 (1.69), TGFBR2 (1.55)
A10.165.114.830.500	Abdominal Fat	Tissues	Connective Tissue	0.04	0.22	CCM2L (3.82), SLC24A3 (2.12), FHL5 (1.86), NRP1 (1.69), TGFBR2 (1.55)
A03.734	Pancreas	Digestive System	Pancreas	0.04	0.21	PLCE1 (1.37), FHL5 (0.94), YAP1 (0.86), HTRA1 (0.75), NBEAL1 (0.71)
A07.541.560	Heart Ventricles	Cardiovascular System	Heart	0.04	0.24	HEY2 (2.72), CCM2L (2.56), HPSE2 (1.88), FHL5 (1.79), FGF6 (1.71)
A07.541.358	Heart Atria	Cardiovascular System	Heart	0.04	0.23	PLCE1 (2.75), CCM2L (2.42), GJA1 (1.44), FHL5 (1.24), ZCCHC14 (1.1)
A05.810	Urinary Tract	Urogenital System	Urinary Tract	0.04	0.22	C7orf10 (1.14), KCNK5 (1.1), PLEKHA1 (1.09), FHL5 (0.98), NRP1 (0.88)
A17.815	Skin	Integumentary System	Skin	0.04	0.22	SDR9C7 (4.24), FHL5 (1.54), GJA1 (1.38), ECM1 (1.29), C1orf51 (1.13)
A05.360.319	Genitalia Female	Urogenital System	Genitalia	0.04	0.21	MPPED2 (1.38), GJA1 (1.01), YAP1 (1.01), HTRA1 (0.98), HEY2 (0.94)
A06.407.071	Adrenal Glands	Endocrine System	Endocrine Glands	0.05	0.23	C7orf10 (1.49), ZCCHC14 (1.15), GJA1 (1.07), CCM2L (1.05), MRPS21 (0.89)
A05.360.319.114.373	Fallopian Tubes	Urogenital System	Genitalia	0.05	0.23	MPPED2 (1.76), YAP1 (1.19), HEY2 (1.12), HTRA1 (0.95), GJA1 (0.85)
A05.810.453	Kidney	Urogenital System	Urinary Tract	0.05	0.23	C7orf10 (1.25), KCNK5 (1.2), PLEKHA1 (1.15), FHL5 (1.06), CFDP1 (0.95)
A03.620	Liver	Digestive System	Liver	0.05	0.22	CYP2C8 (6.14), CYP2C9 (5.51), CYP2C19 (5.21), RDH16 (5.15), CYP2C18 (3.58)
A10.336	Exocrine Glands	Tissues	Exocrine Glands	0.05	0.22	TRPM8 (4.09), ARHGEF26 (2.43), ASTN2 (2.03),

						MPPED2 (1.76), SLC24A3 (1.06)
A10.336.707	Prostate	Tissues	Exocrine Glands	0.06	0.25	TRPM8 (4.42), ARHGEF26 (2.64), ASTN2 (2.16), MPPED2 (1.81), SLC24A3 (1.1)
A14.549	Mouth	Stomatognathic System	Mouth	0.06	0.25	SDR9C7 (3.46), CYP2C18 (3.06), ECM1 (2.2), SLC24A3 (2.01), C1orf51 (1.5)
A04.411	Lung	Respiratory System	Lung	0.07	0.25	ARHGEF26 (0.9), NBEAL1 (0.85), YAP1 (0.8), PLCE1 (0.72), RAPH1 (0.7)
A05.360.319.679.490	Endometrium	Urogenital System	Genitalia	0.07	0.26	MPPED2 (1.83), HEY2 (1.57), ECM1 (1.37), SLC24A3 (1.26), CHST6 (1.18)
A07.541.358.100	Atrial Appendage	Cardiovascular System	Heart	0.07	0.26	PLCE1 (2.87), CCM2L (2.33), GJA1 (1.47), FHL5 (1.4), ZCCHC14 (1.14)
A14.549.167	Dentition	Stomatognathic System	Mouth	0.07	0.26	CYP2C18 (2.44), SDR9C7 (2.12), ECM1 (1.78), NGF (1.5), GJA1 (1.33)
A03.556	Gastrointestinal Tract	Digestive System	Gastrointestinal Tract	0.08	0.30	MYO1A (2.1), CYP2C18 (1.1), PLCE1 (0.95), ECM1 (0.8), SLC24A3 (0.73)
A10.615.550.599	Mouth Mucosa	Tissues	Membranes	0.09	0.31	SDR9C7 (5.89), CYP2C18 (4.23), ECM1 (3.31), SLC24A3 (2.59), C1orf51 (2.26)
A05.810.453.324	Kidney Cortex	Urogenital System	Urinary Tract	0.09	0.31	C7orf10 (3.16), PAPP (1.81), TRIM32 (1.45), CCM2L (1.37), NGF (1.2)
A05.360.444	Genitalia Male	Urogenital System	Genitalia	0.10	0.35	TRPM8 (3.21), ARHGEF26 (2.09), ASTN2 (1.81), MPPED2 (1.39), GJA1 (0.92)
A11.872.580	Mesenchymal Stem Cells	Cells	Stem Cells	0.10	0.35	PAPP (2.61), NGF (2.37), C7orf10 (2.03), TRIM32 (2.01), HTRA1 (1.56)
A05.360.319.114	Adnexa Uteri	Urogenital System	Genitalia	0.11	0.36	MPPED2 (1.33), YAP1 (1.06), HTRA1 (1.05), HEY2 (0.92), GJA1 (0.91)
A02.835.583.443	Joint Capsule	Musculoskeletal System	Skeleton	0.11	0.36	PAPP (2.24), NGF (2.0), ZCCHC14 (1.99), TBC1D12 (1.82), ECM1 (1.57)
A02.835.583	Joints	Musculoskeletal System	Skeleton	0.11	0.35	PAPP (2.24), NGF (2.0), ZCCHC14 (1.99), TBC1D12 (1.82), ECM1 (1.57)
A02.835.583.443.800	Synovial Membrane	Musculoskeletal System	Skeleton	0.11	0.35	PAPP (2.24), NGF (2.0), ZCCHC14 (1.99), TBC1D12 (1.82), ECM1 (1.57)
A06.407	Endocrine Glands	Endocrine System	Endocrine Glands	0.11	0.34	MPPED2 (1.2), YAP1 (0.95), HTRA1 (0.93), GJA1 (0.88), C1orf51 (0.74)
A05.360.319.114.630	Ovary	Urogenital System	Genitalia	0.11	0.34	MPPED2 (1.32), YAP1 (1.06), HTRA1 (1.05), HEY2 (0.91), GJA1 (0.91)
A06.407.900	Thyroid Gland	Endocrine System	Endocrine Glands	0.11	0.34	PRDM16 (1.34), MPPED2 (1.34), PLCE1 (1.18), GJA1 (1.17), RAPH1 (1.14)
A11.620	Muscle Cells	Cells	Muscle Cells	0.11	0.36	PAPP (2.96), C7orf10 (2.71), NGF (2.35), TGFB2 (1.59), ECM1 (1.59)
A11.620.520	Myocytes Smooth Muscle	Cells	Muscle Cells	0.11	0.35	PAPP (2.96), C7orf10 (2.71), NGF (2.35), TGFB2 (1.59), ECM1 (1.59)

A03.556.124.526.767	Rectum	Digestive System	Gastrointestinal Tract	0.11	0.35	MYO1A (2.54), MRVI1 (0.89), KCNK5 (0.88), PLCE1 (0.85), BCAR1 (0.8)
A03.556.500.760.464	Parotid Gland	Digestive System	Gastrointestinal Tract	0.12	0.37	BCAR1 (1.97), ENSG00000237781 (1.81), MPPED2 (1.5), NGF (1.39), ZCCHC14 (1.1)
A06.407.312	Gonads	Endocrine System	Endocrine Glands	0.13	0.42	MPPED2 (1.31), YAP1 (1.04), HTRA1 (1.02), HEY2 (0.93), GJA1 (0.92)
A11.436.275	Endothelial Cells	Cells	Epithelial Cells	0.14	0.45	CCM2L (2.08), TGFB2 (1.98), BCAR1 (1.68), DOCK4 (1.64), GJA1 (1.17)
A07.231.908	Veins	Cardiovascular System	Blood Vessels	0.14	0.44	CCM2L (2.38), DOCK4 (1.98), TGFB2 (1.86), BCAR1 (1.71), C1orf54 (1.42)
A10.690	Muscles	Tissues	Muscles	0.14	0.44	C1orf51 (1.78), SLC24A3 (1.7), FGF6 (1.48), C7orf10 (1.37), NGF (1.16)
A11.329.629	Osteoblasts	Cells	Connective Tissue Cells	0.15	0.47	PAPPA (3.45), NGF (2.93), C7orf10 (2.22), HTRA1 (1.85), TBC1D12 (1.71)
A03.556.249	Lower Gastrointestinal Tract	Digestive System	Gastrointestinal Tract	0.15	0.46	MYO1A (2.53), PLCE1 (0.97), KCNK5 (0.8), BCAR1 (0.76), YAP1 (0.7)
A03.556.124	Intestines	Digestive System	Gastrointestinal Tract	0.16	0.49	MYO1A (2.75), PLCE1 (1.2), KCNK5 (0.86), BCAR1 (0.74), YAP1 (0.65)
A02.165	Cartilage	Musculoskeletal System	Cartilage	0.16	0.48	NGF (6.02), PAPPA (2.04), RAPH1 (1.74), KCNK5 (1.45), IGSF9B (1.27)
A03.556.249.249.356.668	Colon Sigmoid	Digestive System	Gastrointestinal Tract	0.17	0.49	MYO1A (2.73), KCNK5 (0.97), PLCE1 (0.89), MRVI1 (0.85), CYP2C18 (0.84)
A03.556.249.249	Intestine Large	Digestive System	Gastrointestinal Tract	0.17	0.50	MYO1A (2.45), PLCE1 (0.99), KCNK5 (0.78), BCAR1 (0.74), YAP1 (0.7)
A03.556.500.760	Salivary Glands	Digestive System	Gastrointestinal Tract	0.17	0.50	BCAR1 (1.89), ENSG00000237781 (1.69), MPPED2 (1.48), NGF (1.27), ZCCHC14 (0.98)
A08.186.211.730.885.287.249.487	Corpus Striatum	Nervous System	Central Nervous System	0.18	0.51	HPSE2 (3.11), C1orf61 (3.02), TBC1D12 (2.75), MRVI1 (2.4), CHST6 (2.01)
A03.556.249.249.356	Colon	Digestive System	Gastrointestinal Tract	0.18	0.51	MYO1A (2.45), PLCE1 (1.0), KCNK5 (0.78), BCAR1 (0.75), YAP1 (0.71)
A10.615	Membranes	Tissues	Membranes	0.18	0.50	PLCE1 (1.5), MYO1A (1.5), CYP2C18 (1.44), SDR9C7 (1.05), CHST6 (0.93)
A07.231.908.670.874	Umbilical Veins	Cardiovascular System	Blood Vessels	0.20	0.56	CCM2L (2.39), DOCK4 (2.13), TGFB2 (1.99), BCAR1 (1.73), C1orf54 (1.43)
A07.231.908.670	Portal System	Cardiovascular System	Blood Vessels	0.20	0.55	CCM2L (2.39), DOCK4 (2.13), TGFB2 (1.99), BCAR1 (1.73), C1orf54 (1.43)
A03.556.249.249.209	Cecum	Digestive System	Gastrointestinal Tract	0.22	0.61	MYO1A (2.43), TAC3 (1.01), MRVI1 (1.01), PLCE1 (0.85), YAP1 (0.75)
A15.382.520.604.700	Spleen	Hemic and Immune Systems	Immune System	0.23	0.64	CCM2L (3.39), GPR182 (2.32), ENSG00000258442 (1.85), RNF213 (1.0), NOC3L (0.84)
A02.835.232.834.151	Cervical Vertebrae	Musculoskeletal	Skeleton	0.26	0.71	PAPPA (1.39), TRIM32 (1.23), GJA1 (1.15), NGF

		System				(1.04), C7orf10 (1.03)
A14.549.885	Tongue	Stomatognathic System	Mouth	0.26	0.72	CYP2C18 (2.36), SLC24A3 (1.76), MRPS21 (1.29), GJA1 (1.23), CCM2L (1.08)
A02.835.232.834	Spine	Musculoskeletal System	Skeleton	0.26	0.71	PAPPA (1.38), TRIM32 (1.23), GJA1 (1.15), C7orf10 (1.04), NGF (1.04)
A11.329.830	Stromal Cells	Cells	Connective Tissue Cells	0.28	0.76	NGF (2.49), PAPPA (2.15), TRIM32 (1.67), ECM1 (1.52), C7orf10 (1.42)
A08.186.211.730.885 .287.249	Basal Ganglia	Nervous System	Central Nervous System	0.30	0.80	C1orf61 (3.15), HPSE2 (2.29), MRVI1 (2.14), IGSF9B (2.02), TBC1D12 (1.78)
A03.556.124.369	Intestinal Mucosa	Digestive System	Gastrointestinal Tract	0.30	0.80	MYO1A (4.31), PLCE1 (2.77), CFDP1 (1.41), KCNK5 (1.25), CYP2C18 (1.05)
A10.615.550	Mucous Membrane	Tissues	Membranes	0.30	0.79	MYO1A (1.9), CYP2C18 (1.82), PLCE1 (1.64), SDR9C7 (1.31), CHST6 (1.14)
A10.690.552.500	Muscle Skeletal	Tissues	Muscles	0.33	0.86	C1orf51 (2.32), SLC24A3 (2.16), FGF6 (1.83), HEY2 (1.55), MEF2D (1.48)
A10.690.552	Muscle Striated	Tissues	Muscles	0.33	0.85	C1orf51 (2.32), SLC24A3 (2.16), FGF6 (1.83), HEY2 (1.55), MEF2D (1.48)
A11.872.653	Neural Stem Cells	Cells	Stem Cells	0.34	0.87	NAB2 (2.29), MPPED2 (1.87), SLC24A3 (1.61), PRDM16 (1.52), C1orf61 (1.49)
A11.329.171	Chondrocytes	Cells	Connective Tissue Cells	0.37	0.94	NGF (2.72), PAPPA (1.77), PLCE1 (1.74), HTRA1 (1.62), CHST6 (1.33)
A11.436.348	Hepatocytes	Cells	Epithelial Cells	0.38	0.96	CYP2C9 (2.53), CYP2C8 (2.2), CYP2C18 (2.17), CYP2C19 (2.1), WDR12 (1.31)
A02.633.567.850	Quadriceps Muscle	Musculoskeletal System	Muscles	0.39	0.97	C1orf51 (2.42), SLC24A3 (2.24), FGF6 (1.87), HEY2 (1.56), MEF2D (1.5)
A15.382.490.315.583	Neutrophils	Hemic and Immune Systems	Immune System	0.41	1.01	ENSG00000237781 (4.23), TSPAN2 (2.7), PHACTR1 (2.44), NLRP1 (2.09), MRVI1 (1.72)
A10.165.450.300.425	Keloid	Tissues	Connective Tissue	0.41	1.02	NGF (4.77), PAPPA (2.75), ECM1 (1.67), HTRA1 (1.59), TRIM32 (1.53)
A08.186.211.730.885 .287.500.670	Parietal Lobe	Nervous System	Central Nervous System	0.42	1.02	C1orf61 (2.77), MRVI1 (1.9), CHST6 (1.86), HTRA1 (1.62), GJA1 (1.38)
A11.118.637.415	Granulocytes	Cells	Blood Cells	0.44	1.09	ENSG00000237781 (3.85), TSPAN2 (2.61), PHACTR1 (2.22), NLRP1 (1.83), MRVI1 (1.57)
A11.329.114	Adipocytes	Cells	Connective Tissue Cells	0.48	1.16	CCM2L (1.54), HTRA1 (1.46), LRP1 (1.32), YAP1 (1.08), NRP1 (1.04)
A09.371.060	Anterior Eye Segment	Sense Organs	Eye	0.49	1.17	CFDP1 (1.16), HEY2 (1.11), CHST6 (0.83), YAP1 (0.76), PLEKHA1 (0.76)
A11.497.497.600	Oocytes	Cells	Germ Cells	0.49	1.17	HEY2 (2.42), HPSE2 (1.87), PAPPA (1.6), MPPED2 (1.44), GJA1 (1.18)
A05.360.490.690	Ovum	Urogenital System	Genitalia	0.49	1.16	HEY2 (2.42), HPSE2 (1.87), PAPPA (1.6), MPPED2 (1.44), GJA1 (1.18)

A09.371.337	Eyelids	Sense Organs	Eye	0.49	1.15	CFDP1 (1.15), HEY2 (1.13), CHST6 (0.86), YAP1 (0.77), PLEKHA1 (0.76)
A09.371.337.168	Conjunctiva	Sense Organs	Eye	0.49	1.14	CFDP1 (1.15), HEY2 (1.13), CHST6 (0.86), YAP1 (0.77), PLEKHA1 (0.76)
A11.329.228	Fibroblasts	Cells	Connective Tissue Cells	0.50	1.15	PAPPA (2.22), NGF (2.15), TRIM32 (1.58), ECM1 (1.4), C7orf10 (1.32)
A08.186.211.653	Mesencephalon	Nervous System	Central Nervous System	0.50	1.15	C1orf61 (3.44), CHST6 (2.43), HPSE2 (2.08), MRVI1 (1.55), HTRA1 (1.51)
A02.835.232.043	Bones of Lower Extremity	Musculoskeletal System	Skeleton	0.51	1.14	CFDP1 (1.03), HEY2 (1.0), CHST6 (0.8), PLEKHA1 (0.76), YAP1 (0.67)
A10.615.284.473	Chorion	Tissues	Membranes	0.52	1.14	PAPPA (4.84), GJA1 (1.32), BCAR1 (1.13), YAP1 (1.11), NRP1 (0.99)
A10.615.284	Extraembryonic Membranes	Tissues	Membranes	0.52	1.13	PAPPA (4.84), GJA1 (1.32), BCAR1 (1.13), YAP1 (1.11), NRP1 (0.99)
A02.835.232.043.300.710	Tarsal Bones	Musculoskeletal System	Skeleton	0.52	1.13	HEY2 (1.04), CFDP1 (1.03), CHST6 (0.78), PLEKHA1 (0.77), MPPED2 (0.67)
A02.835.232.043.300	Foot Bones	Musculoskeletal System	Skeleton	0.52	1.12	HEY2 (1.04), CFDP1 (1.03), CHST6 (0.78), PLEKHA1 (0.77), MPPED2 (0.67)
A05.360.444.492	Penis	Urogenital System	Genitalia	0.54	1.15	SDR9C7 (2.74), ECM1 (1.4), GJA1 (1.38), PAPPA (1.35), TBC1D12 (1.24)
A10.165.450	Granulation Tissue	Tissues	Connective Tissue	0.54	1.14	NGF (3.27), PAPPA (2.68), ECM1 (1.71), HTRA1 (1.63), NRP1 (1.43)
A10.165.450.300	Cicatrix	Tissues	Connective Tissue	0.54	1.13	NGF (3.27), PAPPA (2.68), ECM1 (1.71), HTRA1 (1.63), NRP1 (1.43)
A08.186.211.464.405	Hippocampus	Nervous System	Central Nervous System	0.58	1.18	SLC24A3 (2.78), C1orf61 (2.41), CHST6 (1.74), HTRA1 (1.45), DOCK4 (1.43)
A11.872.190	Embryonic Stem Cells	Cells	Stem Cells	0.58	1.18	ZBTB39 (1.81), GJA1 (1.43), CHST6 (1.32), CFDP1 (1.24), TAC3 (1.24)
A11.436.397	Keratinocytes	Cells	Epithelial Cells	0.60	1.20	SDR9C7 (4.51), CYP2C18 (1.7), TRIM32 (1.26), ECM1 (1.07), YAP1 (1.06)
A05.360.444.492.362	Foreskin	Urogenital System	Genitalia	0.61	1.21	SDR9C7 (2.76), PAPPA (1.39), ECM1 (1.39), GJA1 (1.39), TBC1D12 (1.31)
A11.872.190.260	Embryoid Bodies	Cells	Stem Cells	0.63	1.24	PAPPA (2.57), BCAR1 (1.52), TAC3 (1.34), GJA1 (1.24), YAP1 (1.06)
A05.360.490	Germ Cells	Urogenital System	Genitalia	0.64	1.24	HEY2 (2.14), PAPPA (1.73), HPSE2 (1.7), MPPED2 (1.26), GJA1 (1.14)
A15.382.680	Phagocytes	Hemic and Immune Systems	Immune System	0.65	1.24	ENSG00000237781 (1.17), PHACTR1 (1.12), DOCK4 (1.03), STAT6 (1.01), ITPK1 (0.79)
A11.118.637.555.567.569.200.700	T Lymphocytes Regulatory	Cells	Blood Cells	0.65	1.24	NLRP1 (1.64), ZCCHC14 (1.57), IGSF9B (1.55), RPRD2 (1.13), RNF213 (0.98)
A08.186.211.730.885	Visual Cortex	Nervous System	Central Nervous System	0.65	1.23	C1orf61 (2.34), PLEKHA1 (1.75), IGSF9B (1.39),

.287.500.571.735						PRDM16 (1.38), GJA1 (1.33)
A15.378.316	Bone Marrow Cells	Hemic and Immune Systems	Hematopoietic System	0.66	1.22	ENSG00000237781 (1.4), PHACTR1 (1.19), STAT6 (0.91), MEF2D (0.76), NLRP1 (0.75)
A15.378	Hematopoietic System	Hemic and Immune Systems	Hematopoietic System	0.66	1.21	ENSG00000237781 (1.4), PHACTR1 (1.19), STAT6 (0.91), MEF2D (0.76), NLRP1 (0.75)
A08.186.211.730.885	Telencephalon	Nervous System	Central Nervous System	0.66	1.21	C1orf61 (2.61), SLC24A3 (1.58), MRVI1 (1.4), HTRA1 (1.38), GJA1 (1.31)
A15.145.300	Fetal Blood	Hemic and Immune Systems	Blood	0.67	1.21	ENSG00000237781 (1.36), FGF6 (0.66), TSPAN2 (0.64), STAT6 (0.62), NLRP1 (0.61)
A08.186.211.730.885 .287	Cerebrum	Nervous System	Central Nervous System	0.67	1.20	C1orf61 (2.6), SLC24A3 (1.59), MRVI1 (1.4), HTRA1 (1.38), GJA1 (1.31)
A15.145.846	Serum	Hemic and Immune Systems	Blood	0.67	1.19	NGF (1.9), BCAR1 (1.67), DOCK4 (1.59), TRIM32 (1.35), NRP1 (1.2)
A08.186.211.730	Prosencephalon	Nervous System	Central Nervous System	0.68	1.19	C1orf61 (2.5), SLC24A3 (1.49), HTRA1 (1.4), MRVI1 (1.33), CHST6 (1.29)
A08.186.211.464	Limbic System	Nervous System	Central Nervous System	0.68	1.19	C1orf61 (2.57), SLC24A3 (1.91), MRVI1 (1.42), HTRA1 (1.39), CHST6 (1.34)
A11.872.700	Pluripotent Stem Cells	Cells	Stem Cells	0.68	1.18	HEY2 (1.94), CHST6 (1.94), HELLS (1.75), GJA1 (1.52), TAC3 (1.51)
A11.872.700.500	Induced Pluripotent Stem Cells	Cells	Stem Cells	0.68	1.17	HEY2 (1.94), CHST6 (1.94), HELLS (1.75), GJA1 (1.52), TAC3 (1.51)
A09.371	Eye	Sense Organs	Eye	0.70	1.18	MPPED2 (0.94), YAP1 (0.73), PLEKHA1 (0.6), TRIM32 (0.58), NBEAL1 (0.57)
A15.145.229.637.555 .567.569.200	CD4 Positive T Lymphocytes	Hemic and Immune Systems	Blood	0.70	1.17	IGSF9B (1.76), ZCCHC14 (1.58), NLRP1 (1.49), RNF213 (0.93), RPRD2 (0.92)
A11.627	Myeloid Cells	Cells	Myeloid Cells	0.70	1.17	ENSG00000237781 (1.1), PHACTR1 (1.06), DOCK4 (0.93), STAT6 (0.9), ITPK1 (0.71)
A08.186.211.730.885 .287.500.571	Occipital Lobe	Nervous System	Central Nervous System	0.70	1.16	C1orf61 (2.4), PLEKHA1 (1.73), IGSF9B (1.48), GJA1 (1.31), NCOA7 (1.26)
A08.186.211	Brain	Nervous System	Central Nervous System	0.70	1.15	C1orf61 (2.48), HTRA1 (1.31), SLC24A3 (1.26), GJA1 (1.16), ASTN2 (1.11)
A08.186.211.730.885 .287.500	Cerebral Cortex	Nervous System	Central Nervous System	0.70	1.15	C1orf61 (2.56), SLC24A3 (1.65), HTRA1 (1.37), MRVI1 (1.34), GJA1 (1.31)
A08.186	Central Nervous System	Nervous System	Central Nervous System	0.70	1.14	C1orf61 (2.46), HTRA1 (1.3), SLC24A3 (1.23), GJA1 (1.15), ASTN2 (1.1)
A15.378.316.580	Monocytes	Hemic and Immune Systems	Hematopoietic System	0.71	1.15	NAB2 (1.18), STAT6 (0.89), DOCK4 (0.84), C1orf54 (0.73), LRP1 (0.7)
A03.734.414	Islets of Langerhans	Digestive System	Pancreas	0.71	1.14	YAP1 (1.3), BCAR1 (0.86), HJURP (0.81), PLCE1 (0.77), PLEKHA1 (0.69)
A11.329	Connective Tissue Cells	Cells	Connective Tissue Cells	0.72	1.14	NRP1 (1.11), PAPPA (0.91), NGF (0.9), TBC1D12 (0.88), ECM1 (0.77)

A08.186.211.730.317	Diencephalon	Nervous System	Central Nervous System	0.74	1.18	IGSF9B (1.97), C1orf61 (1.71), HTRA1 (1.5), HPSE2 (1.27), ASTN2 (1.24)
A15.382.812	Mononuclear Phagocyte System	Hemic and Immune Systems	Immune System	0.74	1.17	TBC1D12 (1.06), DOCK4 (1.01), C1orf54 (0.97), NAB2 (0.91), NRP1 (0.89)
A11.066	Antigen Presenting Cells	Cells	Antigen-Presenting Cells	0.75	1.17	C1orf54 (1.68), TMEM194A (1.2), TBC1D12 (1.19), NRP1 (1.01), DOCK4 (0.95)
A15.382.812.260	Dendritic Cells	Hemic and Immune Systems	Immune System	0.75	1.16	C1orf54 (1.68), TMEM194A (1.2), TBC1D12 (1.19), NRP1 (1.01), DOCK4 (0.95)
A08.186.211.464.710.225	Entorhinal Cortex	Nervous System	Central Nervous System	0.75	1.16	C1orf61 (2.68), MRVI1 (1.51), HTRA1 (1.39), TAC3 (1.39), GJA1 (1.35)
A08.186.211.464.710	Parahippocampal Gyrus	Nervous System	Central Nervous System	0.75	1.15	C1orf61 (2.68), MRVI1 (1.51), HTRA1 (1.39), TAC3 (1.39), GJA1 (1.35)
A09.371.729	Retina	Sense Organs	Eye	0.75	1.14	MPPED2 (4.06), ARHGEF26 (2.45), CFPD1 (1.53), PLEKHA1 (1.33), HEY2 (1.3)
A08.186.211.730.885.287.500.863	Temporal Lobe	Nervous System	Central Nervous System	0.75	1.13	C1orf61 (2.72), TAC3 (1.5), MRVI1 (1.48), HTRA1 (1.39), PLEKHA1 (1.35)
A06.407.312.782	Testis	Endocrine System	Endocrine Glands	0.76	1.14	ZBTB39 (2.03), ASTN2 (1.99), C1orf54 (1.29), HEY2 (1.19), TRIM32 (1.19)
A02.835.583.443.800.800	Synovial Fluid	Musculoskeletal System	Skeleton	0.77	1.14	C1orf54 (2.46), TSPAN2 (1.69), CYP20A1 (1.27), NLRP1 (1.25), TMEM170A (0.8)
A11.118.637.555.567.569	T Lymphocytes	Cells	Blood Cells	0.78	1.14	IGSF9B (1.26), NLRP1 (1.18), RNF213 (0.99), DHX36 (0.77), CYP20A1 (0.71)
A15.382.812.522	Macrophages	Hemic and Immune Systems	Immune System	0.78	1.14	NRP1 (1.29), DOCK4 (1.24), TBC1D12 (1.18), C1orf54 (0.87), NAB2 (0.76)
A11.436.294.064	Glucagon Secreting Cells	Cells	Epithelial Cells	0.79	1.13	YAP1 (1.45), HJURP (1.22), TMEM194A (0.99), PLCE1 (0.94), PLEKHA1 (0.87)
A11.382.625	Enteroendocrine Cells	Cells	Endocrine Cells	0.79	1.13	YAP1 (1.45), HJURP (1.22), TMEM194A (0.99), PLCE1 (0.94), PLEKHA1 (0.87)
A15.382.520	Lymphatic System	Hemic and Immune Systems	Immune System	0.79	1.12	GPR182 (1.7), C1orf54 (0.78), CCM2L (0.73), ENSG00000258442 (0.71), NOC3L (0.58)
A10.549	Lymphoid Tissue	Tissues	Lymphoid Tissue	0.79	1.11	GPR182 (1.7), C1orf54 (0.78), CCM2L (0.73), ENSG00000258442 (0.71), NOC3L (0.58)
A04.623.603	Oropharynx	Respiratory System	Pharynx	0.79	1.11	FAM117B (1.16), PHACTR1 (0.87), C7orf10 (0.73), PRPF3 (0.71), NLRP1 (0.68)
A15.382.520.604.800	Palatine Tonsil	Hemic and Immune Systems	Immune System	0.79	1.11	FAM117B (1.16), PHACTR1 (0.87), C7orf10 (0.73), PRPF3 (0.71), NLRP1 (0.68)
A11.872.378.294	Lymphoid Progenitor Cells	Cells	Stem Cells	0.80	1.11	FAM117B (1.46), PHACTR1 (1.35), NLRP1 (1.33), CYP20A1 (1.27), TMEM170A (1.14)
A11.118.637.555.567.562.440	Precursor Cells B Lymphoid	Cells	Blood Cells	0.80	1.10	FAM117B (1.46), PHACTR1 (1.35), NLRP1 (1.33), CYP20A1 (1.27), TMEM170A (1.14)
A11.627.624.249	Monocyte	Cells	Myeloid Cells	0.80	1.09	PRPF3 (1.06), KCNK5 (0.97), WDR12 (0.93), TARS2

	Macrophage Precursor Cells					(0.72), TMEM170A (0.71)
A15.145.229.188	Blood Platelets	Hemic and Immune Systems	Blood	0.81	1.10	SLC24A3 (3.81), TSPAN2 (3.23), FGF6 (1.94), ENSG00000258442 (1.68), MEF2D (1.48)
A15.145	Blood	Hemic and Immune Systems	Blood	0.83	1.11	NLRP1 (1.15), ENSG00000237781 (0.81), PHACTR1 (0.66), RNF213 (0.57), MEF2D (0.55)
A11.436	Epithelial Cells	Cells	Epithelial Cells	0.83	1.10	CHST6 (0.87), CFDP1 (0.6), YAP1 (0.52), TBC1D12 (0.51), BCAR1 (0.49)
A09.531	Nose	Sense Organs	Nose	0.85	1.12	CHST6 (3.77), NBEAL1 (1.53), PLCE1 (1.47), CYP2C18 (0.97), STAT6 (0.96)
A04.531.520	Nasal Mucosa	Respiratory System	Nose	0.85	1.11	CHST6 (3.77), NBEAL1 (1.53), PLCE1 (1.47), CYP2C18 (0.97), STAT6 (0.96)
A10.615.550.760	Respiratory Mucosa	Tissues	Membranes	0.85	1.11	CHST6 (3.77), NBEAL1 (1.53), PLCE1 (1.47), CYP2C18 (0.97), STAT6 (0.96)
A10.549.400	Lymph Nodes	Tissues	Lymphoid Tissue	0.85	1.10	GPR182 (1.94), C1orf54 (1.2), ENSG00000258442 (0.64), RNF213 (0.59), CCM2L (0.58)
A05.360.319.114.630.535	Ovarian Follicle	Urogenital System	Genitalia	0.86	1.10	PAPPA (2.6), HTRA1 (1.91), GJA1 (1.64), CFDP1 (1.54), HEY2 (1.26)
A11.436.329	Granulosa Cells	Cells	Epithelial Cells	0.86	1.09	PAPPA (2.6), HTRA1 (1.91), GJA1 (1.64), CFDP1 (1.54), HEY2 (1.26)
A06.407.312.497.535.300.500	Cumulus Cells	Endocrine System	Endocrine Glands	0.86	1.09	PAPPA (2.6), HTRA1 (1.91), GJA1 (1.64), CFDP1 (1.54), HEY2 (1.26)
A11.872	Stem Cells	Cells	Stem Cells	0.87	1.08	PAPPA (0.81), WDR12 (0.79), C7orf10 (0.65), NOC3L (0.63), TRIM32 (0.62)
A08.186.211.132	Brain Stem	Nervous System	Central Nervous System	0.87	1.09	C1orf61 (2.62), IGSF9B (2.33), CHST6 (1.6), ASTN2 (1.43), SLC24A3 (1.42)
A15.145.229	Blood Cells	Hemic and Immune Systems	Blood	0.88	1.08	NLRP1 (0.96), PHACTR1 (0.63), RNF213 (0.58), ENSG00000237781 (0.58), MEF2D (0.51)
A11.872.040	Adult Stem Cells	Cells	Stem Cells	0.88	1.08	CHST6 (1.46), HEY2 (1.29), GJA1 (1.27), HELLS (1.25), C1orf51 (1.23)
A11.118.637	Leukocytes	Cells	Blood Cells	0.88	1.08	ENSG00000237781 (0.81), PHACTR1 (0.8), MEF2D (0.75), NLRP1 (0.72), ENSG00000258442 (0.6)
A10.272.497	Epidermis	Tissues	Epithelium	0.88	1.07	SDR9C7 (4.79), ECM1 (2.76), ARHGEF26 (2.17), GJA1 (1.38), SLC24A3 (1.37)
A11.329.372.600	Macrophages Alveolar	Cells	Connective Tissue Cells	0.89	1.07	TBC1D12 (1.95), NRP1 (1.77), DOCK4 (1.33), PHACTR1 (1.19), TMEM170A (0.99)
A08.186.211.730.885.287.500.270	Frontal Lobe	Nervous System	Central Nervous System	0.89	1.06	C1orf61 (2.53), TAC3 (2.01), ITPK1 (1.54), IGSF9B (1.48), GJA1 (1.35)
A08.186.211.730.317.357	Hypothalamus	Nervous System	Central Nervous System	0.90	1.06	IGSF9B (2.16), C1orf51 (1.57), HTRA1 (1.42), ASTN2 (1.22), MPPED2 (1.11)
A11.382	Endocrine Cells	Cells	Endocrine Cells	0.90	1.06	PAPPA (1.31), HTRA1 (1.3), YAP1 (1.23), CFDP1

						(1.14), BCAR1 (0.91)
A08.186.211.865.428	Metencephalon	Nervous System	Central Nervous System	0.90	1.06	IGSF9B (2.77), C1orf61 (2.25), SLC24A3 (1.66), ASTN2 (1.56), NAB2 (1.5)
A08.186.211.865	Rhombencephalon	Nervous System	Central Nervous System	0.90	1.05	IGSF9B (2.77), C1orf61 (2.25), SLC24A3 (1.66), ASTN2 (1.56), NAB2 (1.5)
A11.872.378.590.635	Granulocyte Macrophage Progenitor Cells	Cells	Stem Cells	0.91	1.05	KCNK5 (0.98), WDR12 (0.97), TSPAN2 (0.94), PRPF3 (0.88), TARS2 (0.69)
A08.186.211.132.810.428.200	Cerebellum	Nervous System	Central Nervous System	0.91	1.04	IGSF9B (2.85), C1orf61 (2.11), SLC24A3 (1.74), NAB2 (1.73), ASTN2 (1.54)
A15.382.490.555.567.537	Killer Cells Natural	Hemic and Immune Systems	Immune System	0.92	1.05	RNF213 (1.2), DHX36 (0.94), HELLS (0.77), CYP20A1 (0.68), TMEM170A (0.65)
A10.165	Connective Tissue	Tissues	Connective Tissue	0.93	1.05	SPINK2 (1.15), MEF2D (0.74), PHACTR1 (0.63), FGF6 (0.55), ZBTB39 (0.51)
A15.382	Immune System	Hemic and Immune Systems	Immune System	0.93	1.05	PHACTR1 (0.8), MEF2D (0.78), SPINK2 (0.72), ENSG00000258442 (0.57), FGF6 (0.54)
A08.186.211.730.317.357.352.435	Hypothalamo Hypophyseal System	Nervous System	Central Nervous System	0.93	1.04	IGSF9B (2.27), C1orf51 (1.78), HTRA1 (1.38), MPPED2 (1.32), ASTN2 (1.23)
A08.186.211.730.317.357.352	Hypothalamus Middle	Nervous System	Central Nervous System	0.93	1.04	IGSF9B (2.27), C1orf51 (1.78), HTRA1 (1.38), MPPED2 (1.32), ASTN2 (1.23)
A08.713	Neurosecretory Systems	Nervous System	Neurosecretory Systems	0.93	1.03	IGSF9B (2.27), C1orf51 (1.78), HTRA1 (1.38), MPPED2 (1.32), ASTN2 (1.23)
A10.272	Epithelium	Tissues	Epithelium	0.93	1.03	CHST6 (2.21), NBEAL1 (0.97), PLCE1 (0.86), C1orf51 (0.79), STAT6 (0.78)
A15.145.229.637.555.567.562.725	Plasma Cells	Hemic and Immune Systems	Blood	0.93	1.03	HEY2 (2.01), CYP20A1 (1.86), FGF6 (1.43), ENSG00000258442 (0.95), MEF2D (0.93)
A15.145.693	Plasma	Hemic and Immune Systems	Blood	0.93	1.02	HEY2 (1.99), CYP20A1 (1.86), FGF6 (1.42), ENSG00000258442 (0.95), MEF2D (0.94)
A15.145.229.637.555	Leukocytes Mononuclear	Hemic and Immune Systems	Blood	0.94	1.02	CYP20A1 (0.9), MEF2D (0.58), IGSF9B (0.56), FGF6 (0.48), TMEM170A (0.46)
A02.835	Skeleton	Musculoskeletal System	Skeleton	0.94	1.02	SPINK2 (1.19), MEF2D (0.78), PHACTR1 (0.67), FGF6 (0.58), ZBTB39 (0.55)
A15.382.216	Bone Marrow	Hemic and Immune Systems	Immune System	0.94	1.01	SPINK2 (1.38), MEF2D (0.99), PHACTR1 (0.86), FGF6 (0.72), ZBTB39 (0.62)
A02.835.232	Bone and Bones	Musculoskeletal System	Skeleton	0.94	1.01	SPINK2 (1.23), MEF2D (0.81), PHACTR1 (0.7), FGF6 (0.6), ZBTB39 (0.58)
A11.627.340.360	Granulocyte Precursor Cells	Cells	Myeloid Cells	0.95	1.01	TSPAN2 (1.75), HJURP (1.14), KCNK5 (1.08), WDR12 (1.03), HELLS (0.96)
A15.382.490.555.567	Lymphocytes	Hemic and Immune Systems	Immune System	0.96	1.01	CYP20A1 (1.06), IGSF9B (0.73), ZBTB39 (0.59), MEF2D (0.55), NLRP1 (0.53)

A11.063	Antibody Producing Cells	Cells	Antibody-Producing Cells	0.97	1.01	CYP20A1 (1.51), HEY2 (1.34), FGF6 (0.93), MEF2D (0.83), ZBTB39 (0.8)
A11.118.637.555.567.562	B Lymphocytes	Cells	Blood Cells	0.97	1.00	CYP20A1 (1.51), HEY2 (1.34), FGF6 (0.93), MEF2D (0.83), ZBTB39 (0.8)
A15.382.490.555.567.622	Lymphocytes Null	Hemic and Immune Systems	Immune System	0.97	1.00	HELLS (1.65), TARS2 (1.63), HJURP (1.55), RNF213 (1.34), NOC3L (1.13)
A11.627.635	Myeloid Progenitor Cells	Cells	Myeloid Cells	0.97	1.00	WDR12 (1.26), KCNK5 (1.01), TMEM194A (0.91), TARS2 (0.82), PRPF3 (0.8)
A11.872.378	Hematopoietic Stem Cells	Cells	Stem Cells	0.98	1.00	WDR12 (1.0), PRPF3 (0.8), KCNK5 (0.8), TMEM194A (0.73), NOC3L (0.71)
A11.872.378.590.817	Megakaryocyte Erythroid Progenitor Cells	Cells	Stem Cells	0.99	1.00	WDR12 (1.92), TMEM194A (1.88), HJURP (1.36), NOC3L (1.14), TARS2 (1.11)
A15.378.316.378.590.837.250	Erythroid Precursor Cells	Hemic and Immune Systems	Hematopoietic System	0.99	1.00	WDR12 (1.92), TMEM194A (1.88), HJURP (1.36), NOC3L (1.14), TARS2 (1.11)
A15.145.229.334	Erythrocytes	Hemic and Immune Systems	Blood	0.99	0.99	WDR12 (1.14), HJURP (1.0), TSPAN2 (0.92), SLC24A3 (0.91), KCNK5 (0.85)
A11.443	Erythroid Cells	Cells	Erythroid Cells	0.99	0.99	WDR12 (1.16), HJURP (0.98), TSPAN2 (0.89), SLC24A3 (0.88), TAC3 (0.88)
A14.724.557	Nasopharynx	Stomatognathic System	Pharynx	0.99	0.99	ENSG00000258442 (1.63), CYP2C18 (1.41), CYP2C19 (1.38), TAC3 (1.31), ZBTB39 (1.27)
A14.724	Pharynx	Stomatognathic System	Pharynx	0.99	0.99	ENSG00000258442 (1.06), CYP2C18 (0.9), CYP2C19 (0.87), FAM117B (0.76), CYP2C9 (0.72)

Supplementary Table 21. Enhancer analysis list of tissues and cell lines. The table lists the 56 tissues and cell lines used in the enhancer enrichment analysis, along with the anatomical group and how each cell/tissue type was derived. ESC is embryonic stem cells, iPSC is induced pluripotent stem cells, and GI is gastrointestinal. Migraine credible set SNPs were mapped to sets of enhancers in each tissue and enrichment was assessed empirically by randomly generating a background set of matched SNPs for comparison (10,000 replicates). No tissue/cell type was significant after adjusting for multiple testing. The results are plotted in **Figure 4**.

Tissue no.	Tissue label	Tissue description	Anatomic Group	Type	Enrichment P-value
1	Hippocampus middle	Brain Hippocampus Middle	BRAIN	PrimaryTissue	0.01
2	Anterior caudate	Brain Anterior Caudate	BRAIN	PrimaryTissue	0.49
3	Substantia nigra	Brain Substantia Nigra	BRAIN	PrimaryTissue	0.68
4	Cingulate gyrus	Brain Cingulate Gyrus	BRAIN	PrimaryTissue	0.17
5	Mid frontal lobe	Brain Dorsolateral Prefrontal Cortex	BRAIN	PrimaryTissue	0.01
6	Angular gyrus	Brain Angular Gyrus	BRAIN	PrimaryTissue	0.53
7	Inferior temporal lobe	Brain Inferior Temporal Lobe	BRAIN	PrimaryTissue	0.99
8	Neurosphere	Primary cultured neurospheres	BRAIN	PrimaryCulture	0.09
9	HUES 6	HUES6 Cells	ESC	PrimaryCulture	0.64
10	HUES64	HUES64 Cells	ESC	PrimaryCulture	0.49
11	hiPS-20b	iPS-20b Cells	IPSC	PrimaryCulture	0.99
12	hiPS-18a	iPS-18 Cells	IPSC	PrimaryCulture	0.43
13	H1	H1 Cells	ESC	PrimaryCulture	0.72
14	Kidney	Fetal Kidney	KIDNEY	PrimaryTissue	0.21
15	Pancreatic Islets	Pancreatic Islets	PANCREAS	PrimaryTissue	0.61
16	Liver	Liver	LIVER	PrimaryTissue	0.43
17	Duodenum mucosa	Duodenum Mucosa	GI	PrimaryTissue	0.27
18	Colonic mucosa	Colonic Mucosa	GI	PrimaryTissue	0.16
19	Rectal mucosa	Rectal Mucosa Donor	GI	PrimaryTissue	0.51
20	AdiposeNuclei	Adipose Nuclei	FAT	PrimaryTissue	0.15
21	Skeletal muscle	Skeletal Muscle	MUSCLE	PrimaryTissue	0.11
22	Smooth muscle, Duodenum	Duodenum Smooth Muscle	GI	PrimaryTissue	0.01
23	Smooth muscle, rectal	Rectal Smooth Muscle	GI	PrimaryTissue	0.39
24	Smooth muscle, stomach	Stomach Smooth Muscle	GI	PrimaryTissue	0.28

25	Smooth muscle, colon	Colon Smooth Muscle	GI	PrimaryTissue	0.24
26	BM-MSC	Bone Marrow Derived Cultured Mesenchymal Stem Cells	STROMAL_CONNECTIVE	PrimaryCulture	0.05
27	Chondrogenic dif cells	Mesenchymal Stem Cell Derived Chondrocyte Cultured Cells	STROMAL_CONNECTIVE	PrimaryCulture	0.22
28	NH-Osteoblast	Osteoblast Primary Cells	BONE	PrimaryCulture	0.11
29	NHDF	NHDF-Ad Adult Dermal Fibroblast Primary Cells	SKIN	PrimaryCulture	0.93
30	NHLF	NHLF Lung Fibroblast Primary Cells	LUNG	PrimaryCulture	0.97
31	NH-A	NH-A Astrocytes Primary Cells	BRAIN	PrimaryCulture	0.17
32	HSMM-myotube	HSMM cell derived Skeletal Muscle Myotubes Cells	MUSCLE	PrimaryCulture	0.12
33	HSMM	HSMM Skeletal Muscle Myoblasts Cells	MUSCLE	PrimaryCulture	0.20
34	SK-N-MC	Neuroepithelioma derived from human brain tumor	BRAIN	CellLine	0.91
35	A673	Human muscle sarcoma cell line	MUSCLE	CellLine	0.81
36	K562	K562 Leukemia Cells	BLOOD	PrimaryCulture	0.99
37	HepG2	HepG2 Hepatocellular Carcinoma Cell Line	LIVER	CellLine	0.94
38	Huvec	HUVEC Umbilical Vein Endothelial Primary Cells	VASCULAR	PrimaryCulture	0.90
39	NHEK	NHEK-Epidermal Keratinocyte Primary Cells	SKIN	PrimaryCulture	0.97
40	HMEC	HMEC Mammary Epithelial Primary Cells	BREAST	PrimaryCulture	0.98
41	HeLaS3	HeLa-S3 Cervical Carcinoma Cell Line	CERVIX	CellLine	0.96
42	DND-41	Dnd41 TCell Leukemia Cell Line	BLOOD	CellLine	0.80
43	Mobilized CD34+	Primary hematopoietic stem cells G-CSF-mobilized Male	BLOOD	PrimaryCell	0.79
44	CD14+	Monocytes-CD14+ RO01746 Primary Cells	BLOOD	PrimaryCell	0.70
45	GM12878 lymphoblastoid	GM12878 Lymphoblastoid Cells	BLOOD	PrimaryCulture	0.80
46	CD20+	B cells (CD20+)	BLOOD	PrimaryCell	0.50
47	CD19+	B cells (CD19+)	BLOOD	PrimaryCell	0.72
48	Th2 Tcells	T helper type 2 cells	BLOOD	PrimaryCell	0.74
49	Th1 Tcells	T helper type 1 cells	BLOOD	PrimaryCell	0.73
50	Th0 Tcells	T helper type 0 cells	BLOOD	PrimaryCell	0.84
51	CD25- IL17- Th stim MACS Tcells	Primary T helper cells PMA-I stimulated	BLOOD	PrimaryCell	0.89
52	CD25- IL17+ Th17 stim Tcells	Primary T helper 17 cells PMA-I stimulated	BLOOD	PrimaryCell	0.98
53	CD25int CD127+ memory Tcells	Primary T cells effector/memory enriched from peripheral blood	BLOOD	PrimaryCell	0.96
54	CD25+ CD127- reg Tcells	Primary T regulatory cells from peripheral blood	BLOOD	PrimaryCell	0.95
55	CD25- CD45RA+ naive Tcells	Primary T helper naive cells from peripheral blood	BLOOD	PrimaryCell	0.89
56	CD3+ Tcells	Primary T cells from peripheral blood	BLOOD	PrimaryCell	0.94

Supplementary Table 22. Gene Ontology enrichment analysis. Gene Ontology (GO) pathways significantly enriched for genes found proximal to the 38 migraine loci. Background frequency is the total number of genes out of all genes in the genome that annotated in a particular GO Pathway. The migraine set frequency is the number of genes from the set of 38 genes nearest to the migraine index SNP that are in each GO Pathway. The expected frequency is the number of genes from the migraine set that would be expected by chance to appear in each GO Pathway. The *P*-values from the binomial test were adjusted for the number of independent tests by Bonferroni correction.

Go Pathway	GO Term	Background frequency	Migraine set frequency	Expected frequency	<i>P</i> -value (adjusted)
Circulatory system development	GO:0072359	758	12	1.32	2.7×10^{-5}
Cardiovascular system development	GO:0072358	758	12	1.32	2.7×10^{-5}
Blood vessel morphogenesis	GO:0048514	368	9	0.64	8.7×10^{-5}
Heart development	GO:0007507	432	9	0.75	3.4×10^{-4}
Blood vessel development	GO:0001568	439	9	0.77	3.9×10^{-4}
Vasculature development	GO:0001944	460	9	0.80	5.8×10^{-4}
Endothelium development	GO:0003158	84	5	0.15	2.9×10^{-3}
Artery morphogenesis	GO:0048844	51	4	0.09	1.6×10^{-2}
Stem cell development	GO:0048864	232	6	0.40	2.2×10^{-2}
Single-multicellular organism process	GO:0044707	5874	24	10.24	2.4×10^{-2}
Artery development	GO:0060840	59	4	0.10	2.8×10^{-2}
Tissue morphogenesis	GO:0048729	566	8	0.99	3.8×10^{-2}

Supplementary Table 23. DEPICT enrichment analysis in reconstituted gene sets. The table lists 67 reconstituted gene sets that were identified by DEPICT to be significantly enriched for genes within the 38 migraine loci. To control Type I error due to multiple testing we estimated the false discovery rate (FDR) and applied a threshold for significance at $FDR < 5\%$. The 67 significant gene sets were then clustered by similarity into 10 groups (shaded by similar color in the table) and each cluster is named after the most representative gene set in the group (**Online Methods**). The gene set type column specifies the database where the original gene set was annotated, i.e. Canonical, Mouse Genome Informatics (MGI), and Protein-Protein Interaction (PPI).

Cluster	Reconstituted gene set ID	Reconstituted gene set name	Gene set type	Part of cluster	P	FDR
1	MP:0004883	Abnormal Vascular Wound Healing	MGI	ITGB1 PPI	1.86×10^{-6}	< 0.01
1	ENSG00000082781	ITGB5 PPI	PPI	ITGB1 PPI	9.19×10^{-6}	0.013
1	GO:0032403	Protein Complex Binding	Canonical	ITGB1 PPI	1.95×10^{-5}	0.008
1	ENSG00000087303	NID2 PPI	PPI	ITGB1 PPI	4.17×10^{-5}	0.011
1	MP:0003091	Abnormal Cell Migration	MGI	ITGB1 PPI	4.83×10^{-5}	0.013
1	ENSG00000139626	ITGB7 PPI	PPI	ITGB1 PPI	8.56×10^{-5}	0.023
1	ENSG00000132470	ITGB4 PPI	PPI	ITGB1 PPI	9.07×10^{-5}	0.024
1	ENSG00000123159	GIPC1 PPI	PPI	ITGB1 PPI	9.57×10^{-5}	0.026
1	GO:0005178	Integrin Binding	Canonical	ITGB1 PPI	0.000112	0.026
1	ENSG00000150093	ITGB1 PPI	PPI	ITGB1 PPI	0.000133	0.035
1	REACTOME INTEGRIN CELL SURFACE INTERACTIONS	Integrin Cell Surface Interactions	Canonical	ITGB1 PPI	0.000136	0.035
1	ENSG00000161638	ITGA5 PPI	PPI	ITGB1 PPI	0.000143	0.033
1	ENSG00000056345	ENSG00000056345 PPI	PPI	ITGB1 PPI	0.000166	0.038
1	MP:0000250	Abnormal Vasoconstriction	MGI	ITGB1 PPI	0.000172	0.037
1	GO:0005518	Collagen Binding	Canonical	ITGB1 PPI	0.000239	0.041
2	ENSG00000196411	EPHB4 PPI	PPI	Adherens Junction	1.42×10^{-5}	0.013
2	GO:0005912	Adherens Junction	CC	Adherens Junction	5.94×10^{-5}	0.017
2	GO:0005089	Rho Guanyl-Nucleotide Exchange Factor Activity	Canonical	Adherens Junction	8.83×10^{-5}	0.023
2	GO:0005925	Focal Adhesion	CC	Adherens Junction	0.000138	0.034
2	ENSG00000176105	YES1 PPI	PPI	Adherens Junction	0.000175	0.038
2	GO:0005924	Cell-Substrate Adherens Junction	CC	Adherens Junction	0.000191	0.038
2	GO:0045445	Myoblast Differentiation	Canonical	Adherens Junction	0.000195	0.037

2	GO:0070161	Anchoring Junction	CC	Adherens Junction	0.000205	0.039
2	GO:0017048	Rho Gtpase Binding	Canonical	Adherens Junction	0.000231	0.042
2	GO:0016323	Basolateral Plasma Membrane	CC	Adherens Junction	0.000296	0.049
2	GO:0030055	Cell-Substrate Junction	CC	Adherens Junction	0.000323	0.047
3	GO:0045765	Regulation Of Angiogenesis	Canonical	Blood Vessel Development	7.66×10^{-6}	0.017
3	MP:0003227	Abnormal Vascular Branching Morphogenesis	MGI	Blood Vessel Development	5.09×10^{-5}	0.012
3	GO:0001568	Blood Vessel Development	Canonical	Blood Vessel Development	8.26×10^{-5}	0.024
3	GO:0048514	Blood Vessel Morphogenesis	Canonical	Blood Vessel Development	8.63×10^{-5}	0.022
3	MP:0000291	Enlarged Pericardium	MGI	Blood Vessel Development	9.06×10^{-5}	0.025
3	GO:0022603	Regulation Of Anatomical Structure Morphogenesis	Canonical	Blood Vessel Development	0.00011	0.026
3	GO:0001525	Angiogenesis	Canonical	Blood Vessel Development	0.000139	0.033
3	MP:0002270	Abnormal Pulmonary Alveolus Morphology	MGI	Blood Vessel Development	0.000166	0.039
3	GO:0001944	Vasculature Development	Canonical	Blood Vessel Development	0.000177	0.037
3	GO:0045766	Positive Regulation Of Angiogenesis	Canonical	Blood Vessel Development	0.000208	0.041
3	GO:0019838	Growth Factor Binding	Canonical	Blood Vessel Development	0.000314	0.048
4	ENSG00000171475	WIPF2 PPI	PPI	Transcription Factor Binding	9.89×10^{-6}	0.02
4	GO:0000981	Sequence-Specific Dna Binding Rna Polymerase Ii Transcription Factor Activity	Canonical	Transcription Factor Binding	1.21×10^{-5}	0.014
4	GO:0031490	Chromatin Dna Binding	Canonical	Transcription Factor Binding	2.15×10^{-5}	0.012
4	ENSG00000136352	NKX2-1 PPI	PPI	Transcription Factor Binding	5.35×10^{-5}	0.014
4	ENSG00000096717	SIRT1 PPI	PPI	Transcription Factor Binding	0.000108	0.027
4	GO:0003705	Rna Polymerase Ii Distal Enhancer Sequence-Specific Dna Binding Transcription Factor Activity	Canonical	Transcription Factor Binding	0.000135	0.035
4	ENSG00000100393	EP300 PPI	PPI	Transcription Factor Binding	0.000143	0.033
4	GO:0008134	Transcription Factor Binding	Canonical	Transcription Factor Binding	0.000179	0.036
4	ENSG00000100603	SNW1 PPI	PPI	Transcription Factor Binding	0.000189	0.038
4	GO:0042826	Histone Deacetylase Binding	Canonical	Transcription Factor Binding	0.000217	0.04
5	MP:0011086	Partial Postnatal Lethality	MGI	Partial Postnatal Lethality	9.92×10^{-6}	0.017
5	MP:0001935	Decreased Litter Size	MGI	Partial Postnatal Lethality	1.84×10^{-5}	0.009
5	ENSG00000111676	ATN1 PPI	PPI	Partial Postnatal Lethality	4.85×10^{-5}	0.013

5	MP:0011101	Partial Prenatal Lethality	MGI	Partial Postnatal Lethality	7.71×10^{-5}	0.023
5	MP:0001923	Reduced Female Fertility	MGI	Partial Postnatal Lethality	0.000216	0.04
5	MP:0011108	Partial Embryonic Lethality During Organogenesis	MGI	Partial Postnatal Lethality	0.000238	0.042
6	MP:0005140	Decreased Cardiac Muscle Contractility	MGI	Decreased Cardiac Muscle Contractility	1.83×10^{-5}	0.01
6	MP:0002833	Increased Heart Weight	MGI	Decreased Cardiac Muscle Contractility	0.00017	0.036
6	MP:0005333	Decreased Heart Rate	MGI	Decreased Cardiac Muscle Contractility	0.000183	0.037
6	MP:0000280	Thin Ventricular Wall	MGI	Decreased Cardiac Muscle Contractility	0.000243	0.041
7	GO:0004675	Transmembrane Receptor Protein Serine/Threonine Kinase Activity	Canonical	Transforming Growth Factor Beta-Activated Receptor Activity	2.89×10^{-5}	0.011
7	GO:0005024	Transforming Growth Factor Beta-Activated Receptor Activity	Canonical	Transforming Growth Factor Beta-Activated Receptor Activity	7.41×10^{-5}	0.024
7	GO:0007179	Transforming Growth Factor Beta Receptor Signaling Pathway	Canonical	Transforming Growth Factor Beta-Activated Receptor Activity	8.84×10^{-5}	0.023
8	GO:0035924	Cellular Response To Vascular Endothelial Growth Factor Stimulus	Canonical	Cellular Response To Vascular Endothelial Growth Factor Stimulus	3.12×10^{-5}	0.009
8	GO:0048010	Vascular Endothelial Growth Factor Receptor Signaling Pathway	Canonical	Cellular Response To Vascular Endothelial Growth Factor Stimulus	0.000165	0.039
9	ENSG00000007264	MATK PPI	PPI	Integrin Complex	3.63×10^{-5}	0.012
9	GO:0008305	Integrin Complex	CC	Integrin Complex	0.000128	0.033
9	ENSG00000103653	CSK PPI	PPI	Integrin Complex	0.000195	0.038
10	GO:0010770	Positive Regulation Of Cell Morphogenesis Involved In Differentiation	Canonical	Positive Regulation Of Cell Morphogenesis Involved In Differentiation	5.94×10^{-5}	0.017
10	GO:0010718	Positive Regulation Of Epithelial To Mesenchymal Transition	Canonical	Positive Regulation Of Cell Morphogenesis Involved In Differentiation	0.00012	0.029

Supplementary Table 24. Selected pathways from the DEPICT analysis with previously hypothesized roles in migraine. For each of five previously hypothesized migraine mechanisms (ion homeostasis, glutamate signaling, serotonin signaling, nitric oxide signaling, and oxidative stress) below are shown the lowest *P*-value scoring reconstituted gene sets from the DEPICT gene set enrichment analysis (**Online Methods**), among all sets related to each of the mechanisms. None of the gene sets were even nominally significant. The significant pathways identified in the DEPICT analysis are listed in **Supplementary Table 23**.

Reconstituted gene set ID	Reconstituted gene set name	<i>P</i> -value	FDR	Top migraine loci genes in reconstituted gene sets
REACTOME METABOLISM OF NITRIC OXIDE	Metabolism Of Nitric Oxide	0.07	0.54	<i>NLRP1</i> (3.14), <i>C20orf160</i> (3.0), <i>NBEAL1</i> (2.34), <i>ECM1</i> (2.33), <i>GPR182</i> (2.28)
REACTOME GLUTAMATE NEUROTRANSMITTER RELEASE CYCLE	Glutamate Neurotransmitter Release Cycle	0.19	0.84	<i>MEF2D</i> (3.57), <i>SLC24A3</i> (3.01), <i>ABI2</i> (2.9), <i>IGSF9B</i> (2.75), <i>RAPH1</i> (2.33)
MP:0005322	Abnormal Serotonin Level	0.25	0.92	<i>MYO1A</i> (3.26), <i>ASTN2</i> (2.97), <i>DOCK4</i> (2.31), <i>CYP2C19</i> (2.27), <i>NRP1</i> (2.23)
GO:2000021	Regulation Of Ion Homeostasis	0.30	0.96	<i>TAC3</i> (2.85)
GO:0034599	Cellular Response To Oxidative Stress	0.46	1.00	<i>NCOA7</i> (2.59), <i>TGFBR2</i> (2.04), <i>REST</i> (1.84)

Supplementary Table 25. Specificity of individual gene expression in GTEx tissues. The genes selected were the nearest gene to the index SNP at each migraine locus. Tissues from the GTEx collection were grouped into four categories (brain, vascular, gastrointestinal, and other). For each gene, we used a 1-tailed t-test to assess if the expression level was significantly higher in the brain, vascular, or gastrointestinal tissue groups compared to the control group (“other tissues”). To adjust for multiple testing we used Bonferroni correction for 114 independent tests ($P < 1.3 \times 10^{-3}$). Overall, 13 genes showed significantly high expression in brain, 18 in vascular, and 4 in gastrointestinal tissues. We further defined a gene as tissue-specific if it was significantly expressed in only one tissue group. Of these we identified four in brain and eight in vascular (P -values highlighted in bold).

Selected Gene	Other tissues (reference)	Brain		Vascular		Gastrointestinal	
	Mean RPKM (SE)	Mean RPKM (SE)	P -value	Mean RPKM (SE)	P -value	Mean RPKM (SE)	P -value
<i>PRDM16</i>	1.81 (0.09)	1.40 (0.06)	1	6.35 (0.28)	1.4E-39	1.69 (0.26)	0.67
<i>LRRIQ3</i>	0.14 (0.02)	0.07 (0.004)	1	0.03 (0.002)	1	0.05 (0.004)	1
<i>TSPAN2</i>	3.29 (0.19)	0.85 (0.05)	1	11.29 (0.66)	1.8E-26	7.29 (0.93)	3.0E-05
<i>ADAMTSL4</i>	22.04 (0.56)	1.67 (0.18)	1	20.32 (0.70)	0.97	24.31 (2.25)	0.17
<i>MEF2D</i>	22.84 (0.44)	16.6 (0.56)	1	38.33 (1.32)	7.6E-25	16.63 (1.11)	1
<i>TRPM8</i>	0.08 (0.03)	0.05 (0.01)	0.82	0.001 (4e-4)	0.99	0.45 (0.20)	0.033
<i>TGFB2</i>	63.21 (1.62)	7.55 (0.30)	1	65.35 (2.01)	0.20	38.45 (2.82)	1
<i>GPR149</i>	0.01 (0.001)	0.61 (0.06)	4.4E-20	0.001 (2e-4)	1	0.004 (0.001)	1
<i>REST</i>	4.08 (0.06)	1.33 (0.04)	1	3.58 (0.07)	1	3.85 (0.12)	0.95
<i>PHACTR1</i>	1.25 (0.08)	5.02 (0.27)	1.2E-33	3.43 (0.16)	9.4E-31	0.57 (0.10)	1
<i>NOTCH4</i>	10.14 (0.38)	3.16 (0.12)	1	6.49 (0.32)	1	4.42 (0.45)	1
<i>KCNK5</i>	6.48 (0.36)	0.09 (0.01)	1	0.65 (0.07)	1	7.71 (0.63)	0.05
<i>FHL5</i>	8.51 (0.38)	2.00 (0.13)	1	80.26 (6.14)	9.5E-26	2.63 (0.33)	1
<i>GJA1</i>	53.73 (2.42)	100.77 (4.78)	1.2E-17	49.78 (2.58)	0.87	46.94 (7.28)	0.81
<i>HEY2</i>	2.82 (0.10)	3.47 (0.10)	2.0E-06	28.07 (1.49)	7.2E-44	1.32 (0.07)	1
<i>C7orf10</i>	0.60 (0.04)	0.35 (0.01)	1	1.89 (0.11)	1.3E-23	0.91 (0.10)	2.4E-03
<i>DOCK4</i>	3.46 (0.13)	9.32 (0.29)	1.7E-56	1.76 (0.05)	1	1.59 (0.09)	1
<i>ASTN2</i>	0.77 (0.04)	4.02 (0.10)	8.0E-107	1.38 (0.11)	2.1E-07	0.80 (0.08)	0.38
<i>NRP1</i>	13.56 (0.45)	2.51 (0.11)	1	13.17 (0.38)	0.75	5.39 (0.35)	1
<i>PLCE1</i>	3.20 (0.11)	1.86 (0.06)	1	7.64 (0.37)	1.1E-25	4.76 (0.44)	3.9E-04
<i>HPSE2</i>	0.53 (0.05)	2.15 (0.12)	7.1E-30	3.02 (0.29)	3.6E-16	3.74 (0.73)	1.6E-05
<i>ARMS2</i>	0.10 (0.01)	0.10 (0.01)	0.62	0.10 (0.01)	0.41	0.08 (0.01)	0.93

<i>MRVI1-AS1</i>	1.52 (0.26)	0.91 (0.03)	0.99	1.88 (0.10)	0.10	0.89 (0.10)	0.99
<i>MPPED2</i>	1.12 (0.08)	2.36 (0.09)	5.0E-24	0.66 (0.04)	1	0.42 (0.06)	1
<i>YAP1</i>	24.28 (0.51)	6.44 (0.22)	1	44.53 (1.90)	1.3E-21	24.8 (1.55)	0.38
<i>IGSF9B</i>	0.43 (0.02)	1.47 (0.11)	8.5E-18	2.39 (0.11)	6.3E-48	1.64 (0.23)	6.9E-07
<i>FGF6</i>	0.21 (0.03)	0.005 (7e-4)	1	0.009 (0.005)	1	0.002 (9e-4)	1
<i>LRP1</i>	40.44 (1.24)	25.86 (0.74)	1	51.45 (2.07)	3.3E-06	26.20 (1.84)	1
<i>ITPK1</i>	17.90 (0.40)	45.23 (0.92)	2.7E-98	21.13 (0.56)	1.4E-06	16.44 (1.31)	0.86
<i>CFDP1</i>	11.23 (0.19)	16.98 (0.26)	3.5E-59	10.03 (0.22)	1	11.25 (0.41)	0.48
<i>ZCCHC14</i>	8.06 (0.17)	8.81 (0.30)	0.016	9.37 (0.29)	6.4E-05	6.96 (0.17)	1
<i>WSCD1</i>	0.74 (0.03)	5.67 (0.19)	3.7E-84	1.57 (0.10)	8.2E-14	0.82 (0.12)	0.28
<i>RNF213</i>	12.29 (0.23)	4.16 (0.14)	1	6.23 (0.18)	1	8.94 (0.37)	1
<i>JAG1</i>	17.64 (0.50)	4.17 (0.13)	1	40.29 (2.06)	5.4E-23	15.85 (1.40)	0.88
<i>SLC24A3</i>	4.29 (0.15)	9.21 (0.55)	5.1E-17	8.74 (0.55)	4.9E-14	4.43 (0.46)	0.38
<i>MED14</i>	6.40 (0.10)	3.91 (0.09)	1	5.07 (0.13)	1	4.51 (0.15)	1