SUPPLEMENTARY NOTE

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Supplementary Note

Members of the International Headache Genetics Consortium

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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 and also those who self-reported migraine by questionnaires. 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. Whereas our secondary analyses of 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). Specific IHS diagnostic criteria used to classify migraine with aura and migraine without aura can be found in the 2nd edition of the International Classification of Headache Disorders (ICHD-II)[1]. For the population-based study samples this involved a questionnaire used to assess the necessary criteria, 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 as the migraine aura specifically is quite hard to distinguish from other neurological features that can present as symptoms from unrelated conditions.

Study design

In order to detect common genetic variants of small effect (i.e. odds ratios approximately less than 1.3), we aimed to collect genome-wide association (GWA) study data from as many individuals as possible with migraine information available 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 contain 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), which represent completely new data. The 23andMe GWA study data has been reported previously for other phenotypes, but not for migraine (30,465 new cases), as is similar for the data 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 2013[2] 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.

Defining credible sets

Assume D is the data including the genotype matrix X for all of the P variants (genotype for variant j is denoted as $\boldsymbol{x}_j$) and disease status Y (for N individuals), and β is the model parameters. We define the 'model', denoted A, as the causal status for all the P variants in the locus: $A \equiv \{a_j\}$, in which a_j is the causal status for variant j. $a_j = 1$ if the variant j is causal, whereas $a_j = 0$ if it is not. We assume that there is one and only one genuine signal for each locus, therefore, one and only one of the P variants is causal: $\sum_j a_j = 1$. For convenience, we define A_j as the model that only variant j is causal, and A_0 as the model that no variant is causal (null model). The probability for model A_j (variant j is the only causal variant in this locus) given the data can be calculated using Bayes' rule:

$$\Pr(A_j|D) = \int_\beta \Pr(D, \beta|A_j) \cdot \frac{\Pr(A_j)}{\Pr(D)} \cdot d\beta. \quad (1)$$

We estimate Equation (1) using the steepest descent approach[57]. Making the assumption of a flat prior on the model parameters, we approximate the integral over the model parameters using their maximum likelihood estimator ($\hat{\beta}_j$):

$$\Pr(A_j|D) \approx \Pr(D|A_j, \hat{\beta}_j) \cdot N^{-\frac{|\beta_j|}{2}} \cdot \frac{\Pr(A_j)}{\Pr(D)}, \quad (2)$$

where the sample size is denoted by N and the number of fitted parameters for model A_j is denoted by $|\beta_j|$. $|\beta_j|$ is a constant in this study because model A_j has the same number of parameters across all variants. In the framework of a generalized linear model (including linear and binomial regressions), the deviance for two nested models follows an approximate chi-square distribution. We therefore define ${\chi_j}^2$ as the deviance comparing the null model and the model in which variant j is causal

$${\chi_j}^2 \equiv -2 \log \frac{\Pr(D|A_0, \hat{\beta}_0)}{\Pr(D|A_j, \hat{\beta}_j)}. \quad (3)$$

We further show that ${\chi_j}^2$ can be calculated as the chi-square statistic of fitting a binomial model with the disease status (Y) as the dependent variable and the genotype of variant j as the explanatory variable:

$$\chi_j{}^2 = -2\log\frac{\Pr(\{\boldsymbol{x}_i\}, Y|\{a_i = 0\}, \{\hat{\beta}_{i,0}\})}{\Pr(\{\boldsymbol{x}_i\}, Y|\{a_j = 1, a_{-j} = 0\}, \{\hat{\beta}_j, \hat{\beta}_{-j,0}\})}$$

$$= -2\log\frac{\prod_i \Pr(\boldsymbol{x}_i, Y|a_i = 0, \hat{\beta}_{i,0})}{\Pr(\boldsymbol{x}_j, Y|a_j = 1, \hat{\beta}_j)\prod_{i\neq j}\Pr(\boldsymbol{x}_i, Y|a_i = 0, \hat{\beta}_{i,0})}$$

$$= -2\log\frac{\Pr(\boldsymbol{x}_j, Y|a_j = 0, \hat{\beta}_{j,0})}{\Pr(\boldsymbol{x}_j, Y|a_j = 1, \hat{\beta}_j)}. \quad (4)$$

$\Pr(A_j|D)$ in Equation (2) is then a function of the χ_j^2:

$$\Pr(A_j|D) \approx \exp\left(\frac{\chi_j^2}{2}\right)\cdot l_0 \cdot N^{-\frac{|\beta_j|}{2}}\cdot\frac{\Pr(A_j)}{\Pr(D)}, \quad (5)$$

where $l_0 = \Pr(D|A_0, \hat{\beta}_0)$. We make the assumption that the prior causal probability for all variants is equal, *i.e.*, $\Pr(A_j)$ is the same across all variants j. Equation (5) can then be simplified with a constant for the term $l_0 \cdot N^{-\frac{|\beta_j|}{2}}\cdot\frac{\Pr(A_j)}{\Pr(D)}$ and the probability that variant j is causal can be calculated using

$$\Pr(A_j|D) \propto \exp(\frac{\chi_j^2}{2}), \quad (6)$$

which can be normalized across all variants

$$\mathrm{P}(A_j) \equiv \Pr(A_j|D)/\sum_k \Pr(A_k|D). \quad (7)$$

Finally, the 99% credible set of variants is defined as the smallest set of models, with each model designating one causal variant, $\mathrm{S} = \{A_j\}$, such that

$$\sum_{A_j\in S}\mathrm{P}(A_j) \geq 99\%. \quad (8)$$

This credible set of variants has 99% probability of containing the causal variant, given the assumption that there is a true association and that all possible causal variants have been genotyped (both assumptions are likely to be valid in genome-wide significant regions of data that have been imputed to 1000 Genomes). Finally, note that for fine mapping, we only consider variants for which we have near complete data from the contributing datasets. As a consequence, we cannot unequivocally rule out other variants not in the credible set, as they are incompletely measured for this kind of analysis.

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 ancestry[5]. A maximal set of unrelated individuals was chosen for each analysis using a segmental identity-by-descent (IBD) estimation algorithm[6]. 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 ShapeIt2[7]. 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 algorithm[8], 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 Minimac2[9], using 5 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" and reference the following webpage: http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/.

Centre National de Génotypage (CNG) carried out DNA genotyping on the Illumina human660W-quad 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 1.0e-06. 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 pi-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 program[11]. Association analysis of allelic dosage scores within a logistic regression framework including sex and strata (ATM1/ATM2) as covariates was performed using the PLINK program[12]. 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 1958[14]. 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 sampling[15], 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 Consortium[16], the Type 1 Diabetes Genetics Consortium[17] and the GABRIEL asthma genetics consortium[18]. Imputations were performed using the 1000 Genomes (Phase I, v3, March 2012 release) reference panel by the MACH software[11]. Within-cohort logistic regression analyses for migraine were performed using ProbAbel[19]. 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 studies[20]. The DMQ3 is a comprehensive migraine questionnaire that was designed based on ICHD-II[1], 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 criteria[22], 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% respectively[22]. 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 cancer[23] 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 NFBC1966[24] (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 cohort[25]. Migraine was assessed based on the health questionnaire survey provided by the participants. The sample was originally genotyped for this study[26]. 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 criteria[1]. Details on this procedure can be found in previous work[29]. 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 genotyping[30]. 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 1.07[12]. 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 1[11]. The phased data were then imputed with MINIMAC[31] in batches of around 500 individuals for 561 chromosome chunks obtained by the CHUNKCHROMOSOME program[32]. 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 program[33], as described previously[34]. 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 Netherlands[35]. 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 Registry[37]. 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-II[38]. 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 in included in this study. Migraine cases were defined as those who 1) reported suffering from headache during the last year, and satisfied ICHD criteria[1] 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 Registry[39]. 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 population[39]. 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 migraine[1], 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 IMPUTE[40] version 2 using 1000 Genomes (Phase I, v3, March 2012 release) combined populations reference panel and the 610Q data was use 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 age[41]. 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)[42] 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 $P=10^{-6}$ 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 > 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 adulthood[43]. 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 Welcome 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 (pi-hat > 0.2). 11,766 SNPs were excluded based on Hardy–Weinberg equilibrium (HWE) test ($p = 10^{-6}$), 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 analysis[43]. Genotype imputation was performed using IMPUTE[40] 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[44–46]. 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 student[46]. The migraine diagnoses adhere to the ICHD-2[1]. The 1000 healthy and unrelated controls were recruited among volunteers in the Danish Blood Donor Study (DBDS)[47]. 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 used[48]. 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-II[1]. 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)[49]. 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 I[36]. 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 study[48] 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)[49]. 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 ($FMSQ_{FS}$)[50] and all fulfilled the current International Headache Society diagnostic criteria (ICHD-II[1]) 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 study[51]. 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-II[1] by experienced neurologists with a specialization in headache disorders, as described previously[52]. The diagnosis of MA was obtained either by face-to-face interviews or by telephone interviews.

German controls were obtained from the PopGen study[53] (n = 645) and from the Heinz Nixdorf Recall (HNR) study (n = 365)[54], 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 $FMSQ_{FS}$[50]. 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-II[1] 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/F4[55] (n = 801) as well as from the GSK[56] (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.

Conflicts of interest

Thomas Werge has acted as lecturer and consultant for H. Lundbeck A/S, Valby, Denmark. Markus Schürks is a full-time employee of Bayer HealthCare, Germany.

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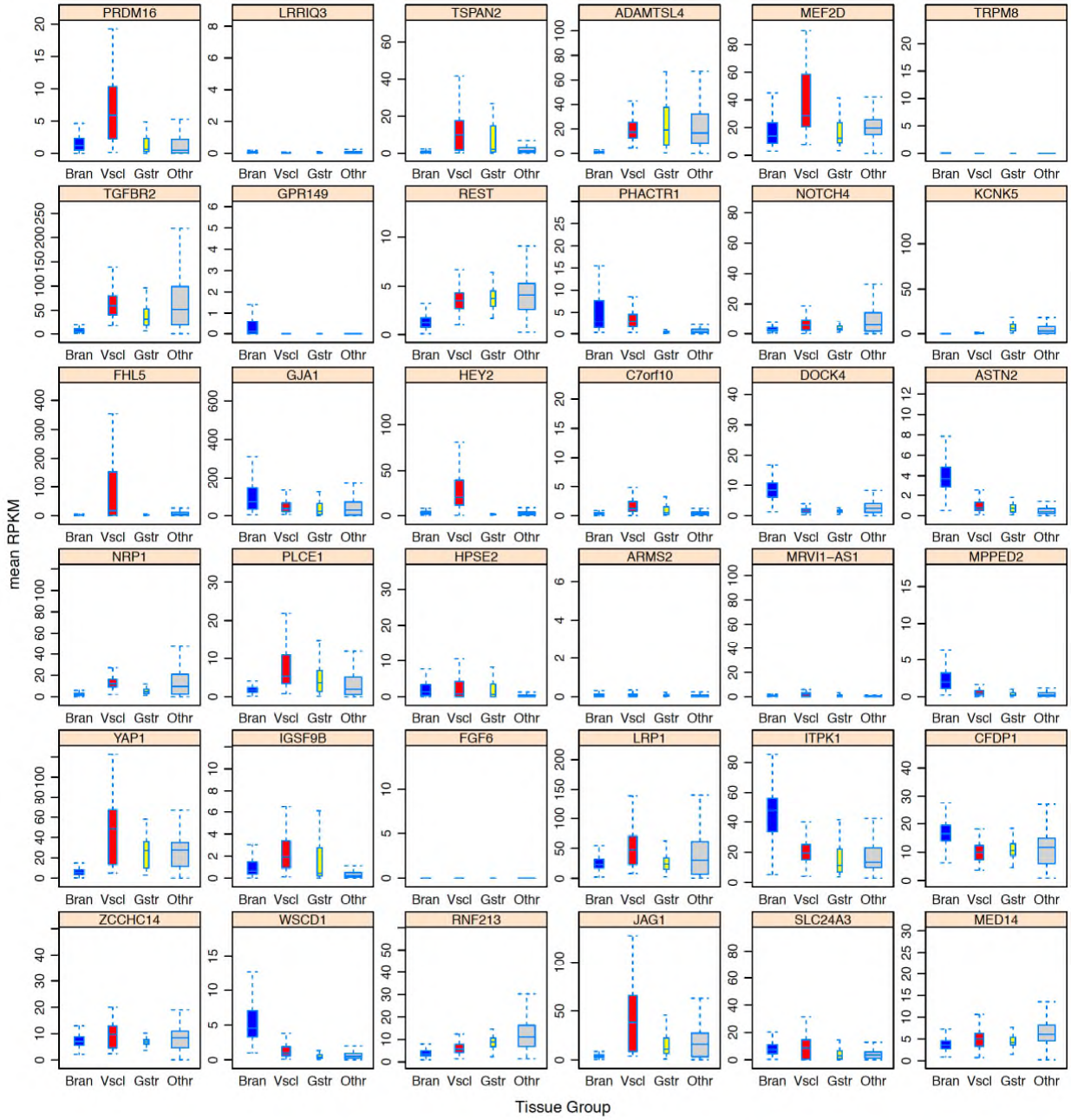
Supplementary Figures

Supplementary Figure 1. Region plots of the 38 genome-wide significant loci (see separate attached PDF document for figure).

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.

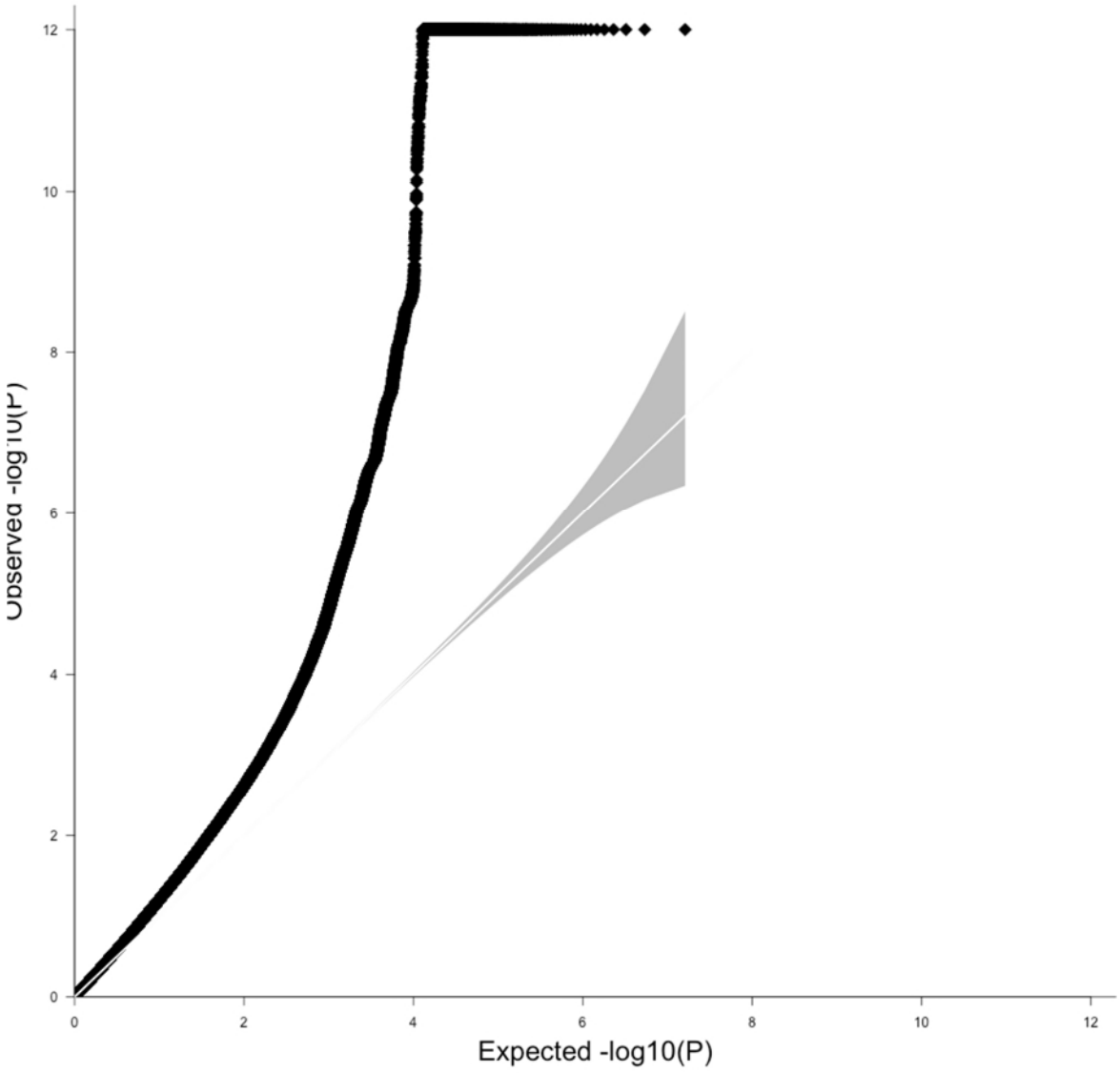
Supplementary Figure 2. Individual gene expression in GTEx tissues.

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 (Gastro), Vascular (Vscl), and Other (Othr). The center values of box-plots represent the median and the box itself outlines the interquartile range.



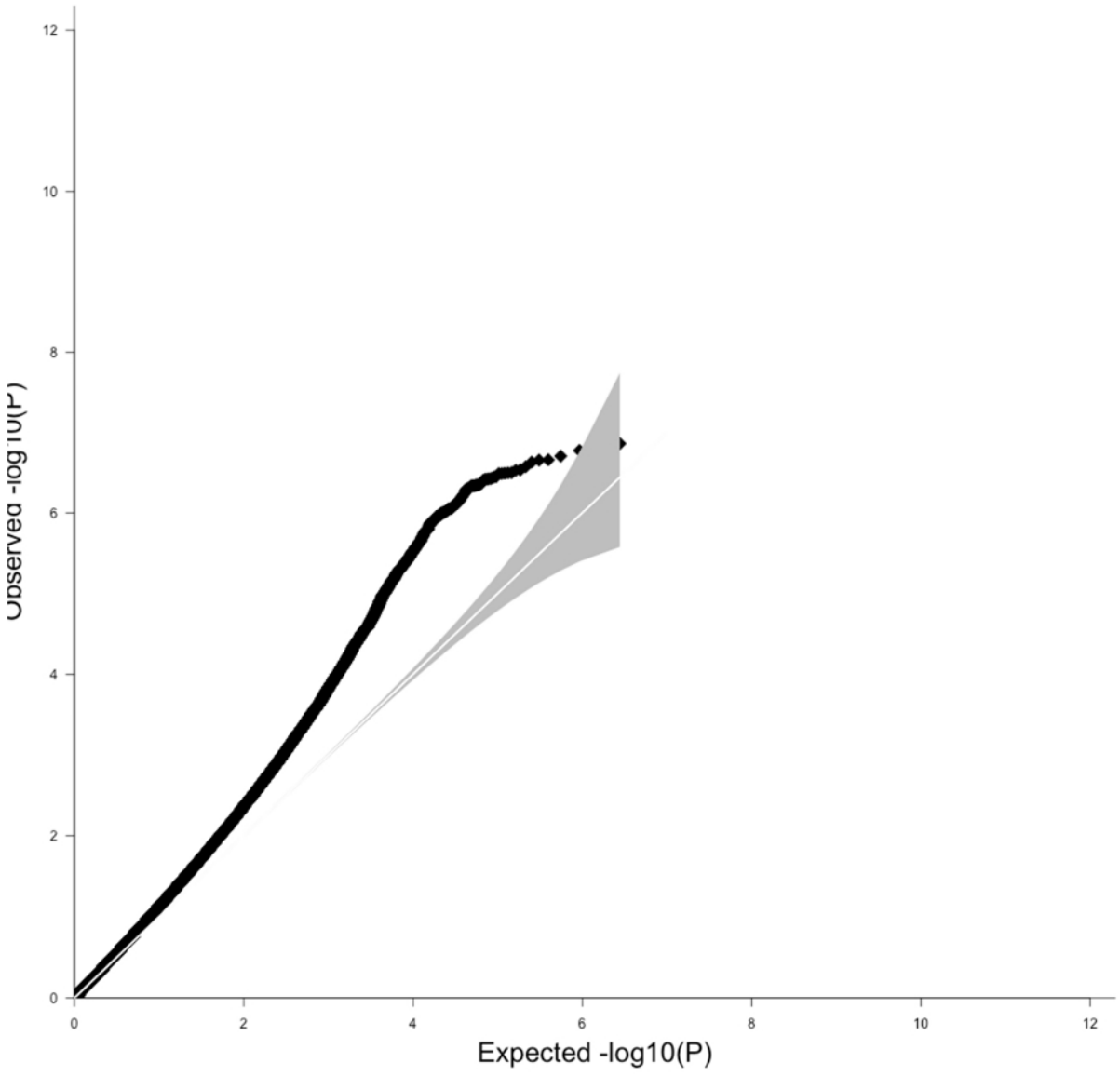
Supplementary Figure 3. QQ-plot of the primary analysis test statistics.

In the analysis of all migraine (59,674 cases vs. 316,208 controls), λ_{GC} = 1.24. For clarity, the observed association p-values along the vertical axis have been limited to a minimum value of $1x10^{-12}$. The shaded area represents the 95% confidence intervals of expected p-values under the null hypothesis.



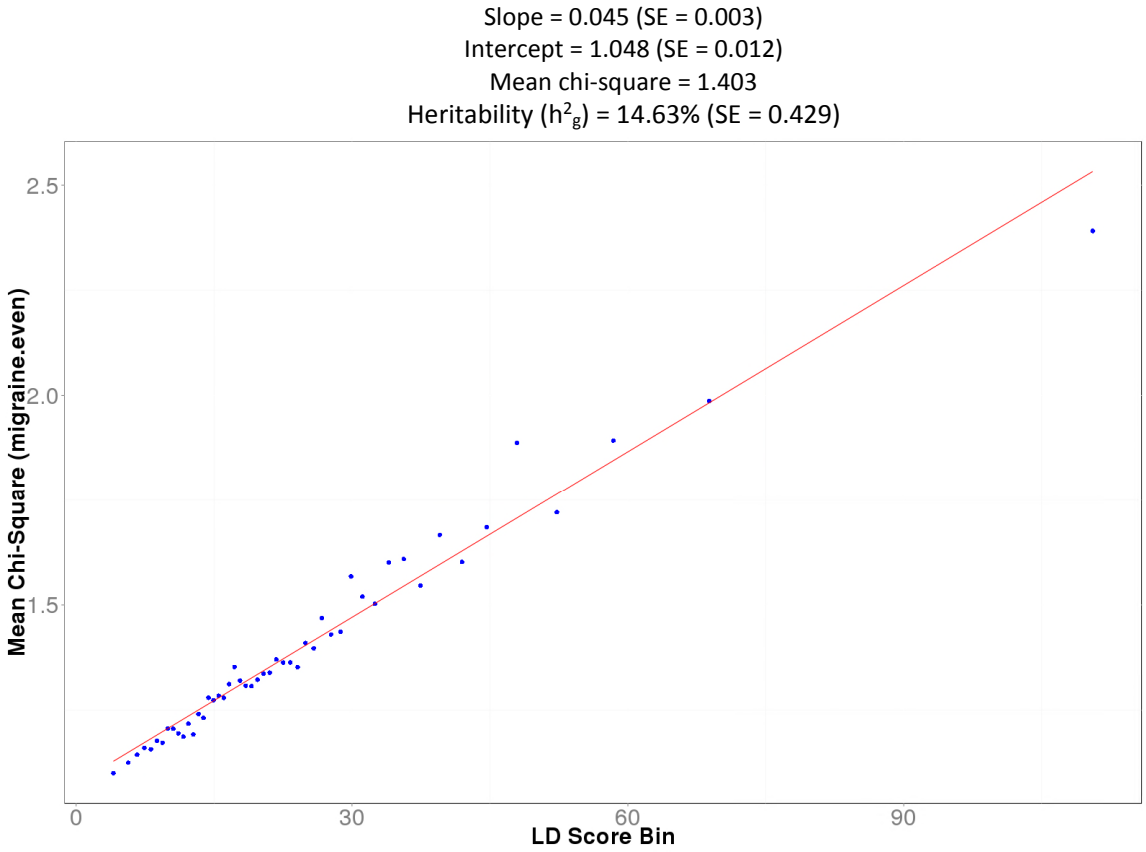
Supplementary Figure 4. QQ-plot of the primary analysis after LD-pruning.

Re-plotting the test statistics for of all migraine (59,674 cases vs. 316,208 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 λ_{GC} = 1.15.



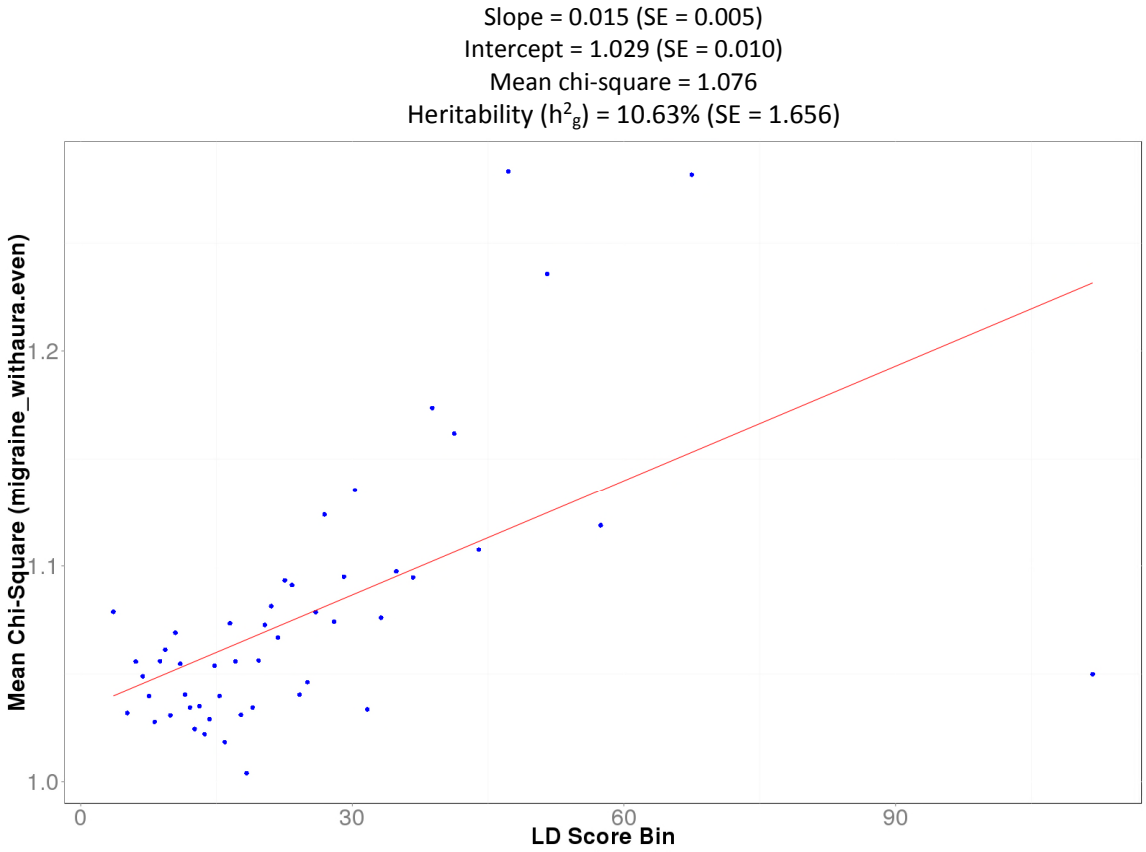
Supplementary Figure 5. LD-score regression plot for all migraine.

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. 316,208 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%CIs = 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).



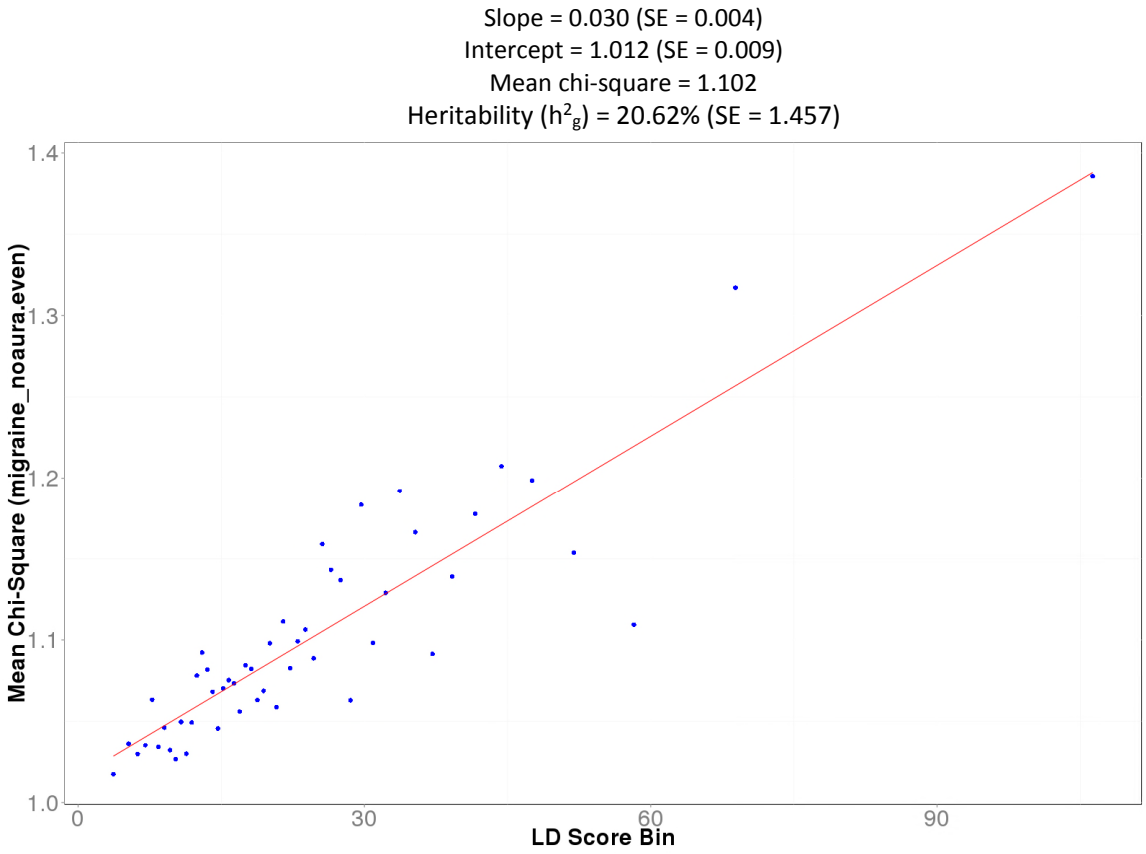
Supplementary Figure 6. LD-score regression plot for the MA subtype.

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 142,817 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%CIs = 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).



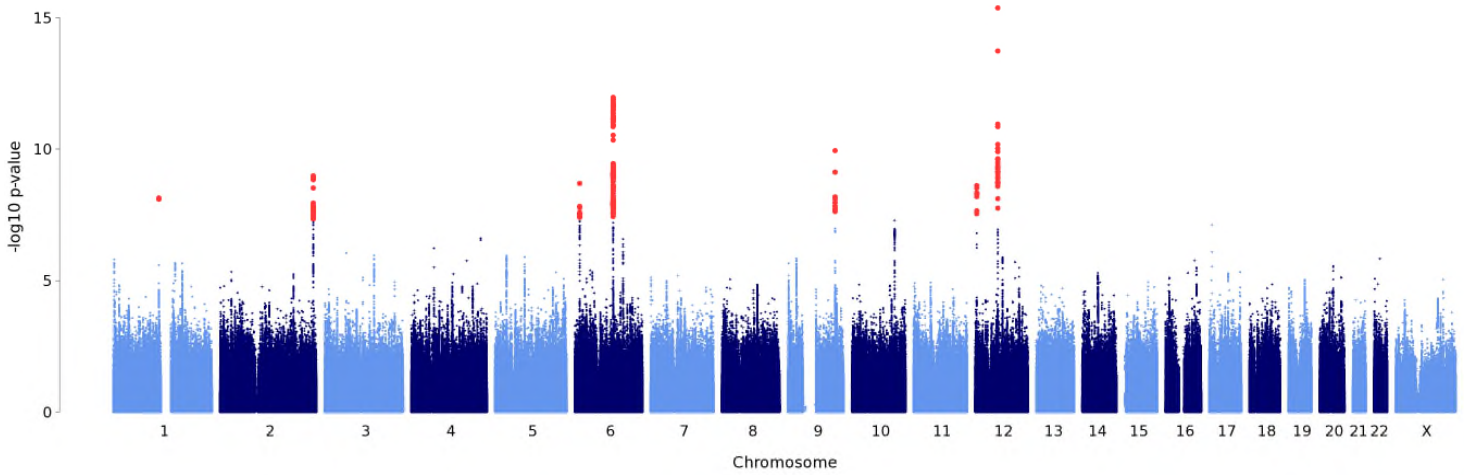
Supplementary Figure 7. LD-score regression plot for the MO subtype.

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 136,758 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%CIs = 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).



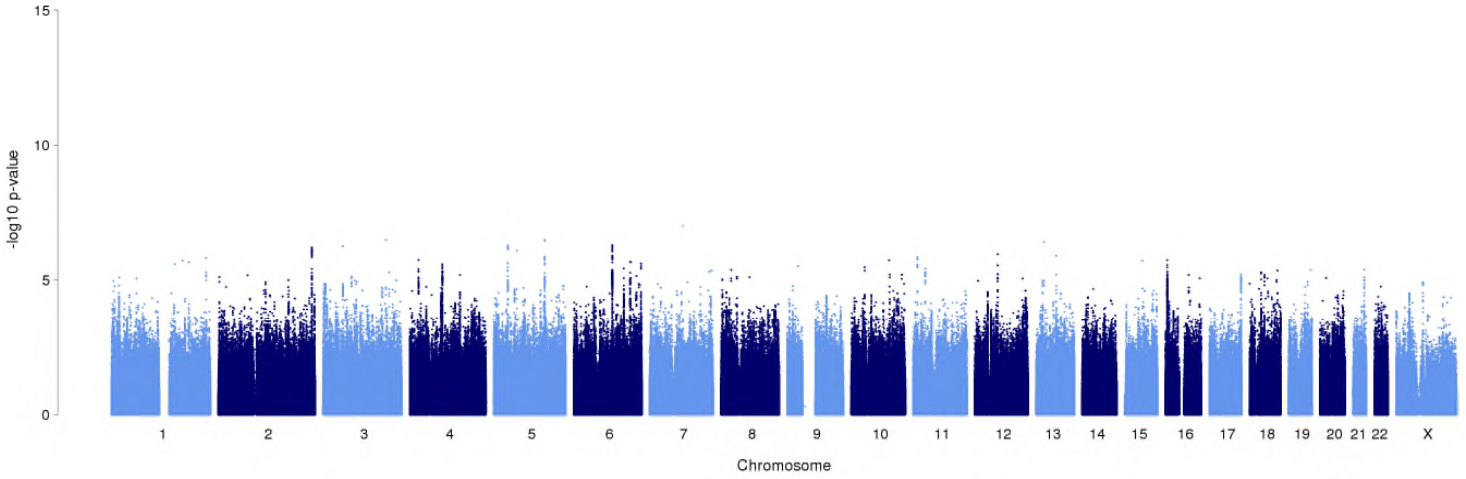
Supplementary Figure 8. Manhattan plot for the MO subset analysis.

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 136,758 controls and seven genome-wide significant loci.



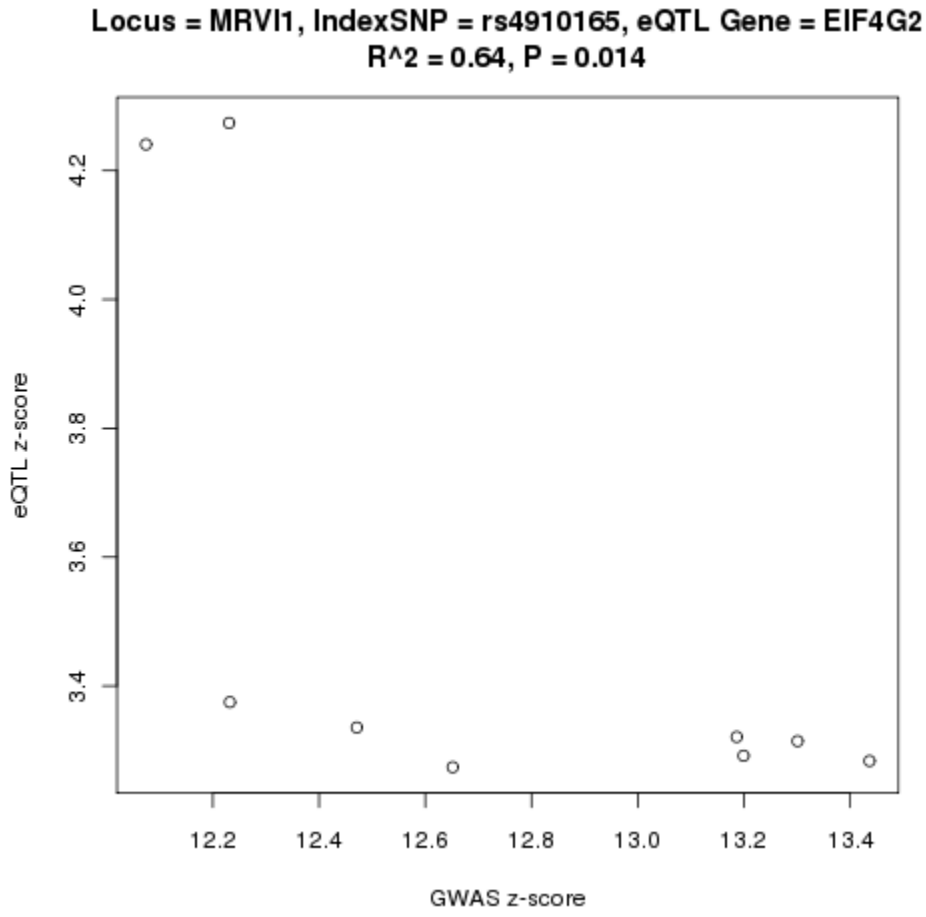
Supplementary Figure 9. Manhattan plot for the MA subset analysis.

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 142,817 controls. No genome-wide significant loci were identified.



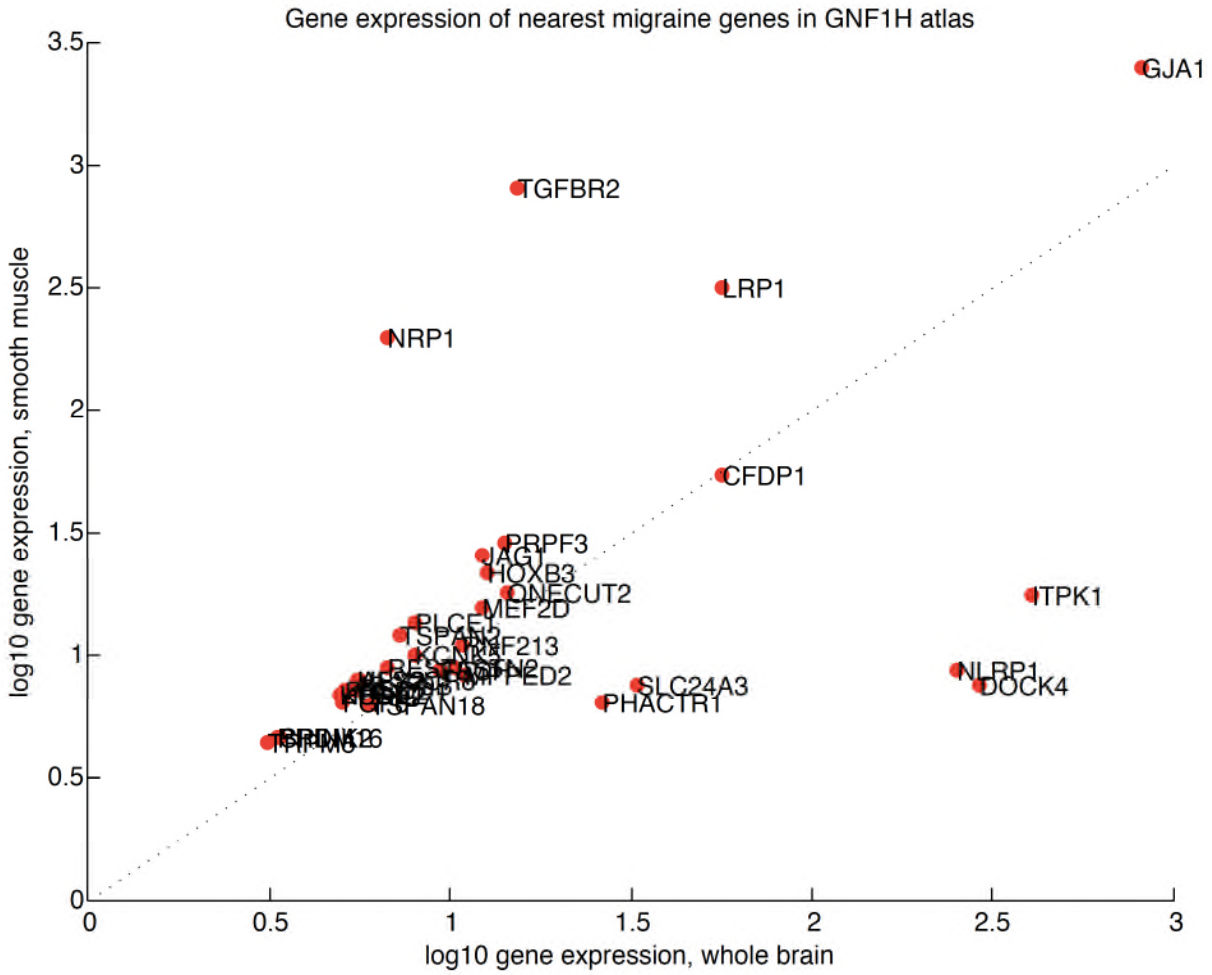
Supplementary Figure 10. Correlation of test statistics between migraine and eQTL SNPs at the *MRVI1* locus.

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.



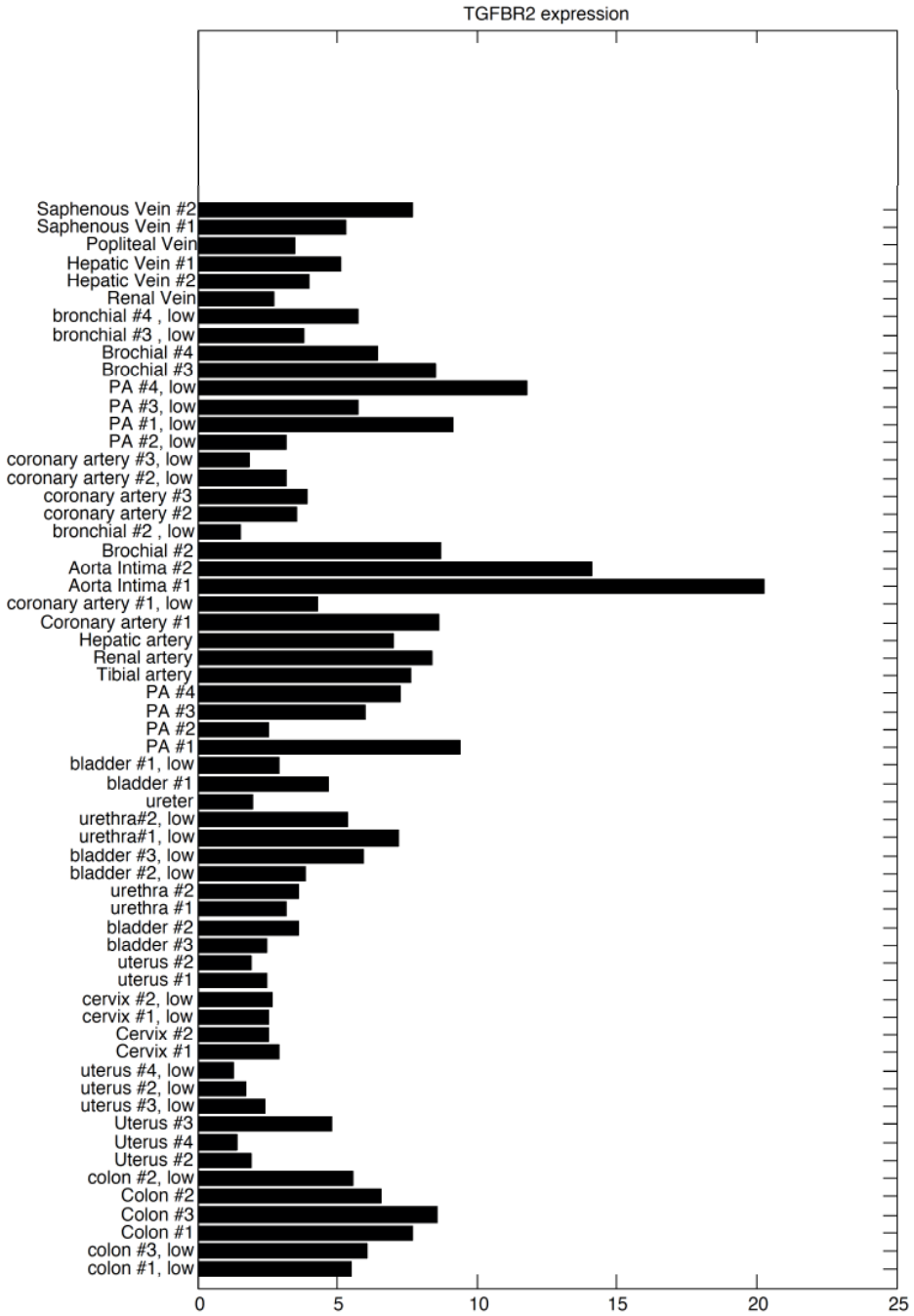
Supplementary Figure 11. Gene expression of the 38 genes nearest to the migraine loci index SNPs.

The expression data used to quantify the degree of brain/smooth muscle tissue expression comes from the GNF1H atlas[58]. The horizontal axis is mean gene-expression in brain tissues and the vertical axis is mean expression in smooth muscle tissues. The plot indicates that *TGFBR2* and *NRP1* are preferentially expressed in smooth muscle tissues.



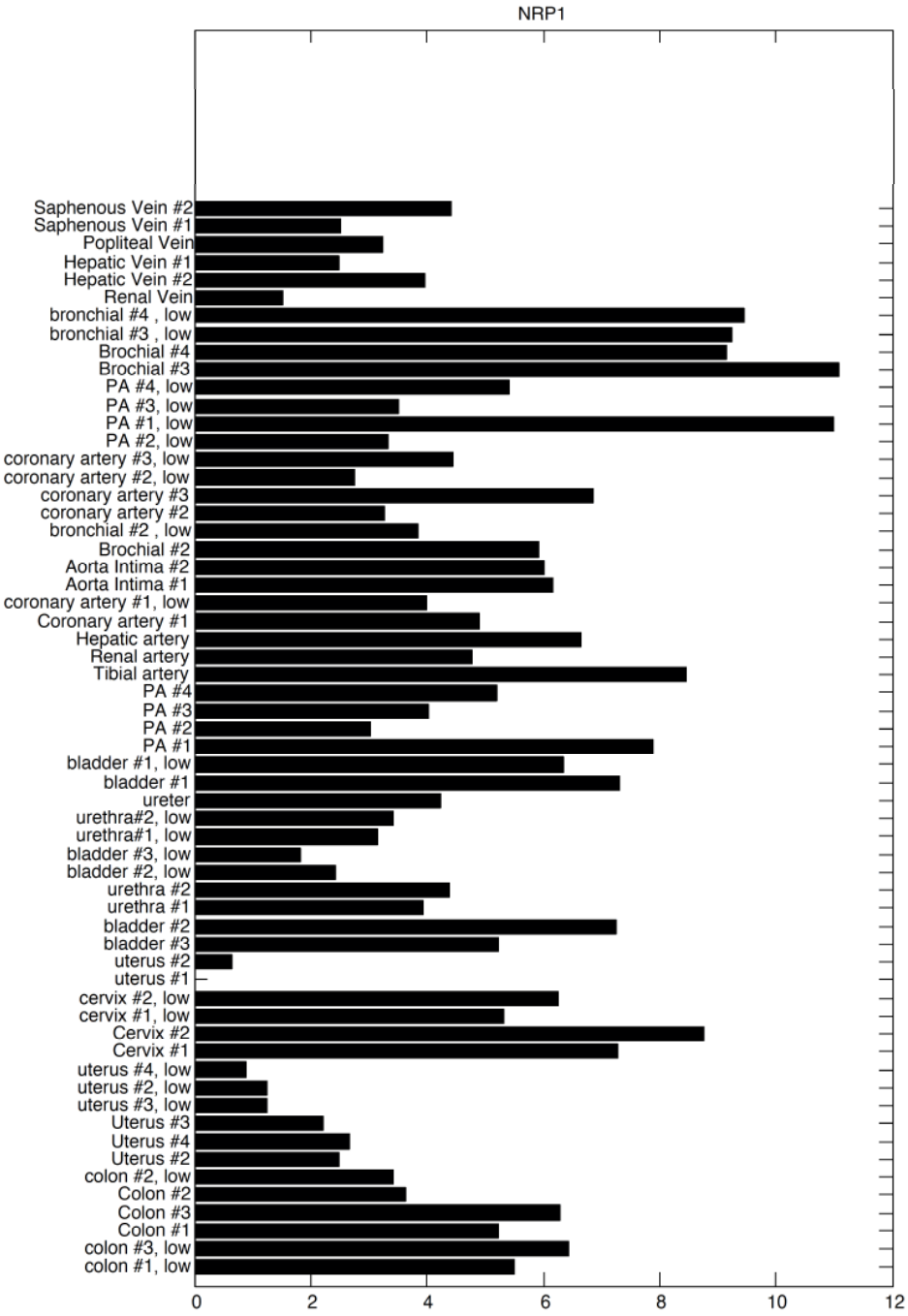
Supplementary Figure 12. Gene expression of *TGFBR2* in 60 types of smooth muscle tissue.

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 13. Gene expression of *NRP1* in 60 types of smooth muscle tissue.

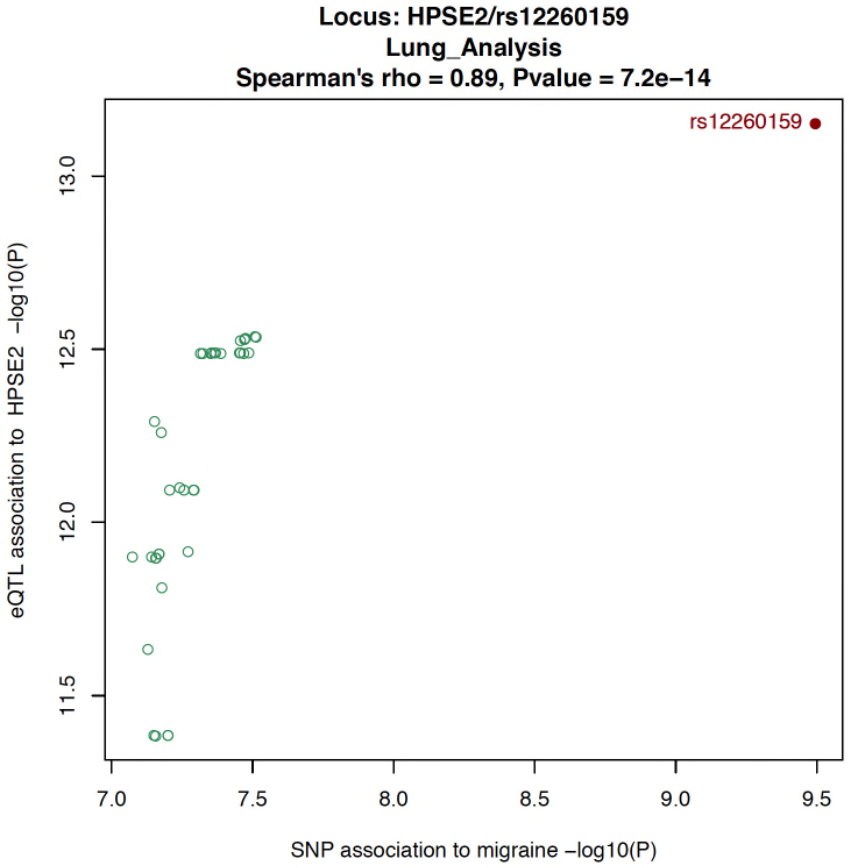
The horizontal bars show gene expression levels per tissue. The top 31 tissues are vascular smooth muscle types while the bottom 29 tissues are visceral smooth muscle types. The expression of *NRP1* appears to be high in many tissues from both the vascular and visceral smooth muscle categories.

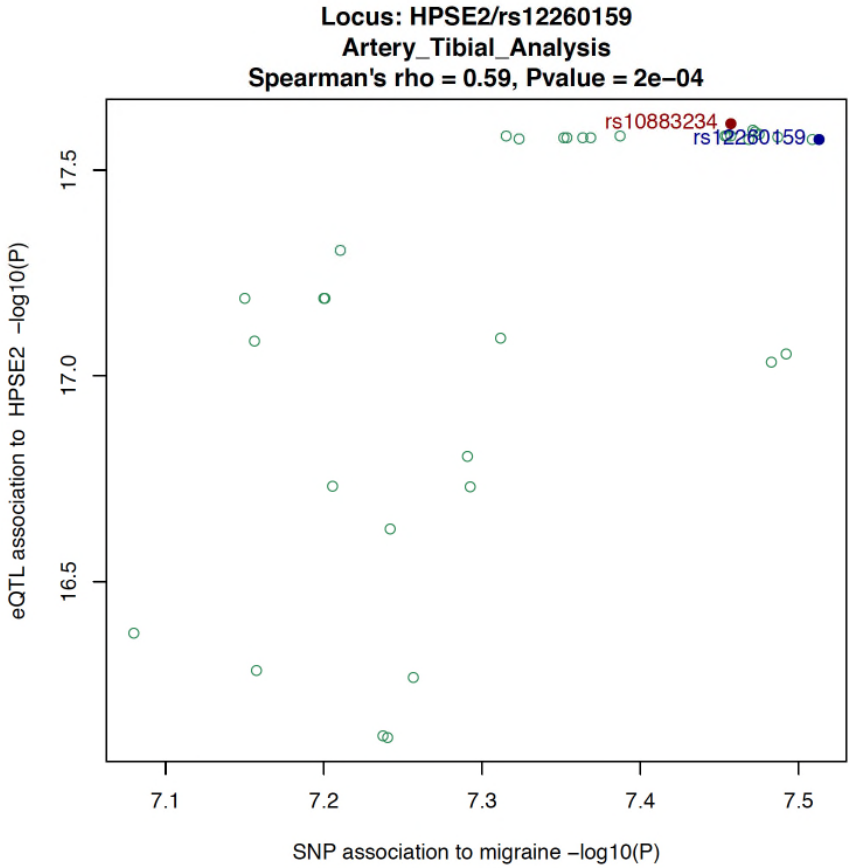


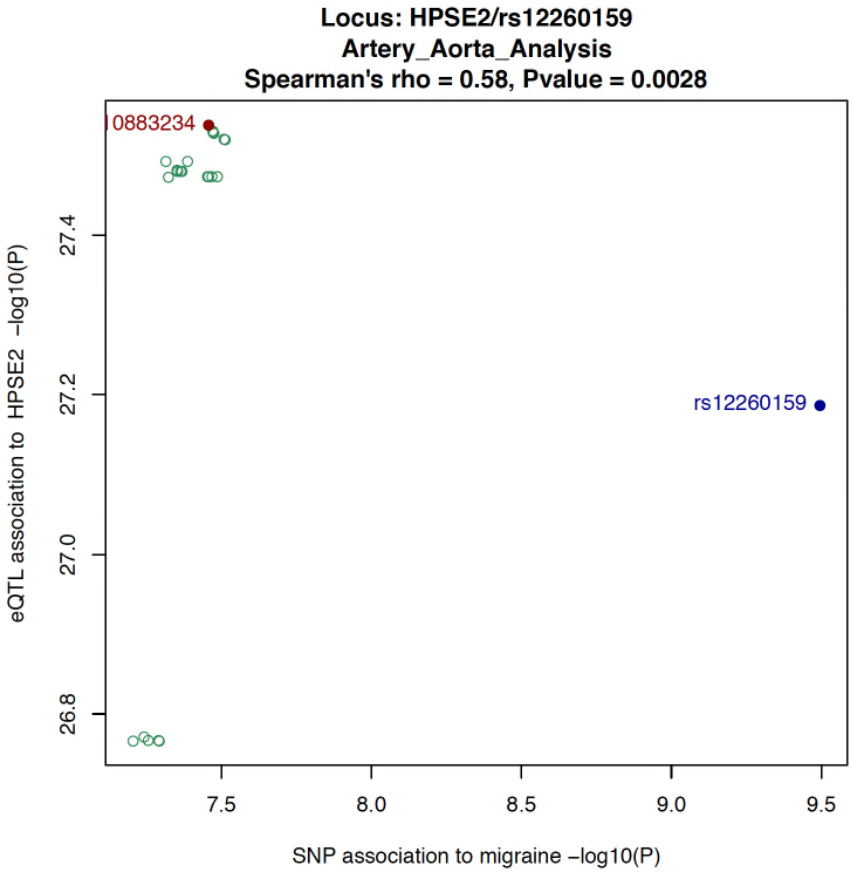
Supplementary Figure 14. Forest plots of the 45 independently associated SNPs (see separate attached PDF document for figure).

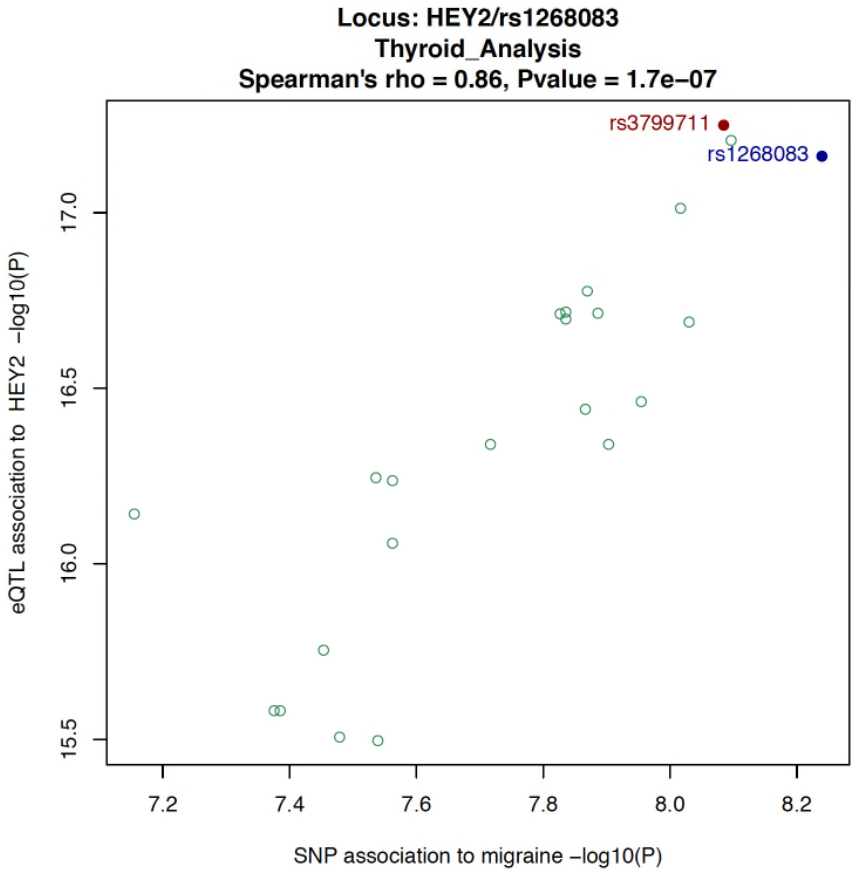
For each SNP we plot the minor allele frequency for cases and controls (MAF[case] and MAF[ctrl] respectively) and the corresponding Odds Ratio (OR) from each of the 22 individual GWA studies. A value of "NA" means that the marker was filtered out of that particular study due to not passing genotyping 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 15. 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 (Lung, Tibial Artery, and Aorta) for the *HPSE2* locus and one tissue (Thyroid) for the *HEY2* 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**.






Locus: HPSE2/rs12260159
Artery_Aorta_Analysis
Spearman's rho = 0.58, Pvalue = 0.0028
0883234
rs12260159
eQTL association to HPSE2 −log10(P)
SNP association to migraine −log10(P)
26.8
27.0
27.2
27.4
7.5
8.0
8.5
9.0
9.5


Locus: HEY2/rs1268083
Thyroid_Analysis
Spearman's rho = 0.86, Pvalue = 1.7e−07
rs3799711
rs1268083
eQTL association to HEY2 −log10(P)
SNP association to migraine −log10(P)
15.5
16.0
16.5
17.0
7.2
7.4
7.6
7.8
8.0
8.2

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-Pval* 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 (%)
PRDM16	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 AJAP1	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 TSPAN2	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
MEF2D	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
TRPM8	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 TGFBR2	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
PHACTR1	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
FHL5	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
C7orf10	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 MMP16	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
ASTN2	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
LRP1	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-quad	1) MAF > 0.01 2) HWE > $1.0\times^{-6}$ 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

			4) IBD < 0.20						

Supplementary Table 4. Covariates and genomic inflation for each individual GWA study.

List of all covariates controlled for in each individual 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 for each study 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 the genomic inflation factor is also shown (λ_{1000}) which denotes the inflation estimated for the same study but rescaled for 1000 cases and 1000 controls[62].

		All migraine studies				MA studies				MO studies			
Study	Covariates	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.

The table shows concordance between the best-guess imputed genotypes and the genotypes obtained for the same individuals by whole-genome sequencing. A total of 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 rates were high (> 85%) for 41 out of 45 migraine-associated index SNPs. The four SNPs with lower concordance rates were found to be multiallelic in the WGS (rs67338227, rs186166891, rs2672599) or in repeat regions (rs111404218) which make them more difficult for correct alignment and calling in sequencing pipelines. For two of these SNPs we identified proxies in high LD (r2 > 0.6 in 1000Genomes) to the original SNP and validated those instead; 99.25% concordance for rs2971606 (proxy to rs67338227) and 99.5% concordance for rs6134000 (proxy to rs111404218). Additionally, rs111404218 was confirmed to exist as a variant in the EGCUT sample by visually inspecting reads using the Integrative Genomics Viewer software.

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
PRDM16	1	rs10218452	G	0.22	72	92	95.73	89	1929	98.76	59	1116	96.31	3357	97.76
PRDM16	1	rs12135062	T	0.23	71	89	85.63	103	2170	96.88	59	1116	88.12	3608	93.53
LRRIQ3	1	rs1572668	A	0.52	70	92	100	112	2410	99.52	59	1116	98.69	3859	99.29
TSPAN2	1	rs2078371	C	0.12	73	94	99.40	115	2446	99.80	59	1116	98.88	3903	99.51
NGF	1	rs7544256	G	0.36	73	96	98.82	115	2383	98.92	59	1116	98.59	3842	98.82
ADAMTSL4	1	rs6693567	C	0.27	72	92	100	107	2344	97.10	59	1116	99.16	3790	97.87
MEF2D	1	rs1925950	G	0.35	72	95	99.40	111	2359	97.65	59	1116	99.51	3812	98.30
CARF	2	rs138556413	T	0.03	68	87	98.71	115	2456	99.69	59	1116	100	3901	99.74
HJURP	2	rs566529	T	0.15	72	96	99.40	112	2452	99.80	59	1116	99.60	3907	99.73
TRPM8	2	rs10166942	C	0.20	72	96	99.40	112	2440	99.88	59	1116	98.72	3895	99.51
TGFBR2	3	rs6791480	T	0.31	73	91	100	112	2415	99.80	59	1116	99.05	3866	99.58
GPR149	3	rs13078967	C	0.03	72	94	97.59	109	2404	98.29	59	1116	86.36	3854	94.62
SPINK2	4	rs7684253	T	0.55	69	93	98.77	107	2382	99.80	59	1116	99.33	3826	99.61
PHACTR1	6	rs9349379	G	0.41	72	94	99.40	101	2138	96.29	59	1116	98.93	3580	97.30
NOTCH4	6	rs140002913	A	0.06	73	96	98.22	104	2197	97.18	59	1116	59.38	3645	85.04
KCNK5	6	rs10456100	T	0.28	72	96	97.02	112	2375	99.60	59	1116	98.21	3830	99.06
FUT9	6	rs2223239	T	0.15	73	95	99.40	114	2433	99.49	59	1116	99.39	3890	99.46
FHL5	6	rs67338227	T	0.23	Not called in WGS			86	1859	56.50	59	1116	2.07	3120	36.00

GJA1	6	rs28455731	T	0.16	71	95	99.40	114	2460	99.65	59	1116	99.30	3915	99.54
HEY2	6	rs1268083	C	0.48	73	96	98.82	115	2446	99.80	59	1116	99.12	3905	99.56
C7orf10	7	rs186166891	T	0.11	25	34	98.31	106	2323	71.93	59	1116	74.15	3663	73.07
DOCK4	7	rs10155855	T	0.05	72	95	99.40	107	2328	99.92	59	1116	97.50	3777	99.14
ASTN2	9	rs6478241	A	0.36	69	90	100	113	2416	99.05	59	1116	98.19	3863	98.83
NRP1	10	rs2506142	G	0.17	72	95	99.40	114	2446	99.80	59	1116	98.68	3902	99.45
PLCE1	10	rs10786156	G	0.45	69	92	100	113	2382	99.64	59	1116	98.91	3831	99.43
PLCE1	10	rs75473620	T	0.04	71	95	98.19	113	2426	98.15	59	1116	94.62	3880	97.08
HPSE2	10	rs12260159	A	0.07	72	94	98.80	112	2415	99.17	59	1116	95.56	3868	98.06
ARMS2	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
MRVI1	11	rs4910165	C	0.33	73	96	99.41	112	2353	99.76	59	1116	99.23	3809	99.58
MPPED2	11	rs11031122	C	0.24	70	94	100	112	2423	99.72	59	1116	98.51	3874	99.37
YAP1	11	rs10895275	A	0.33	71	92	100	111	2428	99.80	59	1116	98.67	3877	99.47
IGSF9B	11	rs561561	T	0.12	Not imputed in GWAS			104	2163	99.96	59	1116	98.95	3442	99.61
FGF6	12	rs1024905	C	0.53	73	96	100	112	2393	99.72	59	1116	98.95	3849	99.50
SDR9C7	12	rs7961602	T	0.41	72	92	98.78	109	2335	96.44	59	1116	93.71	3783	95.69
LRP1	12	rs11172113	C	0.42	73	95	99.40	103	2230	92.33	59	1116	99.09	3676	94.81
ITPK1	14	rs11624776	C	0.31	71	95	100	101	2061	99.31	59	1116	98.69	3503	99.13
CFDP1	16	rs77505915	G	0.55	66	79	93.79	103	2297	97.75	59	1116	94.91	3720	96.70
ZCCHC14	16	rs4081947	G	0.34	Not imputed in GWAS			106	2297	99.13	59	1116	99.22	3578	99.16
WSCD1	17	rs75213074	T	0.03	72	96	100	111	2388	99.92	59	1116	97.78	3842	99.27
RNF213	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
SLC24A3	20	rs4814864	C	0.26	72	95	98.80	110	2414	99.88	59	1116	98.10	3866	99.29
CCM2L	20	rs144017103	T	0.02	73	94	97.01	105	2324	99.75	59	1116	61.76	3771	87.79
MED14	X	rs12845494	G	0.27	68	88	98.72	114	2372	97.30	59	1116	91.98	3817	95.72

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 ($P < 5\times10^{-8}$) 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 *AJAP1*	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 *MMP16*	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 *MTDH*	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 that are significantly associated with migraine ($P < 5\times10^{-8}$).

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. The joint PAR for all SNPs combined was then estimated as 16.65% using $PAR_{joint} = 1 - \prod_k(1 - PAR_k)$. 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 (%)
PRDM16	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
PRDM16	1	3103312	rs12135062	T	0.23	1.05 [1.04-1.07]	3.7×10^{-10}	-	374,810	22	0.58	0	1.17
LRRIQ3	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
TSPAN2	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
NGF	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
ADAMTSL4	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
MEF2D	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
CARF	2	203832867	rs138556413	T	0.03	0.88 [0.84-0.92]	2.3×10^{-08}	-	346,121	14	0.94	0	11.56
HJURP	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
TRPM8	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
TGFBR2	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
GPR149	3	154289946	rs13078967	C	0.03	0.87 [0.83-0.91]	1.8×10^{-09}	-	374,705	22	0.89	0	13.11
SPINK2	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
PHACTR1	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
NOTCH4	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

KCNK5	6	39183470	rs10456100	T	0.28	1.06 [1.04-1.07]	6.9×10^{-13}	-	374,705	22	0.84	0	1.57
FUT9	6	96767685	rs2223239	T	0.15	1.06 [1.04-1.08]	3.2×10^{-10}	-	374,706	22	0.21	0.18	0.91
FHL5	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
GJA1	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
HEY2	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
C7orf10	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
DOCK4	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
ASTN2	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
NRP1	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
PLCE1	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
PLCE1	10	96019029	rs75473620	T	0.04	0.89 [0.86-0.93]	5.8×10^{-09}	-	374,706	22	0.74	0	10.25
HPSE2	10	100702737	rs12260159	A	0.07	0.92 [0.89-0.94]	3.2×10^{-10}	-	374,706	22	0.65	0	7.92
ARMS2	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
MRVI1	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
MPPED2	11	30547438	rs11031122	C	0.24	1.04 [1.03-1.06]	3.5×10^{-08}	-	374,706	22	0.62	0	1.06
YAP1	11	102083608	rs10895275	A	0.33	1.04 [1.03-1.06]	1.6×10^{-08}	-	374,706	22	0.79	0	1.35
IGSF9B	11	133829706	rs561561	T	0.12	0.94 [0.92-0.96]	3.4×10^{-08}	-	368,251	20	0.77	0	5.3
FGF6	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
SDR9C7	12	57273481	rs7961602	T	0.41	0.95 [0.94-0.97]	2.1×10^{-11}	-	374,706	22	0.44	0.02	2.82
LRP1	12	57527283	rs11172113	C	0.42	0.90 [0.89-0.91]	5.6×10^{-49}	-	374,706	22	0.71	0	5.98
ITPK1	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
CFDP1	16	75442143	rs77505915	T	0.45	1.05 [1.03-1.06]	3.3×10^{-10}	-	374,705	22	0.92	0	2.08
ZCCHC14	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
WSCD1	17	5612640	rs75213074	T	0.03	0.89 [0.86-0.93]	7.1×10^{-09}	-	374,706	22	0.86	0	10.2
RNF213	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
JAG1	20	10684159	rs111404218	G	0.34	1.05 [1.03-1.07]	2.0×10^{-09}	-	374,705	22	0.56	0	1.65
SLC24A3	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
CCM2L	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
MED14	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. Overlaps with the NHGRI GWAS catalog and OMIM of all 38 loci identified, rank ordered by lowest p-value of association.

For each locus, the nearest coding gene to the index SNP is given. 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	*LRP1*	chr12:57244168-57545756	301.6	*LRP1, STAT6, NAB2, TMEM194A, MYO1A, TAC3, ZBTB39, HBCBP, GPR182, RDH16, SDR9C7*		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	*PRDM16*	chr1:3065568-3112278	46.7	*PRDM16*		
3	rs67338227	T	0.23	1.09 [1.08-1.11]	2.0E-27	*FHL5*	chr6:96735298-97092478	357.2	*FHL5, UFL1*		
4	rs10166942	C	0.20	0.91 [0.89-0.92]	2.2E-27	*TRPM8*	chr2:234726966-234874402	147.4	*TRPM8, HJURP, MROH2A*	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	*TSPAN2*	chr1:115084796-115829943	745.2	*NGF, TSPAN2, TSHB, SYCP1, SIKE1, CSDE1, NRAS, AMPD1, DENND2C, BCAS2*	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 Hypothryoidism, 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	*PHACTR1*	chr6:12768218-12948388	180.2	*PHACTR1*	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	*CFDP1*	chr16:75304623-75504768	200.2	*CHST6, TMEM170A, CFDP1, BCAR1*	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	*RNF213*	chr17:78235300-78269111	33.8	*RNF213, SLC26A11*	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	*NRP1*	chr10:33464928-33468456	3.5	*NRP1*		
19	rs13078967	C	0.03	0.87 [0.83-0.91]	1.8E-09	*GPR149*	chr3:153891622-154438050	546.4	*GPR149, DHX36, ARHGEF26*		
20	rs111404218	G	0.34	1.05 [1.03-1.07]	2.0E-09	*JAG1*	chr20:10658917-10698494	39.6	*JAG1*	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	*REST*	chr4:57727311-57761417	34.1	*REST*	ARMD pmid=21909106 p=2E-08	
22	rs1268083	C	0.48	0.96 [0.95-0.97]	5.3E-09	*HEY2*	chr6:125988964-126116953	128.0	*NCOA7, HEY2*	Brugada syndrome pmid=23872634 p=5E-17	
23	rs75213074	T	0.03	0.89 [0.86-0.93]	7.1E-09	*WSCD1*	chr17:5603221-5621884	18.7	*NLRP1-WSCD1**		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	*GJA1*	chr6:121782750-121860207	77.5	*GJA1*	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	*TGFBR2*	chr3:30427287-30500279	73.0	*RBMS3-TGFBR2**	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	*ITPK1*	chr14:93591673-93596315	4.6	*ITPK1*	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	*LRRIQ3*	chr1:73458846-74098899	640.1	*NEGR1-LRRIQ3**	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	*MPPED2*	chr11:30492070-30570596	78.5	*MPPED2*		
37	rs140002913	A	0.06	0.91 [0.88-0.94]	3.8E-08	*NOTCH4*	chr6:32200054-32206049	6.0	*NOTCH4*	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	*CCM2L*	chr20:30610164-30628982	18.8	*HCK, CCM2L, XKR7*		

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*<5E-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	***KCNK5*** (PMID: 16239344) ***TRPM8*** (PMID: 23596210)	
Ion homeostasis	***KCNK5*** (ion channel. PMID: 16239344) ***TRPM8*** (ion channel. PMID: 23596210) ***SLC24A3*** (exchanger. PMID: 11294880) ***ITPK1*** (ion flux regulator. PMID: 8816834) ***GJA1*** (Ca2+ oscillations. PMID: 21654699)	*SLC26A11* (Cl^- channel) *JPH3*
NO or oxidative stress	***REST*** (Ox. stress PMID: 24670762) ***GJA1*** (Ox. stress PMID: 23456878) ***YAP1*** (Ox. stress PMID: 24810048) ***PRDM16*** (Ox. stress PMID: 20835244) ***LRP1*** (Ox. stress PMID: 21454812) ***MRVI1*** (NO PMID: 10724174)	*BCAR1* *USP9X* *IMMP2L* *HTRA1*
Vascular diseases	***PHACTR1*** (PMID: 19198609 and 25420145) ***TGFBR2*** (PMID: 16885183) ***LRP1*** (AAA PMID: 22055160) ***PRDM16*** (Cardiomyopathy PMID: 23768516) ***RNF213*** (Moyamoya PMID: 24949311) ***JAG1*** (OMIMs PMID: 12427653) ***HEY2*** (Brugada Sy PMID: 23872634) ***GJA1*** (PMID: 25124494) ***ARMS2*** (Wet AMD. PMID: 20385826)	*HTRA1* (CARASIL)
Regulation of vascular tone	***MRVI1*** (PMID: 20080989) ***GJA1*** (PMID: 17085540) ***SLC24A3*** (PMID 16617138) ***NRP1*** (PMID: 25659123)	*GPR182* *TAC3* *BCAR1*

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 ($P < 5\times10^{-8}$) to other diseases/traits that are also in high LD (allelic $R^2 > 0.8$) with any of the 45 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
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	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	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 i2 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 P-value	i^2 (%)
TSPAN2	1	*115677183*	rs2078371	C	0.11	1.18 [1.12-1.25]	7.4E-09	144,801	11	0.61	0
TRPM8	2	*234820578*	rs6724624	G	0.20	0.86 [0.82-0.90]	1.1E-09	144,703	11	0.003	62.4
PHACTR1	6	*12903957*	rs9349379	G	0.41	0.88 [0.85-0.92]	2.1E-09	144,703	11	0.55	0
FHL5	6	*97056979*	rs7775721	T	0.33	1.15 [1.11-1.20]	1.1E-12	144,702	11	0.26	19.3
ASTN2	9	*119252629*	rs6478241	A	0.35	1.14 [1.09-1.18]	1.2E-10	144,703	11	0.50	0
FGF6	12	*4518140*	rs1024905	G	0.48	1.12 [1.08-1.16]	2.5E-09	144,703	11	0.65	0
LRP1	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 affects between the two groups. The results from this analysis are presented in **Supplementary Table 13**.

GWA study	MA subset		MO subset	
	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 using a previously reported method[59]. 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
PRDM16	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
PRDM16	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
LRRIQ3	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
MEF2D	**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**
TSPAN2	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
ADAMTSL4	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
NGF	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
TRPM8	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
CARF	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
HJURP	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
GPR149	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
TGFBR2	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
SPINK2	**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**
KCNK5	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
HEY2	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
NOTCH4	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
FUT9	6	rs2223239	0.86	0.92	2.4E-02	0.86	0.89	1.6E-03	0.86	0.91	1.4E-04	5.3E-04	4.3E-01
GJA1	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
FHL5	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
PHACTR1	**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**

DOCK4	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
C7orf10	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**
PLCE1	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
HPSE2	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
ARMS2	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
NRP1	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**
YAP1	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**
MRVI1	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
IGSF9B	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
FGF6	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
LRP1	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
SDR9C7	12	rs7961602	0.41	0.95	5.9E-02	0.46	0.93	6.0E-03	0.44	0.94	1.2E-03	3.8E-03	4.4E-01
ITPK1	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
ZCCHC14	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
CFDP1	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
RNF213	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
WSCD1	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
JAG1	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
CCM2L	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
SLC24A3	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	Nearest Gene	Index SNP	No. Credible Set SNPs	List of Credible Set SNPs (posterior probability in brackets)
1	LRP1	rs11172113	1	rs11172113 (0.996),
2	PRDM16	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	FHL5	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	TRPM8	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	TSPAN2	rs2078371	2	rs2078371 (0.560), rs12134493 (0.440),
6	PHACTR1	rs9349379	1	rs9349379 (1.000),
7	MEF2D	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	SLC24A3	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	FGF6	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	C7orf10	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	PLCE1	rs10786156	6	rs10786156 (0.235), rs57866767 (0.206), rs3891783 (0.166), rs11187838 (0.162), rs2274224 (0.131), rs7080472 (0.099),
12	MRVI1	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	KCNK5	rs10456100	4	rs10456100 (0.476), rs733701 (0.264), rs2815116 (0.180), rs9394578 (0.073),
14	ASTN2	rs6478241	3	rs6478241 (0.700), rs1040851 (0.226), rs10817898 (0.073),
15	HPSE2	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	CFDP1	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	RNF213	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	NRP1	rs2506142	7	rs2506142 (0.213), rs2474737 (0.199), rs2474735 (0.185), rs2506144 (0.113), rs2506140 (0.104), rs2474733 (0.092), rs2506143 (0.092),
19	GPR149	rs13078967	5	rs13078967 (0.436), rs144029925 (0.276), rs34097149 (0.154), rs112346815 (0.120), rs71308496 (0.005),
20	JAG1	rs111404218	4	rs111404218 (0.899), rs6134000 (0.048), rs2057053 (0.028), rs8183037 (0.025),
21	REST	rs7684253	2	rs7684253 (0.922), rs2412771 (0.078),
22	HEY2	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	WSCD1	rs75213074	7	rs75213074 (0.611), rs117584668 (0.179), rs79482790 (0.070), rs79022350 (0.064), rs76210292 (0.041), rs78383461 (0.018), rs111501524 (0.017),
24	GJA1	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	TGFBR2	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	ITPK1	rs11624776	3	rs11624776 (0.476), rs28540738 (0.448), rs2402246 (0.076),
27	ADAMTSL4	rs6693567	7	rs6693567 (0.758), rs78976593 (0.135), rs4970996 (0.041), rs698915 (0.022), rs1260387 (0.019), rs12740679 (0.008), rs9436117 (0.008),
28	YAP1	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	DOCK4	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	LRRIQ3	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	CARF	rs138556413	2	rs138556413 (0.595), rs72926788 (0.405),
33	ZCCHC14	rs4081947	3	rs4081947 (0.504), rs8052831 (0.440), rs9929116 (0.050),
34	ARMS2	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	IGSF9B	rs561561	7	rs561561 (0.390), rs79071988 (0.192), rs493888 (0.169), rs678495 (0.104), rs12418760 (0.094), rs329661 (0.040), rs665448 (0.011),
36	MPPED2	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	NOTCH4	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	CCM2L	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[60] 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	*LRP1*	0	Intronic	658	1	*LRP1*	Intronic	-	*LRP1*	0.00007	<0.005
rs10218452	*PRDM16*	0	Intronic	191	8	*PRDM16*	Intronic	-	*PRDM16*	0.004	0.01
rs67338227	*FHL5*	0	Intronic	851	18	*FHL5*	Intronic	-	-	-	-
rs10166942	*TRPM8*	1.0	Upstream	480	11	*TRPM8*	Intronic	-	-	-	-
rs2078371	*TSPAN2*	45.1	Intergenic	712	2	-	-	-	*NGF*	0.0007	<0.005
rs9349379	*PHACTR1*	0	Intronic	474	1	*PHACTR1*	Intronic	-	-	-	-
rs1925950	*MEF2D*	0	Synonymous	196	22	*MEF2D*	Synonymous	rs1925950, rs2274317	-	-	-
rs4814864	*SLC24A3*	0	Intronic	422	21	*SLC24A3*	Intronic	-	-	-	-
rs1024905	*FGF6*	19.2	Intergenic	41	8	-	-	-	*FGF6*	0.01	0.04
rs186166891	*C7orf10*	0	Intronic	223	42	*C7orf10*	Intronic	-	-	-	-
rs10786156	*PLCE1*	0	Intronic	206	6	*PLCE1*	**Missense**	**rs2274224**	*PLCE1*	0.0001	<0.005
rs4910165	*MRVI1*	0	Intronic	152	9	*MRVI1*	**Missense**	**rs4909945**	*MRVI1*	0.002	0.01
rs10456100	*KCNK5*	0	Intronic	283	4	*KCNK5*	Intronic	-	-	-	-
rs6478241	*ASTN2*	0	Intronic	950	3	*ASTN2*	Intronic	-	-	-	-
rs12260159	*HPSE2*	0	Intronic	372	59	*HPSE2*	Intronic	-	*HPSE2*	0.001	0.006
rs77505915	*CFDP1*	0	Intronic	745	238	*CFDP1, TMEM170A*	Intronic	-	-	-	-
rs17857135	*RNF213*	0	**Missense**	113	16	*RNF213*	**Missense**	**rs17857135, rs17853714,** rs17853989, rs17853713	-	-	-
rs2506142	*NRP1*	0	3-prime UTR	29	7	*NRP1*	3-prime UTR	-	*NRP1*	0.003	0.008
rs13078967	*GPR149*	142.4	Intergenic	527	5	-	-	-	*ARHGEF26*	0.008	0.03
rs111404218	*JAG1*	29.5	Intergenic	89	4	-	-	-	*JAG1*	0.00002	<0.005
rs7684253	*SPINK2*	39.4	Intergenic	186	2	-	-	-	*REST*	0.002	0.005

rs1268083	*HEY2*	19.8	Intergenic	291	36	*HEY2, NCOA7*	Intronic	-	*HEY2*	0.002	0.006
rs75213074	*WSCD1*	62.9	Intergenic	96	7	-	-	-	-	-	-
rs28455731	*GJA1*	75.2	Intergenic	255	14	-	-	-	*GJA1*	0.002	0.008
rs6791480	*TGFBR2*	167.4	Intergenic	218	19	-	-	-	*TGFBR2*	0.005	0.02
rs11624776	*ITPK1*	12.9	Intergenic	29	3	-	-	-	-	-	-
rs6693567	*ADAMTSL4*	11.2	Intergenic	766	7	*RPRD2*	Intronic	-	*ECM1*	0.003	0.01
rs10895275	*YAP1*	0	Intronic	285	66	*YAP1*	Intronic	-	*YAP1*	0.0009	0.007
rs12845494	*MED14*	169.6	Upstream	-	-	-	-	-	-	-	-
rs10155855	*DOCK4*	37.8	Intergenic	31	15	-	-	-	-	-	-
rs1572668	*LRRIQ3*	592.0	Intergenic	1176	147	-	-	-	-	-	-
rs138556413	*CARF*	0	Intronic	669	2	*CARF*	Intronic	-	*NBEAL1*	0.0005	<0.005
rs4081947	*ZCCHC14*	54.2	Intergenic	13	3	-	-	-	*ZCCHC14*	0.02	0.05
rs2223089	*ARMS2*	0.4	Upstream	295	31	*PLEKHA1, HTRA1*	Intronic	-	*HTRA1*	0.003	0.007
rs561561	*IGSF9B*	2.8	Upstream	111	7	*IGSF9B*	Intronic	-	-	-	-
rs11031122	*MPPED2*	0	Intronic	125	17	*MPPED2*	Intronic	-	-	-	-
rs140002913	*NOTCH4*	14.2	Intergenic	65	15	-	-	-	-	-	-
rs144017103	*CCM2L*	0.9	Intergenic	36	2	*CCM2L*	Intronic	-	*CCM2L*	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	HRTLV	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 ($P < 1x10^{-4}$) 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 10**) 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
ADAMTSL4	rs6693567	chr1:150250636-150515021	rs12131376	chr1:150262094-150514149	1.68E-10	*FAM63A*
ADAMTSL4	rs6693567	chr1:150250636-150515021	rs72700829	chr1:150345558-150776123	1.55E-15	*CTSS*
ADAMTSL4	rs6693567	chr1:150250636-150515021	chr1_150512316_D	chr1:150387139-150513534	9.20E-13	*RPRD2*
ADAMTSL4	rs6693567	chr1:150250636-150515021	rs145402324	chr1:150495327-150495327	8.34E-84	*MRPS21*
MEF2D	rs1925950	chr1:156403681-156507704	rs6662838	chr1:156403701-156467309	2.26E-05	*NTRK1*
MEF2D	rs1925950	chr1:156403681-156507704	rs115307473	chr1:156470422-156470422	1.60E-06	*GPATCH4*
CARF	rs138556413	chr2:203639395-204040296	rs34349435	chr2:203505125-203864114	4.17E-07	*ABI2*
CARF	rs138556413	chr2:203639395-204040296	rs145743318	chr2:203696281-203778245	1.36E-05	*AC079354.1*
TRPM8	rs10166942	chr2:234726966-234874402	rs7596472	chr2:234722065-234737045	2.26E-06	*TRPM8*
REST	rs7684253	chr4:57727311-57761417	rs28545156	chr4:57709199-57939027	8.02E-17	*REST*
PHACTR1	rs9349379	chr6:12768218-12948388	rs6934996	chr6:12855262-12855262	5.46E-05	*EDN1*
FHL5	rs67338227	chr6:96767685-97092478	rs4240553	chr6:96854444-97067028	1.71E-27	*UFL1*
DOCK4	rs10155855	chr7:111323799-111330237	rs60607828	chr7:111269793-111387274	4.22E-05	*DOCK4*
ASTN2	rs6478241	chr9:119181794-119479868	rs809170	chr9:119266109-119469941	1.24E-06	*TRIM32*
NRP1	rs2506142	chr10:33464928-33468456	rs1015025	chr10:33423206-33485537	1.91E-05	*ITGB1*
PLCE1	rs10786156	chr10:95976903-96074157	rs35348430	chr10:96042893-96345888	5.96E-56	*NOC3L*
ARMS2	rs2223089	chr10:124126358-124232915	rs11200595	chr10:124127990-124198585	3.07E-147	*PLEKHA1*
MRVI1	**rs4910165**	**chr11:10654911-10699750**	**rs1544861**	**chr11:10660840-10699750**	**2.97E-05**	***EIF4G2***
LRP1	rs11172113	chr12:57249600-57545756	rs183314994	chr12:57272508-57272527	5.95E-05	*ERBB3*
LRP1	rs11172113	chr12:57249600-57545756	rs4559	chr12:57489648-57489648	<1.0E-147	*STAT6*
CFDP1	rs77505915	chr16:75304623-75504768	rs247451	chr16:75312136-75490409	1.05E-05	*TMEM170A*
CFDP1	rs77505915	chr16:75304623-75504768	rs4888397	chr16:75332603-75489026	3.81E-13	*CFDP1*
CCM2L	rs144017103	chr20:30610164-30628982	rs12479792	chr20:30593642-30645680	1.36E-09	*HCK*

Supplementary Table 18. Overlap of the migraine and eQTL credible sets in brain tissue.

For each migraine locus we created credible sets of SNPs and then using eQTL data from the human brain cortex of 550 individuals, we searched for significant eQTLs ($P < 1x10^{-4}$) found to genes within a 1Mb window of each migraine credible set. The table lists 29 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. 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
PRDM16	rs10218452	chr1:3065568-3112278	rs2817140	chr1:3106397-3108496	6.01E-05	*MORN1*
PRDM16	rs10218452	chr1:3065568-3112278	rs116525159	chr1:3104972-3107384	2.31E-05	*CCDC27*
TSPAN2	rs2078371	chr1:115630981-115829943	rs147406142	chr1:115697124-115788614	1.73E-05	*CD2*
ADAMTSL4	rs6693567	chr1:150250636-150515021	rs7511649	chr1:150270791-150482738	7.78E-05	*ENSA*
ADAMTSL4	rs6693567	chr1:150250636-150515021	chr1_150375425_D	chr1:150247311-150512346	1.18E-06	*Rprd2*
ADAMTSL4	rs6693567	chr1:150250636-150515021	rs74335909	chr1:150266559-150470296	3.71E-05	*MRPS21*
MEF2D	rs1925950	chr1:156403681-156507704	rs114210236	chr1:156358051-156532657	7.19E-05	*DAP3*
MEF2D	rs1925950	chr1:156403681-156507704	rs7364455	chr1:156495177-156603422	3.08E-05	*KIAA0907*
CARF	rs138556413	chr2:203639395-204040296	rs182823259	chr2:203982049-203982049	3.96E-06	*CD28*
CARF	rs138556413	chr2:203639395-204040296	rs185726277	chr2:203904306-203904306	3.51E-05	*ORC2L*
CARF	rs138556413	chr2:203639395-204040296	rs190660781	chr2:203770182-203770182	1.64E-08	*BZW1*
CARF	rs138556413	chr2:203639395-204040296	rs182405143	chr2:204013299-204013299	1.93E-09	*FASTKD2*
CARF	rs138556413	chr2:203639395-204040296	rs182405143	chr2:204013299-204013299	6.72E-08	*WDR12*
CARF	rs138556413	chr2:203639395-204040296	rs182823259	chr2:203982049-203982049	1.86E-08	*C2orf69*
KCNK5	rs10456100	chr6:39117698-39187886	rs79894111	chr6:39091790-39130651	9.63E-06	*ZFAND3*
KCNK5	rs10456100	chr6:39117698-39187886	rs149096878	chr6:39089907-39152137	1.14E-06	*PTCRA*
KCNK5	rs10456100	chr6:39117698-39187886	rs13213552	chr6:39114475-39157865	6.47E-05	*KIF6*
FHL5	rs67338227	chr6:96767685-97092478	rs60752088	chr6:96702496-97040674	6.33E-05	*POU3F2*
FHL5	rs67338227	chr6:96767685-97092478	rs73488608	chr6:96702496-97040674	1.56E-05	*SFRS18*
PLCE1	rs10786156	chr10:95976903-96074157	rs35084709	chr10:96002360-96293504	1.37E-05	*NOC3L*
HPSE2	rs12260159	chr10:100600946-100792984	rs72838828	chr10:100610752-101042293	9.80E-06	*FRAT1*
HPSE2	rs12260159	chr10:100600946-100792984	rs147998049	chr10:100785193-100785193	8.58E-05	*ARHGAP19*
HPSE2	rs12260159	chr10:100600946-100792984	rs182329697	chr10:100773286-100835791	1.28E-06	*DHDPSL*
IGSF9B	rs561561	chr11:133813808-133846186	rs78510304	chr11:133843529-133843529	3.15E-05	*B3GAT1*
LRP1	rs11172113	chr12:57249600-57545756	rs10506346	chr12:57330858-57330858	4.57E-06	*INHBC*
LRP1	rs11172113	chr12:57249600-57545756	rs34484591	chr12:57290245-57764923	1.95E-05	*RAB5B*

LRP1	rs11172113	chr12:57249600-57545756	rs3024974	chr12:57399556-57492745	9.05E-06	*STAT6*
LRP1	rs11172113	chr12:57249600-57545756	rs7134373	chr12:57306224-57493727	9.77E-05	*ZBTB39*
LRP1	rs11172113	chr12:57249600-57545756	rs58801386	chr12:57272865-57394635	1.74E-05	*GDF11*

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 ($P < 2x10^{-13}$) *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 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 ($P < 7.1x10^{-3}$) the correlation was significant from eQTLs to four tissues (Lung, Thyroid, Tibial Artery, and Aorta) at two migraine loci (*HPSE2* and *HEY2*). Companion plots of the four significantly correlated credible sets are presented in **Supplementary Figure 15**.

Locus	Chr	Locus Index SNP	Migraine *P*-value	eQTL Index SNP	eQTL P-value	eQTL Gene	GTEx Tissue	Spearman's rho	Correlation *P*-value
HPSE2	10	rs12260159	3.20E-10	rs12260159	7.065E-14	HPSE2	Lung	0.89	7.2E-14
HEY2	6	rs1268083	5.25E-09	rs3799711	5.632E-18	HEY2	Thyroid	0.86	1.7E-07
HPSE2	10	rs12260159	3.20E-10	rs10883234	2.438E-18	HPSE2	Artery; Tibial	0.59	2.0E-04
HPSE2	10	rs12260159	3.20E-10	rs10883234	2.899E-28	HPSE2	Artery; Aorta	0.58	2.8E-03
ADAMTSL4	1	rs6693567	1.21E-08	rs6693567	4.653E-33	ADAMTSL4	Esophagus Mucosa	0.8	0.33
HEY2	6	rs1268083	5.25E-09	rs9401845	2.176E-19	HEY2	Testis	-0.38	0.09
HPSE2	10	rs12260159	3.20E-10	rs7091740	1.007E-14	HPSE2	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 asscociated 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), TGFBR2 (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), TGFBR2 (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), TGFBR2 (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), PAPPA (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	PAPPA (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	PAPPA (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	PAPPA (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	PAPPA (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	PAPPA (2.96), C7orf10 (2.71), NGF (2.35), TGFBR2 (1.59), ECM1 (1.59)
A11.620.520	Myocytes Smooth	Cells	Muscle Cells	0.11	0.35	PAPPA (2.96), C7orf10 (2.71), NGF (2.35), TGFBR2

	Muscle					(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), TGFBR2 (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), TGFBR2 (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), TGFBR2 (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), TGFBR2 (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 System	Skeleton	0.26	0.71	PAPPA (1.39), TRIM32 (1.23), GJA1 (1.15), NGF (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)

A08.186.211.730.885.287.500.571.735	Visual Cortex	Nervous System	Central Nervous System	0.65	1.23	C1orf61 (2.34), PLEKHA1 (1.75), IGSF9B (1.39), 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	Connective Tissue Cells	0.72	1.14	NRP1 (1.11), PAPPA (0.91), NGF (0.9), TBC1D12

	Cells					(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), CFDP1 (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 Macrophage Precursor Cells	Cells	Myeloid Cells	0.80	1.09	PRPF3 (1.06), KCNK5 (0.97), WDR12 (0.93), TARS2 (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 that were used for the enhancer enrichment analysis. A description is given for each tissue/cell line, along with the anatomical group and how it was derived. ESC is embryonic stem cells, IPSC is induced pluripotent stem cells, and GI is gastrointestinal. Epigenetic data (H3K27ac histone marks) identifying the genomic locations of active enhancers in each tissue/cell type was obtained from http://www.roadmapepigenomics.org. We then mapped credible sets from the migraine loci to sets of enhancers in each tissue and assessed enrichment empirically using a by randomly generating a background set of matched loci 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.

The set of 38 genes that are nearest to the index SNP in each migraine locus was chosen and tested for over-representation in Gene Ontology (GO) annotations. The PANTHER[61] analysis tool (also available at http://geneontology.org/page/go-enrichment-analysis) was used to perform the analysis which implements a binomial test to determine if the number of genes from the migraine test set found in each GO Pathway is likely to have occurred by chance alone. In the table, the 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 test by Bonferroni correction.

Go Pathway	GO Term	Background frequency	Migraine set frequency	Expected frequency	P-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. 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. A list of the significant results from the DEPICT analysis are provided in **Supplementary Table 24**.

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

Supplementary Table 24. 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). Note that an association identified to one particular gene set (ENSG00000056345 PPI, $P = 1.7\times10^{-4}$, *FDR* = 0.04) has been removed from the table as it is no longer part of the Ensembl database.

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 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 ($P < 1.3\times10^{-3}$). 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
PRDM16	1.81 (0.09)	1.40 (0.06)	1	6.35 (0.28)	**1.4E-39**	1.69 (0.26)	0.67
LRRIQ3	0.14 (0.02)	0.07 (0.004)	1	0.03 (0.002)	1	0.05 (0.004)	1
TSPAN2	3.29 (0.19)	0.85 (0.05)	1	11.29 (0.66)	1.8E-26	7.29 (0.93)	3.0E-05
ADAMTSL4	22.04 (0.56)	1.67 (0.18)	1	20.32 (0.70)	0.97	24.31 (2.25)	0.17
MEF2D	22.84 (0.44)	16.6 (0.56)	1	38.33 (1.32)	**7.6E-25**	16.63 (1.11)	1
TRPM8	0.08 (0.03)	0.05 (0.01)	0.82	0.001 (4e-4)	0.99	0.45 (0.20)	0.033
TGFBR2	63.21 (1.62)	7.55 (0.30)	1	65.35 (2.01)	0.20	38.45 (2.82)	1
GPR149	0.01 (0.001)	0.61 (0.06)	**4.4E-20**	0.001 (2e-4)	1	0.004 (0.001)	1
REST	4.08 (0.06)	1.33 (0.04)	1	3.58 (0.07)	1	3.85 (0.12)	0.95
PHACTR1	1.25 (0.08)	5.02 (0.27)	1.2E-33	3.43 (0.16)	9.4E-31	0.57 (0.10)	1
NOTCH4	10.14 (0.38)	3.16 (0.12)	1	6.49 (0.32)	1	4.42 (0.45)	1
KCNK5	6.48 (0.36)	0.09 (0.01)	1	0.65 (0.07)	1	7.71 (0.63)	0.05
FHL5	8.51 (0.38)	2.00 (0.13)	1	80.26 (6.14)	**9.5E-26**	2.63 (0.33)	1
GJA1	53.73 (2.42)	100.77 (4.78)	1.2E-17	49.78 (2.58)	0.87	46.94 (7.28)	0.81
HEY2	2.82 (0.10)	3.47 (0.10)	2.0E-06	28.07 (1.49)	7.2E-44	1.32 (0.07)	1
C7orf10	0.60 (0.04)	0.35 (0.01)	1	1.89 (0.11)	**1.3E-23**	0.91 (0.10)	2.4E-03
DOCK4	3.46 (0.13)	9.32 (0.29)	**1.7E-56**	1.76 (0.05)	1	1.59 (0.09)	1
ASTN2	0.77 (0.04)	4.02 (0.10)	8.0E-107	1.38 (0.11)	2.1E-07	0.80 (0.08)	0.38
NRP1	13.56 (0.45)	2.51 (0.11)	1	13.17 (0.38)	0.75	5.39 (0.35)	1
PLCE1	3.20 (0.11)	1.86 (0.06)	1	7.64 (0.37)	1.1E-25	4.76 (0.44)	3.9E-04

HPSE2	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
ARMS2	0.10 (0.01)	0.10 (0.01)	0.62	0.10 (0.01)	0.41	0.08 (0.01)	0.93
MRVI1-AS1	1.52 (0.26)	0.91 (0.03)	0.99	1.88 (0.10)	0.10	0.89 (0.10)	0.99
MPPED2	1.12 (0.08)	2.36 (0.09)	**5.0E-24**	0.66 (0.04)	1	0.42 (0.06)	1
YAP1	24.28 (0.51)	6.44 (0.22)	1	44.53 (1.90)	**1.3E-21**	24.8 (1.55)	0.38
IGSF9B	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
FGF6	0.21 (0.03)	0.005 (7e-4)	1	0.009 (0.005)	1	0.002 (9e-4)	1
LRP1	40.44 (1.24)	25.86 (0.74)	1	51.45 (2.07)	**3.3E-06**	26.20 (1.84)	1
ITPK1	17.90 (0.40)	45.23 (0.92)	2.7E-98	21.13 (0.56)	1.4E-06	16.44 (1.31)	0.86
CFDP1	11.23 (0.19)	16.98 (0.26)	**3.5E-59**	10.03 (0.22)	1	11.25 (0.41)	0.48
ZCCHC14	8.06 (0.17)	8.81 (0.30)	0.016	9.37 (0.29)	**6.4E-05**	6.96 (0.17)	1
WSCD1	0.74 (0.03)	5.67 (0.19)	3.7E-84	1.57 (0.10)	8.2E-14	0.82 (0.12)	0.28
RNF213	12.29 (0.23)	4.16 (0.14)	1	6.23 (0.18)	1	8.94 (0.37)	1
JAG1	17.64 (0.50)	4.17 (0.13)	1	40.29 (2.06)	**5.4E-23**	15.85 (1.40)	0.88
SLC24A3	4.29 (0.15)	9.21 (0.55)	5.1E-17	8.74 (0.55)	4.9E-14	4.43 (0.46)	0.38
MED14	6.40 (0.10)	3.91 (0.09)	1	5.07 (0.13)	1	4.51 (0.15)	1