Supplementary data

Populations: subjects and phenotypes

AGES-RS

The Reykjavik Study is a population-based cohort study established in 1967 to prospectively study cardiovascular disease in Iceland. The cohort included a random sample of men and women born between 1907 and 1935 and living in Reykjavik at baseline. In 2002, the Reykjavik Study continued as the AGES-Reykjavik Study to examine risk factors, genetic susceptibility, and gene-environment interactions in relation to disease and disability in old age. Headache data were collected as part of the Reykjavik study. The Reykjavik Study and AGES-Reykjavik Study have been described in detail elsewhere.[1-4] The AGES-Reykjavik study included 357 migraine cases (71 male, 286 female). The control group included 1281 males and 1581 female, a total of 2862 controls. The mean age was 51.03 years (SD = 6.37). All subjects were unrelated.

ERF

The ERF study is a family-based study in a genetically isolated population in the southwest of the Netherlands. This young genetic isolate was founded in the mid 18th century and minimal immigration and/or marriages occurred between surrounding settlements due to social and religious reasons. The ERF population includes 3,465 individuals that are living descendants of 22 couples with at least six children baptized in the community church around 1850–1900. The subjects were unselected with respect to phenotypes. Details about the extensive genealogy and pedigree of the population are described elsewhere.[5]

The present study includes data from 1546 ERF participants; 330 migraineurs and 1216 controls. Of the cases, 81 (25%) were male and 249 (75%) were female; of the controls, 615 (51%) were male and 601 (49%) were female. The mean age was 48.4 years (SD = 14.6).

NESDA

The NESDA sample[6] consisted of 1530 unrelated individuals from the Netherlands (mostly patients with major depressive disorder [MDD]) who were genotyped in the context of the NIH GAIN project, for a GWAS study originally designed to find genes for major depressive disorder (MDD).[7] In the NESDA sample, 1383 subjects had MDD, and 147 were selected for low risk of MDD. In this sample, there were 756 individuals with migraine (713 with MDD

and 43 without MDD) and 774 controls (670 with MDD and 104 without MDD). In the case group, 165 individuals (22%) were male and 591 (78%) were female. In the control group, 322 (42%) were male and 452 (58%) were female. The mean age was 42.9 years (SD = 12.5).

NTR1

The Netherlands Twin Registry collects data in Dutch twins, their parents, siblings and partners. The migraine data were collected in the context of a longitudinal study on health, lifestyle and personality. As the NESDA sample, the first NTR cohort was genotyped as part of the GAIN MDD study.[7] The majority of subjects (N = 1481) were selected for low risk of MDD, 112 subjects were MDD patients. Migraine data were available for 1593 individuals: 378 cases [56 with MDD and 322 without MDD], and 1215 controls [56 with MDD and 1159 without MDD]. In the case group, 69 individuals (18%) were male and 309 (82%) were female. In the control group, 509 (42%) were male and 706 (58%) were female. The mean age was 44.8 years (SD = 15.0). All subjects were unrelated.

NTR2

The second cohort from the Netherlands Twin Registry was an unselected sample. All subjects were unrelated. For 1094 individuals, migraine data were available. There were 276 migraine cases, including 59 (21%) males and 217 (79%) females. The control group consisted of 818 individuals, including 396 (48%) males and 422 (52%) females. The mean age in this cohort was 48.6 years (SD = 14.4).

Rotterdam Study

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.[8] 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. 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 1,998 unrelated individuals, including 349 cases (79 male, 270 female) and 1,649 controls (805 male, 844 female). The mean age of the sample was 55.37 years (SD=4.51).

GEM

The Genetic Epidemiology of Migraine (GEM) cohort is well characterized population-based migraine cohort from the Netherlands.[9] The GEM cohort is embedded in the MORGEN project, a population-based study designed to monitor risk factors for and the prevalence of chronic diseases of public health importance in Dutch adults from 20 to 60 years old. DNA and phenotype data were available for 769 unrelated migraine cases and 940 unrelated non-migraine controls.

Australian Twin Migraine GWA Study

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 = 1851; 389 [21%] male, 1462 [79% female]) were preferentially selected from each family based on migraine severity. The non-migraine controls (N = 1631; 772 [47%] male, 859 [53%] female) were selected from families containing no migraine cases. The unselected controls (N = 2377; 1128 [47%] male, 1249 [53%] female) came from families containing no individuals with migraine information. 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.

NTR replication sample

The third sample from Netherlands Twin Registry consisted of unrelated individuals, unselected with respect to migraine. Migraine data were available for 1163 individuals. There were 337 migraine cases, including 72(21%) males and 265 (79%) females. The control group consisted of 826 individuals, including 347 (42%) males and 479 (58%) females. The mean age in this cohort was 40.5 years (SD = 14.3).

Phenotypes

AGES-RS

Subjects reporting headache at least once a month were asked whether the headaches were accompanied by any of the following migraine features: nausea/vomiting, unilateral location, photophobia, visual disturbance during or preceding headache, and unilateral numbness preceding headache. Individuals were defined as having migraine with aura if they had visual or sensory aura, or both. Subjects with at least 2 of the non-aura symptoms were classified as having migraine without aura. In this study, both migraine with and without aura were included as cases. The remaining individuals were included as controls.[10]

ERF

Migraine was diagnosed according to ICHD-II criteria.[11] Migraineurs were identified using a three-stage screening procedure which has been validated in a population based study [9]. The screening procedure is described in detail by Stam and colleagues.[12] In brief, all participants filled out a concise screening questionnaire on headache and aura symptoms, and those who screened positive also completed a detailed extended questionnaire. The screening questions select primarily on moderate to severe headache. Therefore, patients with aura symptoms without headache will not pass the screening questions positively. Based on the characteristics of this questionnaire, we assumed this screening instrument to have a very high positive predictive value in the ERF population. The extended questionnaire was based on the ICHD-II[11] and included multiple items on primary migraine headache and aura characteristics, premonitory symptoms, trigger factors, and medication use. The questions were to be answered by choosing from categorical alternatives.

All participants who screened positive were telephone-interviewed to clarify their clinical symptoms by trained physicians who are experienced in diagnosing migraine patients. Final diagnosis was always made after this telephone interview and in consultation with a neurologist specialized in headache (GMT). The control group consisted of ERF participants negative for migraine based on the written three-stage screening procedure.

NESDA and NTR (all cohorts)

Migraine was assessed with a questionnaire that provided information on the symptoms listed in the ICHD-II criteria. For the NTR participants, the headache questions were embedded in

surveys that were held in the context of a longitudinal study on health, lifestyle and personality. The data used in this study were collected in two waves that took place in 2002 and 2004. Both surveys included the same set of headache items. Data collection procedures are described in detail elsewhere.[13,14] When a participant answered the headache section in both surveys, the most recent (2004) survey was used.

The NESDA participants underwent a 4-hour baseline assessment at one of seven clinic sites at the beginning of the study. This assessment included an interview on somatic health, functioning and health care use, and the administration of several written questionnaires. Headache data were collected using the same questionnaire that was included in the NTR survey. Further details on the NESDA data collection procedures can be found elsewhere.[9]

The NTR/NESDA migraine questionnaire was preceded by a screening question ("do you ever experience headache attacks, for instance migraine?"). Individuals screening positive subsequently answered a set of more detailed questions about their headaches. This information was used to determine the presence of eight of the symptoms present in the ICHD-II criteria: moderate/severe pain intensity, aggravation by physical activity, pulsating quality, nausea or vomiting, and photo- or phonophobia. The IHS migraine symptom variables were analysed with Latent Class Analysis to determine each participant's affection status for migrainous headache. This method has been described extensively in previous work.[15] The LCA was performed based on headache data from all available NESDA and NTR participants, using the program Latent Gold 4.0 (Statistical Innovations, Inc., Belmont, MA). As in previous studies, four classes of headache sufferers were identified. Participants in the two severest classes (who were positive, on average, for at least half of the symptoms), were classified as affected. The remaining individuals (mild non-migrainous headache and individuals without headaches) were classified as unaffected.

Rotterdam Study

The migraine questionnaire used in the Rotterdam Study was based on the ICHD-II criteria and was a modified questionnaire according to the GEM study of Leiden.[16] The first question was "Have you ever experienced a severe headache that affected your daily activities?" If the answer was negative or if it was clearly indicated that the participants experienced a severe headache due to other causes, such as a tumor, sinusitis, stroke, trauma or meningitis, no further questions on headaches were asked. If the answer to the first question was positive,

headache duration and headache frequency were asked. Next, if a person experienced headaches of which 1) the duration was between four and seventy-two hours (untreated) or the participant did not know the answer to this question, because they always treated their headache attack and 2) the attack frequency was two or more attacks in a lifetime, details on the characteristics and symptoms of the headaches were asked. These included age of onset, unilateral location, pulsating quality, aggravation by daily activities, sensitivity to light and sound, nausea or vomiting. The frequency of the symptoms accompanying the headaches was assessed and defined as never, sometimes, half of the time and more than half of the time. In this group of participants, questions on medication use were assessed. Furthermore, every participant was asked about aura symptoms and physician diagnosis, if they ever had a severe headache. If the participant experienced an aura or the physician had diagnosed migraine, questions on medication use were assessed. Participants whose duration of headache was unknown, because they always used medication to prevent or treat the attack, were considered migraineurs if they fulfilled the remaining IHS criteria. Individuals who were not classified as migraineurs were included as controls.

GEM

Participants for the Genetic Epidemiology of Migraine (GEM) study were identified through the population-based Monitoring Risk Factors for Health in the Netherlands (MORGEN) study[9] - a population-based study designed to monitor risk factors for and the prevalence of chronic diseases of public health importance in Dutch adults 20–65 years of age. The study was approved by the local ethics committee. Respondents signed a general informed consent for the MORGEN project, and a specific informed consent for the GEM Study. For case-finding, MORGEN participants were mailed an extensive self-administered questionnaire that included questions about sociodemographic characteristics, medical history, psychosocial functioning and five migraine screening questions (adapted from Stewart et al.[17]). Screen-positive was defined as those who ever had or had in the last 12 months, a severe headache (excluding those due to hangover or sinus infection) and the pain was 5 or higher on a 10-point pain scale or the participant was diagnosed with migraine by a doctor or used antimigraine medication (including sumatripten and ergotamine compounds). A respondent was also classified as screen-positive if there was a history of severe headache in the last 12 months and the pain was rated between 1 and 4 and one of 10 visual aura symptoms was experienced. Trained field workers at the study center reviewed the screening questions and

identified screen-positive participants. Additional questions regarding medical history were asked in a personal interview, a simple clinical examination was performed, and a blood sample drawn.

Participants that were positive on the screening questionnaire completed a more detailed questionnaire that focused on signs and symptoms of migraine headache and aura as outlined in the IHS criteria.[11] Very special care was given to diagnose aura and those reporting visual aura symptoms were also asked to draw what they saw. The extended questionnaire was based on the IHS criteria[11] and included multiple items on primary migraine headache and aura characteristics, premonitory symptoms, trigger factors, and medication use. The questions were to be answered by choosing from categorical alternatives. A semi-structured telephone interview to validate the questionnaires was obtained in a random sample of screen positive (83%) and screen negative (5%) participants to clarify their clinical symptoms. This interview was done by trained physicians or medical students who are experienced in diagnosing migraine patients. Final diagnosis was always made after this telephone interview and in consultation with a neurologist specialized in headache.

The control sample was drawn from the participants that were screen-negative on the five migraine screening questions and matched the cases for age and gender.

Australian Twin Migraine GWA Study

In the Australian sample, migraine data were collected by means of a semi-structured telephone interview. The questionnaire was based on the symptoms from the ICHD-II diagnostic criteria.[11] Participants were classified as affected or unaffected with latent class analysis, as described for the NTR and NESDA participants. In addition, a diagnosis was made based on the full IHS criteria. The sample was divided into two risk strata: IHS migraine vs. non-migraine controls (narrowly defined) and LCA-migraine vs. unselected controls (broadly defined). This was done to allow for expected differences in migraine risk between these groups. More details on the phenotyping procedures can be found elsewhere.[18,19]

Genotyping and imputation

AGES-RS

Genotyping was performed using the Illumina 370CNV platform. Genotypes for ~ 2.5 million SNPs were imputed using the MACH 1.0.16 program, using HapMap CEU as the reference

set (NCBI build 36, HapMap phase II, release 22). SNPs were excluded in case of a minor allele frequency (MAF) smaller than 1%, call rate < 97%, low imputation quality ($R^2 < 0.3$) or HWE p-value < 1 x 10^{-6}, leaving 2,408,991 SNPs for analysis.

ERF

Genotyping was performed on several different platforms (Illumina HumanHap300, HumanHap370, Affymetrix 250K Nsp array). These sets were merged and genotypes for ~2.5 million SNPs were imputed to (HapMap CEU, phase II, release 22, NCBI build 36) using the MACH program. Data were filtered for rare variants and imputation quality (SNPs with call rate > 95%, MAF≥0.05 and R^2≥0.3 were included), leaving 2,135,034 SNPs for analysis.

NTR1 and NESDA

Individual genotyping for the GAIN sample was conducted by Perlegen Sciences (Mountain View, CA, USA) using a set of four proprietary, high-density oligonucleotide arrays. The SNPs on these arrays were selected to tag common variation in the HapMap European and Asian panels. Of the 3,820 Dutch samples sent to Perlegen, genotypes were delivered for 3,761 samples. After quality control, there were 3,540 subjects in the final analysis dataset (1,738 MDD cases and 1,802 controls).

The unfiltered dataset obtained from dbGaP contained 599,156 unique SNPs. To be included in the final analysis dataset, SNPs were required not to have any of the following features: gross mapping problem, >=2 genotype disagreements in 40 duplicated samples, >=2 Mendelian inheritance errors in 38 complete trio samples, minor allele frequency <0.01, or >0.05 missing genotypes in either cases or controls. A total of 427,049 autosomal SNPs met these criteria and were included in the analyses. Genotypes for ~2.5 million SNPs were imputed using the IMPUTE software, using the HapMap CEU data (phase II, release 22, NCBI build 36), available from the IMPUTE website (https://mathgen.stats.ox.ac.uk/impute/impute.html), as reference. For each SNP an R^2 value was calculated using the QUICKTEST program (http://toby.freeshell.org/software/quicktest.shtml). SNPs were excluded in case of a MAF < 1%, per SNP call rate < 95% or low imputation quality ($R^2 < 0.3$), leaving 2,432,125 SNPs for analysis in the NESDA sample and 2,431,993 in the NTR sample.

NTR2

Genotyping for 657,366 SNPs was performed on the Human660W-Quad BeadChip. SNPs were excluded based on MAF < 0.01, missing genotype rate > 0.05 or a p-value < 1 x 10^{-5} in a test of Hardy-Weinberg equilibrium. After quality control, 515,781 SNPs were left. Genotypes of ~3.8 million SNPS were imputed with the IMPUTE program,[17] using the HapMap CEU data (phase II, release 24, NCBI build 36), available from the IMPUTE website, as reference. Imputed SNPs were excluded if they had a MAF < 0.01, per SNP call rate < 95% or a low imputation quality (R^2 < 0.3), leaving 2,542,087 SNPs for analysis.

Rotterdam Study

Genotyping was performed using the Illumina Infinium II HumanHap550 chip, version 3.0. A total of 572,129 SNPs were genotyped. SNPs were excluded based on the following criteria: HWE p-value < 10-6, call rate < 98% and a minor allele frequency < 0.01. The number of SNPs that survived quality control was 514,139. Genotypes were imputed for 2,543,888 SNPs, using the Hapmap CEU (build 36, phase II, rel. 22) as reference. Imputations were performed in MACH.[20] SNPs were excluded if they had a minor allele frequency < 0.01, per SNP call rate < 98%, HWE p-value < 1 x 10^{-6} or low imputation quality (R^2 < 0.3), leaving a total of 2,450,030 SNPs for analysis.

GEM & NTR replication samples

The top SNP was genotyped in two samples (GEM and NTR replication sample) using TaqMan technology. Probes and primers were designed by Applied Biosystems. A standard PCR reaction was carried out using the TaqMan Universal PCR Master Mix reagent. Genotyping clusters were analysed using the LightScanner480 machine and LightCycler®480 SW 1.5 software (Roche Applied Science). SNPs deviating from Hardy-Weinberg equilibrium (p < 0.01) were excluded from further analysis.

GEM

An additional selection of top SNPs was genotyped by matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry (MS), using the Sequenom MassARRAYtm methodology (Sequenom Inc, San Diego, CA, USA). Amplification reactions and parameters were based on the manufacturer's instructions. Each

384-wells plate contained at least 4 positive (CEPH DNA) and 6 negative controls, to check for assay performance and contaminations, respectively. Spectrocaller software supplied by the manufacturer was used to automatically call the genotypes. Clusters were checked manually and all doubtful calls were evaluated. SNPs deviating from Hardy-Weinberg equilibrium ($p < 0.01$) were excluded from the analyses.

Australian Twin Migraine GWA Study

The ATM GWA cohort was drawn from 9 different projects utilising a variety of Illumina GWA arrays. After stringent quality control (QC) a consensus set of 280,168 SNPs were available for all individuals; which were then utilised to impute up to the August 2009 release of phased data from the 1000 Genomes Project [112 haplotypes from 56 Caucasians, downloaded from http://www.sph. umich.edu/csg/yli/mach/download/1000G-Sanger-0908.html] using the MACH program.[20] A total of 7,365,026 SNPs satisfied the recommended imputation QC threshold of $R^2 \geq 0.3$. SNPs with MAF ≥ 0.05 (N = 6,085,112) were included in the GWA analyses.

Statistical analyses in the individual samples

AGES-RS, Rotterdam

A logistic regression test was performed with sex, age and age2 included as covariates. The analyses were performed in ProbABEL.[21] Uncertainty of imputation was taken into account in the analyses. The genomic inflation factor was 1.002 in AGES-RS and 1.021 in the Rotterdam Study.

ERF

The study-specific genomic inflation factor (λ) in the ERF study was 1.166, reflecting relatedness between study participants. This was corrected for by applying genomic control. Genome-wide association analyses were carried out in ProbABEL,[21] using a logistic regression test with sex and age included as covariates, assuming an additive model, and accounting for uncertainty of imputation.

NESDA, NTR1, NTR2

Genome-wide association testing was performed using SNPTEST.[16] A logistic regression test was used, sex, age, and age^2 were included as covariates and an additive model was assumed.

As in the other samples, uncertainty of imputation was taken into account in the analyses. The genomic inflation factors were 1.006, 1.013 and 1.000 in NESDA, NTR1 and NTR2, respectively.

Replication cohorts

In the GEM and NTR replication samples, association tests were performed using Plink.[22] For each SNP, a logistic regression test was performed, under an additive model, with sex, age and age^2 as covariates. For the ATM GWA sample, association testing was performed with the mach2dat program (http://www.sph.umich.edu/csg/yli/mach/download/), accounting for genotype uncertainty, and adjusting for sex and the risk strata described above.

Power of the replicaton study

The power to replicate the effect of SNP rs9908234 in the GEM sample was calculated using the genetic power calculator (http://pngu.mgh.harvard.edu/~purcell/gpc/). Assuming a migraine prevalence of 12%, an OR of 1.35 and a risk allele frequency of .07 (the average allele frequency in the original samples) the power to detect the effect at an alpha level of .05 was 66%, based on 768 cases and 943 controls. The number of cases required for 80% power was 1072. In the NTR replication sample, based on the same parameters and 337 cases and 826 controls, the power was 44% at an alpha level of .05. For a power of 80%, 798 cases would have been needed. However, this is most likely a conservative estimate, given the more liberal phenotype definition, and therefore higher disease prevalence in the NTR samples. Taken together (1105 cases, 1769 controls) the samples were estimated to have a power of 86%.

Text mining

Relationships between genes (emerging from the meta-analysis) and migraine were studied using the Anni text-mining program (Anni version 2.1).[33] The program generated a concept profile for each gene and for migraine. A concept profile is a summary of all concepts directly co-mentioned with the disease or gene concept (i.e. the main concept) in PubMed abstracts. The strength of association for each concept with the main concept is calculated using 2x2 contingency tables and an uncertainty coefficient. The association between two concept profiles is calculated using vector based matching (e.g. inner product score) over the concepts that the two profiles have in common.

Comparison of results with migraine genes and loci from previous studies

Genome-wide linkage studies for migraine were identified with a literature search in PubMed. Since not all studies clearly specified the confidence intervals of their linkage peaks, the region within 15 Mb of the best linkage marker was inspected. Next, we examined which SNPs with a p-value < 1×10^{-4} coincided with a region containing a published linkage peak. If multiple SNPs had small p-values due to high LD, the SNP with the smallest p-value was retained.

In addition, a selection of candidate genes was made, based on the results of previous association studies (including candidate gene and GWA studies). Genes from candidate gene studies were selected if there was evidence for association with migraine based on one or more studies that included at least 275 migraine cases. Genes were selected only if a study-wide significant result had been obtained in this gene at least once (for MO, MA or MO/MA combined), or if nominal significance was reported in multiple independent studies. We also selected the FHM genes (i.e. *CACNA1A*, *ATP1A2*, and *SCN1A*) and the genes which surfaced as candidates in the first clinic-based GWA study of migraine (*MTHD*, *PGCP* and *SLC1A2*).[17] A gene-based p-value was calculated for each of the selected genes, based on the meta-analysis results of all SNPs tested within the gene. This was done using the VEGAS program (version 0.6.28).[34] This gene-based p-value was used to determine whether the results in a gene were significant after correcting for the number of SNPs tested in a gene, taking the LD structure into account. A Bonferroni correction was applied to the gene-based p-values to account for the fact that thirteen genes were tested.

Finally, we specifically inspected three individual SNPs near the *MTHD* gene that showed a strong association with migraine in the clinic-based migraine GWAS described by Anttila and colleagues.[17]

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