Supplemental Methods:

Genotyping:

For each study in the IHGC migraine analysis, investigators independently performed genome-wide single nucleotide polymorphism (SNP) genotyping using standard technologies and imputed to HapMap release 21 or 22 CEU phased genotype reference panels.[1] Investigators then contributed summary statistic data from association analyses performed using a frequentist additive model based on an expected allelic dosage model for SNP markers, adjusting for sex, age and relatedness where appropriate. SNPs were filtered on per-study levels based on inclusion criteria of minor allele frequencies (MAF)>0.1% and imputation quality measures of IA > 0.6 (IMPUTE 2[2]) or $r^2 > 0.3$ (MaCH[3]). Combined association data for about 2.5 million imputed and genotyped autosomal SNPs were meta-analyzed in a fixed-effects model using GWAMA software.[4] At this stage, SNPs with a heterogeneity coefficient I^2 exceeding 75% or presence in less than five studies were filtered out. In the meta-analysis, there was little evidence of population stratification at the study level (each genomic inflation factor $\lambda \leq 1.1$), though moderate inflation was observed at the meta-analysis level ($\lambda = 1.13$).

In METASTROKE, each cohort was independently genotyped using an Affymetrix or Illumina platform and then performed imputation to the HapMap release 21/22 or the 1000 Genomes reference panels. Association analysis for each study was performed using a log-additive model frequentist test, accounting for the uncertainty of imputed genotypes. Several studies used principal component analysis (PCA) values as covariates in their analyses.[5] Central quality control used

previously agreed upon criteria including check of consistency of the given alleles across all studies, quality of the imputation, deviation from Hardy-Weinberg equilibrium in the controls, minor allele frequency, and call rate. Individual METASTROKE results of association analyses from every center were analyzed using a fixed-effects inverse-variance weighted model with METAL.[6]

References

1. International HapMap Consortium, Frazer KA, Ballinger DG, et al. A second generation human haplotype map of over 3.1 million SNPs. Nature 2007;449:851-861.
2. Howie BN, Donnelly P, Marchini J. A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. PLoS genetics 2009;5:e1000529.
3. Li Y, Willer CJ, Ding J, Scheet P, Abecasis GR. MaCH: using sequence and genotype data to estimate haplotypes and unobserved genotypes. Genetic epidemiology 2010;34:816-834.
4. Magi R, Morris AP. GWAMA: software for genome-wide association meta-analysis. BMC bioinformatics 2010;11:288.
5. Traylor M, Farrall M, Holliday EG, et al. Genetic risk factors for ischaemic stroke and its subtypes (the METASTROKE collaboration): a meta-analysis of genome-wide association studies. Lancet neurology 2012;11:951-962.
6. Willer CJ, Li Y, Abecasis GR. METAL: fast and efficient meta-analysis of genomewide association scans. Bioinformatics 2010;26:2190-2191.