Supplementary information

Genome-wide meta-analysis identifies new susceptibility loci for migraine

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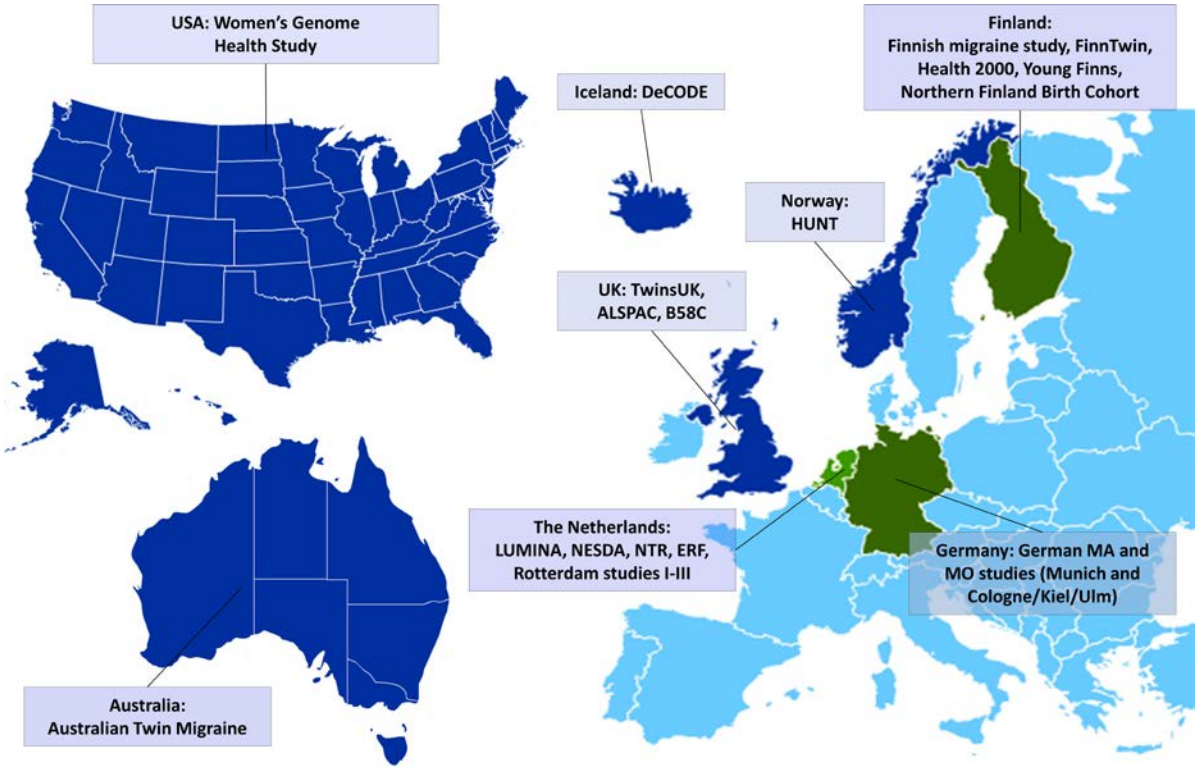
Contents

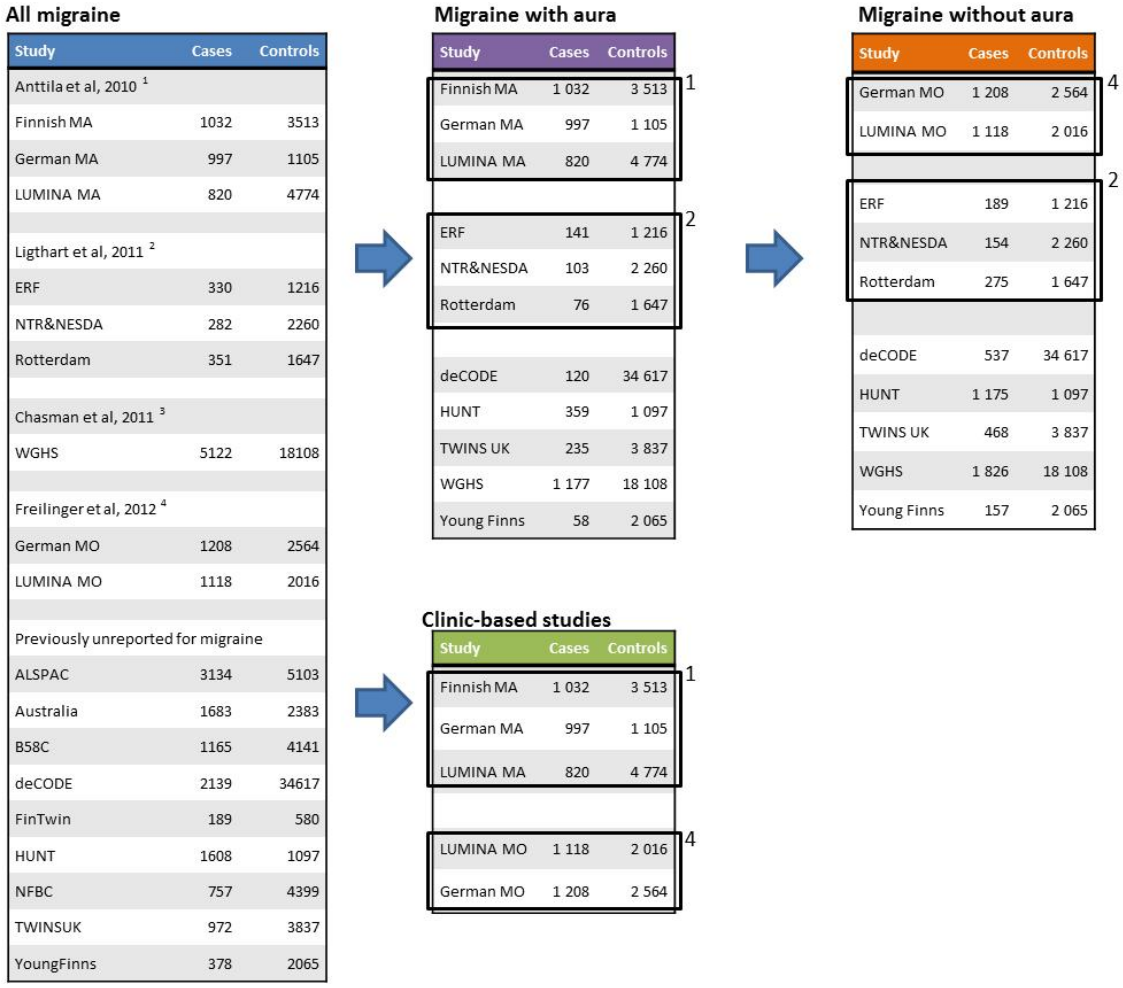
Supplementary Figures

Supplementary Figure 1. Participating studies



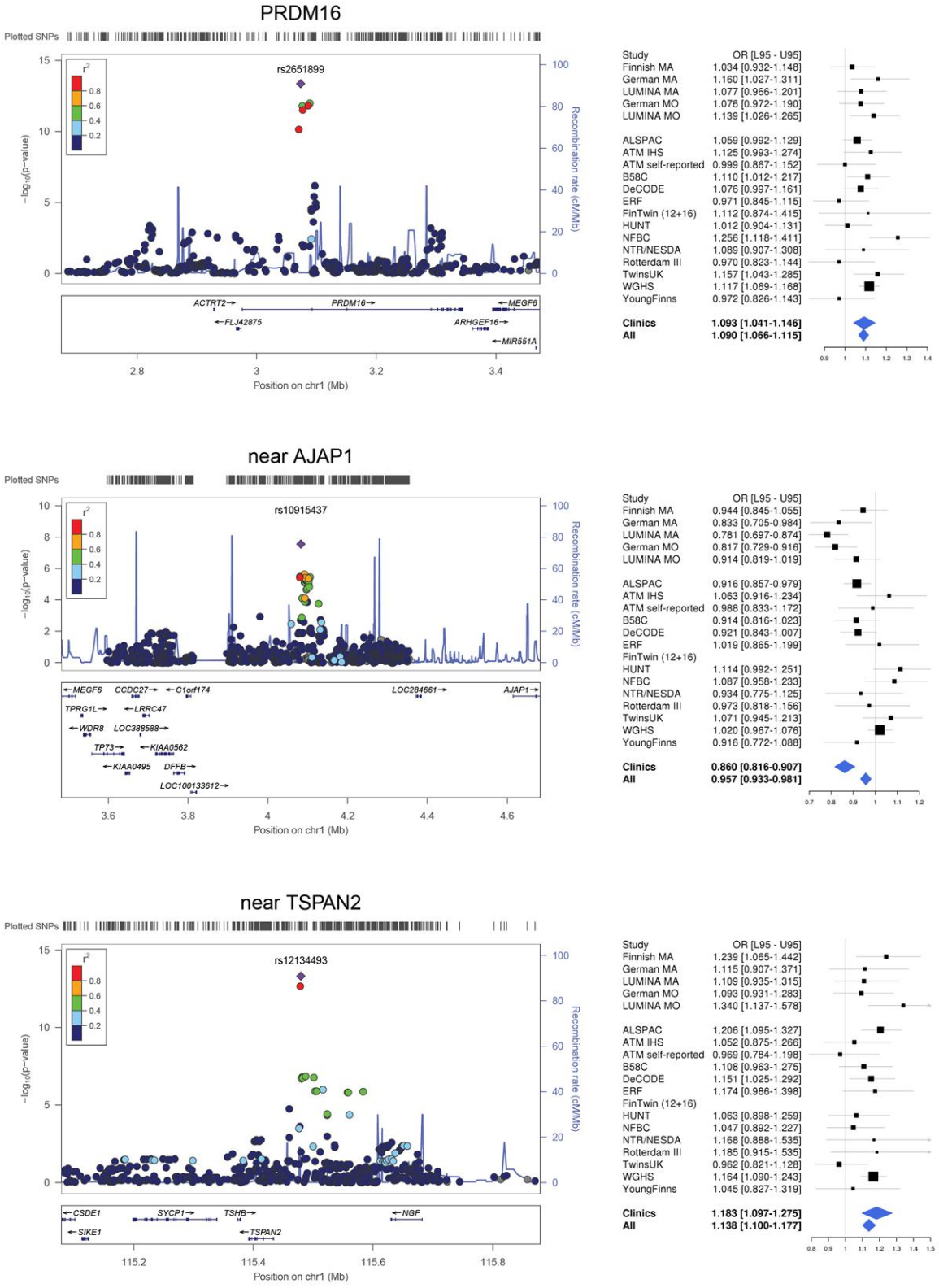
Please see section 'Participating Cohorts' for further information.

Supplementary Figure 2. Previously published study sets within the meta-analysis



The boxes highlight the phenotypic subgroups used in the analysis and their sizes, with black outlines within them denoting which studies have been analysed together in previous publications. The numbers next to the black outlines show the original publications[1-4].

Supplementary Figure 3. Association plots of the identified significant loci



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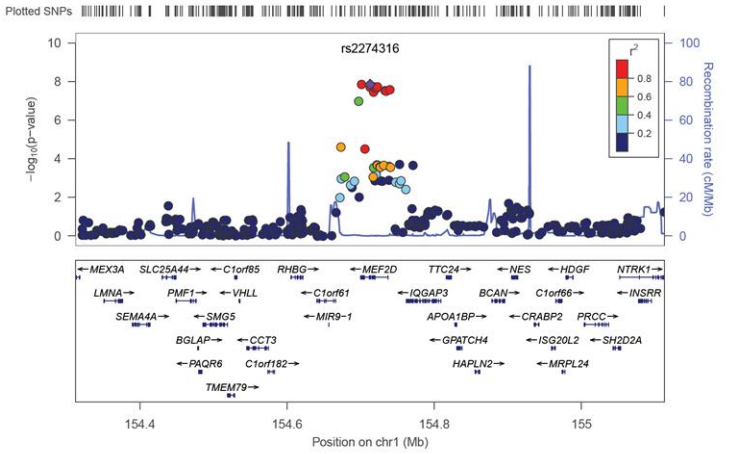
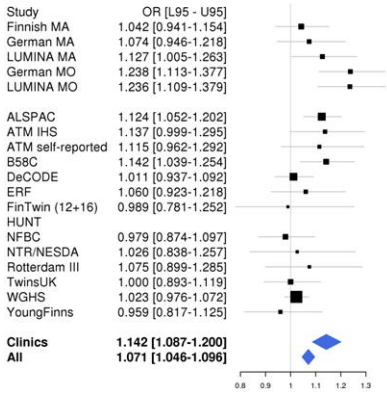
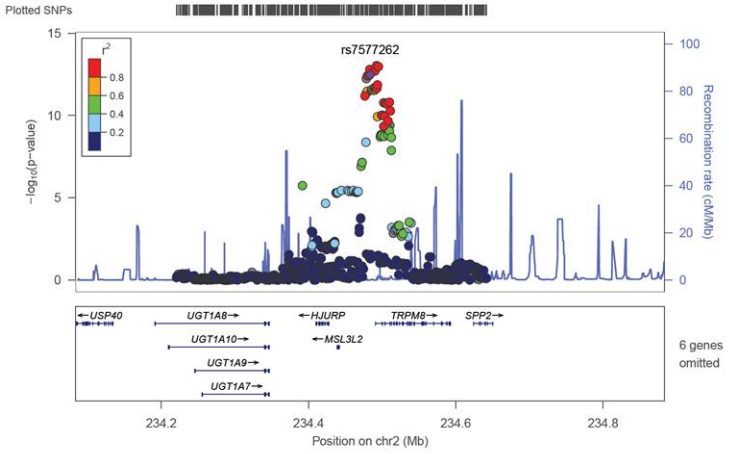
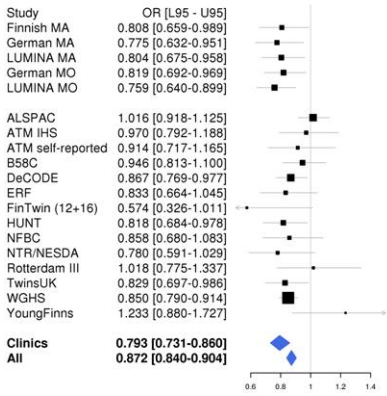


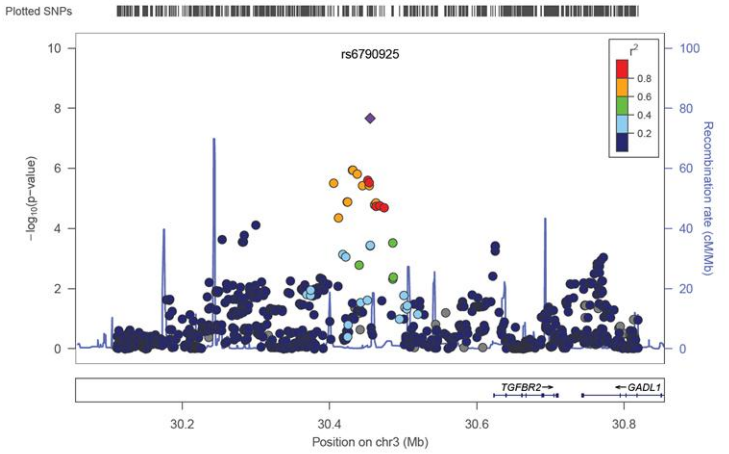


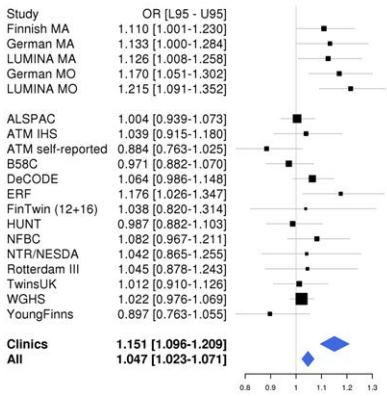
TRPM8



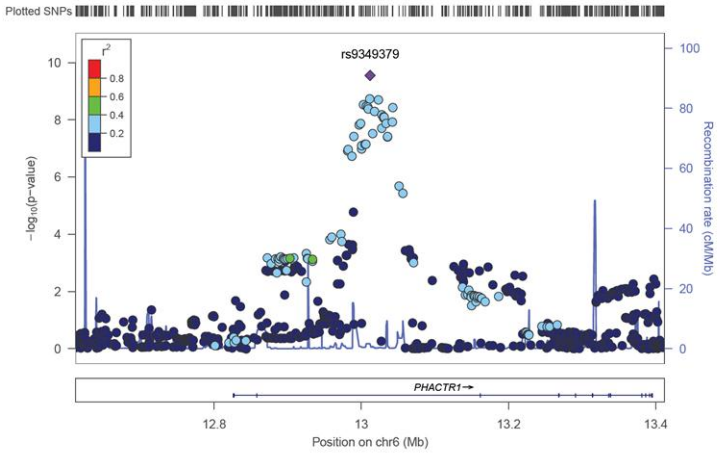


near TGFBR2

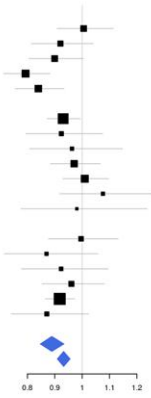




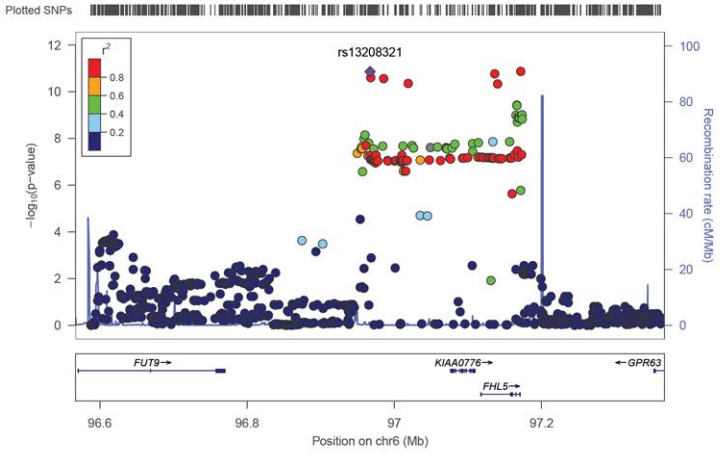
PHACTR1



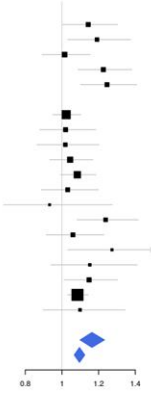
Study	OR [L95 - U95]
Finnish MA	1.005 [0.908-1.113]
German MA	0.921 [0.814-1.041]
LUMINA MA	0.899 [0.805-1.005]
German MO	0.793 [0.713-0.882]
LUMINA MO	0.840 [0.755-0.934]
ALSPAC	0.931 [0.872-0.993]
ATM IHS	0.924 [0.794-1.075]
ATM self-reported	0.963 [0.808-1.147]
B58C	0.971 [0.884-1.066]
DeCODE	1.010 [0.930-1.096]
ERF	1.076 [0.918-1.261]
FinTwin (12+16)	0.981 [0.777-1.237]
HUNT	
NFBC	0.996 [0.877-1.132]
NTR/NESDA	0.870 [0.715-1.057]
Rotterdam III	0.923 [0.778-1.095]
TwinsUK	0.961 [0.854-1.081]
WGHS	0.918 [0.866-0.973]
YoungFinns	0.871 [0.741-1.023]
Clinics	**0.889 [0.847-0.933]**
All	**0.932 [0.909-0.956]**



FHL5



Study	OR [L95 - U95]
Finnish MA	1.143 [1.003-1.303]
German MA	1.191 [1.033-1.375]
LUMINA MA	1.014 [0.892-1.154]
German MO	1.226 [1.088-1.381]
LUMINA MO	1.246 [1.102-1.408]
ALSPAC	1.023 [0.950-1.102]
ATM IHS	1.020 [0.879-1.184]
ATM self-reported	1.019 [0.863-1.202]
B58C	1.045 [0.934-1.169]
DeCODE	1.084 [0.992-1.185]
ERF	1.031 [0.887-1.199]
FinTwin (12+16)	0.933 [0.683-1.274]
HUNT	1.238 [1.083-1.417]
NFBC	1.060 [0.914-1.229]
NTR/NESDA	1.273 [1.032-1.571]
Rotterdam III	1.152 [0.941-1.410]
TwinsUK	1.148 [1.011-1.304]
WGHS	1.085 [1.030-1.142]
YoungFinns	1.099 [0.898-1.344]
Clinics	**1.164 [1.099-1.232]**
All	**1.096 [1.067-1.125]**



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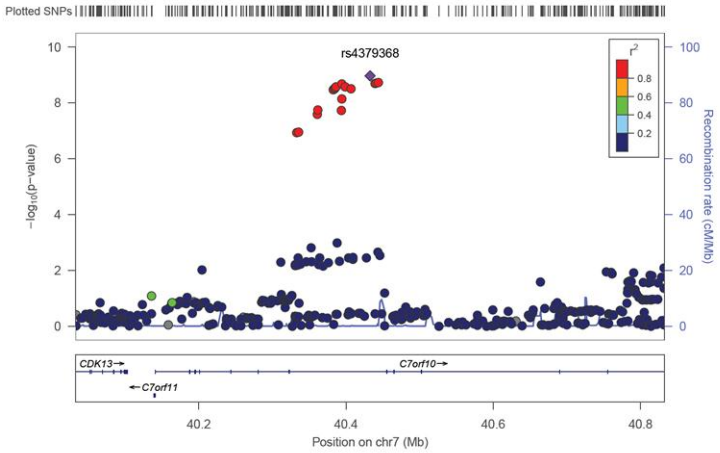
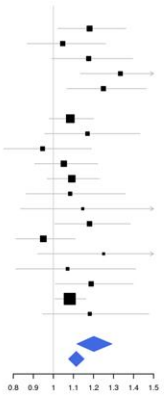
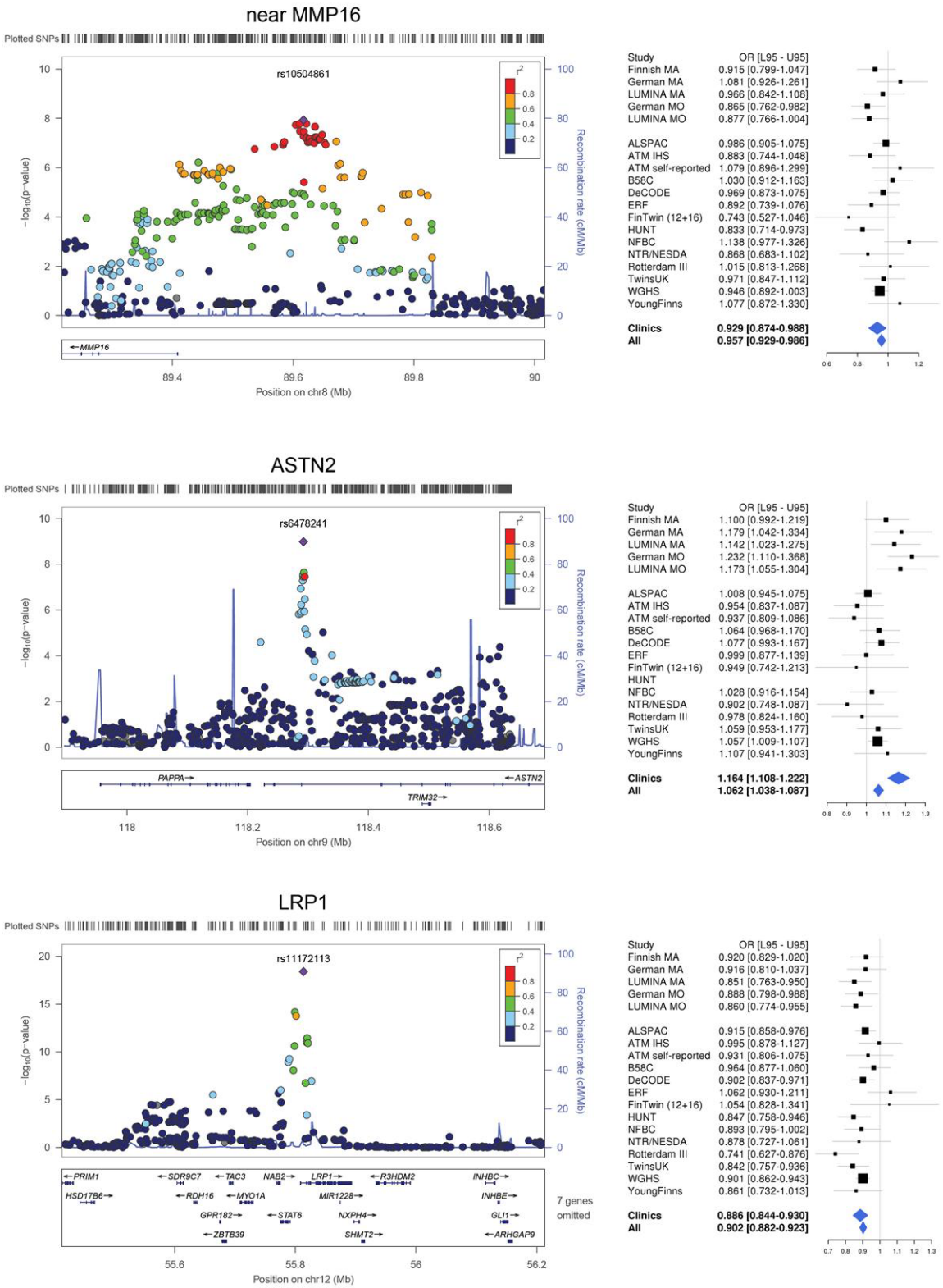


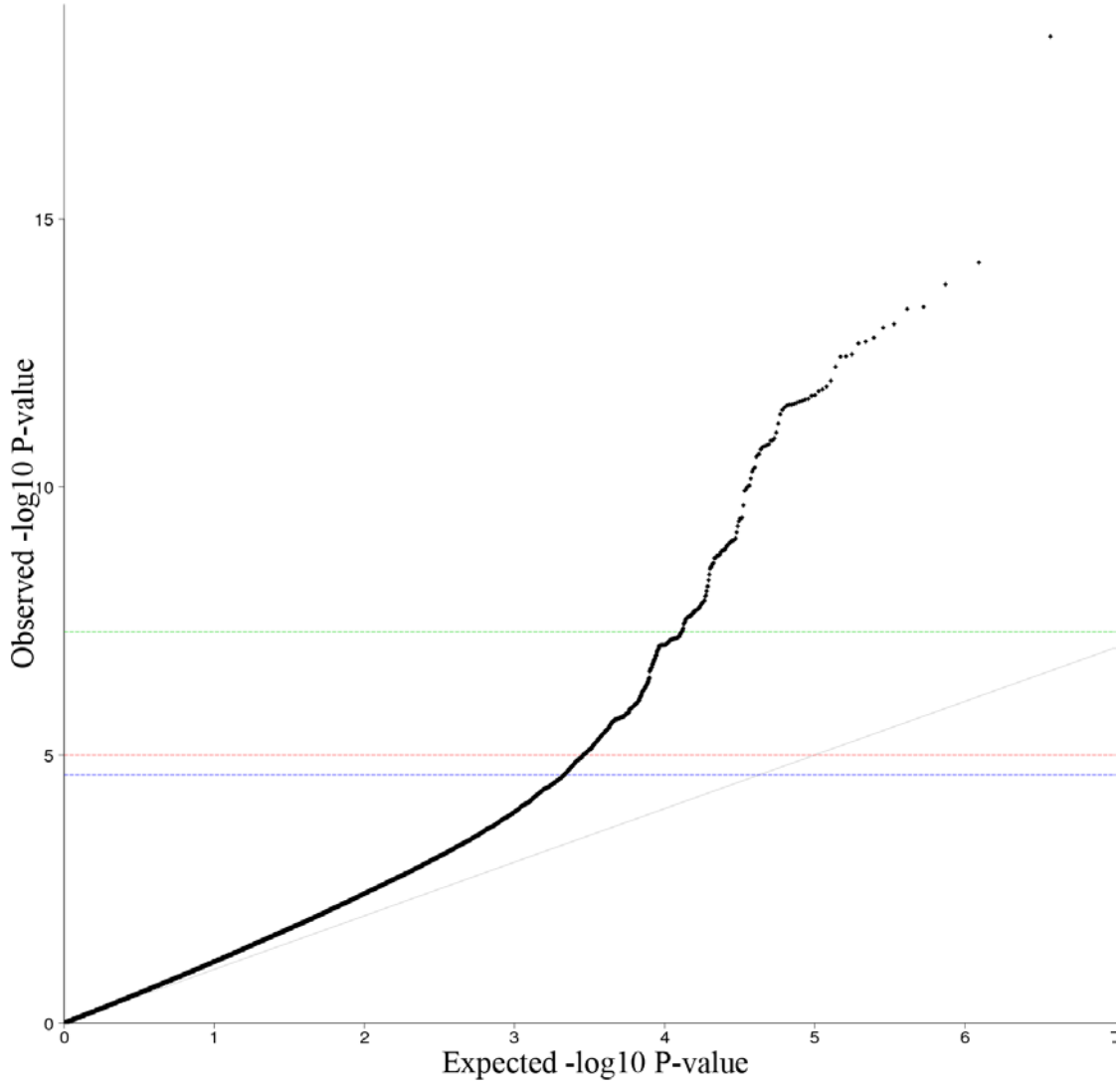
Study	OR [L95 - U95]
Finnish MA	1.181 [1.023-1.363]
German MA	1.047 [0.869-1.261]
LUMINA MA	1.176 [0.991-1.396]
German MO	1.334 [1.135-1.568]
LUMINA MO	1.250 [1.066-1.464]
ALSPAC	1.084 [0.979-1.201]
ATM IHS	1.170 [0.957-1.431]
ATM self-reported	0.946 [0.752-1.190]
B58C	1.052 [0.907-1.221]
DeCODE	1.092 [0.969-1.230]
ERF	1.084 [0.865-1.358]
FinTwin (12+16)	1.146 [0.837-1.571]
HUNT	1.180 [1.007-1.384]
NFBC	0.950 [0.813-1.109]
NTR/NESDA	1.251 [0.922-1.696]
Rotterdam III	1.071 [0.813-1.410]
TwinsUK	1.188 [1.010-1.398]
WGHS	1.082 [1.007-1.162]
YoungFinns	1.182 [0.946-1.476]
Clinics	**1.202 [1.117-1.292]**
All	**1.114 [1.076-1.153]**





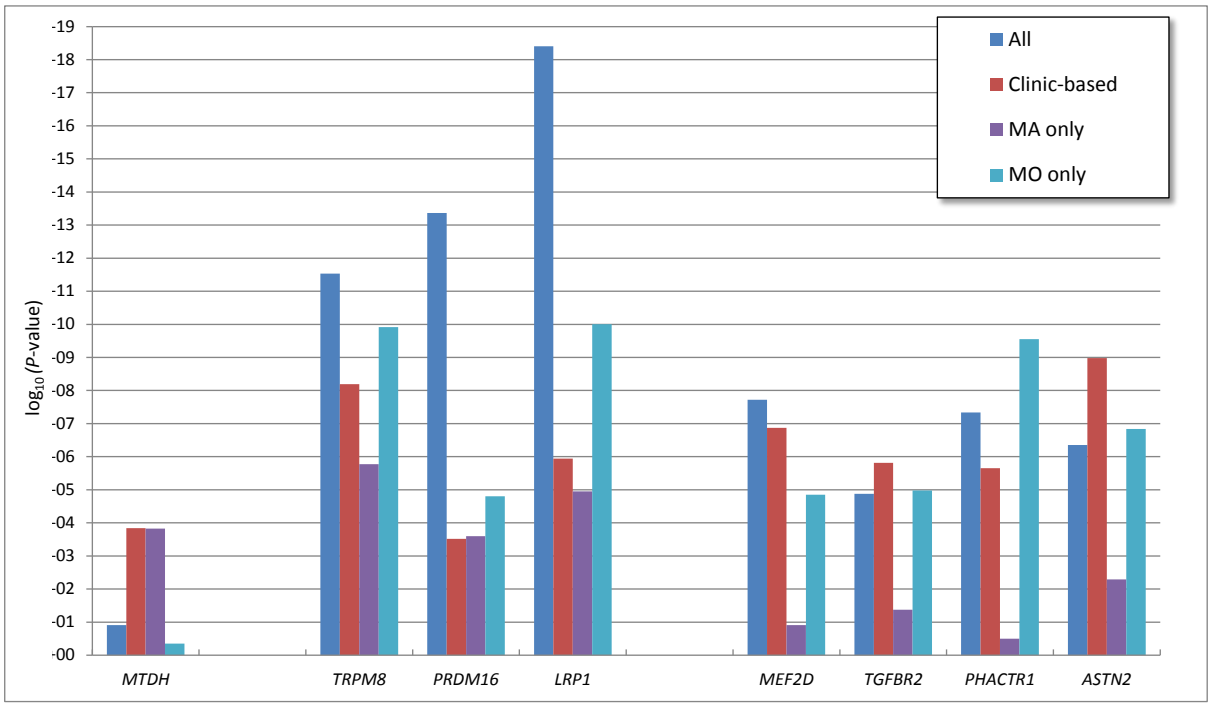
Plots showing the *P* values for association to migraine as well as the local recombination rate (left), together with forest plots showing the odds ratios for migraine in participating studies (clinic-based studies first, followed by the population cohorts) and the meta-analysis for clinic-based samples and all samples (right). Recombination rate data from 1000 Genomes June 2010 release for CEU. Positions are given as in build 36/hg18. The extent of LD to the SNP named in the plot is shown in the shading.

Supplementary Figure 4. Quantile-quantile plot of the meta-analysis results.



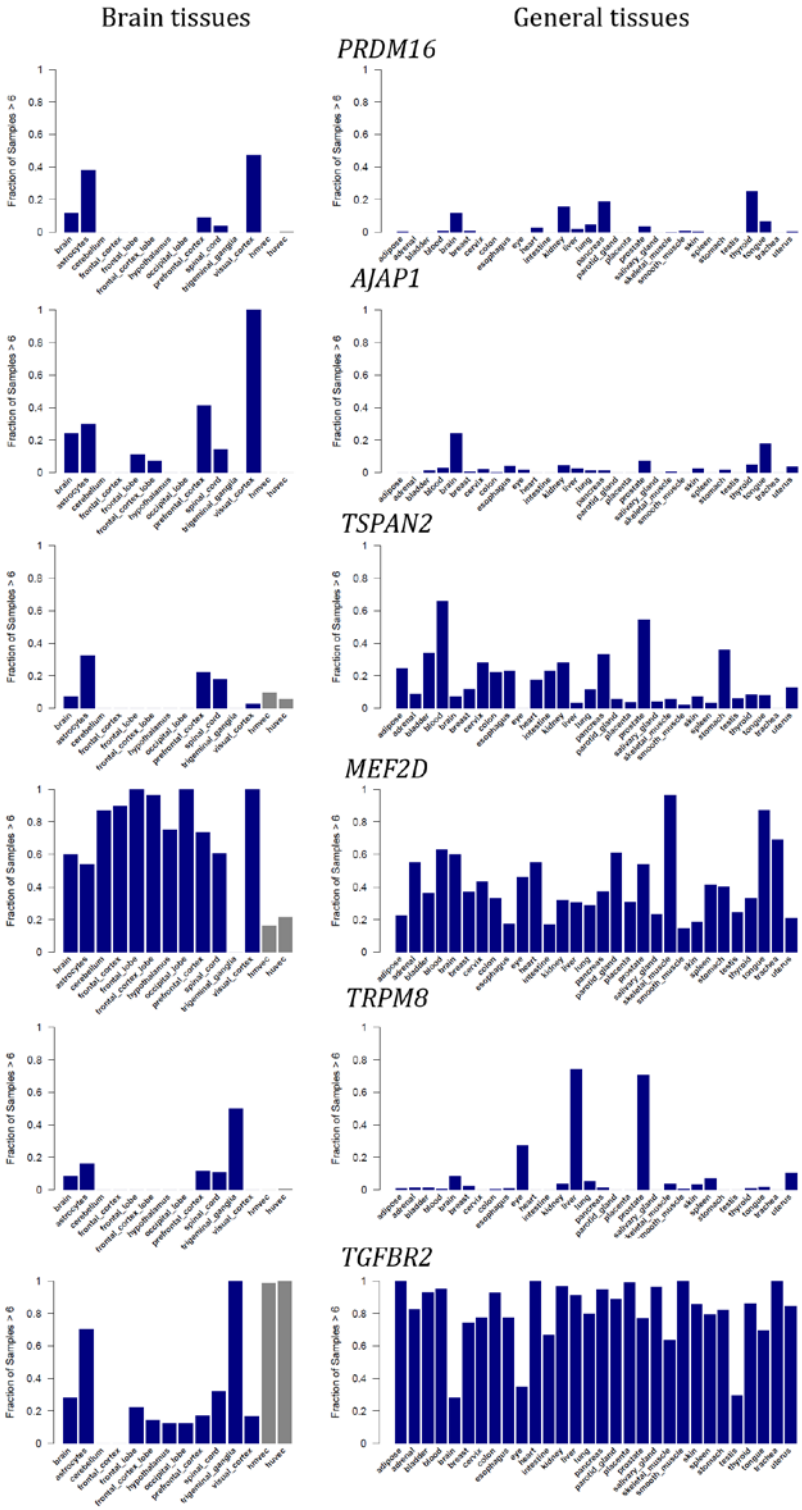
The dashed lines indicate thresholds for genome-wide significance (green; *P* 5.0 x 10^{-8}), suggestive associations (red; *P* 1 x 10^{-5}), and the false discovery rate <0.05 threshold (blue; *P* 2.33 x 10^{-5}).

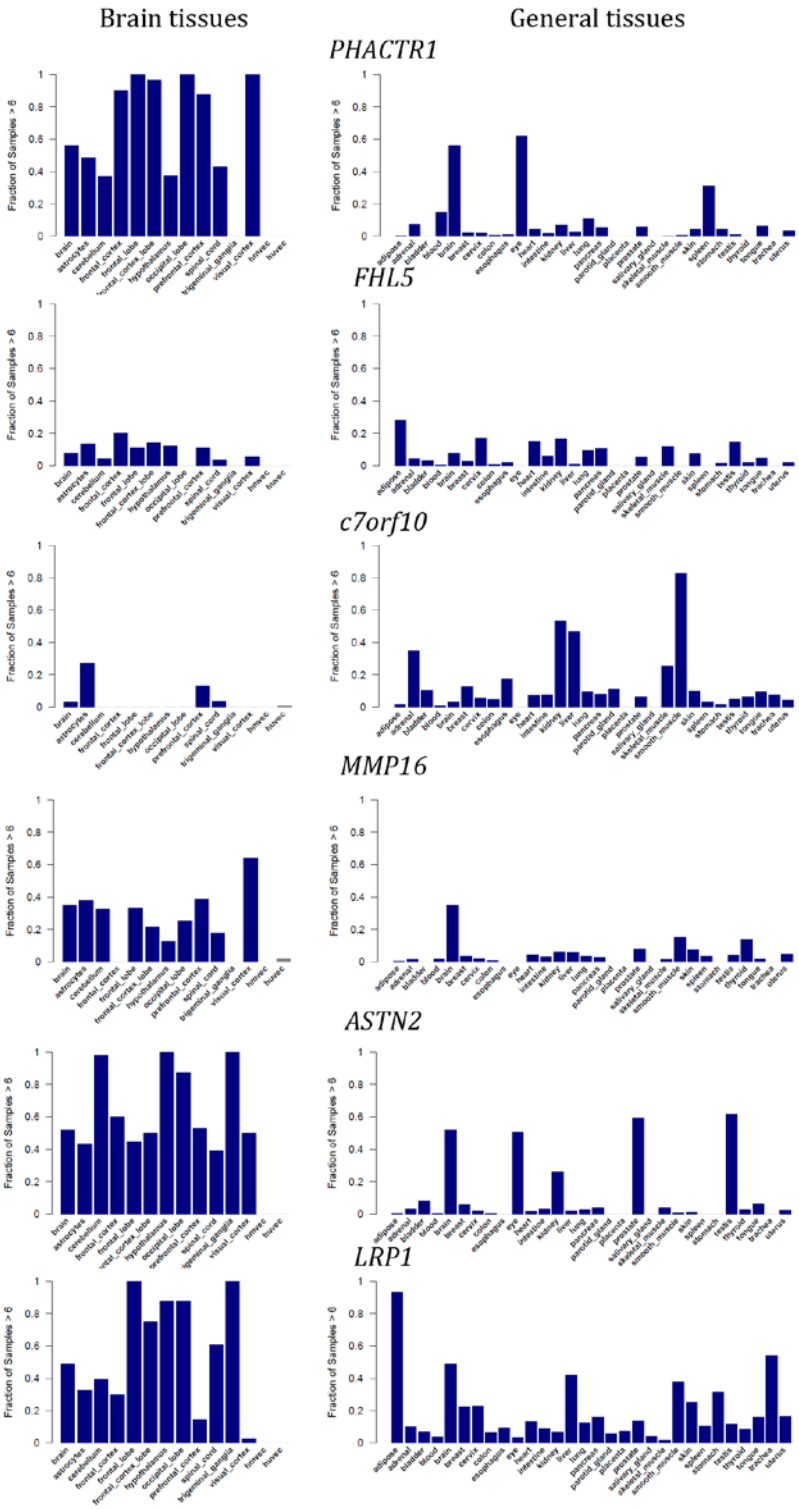
Supplementary Figure 5. Meta-analysis association results at previously reported migraine loci.



Plot showing the *P* values of the previously reported migraine-associated SNPs (see text for references) in order of publication in the meta-analyses of all samples and the three subsets.

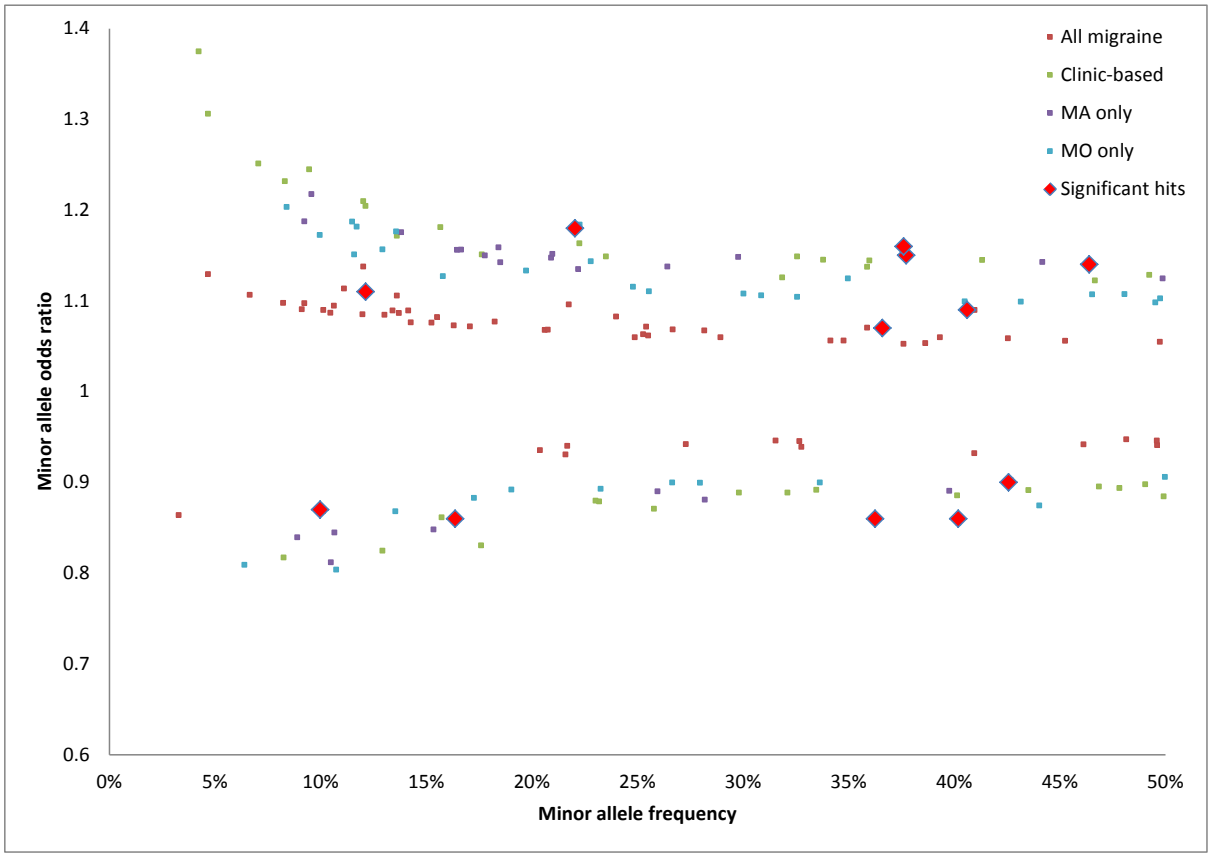
Supplementary Figure 6. Expression of genes with significant association to migraine reported in this study across 55,269 tissue samples





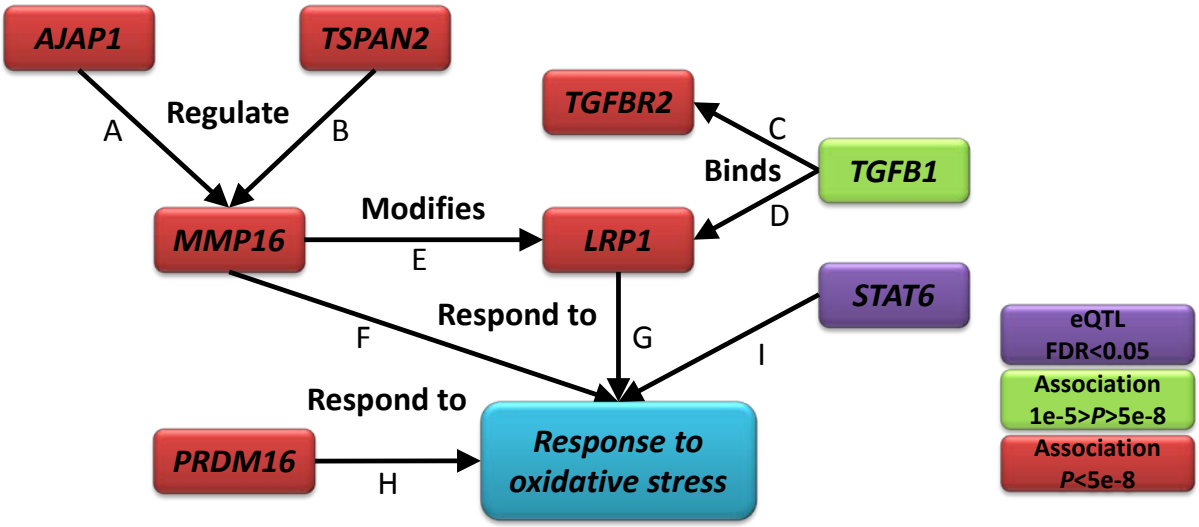
Number of samples for each tissue. Left panel: brain – 1,990; astrocytes – 37; cerebellum – 46; frontal cortex – 28; frontal lobe – 18; frontal cortex/lobe – 10; hypothalamus - 16; occipital lobe – 16; pre-frontal cortex 153; spinal cord – 28; trigeminal ganglia 16; visual cortex – 36; HMVEC (Human Microvascular Endothelial Cells) - 74, HUVEC (Human Umbilical Vein Endothelial Cells) - 310. The left panel contains, in addition to brain tissues, two sets of endothelial tissues (HMVEC and HUMEC). Right panel: adipose – 394; adrenal – 69; bladder – 86; blood – 3327; brain – 1990; breast – 4104; cervix – 53; colon – 1466; esophagus – 97; eye – 63; heart – 178; intestine – 66; kidney – 675; liver – 721; lung – 1442; pancreas – 150; parotid gland – 18; placenta – 107; prostate – 578; salivary gland – 26; skeletal muscle – 793; smooth muscle – 151; skin – 947; spleen – 29; stomach – 67; testis – 102; thyroid – 108; tongue – 62; trachea – 13; uterus – 212.

Supplementary Figure 7. Distribution of minor allele odds ratios (at loci with *P* value < 1 x 10^{-5}) versus allele frequency



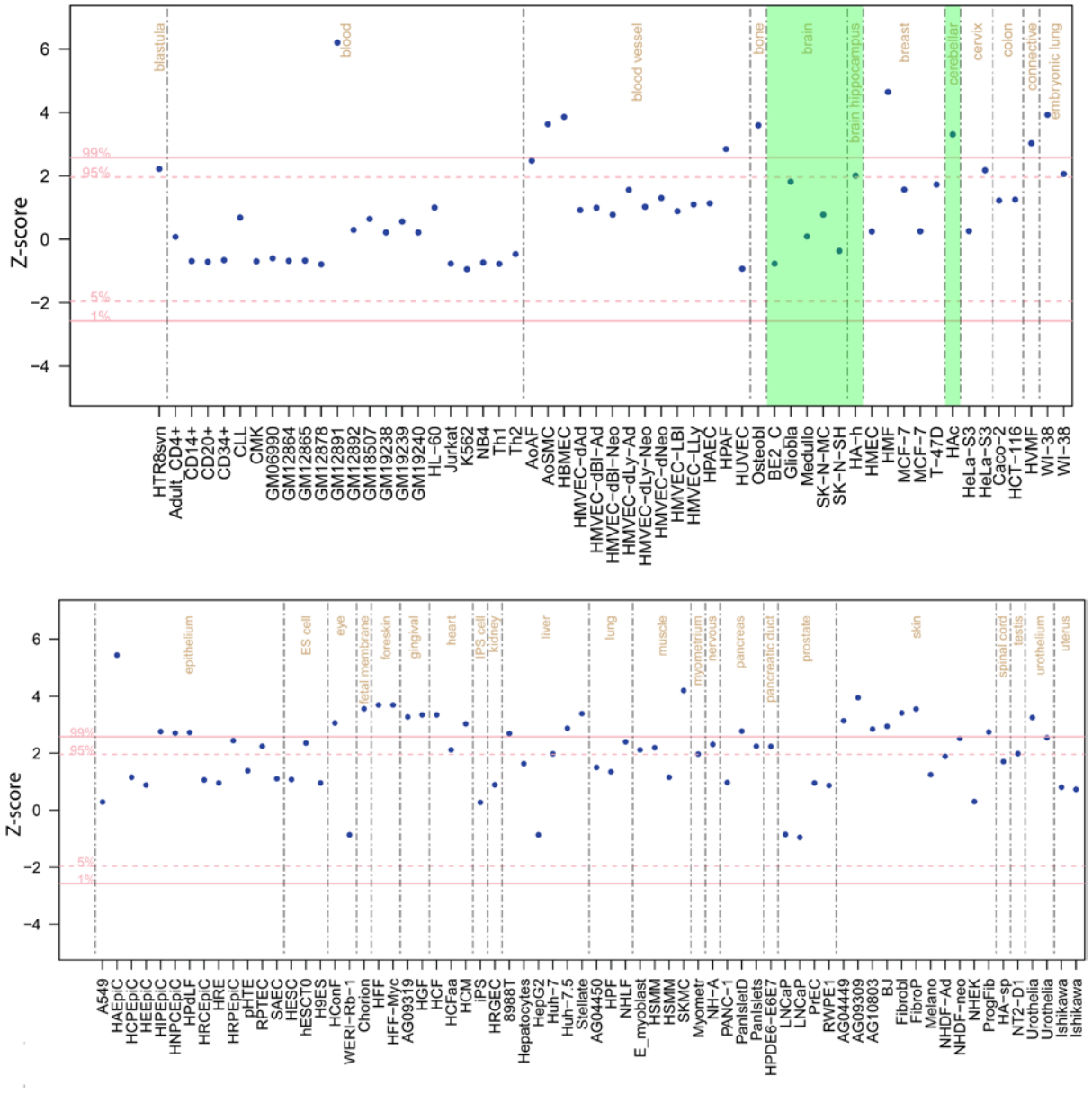
Plot comparing the frequency and odds ratios for the minor alleles reported in this study (suggestive and significant loci), showing an excess of risk increasing variants, especially towards lower frequencies.

Supplementary Figure 8. Hypothesis of how direct connections between genes at loci with significant association to migraine could potentially contribute to responses to oxidative stress.



Genes in red boxes are significantly associated with migraine. References – A[5,6] (via CD147), B[7], C[8], D[9], E[10], F[11], G[12], H[13] ,I[14].

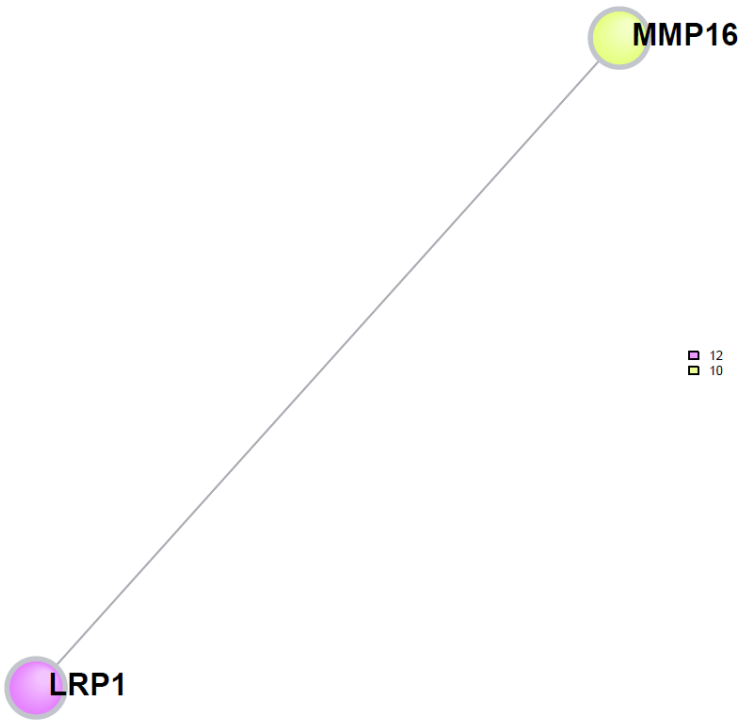
Supplementary Figure 9. DNAse I hypersensitivity site abundance in ENCODE tissue data at migraine loci



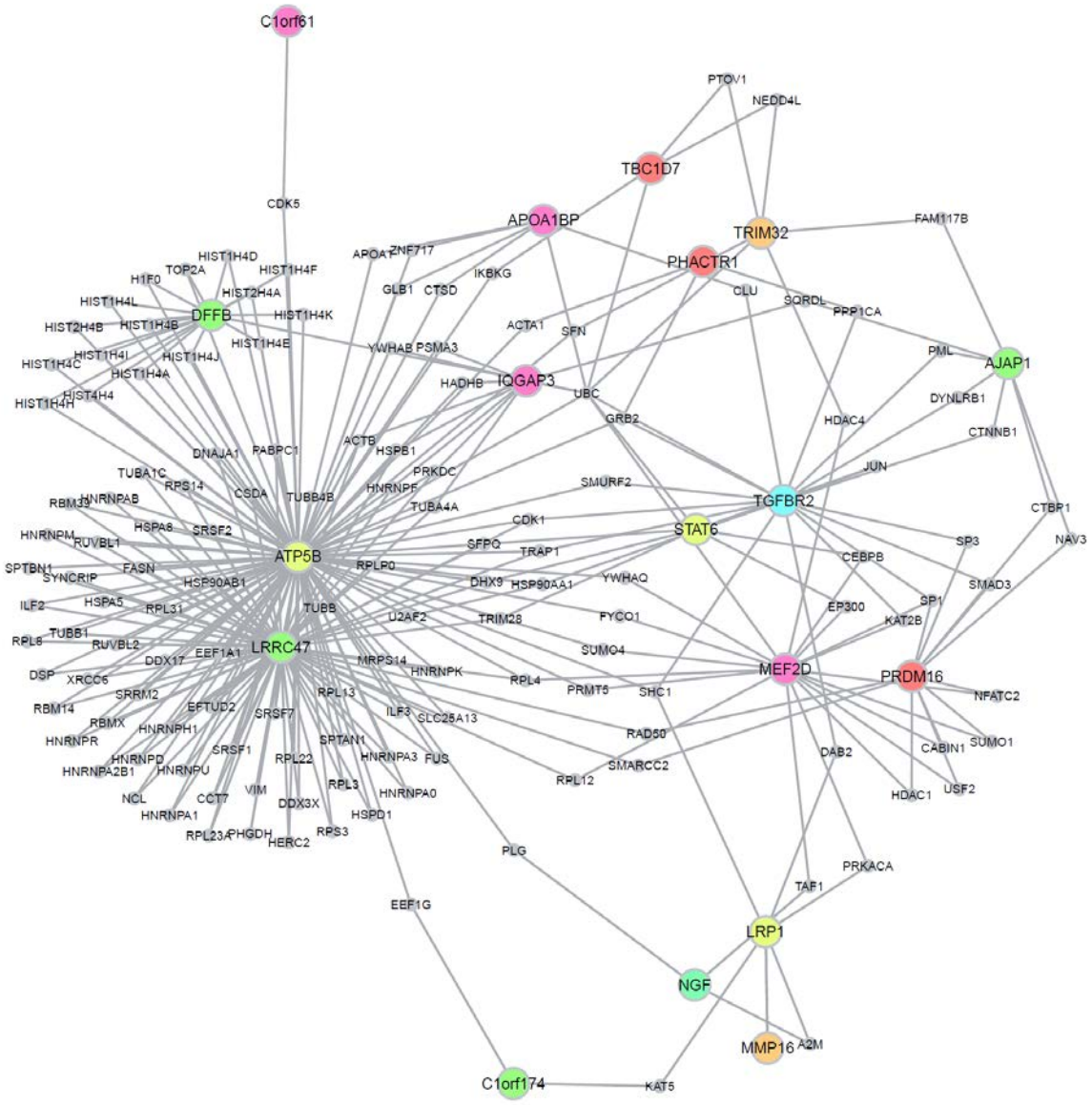
Plots showing the extremity of the proportion of loci containing DNAse I hypersensitivity sites in each tissue for loci with significant association to migraine (*P*-value < 5 x 10^{-8}). The brown text at the top lists the tissue category, while the X-axis lists the exact tissue sample name (for further information, see http://encodeproject.org/ENCODE/dataMatrix/encodeDataMatrixHuman.html). Brain tissues are highlighted in green.

Supplementary Figure 10. Direct protein-protein interactions identified in the DAPPLE analysis

A)



B)



Plot of results from the DAPPLE analysis showing A) direct connections between the significant migraine loci and B) the whole network among significant loci. The colors reflect the different loci used as seeds for the analysis.

Supplementary Tables

Supplementary Table 1: Description of cases and controls from the clinical studies

Study	Cases/ Controls	Migraine %	Female % of		Ethnicity	Migraine definition	Control definition*	Ref study PMID
			Cases	Controls				
German MO	1208/2564	32.0	87.0	55.1				
MO cases	1208/0				European, German	ICHD-II		22683712
GSK	0/861						Pop.	19107115
KORA	0/834						Pop.	16032514
MPIPSYKL	0/489						Pop.	-
HNR	0/380						Pop.	12177636
LUMINA MO	1118/2016	35.7	85.8	54.2				
MO cases	1118/0				European, Dutch	ICHD-II		21914734; 22683712
Rotterdam II	0/2016						Pop.	21877163
Finnish MA	1032/3513	22.7	80.2	52.6				
MA cases	1032/0				European, Finnish	ICHD-II		11509082; 20802479
Health 2000	0/1862						Mig-free	20532202
Helsinki Birth Cohort Study	0/1651						Pop.	16251536
German MA study	997/1105	47.4	81.1	60.8				
MA cases	997/0				European, German	ICHD-II		20802479
PopGen	0/661						Pop.	16490960
Illumina iControlDB	0/444				MDS-filtered Caucasian		Pop.	
LUMINA MA	820/4774	14.7	82.2	58.6				
MA cases	820/0				European, Dutch	ICHD-II		21914734; 20802479
Rotterdam I	0/4774						Pop.	21877163

Where more than one control definition was used, control groups are listed in decreasing size. The indented rows describe studies that were combined together to generate the set named on the first line of the set.
ICHD-II – cases fulfil the International Classification of Headache Disorders, 2nd edition definition for current or past migraine[15]. Pop. – Unscreened population-matched population-based sample. Mig-free pop. – migraine-free population-matched population-based sample. PMID – PubMed ID. MA – migraine with aura. MO – migraine without aura

Supplementary Table 2: Description of cases and controls from the population-based studies

Study	Cases/ Controls	Migraine %	Female % of		Ethnicity	Migraine definition	Control definition*	Ref study PMID
			Cases	Controls				
ALSPAC	3134/ 5103	38.0	100	100	European, British	Self-reported migraine, current or prior	No migraine or use of migraine medications; pop.	22507742
Australia ATM	1683/ 2383	41.4	72.3	48.6	European descent	Modified ICHD-II criteria, current migraine	Pop.	20303062, 18676988
B58C	1165/ 4141	22.0	68.4	44.7	European, British	Self-reported migraine, current or prior	No migraine or severe recurrent headaches	16155052
deCode	2139/ 34617	5.8	73.8	55.4	European, Icelandic	Full ICHD-II criteria, current migraine	Pop.; no migraine	17038039
ERF	330/ 1216	21.3	75.5	50.6	European, Dutch	Full ICHD-II criteria, current migraine	No migraine	20071666
FinnTwin	189/ 580	28.5	63.5	46	European, Finnish	Self-reported migraine, current or prior	No migraine, use of migraine medication or severe recurrent headaches	12537859 , 12537860, 20953688
HUNT	1608/ 1097	59.4	74.9	75	European, Norwegian	Self-reported migraine or fulfilling Modified ICHD-II criteria, current migraine	No migraine; pop.	10999674
NTR	265/ 2128	11.1	85.3	55.2	European, Dutch	Modified ICHD-II criteria, current migraine	No migraine or severe recurrent headache	17254420, 16611468
NESDA	17/ 132	11.4	82.4	56.1	European, Dutch	Modified ICHD-II criteria, current migraine	No migraine or severe recurrent headache	18763692, 20713558
NFBC	757/ 4399	14.7	76.5	48.2	European, Finnish	Self-reported migraine, current or prior	No migraine	4911003
Rotterdam III	351/ 1647	17.6	77.5	51.2	European, Dutch	Modified ICHD-II criteria, current migraine	No migraine	21877163
Twins UK	972/ 3837	20.2	96.2	89.8	European, British	Self-reported migraine or fulfilling Modified ICHD-II criteria, current or prior migraine	No migraine	22253318
WGHS	5122/ 18108	22.0	100	100	European descent	Self-reported migraine or fulfilling Modified ICHD-II criteria,	No migraine	16849661, 18070814
Young Finns	378/ 2065	15.5	79.6	49.3	European, Finnish	Full ICHD-II criteria, current migraine	No migraine	18263651
WGHS	5122/ 18108	22.0	100	100	European descent	Self-reported migraine or fulfilling Modified ICHD-II criteria, current or prior migraine	No migraine	16849661, 18070814

Where more than one control definition was used, control groups are listed in decreasing size.

Pop. – Unscreened population-matched control sample. ICHD-II – International Classification of Headache Disorders, 2nd edition[15].

Supplementary Table 3. Number of samples by phenotypes in study cohorts

	ALSPAC		ATM		B58C		DeCODE		ERF		FinTwin		HUNT	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Final number of samples for analysis	3134	5103	1683	2383	1165	4141	2139	34617	330	1216	189	580	1608	1097
Women	3134	5103	1217	1158	797	1851	1711	19169	249	615	120	267	1204	823
Men	0	0	466	1225	368	2290	428	15448	81	601	69	313	404	274
Samples fulfilling IHS migraine criteria	0	0	886	1586	0	0	1352	34617	330	1216	0	0	1534	1097
Women	0	0	732	763	0	0	1069	19169	249	615	0	0	1140	823
Men	0	0	154	823	0	0	283	15448	81	601	0	0	394	274
Self-reported migraine	3134	5103	797	797	1165	4141	787	34617	0	0	189	580	74	NA
Women	3134	5103	485	395	797	1851	642	19169	0	0	120	267	64	NA
Men	0	0	312	402	368	2290	145	15448	0	0	69	313	10	NA
Samples with migraine with aura	0	0	0	0	0	0	120	34617	141	1216	0	0	359	1097
Samples with migraine without aura analysis	0	0	0	0	0	0	537	34617	189	1216	0	0	1175	1097

	NTR		NESDA		NFBC		Rotterdam III		TwinsUK		WGHS		YoungFinns	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Final number of samples for analysis	265	2128	17	132	757	4399	351	1727	972	3837	5122	18108	378	2065
Women	226	1174	14	74	579	2120	272	844	935	3446	5122	18108	301	1019
Men	39	954	3	58	178	2279	79	803	37	391	0	0	77	1046
Samples fulfilling IHS migraine criteria	265	2128	17	132	0	0	351	1727	703	3837	3003	18108	215	2065
Women	226	1174	14	74	0	0	272	844	684	3443	3003	18108	184	1019
Men	39	954	3	58	0	0	79	803	19	394	0	0	31	1046
Self-reported migraine	0	0	0	0	757	4399	0	0	502	0	2119	0	0	0
Women	0	0	0	0	579	2120	0	0	478	0	2119	0	0	0
Men	0	0	0	0	178	2279	0	0	24	0	0	0	0	0
Samples with migraine with aura	98	2128	5	132	0	0	76	1647	235	3837	1177	18108	58	2065
Samples with migraine without aura analysis	142	2128	12	132	0	0	275	1647	468	3837	1826	18108	157	2065

	Finnish MA		German MA		German MO		LUMINA MA		LUMINA MO	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Final number of samples for analysis	1032	3513	997	1105	1208	2564	820	4774	1118	2016
Women	828	1849	809	672	1051	1412	674	2797	959	1092
Men	204	1664	188	433	157	1152	146	1977	159	924
Samples fulfilling IHS migraine criteria	1032	3513	997	1105	1208	2564	820	4774	1118	2016
Women	828	1849	809	672	1051	1412	674	2797	959	1092
Men	204	1664	188	433	157	1152	146	1977	159	924
Self-reported migraine	0	0	0	0	0	0	0	0	0	0
Women	0	0	0	0	0	0	0	0	0	0
Men	0	0	0	0	0	0	0	0	0	0
Samples with migraine with aura	1032	3513	997	1105	0	0	820	4774	0	0
Samples with migraine without aura analysis	0	0	0	0	1208	2564	0	0	1118	2016

MA – migraine with aura. MO – migraine without aura.

Supplementary Table 4. Association results at the loci with p-values less than 1 x 10^{-5}

Marker					Lowest p-value					All samples		Clinics		MA		MO	
SNP	Chr	Position[a]	Minor allele	Lowest p-value	OR (95% CI)	q/p-value	I^2	Minor allele frequency	Group or subgroup with the lowest p-value	P-value	OR	P-value	OR	P-value	OR	P-value	OR
rs2651899	1	3073572	C	*4.34E-14*	1.09 (1.07 - 1.11)	0.23	0.18	0.41	All	*4.34E-14*	1.09 [1.07 - 1.11]	3.06E-04	1.09 [1.04 - 1.15]	2.54E-04	1.09 [1.04 - 1.14]	1.56E-05	1.09 [1.05 - 1.14]
rs10737909	1	15421223	G	1.89E-07	0.94 (0.92 - 0.96)	0.23	0.19	0.46	All	1.89E-07	0.94 [0.92 - 0.96]	1.08E-02	0.94 [0.90 - 0.99]	9.74E-03	0.94 [0.90 - 0.99]	8.91E-05	0.92 [0.89 - 0.96]
rs1890566	1	54440866	G	7.97E-07	1.06 (1.04 - 1.08)	0.22	0.19	0.43	All	7.97E-07	1.06 [1.04 - 1.08]	1.23E-02	1.06 [1.01 - 1.12]	1.52E-03	1.08 [1.03 - 1.13]	9.74E-02	1.04 [0.99 - 1.08]
rs12134493	1	115479469	A	*4.79E-14*	1.14 (1.1 - 1.18)	0.45	0.00	0.12	All	*4.79E-14*	1.14 [1.10 - 1.18]	1.19E-05	1.18 [1.10 - 1.27]	6.19E-04	1.13 [1.05 - 1.21]	5.29E-08	1.18 [1.11 - 1.26]
rs2274316	1	154712866	C	*1.42E-08*	1.07 (1.05 - 1.1)	0.02	0.47	0.36	All	*1.42E-08*	1.07 [1.05 - 1.10]	1.43E-07	1.14 [1.09 - 1.20]	8.66E-02	1.04 [0.99 - 1.10]	2.31E-05	1.10 [1.05 - 1.15]
rs10442694	1	204800040	T	6.92E-05	0.95 (0.93 - 0.97)	0.62	0.00	0.27	All	6.92E-05	0.95 [0.93 - 0.97]	8.95E-01	1.00 [0.95 - 1.06]	5.18E-02	0.95 [0.90 - 1.00]	9.29E-01	1.00 [0.96 - 1.05]
rs6741751	2	234492400	A	*9.11E-14*	0.87 (0.84 - 0.9)	0.10	0.31	0.10	All	*9.11E-14*	0.87 [0.84 - 0.90]	*1.09E-08*	0.79 [0.73 - 0.86]	1.03E-07	0.81 [0.75 - 0.88]	*8.64E-11*	0.80 [0.75 - 0.86]
rs3923518	3	38861417	A	7.92E-06	1.06 (1.03 - 1.09)	0.29	0.14	0.25	All	7.92E-06	1.06 [1.03 - 1.09]	2.67E-02	1.06 [1.01 - 1.12]	1.79E-02	1.06 [1.01 - 1.12]	2.92E-02	1.05 [1.01 - 1.10]
rs10511112	3	80451153	C	4.71E-06	1.11 (1.06 - 1.16)	0.68	0.00	0.07	All	4.71E-06	1.11 [1.06 - 1.16]	5.82E-03	1.15 [1.04 - 1.26]	2.83E-03	1.15 [1.05 - 1.26]	1.24E-02	1.10 [1.02 - 1.19]
rs273218	5	53416312	T	2.34E-06	0.94 (0.91 - 0.96)	0.19	0.21	0.20	All	2.34E-06	0.94 [0.91 - 0.96]	1.07E-01	0.95 [0.90 - 1.01]	1.07E-02	0.93 [0.88 - 0.98]	1.05E-02	0.94 [0.89 - 0.98]
rs12519773	5	92490172	C	1.93E-06	0.95 (0.93 - 0.97)	0.61	0.00	0.48	All	1.93E-06	0.95 [0.93 - 0.97]	5.96E-03	0.93 [0.89 - 0.98]	3.48E-03	0.93 [0.89 - 0.98]	1.12E-02	0.95 [0.91 - 0.99]
rs2447820	5	122292635	T	4.15E-06	1.09 (1.05 - 1.13)	0.64	0.00	0.10	All	4.15E-06	1.09 [1.05 - 1.13]	7.10E-03	1.11 [1.03 - 1.19]	7.20E-02	1.07 [0.99 - 1.15]	3.80E-03	1.10 [1.03 - 1.18]
rs12153243	5	142879994	T	6.10E-06	1.05 (1.03 - 1.08)	0.32	0.11	0.39	All	6.10E-06	1.05 [1.03 - 1.08]	1.75E-04	1.10 [1.05 - 1.15]	3.66E-04	1.09 [1.04 - 1.14]	6.27E-03	1.06 [1.02 - 1.10]
rs11750092	5	159300549	T	6.51E-06	1.07 (1.04 - 1.11)	0.67	0.00	0.16	All	6.51E-06	1.07 [1.04 - 1.11]	1.23E-03	1.11 [1.04 - 1.19]	3.11E-01	1.03 [0.97 - 1.10]	2.79E-02	1.07 [1.01 - 1.13]
rs10456100	6	39291448	T	5.44E-07	1.07 (1.04 - 1.1)	0.24	0.18	0.27	All	5.44E-07	1.07 [1.04 - 1.10]	2.50E-05	1.13 [1.07 - 1.20]	2.46E-01	1.03 [0.98 - 1.09]	2.06E-04	1.09 [1.04 - 1.14]
rs543844	6	44532778	G	3.41E-06	1.06 (1.03 - 1.08)	0.43	0.02	0.34	All	3.41E-06	1.06 [1.03 - 1.08]	4.01E-02	1.05 [1.00 - 1.11]	4.71E-02	1.05 [1.00 - 1.10]	1.35E-04	1.08 [1.04 - 1.13]
rs13203080	6	136926504	A	5.33E-05	1.07 (1.03 - 1.1)	0.32	0.11	0.15	All	5.33E-05	1.07 [1.03 - 1.10]	9.05E-01	1.00 [0.94 - 1.07]	9.69E-01	1.00 [0.94 - 1.06]	7.32E-03	1.08 [1.02 - 1.14]
rs13196614	6	148965482	T	5.36E-06	1.08 (1.04 - 1.11)	0.41	0.03	0.18	All	5.36E-06	1.08 [1.04 - 1.11]	1.28E-02	1.10 [1.02 - 1.18]	5.15E-02	1.07 [1.00 - 1.14]	1.69E-02	1.07 [1.01 - 1.14]
rs13218732	6	153306903	C	3.44E-06	0.86 (0.81 - 0.92)	0.68	0.00	0.03	All	3.44E-06	0.86 [0.81 - 0.92]	2.24E-04	0.79 [0.70 - 0.89]	-	-	-	-
rs10244428	7	8488468	T	2.27E-05	0.95 (0.93 - 0.97)	0.64	0.00	0.45	All	2.27E-05	0.95 [0.93 - 0.97]	5.81E-01	0.99 [0.94 - 1.04]	1.25E-02	1.06 [1.01 - 1.11]	1.86E-02	0.95 [0.91 - 0.99]
rs4379368	7	40432725	T	*1.07E-09*	1.11 (1.08 - 1.15)	0.44	0.01	0.11	All	*1.07E-09*	1.11 [1.08 - 1.15]	7.18E-07	1.20 [1.12 - 1.29]	1.24E-03	1.12 [1.05 - 1.20]	5.81E-08	1.19 [1.12 - 1.27]
rs9649465	7	123163796	A	1.21E-06	1.06 (1.03 - 1.08)	0.10	0.30	0.45	All	1.21E-06	1.06 [1.03 - 1.08]	1.16E-02	1.06 [1.01 - 1.12]	1.30E-03	1.08 [1.03 - 1.13]	1.63E-02	1.05 [1.01 - 1.09]
rs1861960	7	154977896	T	6.30E-06	1.07 (1.04 - 1.1)	0.08	0.34	0.20	All	6.30E-06	1.07 [1.04 - 1.10]	8.11E-02	1.05 [0.99 - 1.12]	2.27E-02	1.07 [1.01 - 1.13]	3.10E-03	1.08 [1.03 - 1.14]
rs2946505	8	12855523	T	8.94E-06	0.94 (0.92 - 0.97)	0.06	0.36	0.22	All	8.94E-06	0.94 [0.92 - 0.97]	4.74E-01	0.98 [0.92 - 1.04]	1.54E-02	0.93 [0.88 - 0.99]	2.67E-01	0.97 [0.93 - 1.02]
rs12681963	8	30102060	T	2.05E-07	1.11 (1.06 - 1.15)	1.00	0.00	0.14	All	2.05E-07	1.11 [1.06 - 1.15]	5.54E-03	1.12 [1.03 - 1.20]	1.81E-03	1.13 [1.05 - 1.22]	2.56E-02	1.08 [1.01 - 1.16]
rs12681792	8	62217017	A	9.04E-07	0.93 (0.9 - 0.96)	0.00	0.55	0.22	All	9.04E-07	0.93 [0.90 - 0.96]	1.40E-01	0.95 [0.90 - 1.02]	2.27E-02	0.93 [0.88 - 0.99]	1.66E-04	0.90 [0.86 - 0.95]
rs13263568	8	72609972	G	1.84E-06	1.1 (1.06 - 1.14)	0.71	0.00	0.09	All	1.84E-06	1.10 [1.06 - 1.14]	1.25E-03	1.15 [1.06 - 1.26]	9.50E-03	1.11 [1.03 - 1.21]	6.57E-03	1.10 [1.03 - 1.18]
rs6998277	8	103709117	C	2.39E-06	1.07 (1.04 - 1.1)	0.64	0.00	0.21	All	2.39E-06	1.07 [1.04 - 1.10]	2.03E-02	1.07 [1.01 - 1.14]	3.50E-03	1.09 [1.03 - 1.15]	6.89E-03	1.07 [1.02 - 1.12]
rs4733750	8	131008307	G	2.01E-05	1.11 (1.06 - 1.16)	0.30	0.13	0.06	All	2.01E-05	1.11 [1.06 - 1.16]	5.32E-01	1.03 [0.93 - 1.14]	2.22E-01	1.06 [0.97 - 1.16]	7.77E-02	1.08 [0.99 - 1.17]
rs16904191	8	131102678	G	1.64E-07	1.07 (1.04 - 1.09)	0.77	0.00	0.28	All	1.64E-07	1.07 [1.04 - 1.09]	3.88E-01	1.02 [0.97 - 1.08]	7.96E-02	1.05 [0.99 - 1.10]	1.49E-02	1.06 [1.01 - 1.10]
rs12006166	9	117464808	T	8.51E-07	1.08 (1.05 - 1.12)	0.93	0.00	0.16	All	8.51E-07	1.08 [1.05 - 1.12]	3.82E-03	1.11 [1.03 - 1.19]	1.45E-03	1.11 [1.04 - 1.19]	1.51E-02	1.07 [1.01 - 1.14]
rs17303101	9	118221615	A	3.79E-07	1.07 (1.04 - 1.1)	0.18	0.23	0.28	All	3.79E-07	1.07 [1.04 - 1.10]	2.52E-05	1.13 [1.07 - 1.19]	1.98E-02	1.06 [1.01 - 1.12]	3.46E-04	1.09 [1.04 - 1.14]
rs7916968	10	749268	G	6.70E-06	1.09 (1.05 - 1.13)	0.03	0.41	0.09	All	6.70E-06	1.09 [1.05 - 1.13]	1.90E-01	1.05 [0.97 - 1.14]	5.62E-03	1.11 [1.03 - 1.20]	2.65E-02	1.08 [1.01 - 1.16]
rs4880487	10	1236883	T	3.33E-06	1.06 (1.04 - 1.09)	0.00	0.72	0.25	All	3.33E-06	1.06 [1.04 - 1.09]	9.57E-01	1.00 [0.95 - 1.05]	4.64E-02	1.06 [1.00 - 1.11]	1.93E-01	1.03 [0.98 - 1.08]
rs10904077	10	3710304	G	3.57E-05	1.1 (1.05 - 1.15)	0.00	0.62	0.06	All	3.57E-05	1.10 [1.05 - 1.15]	7.91E-01	1.01 [0.92 - 1.12]	6.55E-03	1.13 [1.04 - 1.24]	-	-
rs11816922	10	6964450	A	5.37E-06	1.1 (1.05 - 1.14)	0.01	0.47	0.08	All	5.37E-06	1.10 [1.05 - 1.14]	1.91E-03	1.15 [1.05 - 1.25]	2.06E-04	1.17 [1.08 - 1.27]	7.87E-03	1.11 [1.03 - 1.20]
rs827382	10	8759275	C	9.11E-08	1.07 (1.04 - 1.1)	0.00	0.68	0.25	All	9.11E-08	1.07 [1.04 - 1.10]	9.64E-04	1.09 [1.04 - 1.16]	4.76E-03	1.08 [1.02 - 1.13]	1.26E-04	1.09 [1.04 - 1.14]
rs10906466	10	13830271	A	7.83E-06	1.06 (1.03 - 1.09)	0.06	0.37	0.29	All	7.83E-06	1.06 [1.03 - 1.09]	1.35E-01	1.04 [0.99 - 1.10]	1.16E-03	1.09 [1.03 - 1.15]	-	-
rs11594111	10	14985412	G	1.37E-07	1.09 (1.06 - 1.12)	0.02	0.45	0.14	All	1.37E-07	1.09 [1.06 - 1.12]	6.29E-02	1.07 [1.00 - 1.15]	1.74E-03	1.11 [1.04 - 1.19]	1.25E-04	1.12 [1.06 - 1.18]
rs7068341	10	16674305	T	2.25E-06	1.09 (1.05 - 1.12)	0.00	0.75	0.12	All	2.25E-06	1.09 [1.05 - 1.12]	1.92E-01	1.05 [0.98 - 1.13]	2.42E-03	1.11 [1.04 - 1.20]	2.73E-02	1.07 [1.01 - 1.14]
rs2506155	10	33543185	A	3.30E-06	1.08 (1.04 - 1.11)	0.00	0.72	0.15	All	3.30E-06	1.08 [1.04 - 1.11]	5.57E-03	1.10 [1.03 - 1.17]	1.03E-02	1.09 [1.02 - 1.16]	-	-
rs6479874	10	52459361	T	2.77E-07	1.09 (1.05 - 1.12)	0.00	0.74	0.14	All	2.77E-07	1.09 [1.05 - 1.12]	1.82E-01	1.05 [0.98 - 1.12]	1.52E-02	1.08 [1.02 - 1.16]	2.87E-03	1.09 [1.03 - 1.15]
rs11000137	10	53351800	T	2.86E-06	1.07 (1.04 - 1.1)	0.00	0.70	0.17	All	2.86E-06	1.07 [1.04 - 1.10]	7.24E-02	1.06 [0.99 - 1.13]	2.02E-01	0.96 [0.91 - 1.02]	-	-
rs10763296	10	57444141	G	9.51E-06	1.05 (1.03 - 1.08)	0.00	0.75	0.38	All	9.51E-06	1.05 [1.03 - 1.08]	2.06E-01	1.03 [0.98 - 1.09]	-	-	-	-
rs7900239	10	80185087	A	8.74E-06	1.09 (1.05 - 1.13)	0.00	0.73	0.10	All	8.74E-06	1.09 [1.05 - 1.13]	3.36E-03	1.12 [1.04 - 1.22]	7.25E-02	1.07 [0.99 - 1.16]	2.33E-03	1.12 [1.04 - 1.20]
rs6583954	10	96524253	T	4.15E-06	1.08 (1.04 - 1.11)	0.00	0.74	0.14	All	4.15E-06	1.08 [1.04 - 1.11]	1.57E-02	1.08 [1.02 - 1.16]	1.16E-01	1.05 [0.99 - 1.12]	-	-
rs11188403	10	97365258	G	9.73E-06	1.06 (1.03 - 1.08)	0.00	0.63	0.32	All	9.73E-06	1.06 [1.03 - 1.08]	2.20E-02	1.06 [1.01 - 1.12]	-	-	8.00E-02	1.04 [1.00 - 1.09]
rs577969	10	100281166	T	4.11E-06	1.13 (1.07 - 1.19)	0.00	0.65	0.05	All	4.11E-06	1.13 [1.07 - 1.19]	1.59E-01	1.09 [0.97 - 1.23]	-	-	8.96E-04	1.17 [1.07 - 1.28]
rs1890185	10	104738708	G	3.61E-07	1.06 (1.04 - 1.08)	0.00	0.70	0.39	All	3.61E-07	1.06 [1.04 - 1.08]	1.60E-03	1.08 [1.03 - 1.13]	-	-	4.57E-02	1.04 [1.00 - 1.08]
rs10736184	10	107881592	C	1.68E-05	1.08 (1.04 - 1.12)	0.00	0.66	0.12	All	1.68E-05	1.08 [1.04 - 1.12]	9.57E-01	1.00 [0.93 - 1.07]	5.37E-01	1.02 [0.95 - 1.10]	1.17E-04	1.13 [1.06 - 1.20]
rs12355831	10	114192516	G	1.94E-06	1.09 (1.05 - 1.14)	0.00	0.71	0.11	All	1.94E-06	1.09 [1.05 - 1.14]	2.47E-03	1.13 [1.05 - 1.23]	-	-	-	-
rs705162	10	125241665	A	2.66E-06	1.06 (1.04 - 1.09)	0.00	0.68	0.26	All	2.66E-06	1.06 [1.04 - 1.09]	1.71E-04	1.11 [1.05 - 1.17]	-	-	1.99E-05	1.10 [1.05 - 1.15]
rs4929821	10	125814440	C	2.87E-04	1.05 (1.02 - 1.07)	0.00	0.70	0.34	All	2.87E-04	1.05 [1.02 - 1.07]	3.09E-01	0.97 [0.93 - 1.02]	1.42E-01	1.04 [0.99 - 1.09]	-	-
rs769160	10	127123254	G	6.12E-05	1.06 (1.03 - 1.09)	0.00	0.67	0.19	All	6.12E-05	1.06 [1.03 - 1.09]	9.95E-01	1.00 [0.94 - 1.06]	-	-	-	-
rs11017221	10	132058055	T	1.41E-07	1.09 (1.06 - 1.12)	0.15	0.25	0.13	All	1.41E-07	1.09 [1.06 - 1.12]	2.64E-03	1.12 [1.04 - 1.20]	-	-	1.29E-03	1.10 [1.04 - 1.16]
rs1334911	10	132235669	T	6.63E-05	1.08 (1.04 - 1.12)	0.00	0.69	0.10	All	6.63E-05	1.08 [1.04 - 1.12]	9.97E-01	1.00 [0.92 - 1.09]	1.90E-01	1.06 [0.97 - 1.14]	2.43E-02	1.08 [1.01 - 1.16]
rs7074195	10	132611226	G	1.75E-05	1.05 (1.03 - 1.08)	0.04	0.41	0.40	All	1.75E-05	1.05 [1.03 - 1.08]	4.32E-01	1.02 [0.97 - 1.07]	-	-	2.45E-02	1.05 [1.01 - 1.09]
rs4909945	11	10630315	T	1.86E-07	0.94 (0.92 - 0.96)	0.49	0.00	0.33	All	1.86E-07	0.94 [0.92 - 0.96]	4.72E-04	0.91 [0.87 - 0.96]	1.22E-04	0.91 [0.87 - 0.95]	5.65E-03	0.94 [0.90 - 0.98]
rs12365397	11	43192637	G	9.25E-06	0.95 (0.92 - 0.97)	0.97	0.00	0.32	All	9.25E-06	0.95 [0.92 - 0.97]	4.29E-02	0.95 [0.90 - 1.00]	1.16E-02	0.94 [0.89 - 0.99]	3.63E-02	0.95 [0.91 - 1.00]
rs10849061	12	4393717	T	2.06E-07	0.94 (0.92 - 0.96)	0.03	0.42	0.50	All	2.06E-07	0.94 [0.92 - 0.96]	1.12E-06	0.88 [0.84 - 0.93]	2.83E-04	0.92 [0.88 - 0.96]	2.46E-06	0.91 [0.87 - 0.94]
rs4759042	12	55663614	T	3.06E-06	0.95 (0.92 - 0.97)	0.70	0.00	0.37	All	3.06E-06	0.95 [0.92 - 0.97]	2.17E-01	0.97 [0.92 - 1.02]	1.61E-02	0.94 [0.90 - 0.99]	5.69E-04	0.93 [0.89 - 0.97]
rs11172113	12	55813550	C	*3.94E-19*	0.9 (0.88 - 0.92)	0.20	0.21	0.43	All	*3.94E-19*	0.90 [0.88 - 0.92]	1.15E-06	0.89 [0.84 - 0.93]	1.11E-05	0.90 [0.86 - 0.94]	*9.96E-11*	0.87 [0.84 - 0.91]
rs2723279	12	116757254	A	5.40E-06	0.94 (0.92 - 0.97)	0.52	0.00	0.31	All	5.40E-06	0.94 [0.92 - 0.97]	1.16E-02	0.93 [0.89 - 0.99]	9.60E-05	0.90 [0.86 - 0.95]	4.13E-02	0.95 [0.91 - 1.00]
rs285098	13	97625036	G	6.68E-06	0.95 (0.92 - 0.97)	0.62	0.00	0.33	All	6.68E-06	0.95 [0.92 - 0.97]	6.76E-04	0.92 [0.87 - 0.96]	3.20E-02	0.95 [0.90 - 1.00]	2.89E-04	0.92 [0.88 - 0.96]
rs4984499	15	94448797	T	7.75E-06	1.06 (1.03 - 1.08)	0.33	0.10	0.35	All	7.75E-06	1.06 [1.03 - 1.08]	1.78E-02	1.06 [1.01 - 1.12]	1.95E-02	1.06 [1.01 - 1.11]	6.41E-02	1.04 [1.00 - 1.09]
rs1437588	15	94610786	A	3.36E-06	0.95 (0.93 - 0.97)	0.73	0.00	0.48	All	3.36E-06	0.95 [0.93 - 0.97]	4.29E-02	0.95 [0.90 - 1.00]	1.19E-02	0.94 [0.90 - 0.99]	1.28E-02	0.95 [0.91 - 0.99]
rs4384658	18	9643171	G	6.68E-05	1.06 (1.03 - 1.09)	0.08	0.34	0.20	All	6.68E-05	1.06 [1.03 - 1.09]	9.79E-01	1.00 [0.94 - 1.06]	3.45E-01	1.03 [0.97 - 1.09]	2.76E-02	1.07 [1.01 - 1.13]
rs9947662	18	43114262	A	3.40E-06	0.94 (0.92 - 0.97)	0.54	0.00	0.27	All	3.40E-06	0.94 [0.92 - 0.97]	3.83E-03	0.92 [0.87 - 0.97]	8.44E-04	0.92 [0.87 - 0.96]	3.82E-03	0.94 [0.89 - 0.98]
rs4803455	19	46543349	C	7.66E-07	0.95 (0.93 - 0.97)	0.89	0.00	0.50	All	7.66E-07	0.95 [0.93 - 0.97]	4.06E-02	0.95 [0.91 - 1.00]	4.63E-03	0.94 [0.90 - 0.98]	3.16E-04	0.93 [0.89 - 0.97]
rs10915437	1	4082866	G	*2.81E-08*	0.86 (0.82 - 0.91)	0.11	0.47	0.36	Clinic	6.13E-04	0.96 [0.93 - 0.98]	*2.81E-08*	0.86 [0.82 - 0.91]	1.56E-04	0.90 [0.86 - 0.95]	9.77E-01	1.00 [0.96 - 1.05]
rs516243	1	10673019	A	9.21E-06	0.9 (0.86 - 0.94)	0.70	0.00	0.49	Clinic	1.59E-01	1.02 [0.99 - 1.04]	9.21E-06	1.11 [1.06 - 1.17]	1.14E-02	1.06 [1.01 - 1.11]	5.71E-02	1.04 [1.00 - 1.08]
rs6790925	3	30455089	T	*2.16E-08*	1.15 (1.1 - 1.21)	0.78	0.00	0.38	Clinic	8.74E-05	1.05 [1.02 - 1.07]	*2.16E-08*	1.15 [1.10 - 1.21]	1.54E-02	1.06 [1.01 - 1.11]	8.35E-05	1.09 [1.04 - 1.13]
rs4392363	3	67226528	A	1.28E-06	0.87 (0.82 - 0.92)	0.59	0.00	0.26	Clinic	1.70E-04	0.95 [0.93 - 0.98]	1.28E-06	0.87 [0.82 - 0.92]	8.69E-02	0.96 [0.91 - 1.01]	4.09E-02	0.95 [0.91 - 1.00]

Marker					Lowest p-value					All samples		Clinics		MA		MO	
SNP	Chr	Position[a]	Minor allele	Lowest p-value	OR (95% CI)	q/p-value	I^2	Minor allele frequency	Group or subgroup with the lowest p-value	P-value	OR	P-value	OR	P-value	OR	P-value	*OR*
rs13063872	3	71547025	A	9.25E-06	0.8 (0.73 - 0.89)	0.09	0.50	0.07	Clinic	7.25E-03	0.94 [0.90 - 0.98]	9.25E-06	0.80 [0.73 - 0.89]	3.62E-05	0.82 [0.75 - 0.90]	3.43E-02	0.91 [0.84 - 0.99]
rs6549438	3	72243923	A	3.72E-06	0.89 (0.85 - 0.94)	0.98	0.00	0.48	Clinic	3.41E-01	0.99 [0.97 - 1.01]	3.72E-06	0.89 [0.85 - 0.94]	2.05E-01	0.97 [0.93 - 1.02]	3.54E-01	0.98 [0.94 - 1.02]
rs11726563	4	46518391	C	8.24E-06	0.86 (0.81 - 0.92)	0.98	0.00	0.16	Clinic	1.32E-02	0.96 [0.93 - 0.99]	8.24E-06	0.86 [0.81 - 0.92]	4.72E-02	0.94 [0.88 - 1.00]	1.19E-01	0.96 [0.90 - 1.01]
rs4478147	4	87692800	G	2.18E-06	1.12 (1.07 - 1.18)	0.13	0.43	0.47	Clinic	2.69E-01	1.01 [0.99 - 1.03]	2.18E-06	1.12 [1.07 - 1.18]	1.06E-02	1.06 [1.01 - 1.11]	7.56E-01	0.99 [0.96 - 1.03]
rs4704296	5	75538166	G	5.66E-06	0.9 (0.85 - 0.94)	0.16	0.40	0.47	Clinic	9.24E-02	0.98 [0.96 - 1.00]	5.66E-06	0.90 [0.85 - 0.94]	1.89E-02	0.95 [0.91 - 0.99]	3.58E-01	0.98 [0.94 - 1.02]
rs17608902	5	127744466	A	1.33E-07	1.25 (1.15 - 1.35)	1.00	0.00	0.09	Clinic	1.14E-02	1.05 [1.01 - 1.09]	1.33E-07	1.25 [1.15 - 1.35]	8.59E-06	1.19 [1.10 - 1.28]	6.30E-01	1.02 [0.95 - 1.09]
rs17570583	5	171492136	A	8.78E-06	1.23 (1.12 - 1.35)	0.49	0.00	0.08	Clinic	4.25E-02	1.04 [1.00 - 1.09]	8.78E-06	1.23 [1.12 - 1.35]	1.11E-03	1.16 [1.06 - 1.26]	5.38E-02	1.08 [1.00 - 1.16]
rs602848	6	131488484	C	1.40E-06	1.18 (1.1 - 1.26)	0.60	0.00	0.16	Clinic	1.85E-03	1.05 [1.02 - 1.08]	1.40E-06	1.18 [1.10 - 1.26]	5.40E-06	1.16 [1.09 - 1.24]	3.58E-01	1.03 [0.97 - 1.08]
rs2186141	6	154046664	C	4.12E-06	0.89 (0.85 - 0.94)	0.53	0.00	0.44	Clinic	1.06E-02	0.97 [0.95 - 0.99]	4.12E-06	0.89 [0.85 - 0.94]	3.33E-02	0.95 [0.91 - 1.00]	3.47E-01	0.98 [0.94 - 1.02]
rs11777116	8	24100246	T	6.48E-08	1.27 (1.17 - 1.39)	0.30	0.18	0.08	Clinic	4.56E-03	1.07 [1.02 - 1.11]	6.48E-08	1.27 [1.17 - 1.39]	5.36E-05	1.19 [1.09 - 1.30]	1.34E-01	1.07 [0.98 - 1.16]
rs4738393	8	56762331	A	6.29E-06	1.15 (1.08 - 1.22)	0.20	0.33	0.33	Clinic	-	-	6.29E-06	0.87 [0.82 - 0.92]	2.03E-04	0.89 [0.84 - 0.95]	5.35E-03	0.93 [0.88 - 0.98]
rs400824	8	81520257	T	9.41E-06	0.89 (0.84 - 0.94)	0.31	0.16	0.30	Clinic	9.85E-02	0.98 [0.96 - 1.00]	9.41E-06	0.89 [0.84 - 0.94]	5.59E-02	0.95 [0.91 - 1.00]	2.39E-01	0.97 [0.93 - 1.02]
rs4493873	8	92144819	A	4.58E-06	1.14 (1.08 - 1.2)	0.06	0.59	0.36	Clinic	-	-	4.58E-06	0.88 [0.83 - 0.93]	-	-	-	-
rs12352279	9	668837	C	2.71E-06	1.25 (1.14 - 1.37)	0.42	0.00	0.07	Clinic	4.85E-02	1.05 [1.00 - 1.10]	2.71E-06	1.25 [1.14 - 1.37]	2.08E-03	1.15 [1.05 - 1.26]	1.90E-01	1.06 [0.97 - 1.16]
rs378363	9	9010223	C	7.53E-06	0.88 (0.83 - 0.93)	0.02	0.66	0.23	Clinic	9.26E-01	1.00 [0.97 - 1.03]	7.53E-06	0.88 [0.83 - 0.93]	1.07E-01	0.95 [0.90 - 1.01]	1.11E-01	0.96 [0.91 - 1.01]
rs6478241	9	118292450	A	*1.04E-09*	1.16 (1.11 - 1.22)	0.65	0.00	0.38	Clinic	4.43E-07	1.06 [1.04 - 1.09]	*1.04E-09*	1.16 [1.11 - 1.22]	5.09E-03	1.07 [1.02 - 1.12]	1.45E-07	1.12 [1.08 - 1.18]
rs2274491	10	97186968	T	6.67E-06	1.13 (1.07 - 1.19)	0.53	0.00	0.32	Clinic	-	-	6.67E-06	0.89 [0.84 - 0.94]	7.88E-04	0.92 [0.88 - 0.97]	-	-
rs12282928	11	48288604	G	8.84E-06	0.88 (0.83 - 0.93)	0.83	0.00	0.23	Clinic	7.21E-02	0.98 [0.95 - 1.00]	8.84E-06	0.88 [0.83 - 0.93]	1.02E-01	0.96 [0.91 - 1.01]	2.98E-01	0.98 [0.93 - 1.02]
rs10778070	12	99675606	A	9.84E-06	0.89 (0.85 - 0.94)	0.07	0.54	0.33	Clinic	4.75E-01	0.99 [0.97 - 1.01]	9.84E-06	0.89 [0.85 - 0.94]	5.88E-04	0.92 [0.88 - 0.96]	7.17E-01	0.99 [0.95 - 1.03]
rs17675602	16	81520264	T	5.46E-06	0.83 (0.76 - 0.9)	0.08	0.52	0.13	Clinic	-	-	5.46E-06	1.21 [1.12 - 1.32]	4.19E-01	1.03 [0.95 - 1.12]	3.75E-02	1.08 [1.00 - 1.16]
rs473518	18	18338672	T	8.61E-06	1.21 (1.11 - 1.32)	0.37	0.07	0.12	Clinic	-	-	8.61E-06	0.83 [0.76 - 0.90]	1.31E-02	0.90 [0.83 - 0.98]	1.61E-03	0.88 [0.82 - 0.95]
rs11874712	18	41942574	A	1.58E-07	1.15 (1.09 - 1.2)	0.29	0.19	0.41	Clinic	4.83E-02	1.02 [1.00 - 1.05]	1.58E-07	1.15 [1.09 - 1.20]	3.35E-03	1.07 [1.02 - 1.13]	1.06E-01	1.03 [0.99 - 1.08]
rs12480819	20	17540300	G	3.01E-06	1.15 (1.08 - 1.22)	0.72	0.00	0.24	Clinic	2.20E-02	1.03 [1.00 - 1.06]	3.01E-06	1.15 [1.08 - 1.22]	4.67E-02	1.06 [1.00 - 1.12]	1.55E-02	1.06 [1.01 - 1.11]
rs11906854	20	33847048	G	7.42E-06	1.17 (1.09 - 1.26)	0.74	0.00	0.14	Clinic	5.09E-02	1.03 [1.00 - 1.07]	7.42E-06	1.17 [1.09 - 1.26]	1.86E-01	1.05 [0.98 - 1.12]	1.25E-01	1.05 [0.99 - 1.12]
rs16985493	20	59726958	A	4.37E-06	1.37 (1.2 - 1.57)	0.64	0.00	0.04	Clinic	1.23E-01	1.05 [0.99 - 1.11]	4.37E-06	1.37 [1.20 - 1.57]	-	-	-	-
rs7528859	1	5583596	A	4.81E-06	1.12 (1.07 - 1.18)	0.19	0.29	0.40	MA	1.11E-02	1.03 [1.01 - 1.06]	2.34E-05	1.12 [1.06 - 1.18]	4.81E-06	1.12 [1.07 - 1.18]	7.24E-01	1.01 [0.96 - 1.05]
rs6693295	1	244289743	T	6.09E-06	1.14 (1.08 - 1.21)	0.04	0.50	0.19	MA	2.63E-03	1.05 [1.02 - 1.08]	9.05E-06	1.15 [1.08 - 1.23]	6.09E-06	1.14 [1.08 - 1.21]	2.59E-03	1.08 [1.03 - 1.14]
rs4345220	4	41334273	A	1.70E-06	1.14 (1.08 - 1.21)	0.34	0.11	0.44	MA	-	-	2.34E-02	0.94 [0.89 - 0.99]	1.70E-06	0.87 [0.83 - 0.92]	1.45E-02	0.94 [0.89 - 0.99]
rs2159222	7	15724525	T	8.03E-06	0.86 (0.81 - 0.92)	0.36	0.09	0.18	MA	3.58E-03	0.95 [0.92 - 0.98]	1.96E-03	1.11 [1.04 - 1.19]	8.03E-06	0.86 [0.81 - 0.92]	1.64E-01	0.96 [0.91 - 1.02]
rs1364402	7	136234903	C	3.62E-06	0.84 (0.78 - 0.9)	0.00	0.68	0.09	MA	1.34E-02	0.95 [0.92 - 0.99]	-	-	3.62E-06	0.84 [0.78 - 0.90]	2.27E-01	0.96 [0.90 - 1.03]
rs7015657	8	21011831	G	7.88E-08	1.15 (1.09 - 1.21)	0.63	0.00	0.30	MA	5.91E-02	1.02 [1.00 - 1.05]	1.18E-04	1.11 [1.05 - 1.18]	7.88E-08	1.15 [1.09 - 1.21]	7.96E-01	1.01 [0.96 - 1.05]
rs963265	9	72284355	C	1.06E-06	0.89 (0.85 - 0.93)	0.79	0.00	0.40	MA	8.09E-03	0.97 [0.95 - 0.99]	1.13E-02	0.94 [0.89 - 0.99]	1.06E-06	0.89 [0.85 - 0.93]	9.16E-01	1.00 [0.96 - 1.04]
rs10820447	9	98171865	T	5.84E-06	1.16 (1.09 - 1.23)	0.48	0.00	0.16	MA	5.09E-03	1.04 [1.01 - 1.08]	2.34E-03	1.11 [1.04 - 1.18]	5.84E-06	1.16 [1.09 - 1.23]	8.31E-02	1.05 [0.99 - 1.11]
rs2820651	10	1461765	A	4.02E-07	1.22 (1.13 - 1.31)	0.00	0.75	0.10	MA	4.13E-04	1.07 [1.03 - 1.11]	9.97E-04	1.15 [1.06 - 1.25]	4.02E-07	1.22 [1.13 - 1.31]	1.13E-02	1.09 [1.02 - 1.17]
rs1244181	10	8131383	A	1.71E-06	1.15 (1.09 - 1.22)	0.00	0.70	0.21	MA	-	-	9.15E-02	0.95 [0.89 - 1.01]	1.71E-06	0.87 [0.82 - 0.92]	-	-
rs10826566	10	29404703	A	3.56E-06	1.16 (1.09 - 1.23)	0.01	0.62	0.17	MA	6.42E-03	1.04 [1.01 - 1.08]	1.11E-03	1.11 [1.04 - 1.18]	3.56E-06	1.16 [1.09 - 1.23]	-	-
rs2986961	10	30127365	C	5.15E-07	1.14 (1.08 - 1.2)	0.00	0.73	0.26	MA	2.87E-03	1.04 [1.01 - 1.06]	8.18E-02	1.05 [0.99 - 1.11]	5.15E-07	1.14 [1.08 - 1.20]	2.61E-01	1.03 [0.98 - 1.07]
rs2137920	10	49899644	T	1.14E-06	1.15 (1.09 - 1.22)	0.00	0.72	0.18	MA	-	-	3.71E-03	1.09 [1.03 - 1.16]	1.14E-06	1.15 [1.09 - 1.22]	5.72E-03	0.93 [0.89 - 0.98]
rs12413355	10	117963587	A	2.86E-06	1.14 (1.08 - 1.2)	0.11	0.39	0.22	MA	-	-	4.11E-03	0.92 [0.87 - 0.97]	2.86E-06	0.88 [0.84 - 0.93]	-	-
rs2074193	12	46057696	G	4.94E-07	1.15 (1.09 - 1.21)	0.25	0.22	0.21	MA	8.92E-03	1.04 [1.01 - 1.06]	3.16E-03	1.09 [1.03 - 1.15]	4.94E-07	1.15 [1.09 - 1.21]	7.50E-01	0.99 [0.95 - 1.04]
rs17051917	13	34666789	T	8.59E-06	0.84 (0.78 - 0.91)	0.54	0.00	0.11	MA	8.89E-03	0.95 [0.92 - 0.99]	1.16E-02	0.90 [0.84 - 0.98]	8.59E-06	0.84 [0.78 - 0.91]	2.99E-01	0.97 [0.90 - 1.03]
rs11072158	15	68421763	A	2.86E-06	0.85 (0.79 - 0.91)	0.80	0.00	0.15	MA	1.32E-01	0.97 [0.94 - 1.01]	1.48E-03	0.89 [0.83 - 0.96]	2.86E-06	0.85 [0.79 - 0.91]	8.03E-01	0.99 [0.93 - 1.05]
rs7227892	18	44590700	T	2.10E-06	0.88 (0.84 - 0.93)	0.71	0.00	0.28	MA	3.66E-01	0.99 [0.96 - 1.01]	5.87E-04	0.91 [0.86 - 0.96]	2.10E-06	0.88 [0.84 - 0.93]	6.05E-01	0.99 [0.94 - 1.03]
rs12454023	18	54160584	T	8.01E-07	1.12 (1.07 - 1.18)	0.74	0.00	0.50	MA	5.18E-02	0.98 [0.96 - 1.00]	8.66E-04	0.92 [0.88 - 0.97]	8.01E-07	0.89 [0.85 - 0.93]	2.07E-01	0.97 [0.93 - 1.02]
rs973009	19	43866172	G	4.03E-06	0.85 (0.79 - 0.91)	0.55	0.00	0.13	MA	4.64E-05	0.93 [0.90 - 0.96]	4.19E-05	0.86 [0.81 - 0.93]	4.03E-06	0.85 [0.79 - 0.91]	6.27E-02	0.94 [0.89 - 1.00]
rs2076054	22	31162874	C	8.34E-06	0.89 (0.85 - 0.94)	0.39	0.06	0.26	MA	4.18E-02	0.97 [0.95 - 1.00]	1.24E-02	0.93 [0.89 - 0.99]	8.34E-06	1.12 [1.07 - 1.18]	8.05E-01	0.99 [0.95 - 1.04]
rs17301853	1	172819434	T	1.48E-06	0.86 (0.8 - 0.91)	0.02	0.57	0.12	MO	1.33E-02	0.96 [0.93 - 0.99]	6.56E-06	0.84 [0.78 - 0.91]	1.76E-01	0.95 [0.89 - 1.02]	1.48E-06	0.86 [0.80 - 0.91]
rs6695352	1	213021562	C	4.47E-06	1.1 (1.06 - 1.15)	0.01	0.64	0.50	MO	5.81E-04	0.96 [0.94 - 0.98]	2.53E-03	0.93 [0.88 - 0.97]	1.07E-02	0.94 [0.90 - 0.99]	4.47E-06	0.91 [0.87 - 0.95]
rs6733818	2	179854520	G	6.92E-06	1.1 (1.05 - 1.15)	0.38	0.06	0.40	MO	2.22E-04	1.04 [1.02 - 1.07]	3.39E-02	1.05 [1.00 - 1.11]	9.88E-01	1.00 [0.95 - 1.05]	6.92E-06	1.10 [1.05 - 1.15]
rs488884	5	29075878	T	1.13E-06	0.91 (0.87 - 0.94)	0.33	0.13	0.50	MO	4.03E-05	0.95 [0.93 - 0.98]	9.35E-03	0.94 [0.90 - 0.98]	1.32E-01	0.97 [0.92 - 1.01]	1.13E-06	0.91 [0.87 - 0.94]
rs16879308	5	51272083	T	2.30E-06	0.81 (0.74 - 0.88)	0.51	0.00	0.06	MO	2.93E-02	0.95 [0.91 - 0.99]	5.00E-03	0.86 [0.78 - 0.96]	3.34E-01	0.95 [0.87 - 1.05]	2.30E-06	0.81 [0.74 - 0.88]
rs7718446	5	145729728	G	3.98E-06	0.9 (0.86 - 0.94)	0.94	0.00	0.28	MO	1.41E-05	0.95 [0.92 - 0.97]	1.37E-02	0.94 [0.89 - 0.99]	5.26E-01	0.98 [0.94 - 1.03]	3.98E-06	0.90 [0.86 - 0.94]
rs10037055	5	176623885	T	4.55E-06	0.88 (0.84 - 0.93)	0.77	0.00	0.17	MO	1.16E-02	0.96 [0.94 - 0.99]	3.27E-02	0.93 [0.87 - 0.99]	9.08E-01	1.00 [0.94 - 1.07]	4.55E-06	0.88 [0.84 - 0.93]
rs9349379	6	13011943	G	*2.81E-10*	0.86 (0.82 - 0.9)	0.44	0.00	0.40	MO	*4.60E-08*	0.93 [0.91 - 0.96]	2.22E-06	0.89 [0.85 - 0.93]	3.16E-01	0.97 [0.93 - 1.03]	*2.81E-10*	0.86 [0.82 - 0.90]
rs3095267	6	29715025	C	8.53E-06	0.89 (0.85 - 0.94)	0.86	0.00	0.19	MO	5.82E-03	0.96 [0.93 - 0.99]	5.41E-01	0.98 [0.92 - 1.04]	2.73E-01	1.03 [0.98 - 1.09]	8.53E-06	0.89 [0.85 - 0.94]
rs9260632	6	30031269	T	9.98E-06	0.9 (0.86 - 0.94)	0.17	0.32	0.27	MO	3.86E-03	0.96 [0.94 - 0.99]	1.64E-01	0.96 [0.90 - 1.02]	6.32E-01	0.99 [0.93 - 1.04]	9.98E-06	0.90 [0.86 - 0.94]
rs3094117	6	30845465	C	1.54E-06	0.89 (0.85 - 0.94)	0.83	0.00	0.23	MO	9.47E-02	0.98 [0.95 - 1.00]	-	-	2.30E-01	1.03 [0.98 - 1.09]	1.54E-06	0.89 [0.85 - 0.94]
rs11759769	6	97171933	A	*1.58E-12*	1.18 (1.13 - 1.24)	0.73	0.00	0.22	MO	*1.34E-11*	1.10 [1.07 - 1.13]	4.22E-07	1.16 [1.09 - 1.23]	5.69E-04	1.10 [1.04 - 1.16]	*1.58E-12*	1.18 [1.13 - 1.24]
rs9490306	6	121858578	A	2.95E-07	1.18 (1.11 - 1.25)	0.39	0.06	0.14	MO	7.12E-06	1.08 [1.05 - 1.12]	6.27E-05	1.16 [1.08 - 1.25]	1.41E-02	1.09 [1.02 - 1.18]	2.95E-07	1.18 [1.11 - 1.25]
rs9399032	6	132930632	A	3.66E-06	1.1 (1.06 - 1.15)	0.25	0.22	0.33	MO	2.92E-03	1.04 [1.01 - 1.06]	8.64E-02	1.05 [0.99 - 1.10]	5.60E-01	0.99 [0.94 - 1.03]	3.66E-06	1.10 [1.06 - 1.15]
rs2877098	7	41709819	T	2.38E-06	0.9 (0.86 - 0.94)	0.21	0.28	0.34	MO	9.58E-03	0.97 [0.94 - 0.99]	1.35E-01	0.96 [0.90 - 1.01]	8.11E-01	1.01 [0.96 - 1.06]	2.38E-06	0.90 [0.86 - 0.94]
rs7810727	7	139238329	T	7.86E-06	1.11 (1.06 - 1.16)	0.55	0.00	0.31	MO	6.99E-02	1.02 [1.00 - 1.05]	3.06E-02	1.06 [1.01 - 1.12]	3.64E-01	1.02 [0.97 - 1.08]	7.86E-06	1.11 [1.06 - 1.16]
rs10504861	8	89617048	T	*1.17E-08*	0.86 (0.81 - 0.9)	0.75	0.00	0.16	MO	3.53E-03	0.96 [0.93 - 0.99]	1.87E-02	0.93 [0.87 - 0.99]	1.85E-01	0.96 [0.91 - 1.02]	*1.17E-08*	0.86 [0.81 - 0.90]
rs615552	9	22016077	C	3.64E-06	1.1 (1.06 - 1.14)	0.98	0.00	0.43	MO	4.59E-02	1.02 [1.00 - 1.05]	1.65E-01	1.03 [0.99 - 1.09]	3.06E-01	0.98 [0.93 - 1.02]	3.64E-06	1.10 [1.06 - 1.14]
rs7085387	10	59874608	G	1.63E-06	1.13 (1.08 - 1.19)	0.00	0.75	0.20	MO	-	-	8.99E-02	0.95 [0.90 - 1.01]	1.56E-02	0.93 [0.88 - 0.99]	1.63E-06	0.88 [0.84 - 0.93]
rs10997517	10	68549809	C	5.56E-06	1.14 (1.08 - 1.21)	0.01	0.66	0.23	MO	1.05E-04	1.06 [1.03 - 1.10]	5.15E-02	1.07 [1.00 - 1.14]	-	-	5.56E-06	1.14 [1.08 - 1.21]
rs7075426	10	88206382	A	6.02E-07	1.11 (1.06 - 1.15)	0.00	0.74	0.47	MO	2.68E-03	1.04 [1.01 - 1.06]	8.44E-02	1.04 [0.99 - 1.09]	5.42E-01	1.01 [0.97 - 1.06]	6.02E-07	1.11 [1.06 - 1.15]
rs17470570	10	100570113	G	2.80E-06	1.2 (1.11 - 1.3)	0.03	0.55	0.08	MO	1.20E-03	1.07 [1.03 - 1.12]	5.65E-02	1.10 [1.00 - 1.22]	4.44E-01	1.04 [0.94 - 1.14]	2.80E-06	1.20 [1.11 - 1.30]
rs11189853	10	100636171	G	1.54E-06	1.16 (1.09 - 1.23)	0.04	0.53	0.13	MO	6.44E-05	1.07 [1.03 - 1.11]	6.19E-02	1.07 [1.00 - 1.15]	1.02E-02	1.09 [1.02 - 1.17]	1.54E-06	1.16 [1.09 - 1.23]
rs17770015	10	115228754	G	3.22E-06	1.17 (1.1 - 1.25)	0.37	0.08	0.10	MO	-	-	4.87E-02	0.92 [0.85 - 1.00]	-	-	3.22E-06	1.17 [1.10 - 1.25]
rs7069346	10	124719866	T	3.17E-06	1.11 (1.06 - 1.16)	0.00	0.72	0.30	MO	1.00E-01	1.02 [1.00 - 1.04]	7.43E-01	0.99 [0.94 - 1.04]	5.27E-01	0.98 [0.94 - 1.03]	3.17E-06	1.11 [1.06 - 1.16]
rs1485395	12	52281344	C	7.17E-06	1.13 (1.07 - 1.19)	0.29	0.17	0.16	MO	9.66E-05	1.06 [1.03 - 1.09]	1.60E-04	1.13 [1.06 - 1.21]	4.35E-02	1.06 [1.00 - 1.13]	7.17E-06	1.13 [1.07 - 1.19]
rs11696973	20	53559916	T	8.32E-06	0.87 (0.82 - 0.92)	0.58	0.00	0.14	MO	4.24E-04	0.94 [0.91 - 0.97]	1.51E-01	0.95 [0.88 - 1.02]	8.97E-01	1.00 [0.94 - 1.08]	8.32E-06	0.87 [0.82 - 0.92]

OR – Odds ratio, CI – confidence interval, Clinics – analysis of the samples from headache clinics only, MA – migraine with aura, MO – migraine without aura. Genome-wide significant p-values highlighted in red and italics. Dashes indicate marker was not present in this dataset after filtering. Odds ratios shown for minor alleles.

Supplementary Table 5. Association results at previously reported migraine GWAS loci

		All studies				Excluding original studies			
SNP	Gene	All	Clinic-based	MA only	MO only	All	Clinic studies	MA only	MO only
rs1835740	*MTDH* [a]	0.12217	1.44E-04	1.49E-04	0.447029	0.883	0.754	0.594	0.447
rs10166942	*TRPM8* [b]	2.91E-12	6.39E-09	1.69E-06	1.21E-10	1.12E-04	2.73E-05	0.051	4.99E-07
rs2651899	*PRDM16* [b]	4.34E-14	3.06E-04	2.54E-04	1.56E-05	8.10E-08	0.007	0.417	0.001
rs11172113	*LRP1* [b]	3.94E-19	1.15E-06	1.11E-05	9.96E-11	4.08E-12	4.26E-04	0.005	2.74E-07
rs3790455	*MEF2D* [c]	1.91E-08	1.35E-07	0.123199	1.42E-05	4.12E-05	0.036	0.123	0.139
rs7640543	*TGFBR2* [c]	1.32E-05	1.54E-06	0.041888	1.05E-05	1.96E-03	0.021	0.042	0.025
rs9349379	*PHACTR1* [c]	4.60E-08	2.22E-06	0.316306	2.81E-10	8.92E-05	0.089	0.316	1.56E-04
rs6478241	*ASTN2* [c]	4.43E-07	1.04E-09	0.005093	1.45E-07	2.08E-04	1.12E-04	5.09E-03	3.07E-03

MA – migraine with aura. MO – migraine without aura. P-values for frequentist additive tests shown. Excluding original studies refers to the part of the study data independent of the original reports.
[a] Excluding the Finnish, German and Dutch MA studies[1].
[b] Excluding the Women's Genome Health Study and the Finnish, German and Dutch MA studies[3].
[c] Excluding the German and Dutch MO studies[4].

Supplementary Table 6. SNP with the lowest P value at each locus in the analysed subgroups

						p-values				
SNP	Chr	Position[a]	Location	Minor allele	Gene[b]	All	Clinics	Population	MA	MO
rs2651899	1	3,073,572	Genic	C	*PRDM16*	**4.34E-14**	3.06E-04	**3.30E-11**	2.54E-04	1.56E-05
rs10915437	1	4,082,866	Intergenic	G	*near AJAP1*	6.13E-04	**2.81E-08**	3.79E-01	1.56E-04	9.77E-01
rs12134493	1	115,479,469	Intergenic	A	*near TSPAN2*	**4.79E-14**	1.19E-05	**4.46E-10**	6.19E-04	5.29E-08
rs2274316	1	154,712,866	Genic	C	*MEF2D*	**1.42E-08**	1.43E-07	3.14E-04	8.66E-02	2.31E-05
rs6741751	2	234,492,400	Genic	A	*TRPM8*	**9.11E-14**	**1.09E-08**	**4.97E-08**	1.03E-07	**8.64E-11**
rs6790925	3	30,455,089	Intergenic	T	*near TGFBR2*	8.74E-05	**2.16E-08**	1.35E-01	1.54E-02	8.35E-05
rs9349379	6	13,011,943	Genic	G	*PHACTR1*	**4.60E-08**	2.22E-06	4.15E-04	3.16E-01	**2.81E-10**
rs11759769	6	97,171,933	Genic	A	*FHL5*	**1.34E-11**	4.22E-07	6.35E-07	5.69E-04	**1.58E-12**
rs4379368	7	40,432,725	Genic	T	*c7orf10*	**1.07E-09**	7.18E-07	2.15E-05	1.24E-03	5.81E-08
rs10504861	8	89,617,048	Intergenic	T	*near MMP16*	0.003528	1.87E-02	0.042	0.185	**1.17E-08**
rs17220352	9	118,287,880	Genic	G	*ASTN2*	**5.46E-09**	1.16E-07	1.83E-04	1.10E-02	1.49E-07
rs6478241	9	118,292,450	Genic	A		4.43E-07	**1.04E-09**	1.58E-02	5.09E-03	1.45E-07
rs11172113	12	55,813,550	Genic	C	*LRP1*	**3.94E-19**	1.15E-06	**4.50E-14**	1.11E-05	**9.96E-11**

Chr – chromosome, Clinics – only cases recruited from headache clinics used, Population – samples from population cohorts, MA – migraine with aura, MO – migraine without aura. Bold text indicates genome-wide significant results. N.B. analysis for MA and MO are not independent, because they use some overlapping controls.

Supplementary Table 7. Odds ratios for the SNP with the lowest P value at each locus in the analysed subgroups

SNP	Chr	Position[a]	Location	Minor allele	Gene[b]	Odds ratios All	Clinics	Population	MA	MO
rs2651899	1	3,073,572	Genic	C	*PRDM16*	1.09 [1.07 - 1.11]	1.09 [1.04 - 1.15]	1.09 [1.06 - 1.12]	1.09 [1.04 - 1.14]	1.09 [1.05 - 1.14]
rs10915437	1	4,082,866	Intergenic	G	*near AJAP1*	0.96 [0.93 - 0.98]	0.86 [0.82 - 0.91]	0.99 [0.96 - 1.02]	0.90 [0.86 - 0.95]	1.00 [0.96 - 1.05]
rs12134493	1	115,479,469	Intergenic	A	*near TSPAN2*	1.14 [1.10 - 1.18]	1.18 [1.10 - 1.27]	1.13 [1.09 - 1.17]	1.13 [1.05 - 1.21]	1.18 [1.11 - 1.26]
rs2274316	1	154,712,866	Genic	C	*MEF2D*	1.07 [1.05 - 1.10]	1.14 [1.09 - 1.20]	1.05 [1.02 - 1.08]	1.04 [0.99 - 1.10]	1.10 [1.05 - 1.15]
rs6741751	2	234,483,608	Genic	A	*TRPM8*	0.87 [0.84 - 0.90]	0.79 [0.73 - 0.86]	0.89 [0.85 - 0.93]	0.81 [0.75 - 0.88]	0.80 [0.75 - 0.86]
rs6790925	3	30,455,089	Intergenic	T	*near TGFBR2*	1.05 [1.02 - 1.07]	1.15 [1.10 - 1.21]	1.02 [0.99 - 1.05]	1.06 [1.01 - 1.11]	1.09 [1.04 - 1.13]
rs9349379	6	13,011,943	Genic	G	*PHACTR1*	0.93 [0.91 - 0.96]	0.89 [0.85 - 0.93]	0.95 [0.92 - 0.98]	0.97 [0.93 - 1.03]	0.86 [0.82 - 0.90]
rs11759769	6	96,967,075	Genic	A	*FHL5*	1.10 [1.07 - 1.13]	1.16 [1.09 - 1.23]	1.08 [1.05 - 1.11]	1.10 [1.04 - 1.16]	1.18 [1.13 - 1.24]
rs4379368	7	40,432,725	Genic	T	*c7orf10*	1.11 [1.08 - 1.15]	1.20 [1.12 - 1.29]	1.09 [1.05 - 1.13]	1.12 [1.05 - 1.20]	1.19 [1.12 - 1.27]
rs10504861	8	89,617,048	Intergenic	T	*near MMP16*	0.96 [0.93 - 0.99]	0.93 [0.87 - 0.99]	0.97 [0.93 - 1.00]	0.96 [0.91 - 1.02]	0.86 [0.81 - 0.90]
rs17220352	9	118,287,880	Genic	G	*ASTN2*	1.08 [1.05 - 1.11]	1.16 [1.10 - 1.23]	1.06 [1.03 - 1.09]	1.14 [1.09 - 1.20]	1.07 [1.02 - 1.14]
rs6478241	9	118,292,450	Genic	A		1.06 [1.04 - 1.09]	1.16 [1.11 - 1.22]	1.03 [1.01 - 1.06]	1.07 [1.02 - 1.12]	1.12 [1.08 - 1.18]
rs11172113	12	55,813,550	Genic	C	*LRP1*	0.90 [0.88 - 0.92]	0.89 [0.84 - 0.93]	0.91 [0.88 - 0.93]	0.90 [0.86 - 0.94]	0.87 [0.84 - 0.91]

Chr – chromosome, Clinics – only cases recruited from headache clinics used, Population – samples from population cohorts, MA – migraine with aura, MO – migraine without aura. The intensity of the shading corresponds to the magnitude of the odds ratio. Shades of blue indicate lowered OR and red increased OR. All odds ratios standardized for the minor allele. N.B. analysis for MA and MO are not independent, because they use some overlapping controls.

Supplementary Table 8. SNPs at the loci significantly associated with migraine expected to affect transcription factor binding sites

Chr	Position	SNP	RegulomeDB score
6	96,853,578	rs6924957	eQTL + TF binding / DNase peak
12	57,533,689	rs4759277	eQTL + TF binding / DNase peak
12	57,534,469	rs1466535	eQTL + TF binding / DNase peak
1	156,446,449	rs12131289	TF binding + matched TF motif + matched DNase Footprint + DNase peak
12	57,532,748	rs1385526	TF binding + matched TF motif + matched DNase Footprint + DNase peak
1	3,087,372	rs10909887	TF binding + any motif + DNase Footprint + DNase peak
1	156,446,241	rs2274316	TF binding + any motif + DNase Footprint + DNase peak
2	234,821,529	rs11563063	TF binding + any motif + DNase Footprint + DNase peak
8	89,566,902	rs1352318	TF binding + matched TF motif + DNase peak

List of SNPs at migraine-associated loci expected to change transcription factor binding according to the ENCODE data at RegulomeDB (http://regulome.stanford.edu; showing SNPs with RegulomeDB scores of 2f or higher). All basepair positions are given in build 36/hg18. Chr – chromosome. TF – transcription factor.

Supplementary Table 9. Heterogeneity analysis comparing the results from a fixed effects model and a random effects model between MA and MO

					OR			p-value				
Chr	Position	SNP	EA	EAF	All	MA	MO	MA	MO	FEM	REM	Het.
6	13,011,943	rs9349379	G	0.40	1.10	1.03	1.17	0.32	2.81E-10	1.30E-07	1.33E-09	3.21E-04
6	29,715,025	rs3095267	C	0.19	0.95	1.03	0.89	0.27	8.53E-06	8.69E-03	2.69E-05	1.70E-04
6	30,845,465	rs3094117	C	0.23	1.05	0.97	1.12	0.23	1.54E-06	4.79E-03	4.62E-06	4.64E-05
8	21,011,831	rs7015657	G	0.30	0.94	0.87	0.99	7.88E-08	0.80	1.90E-04	5.18E-07	1.08E-04
9	22,016,077	rs615552	C	0.43	1.04	0.98	1.10	0.31	3.64E-06	5.07E-03	1.29E-05	1.30E-04
9	72,284,355	rs963265	C	0.40	0.95	0.89	1.00	1.06E-06	0.92	1.07E-03	6.57E-06	2.90E-04
12	46,057,696	rs2074193	G	0.21	1.06	1.15	0.99	4.94E-07	0.75	1.87E-03	3.01E-06	7.31E-05

EA – effect allele. EAF – effect allele frequency. MA – migraine with aura. MO – migraine without aura. FEM – fixed effects model. REM – random effects model. Het. – *P* value for the heterogeneity test.

Supplementary Table 10. Pathways associating in the gene set enrichment analysis (GSEA) with a FDR *P* value<0.2 in the MAGENTA analysis

Phenotype	Pathway	GSEA p-value	FDR	Expected	Observed
All migraine	-	-	-	-	-
Clinics only	oxygen binding	6.70E-05	1.05E-01	8	19
MO only	glycogen catabolic process	5.00E-04	1.02E-01	2	6
MO only	traversing start control point of mitotic cell cycle	6.00E-04	1.97E-01	2	6
MA only	nervous system development	1.50E-05	1.83E-01	84	117

Showing only pathways associated with a gene set enrichment analysis (GSEA) *P* value less than 0.2. Expected – expected number of genes below FDR threshold in the pathway. Observed – observed number of genes below the FDR threshold in the pathway. MO – migraine without aura. MA – migraine with aura.

Supplementary Table 11. Genes highlighted by DAPPLE analysis due to significant connectivity

Gene	P-value
SLC43A2	0.001997
TRIM28	0.001997
CDC5L	0.001997
C7orf10	0.001997
ZNF709	0.003992
ATP5B	0.005979
ZNF311	0.009945
SRSF3	0.009945
SMYD5	0.011922
SLC35F2	0.011934
KRT10	0.013896
LRRC47	0.015873
C19orf29	0.015888
DHX16	0.021857
GEMIN4	0.023714
TPPP3	0.035429

Supplementary Table 12. Results of the GRAIL analysis

GENE	GRAIL p-value	Similar genes (overall rank)
PHACTR1	0.001034526	*NRP1(4), C8orf79(68), ASTN2(79), FRMD4A(93), ARL15(94), PPP1R11(130), PTPRD(172), FARP1(186), RBM39(195)*
AS3MT	0.013316371	*SMYD3(12), CDKN2B(85), SUV39H2(92), CYP2C18(110), CYP2C8(178)*
USMG5	0.018108738	*ATP5A1(4), FAM49B(70), KIAA0776(114)*
RASSF5	0.020942561	*RSU1(22), KSR2(41), CASZ1(123), SMYD3(162), KANK1(184), CDKN2B(192)*
C10orf88	0.022462479	*FAM49B(12), ARL15(111), SNX24(151)*

Results of the GRAIL analysis, detailing the genes at each significant locus with the most significantly associated other genes based on text-mining of literature abstracts.

Supplementary Note

Comparing the subgroup results

Since an extensive discussion in the migraine field has concerned whether MA and MO are distinct subtypes or part of the same spectrum (e.g. [16] and [17]), we conducted two exploratory analyses between the two subgroups. As fairly robust study sizes from both migraine subtypes were available, we conducted a heterogeneity analysis[18] at the 146 reported loci (see **Methods**) to look for quantitative differences between the two main types of migraine, MA and MO. By requiring a significance threshold consistent with multiple hypothesis testing ($p < 0.00034$ [=0.05/146 tests]),

significant heterogeneity *P* values between MA and MO were subsequently observed at only seven loci. At these loci, employing a random effects model produced more significant *P* values than the fixed effects model (**Supplementary Table 9**). In addition, we performed an analysis comparing the effect sizes between the MO and MA subgroups. Of the 146 index SNPs for the 12 reported loci, 135 were present in both subgroups and 122 had the same effect direction. Of these 122 SNPs, 62 (51%) had a larger effect size in MA cases compared to MO cases, which does not differ significantly from that expected by chance (two-tailed binomial test $P = 0.928$). While some confounding can be introduced by the different level of difficulty in accurately diagnosing the two forms of migraine, and though significant heterogeneity was observed at a few loci, neither analysis points to clear differences between the two subtypes across these 146 loci. At the 12 significant loci, with the exception of *PHACTR1* (where significant heterogeneity was observed), and near *AJAP1* (where effect size is stronger in the MA group, but the heterogeneity test is not significant, heterogeneity $P = 0.004$), it similarly appears that for common risk variants, MO and MA appear to have a similar genetic loading in terms of liability. However, unlike in the secondary loci, among the 12 significant loci a trend for higher effect sizes in the MO group can be observed, leading to the difference between observed significant loci (**Fig. 2c, d**).

A heterogeneity analysis was also conducted to examine potential effect heterogeneity between men and women. None of the 146 index SNPs displayed genome-wide significant gender heterogeneity (data not shown). The strongest gender disparity was observed at marker rs12153243 on 5q31, with a gender heterogeneity *P* value of 0.004. For each locus where significant heterogeneity between MA and MO was observed, the locus was associated to MO but not MA.

The finding that the index SNPs in the identified loci have more extreme effect sizes in the clinical compared with population-based cohorts (**Supplementary Fig. 5, Supplementary Table 7**) may reflect enrichment of these variants in particularly severe and possibly differentiated subclasses of migraine cases that may be referred for clinic-based care. However, while the benefits of more in-depth phenotyping of the clinic-originated cases (who have, for example, been ascertained for familial aggregation of migraine) may be useful in future studies addressing rare variation, especially in individuals without the identified common genetic risk factors, the relative uniformity of effect sizes across both clinic- and population-based studies suggests that a questionnaire-based approach on larger numbers may yield greater short-term gain for genetic studies of migraine. This agrees with a number of previous studies where a high degree of specificity and sensitivity for diagnosing migraine via well-designed questionnaires (e.g. FMSQ(fs)[19], DMQ3[20], and the Women's Health Study questionnaire[21]) has been demonstrated. In the participating study samples in general, self-reported

migraine has had high concordance when compared to diagnosis made by a headache specialist (see **Supplementary Note** for additional details). However, the lack of findings in the migraine with aura subgroup may suggest that accurately diagnosing aura based on questionnaire data is less successful.

Pathway analyses

We further analysed all 146 loci with a *P* value < 1 x 10^{-5} using pathway analysis methods (MAGENTA Gene Set Enrichment Analysis[22]) as well as protein-protein interactions (DAPPLE[23]) and text-mining (GRAIL[24]). For all pathway analyses, the whole interval containing SNPs with *P* values below the reporting threshold (1 x 10^{-5}), plus 50 kb into each direction, was taken forward, as recommended by the analysis packages. In the MAGENTA analysis, no significant network enrichment was observed (**Supplementary Table 10**), as multiple non-overlapping pathways were among the most associated results, suggesting the genetic susceptibility to migraine is not mediated by any single known pathway. The pathway with the lowest *P* value was "Nervous system development", with an FDR-corrected *P* value of 0.183. In the DAPPLE analysis, 13 individual genes were significantly more connected to other genes in the reported loci than we would expect by chance (FDR<0.05), including *ATP5B* (also identified in the eQTL analysis);(**Supplementary Table 11)**. Additionally, two of the significant genes (*LRP1* and *MMP16*) show strong evidence of direct connectivity (**Supplementary Fig. 10a**). The overall network was not statistically significant (Seed direct degrees *P* value 0.78, indirect degrees *P* value 0.07; **Supplementary Fig. 10b**). While DAPPLE has successfully identified pathways involved in e.g. common autoimmune disorders[23,25], it is possible that the coverage of protein-protein interaction data in the InWeb dataset[26] representing neuronal pathways involved in migraine is currently inadequate to map these molecular processes. In the GRAIL analysis, five genes (e.g. *PHACTR1*, which included *ASTN2* among the most similar genes) showed significant similarity to genes from other reported loci (**Supplementary Table 12**).

Cohort Descriptions

Participating population-based cohorts

ALSPAC

The Avon Longitudinal Study of Parents and Children (ALSPAC)[27] 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".

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 1.0×10^{-6}. Additionally SNPs with a minor allele frequency of less than 1% were removed. Samples were excluded if they displayed more than 5% missingness, had indeterminate X chromosome heterozygosity or extreme autosomal heterozygosity. Samples showing evidence of population stratification were identified by multidimensional scaling of genome-wide IBS pairwise distances using the four HapMap populations as a reference, and then excluded. Cryptic relatedness was assessed, in PLINK, using a 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.

8,340 subjects and 526,688 SNPs passed these quality control filters. We imputed autosomal SNPs against the HapMap CEU population (release 22) using MaCH (v1.0.16). A combination of MaCH and Minimac (v4.4.3) was used to impute X chromosome genotypes against the HapMap CEU population (release 21). Genome-wide SNP data was analysed 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.

Australian Twin cohort

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 HapMap2 (release 22) using the MaCH program[28]. 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[29]. For a detailed description of the QIMR 19K GWA cohort, including QC and imputation methodology, see Medland et al. (2009)[30].

British 1958 Birth Cohort (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[31]. 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[32], from which a DNA collection was established as a nationally representative reference panel (http://www.b58cgene.sgul.ac.uk/). Three non-overlapping subsets of the DNA collection were genotyped as part of case-control studies by the Wellcome Trust Case-Control Consortium[33], the Type 1 Diabetes Genetics Consortium[34] and the GABRIEL asthma genetics consortium[35]. Imputations were performed using the HapMap release 21 CEU haplotypes by the MACH software[28]. Within-cohort logistic regression analyses for migraine were performed using ProbAbel[36].

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[15], 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.

ERF

The Erasmus Rucphen Family (ERF) genetic isolate 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 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[37]. Migraine was diagnosed using a validated three-stage screening method that included a telephone interview[38], which was based on the ICHD-II criteria[15]. The screening procedure is described in detail by Stam and colleagues[39]. In brief, all participants filled out a concise screening questionnaire on headache and aura symptoms. Then, screen-positives received a detailed extended questionnaire. Finally, screen-

positives were telephone interviewed to further clarify their clinical symptoms by trained physicians who are experienced in diagnosing migraine patients. Final diagnosis was only made after the 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. The genome-wide association (GWA) study for migraine includes data from 1546 ERF participants; 330 migraineurs (189 MO and 141 MA) 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.

FinnTwin

The FinnTwin16 subsample included Finnish twins born 1975-79 and migraine was measured by a postal questionnaire (wave 4) when the twins were, on average, 25 years of age (range 22-27 years)[40]. The twins were asked whether a physician had ever told them they had migraine. The type of migraine, symptoms and medication were not asked. The FinnTwin12 subsample included twins born in 1983–1987 and migraine was assessed as part of a structured interview by trained research nurses during a day-long clinical study when they were, on average, 22.4 years of age (range 20-25 years)[41]. They were asked whether they had migraine, whether the diagnosis was made by a health professional and the year it had been made. Medications were asked and coded. Migraine subtypes were not investigated.

HUNT

The 1,608 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[42], 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[42]. The 1,097 Norwegian control samples were recruited from the same HUNT population study (see description above), and included 389 samples previously genotyped as part of a GWA study of lung cancer[43] and 572 samples genotyped as part of an ongoing GWA study of pre-eclampsia, in addition to 136 control samples genotyped for the present study. Participants fulfilling criteria for migraine were excluded from the control population.

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[44,45]. Migraine was assessed with a questionnaire that provided information on the symptoms listed in the ICHD-II criteria. The questionnaire started with a screening question ("do you ever experience headache attacks, for instance migraine?"). Individuals screening positive subsequently 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[15]. Details on this procedure can be found in previous work[46].

Genotyping was performed on the Affymetrix 6.0 (N=298), Affymetrix Perlegen 5.0 (N=3,697), Illumina 370 (N=290), Illumina 660 (N=1,439) and Illumina Omni Express 1M (N=455) platforms. Calls were made with the platform specific software (Genotyper, Beadstudio). Per platform the quality control thresholds for SNPs were MAF > 1%, HWE > 0.00001, call rate >95% and

0.30 < heterozygosity < 0.35. Samples were excluded from the data if their expected sex and IBD status did not match, or if the genotype missing rate was above 10%. For each platform all SNPs were aligned to the positive strand of the HapMap 2 Build 36 release 24 CEU reference set. The alignment was checked using individuals and family members tested on multiple platforms. SNPs were excluded per platform if allele frequencies differed more than 15% with the reference set and/or the other platforms. The data of the platforms were subsequently merged into a single dataset (N=5,856). This merged set was imputed against the reference set using IMPUTE v2. After imputation, genotype dosage was calculated if the highest genotype probability was above 90%. Badly imputed SNPs were removed based on HWE < 0.00001, proper info < 0.40, MAF < 1%, allele frequency difference > 0.15 against reference. Among the NTR participants, related individuals were included in the sample. For the present analyses, unrelated individuals were selected from the sample by including one individual from each NTR family. To maximize the number of migraine cases, the individual with (the most severe) migraine was selected from families with one or more migraineurs. Furthermore, a subset of the NTR/NESDA cohort was originally genotyped for a study on major depressive disorder (MDD)[47], and therefore included MDD patients. Because of the known comorbidity of migraine and MDD, all MDD patients were excluded from the current analyses. The resulting selection included 282 migraine cases (42 males [15%], 240 females [85%], mean age 44.7, SD = 13.3) and 2,260 controls (1,012 males [45%], 1,248 females [55%], mean age 49.3, SD = 14.2). The association analyses were performed using SNPTEST (v 2.1.1)[48].

NFBC

Mothers expected to give birth in the two Northern provinces of Oulu and Lapland in 1966 were enrolled in the NFBC1966[49] (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[50]. Migraine was assessed based on the health questionnaire survey provided by the participants. The study was originally genotyped for the study[51].

Rotterdam

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[52]. 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 3,932 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).[53]

Twins UK

The study population comprised 4,809 individuals (428 males and 4,381 females) from the TwinsUK Adult Twin Registry[54]. 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[54]. 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. Migraine status was ascertained through questionnaires. 703 of the study participants fulfilled the IHS definition of migraine[15], and of these, 235 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[55] version 2 using HapMap2, release 22, combined CEU+YRI+ASN panels and the 610Q data was use as a reference panel for the HumanHap300 data. The imputed genotype data was analyzed with GWAF (Genome-wide association analyses for family data) to test for SNP association with adjustments for age[56]. We used the equations option for logistic regression via generalized estimating of the GWAF software, which incorporates familial clustering.

Women's Genome Health Study

The Women's Genome Health Study (WGHS) is a prospective cohort of initially apparently healthy, female US health care professionals who were at least 45 years old at baseline, representing 72% of 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 randomized controlled trial beginning in 1992-1994 testing the effect of vitamin E and low dose aspirin in the primary prevention of cancer and cardiovascular disease. Information related to health and lifestyle was collected by questionnaire at baseline and during follow-up.

Genotyping in the WGHS sample was performed using the HumanHap300 Duo ''+'' chips or the combination of the HumanHuman300 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 v3.3 software (Illumina, San Diego, CA) for at least 98% of the SNPs. A subset of 23,294 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 v1.06[29]. In the final dataset of these individuals, 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 the final 23,294 individuals of verified European ancestry, genotypes for a total of 2,608,509 SNPs were imputed from the experimental genotypes and LD relationships implicit in the HapMap release 22 CEU samples.

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[57]. The first cross-sectional study was conducted in the year 1980 in five different centres. 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[57]. Genotype imputation was performed using IMPUTE[55] 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.

Clinic-based studies

Finnish MA study

1,032 Finnish patients having either migraine with aura (MA) or migraine with and without aura (MA/MO) were collected nationwide from headache clinics. 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 ($FMSQ_{FS}$)[19] and all fulfilled the current International Headache Society diagnostic criteria (ICHD-II[15]) for MA. In cases of insufficient or conflicting information, a follow-up interview was performed by telephone.

1,862 Finnish control subjects were obtained from the Health2000 study (http://www.terveys2000.fi/julkaisut/baseline.pdf) and 1,651 controls from the Helsinki Birth Cohort study[58].

Written informed consent was obtained from all participants, and the study was approved by the Helsinki University Central Hospital local ethics committee.

German MA study

The Kiel/Ulm sample consists of 758 German patients with MA. The patients were recruited at a single tertiary headache center in Northern Germany (Pain Clinic, Kiel), and first collected at the Universities of Bonn and Cologne. All patients were diagnosed as having MA according to the ICHD-II[15] by experienced neurologists with a specialization in headache disorders, as described previously[59]. The detailed migraine anamnesis was obtained either by face-to-face interviews or by telephone interviews. Interviews were standardized by using a comprehensive migraine questionnaire. All patients gave their written informed consent for participating in the study. The study was approved by the local university ethics committees.

The Munich sample consists of 239 cases with MA. The patients were recruited at the Department of Neurology at the Klinikum Großhadern of the Ludwig-Maximilians-University, Munich, Germany. Both in- and outpatients were recruited. All cases were personally examined by a headache specialist. For establishing the diagnosis of MA, cases were phenotyped with the help of a German translation of the Finnish validated headache questionnaire[19]. Whenever the information from the questionnaire was insufficient or conflicting, an additional telephone interview was performed. Information was thus obtained on all aspects of the ICHD-II[15] criteria as well as on various other aspects (such as age at onset, prodromal symptoms, triggers, acute and prophylactic medication, family history, general past medical history, co-morbidity, place of birth). Written informed consent was obtained from all participants, and the study was approved by the local ethics committee.

German controls were obtained from the PopGen study[60] (n=661), all genotyped on the Illumina 550K platform. In addition, 444 controls were obtained from Illumina iControlDB by querying all Caucasian samples genotyped on the Illumina 550K platform on June 30th, 2008 and filtering these samples based on stratification as observed from multidimensional scaling plots of all existing German samples, and keeping only those identified as being of German descent.

German MO study

The German sample of 1,208 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

$FMSQ_{FS}$[19]. 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[15] 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[61] (n = 834) as well as from the GSK[62] (n = 861), the MPIPSYKL (n = 489) and the HNR[63] (n = 380) studies.

LUMINA MA study

The Dutch MA GWAS contains 879 Dutch MA patients that were available from the clinic-based Leiden University Migraine Neuro Analysis (LUMINA) study. Of the 820 MA cases, 146 (18%) were male and 674 (82%) 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[38]. 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[15]. 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)[64]. A subset of the patients was asked to participate upon visiting the outpatient clinic. Population-matched controls (n=4,774) were obtained from the Rotterdam Study I[53].

LUMINA MO study

The Dutch MO GWAS contains 1,118 Dutch MO patients, of which 159 (14%) were male and 959 (86%) 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[38] 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)[64]. A subset of the patients was asked to participate upon visiting the outpatient clinic. Population-matched controls (n=2,016) were obtained from the Rotterdam Study II (RSII)[53].

Analysis of brain eQTL data

The expression quantitative trait loci (eQTL) analysis sample was composed of 475 neurologically normal Caucasian subjects from the United States and the United Kingdom. Tissue from the cerebellum (CRBLM) and frontal cortex (FCTX) were obtained for all subjects (950 tissue samples). Genotyping was performed from the cerebellum tissue samples using the Illumina HumanHap550 v3, Human610-Quad v1, Human660W-Quad v1 and HumanOmni1-Quad v1 Infinium Beadchips. Expression profiling for mRNA transcripts was assayed using the Illumina HumanHT-12 v3 Expression Beadchip. Processing and analysis of these data were performed in a manner similar to methods previous described for studies including these subjects[65-67] (GEO # GSE36192, dbGaP # phs000249).

Genotype and expression based filtering included subject and SNP filtering based on call rate, expected subject gender, relatedness among subjects, population outliers when combined with HapMap3 genotypes, if a subject was less than 15 years of age or removal of subjects if either of their tissue sample expression profiles were outliers based on mean normalized intensity profile or mean expression detection rate. After filtering 394 subjects remained; 1 subject was removed based on genotype call rate, 3 based on discrepancies between reported and genotyped gender, 1 due to relatedness, 2 as they were duplicates of each other, 10 from being population outliers, 43 based on being an expression outlier or missing expression in one or both tissues and 28 subjects were excluded based on age. Genotype based metrics for filtering was performed using the Plink toolset[29] and R.

A two-step imputation process was performed excluding genotyped SNPs where SNP and subject callrate were less than 95%, MAF was less than 1% and Hardy-Weinberg equilibrium (HWE) *P* values were less than 0.000001. Mach[28] and MiniMac[68] were used to impute genotypes for ~37.4 million autosomal SNPs based on European reference haplotypes from the 1000 Genomes Phase1 v2.20101123 data. Imputed SNPs were excluded if their MAF was less that 0.01964 or the r^2 was less than 0.3 between known and imputed genotypes resulting in ~6.8 million autosomal SNPs available for eQTL analysis. The MAF threshold of 0.01964 is an estimate of the smallest allele frequency testable in this sample series and determined from the typed SNPs (after quality control) where at least 3 minor homozygotes were present.

Prior to eQTL analysis the mRNA expression data were normalized using a cubic spline within BeadStudio. The Illumina HumanHT-12 probes were re-annotated using the ReMOAT tool[69] to identify probes that may have design issues. Filtering based on the ReMOAT quality score field resulted in 14067 of the 48803 probes being excluded from analysis. Additionally to correct for potential hybridization bias resulting from polymorphisms with the mRNA 50mer probe, probes that included a SNP, with a MAF greater than or equal to 0.01964 based on the European subjects from the 1000 Genomes Phase1 v2.20101123 data, within the 50mer design were excluded from the analysis result set. Expression probes were considered reliably detected within a sample if the Illumina Detection *P* value was <= 0.01. An expression probe was selected for eQTL analysis if the probe was reliably detected for 95% of the QC filtered samples within a tissue type. This resulted in 8599 CRBLM and 8696 FCTX probes available to be used for the eQTL analysis. These selected probes expression profiles were then adjusted using known covariates for subject age, gender, post-mortem interval, originating tissue bank, principal components 1 through 12 based on identity-by-state pairwise distances within the filtered subjects genotypes, and the mRNA sample preparation/hybridization batch. The expression profiles were then $\log_2$ transformed and covariates were stepwise fitted in R against the following model:

$$Y = \beta_0 + \beta_1 X_1 + \ldots + \beta_n X_n + \varepsilon$$

where $\beta_0 \ldots \beta_n$ represent the continuous and categorical covariates. The residuals of this model fit for each probe were then standardized, and used as the quantitative trait for the eQTL analysis.

eQTL analysis was then performed using the standardized residuals for every selected and adjusted trait in both brain tissues using mach2qtl[70] to regress the trait with the allele dosage. For each trait analyzed only SNPs that are *cis* to the trait and passed imputation QC were considered in the analysis. In this context *cis* was defined as the region near the trait, +/- 1Mb from the mRNA transcript start or end site, or within the transcript.

Study-specific acknowledgments

ALSPAC: We are extremely grateful to all the families who took part in this study, the midwives for their help in recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists and nurses. The UK Medical Research Council and Wellcome Trust (092731), together with the University of Bristol, provide core support for the ALSPAC study. A grant from the Wellcome Trust funded collection of GWAS data in ALSPAC mothers (WT088806) and a grant from 23andMe, together with support from the Sanger Centre and Centre National de Genotypage funded GWAS data in the offspring. DAL, GMc, GDS, DE, NJT all work in a centre that receives infrastructure funding from the UK Medical Research Council (G0600705).
Australian Twin Migraine: The Australian cohort was supported by National Institutes of Health Grants AA07535, AA07728, AA13320, AA13321, AA14041, AA11998, AA17688, DA012854, and DA019951; by Grants from the Australian National Health and Medical Research Council (241944, 339462, 389927, 389875, 389891, 389892, 389938, 442915, 442981, 496739, 552485, and 552498); by Grants from the Australian Research Council (A7960034, A79906588, A79801419, DP0770096, DP0212016, and DP0343921); and by the EU-funded GenomEUtwin (FP5-QLG2-CT-2002-01254) and ENGAGE (FP7-HEALTH-201413) projects. DRN (FT0991022, 613674), SEM (FT110100548) and GWM (619667) are supported by the Australian Research Council Future Fellowship and NHMRC Fellowship Schemes. We thank P Visscher, D Duffy, A Henders, B Usher, E Souzeau, A Kuot, A McMellon, PAF Madden, MJ Wright, MJ Campbell, A Caracella, L Bowdler, S Smith, S Gordon, B Haddon, D Smyth, H Beeby, O Zheng and B Chapman for their input into project management, databases, phenotype collection, and sample collection, processing and genotyping.
British 58 Birth Cohort: We acknowledge use of phenotype and genotype data from the British 1958 Birth Cohort DNA collection, funded by the Medical Research Council grant G0000934 and the Wellcome Trust grant 068545/Z/02. (http://www.b58cgene.sgul.ac.uk/). Genotyping for the B58C-WTCCC subset was funded by the Wellcome Trust grant 076113/B/04/Z. The B58C-T1DGC genotyping utilized resources provided by the Type 1 Diabetes Genetics Consortium, a collaborative clinical study sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of Allergy and Infectious Diseases (NIAID), National Human Genome Research Institute (NHGRI), National Institute of Child Health and Human Development (NICHD), and Juvenile Diabetes Research Foundation International (JDRF) and supported by U01 DK062418. B58C-T1DGC GWAS data were deposited by the Diabetes and Inflammation Laboratory, Cambridge Institute for Medical Research (CIMR), University of Cambridge, which is funded by Juvenile Diabetes Research Foundation International, the Wellcome Trust and the National Institute for Health Research Cambridge Biomedical Research Centre; the CIMR is in receipt of a Wellcome Trust Strategic Award (079895). The B58C-GABRIEL genotyping was supported by a contract from the European Commission Framework Programme 6 (018996) and grants from the French Ministry of Research.
ERF: The Erasmus Rucphen Family was supported by grants from The Netherlands Organization for Scientific Research (NWO), Erasmus MC and the Netherlands Genomics Initiative (NGI)-sponsored Center of Medical Systems Biology (CMSB). The genotyping for the ERF study was supported by EUROSPAN (European Special Populations Research Network) through the European Commission FP6 STRP grant (018947; LSHG-CT-2006-01947). The ERF study was further supported by grants from the Netherlands Organisation for Scientific Research (NWO), Erasmus MC, the Centre for Medical Systems Biology (CMSB1 and CMSB2) and the Netherlands Genomics Initiative (NGI). We are grateful to all patients and their relatives, general practitioners and neurologists for their contributions and to P. Veraart for her help in genealogy, Jeannette Vergeer for the supervision of the laboratory work and P. Snijders for his help in data collection.
FinTwin: Academy of Finland Center of Excellence in Complex Disease Genetics (grant numbers: 213506, 129680) , the Academy of Finland (grants 205585 and 141054 to JK), ENGAGE – European Network for Genetic and Genomic Epidemiology, FP7-HEALTH-F4-2007, grant agreement number 201413, and U.S.- P.H.S. NIH grants AA-12502, AA-00145, AA-09203, AA15416 and K02AA018755
HUNT: The Nord-Trøndelag Health Study (The HUNT Study) is a collaboration between HUNT Research Centre (Faculty of Medicine, Norwegian University of Science and Technology, NTNU), Nord-Trøndelag County Council, Central Norway Health Authority, and the Norwegian Institute of Public Institute of Public Health. The current study was supported by the South-Eastern Norway Regional Health Authority (2010075 and 2011083 to BW and JAZ), Unger-Vetlesen Medical Fund (to BW), and the Ullevaal fund (to BW). Genotyping was performed by Avazeh Tashakkori-Ghanbarian, Simon Potter and Sarah Hunt (calling and quality control) and Douglas Simpkin (production) at Wellcome Trust Sanger Institute.

Northern Finland Birth Cohort 1966 (NFBC1966): NFBC1966 received financial support from the Academy of Finland (project grants 104781, 120315, 129269, 1114194, 139900/24300796, Center of Excellence in Complex Disease Genetics and SALVE), University Hospital Oulu, Biocenter, University of Oulu, Finland (75617), the European Commission (EURO-BLCS, Framework 5 award QLG1-CT-2000-01643), NHLBI grant 5R01HL087679-02 through the STAMPEED program (1RL1MH083268-01), NIH/NIMH (5R01MH63706:02), ENGAGE project and grant agreement HEALTH-F4-2007-201413, the Medical Research Council, UK (G0500539, G0600705, G0600331, PrevMetSyn/SALVE, PS0476) and the Wellcome Trust (project grant GR069224, WT089549), UK. The DNA extractions, sample quality controls, biobank up-keeping and aliquotting was performed in the National Public Health Institute, Biomedicum Helsinki, Finland and supported financially by the Academy of Finland and Biocentrum Helsinki. The authors would like to acknowledge the contribution of the late Academian of Science Leena Peltonen.

NTR/NESDA: Funding was obtained from the Netherlands Organization for Scientific Research (NWO: MagW/ZonMW grants 904-61-090, 985-10-002,904-61-193,480-04-004, 400-05-717, Addiction-31160008 Middelgroot-911-09-032, Spinozapremie 56-464-14192), Center for Medical Systems Biology (CSMB, NWO Genomics), NBIC/BioAssist/RK(2008.024), Biobanking and Biomolecular Resources Research Infrastructure (BBMRI –NL, 184.021.007), the VU University's Institute for Health and Care Research (EMGO+) and Neuroscience Campus Amsterdam (NCA), the European Science Foundation (ESF, EU/QLRT-2001-01254), the European Community's Seventh Framework Program (FP7/2007-2013), ENGAGE (HEALTH-F4-2007-201413); the European Science Council (ERC Advanced, 230374) and the National Institutes of Health (NIH, R01D0042157-01A). Part of the genotyping and analyses were funded by the Genetic Association Information Network (GAIN) of the Foundation for the US National Institutes of Health, the (NIMH, MH081802).

The infrastructure for the NESDA study (www.nesda.nl) is funded through the Geestkracht program of the Netherlands Organisation for Health Research and Development (Zon-Mw, grant number 10-000-1002) and is supported by participating universities and mental health care organizations (VU University Medical Center, GGZ inGeest, Arkin, Leiden University Medical Center, GGZ Rivierduinen, University Medical Center Groningen, Lentis, GGZ Friesland, GGZ Drenthe, Scientific Institute for Quality of Healthcare (IQ healthcare), Netherlands Institute for Health Services Research (NIVEL) and Netherlands Institute of Mental Health and Addiction (Trimbos Institute).

Rotterdam studies: The generation and management of GWAS genotype data for the Rotterdam Study is supported by the Netherlands Organisation of Scientific Research NWO Investments (nr. 175.010.2005.011, 911-03-012). This study is funded by the Research Institute for Diseases in the Elderly (014-93-015; RIDE2), the Netherlands Genomics Initiative (NGI)/Netherlands Organisation for Scientific Research (NWO) project nr. 050-060-810. The Rotterdam Study is funded by Erasmus Medical Center and Erasmus University, Rotterdam, Netherlands Organization for the Health Research and Development (ZonMw), the Research Institute for Diseases in the Elderly (RIDE), the Ministry of Education, Culture and Science, the Ministry for Health, Welfare and Sports, the European Commission (DG XII), and the Municipality of Rotterdam. The Rotterdam Scan Study is supported by the Netherlands Organization of Scientific Research (NWO) project nrs. 918-46-615, 904-61-096, 904-61-133 and 948-00-010.

TwinsUK: The study was funded by the Wellcome Trust; European Community's Seventh Framework Programme (FP7/2007-2013), ENGAGE project grant agreement (HEALTH-F4-2007-201413). The study also receives support from the Dept of Health via the National Institute for Health Research (NIHR) comprehensive Biomedical Research Centre award to Guy's & St Thomas' NHS Foundation Trust in partnership with King's College London. Genotyping was performed by The Wellcome Trust Sanger Institute, support of the National Eye Institute via an NIH/CIDR genotyping project. This project was part-funded by the Chronic Disease Research Foundation with money raised by the walking twins, Hazel Green and Christine Dafter.

WGHS: Genetic analysis of migraine in the WGHS is supported by a grant from the National Institute of Neurological Disorders and Stroke (NS-061836). The Women's Health Study and the Women's Genome Health Study are supported by grants from the National Heart, Lung, and Blood Institute (HL-043851, HL-080467 and HL-099355) and the National Cancer Institute (CA-47988). Genome-wide genotyping and collaborative scientific support was provided by Amgen.

Young Finns: The Young Finns Study has been financially supported by the Academy of Finland: grants 134309 (Eye), 126925, 121584, 124282, 129378 (Salve), 117787 (Gendi), and 41071 (Skidi), the Social Insurance Institution of Finland, Kuopio, Tampere and Turku University Hospital Medical Funds (grant 9M048 and 9N035 for TeLeht), Juho Vainio Foundation, Paavo Nurmi Foundation, Finnish Foundation of Cardiovascular Research and Finnish Cultural Foundation, Tampere Tuberculosis Foundation and Emil Aaltonen Foundation (T.L). The expert technical assistance in the statistical analyses by Ville Aalto and Irina Lisinen is gratefully acknowledged.

Cologne/Kiel/Ulm clinic-based studies (part of German MA and MO studies): This research was funded by the German Federal Ministry of Education and Research (BMBF) within the framework of the National Genome Research Network (NGFN-Plus; grants 01GS08120 and 01GS1103 to C.K; the German Federal Ministry of Education and Research and by the State of Bavaria and supported within the Munich Center of Health Sciences (MC Health) as part of LMUinnovativ) for the KORA research platform, which was initiated by the Helmholtz Center Munich, German Research Center for Environmental Health; the Center for Molecular Medicine Cologne (to C.K.) and the Heinz Nixdorf Foundation for the Heinz Nixdorf Recall study, and the Deutsche Forschungsgemeinschaft (DFG; to C.K. and H.G.).

Finnish clinic-based study: This work was supported by the Wellcome Trust (grant number WT089062) and, among others, by the Academy of Finland (200923 to AP, 00213 to M.W.); the Helsinki University Central Hospital (to M. Kallela., M.F., V. Artto); the Academy of Finland Center of Excellence for Complex Disease Genetics; the EuroHead project (LSM-CT-2004-504837); the Finnish Cultural Foundation (to V. Anttila); the Finnish Neurology Foundation, Biomedicum Helsinki Foundation (to V. Anttila and V. Artto); the Orion Farmos Research Foundation (to V. Anttila); the Wellcome Trust (grant

number 098051 to AP); the Academy of Finland (grant number 251704 to AP, and 139795 to MW); the Academy of Finland, Center of Excellence in Complex Disease Genetics, (grant numbers 213506 and 129680 to AP and JK); the European Community's Seventh Framework Programme (FP7/2007-2013), ENGAGE Consortium, (grant agreement HEALTH-F4-2007-201413); EU/SYNSYS- Synaptic Systems (grant number 242167 to AP); the Sigrid Juselius Foundation, Finland (to AP); the Folkhälsan Research Foundation, Finland (to MW); Medicinska Understödsföreningen Liv & Hälsa (to MW) and the Helsinki University Central Hospital (to MK, VAr, MF). P.P. was supported by the European Commission FP7 project no. 261123 (gEUVADIS).
LUMINA clinic-based studies: We would like to thank support obtained from the Netherlands Organization for the Health Research and Development (ZonMw) no.90700217 and VIDI (ZonMw) no.91711319 (to G.M.T.); the Netherlands Organisation for Scientific Research (NWO) VICI (918.56.602) and Spinoza (2009) grants (to M.D.F.); the EuroHead project (LSM-CT-2004-504837; the Center for Medical Systems Biology (CMSB) established in the Netherlands Genomics Initiative/Netherlands Organisation for Scientific Research (NGI/NWO), project nr. 050-060-409 (to R.R.F., M.D.F. and A.M.J.M.v.d.M.).
Munich clinic-based studies (part of German MA and MO studies): This work was supported by the German Federal Ministry of Education and Research (BMBF) (grant 01GS08121 to M.D. along with support to H.E.W. in the context of the German National Genome Research Network, (NGFN-2 and NGFN-plus) for the Heinz Nixdorf Recall Study) and an unrestricted grant of the Vascular Dementia Research Foundation (to M.D.).
Brain eQTL data: This research was supported in part by the Intramural Research Program of the NIH, National Institute on Aging (ZO1-AG000947 and Z01-AG000185) and in part by the UK Medical Research Council. This study utilized the high-performance computational capabilities of the Biowulf Linux cluster at the National Institutes of Health, Bethesda, Md. (http://biowulf.nih.gov).

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