Fine-mapping a genome-wide meta-analysis of 98,374 migraine cases identifies 181 sets of candidate causal variants

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Abstract

Migraine is a highly prevalent neurovascular disorder for which genome-wide association studies (GWAS) have identified over one hundred risk loci, yet the causal variants and genes remain mostly unknown. Here, we meta-analyzed three migraine GWAS including 98,374 cases and 869,160 controls and identified 122 independent risk loci of which 35 were new. Fine-mapping of a meta-analysis is challenging because some variants may be missing from some participating studies and accurate linkage disequilibrium (LD) information of the variants is often not available. Here, using the exact in-sample LD, we first investigated which statistics could reliably capture the quality of fine-mapping when only reference LD was available. We observed that the posterior expected number of causal variants best distinguished between the high- and low-quality results. Next, we performed fine-mapping for 102 autosomal risk regions using FINEMAP. We produced high-quality fine-mapping for 93 regions and defined 181 distinct credible sets. Among the high-quality credible sets were 7 variants with very high posterior inclusion probability (PIP > 0.9) and 2 missense variants with PIP > 0.5 (rs6330 in *NGF* and rs1133400 in *INPP5A*). For 35 association signals, we managed to narrow down the set of potential risk variants to at most 5 variants.

Introduction

Migraine is a common neurological disorder characterized by recurrent disabling episodes of severe headache that are typically one-sided, pulsating in nature, and

accompanied by other symptoms such as nausea, and hypersensitivity to light and/or sound. It has two main subtypes, migraine without aura and migraine with aura. The aura is a reversible visual, sensory or speech disturbance, that typically occurs before the headache phase. Migraine attacks last usually from 4 to 72 hours, and can significantly harm daily life of patients[1]. Migraine was ranked as the second most disabling disease worldwide in terms of years lived with disability by Global Burden of Diseases Study in 2019[2]. Its lifetime prevalence has been estimated to be about 15 to 20 % worldwide, and it is three times more common in females than in males[2]. Family and twin studies estimate the heritability to be about 40%[3]. To date, over 100 migraine associated loci have been reported by GWAS[4,5,6,7,8,9,10,11,12,13,14]. The genetic association of migraine has shown a general enrichment in genes highly expressed in vascular and central nervous system related tissues[15,13] but we lack detailed information on specific genetic variants that affect the migraine risk.

Identification of causal genes and variants that have a biological effect on migraine is crucial for understanding the biology of migraine, and for developing new effective treatments for the disorder. Here, we aim to narrow down correlated genetic variation in migraine associated regions to a smaller number of candidate causal variants by applying statistical fine-mapping[16]. Fine-mapping methods evaluate how plausibly each variant in the region is among the causal variants by utilizing the observed association statistics and the LD structure of the region[16]. Multiple methods that can utilize GWAS summary statistics have been developed, including PAINTOR[17], CAVIAR[18], FINEMAP[19], JAM[20] and SuSIE[21]. The optimal way to apply fine-mapping is to compute the LD information from the original GWAS data (in-sample LD), but when the original genotype data are unavailable, approximate LD information is often

obtained from a reference genotype panel (reference LD). However, when reference LD is used, the discrepancy from the in-sample LD can cause errors in fine-mapping and this problem becomes more severe as the GWAS sample size grows[22].

Even though large meta-analyses have become a successful way to increase statistical power of GWAS, they remain difficult to fine-map reliably for several reasons[23]. First, meta-analyses are combinations of multiple studies and typically no single analyst has access to the exact in-sample LD of the whole meta-analysis, which means that reference LD must be used. Second, differences in genotyping platforms and genotype imputation pipelines between the meta-analyzed studies can bias the fine-mapping results. Third, some variants included in the meta-analysis may be present in only a subset of the studies, which leads to variation in information content of the association statistics of different variants. In a landmark fine-mapping study on schizophrenia, Trubetskoy et al. (2022)[24] avoided these problems by collecting all genotype-phenotype data into a single analysis site. Unfortunately, to our knowledge, no other international disease consortium has been able to create a comparable analysis environment that would allow an in-sample fine-mapping of a large meta-analysis. Given that fine-mapping of meta-analysis results typically relies on reference LD, a crucial question is how we can assess when the results of fine-mapping based on reference LD are reliable.

So far, the largest GWAS meta-analysis on migraine contained 102,084 cases and 771,257 controls from 25 study collections[13]. Unfortunately, we cannot perform reliable fine-mapping for that meta-analysis, since the in-sample LD is not available. Instead, we conducted a migraine meta-analysis with 98,374 migraine cases and

869,160 controls by combining data from three sources: 23andMe, Inc., FinnGen, and UK Biobank (UKB). Of these data sets, 23andMe and UKB were included in the earlier meta-analysis of Hautakangas et al. (2022) while FinnGen was not. Statistical power of our meta-analysis was comparable to the previous migraine meta-analysis of Hautakangas et al. (2022), with effective sample sizes of 339,000 and 326,000, respectively. Importantly, we have the full in-sample LD available for 26 risk loci and for the remaining risk loci we have the in-sample LD for FinnGen and UKB but not for 23andMe (Table 1). This set-up allowed us to investigate how different LD reference panels perform compared to the in-sample LD. In particular, we evaluated different statistics that could be used to assess fine-mapping quality when only reference LD is available. Finally, we utilized our results to fine-map 102 migraine risk loci to narrow down the putative causal variants behind the associations. We were able to get reliable fine-mapping results for 93 out of 102 regions and identified 7 variants with a high probability (>90%) of being causal and two missense variants, rs6330 in *NGF* and rs1133400 in *INPP5A,* with a probability > 50% of being causal.

Table 1. Three study collections included in the migraine meta-analysis.

Study	Ancestry	Cases	Controls	N	Case %	Migraine definition	LD availability
UK Biobank	European, British	10,881	330,169	341,050	0.03	Self-reported	In-sample
23andMe, Inc	European descent	53,109	230,876	283,985	0.19	Self-reported	In-sample for 26/102 fine-map regions
FinnGen R8	European, Finnish	34,385	308,114	342,499	0.10	Medication purchases	In-sample
Meta-analysis	European descent	98,374	869,160	967,534	0.10	Self-reported, medication purchases	In-sample 26/102, reference LD 76/102

Results

We conducted an inverse-variance weighted meta-analysis on migraine by combining results from the three GWAS (Table 1): UK Biobank (UKB; 10,881 cases and 330,169 controls), 23andMe, Inc. (53,109 cases and 230,876 controls), and FinnGen Release 8 (34,385 cases and 308,114 controls). The total sample size is 98,374 migraine cases and 869,160 controls. Before meta-analyzing the data, we estimated pairwise genetic correlations between the study collections by LD Score regression (LDSC)[25]. The estimated genetic correlations were 1.00 (s.e. 0.04) between UKB and 23andMe, 0.84 (s.e. 0.05) between UKB and FinnGen, and 0.87 (s.e. 0.03) between 23andMe and FinnGen. The lower genetic correlation between FinnGen and the other two studies could be due to differences in the case definitions (triptan purchases in FinnGen vs. self-reporting in UKB and 23andMe). A comparable level of genetic correlation (0.81) has been reported before between primary care and self-reported migraine cases within UKB[26]. Another source of possible heterogeneity in effect sizes is the difference in genetic ancestry (Finnish in FinnGen vs. Non-Finnish European in the other two).

The genomic inflation factor (λ_{GC}) of the migraine meta-analysis was 1.38. There was a linear relationship between the association statistic and the LD-score (Supplementary Fig 1) indicating that the polygenic background of migraine was the main source of the genomic inflation. However, as the intercept from LDSC was elevated to 1.09 (s.e. 0.01) from its null value of 1.0, some inflation could also be due to confounding factors such as cryptic relatedness, population stratification or other model misspecification. Consequently, we further checked the LDSC intercepts for

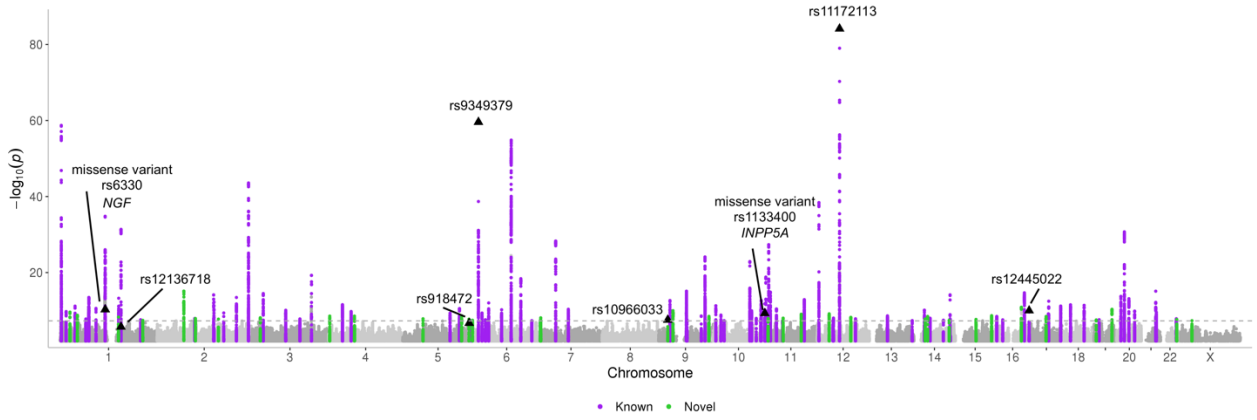
the individual studies: 1.03 (s.e. 0.01) for 23andMe, 1.00 (s.e. 0.01) for UKB and 1.10 (s.e. 0.01) for FinnGen. The higher intercept for FinnGen could be due to a different GWAS analysis method (whole genome-regression by REGENIE[27] including related samples) compared to UKB and 23andMe (logistic regression excluding related samples). Estimated SNP-heritability was 11.49% (s.e. 0.47%) from LDSC when population prevalence was assumed to be 16%.

We followed the locus definition of Hautakangas et al. (2022) and defined the LD-independent genome-wide significant (GWS; $P < 5 \times 10^{-8}$) risk loci from the meta-analysis iteratively by choosing the variant with the smallest P-value as an index variant and excluding all other GWS variants with LD $r^2 > 0.1$ to that index variant from further considerations until no GWS variants remained. Next, we formed a high LD region around each index variant extending to the level of $r^2 > 0.6$, and merged regions that were closer than 250 kb. Lastly, all other GWS variants were included in their closest region, and the region boundaries were updated, and once again regions closer than 250 kb were merged (see further details in Methods). Based on this locus definition, we identified 122 LD-independent risk loci, of which 35 were new (Table 2), and 87 overlapped with the previously known risk loci (Fig 1, Supplementary Table 1, Supplementary Figs 2-4)[4,5,6,7,8,9,10,11,12,13,14].
We observed statistically significant heterogeneity ($P < 0.05/122$) in effect sizes between the study collections only for two lead variants, both of which resided in the previously known migraine loci (PRDM16 and near ZCCHC14)(Supplementary Table 1, Supplementary Fig 3). As external replication data of 34,807 cases and 193,475 controls, we meta-analyzed data from the Trøndelag Health Study (HUNT)[28] and IHGC16 migraine meta-analysis excluding the Finnish cohorts and the 23andMe

data[9]. Of the 35 lead variants of our new loci, 32 were consistent in direction (P = 2.1 × 10^{-7}, one-sided binomial test) and 17 replicated with P < 0.05 (one-sided test; Supplementary Table 2) in the replication data. When we meta-analyzed the discovery and the replication data, 28 out of the 35 novel loci remained GWS (Supplementary Table 2).

To define the fine-map regions, we merged together the risk loci that were closer than 1.5 Mb. This resulted in 102 fine-map regions. To avoid problems due to varying sample sizes across the variants, we included in fine-mapping only autosomal SNPs that were available in all three cohorts. This criterion reduced the number of common variants (MAF>0.05) per regions on average by 19%.

Figure 1. A Manhattan plot of the inverse-variance weighted fixed effects migraine meta-analysis including 98,374 cases and 869,160 controls. X-axis presents the chromosomal location and y-axis the -$\log_{10}$(P-value). Known loci are highlighted in purple and new loci in green. Variants with posterior inclusion probability (PIP) > 0.9 and missense variants with PIP > 0.5 in high-quality fine-mapping regions are annotated.



184 Table 2. New 35 migraine risk loci identified from the meta-analysis of 98,374

185 migraine cases and 869,160 controls.

Locus name	RSID	Chromosome	Position GRCh37	Effect allele	Other allele	Effect allele frequency	Log-odds ratio	S.e.	P-value
near RUNX3	rs71014329	1	25348950	I	D	0.604	0.034	0.005	2.57E-10
ST3GAL3	rs783302	1	44366341	G	A	0.878	0.047	0.008	1.68E-09
SF3B4	rs7544531	1	149897217	T	C	0.084	0.072	0.012	5.08E-09
near DTL	rs61830764	1	212289976	A	G	0.382	0.031	0.006	3.71E-08
near APLF	rs112706954	2	68819969	G	A	0.023	0.137	0.017	7.88E-16
TMEM131	rs2305142	2	98375722	G	A	0.322	0.031	0.005	1.18E-08
near GPD2	rs74482068	2	157560108	D	I	0.039	0.076	0.014	1.76E-08
near RANP7	rs11386839	3	22929430	D	I	0.500	0.029	0.005	7.68E-09
ADD1	rs10026792	4	2862190	G	A	0.687	0.032	0.005	2.79E-09
EPHA5	rs147908403	4	66362482	C	T	0.054	0.069	0.012	2.80E-09
ITGA1	rs4865540	5	52184268	C	A	0.820	0.037	0.007	1.41E-08
near GLRA1	rs372257780	5	151200938	I	D	0.599	0.033	0.006	2.27E-09
KCNIP1	rs78151838	5	170108683	A	G	0.905	0.054	0.010	1.82E-08
MAML1	rs10794701	5	179181061	A	G	0.119	0.043	0.008	3.57E-08
near COX19	rs117303395	7	1001963	A	G	0.019	0.122	0.022	4.40E-08
MAD1L1	rs10479762	7	2045351	T	C	0.419	0.029	0.005	8.01E-09
ELAVL2	rs10966033	9	23705736	G	T	0.617	0.029	0.005	2.70E-08
near ZCCHC7	rs10973207	9	37100525	T	G	0.187	0.042	0.007	1.04E-10
near LMX1B	rs4358894	9	129464802	C	G	0.513	0.030	0.005	3.33E-09
near DENND5A	rs34494849	11	9287030	C	T	0.768	0.034	0.006	1.17E-08
near MTCH2	rs11039324	11	47665686	G	A	0.601	0.030	0.005	9.76E-09
MRE11A	rs639311	11	94205747	C	T	0.681	0.033	0.005	9.02E-10
IPO8	rs12369125	12	30807195	A	C	0.251	0.036	0.006	7.08E-10
MGAT4C	rs73187675	12	86409247	T	A	0.193	0.037	0.006	6.08E-09
RP11-562L8.1	rs1957110	14	29777492	T	C	0.409	0.029	0.005	1.59E-08
INSM2	rs2296919	14	36005659	T	C	0.807	0.038	0.006	3.44E-09
RPS6KA5	rs117151272	14	91415550	A	T	0.026	0.097	0.018	3.59E-08
near ONECUT1	rs1899730	15	53166138	T	G	0.707	0.032	0.006	2.11E-08
FAM174B	rs12910861	15	93218540	C	T	0.227	0.037	0.006	2.15E-09
FAM65A	rs9934328	16	67573367	C	G	0.137	0.049	0.007	1.32E-11
TUBG2	rs2292750	17	40811781	C	T	0.452	0.030	0.005	3.53E-09
near NRTN	rs76899991	19	5822370	G	T	0.963	0.077	0.014	2.89E-08
SYMPK	rs74821481	19	46320041	G	T	0.678	0.036	0.005	4.59E-11
near SERHL2	rs141478056	22	42939927	G	A	0.120	0.046	0.008	2.23E-08
near FTHL17	rs149675702	23	31063624	C	T	0.945	0.079	0.014	4.56E-08

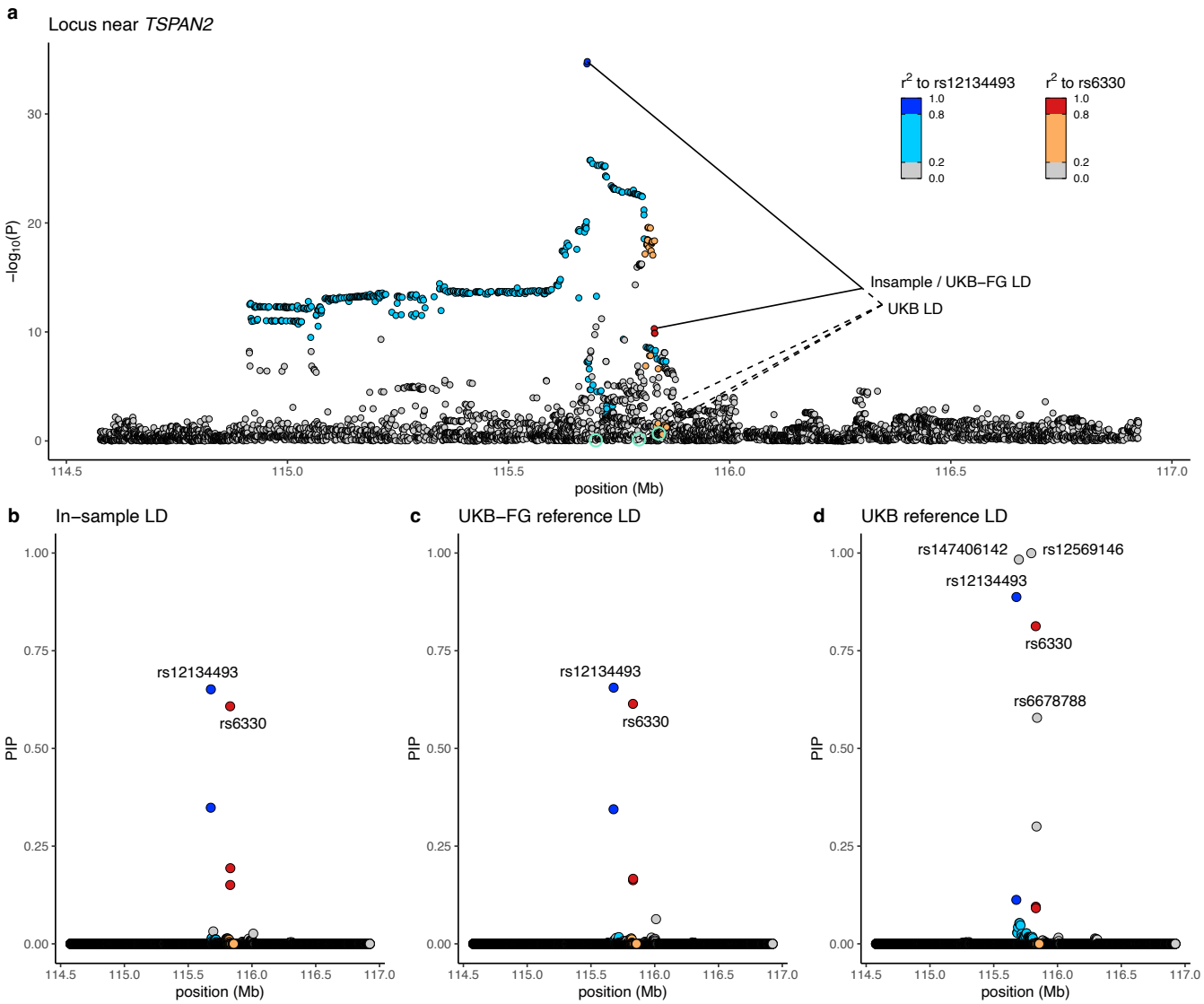
RSID = reference SNP ID, GRCh37 = Genome Reference Consortium Human Build 37, s.e. = standard error. Alleles D and I refer to deletion and insertion, respectively.

Comparison of different LD panels in fine-mapping

A common problem in meta-analyses is that the in-sample LD is not available, and use of reference LD may lead to biased results. Figure 2 demonstrates this problem at the locus around *TSPAN2* where fine-mapping using the in-sample LD disagrees strongly with the UKB reference LD but agrees well with a more accurate UKB-FG reference LD. This shows that, in our setting, fine-mapping based on the UKB-FG reference LD has a potential to yield reliable results but that we need some way to assess, for each region, whether the reference LD has provided reliable results. Therefore, we evaluated whether some statistics, either derived from the GWAS results or from the fine-mapping results, could flag the regions where the reference LD produced unreliable fine-mapping results compared to the in-sample LD. We did this comparison in the 26 regions where the in-sample LD was available. As candidate statistics, we considered: (1) posterior expectation of the number of causal variants (PENC), and, from the top variant(s) of the credible sets, (2) maximum pairwise r^2, (3) maximum marginal *P*-value, and (4) minimum INFO value. We used the maximum difference of the variant-specific posterior inclusion probabilities (maxΔ) between the reference LD and the in-sample LD to assess the quality of the refence LD results. A small maxΔ value (close to 0) indicates high quality (the reference LD produces similar results to the in-sample LD), and a large value (close to 1) indicates low quality (the reference LD produces different results from the in-sample LD).

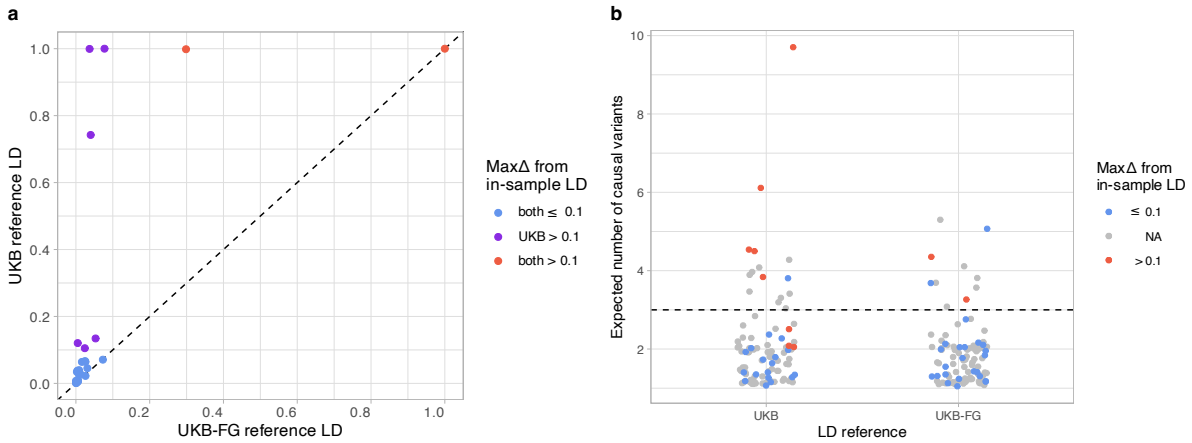
In general, both LD reference panels performed well in most of the 26 regions available for this comparison, but, as expected[22], the more accurate UKB-FG panel performed clearly better than the UKB panel alone. For example, maxΔ was above 0.1 only in 2/26 regions with the UKB-FG panel but in 8/26 regions with the UKB panel (Fig 3a).

Figure 2. Fine-mapping a region near *TSPAN2* at chromosome 1 using three different LD sources. a) Plot of the GWAS results with the chromosomal location on x-axis and the strength of the association as -log10 *P*-values from the inverse-variance weighted fixed-effect meta-analysis with 98,374 migraine cases and 869,160 controls on y-axis. Variants are colored based on the squared correlation (r^2) to the two variants in the top configuration suggested by FINEMAP with the in-sample LD. The suggested top configurations based on three LD panels are marked by lines with the in-sample LD and the UKB-FG reference LD giving the same top configuration and the UKB reference LD including three additional variants (highlighted in green). Posterior inclusion probabilities (PIPs) for the variants based on b) in-sample LD, c) UKB-FG reference LD and d) UKB reference LD.



We then investigated how well the four different statistics could separate the regions with low-quality fine-mapping results from those with high-quality results for the two LD reference panels (Supplementary Fig 5). First, when PENC was used, both LD reference panels performed similarly for the regions where FINEMAP suggested only one or two causal variants (Supplementary Fig 5a). Those results were also close to the in-sample results (maxΔ < 0.07). All low-quality regions (with maxΔ > 0.1) had PENC > 2 with the UKB panel and PENC > 3 with the UKB-FG panel. Thus, we used these PENC thresholds to define low-quality regions when the in-sample LD was not available. We expect that these thresholds have a high sensitivity for low-quality

239 results but will simultaneously exclude some of the regions that truly have many
240 causal variants. The other three statistics are not able to distinguish the low-quality
241 regions as clearly as PENC (Supplementary Figs 5b-d). First, the maximum r^2
242 among the top configuration variants does not distinguish both of the low-quality
243 regions with the UKB-FG panel (Supplementary Fig 5b). Additionally, neither the
244 maximum *P* nor the minimum INFO within the top credible set variants separates
245 well the low-quality regions from the good-quality regions (Supplementary Figs 5c,d).
246 We conclude that PENC gives the best separation among the statistics investigated.
247 Previously, PENC has been used to filter FINEMAP results in the schizophrenia fine-
248 mapping study[24].
249
250 Next, we evaluated how PENC classifies the 76 fine-map regions where only
251 reference LD was available to us. The 76 grey points in Figure 3b show that the fine-
252 map regions without the in-sample LD are typically having PENC < 2.5 and, with the
253 UKB-FG LD, only 6 of the 76 regions have PENC > 3.
254
255 Figure 3. a) Scatter plot comparing the maximum PIP differences (maxΔ) between
256 the in-sample and reference LD for 26 fine-map regions. X-axis shows the UKB-FG
257 reference LD and y-axis the UKB reference LD. b) Strip chart shows the posterior
258 expected number of causal variants (PENC) from fine-mapping for the two LD
259 reference panels for the 102 fine-map regions. Red dots indicate large differences
260 from the in-sample LD (maxΔ > 0.1), and grey color indicates regions for which only
261 reference LD is available and therefore maxΔ is not known. Horizontal line shows
262 PENC = 3 that we use as a threshold to define reliable results with the UKB-FG
263 panel.



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266 FINEMAP results overview

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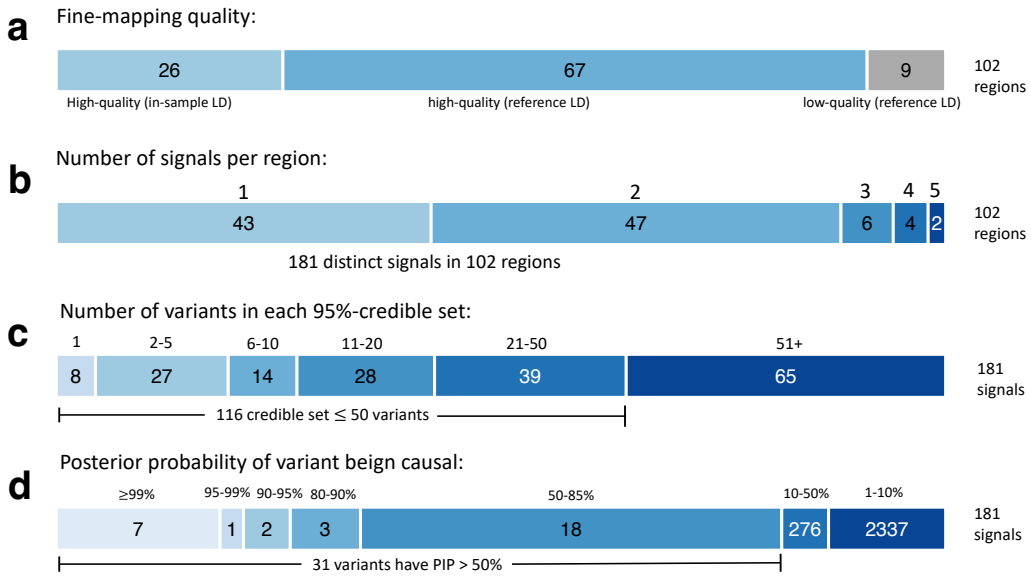
268 Figure 4. Summary of the fine-mapping results across the 102 migraine risk regions.



269

270 Overall, for a majority of the fine-map regions, FINEMAP suggested one (42%) or

271 two (46%) causal variants (Supplementary Table 3, Fig 4.). The 102 fine-map

272 regions together had 181 distinct signals when the signals were defined by the

273 number of causal variants per region with the highest posterior probability. Among

274 the 76 regions without the in-sample LD, 6 had PENC above 3. We flagged these

regions to be of low-quality, and their interpretation requires extra caution. The largest PENC observed was 5 and it occurred for two fine-map regions: *PRDM16* (index variant rs10218452) and *HOXB3* (index variant rs2555111). Of these, *HOXB3* region is flagged as low-quality because there is no in-sample LD available.

The sizes of 95%-credible sets ranged from 1 to 2,787 variants, and 49 credible sets had 10 variants or less. A very high PIP ($\geq$ 0.9) was observed for 10 variants (Supplementary Table 4), of which seven were in the high-quality fine-map regions (Table 3). We conducted a look-up from Variant Effect Predictor (VEP) database for all credible sets to search for variants that could have an impact on the gene transcript. In total, 149 unique missense variants were found of which 3 had PIP > 0.5: rs6330 (PIP=0.59) in *NGF* located at chromosome 1, rs1133400 (PIP=0.93) in *INPP5A* located at chromosome 10 and rs28929474 (PIP=0.64) in *SERPINA1* located in a low-quality fine-map region at chromosome 14 (Table 3, Supplementary Table 5). Of these, rs6330 is a significant *cis*-eQTL for *NGF-AS1* expressed in atrial appendage of heart and rs28929474 for *IFI27L2* expressed in tibial artery and in left ventricle of heart in GTEx v.08 data.

NGF encodes protein nerve growth factor beta (NGHβ) that is important in the development and survival of neurons, and involved in transmission of pain, temperature, and touch sensations via sensory neurons. It binds to two receptors, NTRK1 encoded by *NTRK1* and NGFR/p75^{NTR} encoded by *NGFR*. Of note, two additional missense variants among the credible sets, rs6339 (PIP= 0.48) and rs6336 (PIP=0.39), are located in *NTRK1* in a separate locus. The missense variant rs6330 shows association with multiple diseases of the musculoskeletal system and connective tissue including spinal stenosis, spondylosis, spondylopathies and hallux

valgus in FinnGen R10 PheWAS scan, all to the opposite direction compared to the migraine risk (Supplementary Table 6).

INPP5A encodes a membrane-associated type I inositol 1,4,5-trisphosphate 5-phosphate protein, which hydrolyzes Ins(1,4,5)P3 leading to the mobilization of intracellular calcium. It has a central role in various cellular signaling processes including neurotransmission, hormone secretion, cell proliferation and muscle contraction. *INPP5A* is highly expressed in Purkinje cells of cerebellum, and in mice studies its deletion have been shown to cause ataxia and cerebellar degeneration[29,30].

SERPINA1 encodes an alpha-1 antitrypsin, a serine protease inhibitor protein, that belongs to the serpin superfamily. Its primary target is elastase, and other targets are plasmin and thrombin. Several mutations, including our high-PIP variant rs28929474C>T, in *SERPINA1* can cause an autosomal co-dominant genetic disorder alpha-1 antitrypsin (AAT) deficiency, which can lead to lung or liver disease due to reduced alpha-1 antitrypsin levels[31]. A missense variant rs28929474 is highly pleiotropic and shows associations to multiple disease categories in PheWAS of FinnGen R10 data including, for example, diseases of the respiratory system, diseases of the circulatory system, diseases of digestive system, pregnancy related diseases, diseases of the nervous system, and diseases of musculoskeletal system and connective tissue (Supplementary Tables 6-8).

Five additional high-impact variants on protein function (1 stop gained, 2 start lost, and 2 splice acceptor variants) were among the credible sets, but only with modest PIPs below 0.01 (Supplementary Table 5), and another 5 variants with high-impact on something else than protein coding function (long non-coding RNA, antisense or nonsense mediated decay) with PIPs below 0.02.

Our results provided new information on two of the strongest known migraine risk loci by estimating PIPs of 1.00 for the intronic variants rs9349379 in *PHACTR1* and rs11172113 in *LRP1*. We were able to fine-map both of these loci by using the in-sample LD. The candidate variant in *PHACTR1* is also associated with many vascular diseases and its effects on gene expression of the genes in the locus have been studied in detail but with contradicting results[32,33]. Also, the candidate variant in *LRP1* is associated with several vascular diseases, such as sporadic thoracic aortic dissection, fibromuscular dysplacia and spontaneous coronary artery dissection[34,35,36]. The LDL receptor-related protein 1 (LRP1) is a cell surface receptor and has an important role in vascular and blood brain barrier integrity[37,38,39]. It is expressed in almost every tissue, and most studied in liver and brain. LRP1 is also involved in vascular calcium signaling by regulating smooth muscle cell contractility[38]. A recent study suggested that *LRP1* expression is regulated by allele-specific mechanism of intronic rs11172113 located in an enhancer region through two transcription factors (MECP2 and SNAIL)[40].

Table 3. Variants with high (>0.9) posterior inclusion probability (PIP) and missense variants with PIP > 0.5 among the 93 high-confidence fine-map regions.

Gene (VEP)	Predicted consequence (VEP)	RSID	Chromosome	Position GRCh37	Effect allele	Other allele	PIP	Minor allele frequency	Log-odds ratio	S.E.	P-value	LDsource
PHACTR1	Intron variant	rs9349379	6	12903957	G	A	1.000	0.422	-0.084	0.005	2.59E-60	in-sample
LRP1	Intron variant	rs11172113	12	57527283	C	T	1.000	0.404	-0.101	0.005	7.27E-85	in-sample
-	Intergenic variant	rs12445022	16	87575332	A	G	1.000	0.333	-0.035	0.005	1.04E-10	in-sample
-	Intergenic variant	rs12136718	1	156409585	A	G	0.999	0.072	0.046	0.010	1.95E-06	in-sample
ELAVL2	Intron variant	rs10966033	9	23705736	T	G	0.954	0.383	-0.029	0.005	2.70E-08	UKB-FG
TLX3	3' UTR variant	rs918472	5	170738836	G	A	0.932	0.292	-0.029	0.006	1.95E-07	UKB-FG
INPP5A	missense variant	rs1133400	10	134459388	G	A	0.926	0.198	0.039	0.006	5.06E-10	UKB-FG
NGF	missense variant	rs6330	1	115829313	A	G	0.593	0.461	0.033	0.005	4.97E-11	in-sample

Due to the restriction of including in fine-mapping only the variants that are available in all three data sets, the original lead variant was missing in 17/102 fine-map regions (Supplementary Table 3b). In 14/17 of these regions, the original lead variant was represented by one of the top credible set variants (defined as being in LD with r2 > 0.1 in the UKB data). For the remaining 3 regions, the signal related to the original lead variant may be missing from the fine-mapping results, and we flagged these regions to be of low-quality. Among the fine-map regions for which the lead variant was included in the analysis, the lead variant was within the 95% credible sets in 83/85 fine-map regions and within the top configuration in 73/85 of the regions.

Phenome-wide association scans for the credible set variants

We conducted three separate phenome-wide association studies (PheWAS) by using data from FinnGen Data Freeze 10 including 429,209 individuals. First, by a

PheWAS for the 181 credible set top variants and the list of 2,399 FinnGen endpoints excluding the migraine endpoints, we identified 404 variant-disease associations with $P < 1 \times 10^{-5}$ (Supplementary Table 6, phewas_app). Of these, 108 variant-disease associations belonged to diseases of the circulatory system, including, for example, hypertension and ischemic heart disease, followed by 39 variant-trait associations in a category of quantitative endpoints, including, e.g., height and BMI, 34 in diseases of the musculoskeletal system and connective tissue category, including, e.g., spinal stenosis and rheumatoid arthritis, and 28 associations in diseases of the respiratory system, including, e.g., asthma and COPD.

Second, for the 159 functional variants among the credible sets, we conducted a targeted PheWAS scan within neurological and cardiovascular endpoints, and identified 122 variant-disease associations with $P < 1 \times 10^{-4}$ (Supplementary Table 7, phewas_app), including traits such as sleep apnea and stroke. Third, for the 307 variants with PIP > 0.1, with a similar targeted PheWAS scan within the neurological and cardiovascular endpoints, we identified 330 variant-disease associations with $P < 1 \times 10^{-4}$ (Supplementary Table 8, phewas_app), including, e.g., focal epilepsy and hydrocephalus.

Discussion

Well over one hundred risk loci for migraine have been reported from GWAS, but the causal variants and genes are still mostly unknown[4,5,6,7,8,9,10,11,12,13,14]. Statistical fine-mapping of the GWAS results at the risk loci is a natural next step but reliable fine-

384 mapping of large meta-analysis data has turned out to be very difficult. Our recent
385 migraine meta-analysis of 25 studies[13] illustrated these difficulties as the accurate LD
386 information was not available and the sample size varied considerably across
387 variants. In this study, our goal was to provide reliable fine-mapping for migraine by
388 creating a new migraine meta-analysis for which accurate LD information was
389 available and sample size across variants was more stable. Despite the more
390 stringent selection criteria, the effective sample size of our new meta-analysis
391 (339,000) turned out to be comparable to that of the earlier meta-analysis (326,000).
392
393 A key question in fine-mapping a GWAS meta-analysis is how to assess the
394 reliability of the results. We were able to study this question by directly comparing
395 results between accurate in-sample LD and approximate reference panel LD. We
396 observed that the posterior expected number of causal variants (PENC) as reported
397 by FINEMAP distinguished well the regions with high-quality fine-mapping results
398 from those with low-quality results. We also observed that an appropriate PENC
399 threshold depends on the quality of the reference panel. In our case, we were able to
400 use an upper limit of 3.0 for PENC. While this upper limit restricts our ability to fine-
401 map the migraine risk regions that truly have more than 3 causal signals, we expect
402 that the proportion of such regions is small, as only 3/26 (12%) of the migraine loci
403 with the in-sample LD had PENC over 3 in our analysis.
404
405 Here, we performed the first systematic fine-mapping of a migraine meta-analysis
406 and provided high-quality fine-mapping results for 91% of the migraine risk regions
407 identified by the meta-analysis. Our high-quality results highlight two missense

variants with high PIPs: rs6330 (PIP=0.59) in *NGF* and rs1133400 (PIP=0.93) in *INPP5A.*

The variant rs6330 is only in weak LD (r2 = 0.04) with the lead variant (rs12134493) of its locus and was identified as a secondary signal in our fine-mapping. A recent study[14] has also reported that the migraine association of rs6330 remained statistically significant in a conditional analysis after adjusting for the stronger signal (rs2078371) within the same risk locus. *NGF* has been reported to be highly expressed in hippocampus and cortex[41,42] although according to the GTEx v8 data, *NGF* does not show statistically significant expression in any brain tissue but shows high expression in multiple other tissues, including, for example, ovary, tibial nerve, arteries, visceral adipose, and heart. NGF levels have been reported to be elevated in cerebrospinal fluid in chronic migraine patients compared to controls[43], and decreased in blood serum of episodic migraine patients compared to controls and chronic migraine patients[44]. In addition, we observed two additional missense variants with considerable PIPs, rs6339 (PIP=0.48) and rs6336 (PIP=0.39), located in *NTRK1* which encodes one of the two receptors for NGF. NGF and its receptors have a central role in the pain perception, and elevated NGF levels have been observed also in many other chronic pain conditions, such as osteoarthritis and low back pain[45,46,47]. Multiple antibodies of NGF or small molecular inhibitors of the NGF receptors have been developed and tested in clinical studies to treat chronic pain conditions, including low back pain and osteoarthritis[48,49,50,51,52]. Even though some candidate drugs have shown potential benefit relating to pain relief, an increased risk of progressive osteoarthritis has been observed in a small group of the treated patients[52], and therefore none of the drugs have yet received FDA approval. Currently, other type of drug classes (p75 neurotrophin receptor fusion protein, LEVI-

433 04 (ClinicalTrials.gov ID: NCT05618782) and anti-NGF PEGylated Fab' antibody[53]),
434 are being developed and in pre-clinical or clinical testing. In adults, after pain stimuli,
435 NGF activates overexpression of other neuronal molecules, including calcitonin
436 gene-related peptide (CGRP) and substance P[52]. CGRP is involved in migraine pain,
437 and several effective monoclonal antibodies targeting either CGRP or its receptors
438 have been developed to treat migraine[54,55,56].
439 Gene *INPP5A* is highly expressed in Purkinje cells of cerebellum[57] and involved in
440 multiple cellular signaling processes including neurotransmission, hormone
441 secretion, cell proliferation and muscle contraction through its role in the pathway
442 regulating intracellular calcium levels. The missense variant rs1133400 is in modest
443 LD (r2 = 0.36) with the lead variant of the locus (rs200314499) that was filtered out
444 from fine-mapping due to QC. For this locus, FINEMAP suggested two causal
445 variants (PENC = 1.65). PheWAS showed no other significant associations with this
446 missense variant.
447
448 Another important finding is in the *PHACTR1* locus, which is one of the strongest
449 known migraine risk loci. There our fine-mapping suggested one causal variant
450 (PENC = 1.29), with the lead variant rs9349379 being a clear candidate for being
451 causal with PIP of 1.00. In our FinnGen PheWAS, we detected also strong
452 associations between the variant and, for example, major coronary disease events
453 ($P = 8.22 \times 10^{-52}$), ischemic heart disease ($P = 1.18 \times 10^{-38}$) and angina pectoris (P
454 $= 7.71 \times 10^{-26}$), all to the opposite directions compared to migraine risk. Because of
455 these well-known associations with multiple vascular diseases, this locus has been
456 previously studied in detail but with contradicting results. Gupta et al. (2017)[32]
457 reported that rs9349379 regulates upstream gene *EDN1*, whereas Wang et al.

(2018)[33] reported that they failed to replicate this endothelial rs9349379-EDN1 eQTL, but instead showed that rs9349379 regulates the closest gene *PHACTR1,* confirming previous vascular rs9349379-PHACTR1 eQTLs. Further, Rubin et al (2022)[58] observed that a loss of *PHACTR1* gene does not seem to have any effect on the endothelial or smooth muscle cells of the transgenic mice, and suggested that *PHACTR1* has no contribution to pathological vascular phenotype in mice through cells involved in vascular physiology. Our fine-mapping has provided strong evidence that the lead variant rs9349379 is causal for migraine, but given that the variant is intronic, our fine-mapping results alone do not provide direct evidence through which gene or mechanism this association affects the disease risk.

Our study has some limitations. First, since reliable fine-mapping requires that we exclude variants that are not present in all three component studies of our meta-analysis, it is possible that we exclude also some of the true causal variants. This is a potential problem especially when some of the top variants of the fine-map region have been filtered out from fine-mapping. To identify the regions that are likely to be affected by this problem, we studied the LD patterns between the fine-mapped variants and those top variants from the fine-map regions that were not included in the fine-mapping analysis. For most (14/17) regions where the top variants were missing from fine-mapping, the signal of the top variant was at least partly represented by another variant in LD with the top variant. Additionally, since very rare variants were not included in our analysis, we miss the true causal variants that are rare. Since our variant set is not comprehensive, we must keep in mind that also variants that have a very high probability of being causal in our analysis may still have such variants in high LD that were not included in our analysis. A valid

483 calibration of the PIPs would require that all potential causal variants were included
484 in the analysis. In practice, for common variants, this would require comprehensively
485 imputed data sets with no missing variants in any of the meta-analyzed studies, and,
486 for rare variants, availability of high coverage sequencing data. Currently, we do not
487 yet have such resources available in typical GWAS meta-analyses of common
488 diseases such as migraine.
489 Another limitation of our study relates to the phenotype definitions of different
490 substudies. First, both the UKB and 23andMe GWAS are based on self-reported
491 migraine status, and therefore some other conditions, such as tension headache,
492 may have been wrongly reported as migraine for some cases. Second, the FinnGen
493 GWAS is based on triptan purchase data, which may represent a specific subset of
494 migraine patients. Triptans are not suitable for all migraineurs and, especially, they
495 are contraindicated in patients with cardiovascular diseases. Overrepresentation of
496 migraineurs without any cardiovascular diseases could lead some FinnGen PheWAS
497 associations where migraine risk alleles seem to have protective effect on
498 cardiovascular phenotypes. Observational studies have reported that both migraine
499 and cardiovascular disease risk in women are positively associated[59].
500
501 To conclude, we performed a migraine GWAS meta-analysis with 98,375 migraine
502 cases and 869,159 controls and identified 122 risk loci of which 35 were new. We
503 followed up the meta-analysis by the first systematic fine-mapping analysis of
504 migraine risk loci and identified 7 variants with a high probability of being causal. In
505 addition to providing new information about genetic risk of migraine, we also
506 proposed how one could, in general, evaluate whether the fine-mapping results of
507 each risk loci seem reliable based only on the output from the fine-mapping software

FINEMAP. While a definitive fine-mapping analyses will require more comprehensive data than are currently available for the GWAS meta-analyses of common diseases, our study shows how reliable and novel fine-mapping results can be extracted already from the currently available data sets by a suitable analysis approach.

512 Methods

513

514 Data

515

516 We performed a new migraine meta-analysis by combining summary statistics from
517 three migraine GWAS: UK Biobank (N= 341,050, 10,881 cases and 330,169
518 controls), 23andMe (N=283,985, 53,109 cases and 230,876 controls), and FinnGen
519 R8 (N= 342,499, 34,385 cases and 308,114 controls). By meta-analyzing the three
520 studies, the total sample size was 967,534 including 98,375 migraine cases and
521 869,159 controls.

522

523 UK Biobank: The UK Biobank project is a population-based prospective cohort study
524 that consists of over 500,000 participants aged 40-69 at recruitment collected from
525 several regions across the United Kingdom. The participants completed
526 questionnaires and attended interviews and clinal examinations by a trained staff
527 member. A detailed description of UK Biobank is provided elsewhere[60], and detailed
528 genotyping, quality control and imputation procedures are described at the UK
529 Biobank website (https://www.ukbiobank.ac.uk/). We used the migraine GWAS data
530 described in[13] with self-reported migraine as the phenotype. UK Biobank received
531 ethical approval from the North West Multi-centre Research Ethics Committee
532 (MREC) and informed consent has been obtained from all participants.

533

534 23andMe: 23andMe migraine GWAS was performed by a personal genomics
535 company 23andMe, Inc. (https://www.23andme.com/) and detailed description of the
536 migraine GWAS is provided elsewhere[8]. All participants have provided informed

consent and filled an online survey according to 23andMe's human subjects protocol, which was reviewed and approved by Ethical & Independent Review Services, a private institutional review board. Briefly, migraine cases were assessed from the participants that had reported migraine or answered "Yes" to any of the questions related to migraine, and controls from participants that did not report having migraine or answered "No" to all of the questions related to migraine, excluding participants with discordant answers.

FinnGen: FinnGen (https://www.finngen.fi/en) is a large biobank study that has collected and genotyped 500,000 Finns and combined these data with longitudinal registry data including The National Hospital Discharge Registry, Causes of Death Registry and medication reimbursement registries, all of these linked by unique national personal identification codes. FinnGen includes prospective and retrospective epidemiological and disease-based cohorts and hospital biobank samples. A detailed description of FinnGen is provided in[61]. We used the 8th Data Freeze for the migraine GWAS. The migraine cases were defined as the individuals who had at least one triptan purchase and the remaining individuals without any triptan purchases were defined as controls from the social insurance institution of Finland (KELA) registry including medication reimbursement and drug purchases (https://r8.risteys.finngen.fi/phenocode/MIGRAINE_TRIPTAN).
FinnGen participants provided informed consent under the Finnish Biobank Act. Older cohorts with study-specific consents were transferred to the Finnish biobanks after approval by Fimea, the National Supervisory Authority for Welfare and Health. Recruitment protocols followed the biobank protocols approved by Fimea. The

Coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa (HUS) approved the FinnGen study protocol (Nr HUS/990/2017).

The FinnGen study is approved by Finnish Institute for Health and Welfare (permit numbers: THL/2031/6.02.00/2017, THL/1101/5.05.00/2017, THL/341/6.02.00/2018, THL/2222/6.02.00/2018, THL/283/6.02.00/2019, THL/1721/5.05.00/2019 and THL/1524/5.05.00/2020), Digital and population data service agency (permit numbers: VRK43431/2017-3, VRK/6909/2018-3, VRK/4415/2019-3), the Social Insurance Institution (permit numbers: KELA 58/522/2017, KELA 131/522/2018, KELA 70/522/2019, KELA 98/522/2019, KELA 134/522/2019, KELA 138/522/2019, KELA 2/522/2020, KELA 16/522/2020), Findata permit numbers THL/2364/14.02/2020, THL/4055/14.06.00/2020,,THL/3433/14.06.00/2020, THL/4432/14.06/2020, THL/5189/14.06/2020, THL/5894/14.06.00/2020, THL/6619/14.06.00/2020, THL/209/14.06.00/2021, THL/688/14.06.00/2021, THL/1284/14.06.00/2021, THL/1965/14.06.00/2021, THL/5546/14.02.00/2020, THL/2658/14.06.00/2021, THL/4235/14.06.00/2021 and Statistics Finland (permit numbers: TK-53-1041-17 and TK/143/07.03.00/2020 (earlier TK-53-90-20) TK/1735/07.03.00/2021).

The Biobank Access Decisions for FinnGen samples and data utilized in FinnGen Data Freeze 8 include: THL Biobank BB2017_55, BB2017_111, BB2018_19, BB_2018_34, BB_2018_67, BB2018_71, BB2019_7, BB2019_8, BB2019_26, BB2020_1, Finnish Red Cross Blood Service Biobank 7.12.2017, Helsinki Biobank HUS/359/2017, Auria Biobank AB17-5154 and amendment #1 (August 17 2020), AB20-5926 and amendment #1 (April 23 2020), Biobank Borealis of Northern Finland_2017_1013, Biobank of Eastern Finland 1186/2018 and amendment 22 § /2020, Finnish Clinical Biobank Tampere MH0004 and amendments (21.02.2020 &

06.10.2020), Central Finland Biobank 1-2017, and Terveystalo Biobank STB 2018001.

We have access to the complete in-sample LD information for the UK Biobank and FinnGen samples via the individual-level genotype data. Additionally, we have access to the in-sample LD-matrices in 23andMe data for 26 of our fine-map regions. Thus, for the 26 fine-map regions, we are able to do a high-quality fine-mapping based on the in-sample LD while, for the remaining 76 regions, we need to apply an LD reference panel that does not perfectly match the LD information corresponding to our GWAS summary statistics. To assess the effect of the LD reference panel, we formed two reference panels from the available LD information: one including data only from the UK Biobank (UKB), and the other combining the LD matrices from UK Biobank and FinnGen (UKB-FG), as explained in section “Fine-mapping”.

Genetic association analyses

The UK Biobank and 23andMe GWAS had been conducted by logistic regression on migraine (using PLINK2[62] or custom software of the 23andMe Research Team, respectively), and the FinnGen GWAS by a whole-genome regression model for a binary trait with REGENIE[27].
All the samples were of European descent. Related individuals had been excluded by using a kinship value threshold of 0.0442 computed by KING[63] from UK Biobank, and by using a minimal expected amount of sharing between first cousins from a segmental identity-by descent algorithm from 23andMe. For the FinnGen GWAS

610 analysis, REGENIE accounted for the genetic relatedness by default, and therefore
611 no relatedness exclusions were applied.
612 We excluded multi-allelic variants, and variants with minor allele frequency (MAF) <
613 0.01, IMPUTE2 info or MACH r^2 < 0.6, and when available, missingness > 0.05 and
614 Hardy-Weinberg equilibrium (HWE) $P < 1 \times 10^{-6}$ from each study. Consequently, we
615 are only considering biallelic common variants in this work. We recoded indels as
616 insertions (I) and deletions (D). We mapped the FinnGen GWAS summary statistics
617 positions from hg38 to hg37 by UCSC LiftOver[64]. We excluded the SNPs with an
618 effect allele frequency (EAF) discrepancy of >0.30 and indels with an EAF
619 discrepancy of >0.20 compared to UK Biobank from each study following
620 Hautakangas et al. 2022.
621 We conducted an inverse-variance weighted fixed-effects meta-analysis to combine
622 the three studies by GWAMA[65] with 11,316,120 variants, of which 7,062,924 variants
623 were available in all three studies.
624
625 Genetic correlation and SNP-heritability using LD Score regression
626
627 We estimated genetic correlations between the three GWAS and SNP-heritability
628 from the migraine meta-analysis by LD Score regression v1.0.0[66,25] with
629 precomputed 1000 Genomes European LD Scores
630 (https://data.broadinstitute.org/alkesgroup/LDSCORE/) limiting the analysis to the
631 HapMap3 SNPs. We used munge-tool to reformat and perform additional quality
632 control for all GWAS summary statistics prior to the genetic correlation estimation.
633 We obtained a liability scale SNP-heritability estimate[67] by using a population
634 prevalence of 16% for migraine.

635

636 Locus definition

637

638 We followed the locus definition of Hautakangas et al. (2022) and defined an LD-
639 independent genome-wide significant (GWS, $P < 5 \times 10^{-8}$) risk locus from the meta-
640 analysis by using the UKB LD. Iteratively, we chose the variant with the smallest *P*-
641 value as the index variant and excluded all variants that had $r^2 \geq 0.1$ with the index
642 variant, until no variant had $P < 5 \times 10^{-8}$. Next, we formed high LD regions around
643 each index variant based on the combined UKB-FG LD and r^2 threshold of 0.6. The
644 start of the high LD region was the smallest position, and the end of the region was
645 the largest position where any variant had $r^2>0.6$ with the index variant. Next, we
646 formed the loci by adding $\pm$ 250 kb around the high LD region and merged the
647 overlapping regions. Further, we iteratively added all other GWS variants to their
648 closest loci, and updated the loci boundaries if any of the variants added were
649 outside the existing locus boundaries. Again, the overlapping loci were merged. We
650 named each locus by the lead variant, i.e., the variant with the smallest *P*-value of
651 the locus.

652

653 Replication in HUNT All-in Headache and IHGC16

654

655 To replicate our new loci, we used two independent data sets with no overlaps with
656 our GWAS data: HUNT All-in Headache[28] (N=40,224, 7,801 cases, 32,423 controls)
657 and IHGC16 migraine meta-analysis[9] excluding 23andMe and the Finnish cohorts (N
658 = 189,000, 27,006 migraine cases and 161,994 controls). The meta-analysis of the
659 replication data thus contained N=229,224 samples (34,807 cases and 194,417

controls). We used a one-sided *P*-value threshold of 0.05 to denote a replication and assessed consistency of the effect directions by a sign test. We also reported the two-sided *P*-value of a combined analysis of our discovery and replication results to determine which of the new loci remained GWS after observing the replication data.

Fine-mapping

For fine-mapping, we first merged loci that were closer than 1.5 Mb leading to 102 fine-map regions. We performed fine-mapping for each fine-map region with FINEMAP v1.4[19,22]. FINEMAP is a Bayesian method that uses summary statistics from a GWAS together with LD information to infer which variants are most likely causal within the genomic region. We used the default prior parameters and set the maximum number of causal variants to 10.

We estimated the in-sample LD correlations for the individual GWAS cohorts by using LDStore2[22]. We combined the in-sample LD correlations for the meta-analysis data set by combining the study-specific LD matrices by weighting each matrix in proportion to its effective sample size as follows:

$$\mathbf{R} = (M_1 \mathbf{R}_1 + \ldots + M_C \mathbf{R}_C) / M, \qquad (F1)$$

where $\mathbf{R}_i$ is the LD correlation matrix of study i, $M_i = 4N_i p_i (1-p_i)$ is the effective sample size of study i, with N_i being the total sample size (i.e., the sum of cases and controls) and p_i being the proportion of cases in study i, and $M = M_1 + \ldots + M_C$ is the sum of the effective sample sizes.

For the UK Biobank reference LD (UKB-LD), we used the in-sample LD estimated from the individuals included in the UKB GWAS.

For the combined UKB-FG LD reference panel, we combined the UKB and FG in-sample LD matrices by weighting FG in proportion to its effective sample size, and UKB in proportion to the combined UKB+23andMe effective sample size using the above formula (F1).

LD reference panel sensitivity analyses

We compared the performance of different LD refence panels (UKB LD, UKB-FG LD and in-sample LD) on the FINEMAP results for the 26 fine-map regions for which the in-sample LD was available. We used the maximum difference between the posterior inclusion probabilities (PIPs) from different panels (maxΔ) to compare the performance of the three LD panels.

In addition, we examined the following candidate statistics which could be used for separating the fine-map regions for which the fine-mapping with the reference LD performs poorly when compared to the use of the in-sample LD: 1) the posterior expectation of the number of causal variants (PENC), and, from the top variant(s) of the credible set(s) determined by FINEMAP, 2) the maximum pairwise r^2, 3) the maximum marginal *P*-value from the meta-analysis, or 4) the minimum INFO value.

Variant annotation by VEP and eQTL mapping

FINEMAP reports 95%-credible sets (CS). We searched for coding variants among the CS from the Ensembl VEP

(http://grch37.ensembl.org/Homo_sapiens/Tools/VEP) database by using a default of 5 kb window around the index variant.

For the follow-up analyses, we formed a functional variant group among the CS variants by including the variants that were predicted by VEP to have a moderate or high impact on the transcript (https://www.ensembl.org/info/genome/variation/prediction/predicted_data.html). This includes transcript ablation, splice acceptor or donor variants, stop gained, frameshift variant, stop lost, start lost, transcript amplification, inframe insertion or deletion, and missense variant.

We mapped the functional variant set, and also another set including all variants with PIP > 0.1 (highPIP), to significant eQTLs of the 49 tissues from GTEx v.8 (https://gtexportal.org/home/).

Phenome-wide association scans

We performed three phenome-wide association scans (PheWAS). First, we scanned all 181 candidate variants of the risk loci (top variants of the credible sets) among the 2,399 FinnGen Data Freeze 10 (R10) GWAS endpoints (excluding 9 migraine endpoints) at significance level 1×10^{-5}. Second, we scanned all variants annotated as functional variants with a moderate to high impact on protein function by VEP among neurological and cardiovascular endpoints from FinnGen R10, including the FinnGen endpoint categories Neurological endpoints, VI Diseases of the nervous system (G6_), and IX Diseases of the circulatory system (I9_) with at significance level 1×10^{-4}.

Third, we scanned all variants with PIP > 0.1 among the same FinnGen neurological and cardiovascular endpoints at significance level 1×10^{-4}.
Results can be browsed from PheWAS app https://hhautakangas.github.io/phewas_migraine_tables.html.

Data availability

The access to the UK biobank data can be applied through https://www.ukbiobank.ac.uk/
The GWAS summary statistics for FinnGen R8 are publicly available through https://www.finngen.fi/en/access_results. The Finnish biobank data can be accessed through the Fingenious® services (https://site.fingenious.fi/en/) managed by FINBB. Finnish Health register data can be applied from Findata (https://findata.fi/en/data/).
The GWAS summary statistics for the 23andMe data set will be made available through 23andMe to qualified researchers under an agreement with 23andMe that protects the privacy of the 23andMe participants. Please visit https://research.23andme.com/collaborate/#publication for more information and to apply to access the data.

Acknowledgements

We would like to thank the research participants and employees of 23andMe, Inc. for making this work possible. We thank all the study participants, employees, and investigators of FinnGen and the UK Biobank for their contribution to this research. This research has been conducted using the UK Biobank Resource under Application Number 22627. This work was supported by grants no. 336825, 338507,

352795 from the Research Council of Finland to M.P., by Sigrid Jusélius foundation (M.P. and A.P.) and by the Doctoral School of University of Helsinki (H.H.).

The FinnGen project is funded by two grants from Business Finland (HUS 4685/31/2016 and UH 4386/31/2016) and the following industry partners: AbbVie Inc., AstraZeneca UK Ltd, Biogen MA Inc., Bristol Myers Squibb (and Celgene Corporation & Celgene International II Sàrl), Genentech Inc., Merck Sharp & Dohme LCC, Pfizer Inc., GlaxoSmithKline Intellectual Property Development Ltd., Sanofi US Services Inc., Maze Therapeutics Inc., Janssen Biotech Inc, Novartis AG, and Boehringer Ingelheim International GmbH. Following biobanks are acknowledged for delivering biobank samples to FinnGen: Auria Biobank (www.auria.fi/biopankki), THL Biobank (www.thl.fi/biobank), Helsinki Biobank (www.helsinginbiopankki.fi), Biobank Borealis of Northern Finland (https://www.ppshp.fi/Tutkimus-ja-opetus/Biopankki/Pages/Biobank-Borealis-briefly-in-English.aspx), Finnish Clinical Biobank Tampere (www.tays.fi/en-US/Research_and_development/Finnish_Clinical_Biobank_Tampere), Biobank of Eastern Finland (www.ita-suomenbiopankki.fi/en), Central Finland Biobank (www.ksshp.fi/fi-FI/Potilaalle/Biopankki), Finnish Red Cross Blood Service Biobank (www.veripalvelu.fi/verenluovutus/biopankkitoiminta), Terveystalo Biobank (www.terveystalo.com/fi/Yritystietoa/Terveystalo-Biopankki/Biopankki/) and Arctic Biobank (https://www.oulu.fi/en/university/faculties-and-units/faculty-medicine/northern-finland-birth-cohorts-and-arctic-biobank). All Finnish Biobanks are members of BBMRI.fi infrastructure (www.bbmri.fi). Finnish Biobank Cooperative - FINBB (https://finbb.fi/) is the coordinator of BBMRI-ERIC operations in Finland. The Finnish biobank data can be accessed through the Fingenious® services (https://site.fingenious.fi/en/) managed by FINBB.

The Trøndelag Health Study (HUNT) is a collaboration between HUNT Research Centre (Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology NTNU), Trøndelag County Council, Central Norway Regional Health Authority, and the Norwegian Institute of Public Health. The genotyping was financed by the National Institute of health (NIH), University of Michigan, The Norwegian Research council, and Central Norway Regional Health Authority and the Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology (NTNU). The genotype quality control and imputation has been conducted by the K.G. Jebsen center for genetic epidemiology, Department of public health and nursing, Faculty of medicine and health sciences, Norwegian University of Science and Technology (NTNU).

Consortia

A full list of FinnGen members and their affiliations appears in the Supplementary Data 1.

International Headache Genetics Consortium

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Competing interests

A.P. is the Scientific Director of the public-private partnership project FinnGen that has 12 industry partners that provide funding for the FinnGen project.

Other authors report no conflicts of interests.

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