Genetic variants in migraine: a field synopsis and systematic re-analysis of meta-analyses

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Abstract

Objective: Numerous genetic variants from meta-analyses of observational studies and GWAS were reported to be associated with migraine susceptibility. However, due to the random errors in meta-analyses, the noteworthiness of the results showing statistically significant remains doubtful. Thus, we performed this field synopsis and re-analysis study to evaluate the noteworthiness using a Bayesian approach in hope of finding true associations.

Methods: Relevant meta-analyses from observational studies and GWAS examining correlation between all genetic variants and migraine risk were included in our study by a PubMed search. Identification of noteworthy associations were analyzed by false-positive rate probability (FPRP) and Bayesian false discovery probability (BFDP). Using noteworthy variants, GO enrichment analysis were conducted through DAVID online tool. Then, the PPI network and hub genes were performed using STRING database and CytoHubba software.

Results: As for 8 significant genetic variants from observational studies, none of which showed noteworthy at prior probability of 0.001. Out of 47 significant genetic variants in GWAS, 36 were noteworthy at prior probability of 0.000001 via FPRP or BFDP. We further found the pathways “positive regulation of cytosolic calcium ion concentration” and “inositol phosphate-mediated signaling” and hub genes including MEF2D, TSPAN2, PHACTR1, TRPM8 and PRDM16 related to migraine susceptibility.

Conclusion: Herein, we have identified several noteworthy variants for migraine susceptibility in this field synopsis. We hope these data would help identify novel genetic biomarkers and potential therapeutic target for migraine.

Keywords: Genetic variant, Migraine, Meta-analysis, FPRP, BFDP, GWAS

Introduction

Migraine is a complex and incapacitating neurologic condition with more than one billion individuals suffering from and imposes a huge socioeconomic burden worldwide [1, 2]. It is characterized by recurrent episodes of unilateral throbbing pain often accompanied with nausea, phonophobia and photophobia, leading to a decline in life quality or even disability [3]. In the Global Burden of Disease (GBD) 2015, migraine ranked the seventh among the leading causes of years lived with disability for all ages and the third for ages 15 to 49 years [4]. Recently, it has been reported that, in the United States, migraine affected almost 15% adults and the annual economic cost was over $ 2600 each person diagnosed with episodic migraine and $ 8000 for those with chronic migraine [5, 6]. Thus, a large amount of studies was performed to explore the risk factors and pathogenesis of migraine over the past decades.

Except for the common risk factors such as obesity, medication overuse, poor sleep, caffeine and stressful life events, the genetic factors for migraine susceptibility was drawing more and more attention [7, 8]. Numerous genetic polymorphisms from meta-analyses of observational studies and GWAS were reported to be associated with migraine susceptibility [9]. However, due to the random errors in meta-analyses leading to false-positive results, the noteworthiness of the results with statistical significance remains doubtful. Therefore, in this field synopsis, we summarized and re-analyzed all significant genetic...
variants from meta-analyses of observational studies and GWAS, then assessed their noteworthiness using Bayesian procedures including false-positive rate probability (FPRP) and Bayesian false discovery probability (BFDP) and discussed possible molecular mechanisms for migraine occurrence.

**Methods**

**Search strategy and data extraction**

A comprehensive literature search was conducted in the PubMed database up to 31 July 2019, by using the following terms: “migraine/ headache” and “meta-analysis” and “polymorphism/genome-wide association study/SNP/GWAS/variant/allele/genotype”. Studies were all selected according to the following criteria: (1) meta-analysis design study; (2) evaluating the association between genetic polymorphisms and migraine risk; (3) raw data available including odds ratios (ORs), 95% confidence intervals (CIs) or other information necessary for FPRP and BFDP calculation; (4) studies published in English. Data including author, published year, genetic variant, genetic model, OR, 95% CI, P-value, ethnicity, type of migraine, number of cases and controls, heterogeneity and publication bias were extracted from the meta-analyses included according to above criteria.

**Assessment methods for meta-analysis**

In order to figure out the noteworthiness of meta-analysis on the association between genetic polymorphisms and migraine susceptibility, two novel statistic methods, FPRP and BFDP, were applied in our study. FPRP is the probability that no true association exists between genetic variant and disease drawing a statistically significant finding [10]. The magnitude of the FPRP is determined by prior probability, statistical power and observed P-value. Owing to the highly subjective prior probability, we analyzed a wide range of prior probabilities. We calculated FPRP values using two levels of prior probabilities: at 0.05/0.001 (medium/low prior level) that would be expected for candidate SNPs, and at 0.001/0.000001 (medium/low prior level) for GWAS SNPs. Moreover, the lower the prior probability, the more reliable the result. Besides, we used statistical power to detect ORs of 1.2 and 1.5 for computing FPRP at each prior probability. For the statistically significant SNPs (95% CI that excluded 1 and P-value which was lower than $5 \times 10^{-8}$ for meta-analysis of GWAS or 0.05 for observational studies), we calculated FPRP by using the Excel spreadsheet offered by Wacholder (http://nci.can.cancer.gov/ncifcrf/social.html) [10]. FPRP values lower than 0.2 were considered to be noteworthy.

BFDP is the fact that if an association is reported as noteworthy, BFDP is the probability of a false discovery [11]. Relevant data and prior probability applied in the calculation of BFDP were same as it of FPRP. The BFDP was estimated by using the excel Calculation Spreadsheet (http://faculty.washington.edu/jonno/cv.html) [11]. And BFDP with the values of less than 0.8 were considered to be a noteworthy significant association. Different from FPRP, BFDP is a new statistical method based on logistic regression model rather than standard normal distribution and doesn’t rely on the statistical power. Thus, BFDP has a sounder methodological basis. Nevertheless, Wakefield admits that there is no significant difference in the overall behavior between these two approaches [11]. Therefore, we presented the both results of FPRP and BFDP which allowed readers to reach a more comprehensive judgment.

Besides, for the meta-analysis of observational studies, summary evidence was also evaluated using Venice criteria, which have been described in detail previously [12, 13]. Briefly, we classified the strength of credibility into A, B and C grades that were separately characterized as strong, moderated and weak in three parameters including amount of evidence, replication of association and the protection from bias. According to this criteria, high credibility was defined as including A grades only, intermediate credibility was composed of A and B grades and low credibility was one or more C grades.

**Joint population attributable risk calculation**

We evaluated the cumulative effect of all noteworthy SNPs on migraine susceptibility. We used the minor allelic frequency (MAF) to calculated the population attributable risk (PAR) and further estimated the Joint PAR% for the SNPs showing noteworthiness during the computing of BFDP (BFDP < 0.8) or FPRP (FPRP < 0.2) at a prior probability of $10^{-6}$ assumed for GWAS SNPs and $10^{-3}$ for candidate SNPs at a statistical power to detect the OR of 1.5.

**GO and enrichment pathway analysis and PPI network construction**

Gene ontology (GO) analysis is a useful bioinformatic method for annotating genes. In our study, GO enrichment analyses were carried out using a list of genes with noteworthy SNPs through DAVID online tool (http://david.abcc.ncifcrf.gov/). Then, we applied the STRING 11.0 network database to construct a protein-protein interaction (PPI) network. We set the minimum required interaction score at 0.15, no more than five interactors and four active interaction sources (experiments, text mining, co-expression and database) for PPI construction. Finally, we used the Cytoscape (version 3.4.2) and cytoHubba to detect hub genes meanwhile the cut-off criterion of hub genes was setting as degree ≥7.
Results
First, a total of 89 articles were identified according to our search strategy. Second, 38 obviously irrelevant articles were excluded by screening the titles and abstracts. After reviewing the full-text articles, 16 were further excluded, among which 9 articles were not meta-analyses and 7 were not correlated with migraine susceptibility. At last, 35 articles were selected into our study [14–48]. The screening process of the articles was performed by two independent researchers and shown in Fig. 1. Overall data retrieved from meta-analyses of observational studies and GWAS on risk of migraine were summarized in Additional file 1: Table S1 and Additional file 2: Table S2. Third, when more than one meta-analysis was available for certain SNP, we only included the results from more recent meta-analysis with larger sample size. Finally, the statistically significant results with $P < 0.05$ for observational studies and $P < 5 \times 10^{-8}$ for GWAS were summarized in Tables 1 and 2.

As shown in Table 1, 5 genes with 8 genetic variants from observational studies were found to be significant after excluding the overlapping data. At a prior probability of 0.05, we identified the genetic variants, MTHFR/rs1801133, noteworthy via FPRP estimation with a statistical power to detect OR of 1.2. Likewise, 4 genetic variants including MTHFR/rs1801133, BDNF/rs6265, ESR1/rs1801132 and 5-HTT/VNTR showed noteworthy FPRP values to detect OR of 1.5. As for the statistical method BFDP, the same 4 genetic variants were noteworthy. However, when it comes to the re-analysis at a prior probability of 0.001, no noteworthy relationship between genetic variants and migraine risk could be detected via FPRP and BFDP.

Moreover, we performed subgroup analysis of observational studies based on the migraine subtypes (Table 3). In the migraine with aura subgroup, only 1 (TNF-a/rs1800629) and 3 (MTHFR/rs1801133, ESR1/rs1801132 and TNF-a/rs1800629) genetic variants was noteworthy in FPRP at the prior probability of 0.05 with a statistical power to detect an OR of 1.2 and 1.5, respectively. And all the variants with noteworthy FPRP values were also noteworthy in BFDP estimation. Similarly, none was identified to be noteworthy in FPRP and BFDP when the prior probability was 0.001. In migraine without aura, we did not observe any noteworthy SNPs. Subsequent subgroup analyses based on ethnicity were performed and displayed in Table 4. Compared with 4 noteworthy SNPs identified at the prior probability of 0.05 containing MTHFR/rs1801133, BDNF/rs6265, ESR1/rs1801132 and ESR1/rs2228480 for Caucasian population, none of candidate polymorphisms was considered to be noteworthy in non-Caucasian population.

In addition to FPRP and BFDP, we also used the Venice criteria to evaluate the credibility of the meta-analyses characterized by low, intermediate and high level (Table 1). We observed a consistency between the noteworthiness measured by FPRP and BFDP and Venice criteria score for candidate SNPs, that is, most of the noteworthy SNPs observed in our re-analysis were with high or intermediate level of evidence, with the exception of MTHFR/rs1801133.
Table 1 Meta-analyses results of genetic variants with statistically significance (P-value<0.05) from observational studies

| Author, year | Gene/variant | Comparison | OR (95%CI) | P-value | Ethnicity | No. of cases/controls | BFDP | BFDP Venice criteria | OR 1.2 | OR 1.5 |
|--------------|--------------|------------|------------|---------|-----------|----------------------|------|----------------------|-------|-------|
| Liu L, 2019  | MTHFR/ rs1801133 | T vs. C    | 1.19       | 0.004    | Overall 26 (Caucasian 20, Asian 6) | 10,228/28608 | 0.069 0.795 0.040 0.685 0.476 0.980 A + C + C Low |
| Liu L, 2019  | MTHFR/ rs1801133 | TT vs. CT + CC | 1.29       | 0.010    | Overall 26 (Caucasian 20, Asian 6) | 10,228/28608 | 0.419 0.974 0.149 0.902 0.726 0.993 A + C + C Low |
| Liu L, 2019  | MTHFR/ rs1801133 | TT + CT vs. CC | 1.17       | 0.027    | Overall 26 (Caucasian 20, Asian 6) | 10,228/28608 | 0.485 0.980 0.375 0.969 0.880 0.997 A + C + C Low |
| Liu L, 2019  | MTHFR/ rs1801133 | TT vs. CC | 1.32       | 0.011    | Overall 26 (Caucasian 20, Asian 6) | 10,228/28608 | 0.543 0.984 0.209 0.933 0.778 0.995 A + C + C Low |
| Liu L, 2019  | MTHFR/ rs1801133 | CC vs. AC + AA | 1.82       | 0.022    | Overall 5 (Caucasian 4, Asian 1) | 1368/1411 | 0.883 0.988 0.647 0.990 0.998 0.998 A + C + C Low |
| Liu L, 2019  | MTHFR/ rs1801133 | CC vs. AA | 1.78       | 0.038    | Overall 5 (Caucasian 4, Asian 1) | 1368/1411 | 0.903 0.982 0.729 0.993 0.917 0.998 A + C + C Low |
| Gao X, 2018  | GRI/ rs2195450 | CT vs. CC | 1.23       | 0.03     | Overall 4 (Caucasian 3, Asian 1) | 963/1167 | 0.576 0.986 0.354 0.966 0.862 0.997 A + B + A Intermediate |
| Terrazzino S | BDNF/ rs6265 | A vs. G | 1.17       | 0.014    | Overall 5 (Caucasian 4) | 2884/3760 | 0.408 0.973 0.307 0.959 0.856 0.997 A + A + A High |
| Terrazzino S | BDNF/ rs6265 | AA + GA vs. GG | 1.22       | 0.011    | Overall 5 (Caucasian 4) | 2884/3760 | 0.247 0.945 0.119 0.877 0.694 0.992 A + A + A High |
| Cai X, 2017  | BDNF/ rs2049046 | A vs. T | 0.88       | 0.02     | Overall 4 (Caucasian 4) | 1260/1380 | 0.311 0.960 0.275 0.952 0.855 0.997 A + A + C Low |
| Cai X, 2017  | BDNF/ rs2049046 | AA vs. TA + TT | 0.80       | 0.02     | Overall 4 (Caucasian 4) | 1260/1380 | 0.486 0.980 0.243 0.944 0.809 0.996 A + A + A High |
| Cai X, 2017  | BDNF/ rs2049046 | AA vs. TT | 0.78       | 0.02     | Overall 4 (Caucasian 4) | 1260/1380 | 0.637 0.989 0.345 0.965 0.853 0.997 A + A + A High |
| Cai X, 2017  | BDNF/ rs2049046 | AA vs. TA | 0.81       | 0.03     | Overall 4 (Caucasian 4) | 1260/1380 | 0.658 0.990 0.436 0.976 0.887 0.998 A + A + A High |
| Li L, 2015   | ESR1/ rs1801132 | GG vs. CC | 1.51       | 0.003    | Overall 5 (Caucasian 4, Asian 1) | 2027/1919 | 0.559 0.985 0.119 0.877 0.644 0.990 A + A + A High |
| Li L, 2015   | ESR1/ rs1801132 | GG vs. CC + GC | 1.52       | 0.002    | Overall 5 (Caucasian 4, Asian 1) | 2027/1919 | 0.477 0.980 0.073 0.805 0.542 0.984 A + B + A Intermediate |
| Li L, 2015   | ESR1/ rs2228480 | AG vs. GG | 1.14       | 0.030    | Overall 6 (Caucasian 5, Asian 1) | 2293/2026 | 0.385 0.971 0.336 0.964 0.877 0.997 A + A + A High |
| Li L, 2015   | ESR1/ rs2228480 | AA + AG vs. GG | 1.13       | 0.003    | Overall 6 (Caucasian 5, Asian 1) | 2293/2026 | 0.381 0.970 0.346 0.965 0.885 0.998 A + B + A Intermediate |
| Liu H, 2011  | S-HTT/VNTR | Stin2.12 allele | 1.34       | 0.006    | Overall 4 (Caucasian 3, Asian 1) | 495/729 | 0.377 0.970 0.090 0.840 0.628 0.989 A + A + NA NA |
| Liu H, 2011  | S-HTT/VNTR | 12/12 genotype | 1.55       | 0.002    | Overall 4 (Caucasian 3, Asian 1) | 495/729 | 0.526 0.983 0.090 0.838 0.557 0.986 A + A + NA NA |

OR odds ratio, CI confidence interval, FPRP false-positive rate probability, BFDP Bayesian false discovery probability, NA not available.
As shown in Table 2, within the data extracted from the meta-analyses of GWAS, 40 genes with 47 genetic variants were statistically significant \( (P < 5 \times 10^{-8}) \). According to the results of the re-analyses, 32 and 26 SNPs were found to be noteworthy via FPRP estimation at the statistical power to detect the OR of 1.2 with the prior probability of 0.001 and 0.000001. 34 and 26 SNPs were identified as noteworthy to detect the OR of 1.5 via FPRP. As for BFDP, 40 and 35 SNPs were noteworthy under the prior probability of 0.001 and 0.000001. Almost all noteworthy variants calculated through FPRP also showed noteworthy BFDP values. Only three variants (YAP1/rs10895275, TGFBR2/rs6791480 and MPPED2/rs11031122) were noteworthy in the calculation of FPRP, but not via BFDP. In addition, we detected 9 noteworthy SNPs (LRP1/rs11172113, PRDM16/rs10218452, FHL5/rs67338227, TSPAN2/rs2078371, PLCE1/rs10786156, KCNK5/rs10456100, CFDP1/rs77505915, NRP1/rs2506142 and ADAMTSL4/rs6693567) in the computation of BFDP rather than FPRP, which could be explained by the fact that, in some cases, noteworthiness cannot be assessed on account of a mathematical error during the calculation of the inverse of cumulative normal distribution in FPRP. Furthermore, in the subgroup analysis, we only performed the re-analysis of migraine without aura but not migraine with aura owing to the lack of raw data. We found that all ten statistically significant variants within 8 genes were noteworthy in migraine without aura subgroup (Table 5). In addition, due to the population included in the GWAS were almost Caucasians, subgroup re-analysis based on ethnicity cannot be performed.

In order to provide readers with the predictive potential of the migraine risk, we calculated the joint PAR which was recently argued to be more credible than \( \text{P}\)-values or ORs by combining 36 noteworthy variants via FPRP or BFDP. And the value of joint PAR in our study was 44.2\%, indicating that these involved SNPs together may attribute to an obvious increment in the risk of migraine and this method may be a useful way for screening migraine susceptibility and identify at-risk populations (Table 6).

To explore the potential biology mechanism for migraine, GO enrichment analysis was performed. As shown in Fig. 2, twelve GO terms were identified including “cell-cell signaling” (GO: 0007267), “inositol phosphate-mediated signaling” (GO:0048016), “positive regulation of cytosolic calcium ion concentration” (GO: 0007204), “integral component of plasma membrane” (GO:0005887), “adult heart development” (GO:0007512), “regulation of smooth muscle contraction” (GO: 0006940), “activating transcription factor binding” (GO: 0033613), “sprouting angiogenesis” (GO:0002040), “patternning of blood vessels” (GO:000156), “angiogenesis” (GO:0001525), “receptor activity” (GO:0004872) and “protein kinase C-activating G-protein coupled receptor signaling pathway” (GO:0007205). To detect the interactive relationships and potential hub nodes, PPI network of all genes with noteworthy SNPs were constructed and displayed in Additional file 3: Figure S1. Moreover, when degree \( \geq 7 \) as the cut-off criterion, 5 genes (MEF2D, TSPAN2, PHACTRI, TRPM8 and PRDM16) were selected as hub genes by using CytoHubba software.

**Discussion**

Despite the serious impact of migraine on human health and its burden on public, understanding of the pathogenesis, valid prevention and treatment remains limited [49, 50]. Recent years, the genetic component of migraine has received widespread attention. Moreover, a growing number of meta-analyses from observational studies and GWAS were performed and further identified numerous significant genetic variants, which displayed important insights into the mechanisms underlying migraine development. However, due to false-positive possibility in meta-analyses, we performed the first re-analysis of meta-analyses of genetic association studies in migraine in hope of finding noteworthy associations. We used Bayesian methods and Venice criteria to evaluate the credibility of genetic associations. In this work, we synthesized all relevant data from the meta-analyses which detected the association between genetic polymorphisms and migraine risk before 31 July 2019.

As for the candidate genes, we found 4 genetic variants noteworthy at prior probability of 0.05 which were consistent with the results of Venice criteria. However, when we raised the prior probability standard from 0.05 to 0.001, we did not find any gene noteworthy under FPRP or BFDP, which indicated that the results of observational studies should be interpreted with caution. In comparison to the observational studies, according to GWAS, out of the 47 significant genetic variants, 36 were considered to be noteworthy at prior probability of 0.000001 via FPRP or BFDP. Most significant variants identified in GWAS remained noteworthy at the prior probability of 0.000001 demonstrated that the results from GWAS were more reliable.

We also detected the pathways involved in migraine by conducting functional enrichment analysis and further explore the possible molecular mechanisms. We found several significant pathways (cell-cell signaling, inositol phosphate-mediated signaling, positive regulation of cytosolic calcium ion concentration, integral component of plasma membrane and adult heart development, etc.) and 5 hub genes (MEF2D, TSPAN2, PHACTRI,
| Author, year | Gene/variant | Comparison | OR (95% CI) | P-Value | Ethnicity | No. of cases/controls | FPRP Values at Prior probability | BFDP | BFDP |
|-------------|--------------|------------|-------------|----------|-----------|-----------------------|-----------------------------------|------|------|
|             |              |            |             |          |           |                       | OR 1.2                           | 0.001 | 0.000001 |
|             |              |            |             |          |           |                       | OR 1.5                           | 0.001 | 0.000001 |
| Chang X, 2018 [45] | NMUR2/ rs1946225 | G vs. T | 2.29 (1.73–3.05) | 9.55E-09 | Overall 3 (European 1, African 2) | 1212/13494 | 0.717 1.000 | 0.006 0.851 | 0.027 0.965 | 0.000001 |
| Chang X, 2018 [45] | NMUR2/ rs72793414 | A vs. G | 2.44 (1.85–3.23) | 3.81E-10 | Overall 3 (European 1, African 2) | 1212/13494 | 0.545 0.999 | 0.001 0.541 | 0.003 0.743 | 0.000001 |
| Gormley P, 2016 [40] | LRPI/ rs11172113 | C vs. T | 0.90 (0.89–0.91) | 5.6E-09 | Overall (Caucasian 22) | 59,674/316078 | – – – – | – – – | 6.004E-72 6.011E-69 | 0.000001 |
| Gormley P, 2016 [40] | PRDM16/ rs10218452 | G vs. A | 1.11 (1.10–1.13) | 5.3E-38 | Overall (Caucasian 22) | 59,674/316078 | – – – – | – – – | 8.348E-25 8.356E-22 | 0.000001 |
| Gormley P, 2016 [40] | FHES/ rs67338227 | T vs. A | 1.09 (1.08–1.11) | 2.0E-27 | Overall (Caucasian 22) | 59,674/316078 | – – – – | – – – | 4.430E-15 4.435E-12 | 0.000001 |
| Gormley P, 2016 [40] | TSPAN2/ rs2078371 | C vs. T | 1.11 (1.09–1.13) | 4.1E-24 | Overall (Caucasian 22) | 59,674/316078 | – – – – | – – – | 8.348E-25 8.356E-22 | 0.000001 |
| Gormley P, 2016 [40] | TRPM8/ rs10166942 | C vs. T | 0.94 (0.89–0.99) | 1.0E-23 | Overall (Caucasian 22) | 59,674/316078 | 0.951 1.000 | 0.951 1.000 | 0.998 1.000 | 0.000001 |
| Gormley P, 2016 [40] | PHACTR1/ rs9349379 | G vs. A | 0.93 (0.92–0.95) | 5.8E-22 | Overall (Caucasian 22) | 59,674/316078 | 2.308E-08 2.310E-08 2.308E-08 2.310E-08 | 4.007E-06 3.995E-03 | 0.000001 |
| Gormley P, 2016 [40] | MEF2D/ rs1925950 | A vs. G | 1.07 (1.06–1.09) | 9.1E-22 | Overall (Caucasian 22) | 59,674/316078 | 8.014E-10 8.022E-10 8.014E-10 8.022E-10 | 1.694E-07 1.695E-04 | 0.000001 |
| Gormley P, 2016 [40] | SLC24A3/ rs4814864 | C vs. G | 1.07 (1.06–1.09) | 2.2E-19 | Overall (Caucasian 22) | 59,674/316078 | 8.014E-10 8.022E-10 8.014E-10 8.022E-10 | 1.694E-07 1.695E-04 | 0.000001 |
| Gormley P, 2016 [40] | FG6/ rs1024905 | A vs. G | 1.06 (1.04–1.08) | 2.1E-17 | Overall (Caucasian 22) | 59,674/316078 | 9.959E-07 9.959E-07 9.959E-07 9.959E-07 | 1.767E-04 1.767E-04 | 0.000001 |
| Gormley P, 2016 [40] | C/arr1/ rs186166891 | T vs. A | 1.09 (1.07–1.12) | 9.7E-16 | Overall (Caucasian 22) | 59,674/316078 | 4.933E-07 4.935E-07 4.933E-07 4.935E-07 | 6.430E-05 6.048E-02 | 0.000001 |
| Gormley P, 2016 [40] | PLCE1/ rs10786156 | G vs. C | 0.95 (0.94–0.96) | 2.0E-14 | Overall (Caucasian 22) | 59,674/316078 | – – – – | – – – | 3.842E-16 3.846E-13 | 0.000001 |
| Gormley P, 2016 [40] | KCNKS/ rs10456100 | T vs. C | 1.06 (1.04–1.07) | 6.9E-13 | Overall (Caucasian 22) | 59,674/316078 | – – – – | – – – | 3.372E-28 3.376E-25 | 0.000001 |
| Gormley P, 2016 [40] | ASTN2/ rs6478241 | T vs. A | 1.05 (1.04–1.07) | 1.2E-12 | Overall (Caucasian 22) | 59,674/316078 | 4.011E-04 0.287 4.011E-04 0.287 | 0.055 0.983 | 0.000001 |
| Gormley P, 2016 [40] | MRRV1/ rs4910165 | G vs. C | 0.94 (0.91–0.98) | 2.9E-11 | Overall (Caucasian 22) | 59,674/316078 | 0.783 1.000 | 0.783 1.000 | 0.993 1.000 | 0.000001 |
| Gormley P, 2016 [40] | HPSE2/ rs12260159 | A vs. G | 0.92 (0.89–0.94) | 3.2E-10 | Overall (Caucasian 22) | 59,674/316078 | 2.979E-11 2.982E-11 2.979E-11 2.982E-11 | 5.906E-09 5.912E-06 | 0.000001 |
| Gormley P, 2016 [40] | CFDP1/ rs7750915 | A vs. T | 1.05 (1.03–1.06) | 3.3E-10 | Overall (Caucasian 22) | 59,674/316078 | – – – – | – – – | 3.476E-18 3.479E-15 | 0.000001 |
| Gormley P, 2016 [40] | RNF213/ | C vs. T | 1.06 | 5.2E-10 | Overall | 59,674/9.959E-9.959E-9.959E-9.959E-1.767E-0.150 | 0.000001 | 0.000001 | 0.000001 | 0.000001 | 0.000001 |

Table 2: Meta-analyses results of genetic variants with statistically significance (P-value<5*10^-8) from GWAS
| Author, year | Gene/variant | Comparison | OR (95%CI) | P-Value | Ethnicity | No. of cases/controls | FPRP Values at Prior probability OR 1.2 | BFDP 0.001 | BFDP 0.000001 |
|-------------|--------------|------------|------------|---------|-----------|-----------------------|----------------------------------------|-----------|----------------|
| 2016 [40]   | rs17857135   | G vs. A    | 1.06 (1.04–1.07) | 1.5E-09 | Overall (Caucasian 22) | 59,674/316078 | 07 04 07 04 04       |
| Gormley P,  | NRP1       | G vs. A    | 0.87 (0.83–0.91) | 1.8E-09 | Overall (Caucasian 22) | 59,674/316078 | 1.30E-06 1.29E-06 1.26E-06 1.26E-06 1.117E-04 |
| 2016 [40]   | rs2506142   | G vs. A    | 1.05 (1.03–1.07) | 2.0E-09 | Overall (Caucasian 22) | 59,674/316078 | 4.011E-04 0.287 0.401E-04 0.287 0.055 0.983 |
| Gormley P,  | YAP1       | G vs. C    | 0.96 (0.94–0.97) | 2.5E-09 | Overall (Caucasian 22) | 59,674/316078 | 1.153E-11 1.154E-08 1.153E-08 1.154E-08 4.525E-09 4.530E-06 |
| 2016 [40]   | rs7684253   | T vs. C    | 1.03 (1.00–1.06) | 5.3E-09 | Overall (Caucasian 22) | 59,674/316078 | 0.978 1.000 0.978 1.000 1.000 1.000 |
| Gormley P,  | HEY2       | C vs. T    | 0.96 (0.95–0.97) | 7.1E-09 | Overall (Caucasian 22) | 59,674/316078 | 2.044E-04 0.170 2.040E-04 0.170 0.015 0.937 |
| 2016 [40]   | rs1268083   | T vs. C    | 1.06 (1.04–1.08) | 7.3E-09 | Overall (Caucasian 22) | 59,674/316078 | 9.959E-07 9.959E-07 9.959E-07 9.959E-07 1.767E-04 0.150 |
| Gormley P,  | GJA1       | T vs. G    | 1.04 (1.03–1.06) | 7.8E-09 | Overall (Caucasian 22) | 59,674/316078 | 0.052 0.982 0.052 0.982 0.863 1.000 |
| 2016 [40]   | rs28455731  | T vs. C    | 0.96 (0.94–0.97) | 7.9E-09 | Overall (Caucasian 22) | 59,674/316078 | 1.153E-11 1.154E-08 1.153E-08 1.154E-08 4.525E-09 4.530E-06 |
| Gormley P,  | F2R2       | C vs. A    | 1.05 (1.03–1.06) | 1.2E-08 | Overall (Caucasian 22) | 59,674/316078 | – – – – 3.476E-18 3.479E-15 |
| 2016 [40]   | rs11624776  | T vs. C    | 0.85 (0.76–0.96) | 1.2E-08 | Overall (Caucasian 22) | 59,674/316078 | 0.934 1.000 0.899 1.000 0.993 1.000 |
| Gormley P,  | ITK1       | C vs. A    | 1.04 (1.03–1.06) | 1.6E-08 | Overall (Caucasian 22) | 59,674/316078 | 0.052 0.982 0.052 0.982 0.863 1.000 |
| 2016 [40]   | rs12845494  | G vs. C    | 0.96 (0.95–0.97) | 1.7E-08 | Overall (Caucasian 22) | 59,674/316078 | 1.153E-11 1.154E-08 1.153E-08 1.154E-08 4.525E-09 4.530E-06 |
| Gormley P,  | DOCK4      | T vs. A    | 1.08 (1.05–1.12) | 2.1E-08 | Overall (Caucasian 22) | 59,674/316078 | 0.032 0.971 0.032 0.971 0.688 1.000 |
| 2016 [40]   | rs10155855  | T vs. A    | 1.04 (1.02–1.05) | 2.1E-08 | Overall (Caucasian 22) | 59,674/316078 | 8.873E-13 8.882E-10 8.873E-10 8.882E-10 4.186E-10 4.190E-07 |
| Gormley P,  | LRRQ3      | G vs. A    | 0.88 (0.84–0.92) | 2.3E-08 | Overall (Caucasian 22) | 59,674/316078 | 1.748E-05 0.017 1.733E-05 0.017 1.395E-03 0.583 |
| 2016 [40]   | rs1572668   | G vs. A    | 0.93 (0.91–3.0E-08 | Overall (Caucasian 22) | 59,674/316078 | 2.308E-08 2.310E-05 2.308E-08 2.310E-05 4.007E-06 3.995E-03 |
| Gormley P,  | ARMS2      | C vs. G    | 0.93 (0.91–3.0E-08 | Overall (Caucasian 22) | 59,674/316078 | 2.308E-08 2.310E-05 2.308E-08 2.310E-05 4.007E-06 3.995E-03 |

Table 2: Meta-analyses results of genetic variants with statistically significance (P-value<5x10^-8) from GWAS (Continued)
Circular system [51, 52]. This hypothesis is based on a
activated with activation and sensitization of trigeminovas-
ular system. It suggests that nociceptive effects may be
partially mediated through NMUR2 [58]. Similar with
the activation of nociceptors, these TRPM8-positive
nociceptors release some inflammatory mediators and
vasoactive neuropeptides such as calcitonin gene-related
peptide (CGRP), neurokinin A and substance P causing
vasodilation of dural and pial vessels and neurogenic
inflammation which finally results in central sensitization
causing headache of migraine to some extent [53].

**PLCE1** and **NMUR2**, whose variants showed
noteworthy association with migraine susceptibility, were
found to be involved in two pathways called “positive
regulation of cytosolic calcium ion concentration” and
“inositol phosphate-mediated signaling” detected in our
study. **PLCE1** is a gene encodes an enzyme called
phospholipase C that promotes the generation of inositol
triphosphate (IP3) and further direct the calcium
mobilization by initiate the release of calcium ion stored
in the endoplasmic reticulum through IP3 receptor lead-
ing to the increment of cytosolic calcium concentration
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ing to the increment of cytosolic calcium concentration
in the endoplasmic reticulum through IP3 receptor lead-
in the release of CGRP that finally results in migraine
development [60, 61].
Within the hub genes detected in our study, **TRPM8** gene was found to play an important role in the pathophysiology of migraine. As a cation channel, TRPM8 is characterized as a cold temperature detector firstly [62, 63]. However, recently, it is also discovered as a parameter for ongoing persistent pain with several evidence. **TRPM8** null mice showed a significant decrease in the injury-induced response [64]. On the opposite, the activation of TRPM8 can lead to the depolarization for nerve endings and afferent impulse into central
nervous system. Moreover, these activated neurons by noxious cold temperature have properties similar with nociceptors [65]. Mechanistically, a functional linkage was observed between TRPM8 and CGRP, that is, CGRP release was deficient in neurons without TRPM8 triggering and the release of CGRP was closely related to neurogenic inflammation and future migraine occurrence [66].

As for PHACTR1, it might be involved in migraine attack by regulating vasomotor tone. Concretely, PHACTR1 could bind with protein phosphatase 1 (PP1) and its gene silencing has been demonstrated to decrease the activity of PP1 [67]. In arteries, PP1 may play an important role in vasomotor tone by mediating calcium cycling and contractility in smooth muscle cells [68]. Also, PHACTR1 could regulate dendritic

### Table 4 Subgroup analysis of genetic variants with statistically significance (P-value< 0.05) from observational studies based on ethnicity

| Author, year | Gene/variant | Comparison | OR (95%CI) | P-Value | Ethnicity | No. of cases/controls | FPRP Values at Prior probability | BFDP 0.05 | BFDP 0.001 |
|--------------|--------------|------------|------------|---------|-----------|----------------------|----------------------------------|---------|---------|
| Liu L, 2019 [48] | MTHFR/rs1801133 | T vs. C | 1.18 (1.04–1.34) | 0.012 | Caucasian 20 | 9635/27592 | 0.253 0.947 0.169 0.915 0.766 0.994 |
| Liu L, 2019 [48] | MTHFR/rs1801133 | TT vs. CT + CC | 1.25 (1.02–1.53) | 0.035 | Caucasian 20 | 9635/27592 | 0.626 0.989 0.376 0.969 0.867 0.997 |
| Liu L, 2019 [48] | MTHFR/rs1801133 | TT vs. CC | 1.28 (1.02–1.60) | 0.036 | Caucasian 20 | 9635/27592 | 0.667 0.991 0.384 0.968 0.886 0.997 |
| Dong H, 2018 [46] | eNOS/rs2070744 | CC vs. TC + TT | 1.62 (1.03–2.56) | 0.04 | Caucasian 4 | 435/344 | 0.881 0.997 0.665 0.991 0.908 0.998 |
| Terrazzino S, 2017 [44] | BDNF/rs6265 | A vs. G | 1.17 (1.03–1.34) | 0.014 | Caucasian 5 | 2884/3760 | 0.408 0.973 0.307 0.969 0.867 0.997 |
| Terrazzino S, 2017 [44] | BDNF/rs6265 | AA + GA vs. GG | 1.22 (1.05–1.41) | 0.011 | Caucasian 5 | 2884/3760 | 0.247 0.945 0.119 0.877 0.867 0.997 |
| Cai X, 2017 [42] | BDNF/rs2049046 | A vs. T | 0.88 (0.79–0.98) | 0.2 | Caucasian 4 | 1260/1380 | 0.311 0.960 0.275 0.952 0.856 0.997 |
| Cai X, 2017 [42] | BDNF/rs2049046 | AA + TA vs. TT | 0.80 (0.67–0.96) | 0.02 | Caucasian 4 | 1260/1380 | 0.486 0.980 0.243 0.944 0.809 0.996 |
| Cai X, 2017 [42] | BDNF/rs2049046 | AA vs. TA | 0.78 (0.62–0.97) | 0.02 | Caucasian 4 | 1260/1380 | 0.637 0.989 0.345 0.965 0.853 0.997 |
| Cai X, 2017 [42] | BDNF/rs2049046 | AA vs. TT | 0.81 (0.67–0.99) | 0.03 | Caucasian 4 | 1260/1380 | 0.658 0.990 0.436 0.976 0.887 0.976 |
| Li L, 2015 [37] | ESR1/rs1801132 | GG vs. CC | 1.63 (1.20–2.22) | 0.002 | Caucasian 4 | 1693/1719 | 0.586 0.987 0.110 0.866 0.600 0.988 |
| Li L, 2015 [37] | ESR1/rs1801132 | GG vs. CG + CC | 1.63 (1.21–2.21) | 0.001 | Caucasian 4 | 1693/1719 | 0.564 0.986 0.096 0.848 0.572 0.986 |
| Li L, 2015 [37] | ESR1/rs2228480 | AG vs. GG | 1.19 (1.04–1.35) | 0.009 | Caucasian 5 | 1959/1826 | 0.192 0.926 0.116 0.873 0.696 0.992 |
| Li L, 2015 [37] | ESR1/rs2228480 | AA + AG vs. GG | 1.17 (1.04–1.33) | 0.016 | Caucasian 5 | 1959/1826 | 0.323 0.962 0.237 0.942 0.821 0.996 |
| Chen M, 2015 [35] | TNF-α/rs1800629 | A vs. G | 1.74 (1.13–2.67) | 0.012 | Non-Caucasian 5 | 985/956 | 0.828 0.996 0.462 0.978 0.851 0.997 |
| Chen M, 2015 [35] | TNF-α/rs1800629 | AA+GA vs. GG | 1.82 (1.15–2.87) | 0.010 | Non-Caucasian 5 | 985/956 | 0.838 0.996 0.483 0.980 0.854 0.997 |
| Chen M, 2015 [35] | TNF-α/rs1800629 | GA vs. GG | 1.78 (1.17–2.72) | 0.007 | Non-Caucasian 5 | 985/956 | 0.810 0.996 0.405 0.973 0.828 0.996 |
| Chen M, 2015 [35] | NOS3/rs1799983 | TT vs. GT + GG | 1.84 (1.02–3.33) | 0.043 | Non-Caucasian 3 | 504/339 | 0.914 0.998 0.770 0.994 0.923 0.998 |
| Chen M, 2015 [35] | NOS3/rs1799983 | TT vs. GG | 2.10 (1.14–3.88) | 0.018 | Non-Caucasian 3 | 504/339 | 0.902 0.998 0.706 0.992 0.907 0.998 |
| Liu R, 2014 [32] | TNF-β/rs009253 | GG vs. AG + AA | 1.38 (1.04–1.84) | 0.027 | Non-Caucasian 3 | 746/717 | 0.759 0.994 0.428 0.975 0.869 0.997 |
Table 5 Subgroup analysis results of genetic variants with statistically significance (P-value<5*10^{-8}) from GWAS studies based on migraine subtype

| Author, year | Gene/variant | Comparison | OR (95%CI) | P-value | Subtypes | No. of cases/controls | FPRP Values at Prior probability | BFDP |
|--------------|--------------|------------|------------|---------|----------|----------------------|---------------------------------|------|
| Gormley P, 2016 [40] | LRP1/rs11172113 | C vs. T | 0.85 (0.82–0.89) | 4.3E-16 MO | 8348/139622 | 5.36E-09 | 4.29E-06 | 4.30E-06 | 4.57E-07 | 4.58E-04 |
| Gormley P, 2016 [40] | FHLS/rs7775721 | T vs. A | 1.15 (1.11–1.29) | 1.1E-12 MO | 8348/139622 | 1.25E-04 | 1.22E-04 | 1.22E-04 | 1.21E-04 | 1.30E-05 |
| Gormley P, 2016 [40] | ASTN2/ rs6478241 | G vs. A | 1.14 (1.09–1.18) | 1.2E-10 MO | 8348/139622 | 9.55E-11 | 9.56E-11 | 9.53E-11 | 9.54E-11 | 1.30E-05 |
| Gormley P, 2016 [40] | TRPM8/ rs6724624 | G vs. C | 0.86 (0.82–0.90) | 1.1E-09 MO | 8348/139622 | 8.65E-08 | 7.89E-08 | 7.90E-08 | 7.68E-08 | 7.63E-03 |
| Gormley P, 2016 [40] | PHACTR1/ rs9349379 | A vs. G | 0.88 (0.85–0.92) | 2.1E-09 MO | 8348/139622 | 1.74E-05 | 1.73E-05 | 1.73E-05 | 1.39E-05 | 0.583 |
| Gormley P, 2016 [40] | FG6a/rs1024905 | A vs. G | 1.12 (1.08–1.16) | 2.5E-09 MO | 8348/139622 | 2.45E-07 | 2.45E-07 | 2.45E-07 | 2.68E-05 | 0.026 |
| Gormley P, 2016 [40] | TSPAN2/ rs2078371 | C vs. T | 1.18 (1.12–1.25) | 7.4E-09 MO | 8348/139622 | 2.52E-05 | 1.80E-05 | 1.80E-05 | 1.27E-03 | 0.561 |
| Anttila V, 2013 [29] | TRPM8/ rs6741751 | A vs. G | 0.80 (0.75–0.86) | 8.64E-11 MO | 7107/69427 | 1.09E-05 | 1.46E-06 | 1.46E-06 | 1.14E-03 | 0.103 |
| Anttila V, 2013 [29] | LRP1/rs11172113 | C vs. T | 0.87 (0.84–0.91) | 9.6E-11 MO | 7107/69427 | 1.30E-06 | 1.26E-06 | 1.26E-06 | 1.11E-04 | 0.101 |
| Anttila V, 2013 [29] | PHACTR1/ rs9349379 | G vs. A | 0.86 (0.82–0.90) | 2.8E-10 MO | 7107/69427 | 8.65E-08 | 7.89E-08 | 7.90E-08 | 7.68E-08 | 7.63E-03 |
| Anttila V, 2013 [29] | FHLS/ rs11759769 | A vs. G | 1.18 (1.13–1.26) | 1.5E-12 MO | 7107/69427 | 8.19E-08 | 6.10E-08 | 6.11E-08 | 5.78E-06 | 5.75E-03 |
| Anttila V, 2013 [29] | MMP16/ rs10504861 | T vs. C | 0.86 (0.81–0.90) | 1.1E-08 MO | 7107/69427 | 8.65E-08 | 7.89E-08 | 7.90E-08 | 7.68E-08 | 7.63E-03 |

GWAS genome-wide association studies, MO migraine without aura

morphismology and synaptic activity by interacting with PP1 in nervous system, and was further thought to be implicated with the pathophysiology of migraine [69, 70]. Different with the hub genes mentioned above, PRDM16, a zinc-finger nuclear protein, works as an important activator of brown adipogenesis, and depletion of PRDM16 may lead to a significant loss in brown adipocyte identity [71]. Recently, brown adipose tissue has been in the focus of metabolism research, which can dissipate energy by the regulation of uncoupling protein-1, increase fatty acid oxidation and heat production and counteract obesity [72, 73]. Moreover, PRDM16 rs2651899 is an intron variant that may affect the splicing of PRDM16 and its downstream regulatory elements, reduce PRDM16 expression and thus increase body mass index [74]. Large cohort studies suggest that obesity is a risk factor for migraine even after adjusting for comorbidities [75]. In obese individuals, the expression of many inflammatory mediators was increased including CGRP and interleukins, which in turn could cause central sensitization in migraine pathophysiology [76, 77]. In addition, Obesity is a state of sympathetic activation, that may contribute to increase in migraine attack [78]. For other hub genes for migraine, TSPAN2 is highly expressed in oligodendrocyte cell lines and may regulate the differentiation process of oligodendrocytes to myelin-forming glia [79]. As a transcription factor in neurons, MEF2D is concerned to be involved in neurogenesis, neuronal survival and differentiation by controlling MEF2D-dependent gene transcription [80]. However, up till now, the potential role of TSPAN2 and MEF2D in migraine development still remains unknown. Further functional studies are required to explore the underlying biological mechanisms.

Although our study included a large number of relevant articles on migraine, some limitations should be acknowledged in our re-analysis. First, most of original studies did not consider the potential confounders such as gene-gene and gene-environment interactions. Second, there exist some inherent methodological flaws in observational studies, such as selection bias, publication bias and small sample size. Although Venice criteria
Table 6 Combination of genetic polymorphisms to predict risk of migraine. Calculation of joint PAR% using the SNPs showing noteworthiness during the computing of BFDP (BFDP < 0.8) or FPRP (FPRP< 0.2) at a statistical power to detect the OR of 1.5

| Author, year | Gene/variant | Comparison | MAF | OR (95%CI) | P-value | Ethnicity | No. of cases/controls | PAR (%) | Joint PAR (%) |
|--------------|--------------|------------|-----|-----------|---------|-----------|----------------------|---------|---------------|
| Chang X, 2018 [43] | NMUR2/rs7293414 | A vs. G | 0.1082 | 2.44 (1.85–3.23) | 3.81E-10 | Overall 2 | 1212/13494 | 13.4804396578 | 44.2094776354 |
| Gormley P, 2016 [40] | LRP1/rs11172113 | C vs. T | 0.3894 | 0.90 (0.89–0.91) | 5.6E-49 | Caucasian | 59,674/316078 | 4.0517761638 |
| Gormley P, 2016 [40] | PROM1/6/ rs10218452 | G vs. A | 0.2264 | 1.11 (1.10–1.13) | 5.3E-38 | Caucasian | 59,674/316078 | 2.4298861162 |
| Gormley P, 2016 [40] | FHL5/rs67338227 | T vs. A | 0.0220 | 1.09 (1.08–1.11) | 2.0E-27 | Caucasian | 59,674/316078 | 0.1976087347 |
| Gormley P, 2016 [40] | TSPAN2/rs2078371 | C vs. T | 0.1252 | 1.11 (1.09–1.13) | 4.1E-24 | Caucasian | 59,674/316078 | 1.3584908638 |
| Gormley P, 2016 [40] | PHACTRI1/ rs9349379 | G vs. A | 0.3774 | 0.93 (0.92–0.95) | 5.8E-22 | Caucasian | 59,674/316078 | 2.7134848246 |
| Gormley P, 2016 [40] | MEF2D/rs1925950 | A vs. G | 0.4277 | 1.07 (1.06–1.09) | 9.1E-22 | Caucasian | 59,674/316078 | 2.9068711836 |
| Gormley P, 2016 [40] | SLC24A3/ rs4814864 | C vs. G | 0.3021 | 1.07 (1.06–1.09) | 2.2E-19 | Caucasian | 59,674/316078 | 2.0709065934 |
| Gormley P, 2016 [40] | FGFR10/rs1024905 | A vs. G | 0.3165 | 1.06 (1.04–1.07) | 2.1E-17 | Caucasian | 59,674/316078 | 1.8636100452 |
| Gormley P, 2016 [40] | C7orf10/ rs186166891 | T vs. A | 0.1631 | 1.09 (1.07–1.12) | 9.7E-16 | Caucasian | 59,674/316078 | 1.446664131 |
| Gormley P, 2016 [40] | PLCE1/rs10786156 | G vs. C | 0.4852 | 0.95 (0.94–0.96) | 2.0E-14 | Caucasian | 59,674/316078 | 2.4863180765 |
| Gormley P, 2016 [40] | KCNKS5/rs10456100 | T vs. C | 0.1813 | 1.06 (1.04–1.07) | 6.9E-13 | Caucasian | 59,674/316078 | 1.0760942468 |
| Gormley P, 2016 [40] | HPSE2/rs12260159 | A vs. G | 0.1673 | 0.92 (0.89–0.94) | 3.2E-10 | Caucasian | 59,674/316078 | 1.3565561475 |
| Gormley P, 2016 [40] | CFDP1/rs77505915 | A vs. T | 0.4898 | 1.05 (1.03–1.06) | 3.3E-10 | Caucasian | 59,674/316078 | 2.3904579111 |
| Gormley P, 2016 [40] | RNF213/ rs17857135 | C vs. T | 0.2115 | 1.06 (1.04–1.08) | 5.2E-10 | Caucasian | 59,674/316078 | 1.2530981840 |
| Gormley P, 2016 [40] | NRP1/rs2506142 | G vs. A | 0.1865 | 1.06 (1.04–1.07) | 1.5E-09 | Caucasian | 59,674/316078 | 1.106619563 |
| Gormley P, 2016 [40] | GPR1149/ rs13078967 | C vs. A | 0.0110 | 0.87 (0.83–0.91) | 1.8E-09 | Caucasian | 59,674/316078 | 0.1432047828 |
| Gormley P, 2016 [40] | SPINK2/rs7684253 | T vs. C | 0.4499 | 0.96 (0.94–0.97) | 2.5E-09 | Caucasian | 59,674/316078 | 1.8325790934 |
| Gormley P, 2016 [40] | HEY2/rs1268083 | C vs. T | 0.4419 | 0.96 (0.95–0.97) | 5.3E-09 | Caucasian | 59,674/316078 | 1.7994063059 |
| Gormley P, 2016 [40] | WSCD1/ rs75213074 | T vs. C | 0.0094 | 0.89 (0.86–0.93) | 7.1E-09 | Caucasian | 59,674/316078 | 0.1035070263 |
| Gormley P, 2016 [40] | GJA1/rs28455731 | T vs. G | 0.1302 | 1.06 (1.04–1.08) | 7.3E-09 | Caucasian | 59,674/316078 | 0.7751445706 |
| Gormley P, 2016 [40] | ITPK1/rs11624776 | C vs. A | 0.2278 | 0.96 (0.94–0.97) | 7.9E-09 | Caucasian | 59,674/316078 | 0.9195792057 |
| Gormley P, 2016 [40] | ADAMTS14/ rs6693567 | T vs. C | 0.3037 | 1.05 (1.03–1.06) | 1.2E-08 | Caucasian | 59,674/316078 | 1.4957864823 |
| Gormley P, 2016 [40] | MED14/ rs12845404 | G vs. C | 0.4114 | 0.96 (0.95–0.97) | 1.7E-08 | Caucasian | 59,674/316078 | 1.6731330779 |
| Gormley P, 2016 [40] | LRRK3/rs1572668 | G vs. A | 0.4930 | 1.04 (1.02–1.05) | 2.1E-08 | Caucasian | 59,674/316078 | 1.9338641980 |
| Gormley P, 2016 [40] | CARF/rs138556413 | G vs. A | 0.0104 | 0.88 (0.84–0.92) | 2.3E-08 | Caucasian | 59,674/316078 | 0.1249559450 |
were applied, these potential biases were difficult to measure. Additionally, owing to the inadequate raw data, Venice Score cannot be applied for GWAS. Third, the GWAS involved in our report were mostly performed in Caucasian population, thus, the results of which was restricted to be applied in diverse populations. Also, GWAS included in our study were lack of subgroup analysis on migraine subtype. Thus, we could only study the noteworthiness of GWAS SNPs in migraine without aura subgroup. Lastly, we constructed a PPI network to explore the underlying biological mechanism for migraine. However, the criteria for PPI construction was relatively subjective, so the result of PPI might need to be interpreted with caution.

**Conclusion**

The current findings identify several noteworthy variants for migraine susceptibility. We hope this field synopsis and systematic re-analysis would help identify novel genetic biomarkers and potential therapeutic target for migraine.

### Table 6

Combination of genetic polymorphisms to predict risk of migraine. Calculation of joint PAR% using the SNPs showing noteworthiness during the computing of BFDP (BFDP < 0.8) or FPRP (FPRP< 0.2) at a statistical power to detect the OR of 1.5 (Continued)

| Author, year | Gene/variant | Comparison | MAF | OR (95%CI) | P-value | Ethnicity | No. of cases/controls | PAR (%) | Joint PAR (%) |
|--------------|---------------|------------|-----|------------|---------|-----------|-----------------------|---------|---------------|
| Gormley P, 2016 [40] | ARMS2/rs2223089 | C vs. G | 0.1288 | 0.93 (0.91–0.95) | 3.0E-08 | Caucasian | 22 | 59,674/316078 | 0.9098027819 |
| Gormley P, 2016 [40] | IG5F9B/rs561561 | T vs. A | 0.0827 | 0.94 (0.92–0.96) | 3.4E-08 | Caucasian | 22 | 59,674/316078 | 0.4986744225 |
| Gormley P, 2016 [40] | NOTCH4/rs140002913 | A vs. G | 0.1150 | 0.91 (0.88–0.94) | 3.8E-08 | Caucasian | 22 | 59,674/316078 | 1.0458242813 |
| Anttila V. 2013 [29] | PRDM16/rs2651899 | C vs. T | 0.4708 | 1.09 (1.07–1.12) | 3.28E-14 | Caucasian | 19 | 23,285/95425 | 4.0649595346 |
| Anttila V. 2013 [29] | TSPAN2/rs12134493 | A vs. C | 0.0709 | 1.14 (1.10–1.18) | 6.71E-14 | Caucasian | 19 | 23,285/95425 | 0.9828442876 |
| Anttila V. 2013 [29] | MEF2D/rs2274316 | C vs. A | 0.4289 | 1.07 (1.04–1.09) | 3.14E-08 | Caucasian | 19 | 23,285/95425 | 2.9147892814 |
| Anttila V. 2013 [29] | TRPM8/rs7577262 | A vs. G | 0.2356 | 0.87 (0.84–0.90) | 3.27E-13 | Caucasian | 19 | 23,285/95425 | 3.1595713513 |
| Anttila V. 2013 [29] | FHL5/rs13208321 | A vs. T | 0.2949 | 1.18 (1.13–1.24) | 2.15E-12 | Caucasian | 19 | 23,285/95425 | 5.0406331131 |
| Anttila V. 2013 [29] | c7orf10/rs4379368 | T vs. C | 0.1961 | 1.11 (1.08–1.15) | 1.46E-09 | Caucasian | 19 | 23,285/95425 | 2.1115517179 |
| Anttila V. 2013 [29] | MTDH/rs1835740 | C vs. T | 0.3510 | 1.18 (1.13–1.24) | 1.60E-11 | Caucasian | 7 | 5950/50809 | 5.9425497094 |

*MAF minor allelic frequency, PAR population attributable risk*
Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s10194-020-01087-5.

Additional file 1: Table S1. Overall summary of results from meta-analyses of observation studies on risk of migraine (including duplicates, statistically significant and non-significant results).

Additional file 2: Table S2. Overall summary of results from meta-analyses of GWAS on risk of migraine (including duplicates, statistically significant and non-significant results).

Additional file 3: Figure S1. Protein-protein interaction network of noteworthy genes related with migraine. The active interaction sources included text mining, experiments, databases as well as co-expression. MCL clustering method was used with the inflation parameter setting at 3.

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Authors’ contributions

XL and YZ conceived and designed the study. XL and YZ performed the database search, data extraction, statistical analysis and bioinformatics analysis. XL and YZ wrote the draft and revised the whole manuscript. All authors read and approved the final version of the manuscript.

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Availability of data and materials

The datasets supporting the conclusions of this article are included within the article.

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Competing interests

The authors declare that they have no competing interests.

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