



A conjoint analysis of epilepsy and migraine through network-and-pathway-based method

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Background: Epilepsy and migraine are both considered as paroxysmal neurologic disorders. Previous studies have reported some cases with comorbidity of these two diseases. As the underlying molecular mechanism remains unclear, we performed a network-and-pathway-based method with candidate gene sets of epilepsy and migraine to explore it.

Methods: Comparing the candidate genes between epilepsy and migraine, we identified 21 common genes. Functional enrichment analysis indicated that epilepsy and migraine are dysfunctional in the similar biological processes, such as glutamatergic transmissions, channel activities, and transporter activities. We also explored many shared pathways between these two diseases such as neuroactive ligand-receptor interaction.

Results: By combining systematical analysis and previous studies review, we finally identified six essential genes associated with the comorbidity of epilepsy and migraine.

Conclusions: This is the first time to address the common ground of epilepsy and migraine by a systematic biology method. The present study provides a novel way to explain the potential mechanisms of these two diseases and a new set of therapeutic targets.

Keywords: Epilepsy; migraine; network-and-pathway-based analysis

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Introduction

Migraine and epilepsy are ordinary paroxysmal neurological diseases (1). They both make frequent visits to outpatient clinic and emergency department and increase significant individual and social financial burdens (2). The migraine is defined as recurrent headache disorder manifesting in attacks lasting 4–72 hours; typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia

and phonophobia and it may be preceded by aura (3). Common migraine triggers include delayed or missed meals, menstruation, stress, weather changes, chocolate, soft cheeses, red wine, and artificial sweeteners, alcohol, and certain odors (4,5). And it is suggested that patients write down a headache diary could help their physicians to identify and manage the migraine triggers (2). On the other hand, epilepsy is a symptom complex with multiple risk factors and a strong genetic predisposition rather than a condition with a single expression and cause. A detailed clinical history and a reliable eyewitness account of a

seizure are the cornerstones of the diagnosis. Application of advanced brain imaging and electroencephalogram (EEG) devices can help to distinguish epilepsy from non-epileptic seizures (6).

As we know, in the pathogenesis, epilepsy is characterized by spontaneous, sudden, abnormal, excessive and rapid electrical discharges arising from cerebral neurons (7) while migraine is characterized by a complex and stereotypical, dysfunction of sensory processing (8). Interestingly, several studies have reported comorbidity of these two diseases (9,10). Indeed, since the first report of their co-occurrences in the 19th century, more and more overlap of symptoms between these two disorders has been observed. First, both these disorders are manifested by periodic attacks and return to normality between crises (11,12). Second, they can be induced by similar factors, such as exposure to a flashlight (13), psychological pressure (14,15) and lack of sleep (14,16). Third, they both show abnormal discharge in an EEG (17). Fourth, the presence of Aurae like visual hallucination and dizziness is frequently observed in both disorders (18,19). Fifth, compared to the healthy population, both migraine and epilepsy have a higher prevalence of depression, anxiety and somatization (20,21). Moreover, a recent study reported that a remarkable family history of epilepsy increases the risks of migraine with aura (22). The evidence indicates these two diseases may share common pathogenesis and genetic susceptibilities. However, related studies are rare.

Therefore, it is indispensable to conduct a comprehensive and accurate exploration of the molecular mechanisms of the characteristic features of epilepsy and migraine. We searched the candidate genes manually to perform network and pathway-based analyses. As a result, we identified 21 overlapping genes and several common characteristics between epilepsy and migraine, including extracellular-glutamate-gated ion channel activity, glutamate binding, glutamate receptor activity, cation channel activity, substrate-specific transporter activity and ion transmembrane transporter activity. And among these genes, *TNF*, *VEGFA*, *CACNA1A*, *ATP1A2*, *SCN1A*, *PRRT2* are essential to the comorbidity between epilepsy and migraine. The current study may the underlying mechanisms of these two diseases and indicate the potential target of future prevention and therapy.

Methods

Identification of epilepsy and migraine-related genes

We retrieve the human genetic association studies deposited

in PUBMED (<http://www.ncbi.nlm.nih.gov/pubmed/>). The search strategy is retrieve the researches related to epilepsy with the term (epilepsy[MeSH]) and (polymorphism [MeSH] or genotype [MeSH] or alleles [MeSH]), and (migraine [MeSH] or hemicrania [MeSH] or cephalalgia [MeSH]) and (polymorphism [MeSH] or genotype [MeSH] or alleles [MeSH])) for migraine respectively. The inclusion criteria gene collection runs as follows: (I) at least 5 cases of patients with a specimen of the brain or peripheral blood. (II) All the candidate genes are validated by reliable biological experiments. (III) Candidate genes show a significant difference at the expression level. After reading the abstracts of these acquired publications, we selected the genes published to be associated with epilepsy and migraine. Then the whole reports of the selected publications were reviewed to ensure the conclusions were consistent with the content. The studies reporting nonsignificant or negative associations were excluded to lower the false-positive ratio. In a few studies, some several genes were cooperating to show significant effects on epilepsy and migraine, with each gene having a moderate impact; we also incorporated these genes into our list.

Formation of protein-protein interaction (PPI) network

The Search Tool for the Retrieval of Interacting Genes (STRING) (<http://string-db.org/>) is an online database which can offer a core integration of PPIs with a confidence score and generate a network (23). In the current study, the STRING online database was applied to analyze the PPIs of the candidate genes of epilepsy and migraine. Due to building the PPI network, only the genes with a combined protein interaction score >0.5 were calculated and analyzed. The PPI network was visualized, utilizing Cytoscape 3.4 (24).

Functional enrichment analysis of genes related to epilepsy and migraine

We operate DAVID and KEGG to detect the biological themes of the candidate genes related to epilepsy and migraine. DAVID, a web-based bioinformatic-mining platform, integrates information from multiple resources to analyse the biological processes, including identifying the overrepresented Gene Ontology (GO) terms (25). In the present study, only the enriched GO biological process terms with P value <0.05 meant significant and were reserved KEGG, a platform to calculate and analyze the

enriched biological pathways in the candidate genes, was used synchronously (26). Enriched pathways with P value <0.05 were significantly kept.

We also analysed the interrelations of the enriched pathways. The Fisher's Exact Test with the formula above was used to calculate the overlap between two pathways.

$$P = 1 - \sum_{k=0}^x \frac{\binom{m}{k} \binom{N-m}{n-k}}{\binom{N}{n}}$$

Only pathways with P value <0.05 were considered for crosstalk analysis. Pathways with less than or equal to three candidate genes were discarded since such pathways represent few or biased connections with others. Furthermore, the pathway pairs having the number of common candidate genes less than two were removed.

Results

Identification of candidate genes related to epilepsy and migraine

Discovery of genes linked with epilepsy were completed through searching the published genetic studies associated with epilepsy in PubMed. Only the publications reporting gene(s) significantly associated with the disease were gathered, and those reporting a negative or nonsignificant association were excluded. Altogether, from 545 studies, we collected 171 genes be related to epilepsy (Table S1). Similarly, we collected 70 candidate genes be associated with migraine from 172 studies (Table S2). Comparing two gene lists, we found 21 genes shared by these two disease. These genes are associated with oxidative stress, ion channels and energy metabolism refer to previous studies, partly indicating the complication of the pathogenesis of epilepsy and migraine. The overlapping genes are shown in Table 1.

Construction and analysis of the PPI networks

By mapping the epilepsy-related genes into STRING database, we constructed a PPI network with 156 nodes (epilepsy-related genes) and 1,281 edges (interactions). As for migraine-related genes, the network included 55 nodes (migraine-related genes) and 139 edges (interactions). The plot of the networks is in the Figures S1,S2. The top 10 ranked hub proteins with high degree in the networks of

epilepsy and migraine were shown in Table 2.

Biological functional enrichment analysis of candidate genes

A more detailed biological function pattern of two gene sets was revealed through functional enrichment analysis (Table S3,S4). The GO terms significantly enriched in the epilepsy-related genes and migraine-related genes are partially similar, including those associated with glutamatergic transmission (e.g., glutamate receptor activity, extracellular-glutamate-gated ion channel activity, glutamate binding) and channel activities (e.g., gated channel activity, extracellular ligand-gated ion channel activity, cation channel activity), transporter activities (e.g., substrate-specific transporter activity, metal ion transmembrane transporter activity). These results indicated that complicated connections existed between these two diseases. In addition, these selected genes were relatively credible for following bioinformatics analysis.

Identifying the biochemical pathways enriched in the candidate genes may provide valuable evidence for our understanding of the molecular mechanisms underlying epilepsy and migraine. We searched for enriched pathways in the two sets of candidate genes using KEGG. As a result, we explore 35 significantly enriched pathways for migraine (Table S5) and 129 significantly enriched pathways for epilepsy (Table S6). Interestingly, we found numerous pathways shared by epilepsy and migraine (Table 3).

Crosstalk among significantly enriched pathways in epilepsy and migraine

Detecting the significantly enriched pathways may provide valuable evidence for understanding their interactions, we dealt a pathway crosstalk calculation with the 129 significantly enriched pathways in epilepsy-related genes and 35 significantly enriched pathways in migraine-related genes. Here we assumed that crosstalk existed a pathway pair if they shared a percentage of candidate genes. A plugin of Cytoscape named ClueGO (27) was used for visualization. The results are shown in Figures 1,2.

Discussion

During the past decades, considerable studies have been performed on epilepsy and migraine separately. Nowadays

Table 1 Overlapping genes between epilepsy and migraine

Gene	ID	Description
<i>APOE</i>	348	Apolipoprotein E
<i>ATP1A2</i>	477	ATPase Na ⁺ /K ⁺ transporting subunit alpha 2
<i>CACNA1A</i>	773	Calcium voltage-gated channel subunit alpha1 A
<i>GABRA3</i>	2556	Gamma-aminobutyric acid type A receptor alpha3 subunit
<i>GC</i>	2638	Vitamin D binding protein
<i>GRIA1</i>	2890	Glutamate ionotropic receptor AMPA type subunit 1
<i>GRM7</i>	2917	Glutamate metabotropic receptor 7
<i>HTR1B</i>	3351	5-hydroxytryptamine receptor 1B
<i>KCNN3</i>	3782	Potassium calcium-activated channel subfamily N member 3
<i>MTHFR</i>	4524	Methylenetetrahydrofolate reductase
<i>NOS2</i>	4843	Nitric oxide synthase 2
<i>SCN1A</i>	6323	Sodium voltage-gated channel alpha subunit 1
<i>CCL2</i>	6347	C-C motif chemokine ligand 2
<i>SLC6A4</i>	6532	Solute carrier family 6 member 4
<i>TGFB1</i>	7040	Transforming growth factor beta 1
<i>TGFBR2</i>	7048	Transforming growth factor beta receptor 2
<i>TNF</i>	7124	Tumor necrosis factor
<i>VDR</i>	7421	Vitamin D receptor
<i>VEGFA</i>	7422	Vascular endothelial growth factor A
<i>PRRT4</i>	401399	Proline rich transmembrane protein 4
<i>CCR2</i>	729230	C-C motif chemokine receptor 2

numerous genes/proteins have been identified to associated with these two disorders, however, it remains unclear that a comprehensive understanding of the biological mechanisms related to pathogenesis of these two diseases especially the comorbidity between them. So, it is essential to reveal the underlying molecular processes involved in the epilepsy and migraine by collecting the genes related to these two diseases and systematically exploring the interaction of candidate genes. In the present study, we found several shared characteristics of these two diseases and delineated possible biochemical processes contributing to their comorbidity through network and pathway-based method.

In our study, we selected 171 genes reported to be associated with epilepsy and 70 candidate genes related to migraine. Comparing two gene lists, we found 21 genes shared by these two diseases and former studies have reported that some of them play certain roles in

both epilepsy and migraine (e.g., *CACNA1A*, *ATP1A2*, *SCN1A*, *PRRT2*). The *CACNA1A* gene encodes for the Ca_v2.1 α 1 subunit. It is closely linked with synaptic function of cortical interneurons and function of cortical GABA neurotransmitter (28,29), which ultimately leads to epilepsy and migraine. *ATP1A2* codes for the α 2 subunit of Na⁺/K⁺ ATPase. The dysfunction of Na⁺/K⁺ ATPase damages the K⁺ gradient and impairs glutamate clearance, which could participant in the pathogenesis of migraine and epilepsy by depressing the cortical spreading (30). The *SCN1A* gene encodes for Nav1.1. The dysfunction of Nav1.1 could prolong current duration and increase neuron excitability, which lead to seizures and familial hemiplegic migraine (31). The mutation of *PRRT2* gene impairs SNAP25 function, which alters CaV2.1 activity, enhances neuronal hyper-excitability, and results in epilepsy and hemiplegic migraine (32). Importantly, other unreported

Table 2 The top 10 genes with high node degree in the PPI network of epilepsy and migraine

Epilepsy genes	Degree
<i>TP53</i>	67
<i>AKT1</i>	63
<i>TNF</i>	60
<i>IL6</i>	60
<i>VEGFA</i>	56
<i>BCL2</i>	52
<i>MAPK3</i>	52
<i>CASP3</i>	51
<i>MAPK1</i>	51
<i>APP</i>	50
<i>TNF</i>	21
<i>VEGFA</i>	18
<i>TGFB1</i>	17
<i>NOS3</i>	15
<i>CCL2</i>	13
<i>ACE</i>	12
<i>APOE</i>	11
<i>CCR2</i>	9
<i>NOS2</i>	9
<i>ESR1</i>	9

genes are likely to contribute to epilepsy and migraine through undefined but similar molecular mechanisms. It is worth exploring them in the future.

By mapping the candidate genes into STRING database, we constructed the PPI networks of epilepsy and migraine. Interestingly, we found that several genes serve as hub gene in both networks, such as *TNF* and *VEGFA*. In the past decades, these two genes have been reported to participate in many neurological disorders. *TNF* plays a vital role in the microglia and astrocyte activation which are the initial stages of inflammatory responses in the central nervous system (CNS) (33,34). Several studies indicated that seizures induce the brain-derived TNF expression in animal models (35-37). Balosso *et al.* injected murine-recombinant TNF into the hippocampus of mice and reported a potent prevention of seizures (38). Teocchi *et al.* (39) reported a notable TNF upregulation in the patients of temporal

lobe epilepsy (TLE) and suggested chronic inflammation could be crucial to refractory TLE (40). Moreover, Chen *et al.* reported that some polymorphisms of TNF increase genetic susceptibility to migraine (41). Therefore, we assume that epilepsy and migraine may have similar inflammatory process via TNF signal pathway. Further experiments are needed to verify this point. VEGF is a crucial protein in the angiogenesis and it also participates in neurogenesis (42). And VEGF signaling could take a part in astrocytes activation and astrocyte-related inflammatory reactions (43). Besides, in a case-control study, patients with migraine showed significantly increased levels of VEGF than the control group, which indicates that VEGF is close associated with migraine (44).

Biological function enrichment analysis of candidate genes detected the detailed biological processes. The current GO enrichment analysis demonstrated that both epilepsy-related genes and migraine-related genes participated in glutamatergic transmissions (e.g., glutamate receptor activity, extracellular-glutamate-gated ion channel activity, glutamate binding) and channel activities (e.g., gated channel activity, extracellular ligand-gated ion channel activity, cation channel activity), transporter activities (e.g., substrate-specific transporter activity, metal ion transmembrane transporter activity). This result revealed that epilepsy and migraine shared some similar biological processes in their pathogenesis.

Pathway analysis revealed many common pathways between epilepsy and migraine. Among these common pathways, some are reported to be associated with specific diseases by previous studies such as dopaminergic synapse, serotonergic synapse and estrogen signaling pathway. Dopamine and serotonin are common neurotransmitter with excitatory and inhibitory functions. Once these neurotransmitters interact with the specific receptors, thus triggering various important signaling pathways in the CNS, and then finally regulate a series of physiological processes (45,46). The former studies indicated that they marginally participate in the synaptic plasticity (47,48). Central dopaminergic synapse was considered as a malfunctioning regulatory circuit, insufficient release of feedback control might increase seizure susceptibility (49). Migraine can be affected by fluctuating estrogen levels and high estrogen levels can trigger migraine aura (50,51). Furthermore, down-regulation of serotonergic and GABAergic systems could inhibit the estrogen product, which increases the risk of migraine. Interestingly, some women with

Table 3 Pathways shared by epilepsy and migraine

Pathway ID	Pathway description	Matching genes
4080	Neuroactive ligand-receptor interaction	<i>DRD2, EDNRB, GABRA3, GABRQ, GRIA1, GRIA3, GRM7, HCRTR1, HTR1B, HTR7, OPRM1</i>
4060	Cytokine-cytokine receptor interaction	<i>CCL2, CCR2, IL9, LTA, NGFR, TGFB1, TGFBR2, TNF, VEGFA</i>
5033	Nicotine addiction	<i>CACNA1A, GABRA3, GABRQ, GRIA1, GRIA3</i>
5323	Rheumatoid arthritis	<i>CCL2, CTLA4, HLA-DRB1, TGFB1, TNF, VEGFA</i>
4723	Retrograde endocannabinoid signaling	<i>CACNA1A, GABRA3, GABRQ, GRIA1, GRIA3, KCNJ9</i>
4728	Dopaminergic synapse	<i>CACNA1A, DRD2, GRIA1, GRIA3, KCNJ9, SCN1A</i>
5032	Morphine addiction	<i>CACNA1A, GABRA3, GABRQ, KCNJ9, OPRM1</i>
5142	Chagas disease (American trypanosomiasis)	<i>CCL2, NOS2, TGFB1, TGFBR2, TNF</i>
5144	Malaria	<i>CCL2, LRP1, TGFB1, TNF</i>
4726	Serotonergic synapse	<i>CACNA1A, HTR1B, HTR7, KCNJ9, SLC6A4</i>
5140	Leishmaniasis	<i>HLA-DRB1, NOS2, TGFB1, TNF</i>
4915	Estrogen signaling pathway	<i>ESR1, KCNJ9, NOS3, OPRM1</i>
5152	Tuberculosis	<i>HLA-DRB1, NOS2, TGFB1, TNF, VDR</i>
4020	Calcium signaling pathway	<i>CACNA1A, EDNRB, HTR7, NOS2, NOS3</i>
4940	Type I diabetes mellitus	<i>HLA-DRB1, LTA, TNF</i>
4724	Glutamatergic synapse	<i>CACNA1A, GRIA1, GRIA3, GRM7</i>
4961	Endocrine and other factor-regulated calcium reabsorption	<i>ATP1A2, ESR1, VDR</i>
5145	Toxoplasmosis	<i>HLA-DRB1, NOS2, TGFB1, TNF</i>
4730	Long-term depression	<i>CACNA1A, GRIA1, GRIA3</i>
5212	Pancreatic cancer	<i>TGFB1, TGFBR2, VEGFA</i>
5321	Inflammatory bowel disease (IBD)	<i>HLA-DRB1, TGFB1, TNF</i>
5166	HTLV-I infection	<i>HLA-DRB1, LTA, TGFB1, TGFBR2, TNF</i>
4022	cGMP-PKG signaling pathway	<i>ATP1A2, EDNRB, MEF2D, NOS3</i>
4350	TGF-beta signaling pathway	<i>TGFB1, TGFBR2, TNF</i>
4727	GABAergic synapse	<i>CACNA1A, GABRA3, GABRQ</i>
5168	Herpes simplex infection	<i>CCL2, HLA-DRB1, LTA, TNF</i>
4713	Circadian entrainment	<i>GRIA1, GRIA3, KCNJ9</i>
4066	HIF-1 signaling pathway	<i>NOS2, NOS3, VEGFA</i>
5146	Amoebiasis	<i>NOS2, TGFB1, TNF</i>
4668	TNF signaling pathway	<i>CCL2, LTA, TNF</i>

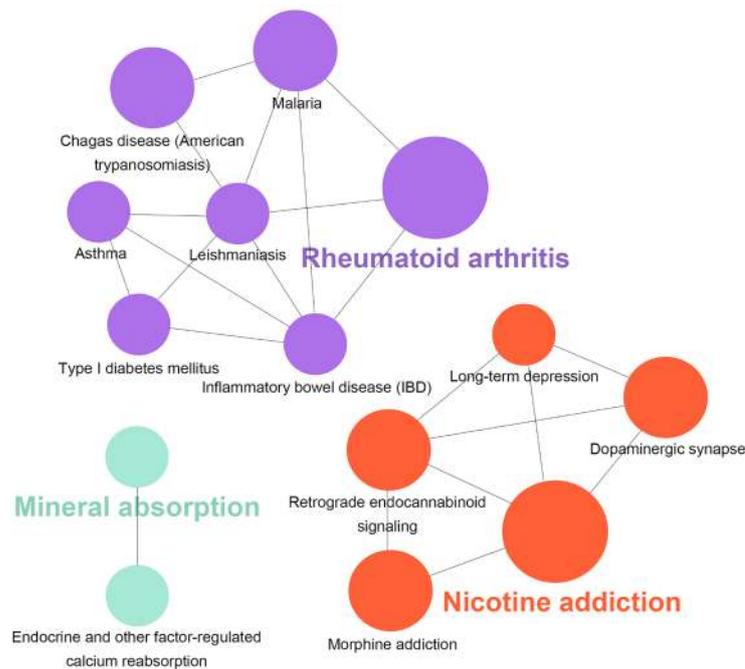


Figure 2 Crosstalk of pathway enriched in migraine-related genes.

and migraine (55). Hopefully, these potential candidate genes are on a list for further exploration. The results are shown in *Figure 3*.

Still, in this study these analysis results of pathways and networks depend entirely on genes in the published data purported to be linked to epilepsy and migraine is a limit. Given that the process of candidate genes identifications is sustaining, the relevant analysis and results should update along with time.

Nowadays, novel drugs for epilepsy and migraine are still urgently needed. The concept of “disease-modifying drugs in epilepsy” is coming up and the mTOR inhibitor *Everolimus* seems to have a similar but slightly delayed antiseizure efficacy in tuberous sclerosis complex disease associated seizures (56). The gut microbiome could give extra assistance to improve the efficacy of the ketogenic diet (57). For migraine, due to advancement in the understanding of migraine pathophysiological mechanisms and identification of hopeful potentially meaningful targets have resulted in a multitude of emerging acute and preventive treatments. The most promising acute therapies which target the Calcitonin-Gen-Related Peptide (CGRP) receptor and ligand and the 5 hydroxytryptamine (5-HT) 1F receptor are two new family of drugs: the Gepants and the Ditans. As preventive treatments, the anti-CGRP

monoclonal antibodies like Erenumab and Fremanezumab is a major milestone since the approval of triptans (58). Surgery is essential for refractory epilepsy treatment. Traditional craniotomy could bring damage to surrounding brain tissue and worsen postsurgical neurological and neuropsychological outcome (59). An abolition of the local epileptogenic zone with non- or less invasive techniques such as stereotactic radiosurgery, radiofrequency thermocoagulation, and laser interstitial thermal therapy, could reduce mentioned risks and have been shown to lead to a favourable seizure outcome in 50–60% of people with drug-resistant focal epilepsy (6). However, the efficacy and safety are currently under investigation with MR-guided ultrasound (60). Furthermore, whatever in epilepsy or migraine, neuromodulatory approaches are alternative treatment strategies when patients are unwilling to accept or tolerate possible drug-induced adverse effect (61).

In summary, we collected some genes existed in epilepsy and migraine from literatures deposited in PubMed and performed a comprehensive and systematic analysis in this study. Then, we integrated the information from GO, KEGG and pathway crosstalk analysis platforms and figured out several biological processes and biochemical pathways related to neuroactive ligand-receptor interaction, dopaminergic synapse and glutamatergic synapse were

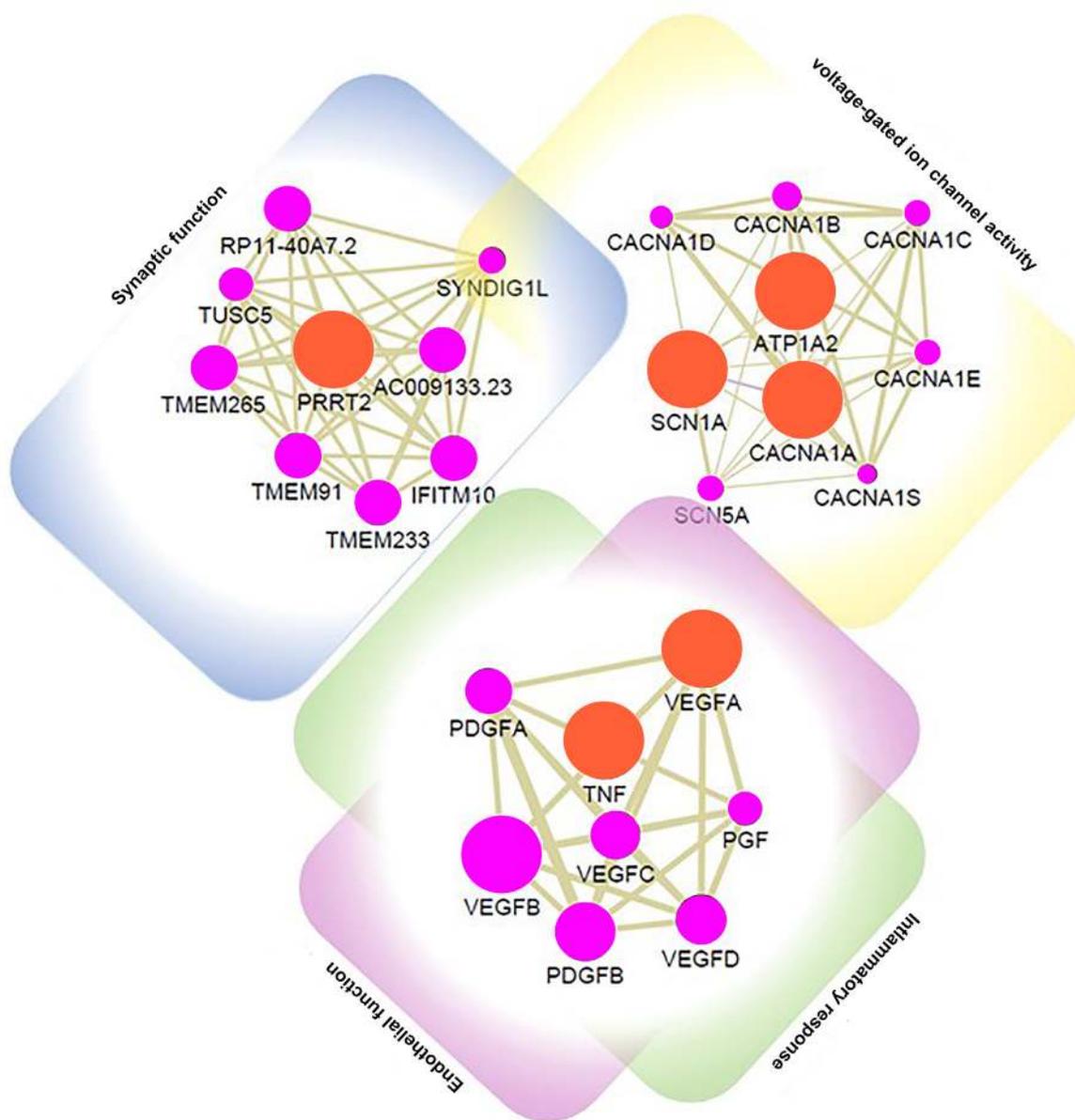


Figure 3 Prediction of genes interact with *TNF*, *VEGFA*, *CACNA1A*, *ATP1A2*, *SCN1A*, *PRRT2* and the potential biological processes involved.

enriched in both epilepsy and migraine genes and revealed the interrelations among these significant pathways. Meanwhile, we highlighted 6 essential genes: *TNF*, *VEGFA*, *CACNA1A*, *ATP1A2*, *SCN1A*, *PRRT2*, which may play an important role in both epilepsy and migraine. Such a network-and-pathway-based method will not only help us to comprehensively understand the contribution of genetic factors and their interaction to the combid mechanisms of epilepsy and migraine but will also provide a way to find

potential therapeutic targets.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Table S1 Identified candidate genes related to epilepsy

No.	Gene	Gene ID	Reference*
1	ASIC1	41	21664108
2	ADK	132	3253237
3	AK2	204	19192410
4	AKT1	207	25903737
5	ANXA7	310	21432772
6	APOE	348	26945380, 19066720
7	APP	351	24566726
8	FAS	355	17660056
9	AQP1	358	18544259
10	AQP4	361	22698689, 19864112
11	RHOA	387	20140537
12	ATP1A2	477	12953268
13	BCL2	596	10908900, 17660056
14	BCL2L1	598	10908900
15	BDNF	627	10082852
16	C3	718	16399808
17	CACNA1A	773	25735478, 3065835, 12461694
18	CACNA1C	775	22698689
19	CANX	821	16651883
20	CAPN1	823	21315622
21	CAPN2	824	22698689
22	CASP1	834	10908900
23	CASP3	836	10908900, 26902190, 20965234, 16651883, 17660056
24	CASP4	837	26902190, 20965234
25	CASP6	839	16651883
26	CASP7	840	16651883
27	CASP9	842	16651883
28	CD74	972	16399808
29	CDC42	998	17925172
30	CNN3	1266	22119193
31	CRMP1	1400	22359051
32	CST3	1471	16049933
33	DBP	1628	25503293
34	DLG2	1740	17506987
35	DMD	1756	22698689
36	DNM1	1759	25318457
37	DNMT1	1786	21826395
38	DNMT3a	1788	21826395
39	DSCAM	1826	21360594
40	EMP1	2012	19288191
41	FGFR3	2261	23165795
42	FHL2	2274	16399808
43	GABBR1	2550	12601092
44	GABRA3	2556	4404495
45	GABRB3	2562	22082659
46	GABRG2	2566	24061200
47	GC	2638	19109932
48	GFAP	2670	21315622, 15668432
49	GJA1	2697	22698689
50	GLUL	2752	15668432
51	GRIA1	2890	22698689, 9761317, 9397013
52	GRIA2	2891	9397013
53	GRIK1	2897	9848088
54	GRIK2	2898	9848088
55	GRIK4	2900	22698689
56	GRIK5	2901	22698689, 9848088
57	GRIN1	2902	8960315, 9397013
58	GRIN2A	2903	10482265
59	GRIN2B	2904	17506987, 10482265, 9397013, 9761317
60	GRM1	2911	10744030
61	GRM2	2912	22698689
62	GRM3	2913	22698689
63	GRM5	2915	22698689, 16311265
64	GRM7	2917	4404495
65	HDAC2	3066	21987499
66	NRG1	3084	26071373
67	HMGB1	3146	20348922
68	HSPA5	3309	22419015, 20965234
69	HSPB2	3316	15571513
70	HTR1A	3350	5465700
71	HTR1B	3351	20435093
72	HTR2A	3356	16399808
73	IL1A	3552	19066720
74	IL1B	3553	21315622, 23982744
75	IL1RN	3557	19066720
76	IL6	3569	21315622
77	IL10	3586	26696826
78	ITGA2	3673	21370991
79	KCNJ10	3766	19864112, 22698689
80	KCNK3	3777	21710317
81	KCNN3	3782	1736047
82	KLK1	3816	21211543
83	LAMB1	3912	21370991, 18691630
84	STMN1	3925	22535533
85	MDM2	4193	17942278
86	MECP2	4204	22707285
87	MAP3K5	4217	22419015
88	CD99	4267	16399808
89	MTHFR	4524	4410915
90	NFE2L2	4780	26149655
91	NFKB1	4790	22698689, 23634661, 23982744
92	NOS1	4842	12121328
93	iNOS	4843	19885009
94	NPY1R	4886	16399808
95	PDYN	5173	26489614, 11835385
96	PGF	5228	22079325
97	ABCB1	5243	24586633
98	MED1	5469	16934225
99	MAPK1	5594	17662006
100	MAPK3	5595	17662006
101	PRNP	5621	14610121
102	RELN	5649	26046367
103	PTGS2	5743	22698689, 12470703
104	RASGRF1	5923	23200899
105	RPS6KB1	6198	25903737
106	SCN1A	6323	10742094, 1125444
107	SCN2A	6326	24220630
108	MCP-1	6347	4038119, 1869627
109	CCL3	6348	18076643
110	CCL4	6351	18076643
111	CX3CL1	6376	22464888
112	SHH	6469	21376786
113	SLC1A2	6506	19338517, 15668432
114	SLC1A3	6507	19338517
115	SLC6A4	6532	21498047
116	SLC16A1	6566	21081165
117	SLC18A2	6571	23504951
118	SNTA1	6640	22698689
119	SOD1	6647	24220630, 19109932
120	SYT1	6857	18779938
121	TACR1	6869	21925840
122	TGFB1	7040	21315622, 22698689
123	TGFBR2	7048	17121744
124	TLR4	7099	20348922, 23982744
125	TNF	7124	23634661
126	TNFRSF1A	7132	27006531
127	TNFRSF1B	7133	27006531
128	TP53	7157	17660056, 17942278
129	HSP90B1	7184	22419015, 20965234
130	TRAF2	7186	22419015
131	TRPC3	7222	25213992
132	TRPC6	7225	25213992
133	VDR	7421	4661623
134	VEGFA	7422	17533168
135	TRPV1	7442	22936245
136	XBP1	7494	20965234
137	ALDH5A1	7915	22082659
138	PPFIA1	8500	21157931
139	APLN	8862	21864607
140	CACNA1H	8912	17696120
141	WASL	8976	18708039
142	SLC16A7	9194	22535546
143	LGI1	9211	15079011
144	SLIT2	9353	20153733
145	KL	9365	23634661
146	GABBR2	9568	18653317
147	KEAP1	9817	26149655
148	GAB2	9846	24327320
149	SV2B	9899	23617838
150	SV2A	9900	19757204, 23617838
151	BCL2L11	10018	16651883
152	GPHN	10243	21404332
153	NES	10763	18719994
154	PHLDA1	22822	17870236
155	SV2C	22987	23617838
156	DICER1	23405	22615744
157	PANX1	24145	24146091
158	AGO2	27161	22615744
159	KCNK9	51305	21710317
160	SOBP	55084	21035105
161	MICAL1	64780	21638339
162	HSPBAP1	79663	17568411
163	TLN2	83660	19109932
164	SNX25	83891	23518199
165	DTNBP1	84062	22337344
166	NTNG2	84628	20382146
167	ABCC11	85320	23982744
168	CALHM1	255022	21439911
169	HCN1	348980	3177145, 2709210
170	PRRT2	401399	3897939, 3257886
171	CCR2	729230	2949152, 4306378

*, references are designated by PMIDs, which are the identifiers of PubMed. PMIDs in each gene term are equal and there're not priorities in the permutation of the corresponding PMIDs of the specified genes.

Table S2 Identified candidate genes related to migraine

No.	Gene	Gene ID	Reference*
1	<i>ADARB2</i>	105	3604878
2	<i>ApoE</i>	348	4534059
3	<i>ATP1A2</i>	477	2034370, 4706665
4	<i>CACNA1A</i>	773	1377706
5	<i>CASQ 1</i>	844	2034370
6	<i>CTLA-4</i>	1493	3452029
7	<i>CYP19A1</i>	1588	3325278
8	<i>ACE</i>	1636	2644823
9	<i>DRD2</i>	1813	3476140
10	<i>EDNRB</i>	1910	2753702
11	<i>ESR1</i>	2099	4616512
12	<i>FMR1</i>	2332	4991825
13	<i>GABRA3</i>	2556	3764027, 1196377
14	<i>GC Globulin</i>	2638	4141767
15	<i>GRIA1</i>	2890	4723374
16	<i>GRIA3</i>	2892	4723374
17	<i>GRM7</i>	2917	3604878
18	<i>HCRTR1</i>	3061	3072499
19	<i>HLA-DRB1</i>	3123	3452004
20	<i>HTR1B</i>	3351	3476140
21	<i>HTR7</i>	3363	3604878
22	<i>IL9</i>	3578	2704575
23	<i>KCN J9</i>	3765	2034370
24	<i>KCN J10</i>	3766	2034370
25	<i>KCNN3</i>	3782	3208049
26	<i>LRP1</i>	4035	3253157
27	<i>TNF-β</i>	4049	4069061
28	<i>MEF2D</i>	4209	3986694
29	<i>MTHFR</i>	4524	2562562, 4231882
30	<i>MTR</i>	4548	4231882
31	<i>MTRR</i>	4552	4231882
32	<i>NGFR</i>	4804	3172930
33	<i>NNMT</i>	4837	5056911
34	<i>iNOS</i>	4843	3356463
35	<i>NOS3</i>	4846	2704575
36	<i>NOTCH4</i>	4855	3620438
37	<i>OPRM1</i>	4988	3444536
38	<i>PROGINS</i>	5241	4337459
39	<i>EDN</i>	6036	2753702
40	<i>SCN1A</i>	6323	4706665
41	<i>MCP-1</i>	6347	4141767
42	<i>SLC6A4</i>	6532	3476140, 3452037
43	<i>SOD2</i>	6648	4283069
44	<i>TARBP2</i>	6895	5541777
45	<i>TGFB1</i>	7040	2704575
46	<i>TGFBR2</i>	7048	3986694
47	<i>TNF</i>	7124	4476787, 2704575
48	<i>VDR</i>	7421	3741896
40	<i>VEGF</i>	7422	3356463
50	<i>NPFF</i>	8620	5541777
51	<i>SLC4A4</i>	8671	2936614
52	<i>FHL5</i>	9457	5541777
53	<i>HEPH</i>	9843	3362572
54	<i>PGCP</i>	10404	3986694
55	<i>UTS2</i>	10911	4835397
56	<i>VSIG4</i>	11326	3362572
57	<i>SYNE1</i>	23345	3986694, 4196204
58	<i>UFL1</i>	23376	5541777
59	<i>NBEA</i>	26960	4394021
60	<i>GABRQ</i>	55879	3764027
61	<i>PRDM16</i>	63976	3986694
62	<i>TRPM8</i>	79054	3986694, 3253157
63	<i>MTDH</i>	92140	3986694, 3172930
64	<i>ZNF555</i>	148254	3604878
65	<i>MGR1</i>	192115	1180504
66	<i>PHACTR1</i>	221692	3986694
67	<i>DAOA</i>	267012	3837682
68	<i>KCNK18</i>	338567	4706665
69	<i>PRRT2</i>	401399	2704575
70	<i>CCR2</i>	729230	2704575

*, references are designated by PMIDs, which are the identifiers of PubMed. PMIDs in each gene term are equal and there're not priorities in the permutation of the corresponding PMIDs of specified genes.

Table S3 GO function enrichment analysis of gene related to epilepsy

Category	Term	Count	%	P value	Genes ID
GOTERM_MF_DIRECT	GO:0042803~protein homodimerization activity	13	18.57	2.63×10 ⁻⁵	4209, 7040, 7422, 4843, 6532, 10404, 729230, 79054, 1813, 2332, 6895, 23345, 348
GOTERM_MF_DIRECT	GO:0050661~NADP binding	4	5.71	3.57×10 ⁻⁴	4846, 4843, 4524, 4552
GOTERM_MF_DIRECT	GO:0010181~FMN binding	3	4.29	1.58×10 ⁻³	4846, 4843, 4552
GOTERM_MF_DIRECT	GO:0050660~flavin adenine dinucleotide binding	4	5.71	2.09×10 ⁻³	4846, 4843, 4524, 4552
GOTERM_MF_DIRECT	GO:0008144~drug binding	4	5.71	3.42×10 ⁻³	3351, 1636, 1813, 477
GOTERM_MF_DIRECT	GO:0005125~cytokine activity	5	7.14	5.25×10 ⁻³	7040, 4049, 7422, 7124, 3578
GOTERM_MF_DIRECT	GO:0005245~voltage-gated calcium channel activity	3	4.29	1.10×10 ⁻²	773, 4988, 2917
GOTERM_MF_DIRECT	GO:0004517~nitric-oxide synthase activity	2	2.86	1.19×10 ⁻²	4846, 4843
GOTERM_MF_DIRECT	GO:0031727~CCR2 chemokine receptor binding	2	2.86	1.19×10 ⁻²	729230, 6347
GOTERM_MF_DIRECT	GO:0005216~ion channel activity	3	4.29	1.26×10 ⁻²	773, 6323, 79054
GOTERM_MF_DIRECT	GO:0005102~receptor binding	6	8.56	1.30×10 ⁻²	8620, 4049, 5241, 10911, 4843, 6347
GOTERM_MF_DIRECT	GO:0004971~AMPA glutamate receptor activity	2	2.86	1.58×10 ⁻²	2892, 2890
GOTERM_MF_DIRECT	GO:0034617~tetrahydrobiopterin binding	2	2.86	1.58×10 ⁻²	4846, 4843
GOTERM_MF_DIRECT	GO:0034714~type III transforming growth factor beta receptor binding	2	2.86	1.58×10 ⁻²	7040, 7048
GOTERM_MF_DIRECT	GO:0005231~excitatory extracellular ligand-gated ion channel activity	2	2.86	1.97×10 ⁻²	2892, 2890
GOTERM_MF_DIRECT	GO:0003707~steroid hormone receptor activity	3	4.29	2.08×10 ⁻²	5241, 7421, 2099
GOTERM_MF_DIRECT	GO:0003725~double-stranded RNA binding	3	4.29	2.44×10 ⁻²	92140, 105, 6895
GOTERM_MF_DIRECT	GO:0034618~arginine binding	2	2.86	2.76×10 ⁻²	4846, 4843
GOTERM_MF_DIRECT	GO:0042802~identical protein binding	8	11.43	2.86×10 ⁻²	7422, 6648, 7124, 1813, 2332, 2099, 6895, 348
GOTERM_MF_DIRECT	GO:0035197~siRNA binding	2	2.86	3.13×10 ⁻²	2332, 6895
GOTERM_MF_DIRECT	GO:0070573~metallopeptidase activity	2	2.86	3.13×10 ⁻²	1636, 10404
GOTERM_MF_DIRECT	GO:0034713~type I transforming growth factor beta receptor binding	2	2.86	3.52×10 ⁻²	7040, 7048
GOTERM_MF_DIRECT	GO:0046982~protein heterodimerization activity	6	8.57	3.72×10 ⁻²	4209, 7040, 4855, 7422, 1813, 2332
GOTERM_MF_DIRECT	GO:0015467~G-protein activated inward rectifier potassium channel activity	2	2.86	3.90×10 ⁻²	3765, 3766
GOTERM_MF_DIRECT	GO:0008066~glutamate receptor activity	2	2.86	4.28×10 ⁻²	2917, 2890
GOTERM_MF_DIRECT	GO:0019899~enzyme binding	5	7.14	4.32×10 ⁻²	7040, 5241, 2099, 6895, 267012
GOTERM_MF_DIRECT	GO:0004970~ionotropic glutamate receptor activity	2	2.86	5.79×10 ⁻²	2892, 2890
GOTERM_MF_DIRECT	GO:0035198~miRNA binding	2	2.86	6.17×10 ⁻²	2332, 6895
GOTERM_MF_DIRECT	GO:0004180~carboxypeptidase activity	2	2.86	6.54×10 ⁻²	1636, 10404
GOTERM_MF_DIRECT	GO:0005234~extracellular-glutamate-gated ion channel activity	2	2.86	6.91×10 ⁻²	2892, 2890
GOTERM_MF_DIRECT	GO:0004890~GABA-A receptor activity	2	2.86	7.28×10 ⁻²	2556, 55879
GOTERM_MF_DIRECT	GO:0005242~inward rectifier potassium channel activity	2	2.86	7.65×10 ⁻²	3765, 3766
GOTERM_MF_DIRECT	GO:0033613~activating transcription factor binding	2	2.86	8.38×10 ⁻²	4209, 63976
GOTERM_MF_DIRECT	GO:0030594~neurotransmitter receptor activity	2	2.86	9.83×10 ⁻²	3351, 3363
GOTERM_MF_DIRECT	GO:0003779~actin binding	4	5.71	9.84×10 ⁻²	221692, 1636, 2638, 23345

Table S4 GO function enrichment analysis of gene related to migraine

Category	Term	Count	%	P value	Genes ID
GOTERM_MF_DIRECT	GO:0042802-identical protein binding	33	19.30	2.27×10 ⁻¹²	7124, 6348, 1788, 6351, 7186, 7422, 2274, 255022, 2901, 6647, 596, 598, 9353, 2670, 7442, 4193, 2752, 839, 1759, 972, 207, 7157, 6857, 348, 351, 5621, 355, 6198, 348980, 4790, 1471, 998, 5594
GOTERM_MF_DIRECT	GO:0005234-extracellular-glutamate-gated ion channel activity	9	5.26	3.27×10 ⁻¹²	2901, 2897, 2902, 2898, 2903, 2904, 2891, 2890, 2900
GOTERM_MF_DIRECT	GO:0004970-ionotropic glutamate receptor activity	7	4.09	4.13×10 ⁻⁹	2897, 2902, 2898, 2903, 2891, 2890, 2900
GOTERM_MF_DIRECT	GO:0008066-glutamate receptor activity	6	3.51	4.05×10 ⁻⁸	2915, 2912, 2913, 2917, 2890, 2911
GOTERM_MF_DIRECT	GO:0097153-cysteine-type endopeptidase activity involved in apoptotic process	6	3.51	1.11×10 ⁻⁷	842, 840, 837, 839, 834, 836
GOTERM_MF_DIRECT	GO:0005515-protein binding	119	69.59	1.07×10 ⁻⁶	7494, 4204, 3146, 6348, 6869, 6351, 41, 3925, 2012, 1826, 5228, 4217, 5743, 9353, 4193, 3552, 2752, 477, 207, 4886, 348, 3351, 3350, 4790, 83660, 824, 6469, 823, 310, 1786, 821, 1788, 3316, 7040, 7186, 6376, 7422, 7421, 2274, 7048, 10018, 4780, 7184, 596, 5243, 598, 9899, 9568, 5621, 718, 7225, 1471, 7222, 998, 10243, 842, 2912, 840, 27161, 7124, 2911, 387, 23405, 8500, 84628, 1756, 2902, 773, 2903, 64780, 2904, 6647, 8976, 4843, 4842, 775, 2670, 2891, 6506, 2890, 9817, 839, 7133, 3309, 834, 972, 1759, 2261, 836, 7132, 9211, 6198, 5595, 2566, 3586, 5594, 79663, 1740, 9846, 2697, 2556, 6640, 3557, 22822, 3673, 2550, 6857, 7157, 351, 5469, 1400, 84062, 355, 3766, 7099, 6532, 358, 3066, 3569
GOTERM_MF_DIRECT	GO:0050998-nitric-oxide synthase binding	5	2.92	8.77×10 ⁻⁶	1756, 6532, 6640, 1759, 972
GOTERM_MF_DIRECT	GO:0015277-kainate selective glutamate receptor activity	4	2.34	9.54×10 ⁻⁶	2901, 2897, 2898, 2900
GOTERM_MF_DIRECT	GO:0005125-cytokine activity	11	6.43	1.07×10 ⁻⁵	7040, 6351, 7422, 3146, 3084, 7124, 3553, 3552, 3586, 3569, 3557
GOTERM_MF_DIRECT	GO:0005262-calcium channel activity	7	4.09	6.88×10 ⁻⁵	2902, 773, 2903, 7225, 7442, 24145, 7222
GOTERM_MF_DIRECT	GO:0016595-glutamate binding	4	2.34	1.10×10 ⁻⁴	2902, 2917, 6507, 2752
GOTERM_MF_DIRECT	GO:0097110-scaffold protein binding	6	3.51	1.10×10 ⁻⁴	8912, 2697, 4842, 5595, 4193, 24145
GOTERM_MF_DIRECT	GO:0042803-protein homodimerization activity	20	11.70	1.23×10 ⁻⁴	4217, 7494, 6647, 596, 598, 4843, 5743, 9353, 348, 7915, 2898, 7040, 3777, 7422, 51305, 6532, 729230, 6566, 4790, 5228
GOTERM_MF_DIRECT	GO:0030165-PDZ domain binding	7	4.09	2.16×10 ⁻⁴	2901, 2697, 2898, 6198, 2917, 2890, 6640
GOTERM_MF_DIRECT	GO:0004197-cysteine-type endopeptidase activity	6	3.51	3.49×10 ⁻⁴	842, 840, 837, 839, 834, 836
GOTERM_MF_DIRECT	GO:0002020-protease binding	7	4.09	5.16×10 ⁻⁴	7494, 596, 7124, 1471, 24145, 7157, 836
GOTERM_MF_DIRECT	GO:0031435-mitogen-activated protein kinase kinase binding	4	2.34	5.94×10 ⁻⁴	7186, 7048, 998, 5594
GOTERM_MF_DIRECT	GO:0005516-calmodulin binding	9	5.26	6.16×10 ⁻⁴	2902, 4843, 775, 4842, 7442, 3782, 6640, 1266, 6857
GOTERM_MF_DIRECT	GO:0005216-ion channel activity	5	2.92	8.63×10 ⁻⁴	6326, 773, 3777, 6323, 7442
GOTERM_MF_DIRECT	GO:0005231-excitatory extracellular ligand-gated ion channel activity	3	1.75	9.65×10 ⁻⁴	2891, 7442, 2890
GOTERM_MF_DIRECT	GO:0005088-Ras guanyl-nucleotide exchange factor activity	7	4.09	1.02×10 ⁻³	9365, 2902, 2903, 2904, 3084, 5923, 2261
GOTERM_MF_DIRECT	GO:0008134-transcription factor binding	10	5.85	2.19×10 ⁻³	596, 4204, 2274, 3146, 3066, 9817, 4790, 7157, 5594, 5469
GOTERM_MF_DIRECT	GO:0051721-protein phosphatase 2A binding	4	2.34	2.38×10 ⁻³	6198, 596, 207, 7157
GOTERM_MF_DIRECT	GO:0046982-protein heterodimerization activity	13	7.60	2.43×10 ⁻³	824, 7494, 3777, 7040, 3673, 596, 7422, 598, 51305, 4790, 24145, 5228, 7157
GOTERM_MF_DIRECT	GO:0035197-siRNA binding	3	1.75	2.65×10 ⁻³	4204, 27161, 23405
GOTERM_MF_DIRECT	GO:0004972-NMDA glutamate receptor activity	3	1.75	2.65×10 ⁻³	2902, 2903, 2904
GOTERM_MF_DIRECT	GO:0005102-receptor binding	11	6.43	2.86×10 ⁻³	2697, 8862, 2902, 9211, 718, 6376, 3084, 4843, 6347, 24145, 351
GOTERM_MF_DIRECT	GO:0034713-type I transforming growth factor beta receptor binding	3	1.75	3.39×10 ⁻³	83891, 7040, 7048
GOTERM_MF_DIRECT	GO:0001948-glycoprotein binding	5	2.92	4.00×10 ⁻³	7040, 6469, 2670, 3309, 821
GOTERM_MF_DIRECT	GO:0051378-serotonin binding	3	1.75	4.20×10 ⁻³	3356, 3351, 3350
GOTERM_MF_DIRECT	GO:0005230-extracellular ligand-gated ion channel activity	4	2.34	4.24×10 ⁻³	2562, 7442, 2556, 2566
GOTERM_MF_DIRECT	GO:0015276-ligand-gated ion channel activity	4	2.34	5.43×10 ⁻³	2901, 2897, 2898, 2900
GOTERM_MF_DIRECT	GO:0008083-growth factor activity	7	4.09	5.67×10 ⁻³	7040, 7422, 3084, 627, 3586, 3569, 5228
GOTERM_MF_DIRECT	GO:0005267-potassium channel activity	4	2.34	5.87×10 ⁻³	3777, 348980, 51305, 358
GOTERM_MF_DIRECT	GO:0005149-interleukin-1 receptor binding	3	1.75	7.15×10 ⁻³	3553, 3552, 3557
GOTERM_MF_DIRECT	GO:0005245-voltage-gated calcium channel activity	4	2.34	7.30×10 ⁻³	773, 2917, 775, 255022
GOTERM_MF_DIRECT	GO:0051087-chaperone binding	5	2.92	8.69×10 ⁻³	6647, 3309, 477, 7157, 5621
GOTERM_MF_DIRECT	GO:0005070-low-density lipoprotein particle receptor binding	3	1.75	1.08×10 ⁻²	7184, 6857, 348
GOTERM_MF_DIRECT	GO:0008009-chemokine activity	4	2.34	1.28×10 ⁻²	6351, 6376, 6347, 6348
GOTERM_MF_DIRECT	GO:0022857-transmembrane transporter activity	4	2.34	1.28×10 ⁻²	22987, 358, 9899, 9900
GOTERM_MF_DIRECT	GO:0015293-symporter activity	4	2.34	1.42×10 ⁻²	9194, 6506, 6566, 6507
GOTERM_MF_DIRECT	GO:0004890-GABA-A receptor activity	3	1.75	1.51×10 ⁻²	2562, 2556, 2566
GOTERM_MF_DIRECT	GO:0005248-voltage-gated sodium channel activity	3	1.75	1.66×10 ⁻²	6326, 348980, 6323
GOTERM_MF_DIRECT	GO:0005507-copper ion binding	4	2.34	1.83×10 ⁻²	6647, 3552, 7157, 5621
GOTERM_MF_DIRECT	GO:0019899-enzyme binding	9	5.26	1.85×10 ⁻²	7040, 7186, 5743, 3066, 4193, 3309, 207, 7157, 351
GOTERM_MF_DIRECT	GO:0001641-group II metabotropic glutamate receptor activity	2	1.17	1.98×10 ⁻²	2912, 2913
GOTERM_MF_DIRECT	GO:0017022-myosin binding	3	1.75	2.00×10 ⁻²	1756, 387, 6532
GOTERM_MF_DIRECT	GO:0005178-integrin binding	5	2.92	2.08×10 ⁻²	3673, 6376, 3084, 2670, 310
GOTERM_MF_DIRECT	GO:0003779-actin binding	8	4.68	2.14×10 ⁻²	1756, 64780, 8976, 2638, 7225, 6640, 83660, 1266
GOTERM_MF_DIRECT	GO:0008201-heparin binding	6	3.51	2.20×10 ⁻²	7422, 9353, 6347, 5228, 348, 351
GOTERM_MF_DIRECT	GO:0005031-tumor necrosis factor-activated receptor activity	3	1.75	2.35×10 ⁻²	355, 7133, 7132
GOTERM_MF_DIRECT	GO:0031625-ubiquitin protein ligase binding	8	4.68	2.48×10 ⁻²	7494, 2898, 7186, 596, 4193, 3309, 7133, 7157
GOTERM_MF_DIRECT	GO:0019903-protein phosphatase binding	4	2.34	2.49×10 ⁻²	4217, 7186, 7184, 7157
GOTERM_MF_DIRECT	GO:0001047-core promoter binding	4	2.34	2.59×10 ⁻²	7494, 27161, 3066, 5469
GOTERM_MF_DIRECT	GO:0030594-neurotransmitter receptor activity	3	1.75	2.74×10 ⁻²	3356, 3351, 3350
GOTERM_MF_DIRECT	GO:0005246-calcium channel regulator activity	3	1.75	2.94×10 ⁻²	2912, 2913, 2917
GOTERM_MF_DIRECT	GO:0042056-chemoattractant activity	3	1.75	2.94×10 ⁻²	7422, 3146, 6348
GOTERM_MF_DIRECT	GO:0004517-nitric-oxide synthase activity	2	1.17	2.96×10 ⁻²	4843, 4842
GOTERM_MF_DIRECT	GO:0031727-CCR2 chemokine receptor binding	2	1.17	2.96×10 ⁻²	729230, 6347
GOTERM_MF_DIRECT	GO:0097200-cysteine-type endopeptidase activity involved in execution phase of apoptosis	2	1.17	2.96×10 ⁻²	840, 836
GOTERM_MF_DIRECT	GO:0015222-serotonin transmembrane transporter activity	2	1.17	2.96×10 ⁻²	6532, 6571
GOTERM_MF_DIRECT	GO:0004965-G-protein coupled GABA receptor activity	2	1.17	2.96×10 ⁻²	2550, 9568
GOTERM_MF_DIRECT	GO:0004993-G-protein coupled serotonin receptor activity	3	1.75	3.14×10 ⁻²	3356, 3351, 3350
GOTERM_MF_DIRECT	GO:0004712-protein serine/threonine/tyrosine kinase activity	3	1.75	3.35×10 ⁻²	6198, 5649, 207
GOTERM_MF_DIRECT	GO:0019901-protein kinase binding	9	5.26	3.47×10 ⁻²	4217, 7494, 842, 7186, 598, 9900, 1759, 998, 7157
GOTERM_MF_DIRECT	GO:0003886-DNA (cytosine-5)-methyltransferase activity	2	1.17	3.92×10 ⁻²	1786, 1788
GOTERM_MF_DIRECT	GO:0004971-AMPA glutamate receptor activity	2	1.17	3.92×10 ⁻²	2891, 2890
GOTERM_MF_DIRECT	GO:0034617-tetrahydrobiopterin binding	2	1.17	3.92×10 ⁻²	4843, 4842
GOTERM_MF_DIRECT	GO:0070326-very-low-density lipoprotein particle receptor binding	2	1.17	3.92×10 ⁻²	5649, 348
GOTERM_MF_DIRECT	GO:0034714-type III transforming growth factor beta receptor binding	2	1.17	3.92×10 ⁻²	7040, 7048
GOTERM_MF_DIRECT	GO:0051434-BH3 domain binding	2	1.17	3.92×10 ⁻²	596, 598
GOTERM_MF_DIRECT	GO:0005172-vascular endothelial growth factor receptor binding	2	1.17	3.92×10 ⁻²	7422, 5228
GOTERM_MF_DIRECT	GO:0001540-beta-amyloid binding	3	1.75	4.49×10 ⁻²	1471, 972, 348
GOTERM_MF_DIRECT	GO:0050661-NADP binding	3	1.75	4.73×10 ⁻²	4843, 4524, 4842
GOTERM_MF_DIRECT	GO:0005314-high-affinity glutamate transmembrane transporter activity	2	1.17	4.88×10 ⁻²	6506, 6507
GOTERM_MF_DIRECT	GO:0009008-DNA-methyltransferase activity	2	1.17	4.88×10 ⁻²	1786, 1788
GOTERM_MF_DIRECT	GO:0005499-vitamin D binding	2	1.17	4.88×10 ⁻²	9365, 2638
GOTERM_MF_DIRECT	GO:0004871-signal transducer activity	6	3.51	5.31×10 ⁻²	9365, 2697, 355, 7186, 3925, 8500
GOTERM_MF_DIRECT	GO:0008234-cysteine-type peptidase activity	3	1.75	5.48×10 ⁻²	824, 840, 839
GOTERM_MF_DIRECT	GO:0032403-protein complex binding	6	3.51	5.52×10 ⁻²	3356, 3673, 7186, 4524, 1759, 836
GOTERM_MF_DIRECT	GO:0008503-benzodiazepine receptor activity	2	1.17	5.83×10 ⁻²	2556, 2566
GOTERM_MF_DIRECT	GO:0005372-water transmembrane transporter activity	2	1.17	5.83×10 ⁻²	358, 361
GOTERM_MF_DIRECT	GO:0043237-laminin-1 binding	2	1.17	5.83×10 ⁻²	6469, 9353
GOTERM_MF_DIRECT	GO:0008233-peptidase activity	4	2.34	6.08×10 ⁻²	842, 6469, 836, 351
GOTERM_MF_DIRECT	GO:0008504-monoamine transmembrane transporter activity	2	1.17	6.76×10 ⁻²	6532, 6571
GOTERM_MF_DIRECT	GO:0034618-arginine binding	2	1.17	6.76×10 ⁻²	4843, 4842
GOTERM_MF_DIRECT	GO:0031726-CCR1 chemokine receptor binding	2	1.17	6.76×10 ⁻²	6351, 6348
GOTERM_MF_DIRECT	GO:0031730-CCR5 chemokine receptor binding	2	1.17	7.69×10 ⁻²	6351, 6348
GOTERM_MF_DIRECT	GO:0042805-actinin binding	2	1.17	9.52×10 ⁻²	7225, 4790
GOTERM_MF_DIRECT	GO:0008331-high voltage-gated calcium channel activity	2	1.17	9.52×10 ⁻²	773, 775
GOTERM_MF_DIRECT	GO:0042975-peroxisome proliferator activated receptor binding	2	1.17	9.52×10 ⁻²	4193, 5469

Table S5 Signaling pathway enrichment analysis related to epilepsy

#Pathway ID	Pathway description	Observed gene count	P value	Matching genes
670	One carbon pool by folate	2	2.10×10^{-2}	<i>MTHFR, MTR</i>
4020	Calcium signaling pathway	5	6.21×10^{-3}	<i>CACNA1A, EDNRB, HTR7, NOS2, NOS3</i>
4022	cGMP-PKG signaling pathway	4	2.20×10^{-2}	<i>ATP1A2, EDNRB, MEF2D, NOS3</i>
4060	Cytokine-cytokine receptor interaction	9	2.38×10^{-5}	<i>CCL2, CCR2, IL9, LTA, NGFR, TGFB1, TGFB2, TNF, VEGFA</i>
4066	HIF-1 signaling pathway	3	4.75×10^{-2}	<i>NOS2, NOS3, VEGFA</i>
4080	Neuroactive ligand-receptor interaction	11	5.18×10^{-7}	<i>DRD2, EDNRB, GABRA3, GABRQ, GRIA1, GRIA3, GRM7, HCRTR1, HTR1B, HTR7, OPRM1</i>
4350	TGF-beta signaling pathway	3	2.40×10^{-2}	<i>TGFB1, TGFB2, TNF</i>
4668	TNF signaling pathway	3	4.86×10^{-2}	<i>CCL2, LTA, TNF</i>
4713	Circadian entrainment	3	3.37×10^{-2}	<i>GRIA1, GRIA3, KCNJ9</i>
4723	Retrograde endocannabinoid signaling	6	5.39×10^{-5}	<i>CACNA1A, GABRA3, GABRQ, GRIA1, GRIA3, KCNJ9</i>
4724	Glutamatergic synapse	4	8.51×10^{-3}	<i>CACNA1A, GRIA1, GRIA3, GRM7</i>
4726	Serotonergic synapse	5	1.03×10^{-3}	<i>CACNA1A, HTR1B, HTR7, KCNJ9, SLC6A4</i>
4727	GABAergic synapse	3	2.87×10^{-2}	<i>CACNA1A, GABRA3, GABRQ</i>
4728	Dopaminergic synapse	6	2.01×10^{-4}	<i>CACNA1A, DRD2, GRIA1, GRIA3, KCNJ9, SCN1A</i>
4730	Long-term depression	3	1.41×10^{-2}	<i>CACNA1A, GRIA1, GRIA3</i>
4915	Estrogen signaling pathway	4	5.99×10^{-3}	<i>ESR1, KCNJ9, NOS3, OPRM1</i>
4940	Type I diabetes mellitus	3	6.21×10^{-3}	<i>HLA-DRB1, LTA, TNF</i>
4961	Endocrine and other factor-regulated calcium reabsorption	3	8.51×10^{-3}	<i>ATP1A2, ESR1, VDR</i>
4964	Proximal tubule bicarbonate reclamation	2	2.10×10^{-2}	<i>ATP1A2, SLC4A4</i>
4978	Mineral absorption	3	9.06×10^{-3}	<i>ATP1A2, HEPH, VDR</i>
5032	Morphine addiction	5	4.95×10^{-4}	<i>CACNA1A, GABRA3, GABRQ, KCNJ9, OPRM1</i>
5033	Nicotine addiction	5	2.38×10^{-5}	<i>CACNA1A, GABRA3, GABRQ, GRIA1, GRIA3</i>
5140	Leishmaniasis	4	2.40×10^{-3}	<i>HLA-DRB1, NOS2, TGFB1, TNF</i>
5142	Chagas disease (American trypanosomiasis)	5	6.21×10^{-4}	<i>CCL2, NOS2, TGFB1, TGFB2, TNF</i>
5144	Malaria	4	6.21×10^{-4}	<i>CCL2, LRP1, TGFB1, TNF</i>
5145	Toxoplasmosis	4	8.93×10^{-3}	<i>HLA-DRB1, NOS2, TGFB1, TNF</i>
5146	Amoebiasis	3	4.75×10^{-2}	<i>NOS2, TGFB1, TNF</i>
5152	Tuberculosis	5	5.99×10^{-3}	<i>HLA-DRB1, NOS2, TGFB1, TNF, VDR</i>
5166	HTLV-I infection	5	1.99×10^{-2}	<i>HLA-DRB1, LTA, TGFB1, TGFB2, TNF</i>
5168	Herpes simplex infection	4	2.87×10^{-2}	<i>CCL2, HLA-DRB1, LTA, TNF</i>
5212	Pancreatic cancer	3	1.56×10^{-2}	<i>TGFB1, TGFB2, VEGFA</i>
5310	Asthma	3	2.83×10^{-3}	<i>HLA-DRB1, IL9, TNF</i>
5321	Inflammatory bowel disease (IBD)	3	1.57×10^{-2}	<i>HLA-DRB1, TGFB1, TNF</i>
5323	Rheumatoid arthritis	6	3.27×10^{-5}	<i>CCL2, CTLA4, HLA-DRB1, TGFB1, TNF, VEGFA</i>
5330	Allograft rejection	2	4.95×10^{-2}	<i>HLA-DRB1, TNF</i>

Table S6 Signaling pathway enrichment analysis related to migraine

#Pathway ID	Pathway description	Observed gene count	P value	Matching genes
330	Arginine and proline metabolism	3	2.82×10 ⁻²	GLUL,NOS1,NOS2
4010	MAPK signaling pathway	23	5.08×10 ⁻¹⁶	AKT1,BDNF,CACNA1A,CACNA1C,CACNA1H,CASP3,CDC42,FAS,FGFR3,IL1A,IL1B,MAP3K5,MAPK1,MAPK3,NFKB1,RASGRF1,STMN1,TGFB1,TGFB2,TNF,TNFRSF1A,TP53,TRAF2
4012	ErbB signaling pathway	5	1.95×10 ⁻³	AKT1,MAPK1,MAPK3,NRG1,RPS6KB1
4014	Ras signaling pathway	15	4.23×10 ⁻⁹	AKT1,BCL2L1,CDC42,FGFR3,GAB2,GRIN1,GRIN2A,GRIN2B,MAPK1,MAPK3,NFKB1,PGF,RASGRF1,RHOA,VEGFA
4015	Rap1 signaling pathway	12	8.66×10 ⁻⁷	AKT1,CDC42,FGFR3,GRIN1,GRIN2A,GRIN2B,MAPK1,MAPK3,PGF,RHOA,TLN2,VEGFA
4020	Calcium signaling pathway	11	1.38×10 ⁻⁶	CACNA1A,CACNA1C,CACNA1H,GRIN1,GRIN2A,GRM1,GRM5,HTR2A,NOS1,NOS2,TACR1
4022	cGMP-PKG signaling pathway	7	1.10×10 ⁻³	AKT1,ATP1A2,CACNA1C,MAPK1,MAPK3,RHOA,TRPC6
4060	Cytokine-cytokine receptor interaction	16	5.13×10 ⁻⁹	CCL2,CCL3,CCL4,CCR2,CX3CL1,FAS,IL10,IL1A,IL1B,IL6,TGFB1,TGFB2,TNF,TNFRSF1A,TNFRSF1B,VEGFA
4062	Chemokine signaling pathway	12	2.24×10 ⁻⁷	AKT1,CCL2,CCL3,CCL4,CCR2,CDC42,CX3CL1,MAPK1,MAPK3,NFKB1,RHOA,WASL
4064	NF-kappa B signaling pathway	10	2.55×10 ⁻⁸	BCL2,BCL2L1,CCL4,IL1B,NFKB1,PTGS2,TLR4,TNF,TNFRSF1A,TRAF2
4066	HIF-1 signaling pathway	10	1.11×10 ⁻⁷	AKT1,BCL2,IL6,MAPK1,MAPK3,NFKB1,NOS2,RPS6KB1,TLR4,VEGFA
4068	FoxO signaling pathway	10	3.99×10 ⁻⁷	AKT1,BCL2L1,GRM1,IL10,IL6,MAPK1,MAPK3,MDM2,TGFB1,TGFB2
4080	Neuroactive ligand-receptor interaction	24	2.53×10 ⁻¹⁶	GABBR1,GABBR2,GABRA3,GABRB3,GABRG2,GRIA1,GRIA2,GRIK1,GRIK2,GRIK4,GRIK5,GRIN1,GRIN2A,GRI2B,GRM1,GRM2,GRM3,GRM5,GRM7,HTR1A,HTR1B,HTR2A,NPY1R,TACR1
4110	Cell cycle	4	4.25×10 ⁻²	HDAC2,MDM2,TGFB1,TP53
4115	p53 signaling pathway	5	7.27×10 ⁻⁴	CASP3,CASP9,FAS,MDM2,TP53
4141	Protein processing in endoplasmic reticulum	9	3.91×10 ⁻⁵	BCL2,CANX,CAPN1,CAPN2,HSPA5,MAP3K5,NFE2L2,TRAF2,XBP1
4144	Endocytosis	7	3.29×10 ⁻³	CDC42,DNM1,FGFR3,MDM2,RHOA,TGFB1,TGFB2
4145	Phagosome	5	1.66×10 ⁻²	C3,CANX,ITGA2,NOS1,TLR4
4150	mTOR signaling pathway	6	4.12×10 ⁻⁵	AKT1,MAPK1,MAPK3,RPS6KB1,TNF,VEGFA
4151	PI3K-Akt signaling pathway	20	1.04×10 ⁻¹⁰	AKT1,BCL2,BCL2L1,BCL2L11,CASP9,FGFR3,IL6,ITGA2,LAMB1,LAMB4,MAPK1,MAPK3,MDM2,NFKB1,PGF,RELN,RPS6KB1,TLR4,TP53,VEGFA
4210	Apoptosis	17	2.39×10 ⁻¹⁷	AKT1,BCL2,BCL2L1,CAPN1,CAPN2,CASP3,CASP6,CASP7,CASP9,FAS,IL1A,IL1B,NFKB1,TNF,TNFRSF1A,TP53,TRAF2
4261	Adrenergic signaling in cardiomyocytes	6	3.33×10 ⁻³	AKT1,ATP1A2,BCL2,CACNA1C,MAPK1,MAPK3
4270	Vascular smooth muscle contraction	4	3.65×10 ⁻²	CACNA1C,MAPK1,MAPK3,RHOA
4320	Dorso-ventral axis formation	2	3.33×10 ⁻²	MAPK1,MAPK3
4350	TGF-beta signaling pathway	7	1.66×10 ⁻⁵	MAPK1,MAPK3,RHOA,RPS6KB1,TGFB1,TGFB2,TNF,CDC42,MAPK1,MAPK3,NTNG2,RHOA,SLIT2
4360	Axon guidance	6	1.77×10 ⁻³	AKT1,CASP9,CDC42,MAPK1,MAPK3,PTGS2,VEGFA
4370	VEGF signaling pathway	7	2.95×10 ⁻⁶	AKT1,FHL2,GAB2,IL1A,IL1B,MAPK1,MAPK3,NFKB1,TGFB1,TGFB2,TNF,TNFRSF1A,TRAF2
4380	Osteoclast differentiation	13	3.75×10 ⁻¹⁰	AKT1,BCL2,CAPN2,CDC42,ITGA2,LAMB1,LAMB4,MAPK1,MAPK3,PGF,RASGRF1,RELN,RHOA,TLN2,VEGFA
4510	Focal adhesion	15	1.45×10 ⁻⁹	AKT1,BCL2,CAPN2,CDC42,ITGA2,LAMB1,LAMB4,MAPK1,MAPK3,PGF,RASGRF1,RELN,RHOA,TLN2,VEGFA
4512	ECM-receptor interaction	6	2.80×10 ⁻⁴	ITGA2,LAMB1,LAMB4,RELN,SV2B,SV2C
4520	Adherens junction	6	1.02×10 ⁻⁴	CDC42,MAPK1,MAPK3,RHOA,TGFB2,WASL
4540	Gap junction	6	2.48×10 ⁻⁴	GJA1,GRM1,GRM5,HTR2A,MAPK1,MAPK3
4611	Platelet activation	6	1.97×10 ⁻³	AKT1,ITGA2,MAPK1,MAPK3,RHOA,TLN2
4612	Antigen processing and presentation	4	6.03×10 ⁻³	CANX,CD74,HSPA5,TNF
4620	Toll-like receptor signaling pathway	10	9.39×10 ⁻⁸	AKT1,CCL3,CCL4,IL1B,IL6,MAPK1,MAPK3,NFKB1,TLR4,TNF
4621	NOD-like receptor signaling pathway	8	1.43×10 ⁻⁷	CASP1,CCL2,IL1B,IL6,MAPK1,MAPK3,NFKB1,TNF
4622	RIG-I-like receptor signaling pathway	3	4.51×10 ⁻²	NFKB1,TNF,TRAF2
4623	Cytosolic DNA-sensing pathway	5	5.12×10 ⁻⁴	CASP1,CCL4,IL1B,IL6,NFKB1
4640	Hematopoietic cell lineage	5	2.13×10 ⁻³	IL1A,IL1B,IL6,ITGA2,TNF
4650	Natural killer cell mediated cytotoxicity	5	9.31×10 ⁻³	CASP3,FAS,MAPK1,MAPK3,TNF
4660	T cell receptor signaling pathway	8	7.78×10 ⁻⁶	AKT1,CDC42,IL10,MAPK1,MAPK3,NFKB1,RHOA,TNF
4662	B cell receptor signaling pathway	4	6.91×10 ⁻³	AKT1,MAPK1,MAPK3,NFKB1
4664	Fc epsilon RI signaling pathway	5	7.27×10 ⁻⁴	AKT1,GAB2,MAPK1,MAPK3,TNF
4666	Fc gamma R-mediated phagocytosis	7	3.65×10 ⁻⁵	AKT1,CDC42,GAB2,MAPK1,MAPK3,RPS6KB1,WASL
4668	TNF signaling pathway	17	6.23×10 ⁻¹⁶	AKT1,CASP3,CASP7,CCL2,CX3CL1,FAS,IL1B,IL6,MAP3K5,MAPK1,MAPK3,NFKB1,PTGS2,TNF,TNFRSF1A,TNFRSF1B,TRAF2
4672	Intestinal immune network for IgA production	3	1.45×10 ⁻²	IL10,IL6,TGFB1
4713	Circadian entrainment	10	3.11×10 ⁻⁸	CACNA1C,CACNA1H,GRIA1,GRIA2,GRIN1,GRIN2A,GRIN2B,MAPK1,MAPK3,NOS1
4720	Long-term potentiation	10	1.10×10 ⁻⁹	CACNA1C,GRIA1,GRIA2,GRIN1,GRIN2A,GRIN2B,GRM1,GRM5,MAPK1,MAPK3
4721	Synaptic vesicle cycle	4	4.32×10 ⁻³	CACNA1A,DNM1,SLC18A2,SYT1
4722	Neurotrophin signaling pathway	10	2.79×10 ⁻⁷	AKT1,BCL2,BDNF,CDC42,MAP3K5,MAPK1,MAPK3,NFKB1,RHOA,TP53
4723	Retrograde endocannabinoid signaling	12	3.16×10 ⁻¹⁰	CACNA1A,CACNA1C,GABRA3,GABRB3,GABRG2,GRIA1,GRIA2,GRM1,GRM5,MAPK1,MAPK3,PTGS2
4724	Glutamatergic synapse	21	7.66×10 ⁻²¹	CACNA1A,CACNA1C,GLUL,GRIA1,GRIA2,GRIK1,GRIK2,GRIK4,GRIK5,GRIN1,GRIN2A,GRIN2B,GRM1,GRM2,GRM3,GRM5,GRM7,MAPK1,MAPK3,SLC1A2,SLC1A3
4725	Cholinergic synapse	6	8.77×10 ⁻⁴	AKT1,BCL2,CACNA1A,CACNA1C,MAPK1,MAPK3
4726	Serotonergic synapse	13	1.04×10 ⁻¹⁰	APP,CACNA1A,CACNA1C,CASP3,GABRB3,HTR1A,HTR1B,HTR2A,MAPK1,MAPK3,PTGS2,SLC18A2,SLC6A4
4727	GABAergic synapse	9	2.08×10 ⁻⁷	CACNA1A,CACNA1C,CAPN1,GABBR1,GABBR3,GABRA3,GABRB3,GABRG2,GLUL,GPHN
4728	Dopaminergic synapse	9	4.89×10 ⁻⁶	AKT1,CACNA1A,CACNA1C,GRIA1,GRIA2,GRIN2A,GRI2B,SCN1A,SLC18A2
4730	Long-term depression	7	2.77×10 ⁻⁶	CACNA1A,GRIA1,GRIA2,GRM1,MAPK1,MAPK3,NOS1
4810	Regulation of actin cytoskeleton	7	5.01×10 ⁻³	CDC42,FGFR3,ITGA2,MAPK1,MAPK3,RHOA,WASL
4912	GnRH signaling pathway	4	1.49×10 ⁻²	CACNA1C,CDC42,MAPK1,MAPK3
4915	Estrogen signaling pathway	6	4.36×10 ⁻⁴	AKT1,GABBR1,GABBR2,GRM1,MAPK1,MAPK3
4917	Prolactin signaling pathway	4	6.91×10 ⁻³	AKT1,MAPK1,MAPK3,NFKB1
4918	Thyroid hormone synthesis	3	4.64×10 ⁻²	ATP1A2,CANX,HSPA5
4919	Thyroid hormone signaling pathway	9	2.77×10 ⁻⁶	AKT1,ATP1A2,CASP9,HDAC2,MAPK1,MAPK3,MDM2,MED1,TP53
4920	Adipocytokine signaling pathway	6	8.15×10 ⁻⁵	AKT1,NFKB1,TNF,TNFRSF1A,TNFRSF1B,TRAF2
4921	Oxytocin signaling pathway	5	2.17×10 ⁻²	CACNA1C,MAPK1,MAPK3,PTGS2,RHOA
4930	Type II diabetes mellitus	5	1.35×10 ⁻⁴	CACNA1A,CACNA1C,MAPK1,MAPK3,TNF
4932	Non-alcoholic fatty liver disease (NAFLD)	16	2.16×10 ⁻¹²	AKT1,BCL2L11,CASP3,CASP7,CDC42,FAS,IL1A,IL1B,IL6,MAP3K5,NFKB1,TGFB1,TNF,TNFRSF1A,TRAF2,XBP1
4940	Type I diabetes mellitus	4	1.05×10 ⁻³	FAS,IL1A,IL1B,TNF
4960	Aldosterone-regulated sodium reabsorption	3	8.35×10 ⁻³	ATP1A2,MAPK1,MAPK3
4961	Endocrine and other factor-regulated calcium reabsorption	5	1.49×10 ⁻⁴	ATP1A2,DNM1,KL,CLK1,VDR
4964	Proximal tubule bicarbonate reclamation	2	2.57×10 ⁻²	AQP1,ATP1A2
4976	Bile secretion	4	6.67×10 ⁻³	ABCB1,AQP1,AQP4,ATP1A2
5010	Alzheimer s disease	18	5.84×10 ⁻¹⁴	APOE,APP,CACNA1C,CAPN1,CAPN2,CASP3,CASP7,CASP9,FAS,GRIN1,GRIN2A,GRIN2B,IL1B,MAPK1,MAPK3,NOS1,TNF,TNFRSF1A
5014	Amyotrophic lateral sclerosis (ALS)	18	6.53×10 ⁻²⁰	BCL2,BCL2L1,CASP1,CASP3,CASP9,GRIA1,GRIA2,GRIN1,GRIN2A,GRIN2B,MAP3K5,NOS1,SLC1A2,SOD1,TNF,TNFRSF1A,TNFRSF1B,TP53
5016	Huntington s disease	9	8.72×10 ⁻⁵	BDNF,CASP3,CASP9,GRIN1,GRIN2B,GRM5,HDAC2,SOD1,TP53
5020	Prion diseases	8	4.23×10 ⁻⁹	HSPA5,IL1A,IL1B,IL6,MAPK1,MAPK3,PRNP,SOD1
5030	Cocaine addiction	10	1.08×10 ⁻¹⁰	BDNF,GRIA2,GRIN1,GRIN2A,GRIN2B,GRM2,GRM3,NFKB1,PDYN,SLC18A2
5031	Amphetamine addiction	8	3.99×10 ⁻⁷	CACNA1C,GRIA1,GRIA2,GRIN1,GRIN2A,GRIN2B,PDYN,SLC18A2
5032	Morphine addiction	6	3.12×10 ⁻⁴	CACNA1A,GABBR1,GABBR2,GABRA3,GABRB3,GABRG2
5033	Nicotine addiction	9	3.16×10 ⁻¹⁰	CACNA1A,GABRA3,GABRB3,GABRG2,GRIA1,GRIA2,GRIN1,GRIN2A,GRIN2B
5034	Alcoholism	9	1.05×10 ⁻⁵	BDNF,GRIN1,GRIN2A,GRIN2B,HDAC2,MAPK1,MAPK3,PDYN,SLC18A2
5100	Bacterial invasion of epithelial cells	4	8.25×10 ⁻³	CDC42,DNM1,RHOA,WASL
5120	Epithelial cell signaling in Helicobacter pylori infection	3	3.91×10 ⁻²	CASP3,CDC42,NFKB1
5130	Pathogenic Escherichia coli infection	4	2.65×10 ⁻³	CDC42,RHOA,TLR4,WASL
5131	Shigellosis	5	3.83×10 ⁻⁴	CDC42,MAPK1,MAPK3,NFKB1,WASL
5132	Salmonella infection	13	2.69×10 ⁻¹²	CASP1,CCL3,CCL4,CDC42,IL1A,IL1B,IL6,MAPK1,MAPK3,NFKB1,NOS2,TLR4,WASL
5133	Pertussis	15	5.08×10 ⁻¹⁶	C3,NFKB1,CASP3,CASP7,IL10,IL1A,IL1B,IL6,MAPK1,MAPK3,NFKB1,NOS2,RHOA,TLR4,TNF
5134	Legionellosis	10	2.28×10 ⁻¹⁰	C3,CASP1,CASP3,CASP7,CASP9,IL1B,IL6,NFKB1,TLR4,TNF
5140	Leishmaniasis	12	8.25×10 ⁻¹²	C3,IL10,IL1A,IL1B,MAPK1,MAPK3,NFKB1,NOS2,PTGS2,TGFB1,TLR4,TNF
5142	Chagas disease (American trypanosomiasis)	7	2.14×10 ⁻¹⁶	AKT1,C3,CCL2,CCL3,FAS,IL10,IL1B,IL6,MAPK1,MAPK3,NFKB1,NOS2,TGFB1,TGFB2,TLR4,TNF,TNFRSF1A
5143	African trypanosomiasis	5	3.34×10 ⁻⁵	FAS,IL10,IL1B,IL6,TNF
5144	Malaria	7	5.89×10 ⁻⁷	CCL2,IL10,IL1B,IL6,TGFB1,TLR4,TNF
5145	Toxoplasmosis	16	3.46×10 ⁻¹⁴	AKT1,BCL2,BCL2L1,CASP3,CASP9,IL10,LAMB1,LAMB4,MAPK1,MAPK3,NFKB1,NOS2,TGFB1,TLR4,TNF,TNFRSF1A
5146	Amoebiasis	11	9.15×10 ⁻⁹	CASP3,IL10,IL1B,IL6,LAMB1,LAMB4,NFKB1,NOS2,TGFB1,TLR4,TNF
5152	Tuberculosis	20	5.08×10 ⁻¹⁶	AKT1,BCL2,C3,CASP3,CASP9,CD74,IL10,IL1A,IL1B,IL6,MAPK1,MAPK3,NFKB1,NOS2,RHOA,TGFB1,TLR4,TNF,TNFRSF1A,VDR
5160	Hepatitis C	8	5.06×10 ⁻⁵	AKT1,MAPK1,MAPK3,NFKB1,TNF,TNFRSF1A,TP53,TRAF2
5161	Hepatitis B	13	1.45×10 ⁻⁹	AKT1,BCL2,CASP3,CASP9,FAS,IL6,MAPK1,MAPK3,NFKB1,TGFB1,TLR4,TNF,TP53
5162	Measles	9	6.59×10 ⁻⁶	AKT1,FAS,IL1A,IL1B,IL6,NFKB1,TACR1,TLR4,TP53
5164	Influenza A	14	1.19×10 ⁻⁹	AKT1,CASP1,CASP9,CCL2,FAS,IL1A,IL1B,IL6,MAPK1,MAPK3,NFKB1,TLR4,TNF,TNFRSF1A
5166	HTLV-I infection	12	6.45×10 ⁻⁶	AKT1,BCL2L1,CANX,IL6,NFKB1,TGFB1,TGFB2,TLN2,TNF,TNFRSF1A,TP53,XBP1
5168	Herpes simplex infection	12	1.82×10 ⁻⁷	C3,CASP3,CCL2,CD74,FAS,IL1B,IL6,NFKB1,TNF,TNFRSF1A,TP53,TRAF2
5169	Epstein-Barr virus infection	9	1.19×10 ⁻⁴	AKT1,BCL2,HDAC2,HSPB2,IL10,MDM2,NFKB1,TP53,TRAF2
5200	Pathways in cancer	27	1.53×10 ⁻¹⁷	AKT1,BCL2,BCL2L1,CASP3,CASP9,CDC42,FAS,FGFR3,HDAC2,IL6,ITGA2,LAMB1,LAMB4,MAPK1,MAPK3,MDM2,NFKB1,NOS2,PGF,PTGS2,RHOA,SHH,TGFB1,TGFB2,TP53,TRAF2,VEGFA
5202	Transcriptional misregulation in cancer	7	1.41×10 ⁻³	BCL2L1,HDAC2,IL6,MDM2,NFKB1,TGFB2,TP53
5203	Viral carcinogenesis	11	2.01×10 ⁻⁶	C3,CASP3,CDC42,HDAC2,MAPK1,MAPK3,MDM2,NFKB1,RHOA,TP53,TRAF2
5205	Proteoglycans in cancer	16	4.71×10 ⁻¹⁰	AKT1,CASP3,CDC42,FAS,HSPB2,ITGA2,MAPK1,MAPK3,MDM2,RHOA,RPS6KB1,TGFB1,TLR4,TNF,TP53,VEGFA
5206	MicroRNAs in cancer	16	1.50×10 ⁻¹²	ABCB1,BCL2,BCL2L11,CASP3,DICER1,DNM1,DNMT3A,FGFR3,MAPK1,MDM2,NFKB1,PTGS2,RHOA,STMN1,TP53,VEGFA
5210	Colorectal cancer	10	4.18×10 ⁻¹⁰	AKT1,BCL2,CASP3,CASP9,MAPK1,MAPK3,RHOA,TGFB1,TGFB2,TP53
5211	Renal cell carcinoma	6	6.34×10 ⁻⁵	AKT1,CDC42,MAPK1,MAPK3,TGFB1,VEGFA
5212	Pancreatic cancer	11	4.95×10 ⁻¹¹	AKT1,BCL2L11,CASP9,CDC42,MAPK1,MAPK3,NFKB1,TGFB1,TGFB2,TP53,VEGFA
5213	Endometrial cancer	5	2.21×10 ⁻⁴	AKT1,CASP9,MAPK1,MAPK3,TP53
5214	Glioma	5	5.12×10 ⁻⁴	AKT1,MAPK1,MAPK3,MDM2,TP53
5215	Prostate cancer	8	2.89×10 ⁻⁶	AKT1,BCL2,CASP9,MAPK1,MAPK3,MDM2,NFKB1,TP53
5216	Thyroid cancer	3	3.96×10 ⁻³	MAPK1,MAPK3,TP53
5218	Melanoma	5	8.77×10 ⁻⁴	AKT1,MAPK1,MAPK3,MDM2,TP53
5219	Bladder cancer	6	2.95×10 ⁻⁶	FGFR3,MAPK1,MAPK3,MDM2,TP53,VEGFA
5220	Chronic myeloid leukemia	11	1.58×10 ⁻¹⁰	AKT1,BCL2L1,GAB2,HDAC2,MAPK1,MAPK3,MDM2,NFKB1,TGFB1,TGFB2,TP53
5221	Acute myeloid leukemia	5	3.26×10 ⁻⁴	AKT1,MAPK1,MAPK3,NFKB1,RPS6KB1
5222	Small cell lung cancer	12	8.44×10 ⁻¹¹	AKT1,BCL2,BCL2L1,CASP9,ITGA2,LAMB1,LAMB4,NFKB1,NOS2,PTGS2,TP53,TRAF2
5223	Non-small cell lung cancer	5	3.06×10 ⁻⁴	AKT1,CASP9,MAPK1,MAPK3,TP53
5321	Inflammatory bowel disease (IBD)	8	2.84×10 ⁻⁷	IL10,IL1A,IL1B,IL6,NFKB1,TGFB1,TLR4,TNF
5322	Systemic lupus erythematosus	5	3.26×10 ⁻³	C3,GRIN2A,GRIN2B,IL10,TNF
5323	Rheumatoid arthritis	9	2.46×10 ⁻⁷	CCL2,CCL3,IL1A,IL1B,IL6,TGFB1,TLR4,TNF,VEGFA
5330	Allograft rejection	3	7.27×10 ⁻³	FAS,IL10,TNF
5332	Graft-versus-host disease	5	4.89×10 ⁻⁵	FAS,IL1A,IL1B,IL6,TNF
5410	Hypertrophic cardiomyopathy (HCM)	6	2.35×10 ⁻⁴	CACNA1C,DMD,IL6,ITGA2,TGFB1,TNF
5412	Arrhythmogenic right ventricular cardiomyopathy (ARVC)	4	8.25×10 ⁻³	CACNA1C,DMD,GJA1,ITGA2
5414	Dilated cardiomyopathy	5	2.47×10 ⁻³	CACNA1C,DMD,ITGA2,TGFB1,TNF
5416	Viral myocarditis	3	2.58×10 ⁻²	CASP3,CASP9,DMD

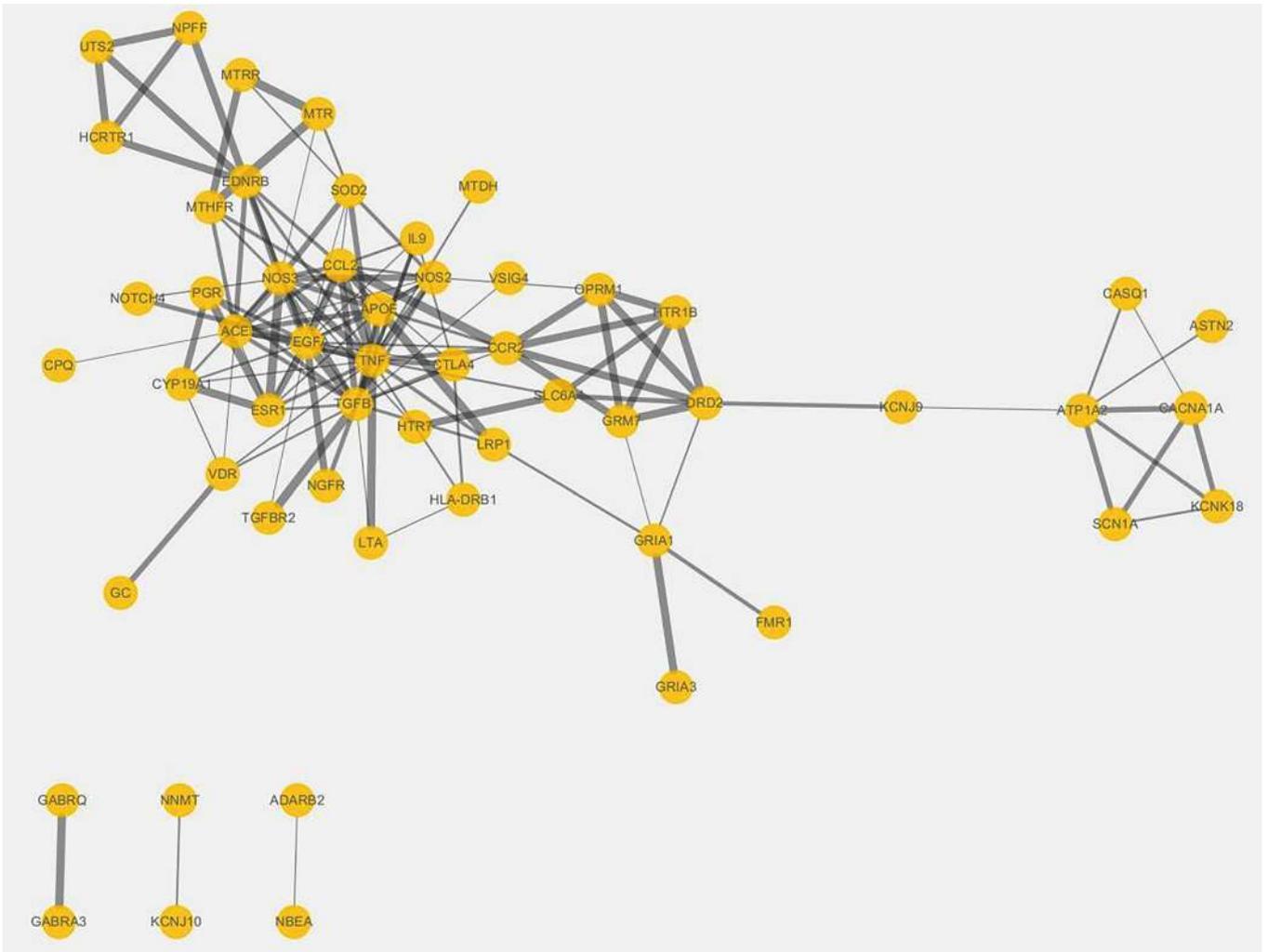


Figure S2 A protein-protein interactions network mapping the migraine-related genes.