Original Article

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, theses 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 dealed 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
APOE	348	Apolipoprotein E
ATP1A2	477	ATPase Na+/K+ transporting subunit alpha 2
CACNA1A	773	Calcium voltage-gated channel subunit alpha1 A
GABRA3	2556	Gamma-aminobutyric acid type A receptor alpha3 subunit
GC	2638	Vitamin D binding protein
GRIA1	2890	Glutamate ionotropic receptor AMPA type subunit 1
GRM7	2917	Glutamate metabotropic receptor 7
HTR1B	3351	5-hydroxytryptamine receptor 1B
KCNN3	3782	Potassium calcium-activated channel subfamily N member 3
MTHFR	4524	Methylenetetrahydrofolate reductase
NOS2	4843	Nitric oxide synthase 2
SCN1A	6323	Sodium voltage-gated channel alpha subunit 1
CCL2	6347	C-C motif chemokine ligand 2
SLC6A4	6532	Solute carrier family 6 member 4
TGFB1	7040	Transforming growth factor beta 1
TGFBR2	7048	Transforming growth factor beta receptor 2
TNF	7124	Tumor necrosis factor
VDR	7421	Vitamin D receptor
VEGFA	7422	Vascular endothelial growth factor A
PRRT4	401399	Proline rich transmembrane protein 4
CCR2	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 Ca2.1α1 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 α2 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
TP53	67
AKT1	63
TNF	60
IL6	60
VEGFA	56
BCL2	52
MAPK3	52
CASP3	51
MAPK1	51
APP	50
TNF	21
VEGFA	18
TGFB1	17
NOS3	15
CCL2	13
ACE	12
APOE	11
CCR2	9
NOS2	9
ESR1	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	*DRD2, EDNRB, GABRA3, GABRQ, GRIA1, GRIA3, GRM7, HCRTR1, HTR1B, HTR7, OPRM1*
4060	Cytokine-cytokine receptor interaction	*CCL2, CCR2, IL9, LTA, NGFR, TGFB1, TGFBR2, TNF, VEGFA*
5033	Nicotine addiction	*CACNA1A, GABRA3, GABRQ, GRIA1, GRIA3*
5323	Rheumatoid arthritis	*CCL2, CTLA4, HLA-DRB1, TGFB1, TNF, VEGFA*
4723	Retrograde endocannabinoid signaling	*CACNA1A, GABRA3, GABRQ, GRIA1, GRIA3, KCNJ9*
4728	Dopaminergic synapse	*CACNA1A, DRD2, GRIA1, GRIA3, KCNJ9, SCN1A*
5032	Morphine addiction	*CACNA1A, GABRA3, GABRQ, KCNJ9, OPRM1*
5142	Chagas disease (American trypanosomiasis)	*CCL2, NOS2, TGFB1, TGFBR2, TNF*
5144	Malaria	*CCL2, LRP1, TGFB1, TNF*
4726	Serotonergic synapse	*CACNA1A, HTR1B, HTR7, KCNJ9, SLC6A4*
5140	Leishmaniasis	*HLA-DRB1, NOS2, TGFB1, TNF*
4915	Estrogen signaling pathway	*ESR1, KCNJ9, NOS3, OPRM1*
5152	Tuberculosis	*HLA-DRB1, NOS2, TGFB1, TNF, VDR*
4020	Calcium signaling pathway	*CACNA1A, EDNRB, HTR7, NOS2, NOS3*
4940	Type I diabetes mellitus	*HLA-DRB1, LTA, TNF*
4724	Glutamatergic synapse	*CACNA1A, GRIA1, GRIA3, GRM7*
4961	Endocrine and other factor-regulated calcium reabsorption	*ATP1A2, ESR1, VDR*
5145	Toxoplasmosis	*HLA-DRB1, NOS2, TGFB1, TNF*
4730	Long-term depression	*CACNA1A, GRIA1, GRIA3*
5212	Pancreatic cancer	*TGFB1, TGFBR2, VEGFA*
5321	Inflammatory bowel disease (IBD)	*HLA-DRB1, TGFB1, TNF*
5166	HTLV-I infection	*HLA-DRB1, LTA, TGFB1, TGFBR2, TNF*
4022	cGMP-PKG signaling pathway	*ATP1A2, EDNRB, MEF2D, NOS3*
4350	TGF-beta signaling pathway	*TGFB1, TGFBR2, TNF*
4727	GABAergic synapse	*CACNA1A, GABRA3, GABRQ*
5168	Herpes simplex infection	*CCL2, HLA-DRB1, LTA, TNF*
4713	Circadian entrainment	*GRIA1, GRIA3, KCNJ9*
4066	HIF-1 signaling pathway	*NOS2, NOS3, VEGFA*
5146	Amoebiasis	*NOS2, TGFB1, TNF*
4668	TNF signaling pathway	*CCL2, LTA, TNF*

Figure 1 Crosstalk of pathway enriched in epilepsy-related genes.

epilepsy showed particular vulnerability to seizures during menstruation and ovulation, which is named catamenial epilepsy (52,53). This phenomenon indicates that epilepsy is also partially influenced by estrogen level. Therefore, estrogen level is very possible to perform as a common trigger of both epilepsy and migraine. In addition, a study of the human partial epilepsy indicated that glutamatergic synaptic transmission increases the hyper-excitability of hippocampal CA1 pyramidal neurons and contribute to seizure (54). Yet, former researches have reported few shared pathways between epilepsy and migraine.

Significantly, pathway crosstalk analysis help us further understanding the interaction between those enriched pathways. We found that pathways in these two diseases can be generally separated into two modules. One includes those pathways explicitly involved in neuron of CNS according to previous studies (e.g., dopaminergic synapse, retrograde endocannabinoid signaling, long-term depression, nicotine addiction). The other is the pathways mainly involved in inflammatory response or some inflammatory disorders (e.g., inflammatory bowel disease, TNF signaling pathway, rheumatoid arthritis). According to the results we further speculate inflammatory response is crucial in epilepsy and migraine.

Through systematic analysis and previous studies review, we considered 6 genes (*TNF*, *VEGFA*, *CACNA1A*, *ATP1A2*, *SCN1A*, *PRRT2*) as important to the comorbidity between epilepsy and migraine. We also predict genes that interact with these 6 essential genes via GeneMania, which may participant in the occurence and development of epilepsy

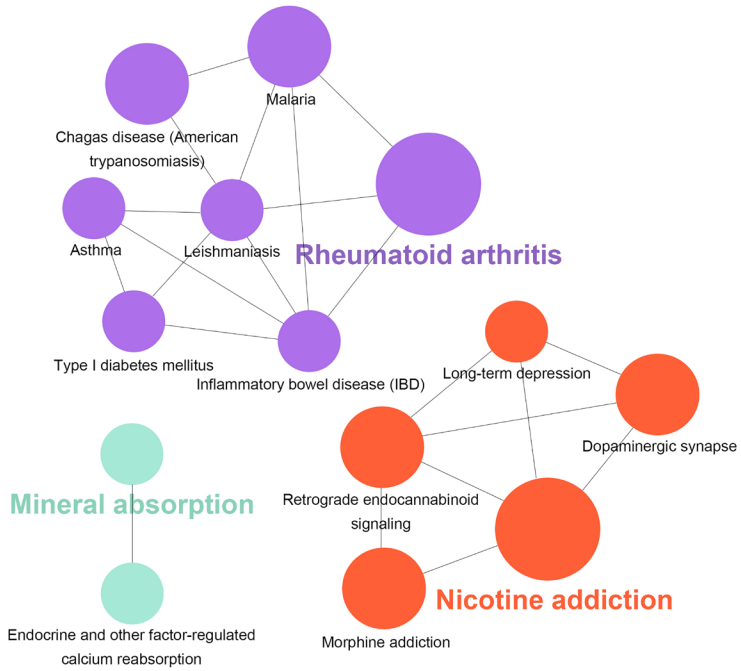

Figure 2 Crosstalk of pathway enriched in migraine-related genes.

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-Gene-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

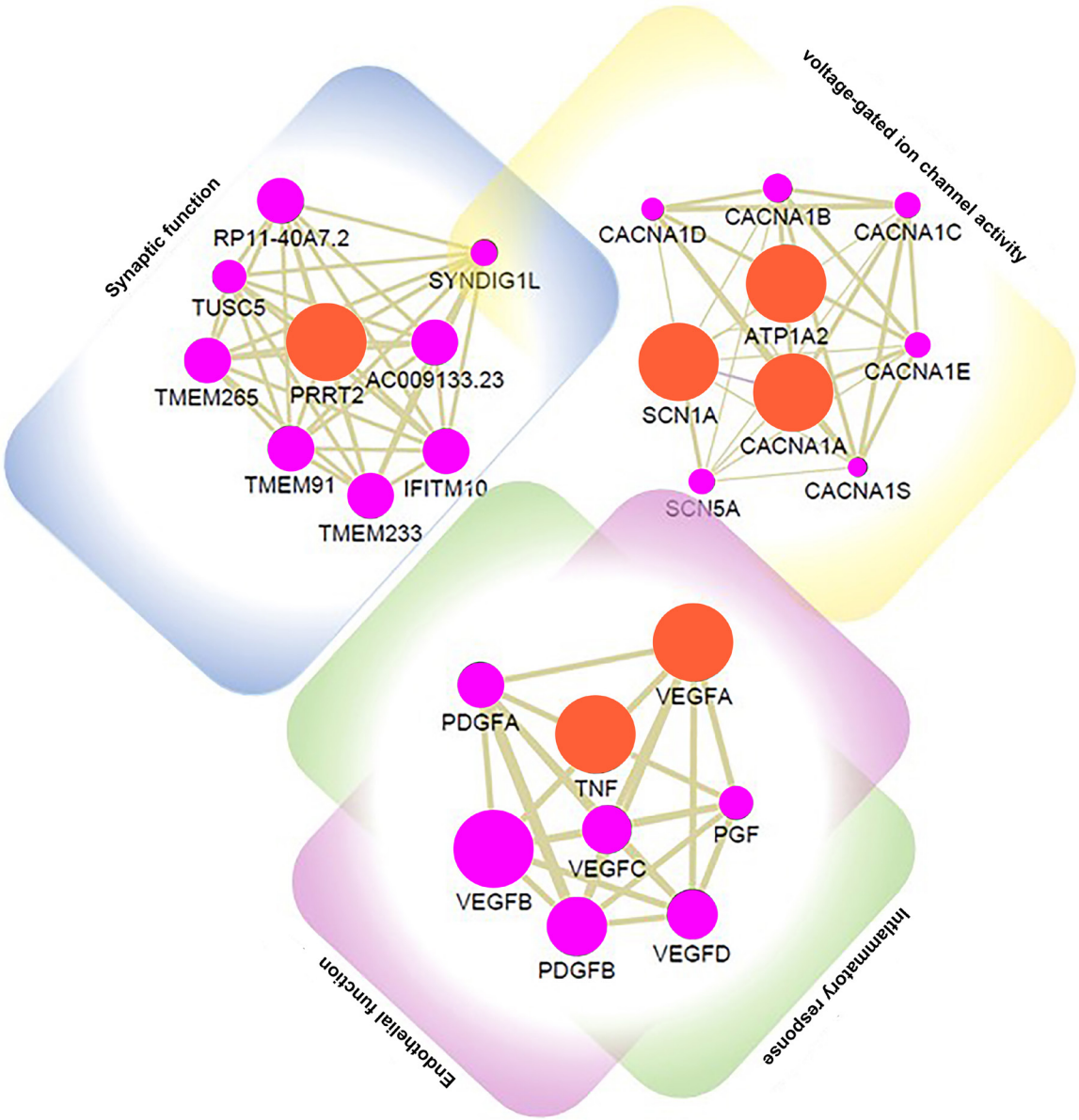

Figure 3 Predition of genes interact with *TNF*, *VEGFA*, *CACNA1A*, *ATP1A2*, *SCN1A*, *PRRT2* and the potential biological processes involved.

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 specified genes.

Table S2 Identified candidate genes related to migraine

No.	Gene	Gene ID	Reference*
1	*ADARB2*	105	3604878
2	*ApoE*	348	4534059
3	*ATP1A2*	477	2034370, 4706665
4	*CACNA1A*	773	1377706
5	*CASQ 1*	844	2034370
6	*CTLA-4*	1493	3452029
7	*CYP19A1*	1588	3325278
8	*ACE*	1636	2644823
9	*DRD2*	1813	3476140
10	*EDNRB*	1910	2753702
11	*ESR1*	2099	4616512
12	*FMR1*	2332	4991825
13	*GABRA3*	2556	3764027, 1196377
14	*GC Globulin*	2638	4141767
15	*GRIA1*	2890	4723374
16	*GRIA3*	2892	4723374
17	*GRM7*	2917	3604878
18	*HCRTR1*	3061	3072499
19	*HLA–DRB1*	3123	3452004
20	*HTR1B*	3351	3476140
21	*HTR7*	3363	3604878
22	*IL9*	3578	2704575
23	*KCN J9*	3765	2034370
24	*KCN J10*	3766	2034370
25	*KCNN3*	3782	3208049
26	*LRP1*	4035	3253157
27	*TNF-β*	4049	4069061
28	*MEF2D*	4209	3986694
29	*MTHFR*	4524	2562562, 4231882
30	*MTR*	4548	4231882
31	*MTRR*	4552	4231882
32	*NGFR*	4804	3172930
33	*NNMT*	4837	5056911
34	*iNOS*	4843	3356463
35	*NOS3*	4846	2704575
36	*NOTCH4*	4855	3620438
37	*OPRM1*	4988	3444536
38	*PROGINS*	5241	4337459
39	*EDN*	6036	2753702
40	*SCN1A*	6323	4706665
41	*MCP-1*	6347	4141767
42	*SLC6A4*	6532	3476140, 3452037
43	*SOD2*	6648	4283069
44	*TARBP2*	6895	5541777
45	*TGFB1*	7040	2704575
46	*TGFBR2*	7048	3986694
47	*TNF*	7124	4476787, 2704575
48	*VDR*	7421	3741896
40	*VEGF*	7422	3356463
50	*NPFF*	8620	5541777
51	*SLC4A4*	8671	2936614
52	*FHL5*	9457	5541777
53	*HEPH*	9843	3362572
54	*PGCP*	10404	3986694
55	*UTS2*	10911	4835397
56	*VSIG4*	11326	3362572
57	*SYNE1*	23345	3986694, 4196204
58	*UFL1*	23376	5541777
59	*NBEA*	26960	4394021
60	*GABRQ*	55879	3764027
61	*PRDM16*	63976	3986694
62	*TRPM8*	79054	3986694, 3253157
63	*MTDH*	92140	3986694, 3172930
64	*ZNF555*	148254	3604878
65	*MGR1*	192115	1180504
66	*PHACTR1*	221692	3986694
67	*DAOA*	267012	3837682
68	*KCNK18*	338567	4706665
69	*PRRT2*	401399	2704575
70	*CCR2*	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~metallodipeptidase 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 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:0050750~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}	*MTHFR, MTR*
4020	Calcium signaling pathway	5	6.21×10^{-3}	*CACNA1A, EDNRB, HTR7, NOS2, NOS3*
4022	cGMP-PKG signaling pathway	4	2.20×10^{-2}	*ATP1A2, EDNRB, MEF2D, NOS3*
4060	Cytokine-cytokine receptor interaction	9	2.38×10^{-5}	*CCL2, CCR2, IL9, LTA, NGFR, TGFB1, TGFBR2, TNF, VEGFA*
4066	HIF-1 signaling pathway	3	4.75×10^{-2}	*NOS2, NOS3, VEGFA*
4080	Neuroactive ligand-receptor interaction	11	5.18×10^{-7}	*DRD2, EDNRB, GABRA3, GABRQ, GRIA1, GRIA3, GRM7, HCRTR1, HTR1B, HTR7, OPRM1*
4350	TGF-beta signaling pathway	3	2.40×10^{-2}	*TGFB1, TGFBR2, TNF*
4668	TNF signaling pathway	3	4.86×10^{-2}	*CCL2, LTA, TNF*
4713	Circadian entrainment	3	3.37×10^{-2}	*GRIA1, GRIA3, KCNJ9*
4723	Retrograde endocannabinoid signaling	6	5.39×10^{-5}	*CACNA1A, GABRA3, GABRQ, GRIA1, GRIA3, KCNJ9*
4724	Glutamatergic synapse	4	8.51×10^{-3}	*CACNA1A, GRIA1, GRIA3, GRM7*
4726	Serotonergic synapse	5	1.03×10^{-3}	*CACNA1A, HTR1B, HTR7, KCNJ9, SLC6A4*
4727	GABAergic synapse	3	2.87×10^{-2}	*CACNA1A, GABRA3, GABRQ*
4728	Dopaminergic synapse	6	2.01×10^{-4}	*CACNA1A, DRD2, GRIA1, GRIA3, KCNJ9, SCN1A*
4730	Long-term depression	3	1.41×10^{-2}	*CACNA1A, GRIA1, GRIA3*
4915	Estrogen signaling pathway	4	5.99×10^{-3}	*ESR1, KCNJ9, NOS3, OPRM1*
4940	Type I diabetes mellitus	3	6.21×10^{-3}	*HLA-DRB1, LTA, TNF*
4961	Endocrine and other factor-regulated calcium reabsorption	3	8.51×10^{-3}	*ATP1A2, ESR1, VDR*
4964	Proximal tubule bicarbonate reclamation	2	2.10×10^{-2}	*ATP1A2, SLC4A4*
4978	Mineral absorption	3	9.06×10^{-3}	*ATP1A2, HEPH, VDR*
5032	Morphine addiction	5	4.95×10^{-4}	*CACNA1A, GABRA3, GABRQ, KCNJ9, OPRM1*
5033	Nicotine addiction	5	2.38×10^{-5}	*CACNA1A, GABRA3, GABRQ, GRIA1, GRIA3*
5140	Leishmaniasis	4	2.40×10^{-3}	*HLA-DRB1, NOS2, TGFB1, TNF*
5142	Chagas disease (American trypanosomiasis)	5	6.21×10^{-4}	*CCL2, NOS2, TGFB1, TGFBR2, TNF*
5144	Malaria	4	6.21×10^{-4}	*CCL2, LRP1, TGFB1, TNF*
5145	Toxoplasmosis	4	8.93×10^{-3}	*HLA-DRB1, NOS2, TGFB1, TNF*
5146	Amoebiasis	3	4.75×10^{-2}	*NOS2, TGFB1, TNF*
5152	Tuberculosis	5	5.99×10^{-3}	*HLA-DRB1, NOS2, TGFB1, TNF, VDR*
5166	HTLV-I infection	5	1.99×10^{-2}	*HLA-DRB1, LTA, TGFB1, TGFBR2, TNF*
5168	Herpes simplex infection	4	2.87×10^{-2}	*CCL2, HLA-DRB1, LTA, TNF*
5212	Pancreatic cancer	3	1.56×10^{-2}	*TGFB1, TGFBR2, VEGFA*
5310	Asthma	3	2.83×10^{-3}	*HLA-DRB1, IL9, TNF*
5321	Inflammatory bowel disease (IBD)	3	1.57×10^{-2}	*HLA-DRB1, TGFB1, TNF*
5323	Rheumatoid arthritis	6	3.27×10^{-5}	*CCL2, CTLA4, HLA-DRB1, TGFB1, TNF, VEGFA*
5330	Allograft rejection	2	4.95×10^{-2}	*HLA-DRB1, TNF*

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,TGFBR2,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,TGFBR2,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,BCL2L11,GRM1,IL10,IL6,MAPK1,MAPK3,MDM2,TGFB1,TGFBR2*
4080	Neuroactive ligand-receptor interaction	24	2.53×10^{-16}	*GABBR1,GABBR2,GABRA3,GABRB3,GABRG2,GRIA1,GRIA2,GRIK1,GRIK2,GRIK4,GRIK5,GRIN1,GRIN2A,GRIN2B,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,TGFBR2*
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,TGFBR2,TNF*
4360	Axon guidance	6	1.77×10^{-3}	*CDC42,MAPK1,MAPK3,NTNG2,RHOA,SLIT2*
4370	VEGF signaling pathway	7	2.95×10^{-6}	*AKT1,CASP9,CDC42,MAPK1,MAPK3,PTGS2,VEGFA*
4380	Osteoclast differentiation	13	3.75×10^{-10}	*AKT1,FHL2,GAB2,IL1A,IL1B,MAPK1,MAPK3,NFKB1,TGFB1,TGFBR2,TNF,TNFRSF1A,TRAF2*
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,TGFBR2,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,GABBR1,GABBR2,GABRA3,GABRB3,GABRG2,GLUL,GPHN*
4728	Dopaminergic synapse	9	4.89×10^{-6}	*AKT1,CACNA1A,CACNA1C,GRIA1,GRIA2,GRIN2A,GRIN2B,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,KLK1,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^{-23}	*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,CASP1,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)	17	2.14×10^{-16}	*AKT1,C3,CCL2,CCL3,FAS,IL10,IL1B,IL6,MAPK1,MAPK3,NFKB1,NOS2,TGFB1,TGFBR2,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,TGFBR2,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,TGFBR2,TP53,TRAF2,VEGFA*
5202	Transcriptional misregulation in cancer	7	1.41×10^{-3}	*BCL2L1,HDAC2,IL6,MDM2,NFKB1,TGFBR2,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,DNMT1,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,TGFBR2,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,BCL2L1,CASP9,CDC42,MAPK1,MAPK3,NFKB1,TGFB1,TGFBR2,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,TGFBR2,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*

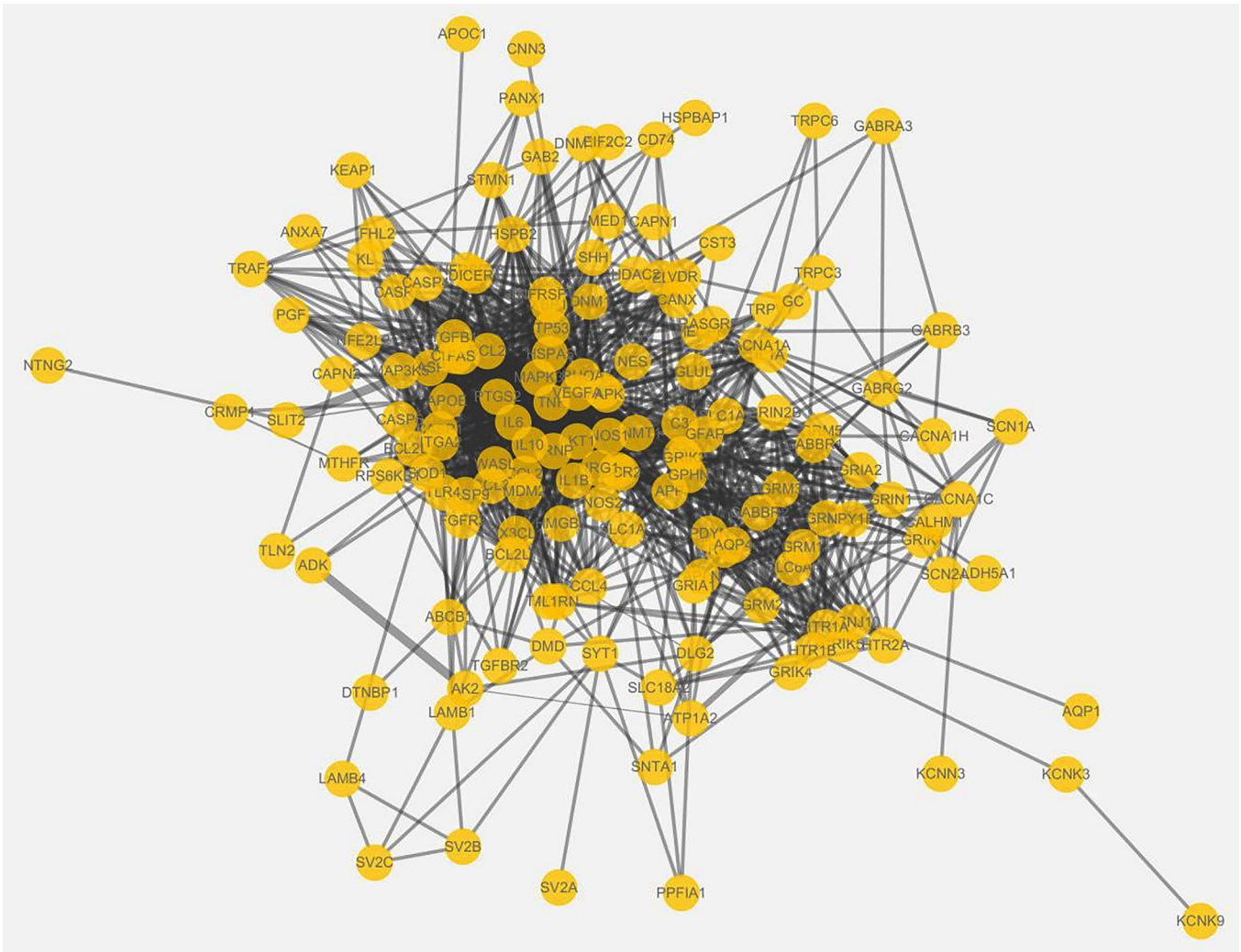

Figure S1 A protein-protein interactions network mapping the epilepsy-related genes.

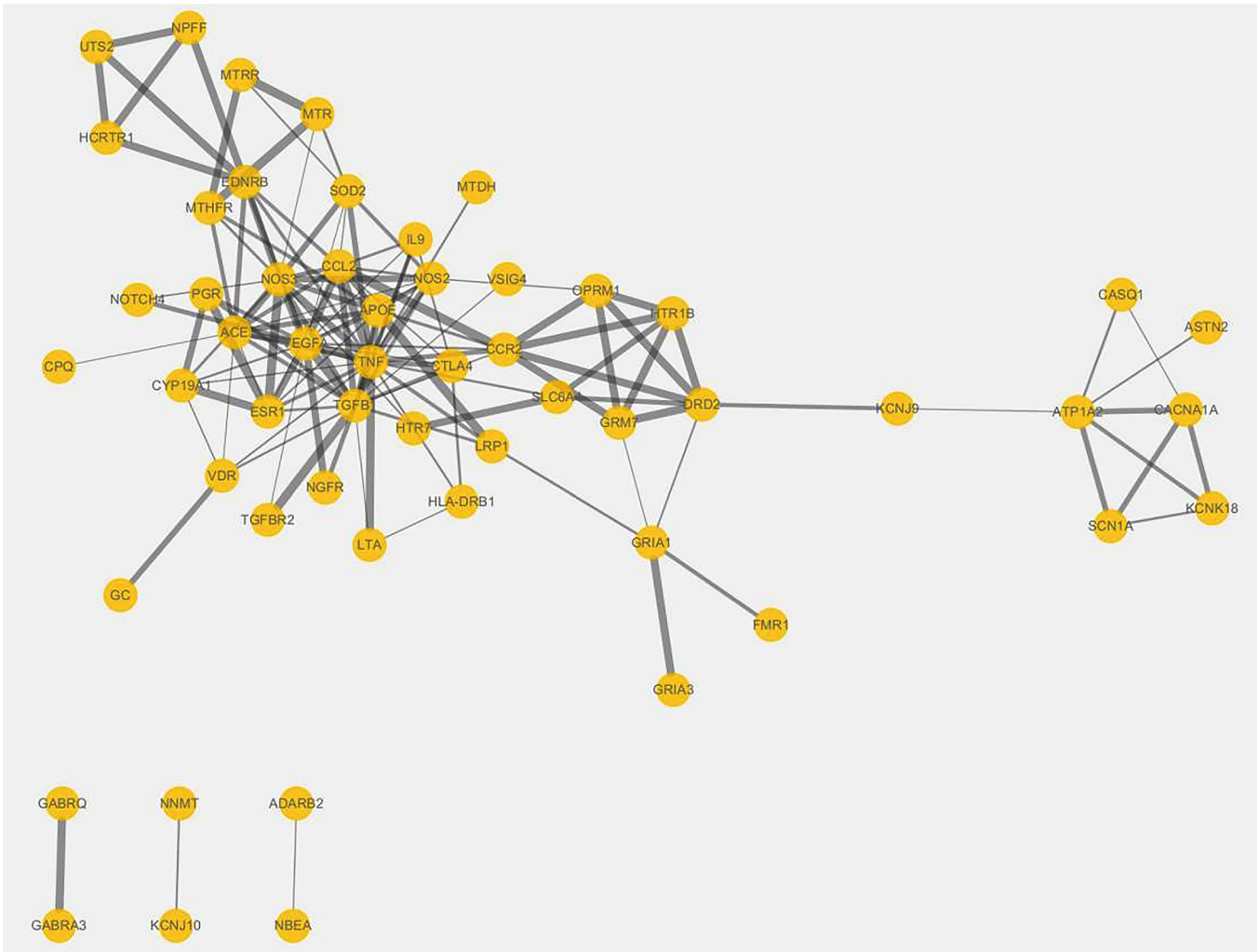

Figure S2 A protein-protein interactions network mapping the migraine-related genes.