Journal of Science Research International (JSRI)
ISSN: 2456-6365 (Online)

OPEN ACCESS

AN INTEGRATED NETWORK AND PATHWAY-BASED BIOINFORMATICS ANALYSIS TO IDENTIFY KEY GENES INVOLVED IN EPILEPSY

Meenakshi Johri*, Bindu Rajaguru and Tejas Sanjay Kadam

Department of Biotechnology,

Pillai College of Arts, Commerce & Science (Empowered Autonomous), New Panvel, Navi Mumbai, Maharashtra

**Corresponding author E-mail: m.johri101@gmail.com*

Received: 12 March 2026	Revised: 26 April 2026	Accepted: 13 May 2026	Published: 26 May 2026

DOI: https://doi.org/10.5281/zenodo.20391281

Abstract:

Epilepsy is a chronic non-communicable neurological disorder characterized by recurrent unprovoked seizures, affecting approximately 50 million people worldwide. It results from a disruption in the balance between excitatory and inhibitory signaling in the brain, often driven by ion channelopathies and synaptic dysfunction. Existing pharmacological treatments fail to control seizures in about 30% of patients and do not address the underlying epileptogenesis; therefore, new mechanism-based interventions are critically necessary. In the present work, an integrated bioinformatics analysis was performed to provide insights into the molecular mechanisms of Epilepsy. A complete list of 30 high-confidence Epilepsy-related genes was compiled from the DisGeNET database and analyzed using GO, KEGG, Reactome, and STRING. Major enriched biological processes were the regulation of membrane potential, ion transmembrane transport, and chemical synaptic transmission; whereas significant molecular functions included gated channel activity and GABA receptor activity. Module analysis revealed a central "Ion Channel" cluster, and topological analysis identified key network hubs including GRIN2B and STXBP1. These results further support the importance of excitation-inhibition imbalance in Epilepsy etiology and indicate voltage-gated sodium channels and GABAergic signaling as top biological targets for therapeutic intervention. This work illustrates the power of integrated bioinformatics in unraveling complex disease mechanisms and expediting the development of targeted therapies.

Keywords: *Epilepsy, Bioinformatics, Ion Channels, PPI Network, Network Pharmacology, Drug Target Discovery.*

1. Introduction

Epilepsy is a prevalent neurological disorder driven by hypersynchronous neuronal activity and disrupted network homeostasis, leading to recurrent seizures and cognitive comorbidities [1]. Despite advances in understanding its pathophysiology, drug-resistant epilepsy remains a profound clinical challenge [2]. Standard anti-seizure medications (ASMs) modulate ion channels or neurotransmitter release but frequently fail to halt underlying disease progression [3].

Consequently, elucidating the exact molecular mechanisms of neuronal hyperexcitability is vital for developing targeted therapeutics [4], [5]. Bioinformatics facilitates this by integrating multi-omics data to map protein-protein interaction (PPI) networks and dysregulated pathways [6]. This study employs an integrated bioinformatics framework to identify key regulatory hubs and biological pathways in epilepsy.

Objective: The objective of this study is to perform a detailed bioinformatics analysis of genes involved in Epilepsy to identify key regulatory hubs and biological pathways. The methods used in this study included:

- identifying core Epilepsy genes from the disgenet database;
- constructing protein-protein interaction networks using STRING;
- extending the network with genemania;
- identifying hub genes using networkanalyst; and
- mapping mechanistic pathways using Reactome.

2. Methodology

2.1 Bioinformatics pipeline and database selection

This study utilized an integrated bioinformatics workflow to transition from static gene-disease associations to a dynamic topological model of epilepsy. DisGeNET was used for clinical gene curation [7], STRING for mapping protein-protein interactions (PPIs) [8], GeneMANIA for network expansion [9], NetworkAnalyst for topological hub identification [10], and Reactome/Enrichr for pathway contextualization [11].

2.2 Gene curation (DisGeNET)

A high-confidence dataset of epilepsy-associated genes was curated using DisGeNET v7.0 [7] with the search term "Epilepsy" (UMLS CUI: C0014544). To minimize false positives, results were strictly filtered by Gene-Disease Association (GDA) scores to prioritize targets with robust experimental and clinical evidence. This yielded a primary seed list of 30 core genes.

2.3 Protein-Protein Interaction (PPI) network (STRING)

To map the molecular architecture of the disease, the 30 seed genes were inputted into the STRING database to construct a foundational PPI network [8]. The network captured both physical and functional associations, utilizing a stringent minimum interaction score to ensure data reliability.

2.4 Functional network expansion (GeneMANIA)

To explore functional redundancy and identify novel genetic candidates, the core PPI network was expanded using GeneMANIA [9]. This platform integrated additional secondary genes into the network based on shared physical interactions, co-localization, and co-expression relationships.

2.5 Network topology and hub identification (NetworkAnalyst)

The expanded network was exported to NetworkAnalyst v3.0 for topological analysis to identify critical regulatory bottlenecks [10]. Treated as an undirected graph, the network was analyzed using Degree Centrality (number of

direct connections) and Betweenness Centrality (shortest paths passing through a node). Nodes ranking in the top percentiles for both metrics were designated as essential structural "hubs."

2.6 Pathway enrichment analysis (Reactome)

Functional contextualization was conducted using the Enrichr platform [12] and the Reactome Pathway Browser [11]. Genes were queried against the Reactome and KEGG databases to identify overrepresented biological cascades. Significance was determined via Fisher's exact test with Benjamini-Hochberg adjustment, retaining only pathways with a stringent False Discovery Rate (FDR) < 0.05.

3. Results

3.1 Core gene set associated with Epilepsy

A total of 30 high-confidence Epilepsy-related genes were identified from the DisGeNET query. This seed set included well-known epileptic encephalopathy genes such as *SCN1A, SCN2A, GABRA1, STXBP1,* and *KCNQ2* [13], [14].

3.2 Protein-Protein Interacton (PPI) and functional enrichment analysis

The PPI network for the Epilepsy-associated genes was constructed using the STRING database with a minimum required interaction score of 0.400 (medium confidence).

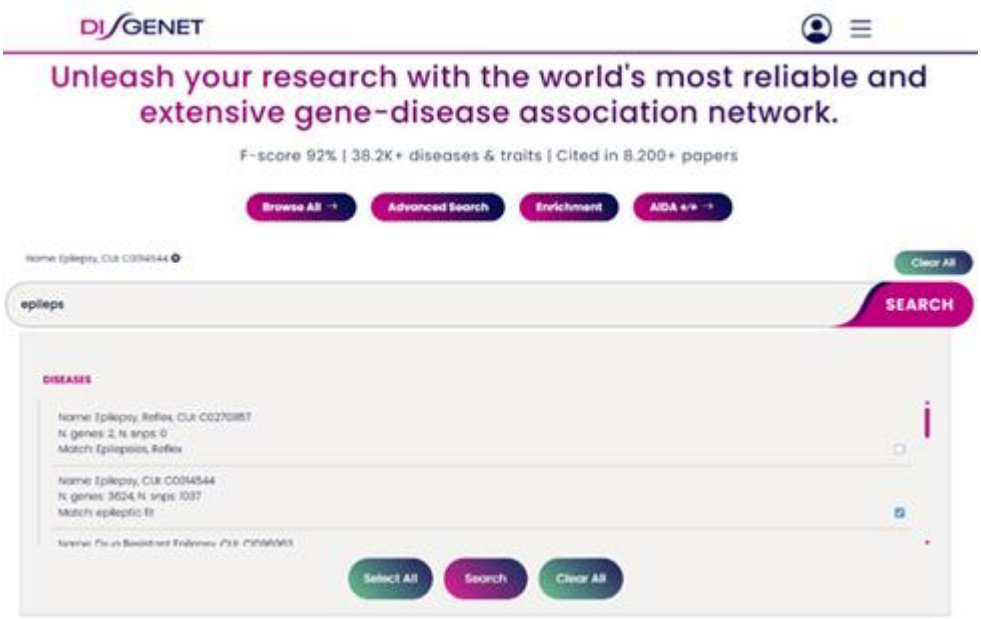


Figure 1: The initial search results for Epilepsy in the DisGeNET database (v7.0). The interface displays the specific disease concept ID(C0014544) and the total no. of available gene-disease associations, which serves as the starting point for Data Mining

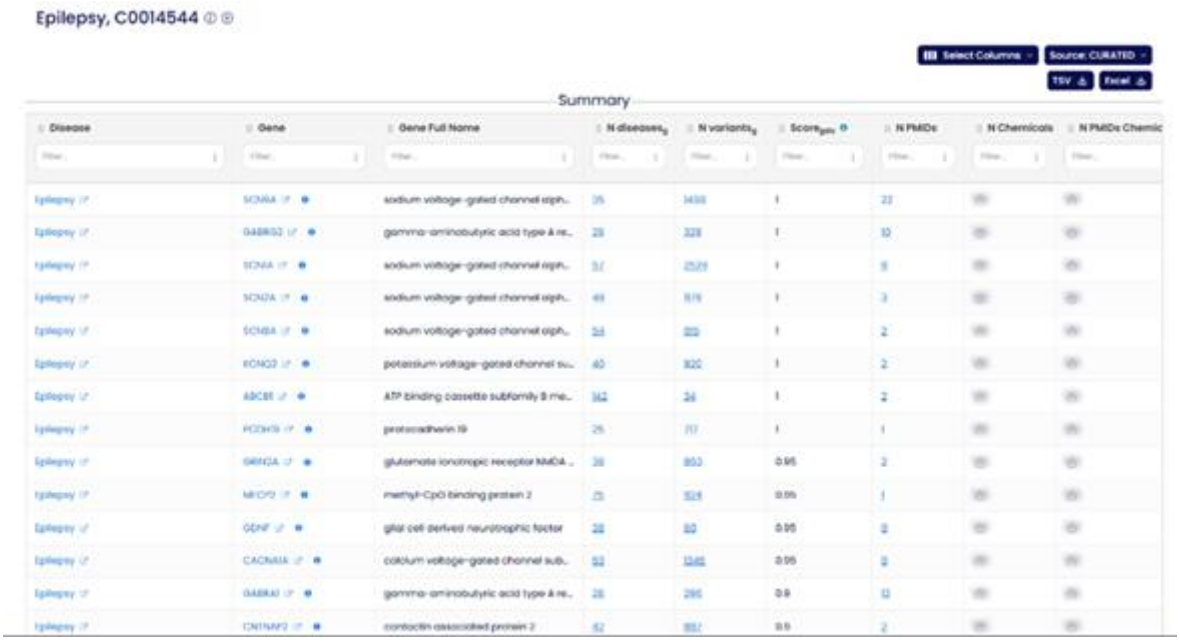


Figure 2: The filtered list of the top 30 high-confidence genes associated with Epilepsy. The table ranks these genes (such as SCN1A, SCN2A, and STXBP1) based on their evidence metrics, illustrating the core genetic dataset selected for this study

Network topology

- Using the STRING database (minimum interaction score ≥ 0.400), the 30 core epilepsy-associated genes were mapped into a highly interconnected interactome comprising 30 nodes and 142 edges. The average node degree was significantly higher than expected by chance ($p < 1.0e^{-16}$), demonstrating that these genes operate as a cohesive biological module driving neuronal excitability [8].
- Subsequent Gene Ontology (GO) and KEGG enrichment analyses strongly supported the hypothesis of epilepsy as a channelopathy [15]. The network was overwhelmingly enriched for Molecular Functions such as "Gated channel activity" (FDR = $6.94e^{-12}$). Similarly, the most significant Biological Processes centered entirely on ionic homeostasis and membrane dynamics, as summarized in Table 1.

Table 1: Summary of Significantly Enriched GO Terms (Biological Process)

GO Term	***Description***	***Count in Network***	***False Discovery Rate (FDR)***
GO:0034220	Ion transmembrane transport	17 of 973	7.18e-11
GO:0042391	Regulation of membrane potential	13 of 428	1.82e-10
GO:0098660	Inorganic ion transmembrane transport	15 of 743	1.82e-10

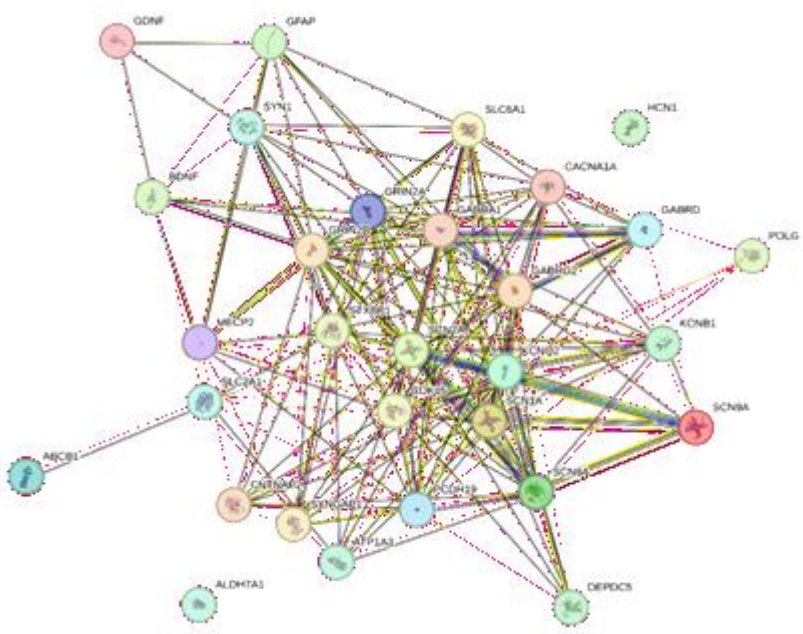


Figure 3: The Protein-Protein Interaction (PPI) network constructed using the STRING database. The colored nodes represent the 30 selected Epilepsy-associated proteins (such as SCN1A, GRIN2A, and STXBP1), and the connecting lines (edges) indicate known and predicted functional interactions. The dense clustering (142 edges) visually confirms that these proteins do not function in isolation but form a highly cohesive biological module regulating neuronal excitability

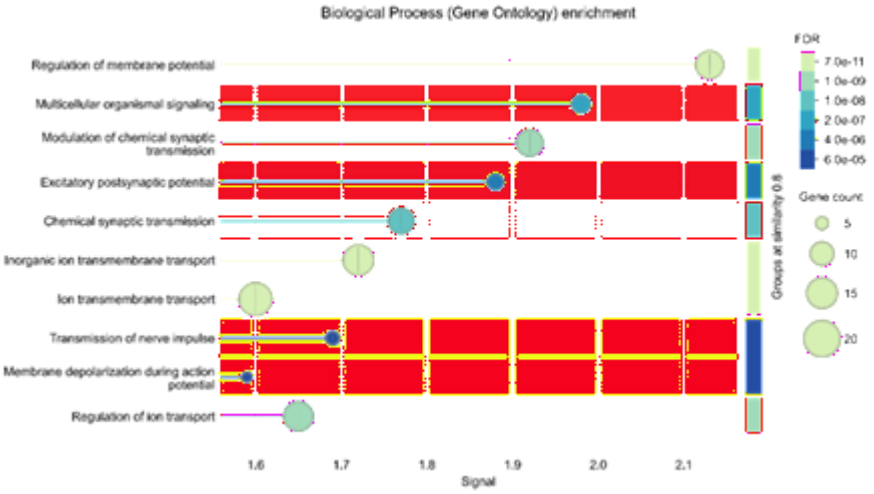


Figure 4: The functional enrichment summary table generated by the STRING database. This data highlights the specific Cellular Components and other enriched domains, confirming that these epilepsy-associated proteins are predominantly localized to the "synaptic membrane" and "ion channel complexes," further emphasizing their structural role in signal transmission between neurons.

3.3 Functional network expansion and gene prediction

To explore functional redundancy and identify novel therapeutic targets, the core gene set was expanded using GeneMANIA, which integrated 20 highly associated secondary genes [9]. Network analysis revealed these genes

are primarily linked via co-expression (37.12%) and co-localization (25.00%), indicating they operate within synchronized transcriptional programs in the brain. Crucially, this expansion predicted significant functional interactors absent from the initial DisGeNET seed list, including:

- ***GABRB2*:** A GABA-A receptor subunit, reinforcing the critical role of inhibitory signaling dysfunction in epileptogenesis [14].
- ***SCN3A, SCN5A, SCN11A*:** Additional voltage-gated sodium channel subunits, highlighting that epilepsy often involves a broad failure of the sodium channel family rather than isolated single-gene defects [16].
- ***HDAC7*:** A histone deacetylase, suggesting a potential novel epigenetic mechanism regulating these ion channels.

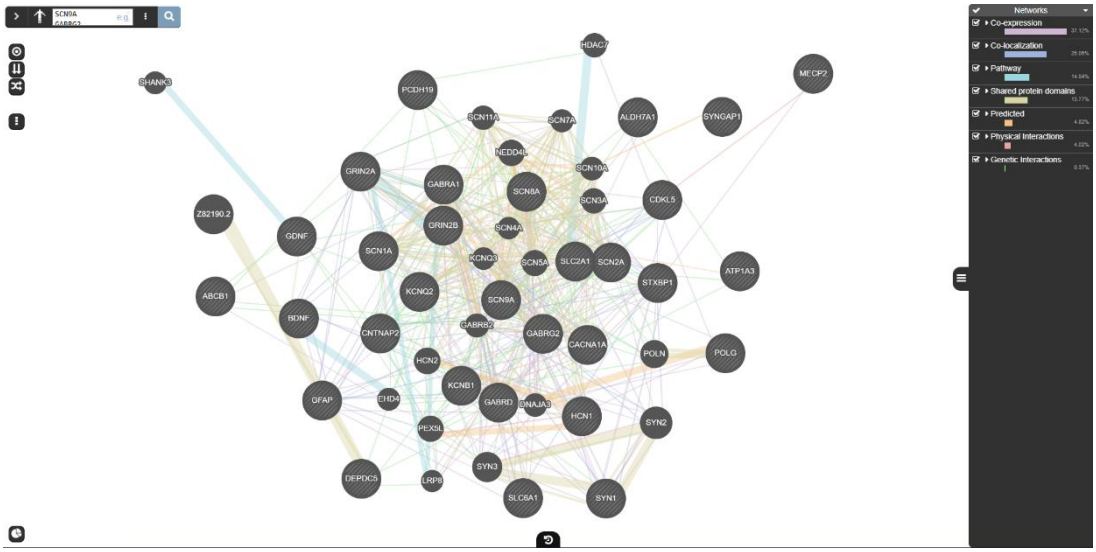


Figure 5: The functional interaction network generated by the GeneMANIA prediction server. The network displays the original 30 epilepsy-associated query genes (inner nodes) alongside newly predicted interacting genes (outer nodes) that are functionally similar. The colored connecting lines represent different types of biological evidence—such as co-expression, physical interactions, and shared protein domains—illustrating the broader functional pathways and complex regulatory mechanisms these genes participate in.

3.4 Network topology and hub gene identification

To pinpoint critical regulatory nodes, topological analysis was executed via NetworkAnalyst. Genes were ranked by Degree Centrality, as high-degree "hubs" are structurally essential to network stability and serve as highly promising therapeutic targets [10]. The analysis identified five major hub genes driving the network:

- ***GRIN2B* (Degree: 29) & *GRIN2A* (Degree: 25):** NMDA receptor subunits critical for excitatory glutamate signaling [17], [18]. Their dominance indicates that dysregulated glutamatergic drive is a primary network convergence point.
- ***STXBP1* (Degree: 14) & *CACNA1A* (Degree: 12):** Essential regulators of the synaptic vesicle cycle and presynaptic neurotransmitter release machinery [19], [20].
- ***KCNQ2* (Degree: 12):** A potassium channel subunit responsible for the "M-current," a critical stabilizer of neuronal excitability [21].

Interpretation: The topological dominance of these specific hubs demonstrates that this epilepsy network is fundamentally driven by a dual failure: hyperactive excitatory synaptic transmission (*GRIN2B/A*) coupled with dysfunctional presynaptic release dynamics (*STXBP1, CACNA1A*).

Node Explorer

Search Delete

ID	Name	Degree	Betweeness	Expr.
2904	GRIN2B	29	1543.833	
2903	GRIN2A	25	985.8333	
6812	STXBP1	14	1502.5	
3785	KCNQ2	12	2639.583	
773	CACNA1A	12	1335.25	
478	ATP1A3	10	882	
6326	SCN2A	8	751.75	
6323	SCN1A	6	763.5	
808	CALM3	5	1982.95	
6334	SCN8A	5	138.75	
3745	KCNB1	5	2146	
6327	SCN2B	4	89.58333	
6853	SYN1	4	203.5	
26047	CNTNAP2	4	303	
6324	SCN1B	4	89.58333	

Page 1 of 4

Figure 6: The Node Explorer table generated by NetworkAnalyst. The table identifies the key "hub" genes within the interaction network by ranking them according to their topological properties, specifically Degree and Betweenness centrality. The top-ranking genes, such as GRIN2B (Degree = 29) and GRIN2A (Degree = 25), are highlighted as the most highly connected and influential structural nodes in this epilepsy-associated network

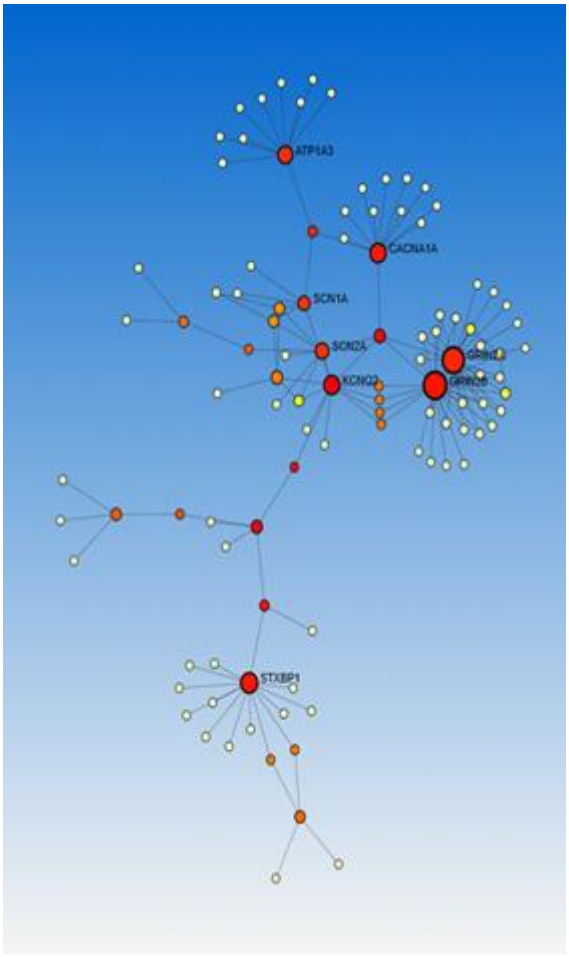
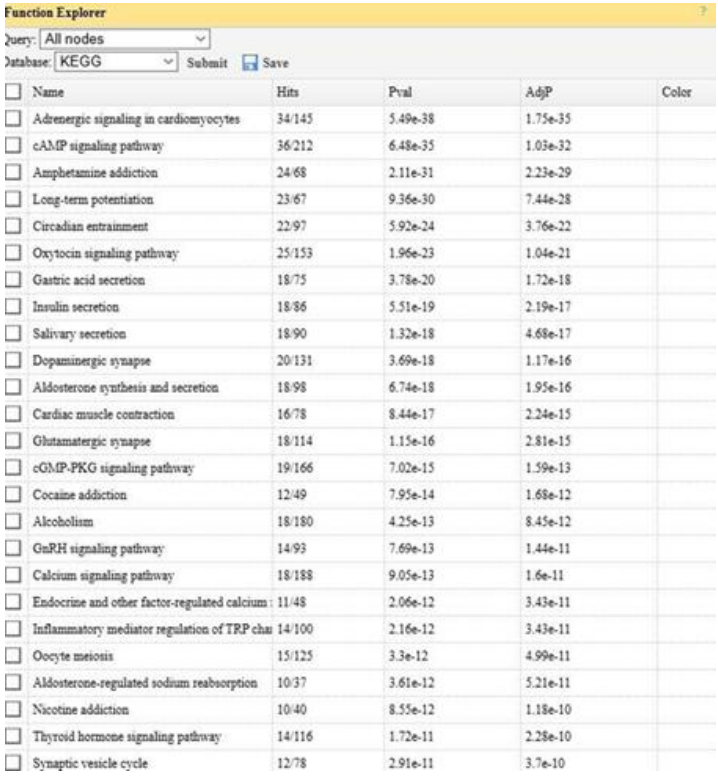


Figure 7: The 2D visualization of the protein-protein interaction network generated by NetworkAnalyst. The graph illustrates the complex interaction architecture among the epilepsy-associated genes, where the size of each node is strictly proportional to its topological significance (specifically, degree centrality). The prominently enlarged nodes—such as GRIN2B, GRIN2A, and STXBP1—visually confirm their status as crucial "hub" genes that are highly interconnected and act as the central anchors for the network's biological functions



Function Explorer

Query: All nodes

Database: KEGG Submit Save

Name	Hits	Pval	AdjP	Color
Adrenergic signaling in cardiomyocytes	34/145	5.49e-38	1.75e-35	
cAMP signaling pathway	36/212	6.48e-35	1.03e-32	
Amphetamine addiction	24/68	2.11e-31	2.23e-29	
Long-term potentiation	23/67	9.36e-30	7.44e-28	
Circadian entrainment	22/97	5.92e-24	3.76e-22	
Oxytocin signaling pathway	25/153	1.96e-23	1.04e-21	
Gastric acid secretion	18/75	3.78e-20	1.72e-18	
Insulin secretion	18/86	5.51e-19	2.19e-17	
Salivary secretion	18/90	1.32e-18	4.68e-17	
Dopaminergic synapse	20/131	3.69e-18	1.17e-16	
Aldosterone synthesis and secretion	18/98	6.74e-18	1.95e-16	
Cardiac muscle contraction	16/78	8.44e-17	2.24e-15	
Glutamatergic synapse	18/114	1.15e-16	2.81e-15	
cGMP-PKG signaling pathway	19/166	7.02e-15	1.59e-13	
Cocaine addiction	12/49	7.95e-14	1.68e-12	
Alcoholism	18/180	4.25e-13	8.45e-12	
GnRH signaling pathway	14/93	7.69e-13	1.44e-11	
Calcium signaling pathway	18/188	9.05e-13	1.6e-11	
Endocrine and other factor-regulated calcium :	11/48	2.06e-12	3.43e-11	
Inflammatory mediator regulation of TRP cha	14/100	2.16e-12	3.43e-11	
Oocyte meiosis	15/125	3.3e-12	4.99e-11	
Aldosterone-regulated sodium reabsorption	10/37	3.61e-12	5.21e-11	
Nicotine addiction	10/40	8.55e-12	1.18e-10	
Thyroid hormone signaling pathway	14/116	1.72e-11	2.28e-10	
Synaptic vesicle cycle	12/78	2.91e-11	3.7e-10	

3.5 Pathway enrichment and visualization

To elucidate the biological mechanisms driving the epileptic network, a multi-stage pathway analysis was conducted utilizing Enrichr and the Reactome Pathway Browser.

3.5.1 Broad Pathway Enrichment (Enrichr)

The core gene set was queried via Enrichr for multi-library enrichment analysis [12]. Analysis of the KEGG library revealed significant enrichment in neurotransmitter-specific systems, prominently featuring "GABAergic synapse" and "Neuroactive ligand-receptor interaction." Expected physiological artifacts, such as addiction-related pathways (e.g., "Nicotine addiction"), were also enriched due to the shared involvement of GABA and glutamate receptors in reward circuitry. Corroborating these findings, the Reactome library identified "Neuronal System" as the most significant term. Subsequent clustergram visualization confirmed that critical network hubs, particularly *GRIN2B* and *SCN1A*, were the primary drivers of these functional enrichments.

3.5.2 Mechanistic pathway mapping (Reactome)

To visualize the precise molecular hierarchy of these systems, the network was mapped into a hierarchical Voronoi diagram using the Reactome Pathway Browser, where region size corresponds to the number of mapped pathway entities [11]. The analysis confirmed the "Neuronal System" (R-HSA-112316) as the paramount parent pathway. Within this overarching system, two distinct functional modules were highly enriched:

- **Transmission across chemical synapses:** Containing the highest density of mapped entities (including *STXBP1, GABRA1,* and *GRIN2A*), confirming a profound localization of defects at the synaptic cleft.
- **Phase 0 - Rapid depolarisation:** Specifically capturing the voltage-gated sodium channels (*SCN1A, SCN2A, SCN8A*), illustrating a fundamental failure in the initial phase of the action potential [22].

Conclusion of pathway analysis: Together, these multi-platform analyses strongly corroborate that epileptogenesis within this network is driven by a dual mechanistic failure: impaired intrinsic neuronal excitability (via sodium channelopathies) compounded by fundamentally dysfunctional synaptic transmission

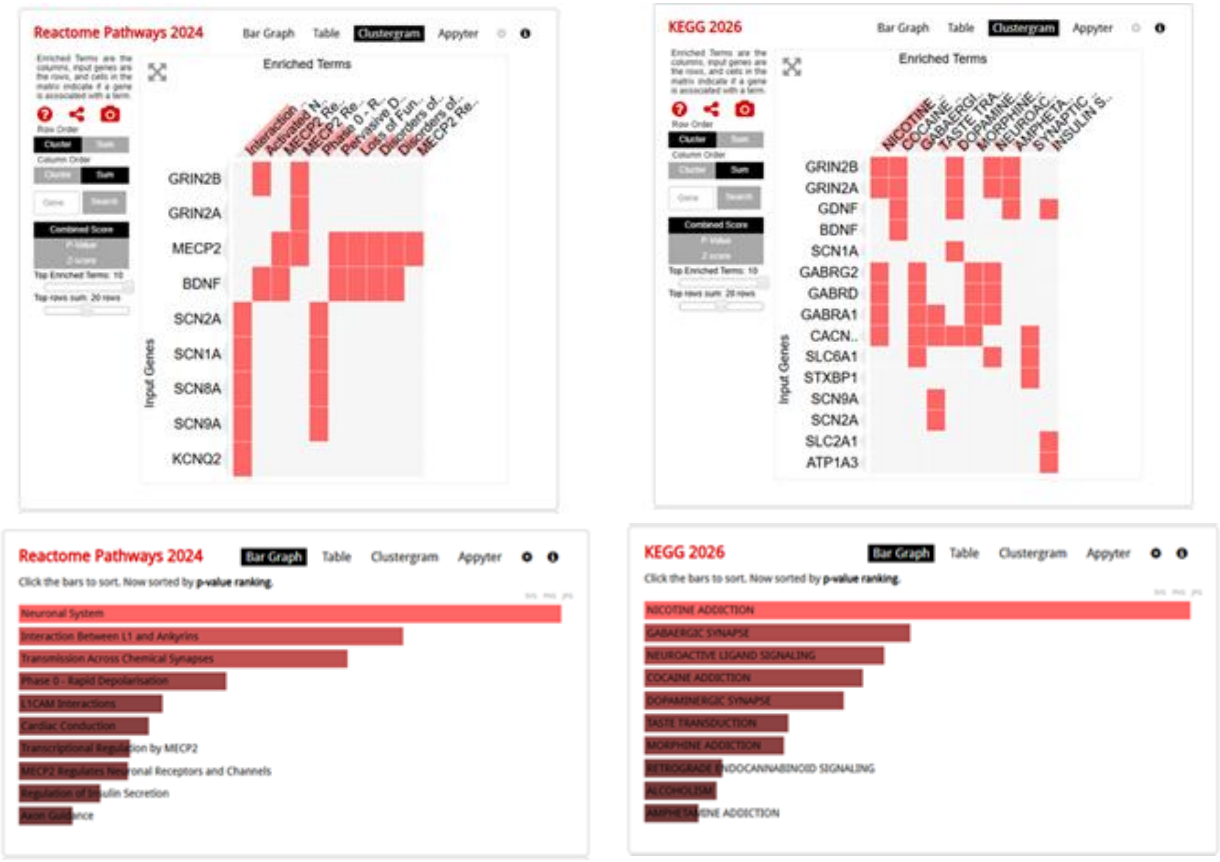
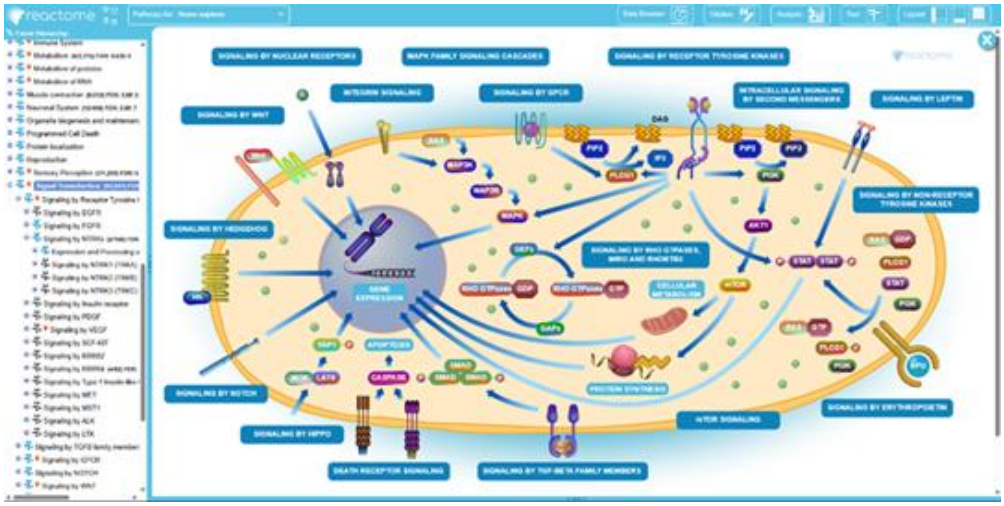


Figure 9 - 12: The Clustergram visualization generated by the Enrichr analysis tool using the Reactome Pathways 2024 database. This matrix maps the input epilepsy-associated genes (rows, such as MECP2, BDNF, and members of the SCN sodium channel family) against the top enriched Reactome pathways (columns, such as "Phase 0 - Rapid Depolarisation" and specific MECP2-regulated functions). The red cells indicate a direct biological association, providing a clear visual representation of how these specific subsets of genes cluster together based on their shared roles in these specialized neurological pathways



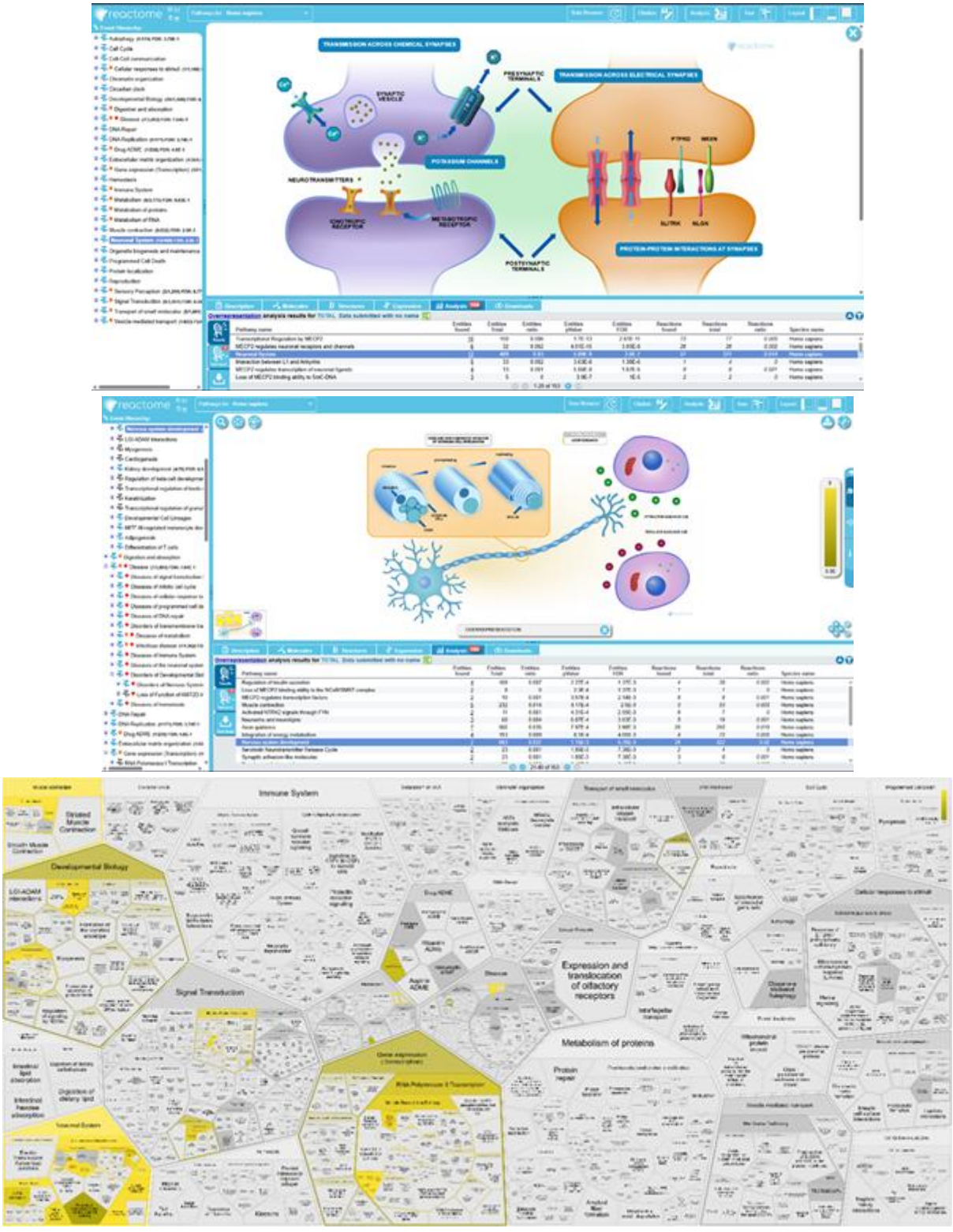


Figure 14: The hierarchical "fireworks" pathway visualization generated by the Reactome database.
In this node-link diagram, human biological pathways are mapped as connected branches extending from major overarching biological categories. The yellow-highlighted trajectories trace the specific pathways significantly enriched by the input epilepsy-associated genes. Prominent yellow clusters are clearly visible within the

"Neuronal System," "Developmental Biology," "Signal Transduction," and "Disease" networks, beautifully illustrating the interconnected, hierarchical role these genes play in nervous system development and complex signaling cascades.

4. Discussion

The integration of multi-omics data through network-based bioinformatics offers a systemic view of epilepsy, shifting the focus from isolated genetic variants to dysregulated functional modules [6]. Our analysis of 30 high-confidence genes reveals a highly cohesive interactome centered on the failure of neuronal homeostasis, specifically driven by ion channel dysfunction and synaptic signaling instability.

4.1 The "Channelopathy" paradigm and action potential dynamics

Both STRING clustering and Reactome pathway analysis highlight the predominance of voltage-gated ion channels, which are heavily populated by sodium (Na_V) and potassium (K_V) subunits [15]. Physiologically, Na_V channels initiate depolarization while K_V channels drive repolarization; their co-clustering suggests epilepsy is often a failure of precise neuronal timing rather than simply "too much excitation." For example, *SCN1A* mutations typically impair the firing of inhibitory interneurons, leading to massive network-wide disinhibition—a mechanism firmly supported by our GO enrichment for membrane potential regulation [16], [22].

4.2 Synaptic vesicle machinery: The presynaptic fault

Beyond simple channel defects, our topological analysis identified *STXBP1* (Syntaxin-binding protein 1) as a critical hub (Degree: 14). Because *STXBP1* is essential for the docking and fusion of synaptic vesicles, its centrality indicates that a significant subset of epilepsy pathology lies in the presynaptic release machinery. Even if ion channels function correctly, a failure in *STXBP1* disrupts the precise release of neurotransmitters into the synaptic cleft [23]. This aligns with the "Transmission across Chemical Synapses" pathway enrichment, highlighting vesicle cycling as a distinct therapeutic target independent of standard ion channel modulators [20].

4.3 Network hubs and the Excitation-Inhibition (E-I) balance

Topological analysis revealed a striking dominance of glutamate receptors (*GRIN2A, GRIN2B*) as the network's primary structural bottlenecks. While many standard anti-seizure medications target sodium channels, our network topology suggests that NMDA receptors act as the central executioners of hyperexcitability. The high connectivity of *GRIN2B* suggests it acts as a functional "convergence point" for upstream signals. Consequently, stabilizing these glutamatergic hubs could effectively dampen the hypersynchrony and excitotoxicity caused by diverse upstream channel mutations [17].

4.4 Functional expansion and epigenetic regulation

GeneMANIA expansion provided critical novel insights by identifying *HDAC7* and *GABRB2* as predicted interactors. The inclusion of the *GABRB2* subunit reinforces the critical role of disrupted phasic inhibition. More notably, the appearance of *HDAC7* (Histone Deacetylase 7) introduces a potential epigenetic layer to epileptogenesis. This implies that the chronic expression of these ion channels may be regulated by ongoing chromatin remodeling, offering a biological explanation for progressive disease severity and why some patients develop acquired drug resistance over time.

Conclusion

This study utilized an integrated bioinformatics pipeline to map the complex molecular architecture of epilepsy, shifting the analytical focus from isolated genetic mutations to a comprehensive model of network failure. By

synthesizing protein-protein interactions, network topology, and pathway enrichment, our results provide robust, multi-layered evidence supporting the "Channelopathy-Synaptopathy" hypothesis of epilepsy [24].

The key conclusions drawn from this network-based analysis are:

- **Pathogenic convergence:** Despite extreme genetic heterogeneity among patients, diverse causative mutations systematically converge onto two primary biological modules: voltage-gated ion transport (governing single-cell excitability) and synaptic vesicle cycling (governing network-wide connectivity).
- **Topological bottlenecks:** Network topology identified specific genes, notably *GRIN2B* and *SCN1A*, as central structural anchors. The exceptionally high centrality of *GRIN2B* suggests the glutamatergic signaling axis serves as a final common pathway for seizure propagation, even when the primary genetic insult originates in distinct systems like sodium channels.
- **Therapeutic validation and expansion:** While validating standard pharmacological targets within the "GABAergic Synapse" pathway, our analysis illuminates vital, underexplored biological avenues. Targeting presynaptic vesicle fusion machinery (*STXBP1*) and epigenetic regulators (*HDAC7*) offers highly promising interventions for drug-resistant [13].
- **A paradigm shift toward precision medicine:** Historically, traditional anti-seizure medications (ASMs) have acted as blunt instruments, achieving seizure control through global neuronal suppression. While effective for some, this non-specific approach fails in approximately 30% of patients and inherently dampens healthy neural circuits, causing severe cognitive and psychiatric side effects. The insights generated from this network architecture emphasize the urgent need for a paradigm shift. Future therapeutic efforts—such as small-molecule modulators, antisense oligonucleotides (ASOs), or viral gene therapies—must strategically target the highly connected network "hubs" identified in this study. This hub-centric approach aims to precisely dismantle pathological seizure networks and restore dynamic synaptic homeostasis without disrupting healthy brain activity, offering a tailored functional cure rather than a systemic chemical restraint [5].

References

1. Fisher, R. S., Acevedo, C., Arzimanoglou, A., Bogacz, A., Cross, J. H., Elger, C. E., Engel, J., Forsgren, L., French, J. A., Glynn, M., Hesdorffer, D. C., Lee, B. I., Mathern, G. W., Moshé, S. L., Perucca, E., Scheffer, I. E., Tomson, T., Watanabe, M., & Wiebe, S. (2014). ILAE official report: A practical clinical definition of epilepsy. *Epilepsia, 55*(4), 475–482. https://doi.org/10.1111/epi.12550
2. Thijs, R. D., Surges, R., O'Brien, T. J., & Sander, J. W. (2019). Epilepsy in adults. *The Lancet, 393*(10172), 689–701. https://doi.org/10.1016/S0140-6736(18)32596-0
3. Löscher, W., Potschka, H., Sisodiya, S. M., & Vezzani, A. (2020). Drug resistance in epilepsy: Clinical impact, potential mechanisms, and new innovative treatment options. *Pharmacological Reviews, 72*(3), 606–638. https://doi.org/10.1124/pr.120.019539
4. EuroEPINOMICS RES Consortium, Epilepsy Phenome/Genome Project, & Epi4K Consortium. (2018). De novo variants in neurodevelopmental disorders with epilepsy. *Nature Genetics, 50*(7), 1048–1053. https://doi.org/10.1038/s41588-018-0143-7
5. Rosch, R. E., Hunter, P. R., Baldeweg, T., Friston, K. J., & Meyer, M. P. (2018). Calcium imaging and dynamic causal modelling reveal brain-wide changes in effective connectivity and synaptic dynamics during

epileptic seizures. *PLOS Computational Biology, 14*(8), e1006375. https://doi.org/10.1371/journal.pcbi.1006375

6. Barabási, A.-L., Gulbahce, N., & Loscalzo, J. (2011). Network medicine: A network-based approach to human disease. *Nature Reviews Genetics, 12*(1), 56–68. https://doi.org/10.1038/nrg2918
7. Piñero, J., Ramírez-Anguita, J. M., Saüch-Pitarch, J., Ronzano, F., Centeno, E., Sanz, F., & Furlong, L. I. (2020). The DisGeNET knowledge platform for disease genomics: 2019 update. *Nucleic Acids Research, 48*(D1), D845–D855. https://doi.org/10.1093/nar/gkz1021
8. Szklarczyk, D., Gable, A. L., Nastou, K. C., Lyon, D., Kirsch, R., Pyysalo, S., Doncheva, N. T., Legeay, M., Fang, T., Bork, P., Jensen, L. J., & von Mering, C. (2021). The STRING database in 2021: Customizable protein–protein networks, and functional characterization of user-uploaded gene/measurement sets. *Nucleic Acids Research, 49*(D1), D605–D612. https://doi.org/10.1093/nar/gkaa1074
9. Warde-Farley, D., Donaldson, S. L., Comes, O., Zuberi, K., Badrawi, R., Chao, P., Franz, M., Grouios, C., Kazi, F., Lopes, C. T., Maitland, A., Mostafavi, S., Montojo, J., Shao, Q., Wright, G., Bader, G. D., & Morris, Q. (2010). The GeneMANIA prediction server: Biological network integration for gene prioritization and predicting gene function. *Nucleic Acids Research, 38*(Suppl. 2), W214–W220. https://doi.org/10.1093/nar/gkq537
10. Zhou, G., Soufan, O., Ewald, J., Hancock, R. E. W., Basu, N., & Xia, J. (2019). NetworkAnalyst 3.0: A visual analytics platform for comprehensive gene expression profiling and meta-analysis. *Nucleic Acids Research, 47*(W1), W234–W241. https://doi.org/10.1093/nar/gkz240
11. Jassal, B., Matthews, L., Viteri, G., Gong, C., Lorente, P., Fabregat, A., Sidiropoulos, K., Cook, J., Gillespie, M., Haw, R., Loney, F., May, B., Milacic, M., Rothfels, K., Sevilla, C., Shamovsky, V., Weiser, J., Williams, M., Wu, G., ... D'Eustachio, P. (2020). The Reactome pathway knowledgebase. *Nucleic Acids Research, 48*(D1), D498–D503. https://doi.org/10.1093/nar/gkz1031
12. Chen, E. Y., Tan, C. M., Kou, Y., Duan, Q., Wang, Z., Meirelles, G. V., Clark, N. R., & Ma'ayan, A. (2013). Enrichr: Interactive and collaborative HTML5 gene list enrichment analysis tool. *BMC Bioinformatics, 14*(1), 128. https://doi.org/10.1186/1471-2105-14-128
13. Balestrini, S., & Sisodiya, S. M. (2018). Pharmacogenomics in epilepsy. *Neuroscience Letters, 667*, 27–39. https://doi.org/10.1016/j.neulet.2017.01.014
14. Carvill, G. L., McMahon, J. M., Schneider, A., Zemel, M., Myers, C. T., Saykally, J., Nguyen, J., Robbiano, A., Zara, F., Specchio, N., Mecarelli, O., Smith, R. L., Leventer, R. J., Møller, R. S., Nikanorova, M., Dimova, P., Jordanova, A., Petrou, S., Helbig, I., ... Mefford, H. C. (2015). Mutations in the GABA transporter SLC6A1 cause epilepsy with myoclonic-atonic seizures. *American Journal of Human Genetics, 96*(5), 808–815. https://doi.org/10.1016/j.ajhg.2015.02.016
15. Wei, F., Yan, L. M., Su, T., He, N., Lin, Z. J., Wang, J., Shi, Y. W., Yi, Y. H., Liao, W. P., & Liu, X. R. (2017). Ion channel genes and epilepsy: Functional alteration, pathogenic potential, and mechanism of epilepsy. *Neuroscience Bulletin, 33*(4), 455–477. https://doi.org/10.1007/s12264-017-0134-1
16. Meisler, M. H., Hill, S. F., & Yu, W. (2021). Sodium channelopathies in neurodevelopmental disorders. *Nature Reviews Neuroscience, 22*(3), 152–166. https://doi.org/10.1038/s41583-020-00418-4
17. Hansen, K. B., Yi, F., Perszyk, R. E., Furukawa, H., Wollmuth, L. P., Gibb, A. J., & Traynelis, S. F. (2021). Structure, function, and pharmacology of glutamate receptor ion channels. *Pharmacological Reviews, 73*(4),

1469–1658. https://doi.org/10.1124/pharmrev.120.000131

18. Lemke, J. R., Lal, D., Reinthaler, E. M., Steiner, I., Nothnagel, M., Alber, M., Geider, K., Laube, B., Schwake, M., Finsterwalder, K., Marino, D., Helbig, I., Heyne, H. O., Schütz, H., Hentschel, J., Møller, R. S., Heron, S. E., Neubauer, B. A., Nürnberg, P., ... Lerche, H. (2013). Mutations in GRIN2A cause idiopathic focal epilepsy with rolandic spikes. *Nature Genetics, 45*(9), 1067–1072. https://doi.org/10.1038/ng.2728
19. Cain, S. M., & Snutch, T. P. (2011). Voltage-gated calcium channels and disease. *BioFactors, 37*(3), 197–205. https://doi.org/10.1002/biof.158
20. Saitsu, H., Kato, M., Mizuguchi, T., Hamada, K., Osaka, H., Tohyama, J., Uruno, K., Kumada, T., Nishiyama, K., Nishimura, A., Okada, I., Yoshimura, Y., Hirai, S., Kumada, S., Hayasaka, K., Fukuda, A., Ogata, K., Saitoh, S., Nagai, T., ... Matsumoto, N. (2008). De novo mutations in the gene encoding STXBP1 (MUNC18-1) cause early infantile epileptic encephalopathy. *Nature Genetics, 40*(6), 782–788. https://doi.org/10.1038/ng.150
21. Millichap, J. J., Park, K. L., Tsuchida, T., Ben-Zeev, B., Carmant, L., Flamini, R., Joshi, N., Levisohn, P. M., Marsh, E. D., Nangia, S., Narula, S., Ng, Y. T., Ortiz-Gonzalez, X. R., Patterson, K., Pearl, P. L., Porter, B. E., Ramsey, K., McGinnis, E., Taglialatela, M., ... Cooper, E. C. (2016). KCNQ2 encephalopathy: Features, mutational hot spots, and ezogabine treatment of 11 patients. *Neurology: Genetics, 2*(5), e96. https://doi.org/10.1212/NXG.0000000000000096
22. Catterall, W. A. (2014). Sodium channels, inherited epilepsy, and antiepileptic drugs. *Annual Review of Pharmacology and Toxicology, 54*(1), 317–338. https://doi.org/10.1146/annurev-pharmtox-011112-140232
23. Stamberger, H., Nikanorova, M., Willemsen, M. H., Accorsi, P., Angriman, M., Baier, H., Benkel-Herrenbrueck, I., Benoit, V., Budetta, M., Caliebe, A., Cariati, E., Coubes, C., Dalla Bernardina, B., Djémié, T., Fannemel, M., Falace, A., Glykantzi, E., Helbig, K. L., Klepper, J., ... Weckhuysen, S. (2016). STXBP1 encephalopathy: A neurodevelopmental disorder including epilepsy. *Neurology, 86*(10), 954–962. https://doi.org/10.1212/WNL.0000000000002457
24. McTague, A., Howell, K. B., Cross, J. H., Kurian, M. A., & Scheffer, I. E. (2016). The genetic landscape of the epileptic encephalopathies of infancy and childhood. *The Lancet Neurology, 15*(3), 304–316. https://doi.org/10.1016/S1474-4422(15)00250-1