

# Knowledge Atlas of the Co-Occurrence of Epilepsy and Autism: A Bibliometric Analysis and Visualization Using VOSviewer and CiteSpace

Yangyang Wang\*, Xianhao Huo\*, Wenchao Li, Lifei Xiao, Mei Li, Chaofan Wang, Yangyang Sun, Tao Sun

Ningxia Key Laboratory of Cerebrocranial Disease, Ningxia Medical University, Yinchuan, People's Republic of China

\*These authors contributed equally to this work

Correspondence: Tao Sun, Ningxia Key Laboratory of Cerebrocranial Disease, Ningxia Medical University, Yinchuan, People's Republic of China, Email [suntao\\_nxmu@163.com](mailto:suntao_nxmu@163.com)

**Objective:** This study aimed to analyze research on epilepsy in autism and autism in epilepsy using VOSviewer and CiteSpace to identify research hotspots and future directions.

**Methods:** We searched the Web of Science Core Collection (WoSCC) for relevant studies about epilepsy in autism and autism in epilepsy published from inception to 31 May 2022. VOSviewer and CiteSpace were used to analyze the authors, institutions, countries, publishing journals, reference co-citation patterns, keyword co-occurrence, keyword clustering, keywords with citation bursts, and other aspects to construct a knowledge atlas.

**Results:** A total of 473 publications related to epilepsy/autism were retrieved. The number of publications about epilepsy/ASD has generally increased over time, with some fluctuations. The USA (202 papers) and University of California-Los Angeles (15 papers) were the leading country and institution, respectively, in this field. Frye, Richard E. was the most published author (9 papers). Notably, collaboration between institutions, countries, and authors does not appear to be active. Hot topics and research frontiers include intellectual disability and exploring the mechanism of epilepsy/ASD from a genetics perspective.

**Conclusion:** This analysis identified the most influential publications, authors, journals, institutions, and countries in the field of epilepsy/ASD research. Using co-occurrence and evolution analyses, the status of the field was identified and future trends were predicted.

**Keywords:** epilepsy, autism, bibliometrics, VOSviewer, CiteSpace, visualization analysis

## Introduction

Epilepsy is a chronic neurological disorder with diverse etiologies, while autism spectrum disorder (ASD) is a collection of neurodevelopmental disorders with multiple etiologies. The prevalence of these conditions in the general population is 0.6% and 1%, respectively.<sup>1,2</sup> Both conditions seriously affect patients' health and life and pose a huge burden on society.<sup>3,4</sup> Notably, epilepsy and autism often co-occur. In recent years, numerous studies have discussed the relationship between epilepsy and autism and the prevalence of their co-occurrence.<sup>5–10</sup> Amiet et al emphasized that epilepsy in autism is associated with intellectual disability (ID) and reported that the prevalence of epilepsy/ASD with ID (21.5%) was higher than epilepsy/ASD without ID (8%).<sup>10</sup> The US National Survey of Children's Health reported that the prevalence of epilepsy with ASD in 2011–2012 was 8.6%.<sup>8</sup> Lukmanji et al demonstrated that the prevalence of epilepsy in patients with autism was 12.1%, while the prevalence of autism in patients with epilepsy was 9.0%.<sup>7</sup> Taken together, these studies indicate that both the prevalence of autism

in patients with epilepsy and the prevalence of epilepsy in patients with autism are higher than the reported rates of both disorders in the general population. At the same time, the prevalence of epilepsy/ASD shows a gradually increasing trend.

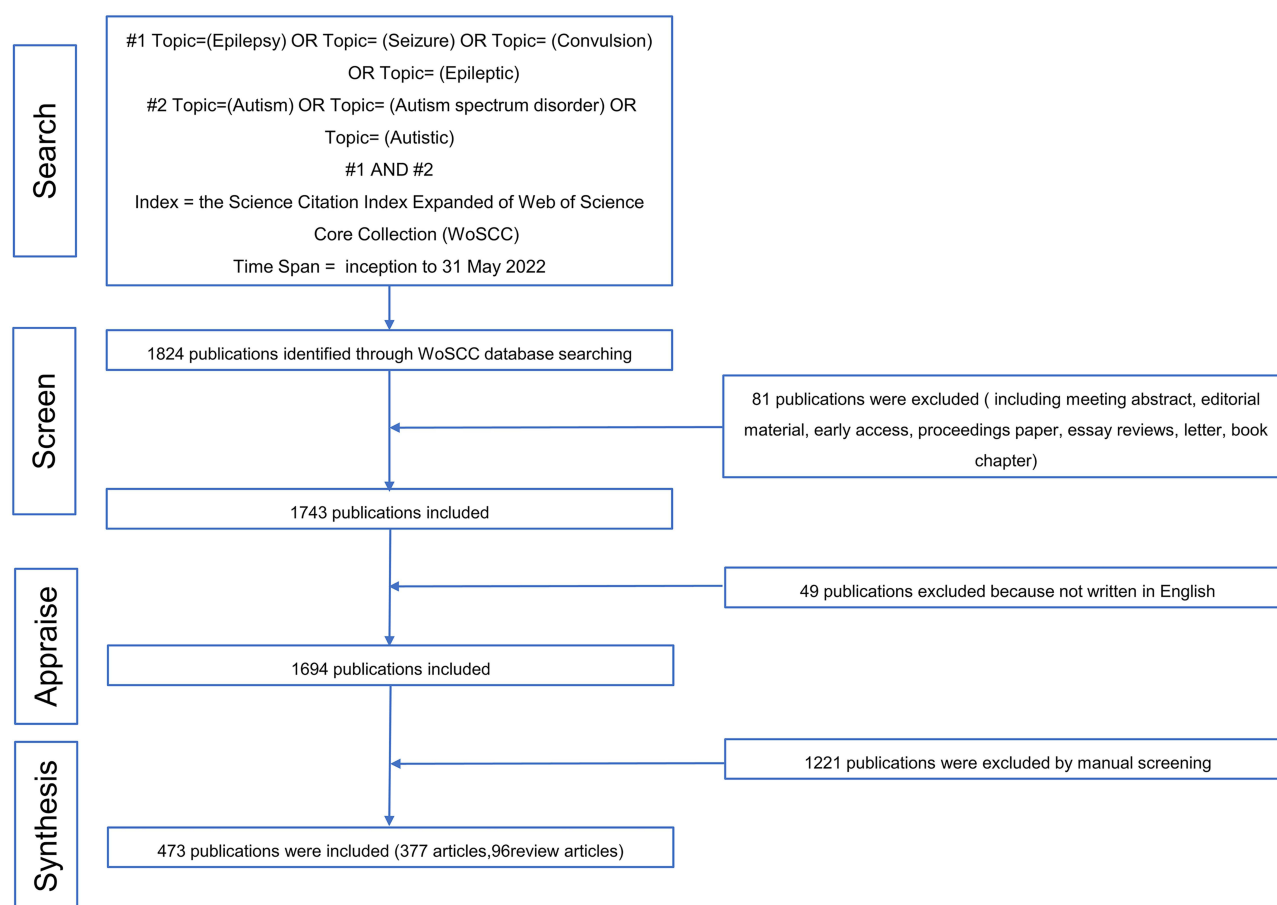
Epilepsy in patients with autism, or autism in patients with epilepsy, often exacerbates cognitive impairment and increases the risk of poor long-term prognosis. Although many studies suggest that epilepsy/ASD comorbidity may be related to genetics, metabolic disorders, infections, and other environmental influences, the details of the underlying mechanisms remain unclear.<sup>11–13</sup> In addition, there is still no effective diagnosis or treatment for epilepsy/ASD, which often depends on which disease occurs first; treatment is often provided according to clinical symptoms, resulting in a low diagnosis rate and poor treatment effects.<sup>14,15</sup> Therefore, it is necessary to summarize the history of the epilepsy/ASD research field and clarify its basis, current hotspots, and potential trends.

Bibliometrics is a quantitative method used to describe and analyze the dynamics and progress of a discipline or research field and to visualize the results of a literature analysis using correlation analysis software.<sup>16,17</sup> In the present study, we used the bibliometrics-related software applications VOSviewer and CiteSpace to perform bibliometric and visual analyses.<sup>18,19</sup> To the best of our knowledge, there is no existing bibliometric analysis of the epilepsy/ASD research field. To fill this gap, we conducted a quantitative analysis and visualization of cooperative networks (countries, institutions, and authors), published journals, co-citation references, keyword clustering, and keyword citation bursts in this research field. In doing so, our study systematically and objectively evaluates the basic, frontier, and hot topics in epilepsy/ASD research.

## Methods

### Data Sources and Search Strategies

As shown in Figure 1, data were retrieved using advanced search strategies in the Web of Science Core Collection (WoSCC), which is an extended version of the Science Citation Index. The following search terms were entered in the topic field: (“Epilepsy”



**Figure 1** Flow chart of the literature screening process.

OR “Seizure” OR “Convulsion” OR “Epileptic”) AND (“Autism Spectrum Disorder” OR “Autistic “OR” Autism”) AND language = English. The time span for publication was from inception to 31 May 2022 and the document types were limited to original articles and reviews. In line with previous studies,<sup>17,20</sup> two independent researchers reviewed the titles and abstracts and excluded any studies unrelated to epilepsy/ASD. As a result, 473 publications were included in the subsequent analysis.

## Data Analysis and Visualization

In this study, VOSviewer (version 1.6.18) and CiteSpace (version 6.1.R2) were used for bibliometric analysis and data visualization. First, we exported the records retrieved from WoSCC in plain text, including the full records and references, named download\_XXX. txt. These data were then imported to VOSviewer and CiteSpace for bibliometric and visual analysis. VOSviewer is used to analyze countries, institutions, journals, co-authors, and co-citation references. CiteSpace identifies research fronts and emerging trends by analyzing annual publication numbers, growth trends, and co-occurring keywords clusters and capturing keywords with strong citation bursts over time.

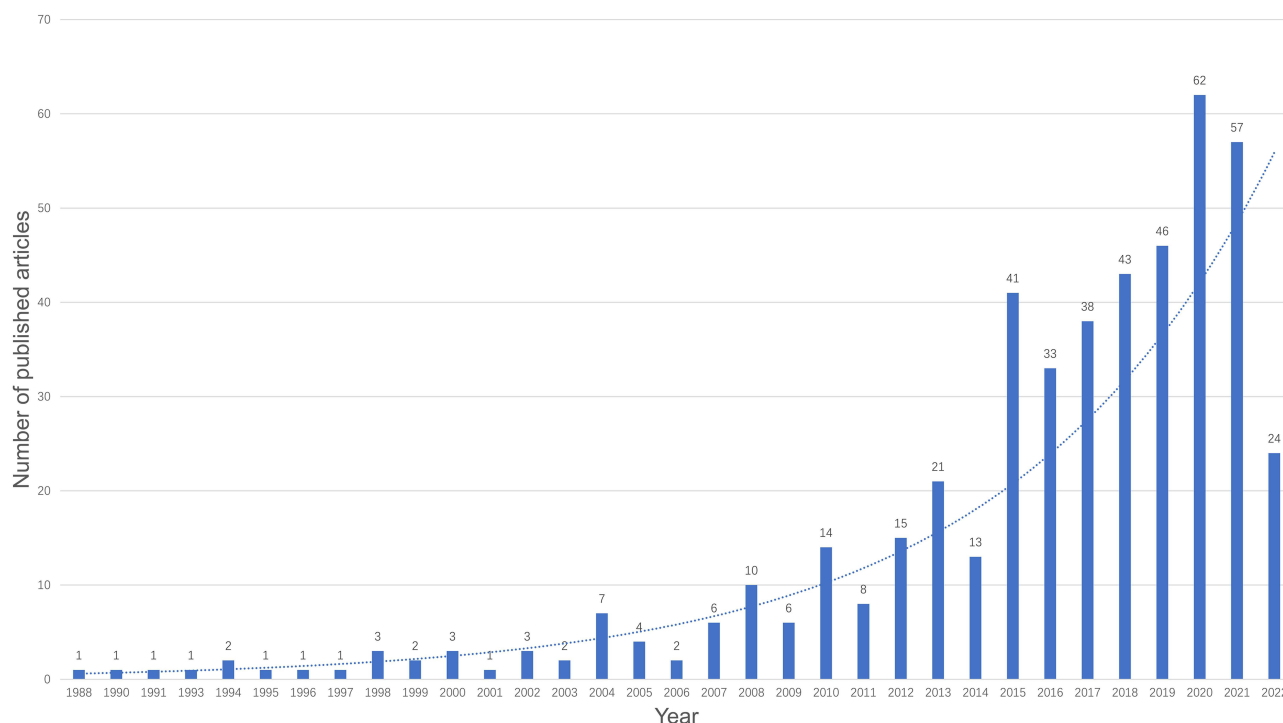
## Results

### Bibliometric Analysis by Publication Year

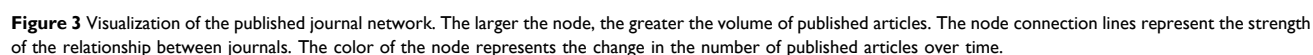
As shown in Figure 2, 473 publications related to epilepsy/ASD were published from inception to 31 May 2022. The number of publications about epilepsy/ASD has generally increased over time, with some fluctuations. Prior to 2007, the number of publications was relatively small with no more than 10 publications published each year. From 2008 to 2014, the annual number of publications began to increase, achieving more than 20 publications in 2013. From 2015 to 2021, more than 30 articles were published each year. Sixty-two articles were published in 2020, which is the year with the most publications. As of 31 May 2022, 24 articles had been published that year.

### Bibliometric Analysis of Journals

The 473 identified publications were published in 195 journals. First, journals with three or more epilepsy/ASD-related publications were visualized using VOSviewer (Figure 3). Next, we summarized the journals with the highest number of



**Figure 2** Annual trends in publications from inception to 31 May 2022.



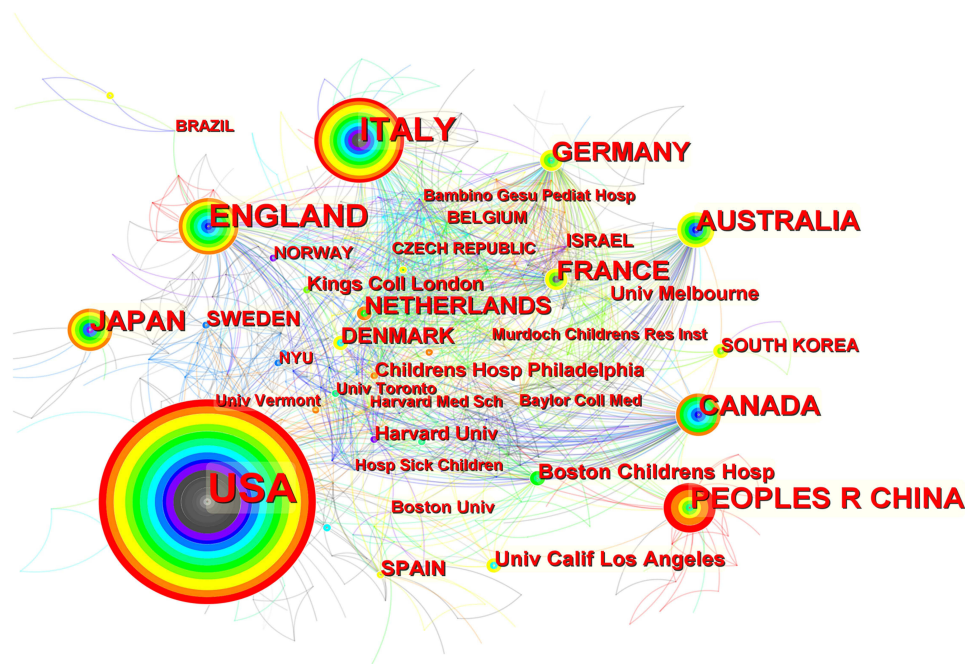
## Bibliometric Analysis of Countries and Institutions

## Bibliometric Analysis of Co-Authors

**Table 1** Journals with More Than 10 Publications in the Field of Epilepsy/ASD

| Rank | Journal   | Publications | Citations | Average Number of Citations per Publication |
|------|---|--------------|-----------|---|
| 1    | <i>Epilepsy &amp; Behavior</i>                    | 46           | 1026      | 22.3  |
| 2    | <i>Epilepsia</i>                                  | 22           | 982       | 44.64                                       |
| 3    | <i>Brain &amp; Development</i>                    | 20           | 1024      | 51.2  |
| 4    | <i>Journal of Child Neurology</i>                 | 14           | 452       | 32.29                                       |
| 5    | <i>Developmental Medicine and Child Neurology</i> | 12           | 788       | 65.67                                       |
| 5    | <i>Pediatric Neurology</i>                        | 12           | 476       | 39.67                                       |





**Figure 4** Network visualization of countries and institutions. The size of the colorful nodes represents the number of articles posted. The node connection lines represent the strength of the relationship between countries and institutions.

## Bibliometric Analysis of Co-Cited References

A total of 18,017 references were co-cited in the 473 publications. Table 4 summarizes the 10 most cited references. The top three co-cited references were Tuchman R (2002) (65 citations), Amiet C (2008) (59 citations), Spence SJ (2009) (43 citations), and Volkmar FR (1990) (43 citations).

## Bibliometric Analysis of Co-Occurring Keywords and Clusters

Table 5 lists the 10 most common keywords; autism spectrum disorder (frequency: 218), children (frequency: 132), epilepsy (frequency: 122), intellectual disability (frequency: 70), seizure (frequency: 62), prevalence (frequency: 54), spectrum disorder (frequency: 43), mutation (frequency: 35), gene (frequency: 33), mouse model (frequency: 32), and de novo mutation (frequency: 32). In CiteSpace, nodes with a centrality that exceeds 0.1 are called “key nodes”. Therefore, Table 5 also summarizes keywords with centrality exceeding 0.1, namely children (centrality: 0.31), autism spectrum disorder (centrality: 0.25), epilepsy (centrality: 0.13), pervasive developmental disorder (centrality: 0.12), prevalence (centrality: 0.10), and spectrum disorder (centrality: 0.10).

We also used CiteSpace to perform cluster analysis of co-occurring keywords. We obtained 11 clusters. The average silhouette (S value) of the cluster is used as an indicator to evaluate clustering. Generally,  $S > 0.5$  clustering is considered reasonable, while  $S > 0.7$  means that clustering is convincing. Each of the obtained clusters has a silhouette value  $> 0.5$ ,

**Table 2** The Top Five Countries and Institutions Publishing Epilepsy/ASD Research

| Rank | Country | Number of Publications | Rank | Institution                          | Number of Publications |
|------|---------|------------------------|------|--------------------------------------|------------------------|
| 1    | USA     | 202                    | 1    | University of California-Los Angeles | 15                     |
| 2    | Italy   | 60                     | 2    | University of Melbourne              | 14                     |
| 3    | England | 53                     | 3    | Kings College London                 | 12                     |
| 4    | China   | 41                     | 4    | Boston Children's Hospital           | 11                     |
| 5    | Canada  | 32                     | 5    | Harvard University                   | 11                     |



**Figure 5** Network visualization of authors. The larger the node, the greater the number of published articles. The node connection lines represent the strength of the relationship between authors.

implying that the results are reasonable (Figure 6, Table 6). To gain further insight into the evolution of these clusters, we visualized the co-clustering timeline view using CiteSpace (Figure 7).

## Bibliometric Analysis of Keywords with Citation Bursts

Lastly, we visualized the top 15 keywords with the strongest citation bursts (Figure 8). The blue line represents the time interval, while the red line represents the time period when the keyword bursts were found. The three most recent citation burst keywords occurred in 2019 (intellectual disability), 2020 (neurodevelopmental disorder), and 2020 (gene) and all lasted until 2022.

**Table 3** Most Important Authors in the Epilepsy/ASD Research Field

| Rank | Author        | Number of Publications | Citations | Average Number of Citations per Publication |
|------|---------------|------------------------|-----------|---|
| 1    | Frye, RE.     | 9                      | 220       | 24.44                                       |
| 2    | Gillberg, C   | 6                      | 111       | 18.5  |
| 3    | Sahin, M      | 6                      | 199       | 33.17                                       |
| 4    | Capal, JK     | 5                      | 107       | 21.4  |
| 4    | Scheffer, IE. | 5                      | 175       | 35  |
| 4    | Scherer, SV.  | 5                      | 111       | 22.2  |
| 4    | Specchio, N   | 5                      | 86        | 17.2  |
| 4    | Trivisano, M  | 5                      | 86        | 17.2  |
| 4    | Tuchman, R    | 5                      | 309       | 61.8  |

**Table 4** The Top 10 Co-Cited References in the Epilepsy/ASD Research Field

| Rank | Co-Cited References  | Citations |
|------|--|-----------|
| 1    | Tuchman R, <sup>31</sup> 2002, lancet neurol, v1, p352, doi 10.1016/s1474-4422(02)00160-6            | 65        |
| 2    | Amiet C, <sup>10</sup> 2008, biol psychiat, v64, p577, doi 10.1016/j.biopsych.2008.04.030            | 59        |
| 3    | Spence SJ, <sup>32</sup> 2009, pediatri res, v65, p599, doi 10.1203/pdr.0b013e31819e7168             | 43        |
| 4    | Volkmar FR, <sup>33</sup> 1990, j am acad child psy, v29, p127, doi 10.1097/00004583-199001000-00020 | 43        |
| 5    | Danielsson S, <sup>34</sup> 2005, epilepsy, v46, p918, doi 10.1111/j.1528-1167.2005.57504.x          | 40        |
| 6    | Hara H, <sup>35</sup> 2007, brain dev-jpn, v29, p486, doi 10.1016/j.braindev.2006.12.012             | 39        |
| 6    | Viscidi EW, <sup>36</sup> 2013, plos one, v8, doi 10.1371/journal.pone.0067797                       | 39        |
| 8    | Chez MG, <sup>37</sup> 2006, epilepsy behav, v8, p267, doi 10.1016/j.yebeh.2005.11.001               | 35        |
| 8    | Rossi PG, <sup>38</sup> 1995, brain dev-jpn, v17, p169, doi 10.1016/0387-7604(95)00019-8             | 35        |
| 10   | Tuchman RF, <sup>39</sup> 1997, pediatrics, v99, p560, doi 10.1542/peds.99.4.560                     | 33        |

**Table 5** The Co-Occurrence Keywords of Epilepsy/ASD Research

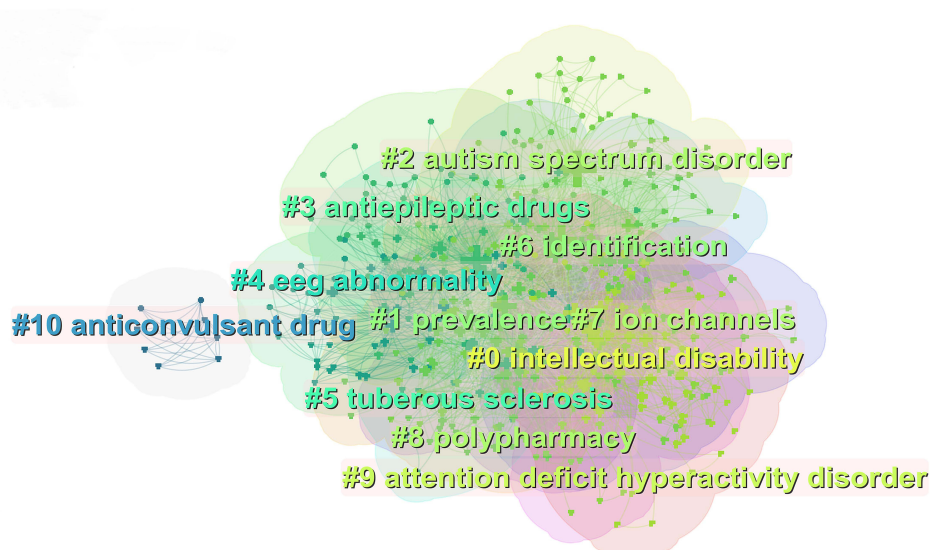
| Rank | Count | Keywords                 | Rank | Centrality | Keywords                         |
|------|-------|--------------------------|------|------------|----------------------------------|
| 1    | 218   | Autism spectrum disorder | 1    | 0.31       | Children                         |
| 2    | 132   | Children                 | 2    | 0.25       | Autism spectrum disorder         |
| 3    | 122   | Epilepsy                 | 3    | 0.13       | Epilepsy                         |
| 4    | 70    | Intellectual disability  | 4    | 0.12       | Pervasive developmental disorder |
| 5    | 62    | Seizure                  | 5    | 0.1        | Prevalence                       |
| 6    | 54    | Prevalence               | 6    | 0.1        | Spectrum disorder                |
| 7    | 43    | Spectrum disorder        |      |            |                                  |
| 8    | 35    | Mutation                 |      |            |                                  |
| 9    | 33    | Gene                     |      |            |                                  |
| 10   | 32    | Mouse model              |      |            |                                  |
| 10   | 32    | De novo mutation         |      |            |                                  |

## Discussion

### General Discussion

To the best of our knowledge, this is the first study to use VOSviewer and CiteSpace to review the field of epilepsy/ASD research and reveal research hotspots and frontiers. Our search of WoSCC identified a total of 473 articles that were published in 195 journals, cited a total of 18,017 references, and had a total of 2584 authors from 1003 institutions and 55 countries.

Based on our findings, the epilepsy/ASD research field can be roughly divided into three stages. From 1998 to 2007, researchers started to recognize epilepsy and autism comorbidities and the number of publications did not exceed 7 per year. From 2008 to 2014, researchers began to pay attention to epilepsy and autism comorbidities and the number of annual publications increased. Since 2015, there has been a rapid increase in the number of published papers. In 2020 and 2021 the number of published papers stabilized at more than 55 each year, indicating recent research attention. The rapid increase in the number of publications since 2015 may be due to several factors. First, the most recent diagnostic criteria for “autism spectrum disorder” in the Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition) (DSM-5) are more extensive, making the rate of ASD diagnosis increase.<sup>11,21,22</sup> Furthermore, awareness of the main behavioral symptoms of ASD, such as social impairment, communication difficulties, and stereotyped repetitive behaviors, has increased in general. Thus, although the prevalence of epilepsy has remained relatively stable, broader diagnostic criteria and better understanding of ASD have led to comorbid epilepsy/ASD receiving increased attention.<sup>11</sup>



**Figure 6** Visualization of the keywords cluster analysis.

## Network

### Journal Network

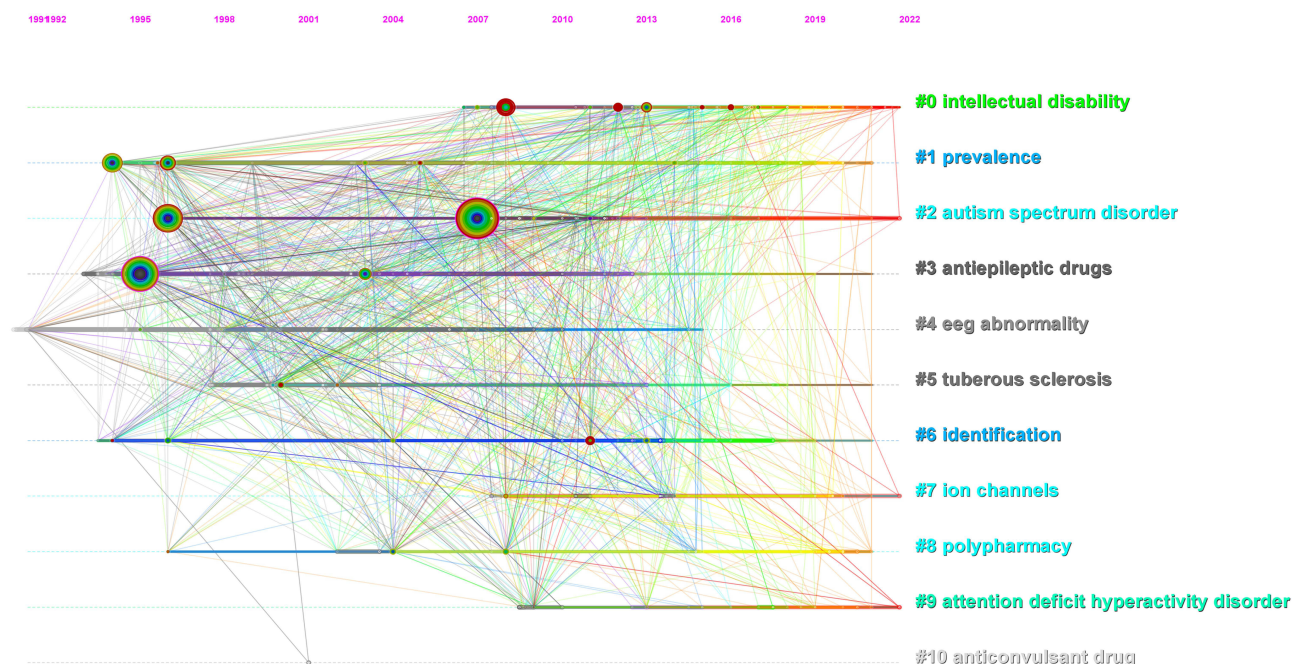
Although analysis of the journals in which epilepsy/ASD research are published cannot help us understand the current state of epilepsy/ASD research, nor can it predict future research trends, it can help us build theoretical foundations and submit high-quality articles. In the journal that published the most articles, *Epilepsy & Behavior*, recent articles include de novo *GRIN2A* variants associated with epilepsy and autism<sup>23</sup> and epilepsy in patients with focal cortical dysplasia that may be associated with ASD.<sup>24</sup>

### Country and Institution Network

From inception to May 2022, the authors of the 473 publications came from 1003 institutions and 55 countries. The top five countries contributed 388 papers, accounting for 82% of all papers; the United States, which ranked first in terms of the number of papers, contributed 202. In addition, three of the top five institutions with the largest number of papers are

**Table 6** Analysis of the Top 10 Clusters of Keywords in the Epilepsy/ASD Research Field

| Cluster ID | Silhouette | Label                                    | Included Keywords (Top 5)   | Mean (Year) |
|------------|------------|--|---|-------------|
| 0          | 0.636      | Intellectual disability                  | Intellectual disability; mutation mouse model; de novo mutation; neurodevelopmental disorder;                 | 2016        |
| 1          | 0.577      | Prevalence                               | Seizure; prevalence; individual; pervasive; developmental disorder  | 2010        |
| 2          | 0.754      | Autism spectrum disorder                 | Autism spectrum disorder; epilepsy; expression; animal model; cognitive impairment                            | 2011        |
| 3          | 0.856      | Antiepileptic drug                       | Children; Spectrum disorder; childhood; EEG; antiepileptic drug   | 2004        |
| 4          | 0.862      | EEG abnormality                          | EEG abnormality; disorder; infantile autism; age; deficit   | 2002        |
| 5          | 0.799      | Tuberous sclerosis                       | Tuberous sclerosis complex; infantile spasm; fragile x syndrome; childhood epilepsy; landau kleffner syndrome | 2004        |
| 6          | 0.827      | Identification                           | Gene; mental retardation; population; identification; association   | 2012        |
| 7          | 0.77       | Ion channels                             | Autism; temporal lobe epilepsy; protein; variant; febrile seizure   | 2015        |
| 8          | 0.786      | Polypharmacy                             | Adolescent; behavior; symptom; adult; anxiety   | 2014        |
| 9          | 0.796      | Attention deficit/hyperactivity disorder | Brain; autism spectrum disorder (asd); adhd; attention deficit/hyperactivity disorder; double blind           | 2015        |



**Figure 7** Co-clustering timeline view from 1988 to 2022. The node size and color indicate the total number of references and individual time slices, respectively. Different colored lines indicate that two articles are co-cited in one article. The solid line and dotted line correspond to clustering topics representing hot topics and non-hot topics, respectively, during the period.

## Top 15 Keywords with the Strongest Citation Bursts

| Keywords                         | Year | Strength | Begin | End  | 1988 - 2022 |
|----------------------------------|------|----------|-------|------|-------------|
| infantile autism                 | 1988 | 5.38     | 1991  | 2009 |             |
| eeg                              | 1988 | 3.94     | 1993  | 2011 |             |
| mental retardation               | 1988 | 4.65     | 1994  | 2016 |             |
| psychiatric disorder             | 1988 | 4.34     | 1995  | 2007 |             |
| childhood                        | 1988 | 4.27     | 1998  | 2013 |             |
| landau kleffner syndrome         | 1988 | 3.62     | 1998  | 2004 |             |
| pervasive developmental disorder | 1988 | 6.03     | 1999  | 2012 |             |
| tuberous sclerosis complex       | 1988 | 4.52     | 2015  | 2017 |             |
| risk                             | 1988 | 4.3      | 2015  | 2016 |             |
| feature                          | 1988 | 4.04     | 2015  | 2018 |             |
| de novo mutation                 | 1988 | 4.27     | 2016  | 2020 |             |
| epileptic encephalopathy         | 1988 | 3.67     | 2017  | 2020 |             |
| intellectual disability          | 1988 | 6.5      | 2019  | 2022 |             |
| neurodevelopmental disorder      | 1988 | 4.9      | 2020  | 2022 |             |
| gene                             | 1988 | 4.21     | 2020  | 2022 |             |

**Figure 8** The top 15 keywords with the strongest citation bursts.



from the United States. These results indicate that the distribution of countries publishing papers in this field is very uneven. Further progress in epilepsy/ASD research requires the participation and collaboration of more institutions and countries.

### Author Network

Through analysis of the authors' collaborative network, we can identify representative scholars in the epilepsy/ASD research field. The author with the highest number of publications is Frye, R. E., who published recent articles discussing the pathogenesis of epilepsy and autism with topics such as metabolism, mitochondrial diseases, central nervous system metabolism, etc.<sup>25–27</sup> The author with the highest average number of citations per publication is Tuchman, R., who mainly discusses the relationship between epilepsy and ASD.<sup>28–30</sup> Although the number of authors of the 473 articles is as high as 2584, the author cooperation network map indicates that only a small number of authors cooperate closely and that most authors do not have cooperative relationships. This may constrain the development of epilepsy/ASD research.

### Co-Cited References Network

By analyzing co-citation references, researchers can quickly grasp the basis of a research field. In the epilepsy/ASD field, the top 5 co-cited references were each cited more than 40 times. The most frequently cited publication is Tuchman, et al, which systematically expounded the relationship between epilepsy and autism.<sup>31</sup> The second most cited is Amiet, et al, which reported that the prevalence of epilepsy and autism comorbidity is related to intellectual disability and gender through meta-analysis.<sup>10</sup> Tied for the third most cited is Spence, et al, which elucidated the role of epilepsy and epileptiform electroencephalography in ASD,<sup>32</sup> and Volkmar, et al, which suggested that children with autism have the highest risk of seizures in early childhood.<sup>33</sup> The fifth most cited is Danielsson, et al, which elaborated the long-term outcome of epilepsy in autism and the epilepsy characteristics of adults with autism through prospective research.<sup>34</sup>

## Hot Topics and Frontiers in Epilepsy/ASD Research

Keywords provide a core, high-level summary of an article. In bibliometrics, high frequency keywords are used to identify hotspots and frontiers in a research field. In this study, we summarized high frequency keywords, performed cluster analysis of these keywords, constructed a keyword clustering timeline graph, and finally analyzed keywords with citation bursts. Our results indicate that the keywords intellectual disability, neurodevelopmental disorder, gene, and mutation may represent hot topics and frontiers in epilepsy/ASD research.

### Intellectual Disability

ID is a topic that cannot be avoided when people discuss the relationship between epilepsy and autism. As mentioned above, the second most co-cited reference is Amiet, et al, which found that the prevalence of epilepsy in autistic patients with ID was 21.5%, while the prevalence of epilepsy in autistic patients without ID was 8%.<sup>10</sup> With the deepening understanding of the relationship between epilepsy and autism, some studies suggest that ID may be a mediator between epilepsy and autism.<sup>36,40–42</sup> A recent study investigating the relationship between epilepsy, autism, and ID is Cogne, et al, which reported that missense variants in the histone acetyltransferase complex component gene *TRRAP* cause concurrent epilepsy, autism, and ID.<sup>43</sup> Brant, et al found that the *IQSEC2* mutation is associated with epilepsy, ID, and autism.<sup>44</sup> Although some scholars have suggested that clinical genetic sequencing of epilepsy/ASD patients with ID,<sup>45</sup> it must be admitted that the relationship between the three is unclear and it thus remains a clinical conundrum.<sup>46</sup> Therefore, more research is needed in the future to clarify the relationship between epilepsy, ID, and autism.

### Genes, Mutation, and Neurodevelopmental Disorders

Although gene, mutation, and neurodevelopmental disorder appeared as three independent high frequency keywords or keywords with citation bursts in our analysis, in the actual publications we found that these three keywords often appeared together. From a genetic point of view, mutations can lead to neurodevelopmental

disorders, which in turn lead to a series of neurological diseases. Therefore, we explore these three keywords together in epilepsy/ASD research. Both epilepsy and autism are neurological disorders with multiple etiologies. However, thanks to advances in gene sequencing technologies and computational approaches, genetics has been shown to play a much greater role in epilepsy and autism than was previously appreciated. Therefore, when studying the underlying mechanism of epilepsy/ASD comorbidity, more and more researchers are adopting a genetic perspective. For example, Penagarikano et al confirmed that the absence of the *Cntnap2* gene can lead to epilepsy/ASD comorbidity by constructing animal models.<sup>47</sup> Stamberger et al<sup>48</sup> confirmed that *STXBP1* mutations can lead to STXBP1 encephalopathy, while Roston et al<sup>49</sup> showed that *SETD1B* mutations can lead to neurodevelopmental disorder, both of which may be risk factors for epilepsy/ASD comorbidity. Multiplex gene and phenotype networks have also been examined for a possible role in the pathogenesis of epilepsy/ASD comorbidity.<sup>50</sup> Many recent review articles have explored the mechanism of epilepsy/ASD comorbidity from a genetics perspective.<sup>51–54</sup> Based on our analysis and the above literature review, the three keywords gene, mutation, and neurodevelopmental disorder have gradually come to reflect hot spots and frontiers in the field of epilepsy/ASD research.

## Limitations

This study is subject to several limitations. First, as our data only comes from the WoSCC database, our analysis may not be comprehensive enough. Second, our search was limited to original articles and reviews published in English, which makes the analysis incomplete to a certain extent. Finally, although VOSviewer and CiteSpace are professional bibliometric analysis software tools that provide objective analysis, since different researchers may have different views and interpretations of the same content, there may be some subjective bias.

## Conclusion

The relationship between epilepsy and autism is extremely complex and the two conditions often co-occur, making it a challenging topic in both clinical and basic research. This study investigated the development of epilepsy/ASD research from its inception to 2022 through bibliometric analysis. Based on 473 articles obtained from WoS, we identified important publications, authors, journals, institutions, and countries and further analyzed the research network. Based on these findings, ID, which is an intermediary factor between epilepsy and autism, and exploring the mechanism of epilepsy/ASD from a genetics perspective are the main hotspot and frontier in this research field, respectively.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Funding

Ningxia Brain plan-The basic and clinical research on tempo-insular neural network and brain recognizing functions (2002170101).

## Disclosure

The authors report no competing interests in this work.

## References

1. Fiest KM, Sauro KM, Wiebe S., et al. Prevalence and incidence of epilepsy: a systematic review and meta-analysis of international studies. *Neurology*. 2017;88(3):296–303. doi:10.1212/WNL.0000000000003509
2. Zeidan J, Fombonne E, Scora J, et al. Global prevalence of autism: a systematic review update. *Autism Res*. 2022;15(5):778–790. doi:10.1002/aur.2696

3. Beghi E. The epidemiology of epilepsy. *Neuroepidemiology*. 2020;54(2):185–191. doi:10.1159/000503831
4. Spain D, Sin J, Paliokosta E, et al. Family therapy for autism spectrum disorders. *Cochrane Database Syst Rev*. 2017;5:CD011894. doi:10.1002/14651858.CD011894.pub2
5. Auvin S. Autism spectrum disorders of patients with epilepsy: the to-be-determined face of the coin. *Epilepsy Behav*. 2021;117:107838. doi:10.1016/j.yebeh.2021.107838
6. Karunakaran S, Menon RN, Nair SS, Santhakumar S, Nair M, Sundaram S. Clinical and genetic profile of Autism Spectrum Disorder-Epilepsy (ASD-E) phenotype: two sides of the same coin *Clin Eeg Neurosci*. 2020;51(6):390–398. doi:10.1177/1550059420909673
7. Lukmanji S, Manji SA, Kadhim S, et al. The co-occurrence of epilepsy and autism: a systematic review. *Epilepsy Behav*. 2019;98(Pt A):238–248. doi:10.1016/j.yebeh.2019.07.037
8. Thomas S, Hovinga ME, Rai D, Lee BK. Brief report: prevalence of co-occurring epilepsy and autism spectrum disorder: the U.S. National survey of children's health 2011–2012. *J Autism Dev Disord*. 2017;47(1):224–229. doi:10.1007/s10803-016-2938-7
9. Jeste SS, Tuchman R. Autism spectrum disorder and epilepsy: two sides of the same coin? *J Child Neurol*. 2015;30(14):1963–1971. doi:10.1177/0883073815601501
10. Amiet C, Gourfinkel-An I, Bouzamoso A, et al. Epilepsy in autism is associated with intellectual disability and gender: evidence from a meta-analysis. *Biol Psychiatry*. 2008;64(7):577–582. doi:10.1016/j.biopsych.2008.04.030
11. Besag F, Vasey MJ. Seizures and epilepsy in autism spectrum disorder. *Psychiatr Clin North Am*. 2021;44(1):51–68. doi:10.1016/j.psc.2020.11.005
12. Lo-Castro A, Curatolo P. Epilepsy associated with autism and attention deficit hyperactivity disorder: is there a genetic link? *Brain Dev*. 2014;36(3):185–193. doi:10.1016/j.braindev.2013.04.013
13. Lin CH, Chou IC, Lee IC, Hong SY. Cytomegalovirus infection in infancy may increase the risk of subsequent epilepsy and autism spectrum disorder in childhood. *Children*. 2021;8(11). doi:10.3390/children8111040
14. Holmes H, Sawyer F, Clark M. Autism spectrum disorders and epilepsy in children: a commentary on the occurrence of autism in epilepsy; how it can present differently and the challenges associated with diagnosis. *Epilepsy Behav*. 2021;117:107813. doi:10.1016/j.yebeh.2021.107813
15. Besag FM. Epilepsy in patients with autism: links, risks and treatment challenges. *Neuropsychiatr Dis Treat*. 2018;14:1–10. doi:10.2147/NDT.S120509
16. Zhan J, Ma Y, Zhao D, et al. Knowledge atlas of post-traumatic epilepsy research: based on citespace visualization analysis. *Epilepsy Res*. 2021;178:106790. doi:10.1016/j.eplepsyres.2021.106790
17. Guo Y, Xu ZY, Cai MT, Gong WX, Shen CH. Epilepsy with suicide: a bibliometrics study and visualization analysis via CiteSpace. *Front Neurol*. 2021;12:823474. doi:10.3389/fneur.2021.823474
18. van Eck NJ, Waltman L. Software survey: vOSviewer, a computer program for bibliometric mapping. *Scientometrics*. 2010;84(2):523–538. doi:10.1007/s11192-009-0146-3
19. Chen C. Searching for intellectual turning points: progressive knowledge domain visualization. *Proc Natl Acad Sci U S A*. 2004;101(Suppl 1):5303–5310. doi:10.1073/pnas.0307513100
20. Xiong HY, Liu H, Wang XQ. Top 100 most-cited papers in neuropathic pain from 2000 to 2020: a bibliometric study. *Front Neurol*. 2021;12:765193. doi:10.3389/fneur.2021.765193
21. Kim YS, Fombonne E, Koh YJ, Kim SJ, Cheon KA, Leventhal BL. A comparison of DSM-IV pervasive developmental disorder and DSM-5 autism spectrum disorder prevalence in an epidemiologic sample. *J Am Acad Child Adolesc Psychiatry*. 2014;53(5):500–508. doi:10.1016/j.jaac.2013.12.021
22. Tsai LY, Ghaziuddin M. DSM-5 ASD moves forward into the past. *J Autism Dev Disord*. 2014;44(2):321–330. doi:10.1007/s10803-013-1870-3
23. Mangano GD, Riva A, Fontana A, et al. De novo GRIN2A variants associated with epilepsy and autism and literature review. *Epilepsy Behav*. 2022;129:108604. doi:10.1016/j.yebeh.2022.108604
24. Fujimoto A, Enoki H, Niimi K, et al. Epilepsy in patients with focal cortical dysplasia may be associated with autism spectrum disorder. *Epilepsy Behav*. 2021;120:107990. doi:10.1016/j.yebeh.2021.107990
25. Brister D, Werner BA, Gideon G, et al. Central nervous system metabolism in autism, epilepsy and developmental delays: a cerebrospinal fluid analysis. *Metabolites*. 2022;12(5):371. doi:10.3390/metabo12050371
26. Frye RE, Casanova MF, Fatemi SH, et al. Neuropathological mechanisms of seizures in autism spectrum disorder. *Front Neurosci*. 2016;10:192. doi:10.3389/fnins.2016.00192
27. Frye RE. Metabolic and mitochondrial disorders associated with epilepsy in children with autism spectrum disorder. *Epilepsy Behav*. 2015;47:147–157. doi:10.1016/j.yebeh.2014.08.134
28. Tuchman R. What is the relationship between autism spectrum disorders and epilepsy? *Semin Pediatr Neurol*. 2017;24(4):292–300. doi:10.1016/j.spen.2017.10.004
29. Tuchman R, Cuccaro M, Alessandri M. Autism and epilepsy: historical perspective. *Brain Dev*. 2010;32(9):709–718. doi:10.1016/j.braindev.2010.04.008
30. Tuchman R, Cuccaro M. Epilepsy and autism: neurodevelopmental perspective. *Curr Neurol Neurosci Rep*. 2011;11(4):428–434. doi:10.1007/s11910-011-0195-x
31. Tuchman R, Rapin I. Epilepsy in autism. *Lancet Neurol*. 2002;1(6):352–358. doi:10.1016/S1474-4422(02)00160-6
32. Spence SJ, Schneider MT. The role of epilepsy and epileptiform EEGs in autism spectrum disorders. *Pediatr Res*. 2009;65(6):599–606. doi:10.1203/PDR.0b013e31819e7168
33. Volkmar FR, Nelson DS. Seizure disorders in autism. *J Am Acad Child Adolesc Psychiatry*. 1990;29(1):127–129. doi:10.1097/00004583-199001000-00020
34. Danielsson S, Gillberg IC, Billstedt E, Gillberg C, Olsson I. Epilepsy in young adults with autism: a prospective population-based follow-up study of 120 individuals diagnosed in childhood. *Epilepsia*. 2005;46(6):918–923. doi:10.1111/j.1528-1167.2005.57504.x
35. Hara H. Autism and epilepsy: a retrospective follow-up study. *Brain Dev*. 2007;29(8):486–490. doi:10.1016/j.braindev.2006.12.012
36. Viscidi EW, Triche EW, Pescosolido MF, et al. Clinical characteristics of children with autism spectrum disorder and co-occurring epilepsy. *PLoS One*. 2013;8(7):e67797. doi:10.1371/journal.pone.0067797
37. Chez MG, Chang M, Krasne V, Coughlan C, Kominsky M, Schwartz A. Frequency of epileptiform EEG abnormalities in a sequential screening of autistic patients with no known clinical epilepsy from 1996 to 2005. *Epilepsy Behav*. 2006;8(1):267–271. doi:10.1016/j.yebeh.2005.11.001

38. Rossi PG, Parmeggiani A, Bach V, Santucci M, Visconti P. EEG features and epilepsy in patients with autism. *Brain Dev.* **1995**;17(3):169–174. doi:10.1016/0387-7604(95)00019-8
39. Tuchman RF, Rapin I. Regression in pervasive developmental disorders: seizures and epileptiform electroencephalogram correlates. *Pediatrics.* **1997**;99(4):560–566. doi:10.1542/peds.99.4.560
40. Berg AT, Plioplys S, Tuchman R. Risk and correlates of autism spectrum disorder in children with epilepsy: a community-based study. *J Child Neurol.* **2011**;26(5):540–547. doi:10.1177/0883073810384869
41. Berg AT, Plioplys S. Epilepsy and autism: is there a special relationship? *Epilepsy Behav.* **2012**;23(3):193–198. doi:10.1016/j.yebeh.2012.01.015
42. Liu X, Sun X, Sun C, et al. Prevalence of epilepsy in autism spectrum disorders: a systematic review and meta-analysis. *Autism.* **2022**;26(1):33–50. doi:10.1177/13623613211045029
43. Cogne B, Ehresmann S, Beauregard-Lacroix E, et al. Missense variants in the histone acetyltransferase complex component gene TRRAP cause autism and syndromic intellectual disability. *Am J Hum Genet.* **2019**;104(3):530–541. doi:10.1016/j.ajhg.2019.01.010
44. Brant B, Stern T, Shekhdem HA, et al. IQSEC2 mutation associated with epilepsy, intellectual disability, and autism results in hyperexcitability of patient-derived neurons and deficient synaptic transmission. *Mol Psychiatry.* **2021**;26(12):7498–7508. doi:10.1038/s41380-021-01281-0
45. Stefanski A, Calle-Lopez Y, Leu C, Perez-Palma E, Pestana-Knight E, Lal D. Clinical sequencing yield in epilepsy, autism spectrum disorder, and intellectual disability: a systematic review and meta-analysis. *Epilepsia.* **2021**;62(1):143–151. doi:10.1111/epi.16755
46. Anand V, Jauhari P. Autism, Epilepsy and Intellectual Disability: a Clinical Conundrum. *Indian J Pediatr.* **2019**;86(10):877–878. doi:10.1007/s12098-019-03045-9
47. Penagarikano O, Abrahams BS, Herman EI, et al. Absence of CNTNAP2 leads to epilepsy, neuronal migration abnormalities, and core autism-related deficits. *Cell.* **2011**;147(1):235–246. doi:10.1016/j.cell.2011.08.040
48. Stamberger H, Nikanorova M, Willemsen MH, et al. STXBP1 encephalopathy: a neurodevelopmental disorder including epilepsy. *Neurology.* **2016**;86(10):954–962. doi:10.1212/WNL.0000000000002457
49. Roston A, Evans D, Gill H, et al. SETD1B-associated neurodevelopmental disorder. *J Med Genet.* **2021**;58(3):196–204. doi:10.1136/jmedgenet-2019-106756
50. Peng J, Zhou Y, Wang K. Multiplex gene and phenotype network to characterize shared genetic pathways of epilepsy and autism. *Sci Rep.* **2021**;11(1):952. doi:10.1038/s41598-020-78654-y
51. Badescu GM, Filfan M, Sandu RE, Surugiu R, Ciobanu O, Popa-Wagner A. Molecular mechanisms underlying neurodevelopmental disorders, ADHD and autism. *Rom J Morphol Embryol.* **2016**;57(2):361–366.
52. Keller R, Basta R, Salerno L, Elia M. Autism, epilepsy, and synaptopathies: a not rare association. *Neurol Sci.* **2017**;38(8):1353–1361. doi:10.1007/s10072-017-2974-x
53. Specchio N, Curatolo P. Developmental and epileptic encephalopathies: what we do and do not know. *Brain.* **2021**;144(1):32–43. doi:10.1093/brain/awaa371
54. Samanta D. PCDH19-related epilepsy syndrome: a comprehensive clinical review. *Pediatr Neurol.* **2020**;105:3–9. doi:10.1016/j.pediatrneurol.2019.10.009

## Neuropsychiatric Disease and Treatment

Dovepress

### Publish your work in this journal

Neuropsychiatric Disease and Treatment is an international, peer-reviewed journal of clinical therapeutics and pharmacology focusing on concise rapid reporting of clinical or pre-clinical studies on a range of neuropsychiatric and neurological disorders. This journal is indexed on PubMed Central, the 'PsycINFO' database and CAS, and is the official journal of The International Neuropsychiatric Association (INA). The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/neuropsychiatric-disease-and-treatment-journal>