Which articles have highly impacted research on genetic generalized epilepsy?

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Background: The purpose of this study was to identify the top-100 cited articles on genetic generalized epilepsy (GGE) published in journals that have made key contributions to the field of epilepsy.

Methods: We searched the Web of Science website produced by Clarivate Analytics for articles on GGE, and sorted them according to the number of citations to identify the top-100 cited articles. We then manually reviewed the contents of the top-100 cited articles, which were designated as “citation classics”.

Results: The top-100 cited articles were published in 27 journals, with the largest proportion appearing in Epilepsia (19 articles). The articles originated from institutions in 17 countries, with 31 articles from the USA. The institution associated with the largest numbers of articles in the field of GGE was the University of Melbourne, Australia (9 articles). Panayiotopoulos C. P. was the first author of three articles, and was listed most frequently in the GGE citation classics. The publication years were concentrated in the 2000s, when 56 articles were published. The most-common study topics were genetics (35 articles) and neuroimaging (17 articles).

Conclusions: This study has identified the top-100 cited articles on GGE. These citation classics represent the landmark articles on GGE, and they provide useful insights into international research leaders and the research trends in the field.

Key words: Publication; Epilepsy, Idiopathic generalized; Retracted publication

INTRODUCTION

The International League Against Epilepsy (ILAE) classification of epilepsies was updated on 2017, and it now classifies epilepsy according to seizure type, epilepsy type, and etiology.1
Generalized epilepsy refers to the seizures originating at some point within or rapidly engaging distributed networks bilaterally, the subcortical or cortical structures, or frequently both of these. A genetic etiology is defined when epilepsy directly results from a known or presumed genetic defect and the seizures are the core symptom of the disorder. The term genetic generalized epilepsy (GGE) is used when a patient has generalized seizures of genetic origin and a well-recognized and established epilepsy syndrome, and includes childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, and epilepsy with tonic-clonic seizures alone. GGE has previously been termed “idiopathic generalized epilepsy,” but the ILAE recommend changing this to “genetic generalized epilepsy” due to “idiopathic” being considered too imprecise. Individuals with GGE account for 20% of all epilepsy cases. GGE occurs mostly in young people, and with a proper diagnosis and management can be controlled with medications in 80% of cases.

The number of times that a previously published work is cited is an indicator of its recognition and impact in an area of investigation. Citation analysis is a systematic approach for identifying scientific studies that have had a high impact in a particular field. Reviewing articles that are cited frequently can provide information about the dominant areas of a discipline, as well as identify growth areas in particular fields. Furthermore, the top-cited articles are often written by recognized experts who can offer novel insight into the future directions of the discipline.

Several recent studies have applied citation analysis or bibliometric analysis to various neurological fields, including stroke, headache disorders, central nervous system inflammatory demyelinating disease, Guillain-Barré syndrome, epilepsy and status epilepticus, and general neurology. However, to the best of our knowledge, no previous study has comprehensively investigated the top-cited articles in the field of GGE. The purpose of this study was to identify the top-100 cited articles (designated as “citation classics”) published in journals on GGE that have made key contributions to the field of epilepsy.

**MATERIALS AND METHODS**

A citation analysis is a bibliometric method that examines the frequency and patterns of citations in articles. We performed a citation analysis in the field of GGE by searching the Web of Science website (https://www.webofknowledge.com) produced by Clarivate Analytics.

In January 2020 we searched for articles published since 1950 with titles that included any of the following expressions: “genetic generalized epilepsy,” “idiopathic generalized epilepsy,” “childhood absence epilepsy,” “juvenile absence epilepsy,” “juvenile myoclonic epilepsy,” “epilepsy with generalized tonic-clonic seizures alone,” or “epilepsy with generalized tonic-clonic seizures on awakening.” The top-100 cited articles were then selected according to the number of citations, and we manually reviewed their contents. We examined various aspects of the articles, such as the number of citations, ranking, authorship, title, year of publication, publishing journal, publication type, and topic categories. The publication types were categorized into original articles, case series, and systematic reviews, and the topics were subtyped as clinical features, epidemiology, pharmacotherapy, laboratory investigations, electrophysiology, neuroimaging, genetics, neuropsychiatry, and general reviews. When the authors of an article had more than one affiliation, the department, institution, and country of origin were defined by either the first or the corresponding affiliation of the first author. Data were presented using descriptive statistics, and no tests of statistical significance were performed. This study did not need to be reviewed by an ethics committee because it performed a bibliometric analysis of existing published studies.

**RESULTS**

We ranked the top-100 cited articles according to the number of citations (Table 1). The most-cited and least-cited articles had been cited 580 and 76 times, respectively. Approximately two-thirds of the articles (64 articles) had been cited more than 100 times.

The top-100 cited articles were published in 27 journals (Table 2), with the largest proportion appearing in *Epilepsia* (19 articles), followed by *Neurology* (15 articles) and *Brain* (10 articles). The top-100 cited articles originated from institutions in 17 countries, with 31 articles from the USA, followed by the UK (14 articles), Germany (11 articles), and...
### Table 1. The top-100 cited articles in the field of GGE

| Rank | Title | First author | Journal | Year | Volume | First page | Last page | Number of citations |
|------|-------|--------------|---------|------|---------|------------|-----------|--------------------|
| 1    | Mutant GABA(A) receptor gamma 2-subunit in childhood absence epilepsy and febrile seizures | Wallace RH | Nature Genetics | 2001 | 28 | 49 | 52 | 580 |
| 2    | Mutation of GABRA1 in an autosomal dominant form of juvenile myoclonic epilepsy | Cossette P | Nature Genetics | 2002 | 31 | 184 | 189 | 403 |
| 3    | Childhood absence epilepsy: genes, channels, neurons and networks | Crunelli V | Nature Reviews Neuroscience | 2002 | 3 | 371 | 382 | 397 |
| 4    | 15q13.3 microdeletions increase risk of idiopathic generalized epilepsy | Helbig I | Nature Genetics | 2009 | 41 | 160 | 162 | 393 |
| 5    | Juvenile myoclonic epilepsy of Janz | Delgadoes-cueta AV | Neurology | 1984 | 34 | 285 | 294 | 310 |
| 6    | Genome-wide copy number variation in epilepsy: novel susceptibility loci in idiopathic generalized and focal epilepsies | Mefford HC | PLOS Genetics | 2010 | 6 | 1 | 9 | 308 |
| 7    | Recurrent microdeletions at 15q11.2 and 16p13.11 predispose to idiopathic generalized epilepsies | de Kovel CG | Brain | 2010 | 133 | 23 | 32 | 293 |
| 8    | Juvenile myoclonic epilepsy (JME) may be linked to the BF and HLA loci on human chromosome 6 | Greenberg DA | American Journal of Medical Genetics | 1988 | 31 | 185 | 192 | 285 |
| 9    | Altered functional-structural coupling of large-scale brain networks in idiopathic generalized epilepsy | Zhang Z | Brain | 2011 | 134 | 2912 | 2928 | 267 |
| 10   | Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy | Glauser TA | New England Journal of Medicine | 2010 | 362 | 790 | 799 | 262 |
| 11   | fMRI activation during spike and wave discharges in idiopathic generalized epilepsy | Aghakhani Y | Brain | 2004 | 127 | 1127 | 1144 | 260 |
| 12   | Mutations in CLCN2 encoding a voltage-gated chloride channel are associated with idiopathic generalized epilepsies (retracted article. See vol 41, pg. 1043, 2009) | Haug K | Nature Genetics | 2003 | 33 | 527 | 532 | 251 |
| 13   | Coding and noncoding variation of the human calcium-channel beta(4)-subunit gene CACNB4 in patients with idiopathic generalized epilepsy and episodic ataxia | Escayg A | American Journal of Medical Genetics | 2000 | 66 | 1531 | 1539 | 248 |
| 14   | Association between genetic variation of CACNA1H and childhood absence epilepsy | Chen YC | Annals of Neurology | 2003 | 54 | 239 | 243 | 246 |
| 15   | Abnormal cerebral structure in juvenile myoclonic epilepsy demonstrated with voxel-based analysis of MRI | Woermann FG | Brain | 1999 | 122 | 2101 | 2107 | 235 |
| 16   | Epilepsy with impulsive petit mal (juvenile myoclonic epilepsy) | Janz D | Acta Neurologica Scandinavica | 1985 | 72 | 449 | 459 | 235 |
| 17   | Mutations in EFHC1 cause juvenile myoclonic epilepsy | Suzuki T | Nature Genetics | 2004 | 36 | 842 | 849 | 229 |
| 18   | Juvenile myoclonic epilepsy: a 5-year prospective study | Panayiotopoulos CP | Epilepsia | 1994 | 35 | 285 | 296 | 225 |
| 19   | Genetic mapping of a major susceptibility locus for juvenile myoclonic epilepsy on chromosome 15q | Elmslie FV | Human Molecular Genetics | 1997 | 6 | 1329 | 1334 | 217 |
| 20   | A splice-site mutation in GABRG2 associated with childhood absence epilepsy and febrile convulsions | Kananura C | Archives of Neurology | 2002 | 59 | 1137 | 1141 | 194 |
### Table 1. Continued

| Rank | Title                                                                 | First author | Journal                          | Year | Volume | First page | Last page | Number of citations |
|------|-----------------------------------------------------------------------|--------------|----------------------------------|------|---------|------------|-----------|---------------------|
| 21   | Localization of idiopathic generalized epilepsy on chromosome 6p in families of juvenile myoclonic epilepsy patients | Durner M     | Neurology                        | 1991 | 41      | 1651       | 1655      | 189                 |
| 22   | Childhood absence epilepsy: behavioral, cognitive, and linguistic comorbidities | Caplan R     | Epilepsia                        | 2008 | 49      | 1838       | 1846      | 185                 |
| 23   | EEG-fMRI of idiopathic and secondarily generalized epilepsies         | Hamandi K    | NeuroImage                       | 2006 | 31      | 1700       | 1710      | 179                 |
| 24   | Interictal mood and personality disorders in temporal lobe epilepsy and juvenile myoclonic epilepsy | Perini G     | Journal of Neurology Neurosurgery and Psychiatry | 1996 | 61      | 601        | 605       | 170                 |
| 25   | Familial and sporadic 15q13.3 microdeletions in idiopathic generalized epilepsy; precedent for disorders with complex inheritance | Dibbens LM   | Human Molecular Genetics         | 2009 | 18      | 3626       | 3631      | 164                 |
| 26   | Confirmation of linkage between juvenile myoclonic epilepsy locus and the HLA region of chromosome 6 | Weisbeder KA | American Journal of Medical Genetics | 1991 | 38      | 32         | 36        | 160                 |
| 27   | Placebo-controlled study of levetiracetam in idiopathic generalized epilepsy | Berkovic SF  | Neurology                        | 2007 | 69      | 1751       | 1760      | 155                 |
| 28   | Levetiracetam for the treatment of idiopathic generalized epilepsy with myoclonic epilepsy | Noachtar S   | Neurology                        | 2008 | 70      | 607        | 616       | 153                 |
| 28   | Epidemiology of idiopathic generalized epilepsies                     | Jallon P     | Epilepsia                        | 2005 | 46      | 10         | 14        | 153                 |
| 28   | Long-term prognosis in two forms of childhood epilepsy: typical absence seizures and epilepsy with rolandic (centrotemporal) EEG foci | Loiseau P    | Annals of Neurology              | 1983 | 13      | 642        | 648       | 153                 |
| 31   | Genome search for susceptibility loci of common idiopathic generalized epilepsies | Sander T     | Human Molecular Genetics         | 2000 | 9       | 1465       | 1472      | 140                 |
| 32   | Reduced cortical inhibition in a mouse model of familial childhood absence epilepsy | Tan HO       | Proceedings of the National Academy of Sciences of the United States of America | 2007 | 104     | 17536      | 17541     | 136                 |
| 33   | Absence and myoclonic status epilepticus precipitated by antiepileptic drugs in idiopathic generalized epilepsy | Thomas P     | Brain                            | 2006 | 129     | 1281       | 1292      | 134                 |
| 34   | MRI volumetry of the thalamus in temporal, extratemporal, and idiopathic generalized epilepsy | Natsume J    | Neurology                        | 2003 | 60      | 1296       | 1300      | 129                 |
| 34   | Some clinical and EEG aspects of benign juvenile myoclonic epilepsy   | Asconape J   | Epilepsia                        | 1984 | 25      | 108        | 114       | 129                 |
| 36   | Functional characterization and neuronal modeling of the effects of childhood absence epilepsy variants of CACNA1H, a T-type calcium channel | Vitko I      | Journal of Neuroscience          | 2005 | 25      | 4844       | 4855      | 128                 |
| 36   | Frontal functions in juvenile myoclonic epilepsy                      | Devinsky O   | Neuropsychiatry Neuropsychology and Behavioral Neurology | 1997 | 10      | 243        | 246       | 128                 |
| 38   | Mapping of spontaneous spike and wave discharges in Wistar rats with genetic generalized nonconvulsive epilepsy | Vergnes M    | Brain Research                   | 1990 | 523     | 87         | 91        | 127                 |

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| Rank | Title                                                                 | First author | Journal                        | Year | Volume | First page | Last page | Number of citations |
|------|----------------------------------------------------------------------|--------------|--------------------------------|------|---------|------------|-----------|--------------------|
| 39   | MR spectroscopy shows reduced frontal lobe concentrations of N-acetyl aspartate in patients with juvenile myoclonic epilepsy | Savic I      | Epilepsia                      | 2000 | 41      | 290        | 296       | 126                |
| 40   | Genome scan of idiopathic generalized epilepsy: evidence for major susceptibility gene and modifying genes influencing the seizure type | Durner M     | Annals of Neurology            | 2001 | 49      | 328        | 335       | 125                |
| 41   | Voltage-gated calcium channels and idiopathic generalized epilepsies  | Khosravani H | Physiological Reviews          | 2006 | 86      | 941        | 966       | 124                |
| 42   | Do carbamazepine and phenytoin aggravate juvenile myoclonic epilepsy? | Genton P     | Neurology                      | 2000 | 55      | 1106       | 1109      | 123                |
| 42   | Long-term prognosis of typical childhood absence epilepsy: remission or progression to juvenile myoclonic epilepsy | Wirrell EC   | Neurology                      | 1996 | 47      | 912        | 918       | 123                |
| 44   | Gating effects of mutations in the Ca(V)3.2 T-type calcium channel associated with childhood absence epilepsy | Khosravani H | Journal of Biological Chemistry | 2004 | 279     | 9681       | 9684      | 121                |
| 45   | Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy: initial monotherapy outcomes at 12 months | Glauser TA   | Epilepsia                      | 2013 | 54      | 141        | 155       | 119                |
| 46   | Primary (idiopathic) generalized epilepsy and underlying mechanisms | Niedermeyer E| Clinical Electroencephalography| 1996 | 27      | 1          | 21        | 118                |
| 47   | Juvenile myoclonic epilepsy 25 years after seizure onset: a population-based study | Camfield CS  | Neurology                      | 2009 | 73      | 1041       | 1045      | 117                |
| 47   | Elevated anxiety and depressive-like behavior in a rat model of genetic generalized epilepsy suggesting common causation | Jones NC     | Experimental Neurology         | 2008 | 209     | 254        | 260       | 117                |
| 49   | Quantitative MRI in patients with idiopathic generalized epilepsy: Evidence of widespread cerebral structural changes | Woermann FG  | Brain                          | 1998 | 121     | 1661       | 1667      | 116                |
| 49   | Juvenile myoclonic epilepsy locus in chromosome 6p21.2-p11: linkage to convulsions and electroencephalography trait | Liu AW       | American Journal of Human Genetics | 1995 | 57     | 368        | 381       | 116                |
| 51   | Extended spectrum of idiopathic generalized epilepsies associated with CACNA1H functional variants | Heron SE     | Annals of Neurology            | 2007 | 62      | 560        | 568       | 115                |
| 52   | Motor system hyperconnectivity in juvenile myoclonic epilepsy: a cognitive functional magnetic resonance imaging study | Vollmar C    | Brain                          | 2011 | 134     | 1710       | 1719      | 114                |
| 52   | Voxel-based morphometry in patients with idiopathic generalized epilepsies | Betting LE  | NeuroImage                     | 2006 | 32      | 498        | 502       | 114                |
| 52   | Mapping of genes predisposing to idiopathic generalized epilepsy | Zara F       | Human Molecular Genetics       | 1995 | 4       | 1201       | 1207      | 114                |
| 55   | BRD2 (RING3) is a probable major susceptibility gene for common juvenile myoclonic epilepsy | Pal DK       | American Journal of Human Genetics | 2003 | 73      | 261        | 270       | 113                |
Table 1. Continued

| Rank | Title                                                                 | First author            | Journal                                         | Year | Volume | First page | Last page | Number of citations |
|------|----------------------------------------------------------------------|-------------------------|-------------------------------------------------|------|---------|------------|-----------|--------------------|
| 56   | From molecules to networks: cortical/subcortical interactions in the pathophysiology of idiopathic generalized epilepsy | Blumenfeld H            | Epilepsia                                       | 2003 | 44      | 7          | 15        | 109                |
| 57   | Cognitive function in idiopathic generalized epilepsy of childhood | Henkin Y                | Developmental Medicine and Child Neurology      | 2005 | 47      | 126        | 132       | 107                |
| 58   | Focal structural changes and cognitive dysfunction in juvenile myoclonic epilepsy | O’Muircheartaigh J     | Neurology                                       | 2011 | 76      | 34         | 40        | 106                |
| 58   | Childhood absence epilepsy and febrile seizures: a family with a GABA(α) receptor mutation | Marini C                | Brain                                           | 2003 | 126     | 230        | 240       | 106                |
| 60   | Hyperglycosylation and reduced GABA currents of mutated GABRB3 polypeptide in remitting childhood absence epilepsy | Tanaka M                | American Journal of Human Genetics              | 2008 | 82      | 1249       | 1261      | 104                |
| 60   | Reproducibility and complications in gene searches: linkage on chromosome 6, heterogeneity, association, and maternal inheritance in juvenile myoclonic epilepsy | Greenberg DA            | American Journal of Human Genetics              | 2000 | 66      | 508        | 516       | 104                |
| 62   | Clinical factors of drug resistance in juvenile myoclonic epilepsy | Gelisse P               | Journal of Neurology Neurosurgery and Psychiatry | 2001 | 70      | 240        | 243       | 102                |
| 63   | Thalamofrontal circuitry and executive dysfunction in recent-onset juvenile myoclonic epilepsy | Pulsipher DT            | Epilepsia                                       | 2009 | 50      | 1210       | 1219      | 100                |
| 63   | Neuropsychological profile of patients with juvenile myoclonic epilepsy: a controlled study of 50 patients | Pascalicchio TF         | Epilepsy and Behavior                           | 2007 | 10      | 263        | 267       | 100                |
| 65   | Genome-wide association analysis of genetic generalized epilepsies implicates susceptibility loci at 1q43, 2p16.1, 2q22.3 and 17q21.32 | Steffens M              | Human Molecular Genetics                        | 2012 | 21      | 5359       | 5372      | 98                 |
| 66   | Childhood absence epilepsy with tonic-clonic seizures and electroencephalogram 3-4-Hz spike and multifocal-slow wave complexes: linkage to chromosome 8q24 | Fong GCY                | American Journal of Human Genetics              | 1998 | 63      | 1117       | 1129      | 97                 |
| 66   | Linkage analysis of idiopathic generalized epilepsy (IGE) and marker loci on chromosome-6p in families of patients with juvenile myoclonic epilepsy: no evidence for an epilepsy locus in the HLA region | Whitehouse WP           | American Journal of Human Genetics              | 1993 | 53      | 652        | 662       | 97                 |
| 66   | Juvenile myoclonic epilepsy: factors of error involved in the diagnosis and treatment | Panayiotopoulos CP     | Epilepsia                                       | 1991 | 32      | 672        | 676       | 97                 |
| 69   | Clinical and EEG asymmetries in juvenile myoclonic epilepsy           | Lancman ME              | Epilepsia                                       | 1994 | 35      | 302        | 306       | 96                 |
| 69   | Juvenile myoclonic epilepsy: long-term response to therapy             | Panayiotopoulos CP     | Epilepsia                                       | 1989 | 30      | 519        | 523       | 96                 |
| 71   | Perampanel for tonic-clonic seizures in idiopathic generalized epilepsy: A randomized trial | Penry JK                | Epilepsia                                       | 2015 | 85      | 950        | 957       | 95                 |
| 71   | Nerve fiber impairment of anterior thalamocortical circuitry in juvenile myoclonic epilepsy | Deppe M                | Neurology                                       | 2008 | 71      | 1981       | 1985      | 95                 |
### Table 1. Continued

| Rank | Title                                                                 | First author | Journal                  | Year | Volume | First page | Last page | Number of citations |
|------|----------------------------------------------------------------------|--------------|--------------------------|------|---------|------------|-----------|---------------------|
| 73   | Regional grey matter abnormalities in juvenile myoclonic epilepsy: a voxel-based morphometry study | Kim JH       | NeuroImage               | 2007 | 37      | 1132       | 1137      | 93                  |
| 73   | The GABA(A) receptor gamma 2 subunit R43Q mutation linked to childhood absence epilepsy and febrile seizures causes retention of alpha 1 beta 2 gamma 2S receptors in the endoplasmic reticulum | Kang JQ      | Journal of Neuroscience   | 2004 | 24      | 8672       | 8677      | 93                  |
| 73   | Magnetic resonance spectroscopy and imaging of the thalamus in idiopathic generalized epilepsy | Bernasconi A | Brain                    | 2003 | 126     | 2447       | 2454      | 93                  |
| 76   | Impaired attention and network connectivity in childhood absence epilepsy | Killory BD   | NeuroImage               | 2011 | 56      | 2209       | 2217      | 92                  |
| 76   | The relationship between treatment with valproate, lamotrigine, and topiramate and the prognosis of the idiopathic generalised epilepsies | Nicolson A   | Journal of Neurology Neurosurgery and Psychiatry | 2004 | 75      | 75         | 79        | 92                  |
| 78   | Thalamo-cortical network pathology in idiopathic generalised epilepsy: insights from MRI-based morphometric correlation analysis | Bernhardt BC | NeuroImage               | 2009 | 46      | 373        | 381       | 91                  |
| 78   | Why does fever trigger febrile seizures? GABA(A) receptor gamma 2 subunit mutations associated with idiopathic generalized epilepsies have temperature-dependent trafficking deficiencies | Kang JQ      | Journal of Neuroscience   | 2006 | 26      | 2590       | 2597      | 91                  |
| 78   | Focal electroencephalographic abnormalities in juvenile myoclonic epilepsy | Alberti V    | Epilepsia                | 1994 | 35      | 297        | 301       | 91                  |
| 78   | Juvenile myoclonic epilepsy: a study in Saudi Arabia                  | Obeid T      | Epilepsia                | 1988 | 29      | 280        | 282       | 91                  |
| 82   | Pretreatment cognitive deficits and treatment effects on attention in childhood absence epilepsy | Masur D      | Neurology                | 2013 | 81      | 1572       | 1580      | 88                  |
| 82   | Electroclinical features of absence seizures in childhood absence epilepsy | Sadleir LG   | Neurology                | 2006 | 67      | 413        | 418       | 88                  |
| 82   | Genetic architecture of idiopathic generalized epilepsy: clinical genetic analysis of 55 multiplex families | Marini C     | Epilepsia                | 2004 | 45      | 467        | 478       | 88                  |
| 82   | Juvenile myoclonic epilepsy. A review                                | Grunewald RA | Archives of Neurology    | 1993 | 50      | 594        | 598       | 88                  |
| 86   | Juvenile myoclonic epilepsy subsyndromes: family studies and long-term follow-up | Martinez-Juarez E | Brain                   | 2006 | 129     | 1269       | 1280      | 86                  |
| 87   | Proton MRS reveals frontal lobe metabolite abnormalities in idiopathic generalized epilepsy | Simister RJ  | Neurology                | 2003 | 61      | 897        | 902       | 85                  |
| 88   | Exacerbation of juvenile myoclonic epilepsy with lamotrigine          | Biraben A    | Neurology                | 2000 | 55      | 1758       | 1758      | 84                  |
| 89   | Multi-site voxel-based morphometry: methods and a feasibility demonstration with childhood absence epilepsy | Pardoe H     | NeuroImage               | 2008 | 42      | 611        | 616       | 83                  |
| 89   | Delayed diagnosis of juvenile myoclonic epilepsy                      | Grunewald RA | Journal of Neurology Neurosurgery and Psychiatry | 1992 | 55      | 497        | 499       | 83                  |
Australia (11 articles) (Table 3). The 100 articles comprised 40 originating from North America (the USA and Canada), 38 from Europe (the UK, Germany, France, Italy, Netherlands, Switzerland, and Sweden), 12 from Oceania (Australia and New Zealand), 8 from Asia (Saudi Arabia, China, South Korea, Israel, and Japan), and 2 from South America (Brazil).

Tables 4 and 5 list the top-ranked institutions and authors for articles published in the field of GGE, respectively. The institution associated with the largest number of articles was the University of Melbourne, Australia (nine articles), followed by the University of California in Los Angeles, USA (seven articles), and University College London, UK (six articles). Panayiotopoulos C. P. was the first author of three articles, and was listed most frequently in the GGE citation classics.

The publication years were mostly concentrated in the 2000s, when 56 articles were published. Twenty-three articles were published in the 1990s, followed by 13 articles in the 2010s, and 8 in the 1980s. The earliest recorded article was published in 1983 and the most-recent article was published in 2015.

Regarding the types of articles, 95 were original articles while 5 were systematic review articles. The subjects of the articles comprised 22 on childhood absence epilepsy, 38 on juvenile myoclonic epilepsy, and 40 on GGE as a whole. The topic subtypes of the articles comprised 35 on genetics, 17 on neuroimaging, 13 on pharmacotherapy, 13 on electrophysiology, 8 on neuropsychiatry, 5 on epidemiology, 5 on general reviews, and 4 on clinical features (Fig. 1).
Table 2. Journals containing at least 2 of the top-100 cited articles in the field of GGE

| Rank | Journal                                | Number of articles |
|------|----------------------------------------|--------------------|
| 1    | Epilepsia                              | 19                 |
| 2    | Neurology                              | 15                 |
| 3    | Brain                                  | 10                 |
| 4    | American Journal of Human Genetics     | 6                  |
| 4    | Annals of Neurology                    | 6                  |
| 4    | NeuroImage                             | 6                  |
| 7    | Human Molecular Genetics               | 5                  |
| 7    | Nature Genetics                        | 5                  |
| 9    | Journal of Neurology Neurosurgery and  | 4                  |
|      | Psychiatry                             |                    |
| 9    | Journal of Neuroscience                | 4                  |
| 11   | American Journal of Medical Genetics   | 3                  |
| 12   | Archives of Neurology                  | 2                  |

GGE, genetic generalized epilepsy.

Table 3. Countries of origin of the top-100 cited articles in the field of GGE

| Rank | Country     | Number of articles |
|------|-------------|--------------------|
| 1    | USA         | 31                 |
| 2    | UK          | 14                 |
| 3    | Germany     | 11                 |
| 3    | Australia   | 11                 |
| 5    | France      | 7                  |
| 6    | Canada      | 9                  |
| 7    | Saudi Arabia| 3                  |
| 8    | Italy       | 2                  |
| 8    | Brazil      | 2                  |
| 8    | Netherlands | 2                  |
| 8    | China       | 2                  |
| 12   | Switzerland | 1                  |
| 12   | New Zealand | 1                  |
| 12   | South Korea | 1                  |
| 12   | Sweden      | 1                  |
| 12   | Israel      | 1                  |
| 12   | Japan       | 1                  |

GGE, genetic generalized epilepsy.

Table 4. Originating institutions with at least 2 of the top-100 cited articles in the field of GGE

| Rank | Institution                  | Number of articles |
|------|------------------------------|--------------------|
| 1    | University of Melbourne      | 9                  |
| 2    | University of California at Los Angeles | 7          |
| 3    | University College London   | 6                  |
| 4    | University of McGill        | 5                  |
| 5    | University of New York      | 4                  |
| 6    | University of King Khalid   | 3                  |
| 6    | University of Humboldt      | 3                  |
| 6    | King’s College London       | 3                  |
| 9    | University of Saint Paul    | 2                  |
| 9    | University of Calgary       | 2                  |
| 9    | University of Cincinnati    | 2                  |
| 9    | University of Virginia      | 2                  |
| 9    | University of Wake Forest   | 2                  |
| 9    | University of Vanderbilt    | 2                  |

GGE, genetic generalized epilepsy.

Table 5. First authors with at least 2 of the top-100 cited articles in the field of GGE

| Rank | First author                | Number of articles |
|------|-----------------------------|--------------------|
| 1    | Panayiotopoulos CP          | 3                  |
| 2    | Dumer M                     | 2                  |
| 2    | Gelisse P                   | 2                  |
| 2    | Glauser TA                  | 2                  |
| 2    | Greengerg DA                | 2                  |
| 2    | Grunewald RA                | 2                  |
| 2    | Janz D                      | 2                  |
| 2    | Kang JQ                     | 2                  |
| 2    | Khojasteh H                 | 2                  |
| 2    | Marini C                    | 2                  |
| 2    | Vitko I                     | 2                  |
| 2    | Woernmann FG                | 2                  |

GGE, genetic generalized epilepsy.
DISCUSSION

This study identified and characterized the top-100 cited articles in the field of GGE. These citation classics may enable the identification of seminal advances in GGE and provide a historical perspective on the scientific progress of the field of epilepsy.

The top-ranked article had a title of “Mutant gamma-aminobutyric acid receptor subtype A (GABA)(A) receptor gamma2-subunit in childhood absence epilepsy and febrile seizure,” its first author was Wallace, it was published in Nature Genetics, and it has been cited 580 times. The authors found a mutation in a gene encoding a GABA(A) receptor subunit in a large family with epilepsy, and the two main phenotypes were childhood absence epilepsy and febrile seizures. The second-ranked article was also published in Nature Genetics, and reported that an Ala322Asp mutation in the GABRA1 gene that encodes the alpha1 subunit of GABA(A) was found in affected individuals of a large French Canadian family with juvenile myoclonic epilepsy. Both of these articles reported on genetic studies. The third-ranked article was a review article on childhood absence epilepsy by Crunelli V that appeared in Nature Reviews Neuroscience.

Citation analysis can identify emerging topics and the relevant trends in a particular field. The present study found that genetics was the most-common topic in the top-100 cited articles on GGE, followed by neuroimaging. Genetics and neuroimaging were the most-common topics for each decade from the 1990s to the 2010s. Since genetic epilepsy directly results from a known or presumed genetic mutation whose core symptom is seizures, it is not surprising that genetics was the most-common topic in the field of GGE. In addition, due to the introduction and advent of next-generation sequencing and genome-wide association studies, the development and application of high-throughput genetic testing has resulted in the discovery of hundreds of epilepsy-associated genes. Thus, we can assume that the number of articles on genetics will increase in the future.

The application of neuroimaging in epilepsy has also increased rapidly and evolved thanks to the substantial advancements in image-analysis techniques in recent decades. Early studies involving brain magnetic resonance
imaging (MRI) did not reveal abnormalities in patients with GGE. However, more-recent voxel-based morphometry and structural/functional connectivity studies based on diffusion-tensor imaging and functional MRI have revealed abnormal morphologies and networks of the brain in GGE.\textsuperscript{17-20} These developments are associated with increasing numbers of related articles being published in scientific journals that could have a great impact on GGE.

The topics addressed in the citation classics varied among the decades, and we discovered some interesting trends in the topics over time. We noted that the most-cited articles on GGE were published during the 2000s. This contrasts with most bibliometric analyses on other topics demonstrating that the most-cited articles are published during the 1990s.\textsuperscript{7,11,21} Thus, we can infer that there have been considerable developments in research on GGE in recent years, which might be attributable to recent developments in research techniques such as genetics and neuroimaging in this field.

We also found that the most-cited articles were published in 	extit{Epilepsia,} which is the official publication of the ILAE. This is perhaps related to the epilepsy-specific journals with high impact factors being focused on GGE. Moreover, we found that about one-third of the 100 top-cited articles originated from institutions in the USA, reflecting the huge influence of the USA in health science research in general, which is probably due to both the large size of the American scientific community and its high research budget.\textsuperscript{22-25} However, a citation analysis in the field of neurology found that from half to two-thirds of the articles originated from the USA. In addition, we found that 20 articles reported on studies performed in Asia and Oceania (12 and 8 articles, respectively), which was a prominently higher ratio than in other citation analyses. We can assume that this finding is associated with the most-cited articles on GGE being published during the 2000s. Recently there have been increasing numbers of articles originating from Asia and Oceania in the field of neurology research, especially from China.\textsuperscript{26}

This study is the first to perform a citation analysis of GGE. The findings could be used to identify recent advances in the field of GGE, provide a historical perspective of its scientific progress, and be used for education purposes. However, there were several inherent limitations in the research methodology. There is ongoing debate about the value of citation rates. A naïve argument is that an article of greater value will be cited more often.\textsuperscript{27} However, the number of citations could be influenced by factors other than the quality and originality of the reported research, such as the characteristics of the involved researchers, institutions, and funding agencies.\textsuperscript{21} Furthermore, analyzing the total number of citations favors older articles.\textsuperscript{28} The citation frequency of a scientific article is typically associated with a time delay of 1-2 years after its publication.\textsuperscript{29} This interval will bias evaluations of the rank and significance of recent publications. However, the use of citation rates is still widely accepted as the best method for judging the impact of the articles, with the impact factor considered indicative of the quality and rank of a given journal in its specific field of interest.\textsuperscript{30}

This study has identified the top-100 cited articles on GGE. The identified citation classics represent landmark articles on GGE, and they provide useful insights into international research leaders and the research trends in the field.

**Author Contributions**

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**Conflict of Interest**

None of the authors has any conflict of interest to disclose.

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