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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]

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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.[1] 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.[1] 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.[1,2] 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.[1] Individuals with GGE account for 20% of all epilepsy cases.[3] GGE occurs mostly in young people, and with a proper diagnosis and management can be controlled with medications in 80% of cases.[3]

The number of times that a previously published work is cited is an indicator of its recognition and impact in an area of investigation.[4-6] 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.[4-6]

Several recent studies have applied citation analysis or bibliometric analysis to various neurological fields, including stroke,[7] headache disorders,[8] central nervous system inflammatory demyelinating disease,[9] Guillain-Barré syndrome,[10] epilepsy and status epilepticus,[11] and general neurology.[12] 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	Delgadoescueta 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
15	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

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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 GI	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	Weissbecker 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 seizures	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 generalised 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

Table 1. Continued

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(A) 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 multispike-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	Penry JK	Epilepsia	1989	30	S19	S23	96
71	Perampanel for tonic-clonic seizures in idiopathic generalized epilepsy. A randomized trial	French JA	Neurology	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 generalized 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	Aliberti 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 IE	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

Table 1. Continued

Rank	Title	First author	Journal	Year	Volume	First page	Last page	Number of citations
91	The idiopathic generalized epilepsies of adolescence with childhood and juvenile age of onset	Janz D	Epilepsia	1997	38	4	11	82
92	Glucose transporter 1 deficiency in the idiopathic generalized epilepsies	Arsov T	Annals of Neurology	2012	72	807	815	81
93	Idiopathic generalized epilepsies recognized by the International League Against Epilepsy	Nordli DR	Epilepsia	2005	46	48	56	80
94	Genome arrays for the detection of copy number variations in idiopathic mental retardation, idiopathic generalized epilepsy and neuropsychiatric disorders: lessons for diagnostic workflow and research	Hochstenbach R	Cytogenetic and Genome Research	2011	135	174	202	79
94	The I-II loop controls plasma membrane expression and gating of Ca(v)3.2 T-type Ca2+ channels: a paradigm for childhood absence epilepsy mutations	Vitko I	Journal of Neuroscience	2007	27	322	330	79
96	Sleep microstructure and EEG epileptiform activity in patients with juvenile myoclonic epilepsy	Gigli GL	Epilepsia	1992	33	799	804	78
96	Juvenile myoclonic epilepsy: an autosomal recessive disease	Panayiotopoulos CP	Annals of Neurology	1989	25	440	443	78
98	Thalamic atrophy in childhood absence epilepsy	Chan CH	Epilepsia	2006	47	399	405	76
98	Worsening of seizures by oxcarbazepine in juvenile idiopathic generalized epilepsies	Gelisse P	Epilepsia	2004	45	1282	1286	76
98	Tiagabine-induced absence status in idiopathic generalized epilepsy	Knake S	Seizure - European Journal of Epilepsy	1999	8	314	317	76

GGE, genetic generalized epilepsy; GABA, gamma-Aminobutyric acid; JME, Juvenile myoclonic epilepsy; Bf, factor B; HLA, human leukocyte antigen; IGE, idiopathic generalized epilepsy; fMRI, functional magnetic resonance imaging; CLCN2, chloride voltage-gated channel 2; CACNB4, calcium voltage-gated channel auxiliary subunit beta 4; EEFHC1, EF-hand domain containing 1; GABRG2, gamma-Aminobutyric Acid type A receptor subunit gamma 2; EEG, electroencephalography; MRI, magnetic resonance imaging; RING3, Really Interesting New Gene 3; MRS, MR spectroscopy.

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 Psychiatry	4
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	Khosravani H	2
2	Marini C	2
2	Vitko I	2
2	Woermann FG	2

GGE, genetic generalized epilepsy.

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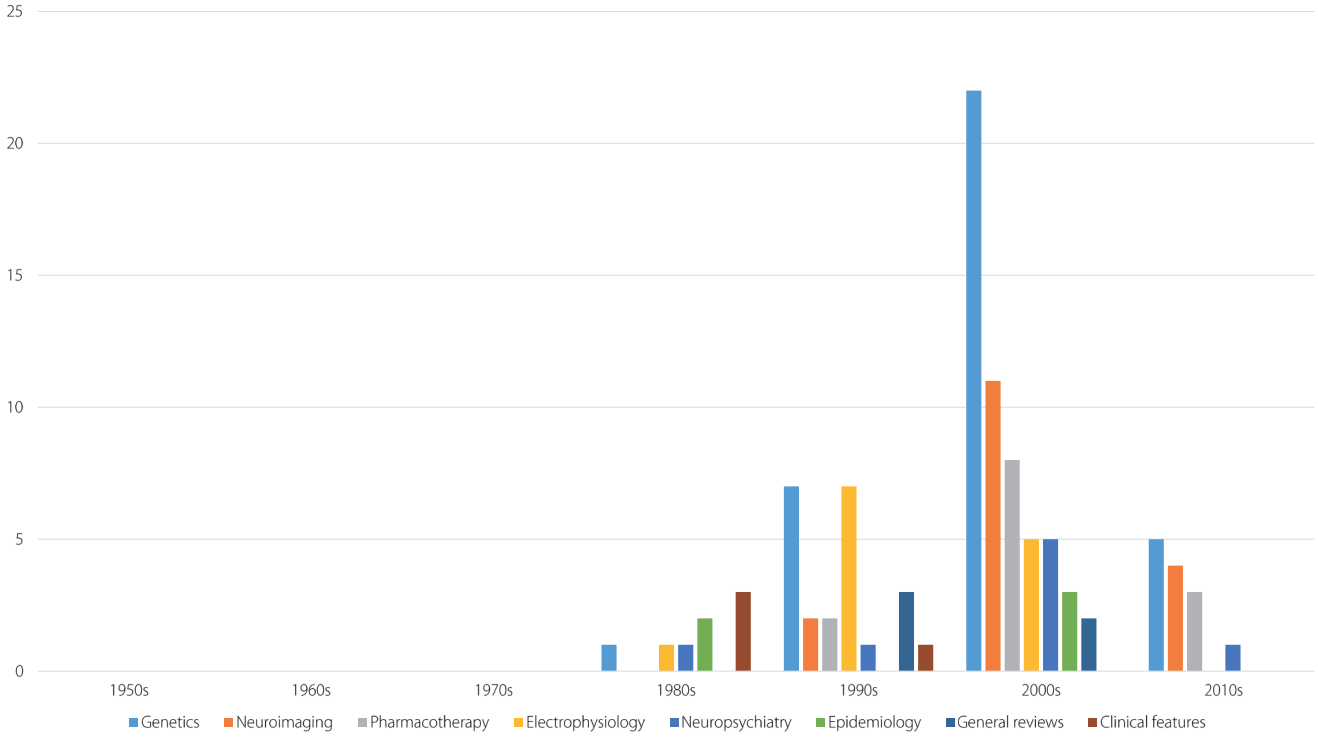

Fig. 1. Number of publications with the top-100 cited articles in the field of genetic generalized epilepsy.

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.[13] 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.[13] 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.[14] 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.[5,6] 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,[1] 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.[15] 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.[16] 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.[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.[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 *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.[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.[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.[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.[21] Furthermore, analyzing the total number of citations favors older articles.[28] The citation frequency of a scientific article is typically associated with a time delay of 1-2 years after its publication.[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.[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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