Review article:

Bibliometric analysis and network visualization on Tuberous Sclerosis Complex

Ninie Nadia Zulkipli[1], Idris Long[2], Habibah A Wahab[3], Teguh Haryo Sasongko[4], Asma Hayati Ahmad[5], Zahiruddin Othman[6], Aidi Ahmi[7], Rahimah Zakaria[8]

Abstract:

Background: Tuberous sclerosis complex (TSC) is a rare autosomal dominant multisystem disease resulting from hyperactivation of the mammalian target of rapamycin (mTOR) signaling pathway. This study aimed to measure the quantitative impact of publications in TSC. ***Materials and methods****:* We analysed TSC literature obtained from the Scopus database using Bibliometrix R Package and VOSviewer software. Annual publication trends, most productive and collaborative authors/institutions/countries, most cited articles, most popular journals and author's keywords were presented using standard bibliometric indicators. ***Results and discussion****:* A total of 5375 documents on TSC were published from 1960 to December 2020, with an increasing trend. The three primary contributing writers were Curatolo P, Kwiatkowski DJ, and Thiele EA, with the United States and its institutions being the largest contributor. The research identified two of the most referenced papers as TSC's seminal pieces. The top journals that published TSC research were medical journals, namely *Journal of Child Neurology, Epilepsia*, and *Pediatric Neurology*. mTOR inhibitor, everolimus, sirolimus, mTORC1, mTOR pathway, autophagy, inflammation, infant, intellectual disability, white matter, TSC-associated neuropsychiatric disorders, TOSCA and quality of life were relatively newer author's keywords and may indicate the future research hotspots in TSC research. ***Conclusion:*** Over the last few decades, TSC research has grown in importance, particularly in the field of clinical medicine. Therapeutic components targeting TSC-related pathways, the utilisation of TSC as disease models and long-term safety studies will be future research areas.

Keywords: TSC, mTOR; Scopus; bibliometrix R; VOSviewer

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Introduction:

Tuberous sclerosis complex (TSC) is an autosomal dominant multisystem disease characterised by tumorigenesis, neurologic and behavioural impairments[1]. It affects both men and women, as well as all ethnic groups[2]. It is a rare disease and affects one

1. Ninie Nadia Zulkipli, School of Biomedicine, Faculty of Health Sciences, Universiti Sultan Zainal Abidin, 21300 Kuala Nerus, Terengganu, Malaysia. Email: nadiazulkipli93@yahoo.com
2. Idris Long, School of Health Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Malaysia. Email: idriskk@usm.my
3. Habibah A Wahab, School of Pharmaceutical Sciences, Universiti Sains Malaysia, 11800 Pulau Pinang, Malaysia. Email: habibahw@usm.my
4. Teguh Haryo Sasongko, School of Medicine, and Institute for Research, Development and Innovation, International Medical University, 57000 Kuala Lumpur, Malaysia. Email: tghsasongko@gmail.com,
5. Asma Hayati Ahmad, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Malaysia. Email: asmakck@usm.my
6. Zahiruddin Othman, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Malaysia. Email: zahirkb@usm.my
7. Aidi Ahmi, Tunku Puteri Intan Safinaz School of Accountancy, Universiti Utara Malaysia 06010 UUM Sintok, Kedah, Malaysia. Email: aidi@uum.edu.my
8. Rahimah Zakaria, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Malaysia. Email: rahimah@usm.my

Correspondence: Asma Hayati Ahmad, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Malaysia. Email: asmakck@usm.my

in every 6000 to 10,000 newborns annually[3]. *TSC1* is located on the long arm of chromosome 9 (9q34), while *TSC2* is on the short arm of chromosome 16. (16p13.3). A mutation in *TSC1* or *TSC2*, which encode the proteins hamartin and tuberin, respectively[4], is the most prevalent cause of TSC[5].

TSC1 mutations are usually nonsense or frameshift mutations that cause protein truncation, whereas *TSC2* mutations are more likely to be missense mutations, substantial deletions, or rearrangements[6]. *TSC1* and *TSC2* mutations have been discovered in 10–20 per cent and 70–90 per cent of TSC patients, respectively[7,8]. However, no mutation is found in 10-15% of individuals with a clinical diagnosis of TSC[98]. These individuals are thought to have somatic mosaicism, which may explain their symptoms. A third candidate gene could also be involved, or the disease could be caused by an intronic mutation[9]. The research on the genetic basis of TSC is still being studied in order to better understand its clinical symptoms.

Pathogenic *TSC2* mutations are associated with a more severe clinical phenotype than mosaic *TSC2* or *TSC1* variations[10-12]. Both *TSC1* and *TSC2* are tumour suppressor genes that, when turned off, cause uncontrolled cell cycle progression and the spread of hamartomas throughout the body[4,13]. The majority of TSC patients have mutations in *TSC1* and *TSC2*, leading to hyperactivation of the mammalian target of rapamycin (mTOR) signalling pathway and abnormalities in a variety of cell functions[14]. Because TSC protein products of *TSC,* hamartin and tuberin, act within the same intracellular pathway, their mutations induce almost similar disease phenotypes[15]. While TSC can affect any organ system in the body, certain organs such as the heart, kidneys and eyes are more vulnerable than others[1].

Bibliometric studies on the mTOR signalling pathway in liver and kidney diseases have recently been published[16,17]. There have, however, been no published bibliometric or visualization studies on TSC research. The purpose of this research is to conduct an in-depth bibliometric analysis and network visualization on TSC literature. The following research questions (RQs) will be addressed: RQ1: What are the general descriptions regarding

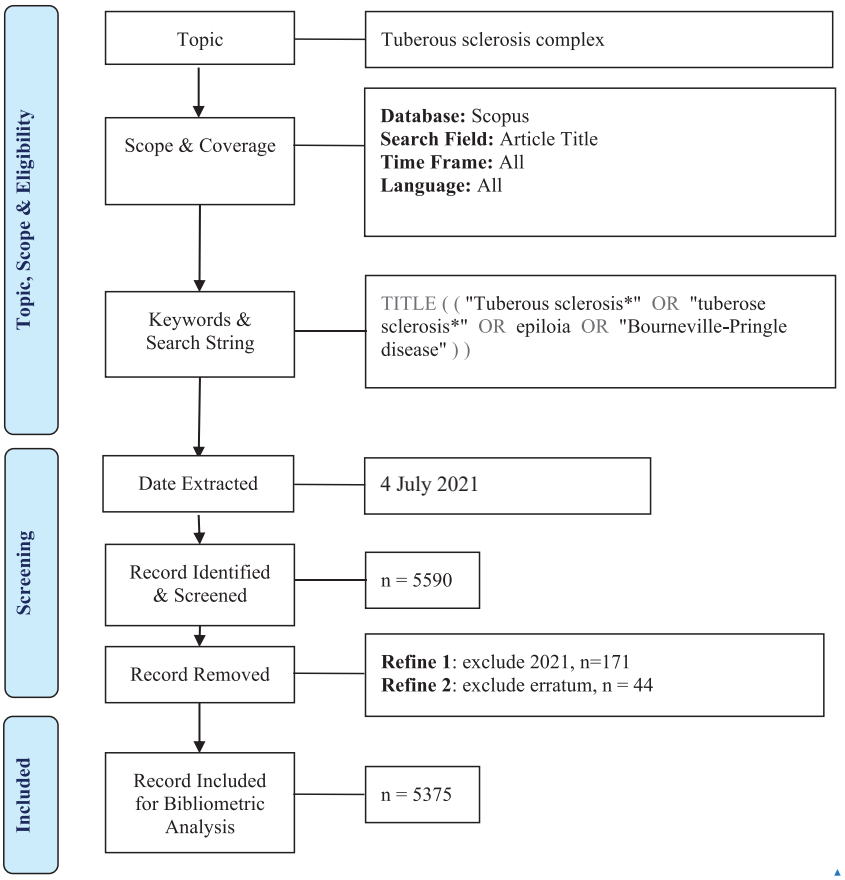

Figure 1 The search strategy used in this study

the TSC documents?, RQ2: What is the annual publication trend in TSC research?, RQ3: Who are the most productive and collaborative authors in TSC research?, RQ4: Which countries/institutions are the most productive and collaborative in TSC research?, RQ5: What are the most cited articles in TSC research?, RQ6: What are the journals that published the most TSC research?, RQ7: What are the most frequently used keywords in TSC research?, and RQ8: What are the main themes of TSC research and their evolution?

Material and Methods:

Search Strategy and Data Extraction:

A literature search for all the published TSC documents was conducted on 4 July 2021, using the Scopus database. The following search terms in the article title were used: ("Tuberous sclerosis*" OR "tuberose sclerosis*" OR epiloia OR "Bourneville-Pringle disease"). A total of 5590 documents were identified throughout the search, however, 215 were excluded including 2021 documents (n = 171) and erratum (n=44). The summary of the search strategy is illustrated in Figure 1. Citation information, bibliographical information, abstract, keywords and other information including references were extracted from each publication and exported in comma-separated values (csv) file format for further analysis.

Data Analysis and Visualization:

The following bibliometric and network analyses were conducted to answer the RQs mentioned earlier. The bibliometric analysis was conducted using R software version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org) via the Bibliometrix R package[18]. While the network analysis was conducted using VOSviewer software (version 1.6.15).

Results:

General description related to TSC documents:

Table 1 presents the main information regarding the retrieved documents. A total of 5375 documents from 1830 sources were retrieved from the Scopus database. All these documents used 11732 keywords plus and 3633 author keywords. The TSC literature we used covered the years 1906 through 2020. These documents were written by 17102 different authors, with just 526 (3.08%) having a single author. The TSC documents have a high collaboration index and only 659 out of 5375 documents (12.26%) were written by a single author. The authors per document were 3.18, which means, on average, more than three authors have written one document.

Table 1 Main information regarding TSC documents

Description	Results
Documents	5375
Sources	1830
Keywords Plus	11732
Author's Keywords	3633
Period	1906:2020
Average citations per document	21.21
Authors	17102
Author Appearances	26385
Authors of single-authored documents	526
Authors of multi-authored documents	16576
Single-authored documents	659
Authors per Document	3.18
Co-Authors per Documents	4.91
Collaboration Index	3.51

Note: Authors per Document index is calculated as the ratio between the total number of authors and the total number of documents. The Co-Authors per Documents index is calculated as the ratio between the author appearances and the total number of documents.

The majority of the retrieved publications were original articles (n = 4328, 80.5%). Other documents were review articles (n = 371, 6.9%), letters (n = 300, 5.6%), notes (n = 134, 2.5%), conference papers (n = 114, 2.1%), and book chapters (n = 60, 1.1%). To a much lesser extent (n = 68, each ≤ 1%), editorials, short surveys and books were also published. Regarding the subject areas, the majority of the publications were classified under medicine (n = 4861, 70.2%), although several documents were published in Neuroscience (n = 818, 11.8%), and Biochemistry, genetics and molecular (n = 688, 9.9%). To a much lesser extent (n = 554, each <2%), the publications were under Arts and humanities, Multidisciplinary, Dentistry, Psychology, and others.

Annual Publication Trends:

Figure 2 depicts the annual publication trends on TSC research. The first publication on TSC dates back to 1906 and the number of publications was small at the start but increased to 2-digit beginning in 1954 and reached 3-digit in 1991.

Table 2 Details of most productive authors

Author	No. of articles	h-index	g-index	m-index	TC	Publication year (no. of articles)
Curatolo P	103	37	79	0.925	6371	1982, 1985, 1987 (2), 1990, 1991 (3), 1993, 1994, 1995, 1996, 1997, 1998, 1999, 2000, 2001 (2), 2002, 2003 (2), 2004 (3), 2005, 2006 (3), 2007, 2008 (4), 2009 (5), 2010 (7), 2011 (3), 2012 (2), 2013 (7), 2014 (3), 2015 (5), 2016 (7), 2017 (4), 2018 (10), 2019 (6), 2020 (11)
Kwiatkowski DJ	90	45	90	1.452	11061	1991, 1992 (2), 1993, 1994 (2), 1995 (5), 1996 (2), 1997 (3), 1998 (2), 1999 (2), 2000, 2001 (3), 2002 (2), 2003 (3), 2004 (3), 2005 (4), 2006, 2007 (3), 2008 (4), 2009 (5), 2010 (7), 2011 (3), 2012 (3), 2013 (3), 2014 (6), 2015 (2), 2016 (5), 2017 (3), 2018, 2019 (4), 2020 (4)
Thiele EA	81	29	62	1.611	3968	2004 (4), 2005 (4), 2006 (3), 2007 (5), 2008 (3), 2009 (7), 2010 (7), 2011 (6), 2012 (7), 2013 (11), 2014 (7), 2015 (4), 2016 (5), 2017 (2), 2018, 2019 (2), 2020 (3)
Sahin M	76	30	69	2	4764	2007 (2), 2008 (5), 2009 (3), 2010, 2011 (3), 2012 (2), 2013 (7), 2014 (3), 2015 (6), 2016 (7), 2017 (7), 2018 (7), 2019 (12), 2020 (11)
Franz DN	68	32	68	1.333	7417	1998, 2000, 2001 (3), 2002 (2), 2004 (3), 2006 (3), 2007 (3), 2008 (2), 2009 (2), 2010 (2), 2011 (4), 2012 (2), 2013 (12), 2014 (3), 2015, 2016 (4), 2017 (4), 2018 (9), 2019 (5), 2020 (2)
Henske EP	59	36	59	1.333	8168	1995 (3), 1996 (2), 1997 (3), 1998 (5), 1999, 2000 (3), 2001 (3), 2002 (3), 2003 (2), 2004 (2), 2005 (3), 2006 (3), 2007, 2009, 2010 (3), 2011 (2), 2012, 2013 (3), 2014 (3), 2015, 2016 (2), 2017 (2), 2018 (3), 2019 (3), 2020
Jozwiak S	58	25	58	0.781	4274	1990 (2), 1995 (3), 1997, 1998 (2), 1999, 2004 (2), 2005, 2006 (3), 2007 (2), 2008 (3), 2009 (2), 2010, 2011, 2013 (2), 2014 (5), 2015 (3), 2016 (3), 2017 (4), 2018 (2), 2019 (7), 2020 (8)
De Vries PJ	56	28	56	1.273	3704	2000, 2001, 2004, 2006, 2007 (5), 2008 (2), 2009 (3), 2010 (2), 2011 (3), 2013 (2), 2014 (3), 2015 (8), 2016 (4), 2017 (4), 2018 (4), 2019 (8), 2020 (4)
Kotulska K	55	25	44	1.389	2034	2004 (2), 2005, 2006 (3), 2007 (5), 2008 (2), 2009 (3), 2010 (2), 2011 (3), 2012 (2), 2013 (2), 2014 (5), 2015 (3), 2016 (9), 2017 (4), 2018 (3), 2019, 2020 (5)
Northrup H	52	25	51	0.714	4053	1987, 1991 (2), 1992 (3), 1993, 1995, 1997 (3), 1998 (3), 1999 (2), 2000, 2001, 2004, 2006, 2007, 200 8(2), 2010, 2011, 2012, 2013 (3), 2016, 2017 (3), 2018 (4), 2019 (6), 2020 (9)

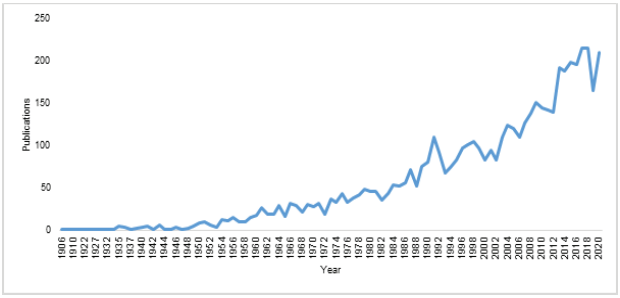

Figure 2 Annual publication trends

Most productive authors:

Table 2 presents the top 10 most productive authors. Curatolo P, Kwiatkowski DJ and Thiele FA were the three major contributing authors based on the number of articles each had written. Curatolo P was also the top author of publication over time; he started in 1982 and was actively publishing until 2020. This was followed by Northrup H (1987), Jozwiak S (1990), Kwiatkowski DJ (1991) and Henske EP (1995).

Figure 3 shows the network visualization map of author co-authorship obtained from VOSviewer. Each node represents an author, the node tag is the author's last name, and the node size is the number of articles published. There were 42 out of 16705 authors who had at least 20 papers and 100 citations. A total of 8 clusters was identified and most of the prolific authors shared the same cluster. For example, Curatolo P, Jozwiak S and Kotulska K belong to the blue cluster, Kwiatkowski DJ and Thiele EA belong to the brown cluster, Sahin M and Northrup H belong to the red cluster, and Franz DN and De Vries PJ belong to the purple cluster.

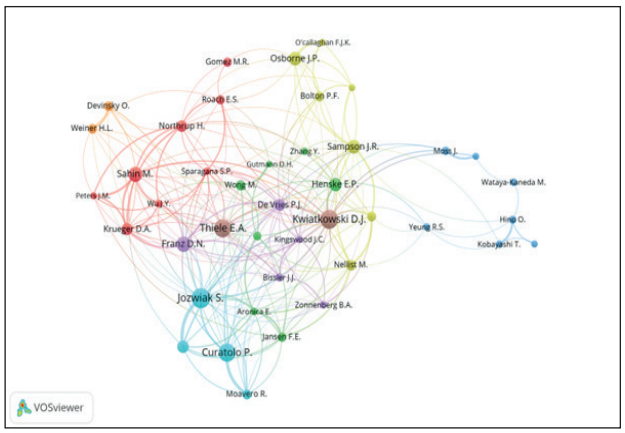

Figure 3 Co-authorship authors network

Most productive countries:

Table 3 presents the most productive countries based on the number of published documents. The United States was the most productive country publishing TSC research. It contributed almost a quarter of the scientific production, followed by Japan, the United Kingdom and Italy. Regarding intra-country collaboration, the United States also had the most documents published by authors from the same country (n = 1060), followed by Japan (n = 299), United Kingdom (n = 250), Italy (n = 216), and China (n = 206). However, in terms of inter-country collaboration, the United Kingdom and Germany (MCP ratio = 0.17, total documents = 51 and 23, respectively) came out tops, followed by United States and Italy (MCP ratio = 0.13, total documents = 163 and 32, respectively).

Table 3 Most productive countries

Country	No of documents	% of documents[a]	SCP	MCP	MCP Ratio[b]
USA	1223	22.8%	1060	163	0.13
Japan	310	5.8%	299	11	0.04
United Kingdom	301	5.6%	250	51	0.17
Italy	248	4.6%	216	32	0.13
China	223	4.1%	206	17	0.08
India	142	2.6%	139	3	0.02
Germany	139	2.6%	116	23	0.17
France	116	2.2%	103	13	0.11
Spain	109	2.0%	101	8	0.07
Turkey	92	1.7%	88	4	0.04

Notes: SCP, single country publications; MCP, multiple country publications. [a]Percentage calculated out of the retrieved 5375 documents. [b]Multiple country publication ratio was calculated as MCP divided by the total of published documents per country.

The network visualization map of country co-authorship produced by VOSviewer is shown in Figure 4. Each node represents a country and the node size is the number of articles published by the country. There were 27 out of 220 countries with at least 20 papers and 100 citations. A total of 4 clusters was identified and most of the productive countries shared the same cluster. For example, United States and Italy belong to the green cluster, Japan, China, India, France and Spain belong to the red cluster, and Germany and Turkey belong to the blue cluster.

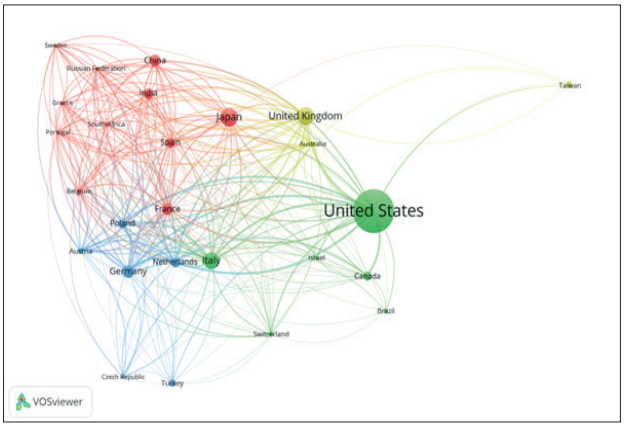

Figure 4 Co-authorship countries network

Most productive institutions:

Table 4 presents the top 10 most productive research institutions in publishing on TSC. Of all the 5375 retrieved documents, these institutions published 1802 references (33.5%), of which 1332 (24.5%) were from institutions located in the United States. The rest of the research findings were published by institutions in Poland (n = 147), United Kingdom (n=134), Netherlands (n=100) and China (n = 89), accounting for 8.7% of the total published references.

Table 4 Most productive institutions

Institutions	Country	No of documents	% of documents[a]
Harvard Medical School	USA	480	8.9
Massachusetts General Hospital	USA	246	4.6
University of California Cincinnati Children's Hospital Medical Center	USA	220	4.1
Children's Memorial Health Institute	Poland	148	2.8
University of Cambridge	UK	147	2.7
Washington University School of Medicine	USA	134	2.5
Brigham and Women's Hospital	USA	120	2.2
University of Amsterdam	Netherlands	118	2.2
Capital Medical University	China	100	1.9

Notes: [a] Percentage calculated out of the retrieved 5375 documents.

Most cited papers:

Table 5 presents the most cited documents. The most cited document authored by the European chromosome 16 Tuberous Sclerosis Consortium and published in *Cell* in 1993 was "Identification and characterization of the tuberous sclerosis gene on chromosome 16". The second most cited document, "Identification of the tuberous sclerosis gene *TSC1* on chromosome 9q34", was authored by Van Slegtenhorst M and published in *Science* in 1997. "The tuberous sclerosis complex", authored by Crino PB and published in *New England Journal of Medicine* in 2006, was the third most cited document.

Most frequent journals:

Table 6 presents the most frequent journals where the 5375 selected documents were published in. *Journal of Child Neurology* was the most frequent journal with the highest h-index, g-index, m-index and total citations, followed by *Epilepsia* and *Pediatric Neurology*.

Most frequent keywords:

Table 7 presents the top 10 frequency of occurrence of the author's keywords and keywords plus. The occurrence of the author's keywords throughout the years is shown in Figure 8. The author keywords "tuberous sclerosis" was prominent from the 1970s until 2012 when "tuberous sclerosis complex" overtook and became the most prominent.

Figure 5 shows an overlay visualisation map of the author's keywords created using VOSviewer. There were 101 out of 3526 keywords with at least 10 co-occurrence. The evolution of the author's keywords revealed that some keywords such as tuberous sclerosis, hamartoma, tuberin, hamartin, Bourneville-pringle disease, mental retardation, computed tomography, phakomatosis and prenatal diagnosis were older (purple), while

Table 5 Most cited documents

Document	Journal	Total Citations (TC)	TC per Year	Reference
Identification and characterization of the tuberous sclerosis gene on chromosome 16	Cell	1397	48.17241	[19]
Identification of the tuberous sclerosis gene *TSC1* on chromosome 9q34	Science	1292	51.68	[20]
The tuberous sclerosis complex	New Engl J Med	1187	74.1875	[21]
Identification of the tuberous sclerosis complex-2 tumor suppressor gene product tuberin as a target of the phosphoinositide 3-kinase/Akt pathway	Mol Cell	1182	59.1	[22]
Phosphorylation and functional inactivation of TSC2 by Erk	Cell	958	56.35294	[23]
Sirolimus for angiomyolipoma in tuberous sclerosis complex or lymphangioleiomyomatosis	New Engl J Med	927	66.21429	[24]
Tuberous sclerosis complex gene products, tuberin and hamartin, control mTOR signalling by acting as a GTPase-activating protein complex toward Rheb	Curr Biol	868	45.68421	[25]
Tuberous sclerosis complex consensus conference: revised clinical diagnostic criteria	J Child Neurol	863	35.95833	[26]
Tuberous sclerosis complex diagnostic criteria update: Recommendations of the 2012 international tuberous sclerosis complex consensus conference	Pediatr Neurol	792	88	[27]
Tuberous sclerosis	Lancet	721	51.5	[28]

Table 6 Most frequent journals

Journal	No of documents	% of documents[a]	h-index	g-index	m-index	TC
Journal of Child Neurology	91	1.7	34	67	1	4651
Epilepsia	70	1.3	32	57	0.593	3337
Pediatric Neurology	65	1.2	24	54	0.649	2983
Brain and Development	56	1	20	33	0.465	1218
Neurology	51	0.9	28	49	0.4	2413
Journal of Medical Genetics	45	0.8	25	42	0.446	1806
Annals of the New York Academy of Sciences	43	0.8	16	41	0.516	1705
Child's Nervous System	38	0.7	15	26	0.405	743
The Lancet	38	0.7	13	38	0.112	2651
Epilepsy and Behavior	35	0.7	14	25	0.875	686

Notes: [a] Percentage calculated out of the retrieved 5375 documents.

mTOR inhibitor, everolimus, sirolimus, mTORC1, mTOR pathway, autophagy, inflammation, infant, intellectual disability, white matter, TSC-associated neuropsychiatric disorders, TOSCA and quality of life were relatively newer (yellow) keywords.

Table 7 Most frequent keywords

Author's keyword	Occurrence	Keywords plus	Occurrence
tuberous sclerosis	1109	tuberous sclerosis	9494
tuberous sclerosis complex	746	human	5316
epilepsy	321	female	4379
angiomyolipoma	204	male	3792
mtor	126	article	3423
tsc2	121	adult	3096
everolimus	104	case report	2673
rapamycin	97	humans	2407
tsc	87	child	2357
subependymal giant cell astrocytoma	83	priority journal	2010
lymphangioleiomyomatosis	82	adolescent	1826
tsc1	80	infant	1386
autism	77	angiomyolipoma	1092
tuberin	68	epilepsy	1087
magnetic resonance imaging	65	nuclear magnetic resonance imaging	899
children	59	clinical article	867
renal angiomyolipoma	58	tuberin	822
hamartoma	56	computer assisted tomography	803
seizures	56	pathology	785
tuberous sclerosis complex (tsc)	56	controlled study	764

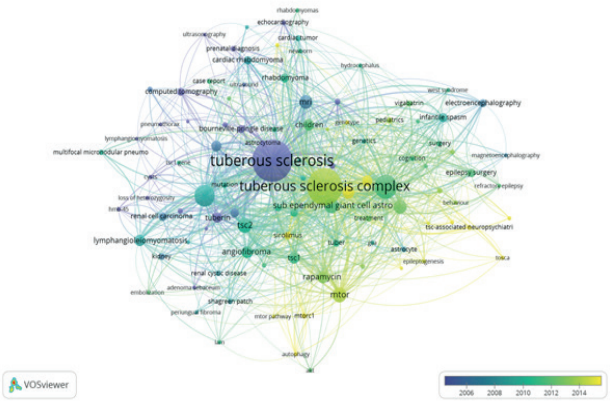

Figure 5 Overlay visualization of authors' keywords.

Discussion:

This bibliometric study presents, for the first time, a comprehensive analysis of TSC research using the Scopus database. The majority of the TSC research documents have been published as original articles in the medical subject field. The development of scientific publications from 1906 to 2020 demonstrates that TSC research has increased in relevance over the recent decades, making it an important research topic. The ability to unravel TSC's genetics and molecular underpinnings may be linked to the rising trend. For instance, DNA was discovered in 1953, the Human Genome Project (HGP) began in 1990, and the NGS application explosion in humans began in 2010.

Curatolo P, Kwiatkowski DJ and Thiele FA were the three main contributors based on the number of publications each author had contributed. The top author production over time, Curatolo P, began publishing in TSC research in 1982 and continued until 2020. His review article, "Tuberous sclerosis", is one of the quoted articles[28]. Kwiatkowski DJ, Thiele FA, Sahin M and Franz DN were the next to perform. In terms of the most impactful author based on the h-index, Kwiatkowski DJ was the most influential followed by Curatolo P, Henske EP, Franz DN, and Sahin M. In a co-authorship network, the authors are the network's nodes, and their connections are the number of their joint works connected by a line. Most of these authors were grouped together in the same cluster; brown (Kwiatkowski DJ, Thiele FA, Henske EP), blue (Curatolo P, Kotulska K, Jozwiak

S), and purple (de Vries PJ, Franz DN), as seen in the co-authorship network of authors. The co-authorship networks are prominent bibliometric indicators for illustrating distinct patterns of co-authorship of academic fields [29,30].

North America (the United States) has the most TSC publications, followed by Europe (the United Kingdom, Italy, Germany, France, Spain and Turkey) and Asia (Japan, China and India). The United States was by far the most productive country in terms of TSC research publications. The country also has the most international collaborations and research institutes. Similarly, while the United States retains a prominent position in the country collaboration networks, Europe and Asia appear to provide a clear counterweight to the research collaboration mapping[31-33] Other famous research institutes in Europe, Asia and South Africa, in addition to select well-known American institutions, contribute to scientific production in TSC research, as evidenced by the institutions' collaborative network.

The most cited document[189], "Identification and characterization of the tuberous sclerosis gene on chromosome 16", received 1397 citations and was written by groups of authors from the University of Wales; Erasmus University and University Hospital, Netherlands; Institute of Molecular Medicine, England; and Leiden University, the Netherlands. According to the study which was published in *Cell* in 1993, *TSC2* is the chromosome 16 TSC gene. This paper was cited by "Atlas of genetics and cytogenetics in oncology and haematology"[34]. "Identification of the tuberous sclerosis gene *TSC1* on chromosome 9q34" was the second most cited document[20], receiving 1292 citations, and was written by a group of authors that included the top authors (Kwiatkowski DJ, Henske EP and Jovaik S). The study, which was reported in *Science* in 1997, identified thirty-two distinct mutations in *TSC1*. These two most cited documents are considered seminal works in TSC research. The other most cited documents include review papers and original articles on the identification of gene products, the role of sirolimus (mTOR inhibitor) in angiomyolipoma and TSC clinical diagnostic criteria.

Interestingly, the results of the most prolific journals revealed that TSC research was published in clinical medicine journals, namely *Journal of Child Neurology, Epilepsia, Pediatric Neurology, Neurology, Child's Nervous System* and *Epilepsy and Behavior,* indicating a greater interest in TSC's clinical neurology aspects, particularly epilepsy and neuro-behavioural/neuro-cognitive manifestations. In terms of productivity, these journals show an increasing trend. On the other hand, high quality, broad-scope journals such as *Lancet, Journal of Medical Genetics* and *Annals of The New York Academy of Sciences* showed decreasing popularity. This could be due to the relative exhaustion of the genetic pathology of the disorders.

The results of the most frequently used keywords provide a clear picture of the current state of TSC research. Essential concepts and knowledge structure of a scientific area could be revealed by examining the connections between keywords in literature[35]. The most frequent author's keywords were TSC, epilepsy, everolimus, angiomyolipoma, mTOR, TSC2, rapamycin, subependymal giant cell astrocytoma, lymphangioleiomyomatosis, TSC1, autism, magnetic resonance imaging, children, renal angiomyolipoma, and seizures. From these keywords, we can deduce that this research field is focused on two primary areas: (i) clinical aspect (children, epilepsy, angiomyolipoma, subependymal giant cell astrocytoma, lymphangioleiomyomatosis, autism, renal angiomyolipoma, seizures and magnetic resonance imaging) and (ii) role of mTOR inhibitors (everolimus and rapamycin) in the treatment of TSC. The evolution of the author's keywords revealed that certain keywords such as mTOR inhibitor, everolimus, sirolimus, mTORC1, mTOR pathway, autophagy, inflammation, infant, intellectual disability, white matter, TSC-associated neuropsychiatric disorders, TuberOus SClerosis Registry to Increase Disease Awareness (TOSCA) and quality of life were relatively new. This suggests that new therapy options targeting vulnerabilities in TSC-related pathways will continue to be developed and TSC serves as a model for many disorders involving the mTOR pathway[1]. In addition, the TOSCA study

was recently initiated to address current gaps in the diagnosis and management of TSC[36].

Conclusion:

TSC research has increased relevance over the last decades especially in the subject related to clinical medicine. Future research hotspots will be in therapeutic aspects targeting TSC-related pathways, the use of TSC as disease models and long-term safety studies such as TOSCA.

Conflict of Interest:

The authors declare no conflict of interests in this study.

Authors' Contribution:

Data gathering and idea owner of this study: Zulkipli NN, Long I, Wahab HA, Sasongko TH, Ahmad AH, Othman Z, Ahmi A, Zakaria R

Study design: Zulkipli NN, Long I, Wahab HA, Sasongko TH, Zakaria R

Writing and submitting manuscript: Ahmad AH, Ahmi A, Sasongko TH, Zakaria R

Editing and approval of final draft: Zulkipli NN, Long I, Wahab HA, Sasongko TH, Ahmad AH, Othman Z, Ahmi A, Zakaria R

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