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Original Article

Characterization of global research hotspots and trends on ten-eleven translocation 2: visualization and bibliometric analysis

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Abstract: Background and objective: Ten-eleven translocation-2 (TET2) is member of the methylcytosine dioxygenase family and plays important roles in a variety of physiological and pathological processes; however, no bibliometric analysis has been performed to methodically evaluate the scientific research on TET2. Therefore, the aim of this study was to conduct a visual and scientometric analysis of TET2 research and to explore its current landscape, future direction, and research frontiers. Methods: Publications related to TET2 research were retrieved from the Web of Science Core Collection (WoSCC) from 2009 to 2021. Excel, CiteSpace, and VOSviewer were utilized to perform the bibliometric visualization analysis. Results: A total of 2384 articles were retrieved. The number of publications on TET2 has been steadily increasing from 2009 to 2021. The USA is the top contributor to the topic, with the largest number of publications. Harvard University and the Institut National de la Santé et de la Recherche Médicale were the leading institutions, while Levine RL of Memorial Sloan-Kettering Cancer Center is the most prolific and influential author. In TET2-related publications, the high-frequency keywords were: "tet2", "DNA methylation", "5-hrdroxymethylcytosine", "5-methylcytosine", "mutations", and "acute myeloid-leukemia". Based on keyword bursts, the emerging TET2 research hotspots include "inflammation", "gene expression", "landscape", and "clonal hematopoiesis". Conclusion: Research on TET2 is constantly growing and evolving during the last decade. Here, we provide an objective and comprehensive analysis of the global status, research hotspots, and potential trends in the field of TET2 research by using a bibliometric approach. These results will assist researchers in mastering the knowledge structure and guiding the future research directions of TET2.

Keywords: TET2, DNA methylation, bibliometric analysis, CiteSpace, VOSviewer

Introduction

DNA methylation is an essential epigenetic mechanism of gene regulation in vertebrates [1], which involves the transfer of a methyl group to the 5th carbon of cytosines to generate 5-methylcytosine (5mC), predominantly at CG dinucleotides (CpG site) [2]. Mounting evidence has shown that the establishment and maintenance of DNA methylation patterns are critical for gene expression, transposon silencing, and genomic imprinting [3-5]. Originally, DNA methylation was considered an irreversible process that was only eliminated passively by dilution during DNA replication [6]. It was not until 2009 that Tahiliani et al. published a paper in *Science* showing that human ten-eleven translocation 1 (TET1), a member of the TET family of dioxygenases, could catalyze the conversion of 5mC to 5-hydroxymethylcytosine (5hmC) and thus actively promote DNA demethylation [7]. Subsequently, Ito et al. found that all members of the mouse TET family, TET1, TET2 and TET3, were able to catalyze DNA demethylation reactions [8]. Currently, TETs are well recognized as epigenetic master regulators capable of regulating the dynamic DNA methylation landscape through various pathways, being intimately involved in a variety of fundamental biological processes [9, 10].

Furthermore, it has been well known that alteration of epigenetic landscapes, such as DNA methylation patterns, is a hallmark of cancer [11]. Interestingly, the activity of TET proteins responsible for the removal of this epigenetic mark has also been identified as a key tumor suppressing mechanism [12]. Among the cancer types studied, hematological malignancies have exhibited the most experimental evidence supporting the role of TET in tumorigenesis, while TET2 is the most frequently mutated member of the TET family in blood malignancies. In 2009, Delhommeau et al. first reported the presence of inactivating mutations in TET2 in myeloproliferative neoplasms (MPN) and acute myeloid leukemia (AML) patients with chromosome 4q24 alterations [13]. In the same year, several other research groups also found deletions and mutations in the *Tet2* gene in patients with myeloid malignancies and myelodysplasia [14-16], demonstrating the role of TET2 in the initiation of these diseases. Further studies have confirmed that somatic mutations of TET2 occur in a variety of hematologic disorders, including lymphoid malignancies, and non-malignant blood diseases [17]. In addition, the emerging role of TET2 dysregulation in non-hematopoietic malignancies has been revealed as well. For example, disruption of TET2 catalytic activity is involved in the carcinogenesis of some solid tumors such as lung cancer, colon cancer, and melanoma [18]. Furthermore, recent studies have shown that *Tet2* deficiency affects the inflammatory process [19]. Enhanced inflammatory response induced by *Tet2* loss has been related to atherosclerosis in mice [20]. Hence, the physiological and pathological functions of TET2 have attracted extensive studies.

Bibliometric analysis is a groundbreaking tool for uncovering a subject's structures and developments through a combination of visualization and statistical methods [21]. A systematic and quantitative analysis of most publications on a given topic through bibliometrics provides valuable information such as the contributions of countries/regions, institutions, authors, and journals [22]. Bibliometric analysis, as opposed to traditional systematic reviews and meta-analyses, is a more efficient approach to reveal key issues and trends in a field, which guides future study [23]. CiteSpace and VOSviewer are visualization software widely used in bibliometrics. CiteSpace software can provide a visual representation of the distribution, pattern, and structure of research fields [24], while VOSviewer is also effective for mapping knowledge domains [25]. With these two tools, a wealth of data can be easily presented, including the information of countries and authors, the collaborative relationships, and visualization of research hotspots and trends.

Although there have been many research articles on TET2 in recent years, no bibliometric analysis in this field has yet been published. Therefore, this study aimed to apply the advantage of bibliometrics to conduct a comprehensive and systematic analysis on the current status and frontiers of TET2 research, highlighting the contributions from different countries, institutions, journals, and authors for overview and spatial-temporal network analysis.

Materials and methods

Data collection

All publications were extracted from Science Citation Index-Expanded (SCI-E) and Social Sciences Citation Index (SSCI) of the Web of Science Core Collection (WoSCC). The search query was Topic = ("TET2") OR ("Ten-eleven translocation 2") OR ("Tet methylcytosine dioxygenase 2"), and a thorough search for relevant papers published in English from 2009 to 2021 was conducted. To eliminate bias caused by regular database updates, document retrieval was finished within one day (January 20, 2022). **Figure 1** provided a comprehensive overview of the workflow for this study. All data were examined independently by two researchers involved in this study.

Bibliometric analysis

All WoSCC data were downloaded in txt format and imported into the analysis software. Briefly, bibliometrics on TET2 were visualized by VOSviewer 1.6.16, CiteSpace 5.8 R3, Microsoft Excel 2019, and other online analysis website for bibliometrics (https://bibliometric.com). Retrieval results regarding the publication of TET2 were analyzed on the year of publication, countries/regions, institutions, journals, core authors, keywords, and key references. Furthermore, the impact factor (IF), H-index, and category quartile of these publications were identified according to the 2020 Journal Citation Reports. A journal's IF is an internation-

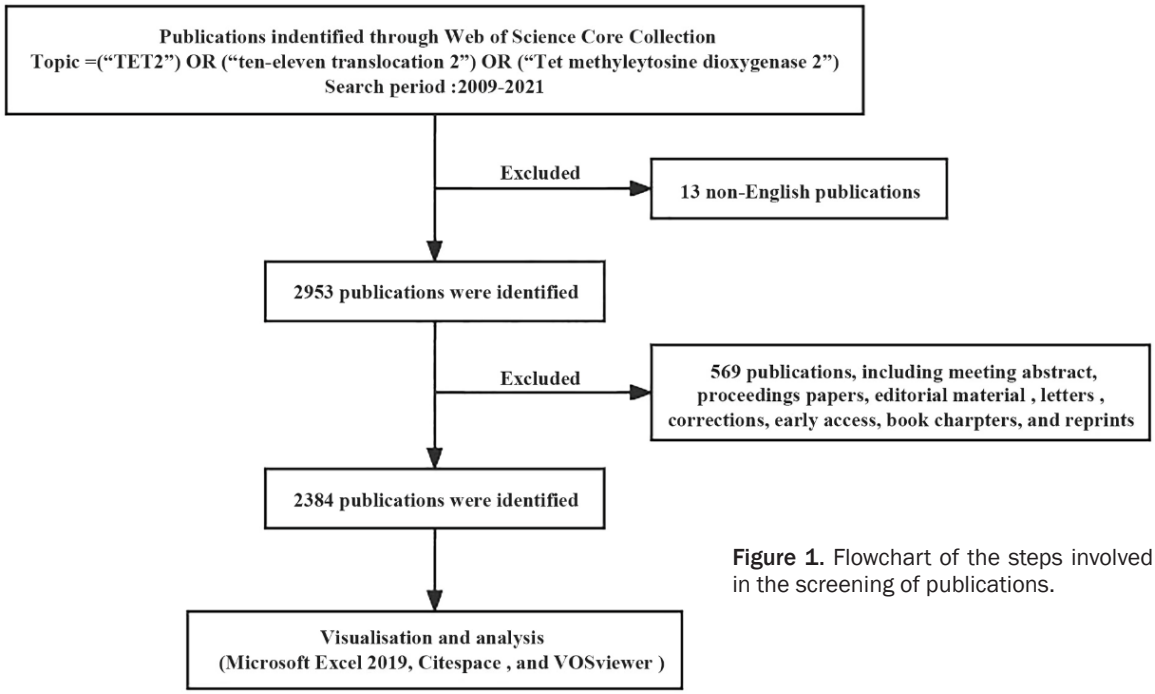


Figure 1. Flowchart of the steps involved in the screening of publications.

ally recognized index to reflect the influence of journals. The H-index is a key indicator of the influence of authors, countries, institutions, and journals [26]. The analysis of trends in annual publications was conducted using Microsoft Office Excel 2019.

The main advantage of VOSviewer lies in its ability to develop visual network maps based on bibliometric networks to achieve an in-depth and comprehensive understanding of the structure evolution of research domains. In this study, we used VOSviewer (version 1.6.16) to build the keyword co-occurrence and cluster map based on text data.

CiteSpace is a powerful bibliometric tool dedicated to exploring priorities, patterns, collaborations, hotspots, and possible trends within a particular field; hence, we employed CiteSpace (version 5.8 R3) for collaboration network analysis (countries/regions, institutions, and authors), co-citation analysis (authors and references), citation burst detection (keywords and references), and dual map. In addition, we used CiteSpace to analyze centrality which assesses the importance of a network node, and the more prominent nodes were counted as higher centrality [27].

Results

Analysis of publication outputs

There were 2384 publications on TET2 between 2009 and 2021, and the number of publications exhibited a rising trend as shown in **Figure 2**. Notably, research activities in TET2 increased dramatically between 2016 and 2021, with 1695 articles published over the five-year period, collectively representing 71.1% of the total number of articles. As for the annual number of publications, the volume of articles peaked in 2021 (367, 15.4%).

Contributions of countries/regions and institutions

The publications were produced by 73 different countries to date, and the top 10 contributing countries were listed in **Table 1**. The USA published the most articles (1057, representing 40% of the publications from the top 10 countries) followed by China (635), Germany (254), Japan (212), and France (192). Using centrality score as the metric to assess the significance of network nodes, Spain (0.36) was at the network core, followed by Germany (0.25), and the UK (0.15). Since more frequent cooperation is correlated with greater centrality in a collabora-

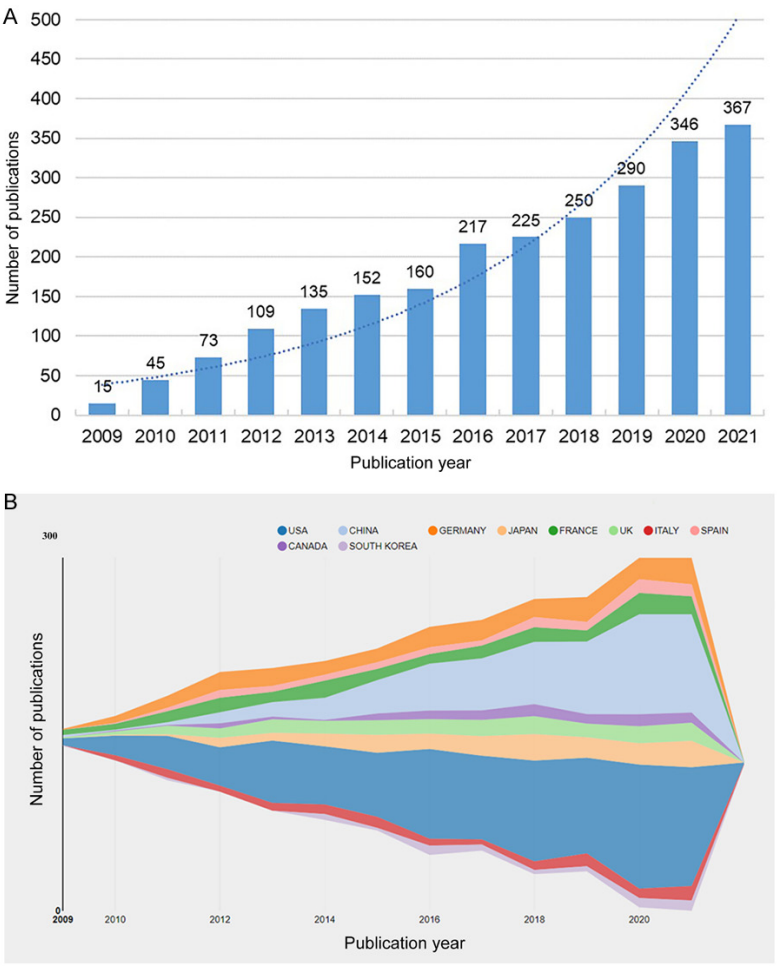


Figure 2. Annual output of TET2 research (A) and the top-10 countries/regions (B) in the field of TET2 from 2009 to 2021.

Table 1. Ranking of top-10 countries that have published the most articles on TET2 research from 2009 to 2021

Rank	Article counts	Centrality score	Country
1	1057	0.09	USA
2	635	0.00	China
3	254	0.25	Germany
4	212	0.00	Japan
5	192	0.09	France
6	172	0.15	UK
7	125	0.00	Italy
8	102	0.36	Spain
9	93	0.00	Canada
10	66	0.00	South Korea

tive network, we analyzed each country's output and the country-collaboration network of TET2 research, as visualized in **Figure 3A**. The low density of the country-collaboration network map suggested that most countries were fragmented and lacked consistent and extensive cooperation.

We next analyzed the number of papers published by institutions, which reflects, to some extent, the scientific competitiveness of the institutions. **Table 2** showed the top 10 institutions and the number of their publications in the field of TET2 research worldwide, including Harvard University (152), Institut National de la Santé et de la Recherche Médicale (152), Memorial Sloan Kettering Cancer Center (124), University of Texas System (114), and Assistance Publique-Hopitaux de Paris (108). Of these 10 institutions, 8 were from the USA, and 2 were from France. The institutions with the highest centrality score were Institut National de la Santé et de la Recherche Médicale (0.07), Mayo Clinic (0.06), Memorial Sloan Kettering Cancer Center (0.04), and Cornell University (0.04). In general, a low degree of centrality was observed in all institutions, indicating less inter-institutional collaboration. The institution-collaboration network (**Figure 3B**) also provided a visual representation of the institutions that contributed most to the TET2 research and the communication between institutions in this area.

Contributions of authors

In total, 14567 authors contributed to the 2384 relevant publications. The top 10 most prolific authors were listed in **Table 3**. In addition, we assessed the influence of authors in the field by 2 indicators: the number of citations and the H-index. R. L. Levine of Memorial Sloan Kettering Cancer Center was the most productive author, with 66 publications, followed by A. Tefferi of Mayo Clinic (51), T. Haferlach of

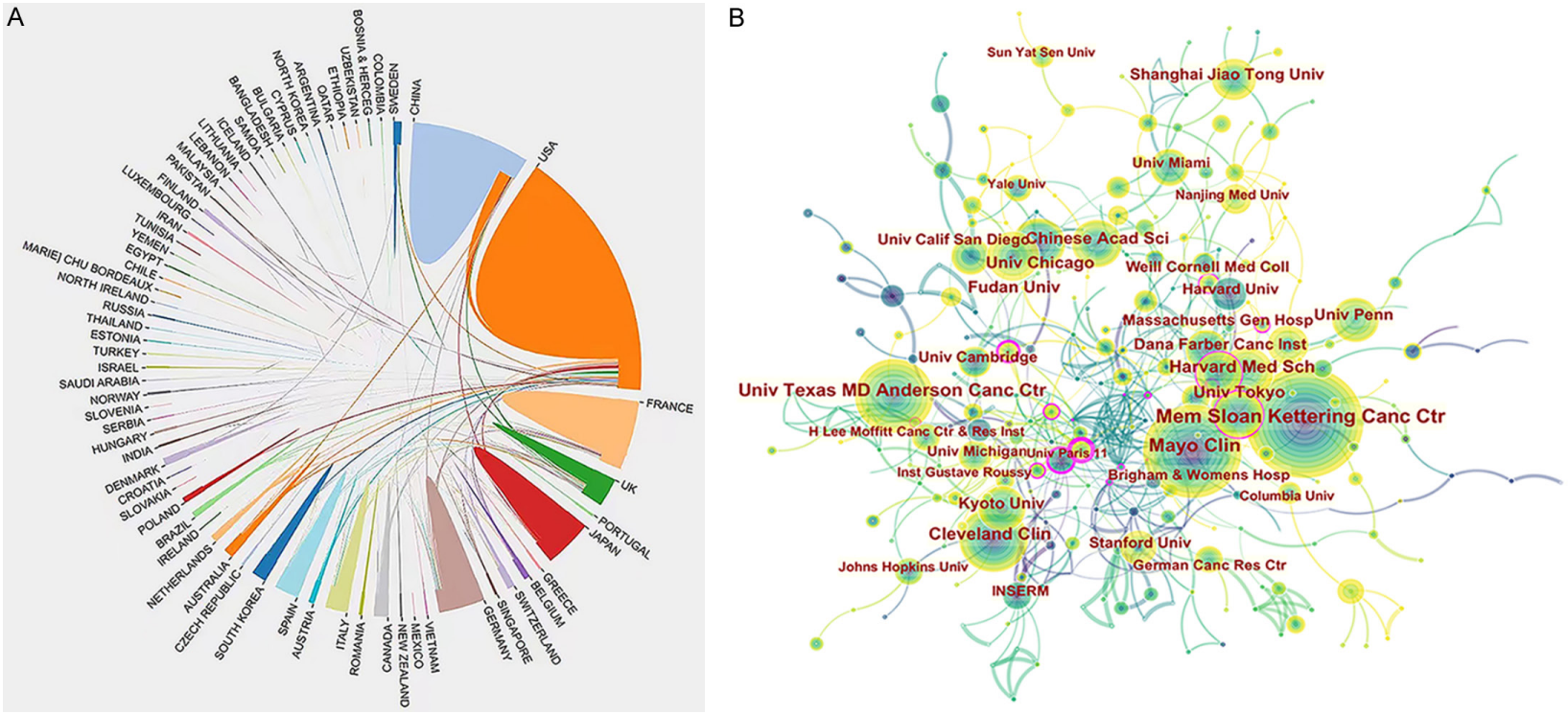


Figure 3. Distribution of countries/regions and institutions involved in research on TET2 from 2009 to 2021. A. Network visualization of the contributions of countries/regions involved in research on TET2. B. Network visualization of the contributions of institutions involved in research on TET2.

Table 2. Ranking of top-10 institutions that have published the most on TET2 research from 2009 to 2021

Rank	Article count	Institution	Country	Centrality score
1	152	Harvard University	USA	0.03
2	152	Institut National de la Santé et de la Recherche Médicale	France	0.07
3	124	Memorial Sloan Kettering Cancer Center	USA	0.04
4	114	University of Texas System	USA	0.02
5	108	Assistance Publique-Hopitaux de Paris	France	0.01
6	97	Cleveland Clinic	USA	0.03
7	94	Mayo Clinic	USA	0.06
8	89	UT MD Anderson Cancer Center	USA	0.02
9	88	University of California System	USA	0.02
10	81	Cornell University	USA	0.04

Table 3. Ranking of top-10 most productive authors on TET2 research from 2009 to 2021

Rank	Author	Article count	Centrality score	Total number of citations	Average number of citations	H-index
1	Levine RL	66	0.35	10273	155.65	36
2	Tefferi A	51	0.00	4027	78.96	33
3	Haferlach T	47	0.01	4452	94.72	30
4	Ogawa S	44	0.15	3339	75.89	23
5	Abdel-wahab O	40	0.00	8615	215.38	28
6	Maciejewski JP	38	0.01	3559	93.66	25
7	Rao A	36	0.03	6452	179.22	29
8	Bernard OA	33	0.10	5098	154.48	24
9	Patnaik MM	32	0.08	1058	33.06	20
10	Haferlach C	31	0.00	3070	99.03	22

Munich Leukemia Laboratory (47), S. Ogawa of Kyoto University (44), and O. Abdel-Wahab of Memorial Sloan-Kettering Cancer Center (40). Importantly, R. L. Levine ranked first in both citations (10273) and the H-index (36).

Furthermore, we identified the core authors and potential collaborators in this field through a visualization map of co-authorship to indicate the cooperative relationships. A visual analysis of authors with ≥ 5 publications and ≥ 500 citations was performed. **Figure 4** depicted the patterns of dominant co-authorship relationships across eight different clusters of authors. R. L. Levine also dominated the first group, whereas O. A. Bernard of the Institut National de la Santé et de la Recherche Médicale dominated the second group. J. P. Maciejewski of the Cleveland Clinic was represented in the third author cluster.

Analysis of journals

The analysis of relevant journals allows for the identification of the leading journals in a certain academic field. The characteristics of the top 10 most prolific journals were presented in **Table 4**. The highest number of TET2-related articles was published in *Blood, Leukemia*, and *Plos One*. Several high impact factor articles on TET2 were published in *Blood*. Furthermore, *Blood* achieved the highest H-index (66) and average number of citations (115.1). *Blood* and *Leukemia* belong to the Journal Citation Report quartile Q1, while *Plos One* was ranked as Q2. Combining the number of publications, citations, impact factor, and H-index, *Blood* was probably the most influential journal in this field and deserved the attention of new researchers.

Analysis of keywords and detection of keyword bursts

The analysis of the keywords covered facilitates the clarification of themes and the establishment of a framework for the research of TET2. We extracted a total of 6919 keywords from 2384 retrieved literatures using VOSviewer, of which 199 items reached a set

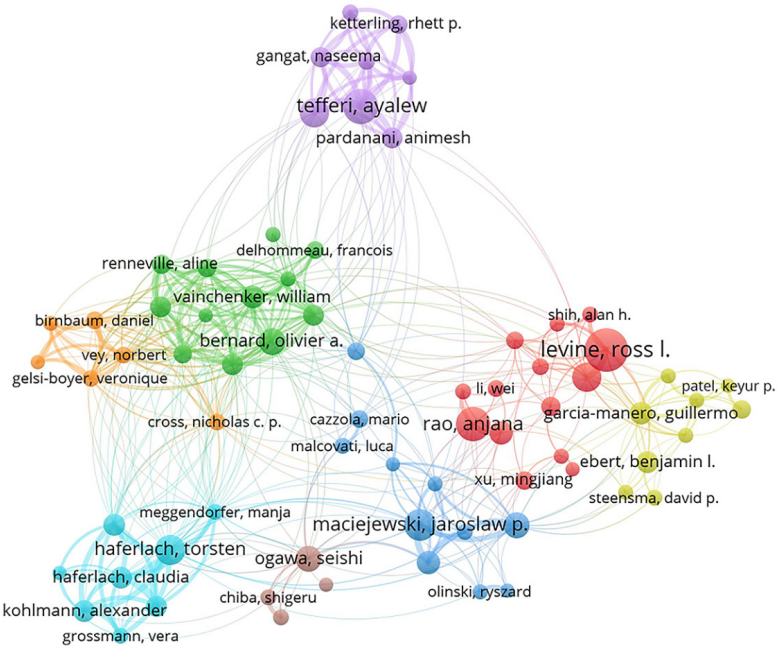


Figure 4. Distribution of authors involved in research on TET2 from 2009 to 2021.

threshold (≥ 20 occurrences). A cluster analysis was performed on these keywords. Different clusters were composed of units of different colors. As shown in **Figure 5A**, the clusters of red, green, yellow, and blue represented four different research scopes: myeloproliferative neoplasm, myeloid malignancies, clonal hematopoiesis, and DNA methylation, respectively.

In the time-overlay network map of the co-occurring keywords, we highlighted the keywords in different colors depending on their average years of publication (**Figure 5B**). Whereas prior to 2015 most of the research was focused on the topics of "genetic mutations" and "myeloid neoplasms", recent trends suggested that "clonal hematopoiesis", "gene expression", and "DNA methylation" were likely to be the future research emphasis. In addition, the frequency of keyword occurrences was presented in the form of a spectral density map using VOSviewer (**Figure 5C**). The "warmer" the color of an area on the map, the higher the density value of that area. Research hotspots typically manifest themselves in higher density values. We found that the high-frequency keywords were "tet2" (636), "DNA methylation" (419), "5-hrdroxymethylcytosine" (392), "5-methylcytosine" (350), "mutations" (349), "acute myeloid-leukemia" (344), "expression" (318), "methylation" (279), "tet2 mutation" (256), and "myelodysplastic syndromes" (254).

Burst term denotes a word or an article that appears to rise dramatically over time, which serves as an important indicator in determining the research frontiers in a particular field of research. Additionally, the burst duration and strength are two key indices to evaluate burst terms. We then investigated the keywords with the strongest citation burst of TET2 research in this study. **Figure 5D** presented a list of burst terms sorted by the time of occurrence, showing the top 20 keywords with the strongest citation burst. Red bars indicated the duration of keyword emergence. Between 2009 and 2021, "polycythemia vera" had the highest burst strength (23.52), followed by "methyltransferase gene ezh2" (16.19) and "jak2" (15.9). We focused on the keywords with citation burst in the last 5 years, including "inflammation" (11.31), "expression" (9.44), "gene expression" (7.57), "landscape" (7.48), and "clonal hematopoiesis" (7.43).

Analysis of co-cited references and reference bursts

Co-cited references are a key indicator in bibliometrics, representing the frequency with which two publications are co-cited by other publications. The clustering analysis can be used to group together a multitude of similar references into several knowledge units, which objectively summarizes the major content of the relevant knowledge unit and reflects the dynamic evolution in a field. We then analyzed the co-citation correlation of 58282 cited references from 2384 articles and generated a cluster network map. As shown in **Figure 6A**, there were 144 nodes and 173 links in the visualized network map of co-cited references. Each node represented a cited reference, and the citations of the same article were shown by links between nodes. The diameter of a node was

Table 4. Ranking of top-10 journals for the number of articles published on TET2 research from 2009 to 2021

Rank	Journal	Article count	Country	Journal citation reports (2020)	Impact factor (2020)	Total number of citations	Mean number of citations	H-index
1	*Blood*	128	USA	Q1	23.629	14733	115.1	66
2	*Leukemia*	84	UK	Q1	11.528	6911	82.27	45
3	*Plos One*	50	USA	Q2	3.240	1654	33.08	22
4	*Oncotarget*	46	USA	-	-	1067	23.2	22
5	*American Journal of Hematology*	40	USA	Q1	10.047	1419	35.48	22
6	*Blood Advances*	40	USA	Q1	6.799	772	19.30	15
7	*Scientific Reports*	36	UK	Q1	4.380	534	14.83	13
8	*Leukemia Research*	35	UK	Q3	3.156	519	14.83	12
9	*British Journal of Hematology*	34	UK	Q1	6.998	1184	34.82	15
10	*Haematologica*	32	Italy	Q1	9.941	796	24.88	18

positively correlated with the total number of co-citations of a reference, and a red circle indicated an "explosion" of citations. We determined that the critical clusters of co-cited references included "mpl", "dna methylation", "clonal hematopoiesis", "vitamin c", and "myelodysplastic syndromes" (**Figure 6B**).

The timeline viewer is based on the mutations and interactions among keywords in a field, which facilitates the exploration of the research hotspots and the evolutionary trajectory of the research field. **Figure 7** plotted the timeline view of TET2 showing that the TET2 research has focused on hematological disorders during the last decade.

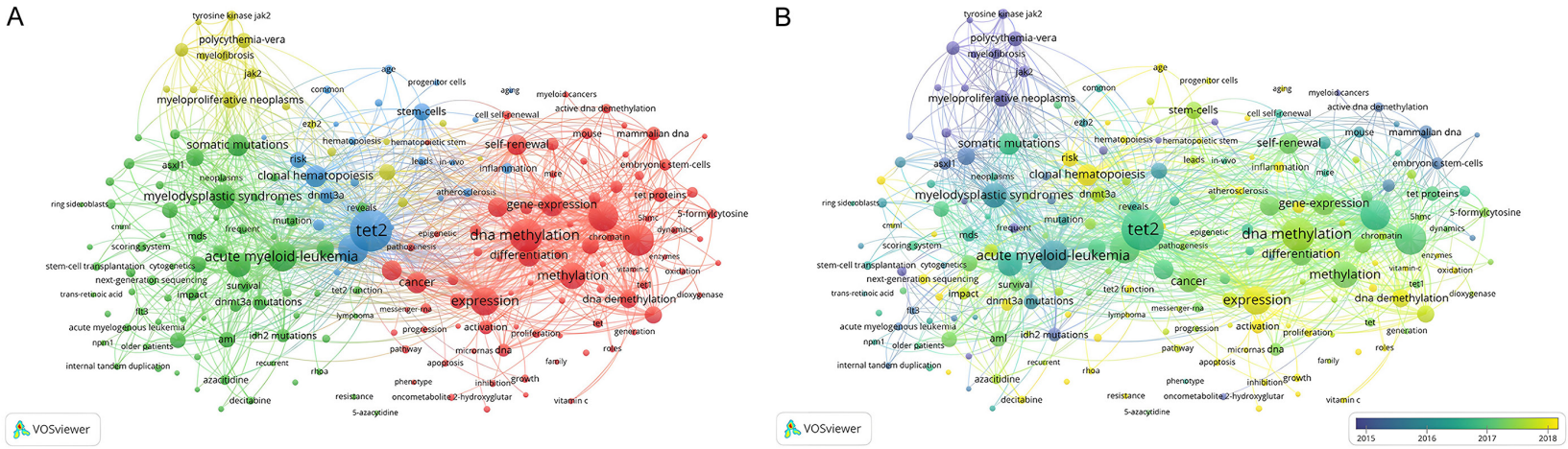
Table 5 presented the ten most frequently cited references. The paper published by Jaiswal et al. [28] in the *New England Journal of Medicine* had the highest number of citations (1980), followed by Figueroa et al. [29] in *Cancer Cell* (1769 citations), and Ito et al. [8] in *Nature* (1718 citations). Eight of these 10 references were about TET2 in hematologic neoplasms. As references with citation bursts refer to references that are frequently cited over a period, we set the burst duration to at least two years in CiteSpace. The top 20 most bursty references were shown in **Figure 8**. Notably, most of these references originated from the top academic journals, including the *New England Journal of Medicine*, *Nature*, and *Science*, indicating that TET2 was a hot research field in medicine and biology.

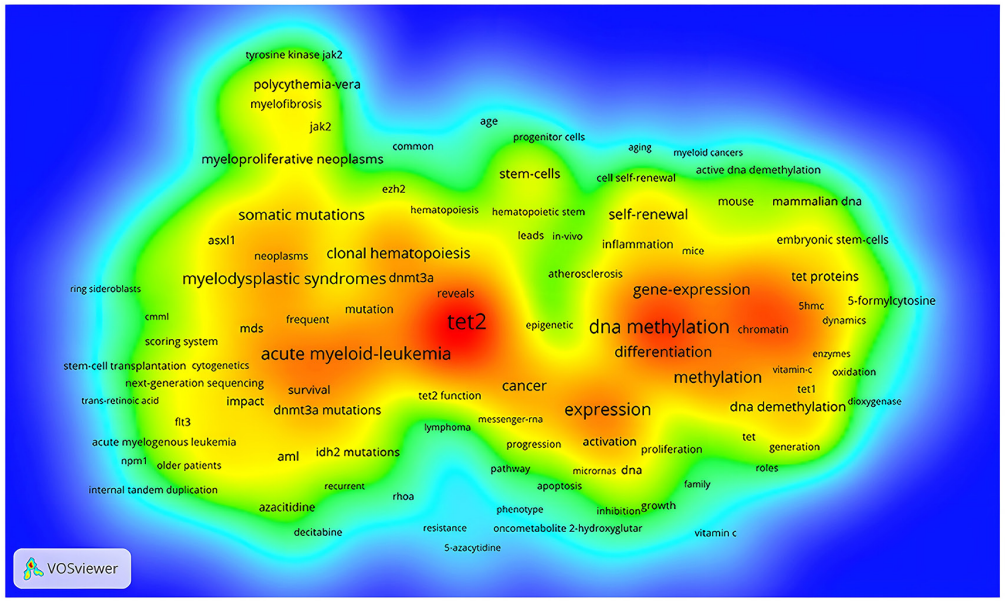
The dual map overlay of academic journals is a representation of the topic distribution of journals. Hence, we created this dual map overlay as shown in **Figure 9**. On the left of the graphic were the citing journals, while on the right were the cited journals with routes indicating the citation relationships between them. There were 2 primary citation paths: the green route indicated that articles published in Molecular/Biology/Genetic journals were generally cited by Medicine/Medical/Clinical journals, and the orange path indicated that publications in Molecular/Biology/Genetic journals were typically cited by Molecular/Biology/Immunology journals.

Discussion

In this age of information explosion, it is increasingly difficult to keep up with the latest research findings and remain at the top of the field. Bibliometrics is a useful method for evaluating the publication trends and relationships between published literature in a field over a certain timeframe. In this study, we performed bibliometric analysis on the current TET2 research and provided quantitative analysis and trend predictions. Our results offer guidance for TET2 research and information which will assist researchers in assessing the significance of research, fostering collaborations among various disciplines, and translating research findings.

The change in the annual number of publications can reflect the trends in the field. TET2 research first emerged in 2009, when several groups reported a strong association between TET2 mutations and hematological disorders such as myeloid malignancies and myelodysplastic syndromes [13, 14]. In the same year, Tahiliani et al. published an article in *Science*





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Top 20 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End	2009 - 2021
polycythemia vera	2009	23.52	2009	2012	
jak2	2009	15.9	2009	2012	
tyrosine kinase jak2	2009	12.72	2009	2012	
myelofibrosis	2009	12.6	2009	2013	
essential thrombocythemia	2009	12.11	2009	2012	
acquired uniparental disomy	2009	10.08	2009	2012	
disorder	2009	9.15	2009	2012	
activating mutation	2009	8.71	2009	2013	
frequent	2009	8.07	2010	2014	
methyltransferase gene ezh2	2009	16.19	2011	2013	
chronic myelomonocytic leukemia	2009	10.42	2011	2013	
idh1	2009	8.97	2011	2012	
idh2 mutation	2009	7.39	2011	2014	
mammalian dna	2009	11.17	2013	2018	
embryonic stem cell	2009	10.25	2013	2017	
gene expression	2009	7.57	2016	2017	
clonal hematopoiesis	2009	7.43	2017	2019	
inflammation	2009	11.31	2019	2021	
expression	2009	9.44	2019	2021	
landscape	2009	7.48	2019	2021	

Figure 5. Keywords analysis in publications related to TET2 worldwide from 2009 to 2021. A. Clustering co-occurrence map of keywords. B. Distribution of keywords based on the average time of appearance. C. Keywords density visualization map. D. Top 20 keywords with the strongest citation bursts.

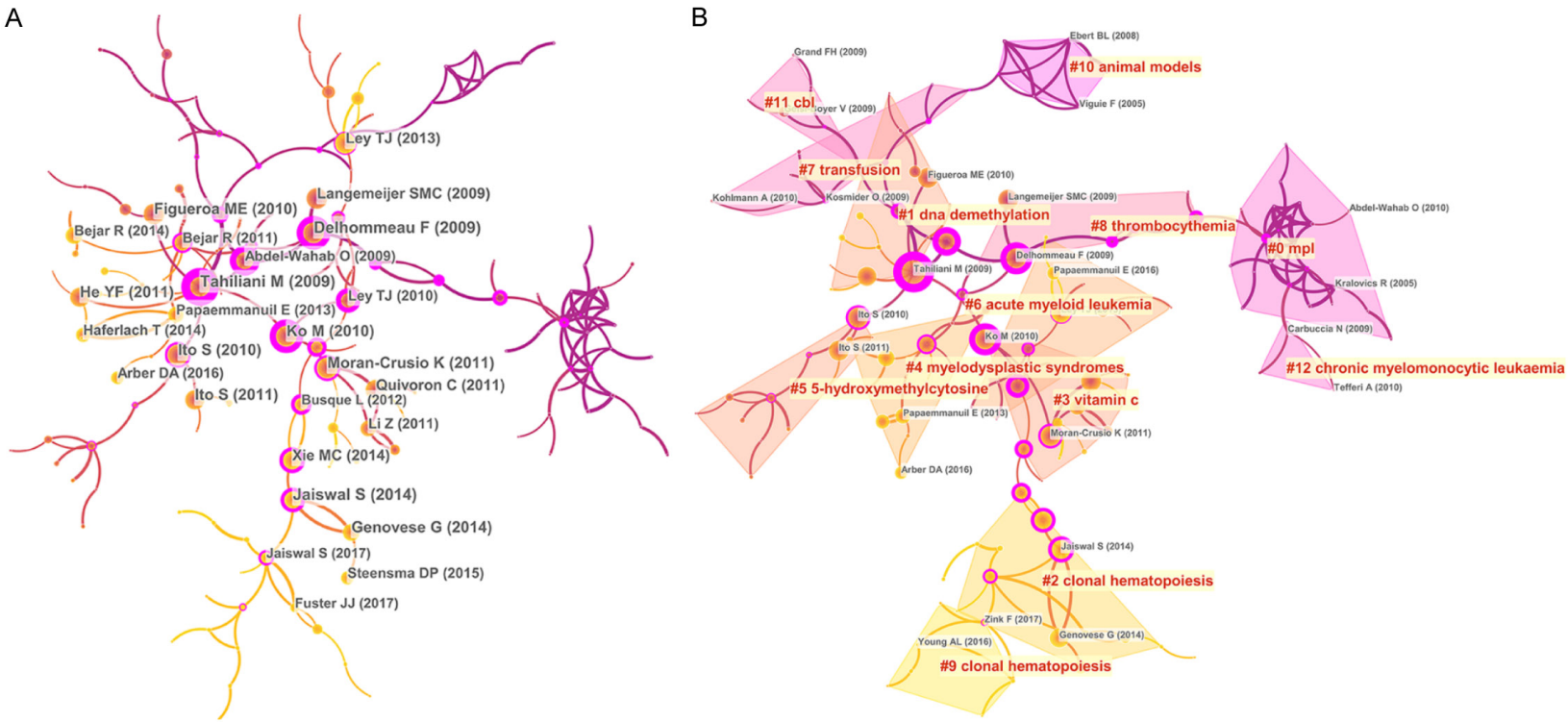

Figure 6. Map of co-cited references (A) and a map of the clustered network of co-cited references (B) related to research on TET2 from 2009 to 2021.

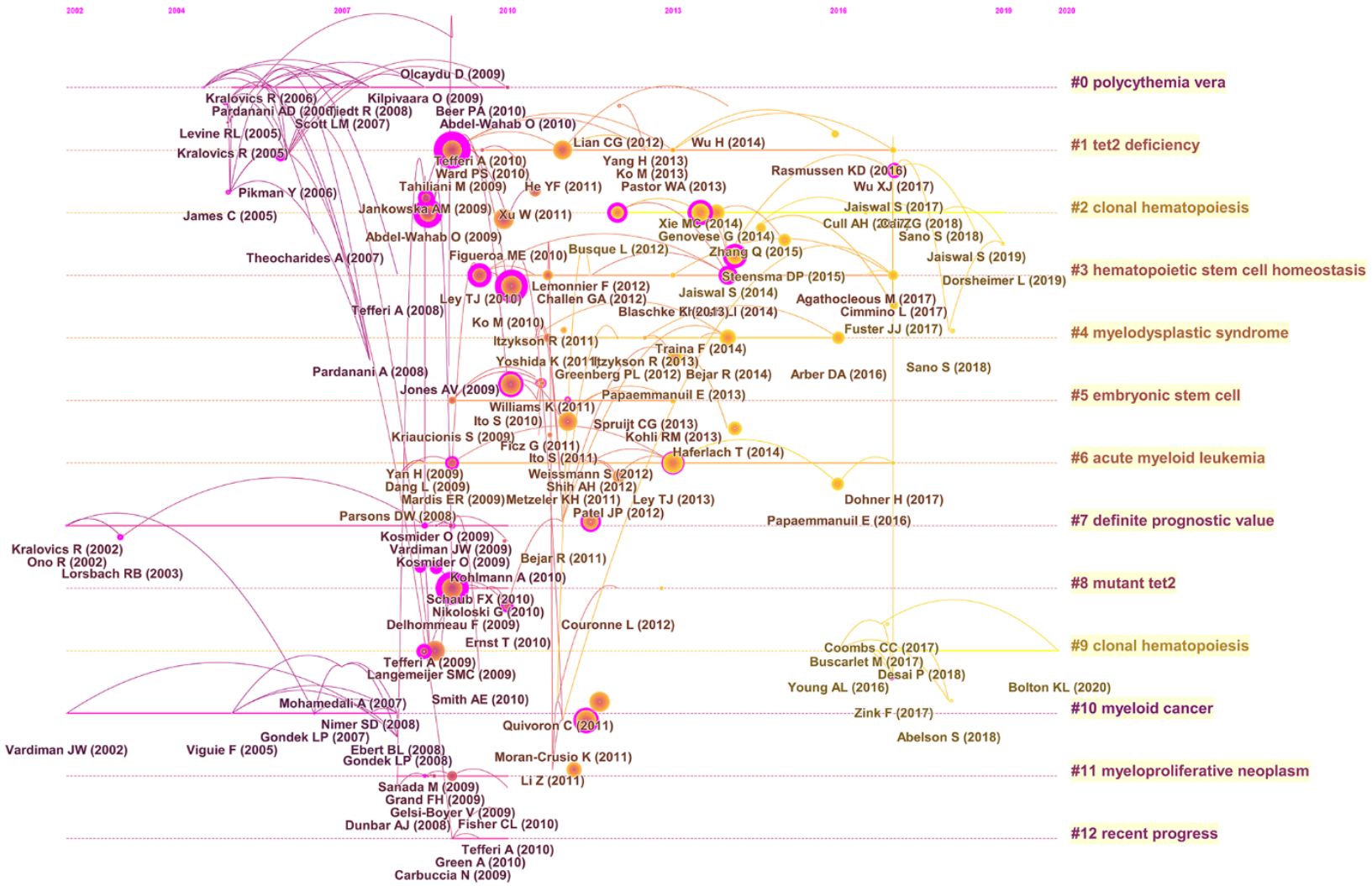

Figure 7. The timeline view of co-citation clusters from 2009 to 2021.

Table 5. Top-10 most cited references on TET2 research from 2009 to 2021

Rank	Title	Author	Year	Journal	Citation frequency
1	Age-Related Clonal Hematopoiesis Associated with Adverse Outcomes	Jaiswal S	2014	*New England Journal of Medicine*	1980
2	Leukemic IDH1 and IDH2 Mutations Result in a Hyper-methylation Phenotype, Disrupt TET2 Function, and Impair Hematopoietic Differentiation	Figueroa ME	2010	*Cancer Cell*	1769
3	Role of Tet proteins in 5mC to 5hmC conversion, ES-cell self-renewal and inner cell mass specification	Ito S	2010	*Nature*	1718
4	Clonal Hematopoiesis and Blood-Cancer Risk Inferred from Blood DNA Sequence	Genovese G	2014	*New England Journal of Medicine*	1581
5	Prognostic Relevance of Integrated Genetic Profiling in Acute Myeloid Leukemia	Patel JP	2012	*New England Journal of Medicine*	1256
6	Mutation in TET2 in Myeloid Cancers	Delhommeau F	2009	*New England Journal of Medicine*	1254
7	Global Epigenomic Reconfiguration During Mammalian Brain Development	Lister R	2013	*Science*	1127
8	Clinical and biological implications of driver mutations in myelodysplastic syndromes	Papaemmanuil E	2014	*Blood*	966
9	Age-related mutations associated with clonal hematopoietic expansion and malignancies	Xie MC	2010	*Nature Medicine*	940
10	Clonal hematopoiesis of indeterminate potential and its distinction from myelodysplastic syndromes	Steensma DP	2015	*Blood*	918

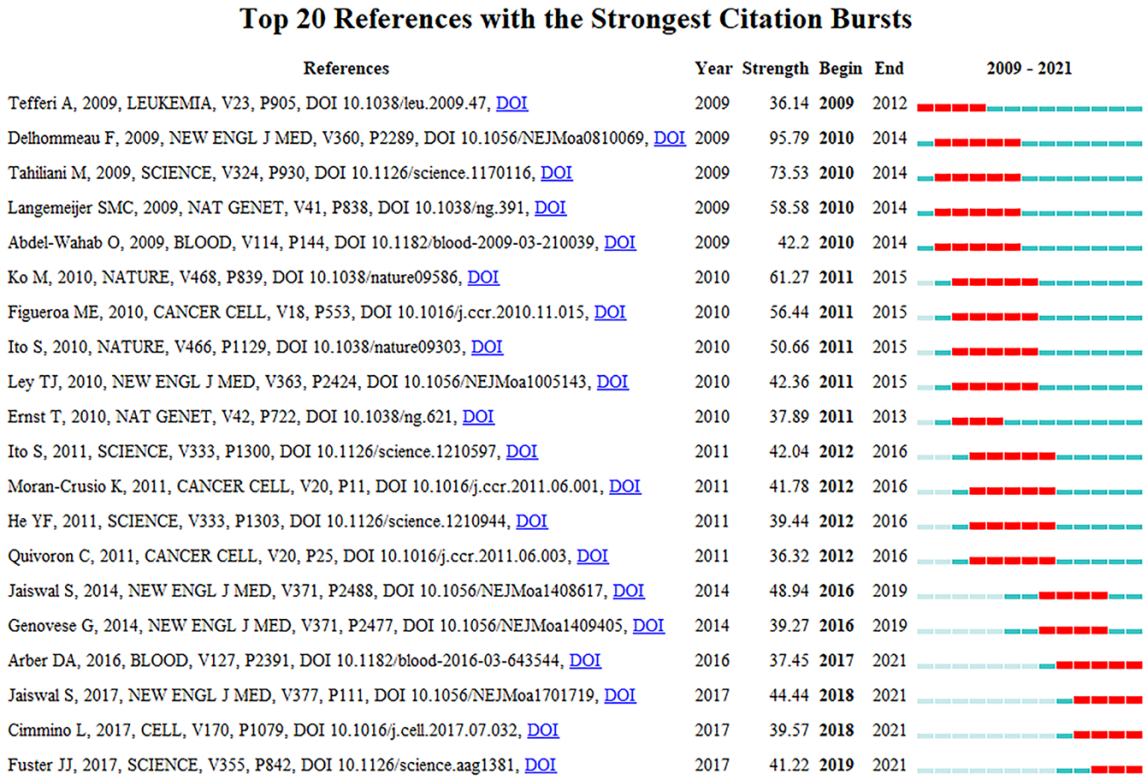

Figure 8. Top 20 cited references with the strongest bursts of citation from 2009 to 2021.

suggesting that the TET family had an active DNA demethylation role [7]. Since these groundbreaking results, there has been rapid growth in publications on TET2. Particularly, during the last five years, there have been an explosion in TET2 research, with 70% of the total number of papers published during this period, indicating that TET2 has been a hot

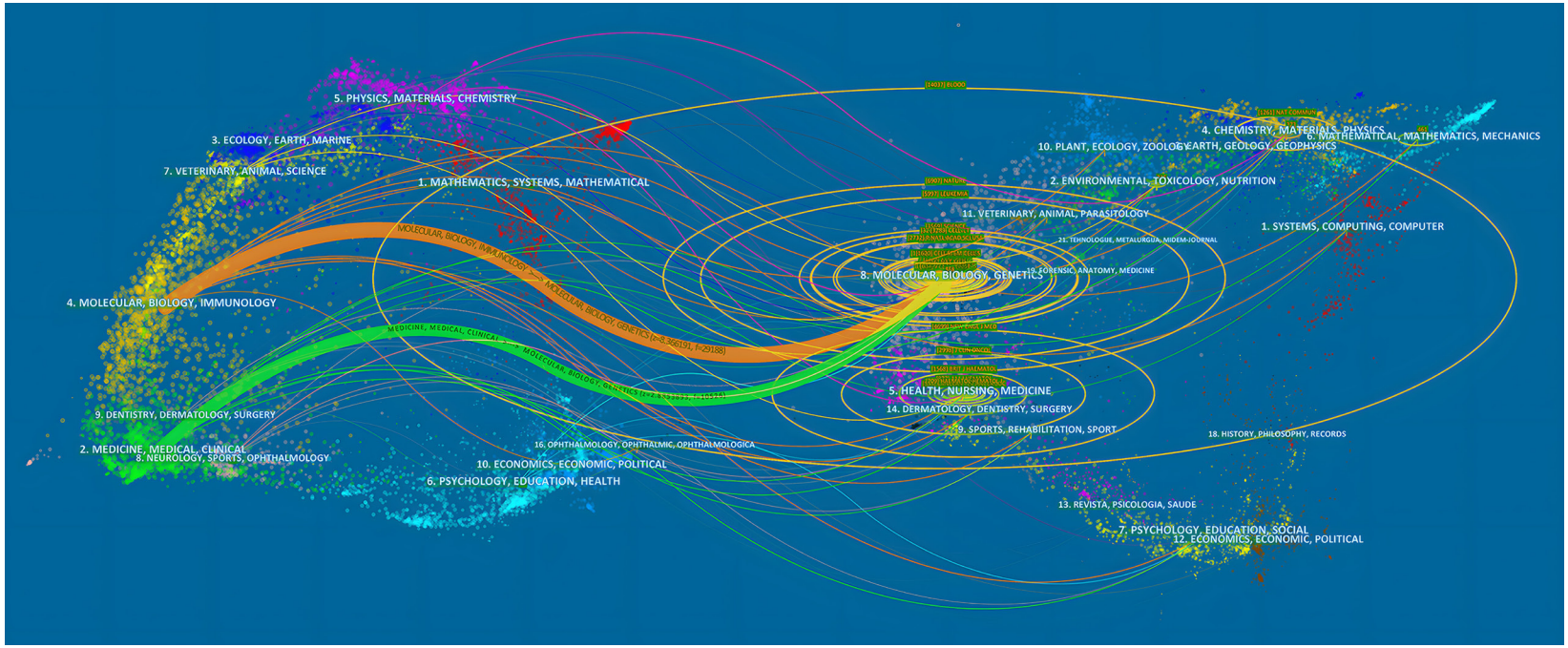

Figure 9. The dual-map overlay of journals publishing papers related to TET2 research from 2009 to 2021.

research area over the past few years. Based on the growth curve of publications, we predicted that more scholars will be involved in this area of research.

When analyzing country/region distribution, we found that the USA published the most articles (1057), followed by China (635), both combined representing 70.9% of the total publication, suggesting that the USA and China lead the research on TET2. However, when calculating the centrality score, which is primarily used to assess the value of the bridge function of a node in terms of the overall network structure, the 2 most prolific countries were not high (below 0.1), as nodes above 0.1 are generally considered to be relatively important nodes, indicating that they need further improvement in academic cooperation and exchange. Among the top 10 countries with the highest number of publications, Spain had the highest centrality score (0.36), suggesting its role as a bridge between the global collaborative network within this field. As for the top 10 research institutions, eight were from the USA, while the other two were from France. Harvard University and the Institut National de la Santé et de la Recherche Médicale were the most influential institutions. Collectively, our analysis indicated that research related to TET2 has attracted a lot of attention worldwide; however, research development was uneven among different countries or regions, and the academic exchange was insufficient, which might negatively impact the development of the field. We therefore strongly suggest that countries and their institutions need to break down academic barriers and expand cooperation and exchange to jointly promote the progress of TET2 research.

This study also highlighted the contributions of influential researchers, who could provide guidance in further research direction. The authors with the most publications were R. L. Levine (66), A. Tefferi (51), T. Haferlach (47), S. Ogawa (44), and O. Abdel-Wahab (40). It is worth noting that R. L. Levine was the most influential scholar in this field as having the highest scores in both the number of citations and the H-index, indicating an outstanding contribution to the field of TET2 research. In addition, our analysis showed a clear geographic pattern in TET2 research among investigators worldwide, with scholars from the USA and Europe dominating the field.

Our results also included an overview of the distribution of publication sources to facilitate the identification of the core journals on TET2 research. Among the journals that published TET2-related articles, *Blood* (128) ranked top, followed by *Leukemia* (84), and *Plos One* (50). Seven of the top 10 journals were in Q1, most of which were journals specialized in hematology. This result also reflected the fact that TET2 was a research focus in hematology. In addition, the top 10 co-cited references were all published in top academic journals, including the *New England Journal of Medicine*, *Nature*, and *Science*, demonstrating that the topic of TET2 is highly regarded in the global academic community. Of interest, most of these publications have focused on the relationship between TET2 mutations and hematological cancers. Furthermore, our dual-map overlay displayed the macroscopic information about the evolution of content at the disciplinary level, and biology, molecular, and genetics were the basic and core disciplines of TET2 research. Analysis of the two main pathways in the map showed that research on TET2 was multidisciplinary.

Since keywords provide an overview of the research themes and basic contents of the article, an analysis of keyword co-occurrences can be used to study the distribution and evolution of different research hotspots within a particular field. Our clustering analysis of high-frequency keywords indicated that the function of TET2 and the role of TET2 in hematological cancers were hot topics of TET2 research. Furthermore, using the burst of keywords, our study predicted the frontiers and emerging trends of TET2 research in 4 arears: “clonal hematopoiesis” (2017-2019), “expression” (2019-2021), “inflammation” (2019-2021), and “landscape” (2019-2021).

It has been well known that DNA cytosine methylation, mainly referred to as 5mC, is one of the most widely studied epigenetic modifications and plays a central role in gene expression [1]. Binding of 5mC to certain proteins restricts the access of transcription factors to the promoter, ultimately repressing transcription [30]. The most basic and important function of TET proteins, including TET2, is the regulation of DNA demethylation. First, TET2 is capable of oxidizing 5mC into 5hmC, 5-formylcytosine (5fC) and 5-carboxycytosine (5caC) sequentially [8]. The thymine DNA glycosylase (TDG) can recognize

and excise these base modifications, resulting in abasic sites; the base excision repair (BER) mechanism then fulfills these sites with unmethylated cytosines [31]. It has been suggested that there are additional mechanisms for active DNA demethylation [32], but further investigation is needed to determine their physiological significance. Second, 5hmC may also promote DNA demethylation passively. This is based on the report that DNA methyltransferase 1 (DNMT1), a maintenance methyltransferase that is responsible for the transfer of a methyl group to unmethylated cytosine, cannot interact with 5hmC. In addition, 5hmC and its oxidized derivatives (oxi-mC) inhibit ubiquitin-like with PHD and ring-finger domain 1 (UHRF1)/DNMT1 from binding to DNA, thereby inhibiting maintenance DNA methylation [33]. Thus, during DNA replication, 5mC is passively diluted when maintenance DNA methylation is halted. Several studies have also revealed that TET2 regulates gene expression by affecting histone modifications. TET2 interacts with O-linked β-N-acetylglucosamine transferase (OGT), and regulates the binding of OGT to the promoter of target genes to modulate gene transcription through histone H2B O-GlcNAcylation or O-GlcNAcylation/proteolytic activation of host cell factor 1 (HCF1) [34, 35]. These studies suggest that TET2 may regulate gene transcription by altering DNA methylation as well as the chromatin landscape. However, the mechanisms involved in the regulation of gene expression by TET2 remain elusive and need to be further investigated.

During the past decade, researchers have provided insight into the complex biological roles of TET2 in the hematological system. It is widely accepted that TET2 is an essential regulator of hematopoiesis, especially myelopoiesis [36]. Multiple blood malignancies are caused by the dysregulation and mutation of TET2 [18]. Our results suggest that clonal hematopoiesis (CH) may be the prospective focus of TET2 in hematology. CH is defined as any state of clonal expansion within the hematopoietic system, functionally characterized by the disproportional proliferation of hematopoietic clones that share a common somatic mutation [37]. Many scholars have suggested that CH may be a pre-malignant state. In fact, it has been reported that patients with CH are approximately tenfold more likely than the general population to develop hematological neoplasms, with an absolute rate of progression of about 0.5-1% per year [38]. TET2 is not only the first gene to be found with somatic mutations in patients with CH but without hematological cancers [39], but also one of the most common mutated genes driving the development of CH [37]. Consistently, studies using mouse models have shown that deletion or haploinsufficiency of TET2 in the hematopoietic system leads to an increased self-renewal of hematopoietic stem and progenitor cells and a tendency to differentiate into the myeloid lineage [40, 41].

Furthermore, TET2 loss-of-function-driven CH has been shown to affect non-malignant geriatric diseases, particularly cardiovascular diseases. Pascual-Figal et al. reported that somatic TET2 mutations in patients with heart failure (HF) appear to contribute to the accelerated HF progression and poorer long-term clinical outcome [42], which was confirmed in a mouse model as hematopoietic or myeloid *Tet2*-loss caused more severe cardiac dysfunction and exacerbated the remodeling process after the induction of HF [43]. In addition, the engraftment of either homozygous or heterozygous *Tet2*-deficiency bone marrow in hypercholesterolemic mice led to larger atherosclerotic plaques when compared with controls, indicating that somatic TET2 mutation-driven CH accelerates atherosclerosis development [20].

Our analysis also suggested that recent study focus on TET2 has been shifted to its role in inflammation. For example, in 2015, Zhang et al. reported that TET2 could inhibit the pro-inflammatory cytokine interleukin-6 (IL-6) expression in innate myeloid cells, including macrophages and dendritic cells, during the resolution stage of inflammation [44]. Mechanistically, TET2 could recruit and bind histone deacetylase (HDAC) 1/2 to promote histone deacetylation, thereby inhibiting IL-6 gene transcription. Furthermore, TET2 deficiency exacerbated the inflammatory response of lipopolysaccharide (LPS)-stimulated bone-marrow-derived macrophages, as evidenced by the increased mRNA levels of interleukin-1β (IL-1β) and IL-6 [45]. Moreover, Fuster et al. showed that *Tet2*-loss macrophages release a large amount of IL-1β in NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome-dependent manner [20]. It has also been

reported that tumor-associated macrophages lacking TET2 expression display a proinflammatory phenotype, including enhanced inflammatory cytokine expression and decreased arginase 1 (ARG-1) expression [46], as well as TET2 modulates innate immune signaling during inflammation initiation [47]. The dysregulation of TET2 has been well established as an important contributor to the development of inflammatory diseases. Studies using stem cell transplantation and *Tet2* loss models have shown that dysregulated inflammation facilitates CH and relevant comorbidities, such as cardiovascular disease and hematological malignancies [48]. Consequently, leukocytes with TET2 mutations contribute to an inflammatory environment, which endows clones with a selective advantage, thereby sustaining a feedback loop of abnormal expansion and inflammation [49]. TET2 has been found to be associated with inflammation in autoimmune diseases, including type I diabetes [50] and Sjögren's syndrome [51]. A recent study showed that knockdown of TET2 and TET3 in regulatory T (Treg) cells severely impairs Treg cell immune homeostasis and induces inflammatory disease in mice [52]. Undoubtedly, further studies need to be undertaken to uncover the potential therapeutic benefit of targeting TET2 for modulating inflammatory responses and treating relevant inflammatory diseases.

Despite the ample information provided by this study, this study had several limitations inherent in bibliometrics. First, although WoSCC database covers the most publications and is commonly used in bibliometric analyses as the primary database, this study only retrieved data from the WoSCC database, missing studies that were not included in the WoSCC. Second, the data in the WoSCC are continuously updated; thus, the search results of this study might differ to some degree from the actual literature included. Lastly, only articles in English were evaluated in this study, which might cause result bias. It is important to note that due to the constant development of scientific research, bibliometrics can only function as a reference for a limited timeframe. Nevertheless, this bibliometric analysis has provided a basis for readers to rapidly grasp the research topics, hotspots, and trends in the field of TET2 research.

Conclusion

TET2 research has undergone a rapid development phase over the last 10 years. Researchers in the USA, Europe, and China have made a significant contribution to the advancement of this field. Harvard University and the Institut National de la Santé et de la Recherche Médicale published the highest number of relevant papers. R. L. Levine of Memorial Sloan Kettering Cancer Center is the most prolific and influential author. Our analysis suggests a need to enhance cooperation and exchanges among different countries and institutions. We also found that many TET2 studies have been published in high impact journals, indicating the significance of TET2 research. Currently, TET2 research is mainly focused on four areas: myeloproliferative neoplasm, myeloid malignancies, clonal hematopoiesis, and DNA methylation. Future study is predicted to concentrate on inflammation, gene expression, and methylation landscape.

In summary, this is the first study to comprehensively assess the literature related to TET2 by bibliometric and visualization analysis. The results of this study can serve as a useful reference for future research.

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Disclosure of conflict of interest

None.

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