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Epigenetics and ischemic stroke: a bibliometric analysis from 2014 to 2024

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Abstract

The importance of epigenetic factors in ischemic stroke has become increasingly prominent. Despite this growing interest, comprehensive bibliometric analyses addressing relationships between epigenetic modification and ischemic stroke are still scarce. This study utilizes a range of bibliometric tools to methodically evaluate research advancements, detect key trends, and delineate both historical and emerging research trajectories in this area. By examining 47 pertinent publications from the Web of Science Core Collection up to July 31, 2024, the present analysis uncovers a consistent rise in global research efforts focused on epigenetics and ischemic stroke. Analyses of co-citation and bibliographic coupling reveal significant research clusters that correspond with current thematic trends. Additionally, scientific mapping and citation burst analyses provide insights into the evolving research landscape and highlight emerging areas of interest. These results emphasize the growing role of epigenetics in understanding the mechanisms of ischemic stroke and developing targeted therapeutic approaches.

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Introduction

Stroke remains a major global health issue, characterized by high incidence rates, significant disability, and substantial mortality. Ischemic stroke (IS), in particular, is a leading cause of death, accounting for ~3.71 million fatalities worldwide per year. The highest mortality rates are observed in Central Asia and Eastern Europe[1]. The 2021 Global Burden of Disease Study reported that IS was responsible for 70.4 million disability-adjusted life years, and 7.81 million new cases, and a troubling 88.0% increase in incident cases since 1990, highlighting the growing impact and urgency of addressing this condition[2].

IS is a complex health condition influenced by numerous factors. While traditional risk factors such as cardiometabolic disorders, lifestyle, and psychosocial issues are well-documented, the precise mechanisms that drive IS remain incompletely understood. Recent advances in epigenetic research are shedding light on these complexities. Epigenetics involves modifications to DNA and histones that impact gene expression and chromatin structure, without altering the DNA sequence itself. Key epigenetic mechanisms include DNA methylation and histone modification. These modifications are dynamic, reversible, and responsive to environmental influences, making them vital for both normal cellular function and disease states[3].

DNA methylation is a critical epigenetic mechanism where methyl groups are added to cytosine residues, where they may influence gene expression without changing the genetic code. Research has shown that alterations in DNA methylation patterns are associated with IS. For example, long interspersed nuclear element-1 (*LINE-1*), the sole autonomous retrotransposon in the human genome, can reshape chromatin and alter genome structure and gene expression. Lower levels of *LINE-1* methylation have been linked to a higher prevalence of IS, with this association remaining significant in males even after adjusting for risk factors[4]. Systematic reviews have also provided evidence for reduced methylation in the promoter regions of key genes such as *tumor necrosis factor* α, *estrogen receptor* α, and *microRNA-223* in stroke patients, and conversely, increased methylation of genes encoding cystathionine β-synthase and ATP-binding cassette G1 (*ABCG1*)[5]. Differential methylation of methylenetetrahydrofolate reductase (*MTHFR*), encoding a critical enzyme in one-carbon metabolism, is also correlated with risk for IS[6]. At the chromatin level, gene expression is regulated by histone modifications, such as those mediated by histone deacetylases (HDACs) which remove acetyl groups from histones. Notably, higher methylation levels of *HDAC9* have been associated with a reduced risk of IS[7]. These findings highlight the critical role of epigenetic mechanisms in understanding and addressing IS.

Bibliometrics involves the systematic application of statistical methods to analyze and quantify scientific and technical outputs across researchers, institutions, and countries. This approach combines qualitative and quantitative evaluations to highlight key metrics such as leading countries, institutions, journals, authors, and keywords over time[8]. By evaluating the current research landscape and trends, bibliometrics provides valuable insights into future research directions, aids in profiling research fields, trend analysis, impact measurement, and identifies emerging areas and collaboration opportunities[8]. While bibliometric analysis has been applied to various aspects of IS, studies specifically focusing on epigenetics in IS are limited. This study seeks to address this gap by employing bibliometric techniques on extensive datasets related to epigenetics in IS. It aims to address recent research, and identify key topics and emerging trends, thereby providing a foundational framework for future research.

As the first bibliometric analysis of its kind, this study aims to explore the following research questions: (i) What are the trends and patterns of advancement in epigenetics research related to IS up to 2024? (ii) Which documents, authors, and countries have made the most significant contributions to the study of epigenetics in IS? (iii) What are the key thematic structures and research themes identified in epigenetics research concerning IS? (iv) What are the

anticipated future research directions and emerging trends in the field of epigenetics and IS?

Materials and methods

Data preparation

The Web of Science Core Collection was used to identify 98 studies on epigenetics in IS as of July 31, 2024. Limiting the search to English-language articles, editorials, abstracts, proceedings, and reviews were excluded. The relevant records-covering countries, institutions, journals, authors, and more, using scientometric tools where then analyzed for a comprehensive evaluation.

Scientometric and bibliometric analyses

After preparing the data, R Studio was utilized with the Bibliometrix R package, an open-source tool for quantitative scientometric and bibliometric analysis. Bibliometrix offers advanced statistical and visualization tools and is complemented by Biblioshiny, a web-based platform for enhanced literature analysis. Using these tools, in-depth analyses were conducted to track research trends, emerging themes, and forecast future directions[8]. The academic impact was assessed with h-index and total citation (TC) metrics, key publications identified by citation analysis and Bradford's Law and Lotka's Law applied to evaluate journal productivity and author output.

VOSviewer 1.6.20[9] and CiteSpace 5.8[10] were utilized to analyze and visualize bibliometric data. VOSviewer created color-coded maps of keyword co-occurrence, highlighting prolific authors, co-cited journals, and key references after refining the dataset[9]. CiteSpace, known for its advanced document analysis features, provided dynamic views of co-citation networks, clustering publications by conceptual themes and revealing research trends over time[10]. While VOSviewer offered clear visualizations, CiteSpace's burst detection and cluster analysis were crucial for identifying significant developments. Together, these tools provided a comprehensive overview of the research landscape, unveiling influential publications and emerging trends.

Results

Overview

This study provides an in-depth assessment of research on epigenetics in IS, analyzing 47 papers from 37 journals published between 2014 and 2024. Key findings include an annual publication growth rate of 14.9%, an average document age of 4.43 years, and an average of 19.21 citations per document. Among the 383 authors, no single author worked alone, with international collaboration at 31.9% and an average of 10 co-authors per paper (Supplementary Fig. S1a). While there has been a consistent increase in global publications on epigenetics, peaking in 2022 with eight papers, citation rates fell sharply from an average of 58.5 per article in 2017 to 15 in 2018 (Supplementary Figs S1b, S1c). The Sankey diagram highlights key metrics, with 'Stroke' as a leading journal and Spain as the top contributor, particularly recognizing Israel Fernandez-Cadenas from Spain as a prominent author (Supplementary Fig. S1d).

Journal rankings and collaboration dynamics

Supplementary Table S1 ranks the most cited journals in epigenetics research related to IS based on h-index, Bradford's Law, and TC. The top 10 journals have h-index values ranging from 1 to 3 and TC from 5 to 206. *Clinical Epigenetics*, *Molecular Neurobiology*, and *Stroke*, all in Zone 1 of Bradford's Law, have the highest h-index of 3. *Molecular Neurobiology* leads in TC, indicating these journals are pivotal in the field.

Institutional contributions reveal that the Hospital Del Mar Research Institute in Spain leads with 12 publications, followed by Autonomous University of Barcelona with 10, and the State University of New York Buffalo with eight (Supplementary Table S2a). Among the 383 authors of 47 research papers, 94.6% have published fewer than two articles in the past decade, in line with Lotka's Law. The top authors by h-index are Fernandez-Cadenas Israel, Jimenez-Conde Jordi, and Roquer Jaume, all from Spain, each with six publications (Supplementary Table S2b).

Supplementary Table 2c summarizes country contributions and collaborations. China leads with 32% of the total publications, followed by Spain at 18%, and India at 10%. While China has the highest publication count (128 total, average 8.0), Spain leads in TC (205, average 22.8) and India also shows high citation rates (103, average 20.6). Supplementary Fig. S1e illustrates the global distribution of publications, with navy blue indicating the highest output, blue for moderate activity, and gray for no publications. Key collaborations include Spain-UK and Spain-USA, each with four co-authored papers, and USA-Sweden with three. Supplementary Table S3 highlights the most cited documents: Patnala et al.[11] in *Molecular Neurobiology* lead with 161 citations.

Scientific mapping and co-citation analysis

Scientific mapping with VOSviewer was used to analyze keyword frequency and co-citation patterns, revealing core knowledge and intellectual structures in the field. Co-citation analysis identified key publications and clusters, highlighting integration patterns and central topics. This approach is crucial for understanding the intersection of epigenetics and IS research, offering insights to guide future research and development.

Figure 1 illustrates the co-citation analysis of 47 journal articles and 2,624 references, identifying 14 key papers with at least five citations each. This analysis uncovered three prominent clusters, connected by 73 links, with a total link strength (TLS) of 130. Each cluster, differentiated by color and node size indicating citation volume, represents a distinct research stream in the field. Red Cluster 1 reveals key insights into IS, including the identification of *LINE-1* methylation as a cardiovascular risk biomarker[12], significant genetic factors associated with stroke subtypes[13], and the impact of DNA methylation on clopidogrel response and stroke recovery[14]. It also emphasizes the role of DNA methylation in stroke pathology[15], its effects on recovery outcomes and stroke subtypes[16,17], regional stroke disparities[18], and its involvement in atherosclerosis[19]. Green Cluster 2 reveals key advancements in methodology, including the TOAST classification for IS subtypes[20], improved normalization techniques for Illumina 450K data preprocessing[21], and breakthroughs in the characterization of the human DNA methylome and histone variants[22]. Blue Cluster 3 focuses on the significant role of *HDAC9* in large-vessel stroke. The studies reveal a connection between *HDAC9* genetic variants and an increased risk of large-vessel IS[23]. Additionally, elevated *HDAC9* expression is noted in carotid plaque and intima-media thickness[24], highlighting the importance of further validating these findings and conducting detailed stroke subtyping[25].

Bibliographic coupling

Bibliographic coupling examines citation patterns to reveal related research. Of the 47 documents reviewed, 43 met the citation threshold, forming a major cluster with 42 interconnected nodes. This cluster, detailed in Fig. 2a, is divided into eight sub-clusters with 199 connections and a TLS of 358, highlighting significant field interrelationships. Network analysis shows that larger nodes indicate higher citation weights, while larger labels represent higher PageRank values[9]. Figure 2b illustrates the overlay network,

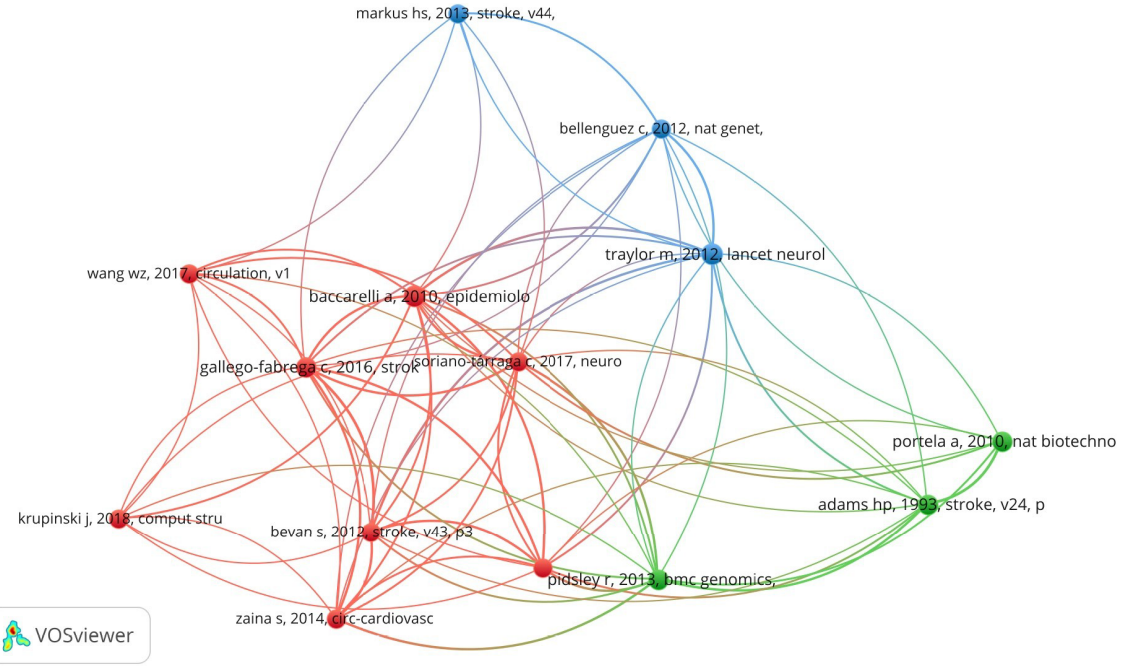

Fig. 1 Co-citation analysis of cited references.

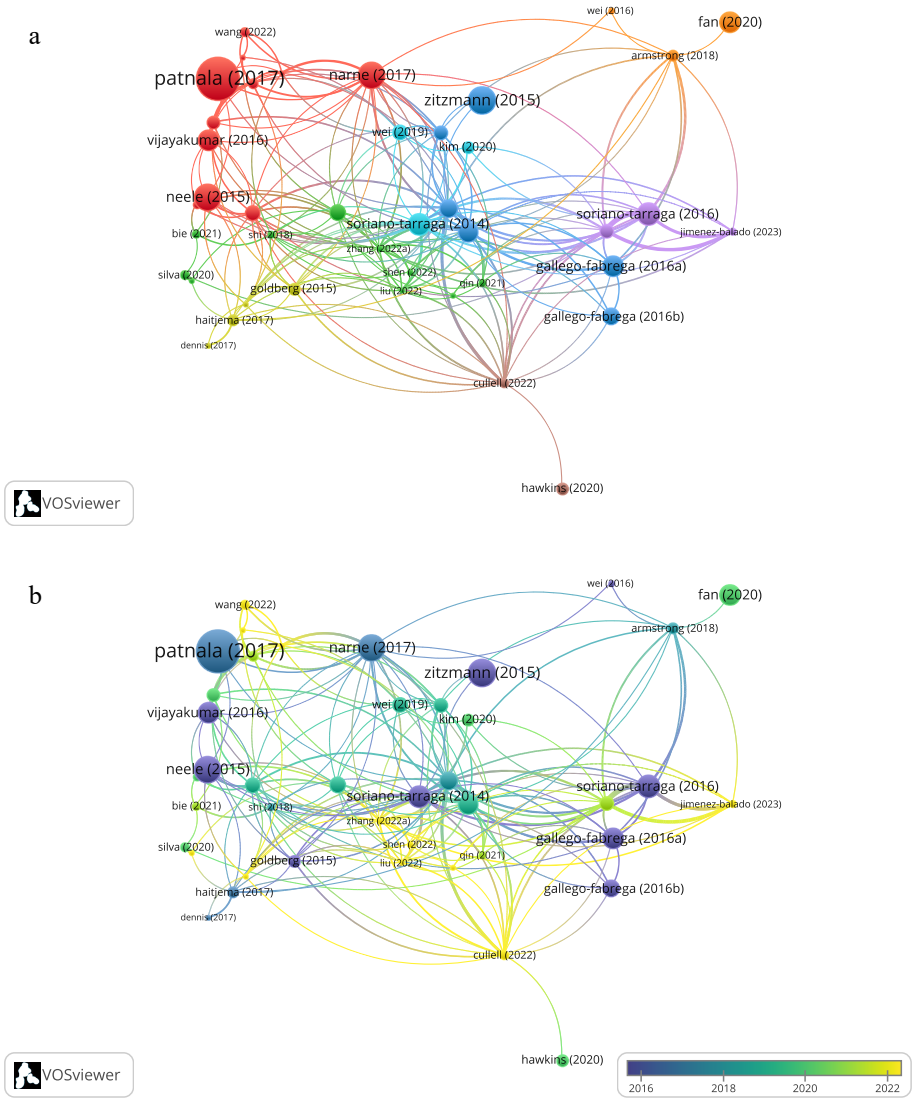

Fig. 2 Bibliographic coupling analysis. (a) Network visualization. (b) Overlay visualization.

mapping publication years and influence. The analysis identified eight sub-research clusters with conceptual similarities and five key themes, offering insights, and suggesting future research directions.

Based on Fig. 2a, Light Green Cluster 1, encompassing 11 articles, focuses on mitochondrial metabolism and epigenetics[26], *HDAC9* polymorphisms[27], histone modifications[28], epigenetic regulation in immune cells[29], and the therapeutic potential of epigenetic modifications[11]. Red Cluster 2 encompasses 10 studies discussing various epigenetic factors in IS, including DNA methylation[7], miRNAs[30], and circular RNAs such as *circRap1b*[31]. It also covers pathways and regulators such as the corin-B type natriuretic peptide (BNP)-neprilysin (NEP) pathway[32], RNA methylation regulators[33], and various types of methylation, including allele-specific methylation, *miR-335* and *miR-495*[34], calmodulin-binding transcription activator 1 (*CAMTA1*) methylation[35], and DNA methylation related to cardiometabolic traits[36]. Blue Cluster 3 highlights five studies on epigenetic modifications in IS. These studies examine the connection between DNA methylation and the *ABCG1* gene[5], reinforcing the significance of DNA methylation research, explore tumor necrosis factor receptor-associated factor 3 (*TRAF3*) methylation and vascular recurrence[14], investigate protein phosphatase Mg^{2+}/Mn^{2+} dependent 1A (*PPM1A*) gene methylation[37], and address hypomethylation of the *MTRNR2L8* gene[38]. Purple Cluster 4 includes four key studies focusing on genetic and epigenetic factors related to vascular and neurological diseases. These studies: identified genes associated with atherosclerosis using advanced chromatin capture techniques[39]; mapped stroke-related single nucleotide polymorphisms (SNPs) to specific genomic regions; reported a GWAS on plasma levels of tissue factor pathway inhibitors, revealing significant SNPs[40]; and highlighted the importance of large-scale genomics in advancing the diagnosis and treatment of neurological disorders. Green Cluster 5 includes three studies focusing on the relationship between biological age (b-Age) and stroke[41], b-Age and white matter hyperintensities[42], and the effectiveness of b-Age as a predictor for stroke recurrence[43]. Light Blue Cluster 6, comprising three studies, highlights that: elevated tumor protein p53 (*TP53*) promoter methylation is observed in IS patients[44]; global DNA methylation levels do not vary significantly across IS subtypes[16]; and significant promoter methylation changes are present in the autoimmune regulator (*AIRE1*) and arachidonate 12-lipoxygenase (*ALOX12*) genes within atherosclerotic plaques[45]. Orange Cluster 7 includes three studies, i.e. development of a rapid pyrosequencing assay to analyze DNA methylation in the *MTHFR* gene[3], identification of *lncRNA_H19* as essential for neurogenesis and stroke recovery, and discovery of ankyrin repeat and SOCS box containing 10 (*ASB10*) and tetratricopeptide repeat domain 37 (*TTC37*) methylation sites as potential biomarkers for stroke risk[46]. Lastly, Light Red-Violet Cluster 8 focuses on advanced research methods and their implications for IS, including epigenome-wide association studies (EWAS), genome editing, advanced sequencing, and single-cell analysis (Fig. 2a).

Thematic analysis and trend topic

CiteSpace was used to map the evolution of research on epigenetics in IS, highlighting key areas and trends. Figure 3a displays the main keywords, while Fig. 3b presents a thematic analysis of nine research clusters organized by density and centrality. Themes such as 'genome-wide association' and 'coronary-artery-disease' are less central, whereas 'cerebral-ischemia', 'methylation', and 'inhibition' are more relevant. Core, but less dense themes such as 'model' and 'focal cerebral-ischemia' show high centrality. Emerging niche areas in the upper left quadrant, like 'cholesterol' and 'histone deacetylase inhibitors', exhibit high density but lower centrality. Dominant themes in the upper right quadrant, including 'expression' and 'gene-expression', have both high density and centrality, outshining 'mechanisms' and 'brain'. Overall, central concepts such as 'ischemic stroke', 'DNA methylation', and 'epigenetics' are crucial, with 'clopidogrel' and 'management' emerging as key themes in the evolving research landscape. Supplementary Table S4 highlights the evolution of key topics in epigenetics and IS from 2014 to 2024. 'Methylation' emerged prominently in early 2016, mid-2018, and late 2020, while 'epigenetics' gained attention in early 2017, mid-2020, and late 2022. The TreeMap visualization in Fig. 3c 'ischemic stroke' as the most frequently used term (14%), followed by 'DNA methylation' and 'epigenetics' (11% each). The TreeMap's color-coded rectangles represent these keywords, with rectangle size indicating the frequency of their occurrence in publications.

Research hotspots and timeline analysis

In CiteSpace, color-coded clusters reveal the emergence of common reference links within specific domains, with prominent works indicated by large nodes due to their high h-index. Figure 4 illustrates the citation network from 2014 to 2024, featuring 13 clusters with parameters set at LRF = 2.5, LBY = 5, L/N = 10, and e = 1.0. CiteSpace analysis shows a highly modular network with a modularity score of 0.78, signifying distinct clusters. The mean silhouette value of 0.94 indicates excellent cluster quality, while a harmonic mean of 0.85 reflects high accuracy and recall. The network, comprising 249 nodes and 806 edges across 47 articles, has a density of 0.03, with no pruning applied to the initial 25 references.

Among the 13 clusters shown in Figs 4 and 5, the timeline for 10 clusters from 2014 to 2024 reveals their evolving themes. Cluster 0, focused on 'cerebral ischemic preconditioning', is the most prominent, while Cluster 9, related to 'transcription' is the smallest. All clusters have been active for at least five years, with Cluster 9 emerging in the past two years. Of which, Cluster 0, with a silhouette value of 0.93, includes 34 members, and Cluster 1, with a silhouette value of 0.99, has 29 members (Supplementary Table S5). This analysis highlights persistent research engagement and thematic concentration in epigenetics.

Citation bursts reveal periods of rapid citation growth, highlighting significant research trends and emerging hotspots. Analyzing these bursts, including factors like author details, publication dates, and burst intensity, helps identify shifts in research focus. Among the 10 bursts analyzed, Pidsley et al.'s publication[21], denoted as a red node in Cluster 3, achieved the highest burst strength of 1.76, marking it as a key influential work with a significant citation surge since 2018 (Fig. 5).

Co-words analysis

Co-words analysis, which examines keyword frequency to reflect article content, was performed using VOSviewer on 47 articles, identifying 75 distinct keywords. This analysis generated seven clusters, with 687 links and a TLS of 987 (Fig. 6a). In the visualization, larger nodes and thicker lines represent higher keyword frequency and stronger relationships. The key clusters identified include: 'epigenetics' (36 occurrences, TLS 210), 'DNA methylation' (19 occurrences, TLS 101), 'stroke' (13 occurrences, TLS 94), 'ischemic stroke' (13 occurrences, TLS 78), and 'risk' (10 occurrences, TLS 69). The overlay visualization demonstrates keyword trends over time: 'ischemic stroke' emerged in 2018, 'epigenetics' in mid-2019, and both 'DNA methylation' and 'stroke' from 2020 onwards (Fig. 6b).

Discussion

Bibliometric analysis

The field of epigenetics in IS has seen substantial growth, attracting significant interest from clinicians, especially neurologists, as

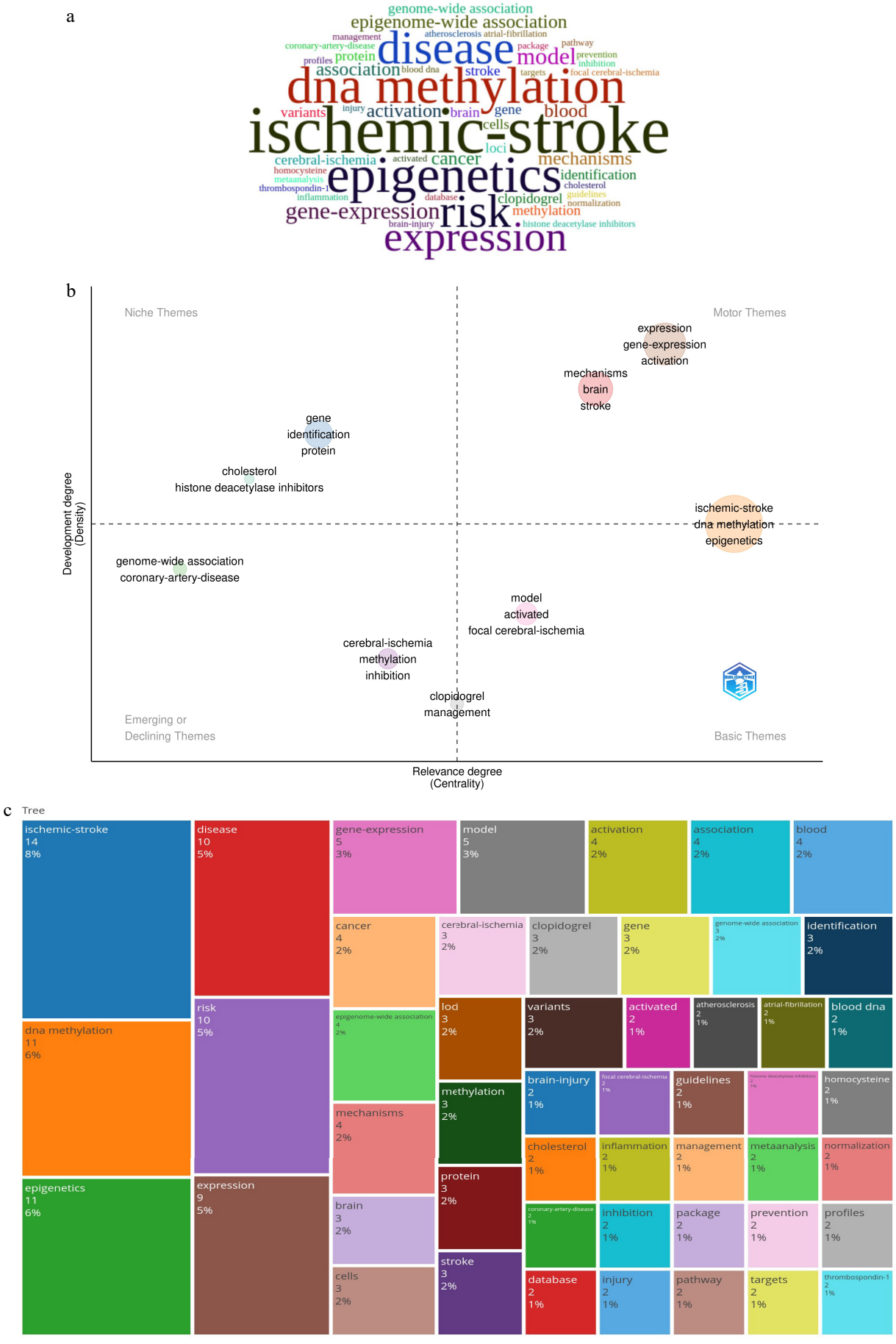

Fig. 3 Research hotspots and future trends. (a) Word frequency, (b) thematic analysis, and (c) TreeMap diagram.

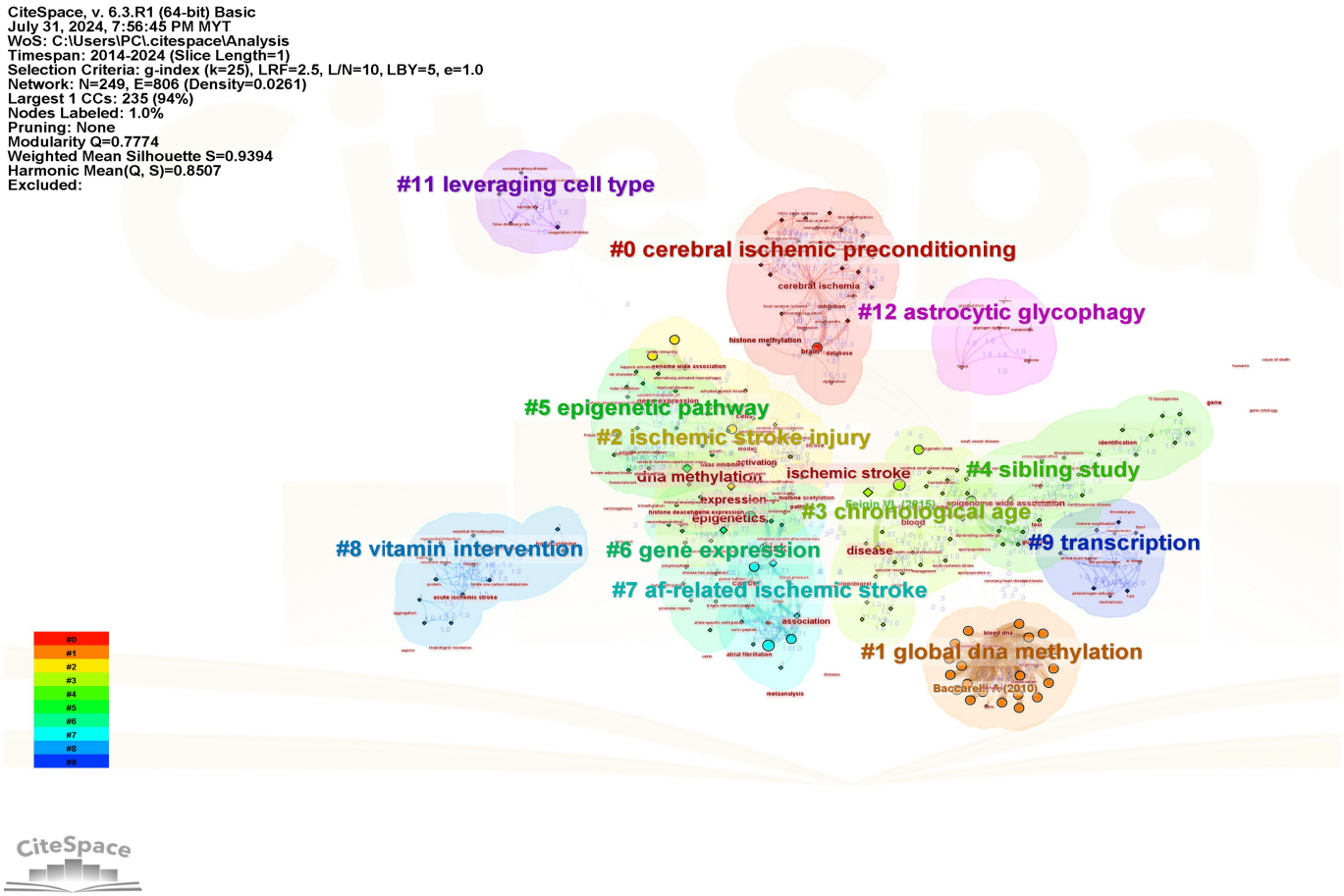

Fig. 4 Panoramic overview of the common keywords and co-cited references.

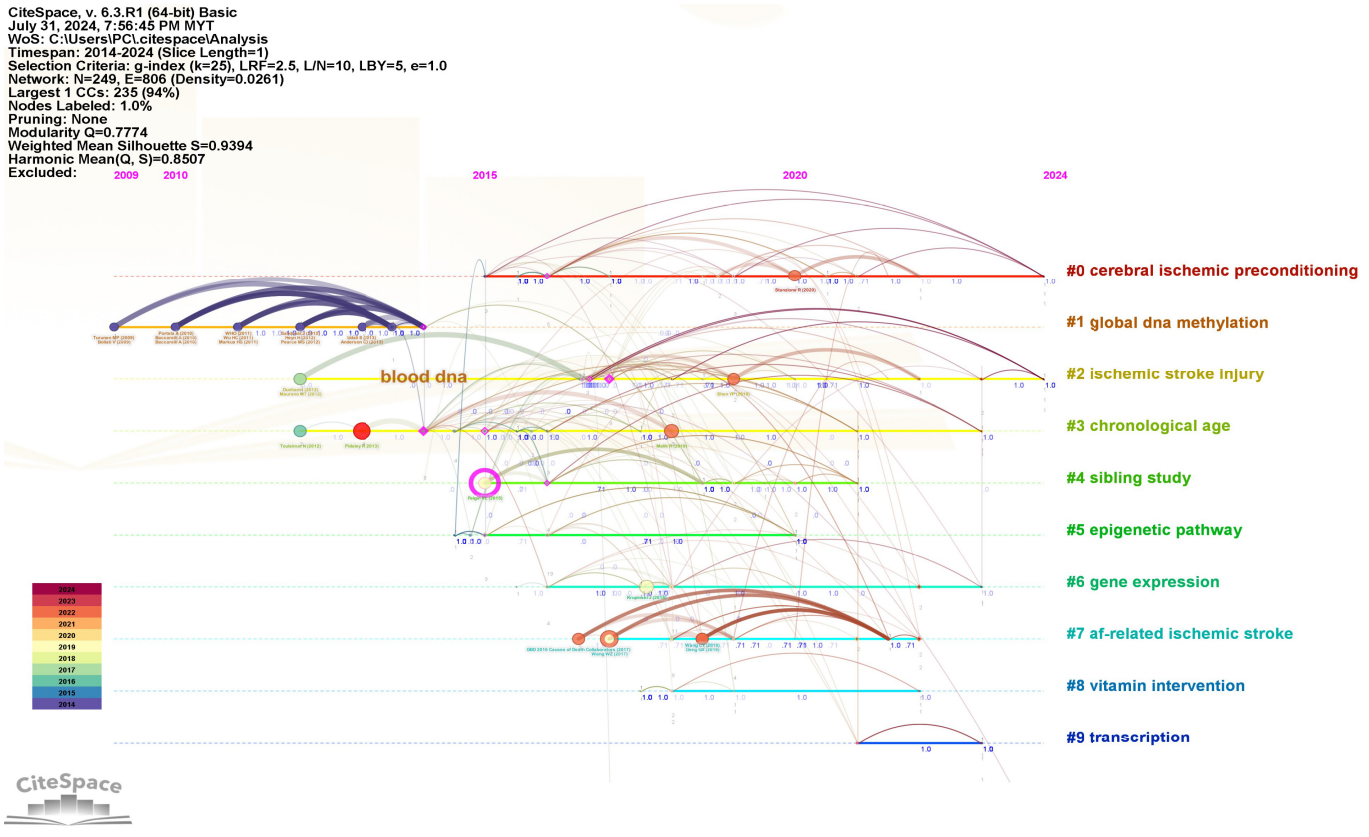

Fig. 5 Timeline analysis and citation burst analysis.

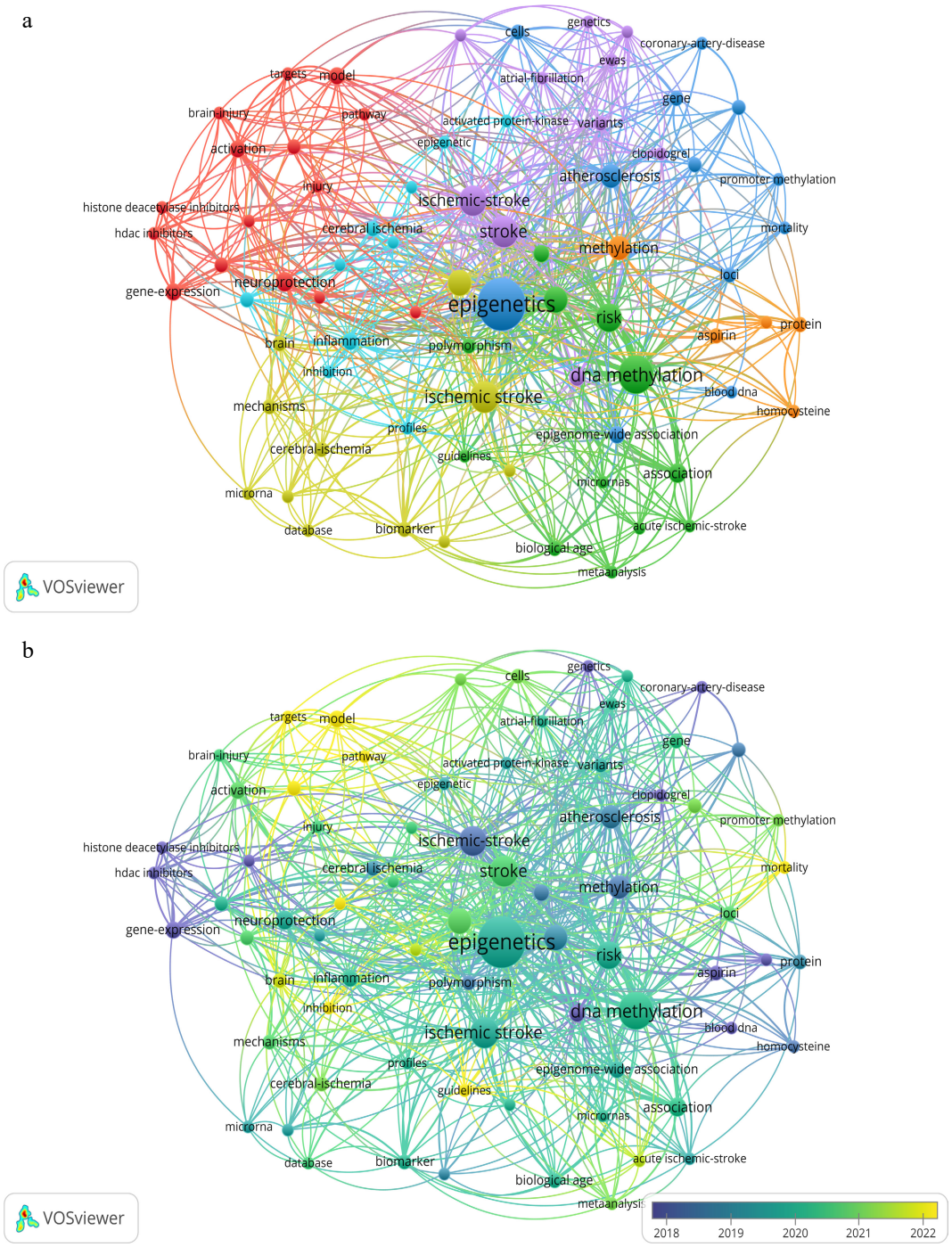

Fig. 6 Co-words analysis. (a) Network visualization, (b) overlay visualization.

well as researchers in neuroscience and medical sciences. This heightened focus has led to a burgeoning body of literature, including diverse articles[14,15], clinical studies[34,36], systematic reviews, and meta-analyses[6] on various aspects of IS. Although the concept of epigenetics emerged decades ago, substantial research in this area, particularly relating to IS, only began to accelerate around 2015. Despite this progress, comprehensive bibliometric analyses of this niche remains sparse, positioning this study as a trailblazer in providing a detailed bibliometric assessment.

The present analysis reveals a steady increase in publications on epigenetics and IS, starting with early works by Turunen et al.[47] and Baccarelli et al.[12]. Since 2022, there has been a consistent rise in the volume of publications, though at a moderate pace. This study offers a foundational bibliometric review, leveraging the epigenetics framework to map out key authors, influential journals, institutions, and countries involved in IS research. By encompassing all relevant publications up to July 31, 2024, the study delivers a comprehensive snapshot of the field's evolution, highlighting key contributors and emerging trends.

The bibliometric data indicates a steady growth in publication volume, with an annual increase of 14.9%. Papers in this field average 4.43 years in age and garner approximately 19.2 citations each. The trend towards collaborative research is evident, with no solo authors and international collaboration comprising 31.9% of co-authorships. The Sankey diagram analysis underscores 'Stroke' as a leading journal and identifies prominent contributors such as Israel

Table 1. Genetic loci associated with ischemic stroke identified in research articles published by the top 10 most cited leading authors.

Authors (reference)	Types of epigenetic modifications	Location of epigenetic modifications	Epigenetic regulatory mechanisms
Fernandez-Cadenas I; Caty C; Natalia C; Jerzy K; Joan M; Elena M[14]	Site specific DNA methylation	CpG sites within the *TRAF* gene	Reduced DNA methylation of *TRAF3*, which activates immune responses, was closely linked to vascular recurrence and increased platelet aggregation in IS patients.
Fernandez-Cadenas I; Jiménez-Conde J; Jaume R; Elisa CG; Natalia C; Eva GS[15]	Site specific DNA methylation	CpG sites within the *THBS2*, *ZFP57*, *ALOX12*, *ABI3*, *ALLC* genes	Reduced DNA methylation at a CpG site in the *THBS2* gene was linked to adverse stroke outcomes at three months. Furthermore, four differentially methylated regions (DMRs) were also associated with stroke outcome at the *ZFP57*, *ALOX12*, *ABI3*, and *ALLC* genes, which have all been implicated in atherogenesis and cognitive impairment.
Fernandez-Cadenas I; Jiménez-Conde J; Jaume R; Caty C; Elisa CG; Eva GS; Joan M[16]	Global DNA methylation	Genome-wide	No global methylation differences were observed among IS subtypes large-artery atherosclerosis, small-artery disease, or cardio-aortic embolism.
Fernandez-Cadenas I; Caty C; Natalia C; Jerzy K; Joan M; Elena M[37]	Site specific DNA methylation	CpG sites within the *PPM1A* gene	*PPM1A* methylation, influencing TGF-β1 signaling and the transcription of plasminogen activator inhibitor-1, was linked to vascular recurrence in aspirin-treated patients.
Fernandez-Cadenas I; Jiménez-Conde J; Jaume R; Jerzy K; Joan M; Elena M[49]	Global DNA methylation	CpG sites within the *ZFHX3* and *MAP3K1* genes	Methylation of *ZFHX3* and *MAP3K1* regulates stroke subtype risk by altering gene expression. Hypomethylation of *ZFHX3*, involved in myogenic and neuronal differentiation, increases cardioembolic stroke risk, while *MAP3K1* shows methylation changes linked to stroke. Mendelian randomization identifies these modifications as key drivers of cardioembolic, atherothrombotic, and lacunar stroke risk.
Jiménez-Conde J; Elisa CG[41]	Global DNA methylation	Genome-wide	IS patients were found to be biologically older than their chronological age, especially in younger individuals, and exhibit significant increases in the Hannum DNA methylation clock.
Jiménez-Conde J; Jaume R; Elisa CG; Eva GS[42]	Global DNA methylation	Genome-wide	The epigenetic clock, determined by DNA methylation, significantly accounts for the burden of white matter hyperintensities, independent of chronological age.
Jiménez-Conde J; Jaume R; Elisa CG; Eva GS[43]	Global DNA methylation	Genome-wide	b-Age is a crucial biomarker for predicting stroke recurrence, with higher b-age associated with elevated risk.

* These top 10 most cited authors were extracted from Supplementary Table S2b. *ABI3*: ABI family member 3, *ALLC*: allantoicase, *ALOX12*: arachidonate 12-lipoxygenase 12S type, b-Age: biological age, *MAP3K1*: mitogen-activated protein kinase kinase kinase 1, *PPM1A*: protein phosphatase, Mg^{2+}/Mn^{2+} dependent 1A, *THBS2*: thrombospondin-2, *TRAF3*: tumor necrosis factor receptor-associated factor 3, protein phosphatase, *ZFP57*: zinc finger protein 57 homolog, TGF-β1: transforming growth factor beta 1, *ZFHX3*: Zinc finger homeobox 3.

Fernandez-Cadenas from Spain. Spain is recognized as a key player, though China leads with 16 publications. The publication of Patnala et al.[11] in *Molecular Neurobiology* has had a significant impact, and top contributing institutions to the topic of epigenetics and IS include Hospital Del Mar Research Institute, Autonomous University of Barcelona, and State University of New York Buffalo.

Past and current research on DNA methylation and ischemic stroke

This study employs CiteSpace to visualize and analyze trends in epigenetics research. By mapping key themes and intellectual structures, it identifies 10 major thematic clusters and examines their evolution over time. The analysis includes timeline and burst detection, which reveal significant trends in epigenetics related to IS, highlighting both the persistence and development of these research areas.

Over the past decade, research into epigenetics and IS has advanced significantly (Table 1), unveiling complex relationships between genetic and environmental factors[13,47,48]. Early studies primarily focused on how epigenetic modifications, such as DNA methylation, influence stroke pathology[16,17]. Recent research has highlighted the crucial role of these modifications in both stroke risk[6] and recovery[48], particularly through mechanisms like cerebral ischemic preconditioning[29]. This approach holds promise for developing novel treatments by inducing a protective state against severe ischemic events[17]. For instance, the discovery of altered global DNA methylation in stroke patients and its association with various stroke subtypes and atherosclerosis highlights the potential for subtype-specific therapies[16]. Moreover, advancements in epigenetic research, including innovations in mapping DNA methylation and histone modifications, provide essential tools for developing and refining these therapeutic strategies[12,24,26]. By integrating these epigenetic insights with strategies like cerebral ischemic preconditioning, researchers can advance treatment methods and improve stroke management. This approach, informed by ongoing epigenetic research, promises to enhance our ability to protect against and treat severe ischemic events.

Likewise, advancing our understanding of global DNA methylation patterns is crucial for improving research and treatment strategies for IS. The ENCODE project has provided invaluable insights into genomic features, including transcription regions and chromatin structures, revealing functional elements across 80% of the human genome[50]. These insights demonstrate how non-coding variants, particularly those active during fetal development, impact gene regulation and are associated with IS[38,50]. Shen et al.[38], identified 1,012 differentially methylated CpG sites related to large-artery atherosclerotic stroke, which highlights the significance of DNA methylation as a diagnostic and therapeutic target. Additionally, the findings of Meng et al.[51] on the effect of electroacupuncture in modulating gene expression through histone acetylation further highlights the importance of epigenetic modifications in stroke recovery. Advances in DNA methylation analysis, including the development of biomarkers such as b-Age for predicting stroke recurrence[43], emphasize the need to integrate these epigenetic insights into stroke prevention and management strategies. Key epigenetic markers, such as allele-specific DNA methylation affecting genes like *ALOX5AP*, have been identified as modulators of stroke phenotypes, suggesting potential targets for intervention[34]. Additionally, hypermethylation of specific genes, including major histocompatibility complex, class II (*HLA*)-DR beta 1 (*DRB1*) and *HLA-DQ beta 1* (*DQB1*), has been linked to IS pathology, offering

potential biomarkers for disease prognosis and targeted therapies[52].

The integration of epigenetic research with non-invasive brain stimulation techniques is also showing promise in enhancing post-stroke rehabilitation[48]. Methods like transcranial magnetic stimulation and transcranial direct-current stimulation are being investigated for their potential to improve recovery from stroke-induced dysphagia. Although results are mixed, this area of research highlights the need for further validation and exploration[48]. Moreover, there is growing interest in how environmental factors and lifestyle interventions, such as vitamin supplementation[53], impact epigenetic modifications and stroke risk[6]. These developments highlight the increasing recognition of epigenetics as a critical factor in stroke research, opening new avenues for personalized treatments and preventive strategies. The trend toward integrating epigenetic insights into clinical practice reflects a broader shift toward more precise and effective approaches in stroke management and prevention.

Future research directions

Future research in IS should prioritize the development of targeted therapies that leverage specific epigenetic modifications. Emphasis should be placed on exploring the potential of HDAC inhibitors[11,24-26] and miRNA-based treatments to craft personalized interventions[30,41]. By tailoring therapies to individual epigenetic profiles, these approaches hold promise for more effective and targeted therapeutic outcomes. In addition to therapy development, there is a pressing need for the validation of new biomarkers that can accurately predict stroke risk and progression[28,31]. Research should focus on confirming the diagnostic and prognostic value of various epigenetic markers, including specific DNA methylation sites and circRNAs[31]. This validation process will require studies involving larger and more diverse cohorts to ensure reliability and applicability[28]. Integrating epigenomic data with existing genomic and clinical information presents an opportunity to enhance stroke risk prediction and treatment strategies[15,38,42,44,45]. Employing advanced methodologies such as EWAS and chromatin capture techniques will be crucial for identifying and mapping new stroke-associated genes and pathways[47]. This integration could lead to more precise risk assessments and tailored treatment approaches. The use of advanced technological tools should also be a priority in future research. Innovations such as genome editing, single-cell sequencing, and rapid pyrosequencing offer the potential to provide deeper insights into the molecular mechanisms underlying stroke[3,47]. These technologies could facilitate the discovery of novel therapeutic targets and improve our overall understanding of stroke pathology. Another important area for exploration is the use of b-Age as a biomarker for stroke risk[42,44]. Investigating how DNA methylation can determine b-Age may improve stroke risk assessment and help develop targeted preventative strategies. This approach is particularly relevant for younger individuals who may be biologically older than their chronological age, indicating a higher risk despite their youth[43]. Finally, a comprehensive investigation into global DNA methylation patterns and specific gene methylation changes is essential[17]. Establishing detailed epigenetic profiles could reveal additional factors relevant to IS and guide the development of personalized treatment and monitoring strategies. In summary, integrating insights from epigenetic research with cutting-edge technologies and biomarker discovery is crucial for advancing stroke prevention, diagnosis, and treatment. By adopting a personalized and targeted approach, future research can lead to more effective and individualized interventions, ultimately improving outcomes for patients with IS.

Study limitations

One limitation of this review reflects the intricate nature of epigenetic modifications and their interactions with other biological factors, which complicates the isolation of specific effects. Although histone modifications and DNA methylation have been identified as key players, they may work interdependently, and their roles are also influenced by a multitude of variables, making it challenging to pinpoint their exact contributions to IS. Additionally, various studies have relied on cross-sectional data, which restricts our ability to establish causal relationships between epigenetic changes and IS. Longitudinal research is needed to better understand how epigenetic modifications evolve and their impact on stroke risk and progression. Likewise, the concept of b-Age as a biomarker for stroke risk, while promising, presents complexities in measurement and interpretation. For example, variability in b-Age assessment methods and a lack of standardization may affect the consistency and clinical relevance of findings. Furthermore, many potential biomarkers, such as specific DNA methylation sites and circRNAs, require validation in larger, more diverse populations to confirm their diagnostic and prognostic value. Thus, while the study offers valuable insights into the role of epigenetics in IS, the limitations such as methodological variability, and the need for further validation underscore the need for future research. Addressing these limitations through larger, more diverse studies and standardized methodologies will be essential for advancing the field and translating findings into effective clinical applications.

Conclusions

This bibliometric analysis has concluded critical advancements in IS research, offering a comprehensive view of emerging trends, influential authors, and key institutions. Notably, Fernandez-Cadenas Israel has emerged as a pivotal figure in this field, with Spain recognized as a leading contributor, particularly through impactful publications in the esteemed journal Stroke. Evolving research, from unraveling the intricate interplay between genetic and environmental factors to focusing on site-specific and global epigenetic modifications such as DNA methylation, has set the stage for innovative stroke subtype-specific therapies and the identification of crucial molecular biomarkers. Recent studies have highlighted the significance of b-Age and vitamin supplementation in stroke research, alongside an increased emphasis on transcriptional regulation. Investigating how DNA methylation affects b-Age could revolutionize stroke risk assessment and enable the formulation of personalized preventative strategies. This study has compiled recent work demonstrating the impact of epigenetic alterations on stroke pathology, and promising therapeutic targets and biomarkers. Furthermore, the integration of epigenomic data with genomic and clinical insights is essential for advancing stroke risk prediction and treatment methodologies. This research outlines the transformative potential of epigenetics in reshaping our understanding of IS, paving the way for more effective prevention and treatment strategies. By focusing on personalized, targeted approaches, future research can leverage these insights to develop more effective interventions, ultimately enhancing patient outcomes in stroke management.

Author contributions

The authors confirm contribution to the paper as follows: Study conception and design, draft manuscript preparation, resources, analysis and interpretation of results: Wei LK; resources, manuscript editing & revision: Sutherland HG, Griffiths LR; study supervision:

Griffiths LR. All authors reviewed the results and approved the final version of the manuscript.

Data availability

All data generated or analyzed are included in this published article.

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Conflict of interest

The authors declare that they have no conflict of interest.

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